# NEW NICKEL COMPOUNDS FOR ALKYLATION AND FLUOROALKYLATION STUDIES

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By

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Finally, I would like to thank my friends from here and back home to make my stay here enjoyable.

# Dedication

To my family members, especially to my niece Kundana Sri Harshini for influencing me in every aspect of life

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| β | Beta |
| α | Alpha |
| º | Degree |
| C | Celsius |
| $ | Dollar |
| EPR | Electron Para Magnetic |
| UV | Ultra violet |
| Vis | Visible |
| % | Percent |
| mL | Milliliter |
| NMR | Nuclear Magnetic Resonance |
| mg | Milligrams |
| mmol | Millimols |
| MHz | Mega Hertz |
| hrs | Hours |
| eV | Electron Volt |
| α | Alpha |
| [ ] | Concentration |
| Aº | Angstroms |
| d | Doublet ( Spectral ) |
| nm | Nanometer |
| Ph | Phenyl |

| | |
|---|---|
| bpy | 2,2’-bipyridine |
| phen | 1,10-Phenanthroline |
| terpy | 2,2’,6’’-terpyrydine |
| bpip | 2,5-bis(1-phenyliminoethyl)pyrazine |
| bdip | 2,5-bis[1-(3,5-demethylphenyl)iminoethyl]pyrizine |
| btip | 2,5-bis[1-(2-methylphenyl)-iminoethyl]pyrazine |
| bxip | 2,5-bis[1-(2,6-dimethylphenyl)iminoehtyl]pyrazine |
| bmip | 2,5-bis[(2,4,6-trimethylphenyl)iminoethyl]pyrazine |
| bpym | 2,2’-bipyrimidine |
| Mes | 2,4,6-trimethylphenyl |
| $PPh_3$ | Triphenylphosphine |
| $P(Cyp)_3$ | Tricycopentylphoshpine |
| $P(^tBu)_3$ | Tri-(tertiarybutyl)phosphine |
| Me | Methyl |
| XPhos | 2-Dicyclohexylphosphino-2’, 4’, 6’-triisopropylbiphenyl |
| Sphos | 2-Dicyclohexylphosphino-2’, 6’-dimethoxybiphenyl |
| dppb | 1, 4-Bis(diphenylphosphino)butane |
| dppe | Ethylenebis(diphenylphosphine) |
| dmpe | 1,2-Bis(dimethylphosphino)ethane |
| dppp | 1,3-Bis(diphenylphosphino)propane |

# Chapter 1

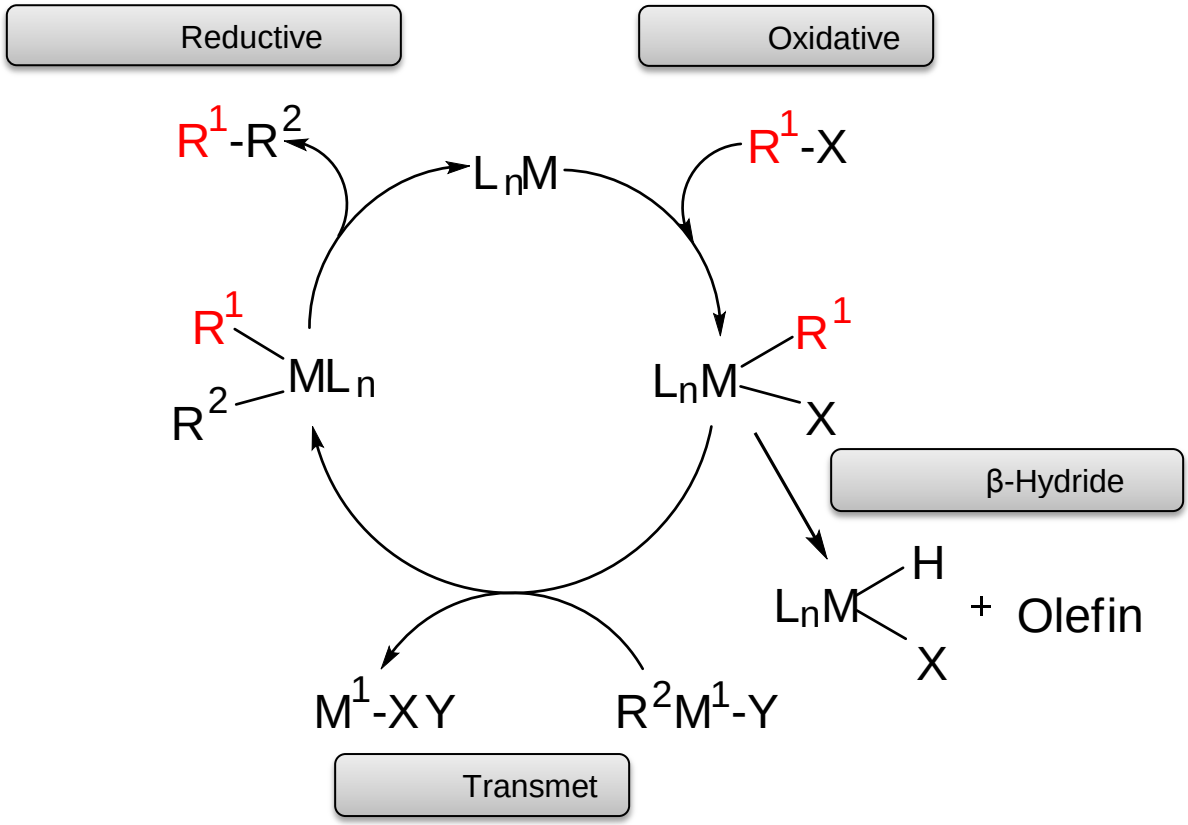
# Introduction to Cross-Coupling Reactions

In the area of drug discovery, synthetic organic chemistry plays a vital role in the preparation of complex molecules. Carbon-carbon bond formation is the major step in making of such complex synthetic organic molecules. In the last three decades, transition metal-catalyzed cross-coupling reactions to form C-C bond by use of an organic electrophile and an organometallic nucleophile has become an important tool in the field of synthetic chemistry. This tool is allowing chemists to make complicated organic frameworks with ease in diversified areas like natural products in the pharmaceutical industry, materials, and nanotechnology.[1] The importance of this area was recognized by the award of the Noble prize in chemistry to Richard Heck, Ei-ichi Negishi, and Akira Suzuki for their contribution in cross-coupling reactions.[2]

Cross-coupling reactions can involve a broad range of substrates. The nucleophiles can be alkyl, alkenyl, alkynyl, allyl, aryl and benzyl groups. Electrophiles are often narrowed to aryl, alkenyl, and activated alkyl groups.[1] $C_{(sp2)}$-$C_{(sp2)}$ bond forming reactions have advanced compared to the $C_{(sp2)}$-$C_{(sp3)}$ bond forming reactions because of limitations associated with the $C_{(sp3)}$ organometallic reagents. Transition-metal alkyls are likely to participate in β-hydride elimination processes. Any cross-coupling reaction that involves activation of alkyl nucleophiles and alkyl electrophiles should consider this undesired side

reaction.[3] Scheme **1.1** shows the general transition-metal catalyzed cross-coupling reaction mechanism.

**Scheme 1.1**: General transition metal-catalyzed cross-coupling reaction mechanism




A typical metal-catalyzed cross-coupling reaction starts with the oxidative addition step, in which the metal atom inserts in between the carbon-halogen bond. In this step the metal changes its oxidation number. Transmetalation is the next step in this mechanism, in which a nucleophile displaces the metal bound

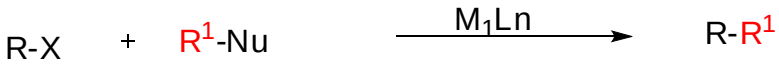
halogen. At the end of this step metal $M^1$ now has a halide co-ordinated to it. Both the organic coupling partners stay on the metal (M) after step.

The desired coupling product is obtained from the reductive elimination step. The metal catalyst gets reduced to give a carbon-carbon bond-coupled product. The big asset of catalytic cross-coupling reaction is that the catalyst can be regenerated at the end of the cycle and can take part in additional catalytic cycles. Historically, the coupling of non-activated alkyl halides, especially those with β-hydrogen atoms, has been challenging because the reductive elimination is not the only pathway in the catalytic cycle. Oxidative addition of alkyl halides is more complex than that of alkenyl and aryl halides. Even if the oxidative addition happens, the resulting metal alkyl species can lose a hydrogen and give unproductive β-hydride elimination.[4-10] In addition to the above problems, alkyl halides are likely to undergo other side reactions, such as base-assisted HX elimination (X=halide) and halide exchange reactions under coupling conditions.[11] Because of the above reasons the coupling of non-activated alkyl halides is less common than that for aryl and vinyl electrophiles.

It is essential to choose reaction conditions that can help to promote reductive elimination over β-hydride elimination and other side reactions in the catalytic cycle. There are several other factors that control the catalytic pathway, such as metal, temperature, ligands, electronic and steric environment on the substrates and so on. The one that will be important and discussed in this chapter is the choice of conditions (choice of solvent, metal, ligand, and etc) used in different catalytic systems.

The following Scheme **1.2** is the basic reaction path for the cross-coupling reactions.

**Scheme 1.2:** Basic cross-coupling reaction




R,$R^1$ = $sp^3$,$sp^2$,sp - hybridized organic substartes

$M_1$ = Pd, Ni, Fe

X = Halides, OTf, $OPO(OEt)_2$

Ln = Ligand

The names of different cross-coupling reactions are based on the nucleophiles used. You can classify the major cross-coupling reactions as follows from Table **1.1**.

| Name of the coupling Reaction | Nu |
|---|---|
| Negishi | -ZnX |
| Suzuki-Miyura | -Boronate |
| Kumada | -MgX |
| Stille | $-SnR_3$ |
| Hiyama | $-SiR_3$ |

**Table 1.1:** Types of cross-coupling reactions

In the 1970's, new processes involving lithium and magnesium reagents with catalytic and stoichiometric amounts of copper halides emerged. Most of these reactions were limited to $sp^3$ electrophiles. The immense basicity and nucleophilicity of the lithium and magnesium reagents limited their usage with a variety of functional groups. The Corey-House coupling reaction between alkyl halides in the presence of cuprates helped to avoid chemoselectivity problems, but couldn't overcome other problems like stoichiometric usage of metal catalyst. In 1971, Kochi reported efficient coupling between 1-alkenyl bromides and Grignard reagents in the presence of iron(III)chloride.[12] In 1972 Kochi reported effective $C_{sp3}$-$C_{sp3}$ coupling with dilithiumtetrachlorocuprate(II) for iodoalkanes and magnesium reagents.[13] Transition metal complexes with Ni, Pd and Fe metals as catalysts open up the scope in cross-coupling reaction field. In 1972 Kumada and Tamao successfully coupled aryl bromides and Grignard reagents using nickel catalysts.[14]

In the early development of cross-coupling reactions, magnesium and lithium based reagents were largely explored, which placed limits on the functional group compatibility, and competition between the halogen and metal exchange led to homo-coupling products. In comparison with nickel derivatives, palladium derivatives were also capable of promoting cross-coupling reactions and showed advantages than nickel derivatives. Palladium catalysts and less reactive organometallic nucleophiles showed encouraging results that broaden the substrate scope in cross-coupling product formation. Negishi reported the efficiency of palladium-catalyzed complexes with vinyl, aryl halides and alkenyl-

zinc,[15] and 1-alkenyl-aluminium.[16] Normat[17] developed alkenyl-copper derivatives "*in situ*", and used them to couple with 1-alkenyl halides with the help of Pd-catalysts.

Migata and Kosugi[18] used organostannane derivatives and Stille[19] extended their work to overcome functional group compatibility in cross-coupling reactions. Organoboron derivatives were introduced by the Suzuki and Miyaura[20] in the presence of base helped to promote cross-coupling smoothly for a wide range of functional groups. During this era, palladium became the metal of choice for Stille and Suzuki-Miyaura coupling reactions.

Negishi[21] introduced zinc reagents as nucleophiles to couple with electrophiles in the formation of C-C bonds. Negishi cross-coupling reactions allowed higher functional group tolerance than other coupling reactions. Negishi used Pd-catalyzed catalysts, homoallylic and homopropargylic alkylzinc reagents and synthesized 1,5-dienes and 1,5-enynes, which constitute the core structure of terpenoids. Negishi found that primary and secondary alkylzinc reagents were more reactive than corresponding alkylmagnesium reagents for the conditions he used. For a very long time coupling reactions were restricted to alkyl-alkyl couplings and $sp^2$ (alkenyl and aryl derivatives) electrophiles. The classical approaches failed in controlling β-hydrogen eliminations when using alkyl halides and pseudohalides. This meant that only methyl, allyl, and benzyl derivatives couple effectively. The problem of β-hydride elimination in palladium-alkyl intermediates could be stopped when used sterically-strong and highly electron donating trialkyl phosphines.[22] In this chapter I will go through the development of

nickel catalyzed Negishi cross-coupling reactions, because much of my work is focused on understanding these reactions in detail.

**1.1 Nickel**:

Along with the palladium-catalyzed couplings, nickel based cross-coupling reactions have gained importance over time, because of the ability to couple to various $C_{sp2}$–X electrophiles during C-C bond formation.[23] The cost per mole of Ni is $1.20, whereas Pd, Pt are precious metals costing $1,500 and $10,000. So in terms of cost efficiency, Ni has advantages over other two metals. Nickel is readily accessible to a greater number of oxidation states (0 to +4), while Pd is generally limited to (0, +2). Many nickel (0,+2) complexes form with ligands such as carbene, olefin, carbon monoxide and nickel (II) with alkyl, allyl, aryl, and hydride as ligands.[24] Nickel (II) complexes with alkyl, aryl, allyl are generally prepared by transmetalation of nickel-halide complexes with Grignard reagents or lithum reagents or hydride sources and by oxidation of Ni(0) complexes.

Nickel complexes, depending on their coordination numbers, oxidation numbers, and geometries, may be paramagnetic or diamagnetic. Many techniques such as EPR spectroscopy, mass spectrometry, X-ray crystallography, and UV-Vis spectroscopy etc are used to characterize these metal complexes.

Organo nickel (IV) complexes are rare, but have been observed in coupling reactions. Figure **1.1** showed some of the nickel (IV) complexes reported.[25]

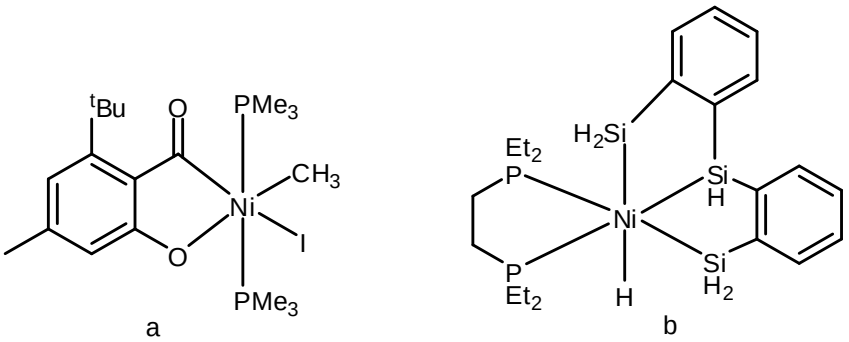
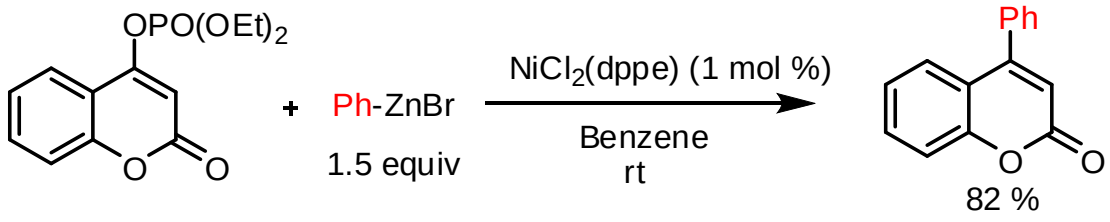



**Figure 1.1:** Examples of nickel (IV) complexes

From Figure **1.1,** complex **a** is distorted octahedral, that is stable in crystalline form in air and decomposes instantly in solution phase. Complex **a** can be prepared by the oxidative addition to the Ni (II) complex by using methyliodide. Complex **b** Ni (IV)-H exists in solution at lower temperatures.

**Scheme 1.3:** Negishi-catalyzed cross-coupling reaction to produce coumoerin derivatives

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Yang *et al*. reported the palladium catalyzed cross-coupling reaction between phosphates and organo zinc reagents to produce coumarins.[26] Phenylzinc halides reacted with phosphates in the presence of nickel catalyst with 82% yield, but in the presence of $Pd(Ph_3P)_4$ the desired 4-phenyl coumarin was obtained 15% and 35% yields. This showed that switching from palladium to nickel resulted in the facile coupling of phenyl zinc reagent with phenyl phosphate (Scheme **1.3**). The palladium-catalyzed system failed for the substrates with nitrogen substituents in Negishi cross-coupling reactions. By considering all of the above, nickel has become the metal of choice for Negishi cross-coupling reactions.

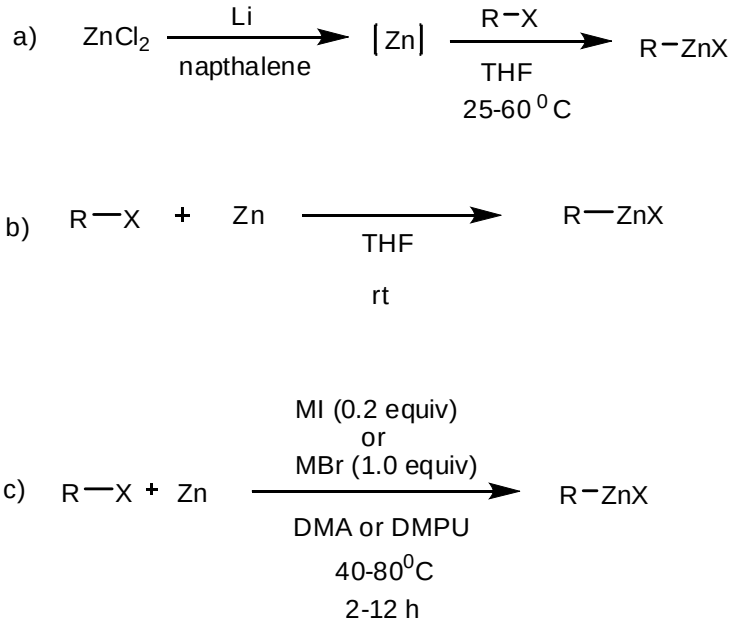
**1.2 Zinc reagents:**

Alkylzinc reagents like $R_2Zn$ or RZnX can bear a variety of functional groups and are widely used as an organometallic reagent in coupling reactions.[27] In 1875 Saytzeff and co-workers[28] synthesized and studied the reactivity of organozinc reagents in addition reactions with electrophiles. Organozinc reagents have low reactivity in addition reactions because of the highly covalent bond between carbon and zinc. Zinc has Lewis acid character, to increase the reactivity towards electrophiles. The empty ground state p orbitals of zinc make these reagents more susceptible to transmetalation than boron or magnesium reagents. This reactivity presents considerable advantages to performing chemo-selective reactions for the direct introduction of the desired functionality into the organic molecule. Because of these advantages, Negishi employed these

nucleophiles in Pd-catalyzed cross-coupling reactions. A convenient way to prepare alkylzinc reagents is the insertion of zinc metal into an alkyl halides.[29]

Rieke et al[30] synthesized 3-substituted thiophenes, useful substrates for pharmaceutical and materials fields. The preparation of the thiophene substrates involves the formation of the alkylzinc reagent and the use of that zinc reagent with electrophiles. The Rieke zinc [Zn*] was synthesized through the reduction of $ZnCl_2$ using Li and naphthalene. Here naphthalene acts as an electron carrier in THF solvent. Scheme **1.4 a** describes the synthetic route for preparation of Rieke zinc.

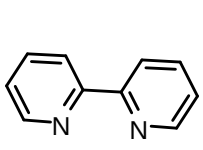
**Scheme 1.4:** Alkylzinc reagents preparative methods



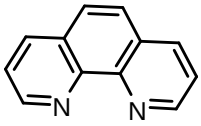
A vast range of organic functional groups, like cyanides, ketones, esters, halides, amides, amines, phthalimides, sulfoxides, sulfides, boronic esters and others are compatible with mild zinc in the above protocol. In contrast, nitro, carboxylic acid, hydroxyl, and azide groups present moieties hindered zinc insertion. Activating zinc before insertion with 1, 2-dibromene helped in faster insertion of zinc into alkyl halides using tetrahydrofuran as a solvent. Zinc can also be activated by hydrochloric acid, mercury alloys and some other methods. Stability of organozinc reagents is a huge problem. Sometimes the reaction required four equivalents to get high yields. Alkylzinc reagents contain one or more functionalities differed in decomposition tendency depending on the functional groups. Organozinc reagents exhibit poor tolerance for acidic proton containing moieties. Solvents with good Lewis basicity like tetrahydrofuran (THF) and dimethylacetamide (DMA) and aprotic co-solvents like dimethyl sulfoxide (DMSO) and N-methyl-2-pyrrolidine (NMP) can help to stabilize the alkylzinc reagent.

Some of the common ligands used in cross-coupling reactions are listed in Chart **1.** Ligands helped to increase the activity of the metal catalytic system. Ligands in stabilizing the Ni (0) intermediate, increase the rate of oxidative addition, and improve the solubility of the catalyst. Phosphines, dienes, pybox, carbenes, nitrogen based ligands like bipyridine derivatives, phenanthroline derivatives, terpyridine derivatives, and pincer type are famous in usage for cross-coupling reactions. Sterically demanding and electron rich diamine and phosphines gained interest, because of effectiveness for less reactive substrates

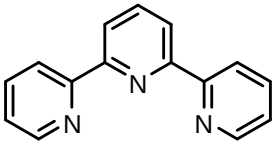
like arylchlorides. Many active catalysts are produced *in situ* from nickel sources and the best ligand combination.



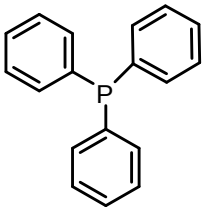

bpy



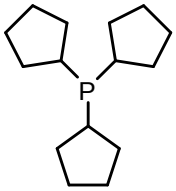

phen



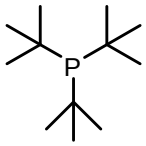

terpy



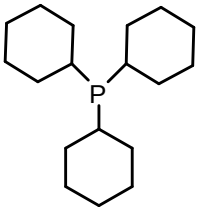

$PPh_3$



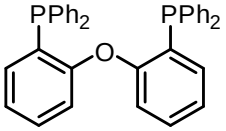

$P(Cyp)_3$



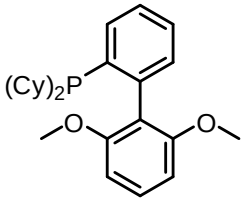

$P(t\text{-}Bu)_3$



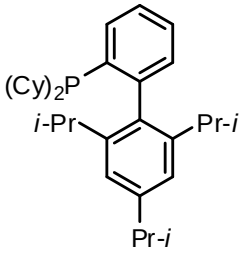

$P(Cy)_3$



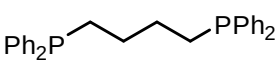

DPEphos



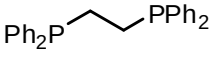

Sphos



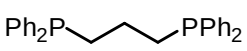

Xphos



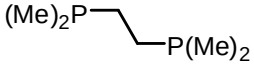

dppb




dppe




dppp



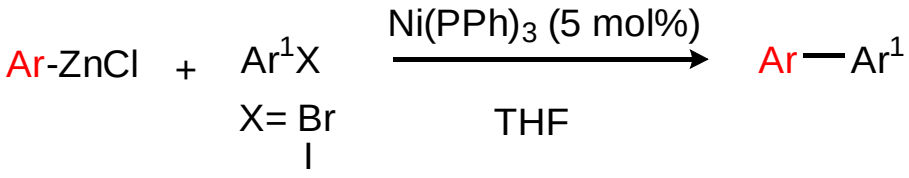

dmpe

**Chart 1:** Some of the common ligands used in the cross-coupling reactions

### 1.3 Nickel-catalyzed aryl $C_{(sp2)}$-aryl $C_{(sp2)}$ and aryl $C_{(sp2)}$-alkenyl $C_{(sp2)}$ Negishi coupling reactions:

Biaryls play a vital role in drug discovery, which is key for the pharmaceutical industry. Negishi methodology is ideal for preparing biaryl derivatives. Negishi[15] submitted the first nickel-catalyzed aryl-aryl coupling reaction which were stereo, chemo, and region-selective paths for the synthesis of unsymmetrical biaryl derivatives. Nickel and palladium catalysts can achieve aryl-aryl couplings with different nucleophilic systems. From Scheme **1.5,** the Negishi group prepared biaryls at room temperature, using aryl halides as an electrophile and arylzinc chloride as a nucleophile. They succeeded in the coupling of aryl halides containing both electron donating and electron withdrawing groups with Ni(0) and Pd(0) complexes.

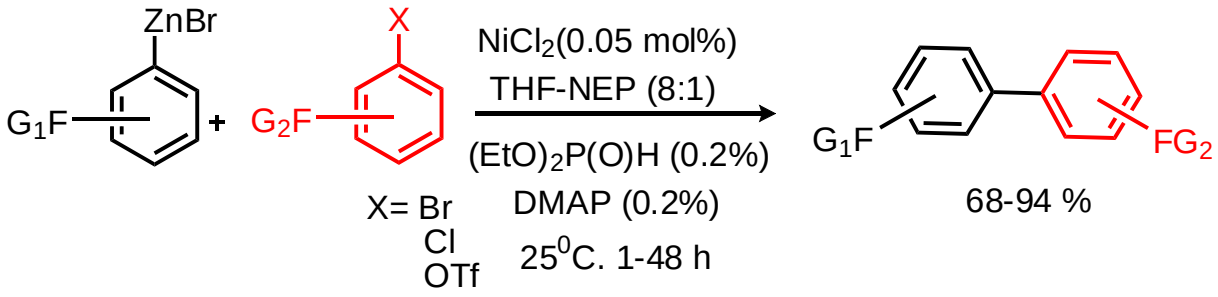
**Scheme 1.5:** Preparation of biaryls with Negishi coupling process




In Scheme **1.5** Negishi generated the nickel catalyst $Ni(PPh)_3$ *in situ* by reacting $Ni(acac)_2$, triphenyl phosphine and DIBAH(di-isobutyl aluminium hydride) in tetrahydrofuran, then used this catalyst for symmetrical and unsymmetrical biaryl synthesis with efficient yields. The same procedure can be used for coupling of benzylzinc halide.

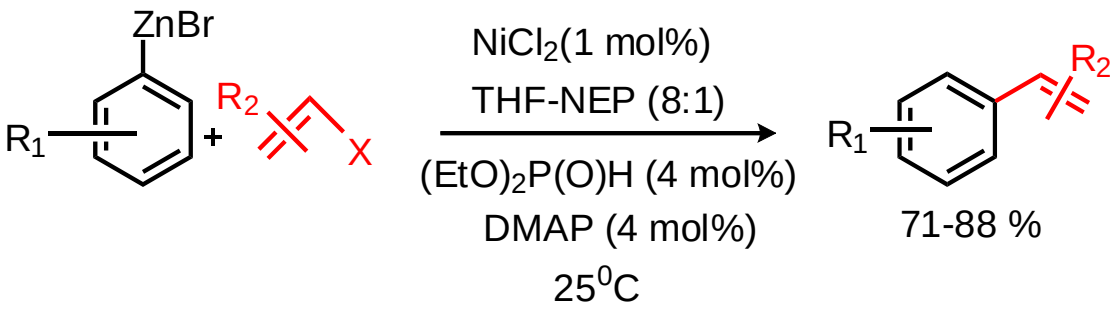
Paul Knochel and co-workers[31] have developed an attractive catalytic system for the cross-coupling reactions (Scheme **1.6**) between aryl bromides, triflates, nontriflates, activated chlorides and functionalized alkylzinc bromides with nickel chloride($NiCl_2$), diethyl phosphite and 4-(dimethylamino)pyridine (DMAP) as solvent. This catalytic system works for wide variety of functional groups at ambient temperatures with very low catalyst loading (0.05%).

**Scheme 1.6:** Cross-coupling reaction between functionalized aryl zinc re-agents and polyfunctional aryl halide electrophiles.



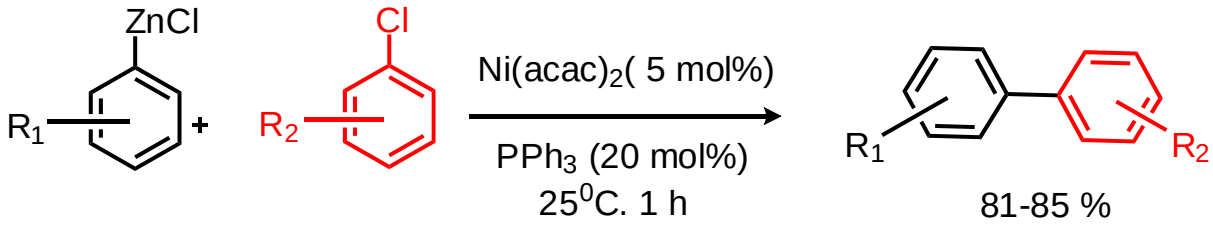

This nickel catalytic system can be applied to the cross-coupling between arylzinc halides and alkenyl halides, triflates, but requires a higher amount of catalyst loading (1 mol%) compared to the arylzinc halides (Scheme **1.7**).

**Scheme 1.7:** Negishi cross-coupling between arylzinc halide and alkenyl electrophiles




Tucker and de Vries[32] have developed an efficient way to couple aryl chlorides or bromides in the presence of nickel catalytic system. They used $Ni(acac)_2$ and triphenyl phosphine catalytic system under very mild conditions, and short reaction times to get the biaryl product (Scheme **1.8**). Aryl chlorides are really cheaper nucleophile sources than bromides and iodides, in making biaryl derivatives.

**Scheme 1.8:** Negishi cross-coupling between arylzinc reagents and aryl chlorides



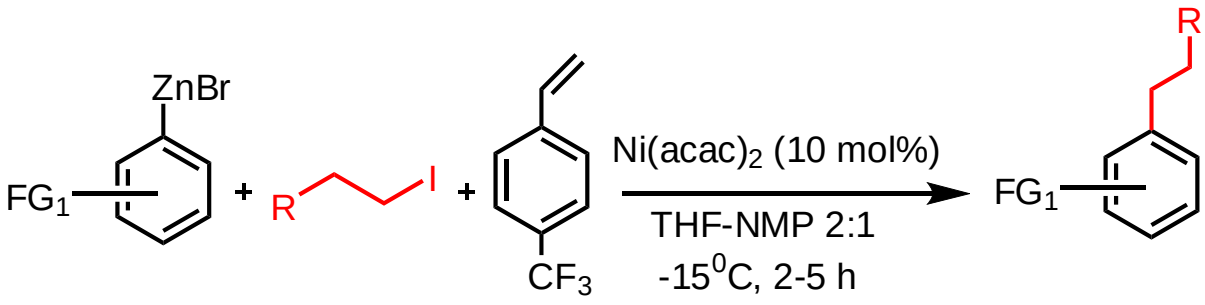

$R_1$= $CH_3$, H  $R_2$= CN, $COC_2H_5$

### 1.4 Nickel-catalyzed aryl $C_{(sp2)}$-alkyl $C_{(sp3)}$ Negishi coupling reactions:

Cross-coupling between alkenyl or aryl halide with alkylzinc reagent can generate a $C_{sp2}$-$C_{sp3}$ bond in the presence of metal catalyst. The major drawback in such coupling procedures that β-hydride elimination of the intermediate alkyl metal complexes can occur. Because of this reason, there are few examples of nickel-catalyzed Negishi cross-coupling reactions of aryl halides for the formation of $C_{sp2}$-$C_{sp3}$ bonds presented.

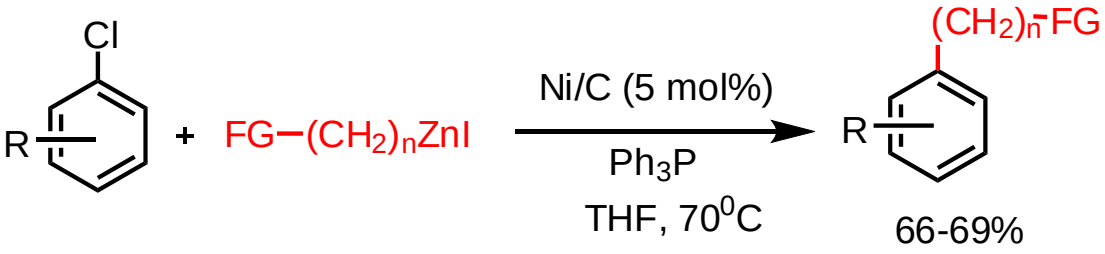
Knochel *et al*[33] reported nickel-catalyzed cross-coupling reaction of polyfunctional alkyl iodides with arylzinc bromides in the presence of $Ni(acac)_2$ (10 mol %), 4-(trifluoromethyl)styrene and tetrahydrofuran(THF)- 1-methyl-2-pyrrolidinone(NMP) used as a solvent (Scheme **1.9**). In this catalytic system 4-(trifluoromethyl)styrene helped to promote reductive elimination over the β-hydride elimination.

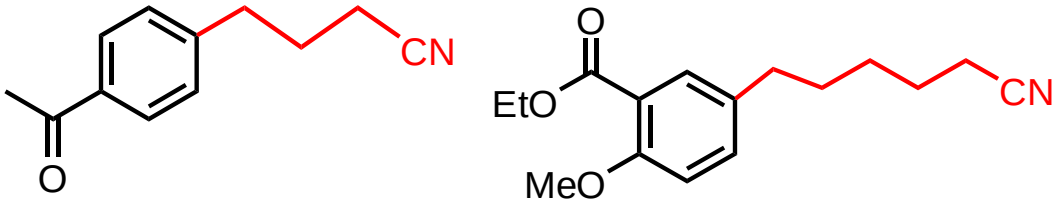
**Scheme 1.9:** Nickel-catalyzed Negishi cross-coupling between primary alkyl iodides and functionalized arylzinc bromides



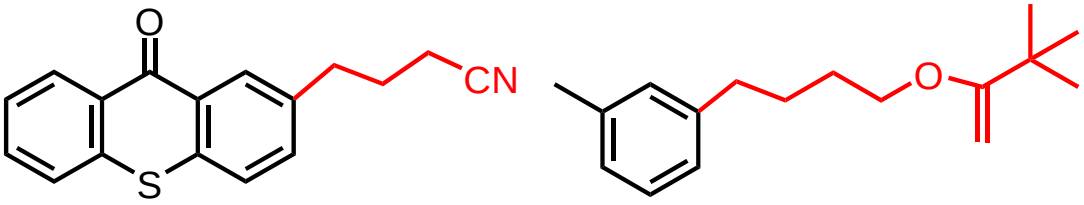
In 1999, Lipshutz and Blomgren[34] have reported cross-coupling between functionalized zinc reagents and several different substituted aryl chlorides in refluxing THF conditions (Scheme **1.10**).

**Scheme 1.10:** Nickel catalyzed coupling of aryl chlorides with functionalized alkyl zinc halides



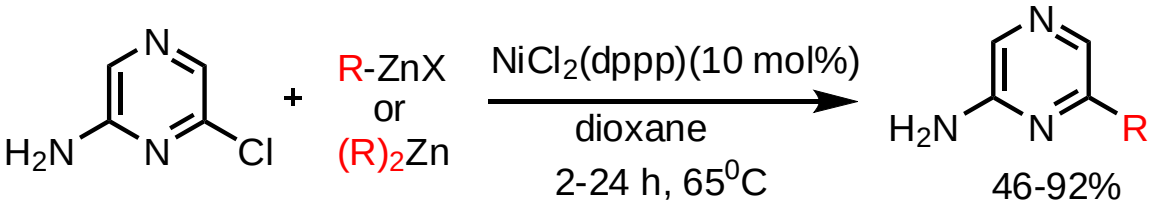

**a** **b**




**c** **d**

The above catalytic system can tolerate different functional groups like aldehydes (entry **a**), esters (entry **b**), nitriles (entry **a, b and c**), sulfar-containing compound (entry **c**).

**Scheme 1.11:** Negishi cross-coupling reaction of aminoheteroaryl chlorides with alkylzinc reagents



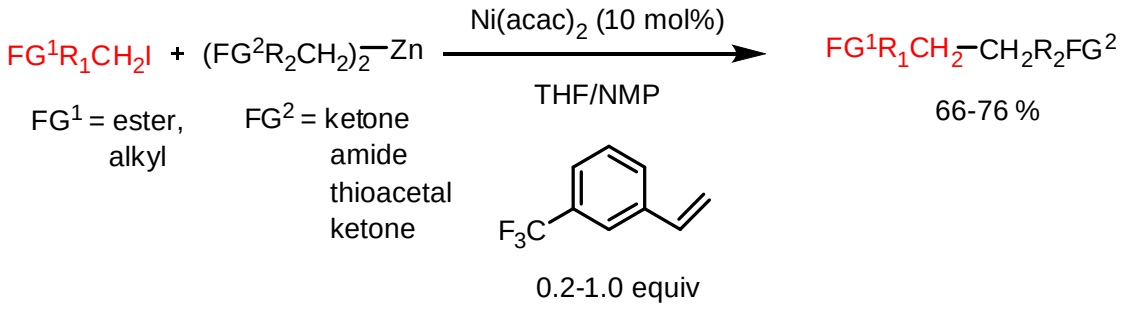

Walters[35] have developed an efficient nickel-catalyzed Negishi cross-coupling between alkylzinc reagents and aminoheteroaryl chlorides in the presence of $NiCl_2$(dppp) in dioxane as solvent (Scheme **1.11**). This reaction is interesting because alkylzinc halides or dialkylzinc halides can be generated *in situ* from the primary alkyl bromides and diethylzinc in the presence of $NiCl_2$(dppp) catalyst, which can also be used as a catalyst in the cross-coupling reaction.

### 1.5 Nickel-catalyzed alkyl $C_{(sp3)}$-alkyl $C_{(sp3)}$ Negishi coupling reactions:

Nickel based Negishi cross-couplings have gained importance in preparing $C_{Sp3}$- $C_{Sp3}$ bonds in recent times. In the preparation of alkyl-alkyl bonds, Knochel[36] and his group have observed that the presence of electron-withdrawing groups or unsaturation (*m*-trifluoromethylstyrene) can help to promote the desired product with higher yields (Scheme **1.12**). To confirm the usage of unsaturated

compounds in the catalytic system, they have tried to couple alkylzinc reagents with alkyl halides in the absence of *m*-triflurомethylstyrene and they ended up with very low amount of cross-coupled product. This result clearly indicated the importance of unsaturated compounds in the catalytic system. The double bond in the *m*-triflurомethylstyrene is acting as a ligand to help stabilize the nickel intermediate, which can then progress to the next steps, transmetalation and reductive elimination. This catalytic system is able to couple with wide range of functionalized organozinc and alkyl halides.

**Scheme 1.12:** Nickel-catalyzed Negishi cross-coupling reaction to form alkyl-alkyl bond




## 1.6 Summary:

In summary, organozinc reagents are easy to prepare and react conveniently with a broad range of functional groups. Oragnozinc reagents are more versatile than the other popular metal nucleophiles. Organozinc reagents fail in some cases, because of their low stability, and may need excess amounts of zinc reagent to give better yields. In addition, zinc reagents shows less tolerance to acidic proton-containing moieties.

Nickel catalytic systems are known to form $C_{Sp2}$-$C_{Sp2}$, $C_{Sp3}$-$C_{Sp2}$, and $C_{Sp3}$-$C_{Sp3}$ bonds with organozinc nucleophiles and organic halides, and are especially reactive towards aryl chloride. Significant advances have been made in nickel-catalyzed cross-coupling reactions. We need to develop better catalytic systems to overcome the challenges in using organozinc reagents to cover a wide range of functional groups. The mechanisms of Ni-catalyzed cross-coupling reactions are complicated and may need to be studied on a case-by-case basis. A clear mechanistic understanding of cross-coupling is important for further development of the field. Stable, recyclable, catalytic systems should be economical and environmental friendly. Moreover, no one has investigated the use of dinuclear metal systems in Negishi reactions, and in particular, whether cooperative effects can aid with the cross-coupling reaction. My research aims to explore if dinuclear nickel systems can mediate Negishi cross-coupling reactions with improved yields under mild conditions.

# Chapter-2

# Exploring the Use of Dinuclear Nickel Complexes in Aryl-Alkyl Cross-Coupling Reactions

## 2.1 Introduction:

In terms of selectivity and efficiency, homogeneous catalysis has been quite successful in C-C and C-P bond forming reactions in synthetic organic chemistry. α-Diimine ligands such as 2,2'-bipyridine (bpy), 1,10-phenanthroline (phen) and diazabutadiene (R-DAB) and nickel complexes thereof have attracted immense interest in the past decade.[1] Important catalytic processes like catalytic carbon-carbon couplings[2-8], olefin polymerization or oligo polymerization, olefin/CO co-polymerisation[9-15] proceed with using nickel complexes with α-diimine ligands.

Dr. Axel Klein's group studies the fundamental electronic properties, reactivity towards ligand exchange, X-ray diffraction, and absorption spectroscopy of α-diimine ligated metal complexes.[16,17] They have intensively studied photophysics and photochemistry using both spectroscopic techniques and quantum chemical calculations.[18,19,20] The redox chemistry of diimine metal complexes was investigated[17,20] with the goal of applying these complexes in electrocatalytic carbon-carbon coupling reactions.[2] Dr. Klein found that the lowest unoccupied molecular orbitals of dinuclear α-diimine ligands are mainly based on (π*) centered orbitals. Moreover, both the intense colors (long-

wavelength absorption bands) and low first potentials and second reduction potentials depend on the nature of the diimine ligands.[16] Because of two metal centers offer the possibility of cooperative effects in catalysis, Klein has begun to focus his efforts on understanding the fundamental features of metal diimine dimers.[16,17,21] In addition to the above, work from Jin and Haung helped us in understanding the higher thermal stability of binuclear complexes, which is advantageous in optimizing coupling reaction conditions.[23]

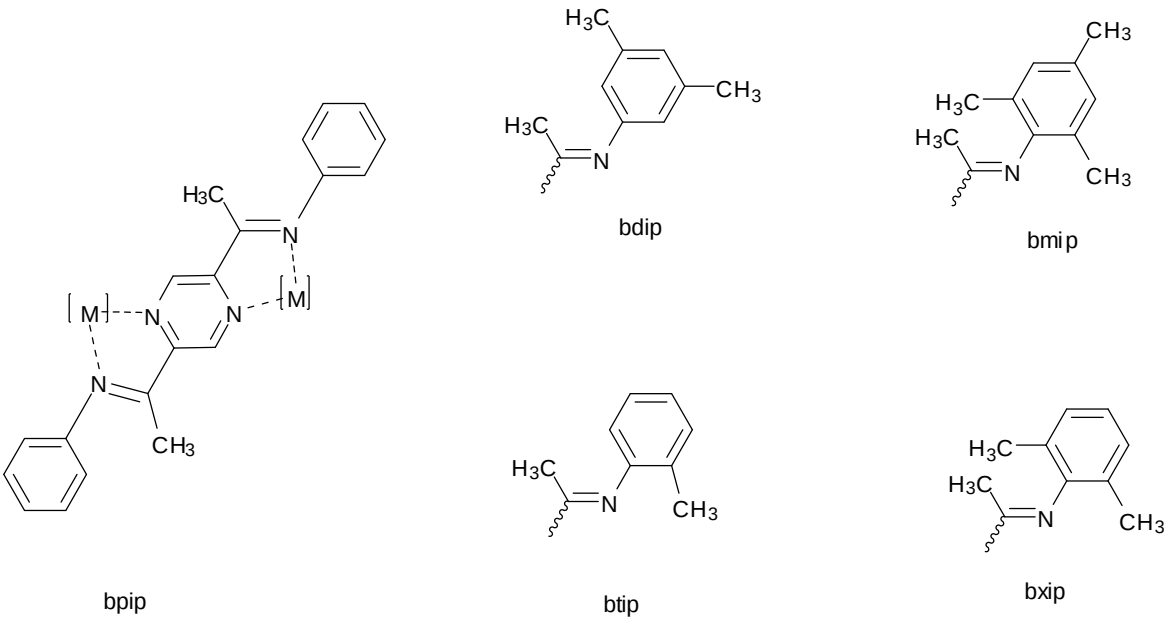
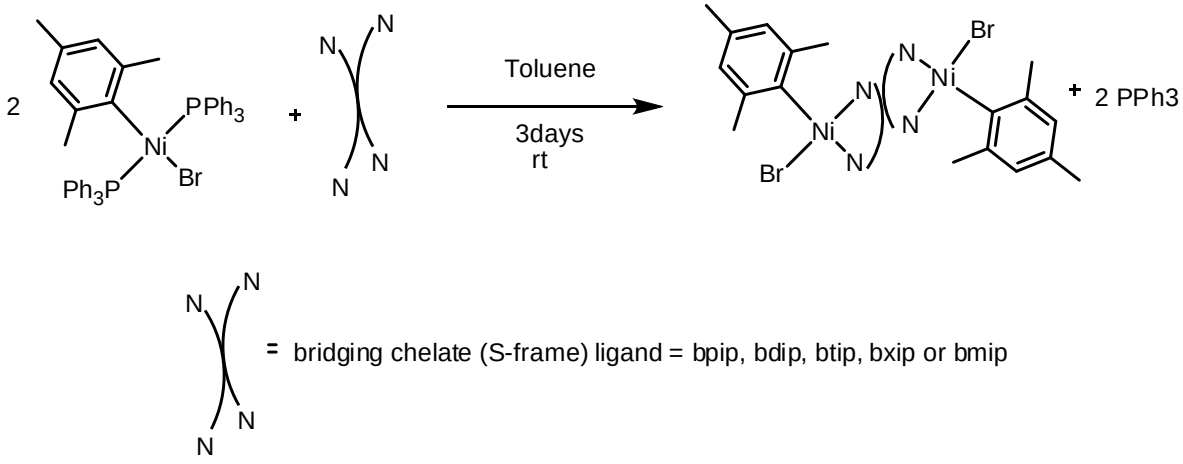



**Figure 2.1:** Bridging diimine ligands[1]. [M] is the potential binding sites of metal.

## 2.2 Properties of the complexes:

**Scheme 2.1:** Preparation of α-diimine nickel complexes




As shown in Scheme **2.1** mononuclear and binuclear nickel complexes were synthesized from the precursor complex $[(PPh_3)_2Ni(Mes)Br]$ by ligand exchange reactions by Dr. Axel's group.[1,19] As described, in the absence of $PPh_3$ or other strong ligands, these nickel complexes are stable in $CH_2Cl_2$, THF, toluene, acetone, and DMF against ligand exchange reactions.[22] Both mononuclear and dinuclear analogue complexes decompose in DMSO, nitriles and alochols.[19,20,22] Thermal studies using differential scanning calorimetry showed that, μ-bxip **5** and μ-bmip **8** derivatives are stable up to 205 ºC, started melting above 220 ºC and decompose at higher temperatures NMR studies showed that μ-bmip **8** (Figure **2.3**) derivatives decompose in DMF solvent with prolonged heating above 152 ºC for more than 8 hours.

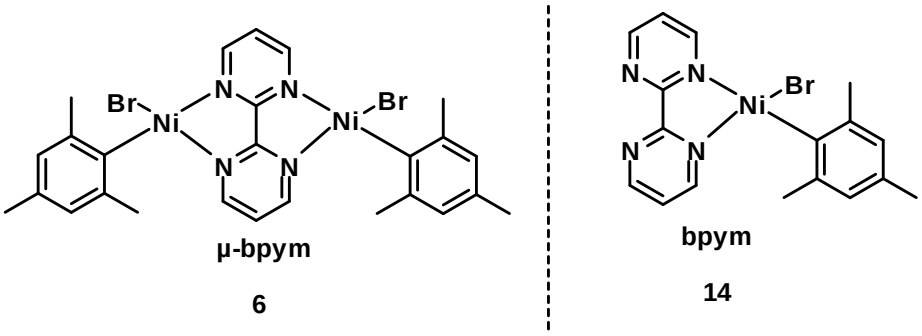



**Figure 2.2:** Mononuclear and dinuclear bpym complexes comparison

In μ-bpym **6** (Figure **2.2**) complexes, the two metal atoms have a metal-metal distance of about 5.5-6 Aº, which is too long for direct metal-metal interactions. On the other hand, the metals could communicate through the ligand via the low-lying lowest unoccupied molecular orbitals of μ-bpym[17] **6** complex (Figure **2.2**)**.** The bromine-nickel bond lengths remain constant for mono bpym **14** and binuclear μ-bpym **6** nickel complexes, but the Debye-Waller factor of the coordination shell of bromine is increased for binuclear μ-bpym **6** complex compared to the mononuclear complex bpym **14**. The complexes displayed very long wavelength absorptions (600-1000 nm), due to metal-to-ligand charge transfer transitions. The low energy of the transitions (1.2-2eV) is attributed to electronic coupling of the two metal centers over the ligand bridge through low-lying π* orbitals. The reductive electrochemistry showed that stable radical anion complexes were formed upon reduction with ligand-centered spin density by ESR-spectroscopy, UV/Vis spectroelectrochemistry and DFT calculations.[1]

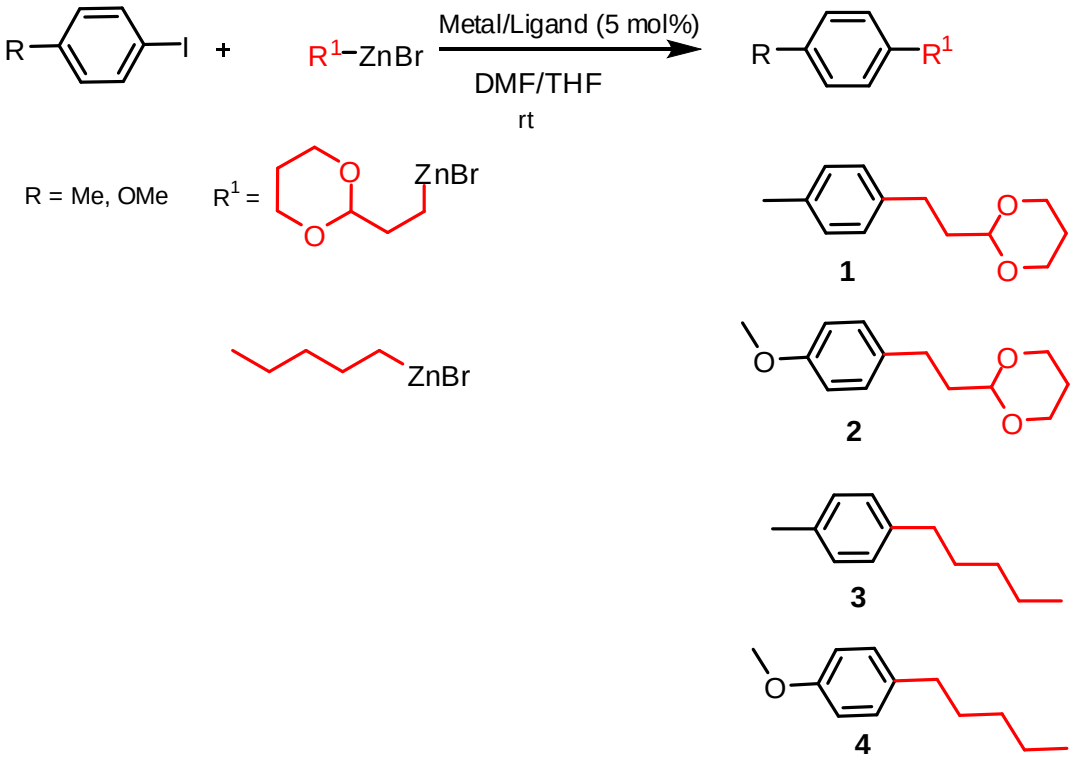
Electrochemical studies of the binuclear complexes exhibits a reversible first reduction wave and second irreversible with DMF or partly reversible wave with THF as a solvent. All waves appeared at far higher (less negative) potentials relative to the mononuclear derivatives.[17] The reversibility suggests that bromide dissociation is largely decreased for the binuclear complex, if not completely inhibited. The reason for this is coordination of a second metal ion, which leads to the stabilization of the ligand's lowest unoccupied orbitals. This leads to higher reduction potentials and helps to decrease the transfer of electron density from the reduced ligand to the nickel atoms (in the reduced complex), important for bromide dissociation.

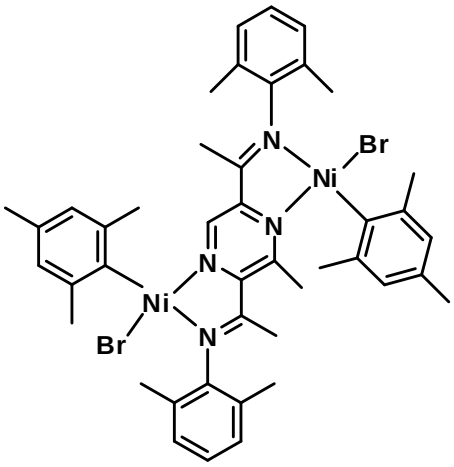
Dr. Vicic's group and Dr. Axel Klein's group collaborated in a project aimed at understanding the reactivity of these new species. For this project, I wanted to study the catalytic activity of C-C bond formation using these bridging diamine nickel complexes. I examined the cross-coupling between aryl halides and alkyl zinc reagents using these dinuclear metal complexes. I have used iodotoluene and electron donating p-iodoanisole as electrophiles in these reactions. I have used simple alkyl zinc halide and highly substituted alkyl zinc reagents (Scheme **2.2)** for checking the catalytic activity of α-diimine nickel complexes. The goal was to compare the reactivity of mononuclear (Figure **2.3)** and dinuclear nickel catalysts (Figure **2.4)** towards cross-coupling reactions.

## 2.3 Experimental and results discussion:

Below in Scheme **2.2**, I have described the type of cross-coupling reaction. We were interested in exploring with the new metal complexes. Figures **2.3** and **2.4** show the catalysts we have tried.

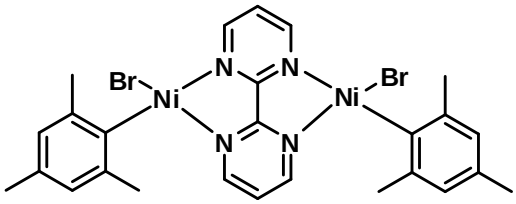
**Scheme 2.2:** Overview of the Negishi reactions we have investigated





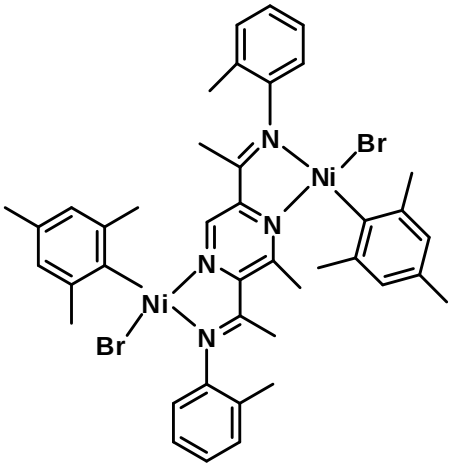

**μ-bxip**

**5**



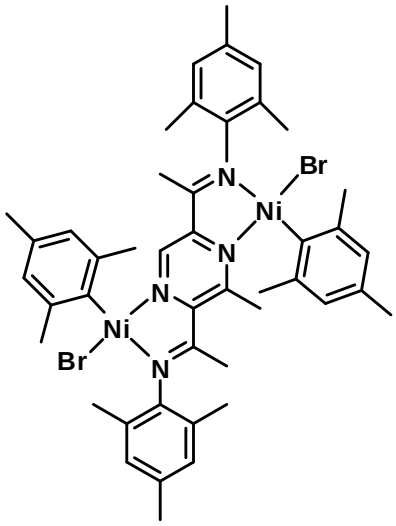

**μ-bpym**

**6**




**μ-btip**

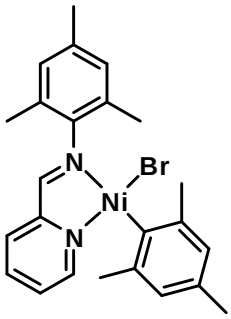
**7**



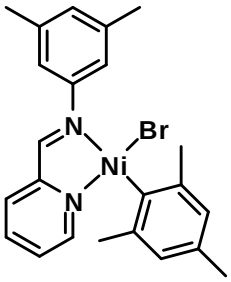

**μ–bmip**

**8**

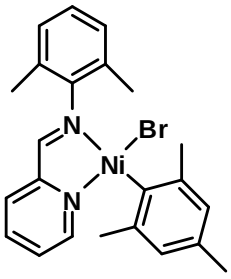
**Figure 2.3:** Binuclear nickel complexes used in this study as a catalyst



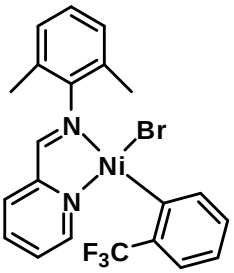

**Mes-Pyma**
**9**



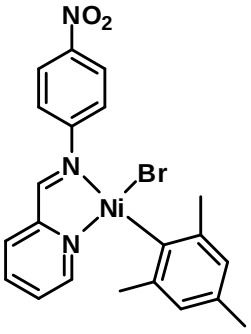

**(3,5-dimethyl)-DAD)Mes**
**10**



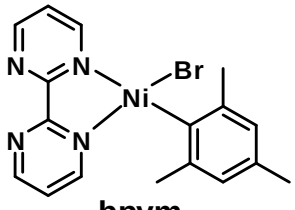

**(Me-DAD)Mes**
**11**




**(Me-DAD)O-$CF_3$Ph**
**12**




**(P-Nitro)-DAD)Mes**
**13**




**bpym**
**14**

**Figure 2.4:** Mononuclear nickel complexes used in this study as a catalyst

## 2.4 General considerations for my experimental conditions:

All manipulations were performed using standard Schlenk techniques or in a nitrogen-filled glove box, unless otherwise noted. Solvents were distilled from Na/benzophenone or $CaH_2$. All reagents were used as received from commercial vendors unless otherwise noted. Aluminum oxide (activated, neutral, Sorbent, 230 x 400 mesh) was dried at 200 ºC under vacuum for two days prior to use. All gas chromatography was completed using Agilent GCMS-7890A. Initial column temp 150 ºC, ramp to 50 ºC for every minute up to 200 ºC, total run time 10 minutes. Injector and detector temperatures were 250 ºC. Each injection was 1 mL of a 0.5 mL aliquot that was diluted with excess THF. I have used the response factor of 1-methoxy-4-pentylbenzene for 1-methyl-4-pentylbenzene to estimate the product yields.

## 2.5 Calibration Curves:

In order to obtain precise yields, calibration curves were performed to best analyze our GC data. Hexamethylbenzene was used as an internal standard in the calibration curves. 0.5 mmol of internal standard and 0.5 mmol, 0.4 mmol, 0.3 mmol, 0.2 mmol and 0.1 mmol of product used to calculate the response factor. The response factor was calculated using the following formula.

$$\mathbf{(m_p/m_{is}) = (A_p/A_{is})\ R_x}$$

**$m_p$ = mass of the product**
**$m_{is}$ = mass of the internal standard**
**$A_p$ = Area of the product**
**$A_{is}$ = Area of the internal standard**
**$R_x$ = Response factor**

Response factor for **2-(4-methylphenethyl)-1-3-dioxane = 0.794**

Response factor for **1-methoxy-4-pentylbenzene = 0.985**

Response factor for **2-(4-methoxyphenethyl)-1-3-dioxane = 0.881**

Response factor for **1-methyl-4-pentylbenzene = 0.985**

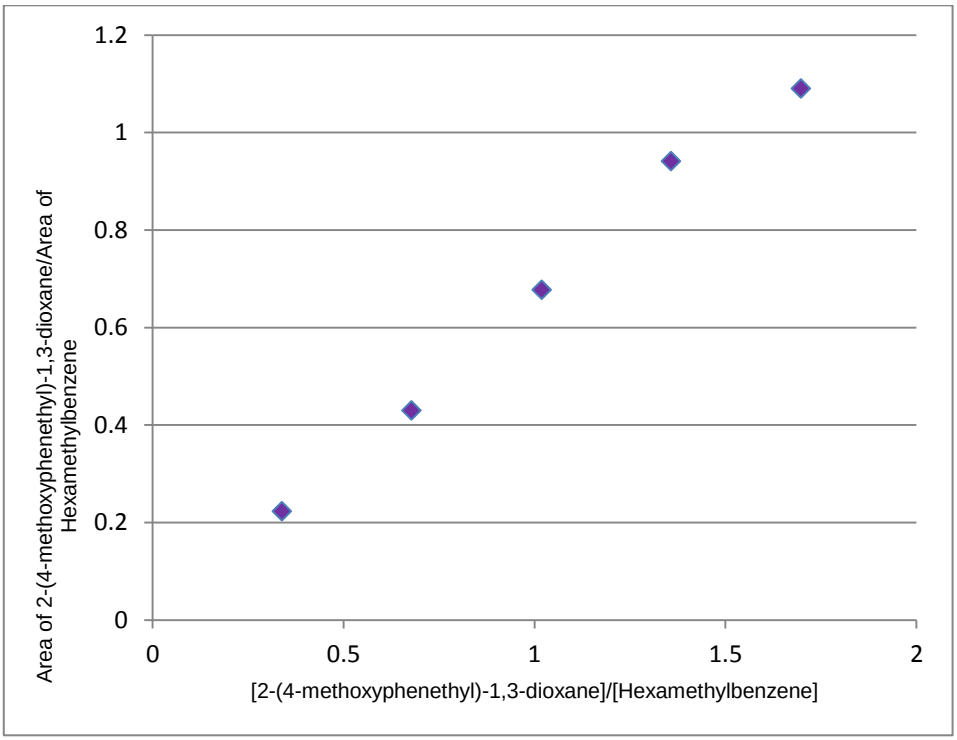



**Figure 2.5:** Calibration curve between hexamethylbenzene and 2-(4-methoxyphenethyl)-1,3-dioxane

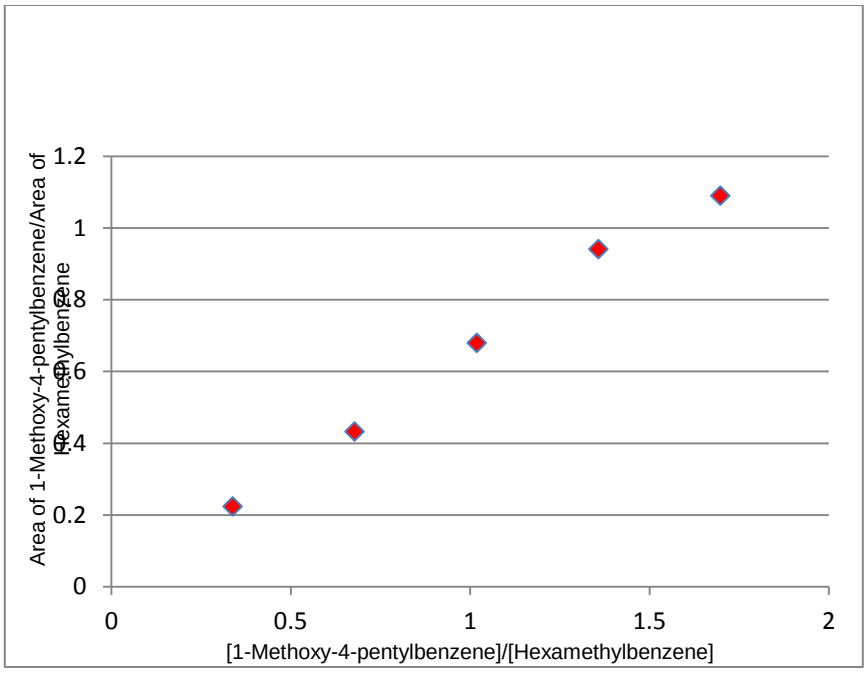



**Figure 2.6:** Calibration curve between hexamethylbenzene and 1-methoxy-4-pentylbenzene

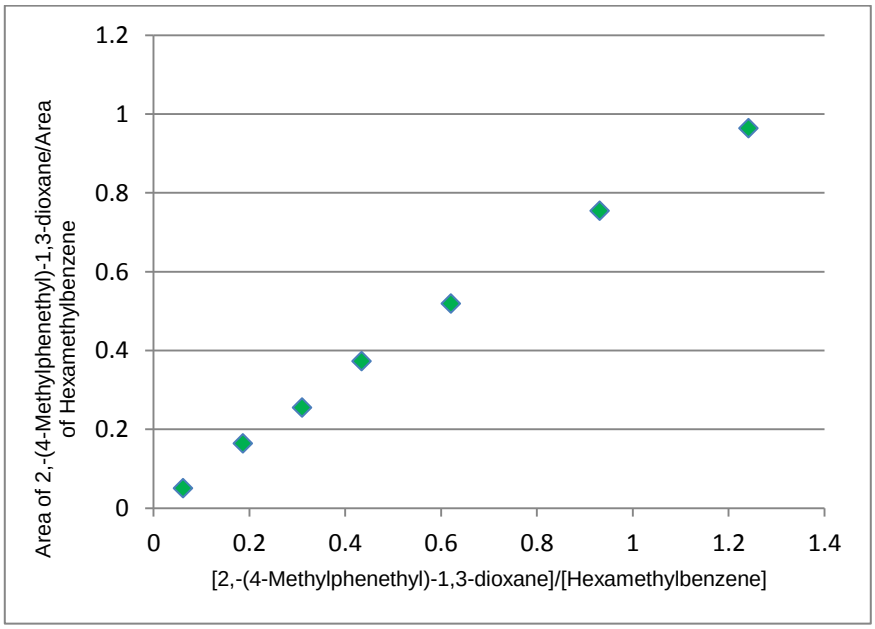
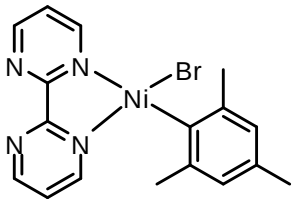



**Figure 2.7:** Calibration curve between hexamethylbenzene and 2-(4-methylphenethyl)-1,3-dioxane

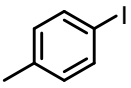
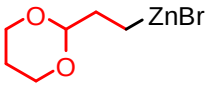
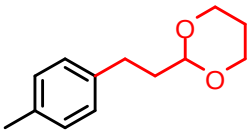
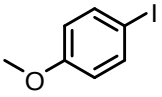
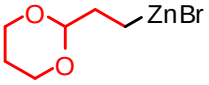
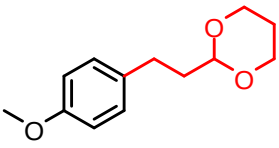
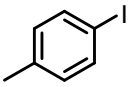
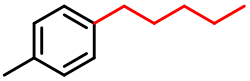
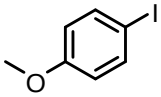
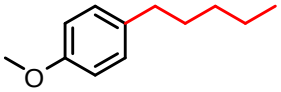
## 2.6 Procedure for Negishi cross-coupling reaction:

A solution of aryl iodide (0.5 mmol) in THF/DMF (1 mL) was added to the alkylzinc bromide reagent (0.5 mmol) in THF/DMF (1mL) at ambient temperatures. To this mixture was added the nickel catalyst (2.5 mol%) and the hexamethylbenzene (0.5 mmol) internal standard. The resulting mixture was stirred at room temperature and aliquots were checked periodically by GC-MS until all aryl iodide was consumed.

**Table 2.1:** Activity towards Negishi cross-coupling with bpym catalyst



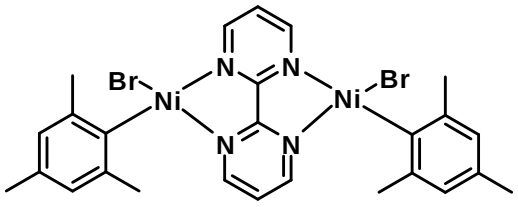

**bpym**
**14**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 56 | 4 |
| (2) |  |  |  2 | 65 | 4 |
| (3) |  |  |  3 | 86 | 4 |
| (4) |  |  |  4 | 66 | 4 |

* THF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard.5 mol% catalyst used for this reaction.

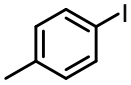
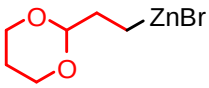
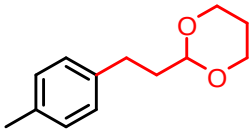
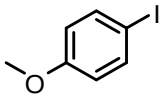
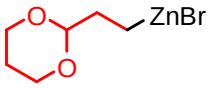
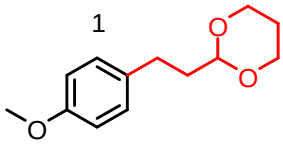
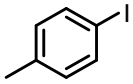
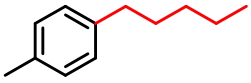
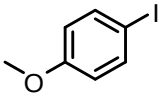
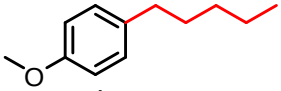
As you can see from Table **2.1,** mononuclear nickel complex, bpym **14** showed good activity towards the cross-coupling reaction. In 4 hours, all of the starting material was consumed. Among all the reaction trials, the substrates shown in entry **3** gave the best yield at 86%.

**Table 2.2:** Activity towards Negishi cross-coupling with μ-bpym catalyst




**μ-bpym**

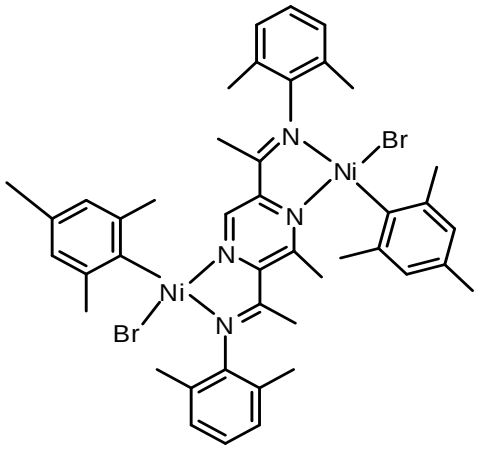
**6**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 63 | 4.5 |
| (2) |  |  |  2 | 68 | 4.5 |
| (3) |  |  |  3 | 51 | 4.5 |
| (4) |  |  |  4 | 36 | 4.5 |

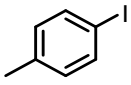
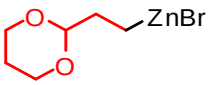
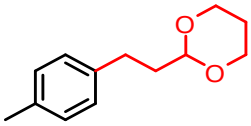
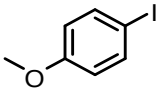
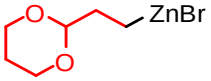
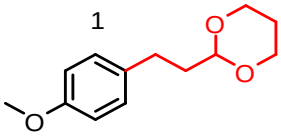
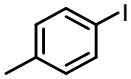
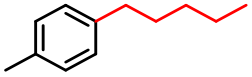
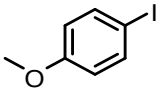
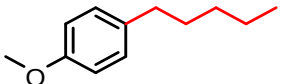
* THF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

As shown in from Table **2.2,** the binuclear bpym **6** afforded similar yields of products **1** and **2** as mononuclear bpym **14** from entry **1** and entry **2.** But for products **3** and **4** from entry **3** and entry **4,** mononuclear bpym **14** worked better (Table **2.1** vs Table **2.2**).

**Table 2.3:** Activity towards Negishi cross-coupling with μ-bxip catalyst




**μ-bxip**
**5**

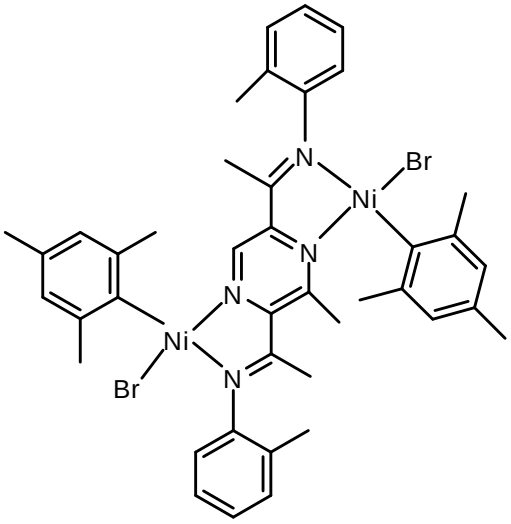
| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1)[a] |  |  |  1 | 19 | 92 |
| (2)[b] |  |  |  2 | 47 | 92 |
| (3) |  |  |  3 | 13 | 2 |
| (4) |  |  |  4 | 13 | 2 |

*THF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction. a, b two equivalents of zinc reagents used on the basis of arylhalide.

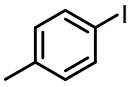
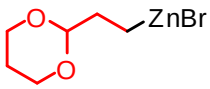
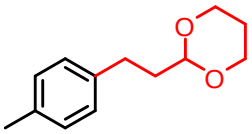
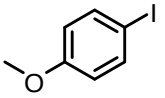
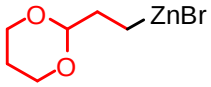
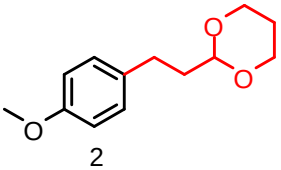
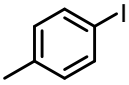
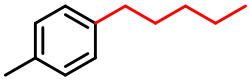
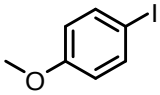
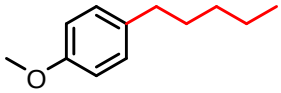
Table **2.3** describes our results using the μ-bxip **5** catalyst for cross-coupling between aryl halides and alkyl zinc reagents. Entries **1** and **2** produced

low yield and took longer to consume the starting material. Entries **3** and **4** gave very low yield and used very short time to coonsume the starting material.

**Table 2.4:** Activity towards Negishi cross-coupling with μ-btip catalyst



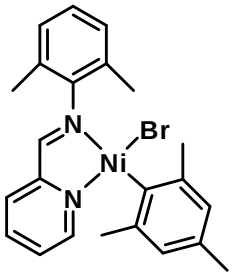

**μ-btip**
**7**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 56 | 92 |
| (2) |  |  |  2 | 17 | 92 |
| (3) |  |  |  3 | 11 | 12 |
| (4) |  |  |  4 | 56 | 24 |

* THF used as a solvent. For a, b 2 equivalents of zinc reagent used. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

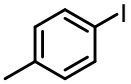
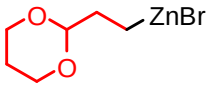
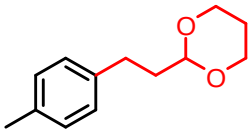
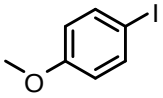
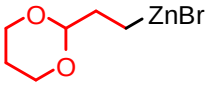
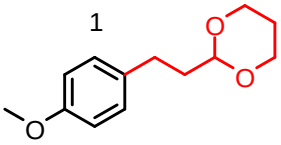
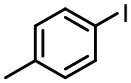
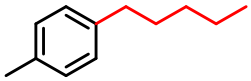
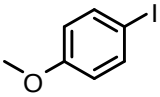
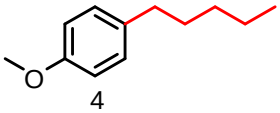
As described in Table **2.4,** complex **7** was less productive for cross-coupling reaction and took longer times to consume aryl iodide. I added excess amount of the zinc reagent after 24 hrs to check the activity of the catalyst. The percentage of the product increased with excess amount of zinc reagent, which indicated that catalyst still showed activity after 24 hrs, but has poor performance towards coupling of the starting materials.

**Table 2.5:** Activity towards Negishi cross-coupling with (Me-DAD)Mes catalyst




**(Me-DAD)Mes**

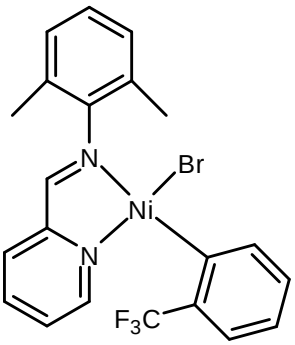
**11**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 70 | 26 |
| (2) |  |  |  2 | 90 | 10.5 |
| (3) |  |  |  3 | 16 | 26 |
| (4) |  |  |  4 | 68 | 68.5 |

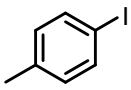
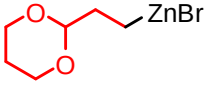
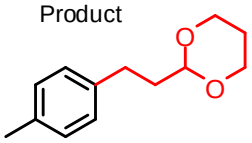
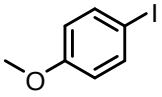
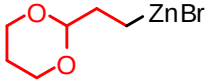
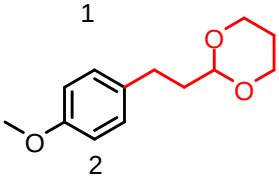
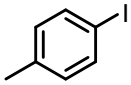
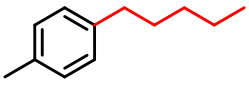
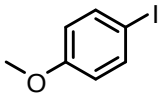
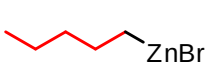
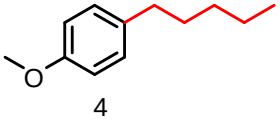
*THF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

As seen in Table **2.5,** complex **11** displayed excellent activity towards electron donating aryl halide and functionalized 2-(1,3-dioxan-2-yl) ethylzinc bromide with 90% yield in entry **2.** Reactions finished within moderate to longer time, based upon consumption of the aryl halide. Reaction with iodotoluene and pentylzinc bromide ended with low 16% yield for entry **3** and I observed homo-coupling of aryl halide.

**Table 2.6:** Activity towards Negishi cross-coupling with (Me-DAD)O-CF3Ph catalyst



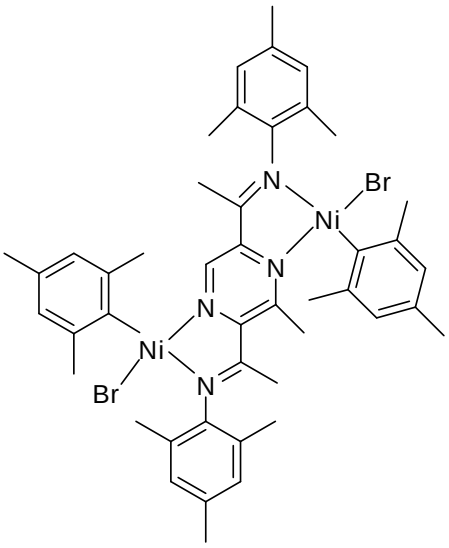

**(Me-DAD)O-$CF_3$Ph**
**12**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 14 | 20 |
| (2) |  |  |  2 | 18 | 27 |
| (3) |  |  |  3 | 72 | 27 |
| (4) |  |  |  4 | 89 | 10.5 |

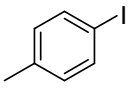
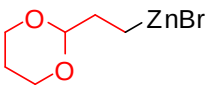
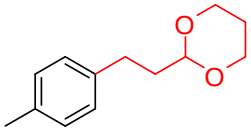
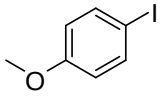
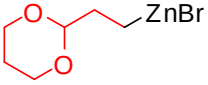
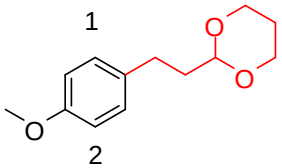
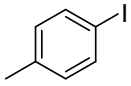
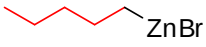
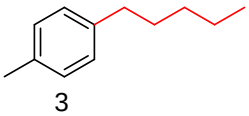
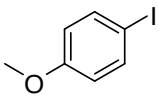
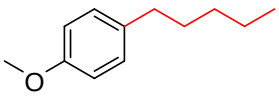
* THF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

As per Table **2.6,** catalyst **12** (Me-DAD)ortho-$CF_3$Ph produced good yields for the pentylzinc bromide nucleophile. Complex **12** gave low yield for highly functionalized 2-(1,3-dioxan-2-yl) ethylzinc bromide reagent (entry **2**).

**Table 2.7:** Activity towards Negishi cross-coupling with μ-bmip catalyst



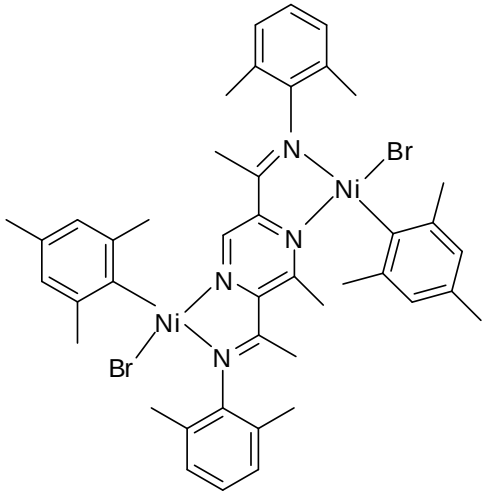

**μ-bmip**
**8**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 77 | 3 |
| (2) |  |  |  2 | 62 | 3 |
| (3) |  |  |  3 | 84 | 3 |
| (4) |  |  |  4 | 87 | 3 |

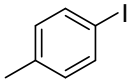
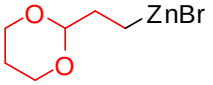
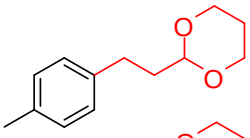
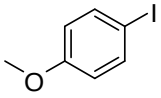
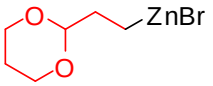
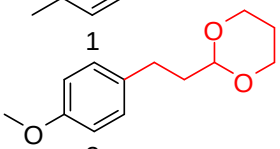
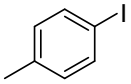
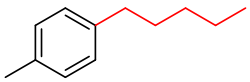
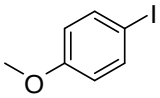
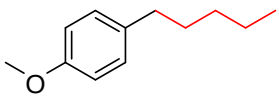
*DMF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

Complex **8** in the presence of DMF solvent yielded attractive results as described in Table **1.6**. it gave better yields starting with pentylzinc bromide as compared to 2-(1,3-dioxan-2-yl) ethylzinc bromide.

**Table 2.8:** Activity towards Negishi cross-coupling with μ-bxip catalyst



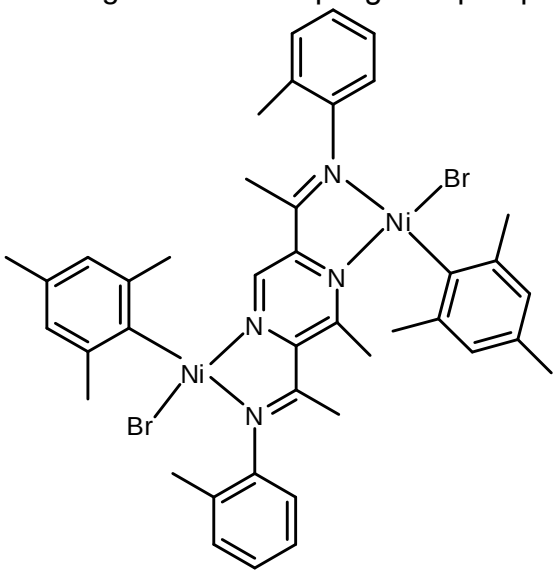

**μ-bxip**
**5**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 71 | 7 |
| (2) |  |  |  2 | 43 | 7 |
| (3) |  |  |  3 | 72 | 4 |
| (4) |  |  |  4 | 69 | 4 |

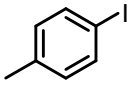
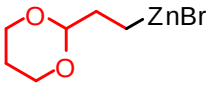
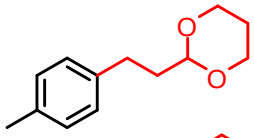
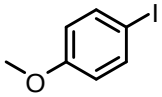
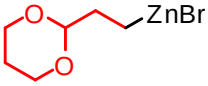
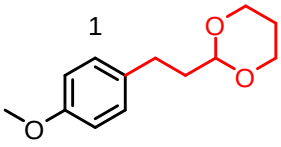
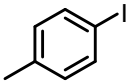
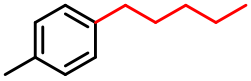
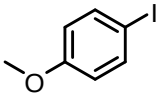
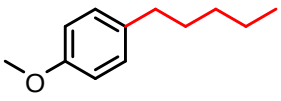
*DMF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction.

Catalyst **5** performed the coupling reaction in less time with moderate yields as described in Table **2.8**. It gave similar amount of product for entries **1, 3** and **4,** apart from entry **2.**

**Table 2.9:** Activity towards Negishi cross-coupling with μ-btip catalyst



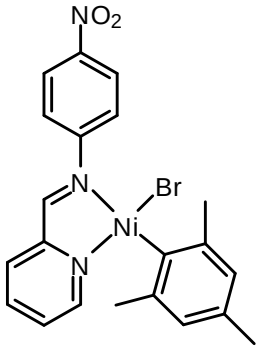

**μ-btip**
**7**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 51 | 24 |
| (2) |  |  |  2 | 50 | 24 |
| (3)[a] |  |  |  3 | 33 | 24 |
| (4)[b] |  |  |  4 | 36 | 24 |

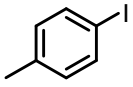
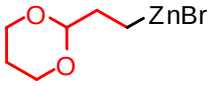
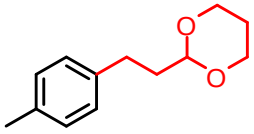
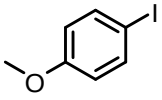
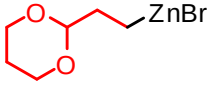
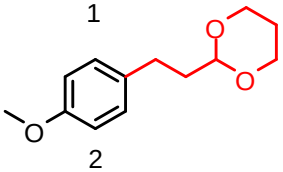
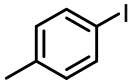
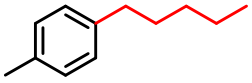
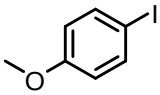
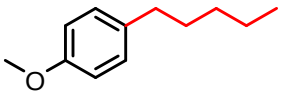
*DMF used as a solvent.Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 2.5 mol% catalyst used for this reaction. For a,b 2 equivalents of pentylzinc bromide used.

From Table **2.9,** binuclear nickel complex **7** catalyzes coupling reactions within one day, but required two equivalents of pentylzinc bromide to consume all of the arylhalide.

**Table 2.10:** Activity towards Negishi cross-coupling with (P-Nitro-DAD)Mes catalyst



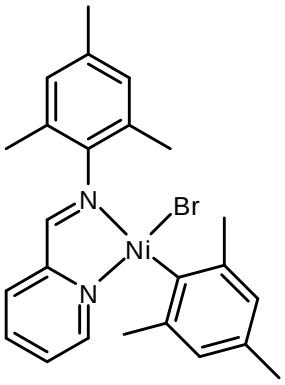

**(P-Nitro-DAD)Mes**
**13**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 65 | 14 |
| (2) |  |  |  2 | 56 | 14 |
| (3) |  |  |  3 | 20 | 14 |
| (4) |  |  |  4 | 44 | 14 |

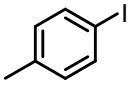
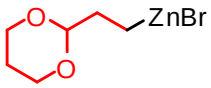
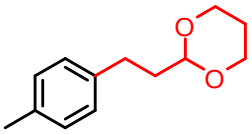
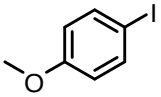
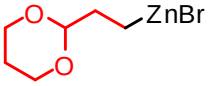
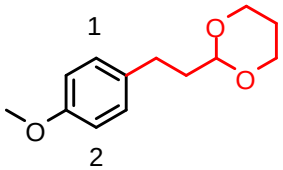
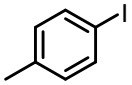
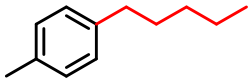
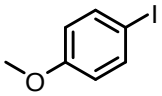
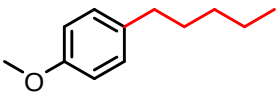
*DMF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 5 mol% catalyst used for this reaction.

From Table **2.10** mononuclear nickel complex **13** performs better on highly functionalized zinc reagents compared to the pentylzinc bromide nucleophiles. Almost all of the reactions were finished in 14 hrs.

**Table 2.11:** Activity towards Negishi cross-coupling with Mes-Pyma catalyst



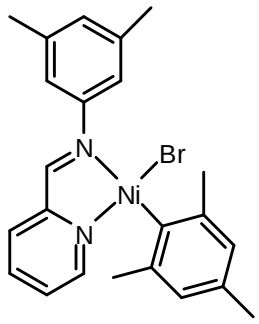

**Mes-Pyma**
**9**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 73 | 22 |
| (2) |  |  |  2 | 56 | 22 |
| (3)[a] |  |  |  3 | 30 | 27 |
| (4)[b] |  |  |  4 | 25 | 27 |

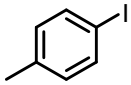
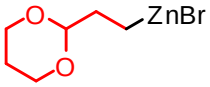
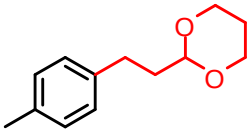
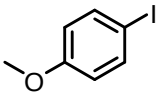
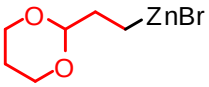
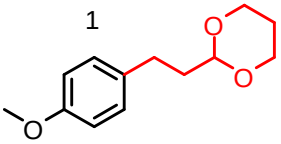
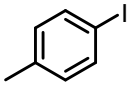
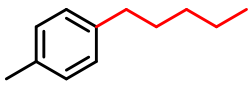
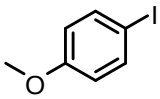
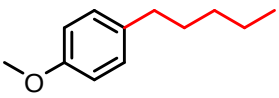
*DMF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 5 mol% catalyst used for this reaction. a,b required two equivalents of zinc reagent.

From Table **2.11,** surprisingly complex **9** has better results for highly functionalized zinc bromides than simple alkylzinc bromides. Entry **1** and **2** ended with 73% and 56% yield and entry 3 and 4 gave low yield 30% and 25%.

**Table 2.12:** Activity towards Negishi cross-coupling with (3,5-Dimethyl)-Pyma catalyst




**(3,5- Dimethyl)-Pyma**
**10**

| entry | Aryl Halide | Zinc Reagent | Product | % Product | Time Hrs |
|---|---|---|---|---|---|
| (1) |  |  |  1 | 57 | 13 |
| (2) |  |  |  2 | 60 | 13 |
| (3) |  |  |  3 | 35 | 10 |
| (4) |  |  |  4 | 37 | 13 |

*DMF used as a solvent. Yields are determined by GC-MS by taking hexamethyl benzene as internal standard. 5 mol% catalyst used for this reaction.

Tables **2.11** and **2.12** show that there was not much difference in activity between complex **9** and **10.** Both of them work better for 2-(1,3-dioxan-2-yl) ethylzinc bromide (entry 1 and 2) compared to pentylzinc bromide ( entry 3 and 4). Reaction completion time is better for complex 10 than 9**.**

**2.7 Discussion:** All of the mononuclear and binuclear nickel complexes showed activity in the formation of aryl-alkyl bonds. All of the complexes were soluble in THF and DMF solvents, but different activity was observed for cross-coupled product formation. Depending on solvent used complex µ-bxip **5** displayed higher activity when the reaction takes place in DMF solvent vs THF solvent. For the entries 1, 2, 3 and 4 yields are 19%, 47%, 13 %, 13% in THF solvent and 71 %, 43%, 72%, 69% in DMF solvent (Table **2.13**).

**Table 2.13:** Complex µ-bxip **5** activity in DMF and THF solvents.

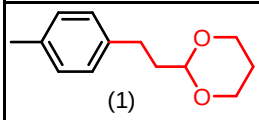
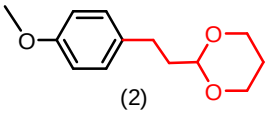
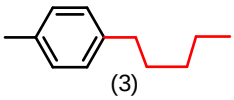
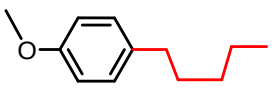
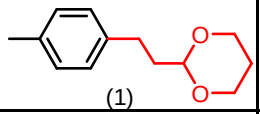
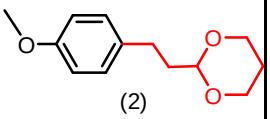
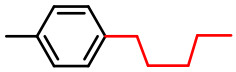
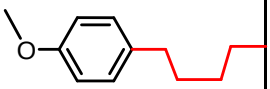
| Product | THF | DMF |
|---|---|---|
|  (1) | 19% | 71% |
|  (2) | 47% | 43% |
|  (3) | 13% | 72% |
|  (4) | 13% | 69% |

**Table 2.14:** Best mononuclear and dinuclear complexes among the complexes I have studied

| Product | bpym(**14**) | μ-bmip(**8**) |
|---|---|---|
|  (1) | 56% | 77% |
|  (2) | 65% | 62% |
|  (3) | 86% | 84% |
|  (4) | 66% | 87% |

In the pool of α-diimine nickel complexes presented in this study, mononuclear nickel complex bpym **14** and binuclear nickel complex μ-bmip **8** have the best reactivity for C-C bond formation in Negishi cross-coupling reaction. Between mononuclear bpym **14** and dinuclear μ-bmip **8** complexes, dinuclear μ-bmip **8** gave better results (Table **2.14**) for some reaction conditions.

Coupling between aryl halides and highly functionalized 2-(1,3-dioxan-2-yl)ethyl zinc reagent supported by complexes ((p-Nitro)-DAD)Mes **13,** Mes-Pyma **9,** ((3,5-Dimethyl)-DAD)Mes **10,** μ-bpym **6,** and (Me-DAD)Mes **11** formed products **1** and **2.** Binuclear nickel complex μ-bpym **6** consumed the starting material in 4.5 hrs and mononuclear complex (Me-DAD)Mes **11** consumed the starting materials in 26 hrs to give product **1 ,** 10.5 hrs to give product **2.** Complex (Me-DAD)O-$CF_3$Ph **12** works better for simple alkyl zinc reagents. By

considering the above results, DMF is the better solvent compared to THF. If the complex has a highly substituted (trisubstituted, disubstituted) aryl ring, then the presence of nitrogen in the α-diimine frame, as in μ-bmip **8** and μ-bxip **5,** presented good results. Sterics also played a crucial role in the activity of the complexes. Sterically-hindered complex μ-btip **7** took 92 hrs to consume half of aryl halide for a highly functionalized zinc reagent and eventually the catalyst died.

### 2.8 Future studies:

Preliminary results showed decent activity for C-C bond formation by these new dinuclear complexes. Further investigation should focus on compatibility with different functional groups and the effect of reaction conditions, such as mole ratio changes, other solvent changes, temperature changes etc.

# Chapter 3

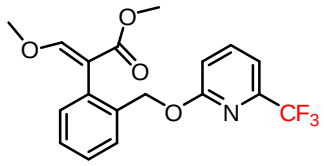
# New Intermediates for Perfluoroalkylation Studies

## 3.1 Introduction:

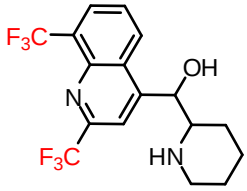
A major challenge for chemists is to make molecules with extraordinary properties which can be used for applications in a wide range of fields. Fluorination often meets this challenge. Fluorine is the 13$^{th}$ most abundant element on the earth.[1] The small size of fluorine atom allows it to be readily incorporated into organic compounds in place of hydrogen. Replacing hydrogen with fluorine in organic compounds often produces molecules with interesting properties in organic and biological chemistry. However organo-fluorine containing molecules are rare in nature. One way to introduce fluorine into molecules is to replace a methyl group with trifluoromethyl group.

Trifluoromethylation is known to alter the liphophilicity of the parent substrate, as well as the acidity, dipole-moment, polarizability, chemical and metabolic stability. The importance of fluorinated organic molecules has increased in the drug industry.[2] Fluorine molecules have many applications in agrochemicals, refrigerants, textile chemicals, surfactants, propellants, polymers and dyes.[3] At present, 30-40% of agrochemicals and 20-30% of pharmaceutical compounds have at least one fluorine atom.[4] The following Figure **3.1** describes some selected fluorine containing bioactive molecules. Picoxystrobin and Fluazinam work as fungicides in crops. Mefloquine is a preventive medicine for

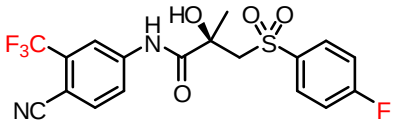
malaria. Bicaluatamide is used to treat prostate cancer. Fluoxetine is an antidepressant. Only a limited number of synthetic methods are available to make fluorinated compounds and all of the $CF_3$ containing molecules have to be prepared synthetically. Because of the need for better synthetic protocols, the field has attracted many scientists. Introduction of fluorine and fluorine containing substituents into organic molecule is correctly an active and challenging area in recent years.



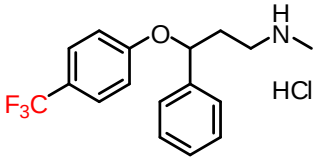

Picoxystrobin



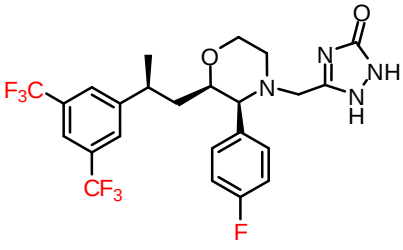

Mefloquine (Lariam®)



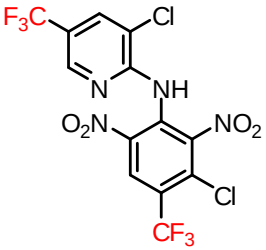

Bicaluatamide (Casodex®)




Fluoxetine (Prozac®)




Aprepitant (Emend®)




Fluazinam

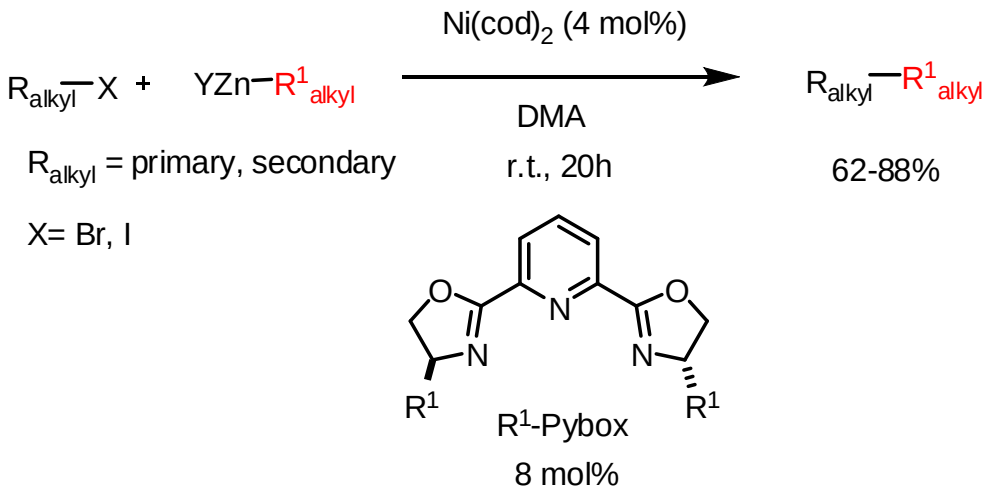
**Figure 3.1:** Fluorine containing pharmaceutical drugs

### 3.2 Alkyl couplings:

To understand fluoroalkylation reactions, one should be aware of the related alkylation reactions that are known in the literature.

In 2003, Fu *et al* [4] developed an efficient nickel catalytic system to form alkyl-alkyl bonds. He successfully coupled primary and secondary alkyl bromides and iodides with alkyl zinc reagents. Fu used $Ni(cod)_2$ (4 mol%) and *s*-Bu-Pybox (8 mol%) in DMA solvent to get high yields of cross-coupled products at room temperatures (Scheme **3.1** ).

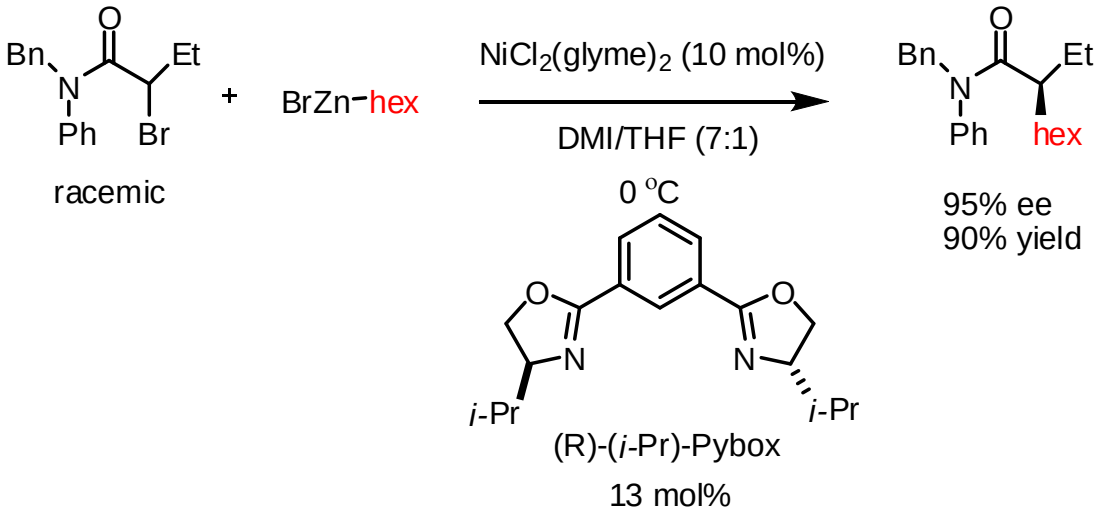
**Scheme 3.1:** Negishi-catalyzed cross-coupling of primary and secondary alkyl halides.




In 2005, Fu *et al* [5] extended the work to cross-couple unsymmetrical secondary electrophiles with alkylzinc reagents in the presence of the nickel-catalytic system. He used (glyme)$NiCl_2$ (10 mol%), (R)-(*i*Pr)-pybox (13 mol%) and DMI (1,3-dimethyl-2-imidazolidinone)/ THF (tetrahydrofuran) as a solvent system to achieve enantioselectivity in the cross-couplings (Scheme **3.2**).

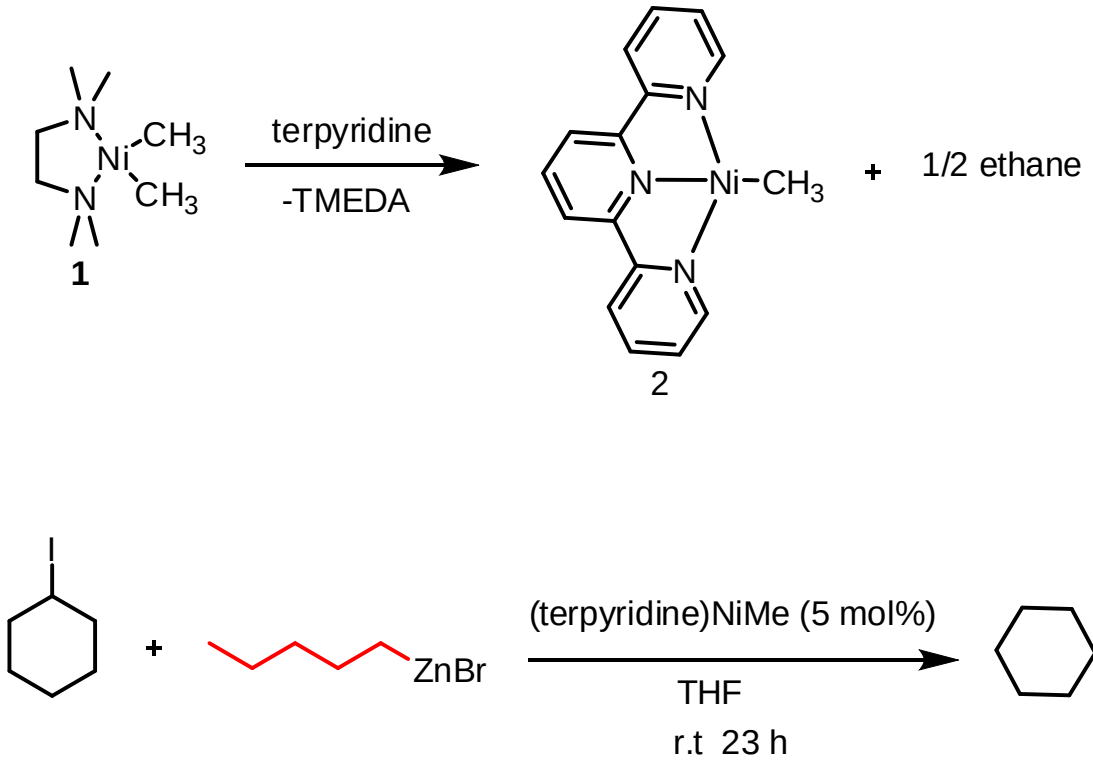
This catalytic system achieves stereoconvergence of the racemic starting material to yield enantiomerically enriched products.

**Scheme 3.2:** Asymmetric Negishi-catalyzed cross-coupling reaction of secondary α-bromo amides and alkylzinc reagents




Because the pybox nickel complexes were difficult to purify and crystalize for fundamental studies of cross-couplings, little was known about the mechanistic details of these reactions. To understand the mechanistic aspects of alkyl-alkyl cross-coupling reactions, Dr. Vicic has developed an efficient catalytic system to examine the formation of alkyl-alkyl bonds with nickel catalysts. He successfully isolated and characterized nickel terpyridine complexes and studied in detail the metal-catalyzed cross-coupling reactions.[6]

**Scheme 3.3:** Catalytic alkyl-alkyl coupling reaction at room temperature

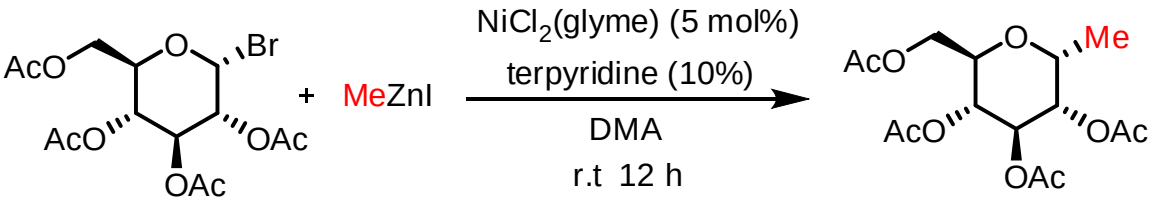



Dr. Vicic prepared nickel terpyridine complex **2** (Scheme **3.3**) from (TMEDA)Ni($CH_3$)$_2$ **1** (TMEDA=*N,N,N',N'*-tetramethylethylenediamine) complex (Scheme **3.3**) in THF solvent and successfully coupled secondary alkyl halides with alkyl zinc halides using this catalyst. Formation of complex **2** in Scheme **3.3** might occur through homolysis of the Ni-C bond, [7,8] resulting from distortion of the Ni(II) dialkyl complex from square planarity. According to this model, the failure of the dimethyl complex to eliminate a full equivalent of ethane upon addition of terpyridine ligand shows that a Ni(II) dialkyl intermediate may not form in the catalytic cross-coupling reaction of saturated

alkyl halides. Terpyridine based nickel catalysts are synthetically very useful ligands in cross-coupling reactions. Dr. Vicic's group first showed the activity of terpyridine nickel catalysts for cross-coupling of alkyl halides with alkyl nucleophiles in Negishi type systems. But others have used this catalyst since this time.

In 2008, Gagné *et al*[9] developed a Negishi type cross-coupling catalytic system to couple between C-alkyl and C-aryl glycosides. Dr. Gagné used a $NiCl_2$(glyme) (5 mol%) and terpyridine catalytic system in DMA (*N,N*-dimethylacetamide) as solvent to achieve higher yields (Scheme **3.4**). This catalytic system improved yields of the selective cross-coupled product, as compared to the $NiCl_2$(glyme)/pybox system.

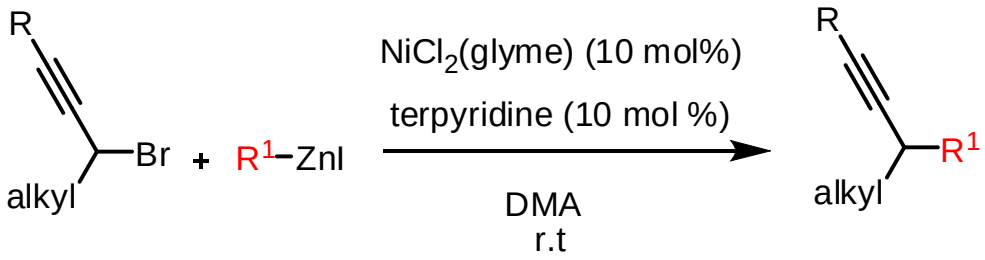
**Scheme 3.4:** Negishi catalyzed cross-coupling reaction between glycosyl bromide and alkyl zinc halide




Fu et al[10] have achieved a nickel-catalytic system to couple secondary alkyl halides with secondary alkyl zinc halides. His group used $NiCl_2$(glyme) (10 mol%), terpyridine (10 mol%), DMA solvent as a catalytic system in cross-

coupling reaction (Scheme **3.5**). This catalytic system works not only for bulky alkyl bromides but also for less hindered alkyl bromides.

**Scheme 3.5:** Room temperature Negishi cross-coupling reaction of secondary propargylic electrophiles with secondary nucleophiles




The above terpyridine based Ni-catalytic system (Scheme **3.5**) works better for secondary alkyl bromide electrophile with secondary alkyl zinc nucleophile compared to pybox based Ni-catalytic system.

All of the above attempts were successful in making $C_{sp}{}^3$-$C_{sp}{}^3$ bonds with nickel based terpyridine catalytic system. Because terpyridine is a good ligand for the formation of alkyl-alkyl bonds, my hypothesis was that a Ni-terpyridine complex would also be good for the coupling of perfluoroalkyl substrates.

### 3.3 Fluoroalkyl couplings:

In the early stages of fluoroalkyl couplings, trifluoromethyl metal (Hg, Cu, Zn and Cd) species were used as nucleophiles to couple with aryl halides. There were lot of limitations applied to the trifluoromethyl usage in fluoroalkyl cross-coupling reactions.[11] They suffered from low yields and various fluorinated side products. Moreover, some reagents were toxic.

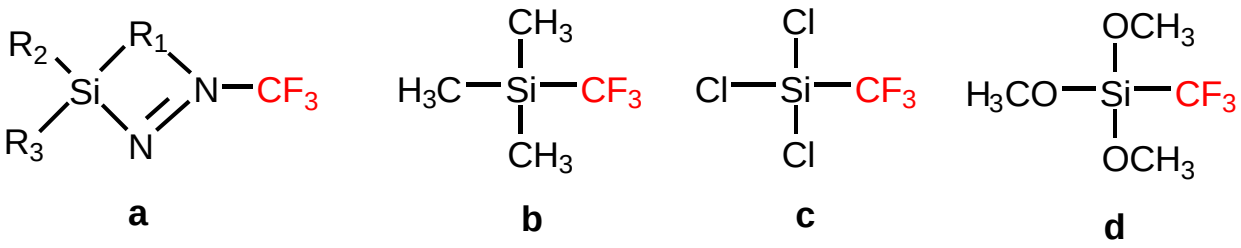
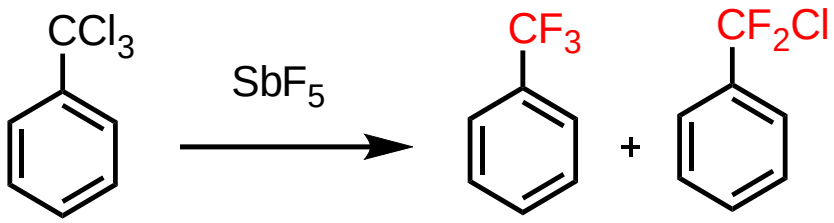



**Figure 3.2:** Some of the common trifluoromethyl sources used in per fluoroalkylation cross-coupling reactions

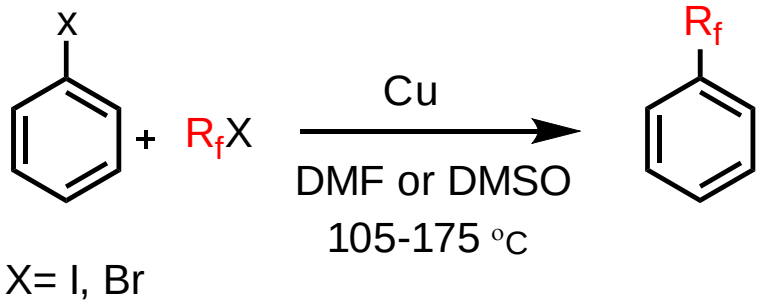
In 1980's several nucleophilic silicon containining trifluoromethyl reagents were reported.[12] Among all, Rupport's group[13,14] and Prakash's group[15] developed trifluoromethyl sources (Figure **3.2 b, c,** and **d**) that gained importance in perfluoroalkylation cross-couplings. The reagents nucleophilicty can be improved by adding CsF, KF, and morpholine based ionic ligands. Also added were $AsPh_3$, $SbPh_3$ and $K_2CO_3$, which act as an initiators for trifluoromethyl sources in coupling reactions.

**Scheme 3.6:** Swarts method to prepare trifluoromethylated aromatic compounds




The simplest trifluoromethylated aromatic compound was first prepared by Swarts.[13] The Swarts method has limitations, leading to side products in addition to the desired product, and required hazardous chemicals and generated large amounts of chlorine waste (Scheme **3.6**).

**Scheme 3.7:** Thrower method to prepare polyfluoroalkylated aromatics

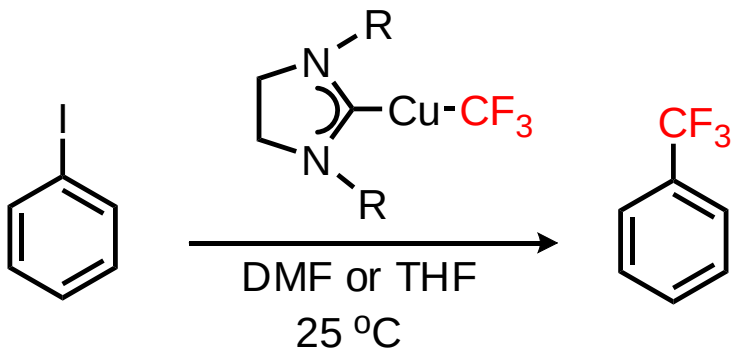



In 1968, McLoughlin and Thrower[14] patented their method to prepare polyfluoalkylated aromatic compounds. It was the first metal mediated polyfluoroalkylation of aromatic organic compounds. In this method the polyfluoroalkyl iodides reductively couple with iodoarenes in the presence of

copper metal (Scheme **3.7**)**.** Super stoichiometric amounts of copper and high temperatures are needed and the method only works for iodoarenes.

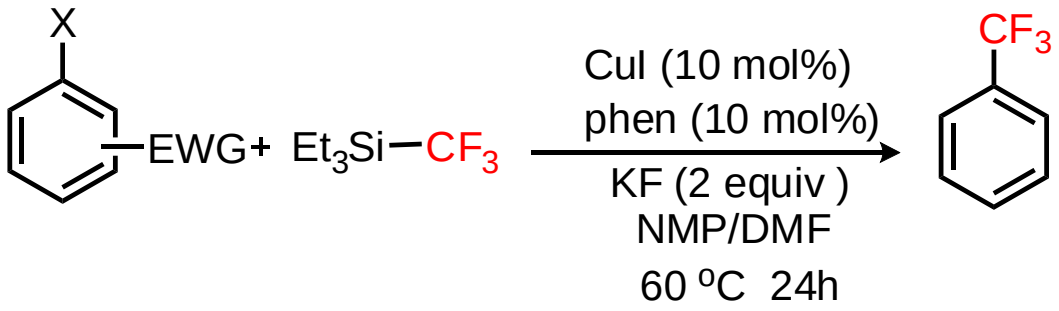
In 2008, Dr. Vicic's group[15,16] reported the first fully characterized Cu(I) trifluoromethyl complex that could effectively be used as a trifluoromethylating agent in fluoroalkylation cross-coupling reactions. A carbene based copper(I) trifluoromethyl complex was generated *in situ* and coupled with the iodoarenes at room temperatures in DMF and THF solvents (Scheme **3.8**).

**Scheme 3.8:** Copper catalyzed fluoroalkyl cross-coupling reactions




In 2009, Amii and co-workers[18] developed a copper catalytic system to couple aryl halides with fluoroalkyls based on a similar ligation strategy. His method was catalytic in copper, but unfortunately this catalytic system only works for electron withdrawing aromatic compounds.

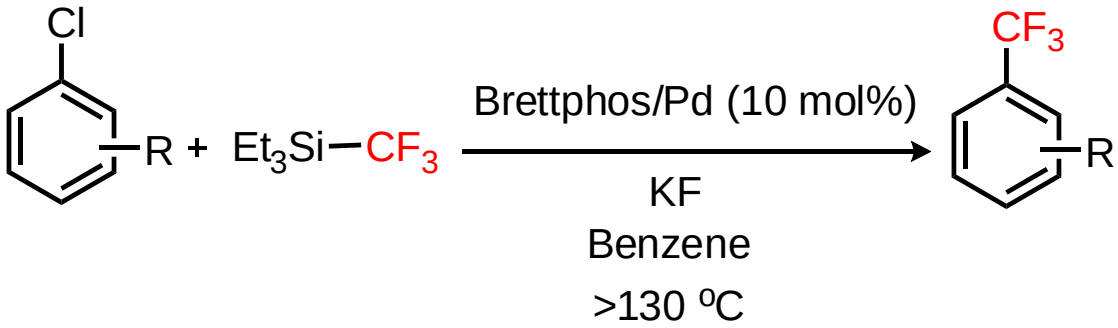
**Scheme 3.9:** Fluoroalkyl cross-coupling reaction with copper metal and phenanthroline as ligand




In this catalytic system (Scheme **3.9**) Dr. Amii used copper as metal with phenanthroline as a ligand. Potassium fluoride was used to activate the fluoroalkyl source. The reaction was performed at 60 ºC and finished in 24 h.

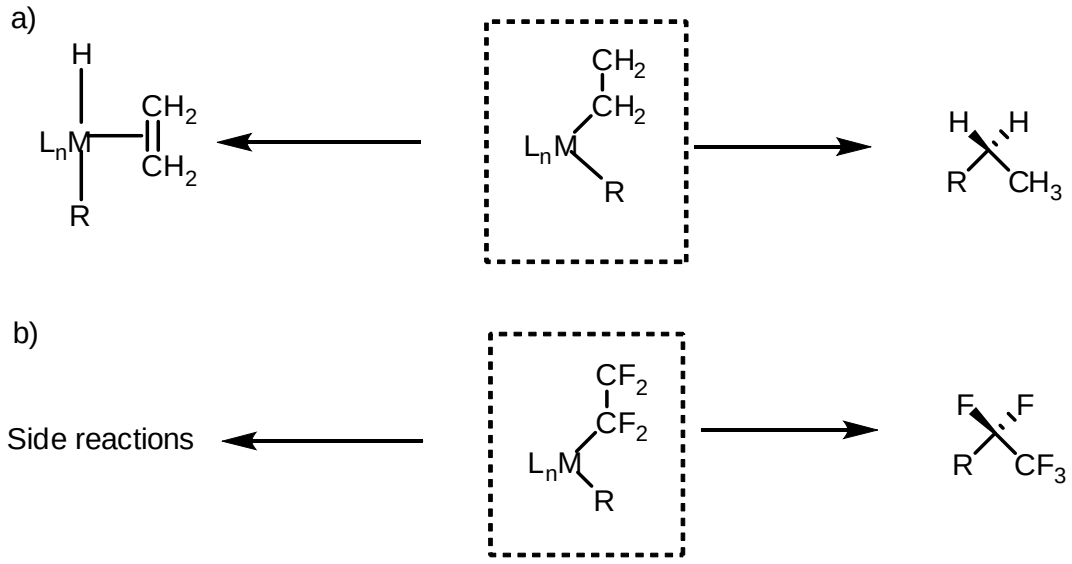
In 2010, Buchwald *et al*[18] developed a palladium catalytic system which can effectively couple chloroarenes with a trifluoromethylating agent. He used Brettphos as a ligand (Scheme **3.10**). Buchwald's system required higher temperatures (130 ºC) and only works for chloroarenes.

**Scheme 3.10:** Palladium catalyzed trifluoromethylation of aryl chlorides



Thus, all of the above reactions dealing with fluroalkyl cross-couplings have limitations.

**Scheme 3.11:** Possible outcomes of alkyl and perfluoroalkyl couplings




After the oxidation step in alkyl-alkyl cross-couplings, electrophiles with β-hydrogen can undergo β-hydride elimination reactions to form olefins rather than the desired cross-coupled product (**Scheme 3.11a**). This is one of the major obstacles one has to deal with in alkyl-alkyl coupling reactions. Perfluoroalkyl couplings are worse compared to alkyl couplings. Metal-perfluoroalkyls undergo β-fluoride elimination, and in addition to this, they can undergo α-fluoride eliminations and undergo irreversible reactions in protic solvents (**Scheme 3.11b**). Developing suitable methods to cross-couple perfluroralkyls is a challenging area in organic synthesis.

Fundamental studies are needed to understand how to better deliver a perfluoroalkyl group to an organic substrate. All of the aforementioned perfluroalkyl cross-couplings are limited to only copper and palladium metals and concentrated only on reductive elimination of aryl-perfluoroalkanes. No active catalytic system is known to perform alkyl-perfluoroalkyl or perfluoroalkyl-perfluoroalkyl coupling reactions. My research has focused in this area. I have worked to make an efficient system to perform perfluoroalkyl-perfluoroalkyl cross-coupling reactions.

### 3.4 Experimental and results discussion:

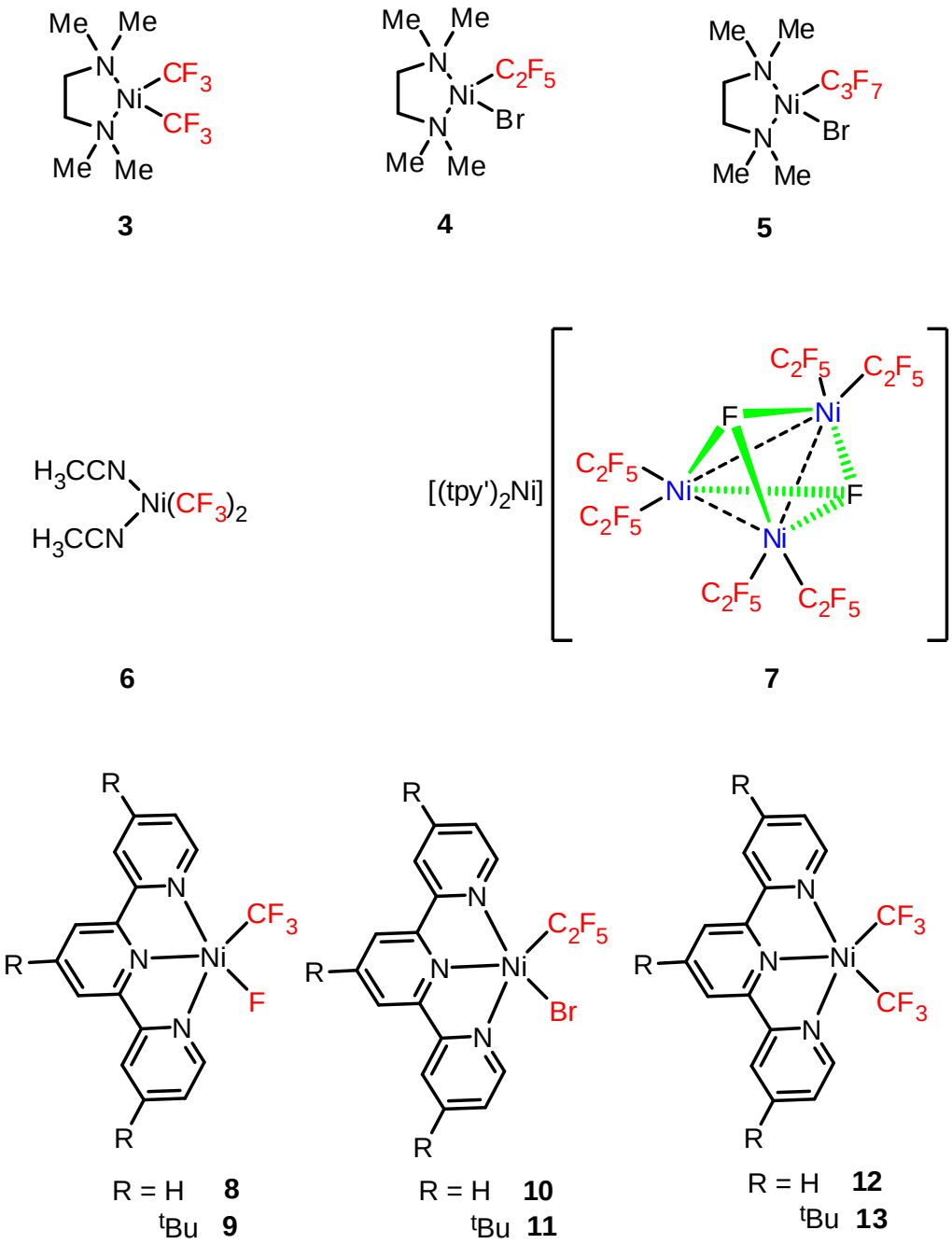
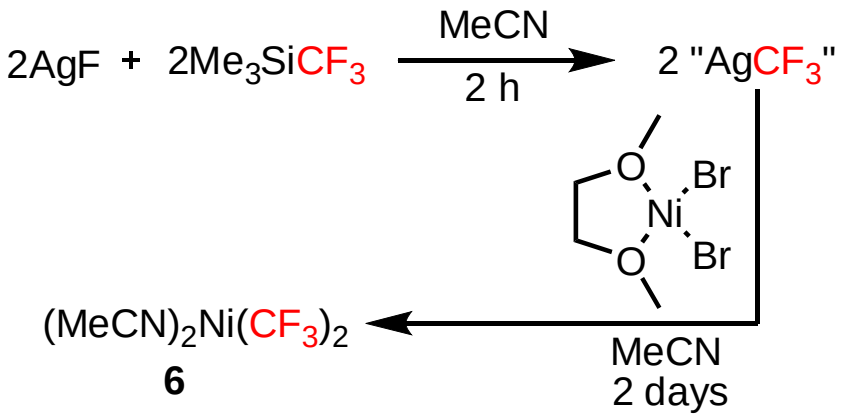



**Figure 3.3:** Nickel complexes I have made as part of the perfluoroalkyl-perfluoroalkyl couplings investigation

To investigate perfluoroalkyl-perfluoroalkyl cross-couplings, I have made the above (Figure **3.3**) fluoroalkyl complexes.

**Scheme 3.12:** Preparation of $(CH_3CN)_2Ni(CF_3)_2$ (**6**)



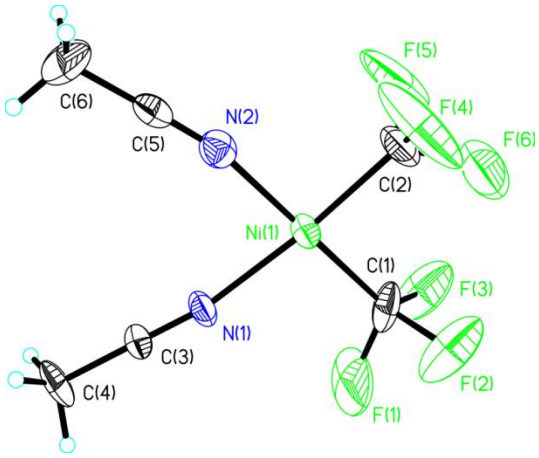




**Figure 3.4:** ORTEP diagram of $[(MeCN)_2Ni(CF_3)_2]$ (**6**). Selected bond lengths (Å): Ni(1)-N(1) 1.971(10); Ni(1)-N(2) 1.889(12); Ni(1)-C(1) 1.853(18); Ni(1)-C(2) 1.903(15). Selected bond angles for **6** (°):N(1)-Ni(1)-N(2) 84.0(5); N(1)-Ni(1)-C(1) 95.6(6); N(1)-Ni(1)-C(2)174.4(6); N(2)-Ni(1)-C(1) 178.5(6); N(2)-Ni(1)-C(2) 90.5(6); C(1)-Ni(1)-C(2) 89.9(7).

Complex **6** is the precursor for most of the nickel complexes I have presented in this chapter. This is a new precursor which hasn't been published yet. I have used trifluoromethyltrimethylsilane as a trifluoromethyl source in making complex **6** (Scheme **3.12**)**.** By using complex **6,** we sought to prepare tetra and penta coordinated nickel-perfluoroalkyl complexes (Figure **3.5**) to investigate perfluoroalkyl-perfluoroalkyl couplings.

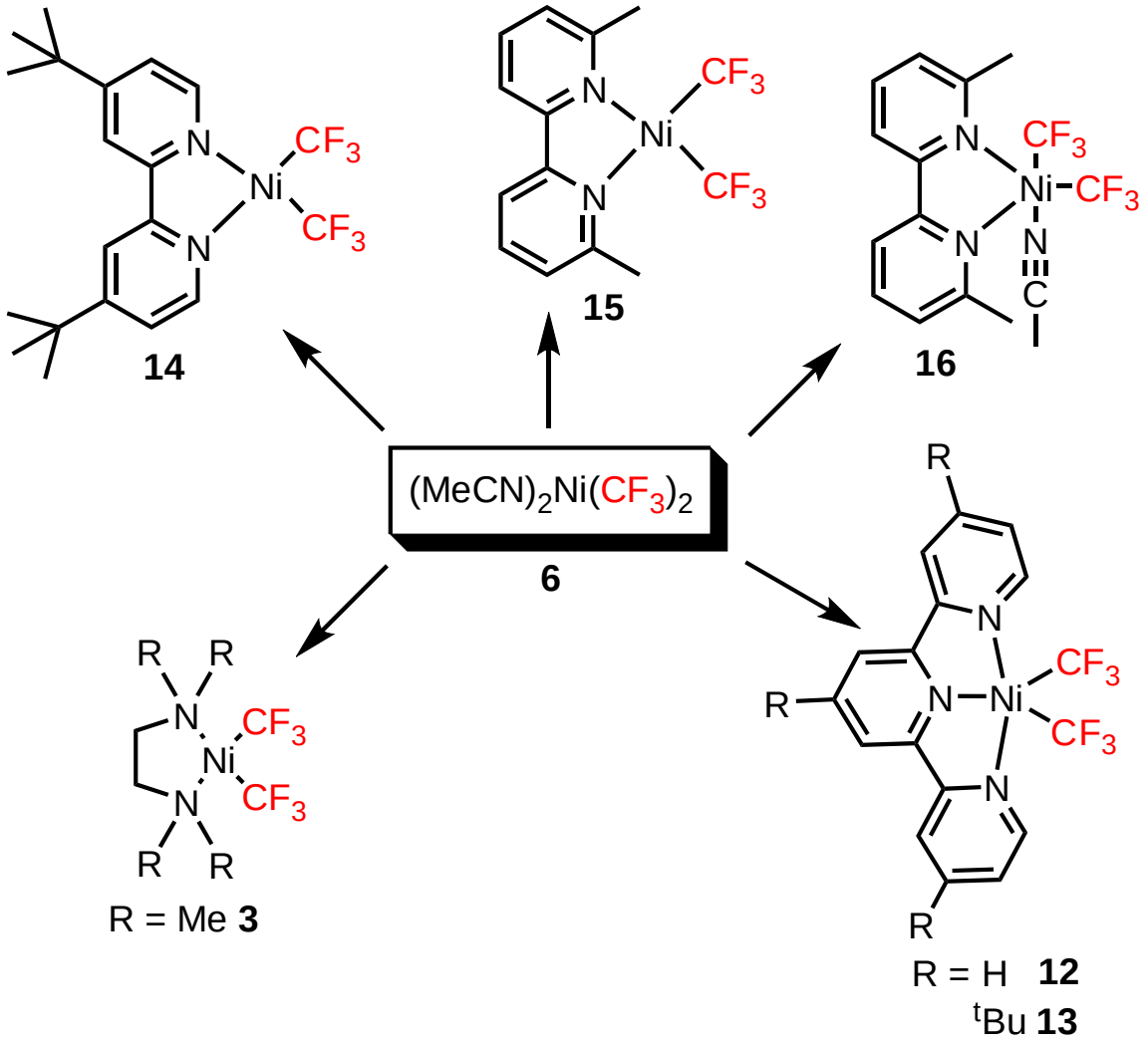
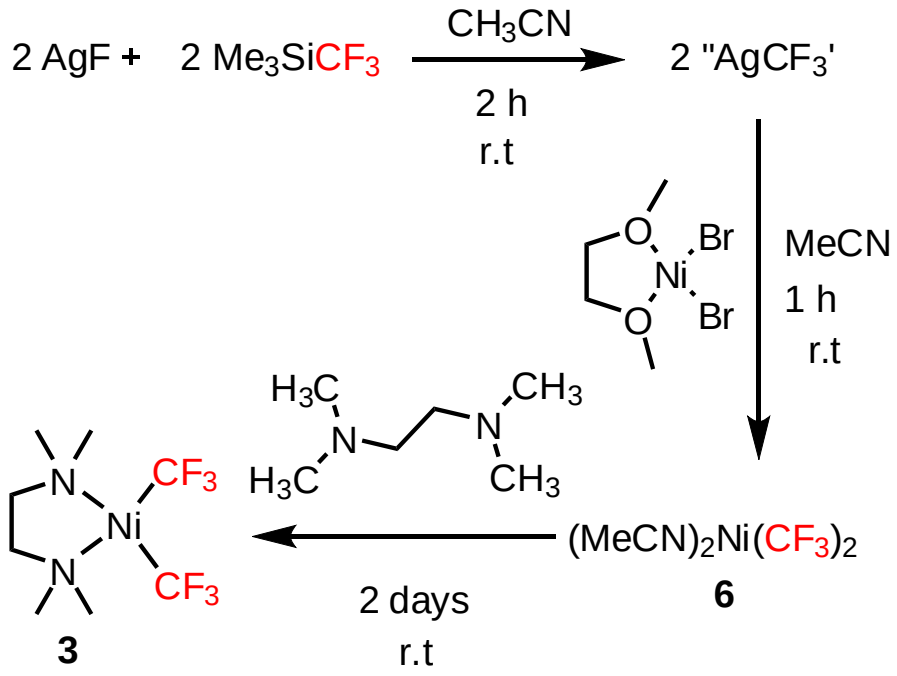



**Figure 3.5:**Nickel-perfluroroalkyl complexes can be generated from complex **6**

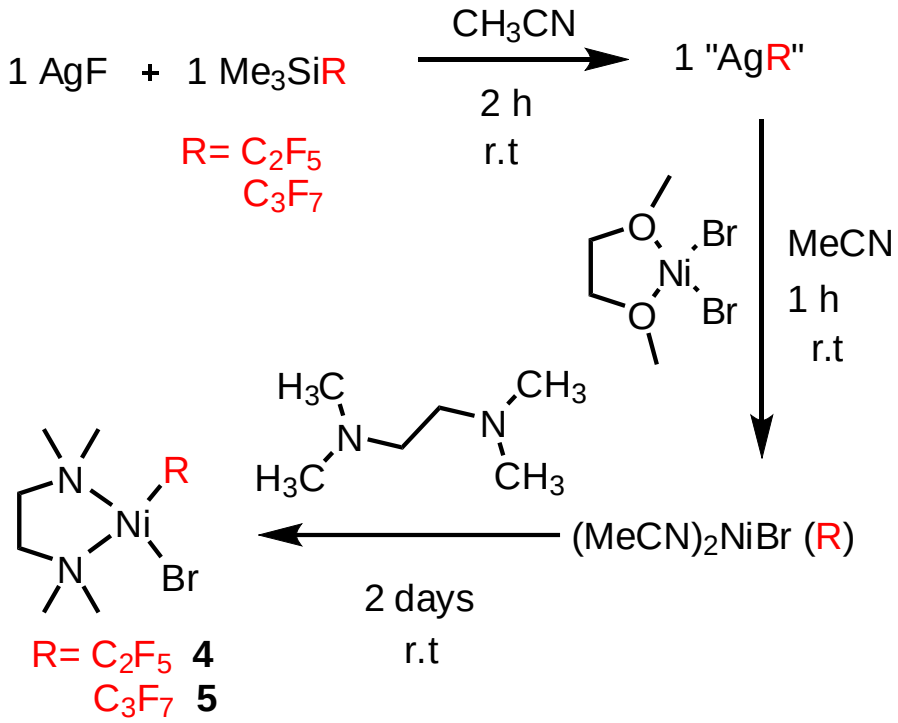
**Scheme 3.13:** Preparation of $(TMEDA)Ni(CF_3)_2$ **(3)**




Complex **3** was prepared by Dr. Cheng-Pan Zhang, a postdoc in Dr. Vicic's lab. The synthesis involved the precursor $(MeCN)_2Ni(CF_3)_2$ , which was generated *in situ* by the above route.

The syntheses of complexes **4** and **5** (Figure **3.3**) are shown below in Scheme **3.14**. To prepare complexes **4** and **5**, I have used pentafluorodimethyltrimethylsilane ($TMSC_2F_5$) and heptafluorotrimethylsilane ($TMSC_3F_7$) as perfluoroalkyl sources. Complex **4** is a yellow color compound and crystallized in a cetonitrile/pentane solvent mixture. Complex **5** is gummy red color compound. Complex **5** is difficult to recrystallize because of it's gummy nature.

**Scheme 3.14:** Preparation of (TMEDA)NiBr($C_2F_5$) **(4)** and (TMEDA)NiBr($C_3F_7$) **(5)**

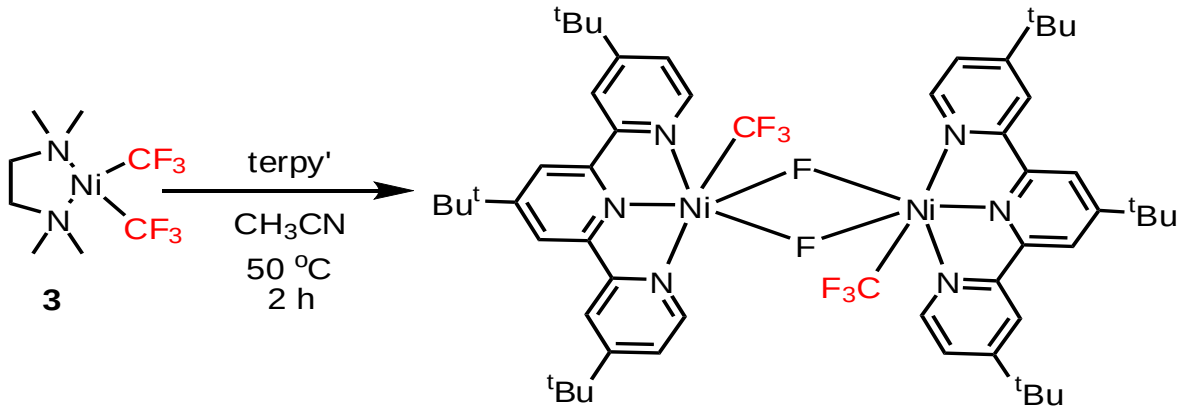



Complex **4** and **5** are good precursors to make perfluoroalkyl-alkyl and perfluoroalkyl-aryl bonds. Although I have successfully prepared complexes **4** and **5,** I need to work more on these complexes to get a reliable preparation and isolation process.

Penta-coordinated nickel complexes are considered promising in the formation of polyfluoroalkyl-polyfluoroalkyl bonds, because they have been successfully used in alkyl-alkyl bond formations. These complexes were recrystallized in a THF/Pentane solvents mixture. For complex **9,** brown colored crystals were obtained. I couldn't get the full crystal structures because the instrument at University of Hawaii at Manoa was not working. I did manage

to get the basic connectivity structure. The following Scheme **3.15** shows the synthetic route.

**Scheme 3.15:** Preparation of $[(terpy')Ni(CF_3)F]_2$ complex (**9)**




**9**

Complex **9** was detected to be a dimer in the solid state by basic X-ray diffraction analysis. The following Figure **3.6** is the ball and stick diagram for complex **9** dimer from DFT studies that were based on the preliminary X-ray structure.

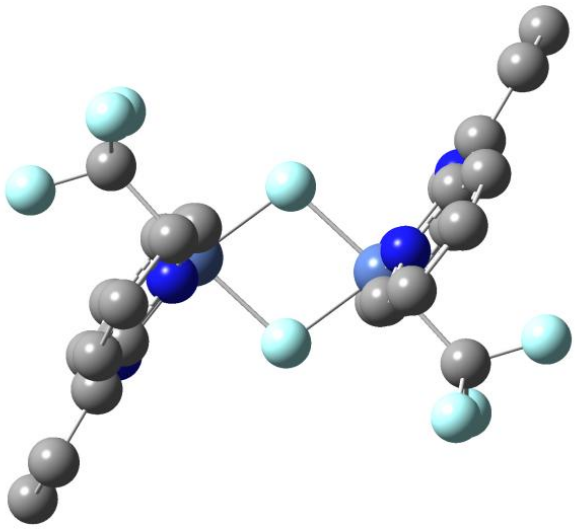
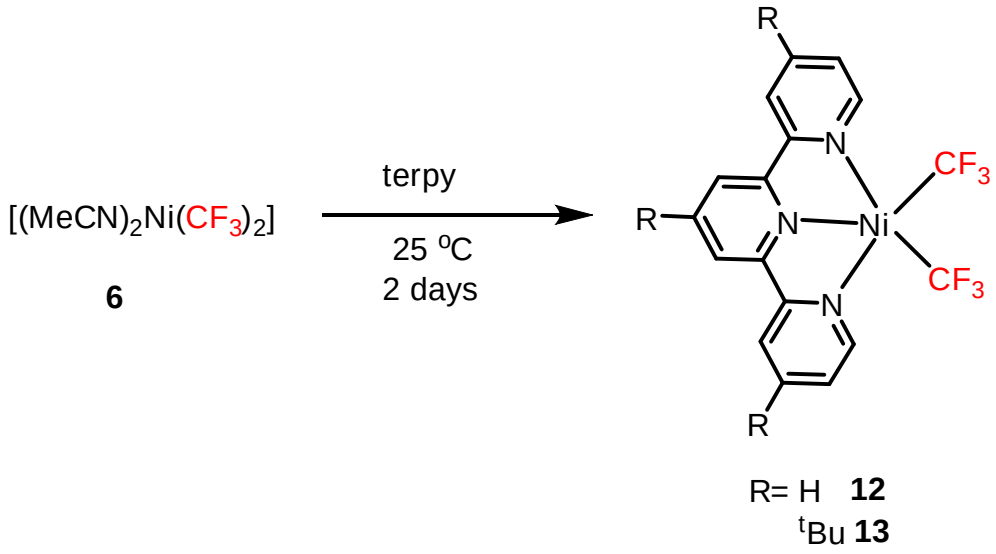


**Figure 3.6:** Ball and stick diagram for complex **8** dimer

**Scheme 3.16**: Preparation of (terpy')Ni($CF_3$)$_2$ complexes **12** and **13**




Complexes **12** and **13** were prepared from complex **6** at ambient temperature as described in Scheme **3.16**. This is the first report of a penta-coordinated nickel-perfluoroalkyl complex. Figure **3.7** shows the DFT optimized geometry of complex **12** as a ball and stick diagram.

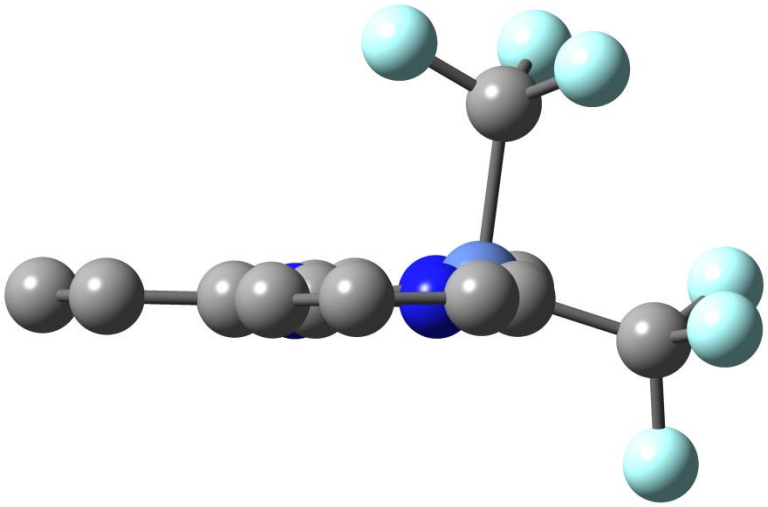
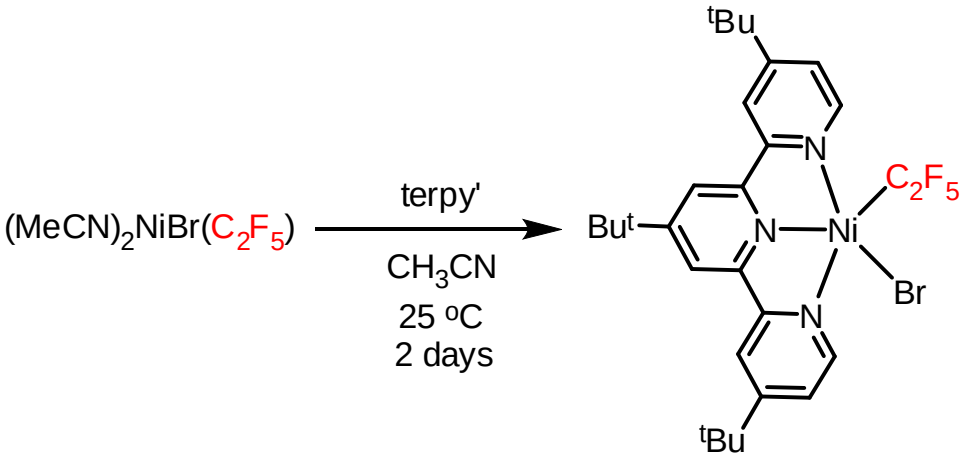


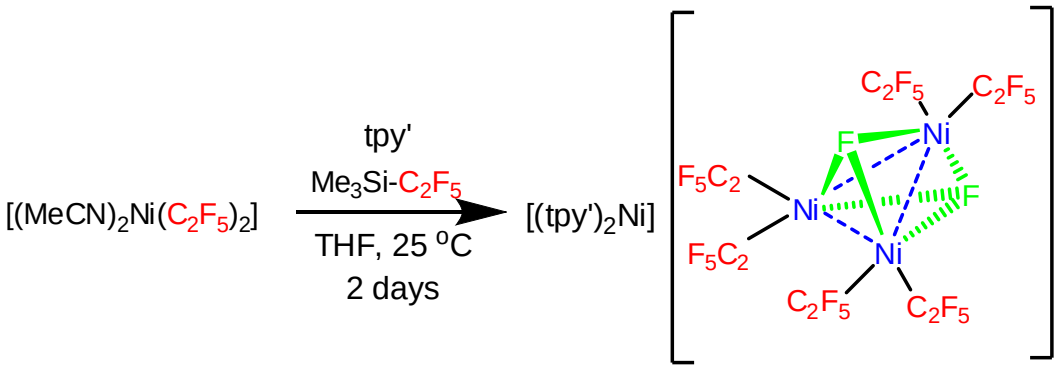
**Figure 3.7:** Ball and stick diagram for complex **12**

**Scheme 3.17:** Preparation of (terpy')Ni($C_2F_5$)Br **11** Complex




I have also prepared the $(MeCN)_2NiBr(C_2F_5)$ complex. I obtained green colored crystals of complex **11** from THF solution, and the structure was determined by X-ray crystallography. This complex is a good precursor for alkyl-perfluoroalkyl cross-couplings because the halide could be replaced by a variety of ligands for future studies.

**Scheme 3.18:** Preparation of $[(terpy')_2Ni][Ni_3F_2(C_2F_5)_6]$ (**7**) Complex




**7**

I have tried to prepare a $[(terpy')Ni(C_2F_5)_2]$ complex. In this process I accidentally made complex **7**. I got red colored crystals after workup of the

reaction. Then I confirmed the basic structure by X-ray diffraction. I need to do more work on reaction optimization to get the pure compound for further analysis.

### 3.5 DFT studies:

Because five-coordinated complexes of nickel terpyridine bearing a nickel-carbon bond were unknown prior to this report, DFT calculations were performed on complexes **8, 12, 14** and **15** (Figure **3.7**) to support basic X-ray data and to provide insight into the electronic structure of these new species. Multiple spin states were explored (Table **3.1**) and both lengths and angles of the lowest energy species are provided in Table **3.2**.

**Table 3.1:** Energies of complexes **8, 12, 14** and **15** at different spin states. The lowest energy state is in red color.

| ***Complex*** | ***Total Energy (Hartrees)*** | | |
|---|---|---|---|
| **12** | singlet: -2925.87160474 | triplet: -2925.87188471 | |
| **14** | doublet: -2925.67871718 | quartet: -2925.57684330 | |
| **8** | singlet: -5376.20118040 | triplet: -5376.26421840 | quintet: -5376.27923028 |
| **15** | singlet -2925.88478685 | triplet -2925.90398964 | |

Table **3.1** shows the energies of complexes **8, 15, 12** and **14** in different spin states. For complex **12** the triplet spin state has lowest energy. For complex **14,** the doublet and complex **8,** the quintet has lowest energy state. Complex **8, 15, 12** are paramagnetic in nature in solution, which supports the DFT studies. Complexes **3, 4, 5** are diamagnetic in nature. Figure **3.8** shows the optimized geometries of the complexes **12**, **14** and **15**. Table **3.2** shows the bond lengths and bond angles of terpyridine derivative complexes **8, 15, 12,** and **14** of their lowest energy spin isomer.

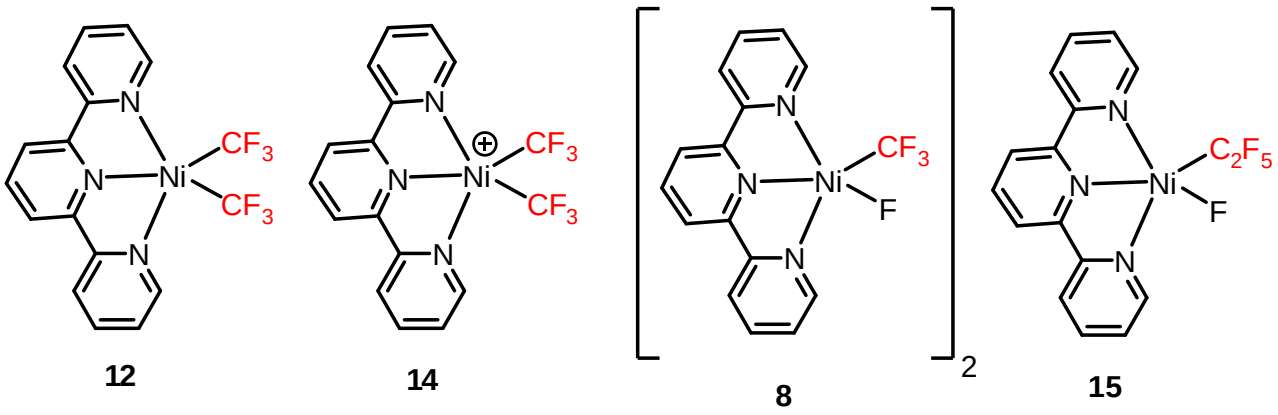



**Figure 3.7:** DFT studies performed on complexes **12, 14, 8,** and **15**

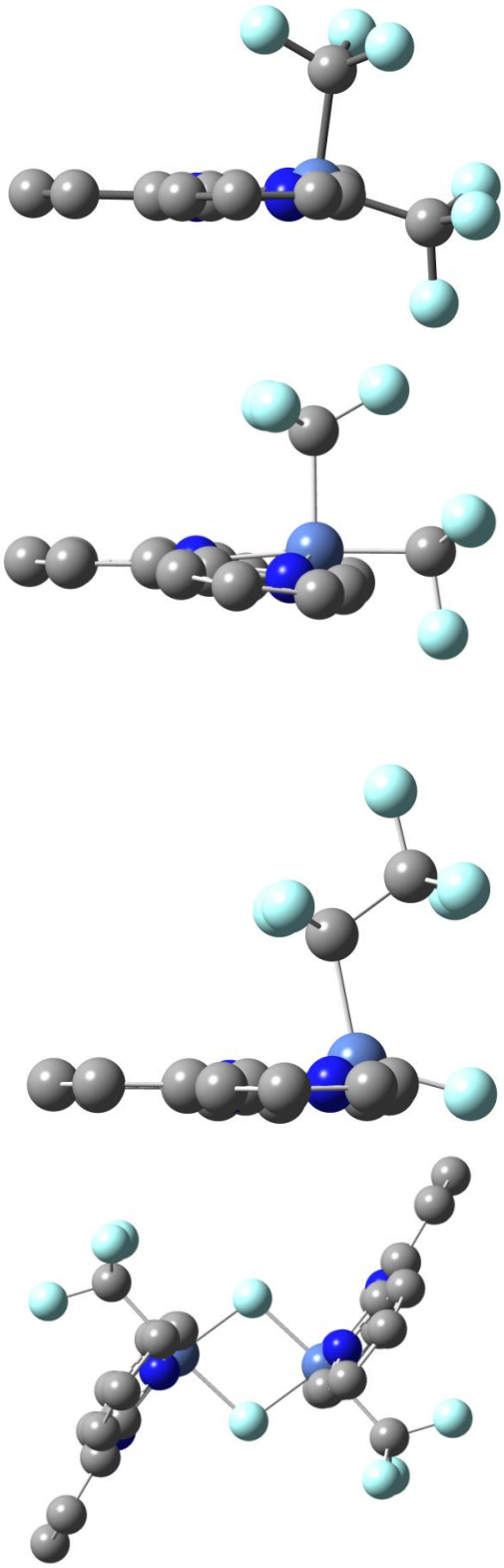
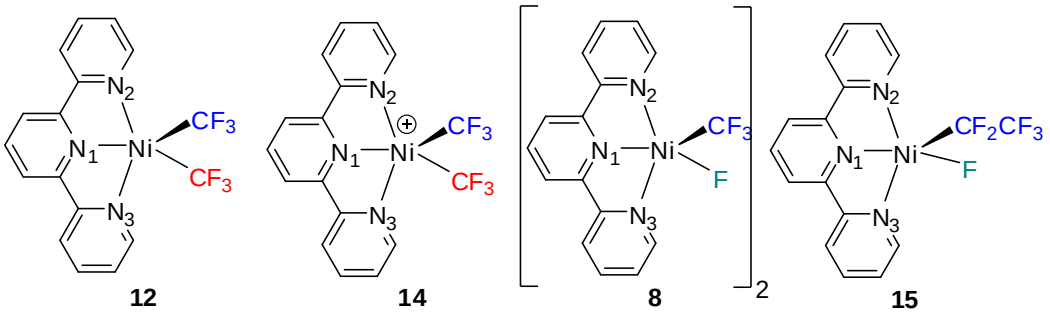


**Figure 3.8:** Optimized geometries (top to bottom) of **12**, **14**, **15**, and **8**. Hydrogen atoms are omitted for clarity.

**Table 3.2:** Comparison of calculated (B3LYP/m6-31g*) bond lengths (Å) and angles (°) in related terpyridine nickel trifluoromethyl complexes.




| ***bond length or angle*** | ***12*** *(triplet)* | ***14*** *(doublet)* | ***8*** *(quintet)* | ***15*** *(triplet)* |
|---|---|---|---|---|
| Ni-C | 1.996 | 1.901 | - | - |
| Ni-C | 1.985 | 1.962 | 2.013 | 2.024 |
| Ni-F | - | - | 1.986 | 1.831 |
| Ni-N1 | 2.034 | 1.952 | 2.055 | 2.013 |
| Ni-N2 | 2.154 | 2.110 | 2.129 | 2.097 |
| Ni-N3 | 2.145 | 2.111 | 2.160 | 2.099 |
| N1-Ni-C | 157.0 | 174.8 | - | - |
| N1-Ni-C | 102.6 | 94.3 | 99.613 | 89.4 |
| C-Ni-C | 100.4 | 90.9 | - | - |
| F-Ni-C | - | - | 95.658 | 116.2 |
| N1-Ni-F | - | - | 164.346 | 154.4 |
| Ni-F-Ni | - | - | 100.343 | - |

### 3.6 Conclusion and future studies:

In conclusion, I have successfully synthesized and isolated tetra and penta coordinated nickel-perfluoroalkyl complexes. DFT studies have been performed on these complexes to support the X-ray diffraction structures and to compare the energies in different spin states. These complexes are useful precursors for further investigation for alkyl-fluoroalkyl, alkyl-perfluoroalkyl, and perfluoroalkyl-perfluoroalkyl cross-coupling reactions.

Selective alkylation and fluoroalkylation methods will continue to play an important role in synthetic organic chemistry, and further development of these methods can impact many areas of basic science. The results described in this chapter serve to aid in understanding at the molecular level the details of these transformations, which could enable reactions that have thus far remained problematic for palladium. In the future, we need to prepare additional perfluoroalkyl nickel complexes using a variety of ligands to understand the roles of geometry and metal oxidation state in the reductive elimination reactions of perfluoroalkyl groups. More synthetic studies are needed to prepare new complexes involving perfluoroalkyl substrates.

### 3.7 Experimental procedures:

**General Considerations:** All manipulations were performed using standard Schlenk and high vacuum techniques or in nitrogen filled glovebox. Solvents were distilled from a benzophenone or $CaH_2$. DMF was distilled over BaO under reduced pressure. All reagents were used as received from commercial vendors, unless otherwise noted. Elemental analyses were performed by olumbia Analytical Services. $^{1}H$ NMR spectra were recorded at ambient temperature (unless otherwise noted) on a Varian Oxford 300 MHz spectrometer and referenced to residual proton solvent signals. $^{13}C$ NMR spectra were recorded on the Varian Oxford spectrometers operating 75 MHz or 126 MHz and referenced to solvent signals. $^{19}F$ spectra were recorded on the Varian Oxford spectrometer operating at 282 MHz and were referenced to α,α,α-trifluorotoluene as an internal standard (δ = -63.7).

**Preparation of [(TMEDA)Ni($CF_3$)$_2$] (3):** $Me_3SiCF_3$ (200 mg, 1.3 mmol) and AgF (130 mg, 1.0 mmol) were added into 10 mL of dry $CH_3CN$. The mixture was stirred at room temperature for 2 hours. Then $NiBr_2$·DME (158 mg, 0.5 mmol) was added. One hour later, *N,N,N,N*-tetramethylethane-1,2-diamine (70 mg, 0.6 mmol) was added. The reaction mixture was kept stirring for 2 days, and filtered. The filtrate was evaporated on a vacuum line. The residue was extracted by dichloromethane (10 mL). The dichloromethane solution was left standing at room temperature for 0.5 h, then filtered and dried on a vacuum line to give a yellow solid (142 mg, 91%). $^{1}H$ NMR ($CD_2Cl_2$, 300 MHz): δ 2.49 (s, 12H), 2.30

(s, 4H). $^{19}F$ NMR ($CD_2Cl_2$, 282 MHz): δ -27.9 (s, 6F). $^{13}C$ NMR ($CD_2Cl_2$, 125 MHz): δ 127.6 (q, *J* = 368 Hz, $CF_3$), 61.4, 49.2. Anal. Calcd (found) for $C_8H_{16}F_6N_2Ni$: C, 30.71 (31.01); H, 5.15 (5.00).

**Preparation of [(TMEDA)Ni($C_2F_5$)Br](4):** $Me_3SiC_2F_5$ ( 414.80 mg, 3 mmol) and AgF (264.64 mg, 2 mmol) were dissolved into 20 mL dry acetonitrile. The reaction mixture was stirred at room temperature for 2 hours. Then $NiBr_2$•DME (300 mg, 1 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. N,N,N,N-tetramethylethane-1,2-diamine (116.24mg, 1.2 mmol) was added and the mixture was stirred at room temperature for two days, and filtered. The filtrate was evaporated on a vacuum line. Charged 10 mL dry THF, filtered and layered with dry 5 mL dry pentane and kept it in the freezer to grow crystals. Dark yellow colored crystals observed (333 mg, 83% crude yield). $^{19}F$ NMR ($CD_2Cl_2$, 282 MHz): δ -80.9 (m, 3F). δ -107.9 (m, 2F).

**Preparation of [(TMEDA)Ni($C_3F_7$)Br] (5):** $Me_3SiC_3F_7$ ( 117.6 mg, 3 mmol) and AgF (42 mg, 2 mmol) were dissolved into 10 mL dry acetonitrile. The reaction mixture was stirred at room temperature for 2 hours. Then $NiBr_2$•DME (50 mg, 1 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. N,N,N,N-tetramethylethane-1,2-diamine (23 mg, 1.2 mmol) was added and the mixture was stirred at room temperature for two days, and filtered. The filtrate was evaporated on a vacuum line. Charged 10 mL dry THF, filtered and layered with dry 5 mL dry pentane and kept it in the freezer to grow crystals. Red colored crystals observed (42 mg, 60% crude yield). $^{19}F$ NMR ($CD_2Cl_2$, 282 MHz): δ -80.9 (m, 3F). δ -103.9 (m, 2F), δ -115.8 (m, 2F).

**Preparation of $[(CH_3CN)_2Ni(CF_3)_2]$ (6):** $TMSCF_3$ (380 mg, 2.5 mmol) and AgF (260 mg, 2.0 mmol) were added into 20 mL of dry $CH_3CN$. The mixture was stirred at room temperature for 2 hours. Then $NiBr_2$·DME (310 mg, 1.0 mmol) was added. The reaction mixture was kept stirring for 2 days, and filtered. The filtrate was evaporated on a vacuum line to give a yellow solid (253 mg, 90%). $^1$H NMR (DMSO-$d_6$, 300 MHz): δ 2.02 (s). $^{19}$F NMR (DMSO-$d_6$, 282 MHz): δ -26.1. $^{13}$C NMR (DMSO-$d_6$, 125 MHz): δ 125.1 (q, $J$ = 368 Hz, $CF_3$), 117.8, 0.78. Anal. Calcd (found) for $C_6H_6F_6N_2Ni$: C, 25.85 (25.65); H, 2.17 (2.25).

**Preparation of $[(tpy')_2Ni][Ni_3F_3(C_2F_5)_6]$ (7):** $[(MeCN)_2Ni(C_2F_5)_2]$ (25 mg, 1 mmol), $^t$Bu-terpyridine (17.9 mg, 2 mmol) and $Me_3SiC_2F_5$ were dissolved 5 mL dry THF at room temperature. Stirred the reaction mixture for two days at ambient temperatures. Filtered and kept it in the freezer (-35 ºC) to grow the crystals. Brownish yellow colored crystals observed.

**Preparation of $[(tpy')Ni(CF_3)F]_2$ (9)**: $[(TMEDA)Ni(CF_3)_2]$(50 mg, 1mmol) and terpyridine' (96.15 mg, 1.5 mmol) were dissolved in 5 mL of dry acetonitrile. The reaction mixture was stirred for 2 hours at 50 ºC under nitrogen. The reaction mixture was filtered and filtrate was evaporated on a vacuum line. Charged 5 mL dry THF solvent and layered with 2 mL dry pentane. The mixture was left in the freezer (-35 ºC) to grow crystals. Finally, greenish brown colored crystals obtained (32.5 mg, 83% crude yield).

**Preparation of [(tpy)Ni($CF_3$)F]$_2$ (10)**: [(TMEDA)Ni($CF_3$)$_2$](50 mg, 1mmol) and terpyridine (55.87 mg, 1.5 mmol) were dissolved in 5 mL of dry acetonitrile. The reaction mixture was stirred for 2 hours at 50 ºC under nitrogen. The reaction mixture was filtered and filtrate was evaporated on a vacuum line. Charged 5 mL dry THF solvent and layered with 2 mL dry pentane. The mixture was left in the freezer (-35 ºC) to grow crystals. Finally, greenish brown colored crystals obtained (45.5 mg, 75% crude yield).

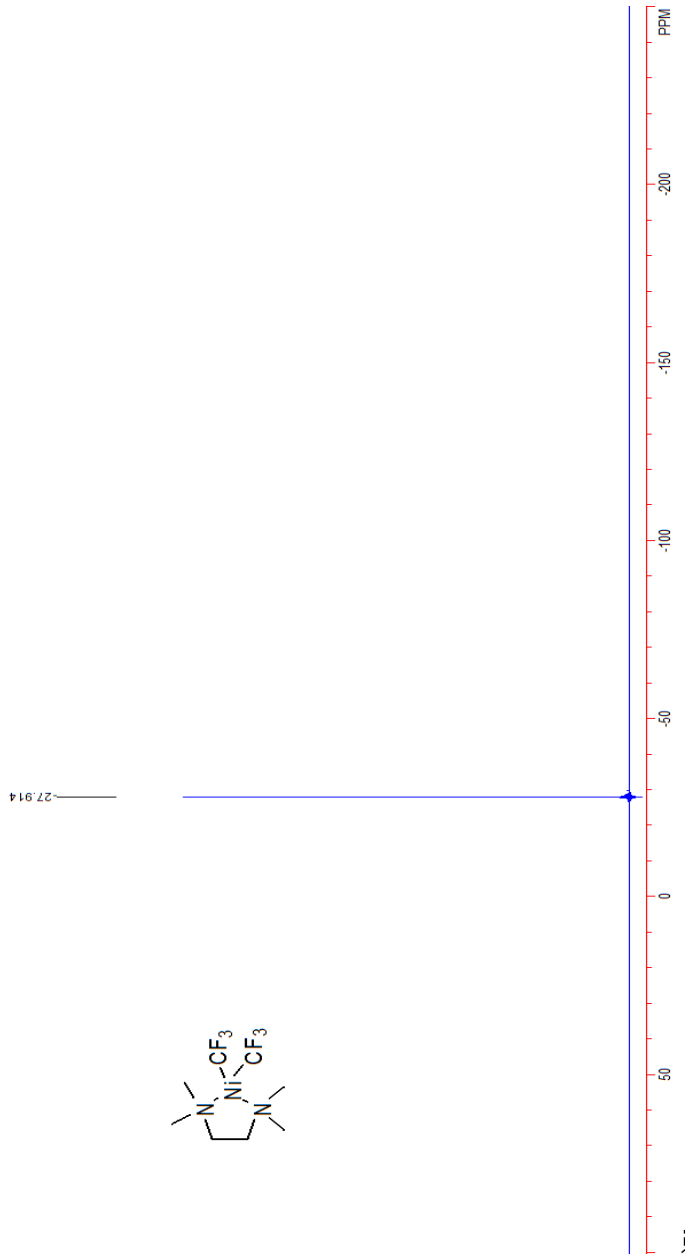
**Preparation of [(tpy')Ni($C_2F_5$)Br] (11):** $Me_3SiC_2F_5$ (93.3 mg, 3 mmol) and AgF (41.1 mg, 2 mmol) were dissolved into 10 mL dry acetonitrile. The reaction mixture was stirred at room temperature for 2 hours. Then $NiBr_2$·DME (50 mg, 1 mmol) was added and the reaction mixture was stirred for 2 hours at room temperature. $^t$Bu-terpyridine (97.56 mg, 1.5 mmol) was added and the mixture was stirred at room temperature for two days, and filtered. The filtrate was evaporated on a vacuum line. Charged 10 mL dry THF and kept it in the freezer to grow crystals. Green colored crystals observed (96 mg, 95% crude yield). Elemental: Anal. Calcd (found) for $C_{29}H_{35}BrF_5N_3Ni$: C, 52.84 (52.36); H, 5.35 (5.36).

**Preparation of [(tpy)Ni($CF_3$)$_2$] (12)**: [$(CH_3CN)_2Ni(CF_3)_2$] (84 mg, 0.3 mmol) and 2:2',6':2''-terpyridine (78 mg, 98%, 0.33 mmol) were dissolved in 6 mL of dry $CH_3CN$. The mixture was stirred at room temperature for 0.5 hour. Then 18mL of dry diethyl ether ($Et_2O$) was added slowly. The mixture was stored in a freezer (-35 $^o$C) in a glove box. Several days later, brown solid was isolated, washed with pentane and dried to give the desired product (104 mg, 0.242

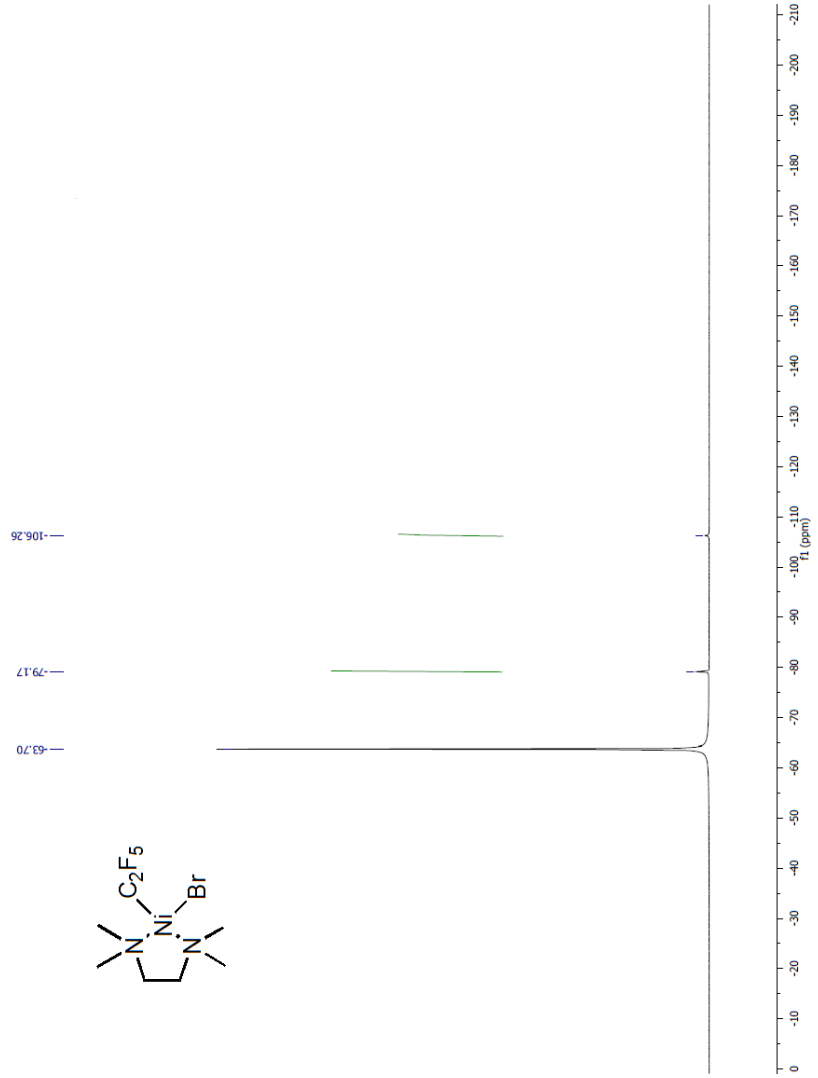
mmol, 81%). Complex is paramagnetic. Anal. Calcd (found) for $C_{17}H_{11}F_6N_3Ni$: C, 47.49 (47.27); H, 2.58 (2.76).

**Electronic structure calculations:** Quantum calculations were performed with the Gaussian09W software. Unconstrained geometry optimizations were performed using the B3LYP exchange-correlation functional.[18,19] The m6-31G* basis set was used for nickel,[20] and the 6-31g* was used for all other atoms. All calculations have been checked for the absence of imaginary frequencies.

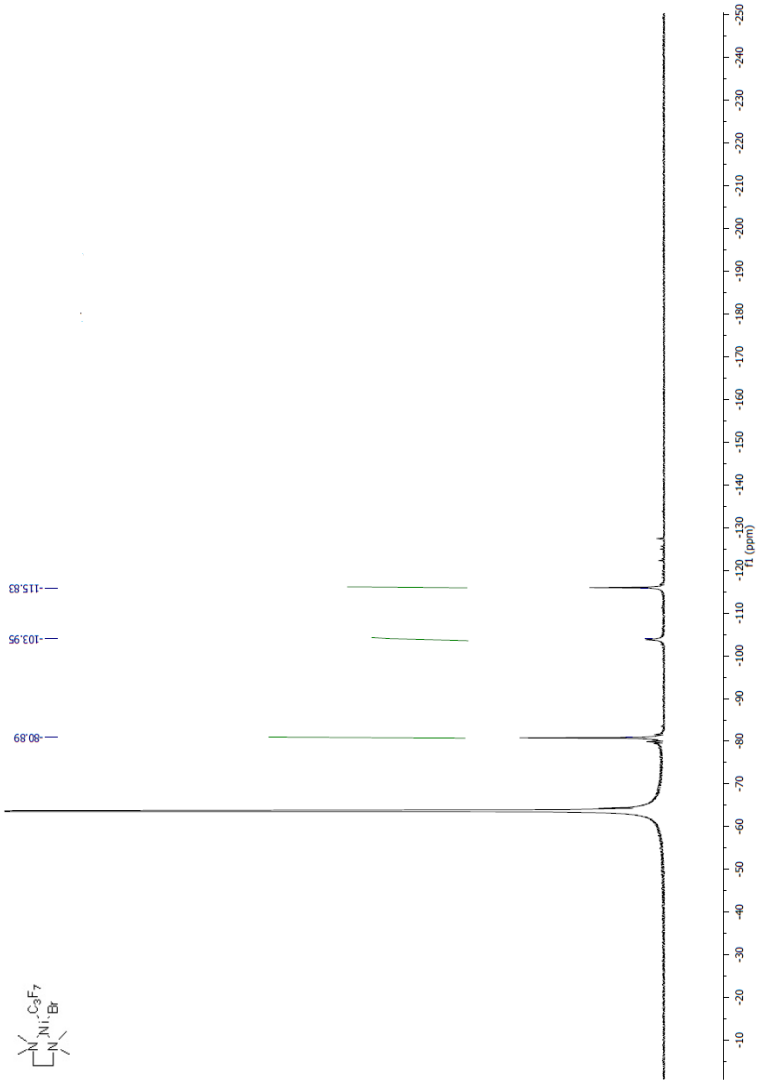
$^{19}F$ NMR for [(TMEDA)Ni($CF_3$)] (**3**):



$^{19}F$ NMR for [(TMEDA)Ni($C_2F_5$)Br] (**4**)**:**



$^{19}F$ NMR for [(TMEDA)Ni($C_2F_5$)Br] (**5**)**:**



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## Chapter 3: New intermediates for Perfluoroalkylation Studies

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