Nickel-catalyzed cross-coupling reactions involving secondary and tertiary alkyl nucleophiles

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Nickel-Catalyzed Cross-Coupling
Reactions Involving Secondary and Tertiary Alkyl Nucleophiles

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ABSTRACT

NICKEL-CATALYZED CROSS-COUPLING REACTIONS
INVolvING SECONDARY AND TERTIARY ALKYL
NUCLEOPHILES

by

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In the first chapter, introduction of transition metal-catalyzed cross-coupling reactions has been given. These transition metal-catalyzed C-C bond forming reactions have been used extensively in organic synthesis. Among them, C(sp²)-C(sp²) bond forming reactions have been widely studied over decades. More recently, some reports have demonstrated the use of
C(sp³) nucleophiles and electrophiles in cross-coupling reactions. However, use of secondary and tertiary alkyl nucleophiles has remained a challenge due to competitive β-hydride elimination and slow transmetallation of bulky secondary and tertiary alkyl organometallic nucleophiles.

In the second chapter, the first general nickel-catalyzed Negishi reaction for the cross-coupling of unactivated, acyclic secondary alkylzinc halides and aryl and hetero-aryl iodides has been reported. This process is the first to overcome the β-hydride elimination problem inherent to the use of the analogous palladium-catalyzed processes. This method is very general and tolerates a wide range of functional groups. A detailed study of the effect of salt additives on these reactions has also been presented.

In the third chapter, this work has been extended to the use of tertiary alkyl nucleophiles and the first metal-catalyzed Kumada cross-coupling reaction of tertiary alkylmagnesium halides and aryl bromides/triflates has been reported. This reaction has very wide substrate scope, and vinyl bromides and vinyl chlorides can also be employed as electrophiles. Here, the effect of catalyst hydration on the reaction yield and selectivity has been demonstrated.

In the fourth chapter, a mild palladium-catalyzed reaction for the monoborylation of primary alkyl halides using bis(pinacolato)diboron as the boron source has been reported. This reaction is very general and can accommodate a wide range of functional groups. To increase the utility of this process, the crude borylation product has been converted into the corresponding boronic acid, trifluoroborate salt and another boronic ester. Additionally, bis(neopentylglycolato)diboron has also been employed as the boron source.
Dedicated to

P. P. Tai, Aie, and Baba
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1 Introduction

1.1 Background

For decades, transition metal-catalyzed cross-coupling reactions have been used as a powerful tool for the formation of carbon-carbon bonds.\(^1\) Metal-catalyzed cross-coupling reactions are broadly defined as a set of reactions in which a new C-C bond is formed via the reaction of a main group organometallic reagent and an organic electrophile (e.g., halide or pseudo halide) in the presence of a transition metal catalyst.

Conventional metal-catalyzed cross-coupling reactions typically proceed via the three fundamental steps shown in figure 1.1. The cycle initiates when an organic halide or pseudo halide \((RX)\) undergoes oxidative addition onto a low valent metal catalyst \((ML_n)\) forming the oxidative addition intermediate \((L_nMRX)\). This intermediate then undergoes transmetallation with the main group organometallic species \((R^1-M^1)\) forming the second intermediate \((L_nMRR^1)\), which undergoes reductive elimination to form the new carbon-carbon bond in the product \((R-R^1)\) and concurrently regenerates the metal catalyst \((ML_n)\). This regenerated catalyst then enters the new catalytic cycle. Hence, very small amount of catalyst is required for a very large scale reaction. The mechanistic details of these fundamental steps differ depending upon the main group organometallic nucleophile and transition metal catalyst employed in the cross-coupling reaction.
The earliest example of the use of metals to form carbon-carbon bond has been traced back to 150 year old literature. The initial discoveries of stoichiometric coupling processes emerged in the areas of organocopper and alkali/alkaline-earth metal organometallics. Examples of these reactions include the Glaser coupling, Ullman coupling, Wurtz and Fittig reaction, and Bennet and Turner reaction. However, these reactions were limited to homodimerization and led to the formation of unwanted side products. At that time, these reactions also suffered from the drawbacks of poor selectivity and requirement of the use of stoichiometric or superstoichiometric metal reagents. Nevertheless, stoichiometric reactions laid the foundation of the conceptual thinking behind making these reactions catalytic. Hence, later efforts were then concentrated on reducing the amount of metal used and making the transformations more selective.

Wollaston discovered the element Palladium (Pd) in 1802, which remained a mere chemical curiosity until its use in the Wacker process post World War II. In later years, Pd contributed greatly to the progress of cross-coupling reactions. In 1971, the Mizoroki-Heck reaction (or Heck reaction) was reported for coupling aryl, benzyl, and styryl halides with alkenes using Pd(0)-Pd(II) catalysis. The Heck reaction differs mechanistically from the other fundamental cross-coupling reactions. In Heck chemistry, after oxidative addition, the reaction undergoes alkene co-ordination, syn-migratory insertion and syn-β-hydride elimination to furnish the alkene product (Figure 1.2). Thus, there is no transmetallation step in the Heck reaction.

![Figure 1.2 Mizoroki-Heck reaction.](image-url)
Alongside the discovery of Heck, the Kumada-Terao-Corriu reaction\textsuperscript{2, 5, 6} was reported for the coupling of organomagnesium reagents using nickel catalysis and a phosphine ligand. This was the first cross-coupling reaction that used a catalytic quantity of metal and addressed the problem of reaction selectivity to a great extent. In 1975, the Pd-catalyzed Sonagashira reaction was reported\textsuperscript{2, 7} for coupling acetylenes with aryl or vinyl halides. The presence of copper co-catalyst was noted to be important for this class of reactions for the \textit{in situ} formation of the transmetallating species. Despite those advances, many challenges still remained. The organomagnesium and organolithium reactions suffered from the drawback of functional group incompatibility due to their high nucleophilicity and reactivity, and the development of Sonagashira reaction was limited to the use of acetylenes. So, clearly there was a further need for the development of more versatile nucleophilic coupling partners. Hence, in later years, chemists sought to develop more stable and functional group tolerant organometallic coupling partners.\textsuperscript{2}

In 1976, Negishi showed that organoaluminium and organozinc reagents are capable of participating in the transmetallation step.\textsuperscript{8} Hence, organomagnesium and organolithium nucleophiles could be replaced by less reactive aluminium and zinc nucleophiles. Negish\textsuperscript{i} and co-workers also carried out a detailed screen of other organometallics and found that tin-, boron-, and zinc-based acetylene nucleophiles were capable of forming the alkyne products.\textsuperscript{2} Taking the advantage of this initial work and high covalent bond character offered by C-Sn bond, the Stille reaction\textsuperscript{2, 9} was reported for the coupling of organostannanes. This reaction was highly versatile with a high degree of functional group compatibility. Despite its great utility for the formation of C-C bonds in complex molecules, toxicity of tin remained a concern. Therefore, there was a need for further development of the nucleophiles. In 1979, the Suzuki-Miyaura reaction was reported, which solved many of the challenges associated with other cross-coupling reactions.\textsuperscript{2, 10} The
Suzuki coupling reaction is arguably the most powerful cross-coupling reaction and offers great advantages over other cross-coupling methods. Boron nucleophiles are air- and moisture-stable, they are easy to handle, and can be stored on the bench top without the requirement of inert conditions. Also, the reaction conditions for their coupling are mild and convenient, and removal of non-toxic inorganic byproducts is typically trivial.²

The base employed in Suzuki-Miyaura cross-coupling reactions often plays a major role in determining the identity and reactivity of the active transmetallating species. More advanced variants of boronic acids are also now available, thus offering a broad choice of boron nucleophiles that can be employed in cross-coupling reactions.² The Hiyama reaction using organosilicon nucleophiles was then reported in later years,¹¹ which is in fact a more environmentally benign alternative to using organozinc, organotin and organoboron nucleophiles. However, this reaction has not been studied in great detail and has thus far found only limited use compared to other cross-coupling reactions.

In general, the cross-coupling reactions have been classified and named based on the main group metal M¹ used to transfer the R¹ group in the transmetallation step (Figure 1.1). These reactions are listed in the table 1.1.
Table 1.1. Named cross-coupling reactions.

<table>
<thead>
<tr>
<th>Organometallic Reagent</th>
<th>Reaction name</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{M}^1 = \text{MgX, Li}$</td>
<td>Kumada Coupling</td>
</tr>
<tr>
<td>$\text{M}^1 = \text{Al(i-Bu)}_2, \text{Zr(Cl)}\text{Cp}_2, \text{ZnX}$</td>
<td>Negishi Coupling</td>
</tr>
<tr>
<td>$\text{M}^1 = \text{SnR}_3$</td>
<td>Stille Reaction</td>
</tr>
<tr>
<td>$\text{M}^1 = \text{SiR}_3$</td>
<td>Hiyama Coupling</td>
</tr>
<tr>
<td>$\text{M}^1 = \text{BX}_2$</td>
<td>Suzuki Reaction</td>
</tr>
<tr>
<td>$\text{M}^1 = \text{Cu (in situ)}$</td>
<td>Sonagashira Reaction</td>
</tr>
</tbody>
</table>

All named reactions undergo the three well known steps of a typical cross-coupling reaction (i.e., oxidative addition, transmetallation and reductive elimination). The sequence of these steps, however, depends upon the type of reaction under study and the transition metal catalyst used for the transformation. Oxidative addition is generally favored on a low valent complex and is supported by electron donating ligands. In this step, the transition metal undergoes an increase in the formal oxidation state. Often, ligand dissociation from a saturated 18 electron complex is required to form the active low valent metal complex. Oxidative addition of the electrophile to a transition metal occurs via one of the three mechanisms (electron transfer, nucleophilic aromatic substitution, or concerted mechanism) depending upon the transition metal employed.

Oxidative addition of aryl and alkenyl halides and triflates onto a coordinatively unsaturated metal complex has been studied widely. However, the oxidative addition of a C(sp$^3$)-X electrophile has been

![Figure 1.3. Oxidative addition to Pd and Ni.](image-url)
less thoroughly explored. It is believed that oxidative addition of an alkyl halide onto Pd(0) takes place usually by associative bimolecular process ($\text{S}_\text{N}2$ reaction). In contrast, with Ni and Cu, radical processes are more evident and may result in loss of stereochemistry (Figure 1.3). The stereochemistry of oxidative addition step influences the stereochemistry of the overall product of the reaction.

The transmetallation step involves transfer of an organic group from the main group element to the transition metal with no change in the formal oxidation state of either of the metals. The transmetallation step, in most cases takes place by sigma bond metathesis. The nucleophilicity of the main group organometallic halide used for the reaction determines the rate of the transmetallation. The more nucleophilic the reagent, the faster is the rate of transmetallation. Figure 1.4 shows the main group metals used in the transmetallation step of the cross-coupling reactions in their order of decreasing covalent character of the C-M bond.\textsuperscript{14} Classically, these nucleophiles have been limited to C(sp\textsuperscript{2})-M species, which decrease in nucleophilicity from Li to B. Therefore, it becomes more difficult to transmetallate an organometallic nucleophile as we move across the series in figure 1.4 from Li to B. When alkyl nucleophiles are employed, additional problem of configurational stability arises. Increasing covalent character increases the configurational stability and decreases the nucleophilicity of organometallic species. However, configurational stability allows for the preparation of chiral nucleophiles required for the formation of optically active cross-coupling products.
The reductive elimination step is favored for electron-deficient complexes and is disfavored for electron-rich complexes since it results in formal two electron reduction of the transition metal. For reductive elimination to take place, the two reductively eliminating moieties are required to be in cis-geometry. Also, the bite angle of ligand used affects the rate of reductive elimination. In complexes bearing ligands with large bite angles, the eliminating groups are forced together, which accelerates reductive elimination. In general, reductive elimination is faster in the order of aryl-aryl > aryl-alkyl > alkyl-alkyl. The transition-metal catalyst is regenerated in this step. The transition metal catalyst must be designed such that all three basic steps of the catalytic cycle can occur efficiently in the absence of undesired side reactions.

A variety of transition metal-catalyzed cross-coupling reactions have been used for the industrial synthesis of pharmaceuticals, agrochemicals, and polymers. In these cross-coupling reactions, palladium, copper, nickel, platinum, iron, and cobalt have been employed as transition metal catalysts. However, these reactions have been mainly limited to the formation of C(sp²)-C(sp²) bonds. Only recently has the use of C(sp³) nucleophiles and electrophiles been investigated in metal-catalyzed cross-coupling reactions.

Transition metal-catalyzed C(sp²)-C(sp³) bond-forming reactions have been extensively studied over the past few decades. Until recently, efficient methods for cross-coupling reactions involving alkyl nucleophiles and electrophiles were scarce. Alkyl electrophiles and nucleophiles containing β-hydrogens are especially more difficult to couple due to the challenges in the oxidative addition and transmetallation step. Also, propensity of these substrates to undergo side reactions like β-hydride elimination, homocoupling, and hydrodehalogenation, presents an added difficulty in their use as electrophilic substrates.
The oxidative addition of alkyl halides to a low-valent transition-metal tends to be more difficult than oxidative addition to aryl or vinyl halides. In the case of aryl or vinyl halides, the complex formed after oxidative addition is stabilized by electronic interaction with d-orbitals on the metal. Since, similar stabilization does not exist in the complex resulting from the oxidative addition of alkyl halide, the oxidative addition complex formed is more reactive and more likely to participate in undesired side reactions like β-hydride elimination. Slow transmetallation of sterically bulky organometallic nucleophile onto the metal catalyst can also slow down the overall transformation. If the reductive elimination is the slow step, side reactions can also potentially take place at this step.

1.2 Nickel-catalyzed Negishi reactions of primary/secondary alkyl nucleophiles and secondary alkyl electrophiles

In the last decade, a transition in the use of electrophiles was seen where conventionally used aryl and alkenyl electrophiles were replaced by the unactivated alkyl electrophiles. Nickel, is by far the most versatile and commonly used transition metal used to couple alkyl electrophiles. Various main group organometallic nucleophiles have been used to transmetallate the alkyl group (see below).

\[ \text{R}_1 \text{X} + \text{YZn} \rightarrow \text{R}_1 \text{YZn} \rightarrow \text{R}_1 \text{Ni} \rightarrow \text{R}_1 \text{R}_2 \]

The first example of the use of an unactivated, β-hydrogen containing secondary alkyl electrophile in cross-coupling reactions with alkyl zinc nucleophiles was reported by Fu and Zhou in 2003. In this reaction both primary and cyclic/acyclic secondary alkyl bromides and iodides could be employed as the electrophilic component (eq. 1). The reaction was performed in
DMA, in the presence of (4 mol %) Ni(0)(cod)₂ and (8 mol %) sec-Bu-pybox ligand at room temperature. It has been reported that this reaction results in lower yields in presence of a Ni(II) catalyst, and that Pd catalysts are ineffective.

In 2005, Fu and Fischer reported the first catalytic enantioselective cross-couplings of secondary α-bromo amides with organozinc reagents in DMI/THF using 10 mol % NiCl₂ and 13 mol % (R)-(i-Pr)-pybox ligand at 0 °C (eq. 2). In an earlier report by Vicic, the cross-coupling of secondary alkyl electrophile and alkyl nucleophile was proposed to proceed via a radical-radical coupling mechanism (Figure 1.5). However, this reaction is suggested to not follow the Vicic pathway due to the high enantioselectivity observed in the reaction.

In the same year, Fu and Arp reported an enantioselective cross-coupling of benzylic bromides and chlorides with functionalized primary alkyl zinc reagents in DMA at 0 °C using NiBr₂•diglyme and (S)-(i-Pr)-pybox ligand (eq. 3). This reaction is stereoconvergent and not very sensitive to air and moisture.
In 2008, Fu and Son reported a nickel-based catalyst for couplings of secondary racemic allylic chlorides with alkyl zinc halides\(^25\) using (S)-(i-Pr)pybox ligand (eq. 4). Here, both enantiomers of the racemic starting material were transformed into the same product with good stereoselectivity. This method has also been applied to the two key steps in the total synthesis of fluvirucinine A\(_1\).

\[
\begin{align*}
\text{R}_1\text{C}^\equiv\text{R}_2\text{Cl} + \text{RZnBr} & \xrightarrow{5\% \text{NiCl}_2\text{glyme}} \xrightarrow{5\% \text{(S)}-\text{BnCH}_2\text{-pybox}} \xrightarrow{\text{NaCl (4 equiv.)}} \xrightarrow{\text{DMA/DMF (1:1), -10 °C}} \text{R}_1\text{C}^\equiv\text{R}_2 \quad \text{--- (4)}
\end{align*}
\]

In 2008, Fu and Smith reported the nickel-catalyzed Negishi cross-couplings of secondary nucleophiles with secondary propargylic electrophiles (eq. 5).\(^18\) The reaction was carried out using NiCl\(_2\)glyme and terpyridine ligand in DMA at room temperature. The conventionally used pybox ligands for the cross-coupling of secondary alkyl electrophiles were ineffective under these conditions. The use of more challenging nucleophiles required the replacement of terpyridine ligand with 2,6-bis-(N-pyrazolyl)pyridine in THF with extra equivalents of nucleophile. Although this is the first example of secondary-secondary cross-couplings, it is limited to the use of propargylic halides and mostly cyclic secondary nucleophiles.
In 2012, enantioselective Negishi cross-couplings of secondary benzylic electrophiles with secondary alkyl nucleophiles were reported (eq. 6).\(^{26}\) Here, racemic benzylic bromides were coupled with achiral alkylzinc reagents in methylene chloride/dioxane at \(-30\) °C with high enantio-convergence. Conventionally used pybox ligands were ineffective for these couplings. To effect this transformation, an isoquinoline-oxazoline ligand in combination with \(\text{NiBr}_2\cdot\text{glyme}\) was used. Both branched acyclic and unbranched nucleophiles were shown to generate the branched isomer of the cross-coupled product in high yields. This preference is thought to arise from the use of bidentate isoquinoline-oxazoline ligand instead of tridentate pybox-type ligand.

In 2012, Fu and Choi reported the Ni-catalyzed stereoconvergent Negishi cross-couplings of racemic \(\alpha\)-halo nitriles with aryl and alkenyl electrophiles using a modified bis-oxazoline
1.3 Palladium and Nickel-catalyzed cross-couplings of secondary alkyl nucleophiles and aryl halides

\[ \text{Ni catalyst} \] \[ \text{P ligand} \]

The original pioneering work of Kumada published in 1972, demonstrated the coupling of chlorobenzene with iso-propyl magnesium chloride using NiCl\(_2\) as a catalyst and a bidentate phosphine as a ligand (eq. 8). It has been shown that the alkyl group isomerization from secondary to primary is strongly dependent on the electronic nature of the ligand. A mechanism involving β-hydride elimination was proposed as the possible pathway for the formation of isomerized linear product.\(^6\)

In 2006, Campos reported the enantioselective arylation of N-Boc-pyrrolidine using zinc reagent generated \textit{in situ} in presence of Pd(OAc)\(_2\) and \(t\)-Bu\(_3\)P•HBF\(_4\) ligand at room temperature (eq. 9). Here, spartine-mediated asymmetric deprotonation precedes transmetallation and Negishi coupling.\(^28\)
In 2007, Aiwen Lei reported the palladium-catalyzed Negishi coupling of alkyl nucleophiles with aryl iodides bearing an ortho substituent (eq. 10). Significant isomerization to the linear product was observed when secondary alkyl zinc nucleophiles were employed. An example with tertiary alkyl nucleophile gave exclusive formation of the rearranged product showing that the palladium catalyzed reactions for these type of couplings tend to undergo a β-hydride elimination/re-insertion sequence.  

\[
\text{Cl} \quad \text{OMe} \quad + \quad \text{Me} \quad \text{BF}_3K \quad \xrightarrow{\text{5\% Pd(OAc)₂ \ 7.5\% t-Bu₂PPh \ 3\ equiv. C₅CO₃}} \quad \text{Me} \quad \text{OMe} \\
\text{100 °C} \quad \text{(11)}
\]

In 2008, Molander and Dreher reported cross-couplings of cyclic secondary alkyl trifluoroborates with aryl chlorides using Pd(OAc)_2 and t-Bu₂PPh in toluene/water at 100 °C (eq. 11). Here, a parallel micro scale experimentation technique with 96-well-plate reactor was used for initial screenings for optimal conditions. When iso-propyl trifluoroborate was used as a nucleophile a very poor ratio of branched to linear isomer (1.4:1) was obtained.  

\[
\begin{align*}
\text{X} & \quad \text{R} \quad + \quad \text{Me} \quad \text{ZnBr} \quad & \xrightarrow{\text{1\% Pd(OAc)₂ \ 2\% CPhos \ THF (0.25 M) \ rt, 30 min}} & \text{Me} \quad \text{Me} \\
& & & \text{R} \quad \text{Me} \quad + \quad \text{Me} \quad \text{Me} \\
& & & \text{(12)}
\end{align*}
\]

In 2009, Buchwald and Han reported Negishi coupling of alkyl zinc halides and aryl bromides/chlorides (eq. 12). The reaction was conducted in presence of Pd(OAc)_2 and CPhos ligand in THF. Here, the THF solution of iso-propyl bromide was prepared by LiCl assisted zinc insertion into iso-propyl bromide using Knochel’s procedure. The product ratio of branched to linear isomer was between 20:1 and 58:1. Most aryl halides used for coupling contained an ortho
substituent or an electron-withdrawing group, each of which is known to accelerate the reductive elimination in palladium catalyzed cross-coupling reactions.\textsuperscript{19}

\[
\begin{align*}
\text{Me} & \quad \text{MgCl} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{BF}_3 \text{K} \\
\text{H} & \quad \text{Ar}X \\
\end{align*}
\]

\[
\begin{align*}
\text{10\% Pd(OAc)}_2 & \quad 20\% \text{XPhos} \\
\text{K}_2 \text{CO}_3 (3 \text{ equiv.}) & \quad \text{Ar} \\
\end{align*}
\]

In 2010, the stereospecific cross-coupling of secondary alkyl β-trifluoroboratoamides with aryl halides was reported using Pd(OAc)\textsubscript{2} and XPhos by Molander and Sandrock (eq. 13). Intramolecular coordination of the carbonyl group to the metal center was proposed to reduce the undesired β-hydride elimination reaction.\textsuperscript{31}

1.4 Nickel-catalyzed cross-couplings of secondary alkyl nucleophiles and aryl halides

\[
\begin{align*}
\text{Me} & \quad \text{MgCl} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{O} & \quad \text{OTf} \\
\text{H} & \quad \text{Ar} & \quad \text{N} & \quad \text{DPE Phos} \\
\end{align*}
\]

\[
\begin{align*}
\text{2.5\% Ni(acac)}_2 & \quad 5\% \text{DPE Phos} \\
\text{ZnBr}_2 (2 \text{ equiv.}) & \quad \text{rt, 72 h} \\
\end{align*}
\]

In 2007, Knochel and Melzig reported the aminoalkylation of arenes via nickel-catalyzed Negishi cross-coupling reactions using Ni(acac)_2 and DPE-Phos (eq. 14).\textsuperscript{32}

\[
\begin{align*}
\text{I} & \quad \text{O} \\
\text{O} & \quad \text{ZnBr} \\
\text{MeO} & \quad \text{ZnBr} \\
\end{align*}
\]

\[
\begin{align*}
\text{3\% [NiCl}_2\text{(py)}_4 & \quad 3\% \text{bipyridine} \\
\text{THF, 23}^\circ \text{C} & \quad \text{MeO} \\
\end{align*}
\]

In 2009, Cardenas and Phapale reported a catalytic system for the cross-coupling of aryl bromides and iodides with alkyl zinc reagents using [NiCl\textsubscript{2}(py)_4] and bipyridine as ligand in THF at room temperature (eq. 15).\textsuperscript{33} Here, only a few examples of the cross-coupling reactions using
secondary alkyl zinc nucleophiles were reported, each using activated electrophiles. In cases where less activated electrophiles were used, the yields were shown to diminish. Moreover, no discussion about the ratio of branched to linear product formation was detailed. Energy calculations using DFT models suggested that the reaction is more likely to occur via a Ni$^I$-Ni$^{II}$ cycle than a Ni$^0$-Ni$^{II}$ cycle.

\[
\text{MeZnCl} + \text{Ar-I} \xrightarrow{1\% \text{Pd(dba)}_2, 1\% \text{S-Phos}} \text{THF, NEP (6 vol%), -25 °C, 12 h then -15 °C, 6 h} \rightarrow \text{Me,Ar} \quad \text{(16)}
\]

In 2010, Knochel and Thaler reported diastereoselective Negishi cross-couplings of various substituted cyclohexylzinc reagents with aryl halides forming thermodynamically stable stereoisomer in most cases (eq. 16).

### 1.5 Cross-couplings of tertiary alkyl nucleophiles

\[
\text{N-Cl} + \text{t-BuMgCl} \xrightarrow{5\% \text{CuI}} \text{THF, 0 °C to rt, 3 h} \rightarrow \text{N-Cl, t-Bu} \quad \text{(17)}
\]

At the time we began to look in the literature for cross-couplings using tertiary alkyl nucleophiles, there was no efficient method reported for their use in cross-coupling reactions. The only method that successfully employed tertiary alkyl nucleophiles in a cross-coupling type reaction was the copper-catalyzed method reported by Hintermann. However, this method was limited only to the use of tertiary alkylmagnesium nucleophiles and poly-chlorinated aza-aryl electrophiles (eq. 17).
In 2007, Lei tried to employ $t$-BuZnCl in palladium-catalyzed Negishi reaction with aryl iodide. A hemi-labile bidentate ligand with palladium catalyst was used in this reaction. This reaction resulted in exclusive formation of the *iso*-butyl product which forms *via* a $\beta$-hydride elimination/reinsertion sequence (eq. 18). 29

In 2010, Hu group reported the stoichiometric reaction of a pincer Ni complex with $t$-BuMgCl (eq. 19). The desired $t$-Bu-Ni complex was not observed. Instead, the complex obtained showed complete rearrangement of the $t$-butyl nucleophile to an *iso*-butyl group. 35

The above examples demonstrate the difficulty of employing tertiary alkyl nucleophiles in palladium- and nickel-catalyzed cross-coupling reactions. No palladium- or nickel-catalyzed process showed even a trace of tertiary alkyl product in cross-coupling reactions. The only method that could overcome this challenge to a certain extent is the copper-catalyzed reaction developed by Hintermann, which is limited to the use of poly-chlorinated aza-aryl electrophiles.
1.6 General reaction scheme for the metal-catalyzed cross-coupling of secondary/tertiary alkyl nucleophiles and aryl halides

A plausible mechanism for the coupling of an aryl halide and an organometallic alkyl nucleophile containing β-hydrogens is shown in figure 1.6. When using branched alkyl nucleophiles or electrophiles as coupling partners in cross-coupling reactions, it is essential to prevent the undesired isomerization side reaction. Here, the complex formed after oxidative addition or transmetallation can undergo β-hydride elimination followed by re-insertion to give the linear isomer of the desired product. Reduction product can also be formed as another side product in this process, which coincides with olefin formation. Therefore, an efficient catalyst must enhance the rate of oxidative addition, transmetallation, and reductive elimination and suppress the rate of β-hydride elimination, which would then minimize the formation of undesired side products. The plausible catalytic cycle for such a transformation would resemble the one shown in figure 1.6.

Although there are many protocols for the cross-coupling of secondary alkyl halides with aryl nucleophiles, cross-coupling of secondary/tertiary alkyl metallic nucleophiles with aryl halides or pseudo halides still remains a challenge. The difficulty in this transformation arises from two factors: (a) slow transmetallation in case of sterically demanding secondary organometallic nucleophile and (b) reductive elimination competing with facile β-hydride elimination.
Figure 1.6. Cross-coupling of an aryl halide with secondary alkyl metallic nucleophile.
2 Nickel-Catalyzed Negishi Cross-Coupling Reactions of Secondary Alkylzinc Halides and Aryl Iodides

2.1 Introduction

Among the various transition metal-catalyzed reactions listed in Chapter 1 for the formation of a new C-C bond between a sp$^2$-hybridized carbon and a sp$^3$-hybridized carbon, Molander and Buchwald have conducted the most comprehensive studies. Molander et al. reported$^{30}$ the palladium catalyzed cross-coupling of secondary alkyltrifluoroborates with aryl chlorides. This reaction was shown to tolerate many functional groups on the aryl chloride when coupled with cyclohexyltrifluoroborates. However, when the coupling partner was iso-propyl trifluoroborate, the reaction suffered from a lower yield as a result of significant isomerization of the branched product to the linear. An example of palladium based Negishi coupling of secondary alkyl zinc halides with aryl bromides and chlorides was reported by Buchwald et al. wherein the isomerization to linear products was significantly decreased, yet not eliminated.$^{19}$ This method required the presence of an ortho group on the electrophilic component which is known to speed up the reductive elimination owing to its steric contribution.$^{36}$ Also, the presence of activating groups such as an ortho substituent or an electron withdrawing functional groups at the ortho or para position produced good yields of the product.

In 1972, Kumada had reported that the secondary alkyl Grignard reagent can undergo nickel-based cross-coupling reaction with aryl chlorides but suffers from isomerization of the desired product.$^{6}$ Moreover, this method was limited in the substrate scope and the study was not
expanded to substrates containing any functional groups. A separate study by Cardenas was
dedicated towards the use of primary alkyl nucleophiles, and had only a few examples of the
coupling of secondary alkyl nucleophiles with highly activated electrophiles. Reactions using
secondary alkyl nucleophiles suffered from poor yields and were limited to highly activated
electrophiles.\(^{33}\)

No general method for the cross-coupling of aryl halides with secondary and tertiary
alkyl organometallic nucleophiles that allowed the broad use of electrophilic and nucleophilic
components existed. Therefore, we decided to investigate whether a nickel-based catalyst in
combination with nitrogen or phosphorus containing supporting ligands could facilitate
cross-couplings of non-cyclic secondary and tertiary alkyl nucleophiles with aryl halides. Nickel
had already shown promise in cross-couplings of secondary alkyl electrophiles and nucleophiles
and therefore was a good catalyst to begin the screening (see Chapter 1). Such a method would
be required to overcome the known problems of slow transmetallation and product isomerization
for this transformation.

It has been suggested that a radical mechanism is involved in the cross-couplings of
secondary alkyl electrophiles and aryl nucleophiles (see figure 1.5).\(^{17, 21, 37}\) Therefore, optically
active electrophiles would undergo racemization during this process. Hence, we decided to
exploit the possibility of using secondary alkyl nucleophiles and aryl halides in the presence of
transition metal catalyst to form aryl substituted tertiary centers. Since, most biologically active
molecules are chiral and are required to be synthesized with high enantiopurity, expansion of
such a method to using optically active secondary alkyl nucleophiles would be a value addition
to the field.
The use of nickel catalysis by Fu group, in combination with bidentate and tridentate nitrogen ligands used in the cross-coupling of alkyl electrophiles with alkyl/aryl nucleophiles showed that this catalytic system supports the transmetallation of secondary alkyl nucleophiles onto the transition metal and also effects the reductive elimination of alkyl-alkyl and alkyl-aryl group from nickel catalyst. Since reductive elimination of a secondary alkyl unit readily occurs in this chemistry, we decided to explore the potential of Ni-catalysis to effect cross-coupling reactions involving secondary alkyl nucleophiles. Nickel catalysis was also used in the cross-coupling of aryl nucleophiles and secondary alkyl electrophiles. Both of these cross-coupling reactions proceed via a common intermediate before reductive elimination (shown in box in figure 2.1). Therefore, we speculated that a nickel catalyst would efficiently support the reductive elimination step of such a reaction.

![Figure 2.1. Reductive elimination of secondary alkyl groups from nickel.](image)

Palladium is known to undergo a Pd(0)-Pd(II) catalytic cycle for the cross-coupling reactions. However, with nickel catalysts the mechanism of a cross-coupling reaction is not as straightforward because of the number of oxidation states accessible to nickel vs palladium. Therefore, the possibility of a Ni(0)-Ni(II) or a Ni(I)-Ni(III) catalytic cycle exists. Certain reports in the literature support the mechanism undergoing by a Ni(I)-Ni(III) cycle both experimentally and computationally. It has also been stated that for catalytic cycle involving Ni(I)-Ni(III) cycle, transmetallation precedes the oxidative addition step. Based upon these reports, we
thought that the Ni(I) catalyst might be able to undergo the transmetallation of sterically demanding secondary alkyl nucleophile prior to the oxidative addition step and also support the reductive elimination of the two bond forming species (see figure 2.1). Therefore, while a Ni(0)-Ni(II) catalytic cycle cannot be conclusively ruled out, we proposed that a successful cross-coupling reaction between alkyl nucleophiles and aryl electrophiles would be more likely to follow a Ni(I)-Ni(III) pathway. A general nickel-catalyzed reaction for cross-coupling aryl halide and secondary alkyl nucleophile undergoing transmetallation before oxidative addition is shown in Figure 2.2.

![Figure 2.2. Proposed catalytic cycle for cross-coupling of secondary alkyl nucleophiles and aryl halides.](image)

### 2.2 Initial choice of nucleophile

For the formation of C(sp²)-C(sp³) bond using a secondary alkyl nucleophile, the nickel-catalyzed Stille reaction was thought to be a good starting point. Since tin nucleophiles have high covalent character in the C-M bond, they are less labile and less nucleophilic as compared to the lithium and magnesium reagents. This property makes them attractive to be considered as nucleophilic partners. Extension of a developed cross-coupling reaction to stereoretentive transformations could then also become possible.⁴⁰
Figure 2.3 shows the scheme for the formation of chlorostannatrane (2) from triallyl amine via a tris-hydrozirconation reaction followed by reaction with tin tetrachloride. Reaction of (2) with a secondary alkyl magnesium chloride then furnished the corresponding alkyl stannatrane nucleophile (3) to be used as an organometallic coupling reagent in the Stille reaction. The alkyl stannatranes, which were developed by Jurkschat and later employed by Vedejs, were used to ensure transfer of a secondary alkyl unit from tin.

![Synthetic route for the formation of tin reagent from triallyl amine](image)

This preparation of stannatrane nucleophiles suffered from two major drawbacks: i) the yield of the first step for the formation of 2 was consistently low, between 30-35% (reported yield was 50%) after recrystallization from methanol and ii) the Schwartz reagent, Cp₂Zr(H)Cl (1) was very expensive. Hence, we decided to synthesize the Schwartz reagent from a cheaper precursor. Figure 2.4 shows the synthetic route for the synthesis of Schwartz reagent. However, when this zirconium reagent prepared in laboratory was used in the next step, the yield of the subsequent step (formation of tin reagent) further dropped to 14%.
Initial ligand screen with tin nucleophile

Due to their success in Ni-catalyzed cross-coupling reactions involving alkyl partners, different nitrogen based bidentate and tridentate ligands were screened in order to identify the ligand class effective for this transformation (eq. 20). Initial screens were performed on 0.025 mmol scale using 5 mol% Ni(cod)₂ in two solvents of different polarity, THF (0.3 ml) and DMA (0.3 ml). The electrophiles chosen were bromobenzene and phenyl triflate, and reactions were conducted under reflux conditions. Ligands (10 mol%) used for first screen are listed in figure 2.5. Formation of product was monitored by gas chromatography and a commercially available sample of the desired product was calibrated using dodecane as internal standard.
standard. These ligands were also screened in the presence of CuI and 1-phenylpropyne\textsuperscript{44} with the thought that the copper might actually help speed up the transmetallation step.

The first screen did not show any signs of product formation. For the second screen, 10 mol % of Ni(cod)$_2$ was used along with 10 mol % of bidentate nitrogen/phosphorus ligands or 20 mol % of the monodentate ligands. The ligands used for second screen are listed in figure 2.6. None of the ligands showed any signs of the desired product formation when run in the presence or absence of CuI.

![Figure 2.6. Various phosphorus and nitrogen ligands used for screening.](image)

### 2.4 Change of nucleophile

After seeing no product formation with the tin nucleophile, we suspected that the transmetallation of sterically bulky secondary alkyl group from the tin nucleophile onto the nickel center could be a problem. Because of the literature precedence\textsuperscript{18, 19} for the transmetallation of the secondary alkylzinc nucleophiles onto palladium and nickel, the tin nucleophile was then replaced with a zinc nucleophile. Secondary zinc nucleophiles were
prepared using a reported procedure and the molarity of the resulting zinc reagent was determined using iodine titration. Preparation of zinc reagents in THF and DMA as shown in eq. 21 and eq. 22 was efficient, providing high yields in one step.

\[
\begin{align*}
\text{Zn} & \quad \xrightarrow{6 \text{ h}, 80 \degree \text{C}} \quad \text{I}_2, \text{DMA} \\
\text{Zn} & \quad \xrightarrow{30 \text{ min}, 80 \degree \text{C}} \quad \text{I}_2, \text{THF} \\
\text{cyclohexyl iodide} & \quad 12 \text{ h}, \text{rt} \\
\end{align*}
\]

The cyclohexyl zinc iodide nucleophile was then treated with bromobenzene and phenyl triflate using NiCl$_2$•glyme (10 mol %), in the presence of different ligands (15 mol %). Reactions were performed in the presence and absence of CuI to see if the copper salts have any effect on the reaction since the copper salts have been reported to help the transmetallation step. Two solvents, DMA and THF, were employed for the screen (eq. 23). The list of nitrogen and phosphorus ligands screened with the zinc nucleophile is given in figure 2.7. Product formation was monitored by gas chromatography where the reaction chromatogram was compared to the one resulting from the commercially available product of the reaction under development.
With bromobenzene as the electrophile, the first ligand screen using cyclohexyl zinc iodide prepared in DMA, gave us two hits. These ligands are shown in blue in figure 2.7. The
reactions were repeated with 10 mol % NiCl₂•glyme, 15 mol % ligand using 2 equivalents of cyclohexylzinc nucleophile to check the reproducibility of the results. The calibrated GC product yield with ligand hit 1, of the reaction using bromobenzene as electrophile in THF was 22% with 83% conversion. The ligand hit 2 gave 11% yield with bromobenzene in THF. No product formation was observed when reactions were screened in DMA. Hence, use of DMA as solvent for further screens was discontinued.

Cyclohexylzinc iodide is a symmetrical cyclic nucleophile. Hence, the desired secondary branched product resulting from its reaction with aryl electrophile is the same as the one that would form after β-hydride elimination and reinsertion (as shown in figure 1.6). Therefore, in order to observe the ratio of the desired branched product to the undesired linear product, the zinc reagent was changed from cyclohexylzinc iodide to sec-butylzinc iodide.

Keeping the other reaction conditions the same (eq. 24), ligand hit 1 was then screened for different nickel sources tabulated in table 2.1. As none of the other nickel sources was better than NiCl₂•glyme, the use of NiCl₂•glyme for screening optimal conditions was continued. Several other variations with respect to the amounts of NiCl₂•glyme, amount of ligands used, equivalents of zinc reagent, temperature, and reaction time did not result in an increase in the amount of product formed.
Table 2.1. Different nickel sources screened.

<table>
<thead>
<tr>
<th>Nickel Source (10 mol %)</th>
<th>Structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bis (triphenylphosphine) Ni (II) chloride</td>
<td>( \text{Ph}_3\text{P} \quad \text{Ni} \quad \text{PPh}_3 ) ( \text{Cl} \quad \text{Cl} )</td>
</tr>
<tr>
<td>Nickel (II) Bromide, anhydrous</td>
<td>( \text{NiBr}_2 )</td>
</tr>
<tr>
<td>1,2-Bis-(diphenylphosphino)ethane Nickel (II) chloride</td>
<td>( \text{Ph}_2\text{P} \quad \text{Ni} \quad \text{PPh}_2 ) ( \text{Cl} \quad \text{Cl} )</td>
</tr>
<tr>
<td>Nickel (II) Chloride, anhydrous</td>
<td>( \text{NiCl}_2 )</td>
</tr>
<tr>
<td>Nickel (II) Acetylacetonate, anhydrous</td>
<td>( \text{Ni} \quad \text{O} \quad \text{O} )</td>
</tr>
<tr>
<td>Nickel (II) Iodide</td>
<td>( \text{NiI}_2 )</td>
</tr>
<tr>
<td>Nickel (II) Triflate</td>
<td>( \text{Ni(OTf)}_2 )</td>
</tr>
</tbody>
</table>

2.5 Effect of additives

In order to determine if the use of additives help improve the reaction yield, styrene based additives such as 4-fluorostyrene and 4-(trifluoromethyl) styrene which have been suggested to facilitate reductive elimination from nickel, were added to the reaction mixture (eq. 25).\(^{47}\) Also, addition of excess zinc granules and pyridine was tested for its effect on reaction yield and product distribution.\(^{33,48}\) The results obtained are tabulated in table 2.2. As we see from entries 1, 2, 5, and 6, styrene additives helped to increase the yield but the ratio of branched to linear product was adversely affected. Gas chromatograms for these reactions also showed formation of new unidentified peaks. Styrene-based additives not only favored β-hydride elimination but also promoted the formation of homo-coupling product. Using pyridine and zinc granules, the ratio of
branched/linear was comparatively better, but yields were poor. Overall, the additives neither improved the reaction yield nor lowered the formation of the side products.

![Reaction Scheme](image)

Table 2.2. Effect of additives on reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Additive</th>
<th>Conversion</th>
<th>Yield</th>
<th>Branched/Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Ligand 1" /></td>
<td><img src="image" alt="Additive 1" /></td>
<td>66%</td>
<td>34%</td>
<td>0.9:1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Ligand 2" /></td>
<td><img src="image" alt="Additive 2" /></td>
<td>32%</td>
<td>21%</td>
<td>1.3:1</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ligand 3" /></td>
<td>Zinc granules (2 equiv.)</td>
<td>62%</td>
<td>25%</td>
<td>3.2:1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ligand 4" /></td>
<td>Pyridine (0.5 equiv.)</td>
<td>6%</td>
<td>4%</td>
<td>Nd</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Ligand 5" /></td>
<td><img src="image" alt="Additive 3" /></td>
<td>43%</td>
<td>40%</td>
<td>0.6:1</td>
</tr>
<tr>
<td>6</td>
<td><img src="image" alt="Ligand 6" /></td>
<td><img src="image" alt="Additive 4" /></td>
<td>50%</td>
<td>40%</td>
<td>0.7:1</td>
</tr>
<tr>
<td>7</td>
<td><img src="image" alt="Ligand 7" /></td>
<td>Zinc granules (2 equiv.)</td>
<td>41%</td>
<td>16%</td>
<td>7:1</td>
</tr>
<tr>
<td>8</td>
<td><img src="image" alt="Ligand 8" /></td>
<td>Pyridine (0.5 equiv.)</td>
<td>100%</td>
<td>22%</td>
<td>1.4:1</td>
</tr>
</tbody>
</table>
2.6 Change of electrophile

After seeing no further improvement in results, the electrophile used for screening was changed from bromobenzene to more reactive iodobenzene. We were pleased to see significant improvement in the product formation with iodobenzene raising the overall yield of the desired product to 52% with 97% conversion. With this result, we wanted to check if the ligand hits that we had obtained for bromobenzene were consistent using iodobenzene (Figure 2.8). We therefore screened a variety of nitrogen ligands (15 mol %) again with NiCl$_2$•glyme (10 mol %) and 2 equiv. $iso$-propyl zinc iodide on 0.01 mmol scale using 1.2 mL THF solvent at 60 °C for

![Figure 2.8. Ligands screened for iodobenzene as electrophile.](image-url)
20 h (eq. 26). The ligand screen for iodobenzene gave two hits, i.e. bathophenanthroline and terpyridine, neither of which had worked well for bromobenzene. Therefore, the new ligand screen for iodobenzene proved to be very helpful to identify the optimal ligand for this transformation.

![Chemical reaction diagram]

Table 2.3. Results obtained from initial ligand screen for iodobenzene.

<table>
<thead>
<tr>
<th>Ligand (15%)</th>
<th>Calibrated Yield</th>
<th>Homocoupling</th>
<th>Branched/Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>34%</td>
<td>4%</td>
<td>34/1</td>
</tr>
<tr>
<td>MeO</td>
<td>40%</td>
<td>4%</td>
<td>32/1</td>
</tr>
<tr>
<td>t-Bu</td>
<td>54%</td>
<td>3%</td>
<td>73/1</td>
</tr>
<tr>
<td>H₂C(H₂O)₈(CH₂)₃CH₃</td>
<td>46%</td>
<td>4%</td>
<td>52/1</td>
</tr>
<tr>
<td></td>
<td>46%</td>
<td>4%</td>
<td>42/1</td>
</tr>
<tr>
<td>MeO</td>
<td>44%</td>
<td>4%</td>
<td>37/1</td>
</tr>
<tr>
<td>Me</td>
<td>50%</td>
<td>4%</td>
<td>54/1</td>
</tr>
<tr>
<td>Ph</td>
<td>52%</td>
<td>3%</td>
<td>63/1</td>
</tr>
<tr>
<td></td>
<td>59%</td>
<td>-</td>
<td>385/1</td>
</tr>
</tbody>
</table>
The yields and product ratios obtained from cross-coupling reactions using various nitrogen ligands are given in table 2.3. Although the product yield with bathophenanthroline ligand improved to 73% after few other optimization efforts, the use of the terpyridine ligand with lower yield of 59% became more attractive. With terpyridine ligand formation of homocoupled product was completely suppressed. The amount of reduction of electrophile was also lowered leaving significant amount of unreacted starting material in the reaction mixture. Using terpyridine, the product ratio increased dramatically (>300:1), showing practically no detectable trace of the linear product formation. We continued the method optimization with both of these ligands.
Table 2.4. Yields and product distribution obtained when bathophenanthroline and terpyridine were screened for different nickel sources.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nickel source</th>
<th>Structure</th>
<th>Bathophenanthroline</th>
<th>Terpyridine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Conv.</td>
<td>Yield</td>
</tr>
<tr>
<td>1</td>
<td>Nickel (II) chloride•glyme</td>
<td><img src="" alt="Structure" /></td>
<td>100%</td>
<td>66%</td>
</tr>
<tr>
<td>2</td>
<td>Nickel (II) Bromide, 1,2-Bis (diphenyl-phosphino)</td>
<td><img src="" alt="Structure" /></td>
<td>48%</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>Nickel (II) Chloride, anhyd.</td>
<td><img src="" alt="Structure" /></td>
<td>100%</td>
<td>62%</td>
</tr>
<tr>
<td>4</td>
<td>Nickel (II) Acetylacetonate, anhydrous</td>
<td><img src="" alt="Structure" /></td>
<td>60%</td>
<td>24%</td>
</tr>
<tr>
<td>5</td>
<td>Nickel (II) Iodide</td>
<td><img src="" alt="Structure" /></td>
<td>89%</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>Nickel (II) Triflate</td>
<td><img src="" alt="Structure" /></td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

With these results, we then screened different nickel sources for iodobenzene electrophile using isopropylzinc iodide with both bathophenanthroline and terpyridine ligands on 0.05 mmol scale in 0.6 mL THF at room temperature for 4 hours (eq. 27). These results are tabulated in table 2.4. All nickel complexes tested furnished results comparable to or worse than NiCl₂•glyme. Hence, we continued to use NiCl₂•glyme as our nickel source for further optimizations.
2.7 Terpyridine analogues

In order to see if changing the electronic properties of terpyridine ligand improved the yield, different terpyridine analogues were prepared by substituting position 4 of 2,2’-terpyridine with diverse electronic groups. Also, two pyridine rings on the two sides of 2,2’-terpyridine were replaced with pyrazole rings at 2 and 2’ positions to find out if this has any effect on the reaction. These analogues (15 mol %) were then tested in the reaction with (10 mol %) NiCl₂•glyme and 2 equiv. iso-propylzinc iodide on 0.01 mmol scale using 1.2 mL THF solvent at 60 °C for 20 h (eq. 28).

Unfortunately, none of the terpyridine analogues listed in figure 2.9 performed any better than terpyridine (Table 2.5). Also, additional reaction and purification steps were needed for their preparation. Therefore, it was concluded that these changes in the electronics of terpyridine scaffold do not have a huge effect on the reaction and further screens were continued using the unsubstituted terpyridine ligand.

![Figure 2.9. Analogues of 2,2'-terpyridine.](image-url)
Table 2.5. Results obtained from screening terpyridine analogues for iodobenzene.

<table>
<thead>
<tr>
<th>Ligand (15%)</th>
<th>Calibrated Yield</th>
<th>Unreacted SM</th>
<th>Homocoupling</th>
<th>Branched/Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Ligand 1" /></td>
<td>27%</td>
<td>21%</td>
<td>-</td>
<td>&gt;300/1</td>
</tr>
<tr>
<td><img src="image2.png" alt="Ligand 2" /></td>
<td>25%</td>
<td>19%</td>
<td>&lt;1%</td>
<td>26/1</td>
</tr>
<tr>
<td><img src="image3.png" alt="Ligand 3" /></td>
<td>35%</td>
<td>19%</td>
<td>-</td>
<td>&gt;300/1</td>
</tr>
<tr>
<td><img src="image4.png" alt="Ligand 4" /></td>
<td>54%</td>
<td>11%</td>
<td>-</td>
<td>30/1</td>
</tr>
<tr>
<td><img src="image5.png" alt="Ligand 5" /></td>
<td>59%</td>
<td>12%</td>
<td>-</td>
<td>&gt;300/1</td>
</tr>
<tr>
<td><img src="image6.png" alt="Ligand 6" /></td>
<td>38%</td>
<td>-</td>
<td>-</td>
<td>&gt;300/1</td>
</tr>
<tr>
<td><img src="image7.png" alt="Ligand 7" /></td>
<td>59%</td>
<td>-</td>
<td>-</td>
<td>&gt;300/1</td>
</tr>
</tbody>
</table>
2.8 Effect of Concentration

To further increase the yield, we tried to vary the concentration of reaction mixture by changing the amount of THF externally added. Reactions involving bathophenanthroline did not show a large dependence on the concentration of reaction. However, reactions involving terpyridine were highly dependent on the amount of solvent present in the reaction. Concentration effects on these ligands are shown in table 2.6. These reactions were performed on 0.075 mmol scale with 10 mol % NiCl$_2$•glyme using 2 equivalents of sec-butyl zinc iodide at room temperature for 24 hours (eq. 29).

![Chemical reaction diagram]

Table 2.6. Effect of concentration on bathophenanthroline and terpyridine ligands.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand (15%)</th>
<th>THF (mL)</th>
<th>Conversion</th>
<th>Desired Product.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bathophenanthroline</td>
<td>0.6</td>
<td>100%</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>bathophenanthroline</td>
<td>1.0</td>
<td>92%</td>
<td>49%</td>
</tr>
<tr>
<td>3</td>
<td>bathophenanthroline</td>
<td>1.5</td>
<td>100%</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>bathophenanthroline</td>
<td>2.0</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>5</td>
<td>terpyridine</td>
<td>0.6</td>
<td>100%</td>
<td>78%</td>
</tr>
<tr>
<td>6</td>
<td>terpyridine</td>
<td>1.0</td>
<td>80%</td>
<td>57%</td>
</tr>
<tr>
<td>Entry</td>
<td>Ligand (15%)</td>
<td>THF (mL)</td>
<td>Conversion</td>
<td>Desired Product.</td>
</tr>
<tr>
<td>-------</td>
<td>--------------</td>
<td>----------</td>
<td>------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>7</td>
<td>terpyridine</td>
<td>1.5</td>
<td>82%</td>
<td>59%</td>
</tr>
<tr>
<td>8</td>
<td>terpyridine</td>
<td>2.0</td>
<td>51%</td>
<td>21%</td>
</tr>
</tbody>
</table>

With terpyridine, increase in reaction concentration helped to improve the reaction yield. After noticing this dependence on the concentration of reaction, the reaction was performed without adding any external THF to further lower the quantity of solvent (eq. 30). Therefore, the solvent present in the reaction mixture was only the amount that originated from the zinc nucleophile prepared in THF. The molarities of zinc reagents prepared in THF were typically between 0.75-0.9 M. This improved the yields dramatically for reactions using the terpyridine ligand. Also, the ratio of branched product to linear product increased. The improved results obtained without adding excess THF are shown in table 2.7.
Table 2.7. Improved yields with no external THF in reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Scale (mmol)</th>
<th>Zinc nucleophile</th>
<th>Conversion</th>
<th>Yield</th>
<th>Branched/Linear</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bathophenanthroline</td>
<td>0.1</td>
<td>ZnI</td>
<td>100%</td>
<td>60%</td>
<td>15:1</td>
</tr>
<tr>
<td>2</td>
<td>bathophenanthroline</td>
<td>0.5</td>
<td>ZnI</td>
<td>100%</td>
<td>60%</td>
<td>12:1</td>
</tr>
<tr>
<td>3</td>
<td>bathophenanthroline</td>
<td>0.1</td>
<td>ZnI</td>
<td>100%</td>
<td>64%</td>
<td>50:1</td>
</tr>
<tr>
<td>4</td>
<td>bathophenanthroline</td>
<td>0.5</td>
<td>ZnI</td>
<td>100%</td>
<td>58%</td>
<td>40:1</td>
</tr>
<tr>
<td>5</td>
<td>terpyridine</td>
<td>0.1</td>
<td>ZnI</td>
<td>100%</td>
<td>87%</td>
<td>23:1</td>
</tr>
<tr>
<td>6</td>
<td>terpyridine</td>
<td>0.5</td>
<td>ZnI</td>
<td>100%</td>
<td>91%</td>
<td>49:1</td>
</tr>
<tr>
<td>7</td>
<td>terpyridine</td>
<td>0.1</td>
<td>ZnI</td>
<td>100%</td>
<td>96%</td>
<td>158:1</td>
</tr>
<tr>
<td>8</td>
<td>terpyridine</td>
<td>0.5</td>
<td>ZnI</td>
<td>100%</td>
<td>quant.</td>
<td>206:1</td>
</tr>
</tbody>
</table>

With high yielding results in hand, further optimization regarding the catalyst loading and the equivalents of zinc nucleophile was needed. Without compromising the current yields and product distribution the catalyst loading was lowered to 2 mol % using 1.5 equiv. of nucleophile (eq. 31). The same reaction was performed using NiCl$_2$ instead of NiCl$_2$·glyme. The yields were not affected and there was further improvement in ratio of branched product/linear product. This
was an interesting observation as the use of \( \text{NiCl}_2 \) instead of \( \text{NiCl}_2 \cdot \text{glyme} \) for coupling reactions is very cost effective. The cost of \( \text{NiCl}_2 \cdot \text{glyme} \) is \$13.12/gram whereas that of \( \text{NiCl}_2 \) is only \$0.36/gram.\(^{50}\) For further reactions, 2\% \( \text{NiCl}_2 \) was used as the nickel source.

\[
\begin{align*}
\text{R} \text{I} & \quad \text{RZnI} \\
(0.05-0.2 \text{ mmol}) & \quad (1.5 \text{ equiv.}) \\
\text{R} & = \text{i-Pr or sec-Bu}
\end{align*}
\]

\[
(2\% \text{NiCl}_2 \cdot \text{glyme}) \quad 2\% \text{terpyridine} \quad 80 \degree \text{C, 2 h} \quad \text{> 95\% yields (31)}
\]

The addition of small amount of co-solvents such as DME, DMF, NMP, and DMA resulted in decreased yields and lower ratios of branched/linear products. Hence, the optimized conditions from eq. 31 were then applied on a variety of substrates to test the generality of process. When some functionalized aryl iodide electrophiles were reacted with zinc nucleophiles using conditions in eq. 31, they formed significant amount of reduced electrophile. Amount of this reduction side product further increased when the reactions were scaled up to 1 mmol scale. Therefore, to solve this problem the reaction temperature was then lowered from 80 \degree \text{C} to 40 \degree \text{C}. With this new set of conditions shown in eq. 32, the side product formation was lowered to negligible amounts.

\[
\begin{align*}
\text{R}_1 \text{I} & \quad \text{RZnI} \\
(1 \text{ mmol}) & \quad (1.5 \text{ equiv.}) \\
\text{R} & = \text{i-Pr or sec-Bu}
\end{align*}
\]

\[
(2\% \text{NiCl}_2 \cdot \text{anhyd.}) \quad 2\% \text{terpyridine} \quad 40 \degree \text{C, overnight} \quad \text{> 95\% yields (32)}
\]

### 2.9 Substrate Scope

Scheme 2.1 shows various functionalized arenes used as electrophilic substrates coupled with zinc nucleophiles. Each substrate is coupled with \textit{iso}-propyl and \textit{sec}-butyl zinc iodide to test the sensitivity of method to \( \alpha \)-branching. As we see here, both electron withdrawing, electron
donating and heterocyclic substrates are well tolerated. In each case, the ratio of the desired branched secondary product to the undesired linear primary product is greater than 100:1, as determined by gas chromatography technique. In very few cases, where the ratio was lower than 100:1 (7a, 10a, 15a), an equivalent of exogenous LiBF₄ was added to enhance formation of desired branched product. Details about the effect of salt additives on the product formation are given in the later part of this chapter.

As we see from scheme 2.1, substrates that have been traditionally difficult to couple are well tolerated by this method giving good to excellent yield of products. The presence of an electron donating group on the electrophile makes it more electron-rich and thereby more

**Scheme 2.1.** Ni-catalyzed cross-coupling reactions of i-PrZnI and sec-BuZnI with aryl and heteroaryl iodides.

\[
\begin{align*}
R-\text{ZnI} & \quad \xrightarrow{(R=\ i-\text{Pr}, \ s-\text{Bu})} \quad \text{NiCl}_2 (2-5 \text{ mol } \% ) \\
\text{ArI} & \quad \xrightarrow{\text{Terpyridine (2-5 mol } \% )} \quad \text{THF, 40-80 }{^\circ}\text{C} \quad \xrightarrow{R-\text{Ar}}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>91%</td>
</tr>
<tr>
<td>4b</td>
<td>87%</td>
</tr>
<tr>
<td>5a</td>
<td>83%</td>
</tr>
<tr>
<td>5b</td>
<td>82%</td>
</tr>
<tr>
<td>6a</td>
<td>67%</td>
</tr>
<tr>
<td>6b</td>
<td>68%</td>
</tr>
<tr>
<td>7a</td>
<td>88%</td>
</tr>
<tr>
<td>7b</td>
<td>83%</td>
</tr>
<tr>
<td>8a</td>
<td>82%</td>
</tr>
<tr>
<td>8b</td>
<td>82%</td>
</tr>
<tr>
<td>9a</td>
<td>89%</td>
</tr>
<tr>
<td>9b</td>
<td>87%</td>
</tr>
<tr>
<td>10a</td>
<td>91%</td>
</tr>
<tr>
<td>10b</td>
<td>91%</td>
</tr>
<tr>
<td>11a</td>
<td>92%</td>
</tr>
<tr>
<td>11b</td>
<td>92%</td>
</tr>
<tr>
<td>12a</td>
<td>91%</td>
</tr>
<tr>
<td>12b</td>
<td>93%</td>
</tr>
<tr>
<td>13a</td>
<td>74%</td>
</tr>
<tr>
<td>13b</td>
<td>68%</td>
</tr>
<tr>
<td>14a</td>
<td>73%</td>
</tr>
<tr>
<td>14b</td>
<td>75%</td>
</tr>
<tr>
<td>15a</td>
<td>61%</td>
</tr>
<tr>
<td>15b</td>
<td>71%</td>
</tr>
</tbody>
</table>
difficult to undergo the elementary steps of a cross-coupling reaction. Here, the presence of a para (4a, 4b) methoxy group is well tolerated giving excellent isolated product yields. Aniline (6a, 6b), which is a more difficult case also gives good product yield. Electron withdrawing para ester (10a, 10b) and meta (7a, 7b) methoxy group gives excellent yield. Meta (8a, 8b) and para (5a, 5b) phenols could be coupled without protecting the hydroxyl functionality. Here, an extra equivalent of nucleophile was added to deprotonate the hydroxyl proton which was reestablished upon quenching the reaction with mildly acidic saturated aqueous ammonium chloride solution. Other functional groups like bis(pinacolato)diboron (9a, 9b) and TMS acetylene (11a, 11b) gave very good product yields. These products can be further used as building blocks in other reactions such as Suzuki cross-coupling reactions.

The utility of the method increases considerably if the method is broad in substrate scope and accommodates heterocyclic substrates. Also, the medicinal chemistry research in pharmaceutical industry deals primarily with complex heterocyclic ring structures. With this knowledge, we then wanted to test various rings containing heteroatoms such as O, S, N as our electrophiles. We were able to couple indole (13a, 13b), furaldehyde (14a, 14b) and thiophene (15a, 15b) in very good product yields and ratios.

Although the method is very general in terms of the electrophilic scope, like any other method, it suffers from some limitations. Here, a few substrates such as 3’-iodo-4’-methoxyacetophenone, 1-iodonaphthalene, and 4-iodobenzonitrile produced complex mixture of products with very small amount of desired product. The reaction is not very general in coupling nitrogen-heterocycles. Repeated optimization efforts using various heterocyclic electrophiles such as 2-iodopyridine, 3-iodopyridine, 3-iodo-7-azaindole, and 2-iodopyrazine could not provide efficient
cross-coupling conditions. Various attempts to couple substrates containing ortho substituents using 1-iodo-2,4-dimethoxybenzene, 2-ethyliodobenzene, 2-iodobenzaldehyde, and 2-iodobenzaldehyde were also not successful. Here, ortho-groups containing carbonyl functionalities were also used with the thought that they might chelate to the catalyst and facilitate the reaction. Since the presence of coordinating ortho substituents have been shown to facilitate Ni-catalyzed cross-coupling reactions. However, such substrates were not tolerated in this reaction. Because electrophiles bearing ortho substituents tend to couple efficiently in analogous Pd-catalyzed reactions, our method can be used as a complementary method to the palladium-catalyzed reactions.

To expand the scope of nucleophilic coupling partners of the reaction, we prepared the zinc reagents of various acyclic secondary alkyl halides other than $i$-PrZnI and sec-BuZnI and coupled them with 1-iodo-3,5-dimethylbenzene using the optimized reaction conditions (Scheme 2.2). Here, the presence of alpha functionality on one alkyl group (16) as well as both alkyl groups (18) was well tolerated. In each case, the ratio of desired branched product to its linear isomer was more than 100:1. The presence of ester functionality was also well tolerated. One of the challenges faced here was the preparation of THF solution of substituted secondary alkyl zinc nucleophiles in high molarity. Since this method is highly dependent on the reaction concentration, lower molarity of reagent means dilute reaction conditions, lower yields and lower product ratios.
As we are interested in operational simplicity and high utility of the process, all the reactions were carried out outside of the glove box without the requirement of any specially designed apparatus or glassware. The reactions were run in disposable screw-top vials with septum caps on the bench-top. The reactions were run under argon without the requirement of any additional argon pressure during the course of reaction. To get an idea about sensitivity of the reaction, we set up the reactions in an open vial without any precautions to exclude air or moisture. We observed that the yield of such a reaction dropped by only 5% compared to the one obtained using standard reaction conditions. Therefore, while it is advised that these reactions be carried out under inert argon atmosphere, exposure to air and moisture has a small effect on the product yield.

2.10 Role of Salts

During our initial efforts to arrive at optimized reaction conditions, we had prepared the zinc nucleophiles using different reported methods. One of those methods was LiCl assisted insertion (eq. 33) reported by Knochel. However, when this reagent was employed in the Ni-catalyzed cross-coupling reactions, the reaction resulted in lower yields and poor product ratios.
Therefore, to investigate if there is any role of the LiCl salt in changing the product distribution, we added one equivalent of exogenous LiCl salt to the reaction, set up using the zinc reagent prepared by direct insertion method (eq. 21) to mimic the conditions in eq. 33. We saw that external LiCl addition has deleterious effect on the reaction. The product ratio had gone down by more than 3 fold producing 5-10% of the linear product.

![Chemical Reaction](image)

The salt additives have been reported to have an effect on the Negishi reaction and nickel-catalyzed cross-coupling reactions. Therefore, based on these reports and our observation with LiCl salt, we decided to look more closely into the effect of various salts on the reaction by adding one equivalent of salt exogenously in the reaction. The salts were stored and weighed out in the glove box due to their hygroscopic nature. The yields and product distribution obtained in salt experiments are shown in scheme 2.3. Although most substrates gave very high ratio of branched to linear products using our standard conditions, the coupling product (10a) obtained from the cross-coupling of 4-iodoester and i-PrZnI resulted in more substantial isomerization. Therefore, for this study, 10a was chosen as the electrophile in order to clearly identify the change in ratio upon addition of salt.
While most salts did not alter the yield and selectivity significantly, some salts had enhancing effect and some had deleterious effect on the reaction. As we had observed earlier, the yield and the selectivity dropped greatly with addition of 1 equiv. of LiCl and worsened with 3 equiv. of LiCl. LiI behaved similar to LiCl, adversely affecting the yield and product isomerization. With Bu₄NCl the yield was not as greatly affected but the ratio lowered in similar fashion to the LiCl. Zinc salts on the other hand helped improve the reaction yield and gave high ratios. Since lithium halide salts have shown to facilitate Pd-catalyzed Negishi cross-coupling reactions, it was surprising to see this deleterious LiCl effect on Ni-catalyzed Negishi cross-couplings.

While Zn(OTf)₂ did not have a dramatic effect, ZnI₂ and ZnCl₂ improved the yield and the ratio. By far the best salt additive was LiBF₄, which increased the yield from 86% to 95% by lowering the formation of reduced electrophile product. The ratio of desired to undesired isomer increased dramatically from 33:1 to >300:1, giving more than 10 fold improvement. Therefore, in cases where the ratio of desired product to isomerized product was <100:1, an equivalent of exogenous LiBF₄ was added in the reaction (products 7a, 10a, and 15a from scheme 2.1).
most substrates can be coupled in high yields and high ratios using the standard nickel-catalyzed cross-coupling conditions, an equivalent of LiBF₄ can be added to the reactions that form higher amounts of isomerized products. ZnCl₂ and LiBF₄ were the best additives among all the salts tested to improve the product ratio. In order to test if the Lewis acidity of these salts is responsible for this effect, two other non-coordinating Lewis acidic salts, LiSbF₆ and AgSbF₆ were additionally tested. While the lithium salt showed slight improvement in the ratio (63/1) the yield was lowered to 66%. The silver salt improved the ratio greatly (>200:1) but gave lower conversion and yield of 29%. To determine if very small amount of fluoride ion is leaching from the LiBF₄ solution and affecting the product ratio, an equivalent of CsF was used as an additive. However, with CsF, both yield and ratio diminished to 20% (23:1).

2.11 Plausible Catalytic Cycle

The catalytic cycle for the Nickel-catalyzed cross-coupling reaction of secondary and tertiary alkyl nucleophiles and aryl halides can occur by two pathways as shown in figure 2.10. The catalytic cycle shown in the left half of figure 2.10 initiates with the oxidative addition of an
aryl halide onto a \( \text{Ni}(0) \) to give an oxidatively added \( \text{Ni}(II) \) intermediate (1b). This intermediate then undergoes transmetallation followed by reductive elimination to yield the desired cross-coupled product and regenerate the catalyst. Another mechanistic possibility for this transformation could be the \( \text{Ni}(I)-\text{Ni}(III) \) catalytic cycle shown on the right. Here, transmetallation of the secondary/tertiary alkyl nucleophile takes place on a \( \text{Ni}(I) \) center to give transmetallated \( \text{Ni}(I) \) intermediate 1a. This intermediate undergoes oxidative addition to give a second intermediate with a \( \text{Ni}(III) \) center. This intermediate then furnishes the cross-coupled product regenerating \( \text{Ni}(I) \) catalyst. While neither of the possibilities can be conclusively ruled out, we support the mechanistic possibility of the catalytic cycle in \( \text{Ni}(I)-\text{Ni}(III) \) based on the prior experimental and computational work reported by other groups.\textsuperscript{23, 33, 39, 54}

*Kinetic studies to evaluate the role of salt additives:*

When the reactions were conducted using a reaction calorimeter, the observations included in table 2.8 were made. Results obtained for initial and overall rates of the reaction are compared to those obtained for the standard reaction conditions.

**Table 2.8.** Results obtained from experiments performed inside the calorimeter.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Change in conditions compared to standard</th>
<th>Initial Rate comparison</th>
<th>Uncalibrated Results</th>
<th>Overall reaction time (comparison with standard)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Standard Conditions: 4-Iodoanisole (0.6 mmol); ( \text{NiCl}_2 ), anhyd. (5 mol %); Terpyridine (5 mol %); ( i-\text{PrZnI} ) (1.5 equiv.); THF (0.3 ml)</td>
<td>Standard reaction used for comparison</td>
<td>Conv. = 100% Reduction = 4 % Product = 96 %</td>
<td>Standard reaction time 8-10 hours</td>
</tr>
<tr>
<td>2</td>
<td>( \text{LiBF}_4 ) (1 equiv.)</td>
<td>Slightly slower</td>
<td>Conv. = 100 % Reduction = 2 % Pdts. = 98 %</td>
<td>Time = 0.66 times standard</td>
</tr>
<tr>
<td>Entry</td>
<td>Change in conditions compared to standard</td>
<td>Initial Rate comparison</td>
<td>Uncalibrated Results</td>
<td>Overall reaction time (comparison with standard)</td>
</tr>
<tr>
<td>-------</td>
<td>------------------------------------------</td>
<td>------------------------</td>
<td>----------------------</td>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>3</td>
<td>LiCl (1 equiv.)</td>
<td>Fastest initial rate</td>
<td>Conv. = 100 %</td>
<td>Time = 0.5 times standard,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 46 %</td>
<td>isomerization homocoupling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 43 % (11/1)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Homo = 11 %</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LiI (1 equiv.)</td>
<td>Very fast initial rate for few minutes</td>
<td>Conv. = 100 %</td>
<td>Time = 0.33 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 36.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 63.7 %</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>ZnCl₂ (1 equiv.)</td>
<td>Very slow initial rate</td>
<td>Conv. = 100 %</td>
<td>Time = 1.3 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 5 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Products = 95 %</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂, anhyd. (2 mol %) Terpyridine (2 mol %)</td>
<td>Comparable initial rate</td>
<td>Conv. = 100 %</td>
<td>Time = 0.66 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 2.4 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Products = 97.6 %</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>NiCl₂, anhyd. (2 mol %) Terpyridine (5 mol %)</td>
<td>Comparable initial rate</td>
<td>Conv. = 100 %</td>
<td>Time = 0.66 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 4.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 95.7 %</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>NiCl₂, anhyd. (5 mol %) Terpyridine (2 mol %)</td>
<td>Initial rate ~ double of standard</td>
<td>Conv. = 100 %</td>
<td>Time = 0.4 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 3.3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 96.7 %</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>NiCl₂, anhyd. (5 mol %) Terpyridine (1 mol %)</td>
<td>Slightly faster than standard</td>
<td>Conv. = 100 %</td>
<td>Time = 0.4 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 3 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 97 %</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>NiCl₂, anhyd. (5 mol %) Terpyridine (0.5 mol %)</td>
<td>Very slow start, incubation period (1/2 h)</td>
<td>Conv. = 100 %</td>
<td>Time = 0.5 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 3.9 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 96.1 %</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>NiCl₂, anhyd. (10 mol %) Terpyridine (10 mol %)</td>
<td>Very fast</td>
<td>Conv. = 100 %</td>
<td>Time = 0.33 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 6.8 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 93.1 %</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>i-PrZnI (1.2 equiv.)</td>
<td>Incubation period for 15-20 mins. Very sluggish start</td>
<td>Conv. = 100 %</td>
<td>Time = 0.5 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 5.5 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 94.5 %</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>i-PrZnI (2 equiv.)</td>
<td>Comparable initial rate</td>
<td>Conv. = 100 %</td>
<td>Time = 0.5 times standard</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Reduction = 2.9 %</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pdts. = 97.1 %</td>
<td></td>
</tr>
</tbody>
</table>
When the reactions were conducted outside the reaction calorimeter, the observations included in table 2.9 were made. Results obtained for initial and overall rates of the reaction are compared to those obtained for the standard reaction conditions. Each reaction was set in two different vials. First vial was used for sampling the aliquot after specific time intervals. Reaction in second vial was stopped and analyzed after 3 hours and used as control experiment.

**Table 2.9.** Results obtained from crude kinetic experiments performed outside the calorimeter.

**Variation from Standard Reaction Conditions:** None

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (5 mol %), $i$-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.

<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td></td>
<td>% Redced product (uncalibrated)</td>
</tr>
<tr>
<td></td>
<td>% Desired product (uncalibrated)</td>
</tr>
<tr>
<td></td>
<td>% Starting material (uncalibrated)</td>
</tr>
<tr>
<td></td>
<td>% Homo-coupled product (uncalibrated)</td>
</tr>
<tr>
<td>25 min</td>
<td>19.7</td>
</tr>
<tr>
<td>1 h</td>
<td>46.6</td>
</tr>
<tr>
<td>2 h</td>
<td>73</td>
</tr>
<tr>
<td>3 h</td>
<td>82.8</td>
</tr>
<tr>
<td></td>
<td>91.8</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours.

**Variation from Standard Reaction Conditions:** 1 equiv. LiBF$_4$

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (5 mol %), $i$-PrZnI (1.5 equiv.), THF (0.15 mL), 1 equiv. LiBF$_4$, 40 °C, 3 h.
<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td>25 min</td>
<td>1</td>
</tr>
<tr>
<td>1 h</td>
<td>9</td>
</tr>
<tr>
<td>2 h</td>
<td>29.2</td>
</tr>
<tr>
<td>3 h</td>
<td>43.7</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>59.7</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours

Variation from Standard Reaction Conditions: 1 equiv. LiCl

4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (5 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 1 equiv. LiCl, 40 °C, 3 h.

<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td>25 min</td>
<td>2</td>
</tr>
<tr>
<td>1 h</td>
<td>53.6</td>
</tr>
<tr>
<td>2 h</td>
<td>75</td>
</tr>
<tr>
<td>3 h</td>
<td>86.5</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>100</td>
</tr>
</tbody>
</table>
**Variation from Standard Reaction Conditions:** 1 equiv. ZnCl₂

4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (5 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 1 equiv. ZnCl₂, 40 °C, 3 h.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td>1</td>
<td>-</td>
<td>2</td>
<td>98</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td>3</td>
<td>-</td>
<td>12.3</td>
<td>87.7</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td>12</td>
<td>2</td>
<td>20</td>
<td>78</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours

| 3 h    | 16.5                      | 1.8                             | 23.5                            | 74.6                              | -                                   |

**Variation from Standard Reaction Conditions:** 1 equiv. LiI

4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (5 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 1 equiv. LiI, 40 °C, 3 h.
<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td>25 min</td>
<td>15.6</td>
</tr>
<tr>
<td>1 h</td>
<td>45.4</td>
</tr>
<tr>
<td>2 h</td>
<td>63</td>
</tr>
<tr>
<td>3 h</td>
<td>73.8</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours

<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td>3 h</td>
<td>73.6</td>
</tr>
</tbody>
</table>

Variation from Standard Reaction Conditions: 100 °C

4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (5 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 100 °C, 3 h.
Variation from Standard Reaction Conditions: room temperature

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (5 mol %), $i$-PrZnI (1.5 equiv.), THF (0.15 mL), rt, 3 h.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min</td>
<td>7.6</td>
<td>0.8</td>
<td>14.9</td>
<td>84.3</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td>26</td>
<td>1.2</td>
<td>35</td>
<td>63.8</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td>44.6</td>
<td>1.8</td>
<td>53.5</td>
<td>44.7</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td>52.3</td>
<td>1.9</td>
<td>60.7</td>
<td>37.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 h</td>
<td>44.6</td>
<td>1.8</td>
<td>52.6</td>
<td>45.5</td>
<td>-</td>
</tr>
</tbody>
</table>

Variation from Standard Reaction Conditions: $i$-PrZnI (1.2 equiv.)

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (5 mol %), $i$-PrZnI (1.2 equiv.), THF (0.15 mL), 40 °C, 3 h.
<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 min</td>
<td></td>
<td>28</td>
<td>1.3</td>
<td>30.2</td>
<td>68.5</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td>49.6</td>
<td>2.1</td>
<td>54.3</td>
<td>43.5</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td></td>
<td>72.5</td>
<td>3.2</td>
<td>74.6</td>
<td>22.1</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td></td>
<td>83</td>
<td>3.8</td>
<td>83.1</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reaction stopped after 3 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td></td>
<td>77.2</td>
<td>3.5</td>
<td>79.6</td>
<td>16.9</td>
<td>-</td>
</tr>
</tbody>
</table>

Variation from Standard Reaction Conditions: \( i\)-PrZnI (2 equiv.)

4-Iodoanisole (0.3 mmol), NiCl\(_2\), anhyd. (5 mol %), Terpyridine (5 mol %), \( i\)-PrZnI (2 equiv.), THF (0.15 mL), 40 °C, 3 h.
**Variation from Standard Reaction Conditions:** NiCl$_2$, anhyd. (10 mol %), Terpyridine (10 mol %)

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (10 mol %), Terpyridine (10 mol %), $i$-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min</td>
<td>23</td>
<td>1.2</td>
<td>29.2</td>
<td>69.6</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td>49.3</td>
<td>2.3</td>
<td>57.3</td>
<td>40.4</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td>82.2</td>
<td>3</td>
<td>84.6</td>
<td>12.4</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td>91.6</td>
<td>3.5</td>
<td>90.8</td>
<td>5.7</td>
<td>-</td>
</tr>
</tbody>
</table>

Reaction stopped after 3 hours

<table>
<thead>
<tr>
<th>Time</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 h</td>
<td>90.3</td>
<td>4.4</td>
<td>88.8</td>
<td>6.8</td>
<td>-</td>
</tr>
</tbody>
</table>

**Variation from Standard Reaction Conditions:** NiCl$_2$, anhyd. (2 mol %), Terpyridine (5 mol %)

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (2 mol %), Terpyridine (5 mol %), $i$-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.
<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Conversion (Calibrated)</td>
</tr>
<tr>
<td>25 min</td>
<td>4.1</td>
</tr>
<tr>
<td>1 h</td>
<td>27.7</td>
</tr>
<tr>
<td>2 h</td>
<td>46.6</td>
</tr>
<tr>
<td>3 h</td>
<td>61.8</td>
</tr>
<tr>
<td></td>
<td>Reaction stopped after 3 hours</td>
</tr>
<tr>
<td>3 h</td>
<td>65.6</td>
</tr>
</tbody>
</table>

Variation from Standard Reaction Conditions: NiCl₂, anhyd. (2 mol %), Terpyridine (2 mol %)
4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (2 mol %), Terpyridine (2 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.
Variation from Standard Reaction Conditions: NiCl$_2$, anhyd. (5 mol %), Terpyridine (2 mol %)

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (2 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.

<table>
<thead>
<tr>
<th>Time</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min</td>
<td>16.8</td>
<td>-</td>
<td>22</td>
<td>78</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td>42.6</td>
<td>1.7</td>
<td>50.2</td>
<td>48</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td>74</td>
<td>2.4</td>
<td>78.4</td>
<td>19.2</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td>82.8</td>
<td>2.6</td>
<td>85.2</td>
<td>12.2</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reaction stopped after 3 hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 h</td>
<td>95</td>
<td>3.7</td>
<td>93</td>
<td>3.4</td>
<td>-</td>
</tr>
</tbody>
</table>

Variation from Standard Reaction Conditions: NiCl$_2$, anhyd. (5 mol %), Terpyridine (1 mol %)

4-Iodoanisole (0.3 mmol), NiCl$_2$, anhyd. (5 mol %), Terpyridine (1 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.
<table>
<thead>
<tr>
<th>Time</th>
<th>Reaction sampled out after specific time interval</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 min</td>
<td></td>
<td>22.7</td>
<td>11.8</td>
<td>33.6</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>1 h</td>
<td></td>
<td>70</td>
<td>3.3</td>
<td>74.9</td>
<td>21.8</td>
<td>-</td>
</tr>
<tr>
<td>2 h</td>
<td></td>
<td>89.8</td>
<td>4.6</td>
<td>88.4</td>
<td>7.1</td>
<td>-</td>
</tr>
<tr>
<td>3 h</td>
<td></td>
<td>95.8</td>
<td>4.8</td>
<td>92.3</td>
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<tr>
<td>3 h</td>
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<td>96.9</td>
<td>3.9</td>
<td>94</td>
<td>2.1</td>
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Variation from Standard Reaction Conditions: NiCl₂, anhyd. (5 mol %), Terpyridine (0.5 mol %), 4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (0.5 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.

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<th>Reaction sampled out after specific time interval</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
<th>% Homo-coupled product (uncalibrated)</th>
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<td>62</td>
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<td>96.1</td>
<td>4.5</td>
<td>92.9</td>
<td>2.6</td>
<td>-</td>
</tr>
</tbody>
</table>
Variation from Standard Reaction Conditions: NiCl₂, anhyd. (5 mol %), Terpyridine (0 mol %)

4-Iodoanisole (0.3 mmol), NiCl₂, anhyd. (5 mol %), Terpyridine (0 mol %), i-PrZnI (1.5 equiv.), THF (0.15 mL), 40 °C, 3 h.

<table>
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<th>Time</th>
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<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
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Reaction stopped after 3 hours

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<tr>
<th>Time</th>
<th>% Conversion (Calibrated)</th>
<th>% Reduced product (uncalibrated)</th>
<th>% Desired product (uncalibrated)</th>
<th>% Starting material (uncalibrated)</th>
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<td>3 h</td>
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<td>3.1</td>
<td>17.3</td>
<td>79.6</td>
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</table>

Discussion of results:

Figure 2.11 shows a detailed mechanism of a Ni(I)-Ni(III) catalytic cycle discussed above. Here transmetallation of the alkyl nucleophile on Ni(I) complex D gives rise to intermediate A. This intermediate A is a Ni(II) complex with reduced terpyridine ligand. Oxidative addition of aryl halide onto A then takes place as a two-step process leading to a Ni(III) intermediate C. Reductive elimination of R-Ar from C can then produce the desired product. We postulate that formation of intermediate C from intermediate A could be a reversible process.
Kinetic data obtained by adding various salts to the standard reaction also supports this assumption. As mentioned in the earlier section, some salts like LiBF$_4$ and ZnCl$_2$ help the reaction by reducing the formation of undesired isomeric product and increase the yield by decreasing the formation of reduced electrophile. Lewis acidic salts like ZnCl$_2$ can undergo complexation with the $X^-$ from intermediate C resulting in formation of higher order zincates. Reductive elimination of R-Ar from the cationic nickel from intermediate C can then form the desired product.

However, when halide salts like LiCl and LiI are added to the reaction, the equilibrium of the reversible reaction will be pushed backwards towards intermediate A due to the presence of excessive amount of halide ion coming from added salts. If the concentration of intermediate A thus increases, the propensity of it undergoing β-hydride elimination leading to the product isomer also increases. If during the process of formation of intermediate A from intermediate C, an alkyl radical falls off instead of an aryl radical, an intermediate analogous to A with an aryl group will be formed. However, our experimental work suggests that the same catalyst system consisting of nickel and terpyridine ligand does not support the cross-coupling event when the nucleophilic and the electrophilic reaction partners are interchanged. Therefore, this intermediate may not undergo further reaction steps and can thus participate in other side-reactions leading to reduction or homo-coupling of the electrophile. This can then explain the observation that addition of an equivalent of LiCl or LiI reduces the product yield and the ratio of desired to isomerized product and leads to the formation of homo-coupled and reduced electrophilic products.
2.12 Conclusions

A general method for cross-coupling various aryliodides with acyclic secondary alkylzinc nucleophiles has been developed using NiCl$_2$ and terpyridine. This method is very mild, functional group tolerant and easy to set up. Various electron donating, electron withdrawing and heteroaryl functionalities on the electrophile are well tolerated. Many traditionally difficult electrophiles were coupled in good to excellent product yields with very high (>100:1) ratio of the desired branched secondary product to the undesired primary linear product.

While this reaction has broad scope, it also has some limitations. The reaction is sensitive to the presence of ortho-substituents on the electrophile. Also, it does not work well with some nitrogen containing heterocyclic substrates. To further expand the scope of the method, more substituted nucleophiles containing functionalities or alpha-branching on one and both sides
were coupled in high yields and ratios. In cross-coupling secondary alkyl nucleophiles the biggest challenge lies in preparation of their solution in high concentration.

A thorough study of the effect of salt additives on the conversion and product distribution was carried out. It was concluded that exogenous addition of some salts like LiCl and LiI is detrimental to the reactions. Some Lewis acidic salts like ZnCl₂ and LiBF₄ help the reaction by improving the product ratio and reducing the reduction of electrophile. LiBF₄ can be added to the reaction if problems of isomerization arises for some substrates.

2.13 Supporting Information

General Reagent Information

BDH brand toluene was purchased from VWR. EMD brand Omnisolv THF (unstabilized) was also purchased from VWR. These solvents were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene). All reagents and solvents were used as received unless otherwise noted. Anhydrous NiCl₂ was purchased from Strem, terpyridine was purchased from Sigma-Aldrich. Flash chromatography was performed using Silicycle silica gel (ultra-pure grade).

General Analytical Information

All compounds were characterized by ¹H NMR and ¹³C NMR spectroscopy. Copies of the ¹H and ¹³C spectra can be found at the end of the Supporting Information. All previously unreported compounds were additionally characterized by IR spectroscopy and elemental
analysis. Nuclear Magnetic Resonance spectra were recorded on a Varian 300 or 500 MHz instrument. All $^1$H NMR experiments are reported in $\delta$ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm). All $^{13}$C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm), and were obtained with $^1$H decoupling. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase. IR spectra were obtained on a Perkin-Elmer Model 2000 FT-IR using NaCl plates (thin film).

**General Procedural Information**

**General procedure for the preparation of isopropyl and sec-butylzinc iodide**

Zinc granules (3 g, 45 mmol) were added to a flame dried 100 mL Schlenk flask with a stir bar and heated at 80 °C under vacuum for 1 h while stirring. After the flask was cooled to room temperature under argon, iodine crystals (3.8 g, 15 mmol) were added, and the flask was evacuated and backfilled with argon 3 times. The flask was cooled using an ice bath and dry THF (24 mL) was then added via syringe. The reaction mixture was stirred until the red color of the solution faded to colorless-yellow. The secondary alkyl iodide (30 mmol) was then added via syringe. The reaction mixture was stirred at room temperature until complete consumption of the alkyl halide (1-2 days) as judged by GC. The solution was transferred into a flame dried pear shaped flask via cannula and stored under argon on the bench-top. The molarity of the resulting solution was determined using iodine titration. The molarities were typically between 0.8 M and 1.0 M.
General procedure for the preparation of alkylzinc iodides from scheme 2.2:

Zinc granules (1.96 g, 30 mmol) were added to a flame dried 50 mL 2-neck round bottom flask equipped with a condenser and a stir bar. Under vacuum, the flask was heated to 80 °C for 1 h while stirring. The flask was backfilled with argon and the temperature was lowered to 60 °C. A solution of iodine (3 g, 12 mmol) in THF (6 mL) was added via syringe. The reddish color of the solution faded to colorless within a few minutes. The secondary alkyl iodide (6 mmol) in THF (2 mL) was then added via syringe and the reaction mixture was refluxed at 60 °C for 20 h. The solution was transferred while hot* into a flame dried round bottom flask via syringe/needle and stored under argon. Molarity of the resulting solution was determined by iodine titration. The molarities of these alkyl zinc iodides typically ranged from 0.4 M to 0.7 M.

*Note: If the solution is cooled, a solid precipitate may form, which will clog the syringe. Hence, it is necessary to transfer the organozinc solution while it is hot. If solid precipitate forms in the round bottom receiving flask, extra THF can be added.

General procedure for the cross-coupling of aryl iodides and secondary alkylzinc iodides:

Anhydrous NiCl$_2$ (2.6 mg, 0.02 mmol) and terpyridine (4.6 mg, 0.02 mmol) were weighed out on the benchtop in a flame-dried 1 dram vial with stir bar. The aryl iodide (1 mmol) was then added to the vial. The vial was sealed using a screw cap lined with a teflon septum. The vial was evacuated and backfilled with argon using a needle attached to a vacuum manifold. If the aryl iodide was a liquid, it was added via microsyringe after having backfilled the vial with argon. The secondary alkylzinc iodide (1.5 mmol) was then added via syringe under a positive pressure of argon. The vial was sealed with electrical tape and the reaction mixture was stirred.
for 17 h on the benchtop at 40 °C with no additional argon pressure. Progress of the reaction was monitored by GC. The reaction mixture was poured into a separatory funnel containing saturated aqueous NH₄Cl (ca. 10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude product was purified by column chromatography.

**General procedure for experiments of scheme 2.3:**

Anhydrous NiCl₂ (1.6 mg, 0.0125 mmol), terpyridine (2.9 mg, 0.00125 mmol), and methyl 4-iodobenzoate (65.5 mg, 0.25 mmol) were weighed out on the benchtop into an oven-dried 1 dram vial with stir bar. The reaction vial was transferred to a nitrogen-filled glovebox. The salt (0.25 mmol) was added to the vial. The vial was capped with a screw cap lined with a teflon septum. This screw cap was additionally sealed with electrical tape and was removed from the glovebox. i-PrZnI in THF (1.0 M, 400 ml, 0.400 mmol) was added via syringe to the reaction vial. The vial was heated to 40 °C for 20 h in a reactor block. The reaction mixture was poured into a 2 dram vial containing saturated aqueous NH₄Cl (ca. 1 mL) and extracted with EtOAc (ca. 1 mL). The EtOAc layer was analyzed by GC.

**Spectral Data**

![Terpyridine Structure](image)

4′-(Trifluoromethyl)-2,2′:6′,2″-terpyridine. To a flame dried 50 mL 2-neck round bottom flask equipped with a stir bar and a condenser, 2,6-dichloro-4-
trifluoromethylpyridine (120 mg, 0.56 mmol), 2-pyridyl-tributyl stannane (511 mg, 1.39 mmol) and toluene (10 mL) was added. The flask was evacuated/ backfilled with argon thrice. Palladium tetrakistriphenylphosphine was then added in one portion under argon pressure and the reaction mixture was heated to reflux for 20 h. The reaction was monitored by proton NMR. When no more starting material was left, the reaction was quenched by adding saturated aqueous NH₄Cl (ca. 5 mL). The mixture was then poured into a separatory funnel and extracted three times with EtOAc. The combined organic layers were washed with brine and dried over Na₂SO₄. After column chromatography (20:1 CH₂Cl₂: MeOH), the desired product was obtained as a solid (90 mg, 30%). The product was then digested in hexane (ca. 1-2 mL) to provide off-white solid. ¹H NMR (500 MHz, CDCl₃) δ: 8.74 (m, 2H), 8.72 (s, 2H), 8.64 (d, J = 8.3 Hz, 2H), 7.90 (td, J = 7.8, 1.5 Hz, 2H), 7.40 (m, 2H) ppm. Anal. Calcd. for C₁₆H₁₀N₃F₃: C, 63.79; H, 3.35. Found: C, 63.24; H, 3.49.

1-(iso-Propyl)-4-methoxybenzene (4a). The general procedure was employed with the following modification: ether used for extractions during work-up. A colorless liquid (138 mg, 92%) was isolated by column chromatography (95:5 Hex:Ether). ¹H NMR (500 MHz, CDCl₃) δ: 7.17 (d, J = 8.3 Hz, 2H), 6.86 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 2.88 (septet, J = 6.8 Hz, 1H), 1.25 (d, J = 6.8 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 157.8, 141.2, 127.4, 113.8, 55.4, 33.4, 24.2 ppm.
1-(sec-Butyl)-4-methoxybenzene (4b). The general procedure was employed with the following modification: ether used for extractions during work-up. A colorless liquid (149 mg, 91%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.11 (d, $J$ = 8.7 Hz, 2H), 6.85 (d, $J$ = 8.7 Hz, 2H), 3.80 (s, 3H), 2.56 (app. sextet, $J$ = 7.1 Hz, 1H), 1.57 (app. pentet, $J$ = 7.4 Hz, 2H), 1.22 (d, $J$ = 6.9 Hz, 3H), 0.83 (t, $J$ = 7.4 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 157.8, 139.9, 128.0, 113.8, 55.4, 41.0, 31.5, 22.2, 12.4 ppm.

![Structure of 1-(sec-Butyl)-4-methoxybenzene](image)

4-(iso-Propyl)phenol (5a). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl$_2$ and terpyridine employed, 22 h reaction time. A white solid (115 mg, 85%) was isolated by column chromatography (gradient from 70:30 to 65:35 Hex:EtOAc). Mp: 62-64 ºC. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.10 (d, $J$ = 8.3 Hz, 2H), 6.76 (d, $J$ = 8.8 Hz, 2H), 4.54 (s, 1H), 2.85 (septet, $J$ = 7.3 Hz, 1H), 1.22 (d, $J$ = 7.3 Hz, 6H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 153.6, 141.4, 127.6, 115.2, 33.4, 24.4 ppm.

![Structure of 4-(iso-Propyl)phenol](image)

4-(sec-Butyl)phenol (5b). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl$_2$ and terpyridine employed, 40 h reaction time. A white solid (123 mg, 87%) was isolated by column chromatography (gradient from 70:30 to 65:35 Hex:EtOAc). Mp: 58-60 ºC. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.05 (d, $J$ = 8.5 Hz, 2H), 6.76 (d, $J$ = 8.5 Hz, 2H), 4.53 (bs, 1H), 2.53 (m, 1H), 1.54 (m, 2H), 1.20 (d,
\[ J = 6.8 \text{ Hz}, \ 3\text{H}, \ 0.81 \ (t, \ J = 7.3 \text{ Hz}, \ 3\text{H}) \ \text{ppm}. \]

\(^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3\) \(\delta: 153.5, 140.1, \ 128.2, \ 115.1, \ 41.0, 31.5, 22.2, 12.4 \ \text{ppm}. \)

**4-(iso-Propyl)aniline (6a).** The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl\(_2\) and terpyridine employed, reaction conducted at 80 °C, 14 h reaction time, reaction quenched with saturated aqueous NaHCO\(_3\). A yellow-orange liquid (91 mg, 67%) was isolated by column chromatography (gradient from 75:25 to 70:30 Hex:EtOAc). \(^1\text{H} \text{ NMR (500 MHz, CDCl}_3\) \(\delta: 7.03 \ (d, \ J = 8.3 \text{ Hz}, \ 2\text{H}), \ 6.65 \ (d, \ J = 8.7 \text{ Hz}, \ 2\text{H}), \ 3.57 \ (bs, \ 2\text{H}), \ 2.82 \ (septet, \ J = 6.8 \text{ Hz}, \ 1\text{H}), \ 1.21 \ (d, \ J = 6.8 \text{ Hz}, \ 6\text{H}) \ \text{ppm}. \)

\(^{13}\text{C} \text{ NMR (125 MHz, CDCl}_3\) \(\delta: 144.3, 139.3, 127.3, 115.3, 33.4, 24.4 \ \text{ppm}. \)

**4-(sec-Butyl)aniline (6b).** The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl\(_2\) and terpyridine employed, reaction conducted at 80 °C, 15 h reaction time, reaction quenched with saturated aqueous NaHCO\(_3\). A yellow-orange liquid (93 mg, 62%) was isolated by column chromatography (gradient from 70:30 to 65:35 Hex:EtOAc). \(^1\text{H} \text{ NMR (500 MHz, CDCl}_3\) \(\delta: 6.99 \ (d, \ J = 8.4 \text{ Hz}, \ 2\text{H}), \ 6.65 \ (d, \ J = 8.5 \text{ Hz}, \ 2\text{H}), \ 3.57 \ (bs, \ 2\text{H}), \ 2.50 \ (app. sextet, \ J = 7.1 \text{ Hz}, \ 1\text{H}), \ 1.55 \ (m, \ 2\text{H}), \ 1.20 \ (d, \ J = 7.0 \text{ Hz}, \ 3\text{H}), \ 0.82 \ (t, \ J = 7.4 \text{ Hz}, \ 3\text{H}) \ \text{ppm}. \)

\(^{13}\text{C} \text{ NMR (75 MHz, CDCl}_3\) \(\delta: 144.3, 138.1, 127.9, 115.3, 40.9, 31.5, 22.1, 12.4 \ \text{ppm}. \)
1-(*iso*-Propyl)-3-methoxybenzene (7a). The general procedure was employed with the following modifications: LiBF<sub>4</sub> (93.7 mg, 1mmol) was weighed out and added to the reaction vial in a nitrogen-filled glove box, 30 h reaction time, ether used for extractions during work-up. A pale yellow liquid (136 mg, 91%) was isolated by column chromatography (95:5 Hex:Ether).<br />

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.23 (t, <i>J</i> = 7.8 Hz, 1H), 6.84 (d, <i>J</i> = 7.5 Hz, 1H), 6.79 (m, 1H), 6.73 (d, <i>J</i> = 7.8 Hz, 1H), 3.82 (s, 3H), 2.89 (septet, <i>J</i> = 6.8 Hz, 1H), 1.26 (d, <i>J</i> = 6.8 Hz, 6H) ppm. <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ: 159.8, 150.8, 129.4, 119.0, 112.6, 110.9, 55.3, 34.3, 24.1 ppm.

1-(sec-Butyl)-3-methoxybenzene (7b). The general procedure was employed with the following modifications: 18 h reaction time, ether used for extractions during work-up. A colorless liquid (141 mg, 86%) was isolated by column chromatography (95:5 Hex:Ether). <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ: 7.22 (td, <i>J</i> = 7.6 Hz, 0.9 Hz, 1H), 6.79 (d, <i>J</i> = 7.6 Hz, 1H), 6.75 (d, <i>J</i> = 0.9 Hz, 1H), 6.73 (dd, <i>J</i> = 2.6 Hz, 0.9 Hz, 1H), 3.81 (s, 3H), 2.58 (app. sextet, <i>J</i> = 7.1 Hz, 1H), 1.60 (m, 2H), 1.24 (d, <i>J</i> = 7.0 Hz, 3H), 0.84 (t, <i>J</i> = 7.4 Hz, 3H) ppm. <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ: 159.7, 149.6, 129.3, 119.7, 113.2, 110.8, 55.2, 41.9, 31.2, 22.0, 12.4 ppm.
3-(*iso-Propyl*)phenol (8a). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl₂ and terpyridine employed, reaction conducted at 80 °C, 17 h reaction time. A colorless liquid (110 mg, 81%) was isolated by column chromatography (gradient from 70:30 to 65:35 Hex:EtOAc). ¹H NMR (500 MHz, CDCl₃) δ: 7.16 (t, J = 7.8 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.71 (m, 1H), 6.67 (m, 1H), 4.70 (bs, 1H), 2.86 (septet, J = 6.8 Hz, 1H), 1.24 (d, 6.8 Hz, 6H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 155.6, 151.1, 129.6, 119.2, 113.5, 112.7, 34.1, 24.0 ppm.

3-(*sec-Butyl*)phenol (8b). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol % NiCl₂ and terpyridine employed, reaction conducted at 80 °C, 14 h reaction time. A colorless liquid (120 mg, 80%) was isolated by column chromatography (gradient from 70:30 to 65:35 Hex:EtOAc). ¹H NMR (500 MHz, CDCl₃) δ: 7.16 (t, J = 7.8 Hz, 1H), 6.77 (d, J = 7.3 Hz, 1H), 6.66 (m, 2H), 4.86 (s, 1H), 2.55 (app. sextet, J = 7.3 Hz, 1H), 1.58 (m, 2H), 1.22 (d, J = 6.8 Hz, 3H), 0.83 (t, J = 7.6 Hz, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ: 155.5, 150.0, 129.5, 119.9, 114.1, 112.8, 41.7, 31.2, 21.9, 12.4 ppm.

2-(4-(*iso-Propyl*)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9a). The general
procedure was employed with the following modification: 30 h reaction time. A white solid (211 mg, 86%) was isolated by column chromatography (gradient from 93:7 to 90:10 Hex:EtOAc). Mp: 78-80 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.76 (d, $J = 7.8$ Hz, 2H), 7.25 (d, $J = 7.8$ Hz, 2H), 2.95 (septet, $J = 6.8$ Hz, 1H), 1.34 (s, 12H), 1.26 (d, $J = 6.8$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 152.5, 135.1, 126.1, 83.7, 34.5, 25.0, 24.0 ppm. $^{11}$B NMR (160 MHz, CDCl$_3$) δ: 30.9 ppm.

2-(4-(sec-Butyl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (9b). The general procedure was employed with the following modification: 30 h reaction time. A white solid (238 mg, 92%) was isolated by column chromatography (gradient from 93:7 to 90:10 Hex:EtOAc). Mp: 88-91 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.74 (d, $J = 8.5$ Hz, 2H), 7.20 (d, $J = 8.0$ Hz, 2H), 2.60 (m, 1H), 1.60 (m, 2H), 1.34 (s, 12H), 1.23 (d, $J = 7.3$ Hz, 3H), 0.81 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) δ: 151.3, 135.0, 126.7, 83.7, 42.1, 31.1, 25.0, 21.9, 12.4 ppm. $^{11}$B NMR (160 MHz, CDCl$_3$) δ: 31.0 ppm. IR (neat, cm$^{-1}$): 3047, 2961, 2930, 2866, 1611, 1460, 1398, 1360, 1323, 1271, 1143, 1107, 1090, 859, 740, 662. Anal. Calcd. for C$_{16}$H$_{25}$BO$_2$: C, 73.86; H, 9.69. Found: C, 74.14; H, 9.64.

Methyl 4-(iso-propyl)benzoate (10a). The general procedure was employed with the following modifications: LiBF$_4$ (93.7 mg, 1 mmol) was weighed out and added to the reaction vial in a nitrogen-filled glove box, 5 mol% NiCl$_2$ and terpyridine employed, 40 h reaction time.
A colorless liquid (163 mg, 91%) was isolated by column chromatography (85:15 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.97 (d, $J = 8.7$ Hz, 2H), 7.29 (d, $J = 8.4$ Hz, 2H), 3.90 (s, 3H), 2.96 (septet, $J = 6.8$ Hz, 1H), 1.27 (d, $J = 6.8$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 167.3, 154.4, 129.9, 127.9, 126.6, 52.1, 34.4, 23.8 ppm.

**Methyl 4-(sec-butyl)benzoate (10b).** The general procedure was employed with the following modifications: 5 mol% NiCl$_2$ and terpyridine employed, 30 h reaction time. A yellow-orange liquid (180 mg, 86%) was isolated by column chromatography (85:15 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.96 (d, $J = 8.3$ Hz, 2H), 7.25 (d, $J = 8.3$, 2H), 3.90 (s, 3H), 2.65 (m, 1H), 1.61 (m, 2H), 1.25 (d, $J = 7.3$ Hz, 3H), 0.81 (t, $J = 7.5$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 167.4, 153.5, 129.8, 127.9, 127.2, 52.1, 41.9, 31.1, 21.7, 12.3 ppm.

$^{((4\text{-iso-Propylphenyl})\text{ethynyl})\text{trimethylsilane}}$ (11a). The general procedure was employed with the following modification: 42 h reaction time. A yellow liquid (197 mg, 91%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.39 (d, $J = 7.8$ Hz, 2H), 7.15 (d, $J = 7.8$ Hz, 2H), 2.89 (septet, $J = 6.9$ Hz, 1H), 1.23 (d, $J = 6.9$ Hz, 6H), 0.24 (s, 9H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 149.7, 132.1, 126.5, 120.6, 105.5, 93.3, 34.2, 23.9, 0.2 ppm.
((4-(sec-Butyl)phenyl)ethynyl)trimethylsilane (11b). The general procedure was employed with the following modification: 36 h reaction time. A yellow liquid (215 mg, 93%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.39 (d, $J = 8.3$ Hz, 2H), 7.10 (d, $J = 8.3$ Hz, 2H), 2.59 (m, 1H), 1.56 (m, 2H), 1.21 (d, $J = 6.8$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H), 0.24 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.5, 132.0, 127.1, 120.5, 105.5, 93.3, 41.8, 31.1, 21.8, 12.3, 0.2 ppm. IR (neat, cm$^{-1}$): 3081, 3028, 2961, 2929, 2875, 2158, 1501, 1460, 1250, 842, 900, 760. Anal. Calcd. for C$_{15}$H$_{22}$Si: C, 78.19; H, 9.62. Found: C, 77.55; H, 9.45.

1-(iso-Propyl)-3,5-dimethylbenzene (12a). The general procedure was employed with the following modification: ether used for extractions during work-up. A colorless liquid (133 mg, 90%) was isolated by column chromatography (97:3 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 6.87 (m, 3H), 2.87 (septet, $J = 6.8$ Hz), 2.33 (s, 6H), 1.27 (d, $J = 6.8$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 150.0, 137.9, 127.6, 124.4, 34.1, 24.2, 21.5 ppm.

1-(sec-Butyl)-3,5-dimethylbenzene (12b). The general procedure was employed with
the following modification: ether used for extractions during work-up. A colorless liquid (149 mg, 92%) was isolated by column chromatography (97:3 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 6.86 (s, 1H), 6.83 (s, 2H), 2.54 (app. sextet, $J = 7.3$ Hz, 1H), 2.33 (s, 6H), 1.61 (m, 2H), 1.24 (d, $J = 6.8$ Hz, 3H), 0.86 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 147.9, 137.7, 127.6, 125.0, 41.7, 31.3, 22.0, 21.5, 12.5 ppm.

5-(iso-Propyl)-1H-indole (13a). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl$_2$ and terpyridine employed, 48 h reaction time. A yellow-brown liquid (120 mg, 75%) was isolated by column chromatography (gradient from 75:25 to 70:30 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.04 (bs, 1H), 7.51 (s, 1H), 7.33 (d, $J = 8.4$ Hz, 1H), 7.18 (t, $J = 2.8$ Hz, 1H), 7.12 (dd, $J = 8.4$ Hz, 1.6 Hz, 1H), 6.52 (m, 1H), 3.03 (septet, $J = 6.9$ Hz, 1H), 1.33 (d, $J = 6.9$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 140.6, 134.5, 128.1, 124.4, 121.4, 117.7, 110.9, 102.5, 34.3, 24.8 ppm.

5-(sec-Butyl)-1H-indole (13b). The general procedure was employed with the following modifications: 2.5 equiv. alkylzinc reagent employed, 5 mol% NiCl$_2$ and terpyridine employed, 48 h reaction time. A yellow liquid (130 mg, 75%) was isolated by column chromatography (gradient from 75:25 to 70:30 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ: 8.04 (bs, 1H), 7.47 (s, 1H), 7.33 (d, $J = 8.3$ Hz, 1H), 7.18 (m, 1H), 7.08 (dd, $J = 8.8$ Hz, 1.5 Hz, 1H), 6.52 (m, 1H), 2.71
(m, 1H), 1.67 (m, 2H), 1.32 (d, $J = 6.8$ Hz, 3H), 0.87 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 139.3, 134.5, 128.0, 124.3, 121.8, 118.6, 110.8, 102.4, 41.9, 31.8, 22.7, 12.6 ppm. IR (neat, cm$^{-1}$): 3415, 2960, 2927, 2872, 1475, 1455, 1414, 1354, 1092, 894, 805, 726. Anal. Calcd. for C$_{12}$H$_{15}$N: C, 83.19; H, 8.73. Found: C, 82.76; H, 8.87.

5-(iso-Propyl)furan-2-carbaldehyde (14a). The general procedure was employed with the following modification: 12 h reaction time. A brown oil (111 mg, 73%) was isolated by column chromatography (gradient from 75:25 to 70:30 Hex:EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.52 (s, 1H), 7.17 (d, $J = 3.3$ Hz, 1H), 6.22 (d, $J = 3.3$ Hz, 1H), 3.04 (septet, $J = 6.9$ Hz, 1H), 1.31 (d, $J = 6.9$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 177.2, 169.1, 151.8, 123.6, 106.8, ppm.

5-(sec-Butyl)furan-2-carbaldehyde (14b). The general procedure was employed with the following modifications: 5 mol% NiCl$_2$ and terpyridine employed, 22 h reaction time. A brown oil (118 mg, 71%) was isolated by column chromatography (gradient from 75:25 to 70:30 Hex:EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$: 9.50 (s, 1H), 7.15 (d, $J = 3.5$ Hz, 1H), 6.20 (d, $J = 3.5$ Hz, 1H), 2.81 (app. sextet, $J = 6.9$ Hz, 1H), 1.66 (m, 2H), 1.26 (d, $J = 7.1$ Hz, 2H), 0.87 (t, $J = 7.4$ Hz, 3H) ppm. $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$: 177.1, 168.2, 151.8, 123.5, 107.6, 35.3, 28.4, 18.3, 11.5 ppm.
3-(iso-Propyl)thiophene (15a). The general procedure was employed with the following modifications: LiBF$_4$ (93.7 mg, 1mmol) was weighed out and added to the reaction vial in a nitrogen-filled glove box, 5 mol% NiCl$_2$ and terpyridine employed, 19 h reaction time, ether used for extractions during work-up. A pale yellow liquid (77 mg, 61%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.25 (dd, $J = 5.0, 2.9$ Hz, 1H), 7.01 (dd, $J = 5.0, 1.3$ Hz, 1H), 6.95 (m, 1H), 2.99 (septet, $J = 6.9$ Hz, 1H), 1.27 (d, $J = 6.9$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 150.0, 127.1, 125.3, 118.3, 29.8, 23.8 ppm.

3-(sec-Butyl)thiophene (15b). The general procedure was employed with the following modifications: 5 mol% NiCl$_2$ and terpyridine employed, 26 h reaction time, ether used for extractions during work-up. A pale yellow liquid (77 mg, 61%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.26 (m, 1H), 6.99 (dd, $J = 5.0, 1.3$ Hz, 1H), 6.95 (m, 1H), 2.78 (app. sextet, $J = 7.0$ Hz, 2H), 1.62 (m, 2H), 1.27 (d, $J = 7.0$ Hz, 3H), 0.88 (t, $J = 7.4$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.7, 127.0, 125.1, 119.0, 37.0, 31.1, 21.4, 12.1 ppm.
**1,3-Dimethyl-5-(4-phenylbutan-2-yl)benzene (16).** The general procedure was employed with the following modifications: 1.3 equiv. of alkylzinc reagent employed, reaction conducted at 80 °C, 15 h reaction time, ether used for extractions during work-up. A colorless liquid (215 mg, 90 %) was isolated by column chromatography (95:5 Hex:Ether). \(^1\)H NMR (500 MHz, CDCl₃) δ: 7.29 (m, 2H), 7.18 (m, 3H), 6.86 (m, 3H), 2.69 (m, 1H), 2.58 (m, 2H), 2.35 (s, 3H), 1.88–2.01 (m, 2H), 1.30 (d, \(J = 6.8\) Hz) ppm. \(^{13}\)C NMR (125 MHz, CDCl₃) δ: 147.5, 142.8, 137.9, 128.5, 128.4, 127.8, 125.7, 125.0, 40.1, 39.6, 34.2, 22.6, 21.5 ppm. IR (neat, cm\(^{-1}\)): 3085, 3062, 2960, 2917, 1605, 1496, 1454, 847, 746, 699. Anal. Calcd. for C\(_{18}\)H\(_{22}\): C, 90.70; H, 9.30. Found: C, 90.86; H, 9.28.

![Chemical structure](image)

**Ethyl 3-(3,5-dimethylphenyl)butanoate (17).** The general procedure was employed with the following modifications: 5 mol% NiCl₂ and terpyridine employed, 15 h reaction time, reaction conducted at 80 °C. \(^1\)H NMR (500 MHz, CDCl₃) δ: 6.84 (app. s, 3H), 4.10 (q, \(J = 7.3\) Hz, 2H), 3.21 (m, 1H), 2.50–2.60 (m, 2H), 2.30 (s, 6H), 1.28 (d, \(J = 6.8\) Hz, 3H), 1.21 (t, \(J = 7.3\) Hz, 3H) ppm. \(^{13}\)C NMR (125 MHz, CDCl₃) δ: 172.6, 145.9, 138.0, 128.1, 124.7, 60.3, 43.2, 36.5, 21.9, 21.5, 14.3 ppm. IR (neat, cm\(^{-1}\)): 2967, 2920, 2872, 1736, 1606, 1462, 1286, 1176, 1159, 1030, 847, 704. Anal. Calcd. for C\(_{14}\)H\(_{20}\)O\(_2\): C, 76.33; H, 9.15. Found: C, 76.53; H, 9.26.
1,3-Dimethyl-5-(octan-3-yl)benzene (18). The general procedure was employed with the following modifications: 5 mol% NiCl$_2$ and terpyridine employed, 15 h reaction time, reaction conducted at 80 °C, ether used for extractions during work-up. A pale yellow liquid (199 mg, 91%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 6.84 (s, 1H), 6.76 (s, 2H), 2.34 (m, 1H), 2.32 (s, 6H), 1.60-1.68 (m, 2H), 1.52-1.58 (m, 2H), 1.18-1.28 (m, 6H), 0.87 (t, $J = 6.8$ Hz, 3H), 0.79 (t, $J = 7.3$ Hz, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 146.3, 137.5, 127.5, 125.7, 47.9, 36.6, 32.2, 29.8, 27.5, 22.7, 21.5, 14.3, 12.4 ppm.
$\text{H}_3\text{C}-\text{CH}_3$
H₃C₆CH₃₆O₇Me
H₃C–CH₃

OMe
3 Nickel-catalyzed Kumada cross-coupling reactions of Tertiary Alkyl Magnesium Halides and Aryl Bromides/Triflates

3.1 Introduction

Traditionally, it has been difficult to use secondary and tertiary alkyl nucleophiles and electrophiles in cross-coupling reactions to form a new C-C bond. Most efforts dedicated in the field over the years have concentrated on developing the reactions forming (sp$^2$)-(sp$^2$) carbon-carbon bonds. Until the last decade, examples involving the use of secondary and tertiary alkyl nucleophilic and electrophilic coupling partners were very scarce. The main concern in their use arises from their tendency to form less branched isomer of the branched nucleophile. As described in the earlier chapter, we began addressing this problem by looking into using secondary alkyl zinc reagents and developed the first general Ni-catalyzed Negishi cross-coupling methodology to form secondary alkyl substituted aryl and heteroaryl rings.$^56$

After gaining some insights into the catalyst system capable of carrying out such a transformation, we then wanted to use this experience to explore the possibility of developing a nickel-catalyzed method to cross-couple aryl electrophiles and tertiary alkyl nucleophiles to form aryl substituted quaternary centers. At the time we began to look into the literature, there was no efficient method for cross-coupling of tertiary alkyl nucleophiles. The few published reports for cross-coupling tertiary alkyl nucleophiles were limited to using specific electrophiles or produced isomeric products exclusively.$^{29, 34, 35}$ In an attempt to build upon our previous work, we explored the possibility of developing a Ni-catalyzed direct cross-coupling reaction of tertiary alkyl nucleophiles and aryl halides to form aryl-substituted quaternary centers.
3.2 Initial Screens

Based upon our prior method development experience, we started our screens with a nickel catalyst to identify the appropriate ligand for this transformation. Since transmetallation of sterically demanding tertiary nucleophiles is difficult, we decided to start with more nucleophilic alkyl magnesium nucleophiles. In the initial screens, reactions of bromobenzene with tertiary butyl magnesium chloride were performed on a 0.5 mmol scale using various phosphorus ligands (eq. 34). For salts of alkyl phosphine ligands, potassium phosphate base was added to aid the deprotonation. Unlike the initial screens for the previous project using secondary alkyl zinc nucleophiles, these screens showed product formation with quite a few different ligands in varying proportions. These ligands along with uncalibrated product yield obtained and the ratio of desired product to its isomer for each are listed in figure 3.1.

\[
\begin{align*}
\text{Cy}_2\text{P} & \quad \text{PCy}_2 & \quad \text{P(t-Bu)}_3 \\
\text{HBF}_4 & \quad \text{HBF}_4 & \quad \text{HBF}_4 \\
Pdt = 15\% (8.1:1) & \quad Pdt = 12\% (1.7:1) & \quad Pdt = 20\% (10.8:1) \\
\text{Ph}_2\text{P} & \quad \text{PPh}_2 & \quad \text{PCy}_3 & \quad (\text{C}_6\text{F}_5)_3\text{P} \\
\text{HBF}_4 & \quad \text{HBF}_4 & \quad & \quad \text{HBF}_4 \\
Pdt = 8\% (\text{n.d.}) & \quad Pdt = 34\% (3.3:1) & \quad Pdt = 36\% (6.7:1)
\end{align*}
\]

Figure 3.1. Phosphorus ligands used for first screen.

For the next screen of phosphorus ligands, the catalyst loading was increased to 10 mol % and reactions were carried out on 0.1 mmol scale using 0.2 mL THF. The ligands used for the
second screening are listed in figure 3.2 along with the observed product yields and the ratio of desired product to its isomer in parenthesis.

![Figure 3.2. Phosphorus ligands used for second screen.](image)

Figure 3.3 shows phosphorus and nitrogen ligands that did not show significant product formation. Although different phosphorus ligand leads were obtained in first two screens, we decided to thoroughly screen the (N-heterocyclic) ligands since such ligands have been implicated in Ni(I)-Ni(III) cycles.

Figure 3.4 shows NHC ligands screened along with the product yields and ratios of desired to isomerized products obtained. Screenings were performed on 0.01 mmol scale with 10 mol % catalyst loading for 2 h.
Figure 3.3. Phosphorus and nitrogen ligands that did not show product formation.

Figure 3.4. N-Heterocyclic carbene ligands used for screening.
As we see from the screening results, a few NHC and phosphorus ligands produced more than 20% product in the very first screen with nickel catalyst. However, cyclohexyl substituted N-heterocyclic carbene ligand with/without phenyl backbone (ligands A and B from figure 3.4) produced the highest yield. Additionally, a low percentage of isomerized product was observed alongside some unreacted starting material. Therefore, these two ligands were considered for further optimization of the method.

3.3 Reaction Optimization

With these results in hand, we then tested different nickel sources to find out if any other nickel catalyst is better than NiCl$_2$•glyme for the reaction. Table 3.1 gives the results obtained from testing the two best ligands i.e. ligands A and B from figure 3.4 for different nickel catalysts. The reactions were performed on 0.2 mmol of bromobenzene using 10 mol % catalyst loading and 2 equiv. tertiary butyl nucleophiles in 1 mL THF at 0 °C for 1 hour (eq. 35). For each trial, uncalibrated amounts of products (branched and linear) formed and their ratio have been given. The reduction product of electrophile, benzene, was not detectable using our standard GC method. As we see from this table, entry 7 where 10 mol % ligand B was used with 10 mol % Ni(II)Cl$_2$, anhyd. produced the best results where the product yield was increased to 72% with the ratio of 10:1. Therefore, for further optimization attempts we used this catalyst system.

![Chemical reaction equation]

\[ \text{Br} \quad \text{0.2 mmol} \quad + \quad \text{t-BuMgCl} \quad 1 \text{M in THF} \quad \text{2 equiv.} \quad \xrightarrow{10 \% \text{Ni} \quad \text{10 \% ligand}} \quad t^\text{-Bu} \quad + \quad i^\text{-Bu} \quad \text{--- (35)} \]
Table 3.1. Different nickel sources tested in reaction optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Nickel source</th>
<th>Unreacted SM</th>
<th>Products</th>
<th>Homocoupling</th>
<th>(Branched/Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>Bis(triphenylphosphine) Ni(II)chloride</td>
<td>92%</td>
<td>8%</td>
<td>-</td>
<td>5/1</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>Bis(triphenylphosphine) Ni(II)chloride</td>
<td>85%</td>
<td>6%</td>
<td>9%</td>
<td>0.4/1</td>
</tr>
<tr>
<td>3</td>
<td>B</td>
<td>Ni(II)Br₂, anhyd.</td>
<td>75%</td>
<td>25%</td>
<td>-</td>
<td>16/1</td>
</tr>
<tr>
<td>4</td>
<td>A</td>
<td>Ni(II)Br₂, anhyd.</td>
<td>89%</td>
<td>11%</td>
<td>-</td>
<td>5/1</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>1,2-Bis(diphenylphosphino) ethane Ni(II)Cl₂</td>
<td>92%</td>
<td>11%</td>
<td>8%</td>
<td>1/1</td>
</tr>
<tr>
<td>6</td>
<td>A</td>
<td>1,2-Bis(diphenylphosphino) ethane Ni(II)Cl₂</td>
<td>85%</td>
<td>9%</td>
<td>6%</td>
<td>0.1/1</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>Ni(II)Cl₂, anhyd.</td>
<td>28%</td>
<td>72%</td>
<td>-</td>
<td>10/1</td>
</tr>
<tr>
<td>8</td>
<td>A</td>
<td>Ni(II)Cl₂, anhyd.</td>
<td>70%</td>
<td>30%</td>
<td>-</td>
<td>1/1</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>Ni(II)acetylacetonate, anhyd.</td>
<td>71%</td>
<td>29%</td>
<td>-</td>
<td>19/1</td>
</tr>
<tr>
<td>10</td>
<td>A</td>
<td>Ni(II)acetylacetonate, anhyd.</td>
<td>65%</td>
<td>35%</td>
<td>-</td>
<td>7/1</td>
</tr>
<tr>
<td>11</td>
<td>B</td>
<td>Ni(II)I₂</td>
<td>100%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
While we were developing the cross-coupling method to couple secondary alkyl zinc nucleophiles and aryl iodides using nickel catalyst, we had observed the dependence of such a system on salt additives. After carrying out a thorough study, LiBF₄ was found to improve the secondary alkyl Negishi reaction by reducing the isomerization and reduction events. Based on this experience we decided to first test the reaction for its dependence of salt additives. However, unlike the previous experience, this reaction does not depend on the presence of salt additives.
Table 3.2. Reaction conditions tested for further reaction optimization.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard reaction conditions in eq. 36</th>
<th>Unreacted SM</th>
<th>Products</th>
<th>Homocoupling</th>
<th>(Branched/Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>No change</td>
<td>65%</td>
<td>34%</td>
<td>1%</td>
<td>13/1</td>
</tr>
<tr>
<td>2</td>
<td>NiCl$_2$, anhyd. 1 mol %</td>
<td>67%</td>
<td>34%</td>
<td>-</td>
<td>6/1</td>
</tr>
<tr>
<td>3</td>
<td>NiCl$_2$, anhyd. 5 mol %</td>
<td>47%</td>
<td>51%</td>
<td>2%</td>
<td>9/1</td>
</tr>
<tr>
<td>4</td>
<td>NiCl$_2$, anhyd. 10 mol %, 1.5 equiv. nucleophile</td>
<td>67%</td>
<td>31%</td>
<td>2%</td>
<td>10/1</td>
</tr>
<tr>
<td>5</td>
<td>10 mol % NiCl$_2$, anhyd. after 0.5 hrs, total time: 1 h.</td>
<td>52%</td>
<td>46%</td>
<td>2%</td>
<td>11/1</td>
</tr>
<tr>
<td>6</td>
<td>10 mol % NiCl$_2$, anhyd. after 0.5 h., additional 10 mol % NiCl$_2$, anhyd. after 1 h., total time: 1.5 h.</td>
<td>50%</td>
<td>47%</td>
<td>2%</td>
<td>11/1</td>
</tr>
<tr>
<td>7</td>
<td>Bis(triphenylphosphine) Ni(II)Cl$_2$ 10 mol %</td>
<td>83%</td>
<td>11%</td>
<td>6%</td>
<td>2/1</td>
</tr>
<tr>
<td>8</td>
<td>Ni(II)Br$_2$, anhyd. 10 mol %</td>
<td>65%</td>
<td>33%</td>
<td>2%</td>
<td>14/1</td>
</tr>
<tr>
<td>9</td>
<td>1,2-(Bisdiphenylphosphino) ethane Ni(II)Cl$_2$ 10 mol %</td>
<td>88%</td>
<td>8%</td>
<td>5%</td>
<td>0.5/1</td>
</tr>
<tr>
<td>10</td>
<td>Ni(II) acetylacetonate, anhyd. 10 mol %</td>
<td>76%</td>
<td>23%</td>
<td>1%</td>
<td>10/1</td>
</tr>
<tr>
<td>11</td>
<td>Ni(II)I$_2$ 10 mol %</td>
<td>100%</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Ni(II)(OTf)$_2$ 10 mol %</td>
<td>96%</td>
<td>4%</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Other conditions tested by changing reaction parameters and the catalyst did not improve the yield further (Table 3.2). In next set of trials, the bromobenzene electrophile was replaced by 4-bromoanisole. With 4-bromoanisole, all the possible side products arising from β-hydride elimination, reduction and homocoupling were detectable using gas chromatography. Therefore, it is easier to study the behavior of reaction with changing parameters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard reaction conditions in eq. 36</th>
<th>Unreacted SM</th>
<th>Products</th>
<th>Homocoupling</th>
<th>(Branched /Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Pd(II)Cl₂ 10 mol %</td>
<td>89%</td>
<td>7%</td>
<td>4%</td>
<td>-</td>
</tr>
<tr>
<td>14</td>
<td>Pd(II)OAc₂ 10 mol %</td>
<td>83%</td>
<td>7%</td>
<td>11%</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>Pd(II)(dba)₂ 10 mol %</td>
<td>81%</td>
<td>0%</td>
<td>19%</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td>CuCl₂, dihydrate 10 mol %</td>
<td>66%</td>
<td>33%</td>
<td>1%</td>
<td>6/1</td>
</tr>
<tr>
<td>17</td>
<td>CuI₂ 10 mol %</td>
<td>98%</td>
<td>2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>18</td>
<td>CuCN 10 mol %</td>
<td>100%</td>
<td>0%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>4-Bromoanisole electrophile used</td>
<td>57%</td>
<td>31%</td>
<td>-</td>
<td>6/1</td>
</tr>
</tbody>
</table>

![Diagram](image_url)
Table 3.3. Different reaction conditions tested to improve reaction yield and isomerization ratio.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard reaction conditions in eqn. 37</th>
<th>Unreacted SM</th>
<th>Products</th>
<th>Reduction</th>
<th>(Branched/Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-20 °C, 25 min</td>
<td>91%</td>
<td>7%</td>
<td>3%</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>-20 °C, 80 min</td>
<td>40%</td>
<td>40%</td>
<td>20%</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>Electrophile added at rt, then stirred at -5 °C</td>
<td>&lt;1%</td>
<td>83%</td>
<td>16%</td>
<td>25/1</td>
</tr>
<tr>
<td>4</td>
<td>-5 °C</td>
<td>-</td>
<td>89%</td>
<td>11%</td>
<td>33/1</td>
</tr>
<tr>
<td>5</td>
<td>At -5 °C, nucleophile, then electrophile, ligand and NiCl₂</td>
<td>32%</td>
<td>51%</td>
<td>17%</td>
<td>n.d.</td>
</tr>
<tr>
<td>6</td>
<td>With 3 uL H₂O</td>
<td>16%</td>
<td>70%</td>
<td>15%</td>
<td>20/1</td>
</tr>
<tr>
<td>7</td>
<td>With 0.2 equiv. NaOt-Bu</td>
<td>51%</td>
<td>32%</td>
<td>17%</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>At -4 °C, 100 uL THF</td>
<td>2%</td>
<td>77%</td>
<td>21%</td>
<td>22/1</td>
</tr>
<tr>
<td>9</td>
<td>At -4 °C, 100 uL THF, 1 uL H₂O</td>
<td>43%</td>
<td>40%</td>
<td>17%</td>
<td>27/1</td>
</tr>
<tr>
<td>10</td>
<td>At -4 °C, 100 uL THF, 0.5 uL H₂O</td>
<td>6%</td>
<td>75%</td>
<td>19%</td>
<td>23/1</td>
</tr>
<tr>
<td>11</td>
<td>At -4 °C, 100 uL THF, no ligand</td>
<td>16%</td>
<td>8%</td>
<td>66%</td>
<td>2/1</td>
</tr>
<tr>
<td>12</td>
<td>no change</td>
<td>2%</td>
<td>83%</td>
<td>13%</td>
<td>36/1</td>
</tr>
</tbody>
</table>
As we see from table 3.3, with multiple changes in conditions, we were able to obtain the product yield of 83% with 33/1 ratio of desired product to its isomer (Entry 4). However, when the same reaction was repeated using a fresh sample of NiCl₂, anhydrous from glove box, the reaction yield dropped drastically. Also, there was visual difference between the colors of both nickel samples. While the sample that was left outside of the glove box inside the desiccator for extended period of time and used for reaction optimization was orange, fresh NiCl₂ from glove box was pale yellow. Due to these observed differences in yield we thought that the water of hydration associated with the nickel left outside the glove box had something to do with the optimal reaction condition.

To investigate further, we prepared samples of NiCl₂ with different extents of hydration by heating nickel chloride hexahydrate (green in color) under vacuum and sampling out the catalyst after certain time intervals. Difference in the mass would then give the hydration associated with nickel. As we decreased the water content, the color changed from green to different shades of yellow to orange. These samples were then stored in dry conditions and immediately tested in reaction. The reactions were performed on 0.2 mmol scale using conditions given in eqn. 38 and yields and ratios obtained from samples having different hydrations of nickel are tabulated in table 3.4. These reactions were performed using 4-bromoanisole, as the reduction product of electrophile (i.e. anisole) is detectable on GC. No homocoupling product was observed on GC.
Table 3.4. Results obtained from reactions using nickel chloride with different hydrations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard reaction conditions in eq. 38</th>
<th>Unreacted SM</th>
<th>Products</th>
<th>Reduction (Branched/Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{4.39}</td>
<td>30%</td>
<td>52%</td>
<td>18% 53/1</td>
</tr>
<tr>
<td>2</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{2.13}</td>
<td>8%</td>
<td>83%</td>
<td>9% 58/1</td>
</tr>
<tr>
<td>3</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{2.01}</td>
<td>1%</td>
<td>85%</td>
<td>14% 64/1</td>
</tr>
<tr>
<td>4</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{1.84}</td>
<td>6%</td>
<td>85%</td>
<td>9% 59/1</td>
</tr>
<tr>
<td>5</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{1.75}</td>
<td>1%</td>
<td>87%</td>
<td>10% 69/1</td>
</tr>
<tr>
<td>6</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{1.49}</td>
<td>-</td>
<td>89%</td>
<td>11% 54/1</td>
</tr>
<tr>
<td>7</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{1.32}</td>
<td>-</td>
<td>86%</td>
<td>14% 49/1</td>
</tr>
<tr>
<td>8</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{1.21}</td>
<td>-</td>
<td>87%</td>
<td>13% 39/1</td>
</tr>
<tr>
<td>9</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{0.67}</td>
<td>-</td>
<td>81%</td>
<td>19% 34/1</td>
</tr>
<tr>
<td>10</td>
<td>NiCl₂((\text{H}<em>2\text{O}))</em>{0.19}</td>
<td>48%</td>
<td>13%</td>
<td>39% 31/1</td>
</tr>
</tbody>
</table>

From this study, we observed that for the reaction to produce a high yield of desired product, it is ideal to used nickel chloride with 1.2 to 1.8 water molecules per Ni. NiCl₂ with a lower water content resulted in incomplete conversion and extensive reduction product. Therefore, we prepared a bulk sample of NiCl₂(\(\text{H}_2\text{O}\))_{1.5} which was used for all large scale reactions. Final optimizations carried out to maximize the yield and ratios of desired product to
isomerized product are listed in table 3.5. Further attempts to reduce the catalyst loading were not successful.

![Chemical reaction diagram](image)

**Table 3.5.** Final Reaction optimization using NiCl₂(H₂O)₁.₅ as nickel source.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard reaction conditions in eq. 39</th>
<th>Yield</th>
<th>(Branched/Linear)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>90%</td>
<td>40/1</td>
</tr>
<tr>
<td>2</td>
<td>0 °C</td>
<td>84%</td>
<td>25/1</td>
</tr>
<tr>
<td>3</td>
<td>0 °C, 5 % cat., 5 % ligand</td>
<td>77%</td>
<td>24/1</td>
</tr>
<tr>
<td>4</td>
<td>5 % cat., 5 % ligand</td>
<td>68%</td>
<td>26/1</td>
</tr>
<tr>
<td>5</td>
<td>4 % cat., 5 % ligand</td>
<td>72%</td>
<td>23/1</td>
</tr>
<tr>
<td>6</td>
<td>8.5 % cat., 10 % ligand</td>
<td>86%</td>
<td>40/1</td>
</tr>
<tr>
<td>7</td>
<td>10% Ni(COD)₂</td>
<td>&lt;5%</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>10% NiBr₂</td>
<td>17%</td>
<td>18/1</td>
</tr>
<tr>
<td>9</td>
<td>10% NiBr₂•H₂O</td>
<td>83%</td>
<td>38/1</td>
</tr>
<tr>
<td>10</td>
<td>NiCl₂, NaOt-Bu</td>
<td>32%</td>
<td>35/1</td>
</tr>
<tr>
<td>11</td>
<td>No ligand</td>
<td>17%</td>
<td>3/1</td>
</tr>
</tbody>
</table>
3.4 Substrate Scope

As we see from scheme 3.1, a variety of functional groups on the electrophile are well tolerated in this cross-coupling reaction. Deactivated electron-rich substrates like 4-bromoanisole (24) and 4-bromo-N,N-dimethyl aniline (28) gave coupling yields of 76% with 36:1 ratio. Other substituents such as 4-ester (21), 4-trifluoromethyl (23), 3-methoxy (22), 3-trifluoromethoxy (27), and 3-silyl protected alcohol (30) were well tolerated and provided the cross-coupling product in very good yields. 4-Chlorobromobenzene (25) underwent coupling with complete selectivity for the bromide, thus showing that quaternary centers bearing chloroarenes can be produced for use in subsequent cross-coupling reactions to form more complex products. 2-Bromonaphthalene (19), 3,5-dimetyl (34), and acetal (26 & 31) and pyrrole substitution (32) produced coupling products in good yield and ratios. Although this method has excellent substrate scope, it also has its limitations. With heterocyclic substrates, the method is more sensitive and in some cases the reactions did not go to completion. As we see from the table, the yields and ratios for sulphur (29) and nitrogen (33) heterocyclic substrates are significantly lower than all other cases. Also for (29) only 90% conversion was obtained by proton NMR after 24 h. For 3-bromothiophene only 64% calibrated GC yield was obtained after 24 h. Also, since the tertiary alkyl nucleophile is significantly bulky, ortho-substitution is not as well tolerated. Nevertheless, we were able to get a 55% yield when 2,4-dimethyl bromobenzene was employed, although a lower ratio of retention to isomerization (10:1) resulted. Also 6-methoxy-1-bromonaphthalene (36) was coupled in excellent yield and ratio despite the location of the bromide at sterically demanding position. Most of the cross-coupling reactions took place with over 30:1 ratio of desired to undesired isomer of the product. Therefore, product isomerization was not one of the major problems observed. Reduction of electrophile however reduced the
product yield significantly in some cases producing products that were difficult to separate by column chromatography.

**Scheme 3.1.** Ni-catalyzed cross-coupling reactions of t-BuMgCl with aryl and heteroaryl bromides.

In order to determine if tertiary alkyl nucleophiles other than t-butyl magnesium chloride can be employed in the Ni-catalyzed couplings, we employed more substituted nucleophiles in the reaction. As shown in scheme 3.2, a cyclic nucleophile underwent cross-coupling in good yield though isomerization increased. One alpha-branch (37) is well tolerated in the reaction. As
the branching and the steric bulk around the nucleophile increases, more β-hydride elimination/reinsertion occurs affecting the ratio of desired to undesired isomer drastically. When one more alpha branch was present on nucleophilic component around 15% of isomerized product was concurrently formed (39).

Scheme 3.2. Ni-catalyzed cross-coupling reactions of aryl bromides with different tertiary alkylmagnesium halides.

We then investigated whether electrophiles other than bromides could be employed in these cross-coupling reactions. As given in scheme 3.3 we see that non-deactivated 4-phenyl substituted (42), 3-anisyl (44), and non-hindered β-napthalene (40) triflates performed well in the reaction. However, for the sterically hindered alpha-napthalene substrate (41) and deactivated 4-anisyl triflate (43), more isomerized product was formed and the yield was drastically affected as well. Overall, it appears that the triflates are more sensitive to the steric and electronics of the electrophilic substrate than the bromides.
To further extend the utility of the reaction we applied the same optimized reaction conditions to vinyl chlorides and bromides. Very good product yields were produced in excellent ratios without altering the reaction conditions (Scheme 3.4). Thus, the same optimized conditions were applied to the bromides, triflates, and vinyl electrophiles.

### Scheme 3.3. Ni-catalyzed cross-coupling reactions of aryl triflates with t-BuMgCl.

![Scheme 3.3](image)

### Scheme 3.4. Ni-catalyzed cross-coupling reactions of vinyl electrophiles with t-BuMgCl.

![Scheme 3.4](image)

### 3.5 Conclusions

In conclusion, we have developed the first general method to cross-couple tertiary alkyl magnesium halides and aryl bromides using nickel chloride and cyclohexyl-NHC ligand. This method circumvents the undesired β-hydride elimination reaction and produces products in >50:1 ratios of the desired cross-coupled product to its isomer. The process is very general and tolerates a variety of functional groups on the electrophilic partner that are compatible with Grignard’s reagent. This process tolerates the presence of one α-branching on nucleophilic component. However, as the α-branching increases, the ratio of product to its isomer goes down.
The utility of the method has been further increased by applying the cross-coupling conditions to the aryl triflates. Triflates are more sensitive to the coupling conditions than the bromides where product yield and ratio decreases as the substrate becomes more challenging sterically or electronically. Additionally, the vinyl chlorides and bromides electrophiles also participate in the cross-coupling reaction producing high product yields and ratios.

3.6 Supporting Information

General Reagent Information

Toluene and THF (unstabilized) were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 h. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene). All reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using silica gel (ultra-pure grade).

General Analytical Information

All compounds were characterized by $^1$H NMR, $^{11}$B NMR, and $^{13}$C NMR spectroscopy. Copies of the $^1$H, $^{11}$B, and $^{13}$C spectra can be found at the end of the supporting information. Nuclear magnetic resonance spectra were recorded on a Varian 500 MHz instrument. All $^1$H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm), dimethyl sulfoxide (2.50 ppm) or acetonitrile (1.94 ppm). All $^{13}$C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm), dimethyl sulfoxide (39.52 ppm) or acetonitrile (118.26 ppm) and were obtained with $^1$H
decoupling. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

*General Procedural Information*

$t$-BuMgCl (1M in THF) was purchased from Sigma-Aldrich. All NHC ligands were purchased from Strem. All nickel compounds with the exception of NiCl$_2$(H$_2$O)$_6$ (Fisher Scientific) were purchased from Strem. Grignard reagents were prepared from their corresponding $t$-alkyl chlorides or bromides using a literature procedure.$^{57}$ Molarities of Grignard reagents (typically between 0.8 M and 1.0 M) were determined using iodine titration.$^{45}$ Reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using Silicycle silica gel (ultra-pure grade).

*General procedure for the preparation of NiCl$_2$•(H$_2$O)$_n$*

NiCl$_2$•(H$_2$O)$_6$ (2 g, 8.4 mmol) was finely ground using a mortar and pestle and transferred to a 50 mL round bottom flask containing a stirbar. The flask was place under high vacuum (0.5-1.0 torr) and immersed into a 100 °C oil bath for 20 minutes. The contents of the flasks were vigorously mixed to ensure homogenous heating. The color of the nickel complex changed from bright green to yellow to yellow-orange as water was removed. The flask was removed from the oil bath and allowed to cool. Loss of water was determined by measuring mass lost during the heating process. In general, after 20 min, ca. 2 equiv. water remained for each equivalent of NiCl$_2$. After loss of 4 equivalents of water, dehydration becomes slower. After having determined the extent of remaining hydration, the temperature of the oil bath was
increased to 120 °C. The flask was re-immersed in the heated oil bath for 5-10 min to generate NiCl$_2$•(H$_2$O)$_n$ where $n = 1.4 – 1.7$. NiCl$_2$ samples with different extents of hydration were achieved by sampling the heated reaction flask more frequently. In order to thoroughly dehydrate the NiCl$_2$, the temperature of the oil bath was increased to 150 °C and the flask was heated for at least 2 h. In its anhydrous state, NiCl$_2$ is orange.

*General procedure for the cross-coupling of aryl/vinyl halide/triflates and tertiary alkylmagnesium halides:*

Because we are interested in developing methods of high operational simplicity as well as generality, we performed each of the reactions on the benchtop, using readily available disposable vials with screw-top septa. NiCl$_2$•(H$_2$O)$_{1.54}$ (16 mg, 0.1 mmol) and NHC ligand B (32 mg, 0.1 mmol) were weighed out on the benchtop in an oven-dried 10 mL screw top test tube with stir bar. The aryl bromide/triflate (1 mmol) was then added to the vial. The vial was sealed using a screw cap lined with a teflon septum. The reaction vial was evacuated and backfilled three times with argon using a needle attached to a vacuum manifold, and cooled to –10 °C in NaCl/ice slurry prior to the addition of the alkylmagnesium reagent. If the aryl bromide/triflate were a liquid, it was added via microsyringe after having backfilled the vial with argon. The tertiary alkylmagnesium halide (2.0 mmol) was then added via syringe under a positive pressure of argon. The vial was sealed with electrical tape and the reaction mixture was stirred for 90 minutes on the benchtop at –10 °C with no additional argon pressure. The reaction mixture was quenched through the addition of ice chips, then poured into a separatory funnel containing saturated aqueous NH$_4$Cl (ca. 10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The crude product was purified
by column chromatography. Extent of isomerization can be easily determined via $^1$H NMR spectroscopy by comparison of the integral of the singlet from the $t$-butyl group (1.3-1.4 ppm, 9H) to the integral of the doublet from the benzylic protons of the iso-buty1 group (2.4-2.5 ppm, 2H). The doublet from the methyls of the iso-buty1 group could additionally be used (ca. 0.8 ppm, 6H).

Spectral Data

**2-(tert-Butyl)naphthalene (19).** The general procedure was employed. A oily, white solid was isolated by column chromatography (96:4 Hex:Ether). This product consisted of 142 mg desired product (77% yield) and 15 mg reduction product. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.77-7.84 (m, 4H), 7.57 (dd, $J = 8.4, 1.9$ Hz, 1H), 7.39-7.47 (m, 2H), 1.43 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 133.6, 131.9, 128.2, 127.9, 127.6, 127.5, 126.0, 125.4, 125.0, 123.1, 35.0, 31.5 ppm.

**1,4-di-tert-Butylbenzene (20).** The general procedure was employed. A oily, white solid (147 mg, 77%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.34 (s, 4H), 1.34 (s, 18H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 148.2, 125.1, 34.5, 31.6 ppm.
Ethyl 4-(tert-butyl)benzoate (21). The general procedure was employed. A yellow liquid (167 mg, 81%) was isolated by column chromatography (80:20 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.98 (d, $J$ = 8.6 Hz, 2H), 7.45 (d, $J$ = 8.6 Hz, 2H), 4.36 (q, $J$ = 7.2 Hz, 2H), 1.38 (t, $J$ = 7.2 Hz, 3H), 1.34 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 166.7, 156.5, 129.5, 127.9, 125.4, 60.8, 35.1, 31.2, 14.5 ppm.

1-(tert-Butyl)-3-methoxybenzene (22). The general procedure was employed. A colorless liquid (138 mg, 84%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.23 (t, $J$ = 7.9 Hz, 1H), 6.99 (ddd, $J$ = 7.8 Hz, 1.8 Hz, 0.9 Hz, 1H), 6.95 (m, 1H), 6.73 (ddd, $J$ = 8.1 Hz, 2.6 Hz, 0.9 Hz, 1H), 3.81 (s, 3H), 1.31 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 159.6, 153.1, 129.1, 118.0, 112.2, 110.1, 55.2, 34.9, 31.5 ppm.

2-(3-(tert-Butyl)phenyl)-1,3-dioxolane (31). The general procedure was employed. The general procedure was employed. A colorless liquid (165 mg, 80%) was isolated by column chromatography (95:5 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.49 (m, 1H), 7.40 (dt, $J$ = 7.2 Hz, 1.6 Hz, 1H), 7.31 (m, 2H), 5.81 (s, 1H), 4.10 (m, 4H), 1.33 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 151.4, 137.5, 128.3, 126.5, 123.7, 123.5, 104.3, 65.5, 34.9, 31.5 ppm. HRMS (ESI$^+$): (M+H)$^+$: 207.1380 (calc.); 207.1382 (found); diff (ppm) = 1.31.
1-(tert-Butyl)-4-methoxybenzene (24). The general procedure was employed. A colorless liquid (126 mg, 77%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.34 (d, $J = 8.9$ Hz, 2H), 6.88 (d, $J = 8.9$ Hz, 2H), 3.82 (s, 3H), 1.34 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 157.5, 143.5, 126.4, 113.5, 55.4, 34.2, 31.7 ppm.

1-(tert-Butyl)-3-(trifluoromethoxy)benzene (27). The general procedure was employed. A colorless liquid (153 mg, 70%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.32 (m, 2H), 7.22 (s, 1H), 7.05 (m, 1H), 1.33 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 153.9, 149.5, 129.4, 123.9, 118.4, 118.0, 35.1, 33.4 ppm. $^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$: -58.2 ppm. HRMS (APPI$^+$): M$^+$: 218.0918 (calc.); 218.0915 (found); diff (ppm) = -1.49.

1-(tert-Butyl)-4-chlorobenzene (25). The general procedure was employed. A pale yellow liquid (142 mg, 84%) was isolated by column chromatography (96:4 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.33 (d, $J = 8.8$ Hz, 2H), 7.27 (d, $J = 8.8$ Hz, 2H), 1.32 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 149.8, 131.3, 128.3, 126.9, 34.7, 31.5 ppm.
5-(tert-Butyl)benzo[d][1,3]dioxole (26). The general procedure was employed. A purple liquid was isolated by column chromatography (90:10 Hex:EtOAc). This liquid consisted of 130 mg desired product (73% yield) and 17 mg reduction product. $^1$H NMR (500 MHz, CDCl$_3$) δ: 6.90 (d, $J = 2.0$ Hz, 1H), 6.82-6.84 (m, 2H), 5.92 (s, 2H), 1.28 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 147.6, 145.5, 145.3, 118.0, 107.8, 106.5, 100.9, 34.8, 31.8 ppm.

4-(tert-Butyl)-N,N-dimethylaniline (28). The general procedure was employed. A pale yellow liquid was isolated by column chromatography (90:10 Hex:EtOAc). This liquid consisted of 135 mg desired product (76% yield) and 17 mg reduction product. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.39 (d, $J = 8.8$ Hz, 2H), 6.83 (d, $J = 8.8$ Hz, 2H), 3.02 (s, 6H), 1.42 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.7, 139.5, 126.0, 112.8, 41.2, 33.9, 31.7 ppm.

1-(tert-Butyl)-4-(trifluoromethyl)benzene (23). The general procedure was employed. A colorless liquid (164 mg, 81%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.60 (d, $J = 8.3$ Hz, 2H), 7.54 (d, $J = 8.3$ Hz, 2H), 1.39 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 155.4, 128.1 (q, $J = 32$ Hz), 125.9, 125.2 (q, $J = 4$ Hz), 124.7 (q, $J = 270$ Hz), 35.2, 31.3 ppm.
**tert-Butyl(3-(tert-butyl)phenoxy)dimethylsilane (30).** The general procedure was employed. A colorless liquid was isolated by column chromatography (90:10 Hex:EtOAc). This liquid consisted of 177 mg desired product (67% yield) and 29 mg reduction product. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.20 (t, $J = 7.9$ Hz, 1H), 7.03 (ddd, $J = 7.8$ Hz, 1.9 Hz, 1.0 Hz, 1H), 6.93 (app. t, $J = 2.1$ Hz, 1H), 6.71 (ddd, $J = 8.0$ Hz, 2.4 Hz, 1.0 Hz, 1H), 1.36 (s, 9H), 1.06 (s, 9H), 0.27 (s, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 155.6, 153.0, 129.0, 120.3, 118.4, 117.6, 117.2, 34.8, 31.6, 26.0, 18.5, 4.1 ppm.

![tert-Butyl(3-(tert-butyl)phenoxy)dimethylsilane](image)

**1-(4-(tert-Butyl)phenyl)-1H-pyrrole (32).** The general procedure was employed. A pale yellow solid was isolated by column chromatography (98:2 Hex:Ether). Mp: 55-58 °C. This solid consisted of 149 mg desired product (75% yield) and 29 mg reduction product. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.46 (d, $J = 8.6$ Hz, 2H), 7.34 (d, $J = 8.6$ Hz, 2H), 7.09 (t, $J = 7.1$ Hz, 2H), 6.36 (t, $J = 7.1$ Hz, 2H), 1.37 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 148.9, 129.7, 126.6, 120.5, 119.6, 110.2, 34.7, 31.6 ppm.

![1-(4-(tert-Butyl)phenyl)-1H-pyrrole](image)

**1-(tert-Butyl)-3,5-dimethylbenzene (34).** The general procedure was employed with the following modification: the reaction mixture was allowed to warm to rt and stir overnight (10h). A colorless liquid (138 mg, 85%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.21 (s, 2H), 7.02 (s, 1H), 2.52 (s, 6H), 1.51 (s, 9H) ppm. $^{13}$C NMR
(125 MHz, CDCl₃) δ: 151.3, 137.5, 127.3, 123.3, 34.6, 31.6, 21.7 ppm.

1-(tert-Butyl)-2,4-dimethylbenzene (35). The general procedure was employed. A colorless liquid (89 mg, 55%) was isolated by column chromatography (98:2 Hex:Ether). ¹H NMR (500 MHz, CDCl₃) δ: 7.28 (d, J = 7.7 Hz, 1H), 6.96 (m, 2H), 2.53 (s, 3H), 2.29 (s, 3H), 1.41 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 145.2, 136.3, 135.4, 133.8, 126.5, 126.2, 42.4, 35.7, 31.2 ppm.

1-(tert-Butyl)-6-methoxynaphthalene (36). The general procedure was employed. A white solid was isolated by column chromatography (96:4 Hex:Ether). Mp: 63-65 ºC. This white solid consisted of 184 mg desired product (86% yield) and 13 mg reduction product. ¹H NMR (500 MHz, CDCl₃) δ: 7.70 (app. t, J = 8.0 Hz, 3H), 7.54 (dd, J = 8.6, 2.0 Hz, 1H), 7.11-7.14 (m, 2H), 3.92 (s, 3H), 1.41 (s, 9H) ppm. ¹³C NMR (125 MHz, CDCl₃) δ: 157.5, 146.5, 132.8, 129.6, 129.0, 126.7, 125.5, 122.9, 118.7, 101.6, 55.5, 34.8, 31.5 ppm. HRMS (ESI⁺): (M+H)⁺: 215.1430 (calc.); 215.1432 (found); diff (ppm) = 0.70.

1-Chloro-4-(tert-pentyl)benzene (37). The general procedure was employed. A pale yellow liquid (133 mg, 73%) was isolated by column chromatography (99:1 Hex:Ether). ¹H
NMR (500 MHz, CDCl$_3$) δ: 7.29 (app. s, 4H), 1.66 (q, $J = 7.3$, 2H), 1.30 (s, 6H), 0.71 (t, $J = 7.3$, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 167.4, 153.5, 129.8, 127.9, 127.2, 52.1, 41.9, 31.1, 21.7, 12.3 ppm.

**Ethyl 4-(1-methylcyclohexyl)benzoate (38).** The general procedure was employed. A colorless liquid (187 mg, 76%) was isolated by column chromatography (90:10 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.99 (d, $J = 8.7$ Hz, 2H), 7.44 (d, $J = 8.7$ Hz, 2H), 4.37 (q, $J = 7.1$, 2H), 2.02 (m, 2H), 1.55-1.61 (m, 4H), 1.39-1.50 (m, 4H), 1.38 (t, $J = 7.1$, 3H), 1.19 (s, 3H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 166.9, 155.6, 129.7, 127.7, 126.1, 60.9, 38.6, 37.5, 33.3, 26.5, 22.8, 14.6 ppm. HRMS (ESI$^+$): (M+H)$^+$: 247.1693 (calc.); 247.1696 (found); diff (ppm) = 1.22.

**2-(3-(3-Methylpentan-3-yl)phenyl)-1,3-dioxolane (39).** The general procedure was employed with the following modification: the reaction mixture was allowed to warm to rt and stirred overnight (10h). An oily, colorless solid (121 mg, 51%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.39 (s, 1H), 7.28-7.34 (m, 3H), 5.81 (s, 3H), 4.13-4.17 (m, 2H), 4.02-4.06 (m, 2H), 1.72-1.80 (m, 2H), 1.54-1.62 (m, 2H), 1.27 (s, 3H), 0.68 (t, $J = 7.4$ Hz, 6H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 148.0, 137.4, 128.1, 127.7, 125.0, 123.5, 104.4, 65.4, 41.5, 38.6, 35.3, 23.0, 8.9 ppm. HRMS (ESI$^+$): (M+H)$^+$: 235.1693 (calc.); 235.1691 (found); diff (ppm) = -0.65.
(E)-1-(3,3-Dimethylbut-1-en-1-yl)-4-methoxybenzene (Scheme 3.4). The general procedure was employed. A white solid (Cl: 158 mg, 83%; Br: 133 mg, 70%) was isolated by column chromatography (98:2 Hex:Ether). Mp: 48-50 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.30 (d, $J = 8.7$ Hz, 2H), 6.84 (d, $J = 8.7$ Hz, 2H), 6.25 (d, $J = 16$ Hz, 1H), 6.12 (d, $J = 16$ Hz, 1H), 3.80 (s, 3H), 1.11 (s, 9H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 158.8, 140.0, 131.1, 127.3, 124.0, 114.1, 55.5, 33.4, 29.9 ppm.
F₃CO-t-Bu

isomerization

isomerization
$^{19}$F NMR
isomerization

reduction

MeO
w/ 8% reduction product

isomerization
MeO-t-Bu w/ 8% reduction product
EtO₂C

Me

isomerization
isomerization
peaks from major isomer indicated
4 Palladium-Catalyzed Borylation of Primary Alkyl Halides Using Bis(pinacolato)diboron as the Boron Source

4.1 Introduction

After gaining some insights into the development of novel methods for the construction of new carbon-carbon bonds via metal-catalyzed cross-coupling reactions, we then decided to look into developing a method for monoborylation of alkyl halides. In earlier years, we had addressed the challenge of averting β-hydride elimination reaction associated with the use of secondary and tertiary alkyl nucleophiles. We reported a nickel-catalyzed Negishi reaction for the cross-coupling of aryl iodides and non-cyclic secondary alkylzinc halides. Based on this experience, we subsequently developed the nickel-catalyzed Kumada reaction to cross-couple aryl and hetero aryl bromides with tertiary alkyl halides. Both of these methods have been able to successfully overcome the problem of β-hydride elimination/re-insertion that leads to the formation of the inseparable isomers of the desired product.

However, since the magnesium and zinc nucleophiles used in these projects are labile, expansion of these methods to the use of their optically active variant using chiral nucleophiles is very difficult. Boronic esters on the other hand are stable, easy to handle and store, and are known to exist as a variety of boronic ester derivatives. Their high covalent bond character makes them configurationally stable and imparts air and moisture stability. They are compatible with a wide range of functional groups and serve as important synthetic intermediates for industrial use. Their increasing application in the field of organic and organometallic reactions over past few years has made them important to the scientific community. The Suzuki-
Miyaura reaction has now become a versatile and widely used cross-coupling reaction.\textsuperscript{1, 60} Aryl and vinyl boronic esters have been used as nucleophiles in metal-catalyzed Suzuki cross-coupling reactions for many years. More recently, alkyl boronic esters have also been employed but their use has been limited to only a few methods.\textsuperscript{61} The expansion of their use in cross-coupling methodologies by taking advantage of various attractive features they offer would be a value addition to the coupling reactions.

Boronic esters have classically been prepared from the corresponding lithium and magnesium reagents. Therefore, the scope of their use was limited by incompatibilities associated with use of lithium and magnesium bases.\textsuperscript{62} Over the past few years, significant progress has been made in this field, and various other methods for the preparation of boronic esters have been developed. Some of the important examples include Ir- and Rh-catalyzed hydroboration of alkenes,\textsuperscript{63} Rh-, Ir-, Re-, Pd-, and Ni-catalyzed C-H activation/borylation,\textsuperscript{64} and Pt-, Cu-, Rh-, Ni-, and Pd-catalyzed $\beta$-borylation of $\alpha,\beta$-unsaturated compounds.\textsuperscript{65}

Very recently, a copper-catalyzed method for the monoborylation of primary and secondary alkyl halides has been reported.\textsuperscript{66} In this report, the boronic ester products have also been shown to be used in the subsequent Suzuki reaction to form the cross-coupled product. However, since this reaction proceeds \textit{via} a radical pathway, its use for the synthesis of optically active drug products is limited. Biologically active molecules are chiral in nature and are often required to be prepared with high enantiopurity. In such cases, use of copper-catalyzed borylation method for the preparation of optically active boronic esters will result in loss of optical activity yielding racemized product.

We therefore decided to look into the development of a palladium-catalyzed monoborylation reaction of primary alkyl halides using bis(pinacolato)diboron as boron source.
Pd-catalyzed borylation reaction of alkyl halides had not been reported prior to our studies. Bis(pinacolato) diboron was chosen as the borylation agent because the boronic ester product formed after the reaction was thought to be stable and hence isolable under the reaction conditions. Also, bis(pinacolato)diboron has been previously used in similar reaction for the formation of aryl boronic esters from aryl halides. In addition, the oxidative addition of Pd to primary halides has been extensively investigated and demonstrated by the Fu group.

4.2 Reaction Optimization

Table 4.1. Reaction optimization for palladium-catalyzed borylation of (3-bromopropyl)benzene using bis(pinacolato)diboron.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Variation from standard conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>10 µL water instead of 50 µL</td>
<td>93%</td>
</tr>
<tr>
<td>3</td>
<td>NMP used as solvent, 10 µL water</td>
<td>29%</td>
</tr>
<tr>
<td>4</td>
<td>Toluene used as solvent, 10 µL water</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>DMA used as solvent, 10 µL water</td>
<td>70%</td>
</tr>
<tr>
<td>6</td>
<td>DMF used as solvent, 10 µL water</td>
<td>44%</td>
</tr>
<tr>
<td>7</td>
<td>DMF used as solvent, no water</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>8</td>
<td>PCy₃·HBF₄ ligand used</td>
<td>34%</td>
</tr>
<tr>
<td>9</td>
<td>Pr-Bu₃·HBF₄ ligand used</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Pr-Bu₃·HBF₄ used as ligand</td>
<td>-</td>
</tr>
</tbody>
</table>

In studies by the Fu group, it was determined that trialkyl phosphine ligands best supported the oxidative addition of Pd. Therefore, we focused our attention on the use of trialkyl
phosphine ligands. The initial ligand screen was performed on 0.2 mmol scale using (3-
bromopropyl)benzene as the electrophile, with Pd$_2$(dba)$_3$, potassium phosphate, and trialkyl
phosphines (Table 4.1). Easy detection of the side products resulting from reduction, β-hydride
elimination and homo-coupling side reactions on GC was helpful for reaction optimization. Any
variation from the optimized standard conditions resulted in lower yields. When 10 µL H$_2$O was
used instead of 50 µL, the yield dropped only slightly (Entry 2). The reaction carried out in
DMA with 10 µL water yielded 70% product (Entry 6). Use of other polar and non-polar
solvents lowered the yields as well (Entries 3, 4, and 6). When DMF was used as solvent with no
additional water, less than 10% product was formed (Entry 7). While tricyclohexyl phosphine
ligand gave 34% product and lower conversion, tri-$n$-butylphosphine and tri-$t$-butyl phosphine
ligands showed no signs of product formation.

### 4.3 Substrate Scope

With the optimized conditions in hand, we then tested the reaction for its substrate scope.
The reaction showed very good compatibility with a wide range of functional groups and
produced borylated products in very high yields. (3-Bromopropyl)benzene (46), (2-
bromoethyl)cyclohexane (47), and 1-bromo-3-methylbutane (49) reacted well to form products
in high yields. Primary alkyl bromides bearing an ester group (50) and a nitrile group (54)
yielded high amounts of borylated products. 1-bromo-5-chloropentane (51) underwent borylation
only at the bromide giving 91% product leaving the chloride unreacted. This chloride can then be
used as the substrate for further transformations. (4-Bromobutoxy) benzene (58) and 10-
bromodecanamide (57) showed very high reactivity giving excellent product yields of 94% each.
With 6-bromohexan-1-ol (48), a moderate yield of 61% was obtained.
Palladium-catalyzed borylation also works well with primary alkyl electrophiles containing heterocyclic components. 2-(2-Bromoethyl) thiophene (53), 2-(4-bromobutyl) isoindoline1,3-dione (55) and 7-(4-bromobutoxy)-3,4-dihydroquinolin-2(1H)-one (56) gave moderate to good yields of borylated products. 1,4-dibromopentane containing both primary and
secondary bromides formed the primary borylated product (52) exclusively, whereas the secondary bromide remained unreacted throughout the reaction. This suggests a non-radical pathway for the palladium-catalyzed borylation reaction.\textsuperscript{66} Also, the borylated product containing a secondary bromide can be used for further reactions to build complex organic frameworks. Overall, the palladium-catalyzed monoborylation reaction is very general and works well with a wide variety of bromides.

In order to expand the scope of the reaction, we also tested the optimized conditions for borylation of electrophiles other than the primary alkyl bromides (Table 4.3). (3-Iodopropyl)benzene and 3-phenylpropyl-4-methylbenzene-sulfonate reacted to form products in (46a) 63\% and (46b) 75\% yields respectively. The reactivity of the tosyl group is especially interesting as it allows for the late stage borylation of molecules containing alcohol functionality, by converting it into the corresponding tosylate.

During the initial screenings, we had observed that the use of anhydrous potassium phosphate occasionally leads to clumping of the reaction. Such reactions then often had lower conversions and required longer reaction times due to poor mixing. To address this problem, we replaced anhydrous potassium phosphate with potassium phosphate monohydrate.

\begin{center}
\textbf{Scheme 4.2.} Palladium-catalyzed monoborylation of primary alkyl halides with bis(pinacolato)diboron.
\end{center}

\begin{center}
\begin{tabular}{ccc}
\textbf{44} & \textbf{45} & \textbf{46} \\
0.75 mmol & 1.2 equiv & \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{c}
\textbf{X=I, 46a: 63\%} \\
\textbf{X=OTs, 46b: 76\%} \\
\textbf{X=Br, 46c: 76\%} \\
\end{tabular}
\end{center}

During the initial screenings, we had observed that the use of anhydrous potassium phosphate occasionally leads to clumping of the reaction. Such reactions then often had lower conversions and required longer reaction times due to poor mixing. To address this problem, we replaced anhydrous potassium phosphate with potassium phosphate monohydrate. During
subsequent studies, we found that potassium carbonate also serves as a competent base and gives good yield of the product. There are no clumping issues associated with the use of potassium carbonate and hence it provides a good alternative to the reactions that result in low product yields due to reaction clumping.

![Scheme 4.3. Conversion of boronic ester into trifluoroborate.](image)

To further extend the utility of this method, the borylation product of (3-bromopropyl)benzene was formed using the standard reaction conditions (Scheme 4.3) and the crude product was then converted into the corresponding trifluoroborate salt (59) by the treatment of aqueous KHF$_2$.

![Scheme 4.4. Conversion of boronic ester into boronic acid.](image)

In a separate reaction, the crude borylated product (Scheme 4.4) was treated with sodium periodate and aqueous hydrochloride acid to yield 89% of 3-phenylpropylboronic acid (60).
In an independent reaction, the boronic acid (60) formed using conditions in scheme 4.4 was then refluxed without further purification with 1,3-propanediol using Dean-Stark apparatus to form 2-(3-phenylpropyl)-1,3,2-dioxaborinane (61) in 60% overall yield (Scheme 4.5).\textsuperscript{72} The easy conversion of boronic ester formed by palladium-catalyzed borylation reaction into the corresponding boronic acid, trifluoroboronate and other boronic ester widens the choices of nucleophiles that can be potentially used by the synthetic and medicinal chemists to carry out the transformations.

Next, we explored the borylation of primary alkyl bromides with bis(neopentylglycolato)diboron (62, Scheme 4.6). This reaction requires the use of 1 mol % Pd and 6 mol % ligand at 80 °C. The primary alkyl bromides containing ester (63) and nitrile (65)
functionality gave moderate to good yields whereas highest yield of 70% was obtained with (3-bromopropyl)benzene (64). In general, the yields with bis(neopentlyglycolato) diboron were lower compared to the analogous reaction with bis(pinacolato)diboron. Side products formed from reduction, β-hydride elimination and homocoupling reactions consumed the remaining starting material. The problem of competing side reactions is thought to primarily arise due to the high reactivity of the neopentylglycol ester product under the reaction conditions. The neopentylglycol boronic ester is less stable compared to the pinacol boronic ester and hence further takes part in the subsequent reactions forming undesired side products. This lowers the overall yield of the desired product.

4.4 Conclusions

In conclusion, we have developed the first palladium-catalyzed monoborylation reaction of primary alkyl bromides with bis(pinacolato)diboron. This novel reaction is very general, requires low catalyst loading, and works with various different electrophiles. Easy conversion of pinacolboronic ester product into the corresponding boronic acid, trifluoroboronate, and other boronic ester makes this method even more useful. Extension of borylation reaction to the formation of neopentylglycol esters further increases the utility of the method.

4.5 Supporting Information

General Reagent Information
Toluene and THF (unstabilized) were transferred to separate 20 L solvent-delivery kegs and vigorously purged with argon for 2 hours. The solvents were further purified by passing them under argon pressure through two packed columns of neutral alumina (for THF) or through neutral alumina and copper (II) oxide (for toluene). All reagents and solvents were used as received unless otherwise noted. Flash chromatography was performed using silica gel (ultra-pure grade).

General Analytical Information

All compounds were characterized by $^1$H NMR, $^{11}$B NMR, and $^{13}$C NMR spectroscopy. Copies of the $^1$H, $^{11}$B, and $^{13}$C spectra can be found at the end of the supporting information. Nuclear magnetic resonance spectra were recorded on a Varian 500 MHz instrument. All $^1$H NMR experiments are reported in δ units, parts per million (ppm), and were measured relative to the signals for residual chloroform (7.26 ppm), dimethyl sulfoxide (2.50 ppm) or acetonitrile (1.94 ppm). All $^{13}$C NMR spectra are reported in ppm relative to deuterochloroform (77.16 ppm), dimethyl sulfoxide (39.52 ppm) or acetonitrile (118.26 ppm) and were obtained with $^1$H decoupling. All GC analyses were performed on a Shimadzu GC-2010 gas chromatograph with an FID detector using a 25 m x 0.20 mm capillary column with cross-linked methyl siloxane as the stationary phase.

General Procedural Information

General Procedure for borylation of primary alkyl bromides with bis(pinacolato)diboron:
Pd$_2$(dba)$_3$ (4.6 mg, 0.005 mmol), di-tert-butyl(methyl)phosphonium tetrafluoroborate ligand (7.4 mg, 0.03 mmol), (BPin)$_2$ (305 mg, 1.2 mmol) and K$_3$PO$_4$•H$_2$O (460 mg, 2 mmol) were weighed out on the benchtop in an oven-dried 10 mL screw top test tube with stir bar. The test tube was sealed using a screw cap lined with a teflon septum. The reaction was stirred on a stir plate and the test tube was evacuated (100 mTorr) and backfilled three times with argon using a needle attached to a vacuum manifold. The alkyl bromide (1 mmol) was then added to the test tube via a microsyringe followed by degassed tertiary butyl alcohol (3 mL) and degassed water (0.25 mL). If the alkyl bromide was a solid, it was weighed out after K$_3$PO$_4$•H$_2$O before evacuating the test tube. The test tube was sealed with an electrical tape and the reaction mixture was stirred overnight on the benchtop at 60 °C with no additional argon pressure. The reaction mixture was quenched through the addition of saturated aqueous NH$_4$Cl (ca. 5 mL), then poured into a separatory funnel and extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. The crude product was purified by column chromatography. Because we are interested in developing methods of high operational simplicity as well as generality, we performed each reaction on the benchtop, using readily available disposable vials with screw-top septa.

Note: Ensure that the K$_3$PO$_4$•H$_2$O does not clump while reaction is in progress. If clumping occurs, K$_2$CO$_3$ may be used in place of K$_3$PO$_4$•H$_2$O.

*General procedure for trifluoroborate salt:* $^{56}$
Borylation reaction was performed as described above. Crude borylated product (0.75 mmol) was dissolved in 5 mL methanol. To this, aqueous solution of KHF$_2$ (2.25 equiv, 4.5 M) was added and the reaction mixture was stirred at room temperature for 2 h. Reaction was monitored for disappearance of starting material by gas chromatography. Solvent was evaporated in vacuo and the crude product was purified by recrystallization from hot acetone. Excess acetone was evaporated to give the concentrated slurry of product. Solid crystals were obtained by slowing adding diethyl ether to the product slurry. The crystals were then filtered and dried under vacuum to give pure product.

*General procedure for boronic acid:* $^{71}$

Borylation reaction was performed as described above. Sodium periodate (213 mg, 2.25 mmol) was added to the crude borylated product (0.75 mmol) in THF/H$_2$O (4:1 mixture, 6.25 mL) under argon and stirred for half hour at room temperature. To this, 2N HCl (0.25 mL) was added dropwise and the reaction mixture was stirred at room temperature for 3 hours. Reaction was monitored for disappearance of starting material by gas chromatography and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were washed with water and brine, dried over Na$_2$SO$_4$, and concentrated in vacuo.

*General procedure for boronic ester formation:* $^{72}$

The boronic acid (0.75 mmol) was prepared using the procedure above. The crude boronic acid was then refluxed overnight with 1,3-propanediol (162 µL, 3 equiv.) and catalytic $p$-
toluenesulfonic acid (0.05 mmol) in benzene using Dean-Stark apparatus. Benzene was evaporated and concentrated product was then washed with 10% aq. NaHCO₃. The aqueous layer was extracted with dichloromethane (3 x 15 mL) and dried over Na₂SO₄. The product was further purified by column chromatography (90:10 Hex:Ether).

General Procedure for borylation of primary alkyl bromides with bis(neopentylglycolato) diboron:

Pd₅(dba)₃ (1.83 mg, 0.002 mmol), di-tert-butyl(methyl)phosphonium tetrafluoroborate ligand (3 mg, 0.12 mmol), (BNeop)₂ (54 mg, 1.2 mmol) and K₃PO₄, anhydrous (85 mg, 0.4 mmol) were weighed out in the glove-box in an oven-dried 10 mL screw top test tube with stir bar. The test tube was sealed using a screw cap lined with a teflon septum. The reaction was stirred on a stir plate and alkyl bromide (0.2 mmol) was then added to the vial via a microsyringe. Degassed tertiary butyl alcohol (1 mL) and degassed water (20 μL) were then added under argon, outside of the glove box. The test tube was sealed with an electrical tape and the reaction mixture was stirred for 5 hours on the benchtop at 80°C with no additional argon pressure. The reaction mixture was quenched through the addition of saturated aqueous NH₄Cl (ca. 4 mL), then poured into a separatory funnel and extracted with diethyl ether (3 x 10 mL). The combined organic layers were washed with brine and dried over Na₂SO₄. The crude product was purified by column chromatography.

Spectral Data
4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (46). The general procedure was employed. A brownish yellow liquid (236 mg, 96%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.27 (t, $J = 7.5$ Hz, 2H), 7.16-7.20 (m, 3H), 2.63 (t, $J = 7.5$ Hz, 2H), 1.76 (quint., $J = 7.5$ Hz, 2H), 1.26 (s, 12H), 0.85 (t, $J = 7.5$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 142.76, 128.64, 128.25, 125.65, 83.00, 38.69, 26.22, 24.89 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 33.25 ppm.

2-(2-Cyclohexylethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (47). The general procedure was employed with following modifications: Pd$_2$(dba)$_3$ (14 mg, 0.015 mmol), tricyclohexyl phosphonium tetrafluoroborate ligand (33 mg, 0.09 mmol). A pale yellow liquid (198 mg, 83%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 1.61-1.72 (m, 5H), 1.11-1.31 (m, 18H), 0.83 (q, $J = 12$ Hz, 2H), 0.75 (t, $J = 8.5$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 82.95, 40.09, 33.12, 31.51, 26.90, 26.58, 24.94 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 33.43 ppm.

6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-1-ol (48). The general procedure was employed. A brown liquid (139 mg, 61%) was isolated by column chromatography (gradient from 80:20 to 75:25 Hex:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.63 (app. q, $J = 6.5$ Hz, 2H),
1.53-1.59 (m, 2H), 1.38-1.45 (m, 2H), 1.29-1.36 (m, 4H), 1.24 (s, 12H), 0.77 (t, \( J = 7.5 \) Hz, 2H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 83.00, 63.15, 32.81, 32.17, 25.56, 24.93, 24.71, 24.03 ppm. \(^{11}\)B (MHz, CDCl\(_3\)) \( \delta \): 33.18 ppm.

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{B} \\
\end{align*}
\]

2-iso-Pentyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (49). The general procedure was employed. A yellow liquid (147 mg, 74%) was isolated by column chromatography (99:1 Hex:Ether). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 1.45 (m, \( J = 6.5 \) Hz, 1H), 1.21-1.3 (m, 2H), 1.23 (s, 12H), 0.84 (d, \( J = 6.5 \) Hz, 6H), 0.74 (t, \( J = 8.5 \) Hz, 2H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 82.98, 33.05, 30.35, 24.95, 24.71, 22.35 ppm. \(^{11}\)B (MHz, CDCl\(_3\)) \( \delta \): 33.32 ppm.

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{B} \\
\end{align*}
\]

Ethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (50). The general procedure was employed with following modification: The ligand used in this reaction is tricyclohexylphosphonium tetrafluoroborate (11 mg, 0.03 mmol). A bright yellow liquid (215 mg, 89%) was isolated by column chromatography (95:5 Hex:Ether). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 4.10 (q, \( J = 7 \) Hz, 2H), 2.31 (t, \( J = 7.5 \) Hz, 2H), 1.74 (quint., \( J = 7.5 \) Hz, 2H), 1.23-1.26 (m, 15H), 0.81 (t, \( J = 8 \) Hz, 2H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 173.79, 83.14, 60.18, 36.71, 24.83, 19.77, 14.37 ppm. \(^{11}\)B (MHz, CDCl\(_3\)) \( \delta \): 32.77 ppm.

\[
\begin{align*}
\text{Me} & \quad \text{O} \\
\text{Me} & \quad \text{B} \\
\end{align*}
\]

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2-(5-Chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (51). The general procedure was employed with following modification: The ligand used in this reaction is tricyclohexylphosphonium tetrafluoroborate (11 mg, 0.03 mmol). A yellowish orange liquid (211 mg, 91%) was isolated by column chromatography (98:2 Hex:Ether) $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 3.50 (t, $J = 7$ Hz, 2H), 1.75 (quint., $J = 7$ Hz, 2H), 1.41 (m, 4H), 1.23 (s, 12H), 0.77 (t, $J = 7$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 83.06, 45.23, 32.55, 29.64, 24.93, 24.69, 23.41 ppm. $^{11}$B (MHz, CDCl$_3$) $\delta$: 32.89 ppm.

[Diagram of 2-(5-Chloropentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane]

2-(4-Bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (52). The general procedure was employed. A bright yellow liquid (219 mg, 79%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 4.13 (sextet, $J = 6.5$ Hz, 1H), 1.82-1.90 (m, 1H), 1.73-1.80 (m, 1H), 1.70 (d, $J = 7$ Hz, 3H), 1.48-1.66 (m, 2H), 1.24 (s, 12H), 0.73-0.84 (m, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 83.12, 51.61, 43.84, 26.50, 24.94, 22.34 ppm. $^{11}$B (MHz, CDCl$_3$) $\delta$: 33.19 ppm. HRMS (EI$^+$): Calcd. (C$_{11}$H$_{22}$BBrO$_2$-CH$_3$) $261.0661$; Found 261.0656.

[Diagram of 2-(4-Bromopentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane]

4,4,5,5-Tetramethyl-2-(2-(thiophen-2-yl)ethyl)-1,3,2-dioxaborolane (53). The general procedure was employed. An orange yellow liquid (149 mg, 63%) was isolated by column chromatography (98:2 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.08 (dd, $J = 5$ Hz, 1.5 Hz, 1H), 6.88 (m, 1H), 6.79 (m, 1H), 2.96 (t, $J = 8$ Hz, 2H), 1.24 (m, 14H), ppm. $^{13}$C NMR (125
MHz, CDCl$_3$) $\delta$: 147.87, 126.64, 123.51, 122.70, 83.33, 24.93, 24.48 ppm. $^{11}$B (MHz, CDCl$_3$) $\delta$: 32.94 ppm.

$6$-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)hexanenitrile (54). The general procedure was employed. A golden yellow liquid (214 mg, 96%) was isolated by column chromatography (gradient from 95:5 to 93:7 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 2.30 (t, $J = 7$ Hz, 2H), 1.63 (quint., $J = 7.0$ Hz, 2H), 1.40-1.43 (m, 4H), 1.22 (s, 12H), 0.76 (t, $J = 7.0$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 119.90, 83.09, 31.25, 25.22, 24.89, 17.08 ppm. $^{11}$B (MHz, CDCl$_3$) $\delta$: 33.08 ppm.

$2$-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)butyl)isoindoline-1,3-dione (55). The general procedure was employed with following modification: The ligand used in this reaction is tricyclohexylphosphonium tetrafluoroborate (11 mg, 0.03 mmol). A dark brown liquid (260 mg, 79%) was isolated by column chromatography (gradient from 85:15 to 80:20 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.80 (dd, $J = 8.5$ Hz, 3 Hz, 2H), 7.67 (dt, $J = 8.5$ Hz, 2.5 Hz, 2H), 3.64 (t, $J = 7.5$ Hz, 2H), 1.66 (quint., $J = 7.5$ Hz, 2H), 1.44 (quint., $J = 8$ Hz, 2H), 1.20 (s, 12H), 0.79 (t, $J = 7.5$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 168.48, 133.85, 132.32, 123.18, 83.06, 38.03, 31.16, 24.89, 24.68, 21.44 ppm. $^{11}$B (MHz, CDCl$_3$) $\delta$: 32.99 ppm. Anal. Calcd. for C$_{18}$H$_{24}$BNO$_4$: C, 65.67; H, 7.35. Found: C, 65.45; H, 7.28.
7-(4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)-3,4-dihydroquinolin-2(1H)-one (56). The general procedure was employed with following modifications: 0.75 mmol scale, Pd\(_2\)(dba)\(_3\) (10.3 mg, 0.01125 mmol), di-tert-butyl(methyl)phosphonium tetrafluoroborate (11.16 mg, 0.045 mmol), DMA (3mL) used as solvent. A thick yellow liquid (186 mg, 72\%) was isolated by column chromatography (CH\(_2\)Cl\(_2\):MeOH: 99:1) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:7.44\) (bs, 1H), 7.03 (d, \(J = 8.5\) Hz, 1H), 6.51 (dd, \(J = 8.5\)Hz, 2.5Hz, 1H), 6.27 (d, \(J = 2\)Hz, 1H), 3.91 (t, \(J = 6.5\) Hz, 2H), 2.89 (t, \(J = 7\) Hz, 2H), 2.61 (t, \(J = 8\) Hz, 2H), 1.73-1.80 (m, 2H), 1.54-1.60 (m, 2H), 1.24 (s, 12H), 0.84 (t, \(J = 8\) Hz, 2H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta:172.03, 158.91, 138.20, 128.69, 115.65, 108.85, 102.36, 83.13, 68.10, 31.82, 31.24, 25.00, 24.71, 20.68\) ppm. \(^{11}\)B (MHz, CDCl\(_3\)) \(\delta:33.26\) ppm.

10-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)decanamide (57). The general procedure was employed. A white solid (279 mg, 94\%) was isolated by column chromatography (95:5 CH\(_2\)Cl\(_2\):MeOH). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta:5.32\) (broad d, 2H), 2.21 (t, \(J = 7.5\) Hz, 2H), 1.60-1.66 (m, 2H), 1.22-1.26 (m, 22H), 0.76 (m, \(J = 7.5\) Hz, 2H) ppm. \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta:175.57, 82.98, 36.09, 32.55, 29.62, 29.59, 29.50, 29.46, 29.38, 25.70, 24.97, 24.14\) ppm. The carbon atom directly attached to the boron atom was not detected, likely due to quadrupolar broadening. \(^{11}\)B (MHz, CDCl\(_3\)) \(\delta:33.69\) ppm. Anal. Calcd. for C\(_{16}\)H\(_{32}\)BNO\(_3\): C, 64.65; H, 10.85. Found: C, 64.41; H, 10.99.
4,4,5,5-Tetramethyl-2-(4-phenoxybutyl)-1,3,2-dioxaborolane (58). The general procedure was employed. A bright yellow liquid (259 mg, 94%) was isolated by column chromatography (99:1 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 7.26 (dt, $J = 7.5$ Hz, 1 Hz, 2H), 6.88-6.93 (m, 3H), 3.95 (t, $J = 6.5$ Hz, 2H), 1.80 (quint., $J = 6.5$ Hz, 2H), 1.59 (quint., $J = 8$Hz, 2H), 1.25 (s, 12H), 0.86 (t, $J = 8$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 159.29, 129.52, 120.53, 114.66, 83.14, 67.79, 31.96, 25.20, 25.00, 20.76 ppm. The carbon atom directly attached to the boron atom was not detected, likely due to quadrupolar broadening. $^{11}$B (MHz, CDCl$_3$) δ: 33.05 ppm.

4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (46a). The general procedure was employed with following modifications: tricyclohexyl phosphonium tetrafluoroborate ligand (8.3 mg, 0.0225 mmol), and DMA solvent (3 mL) were employed in the reaction. A reddish yellow liquid (155 mg, 63%) was isolated by column chromatography (98:2 Hex:Ether).

4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (46b). The general procedure was employed with following modifications: Pd$_2$(dba)$_3$ (10.3 mg, 0.01125 mmol), di-tert-butyl(methyl)phosphonium tetrafluoroborate ligand (16.7 mg, 0.0675 mmol) were employed in
the reaction. A reddish yellow liquid (141 mg, 76%) was isolated by column chromatography (98:2 Hex:Ether).

![Structure of 4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane](image)

4,4,5,5-Tetramethyl-2-(3-phenylpropyl)-1,3,2-dioxaborolane (46c). The general procedure was employed with following modifications: K$_2$CO$_3$, anhydrous was used instead of K$_3$PO$_4$·H$_2$O. A reddish yellow liquid (141 mg, 76%) was isolated by column chromatography (98:2 Hex:Ether).

![Structure of Potassium-3-Phenyl-trifluoroboratopropane](image)

Potassium-3-Phenyl-trifluoroboratopropane (59). The general procedure was employed. A white solid (118 mg, 70%) $^1$H NMR (500 MHz, DMSO) δ: 7.20-7.23 (t, $J = 7.5$ Hz, 4H), 7.08-7.12 (m, 3H), 2.45 (t, $J = 8.0$ Hz, 2H), 1.40 (quint., $J = 7.5$ Hz, 2H), 0.02 (m, 2H) ppm. $^{13}$C NMR (125 MHz, DMSO) δ: 144.14, 128.26, 127.88, 124.94, 28.25, 28.24 ppm. $^{11}$B (MHz, DMSO) δ: 9.25 ppm.

![Structure of 3-Phenylpropylboronic acid](image)

3-Phenylpropylboronic acid (60). The general procedure was employed. A yellowish white solid (109 mg, 89%) $^1$H NMR (500 MHz, DMSO) δ: 7.40 (s, 2H), 7.25 (t, $J = 8$ Hz, 2H), 7.13-7.16 (m, 3H), 2.50 (m, 2H), 1.60 (quint., $J = 7.5$ Hz, 2H), 0.60 (t, $J = 8.0$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CD$_3$CN) δ: 143.91, 129.36, 129.11, 126.46, 39.15, 27.29 ppm. The carbon atom directly attached to the boron atom was not detected, likely due to quadrupolar broadening. $^{11}$B (MHz, CD$_3$CN) δ: 36.96 ppm.
2-(3-Phenylpropyl)-1,3,2-dioxaborinane (61). The general procedure was employed. (92 mg, 60%) $^1$H NMR (500 MHz, CD$_3$CN) δ: 7.24-7.27 (m, 2H), 7.13-7.18 (m, 3H), 3.95 (t, $J = 5.0$ Hz, 4H), 2.58 (t, $J = 7.5$ Hz, 2H), 1.90 (quint., $J = 6.0$ Hz, 2H), 1.68 (quint., $J = 8.0$ Hz, 2H), 0.73 (t, $J = 8.0$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CD$_3$CN) δ: 143.10, 128.71, 128.21, 125.56, 61.70, 38.74, 27.50, 26.10 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 29.94 ppm.

Ethyl 4-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)butanoate (63). The general procedure was employed. A yellow liquid (28 mg, 62%) was isolated by column chromatography (90:10 Hex:Ether). $^1$H NMR (500 MHz, CD$_3$CN) δ: 4.11 (q, $J = 7$ Hz, 2H), 3.58 (s, 4H), 2.29 (t, $J = 7.5$ Hz, 2H), 1.70 (quint., $J = 7.5$ Hz, 2H), 1.25 (t, $J = 7$ Hz, 3H), 0.95 (s, 6H), 0.75 (t, $J = 8$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CD$_3$CN) δ: 174.09, 72.11, 60.17, 36.90, 31.75, 29.83, 21.97, 19.91, 14.41 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 29.37 ppm. HRMS (FAB$^+$) Calcd. (for C$_{11}$H$_{21}$BO$_4$ + H$^+$) 229.161; Found 229.1622.

5,5-Dimethyl-2-(3-phenylpropyl)-1,3,2-dioxaborinane (64). The general procedure was employed. A yellowish liquid (32 mg, 70%) was isolated by column chromatography (90:10 Hex:Ether). $^1$H NMR (500 MHz, CD$_3$CN) δ: 7.24-7.27 (m, 2H), 7.14-7.19 (m, 3H), 3.57 (s, 4H), 2.60 (t, $J = 8$ Hz, 2H), 1.70 (quint., $J = 8$ Hz, 2H), 0.95 (s, 6H), 0.76 (t, $J = 8$ Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CD$_3$CN) δ: 143.13, 128.71, 128.26, 125.60, 72.12, 38.85, 31.76, 29.85, 26.31,
22.00 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 29.68 ppm. Anal. Calcd. for C$_{14}$H$_{21}$BO$_2$: C, 72.44; H, 9.12. Found: C, 72.45; H, 9.23.

6-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)hexanenitrile (65). The general procedure was employed. A yellow liquid (18 mg, 42%) was isolated by column chromatography (90:10 Hex:Ether). $^1$H NMR (500 MHz, CDCl$_3$) δ: 3.59 (s, 4H), 2.32 (t, $J$ = 7.5 Hz, 2H), 1.65 (quint., $J$ = 7 Hz, 2H), 1.37-1.47 (m, 4H), 0.95 (s, 6H), 0.72 (t, $J$ = 8 Hz, 2H) ppm. $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 120.09, 72.13, 31.76, 31.43, 29.84, 25.37, 23.33, 21.97, 17.16 ppm. $^{11}$B (MHz, CDCl$_3$) δ: 29.37 ppm. HRMS (FAB$^+$) Calcd. (C$_{11}$H$_{20}$BNO$_2$ + H$^+$) 210.1665; Found 210.1660.
5 Bibliography


50. Prices from Strem Chemicals Catalogue.


6 Autobiographical statement

Amruta Ajit Joshi was born on August 1st, 1985 in Sangli, India. She obtained her Bachelors in Pharmaceutical Sciences and Technology from Institute of Chemical Technology (ICT-Formerly known as UDCT), Mumbai, India in May 2007. Later she joined the chemistry department of as a doctoral student in August 2007.

HONOURS AND AWARDS

- Doctoral Dissertation Fellowship (2012) - Awarded from 263 applicants
- Doctoral Students Research Grant (2011 & 2009) - Awarded for best research proposal
- Research Excellence Award (2010) - Special award for research excellence

PUBLICATIONS


Palladium-catalyzed Suzuki cross-coupling reaction of aryl chlorides and chiral/achiral secondary alkyl boronic acids & trifluoroboronates (*Manuscript in preparation*)

**POSTER PRESENTATIONS**

- Graduate Research Symposium, Santa Barbara, CA, **July 2011**
  (competitive selection from over 100 applications)
- 42**nd** National Organic Symposium, Princeton, NJ, **June 2011**
- 240**th** American Chemical Society (ACS) National Meeting, Boston, MA, **August 2010**