Oxidative Generation of Reactive Iminium-Intermediates: A Powerful Strategy for C-H Bond Functionalization

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Abstract


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This thesis is an investigation on the generation and reactivity of carbocations adjacent to a trisubstituted nitrogen atom (iminium).

In the first part of this thesis, a copper-catalyzed oxidative alkylation of sp\(^3\) C-H bond adjacent to a nitrogen atom is described. This environmentally respectful process used molecular oxygen as oxidant and water as solvent.

In the second part of the thesis, an aerobic sp\(^3\) C-H bond phosphonation reaction is presented. This process catalyzed by copper(I) bromide using dialkylphosphites as nucleophiles offered direct C-P bond formation via direct oxidative coupling of C-H and P-H bonds.

In the third part of the thesis, a copper-catalyzed sp\(^3\) C-H bond arylation with boronic acids in absence of directing group is described. The oxidative arylation reaction provided easy access to biologically active tetrahydroisoquinoline derivatives and can either use peroxide or molecular oxygen as oxidant.

In the last part of the thesis, the aerobic and electrochemical Cross-Dehydrogenative-Coupling in ionic liquids is presented. Ionic liquids have demonstrated high efficiency when applied as solvent and electrolyte solvent for the oxidative nitro-Mannich carbon-carbon bond formation.
**Resumé**

**Génération Oxydante d’Intermédiaires Iminium Réactifs : Stratégie Efficace pour la Fonctionnalisation de Liaisons C-H.**

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Cette thèse est une investigation sur la génération et la réactivité de carbocations adjacents à un atome d’azote trisubstitué (iminium).

Dans la première partie de cette thèse, une alkylation d’une liaison sp³ C-H adjacente à un atome d’azote catalysée au cuivre est décrite. Ce procédé respectueux de l’environnement utilisa l’oxygène comme oxydant et l’eau comme solvant.

Dans la deuxième partie de cette thèse, une réaction aérobique de phosphonation de liaison sp³ C-H est présentée. Ce procédé catalysé par un sel de bromure de cuivre(I) et utilisant des bis-alkylphosphites comme nucléophiles permit la synthèse directe de liaisons C-P via le couplage oxydant de liaisons carbone-hydrogène et phosphore-hydrogène.

Dans la troisième partie de cette thèse, une réaction d’arylation de liaison sp³ C-H, catalysée par le cuivre, avec des acides boroniques en absence de groupement directeur est décrite. Cette réaction d’arylation, utilisant soit un peroxide soit l’oxygène comme oxydant, donna des dérivés de la tétrahydroisoquinoline biologiquement actifs.

Dans la dernière partie de cette thèse, le couplage croisé déshydrogénant aérobique et électrochimique en liquides ioniques est présenté. Les liquides ioniques ont démontré une grande efficacité pour la formation de liaisons C-C (nitro-Mannich oxydante) lors de leurs utilisations comme solvant et solvant électrolyte.
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The successful completion of this thesis would not have been made possible without the support and assistance of many people.

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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>[BMIm][BF₄]</td>
<td>Butyl-methylimidazolium tetrafluoroborate</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>BOC</td>
<td>tert-butoxycarbonyl</td>
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<tr>
<td>BQ</td>
<td>1,4-benzoquinone</td>
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<td>&quot;Bu</td>
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<td>′Bu</td>
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<td>C-C</td>
<td>carbon-carbon</td>
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<td>CDC</td>
<td>Cross-Dehydrogenative-Coupling</td>
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<td>CE</td>
<td>counter electrode</td>
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<tr>
<td>C-H</td>
<td>carbon-hydrogen</td>
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<td>C-P</td>
<td>carbon-phosphorus</td>
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<td>CV</td>
<td>cyclic voltammogram</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexyl</td>
</tr>
<tr>
<td>d</td>
<td>doublet (¹ HNMR)</td>
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<td>DCE</td>
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<td>DMBQ</td>
<td>2,6-dimethyl-1,4-benzoquinone</td>
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<td>DME</td>
<td>1,2-dimethoxyethane</td>
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<td>DMSO</td>
<td>dimethyl sulfoxide</td>
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<td>ee</td>
<td>enantiomeric excess</td>
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<td>Et</td>
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<td>equiv.</td>
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<td>GC electrode</td>
<td>glassy carbon electrode</td>
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<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
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<td>HRMS</td>
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<td>m.p.</td>
<td>melting point</td>
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<td>NHPI</td>
<td>N-hydroxyptalimide</td>
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<td>Definition</td>
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<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>Nu</td>
<td>nucleophile</td>
</tr>
<tr>
<td>[O]</td>
<td>oxidation</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
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<tr>
<td>OTf</td>
<td>trifluoromethanesulfonate</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
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<tr>
<td>PG</td>
<td>protecting group</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
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<tr>
<td>PMP</td>
<td>para-methoxyphenyl</td>
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<td>ppm</td>
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<tr>
<td>'Pr</td>
<td>isopropyl</td>
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<tr>
<td>PyBox</td>
<td>2,6-Bis[(4R)-4-phenyl-2-oxazolinyl]pyridine</td>
</tr>
<tr>
<td>q</td>
<td>quartet ((^1) HNMR)</td>
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<tr>
<td>RE</td>
<td>reference electrode</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>s</td>
<td>singlet ((^1) HNMR)</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>t</td>
<td>triplet ((^1) HNMR)</td>
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<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>T-HYDRO</td>
<td>tert-butyl hydroperoxide, 70 wt% in water</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>TLC</td>
<td>thin-layer-chromatography</td>
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<td>working electrode</td>
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Part I. Cross-Dehydrogenative-Coupling for C-C Bond Formation.
Chapter 1 – Introduction to Oxidative Cross-Coupling Reactions

The carbon-carbon bond constitutes the backbone of organic chemistry and carbon-carbon bond formation plays a critical part in the syntheses of many organic molecules, which are designed in agreement with the tools available to organic chemists. Therefore, the development of new strategies for C-C bond formation to improve overall synthetic efficiency constitutes a critical research area in order to provide alternatives toward traditional methodologies.

The common route into C-C bond formation occurs through the coupling of various pre-synthesized nucleophiles and pre-synthesized electrophiles. In pursuance of maximizing resource and energy efficiencies by eliminating unnecessary pre-activation steps, recent years have witnessed a considerable effort in the direct use of carbon-hydrogen bonds. Nevertheless, most of these reactions still require a functionalized partner to generate the desired C-C bond coupling-product.

In recent years, Professor Chao-Jun Li and others have been exploring the possibility of constructing new carbon-carbon bonds directly from two different C-H bonds under oxidative conditions via Cross-Dehydrogenative-Coupling (CDC). This chapter intends to present examples based on this new methodology employing organic peroxide, oxygen and in particular hydrogen acceptors as oxidants.

In regards to the myriad of C-H bonds available as potential coupling partners, the challenge resides in the selective functionalization of the desired position. According to their bond-dissociation-energies, C-H bonds adjacent to heteroatom, double bonds (allylic) and aromatics (benzylic) are potentially easier to functionalize.
1.1 – Oxidative Cross-Dehydrogenative-Coupling with Allylic and Benzylic C-H Bonds

Since 1958, when Kharasch and Sosnovsky demonstrated that tert-butyl perbenzoate in the presence of a copper salt catalyst reacts with various olefins to give the corresponding allylic benzoates as a single isomer, selective allylic carbon-heteroatom bond formation has attracted considerable interest. Nevertheless, the oxidative carbon-carbon bond formation of allylic C-H bond has only been recently reported.

Inspired by the pioneering work of Trost and co-workers using allylic sp$^3$C-H bonds to form π-allyl palladium complexes, Li and coworker developed a catalytic allylic alkylation with allylic sp$^3$ C-H and methylenic sp$^3$ C-H bond. The difficulty to reoxidize Pd(0) to Pd(II) was overcome by the use of an alternative system catalyzed by copper and cobalt salts (Scheme 1.1).

\[
\begin{align*}
\text{R}_1\text{O} & + \text{R}_2\text{O} \\
\text{Diketone} \quad \text{or} \quad \text{Diketoester} \\
& \xrightarrow{\text{cat CuBr/CoCl}_2} \text{TBHP, 80 °C} \\
& \text{R}_1\text{R}_2\text{Yield: 35-71 %}
\end{align*}
\]

**Scheme 1.1 – Oxidative Allylic Alkylation of Cyclic Alkenes**

Following the work by Li and inspired by the allylic C-O/N bond formation reported by White and co-workers, Shi and coworkers published the intra/intermolecular oxidative allylic alkylation catalyzed by bis-sulfoxide palladium acetate complex. This methodology required the presence of both 1,4-benzoquinone (BQ) and oxygen gas as oxidants (Scheme 1.2).
In a similar fashion, White and co-workers reported the use of electron poor nitroalkanes as nucleophiles. The sterically hindered 2,6-dimethylbenzoquinone (DMBQ) was found most effective under the described conditions (Scheme 1.3).\(^9\)

**Scheme 1.2 – Palladium-Catalyzed Intra/Intermolecular Oxidative Allylic Alkylation**

**Scheme 1.3 - Palladium-Catalyzed Intermolecular Oxidative Allylic Alkylation**
Benzylic C-H bonds, similar to allylic C-H in bond-dissociation-energy, were also investigated for oxidative alkylation reaction. Li and co-workers published the use of iron(II) chloride, which is cheap and of low toxicity, to catalyze the oxidative Cross-Dehydrogenative-Coupling between activated methylene nucleophiles and benzylic C-H bonds (Scheme 1.4).\(^\text{10}\)

\[
\begin{align*}
\text{Ar} & \text{-R}^1 + \text{R}^2\text{O} \text{-O} \text{R}^3 & \text{FeCl}_2 (20 \text{ mol}\%) \quad \text{tBuOOtBu} \\
\text{Yield: 25-87 \%}
\end{align*}
\]

**Scheme 1.4 – Iron-Catalyzed Oxidative Benzylic Alkylation**

Rather than iron, Powell and co-worker demonstrated that a similar reaction can be realized in the presence of copper(II) perchlorate catalyst and t-butylbenzoate peroxide as the oxidant (Scheme 1.5).\(^\text{11}\)

\[
\begin{align*}
\text{Ar} & \text{-R}^1 + \text{R}^2\text{O} \text{-O} \text{R}^3 & \text{Cu(ClO}_4\text{)} (20 \text{ mol}\%) \quad \text{Ligand (5 mol\%)} \quad \text{tBuOOBz} \\
\text{neat, 60°C} & \text{Yield: 51-75 \%}
\end{align*}
\]

**Scheme 1.5 – Copper-Catalyzed Oxidative Benzylic Alkylation**
The proposed reaction intermediate was subjected to the standard conditions and the desired coupling product was obtained in 76% yield demonstrating the implication of the ester intermediate in the catalytic cycle.

Combining both principles, an interesting metal free procedure for oxidative benzylic /allylic C-H bond alkylation was recently reported by Bao and co-worker. The well-known oxidation reagent, 2,3-dichloro-5,6-dicyanoquinone (DDQ) mediated efficient and concise oxidative-coupling reaction between diarylallylic sp$^3$ C-H and active methylenic sp$^3$ C-H bonds in absence of any metal catalyst (Scheme 1.6).\(^\text{12}\)

\[
\begin{align*}
\text{Ar}^1\text{C} & \text{C} & \text{Ar}^2 + \text{O} & \text{O} & \text{R}^1 & \text{R}^2 \\
\text{DDQ, CH}_2\text{Cl}_2, \text{rt} & \rightarrow & \text{O} & \text{O} & \text{R}^1 & \text{R}^2 \\
\text{Ar}^1 & \text{C} & \text{C} & \text{Ar}^2
\end{align*}
\]

Yield: 71-98 %

**Scheme 1.6 – DDQ-Mediated Oxidative Alkylation**

1.2 – Oxidative Cross-Dehydrogenative-Coupling with C-H Bond Adjacent to Heteroatoms

Direct functionalization of tertiary amines is of importance both enzymatically and synthetically. In 1993, Miura and co-workers reported the first example of oxidative C-C cross-coupling reaction between 4-substituted \(N,N\)-dimethylaniline and terminal alkynes.\(^\text{13}\) Using copper(II) chloride in an oxygen atmosphere, they managed to obtain in low to moderate yields the propargylamine products together with the \(N\)-methylformanilides and \(N\)-methylanilines (Scheme 1.7).
In an early work, Murahashi and co-workers had established that a C-H bond adjacent to a nitrogen atom can be selectively oxidized in the presence of peroxide and ruthenium catalyst. Substituted anilines and amides were efficiently functionalized by excess tert-butyl hydroperoxide (TBHP) playing both roles of oxidant and nucleophile in this system (Scheme 1.8).\textsuperscript{14}

The key intermediate of this transformation was proposed to be the corresponding iminium type intermediate derived from the amine oxidation. Murahashi expanded this methodology to the use of different peroxides, but more importantly, in 2003 C-C bond formation was achieved by trapping the postulated electrophilic intermediate with cyanide (Scheme 1.9).\textsuperscript{15} The very interesting feature of this new strategy was the use of molecular oxygen as an efficient oxidant, providing $\alpha$-aminonitriles in good to excellent yields. Later hydrogen peroxide was described as a more versatile oxidant, in particular for the selective alpha-cyanation of cyclic amines.\textsuperscript{16}
Scheme 1.9 – Ruthenium-Catalyzed Aerobic Cyanation of Tertiary Amines

In our own laboratory Li and co-workers have developed the Cross-Dehydrogenative-Coupling method. This oxidative C-C bond formation offered a large number of different $\alpha$-substituted tertiary amines through the catalytic use of copper(I) bromide and TBHP as the oxidant (Scheme 1.10).\textsuperscript{2,17}

Scheme 1.10 – Copper-Catalyzed Cross-Dehydrogenative-Coupling
This coupling in the presence of different nucleophiles such as terminal alkynes,\textsuperscript{18} nitroalkanes,\textsuperscript{19} indoles\textsuperscript{20} and malonates,\textsuperscript{21} also found an interesting application in the direct synthesis of chiral $\alpha$-functionalized tertiary amines in presence of chiral bis(oxazoline) ligands for copper catalyst.\textsuperscript{22}

Sodeoka and co-workers described the asymmetric coupling of BOC protected tertiary amines with malonates. The chiral cationic palladium complex catalyzed the oxidative alkylation reaction with high efficiency and enantioselectivity (Scheme 1.11).\textsuperscript{23}

\begin{equation}
\begin{array}{c}
\text{catalyst} = \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \quad \text{Pd}^{2+}(\text{OH}_2)_2 \\
\text{Ar} = 3,5-\text{Me}_2\text{C}_6\text{H}_3
\end{array}
\end{equation}

\textbf{Scheme 1.11} – Palladium-Catalyzed Asymmetric Oxidative Alkylation

Doyle and co-workers reported the use of a rhodium-dimer caprolactamate ($\text{Rh}_2(\text{cap})_4$) complex to catalyze the oxidative coupling between tertiary amines and 2-siloxyfurans to generate $\gamma$-butyrolactones in a racemic fashion (Scheme 1.12).\textsuperscript{24}

\begin{equation}
\begin{array}{c}
\text{Yield: 50-89 %}
\end{array}
\end{equation}

\textbf{Scheme 1.12} – Rhodium-Catalyzed Oxidative $\gamma$-Butyrolactones Synthesis
The Cross-Dehydrogenative-Coupling method to functionalize tertiary amines has attracted a lot of interest in recent years. Recently, Guo and co-workers demonstrated the possibility of using a simple copper salt to catalyze the exact same reaction.\textsuperscript{25} Employing a similar strategy, Qing and co-workers described the copper(I) bromide catalyzed coupling of difluoro silyl ethers and tertiary amines with TBHP to produce $\beta$-amine-ketones (Scheme 1.13).\textsuperscript{26}

\[ \begin{align*}
\text{R}_1\text{N}_\text{H} & + \text{F}_\text{OTMS} \quad \text{CuBr (10 mol\%)} \quad \text{TBHP} \\
& \quad \text{CH}_2\text{Cl}_2, \text{rt} \\
\text{R}_2\text{F} & \text{F} \\
\text{R}_3 & \text{F} \\
\text{R}_4 & \text{F} \\
\text{Yield: 13-88 \%}
\end{align*} \]

\textbf{Scheme 1.13} – Copper-Catalyzed Oxidative Coupling with Silyl Ethers

Guo and co-workers synthesized $\beta$-amine-ketones from coupling with unmodified methylketones and molecular oxygen as oxidant (Scheme 1.14).\textsuperscript{27} They believed that acetic acid could facilitate the methyl ketone enolization, thus making the trapping of the iminium intermediate faster.

\[ \begin{align*}
\text{R}_1\text{N}_\text{H} & + \text{R}_4 \quad \text{Cul (5 mol\%)} \quad \text{O}_2 \text{ (1 atm)} \\
& \quad \text{AcOH, 80 }\text{oC} \\
\text{R}_2 & \text{R}_3 \\
\text{R}_4 & \text{R}_4 \\
\text{Yield: 24-73 \%}
\end{align*} \]

\textbf{Scheme 1.14} – Copper-Catalyzed Aerobic $\beta$-Amine-Ketones Syntheses

The DDQ-mediated coupling between tetrahydroisoquinolines and nitromethane was recently described by Todd and co-worker.\textsuperscript{28} NMR monitoring of this reaction suggested that the DDQ oxidation of the tertiary amine was fast and gave an intermediate iminium ion, probably as a salt. Reaction with nitromethane occurred during the basic work-up (Scheme 1.15).
The oxidative functionalization of secondary amines was recently achieved by Li and Zhao utilizing copper(I) bromide as catalyst and TBHP as oxidant. This new method provided peptido-amides functionalization through the direct reaction at the α-peptido C-H bonds to give C-C bonds in a Cross-Dehydrogenative-Coupling process (Scheme 1.16).

In an effort to functionalize the C-H bond of ether and related oxygen-containing compounds directly, Li and co-worker reported the construction of β-diester ether catalyzed by a combination of indium and copper catalysts in the presence of DDQ (Scheme 1.17). Previously, simple ketones were shown to undergo oxidative coupling with benzyl ether under metal-free condition with DDQ.

Scheme 1.15 – DDQ-Mediated Oxidative Alkylation of Tertiary Amines

Scheme 1.16 – Copper-Catalyzed α-Functionalization of Short Peptides

Scheme 1.17 – Copper/Indium-Catalyzed Oxidative Benzyl Ether Alkylation
More recently, the addition of N-hydroxyphthalimide (NHPI) as a co-catalyst allowed the reaction to proceed in presence of molecular oxygen at atmospheric pressure to act at the terminal oxidant. Li and co-workers showed that the potential intermediate of this reaction was the benzylic alcohol derived from the oxidation of the cyclic benzyl ether (Scheme 1.18).\(^{33}\)

**Scheme 1.18 - Copper/Indium/NHPI-Catalyzed Aerobic Benzyl Ether Alkylation**

1.3 – Oxidative Cross-Dehydrogenative-Coupling With Simple Alkanes.

*It is a great challenge to use simple alkanes without any functional groups to form C-C bonds.* Li and co-worker recently achieve this challenge by employing a method inspired from the pioneering work of Fenton chemistry\(^ {34}\) and the Gif process.\(^ {35}\) Simple alkanes were efficiently cross-coupled with β-ketoesters using iron(II) chloride catalyst in presence of a stoichiometric peroxide oxidant (Scheme 1.19).\(^ {36}\)
Scheme 1.19 – Iron-Catalyzed Oxidative Coupling of Cyclic Alkanes with β-Ketoesters

Iron(II) can catalyze the decomposition of the peroxide to give the tert-butoxy radical, which then reacts with a cyclic alkane to give a cycloalkyl radical as the key intermediate.

To extend the concept of trapping alkane radical intermediates, Li and co-worker reported the direct oxidative alkylation of aromatic C-H bonds. In presence of peroxide, a pyridine-directing-group assisted the formation of a ruthenacycle, which cross-coupled with the postulated alkyl radical to regioselectively generate the desired C-C bond (Scheme 1.20).

Scheme 1.20 – Ruthenium-Catalyzed Oxidative Alkylation of 2-Phenylpyridines With Cyclic Alkanes

Itami, Li and co-workers described a transition metal free system for the cross-coupling reactions of nitrogen heteroaromatics and alkanes. Under the
influence of tert-butyl peroxide the formation of the reactive alkyl radical occurred and efficiently reacted with the electrophilic pyridine N-oxide derivatives (Scheme 1.21).

![Scheme 1.21 – Oxidative Cross-Coupling of Pyridine N-Oxide With Cyclic Alkanes](image)

However, under similar conditions unactivated pyridines or quinolines did not react with simple alkanes. Li and Deng, considered the possibility of increasing the acidity of the C(2)-H bond of heteroaromatic rings by using a Lewis acid catalyst. Sc(OTf)₃ showed the best catalytic activity offering the Cross-Dehydrogentaive-Coupling product in good to excellent yields (Scheme 1.22).³⁹

![Scheme 1.22 – Scandium-Catalyzed Oxidative Coupling of Pyridine Derivatives with Cyclic Alkanes](image)

In comparison to the metal-free/pyridine N-oxide process, a better regioselectivity was observed when using scandium(III) triflate as Lewis acid catalyst. In fact, the alkylation occurred selectively at the carbon adjacent to the nitrogen atom.
References for Chapter 1


Chapter 2 – Copper Catalyzed Oxidative Alkylation of \( \text{sp}^3 \) C-H Bond Adjacent to a Nitrogen Atom Using Molecular Oxygen in Water.

As illustrated in the chapter 1, peroxides and hydrogen acceptors are the most commonly used oxidants for the direct selective functionalization of C-H bond adjacent to a heteroatom or a double bond. Nevertheless, the use of peroxide is potentially dangerous in large-scale reactions and the replacement of peroxides by molecular oxygen (in water) would offer a more atom-economical and safer process.\(^1\)

2.1 – Background

In 2003, Murahashi and co-workers reported the ruthenium-catalyzed oxidative cyanation of tertiary amines with sodium cyanide. The aerobic method occurs to give the corresponding \( \alpha \)-aminonitriles with high yield under an atmosphere of oxygen. This process represented at this time the first example of efficient aerobic transformation of tertiary amines (Scheme 2.1).\(^2\)

\[
\begin{array}{c}
\text{R}_1 \text{N}^\text{H} \text{R}_2 + \text{NaCN} \xrightarrow{\text{cat. RuCl}_3} \text{O}_2 (1 \text{ atm}) \xrightarrow{\text{AcOH, MeOH, 60°C}} \text{R}_1 \text{N}^\text{CN} \text{R}_2 \\
\text{R}_3
\end{array}
\]

Scheme 2.1 – Ruthenium-Catalyzed Aerobic Oxidative Cyanation of Tertiary Amines with Sodium Cyanide

The direct carbon-carbon bond formation was postulated to occur by trapping the iminium ion intermediates with a carbon nucleophile under oxidative conditions.

\[
\begin{bmatrix}
\text{R}_2 \\
\text{R}_1 \\
\text{R}_3
\end{bmatrix}
\]

Postulated iminium ion type intermediate.
Previously, we reported the copper-catalyzed CDC reaction between tertiary-amines and nitroalkanes to generate β-nitroamines. The in situ oxidation of tertiary amine in presence of peroxide was postulated to generate a similar iminium ion key intermediate (Scheme 2.2).

$$\text{Scheme 2.2} - \text{Copper-Catalyzed Oxidative Alkylation of Tertiary Amines with Nitroalkanes}$$

In a search for a more environmentally benign and effective method for oxidative transformation of amines, we aimed at accomplishing two tasks at once: (1) oxidation with molecular oxygen in place of peroxides and (2) the use of water as solvent.

2.2 – Optimization of the Reaction Conditions

Tetrahydroisoquinoline, a common substructure in natural compounds, was the tertiary amines of choice. Inspired by the work of Murahashi and co-workers, we examined the CDC reaction between such compounds with nitromethane in the presence of 5 mol% of ruthenium chloride and under one-atmosphere of oxygen gas in water to give 45% yield of the desired CDC reaction product in 18 h. Encouraged by this initial result, we began to optimize the reaction (Table 2.1). The addition of 1 mol % of CuBr significantly increased the yield of the desired product (nearly the same as the result obtained with 10 mol% RuCl₃). With 5 mol % RuCl₃ and 5 mol % CuBr as co-catalysts, 90% of the corresponding CDC product was obtained after 18 h. Interestingly, the use of 5 mol % of CuBr in the absence of RuCl₃ increased the
rate of the reaction to generate 90% of the desired product after 16 h in both methanol and water. It is important to note that the CDC reaction also proceeded efficiently in air and water without the need of oxygen gas, albeit with a reduced reaction rate. After 24 h, 85% of the desired product was obtained with a 99% conversion of the starting material.

**Table 2.1 – Optimization of the Reaction Conditions**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>RuCl₃ (mol %)</th>
<th>CuBr (mol %)</th>
<th>Reaction time (h)</th>
<th>NMR yieldb</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O</td>
<td>5</td>
<td>0</td>
<td>18</td>
<td>45</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>0</td>
<td>0</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>H₂O</td>
<td>10</td>
<td>0</td>
<td>18</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>H₂O</td>
<td>5</td>
<td>1</td>
<td>18</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>H₂O</td>
<td>5</td>
<td>2</td>
<td>18</td>
<td>73</td>
</tr>
<tr>
<td>6</td>
<td>H₂O</td>
<td>5</td>
<td>5</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>H₂O</td>
<td>0</td>
<td>5</td>
<td>16</td>
<td>90</td>
</tr>
<tr>
<td>8</td>
<td>MeOH</td>
<td>0</td>
<td>5</td>
<td>16</td>
<td>90</td>
</tr>
</tbody>
</table>

a Tertiary amine (0.2 mmol) and nitroalkane (0.4 mmol) were stirred under O₂ (1 atm) at 60°C in 0.6 mL of water; b NMR yields based on tetrahydroisoquinoline using an internal standard

**2.3 – Scope of the Oxidative Alkylation of sp³ C-H Bond Using Molecular Oxygen in Water**

Subsequently, oxidative Cross-Dehydrogenative-Coupling between various tertiary amines and nitro-alkanes were examined under the standard conditions of 1 atmosphere oxygen gas in water (Table 2.2). The reaction of 1,2,3,4-tetrahydroisoquinoline derivatives with two equivalents of nitromethane generated the desired coupling products 3a and 3d in excellent yields (entries 1 and 4). Similar
excellent results were obtained in the presence of five equivalents of nitroethane or nitropropane (the ratio of the two diastereoisomers are 3:2) (entries 2, 3, 5 and 6). Substrate 1b with an $N$-$\beta$-methoxyphenyl substituent was found to be more reactive than the simple phenyl substituted analogue for the CDC reaction. In this case, the reactions were highly effective even at 40°C (entries 4, 5, and 6). For the symmetrical $N,N$-dimethyltoluidine, although there is a great potential for forming the bisalkylation by-product, the use of 1 mL (92 equiv) of nitromethane with 0.2 mmol of $N,N$-dimethyltoluidine offered product 3h with good yield in water (entry 8). Nevertheless, in the case of $N,N$-dimethylaniline, the reaction was less efficient. The selectivity for the formation of the CDC product in the absence of a 4-substituted $N,N$-dimethylaniline derivative decreased considerably.
Table 2.2 – Scope of the Oxidative Alkylation of sp³ C-H Bond Using Molecular Oxygen in Water

<table>
<thead>
<tr>
<th>entry</th>
<th>nitroalkanes</th>
<th>T°C</th>
<th>products</th>
<th>yield(%)d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeNO₂</td>
<td>60</td>
<td><img src="image" alt="Product 3a" /></td>
<td>90 (79)b</td>
</tr>
<tr>
<td>2</td>
<td>EtNO₂</td>
<td>60</td>
<td><img src="image" alt="Product 3b" /></td>
<td>90 (75)</td>
</tr>
<tr>
<td>3</td>
<td>PrNO₂</td>
<td>60</td>
<td><img src="image" alt="Product 3c" /></td>
<td>95 (82)</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>40</td>
<td><img src="image" alt="Product 3d" /></td>
<td>95 (72)b</td>
</tr>
<tr>
<td>5</td>
<td>2b</td>
<td>40</td>
<td><img src="image" alt="Product 3e" /></td>
<td>80 (67)</td>
</tr>
<tr>
<td>6</td>
<td>2c</td>
<td>40</td>
<td><img src="image" alt="Product 3f" /></td>
<td>85 (69)</td>
</tr>
<tr>
<td>7</td>
<td>2a</td>
<td>60</td>
<td><img src="image" alt="Product 3g" /></td>
<td>(30)c</td>
</tr>
<tr>
<td>8</td>
<td>2a</td>
<td>60</td>
<td><img src="image" alt="Product 3h" /></td>
<td>75 (63)c</td>
</tr>
</tbody>
</table>

Tertiary amine (0.2 mmol), nitroalkane (1 mmol), CuBr (5 mol%), under O₂ (1 atm) at 60°C for 16 h in 0.6 mL of water; nitromethane (0.2 mmol) was used; nitromethane (1.0 mL, 92 equiv) was used; NMR yields based on tertiary amines with an internal standard (isolated yields are given in brackets).
In addition to nitroalkanes, the oxidative CDC reaction in water with oxygen was also applicable to dialkyl malonate derivatives (Table 2.3). The reactions of dimethyl- and diethylmalonate with 2-phenyl-1,2,3,4-tetrahydroisoquinoline generated β-diester products in good yields in water and with oxygen gas.

**Table 2.3 – CDC Reaction of Tetrahydroisoquinoline with Malonate**

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>EWG</th>
<th>CuBr (5 mol%)</th>
<th>H₂O, 60°C, 24h</th>
<th>O₂ (1 atm)</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>EWG</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td></td>
<td></td>
<td></td>
<td>N</td>
<td>H</td>
<td>H</td>
<td>EWG</td>
</tr>
<tr>
<td>Ph</td>
<td>O</td>
<td>O</td>
<td>O</td>
<td></td>
<td></td>
<td></td>
<td>Ph</td>
<td>O</td>
<td>O</td>
<td>Et</td>
</tr>
<tr>
<td>MeO</td>
<td>O</td>
<td>O</td>
<td>OMe</td>
<td></td>
<td></td>
<td></td>
<td>82</td>
<td>(63)</td>
<td></td>
<td>80</td>
</tr>
</tbody>
</table>

*aTetrahydoisoquinoline (0.2 mmol) and malonate (0.2 mmol) under O₂ at 60°C for 24 h in water;*  
*bNMR yields based on tertiary amines with an internal standard (isolated yield are given in brackets).*

### 2.4 – Proposed Reaction Mechanism

In order to explore the mechanism, measurement of the molecular oxygen uptake was undertaken (Graph 2.1). This study showed that 0.5 mol of molecular oxygen is consumed for the oxidation of 1 mol of 2-phenyl-1,2,3,4-tetrahydroisoquinoline under the standard reaction conditions (For more details concerning the calculations, please see the experimental section 2.6.3).
This suggests that the reaction proceeds via the copper-catalyzed generation of possible iminium-type intermediate $6$ with half of an oxygen molecule. Then, copper can also catalyze a subsequent Henry-type reaction in situ by facilitating the deprotonation of nitroalkanes to generate intermediate $2'$ as reported earlier by Evans (Scheme 2.3).$^7$

$\text{Scheme 2.3} – \text{Proposed Mechanism for the Oxidative sp}^3 \text{ C-H bond Alkylation with Molecular Oxygen in Water.}$
2.5 - Conclusion

In conclusion, a simple and highly efficient C-C bond formation was developed via the reaction of two sp³ C-H bonds catalyzed by copper bromide under an oxygen atmosphere in water. The oxidative CDC reaction appears to be a combination of a copper-catalyzed oxidative transformation of amines to iminium-type intermediates followed by a copper-catalyzed Henry-type reaction. Moreover, this new methodology represented at this time the first example of sp³ C-H functionalization in water.

2.6 – Experimental Section

2.6.1 – General Information

All the experiments were carried out under an atmosphere of oxygen gas. Standard column chromatography was performed on 20-60 µm silica gel (obtained from Silicycle Inc.) using standard flash column chromatography techniques. ¹H NMR spectra were recorded on Varian 300 and 400 MHz spectrometers in CDCl₃ solution and the chemical shifts were reported in parts per million (δ) referenced to the internal solvent signal (peak at 7.26 ppm). ¹³C NMR were obtained at 75 MHz and 100 MHz and referenced to the internal solvent signal (central peak is 77.00 ppm). HRMS were made by McGill University. All reagents were weighed and handled in air, and backfilled under an oxygen atmosphere at room temperature. All reagents were purchased from Aldrich and Across and used without further purification. 2-Aryl-1,2,3,4-tetrahydro-isoquinolines were prepared by the literature method.
2.6.2 – General Procedure for the Oxidative sp³ C-H bond Alkylation with Molecular Oxygen in Water.

To a mixture of CuBr (1.4 mg, 0.01 mmol), 2-phenyl-tetrahydroisoquinoline (42 mg, 0.2 mmol), 0.6 mL of distilled water and CH₃NO₂ (21.5 µL, 0.4 mmol) was added. Then the 20 mL test-tube was sealed and filled up with molecular oxygen. The reaction was stirred using a magnetic stirrer at 60°C for 16h. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel and eluted with ethyl acetate. Solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 5:1), and the fraction with an Rₐ = 0.5 was collected and concentrated to give the desired product 3a.

1,2,3,4-Tetrahydro-1-(nitromethyl)-2-phenylisoquinoline (3a)

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, Rₐ = 0.5). ¹H NMR (400 MHz, ppm) δ 7.25-7.20 (m, 2H), 7.18 (dd, J = 4.4, 1.6 Hz, 1H), 7.16-7.13 (m, 2H), 7.08(d, J = 7.6 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.81 (dd, J = 7.4, 7.4 Hz, 1H), 5.51 (dd, J = 7.6, 6.8 Hz, 1H), 4.81 (dd, J = 12.0, 7.6 Hz, 1H), 4.50 (dd, J = 12.0, 6.8 Hz, 1H), 3.64-3.53 (m, 2H), 3.04 (ddd, J = 14.0, 8.6, 5.2 Hz, 1H), 2.74 (dt, J = 16.4, 4.8 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ ppm 148.2, 135.1, 132.7, 129.3, 129.0, 127.9, 126.8, 126.5, 119.2, 114.9, 78.6, 58.2, 42.0, 26.5. This is a known compound and the spectral data is consistent with the literature.³
1,2,3,4-Tetrahydro-1-(1-nitroethyl)-2-phenylisoquinoline (3b)

The ratio of isolated diastereoisomers is 1.7. Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, \( R_f = 0.6 \)). The major isomer: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) ppm 5.21 (d, \( J = 7.8 \) Hz, 1H), 5.03 (dq, \( J = 8.4, 6.6 \) Hz, 1H), 3.62-3.49 (m, 2H), 1.53 (d, \( J = 6.6 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) ppm 148.7, 135.5, 131.9, 129.3, 129.2, 128.2, 128.1, 126.0, 119.2, 115.3, 85.4, 62.7, 42.7, 26.4, 16.5; The minor isomer: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) ppm 5.24 (d, \( J = 7.8 \) Hz, 1H), 4.87 (dq, \( J = 8.7, 6.9 \) Hz, 1H), 3.82 (ddd, \( J = 13.5, 8.1, 5.7 \) Hz, 2H), 1.69 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) ppm 148.9, 134.6, 133.7, 129.2, 129.0, 128.6, 127.1, 126.5, 118.6, 114.3, 88.9, 61.1, 43.6, 26.8, 17.5; Other overlapped peaks: \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) ppm 7.28-7.18 (m), 7.16-7.06 (m), 7.00-6.95 (m), 6.83-6.76 (m), 3.09-2.99 (m), 2.94-2.81(m). This is a known compound and the spectral data is consistent with the literature.³

1,2,3,4-Tetrahydro-1-(1-nitropropyl)-2-phenylisoquinoline (3c)

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, \( R_f = 0.6 \)). The ratio of diastereomers is 1.4. IR (neat liquid): \( \nu_{\text{max}} \) 3061, 3036, 3024, 2973, 2936, 2879, 2856, 1598, 1577, 1549, 1503, 1494, 1475, 1457, 1438, 1390, 1370, 1346, 1320, 1298,
1269, 1218, 1149, 1122, 1111, 1081, 986 cm⁻¹; The major isomer: ¹H NMR (400 MHz, CDCl₃) δ ppm 5.15 (d, J = 9.6 Hz, 1H), 4.88 (t, J = 9 Hz, 1H), 3.88-3.83 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) δ ppm 149.4, 135.8, 132.8, 129.7, 129.5, 128.9, 128.4, 126.2, 119.7, 116.1, 93.3, 62.5, 42.6; The minor isomer: ¹H NMR (400 MHz, CDCl₃) δ ppm 5.26 (d, 9.6 Hz, 1H), 4.67 (t, 9 Hz, 1H). ¹³C NMR (75 MHz, CDCl₃) δ ppm 149.3, 135.0, 134.2, 129.6, 128.9, 128.5, 127.5, 126.9, 118.9, 114.4, 96.4, 61.0, 43.8, 27.1, 25.3, 11.0. Other overlapped peaks: ¹H NMR (400 MHz, CDCl₃) δ ppm 3.71-3.51 (m), 3.13-2.85 (m), 2.27-2.09 (m), 1.88-1.80 (m), 0.98-0.93 (m); ¹³C NMR (75 MHz, CDCl₃) δ ppm 129.9, 129.6, 129.5, 128.9, 128.5, 127.5, 126.9, 126.2, 27.1, 26.0, 25.3, 24.9, 10.9. HRMS calculated for C₁₈H₂₀O₂N₂: [M⁺] = 296.1525; found: [M⁺] = 296.1511.

1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-(nitromethyl)-isoquinoline (3d)

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, Rᵣ = 0.4). ¹H NMR (400 MHz, CDCl₃) δ ppm 7.24-7.17 (m, 2H), 7.16-7.11 (m, 2H), 6.89 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.37 (dd, J = 8.4, 6.0 Hz, 1H), 4.80 (dd, J = 12.0, 8.8 Hz, 1H), 4.54 (dd, J = 12.0, 6.0 Hz, 1H), 3.73 (s, 3H), 3.60-3.50 (m, 2H), 3.00 (ddd, J = 16.4, 8.8, 6.4 Hz, 1H), 2.68 (dt, J = 16.4, 4.0 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ ppm 153.7, 142.8, 135.2, 132.7, 129.3, 127.7, 126.7, 126.4, 118.7, 114.6, 78.9, 58.9, 55.6, 43.2, 25.9. This is a known compound and the spectral data is consistent with the literature.³
1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-(1-nitroethyl)-isoquinoline (3e)

The ratio of isolated diastereoisomers is 1.7. Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, R_f = 0.4). The major isomer: ^1^H NMR (300 MHz, CDCl₃) δ ppm 3.72 (s, 3H), 3.53-3.44 (m, 2H), 1.52 (d, J = 6.6 Hz, 3H); ^13^C NMR (75 MHz, CDCl₃) δ ppm 153.6, 143.3, 135.7, 131.9, 129.1, 128.3, 127.9, 125.9, 118.7, 114.4, 85.7, 63.4, 55.5, 44.0, 26.0, 16.7; The minor isomer: ^1^H NMR (300 MHz, CDCl₃) δ ppm 4.85 (dq, J = 8.6, 6.6 Hz, 1H), 3.81-3.75 (m, 2H), 3.74 (s, 3H), 1.67 (d, J = 6.9 Hz, 3H); ^13^C NMR (75 MHz, CDCl₃) δ ppm 153.3, 143.7, 134.9, 133.5, 128.8, 127.8, 127.1, 126.4, 118.1, 114.6, 88.8, 62.1, 56.6, 45.0, 26.3, 17.2; Other overlapped peaks: ^1^H NMR (300 MHz, CDCl₃) δ ppm 7.25-7.07 (m), 7.01-6.98 (m), 6.92-6.87 (m), 6.83-6.75 (m), 5.06-4.93 (m), 3.02-2.92 (m), 2.84-2.72(m). This is a known compound and the spectral data is consistent with the literature.³

1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)-1-(1-nitropropyl)-isoquinoline (3f)

Isolated by flash column chromatography (eluent: hexane/ethyl acetate = 5:1, R_f = 0.4). The ratio of diastereomers is 1.4. IR (neat liquid): ν_max 3062, 3042, 3021, 2952, 2932, 2852, 2834, 1607, 1581, 1556, 1553, 1549, 1514, 1506, 1493, 1463, 1441, 1386, 1371, 1347, 1293, 1267, 1246, 1183, 1146, 1120, 1038 cm⁻¹; The major isomer: ^1^H NMR
(300 MHz, CDCl$_3$) $\delta$ ppm 4.93-4.8 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 154.1, 136.0, 132.8, 129.0, 128.3, 126.1, 119.4, 114.7, 93.5, 63.2, 55.8, 43.8, 25.6, 24.9, 11.0. The minor isomer: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 5.03 (d, $J = 9$ Hz, 1H), 4.67 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 153.5, 135.1, 134.0, 129.1, 127.5, 126.8, 117.8, 115.0, 96.3, 61.8, 55.9, 44.9, 26.5, 25.2, 10.9. Other overlapped peaks: $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.26-7.18 (m), 7.16-6.74 (m), 3.87-3.72 (m), 3.61-3.47 (m), 3.06-2.95 (m), 2.83-2.73 (m), 1.86-1.80 (m), 0.97-0.94 (m); $^{13}$C NMR (75 MHz, CDCl$_3$). $\delta$ ppm 144.0, 129.7. HRMS calculted for C$_{19}$H$_{22}$O$_3$N$_2$: [M$^+$] = 326.1630; found: [M$^+$] = 326.1617.

$N$-Methyl-$N$-(2-nitroethyl)benzenamine (3g)

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.4$). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.28-7.22 (m, 2H), 6.78 (dd, $J = 7.2$, 7.2 Hz, 1H), 6.72 (dd, $J = 9.0$, 0.9 Hz, 2H), 4.56 (t, $J = 6.3$ Hz, 2H), 4.00 (td, $J = 6.6$ Hz, 2H), 2.98 (s, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 147.6, 129.4, 117.9, 112.5, 72.6, 50.6, 38.9. This is a known compound and the spectral data is consistent with the literature.$^3$
**N,4-Dimethyl-N-(2-nitroethyl)benzenamine (3h)**

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, Rf = 0.5). $^1$H NMR (300 MHz, CDCl$_3$) δ ppm 7.05 (d, $J = 8.7$ Hz, 2H), 6.64 (d, $J = 8.7$ Hz, 2H), 4.52 (t, $J = 6.3$ Hz, 2H), 3.93 (t, $J = 6.3$ Hz, 2H), 2.92 (s, 3H), 2.25 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 145.6, 129.9, 127.3, 113.0, 73.0, 51.0, 39.0, 20.3. This is a known compound and the spectral data is consistent with the literature.$^3$

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**2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid dimethyl ester (5a)**

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, Rf = 0.5). $^1$H NMR (400 MHz, CDCl$_3$) δ ppm 7.23-7.17 (m, 3H), 7.14-7.05 (m, 3H), 6.98 (d, $J = 8.0$ Hz, 2H), 6.76 (dd, $J = 7.2$, 7.2 Hz, 1H), 5.70 (d, $J = 9.2$ Hz, 1H), 3.95 (d, $J = 9.2$ Hz, 1H), 3.76-3.60 (m, 2H), 3.66 (s, 3H), 3.55 (s, 3H), 3.08 (ddd, $J = 16.0$, 8.4, 6.3 Hz, 1H), 2.90 (dt, $J = 16.0$, 5.1 Hz, 1H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ ppm 168.0, 167.1, 148.6, 135.5, 134.6, 128.9, 128.8, 127.5, 126.9, 125.9, 118.5, 115.0, 59.1, 58.1, 52.5, 52.5, 42.1, 26.1. This is a known compound and the spectral data is consistent with the literature.$^6$
2-(2-Phenyl-1,2,3,4-tetrahydro-isoquinolin-1-yl)-malonic acid diethyl ester (5b)

Isolated by flash column chromatography (hexane/ethyl acetate = 5:1, Rf = 0.5). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ ppm 7.24-7.05 (m, 6H), 6.96 (d, $J = 8.1$ Hz, 2H), 6.72 (dd, $J = 7.2$, 7.2 Hz, 1H), 5.71 (d, $J = 9.3$ Hz, 1H), 4.17-3.93 (m, 4H), 3.88 (d, $J = 9.0$ Hz, 1H), 3.74-3.58 (m, 2H), 3.06 (ddd, $J = 16.5$, 8.7, 6.3 Hz, 1H), 2.87 (dt, $J = 16.5$, 5.1 Hz, 1H), 1.16 (t, $J = 7.2$ Hz, 3H), 1.08 (t, $J = 7.2$ Hz, 3H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ ppm 167.7, 166.9, 148.6, 135.8, 134.6, 128.9, 128.7, 127.4, 127.0, 125.9, 118.3, 114.9, 61.6, 59.5, 57.8, 42.3, 26.1, 14.0, 13.9. This is a known compound and the spectral data is consistent with the literature.$^6$

2.6.3 – Measurement of Molecular Oxygen Uptake for Copper-Catalyzed Aerobic Alkylation of Csp$_3$-H Bond

In a 10 mL schlenk flask equipped with a magnetic stirring bar and connected to a gas pressure sensor (Vernier; GPS-BTA), CuBr (1.4 mg, 0.01 mmol) was added ($V_{\text{tot}} = 17$ mL). After the reaction was flushed with molecular oxygen (1 atm), methanol (0.6mL) was added. After the flask was immersed in an oil bath at 60 °C, for 1h to stabilize, 2-phenyl-tetrahydroisoquinoline (42 mg, 0.2 mmol), dissolved in diethylphosphonate (21.5 µL, 0.4 mmol), was injected with a micro-syringe to start the reaction. The consummation of oxygen was monitored every minute using logger Pro 3.0. The decrease of pressure in the system represented the amount of oxygen consumed during the process.

\[ pV = nRT \]

$Vi$ : initial Volume = $V_f$ : final volume = $V$

$T_i$ : initial Temperature = $T_f$ : final Temperature = $T$

$n_i$ : initial moles of $O_2$ $n_f$ : final moles of $O_2$

moles of oxygen consumed = $(n_f-n_i) = [(p_i-p_f)V]/(RT)$
Reference for Chapter 2


Part II. Cross-Dehydrogenative-Coupling for C-P Bond Formation
Chapter 3 – Introduction to Phosphorus-Carbon Bond Formation.

Interest in the preparation of organophosphorus compounds has continued to expand in recent years. This is a direct result of developing applications for phosphorus compounds in numerous synthetic procedures as well as an understanding of the role of the element biological systems.

The Arbuzov reaction (Michaelis-Arbuzov reaction) of trialkyl phosphate with an alkyl halide to produce an alkyl phosphonate represents the most famous example of carbon-phosphorus bond formation. The first step involves nucleophilic attack by the phosphorus on the alkyl halide, followed by the ion dealkylation of the resulting trialkyloxyphosphonium salt (Scheme 3.1).1

![Scheme 3.1 – The Arbuzov Reaction](image)

This reaction has found extensive applications in the preparation of phosphate esters for the use in the Horner-Emmons Reaction.

Research in the concept of carbon-phosphorus bond formation attracted considerable attention in recent decades. In regards to our research presented in chapter 4, the following brief overview, will focus on the most recent work using H-phosphonate (dialkyl phosphonate) as the phosphorus source.

3.1 – Metal-Catalyzed Arbuzov-Type Reaction

Stawinski and co-workers recently reported a representative example of palladium-catalyzed C-P bond formation. They described a microwave-assisted
palladium-catalyzed cross-coupling of aryl and vinyl halides with H-phosphonate diesters. The procedure is highly efficient and provides rapid access to broad spectrum of phosphonate diesters (Scheme 3.2).²

![Chemical Reaction Diagram]

**Scheme 3.2 – Palladium-Catalyzed Arbuzov-Type Reactions**

There is a consensus that palladium-catalyzed cross-coupling reactions with heteroatom nucleophiles follow a three-step catalytic cycle, which for the example of H-phosphonates, is depicted in scheme 3.3.³
3.2 – Addition of H-Phosphonates to Unsaturated Hydrocarbons.

H-phosphonate addition to alkenes, allenes, and alkynes has been, and continues to be an area of intensive research, because it is the most atom-economical way to prepare organophosphonate diesters.

In 1958, Stiles and co-workers reported the first study of radical addition of H-phosphonates to alkenes. Moderate yields were obtained for the addition of different H-phosphonates to various terminal and internal alkenes in the presence of tert-butyl peroxide. Nifant’ev and co-workers reported an improvement in the radical reaction induced by decomposition of the benzoyl prooxide, by addition of a catalytic amount of acetic or oxalic acid (Scheme 3.4).
Scheme 3.4 – Radical Addition of H-Phosphonates to Cyclic Alkenes.

In 2004, an efficient radical hydrophosphonation was published by Ishii and co-workers with the use of Mn(OAc)$_2$ in air. The authors suggested that Mn$^{II}$ was oxidized from air to Mn$^{III}$, which catalyzed the addition. Ishii and coworkers described one example of a terminal alkyne. Under these conditions, the addition led to anti-Markovnikov products in good yields (Scheme 3.5).

Scheme 3.5 – Manganese-Catalyzed Addition of H-Phosphonates to Alkenes and Alkynes

A large number of studies have been reported on the transition-metal-catalyzed addition of H-phosphonates to alkynes. Depending on the metal (Pd, Ni, Rh) employed, it gives the opportunity to tune the regio- and stereoselectivity of the addition.
3.3 – Oxidative Dialkylarylphosphonate Synthesis

After the discovery of the Mn$^{II}$/Co$^{II}$/O$_2$ redox system for the addition of diethyl phosphite to alkenes, Ishii and his group developed a catalytic phosphonation of benzenes with dialkylphosphites such as HP(O)(OEt)$_2$ by the same redox system under mild conditions (Scheme 3.6).$^7$

![Scheme 3.6 – Manganese-Catalyzed Oxidative Phosphonation of benzenes](image)

In a stoichiometric fashion, Zhang and co-workers reported in 2006 the manganese(III) acetate promoted regioselective phosphonation of heteroaryl compounds. Reaction of thiazoles, furans and pyrroles with dimethyl or diethylphosphites gave phosphonated products in high yield and good regioselectivity (Scheme 3.7).$^8$

![Scheme 3.7 – Manganese-Mediated Phosphonation of Heteroaryl Compounds](image)
3.4 – The Kabatschnick–Fields Reaction

Numerous Lewis-acid metal catalysts have shown efficiency in the synthesis of α-amino phosphonates from the addition of dialkyl phosphites (H-phosphonates) to isolated and in situ generated imines. One of the most recent example of metal-catalyzed the three-component (aldehyde-amine-phosphonate) reaction was published by Feng and co-workers. The $N,N'$-dioxide-Sc(III) complex catalyzed the reaction of aldehydes, 2-aminophenol and diphenyl phosphite to produce the corresponding α-amino phosphonates in good yields with high enantioselectivities (Scheme 3.8).

$$\begin{align*}
\text{R} &= \text{benzene derivatives} \\
\text{O} + \text{OH} + \text{NH}_2 + \text{O} &\rightarrow \text{O}_\text{P} \text{(OPh)}_2 \\
\text{THF, } -20 \, ^\circ \text{C, 1 h} &\rightarrow \text{HN}_\text{P} \text{(OPh)}_2 \text{O} \\
3: \text{Ar} &= 2,6-\text{iPr}_2\text{C}_6\text{H}_3
\end{align*}$$

**Scheme 3.8** – Scandium-Catalyzed Asymmetric α-Amino Phosphonates Synthesis

The asymmetric organocatalysis using a wide range of small molecules has recently emerged as an essential tool of asymmetric organic synthesis. Jacobsen et al reported the use of chiral thiourea as the efficient catalyst for the enantioselective hydrophosphonylation of benzylimines. Petterson and coworkers demonstrated a simple and efficient organocatalytic enantioselective hydrophosphonylation of imines by using commercially available quinine as the catalyst. Most recently, the analogous chiral phosphoric acid catalyzed direct asymmetric Kabachnik-Fields reaction of aldehydes, anisidine ad di(3-pentyl)phosphite has been reported by List and coworkers. The chiral phosphoric acid bifunctional catalyst activated simultaneously both the electrophile and the nucleophile (Scheme 3.9).
Scheme 3.9 – Organocatalytic Enantioselective Hydrophosphonylation of Imines
References for Chapter 3

Chapter 4 – Copper-Catalyzed Aerobic Phosphonation of \( \text{sp}^3 \) C-H Bond.

As illustrated in chapter 3, the development of new methods to create a phosphorus-carbon bond has attracted considerable attention in the past and remains a challenge for organic chemists. Therefore, we became interested in developing a new environmentally friendly process for the formation of C-P bond via direct oxidative coupling of C-H bond and P-H bond.

4.1 - Background

\( \alpha \)-Aminophosphonates and their corresponding \( \alpha \)-amino-phosphonic acids have received much interest in organic and medicinal chemistry because they are analogous to both natural and unnatural amino acids.\(^1\) Moreover, \( \alpha \)-aminophosphonates have broad applications due to their antibacterial,\(^2\) antifungal,\(^3\) enzyme inhibitory\(^4\) and catalytic antibody activities.\(^5\) One of the most convenient methods for synthesizing such compounds is the nucleophilic addition of phosphonate to imine (generated in situ) catalyzed by Lewis acid (Kabatchnick–Fields reaction).\(^6\)

\[
\begin{array}{c}
\text{N}^+ \text{N} \\
\text{R}_2 \\
\text{R}_1 \\
\text{H} \\
\text{P(OR)}_2 \\
\text{O} \\
\text{H} \\
\text{R}_2 \\
\text{R}_1 \\
\text{Cat. Lewis Acid} \\
\end{array}
\]

**Scheme 4.1 -** Lewis Acid-Catalyzed H-Phosphonate Addition to Imine

As part of our continued interest in using molecular oxygen as a terminal oxidant we decided to investigate the dehydrogenative C-P bond formation.

\[
\text{C-H} + \text{H-P} \xrightarrow{\text{cat. M}} \text{[O]} \text{C-P}
\]
4.2 - Optimization of the Reaction Conditions

We postulated the applicability of the simple, environmentally healthy and safe selective aerobic Cross-Dehydrogenative-Coupling method in water to the direct synthesis of α-aminophosphonates.\(^7\)

![Scheme 4.2 - Postulated Aerobic Carbon-Phosphorous Bond Formation.](image)

For the purpose of optimization of the experimental conditions, we chose a model coupling reaction between N-phenyltetrahydroisoquinoline 1a and diethylphosphite 7a. We were pleased to observe the excellent efficiency of copper bromide to catalyze, in water, the desired reaction under an atmosphere of oxygen (Table 4.1, entry 1). Unfortunately, water did not appear to be a suitable solvent for all phosphite substrates. In fact, when dimethylphosphite was used instead of diethylphosphite 7a, under the same conditions the desired product was obtained in a low 30% NMR yield (entry 2). Surprisingly, the yield could be increased to 65% by lowering the excess of dimethylphosphite 7b (entry 3). Nevertheless, the conditions were not applicable to PMP-tetrahydroisoquinoline 1b, for which no product was obtained in the presence of 7b.

We postulated that 7b was easily hydrolyzed in water under the reaction conditions and the phosphoric acid generated \textit{in-situ} interfered with the basic tertiary amine substrate. To overcome this issue we decided to perform the reaction in non-aqueous conditions. Methanol was shown to be an efficient solvent for a number of oxidative couplings\(^7\)\(^8\) and gratifying, excellent yields were obtained when reacting 7b
and 1b in methanol (entries 7-10). Other copper salts were also investigated as catalysts. Interestingly, most of the other copper salts investigated could catalyze the C-P bond formation in good to excellent yields (entries 9-12). On the other hand, only a trace amount of the desired product was detected in the absence of either oxygen or copper.

**Table 4.1 - Optimization of the Reaction Conditions**

<table>
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<tr>
<th>Entry</th>
<th>[Cu]</th>
<th>Ar</th>
<th>R</th>
<th>Equiv. of 7</th>
<th>Solvent</th>
<th>NMR Yieldb</th>
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<tr>
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<td>Me (7b)</td>
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<td>30</td>
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<tr>
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<td>H2O</td>
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<td>Ph</td>
<td>Et</td>
<td>2</td>
<td>MeOH</td>
<td>&lt;10</td>
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</table>

a Tetrahydroisoquinoline (0.1 mmol). b NMR yields using an internal standard. c Not determined. d Under nitrogen.
4.3 – Scope and Limitations of the Aerobic Phosphonation

Under the optimized conditions the new Cross-Dehydrogenative-Coupling method to create new sp$^3$ C-P bonds was efficient for a number of different phosphites (Table 4.2). Not only diethylphosphite offered almost quantitative yield by NMR, but dimethyl-, diisopropyl- and dibenzylphosphites were also employed with high efficiency using the new methodology (entries 1-4). Interestingly, replacement of dialkylphosphite with trialkylphosphite failed to generate the phosphonated product.

Table 4.2 – Scope of the Aerobic Phosphonation Reaction.

<table>
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<tr>
<th>Entry</th>
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<th>Product</th>
<th>Yield$^b$</th>
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<td>H$_2$P(OEt)$_2$</td>
<td>8a</td>
<td>(95) 79</td>
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<td></td>
<td></td>
<td></td>
<td>7a</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>H$_2$P(OMe)$_2$</td>
<td>8b</td>
<td>(90) 74</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>7b</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>H$_2$P(OiPr)$_2$</td>
<td>8c</td>
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<tr>
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<td>(80) 69</td>
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<td></td>
<td></td>
<td>7d</td>
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$^a$ Tetrahydroisoquinoline (0.2 mmol).$^b$ Isolated yields (NMR yields based on tertiary amines with an internal standard).
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<tbody>
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<td>7a</td>
<td>8e</td>
<td>(75) 67</td>
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<tr>
<td>6</td>
<td>1b</td>
<td>7b</td>
<td>8f</td>
<td>(75) 69</td>
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<tr>
<td>7</td>
<td>1b</td>
<td>7c</td>
<td>8g</td>
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</tr>
<tr>
<td>8</td>
<td>1b</td>
<td>7d</td>
<td>8h</td>
<td>(85) 55</td>
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<td>8i</td>
<td>(75) 61</td>
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<td>1c</td>
<td>7b</td>
<td>8j</td>
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</tr>
<tr>
<td>11</td>
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<tr>
<td>12</td>
<td>1c</td>
<td>7d</td>
<td>8l</td>
<td>(75) 69</td>
</tr>
</tbody>
</table>

<sup>a</sup> Tetrahydroisoquinoline (0.2 mmol),<sup>b</sup> Isolated yields (NMR yields based on tertiary amines with an internal standard).
The desired coupling products were also obtained in good yield when \( p \)-methoxyphenyl-tetrahydroisoquinoline (7b) was employed in place of \( N \)-phenyltetrahydroisoquinoline (7a) (entries 5-8). The use of this particular amine protecting group constitutes an undoubtable advantage since it can be easily removed, offering ready access to the secondary amine. Moreover, aryl-protected amines are an important feature in the efficiency of the aerobic Cross-Dehydrogenative-Coupling method. They facilitate the reaction by stabilizing the oxidized forms of the tertiary amine.\(^9\) As a representative example, when \( N \)-methyltetrahydroisoquinoline was employed, no coupling product was detected by \(^1\)H and \(^{31}\)P NMR (Scheme 4.3).

\[
\begin{align*}
\text{N} & \quad \text{Me} \\
\text{Me} & \quad \text{H} \\
\text{P(OEt)}_2 & \quad \text{CuBr (5 mol %)} \\
\text{MeOH}; \text{O}_2 (1 \text{ atm.}) & \quad 60^\circ \text{C}, 16 \text{ h} \\
\text{No desired product}
\end{align*}
\]

**Scheme 4.3** - Unsuccessful \( N \)-Methyltetrahydroisoquinoline.

The possibility of a stabilized radical and/or cation intermediate may explain the regioselectivity observed for the benzylic position over the aliphatic one. In fact, saturated cyclic amines such as \( N \)-phenylpyrrolidine and \( N \)-phenylpiperidine were inefficient substrates for the aerobic sp\(^3\)C-H bond phosphonation (Scheme 4.4).

\[
\begin{align*}
\text{N-phenylpiperidine} & \quad \text{N-phenylpyrrolidine}
\end{align*}
\]

**Scheme 4.4** - Unsuccessful Saturated Cyclic Amines.
Interestingly, the cross-coupling product could also be obtained in good yields when the more sterically hindered $o$-methoxyphenyl-amine protecting group was tested (entries 9-12). It is important to note that, $o$-methoxyphenyl represents another example of a removable protecting group (Table 4.2).

4.4 – Mechanism of the Aerobic Phosphonation Reaction

The mechanism remains uncertain at this time. Nevertheless, in order to acquire a better understanding of the overall oxidation process, we performed the molecular oxygen uptake experiment. We and Murahashi previously demonstrated the necessity to consume only half an equivalent of molecular oxygen in the presence of metal catalyst to generate one equivalent of the now well-established iminium-type intermediate 6.

![Graph 4.1](image)

**Graph 4.1** – Molecular Oxygen Uptake Experiment for the Aerobic Phosphonation Reaction (see experimental section 4.6.3 for details concerning the calculations)

Surprisingly, the result of the molecular oxygen uptake in the standard reaction conditions for the Cross-Dehydrogenative-Coupling between 1a and 7a revealed a
total consumption of one equivalent of oxygen for the generation of one equivalent of the desired product (Graph 4.1). The explanation for this interesting result resides in the excess of the substrate 7a. In fact, concurrently with the oxygen consumption for the desired coupling reaction, oxygen is also involved in the oxidation of the excess diethylphosphonate 7a with methanol to methyl-diethylphosphate 10. This result successfully corroborates our first hypothesis of in situ generation in water of dialkylphosphoric acid which interferes with the oxidation of the tertiary amine substrate 1a; a phenomenon which could be avoided by the use of methanol as solvent.

![Scheme 4.5 – Copper-Catalyzed Oxidation of H-Phosphonate](image)

Moreover, in the presence of 1 equivalent of 1a and only 1 equivalent of 7, the molecular oxygen uptake experiment revealed the consumption of exactly half an equivalent of oxygen offering respectively 70% of the desired product and 30% of trialkylphosphate.

On the other hand, the phosphonate 7 is known to be in equilibrium with the nucleophilic phosphite species. The reactive phosphite form reacts with intermediate 6 to produce the desired coupling product and one molecule of water. It is important to note that the addition of dialkylphosphite on the corresponding preformed iminium salt of 1a in presence of triethylamine, offered 8a, demonstrating the sufficient nucleophilicity of dialkylphosphite under these conditions (Scheme 4.6).
Scheme 4.6 - Phosphonate Addition With Preformed Iminium Salt

Nevertheless, copper catalyst might also play a role in the phosphonate/phosphite equilibrium by facilitating the deprotonation of the former and subsequently accelerate the rate of the reaction.

Scheme 4.7 – Tentative Mechanism for the Aerobic Phosphonation Reaction
4.5 – Conclusion

In summary, an unprecedented copper catalyzed aerobic phosphonation of $sp^3$C-H bond adjacent to a nitrogen atom has been developed. This new method provides a simple way to synthesize biologically important $\alpha$-aminophosphonates. The use of a relatively cheap copper salt as catalyst, oxygen as a safe oxidant and high regioselectivity are some of the numerous advantages of this new method.

4.6 – Experimental Section

4.6.1 - General Information

All experiments procedures were carried out under an atmosphere of oxygen gas. Standard column chromatography was performed on 20-60 µm silica gel (obtained from Silicycle Inc.) using standard flash column chromatography techniques. $^1$H NMR spectra were recorded on Varian 400 MHz spectrometers in CDCl$_3$ solution and the chemical shifts were reported in parts per million (δ) referenced to the internal solvent signal (peak at 7.26 ppm). The peak patterns are indicated as following: s, singlet; d, doublet; t, triplet; The coupling of constants, $J$, are reported in Hertz (Hz). $^{13}$C NMR were obtained at 75 MHz and 125 MHz and referenced to the internal solvent signal (central peak is 77.00 ppm). $^{31}$P NMR were obtained at 81 MHz and calibrated with (peak at 0.00 ppm). MS data were obtained by Agilent 6890N Network GC/ System/Agilent 5973 Mass Selective Detector. HRMS were made by McGill University. IR spectra were recorded by an ABB Bomem MB100 instrument. All reagents were weighed and handled in air at room temperature. All reagents were purchased from Aldrich and Acros and used without further purification. 2-Aryl-1,2,3,4-tetrahydro-isoquinolines were prepared by the literature method.$^{[1]}$
4.6.2 - General Procedure

To a mixture of CuBr (1.4 mg, 0.01 mmol), 2-phenyl-tetrahydroisoquinoline (42 mg, 0.2 mmol), 0.6 mL of dried methanol and (51.5 µL, 0.4 mmol) HPO(OEt)$_2$ was added. Then the 20 mL test-tube was sealed and filled up with molecular oxygen. The reaction was stirred using a magnetic stirrer at 60°C for 16h. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel and eluted with ethyl acetate. Solvent was evaporated and the residue was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate = 1:1), and the fraction with an $R_f = 0.2$ was collected and concentrated to give the desired product 8a.

1-Phenyl-2-diethylphosphonate -1,2,3,4-tetrahydroisoquinoline (8a).

$^1$H NMR (400MHz, CDCl$_3$, 293K): δ ppm 7.36-7.38 (m, 1H), 7.13-7.27 (m, 5H), 6.97 (d, 2H, $J = 8.8$ Hz), 6.79 (t, 1H, $J = 7.6$ Hz), 5.26 (d, 1H, $J = 20.4$ Hz), 3.84-4.13 (m, 5H), 3.59-3.65 (m, 1H) 2.95- 3.11 (m, 2H), 1.24 (t, 3H, $J = 6.8$Hz), 1.15 (t, 3H, $J = 6.8$Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$, 293K): δ ppm 149.3 (d, $J = 6$ Hz), 136.4 (d, $J = 5.4$ Hz), 130.6, 129.1, 128.7 (d, $J = 2.5$ Hz), 128.1(d, $J = 4.6$ Hz), 127.4 (d, $J = 3.7$ Hz), 125.8 (d, $J = 2.9$ Hz), 118.4, 114.6 (d, $J = 6.9$ Hz), 63.2 (d, $J = 7.1$ Hz), 62.2 (d, $J = 7.3$ Hz), 58.8 (d, $J = 158$ Hz), 43.4, 26.7, 16.4 (d, $J = 6.3$ Hz), 16.3 (d, $J = 6.3$).

$^{31}$P NMR 81 MHz, CDCl$_3$, 293K): δ ppm 23.3 (s) IR: $\nu_{max}$/cm$^{-1}$ 3062, 3037, 2980, 2908, 2862, 1593, 1505, 1232, 1021, 959, 743. HRMS: Calculated for C$_{19}$H$_{24}$NO$_3$P: [M$^+$] = 345.1494; Found: [M$^-$] = 345.1481.
1-Phenyl-2-dimethylphosphonate-1,2,3,4-tetrahydroisoquinoline (8b).

$^1$H NMR (400 MHz, CDCl$_3$, 293K): $\delta$ ppm 7.35-7.37 (m, 1H), 7.15-7.29 (m, 5H), 6.98 (d, 2H, J = 8.4 Hz), 6.81 (t, 1H, J = 7.2 Hz), 5.20 (d, 1H, J = 19.6 Hz), 3.98-4.05 (m, 1H), 3.61-3.67 (m, 7H), 2.99-3.11 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K, TMS): $\delta$ ppm 149.2 (d, $J = 6$ Hz), 136.4 (d, $J = 5.7$ Hz), 130.33, 129.21, 128.8 (d, $J = 2.6$ Hz), 127.9 (d, $J = 4.5$ Hz), 127.5 (d, $J = 3.4$ Hz), 126.0, (d, $J = 2.7$ Hz), 118.6, 114.7, 58.7 (d, $J = 160$ Hz), 53.9 (d, $J = 7.2$ Hz), 52.9 (d, $J = 7.7$ Hz), 43.5, 26.6. $^{31}$P NMR 81 MHz, CDCl$_3$, 293K): $\delta$ ppm 25.5 (s). IR: $\nu_{\text{max}}$/cm$^{-1}$ 3054, 3033, 2950, 2896, 2856, 1593, 1504, 1236, 1062, 1001, 738. HRMS: Calculated for C$_{17}$H$_{20}$NO$_3$P: [M$^+$] = 317.1181; Found: [M$^+$] = 317.1178.

1-Phenyl-2-diisopropylphosphonate-1,2,3,4-tetrahydroisoquinoline (8c):
1H NMR (400MHz, CDCl₃, 293K):
δ ppm 7.39-7.41 (m, 1H), 7.11-7.25 (m, 5H), 6.95 (d, 2H,  J = 8 Hz), 6.76 (t, 1H,  J = 7.0 Hz), 5.14 (d, 1H,  J = 21.2 Hz), 4.57-4.66 (m, 2H), 4.01- 4.08 (m, 1H), 3.61-3.68 (m, 1H), 2.92-3.06 (m, 2H), 1.29 (d, 3H,  J = 6 Hz), 1.28 (d, 3H,  J = 7.2 Hz), 1.16 (d, 3H,  J = 6 Hz), 0.94 (d, 3H,  J = 6 Hz).

13C NMR (75 MHz, CDCl₃, 293K, TMS):
δ ppm 149.5 (d,  J = 6.6 Hz), 136.4 (d,  J = 5.4 Hz), 130.9 (d,  J = 1.4 Hz), 128.9, 128.6 (d,  J = 2.5 Hz), 128.4 (d,  J = 4.3 Hz), 127.2 (d,  J = 3.8 Hz), 125.5 (d,  J = 2.8 Hz), 118.2, 114.8 (d,  J = 0.8 Hz), 72.2 (d,  J = 7.8 Hz), 70.8 (d,  J = 8.3 Hz), 57.7 (d,  J = 166 Hz), 43.4, 26.5, 24.5 (d,  J = 2.9 Hz), 24.1 (d,  J = 3.1 Hz), 23.7 (d,  J = 5.6 Hz), 23.2 (d,  J = 5.7 Hz).

31P NMR 81 MHz, CDCl₃, 293K):
δ ppm 22.0 (s).

IR: νmax /cm⁻¹ 3035, 2973, 2928, 2866, 1594, 1504, 1233, 982, 745. HRMS: Calculated for C₂₁H₂₈NO₃P: [M⁺] = 373.1807; Found: [M⁺] = 373.1802.

1-Phenyl-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (8d).

1H NMR (400MHz, CDCl₃, 293K):
δ ppm 7.11-7.34 (m, 16H), 6.97 (d, 2H,  J = 8.0 Hz), 6.79 (t, 1H,  J = 7.2 Hz), 5.28 (d, 1H,  J = 19.6 Hz), 4.74-5.31 (m, 4H), 3.98-4.05 (m, 1H), 3.59-3.64 (m, 1H), 2.96-3.09 (m, 2H).

13C NMR (75 MHz, CDCl₃, 293K):
δ ppm 149.1 (d,  J = 5.7 Hz), 136.4 (d,  J = 5.7 Hz), 136.2 (d,  J = 6 Hz), 136.1 (d,  J = 6 Hz), 130.3, 129.1, 128.7 (d,  J = 2.9 Hz), 128.3 (d,  J = 6.8 Hz), 128.2, 128.1, 128.1, 127.9 (d,  J = 3.7 Hz), 127.5, (d,  J = 3.4 Hz), 125.9, (d,  J = 2.9 Hz), 118.5, 114.8, 68.5 (d,  J = 7.2 Hz), 67.6 (d,  J = 8 Hz), 59.0 (d,  J = 158 Hz), 43.5, 26.7.

31P NMR 81 MHz, CDCl₃, 293K):
δ ppm 24.1 (s). IR: νmax /cm⁻¹ 3063, 3032, 2851,
1594, 1503, 1453, 1384, 1234, 1209, 1172, 1011, 981, 727. **HRMS:** Calculated for C_{29}H_{28}NO_{3}P: \([M^+]= 469.1807\); Found: \([M^+]= 469.1791\).

![Chemical Structure](image)

1-(4-Methoxyphenyl) -2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (8e)

\(^1\)H NMR (400MHz, CDCl\(_3\), 293K): \(\delta\) ppm 7.37-7.39 (m, 1H), 7.12-7.21 (m, 3H), 6.9-6.93 (m, 2H), 6.79-6.83 (m, 2H), 5.02 (d, 1H, \(J = 21.6\) Hz), 3.84-4.15 (m, 5 H), 3.75 (s, 3H), 3.52-3.57 (m, 1H), 2.91-2.93 (m, 2H), 1.25 (t, 3H, \(J = 6.8\) Hz), 1.16 (t, 3H, \(J = 6.8\) Hz). \(^{13}\)C NMR (125 MHz, CDCl\(_3\), 293K): \(\delta\) ppm 153.0, 144.1 (d, \(J = 7.9\) Hz), 136.4 (d, \(J = 6.0\) Hz), 130.5, 128.9 (d, \(J = 2.3\) Hz), 128.1(d, \(J = 4.6\) Hz), 127.2 (d, \(J = 3.6\) Hz), 125.8 (d, \(J = 2.8\) Hz), 117.6, 114.5, 63.4 (d, \(J = 7.1\) Hz), 62.2 (d, \(J = 7.8\) Hz), 59.4 (d, \(J = 159\) Hz), 55.6, 44.6, 26.1, 16.5 (d, \(J = 5.5\) Hz), 16.4 (d, \(J = 5.5\) Hz). \(^{31}\)P NMR 81 MHz, CDCl\(_3\), 293K): \(\delta\) ppm 23.3 (s). **IR:** \(\nu_{\text{max}}/\text{cm}^{-1}\) 3063, 3033, 2929, 2850, 1594, 1576, 1504, 1454, 1384, 1234, 1210, 1029, 1011, 981. **HRMS:** Calculated for C_{20}H_{26}NO_{4}P: \([M^+]= 375.1599\); Found: \([M^+]= 375.1602\).
1-(4-Methoxyphenyl)-2-diisopropylphosphonate-1,2,3,4-tetrahydroisoquinoline (8g):

$^1$H NMR (400MHz, CDCl$_3$, 293K): δ ppm 7.35-7.38 (m, 1H), 7.15-7.29 (m, 5H), 6.92 (d, 2H, J = 9.2 Hz), 6.82 (d, 2H, J = 9.2 Hz), 5.05 (d, 1H, J = 21.6 Hz), 3.98-4.05 (m, 1H), 3.74 (s, 3H), 3.64-3.68 (m, 6H) 3.51-3.57 (m, 1H), 2.90-2.92 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K, TMS): δ ppm 153.1, 143.8 (d, $J$ = 8.5 Hz), 136.3 (d, $J$ = 6.0 Hz), 130.1, 128.9 (d, $J$ = 2.6 Hz), 127.9 (d, $J$ = 4.3 Hz), 127.3 (d, $J$ = 3.4 Hz), 125.9, (d, $J$ = 2.9 Hz), 117.5, 114.4, 59.3 (d, $J$ = 159 Hz), 55.5, 54.0 (d, $J$ = 7.2 Hz), 52.8 (d, $J$ = 7.5 Hz), 44.6, 25.9. $^{31}$P NMR 81 MHz, CDCl$_3$, 293K): δ ppm 25.5 (s).

IR: $\nu_{\text{max}}$ /cm$^{-1}$ 2992, 2951, 2832, 1511, 1482, 1241, 1012, 933. HRMS: Calculated for C$_{18}$H$_{22}$NO$_4$P: [M$^+$] = 347.1287; Found: [M$^+$] = 347.1292.
$^1$H NMR (400MHz, CDCl$_3$, 293K): $\delta$ ppm 7.42-7.43 (m, 1H), 7.09-7.18 (m, 3H), 6.89 (d, 2H, $J = 9.2$ Hz), 6.79 (d, 2H, $J = 9.2$ Hz) 4.96 (d, 1H, $J = 22.8$ Hz), 4.58-4.69 (m, 2H), 4.04-4.11 (m, 1H), 3.73 (s, 3H), 3.53-3.59 (m, 1H), 2.81-2.95 (m, 2H), 1.30 (m, 6H), 1.18 (d, 3H, $J = 6$ Hz), 1.02 (d, 3H, $J = 6.4$ Hz). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K, TMS): $\delta$ ppm 152.9, 144.2 (d, $J = 9.4$ Hz), 142.8, 136.4 (d, $J = 5.7$ Hz), 130.7, 128.82, 128.4 (d, $J = 4.2$ Hz), 127.1 (d, $J = 3.4$ Hz), 125.5 (d, $J = 2.6$ Hz), 117.8, 114.3, 72.1 (d, $J = 4.6$ Hz), 70.6 (d, $J = 5.5$ Hz), 59.3 (d, $J = 166$ Hz), 55.5, 44.7, 25.8, 24.6 (d, $J = 2.9$ Hz), 24.1 (d, $J = 3.1$ Hz), 23.7 (d, $J = 5.4$ Hz), 23.3 (d, $J = 5.7$ Hz). $^{31}$P NMR 81 MHz, CDCl$_3$, 293K): $\delta$ ppm 21.9 (s). IR: $\nu_{\text{max}}$/cm$^{-1}$ 2977, 2931, 2832, 1508, 1464, 1383, 1238, 1104, 975, 726. HRMS: Calculated for C$_{17}$H$_{20}$NO$_3$P: [M$^+$] = 403.1913; Found: [M$^+$] = 403.1906.

![Chemical structure](image)

1-(4-Methoxyphenyl)-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (8h):

$^1$H NMR (400MHz, CDCl$_3$, 293K): $\delta$ ppm 7.11-7.35 (m, 14H), 6.90 (d, 2H, $J = 8.8$Hz), 6.78 (d, 2H, $J = 8.8$Hz), 5.12 (d, 1H, $J = 20.0$ Hz), 4.80-5.05 (m, 4H), 4.00-4.07 (m, 1H), 3.73 (s, 3H), 3.51-3.56 (m, 1H), 2.86-2.98 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K): $\delta$ ppm 153.1, 143.9 (d, $J = 8.0$ Hz), 136.4 (d, $J = 5.7$ Hz), 136.2 (d, $J = 6.3$ Hz), 130.1, 128.9 (d, $J = 3.0$ Hz), 128.3 (d, $J = 6.8$ Hz), 128.2, 128.1, 128.0, 127.8, 127.3, (d, $J = 3.4$ Hz), 125.8, (d, $J = 2.9$ Hz), 117.6, 114.5, 68.6 (d, $J = 7.4$ Hz), 67.6 (d, $J = 7.8$ Hz), 59.7 (d, $J = 158$ Hz), 55.6, 44.7, 26.1. $^{31}$P NMR
### 1-(2-Methoxyphenyl)-2-diethylphosphonate-1,2,3,4-tetrahydroisoquinoline (8i):

**1H NMR (400MHz, CDCl₃, 293K):** δ ppm 7.44-7.46 (m, 1H), 7.18-7.20 (m, 2H), 7.10-7.12 (m, 1H), 6.95-6.99 (m, 1H), 6.80-6.90 (m, 3H), 5.16 (d, 1H, J = 24Hz), 3.77-4.10 (m, 5H), 3.82 (s, 3H), 3.56-3.61 (m, 1H), 2.86-2.94 (m, 1H), 2.70-2.75 (m, 1H), 1.17 (t, 3H, J = 7.2Hz), 1.06 (t, 3H, J = 7.2Hz). **13C NMR (75 MHz, CDCl₃, 293K):** δ ppm 152.4, 140.0 (d, J = 7.7 Hz), 135.8 (d, J = 6.3 Hz), 130.6, 129.2 (d, J = 2.6 Hz), 128.1 (d, J = 4.1 Hz), 126.9 (d, J = 3.7 Hz), 125.5 (d, J = 3.2 Hz), 123.0, 121.7, 120.8, 111.5, 63.0 (d, J = 7.4 Hz), 61.8 (d, J = 7.2 Hz), 58.7 (d, J = 143 Hz), 55.3, 44.3, 26.4, 16.2 (d, J = 5.9 Hz). **31P NMR 81 MHz, CDCl₃, 293K:** δ ppm 24.2(s) **IR:** ν_{max} /cm⁻¹ 3061, 2977, 2929, 2834, 1592, 1498, 1453, 1389, 1366, 1238, 1048, 1020, 962, 908, 725. **HRMS:** Calculated for C₂₀H₂₆NO₄P: [M⁺] = 375.1599; Found: [M⁺] = 375.1589.
1-(2-Methoxyphenyl)-2-dimethylphosphonate-1,2,3,4-tetrahydroisoquinoline (8j):

$^1$H NMR (400MHz, CDCl$_3$, 293K, TMS): $\delta$ ppm 7.41-7.43 (m, 1H), 7.19-7.21 (m, 2H), 7.11-7.13 (m, 1H), 6.97-7.01 (m, 1H), 6.81-6.89 (m, 3H), 5.15 (d, 1H, $J = 22.4$Hz), 4.03 (dt, 1H, $J_1 = 4.4$ Hz, $J_2 = 12.4$Hz), 3.83 (s, 3H), 3.54-3.63 (m, 7H), 2.85-2.95 (m, 1H), 2.70-2.74 (m, 1H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K, TMS): $\delta$ ppm 152.4, 139.8 (d, $J = 8.5$ Hz), 135.7 (d, $J = 6$ Hz), 130.4, 129.3(d, $J = 2.6$ Hz), 127.8 (d, $J = 4.1$ Hz), 127.0 (d, $J = 3.8$ Hz),125.6 (d, $J = 3.2$ Hz), 123.2, 121.7, 120.8, 111.5, 58.7 (d, $J = 151$ Hz), 55.3, 53.8 (d, $J = 7.2$ Hz), 52.5 (d, $J = 7.2$ Hz), 44.4, 26.2. $^{31}$P NMR 81 MHz, CDCl$_3$, 293K): $\delta$ ppm 26.5 (s). IR: $\nu_{\max}$/cm$^{-1}$ 3060, 3000, 2951, 2853, 1592, 1497, 1452, 1360, 1238, 1177, 1110, 1055, 1021, 908, 723. HRMS: Calculated for C$_{18}$H$_{22}$NO$_4$P: [M$^+$] = 347.1286; Found: [M$^+$] = 347.1275.
1-(4-Methoxyphenyl)-2-diisopropylphosphonate-1,2,3,4-tetrahydroisoquinoline (8k):

$^1$H NMR (400MHz, CDCl$_3$, 293K): $\delta$ ppm 7.26-7.51 (m, 1H), 7.09-7.19 (m, 2H), 7.08-7.09 (m, 1H), 6.92-6.96 (m, 1H), 6.76-6.83 (m, 3H), 5.05 (d, 1H, $J = 23.6$ Hz), 4.57-4.69 (m, 2H), 4.04-4.13 (m, 1H), 3.81 (s, 3H), 3.61-3.66 (m, 1H), 2.79-2.90 (m, 1H), 2.64-2.68 (m, 1H), 1.26 (m, 6H), 1.10 (d, 3H, $J = 6.4$ Hz), 0.91(d, 3H, $J = 6.0$ Hz).

$^{13}$C NMR (75 MHz, CDCl$_3$, 293K, TMS): $\delta$ ppm 152.3, 140.1 (d, $J = 9.4$ Hz), 135.9 (d, $J = 6.0$ Hz), 130.9 (d, $J = 1.4$ Hz), 129.1 (d, $J = 2.6$ Hz), 128.4 (d, $J = 3.7$ Hz), 126.7 (d, $J = 3.5$ Hz), 125.3 (d, $J = 3.2$ Hz), 122.7, 121.5, 120.6, 111.2, 72.0 (d, $J = 7.4$ Hz), 70.4 (d, $J = 8.1$ Hz), 59.2 (d, $J = 151$ Hz), 55.1, 44.1, 26.1, 24.6 (d, $J = 1.7$ Hz), 24.0 (d, $J = 3.4$ Hz), 23.5 (d, $J = 5.4$ Hz), 23.2(d, $J = 6.3$ Hz).

$^{31}$P NMR 81 MHz, CDCl$_3$, 293K): $\delta$ ppm 21.2 (s). IR: $\nu_{\text{max}}$ cm$^{-1}$ 2975, 2924, 2833, 1590, 1497, 1451, 1373, 1240, 1104, 998, 972, 886, 748, 735, 736. HRMS: Calculated for C$_{22}$H$_{30}$NO$_4$P: [M$^+$] = 403.1912; Found: [M$^+$] = 403.1901.

1-(2-Methoxyphenyl)-2-dibenzylphosphonate-1,2,3,4-tetrahydroisoquinoline (8l).

$^1$H NMR (400MHz, CDCl$_3$, 293K): $\delta$ ppm 7.42 (d, 1H, $J = 7.2$ Hz), 7.06-7.29 (m, 12H), 6.95-6.99 (m, 1H), 6.77-6.88 (m, 3H), 5.25 (d, 1H, $J = 22.0$ Hz), 4.87-5.02 (m, 3H), 476-4.81 (m, 1H), 4.07-4.15 (m, 1H), 3.74 (s, 3H), 3.58-3.62 (m, 1H), 2.85-2.93 (m, 1H), 2.67-2.71 (m, 1H).

$^{13}$C NMR (75 MHz, CDCl$_3$, 293K): $\delta$ ppm 152.5, 142.7, 139.7 (d, $J = 8.9$ Hz), 136.8 (d, $J = 6.5$ Hz), 136.4 (d, $J = 6.3$ Hz), 135.9 (d, $J = 5.3$ Hz).
Hz), 130.3, 129.8, 128.3, 128.2, 128.1, 128.0, 127.9, 127.8, 127.5, 127.1 (d, \( J = 3.7 \) Hz), 125.6 (d, \( J = 3.0 \) Hz), 123.3, 121.7, 120.8, 111.4, 68.4 (d, \( J = 7.1 \) Hz), 67.2 (d, \( J = 7.7 \) Hz), 59.2 (d, \( J = 151 \) Hz), 55.2, 44.5, 26.2. \( ^{31}\text{P} \text{NMR 81 MHz, CDCl}_3, 293K): \delta \text{ ppm} 24.4 \text{ (s)}. \text{IR}: \nu_{\text{max}} / \text{cm}^{-1} 3062, 3030, 2936, 2833, 1591, 1497, 1453, 1239, 988, 907, 724, 694. \text{HRMS}: \text{Calculated for C}_{30}\text{H}_{30}\text{NO}_4\text{P: } [\text{M}^+] = 499.1912; \text{Found: } [\text{M}^+] = 499.1904.

4.6.3 – Measurement of Molecular Oxygen Uptake for Copper-Catalyzed Aerobic Phosphonation of Csp\(^3\)-H Bond

In a 10 mL Schlenk flask equipped with a magnetic stirring bar and connected to a gas pressure sensor (Vernier; GPS-BTA), CuBr (1.4 mg, 0.01 mmol) was added (\( V_{\text{tot}} = 15 \text{ mL} \)). After the reaction was flushed with molecular oxygen (1 atm), methanol (0.6mL) was added. After the flask was immersed in an oil bath at 60 °C, for 1h to stabilize, 2-phenyl-tetrahydroisoquinoline (42 mg, 0.2 mmol), dissolved in diethylphosphonate (51.5 µL, 0.4 mmol), was injected with a micro-syringe to start the reaction. The consumption of oxygen was monitored every minute using logger Pro 3.0. The decrease of pressure in the system represented the amount of oxygen consumed during the process.

\[ pV = nRT \]

\( V_i \): initial Volume = \( V_f \): final volume = \( V \)
\( T_i \): initial Temperature = \( T_f \): final Temperature = \( T \)
\( n_i \): initial moles of \( \text{O}_2 \) \( n_f \): final moles of \( \text{O}_2 \)

mole of oxygen consumed = \( (n_i-n_f) = [(p_i-p_f)V]/(RT) \)
References for chapter 4.


6. See chapter 3.


Part III. Arylation of sp$^3$ C-H Bonds
Chapter 5. Introduction to Metal-Catalyzed Arylation of sp\textsuperscript{3} C-H Bond.

Environmental consciousness has given rise to much interest in the direct arylation of selective C-H bonds\textsuperscript{1}. Analogous catalytic functionalization processes provide an economical alternative to traditional organic chemistry\textsuperscript{2}. Recent efforts have been made toward direct cross-coupling using sp\textsuperscript{3} C-H bonds and in particular, palladium catalyzed regioselective phenylation and arylation of sp\textsuperscript{3} C-H bonds has frequently been reported.

5.1 – Palladium-Catalyzed Arylation of sp\textsuperscript{3} C-H Bond.

One of the first examples of catalytic sp\textsuperscript{3} C-H bond arylation was reported by Dyker in 1992\textsuperscript{3}. The C-H activation of methoxy groups described in this communication represented a new reaction principle for palladium-catalyzed processes. This new methodology was applied for the domino synthesis of polycyclic products (Scheme 5.1).

![Scheme 5.1- Palladium-Catalyzed Domino synthesis of Polycyclic Products](image)

More than ten years later, Baudoin and co-workers reported in 2003, the intramolecular catalytic C-H activation of *gem*-dialkyl groups, which occurred by transformation of five-membered palladacycles and gave rise to benzocyclobutadienes (Scheme 5.2)\textsuperscript{4}.
Scheme 5.2 – Palladium-Catalyzed C-H Activation of gem-Dialkyl Groups

In early 2005, Buchwald and co-workers discovered the intermolecular sp³ C-H bond arylation via transmetallation of the alkyl Pd(II) species with the boronic acid substrate (Scheme 5.3). This efficient cross-coupling transformation was made possible by the effect of the bulky phosphine ligand structure.

Scheme 5.3 – Palladium-Catalyzed Cross-Coupling with Boronic Acids

In 2005, Sanford and co-workers reported an impressive palladium-catalyzed C-H bond activation / C-C bond formation involving Pd(IV)-Aryl intermediates (with iodine (III) reagent [Ph₂I]BF₄ as source of Ph⁺ and oxidizing agent).
Scheme 5.4 – Mechanism for Palladium-Catalyzed Arylation with Iodine(III) Reagents

Despite the fact that the majority of the examples presented in this particular report focused on the sp\textsuperscript{2} C-H bond functionalization, the reaction also proceeded efficiently with activated benzylic sp\textsuperscript{3} C-H substrates (Scheme 5.5).

Scheme 5.5 – Palladium-Catalyzed Arylation of Benzylic sp\textsuperscript{3}C-H Substrates with Iodine(III) Reagents

In 2006, Knochel and co-workers developed an intramolecular benzylic C-H activation for the preparation of condensed N-heterocycles (Scheme 5.6).\textsuperscript{7}

Scheme 5.6 – Palladium-Catalyzed Condensed N-Heterocycles Synthesis
Remarkably, this activation of the 2-methyl substituent of pyrroles can be extended to \(N\)-acyl-2,5-pyrrole derivatives. Under the usual conditions, these readily available amides are converted to the pyrrolo[1,2-b]isoquinolines in yield of 75–81 \%, demonstrating the broad scope of this type of ring closure (Scheme 5.7).

![Scheme 5.7](image)

The key step in these ring closures is a chemoselective intramolecular C-H activation of a methyl group at position 2.

Daugulis and co-workers demonstrated the efficiency of palladium(II) acetate to catalyze the coupling of \(sp^3\) C-H and C-I bonds using pyridine as a directing group (Scheme 5.8).

![Scheme 5.8](image)

This methodology was not only applicable to benzylic position. In fact, simple aliphatic C-H bonds were also arylated with satisfactory yields. Nevertheless, the described conditions required a considerably long reaction time.
A high regioselectivity arylation of sp³ C-H bond with acceptable reaction time was later reported by the same group.⁹ Previous limitations were overcome by the use of pyridine-amide functionalities to generate a chelated palladium intermediate. Under the described conditions high yields for the arylation of unactivated sp³ C-H bonds were obtained. Similar to the mechanism proposed by Sanford, Pd(IV) species are assumed to be involved in the catalytic cycle.

\[
\begin{array}{c}
\text{N} \quad \text{X} \\
\text{NH} \quad \text{Pd(II) cat., AgOAc} \\
\text{H}_2\text{CH}_2\text{C} \quad \text{Y} \\
\text{ArI} \\
70-130 \, ^\circ\text{C} \\
5 \, \text{min}-16 \, \text{h} \\
\text{ArH}_2\text{CH}_2\text{C} \quad \text{via} \\
\text{Y} = \text{C}=\text{O}, \text{carboxylic acid } \beta\text{-arylation} \\
\text{Y} = \text{CH}_2, \text{amine } \gamma\text{-arylation}
\end{array}
\]

\[\text{Scheme 5.9}\]

In the investigation of the cross-coupling of aromatic C-H substrates, Sanford and co-worker reported an example with an activated benzylic C-H bond. The regioselective oxidative cross-coupling proceed via two discrete C-H activation steps whose selectivities are predominantly controlled by a benzoquinone ligand (Scheme 5.10).¹⁰

\[
\begin{array}{c}
\text{N} \quad \text{X} \\
\text{Ar} \quad \text{Pd(OAc)}_2 (10 \, \text{mol} \, \% ) \\
\text{BQ (0.5 equiv)} \\
\text{Ag}_2\text{CO}_3 (2 \, \text{equiv}) \\
\text{DMSO (4 equiv)} \\
130 \, ^\circ\text{C}, 12 \, \text{h} \\
\text{Ph} \\
48 \, \% \, \text{Yield}
\end{array}
\]

\[\text{Scheme 5.10} – \text{Palladium-Catalyzed Oxidative Arylation Reaction}\]
The mechanism of the benzoquinone-promoted, palladium-catalyzed oxidative cross-coupling reaction was largely investigated. The work more recently reported provided key insights into the selectivity-determining steps of this transformation.

\[
\text{C}_L\text{Pd}^\text{II} \text{Ac-O} \xrightleftharpoons{\text{+ Ar-H}} \text{L C Ar} + \text{AcOH} - \text{AcOH} \xrightleftharpoons{\text{-AcOH} \text{+ Ar-H}} \text{C}_L\text{Pd}^\text{IV} \text{Ar} + \text{BQ} \xrightarrow{\text{fast}} \text{C}_L\text{Pd}^\text{IV} \text{Ar} \text{BQ} \xrightarrow{\text{- [Pd}^0\text{]}} \text{L C Ar}
\]

Scheme 5.11 – Mechanism for Palladium-Catalyzed Oxidative Arylation Reaction

Instead of using pyridine directing groups, which seriously restrict the substrate scope, Yu and co-workers reported a palladium-catalyzed arylation of sp\(^3\) C-H bonds in simple carboxylic acids.\(^{11}\) Carboxylic acids are readily available, and the development of Pd(OAc)\(_2\)-catalyzed C-H functionalization processes directed by carboxyl groups represent a practically appealing approach (Scheme 5.12).

\[
\text{H}_3\text{C}\begin{array}{c} \text{CH}_3 \text{OH} \end{array} + \text{Ph-B-O-} \xrightarrow{\text{Pd(OAc)}_2 (10 \text{ mol } \%) \text{ BQ, Ag_2CO_3, K}_2\text{HPO}_4} \text{H}_3\text{C}\begin{array}{c} \text{R} \end{array} \text{CO} \xrightarrow{^1\text{BuOH, 100 } \degree\text{C, 3 h}} \text{Ph} \text{CO} \text{20-38 }\%\text{ yield}
\]

Scheme 5.12 – Palladium-Catalyzed Arylation of sp\(^3\) C-H Bonds in Simple Carboxylic Acids with Boronic Esters

This coupling reaction provided the first example for carboxyl-directed Pd-insertion into sp\(^3\) \(\beta\) C-H bonds in simple aliphatic acids. To demonstrate the generality of this C-H cleavage, the Yu Group also carried out arylation using iodoarenes as arylating agents. They obtained a mixture of the mono- and diarylated product in good yields.
Scheme 5.13 - Palladium-Catalyzed Arylation of sp\(^3\) C-H Bonds in Simple Carboxylic Acids with Iodoarenes

In 2007, Fagnou and co-workers reported the palladium-catalyzed intramolecular alkane arylation (Scheme 5.14).\(^\text{12}\)

Scheme 5.14 – Palladium-Catalyzed Intramolecular Alkane Arylation

The density functional theory (DFT) calculation demonstrated the critical role of the insoluble carbonate base together with pivalic acid for the reaction to occur. In fact the intimate role of the \textit{in situ} generated carboxylate base in the transition state was to promote the desired C-H bond cleavage by coordination to the Pd(II) intermediate (Scheme 5.15).
This methodology was recently applied to indoline derivatives synthesis. In fact, Ohno and co-worker reported the palladium-catalyzed sp\(^3\) C-H bond activation of N-alkyl-2-bromonilines.\(^{13}\)

During the course of our research on copper-catalyzed sp\(^3\) C-H bond arylation (see chapter 6), a considerable number of impressive site selective arylation reactions were reported. At the same time, the Fagnou and Charette groups described the palladium-catalyzed sp\(^3\) arylation of 2-alkyl-pyridine derivatives with haloarenes as arylation agents. Nevertheless, two different strategies were considered in order to reach this particular objective.

Toward this goal, Fagnou and co-workers reported the use of pyridine N-oxides to direct the benzylic activation via formation of the palladacycle intermediate described below.\(^{14}\) On the other hand, Charette and co-workers described the same selectivity with 2-alkyl substituted N-iminopyridinium ylides.\(^{15}\) In both cases, the
survey of ligands revealed the critical role of bulky phosphine coordination to the metal center (Scheme 5.16).

Scheme 5.16 – Palladium-Catalyzed Arylation of 2-Alkyl Substituted Pyridine

In 2008, Hartwig and co-workers reported simultaneously two complementary methods for the α-arylation of esters catalyzed by palladium complexes. The described methodologies involved a two step process. Firstly, the α-acidic position is \textit{in situ} deprotonated in the presence of a strong bulky base, followed by the catalytic arylation using either bromo- or chloroarenes (Scheme 5.17).
Interestingly, the turnover numbers for these processes were high for these types of coupling reactions. In fact, the desired products were produced in high yields in the presence of low catalyst loading (<0.1 % Pd).

Very recently, the Yu group reported an example of Pd(0)-catalyzed intermolecular arylation of β-C-H bonds in a wide range of amide substrates. The development of a simple and readily removable amide directing group was crucial for enabling facile C-H activation under the described conditions.

In the presence of two similar β-C-H bonds, a mixture of the mono- and diarylated cross-coupling product was obtained.
5.2 – Alternatives to Palladium-Catalyzed Arylation Reaction

In fact, palladium does not constitute the unique transition metal catalyst able to directly functionalize sp$^3$ C-H bonds. Nevertheless, only rare examples reported the use of different transition metal for the direct sp$^3$ C-H bond arylation. These alternatives to the palladium-catalyzed sp$^3$C-H bond arylation reaction are presented in the background of the next chapter.
References for Chapter 5

Chapter 6 – Copper-Catalyzed \( sp^3 \) C-H Bond Arylation with Boronic Acids.

As illustrated in chapter 5, numerous techniques have been recently developed for the direct arylation of \( sp^3 \) C-H bond. Nevertheless, two years ago, the state of the art in this direct functionalization was represented by the palladium-catalyzed arylation reaction. Only a few examples that referred to the use of low cost and low toxicity copper catalysts were reported at that time. Therefore, we became interested in developing a new method in order to achieve this challenging process.

6.1 – Background

An alternative to the use of palladium was reported in 2006 by Sames and co-workers in which \( \alpha \)-arylation of saturated cyclic amine was efficiently achieved using low valent ruthenium catalyst with boronic esters directed by removable amidine protecting group (Scheme 6.1).\(^1\)

![Scheme 6.1 – Ruthenium-Catalyzed \( \alpha \)-Arylation of Saturated Cyclic Amine](image)

The first elemental step of the proposed scheme involves the insertion of a low-valent transition metal into the desired \( sp^3 \) C-H bonds.

![Scheme 6.2 - First Elemental Step of Ruthenium-Catalyzed \( \alpha \)-Arylation of Saturated Cyclic Amine](image)
There have been only few reports employing copper for the selective arylation of \( \text{sp}^3 \text{C-H} \) bond. Ma and co-workers reported the Cul-catalyzed coupling of aryl halides with \( \beta \)-ketoesters assisted by L-proline.\(^2\) Later, they envisioned the asymmetric induction of the chiral ligand.\(^3\) The Ullmann-type coupling offered good yield and enantioselectivity with 2-iodotrifluoroacetanilides and 2-methylacetoacetates when \textit{trans}-4-hydroxyproline was used as a ligand for the copper catalyst (Scheme 6.3).

\[
\text{O} \quad \text{O} \\
\begin{array}{c}
\text{OR} \\
\text{CuI/(2S,4R)-4-hydroxyproline} \\
\text{NaOH, DMF, H}_2\text{O, -45 °C}
\end{array}
\text{O} \quad \text{OR} \\
\text{NHCOCF}_3
\]

\text{Yield: 29-82 %} \\
\text{ee: 60-93 %}

\textbf{Scheme 6.3} – Copper-Catalyzed Ullmann-Type Coupling

We previously reported a copper-catalyzed reaction of indoles with tetrahydroisoquinoline via Cross-Dehydrogenative-Coupling (CDC). This transformation led to the direct indolization (arylation) of an \( \text{sp}^3 \) centre (Scheme 6.4).\(^4\)

\[
\text{N} \quad \text{Ar} \\
\begin{array}{c}
\text{CuBr (5 mol %)} \\
\text{TBHP (1.3 equiv)}
\end{array}
\text{50 °c, overnight}
\]

\text{R = H, Me}

\text{44-85 % yield}

\textbf{Scheme 6.4} – Copper-Catalyzed Cross-Dehydrogenative-Coupling with indoles
Interestingly, protection-free N-H indoles can be used in this coupling, eliminating protection-deprotection processes. The reactions selectively occur at the C3 position of indoles if both C2 and C3 positions of indoles are unoccupied. Nevertheless, when the C3 position of indoles was substituted, the C2 products were obtained.

Tetrahydroisoquinoline derivatives mediate useful pharmacological and physiological effects. As representative examples, 1-phenyl-1,2,3,4-tetrahydroisoquinoline displays high affinity to the PCP binding site of the NMDA receptor and also constitutes the starting building block for synthesizing attractive estrogen receptor modulators (Figure 6.1).

![Chemical structures](image)

**Fig 6.1** – Representative structures of Known Biologically Active 1-Aryl-1,2,3,4-Tetrahydroisoquinolines.

### 6.2 – Optimization of The Reaction Conditions

We envisioned a direct arylation of the sp³ C-H bond adjacent to the nitrogen atom to synthesize these biologically active molecules via the coupling of phenylboronic acid (11a) with N-phenyl-tetrahydroisoquinoline (1a). Similar to a Petasis borono-Mannich reaction, we postulated the nucleophilic addition of the arylboronic acid to an in situ generated iminium type intermediate via oxidation of the tertiary amine in the presence of a peroxide and a copper salt. The key challenge
was the absence of a neighboring heteroatom directing group generally required in the Petasis reaction to form the more active tetracoordinated borate species. We reasoned that copper would compensate for this absence.

Considering previous work on transition metal catalyzed sp³ C-H bond activation for C-C bond formation, we began our investigation using tert-butyl hydroperoxide (TBHP) as a stoichiometric oxidant. While optimizing the reaction conditions, we discovered the critical role of water in the oxidative arylation reaction. In the absence of water, only 15% of the benzylic α-arylated product was obtained when the CuBr/TBHP system was tested in DME at 95 °C (Table 6.1, entry 1). Interestingly, when the solvent of the oxidant was switched from decane to water, the efficiency of the reaction dramatically increased, providing the arylated product in 75% yield (Table 6.1, entry 2). Increasing the reaction temperature to 120 °C lowered the yield due to an increase of biphenyl by-product formation (table 6.1, entry 3). Instead of using tert-butyl hydroperoxide, 70 wt. % in water (T-HYDRO®), adding a small amount of water with anhydrous TBHP in decane was also effective (entry 4). However, a large amount of water prevents the reaction from occurring (Table 6.1, entry 5).
Table 6.1 – Optimization of the Oxidative Arylation Reaction.

<table>
<thead>
<tr>
<th>entry</th>
<th>2a</th>
<th>cat.[Cu]</th>
<th>[O] (equiv)</th>
<th>solvent (conc.)</th>
<th>temp. (°C)</th>
<th>3a (%)&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2</td>
<td>CuBr</td>
<td>TBHP (1.2)</td>
<td>DME (1M)</td>
<td>95</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.2)</td>
<td>DME (1M)</td>
<td>95</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>1.2</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.2)</td>
<td>DME (1M)</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>CuBr</td>
<td>TBHP (1.2)</td>
<td>DME (+ 5 μL H₂O)</td>
<td>95</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>1.2</td>
<td>CuBr</td>
<td>TBHP (1.2)</td>
<td>H₂O</td>
<td>95</td>
<td>&lt;5</td>
</tr>
<tr>
<td>6</td>
<td>1.2</td>
<td>CuI</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.2)</td>
<td>DME (1M)</td>
<td>95</td>
<td>10&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>1.5</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.5)</td>
<td>DME (1M)</td>
<td>95</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>1.5</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.6)</td>
<td>DME (1M)</td>
<td>95</td>
<td>85</td>
</tr>
<tr>
<td>9</td>
<td>1.6</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.6)</td>
<td>DME (2M)</td>
<td>95</td>
<td>90</td>
</tr>
<tr>
<td>10</td>
<td>1.5</td>
<td>CuBr</td>
<td>T-HYDRO&lt;sup&gt;®&lt;/sup&gt; (1.6)</td>
<td>Neat</td>
<td>95</td>
<td>30</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions scale: tertiary amine (0.1 mmol).  
<sup>b</sup> Use of other copper(I) salts resulted in decreased yield.  
<sup>c</sup> NMR yields based on tetrahydroisoquinoline using an internal standard

It is also important to note that no product was obtained when 11a was replaced by its corresponding ester. The optimized reaction conditions required 1.6 equivalents of phenylboronic acid in the presence of an equivalent amount of T-HYDRO<sup>®</sup> in DME (2M) at 95 °C (Table 6.1, entry 9).

6.3 - Scope of the Oxidative Arylation Reaction

Next, we examined the scope of the oxidative arylation reaction with a variety of substituted aryl boronic acids. Both electron-withdrawing and electron-donating substituted arylboronic acids were successfully coupled to tetrahydroisoquinolines. Both *N*-phenyl protected and *N*-PMP protected tetrahydroisoquinolines were effective for this transformation. *N*-PMP can easily be deprotected to give the α-arylated free
Interestingly, the very sterically hindered 2-naphthylboronic was coupled in good yields under the optimized conditions.

**Table 6.2 - Scope of the Oxidative Arylation Reaction**

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>NMR Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>12a</td>
<td>90</td>
<td>75</td>
</tr>
<tr>
<td>12b</td>
<td>80</td>
<td>62</td>
</tr>
<tr>
<td>12c</td>
<td>85</td>
<td>64</td>
</tr>
<tr>
<td>12d</td>
<td>75</td>
<td>54</td>
</tr>
<tr>
<td>12e</td>
<td>70</td>
<td>52</td>
</tr>
<tr>
<td>12f</td>
<td>80</td>
<td>61</td>
</tr>
<tr>
<td>12g</td>
<td>60</td>
<td>47</td>
</tr>
<tr>
<td>12h</td>
<td>60</td>
<td>52</td>
</tr>
<tr>
<td>12i</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>12j</td>
<td>70</td>
<td>51</td>
</tr>
<tr>
<td>12k</td>
<td>90</td>
<td>72</td>
</tr>
<tr>
<td>12l</td>
<td>80</td>
<td>59</td>
</tr>
</tbody>
</table>

* Tetrahydroisoquinolines (0.2 mmol). NMR yields using an internal standard presented in brackets.

6.4 – Aerobic Oxidative Arylation

Furthermore, we considered the use of molecular oxygen for the oxidative arylation reaction. Unfortunately, no product could be detected under the previously
reported CuBr/O₂/water system (Table 6.2, entry 1). Nevertheless, when the reaction was performed in DME as solvent, 20 % of the desired arylated product was obtained (entry 2). The role of water was also critical under aerobic conditions. In fact, addition of a small amount of water to the previous conditions increased the yield to 60 % (entry 3). The yield was further improved to generate 80 % of the desired product when a catalytic amount of peroxide was used (Table 6.2, entry 4).

**Table 6.3 – Aerobic Oxidative Arylation**

<table>
<thead>
<tr>
<th>entry</th>
<th>[O] (equiv)</th>
<th>solvent</th>
<th>12a (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>O₂ (1 atm)</td>
<td>H₂O</td>
<td>&lt;5</td>
</tr>
<tr>
<td>2</td>
<td>O₂ (1 atm)</td>
<td>DME</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>O₂ (1 atm)</td>
<td>DME (+ 5 μL H₂O)</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>O₂ (1 atm)+ 20 mol % T-HYDRO®</td>
<td>DME (+ 5 μL H₂O)</td>
<td>80</td>
</tr>
</tbody>
</table>

<sup>a</sup>NMR yields based on tetrahydroisoquinoline using an internal standard.

### 6.5 – Asymmetric Oxidative Arylation.

To have a better understanding of the reaction mechanism and since the biological potency of 1-phenyl-1,2,3,4-tetrahydroisoquinoline is highly enantioselective,<sup>5</sup> we briefly investigated the asymmetric oxidative arylation reaction. Interestingly, lowering the temperature to 50 °C together with addition of (R,R)-2,6-bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine ligand (PhPyBox) provided the desired product with 30 % ee and a 50 % conversion. After CuOTf replaced CuBr the enantiomeric excess was further improved to provide the α-arylation product with 44 % ee (Scheme 6.5).<sup>13</sup>
Scheme 6.5 – Asymmetric Oxidative Arylation

6.6 – Mechanism of the Oxidative Arylation Reaction.

The mechanism of the oxidative arylation reaction remains uncertain at this time. Nevertheless, two possible pathways can be considered (Scheme 6.6). First, a well established iminium type intermediate 6 is generated by the oxidation of the tertiary amine 1 in the presence of peroxide and copper catalyst. The possibility of a stabilized radical and/or cation intermediate may explain the regioselectivity observed for the benzylic position over the aliphatic one. In Pathway A, nucleophilic attack of 6 by a water molecule would generate the $\alpha$-hydroxy amine intermediate 13. This intermediate could either be further oxidized to the observed amide 15 byproduct or react with arylboronic acid to form boronate 14. Intermediate 14, through an addition-elimination type mechanism that results in an overall ipso substitution, would produce product 12. Alternatively, in pathway B, 6 reacts directly with arylboronic acid catalyzed by copper. Pathway B, which involves [Cu] with C-C bond formation, would more easily account for the enantioselectivity obtained in the presence of chiral ligands.
Scheme 6.6 – Mechanistic Proposal for the Oxidative Arylation Reaction.

6.7 – Conclusion

In summary, an unprecedented copper-catalyzed arylation of sp³ C-H bonds adjacent to a nitrogen atom in the absence of a directing group with boronic acids was developed. This new method provides a simple way to synthesize potential biologically active 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives. The method has numerous advantages: the use of a minimally toxic and relatively cheap copper salt as a catalyst; high regioselectivity; ready generation of free amine; and potential asymmetric synthesis. The scope, applications and mechanism of this reaction are under investigation.
6.8 – Experimental Section

6.8.1 – General Information

All procedures were carried out under an atmosphere of oxygen gas. Standard column chromatography was performed on 20-60 \( \mu m \) silica gel (obtained from Silicycle Inc.) using standard flash column chromatography techniques. \(^1\)H NMR spectra were recorded on Varian 300 and 400 MHz spectrometers in CDCl\(_3\) solution and the chemical shifts were reported in parts per million (\( \delta \)) referenced to the internal solvent signal (peak at 7.26 ppm). The peak patterns are indicated as following: s, singlet; d, doublet; t, triplet; m, multiplet; the coupling of constants, \( J \), are reported in Hertz (Hz). \(^{13}\)C NMR were obtained at 75 MHz and referenced to the internal solvent signal (central peak is 77.00 ppm). MS data were obtained by Agilent 6890N Network GC/System/Agilent 5973 Mass Selective Detector. HRMS were made by McGill University. IR spectra were recorded using an ABB Bomem MB100 instrument. Enantiomeric excesses were determined with Varian Polaris Prostar HPLC using a chiral AD column, 99.5/0.5 hexane/isopropanol and 0.4 mL/min flow rate. All reagents were weighed and handled in air, and refilled with an inert atmosphere of nitrogen at room temperature.

6.8.2 - General Procedure for the Synthesis of Amine Substrates

Copper(I) iodide (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were put into a Schlenk tube. The tube was evacuated and refilled with nitrogen. 2-Propanol (10 mL), ethylene glycol (1.11 mL, 20.0 mmol), 1,2,3,4-tetrahydro-isoquinoline (2.0 mL, 15.0 mmol) and iodobenzene (1.12 mL, 10.0 mmol) were added successively using a syringe at room temperature. The reaction mixture was heated at 85-90 °C for 24 h and then allowed to cool down to room temperature. Diethyl ether (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted by diethyl ether (2 \( \times \) 20 mL). The combined organic
phases were washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (hexane/ethyl acetate=20:1), and the fraction with an $R_f = 0.7$ was collected to give the desired product 1a in 60-80% isolated yields.

6.8.3 – General Procedure for Arylation of $sp^3$ C-H Bond

CuBr (2.8 mg, 0.02 mmol), 2-phenyl-tetrahydroisoquinoline (21 mg, 0.1 mmol), and phenylboronic acid (19.5 mg, 0.16 mmol) were weighed under air and placed inside a 7 mL conical glass vial. The vial equipped with a cap (Teflon septum inside) was evacuated under vacuum and refilled with nitrogen via a needle through the septum (The reaction is not sensitive to a small amount of oxygen). At room temperature and with stirring, DME (500 µL) was added with a syringe, followed by drop-wise addition of T-HYDRO® (23 µL, 0.16 mmol). Product formation was sensitive to the stirring efficiency. Then, the vial was immersed in an oil bath at 95°C under stirring for 24 hours. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel eluting with ethyl acetate. The solvent was evaporated, the residue was purified by column chromatography on silica gel (eluent: hexane/methylene chloride = 5:3), and the fraction with an $R_f = 0.4$ was collected and concentrated to give the desired product 3a.

![1-Phenyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline (12a).](image-url)
Isolated by flash column chromatography (hexane/methylene chloride = 5:3, R<sub>f</sub> = 0.3). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 293K): δ ppm 7.27-7.11 (m, 11H), 6.82 (d, 2H, <i>J</i> = 8 Hz), 6.73 (t, 1H, <i>J</i> = 7.4 Hz), 5.81 (s, 1H), 3.72-3.67 (m, 1H), 3.50-3.44 (m, 1H), 2.94-2.83 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 293K): δ ppm 149.4, 143.0, 137.8, 135.7, 129.1, 128.2, 128.1, 127.7, 127.2, 127.0, 126.7, 126.1, 124.7, 117.4, 113.7, 62.7, 43.7, 27.9. IR (ATR): <i>ν</i><sub>max</sub> / cm<sup>-1</sup> 3648, 3057, 3021, 2958, 2888, 2853, 1593, 1573, 1503, 1490, 1471, 1456, 1444, 1381, 1360, 1342, 1325, 1360, 1342, 1299, 1268, 1251, 1208, 1171, 1150, 1111, 1076, 1032, 1009, 987, 934, 853, 775, 746, 730, 692, 610, 571. HRMS: Calculated for C<sub>21</sub>H<sub>19</sub>N: [M<sup>+</sup>] = 285.1152; Found: [M<sup>+</sup>] = 285.1513.

![Structure](image)

1-Phenyl-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (12b).

Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, R<sub>f</sub> = 0.5). <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>, 293K): δ ppm 7.23-7.14 (m, 9H), 6.82-6.77 (m, 4H), 5.66 (s, 1H), 3.73 (S, 3H), 3.6-3.54 (m, 1H), 3.4-3.37 (m, 1H), 3.0-2.88 (m, 2H). <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>, 293K): δ ppm 152.8, 144.4, 143.2, 137.6, 135.5, 128.3, 128.1, 128.0, 127.9, 126.8, 126.7, 125.9, 117.6, 114.4, 64.3, 55.6, 44.5, 28.1. IR (ATR): <i>ν</i><sub>max</sub> / cm<sup>-1</sup> 3064, 3023, 3004, 2956, 2909, 2823, 1598, 1580, 1507, 1493, 1463, 1450, 1440, 1368, 1334, 1292, 1263, 1242, 1216, 1203, 1178, 1168, 1160, 1122, 1106, 1075, 1054, 1031, 1008, 951, 935, 910, 879, 866, 825, 766, 752, 731, 700, 648, 640, 621, 595, 568. HRMS: Calculated for C<sub>22</sub>H<sub>21</sub>ON: [M<sup>+</sup>] = 315.1623; Found: [M<sup>+</sup>] = 315.1618.
1-(4-Methoxyphenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (12c).
Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, R_f = 0.5). \( ^1H \) NMR (400MHz, CDCl_3, 293K): \( \delta \) ppm 7.26-7.12 (m, 8H), 6.85 (d, 2H, \( J = 7.6 \)Hz), 6.78-6.73 (m, 3H), 5.79 (s, 1H), 3.73 (s, 3H), 3.71-3.65 (m, 1H), 3.50-3.49 (m, 1H), 2.98-2.86 (m, 2H).
\( ^{13} \)C NMR (75 MHz, CDCl_3, 293K): \( \delta \) ppm 158.4, 149.6, 138.0, 135.6, 135.1, 129.2, 128.4, 128.1, 127.7, 126.9, 126.1, 117.5, 114.0, 113.5, 62.2, 55.2, 43.5, 27.9. IR (ATR): \( \nu_{\text{max}} / \text{cm}^{-1} \) 3060, 3021, 2936, 2835, 1595, 1501, 1466, 1452, 1439, 1418, 1384, 1357, 1329, 1301, 1257, 1248, 1229, 1191, 1170, 1154, 1113, 1033, 988, 937, 909, 867, 858, 822, 806, 789, 767, 739, 690, 660, 633, 607, 584, 566. HRMS: Calculated for C_{23}H_{21}ON: [M^+] = 315.1623; found: [M^+] = 315.1620.

1-(4-Methoxyphenyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (12d).
Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, R_f = 0.4). \( ^1H \) NMR (400MHz, CDCl_3, 293K): \( \delta \) ppm 7.2-7.12 (m, 4H), 7.05 (d, 2H, \( J = 8.4 \)Hz), 6.86-6.80 (m, 4H), 6.76 (d, 2H, \( J = 8.4 \) Hz), 5.64 (s, 1H); 3.76 (s,
3H), 3.75 (s, 3H), 3.58-3.52 (m, 1H), 3.44-3.37 (m, 1H), 3.01-2.93 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K): δ ppm 158.4, 152.9, 144.5, 137.8, 135.4, 135.2, 129.3, 128.4, 128.1, 126.6, 125.9, 118.2, 114.4, 113.6, 63.9, 55.6, 55.1, 44.3, 28.1. IR (ATR): $\nu_{\text{max}}$/cm$^{-1}$ 2996, 2904, 2832, 1607, 1581, 1505, 1461, 1440, 1382, 1327, 1299, 1240, 1168, 1113, 1033, 941, 907, 821, 785, 727, 647, 560. HRMS: Calculated for C$_{23}$H$_{23}$O$_2$N: [M$^+$] = 345.1729; Found: [M$^+$] = 345.1723.

1-(Biphenyl-4-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (12e).

Isolated by flash column chromatography (hexane/methylene chloride) = 5:2, R$_f$ = 0.6). $^1$H NMR (400MHz, CDCl$_3$, 293K): δ ppm 7.53-7.16 (m, 15H), 6.87 (d, 2H, J = 8.2 Hz), 6.76 (t, 1H, J = 7.2 Hz), 5.86 (s, 1H), 3.78-3.73 (m, 1H), 3.55-3.47 (m, 1H), 2.97-2.93 (m, 2H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K): δ ppm 149.5, 142.2, 140.7, 139.7; 137.8, 135.8, 129.1, 128.7, 128.1, 127.8; 127.7, 127.15, 127.1, 127, 126.9, 126.2, 117.4, 113.8, 62.6, 43.8, 28.0. IR (ATR): $\nu_{\text{max}}$/cm$^{-1}$ 3053, 3023, 2917, 2850, 1593, 1570, 1559, 1501, 1485, 1469, 1457, 1403, 1378, 1357, 1344, 1323, 1330, 1263, 1203, 1147, 1109, 1074, 1038, 986, 932, 879, 861, 851, 755, 744, 693. HRMS: Calculated for C$_{27}$H$_{23}$N: [M$^+$] = 361.1831; found: [M$^+$] = 361.1825.
1-(Biphenyl-4-yl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (12f):

Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, \( R_f = 0.6 \). \(^1\)H NMR (400MHz, CDCl\(_3\), 293K): \( \delta \) ppm 7.52 (d, 2H, \( J = 8\)Hz), 7.44 (d, 2H, \( J = 8\)Hz), 7.29 (m, 1H), 7.23-7.19 (m, 6H), 6.82 (m, 4H), 5.72 (s, 1H), 3.73 (s, 3H), 3.63-3.57 (m, 1H), 3.45-3.39 (m, 1H), 3.02-2.89 (m, 2H). \(^13\)C NMR (75 MHz, CDCl\(_3\), 293K): \( \delta \) ppm 152.8, 144.3, 142.3, 140.8, 139.6, 137.6, 135.5, 128.7, 128.4, 128.3, 128.1, 127.1, 127.0, 126.8, 126.0, 117.6, 114.5, 64.0, 55.6, 44.5, 28.1. IR (ATR): \( \nu_{\text{max}} /\text{cm}^{-1} \) 3032, 2989, 2921, 2830, 1599, 1576, 1560, 1505, 1485, 1465, 1449, 1403, 1365, 1333, 1291, 1272, 1245, 1195, 1176, 1132, 115, 1076, 1027, 986, 952, 939, 830, 814, 768, 749, 689, 656, 635, 628, 577. HRMS: Calculated for C\(_{28}\)H\(_{25}\)ON: [M+] = 391.1936; found: [M+] = 391.1931.

1-(4-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl)ethanone (12g).

Isolated by flash column chromatography (hexane/methylene chloride) = 5:2, \( R_f = 0.5 \). \(^1\)H NMR (400MHz, CDCl\(_3\), 293K): \( \delta \) ppm 7.84 (d, 2h, \( J = 8.4\)Hz), 7.37 (d, 2H,
$J = 8.4\text{Hz}$), 7.30-7.17 (m, 6H), 6.82 (d, 2H, $J = 8\text{Hz}$), 6.78 (t, 1H, $J = 8\text{Hz}$), 5.84 (s, 1H), 3.77-3.71 (m, 1H), 3.54-3.47 (m, 1H), 3.01-2.87 (m, 2H), 2.54 (s, 3H). \textbf{\textsuperscript{13}C NMR (75 MHz, CDCl$_3$, 293K):} δ ppm 197.7, 149.2, 148.8, 137.1, 135.8, 135.7, 129.2, 128.4, 128.2, 127.7, 127.4, 127.3, 126.4, 117.8, 113.9, 62.9, 44.1, 28.2, 26.6. \textbf{IR (ATR):} $\nu_{\text{max}} / \text{cm}^{-1}$ 3340, 3023, 2847, 2359, 1676, 1596, 1573, 1503, 1492, 1452, 1430, 1411, 1384, 1356, 1297, 1266, 1228, 1193, 1153, 1115, 1035, 1014, 988, 956, 935, 879, 436, 817, 781, 753, 690, 658, 607, 590, 567. \textbf{HRMS:} Calculated for C$_{23}$H$_{21}$ON: [M$^+$] = 327.1623; found: [M$^+$] = 327.1618.

![Image](image_url)

1-(4-(2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)phenyl)ethanone (12h)

Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, $R_f = 0.3$). \textbf{\textsuperscript{1}H NMR (400MHz, CDCl$_3$, 293K):} δ ppm 7.82-7.79 (m, 2H), 7.27 (d, 2H, $J = 8.4$ Hz), 7.23-7.16 (m, 3H), 7.13-7.10 (m, 1H), 6.2-6.77 (m, 4H), 5.67 (s, 1H), 3.73 (s, 3H), 3.59-3.53 (m, 1H), 3.43-3.37 (m, 1H), 3.02-2.90 (m, 2H), 2.53 (s, 3H). \textbf{\textsuperscript{13}C NMR (75 MHz, CDCl$_3$, 293K):} δ ppm 198.1, 153.5, 149.1, 144.4, 137.2, 136.0, 135.7, 128.8, 128.5, 128.4, 128.3, 127.3, 126.4, 118.3, 114.8, 64.7, 55.9, 45.3, 28.6, 26.8. \textbf{IR (ATR):} $\nu_{\text{max}} / \text{cm}^{-1}$ 3058, 3008, 2949, 2935, 2824, 1670, 1603, 1578, 1503, 1458, 1447, 1416, 1359, 1303, 1271, 1235, 1197, 1182, 1125, 1112, 1053, 1031, 956, 938, 908, 865, 841, 823, 812, 786, 760, 740, 723, 632, 598, 588, 571. \textbf{HRMS:} Calculated for C$_{24}$H$_{23}$O$_2$N: [M$^+$] = 357.1729; found: [M$^+$] = 357.1725.
1-(Naphthalen-1-yl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (12i)

Isolated by flash column chromatography (hexane/methylene chloride) = 5:2, R_f = 0.3).

^1H NMR (400MHz, CDCl₃, 293K): δ ppm 8.13-8.1 (m, 1H), 7.86-7.84 (m, 1H), 7.37 (d, 1H, J = 8Hz), 7.49-7.42 (m, 2H), 7.30-7.1 (m, 9H), 6.86-6.83 (m, 2H), 6.49 (s, 1H), 3.71-3.67 (m, 1H), 3.58-3.50 (m, 1H), 3.00-2.92 (m, 1H), 2.71-2.67 (m, 1H). ^13C NMR (75 MHz, CDCl₃, 293K): δ ppm 149.6, 139.8, 136.2, 136.1 133.9, 132.2, 129.3, 129.1, 128.9, 128.6, 128.1, 128.0, 126.8, 126.3, 126.0, 125.6, 124.7, 124.4, 119.4, 117.5, 58.7, 43.5, 25.47. IR (ATR): νmax /cm⁻¹ 3040, 3006, 2967, 2921, 2885, 2825, 1595, 1576, 1497, 1473, 1451, 1423,1392, 1366, 1305, 1275, 1209, 1199, 1169, 1156, 1132, 1111, 1029, 935, 885, 858, 789, 775, 762, 752, 738, 687, 661, 645, 623. HRMS: Calculated for C₂₅H₂₁N: [M⁺] = 335.1674; found: [M⁺] = 335.1670.

2-(4-Methoxyphenyl)-1-(naphthalen-1-yl)-1,2,3,4-tetrahydroisoquinoline (12j)
Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, Rf = 0.7).  

$^1$H NMR (400MHz, CDCl$_3$, 293K): δ ppm 8.12 (d, 1H, 8.4Hz), 7.85-7.82 m (m, 1H), 7.73-7.71 (d, 1H, 8.4Hz), 7.85-7.40 m (m, 2H), 7.29-7.11 (m, 4H), 7.03-6.98 (m, 3H), 6.95 (d, 1H, J = 6.8Hz), 6.76 (d, 2H, 8.8Hz), 6.23 (s, 1H), 3.73(s, 3H), 3.51-3.48 (m, 2H), 2.94-2.86 (m, 1H), 2.77-2.71 (m, 1H).  

$^{13}$C NMR (75 MHz, CDCl$_3$, 293K):  δ ppm 154.0, 144.2, 139.9, 136.6, 136.1, 134.0, 132.2, 129.0, 128.7, 128.6, 128.2, 128.0, 126.0, 126.1, 125.5, 124.8, 124.7, 120.9, 114.3, 60.7, 55.4, 45.7, 25.7.  

IR (ATR): $v_{\text{max}}$/cm$^{-1}$ 3046, 2984, 2908, 2830, 1594, 1506, 1475, 1454, 1391, 1366, 1320, 1277, 1238, 1204, 1183, 1137, 1113, 1031, 987, 939, 885, 860, 821, 790, 777, 752, 716, 652, 620, 580.  

HRMS: Calculated for C$_{26}$H$_{23}$ON: [M$^{+}$] = 365.1766; found: [M$^{+}$] = 365.1772.

1-(4-Tert-butylphenyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline (12k)

Isolated by flash column chromatography (hexane/methylene chloride) = 5:2, Rf = 0.6).  

$^1$H NMR (400MHz, CDCl$_3$, 293K): δ ppm 7.3-7.13(m,10H), 6.85(d, 2H, J = 7.6Hz), 5.81 (s, 1H), 3.75-3.69 (m, 1H), 3.54-3.47 (m, 1H), 2.97-2.84 (m, 2H).  

$^{13}$C NMR (75 MHz, CDCl$_3$, 293K): δ ppm 149, 149, 139.5, 137.6, 135.4, 128.7, 127.6, 127.3, 126.5, 126.4, 125.6, 124.7, 116.7, 113.1, 61.8, 43.2, 33.9, 30.9, 27.4.  

IR (ATR): $v_{\text{max}}$/cm$^{-1}$ 3024, 2959, 2903, 2865, 2359, 2340, 2243, 1595, 1501, 1473, 1407, 1382, 1360, 1326, 1298, 1268, 1218, 1152, 1111, 1016, 987, 937, 906, 855, 813, 720, 689, 648, 610, 564.  

HRMS: Calculated for C$_{25}$H$_{27}$N: [M$^{+}$] = 341.2144; found: [M$^{+}$] =341.219.
1-(4-Tert-butylphenyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroisoquinoline (12l)

Isolated by flash column chromatography (hexane/methylene chloride/diethyl ether) = 5:2:1, R_f = 0.7). $^1$H NMR (400MHz, CDCl$_3$, 293K): $\delta$ ppm 7.24-7.22 (d, 2H, 8.8Hz), 7.18-7.15 (m, 4H), 7.08 (d, 2H, J = 8Hz), 6.84-6.78 (m, 4H), 5.66 (s, 1H), 3.74 (s, 3H), 3.61-3.57 (m, 1H), 3.45-3.39 (m, 1H), 2.97-2.84 (m, 2H), 1.26 (s, 9H). $^{13}$C NMR (75 MHz, CDCl$_3$, 293K): $\delta$ 152.7, 149.7, 144.7, 140.5, 138.0, 135.9, 128.6, 128.3, 127.8, 127.0, 126.2, 125.2, 117.2, 114.8, 63.8, 55.9, 44.4, 34.6, 31.6, 28.0. IR (ATR): $\nu_{\max}$/cm$^{-1}$ 3024, 2956, 2902, 2866, 2830, 1609, 1579, 1507, 1461, 1440, 1406, 1382, 1361, 1326, 1292, 1267, 1240, 1180, 1152, 1111, 1037, 940, 907, 878, 812, 770, 752, 728, 686, 646, 583, 564. HRMS: Calculated for C$_{26}$H$_{29}$ON: [M$^+$] = 371.2249; found: [M$^+$] = 371.2245.

6.8.4 - General Procedure for the Aerobic sp$^3$ C-H Bond Arylation

CuBr (2.8 mg, 0.02 mmol), 2-phenyl-tetrahydroisoquinoline (21 mg, 0.1 mmol), and phenylboronic acid (19.5 mg, 0.16 mmol) were weighed under air and placed inside a 7 mL conical glass vial. The vial equipped with a cap (Teflon septum inside) was evacuated under vacuum and refilled with oxygen via a needle through the septum. At room temperature, and with stirring, DME (500 µL) was added with a syringe, followed by addition of H$_2$O (5 µL, mmol). Product formation was sensitive to the
stirring efficiency. Then, the vial was immersed in an oil bath at 95°C, under stirring, for 24 hours. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel eluting with ethyl acetate. Solvent was evaporated, the residue was purified by column chromatography on silica gel (eluent: hexane/methylene chloride = 5:3), and the fraction with an $R_f = 0.4$ was collected and concentrated to give the desired product 12a.

6.8.5 - General Procedure for the Asymmetric $sp^3$ C-H Bond Arylation

CuBr (2.8 mg, 0.02 mmol) and “PhPyBox” (5.5 mg, 0.03 mmol) were weighed under air and placed inside a 7 mL conical glass vial. The vial equipped with a cap (Teflon septum inside) was evacuated under vacuum and refilled with nitrogen via a needle through the septum. DME (500 µL) was added with a syringe, and the mixture was stirred at room temperature for 2 hours. The vial was opened and then 2-phenyl-tetrahydroisoquinoline (21 mg, 0.1mmol) and phenylboronic acid (19.5 mg, 0.16 mmol) were rapidly added to the preformed copper complex in solution before resealing the vial (The reaction is not sensitive to a small amount of oxygen). The drop-wise addition of T-HYDRO® (23 µL, 0.16 mmol) was performed with a micro-syringe over 30 minutes. Then, the vial was immersed in an oil bath at 50°C for 2 days. The resulting mixture was extracted with ethyl acetate and filtered through a short layer of silica gel, eluting with ethyl acetate. Solvent was evaporated, the residue was purified by Thin Layer Chromatography (eluent: hexane/methylene chloride: 5/2) and the fraction with an $R_f = 0.3$ was collected to give the desired product 3a.

“PhPybox”
(R,R)-2,6-Bis(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine

[Chemical Structure Image]
References for Chapter 6

11. Phenylboronic acid pinacol ester and phenylboronic acid glycol ester were inefficient under the optimized conditions.
Part IV. Electrochemical Cross-Dehydrogenative-Coupling
Chapter 7 – Electrochemical C-C Bond Formation via Generation of Carbocation Intermediates.

Electron-transfer-driven reactions have been widely used for various transformations, although their potential has not yet been fully utilized. Among several methods for electron-driven-transfer reactions, electrochemistry serves as a straightforward and powerful method. In fact, radical cations can be generated by electrochemical electron-transfer reactions of neutral organic compounds, and carbocations can also be generated by subsequent bond-dissociation process. These reactive carbon species are utilized in various synthetic transformations, especially carbon-carbon bond formations.1-16

7.1 - Direct Oxidative Cyanation

Electrochemical oxidation has been largely investigated for the generation of carbocation intermediates and the electrochemical cyanation of tertiary amines constitutes a representative example of C-C bonds formation employing this method.1-8

Natural and unnatural α-amino acids are widely used as chiral building blocks for natural products synthesis. α-Amino acids can be prepared by cyanation at the α-position of alkyl-amines. The first example of electrochemical anodic cyanation of tertiary amines was reported in 1969. Andreades an Zahnow investigated the electrochemical cyanation of N,N-dimethylaniline and N-methyl-N-ethylaniline and found that the introduction of the cyanide group occurred preferentially at the primary position of the side chain.1 α-Aminonitriles were obtained by Chiba and Takata from potential controlled oxidation of various aliphatic and heterocyclic tertiary amines at a platinum anode in a sodium cyanide methanolic solution.2 Under similar conditions Yoshida observed a regiospecific cyanation of pyrrole and indole derivatives.3 In 1990, Fuchigami and co-workers studied the regioselectivity of the anodic cyanation
of 2,2,2-trifluoroethylamine and contrary to the methoxylation which took place at the α-position of the trifluoromethyl group, the cyanation occurred at the α-position of the amine.⁴

The methods described above are relatively simple. Nevertheless, most of them suffer from long reaction times, low yields and low current efficiencies due to electrode passivation and cyanide oxidation.

To prevent electrode anode passivation, Hurvois and co-workers developed a flow cell method for the macroscale electrochemical cyanation of cyclic aniline derivatives. This method found an interesting application in the total synthesis of alkaloid 241D (Scheme 7.1).⁵

![Scheme 7.1 – Electrochemical Cyanation of Cyclic Anilines Derivatives](image)

The generation of carbocation must be carried out in the presence of carbon nucleophiles owing to their instability. Direct oxidative carbon-carbon bond formation is generally difficult because carbon nucleophiles are easily oxidized and prevent oxidative generation of carbocations. In order to achieve anodic carbon-carbon bond formation with high efficiency, two different methods were developed: the “site isolation” concept and “the cation pool” technique.

The concept of “site isolation” (attachment of opposing reagents to the respective insoluble polymers suppresses their mutual destruction) was recently
applied to the anodic cyanation of cyclic amides. Tajima and Nakajima reported the use of a polystyrene-supported quaternary ammonium cyanide as a heterogeneous cyanide source. The active Bu₄NCN cyanating agent was generated in situ via anion exchange reaction (Scheme 7.2).⁶

![Scheme 7.2 – The Site Isolation Concept](image)

Pilli and Santos published their work on electrochemical cyanation, where, in the case of “cation pool” method (discussed in part 7.2 of this chapter) using a combination of TMSCN and TMSOTf, they achieved high yield and regioselectivity.⁷

![Scheme 7.3](image)
Recently, Onomura reported α-cyanation of N-protected cyclic amines using a direct electrochemical method. With methane sulfonic acid (MeSO$_3$H) as additive, cyclic α-cyanoamines were obtained with high yield and high regioselectivity.$^8$

\[
\text{O}_\text{OR} \xrightarrow{-2e, -H^+} \text{TMSCN, MeSO}_3\text{H} \xrightarrow{\text{MeCN/CH}_2\text{Cl}_2, 0^\circ\text{C}} \text{O}_\text{OR}
\]

\[
\text{n = 1, 2, 3, 4} \quad 67-98 \% \text{ yield}
\]

**Scheme 7.4**

### 7.2 – The Cation Pool Method

In 1999, Yoshida and co-workers reported the development of a method that involves the generation of a “cation pool” using low-temperature electrolysis, and then its reaction with nucleophiles under non-oxidative conditions (Figure 7.1). This one-pot/two-step method solves problems associated with conventional oxidative generation of cations and their in situ reaction with nucleophiles, and provides an efficient method for direct oxidative carbon-carbon bond formation.$^9$

![Figure 7.1 – “Cation Pool” Method for the Oxidative Carbon-Carbon Bond Formation](image)

**Figure 7.1** – “Cation Pool” Method for the Oxidative Carbon-Carbon Bond Formation.
This one-pot method has an advantage over conventional processes because nucleophiles that might be otherwise oxidized during an in situ process can be used without any difficulty. A representative example of this powerful method is presented in scheme 7.5. The carbamate substrate with an oxidation potential much higher than the allylsilane nucleophile was efficiently oxidized to produce the desired coupling product in high yield.

![Scheme 7.5](image)

In this early publication Yoshida and co-workers reported the functionatization of carbamate with electron-rich arenes, 1,3 diketones, 1,3 diketoesters, allylsilanes, enol silyl ethers, and related compounds, demonstrating the broad application of the procedure. This technique has found numerous applications in oxidative carbon-carbon bond formation, including the α-cyanation of N-protected cyclic amines (see chapter 7.1).
Figure 7.2 – Selected Examples of Carbon-Carbon Bond Coupling Products Generated via the Cation-Pool of N-Acyliminium

ref. 14  
ref. 14  
ref. 14  
ref. 14
References for Chapter 7

Chapter 8. Aerobic and Electrochemical Oxidative Cross-Dehydrogenative-Coupling (CDC) in Ionic Liquids.

As illustrated in the previous chapters of this thesis, the generation of carbocation intermediates followed by their reaction with carbon nucleophiles is one of the most powerful strategies for the formation of C-C bonds. The use of organic reagents as oxidants does not constitute a unique method. In fact, electrochemical oxidation has been also largely investigated for the generation of these carbocation intermediates (see Chapter 7).

On the other hand, room temperature ionic liquids composed entirely of ions and existing in the liquid state at and around room temperature have several archetypal properties such as intrinsic conductivity, high thermal stability, low-volatility, high polarity and wide electrochemical windows. As a result, they are being increasingly used in many electrochemical experiments. Combining the above principles, we envisaged an oxidative carbon-carbon bond formation in ionic liquids via the anodic oxidation of an amine 1, N-phenyltetrahydroisoquinoline (1a) (see Table 8.1), to generate the corresponding iminium intermediate 16, which would subsequently react with a carbon nucleophile (Scheme 8.1).

Scheme 8.1 – Carbon-Carbon Bond Formation via Generation of Carbocations in Ionic Liquids.
8.1 – Background

The chemical CDC reaction has been performed so far in water or in an organic solvent. For our investigation in ionic liquids, it was necessary to determine the feasibility of the chemical CDC reaction in this medium. We therefore selected a well established coupling reaction between N-phenyl-tetrahydroisoquinoline (1a) and nitromethane, giving the β-nitroamine 3a, which had been carried out in water under an atmosphere of oxygen using CuBr as catalyst (see chapter 2). β-Nitroamines such as 3a can be readily reduced to 1,2-diamines, which are important molecules in medicinal chemistry and are useful ligands for catalysis.

\[
\begin{align*}
&\text{CuBr (5 mol %)} \\
&2 \text{ equiv MeNO}_2 \\
&\text{O}_2 (1 \text{ atm}) \\
&\text{H}_2\text{O, 60°C}
\end{align*}
\]

Scheme 8.2 – Oxidative Alkylation of sp\textsuperscript{3} C-H Bond Using Molecular Oxygen in Water

8.2 – Aerobic Cross-Dehydrogenative-Coupling in Ionic Liquid

Consequently, the above reaction was performed in Butyl-methylimidazolium tetrafluoroborate ([BMIm][BF\textsubscript{4}]) as solvent. Such 1-3 dialkyl imidazolium based ionic liquids have considered interest in both catalysis and electrochemistry. [BMIm][BF\textsubscript{4}] was synthesized according to the reported method and was obtained as a colorless liquid. The ionic liquid [BMIm][BF\textsubscript{4}] appeared as an effective solvent for the CDC reaction between tertiary amine 1a and nitromethane and the desired product 3a was obtained in 80 % yield (Table
8.1, run 1) compared to 90% NMR yield in water. Interestingly, the ionic liquid and the catalyst could be recycled 10 times with almost no loss of activity (Table 8.1). It is also important to note that an increase of yield was observed after the first recycling. In fact, a better yield of the desired coupling product 3a was obtained in runs 2 to 6, suggesting a possible activation of the copper catalyst by the ionic liquid solvent. Imidazolium based ionic liquids can exhibit dramatic acceleration effect on the electron transfer from metal complexes to oxygen molecule.\textsuperscript{6} Moreover, the \textit{in situ} generation of a carbene intermediate in ionic liquid which can play the role of ligand for metal centers has also been clearly demonstrated.\textsuperscript{7}

\textbf{Table 8.1} – Copper-Catalyzed Aerobic Alkylation of Tertiary Amines in Ionic Liquid

\begin{center}
\begin{tabular}{|c|c|c|c|c|c|c|c|c|c|}
\hline
Run & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\hline
Yield\textsuperscript{a} & 80 & 90 & >99 & >99 & >99 & 95 & 90 & 85 & 80 & 70 \\
\hline
\end{tabular}
\end{center}

\textbf{8.3 – Electrochemical Cross-Dehydrogenative-Coupling in Ionic Liquid}

\textbf{8.3.1 – Cyclic Voltammetry Studies}

The results of Table 8.1 clearly show that the chemical CDC reaction between a tertiary amine and nitromethane is also efficient in an ionic liquid. The next step was to verify if such an oxidative coupling could be carried out electrochemically.
Ionic liquids as electrolytes are known to have a wide electrochemical window. Indeed, the electrochemical window of the \([\text{BMIm}][\text{BF}_4]\) ionic liquid covers about 4 V (from -2.5 to 2.2 V vs. Ag/AgNO\(_3\) 0.01 M at a glassy carbon (GC) electrode (Figure 8.1). The oxidation limit occurs at a potential significantly more positive than those of the tertiary N-phenylamine 1a and of the \(\beta\)-nitroamine 3a (see Figs 8.2 and 8.3).

![Figure 8.1 – Cyclic Voltammogram of \([\text{BMIm}][\text{BF}_4]\) at GC Electrode and a Scan Rate of 0.1 Vs\(^{-1}\).](image)

As seen in Fig. 8.2, the cyclic voltammogram (CV) of amine 1a in \([\text{BMIm}][\text{BF}_4]\) at a GC electrode reveals a non-reversible oxidation peak at a potential of 0.55 V vs. Ag/AgNO\(_3\), which corresponds to the oxidation of a tertiary N-phenylamine. The CV of the \(\beta\)-nitroamine 3a (Fig. 8.3) shows a similar oxidation peak but at a more positive potential of 0.75 V. The tertiary N-phenyl nitroamine 3a is more difficult to oxidize due to the inductive effect of the nitro group. In the CVs of Fig. 8.2 and Fig. 8.3, on the first negative scan after reversal of the potential, a reduction peak appear around 0.2 V (Fig. 8.2) and 0.3 V (Fig. 8.3) to which corresponds an oxidation peak at 0.2 and 0.4 V respectively.
in the second positive scan. The increase of current of these redox couples upon
cycling indicates that the species giving rise to these reversible systems to
accumulate on the electrode. This is most probably due to the formation of
conducting polymers or oligomers on the electrode surface. Such
polymerization/oligomerization would be responsible for the partial passivation of
the electrode seen in these CVs by the decrease of the peak current for the
oxidation of amines 1a and 3a and the decrease of the reduction current of the
nitro group of 3a at −1.7-1.8 V. An important feature of the CVs of amines 1a and
3a is the reduction peak at −1.2 V in the reverse scans which, as will be seen
below, corresponds to the iminium cation generated by oxidation of the amine:
iminium cation 16 from the oxidation of 1a (see Scheme 2) and the iminium
cation generated by oxidation of the β-nitroamine 3a.

![Cyclic Voltammogram of the N-Phenyltetrahydroisoquinoline 1a, [1a] = 5.10^2 M) in [BMIm][BF4] at GC Electrode and a Scan Rate of 0.1 Vs^{-1}.](image)
Next, the cyclic voltammogram of a solution of the amine 1a plus 2 equivalents of nitromethane in [BMIm][BF₄] was recorded in order to see if the β-nitroamine 3a could be formed in situ upon oxidation of the amine 1a. This CV did not show any peak corresponding to the β-nitroamine 3a (voltammogram not shown). The latter was not formed under these conditions. These results will be discussed below together with the potentiostatic electrolysis results.

8.3.2 – Anodic Nitro-Mannich Reaction in Ionic Liquids.

An electrolysis of the amine 1a was then performed under controlled potential (potentiostatic electrolysis) in a standard two-compartment electrochemical H-cell. A large area Pt electrode was used as working electrode instead of a GC electrode for practical reasons. The CV behavior on a Pt microelectrode was identical to that on a GC electrode. The anodic potential was fixed at 0.7 V, 150 mV more positive than the oxidation peak potential of the
amine 1a (see the Experimental Section for details). The number of coulombs consumed corresponded to the exchange of one electron per molecule of 1a. In fact, in regard to the expected 14.5 coulombs necessary for the one-electron oxidation of 1.5 mmol of the amine 1a, a total of 15.5 coulombs was observed.

After the electrolysis, 2 equivalents of nitromethane were added to the cathodic compartment and the resulting mixture was stirred for 2 hours. No organic compound (other than nitromethane) was detected after extraction with diethyl ether, suggesting that only charged species insoluble in ether and stabilized in the ionic liquid were present in the final electrolytic solution. On the other hand, when 2 equivalents of both triethylamine and nitromethane were added to the solution after electrolysis, the CV of Fig. 8.4 was obtained showing the presence of an equimolar ratio of the desired β-nitroamine 3a and starting amine 1a (oxidation peaks of the amine 1a and the β-nitroamine 3a of equal intensity). Other features of this CV are the cathodic peak at –1.2 V corresponding to the reduction of the iminium cation 16 and the iminium cation generated by the oxidation of 3a, the peak corresponding to the reduction of the nitro group of 3a, and the nitromethane reduction peak. Note that there is no iminium cation present in the solution since the first scan of Fig. 8.4 recorded towards the negative potentials does not show any reduction peak at –1.2 V. The iminium reduction peak is generated only after the first cycle in oxidation. The formation of an equimolar amount of the β-nitroamine 3a and the starting amine 1a was confirmed by ether extraction of the final solution and NMR analysis of the crude product.
8.3.3 – Postulated Mechanism for the Formation of $\beta$-nitroamine 3a by Oxidation of Amine 4.

According to the electrolysis and voltammetric results, a possible reaction mechanism can be postulated and is shown in Scheme 8.3. It involves the generation of the radical cation 1a$^+$ by a one-electron oxidation of the amine 1a which would be deprotonated to the radical intermediate (1a') through deprotonation by the amine 1a. Thus one equivalent each of radical 1a' and the protonated amine 1aH$^+$ would be formed. The neutral radical 1a' would be further oxidized to the iminium cation 16. In the absence of Et$_3$N, there is no nucleophile present in the solution to react with the iminium cation 16 and the charged species 1aH$^+$ and 16 are much more soluble in the ionic liquid than in ether. The protonated amine 1aH$^+$ is not oxidized in the potential region studied as evidenced by the absence of an oxidation peak in the CV of 1aH$^+$ BF$_4^-$ in [BMIIm][BF$_4$] (voltammogram not shown). In the presence of 2 equivalents of
$\text{Et}_3\text{N}, \text{1aH}^+$ and nitromethane would be deprotonated to regenerate the starting amine $\text{1a}$ and form the nucleophilic nitronate anion. The latter then would react with the iminium cation $\text{16}$ to generate the desired $\beta$-nitroamine $\text{3a}$. Hence a total of one electron per molecule of amine $\text{1a}$ is consumed to produce an equimolar amount of the $\beta$-nitroamine $\text{3a}$ and the starting amine $\text{1a}$.

**Scheme 8.3** – Postulated Mechanism for the Formation of $\beta$-Nitroamine $\text{3a}$ by the Oxidation of the Amine $\text{1a}$.
A similar mechanism involving the radical cation 1a$^{+}$ and the radical 1a$^-$ might also take place in the copper catalyzed aerobic chemical Cross-Dehydrogenative-Coupling reaction. In fact, the addition of radical scavengers like 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and 4-methyl-2,6-di-tert-butyl phenol (BHT) to the standard conditions of copper-catalyzed nitro-Mannich reaction decreased significantly the yield of the coupling product in both ionic liquid and water. There would be a competition between oxidation of the radical 1a$^-$ to the iminium cation 16 and its reaction with the scavengers (coupling with TEMPO and H-abstraction with BHT).

8.3.4 – Cation Pool Method in Ionic Liquid

Taking the proposed mechanism in consideration, we postulated the possibility of generating and accumulating carbocations electrochemically in [BMImBF$_4$] in the absence of nucleophiles (“cation pool”). Since the conditions described above were producing 50% of the unreactive protonated amine 1aH$^+$, we envisaged the addition of triethylamine in the electrolysis solution. The addition of such a base to the iminium cation 16 would be reversible and the base would then deprotonate 1aH$^+$ to regenerate the starting amine 1a, which would allow the complete anodic oxidation of the amine 3a to the iminium cation 16. Cyclic voltammetric studies demonstrated that triethylamine was not oxidized at the selected potential. Consequently, triethylamine was added to the [BMIm][BF$_4$] ionic liquid containing the amine 1a and the reaction mixture was subjected to potentiostatic anodic oxidation. The coulometry corresponded to the expected consumption of 2 electrons per molecule of 1a.

The starting amine 1a and the protonated amine 1aH$^+$ were not detected and only the iminium cation 16 reduction peak could be observed in the CV, thus clearly showing that the cation 16 has been preformed in [BMIm][BF$_4$] (cation pool) by complete oxidation of 1a.
Then, the addition of 2 equivalents of nitromethane and triethylamine to the ionic liquid cation pool produced the β-nitroamine product 3a in 80 % NMR yield (Scheme 8.4).

Scheme 8.4 – Results of the Cation Pool Method in an Ionic Liquid.
To evaluate further the potential of this new cation pool method, we investigated the formation of a new C-P bond using diethylphosphite as nucleophile in place of the conjugate base of nitromethane using the same conditions and procedure described above. The biologically important α-aminophosphonate 8a was synthesized in a high 85 % NMR yield (Scheme 8.4). It is important to note that the addition of nitromethane or diethylphosphite with the chemically preformed iminium salt 16 generated also the desired coupling products with high efficiency.

8.4 – Conclusion

To conclude, we have demonstrated that ionic liquids and in particular [BMIm][BF₄] are highly effective solvents for copper-catalyzed Cross-Dehydrogenative-Coupling (CDC) with oxygen as terminal oxidant. By using ionic liquids as such, both the solvent and the copper catalyst can be recycled 10 times without significant lost of activity. Furthermore, we have also demonstrated the possibility of using an electrochemical method rather than a metal catalyst, to carry out CDC in ionic liquids as solvent and electrolyte. Finally, a detailed mechanism of the anodic nitro-Mannich carbon-carbon bond formation process was described. Further studies for the detection and the characterization of the proposed intermediates along with the extension of the scope of the CDC reaction in ionic liquids are being pursued.
8.5 – Experimental Section

8.5.1 – General Information

1H NMR spectra were recorded on Varian 400 MHz spectrometers in CDCl₃ solution and the chemical shifts were reported in parts per million (δ) referenced to the internal solvent signal (peak at 7.26 ppm). The peak patterns are indicated as following: s, singlet; d, doublet; t, triplet; the coupling of constants, J, are reported in Hertz (Hz). Flash column chromatography was performed using Sorbent Silica Gel 60 F₂₅₄ TLC plates and visualized with ultraviolet light. All reagents were weighed and handled in air at room temperature and were later degassed with Argon. All reagents were purchased from Aldrich and Acros and used without further purification. 2-Aryl-1,2,3,4-tetrahydroisoquinoline (4) was prepared by the literature method.[¹] Ionic liquids were prepared according to the reported method. All the cyclic voltammetry studies were performed in a non-divided cell containing the [BMIm][BF₄] ionic liquid. The electrochemical behaviors of the organic molecules (C = 5.10⁻² M) were studied using a 3 mm diameter glassy carbon disk working electrode.

8.5.2 – General Procedure for the Anodic Nitro-Mannich Reaction in Ionic Liquids

![Figure 8.6 – Setup of the Bulk Electrolysis.](image-url)

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In a two-compartment electrochemical cell with a glass fritt as separator, the ionic liquid [BMIm][BF$_4$] (3 mL) was added to the three neck anodic compartment containing 2-phenyl-tetrahydroisoquinoline (1a) (31 mg, 0.15 mmol). The amine 1a was carefully dissolved upon heating by stirring using a magnetic stirrer under an argon atmosphere. The cathodic compartment was filled with [BMIm][BF$_4$] (3 mL). Platinum mesh wire-netting working electrode was positioned in the anodic compartment and the platinum auxiliary electrode in the cathodic compartment (see Figure 8.6). The oxidation potential was fixed at 0.7V (vs. Ag/AgNO$_3$) and the colorless solution was stirred at room temperature until the current reached less than 1% of its initial intensity. To the orange product mixture, nitromethane (16 µL, 0.3 mmol) and triethylamine (44 µL, 0.315 mmol) were added and the solution was stirred for 12h at room temperature. The resulting mixture was extracted with diethylether and filtered through a short layer of silica gel and eluted with diethylether. The solvent was evaporated and the residue was analyzed by thin layer chromatography and $^1$H NMR spectroscopy.

**Graph 8.1** – Coulometry of the Potentiostatic Electrolysis.
8.5.3 – General Procedure for the Cation Pool Method in Ionic liquids.

![Diagram of the Cation Pool Method](image)

**Figure 8.7** – Set up of the Cation Pool Method.

In the electrochemical cell, the electrodes and the procedure were the same as those described above except that triethylamine (28 µL, 0.3 mmol) was added to the anodic compartment. After completion of the electrolysis, nitromethane (16 µL, 0.3 mmol) or diethylphosphite (26 µL, 0.3 mmol) and triethylamine (44 µL, 0.315 mmol) were added and stirred for 12h at room temperature. The resulting mixture was extracted with diethylether and filtered through a short layer of silica gel and eluted with diethylether. The solvent was evaporated and the residue was analyzed by thin layer chromatography and $^1$H NMR spectroscopy.
8.5.4 – General Procedure for the Addition With Preformed Iminium

As mentioned previously in this chapter, the addition of nitromethane or diethylphosphite with the preformed iminium salt generated also the desired coupling products with high efficiency.
In a 10 mL test tube, 3,4-dihydro-2-phenyl-isoquinolinium bromide salt (16) (0.2 mmol) (58 mg, 0.2 mmol), 0.4 mL of [BMIm][BF₄], (21.5 µL, 0.4 mmol) or (51.5 µL, 0.4 mmol) HPO(OEt)₂ and NEt₃ (0.4 mmol) was added. The reaction was stirred using a magnetic stirrer at room temperature overnight. The resulting mixture was extracted with diethyl ether and filtered through a short layer of silica gel and eluted with ethyl acetate. Solvent was evaporated and the NMR yields were determined using an internal standard (90% NMR yield).

8.5.5 – General Procedure for 1-Butyl-3-Methylimidazolium Tetrafluoroborate [BMIm][BF₄] Synthesis.

A solution of 1-bromobutane (119 mL, 1.1 equiv.) was added slowly to 1-methylimidazole (78 mL, 1 mol) in acetone (500 mL) in a 1L round bottle flask (1-methylimidazole was first distilled under vacuum to give a clear colourless oil). The mixture was gently refluxed under argon for 24 hours. After cooling to room temperature, the solvent was removed and the 1-butyl-2-methylimidazolium bromide ([BMIm][BF₄]) was washed thoroughly with ether (3*300 mL ). A 2 L roundbottom flask was charged with 1.5 L acetonitrile, [BMIm][Br] and sodium tetrafluoroborate (150g, 1.4 equiv.), and the mixture was allowed to stand at room temperature for 3 days with stirring. The precipitate (NaBr) was then filtered off and the filtrate was concentrated by rotary evaporation. More NaBr was precipitated by adding dichloromethane (1L) and cooling down in a ice bath. The crude IL was further purified on a silica column using cold dichloromethane as eluent to give a colourless liquid.

1-Butyl-3-methylimidazolium tetrafluoroborate [BMIm][BF₄].

\[
\begin{align*}
\text{BF}_4^- \\
\text{N} & \quad \text{N} \\
\end{align*}
\]

\[\text{H NMR (400 MHz, d₆ acetone, 293 K)} \delta \text{ ppm: } 9.00 (s, 1H), 7.73 (d, 2H, J = 22.4 Hz), 4.35 (t, 2H, 7.2 Hz), 4.04 (s, 3H), 1.91 (m, 2H), 1.37 (m, 2H), 0.94 (t, 3H, 6.8 Hz).\]
References for Chapter 8


Conclusion and Claims to Original Knowledge

The oxidative C-C bond formation was developed between tertiary amines and nitroalkanes to produce \( \beta \)-nitroamines. This environmentally respectful method was catalyzed by copper bromide using oxygen gas as oxidant and water as solvent. The molecular oxygen uptake demonstrated that water was the only byproduct of this highly efficient Cross-Dehydrogenative-Coupling reaction.

Based on the above aerobic methodology, we were also able to generate a variety of different \( \alpha \)-aminophosphonates from the oxidative coupling of tertiary amines and H-phosphonates. This new strategy for carbon-phosphorus bond formation used a relatively cheap copper salt as catalyst and oxygen as a safe oxidant.

Potential biologically active 1-aryl-1,2,3,4-tetrahydroisoquinoline derivatives were generated from a copper-catalyzed arylation of \( \text{sp}^3 \) C-H bonds adjacent to a nitrogen atom in the absence of a directing group with boronic acids. Some important features of the unprecedented oxidative arylation methodology were the possibility to use either peroxide or molecular oxygen as oxidant and its potential asymmetric synthesis in presence of chiral ligands for the copper catalyst. This methodology found an interesting application in the direct \( \alpha \)-functionalization of glycine derivatives and short peptides.

Additional to the precedent mechanistic studies, the electrochemical behaviour of the tertiary amine substrate and the \( \beta \)-nitroamine product was investigated employing \([\text{BMIm}]\text{[BF}_4\text{]}\) as electrolyte solvent. The potentiostatic electrolysis in ionic liquid afforded the desired product with a high yield. This result and the cyclic voltammetric investigation provided a better understanding of the reaction mechanism involving radicals. Ionic liquids have also demonstrated high efficiency when applied as solvent for the aerobic nitro-Mannich carbon-carbon bond formation.
During the course of this thesis, the following articles were published:


