Nickel-catalyzed decarbonylative coupling for access to biaryl motifs

by

NICOLE LABERGE

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF
THE REQUIREMENTS FOR THE DEGREE OF
MASTER OF SCIENCE

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Chemistry)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

July 2015

© Nicole LaBerge, 2015
Abstract

The goal of this research project was to design a sustainable catalytic cross-coupling reaction using nickel and carboxylic acid derivatives and apply it to the synthesis biaryls. A low-cost route to a variety of functionalized bis(hetero)aryl and biaryl motifs has been developed using aryl esters and boronic acids. This Suzuki-Miyaura-type decarbonylative cross-coupling is catalyzed by an affordable low-toxic catalyst system composed of Ni(cod)$_2$ and PCy$_3$. Electron-rich arylboronic acids gave the highest yields. A variety of functional groups including methyl ethers, esters, fluorine substituents and acetals are compatible with the reaction conditions. The reaction did not tolerate boronic acids possessing halogen or cyano functionalities. Aryl esters with and without nitrogen atoms were also accommodated in the reaction. The methodology reveals challenges associated with nickel and esters in cross-coupling chemistry. Additionally, it presents an attractive alternative to the use of palladium catalysis currently used in industry to acquire such biaryls.
Preface

Work presented in Chapter 2 has been accepted for publication as a full paper in European Journal Organic Chemistry (LaBerge, N.A.; Love, J. A. *Eur. J. Org. Chem.* **2015**, *in-press* DOI: 10.1002/ejoc.201500630). Tables have been modified compared to the published version. I assembled the manuscript and Prof. Jennifer Love edited prior to submission. The results disclosed in the chapter are extended in scope and discussion compared to the published data. I was the lead investigator, responsible for all major areas of concept formation, synthesis, data collection and analysis.
# Table of Contents

Abstract........................................................................................................................................ ii

Preface ........................................................................................................................................... iii

Table of Contents........................................................................................................................ iv

List of Tables .................................................................................................................................. vi

List of Figures ............................................................................................................................... vii

List of Schemes ............................................................................................................................ viii

List of Symbols and Abbreviations .............................................................................................. x

Acknowledgements ....................................................................................................................... xiii

Chapter 1: Introduction ................................................................................................................1

1.1 Generation of metal aryl species .......................................................................................... 3

1.2 Decarboxylative cross-couplings ...................................................................................... 5

1.3 Decarboxylative coupling .................................................................................................. 17

1.3.1 Decarboxylative coupling with esters ....................................................................... 19

1.4 Decarboxylative reaction design ...................................................................................... 22

Chapter 2: Ni(0)-catalyzed decarboxylative coupling with esters ........................................ 23

2.1 Introduction ......................................................................................................................... 23

2.2 Results and discussion ....................................................................................................... 24

2.2.1 Reaction design ........................................................................................................... 24

2.2.2 Reaction optimization ................................................................................................ 26

2.2.3 Substrate scope ........................................................................................................... 32

2.2.4 Mechanistic inquiry .................................................................................................... 38

Chapter 3: Summary and Future Work ....................................................................................... 43

3.1 Summary and conclusions .............................................................................................. 43

3.2 Future work ....................................................................................................................... 43

Chapter 4: Experimental Procedures ......................................................................................... 45

4.1 General procedures .......................................................................................................... 45

4.2 Materials and methods .................................................................................................... 45

4.3 Preparation of aryl esters ............................................................................................... .46

4.4 Experimental procedure for decarboxylative coupling .................................................... 51
4.5 Experimental procedure for decarbonylative coupling (2a, large scale) ..................58
4.6 Stoichiometric experiments ..................................................................................58
4.7 Procedure for $^1$H NMR spectroscopy yields .....................................................59
4.8 Description of GC FID study ................................................................................63

References ..................................................................................................................65
Appendix 1 NMR Spectra .........................................................................................68
List of Tables

Table 2.1  Optimization of reaction conditions (ligand, temperature) ..................27
Table 2.2  Optimization of reaction conditions (base with PCy₃ or PPh₃) ...............29
Table 2.3  Optimization of reaction conditions (other ligands) .........................32
Table 2.4  Substrate scope and limitation of boronic acids .............................34
Table 2.5  Scope and limitation of heteroaryl esters ...................................36
Table 2.6  Scope and limitation of aryl esters .............................................37
### List of Figures

| Figure 1.1 | Molecules possessing biaryl motifs | 1 |
| Figure 1.2 | Possible four-membered transition state | 13 |
| Figure 2.1 | Decarboxylative coupling | 23 |
| Figure 2.2 | Transmetallating reagents screened | 25 |
| Figure 2.3 | Buchwald, NHC, and bidentate N ligands | 31 |
| Figure 2.4 | Variable temperature $^{31}$P{$^1$H} NMR spectra for the reaction of phenyl nicotinate, Ni(cod)$_2$ and PCy$_3$(162 MHz, tol-$d_8$) | 39 |
| Figure 2.5 | ORTEP depiction of Ni(PCy$_3$)$_2$(CO)$_2$ | 41 |
| Figure 2.6 | Possible mechanism | 42 |
| Figure 2.7 | Possible bond cleavages for an aryl ester | 42 |
| Figure 4.1 | Representative $^1$H NMR spectrum for biaryl products 3d and 4d | 60 |
| Figure 4.2 | Enhancement of Figure 4.1 from 0.5 to 5 ppm | 60 |
| Figure 4.3 | GC calibration curve for 3-phenylpyridine | 64 |
**List of Schemes**

<table>
<thead>
<tr>
<th>Scheme</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 1.1</td>
<td>Traditional biaryl cross-coupling</td>
<td>2</td>
</tr>
<tr>
<td>Scheme 1.2</td>
<td>Decarboxylative cross-coupling with aryl halides</td>
<td>3</td>
</tr>
<tr>
<td>Scheme 1.3</td>
<td>Routes to metal aryl species from aryl carboxylic acids and derivatives</td>
<td>4</td>
</tr>
<tr>
<td>Scheme 1.4</td>
<td>Cu-mediated decarboxylative arylation of 2-nitrobenzoic acid and ( p )-iodoanisole</td>
<td>5</td>
</tr>
<tr>
<td>Scheme 1.5</td>
<td>Proposed mechanism for bimetallic decarboxylative cross-coupling</td>
<td>6</td>
</tr>
<tr>
<td>Scheme 1.6</td>
<td>Decarboxylative coupling of ortho-substituted benzoic acids and aryl bromides</td>
<td>7</td>
</tr>
<tr>
<td>Scheme 1.7</td>
<td>Proposed decarboxylative cross-coupling mechanism with Pd and Cu</td>
<td>7</td>
</tr>
<tr>
<td>Scheme 1.8</td>
<td>Decarboxylative coupling of aryl triflates and potassium carboxylates</td>
<td>8</td>
</tr>
<tr>
<td>Scheme 1.9</td>
<td>Decarboxylative coupling of aryl mesylates and potassium carboxylates</td>
<td>9</td>
</tr>
<tr>
<td>Scheme 1.10</td>
<td>Decarboxylative coupling of aryl iodides and benzoic acids</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 1.11</td>
<td>Pd and Ag mediated decarboxylative coupling of aryl iodonium species</td>
<td>11</td>
</tr>
<tr>
<td>Scheme 1.12</td>
<td>Decarboxylative coupling of aryl triflates and potassium carboxylates</td>
<td>11</td>
</tr>
<tr>
<td>Scheme 1.13</td>
<td>Decarboxylative Hiyama cross-coupling with Pd, Cu and Ag</td>
<td>12</td>
</tr>
<tr>
<td>Scheme 1.14</td>
<td>Decarboxylative arylation of heteroaromatic carboxylic acids and aryl bromides</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 1.15</td>
<td>Decarboxylative coupling of fluoroarenes with aryl bromides, chlorides and triflates</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 1.16</td>
<td>Direct arylation of aryl benzoic acids via decarboxylative coupling</td>
<td>15</td>
</tr>
<tr>
<td>Scheme 1.17</td>
<td>Decarboxyaltive arylation with boronic esters</td>
<td>17</td>
</tr>
<tr>
<td>Scheme 1.18</td>
<td>Transition-metal mediated decarbonylation reactions</td>
<td>18</td>
</tr>
<tr>
<td>Scheme 1.19</td>
<td>Decarbonylative coupling to generate biaryls</td>
<td>19</td>
</tr>
<tr>
<td>Scheme 1.20</td>
<td>Pd-catalyzed decarbonylative waste free Heck olefination</td>
<td>20</td>
</tr>
<tr>
<td>Scheme 1.21</td>
<td>Ru-catalyzed decarbonylative coupling of esters and boronic acids</td>
<td>20</td>
</tr>
<tr>
<td>Scheme 1.22</td>
<td>Ni-catalyzed decarbonylative coupling of aryl esters and azoles</td>
<td>21</td>
</tr>
<tr>
<td>Scheme 1.23</td>
<td>Ni-catalyzed decarbonylative C-H alkenylation</td>
<td>21</td>
</tr>
<tr>
<td>Scheme 2.1</td>
<td>Formation of ([\text{Ni(O)PCy}_3]_4)</td>
<td>38</td>
</tr>
<tr>
<td>Scheme 2.2</td>
<td>Formation of ((\text{PCy}_3)_2\text{Ni(}CO\text{)}_2)</td>
<td>40</td>
</tr>
</tbody>
</table>
Scheme 3.1  Decarbonylative coupling of acyl chlorides and alkyl esters…………………44
# List of Symbols and Abbreviations

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acac</td>
<td>Acetylacetone</td>
<td></td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
<td></td>
</tr>
<tr>
<td>BINAP</td>
<td>(2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl)</td>
<td></td>
</tr>
<tr>
<td>Calc’d</td>
<td>Calculated</td>
<td></td>
</tr>
<tr>
<td>cat.</td>
<td>Catalyst</td>
<td></td>
</tr>
<tr>
<td>δ</td>
<td>Chemical shift</td>
<td></td>
</tr>
<tr>
<td>CDCl₃</td>
<td>Deuterated chloroform</td>
<td></td>
</tr>
<tr>
<td>cod</td>
<td>Cycloocta-1,5-diene</td>
<td></td>
</tr>
<tr>
<td>Cy</td>
<td>Cyclohexyl</td>
<td></td>
</tr>
<tr>
<td>°C</td>
<td>Degrees Celsius</td>
<td></td>
</tr>
<tr>
<td>dba</td>
<td>Dibenzylideneacetone</td>
<td></td>
</tr>
<tr>
<td>dctype</td>
<td>1,2-Bis(dicyclohexylphosphino)ethane</td>
<td></td>
</tr>
<tr>
<td>DFT</td>
<td>Density Functional Theory</td>
<td></td>
</tr>
<tr>
<td>DIPHOS</td>
<td>1,2-Bis(diphenylphosphino)ethane</td>
<td></td>
</tr>
<tr>
<td>DMAc</td>
<td>Dimethylacetamide</td>
<td></td>
</tr>
<tr>
<td>DMAP</td>
<td>Dimethylaminopyridine</td>
<td></td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
<td></td>
</tr>
<tr>
<td>DPEPhos</td>
<td>Oxybis(2,1-phenylene)bis(diphenylphosphine)</td>
<td></td>
</tr>
<tr>
<td>dppb</td>
<td>1,4-Bis(diphenylphosphino)butane</td>
<td></td>
</tr>
<tr>
<td>dppm</td>
<td>1,2-Bis(diphenylphosphino)methane</td>
<td></td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
<td></td>
</tr>
<tr>
<td>Equiv.</td>
<td>Equivalents</td>
<td></td>
</tr>
<tr>
<td>FG</td>
<td>Functional group</td>
<td></td>
</tr>
<tr>
<td>g</td>
<td>Gram</td>
<td></td>
</tr>
<tr>
<td>GC</td>
<td>Gas Chromatography</td>
<td></td>
</tr>
<tr>
<td>HRMS</td>
<td>High-Resolution Mass Spectrometry</td>
<td></td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
<td></td>
</tr>
<tr>
<td>IAd</td>
<td>1,3-Bis(2,6-adamantyl) imidazole-2-ylidene</td>
<td></td>
</tr>
<tr>
<td>ICy</td>
<td>1,3-Bis(2,6-cyclohexyl) imidazole-2-ylidene</td>
<td></td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
<td></td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
<td></td>
</tr>
<tr>
<td>IMes</td>
<td>1,3-Bis(2,6-mesityl) imidazole-2-ylidene</td>
<td></td>
</tr>
<tr>
<td>IPr</td>
<td>1,3-Bis(2,6-diisopropylphenyl) imidazole-2-ylidene</td>
<td></td>
</tr>
<tr>
<td>$J$</td>
<td>Coupling constant (NMR spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>LR ESI-MS</td>
<td>Low-resolution electrospray mass spectrometry</td>
<td></td>
</tr>
<tr>
<td>[M]</td>
<td>Metal in ligand environment</td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>Molar</td>
<td></td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
<td></td>
</tr>
<tr>
<td>MHz</td>
<td>Megahertz (NMR spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>mL</td>
<td>Milliliter</td>
<td></td>
</tr>
<tr>
<td>μL</td>
<td>Microliter</td>
<td></td>
</tr>
<tr>
<td>mmol</td>
<td>Millimole</td>
<td></td>
</tr>
<tr>
<td>mol</td>
<td>Mole</td>
<td></td>
</tr>
<tr>
<td>m</td>
<td>Multiplet (NMR spectroscopy)</td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
<td></td>
</tr>
<tr>
<td>Mes</td>
<td>Mesityl</td>
<td></td>
</tr>
<tr>
<td>MIDA</td>
<td>N-methyliminodiacetic acid</td>
<td></td>
</tr>
<tr>
<td>Ms</td>
<td>Mesylate</td>
<td></td>
</tr>
<tr>
<td>MS</td>
<td>Molecular sieves</td>
<td></td>
</tr>
<tr>
<td>MW</td>
<td>Microwave</td>
<td></td>
</tr>
<tr>
<td>NHC</td>
<td>N–heterocyclic carbene</td>
<td></td>
</tr>
<tr>
<td>Ni(cod)$_2$</td>
<td>Bis(1,5-cyclooctadiene)nickel(0)</td>
<td></td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl-2-pyrrolidone</td>
<td></td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
<td></td>
</tr>
<tr>
<td>NQ</td>
<td>Napthoquinone</td>
<td></td>
</tr>
<tr>
<td>ORTEP</td>
<td>Oak Ridge Thermal Ellipsoid Plot</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
<td></td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
<td></td>
</tr>
<tr>
<td>RT</td>
<td>Room temperature</td>
<td></td>
</tr>
<tr>
<td>TBAC</td>
<td>Tetrabutylammonium chloride</td>
<td></td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
<td></td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>TBDMS</td>
<td>tButyldimethylsilyl</td>
<td></td>
</tr>
<tr>
<td>TBHAB</td>
<td>Tri-\textit{n}-butyl(2-hydroxyethyl)ammonium bromide</td>
<td></td>
</tr>
<tr>
<td>\textit{tBu}</td>
<td>\textit{Tert}-butyl</td>
<td></td>
</tr>
<tr>
<td>\textit{tBu}XPhos</td>
<td>2-Di-\textit{t}ert-butyphosphino-2',4',6'-triisopropylbiphenyl</td>
<td></td>
</tr>
<tr>
<td>Tf</td>
<td>Triflate</td>
<td></td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetatic acid</td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
<td></td>
</tr>
<tr>
<td>Ts</td>
<td>Tosylate</td>
<td></td>
</tr>
<tr>
<td>XPhos</td>
<td>Dicyclo-hexyl(2'4'6'-triisopropyl[1,1'-biphenyl]-2yl)phosphine</td>
<td></td>
</tr>
</tbody>
</table>
Acknowledgements

First, I owe great thanks to Dr. Jennifer A. Love for her unconditional support and mentorship over the course of my master’s degree. Her enthusiasm, motivation and knowledge were highly inspirational and encouraging.

I owe thanks to Dr. Laurel L. Schafer for inspiration and support during my master’s degree. Also, I thank Dr. Gregory R. Dake for first introducing me to the exciting world of organic chemistry. His passion and discipline towards the subject was greatly admirable and motivating.

My group members, both past and present have been an immense support while working in the lab. Thanks to Alex Dauth, Lauren Keyes, Matthew Wathier, Tin Nguyen, Addison Desnoyer, Philip Provencher, Eric Bowes, Dawson Beattie, Weiling Chiu, Marcus Drover and Shrin Pal. Thanks also goes to Joseph Clarkson for support with the GC FID instrument in the shared instrument facility. Without his help I wouldn’t have been able to do my research.

The UBC support staff also deserves a note of gratitude. Thanks to Maria Ezhova for assisting me with NMR experiments, Ken Love for repairing my vacuum pump on several occasions, and Brian Ditchburn for making specialized glassware for my reactions. I also appreciated the assistance of Dr. Brian O. Patrick with collecting X-ray data.

I thank my parents for their absolute and undying support in whatever I choose to pursue. Thank you to my brother, Alan for keeping me in check. Last but certainly not least, thank you to Marcus Drover who is an incredible support in my life; words cannot describe how grateful I am for you.
Chapter 1: Introduction

A congener to palladium (Pd), nickel (Ni) is an increasingly sought alternative for use in cross-coupling methodologies due to its low toxicity, abundance (84 ppm for Ni vs. 0.015 ppm for Pd in the earth’s crust) and affordability ($7.70/100 g for Ni vs. $5833.00/100 g for Pd).\textsuperscript{1,2} Nickel is able to access a variety of oxidation states, which allows for catalytic application over a broad range of synthetically useful transformations.\textsuperscript{3} Despite a surge of reports on nickel catalysis, to date, catalytic strategies using nickel remain much less studied than with palladium. Thus, there lies great demand in further exploring the reactivity and catalytic potential of nickel.

Biaryls are considered ‘privileged structures’ because of their prominence in pharmaceuticals.\textsuperscript{4} In many cases, one or both of the aryl groups contain a hetero atom. Relevant examples include Gleevec, a tyrosine kinase inhibitor used to treat various types of cancers, as well as Atazanavir, an anti-retroviral agent used to treat human immunodeficiency virus (HIV) (Figure 1).\textsuperscript{5}

![Figure 1.1 Molecules possessing biaryl motifs](image-url)
Presently, the most common route to biaryl scaffolds is through cross-coupling of an aryl halide and a stoichiometric amount of organometallic reagent (M) such as Mg, Zn, Sn, B, or Si in the presence of a Pd catalyst (Scheme 1.1). These methods incur several disadvantages including the formation of MXₙ waste, the necessity of pre-functionalized starting materials, and poor atom/step economy. In addition, aryl chlorides exhibit lower reactivity in cross-coupling methodologies, presumably due to a strong Ar-Cl bond (97 kcal/mol) relative to Ar-Br (83 kcal/mol) and Ar-I (67 kcal/mol) bonds. Due to the low reactivity of the Ar-Cl bond, specialized ligands that are often air and moisture sensitive are typically employed.

Scheme 1.1 Traditional biaryl cross-coupling

Since Gooßen’s groundbreaking report on decarboxylative coupling of carboxylic acids with aryl halides in 2006, the use of carboxylic acid derivatives as electrophilic partners in cross-coupling reactions has increased dramatically (Scheme 1.2). In contrast to standard cross-coupling methodologies, which employ aryl halides (Suzuki-Miyuara coupling, Negishii coupling, etc.), the use of carboxylic acid-based cross-coupling partners has been studied to a lesser extent. The use of carboxylic acids in such a protocol has many appealing features: they are widely available, inexpensive and generate CO₂ when used in cross-coupling reactions (Scheme 1.1). In combination with Ni catalysis, the replacement of
aryl halides with aryl carboxylic acids, provides an attractive alternative to the traditional methods used to access biaryls. This chapter will survey cross-coupling methods that use carboxylic acid derivatives as alternative sources of metal aryl species in the formation of biaryl scaffolds.

![Scheme 1.2 Decarboxylative cross-coupling with aryl halides](image)

### 1.1 Generation of metal aryl species

Metal aryl (M-Ar) species may be generated from carboxylic acids or derivatives thereof in one of three ways. Depending on the method used, the resulting M-Ar fragment may be considered electrophilic or nucleophilic in character. If the M-Ar fragment is nucleophilic in character, it can replace standard transmetallation reagents in cross-coupling reactions. A nucleophilic M-Ar (I) species is formed when the acid derivative is bonded to an electron-rich metal, *i.e.* the metal is in the zero oxidation state (Scheme 1.3, Route A). This route is termed redox-neutral decarboxylative coupling, where redox-neutral implies the metal does not need to be oxidized between reductive elimination and oxidative addition steps. If the M-Ar fragment is electrophilic in character it may replace aryl halides in a coupling reaction. An electrophilic M-Ar species (II) is generated when CO₂ is extruded from the acid, and the resulting aryl fragment bonds to an electron-poor metal, *i.e.* the metal is in the +2 oxidation state (Scheme 1.3, Route B). This route is termed oxidative decarboxylative coupling where ‘oxidative’ specifies that the metal must be oxidized before
it can interact with the carboxylic acid derivative. This species (II) is analogous to those generated when an aryl halide is oxidatively added across a metal.

**Scheme 1.3 Routes to metal aryl species from aryl carboxylic acids and derivatives**

The same species II may also be generated when a metal catalyst inserts into a C-O bond of an activated carboxylic acid derivative such as those found in an ester or anhydride under redox neutral conditions (Scheme 1.3, Route C). Following insertion of the metal catalyst, CO extrusion occurs to give a metal aryl species that is electrophilic in nature - this pathway is termed decarbonylation.

As outlined above, the three routes to access M-Ar species include a) redox neutral decarboxylation, b) oxidative decarboxylation, and c) redox-neutral decarbonylation. In the first case a nucleophilic M-Ar species forms, providing an alternative to the use of organometallic transmetallating agents required by cross-coupling reactions. The last two routes offer access to electrophilic M-Ar fragments that may replace aryl halides in cross-coupling reactions. These three complementary routes form the basis from which a variety of
synthetic transformations can be realized using aryl carboxylates as replacements for organometallic reagents or aryl halides.

1.2 Decarboxylative cross-couplings

1.2.1 Redox-neutral cross-couplings

Initial reports of decarboxylative cross-coupling date back to the mid-1960s, when Nilson et al. reported the formation of biaryls from benzoic acids and aryl iodides using stoichiometric amounts of Cu$_2$O in quinoline at 240 °C (Scheme 1.4). It wasn’t until 40 years later that Gooßen et al. reported the first catalytic example of a redox-neutral decarboxylative cross-coupling process using a bimetallic Pd/Cu catalyst. Since then, decarboxylative coupling has evolved into a new and reliable route for access to biaryl motifs.

Scheme 1.4 Cu-mediated decarboxylative arylation of 2-nitrobenzoic acid and p-iodoanisole

Until recently, most examples of decarboxylative coupling have relied on bimetallic systems composed of either Pd and Cu or Pd and Ag. The use of Cu or Ag helps to facilitate the decarboxylation step while Pd facilitates the transmetallating step (Scheme 1.5). The decarboxylation step occurs within the inner-coordination sphere of either Cu or Ag. This generates intermediate c that is transferred to the Pd-Ar species to give the biaryl Pd complex d that subsequently undergoes reductive elimination to give the desired product and catalyst.
The following sections will review examples of bimetallic and monometallic catalyst systems for redox-neutral decarboxylative coupling relevant to the synthesis of biaryls.

Scheme 1.5 Proposed mechanism for bimetallic decarboxylative cross-coupling

Palladium and Copper systems

As mentioned previously, the first catalytic example of decarboxylative coupling was reported in 2006 in a groundbreaking report by Gooßen and colleagues. The catalytic cross-coupling of ortho-substituted benzoic acids and aryl bromides proceeded in the presence of 1 mol% Pd(acac)$_2$ or PdBr$_2$, 3 mol% CuI or CuBr, 1,10-phenanthroline, K$_2$CO$_3$, and 3 Å MS (Scheme 1.6). The reaction required heating for 24 h at temperatures ranging from 160-170 °C. Molecular sieves are used to trap H$_2$O that is formed upon deprotonation of the carboxylic acid by K$_2$CO$_3$. 
Scheme 1.6 Decarboxylative coupling of ortho-substituted benzoic acids and aryl bromides

The mechanism for this process is thought to involve a dual Pd/Cu catalytic cycle such as that discussed in Scheme 1.5 (Scheme 1.7). A Cu(I) or Cu(II) species mediates the decarboxylation step to give a Cu-Ar species \(c\), which is cross-coupled with an analogous Pd-Ar complex \(f\) formed from oxidative addition of an aryl bromide to Pd(0). Interestingly, addition of exogenous halide sources retards the decarboxylation step, presumably resulting from the formation of inactive Cu X\(_2\) salts.

Scheme 1.7 Proposed decarboxylative cross-coupling mechanism with Pd and Cu
A variant of this reaction has also been reported using aryl chlorides. Ortho-substituted benzoic acids were cross-coupled with aryl chlorides in the presence of 2 mol% PdI$_2$ or PdBr$_2$, 2-10 mol% CuI or CuBr, PtBu$_2$Ph (bis(t-butyl)phenyl phosphine) and a solvent mixture of NMP (N-methyl-2-pyrrolidone) and quinoline at 160 °C. The best yields were obtained when benzoic acids possessing ortho substitution patterns were used suggesting pre-coordination via a directing effect. As a result, the cross-coupling of benzoic acids devoid of ortho substitution gave poor yields. Nonetheless, this protocol expands the substrate scope to include inexpensive aryl chlorides.

Thus far, examples outlined for redox-neutral decarboxylative coupling methods are limited to benzoic acids having ortho-substitution patterns. This limitation was overcome in 2008 when aryl triflates (Ar-OTf; OTf = CF$_3$SO$_2$) were used in-lieu of aryl halides as the electrophilic cross-coupling partner (Scheme 1.8). In this instance, CuOTf, is formed rather than CuX allowing for facile displacement by a carboxylate. A wide selection of heteroaromatic benzoic acids was tolerated in the reaction.

![Scheme 1.8 Decarboxylative coupling of aryl triflates and potassium carboxylates](image)

Although aryl triflates enhance the benzoic acid substrate scope they suffer from high cost and laborious preparation. To alleviate this drawback, in 2010 aryl tosylates (OTs = p-CH$_3$C$_6$H$_4$SO$_2$) were introduced as electrophilic coupling partners. In the presence of a Pd(acac)$_2$, Cu$_2$O, XPhos (dicyclo-hexyl(2′4′6′-triisopropyl[1,1′-biphenyl]-2yl)phosphine) and
NMP a variety of potassium carboxylates were cross-coupled with aryl tosylates. The reaction has also been extended to include aryl mesylates (OMs = CH$_3$SO$_2$O). Using a customized imidazolyl phosphine ligand (2-(2-(dicyclohexylphosphino)phenyl)-5,6-dimethyl-1-octyl-1H-benzo[d]imidazole L$_1$) (Scheme 1.9) and a bimetallic catalyst system comprised of [Pd(dba)$_2$] and Cu$_2$O, aryl and heteroaryl carboxylates were coupled with aryl mesylates affording the corresponding biaryl.$^{17}$ Although mesylates possess the lowest molecular weight of the sulfonyl leaving group family, specialized ligands are required to aid in cleavage of the strong C-O bond. In this example a rigorous ligand screening protocol was performed, indicating the optimal ligand to be the imidazolyl phosphine L$_1$ (Scheme 1.9).

![Chemical reaction diagram](image)

**Scheme 1.9 Decarboxylative coupling of aryl mesylates and aryl potassium carboxylates**

Continuing their fruitful pursuits in the field, the Gooßen group extended decarboxylative coupling to an industrial scale. In 2011, the group reported a continuous flow reaction set-up capable of performing decarboxylative coupling reactions on a gram scale in less time than typical batch reactions.$^{18}$

The reactions discussed thus far have required high temperatures (up to 170 °C), which were originally attributed to the decarboxylation step. Density functional theory (DFT)
studies, however, could not decipher whether the decarboxylation step or the transmetallating step was rate limiting.\textsuperscript{19} Thus, reaction improvement should not exclusively focus on the decarboxylation step, but also the transmetallating step. This was confirmed when a bidentate ligand designed to facilitate adduct formation between Cu and Pd enabled the reaction to proceed at 100 °C, rather than 170 °C. This finding provides pivotal information for further development of decarboxylative cross-coupling reactions, as high temperatures are a substantial drawback of current methods.

**Palladium and silver systems**

Becht and Wagner described the first example of decarboxylative coupling involving Pd and Ag in 2007. Aryl iodides were cross-coupled with benzoic acids to give a diverse selection of functionalized biaryls having electron-rich or -poor character (Scheme 1.10).\textsuperscript{20} The method, however, requires a high catalytic loading of PdCl\(_2\), AsPh\(_3\) and 3 equiv. of Ag\(_2\)CO\(_3\). The authors believe that the Ag salt serves as a source of base, although there have been reports where Ag has performed the decarboxylation.\textsuperscript{21} Given these findings, halide abstraction of Pd(Ar)(I) to give AgI, cannot be ruled out.

![Scheme 1.10 Decarboxylative coupling of aryl iodides and benzoic acids](image)

In a related report, Wu et al. revealed a different procedure for the coupling of aryl iodides with benzoic acids.\textsuperscript{22} This method uses lower amounts of Pd - an improvement to
Becht’s previously described method, yet still requires 3 equiv. of Ag$_2$CO$_3$. It is also possible to couple carboxylic acids with bis(aryl)iodonium(III) zwitterions (Scheme 1.11). This reaction employs a bimetallic catalyst system composed of 20 mol% PdCl$_2$, 20 mol% of the bidentate phosphine ligand DPEPhos (oxybis(2,1-phenylene)]bis(diphenylphosphine) and 3 equiv. of Ag$_2$CO$_3$.

**Scheme 1.11 Pd and Ag mediated decarboxylative coupling of aryl iodonium species**

Examples showcased thus far have been catalytic in Pd and have required stoichiometric amounts of Ag salts to proceed. The first instance of a decarboxylative coupling reaction catalytic in both Pd and Ag was communicated in 2010, where Gooßen and co-workers used aryl triflates as the electrophilic coupling partner (Scheme 1.12). Use of triflates prevents AgI formation similar to the cases with Cu. The reaction is thought to proceed through a bimetallic dual catalytic cycle similar to that described previously for Cu and Pd (Scheme 1.6).

**Scheme 1.12 Decarboxylative coupling of aryl triflates and potassium carboxylates**
Just recently, Gooßen and colleagues reported the first example of decarboxylative Hiyama cross-coupling reaction using a trimetallic catalyst system involving Pd, Cu, and Ag (Scheme 1.13).\(^2\) 2-Nitrocarboxylates were cross-coupled with various electron-neutral and -rich organosilanes to generate the corresponding biaryl. The substrate scope was limited to carboxylates having a nitro functional group in the ortho position. The exact role of each metal is not understood, though the authors speculate that Ag reoxidizes Pd(0) to Pd(II), closing the catalytic cycle.

\[
\text{FG'NO}_2 \text{CO}_2\text{K} + \text{(MeO)}_3\text{Si} \text{FG} \rightarrow \text{FG'NO}_2 \text{FG} \]

\[
\frac{\text{[Pd(IPr)NO]}_2 (1.5 \text{ mol\%}) \quad \text{CuF}_2 (1.5 \text{ equiv.}) \quad \text{Ag}_2\text{CO}_3 (25 \text{ mol\%}) \quad \text{DMAC} \_130 {^\circ}\text{C}, 19 \text{ h}}{\text{FG'NO}_2 \text{FG}}
\]

\text{22 examples} \quad 56-95\% \text{ yield}

**Scheme 1.13 Decarboxylative Hiyama cross-coupling with Pd, Cu, and Ag**

**Palladium-only systems**

Decarboxylative cross-coupling using only Pd was first reported by Steglich et al. in 1997. This protocol was used in a decarboxylative arylation step in the synthesis of *lamellarin G trimethyl ether*, an alkaloid exhibiting anti-tumor activity.\(^2\) Since this report, a number of decarboxylative couplings catalytic in Pd have been reported. The first catalytic variant was described by Forgione and Bilodeau in 2006 where heteroaromatic carboxylic acids were coupled to benzoic acids (Scheme 1.14).\(^2\) The reaction occurs under microwave heating using 5 mol\% [Pd(PrBu\(_3\))\(_2\)], TBAC (tetrabutylammonium chloride), Cs\(_2\)CO\(_3\) and DMF (\(N,N\)-dimethylformamide) at 170 \(^\circ\)C. The reaction was limited to acids having a heteroatom α to the carboxylate.
Scheme 1.14 Decarboxylative arylation of heteroaromatic carboxylic acids

Liu et al. illustrated it is also possible to couple severely electron-deficient potassium benzoates having fluorine substitution with aryl bromides, chlorides, and triflates (Scheme 1.15). The method uses between 1-2 mol% Pd(OAc)$_2$ and either 2-4 mol% of PCy$_3$ or P(o-tolyl)$_3$ in diglyme at 130 °C. Based on computational studies, the authors suggest the decarboxylation step proceeds through a four-membered transition state (Figure 1.2). This transformation is highly relevant as the incorporation of aryl fluorides into molecules of increasing complexity is a non-trivial task.

Scheme 1.15 Decarboxylative coupling of fluoroarenes with aryl bromides, chlorides and triflates

Figure 1.2 Possible four-membered transition state
While Pd-catalyzed decarboxylative cross-coupling provides an alternative route to the synthesis of biaryls, the requirement of high temperatures, and non-user friendly solvents still remains a challenge. Pd is also expensive and toxic,\textsuperscript{1,2} thus making it attractive to explore first row transition metals such as Cu and Ni for such transformations.

**Copper-only systems**

Relative to decarboxylative cross-coupling reports using Pd, examples using Cu are sparse. The first example of an Ullman-type decarboxylative process wasn’t described until 2009. Continuing their work in the area, Liu and colleagues revealed aryl iodides and aryl bromides could be cross-coupled with polyfluorinated aromatic carboxylates.\textsuperscript{29} When aryl bromides were used, greater amounts of catalyst and ligand were required for the reaction to proceed. Similar to the computational studies on their system with Pd,\textsuperscript{28} the mechanism is believed to involve a decarboxylation \textit{via} a four-membered transition state.

**1.2.2 Oxidative decarboxylative cross-couplings**

In oxidative decarboxylative cross-coupling reactions, carboxylic acid derivatives can also be coupled to organometallic reagents. Presently, there are several variations of this reaction, where carboxylic acid derivatives serve as “pseudohalides” and are coupled to arenes \textit{via} C-H activation or using aryl boronic esters (ArB(OR)\textsubscript{2}). The following sections will survey literature from the last 5 years.
Direct arylation via C-H activation

In direct arylation reactions, aryl carboxylic acids are coupled with arenes via C-H activation. A coupling reaction combining aryl carboxylic acid derivatives and C-H activation is highly desirable as halogen waste is limited, pre-functionalization of starting material is not required, and H₂O and CO₂ are by-products. The first example of such a transformation was reported in 2008 when Crabtree et al. showed that aromatic carboxylic acids could be coupled to arenes using 10 mol% Pd(OAc)₂ and 20 mol% tBuXPhos (2-Di-tert-butylphosphino-2′,4′,6′-triisopropylbiphenyl) (Scheme 1.16). This method was applied to both inter- and intramolecular examples, however, it suffered from a limited substrate scope and low yields. Unfortunately protodecarboxylation was a competing reaction in this method, generating 1,3-dimethoxybenzene as an undesired by-product. Nonetheless, this report provided proof-of-concept for the cross-coupling of carboxylic acids and arenes.

\[
\begin{align*}
\text{Pd(OAc)}_2 (10 \text{ mol\%}) & \quad \text{tBuXPhos (20 mol\%)} \\
\text{Ag}_2\text{CO}_3 (1.25 \text{ equiv.}) & \quad \text{DMF-DMSO (9:1)} \\
200 \text{ °C, MW, 5 min} & \quad 10 \text{ examples} \\
\end{align*}
\]

12-81\% yield

Scheme 1.16 Direct arylation of aryl benzoic acids via decarboxylative coupling

Glorius et al. also reported an intramolecular direct arylation of 2-phenoxybenzoic acids for the synthesis of dibenzofurans. In order for high yields to be obtained, the reaction required 15 mol% Pd(TFA)₂ (TFA = O₂CCF₃) with three equiv. of Ag₂CO₃. It is believed that one equiv. of Ag serves to reoxidize Pd(0) to close the catalytic cycle.
It is also possible to arylate various indoles using electron-deficient benzoic acids containing chloro, fluoro, or nitro at the ortho position. The reaction is highly regioselective and only arylates the indole at the 3-position. Later, Su et al. devised a method to accommodate a greater selection of carboxylic acid derivatives and indoles. Curiously, when electron-rich carboxylic acids were used, arylation occurred at the 2-position of the indole. When electron-poor carboxylic acids were used, arylation occurred at the 3-position. This difference in regioselectivity is attributed to competing catalytic pathways. Moreover, when Ag₂CO₃ and Pd(TFA)₂ are absent from the reaction, electron-rich carboxylic acids are immune to decarboxylation. The authors suggest Ag₂CO₃ may mediate the decarboxylation of electron-poor benzoic acids.

More recently, Su et al. provided the first example of a Ag-catalyzed decarboxylative system capable of coupling aromatic benzoic acids with electron-deficient heteroarenes. This example is particularly noteworthy as C-H activation of electron-poor arenes and heteroarenes is a challenging endeavor. The method tolerates a variety of functional groups including nitrile, nitro, and ester groups.

Decarboxylative Suzuki cross-coupling

In 2011, Liu et al. provided an example of decarboxylative Suzuki cross-coupling. The method is capable of coupling various aryl boronic esters to ortho-methoxy benzoic acids. The reaction uses 20 mol% Pd(TFA)₂ and three equiv. of Ag₂CO₃ in DMSO (dimethylsulfoxide) at 120 °C for 2 h (Scheme 1.17). This remains the only example of such a Suzuki-type decarboxylative cross-coupling reaction.
Scheme 1.17 Decarboxylative arylation with boronic esters

As illustrated in the examples previous, much remains to be elucidated regarding redox-neutral and oxidative decarboxylative cross-coupling reactions. Many of the examples provide proof-of-concept, however, lack broad substrate applicability. As well, the use of high temperatures is undesirable for a late-stage synthetic transformation. Nonetheless, the current literature lays an important foundation for future discoveries in decarboxylative coupling, whose ultimate goal is to improve upon traditional cross-coupling methods.

1.3 Decarbonylative coupling

Carboxylic acid derivatives may also participate in decarbonylative cross-coupling.\textsuperscript{36} This involves oxidative addition of the aroyl compound to a metal followed either by transmetallation or CO extrusion and finally, reductive elimination to afford the desired product. This type of reaction dates back to the late 50s when Eschinazi illustrated the first examples of a transition-metal mediated decarbonylation of aldehydes using Pd(OH)\textsubscript{2} and BaSO\textsubscript{4}.\textsuperscript{37} Using this method, the terpene, apopinene was accessed through decarbonylation of myrtenal (Scheme 1.18, eq. 1).\textsuperscript{38} Following this, Hawthorne and Hoffman conducted a series of kinetic and substrate scope studies where they found decarbonylation of aldehydes to be first order.\textsuperscript{39,40}
Tsuji and Ohno reported decarbonylation of aldehydes and alkyl acyl halides using Wilkinson’s catalyst ($\text{RhCl}(\text{PPh}_3)_3$) and Pd/C or PdCl$_2$ (Scheme 1.1, eq. 2 and 3). Blum and co-workers extended the scope to include aryl chlorides using Wilkinson’s catalyst (Scheme 1.1, eq. 4). Ruthenium was also found to decarbonylate aldehydes affording CO and olefins (Scheme 1.1, eq. 5).

Since these initial reports, a number of carboxylic acid derivatives have been used in decarbonylative cross-coupling reactions. Compounds including acyl halides, anhydrides, and esters have been coupled to organometallic and organic reagents through stoichiometric loss of CO (Scheme 1.19). Biaryls may be accessed through decarbonylative couplings of acyl halides, esters, and anhydrides with boronic acids, boronic esters, and aryl zinc reagents (Scheme 1.19, Route A and B). Direct arylation is also possible in decarbonylative coupling...
reactions (Scheme 1.19, Route C). Notably, carboxylic acids cannot be used directly in decarbonylative cross-coupling reactions without first being converted to a more activated group such as an anhydride or ester.

Scheme 1.19 Decarbonylative cross-coupling to generate biaryls

1.3.1 Decarbonylative coupling with esters

Relative to acyl halides and anhydrides, the use of esters in decarbonylative coupling reactions has been far less studied. Esters offer additional advantages, for instance they are easily accessible from carboxylic acids, are ubiquitous in nature and can be used in orthogonal couplings reactions. This section will survey examples of decarbonylative coupling with esters from the last decade.

In 2002, Gooßen and Paetzold reported a waste-free Heck decarbonylation reaction of aryl esters catalyzed by Pd (Scheme 1.20, eq. 1).\textsuperscript{44} Acetone and CO were the only
by-products and could be burned to give CO₂ and H₂O. Although this reaction accommodated a variety of olefins it was limited to aryl esters. In a follow-up report, Gooßen and Paetzold extended the scope of this reaction to include olefinic esters (Scheme 1.20, eq. 2).⁴⁵

![Scheme 1.20 Pd-catalyzed decarbonylative waste free Heck olefination](image)

In 2007, the Sames group provided an example of Ru-catalyzed decarbonylative coupling of sp³ carbon centers in pyrrolidine and piperidine heterocycles using boronic acids as the transmetallating agent (Scheme 1.21).⁴⁶ The reaction was able to couple a variety of α-amino esters with boronic acids and esters to afford new C(sp³)-C(sp²) bonds, albeit with poor stereochemical control. Nevertheless, the reaction provides a route for the functionalization of cyclic amines that are important building blocks for biologically-active compounds, such as alkaloids.

![Scheme 1.21 Ru-catalyzed decarbonylative coupling of esters and boronic acids](image)
More recently, Itami and colleagues described the first example of Ni-catalyzed decarbonylative coupling of azoles and aryl esters to afford bis(hetero)aryls (Scheme 1.22).\textsuperscript{47} The method combined a variety of electron-rich and -poor azoles to heteroaryl esters and was applied to the synthesis of *Muscoride A*, a natural product exhibiting anti-bacterial activity.

\[
\begin{align*}
\begin{array}{c}
\text{Z} = \text{O, S} \\
\end{array}
\end{align*}
\]

Scheme 1.22 Ni-catalyzed decarbonylative coupling of aryl esters and azoles

Itami and co-workers also reported a decarbonylative coupling of alkenyl esters to azoles (Scheme 1.23).\textsuperscript{48} The decarbonylative C-H alkenylation process tolerated a wider substrate scope coupling various \(\alpha-\beta\) unsaturated esters to benzoazoles. This method was also applied to the convergent synthesis of *Siphonazole B*, a natural product isolated from the metabolite *Heroetosiphone sp.*

\[
\begin{align*}
\begin{array}{c}
\text{Z} = \text{O, S} \\
\end{array}
\end{align*}
\]

Scheme 1.23 Ni-catalyzed decarbonylative C-H alkenylation

As can be surmised from the above examples, decarbonylative coupling of esters is still in its infancy - much remains to be learned with respect to both reaction scope and mechanism. Further studies are warranted before these types of transformations may be applied to complex molecule synthesis and industrial scale processes.
1.4 Decarbonylative reaction design

Aromatic carboxylic acid derivatives are an attractive alternative to aryl halides and organometallic reagents in cross-coupling reactions due to their wide availability, stability and low cost. Given these advantages, they are an important class of compounds that should be studied further to improve already existing cross-coupling technologies. Combined with the benefits of using nickel (affordable, less toxic than Pd, and more abundant)\textsuperscript{1-3} and the motivation to develop sustainable synthetic methods, we sought to investigate the less studied area of Ni-catalyzed decarbonylative coupling with aryl esters. From this, we aimed to achieve a synthetic route to biaryls, a common scaffold in biologically-relevant molecules, and pharmaceuticals.\textsuperscript{4}
Chapter 2: Ni(0)-catalyzed decarbonylative coupling with esters

2.1 Introduction

Decarbonylative coupling, as discussed in Chapter 1, involves the cross-coupling of an electrophilic carbonyl-containing species, upon loss of CO, with a nucleophilic transmetallating reagent to afford a new C-C bond (Figure 2.1). This transformation allows the coupling of several carbonyl-containing compounds, including aldehydes, ketones, acyl chlorides, and anhydrides, to a variety of nucleophilic reagents containing zinc and boron.\(^{35}\) Carbonyl-containing compounds may also be added across points of unsaturation including alkenes and alkynes.\(^{49}\) Remarkably, decarbonylative coupling of esters has been less studied.\(^{44-48}\)

\[
\begin{align*}
\text{Y} = &\text{Cl, Br, I} \\
&\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} \\
\text{R'--} &\quad \text{or} \\
\text{R--} &\quad \text{or}
\end{align*}
\]

\[
\begin{align*}
\text{Y} = \text{Cl, Br, I} \\
\text{O(CO)R', R'} \\
\text{etc...}
\end{align*}
\]

\[
\begin{align*}
\text{R'--M} &\quad \text{or} 

order to mitigate toxic waste. Given the Love group’s success with Ni catalysts for the activation of $C(sp^2)$-F bonds\textsuperscript{50} we wanted to investigate the reactivity of these catalysts towards $C(sp^2)$-O bonds and determine if catalytic reactivity could be realized. With this motivation, and the lack of decarbonylative cross-coupling examples employing esters, we sought to determine if Ni could catalytically cross-couple aryl esters to nucleophilic cross-coupling partners such as boronic acids, or organic zinc reagents.

2.2 Results and discussion

2.2.1 Reaction design

Our first task was to identify a suitable transmetallating reagent that could be cross-coupled to an aryl ester. We employed the conditions of Itami’s decarbonylative cross-coupling of heteroaryl esters with azoles as a model reaction (Figure 2.2).\textsuperscript{47} Once having successfully repeated this reaction we used these conditions to investigate other possible nucleophilic cross-coupling partners (Figure 2.2).
Figure 2.2 Transmetallating reagents screened

Reagents screened included substrates bearing acidic C(sp²)-H bonds, organozinc, organoboron reagents, as well as amines. The successful formation of product was determined using LRMS (low-resolution mass-spectrometry). Interestingly, pentafluorobenzene (pKa = 23.1) did not cross-couple to phenyl nicotinate when reacted under the same conditions as benzoazole (pKa = 24.4), which was employed by Itami and co-workers.⁴⁷ Alkyl zinc reagents did not afford the desired cross-coupling product but formation of the corresponding ketone was observed. The use of ZnPh₂ generated 3-phenylpyrididine; however, phenyl-3-pyridinyl methanone was also formed. When the reaction was run in the presence of phenyl boronic acid or phenyl boronic acid MIDA (N-methyliminodiacetic acid) ester, the desired product, 3-phenylpyrididine was observed. Other boron-containing reagents, such as boronate salts and pinacol ester did not afford the desired product. Lastly, when 4-aminopyridine was tested no reaction was observed. Given the
success with phenylboronic acid, arylboronic acids were used as the nucleophilic transmetallating partner. Markedly, boronic acid reagents offer several advantages since they are readily available, affordable, and exhibit air and moisture stability.

2.2.2 Reaction optimization

Having determined boronic acids as the most suitable transmetallating reagent, we next wished to optimize the reaction yield. Our first task was to identify the optimal catalyst ligand combination. The necessity of Ni was confirmed in the control experiment (Table 2.1, entry 1) where no product was observed. In the absence of ligand, < 5% of product was formed confirming the requirement of ligand (Table 2.1, entry 2). A variety of bidendate as well as monodentate phosphine ligands were screened in the presence of 10 mol% Ni(cod)$_2$. Of the bidendate phosphine ligands screened, only dcype (1,2-bis(dicyclohexylphosphino)ethane) generated the desired product, albeit in < 5% (Table 2.1, entry 3). By contrast, Itami et al. found dcype to be essential for the Ni-catalyzed decarbonylative coupling of aryl esters and azoles.$^{46,47}$ When our reaction was run with PPh$_3$ or PCy$_3$ at 100 °C, 3-phenylpyridine was generated in 11% and 23%, respectively (Table 2.1, entries 8 and 9). When the reaction was conducted at 150 °C in the presence of PCy$_3$ and K$_3$PO$_4$ product conversion increased to 26%. The Ni(II) salt, NiCl$_2$(PCy$_3$)$_2$ was found to be catalytically inactive for the reaction (Table 2.1, entry 11). Other late transition metal catalysts were considered, (Table 2.1, entries 12 - 14) however, were not successful in performing the desired transformation. With the best result being 26% conversion at 150 °C using PCy$_3$, we next examined choice of base.
Table 2.1 Optimization of reaction conditions (ligand, temperature)

**Reaction conditions:** To a sealed tube was added phenyl nicotinate (0.5 mmol), phenyl boronic acid (0.75 mmol), Ni(cod)$_2$ (0.05 mmol), ligand (0.1 mmol), base (1 mmol), and solvent (2 mL).

<table>
<thead>
<tr>
<th>entry</th>
<th>nickel source</th>
<th>ligand</th>
<th>base</th>
<th>solvent</th>
<th>T(°C)</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>none</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>Ni(cod)$_2$</td>
<td>none</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>3</td>
<td>Ni(cod)$_2$</td>
<td>dctype</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>4</td>
<td>Ni(cod)$_2$</td>
<td>DIPHOS</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>Ni(cod)$_2$</td>
<td>dppb</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Ni(cod)$_2$</td>
<td>dppm</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>Ni(cod)$_2$</td>
<td>DPEPHos</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Ni(cod)$_2$</td>
<td>PPh$_3$</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>11%</td>
</tr>
<tr>
<td>9</td>
<td>Ni(cod)$_2$</td>
<td>PCy$_3$</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>23%</td>
</tr>
<tr>
<td>10</td>
<td>Ni(cod)$_2$</td>
<td>PCy$_3$</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>26%</td>
</tr>
<tr>
<td>11</td>
<td>Ni(PCy$_3$)$_2$Cl$_2$</td>
<td>none</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)$_2$</td>
<td>PCy$_3$</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>13</td>
<td>Rh(nbd)$_2$Cl$_2$</td>
<td>none</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
<tr>
<td>14</td>
<td>Rh(PPh$_3$)$_3$Cl</td>
<td>none</td>
<td>K$_3$PO$_4$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>0%</td>
</tr>
</tbody>
</table>

$^a$ GC yield using n-dodecane as an internal standard based upon two runs.

A variety of inorganic bases were screened in the presence of Ni(cod)$_2$ and PPh$_3$ or PCy$_3$. When CsF or KOrBu (Table 2.2, entries 8 and 9) was used no reaction occurred. The presence of K$_2$CO$_3$ and Na$_2$CO$_3$ (Table 2.2, entries 6 and 7) resulted in 3-phenylpyridine, in 10 and 12%. When 2,6-lutidine was used as a soluble organic base no reaction occurred (Table 2.2, entry 10). Unfortunately, use of PPh$_3$ with varying bases (Table 2.2, entries 11-
16) did not provide any reaction improvement. The best result occurred when PCy$_3$ and Cs$_2$CO$_3$ were used generating 3-phenylpyridine in 28%. Using toluene as the solvent increased product yield to 31% (Table 2.2, entry 3).
Table 2.2 Optimization of reaction conditions (base with PCy₃ or PPh₃)

Although a small increase was observed when Cs₂CO₃ was employed, (Table 2.2, entry 2) modifying the base did not provide significant reaction improvement. Since the
reaction required a high temperature for CO extrusion to occur, we postulated CO could be irreversibly poisoning the Ni catalyst and inhibiting reactivity. To circumvent this problem two approaches were taken; first, the reaction was microwaved for 45 min at 150°C. This yielded the same result as conventional heating (Table 2.2, entry 4). To allow CO to exit the system the reaction was carried out under a continuous flow of N₂ (Table 2.2, entry 5). This improved the reaction significantly providing 3-phenylpyridine in 60% yield. As postulated, performing the reaction under a constant flow of N₂ facilitates CO removal from the flask, mitigating catalyst poisoning. Photolysis of a possible Ni-CO intermediate using a broadband halogen lamp was also attempted; however, no improvement in yield was observed. Likewise, CO displacement from Ni was attempted using 10 mol% pyridine, but no reaction enhancement was observed. To further improve yield a series of Buchwald ligands, NHCs (N-heterocyclic carbene), and bidentate nitrogen ligands were screened (Figure 2.3).
The use of 2,2′-bipyridine provided 3-phenylpyridine in 33%, however, proved difficult to remove during product isolation (Table 2.3, entry 1). Neocuproine did not catalyze the reaction (Table 2.3, entry 2). Buchwald phosphine ligands of varying steric and electronic properties including XPhos, RuPhos, JohnPhos, and BrettPhos (Table 2.3, entries 3-6) also failed to provide the desired product in good yield. A series of NHC ligands were also considered, but were unsuccessful in improving the reaction outcome (Table 2.3, entries 7-10). Despite the promise of these additional ligands screened, the ligands did not support the catalytic reaction. In accordance with these optimizations, the reaction conditions used

**Figure 2.3 Buchwald, NHC, and bidentate N ligands**

The use of 2,2′-bipyridine provided 3-phenylpyridine in 33%, however, proved difficult to remove during product isolation (Table 2.3, entry 1). Neocuproine did not catalyze the reaction (Table 2.3, entry 2). Buchwald phosphine ligands of varying steric and electronic properties including XPhos, RuPhos, JohnPhos, and BrettPhos (Table 2.3, entries 3-6) also failed to provide the desired product in good yield. A series of NHC ligands were also considered, but were unsuccessful in improving the reaction outcome (Table 2.3, entries 7-10). Despite the promise of these additional ligands screened, the ligands did not support the catalytic reaction. In accordance with these optimizations, the reaction conditions used
were Ni(cod)$_2$ (10 mol%), PCy$_3$ (20 mol%), Cs$_2$CO$_3$ (2.0 equiv.) using toluene at reflux for 24 h under a dynamic flow of N$_2$.

### Table 2.3 Optimization of reaction conditions (other ligands)

<table>
<thead>
<tr>
<th>entry</th>
<th>nickel source</th>
<th>ligand</th>
<th>base</th>
<th>solvent</th>
<th>T($^\circ$C)</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(cod)$_2$</td>
<td>bpy</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>33%</td>
</tr>
<tr>
<td>2</td>
<td>Ni(cod)$_2$</td>
<td>neocuprione</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>0%</td>
</tr>
<tr>
<td>3</td>
<td>Ni(cod)$_2$</td>
<td>XPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>Ni(cod)$_2$</td>
<td>RuPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>Ni(cod)$_2$</td>
<td>JohnPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>6</td>
<td>Ni(cod)$_2$</td>
<td>BrettPhos</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>7</td>
<td>Ni(cod)$_2$</td>
<td>IPr</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>8</td>
<td>Ni(cod)$_2$</td>
<td>IMes</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>9</td>
<td>Ni(cod)$_2$</td>
<td>IAd</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>100</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>10</td>
<td>Ni(cod)$_2$</td>
<td>ICy</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>11</td>
<td>Ni(cod)$_2$</td>
<td>L1</td>
<td>Cs$_2$CO$_3$</td>
<td>1,4-dioxane</td>
<td>150</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

Reaction conditions: To a sealed tube was added phenyl nicotinate (0.5 mmol), phenyl boronic acid (0.75 mmol), Ni(cod)$_2$ (0.05 mmol), ligand (0.1 mmol), base (1 mmol), and solvent (2 mL)

$^a$ GC yield using n-dodecane as an internal standard based upon two runs

L1 = 1,1'-Di-terf-butyl-3,3'methyleneimidotiazolium dibromide

#### 2.2.3 Substrate scope

With the optimized reaction conditions in hand, the substrate scope with respect to boronic acid and aryl ester was considered. A variety of boronic acids possessing different electronic, and steric properties were screened (Table 2.4). Electron-rich, and neutral acids resulted in the highest isolated yields (Table 2.4, 2a, 2b, 2c, 2d, 2e, 2f). Aryl methoxy ethers
were tolerated in the reaction, and were not susceptible to cleavage by Ni (Table 2.4, 2f and 2g). Use of a boronic acid bearing a TBDMS (tButyldimethylsilyl) protected alcohol was also tolerated in the reaction, giving 2h, providing a site for further functional group conversion (Table 2.4). Methyl esters were also accommodated illustrating chemoselectivity for aryl ester activation (Table 2.4, 2i). This reaction could also be performed on a gram scale, providing 3-phenylpyridine in 50% (380 mg) isolated yield.

A limitation of scope was observed when electron-deficient boronic acids were used. Boronic acids possessing various fluorine substitution patterns gave poor yields (Table 2.4, 2k, 2l, 2q). Challenging substrates such as benzofuran, and benzothiophene were also coupled to phenyl nicotinate (Table 2.4, 2m and 2n). Ortho substituted boronic acids (Table 2.4, 2g and 2p) could also be used as nucleophilic partners, however, showed low yields presumably due to steric congestion. Methylenedioxy acetal is additionally tolerated (Table 2.4, 2o.)
Table 2.4 Scope and limitation of boronic acids

\[
\text{Ni(cod)}_2 (10 \text{ mol\%}) \quad \text{PCy}_3 (20 \text{ mol\%}) \\
\text{Cs}_2\text{CO}_3 (2 \text{ equiv.}) \\
toluene, reflux, 24 \text{ h}
\]

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>51%</td>
</tr>
<tr>
<td>2b</td>
<td>47%</td>
</tr>
<tr>
<td>2c</td>
<td>39%</td>
</tr>
<tr>
<td>2d</td>
<td>41%</td>
</tr>
<tr>
<td>2e</td>
<td>38%</td>
</tr>
<tr>
<td>2f</td>
<td>45%</td>
</tr>
<tr>
<td>2g</td>
<td>27%</td>
</tr>
<tr>
<td>2h</td>
<td>31%</td>
</tr>
<tr>
<td>2i</td>
<td>22%</td>
</tr>
<tr>
<td>2j</td>
<td>27%</td>
</tr>
<tr>
<td>2k</td>
<td>23%</td>
</tr>
<tr>
<td>2l</td>
<td>23%</td>
</tr>
<tr>
<td>2m</td>
<td>10%</td>
</tr>
<tr>
<td>2n</td>
<td>8%</td>
</tr>
<tr>
<td>2o</td>
<td>41%</td>
</tr>
<tr>
<td>2p</td>
<td>10%</td>
</tr>
<tr>
<td>2q</td>
<td>trace</td>
</tr>
</tbody>
</table>

\(X = \text{Br, Cl, NO}_2, \ 
\text{CN, OH, NMe}_2, \ 
\text{SCH}_3, \ 
\text{CHO, COCH}_3, \ 
\text{n.r.}\)

\(\text{a Yields are reported for isolated products and are the average of two runs}\)
The scope of heteroaryl ester was also considered. Substitution of the pyridine aryl ester is not limited to the 3-position. The nitrogen substituent in the 4-position is tolerated giving 4-phenylpyridine in 49% yield (Table 2.5, 2s). Aryl esters having a nitrogen atom ortho to the ester were not accommodated in the reaction (Table 2.5, 1b and 1d). Presence of nitrogen in this position probably shuts down anticipated reactivity due to preemptive coordination to nickel.

Altering the electronic nature of the (O-Ar) fragment of the aryl ester appeared to influence the reaction outcome. Substitution of a fluorine atom in the para position resulted in lower product yield (Table 2.5, 1e). The presence of a methoxy substituent in the para position gave 51% - a similar yield obtained using phenyl nicotinate (Table 2.5, 1f). Sterics of the ester cross-coupling partner proved to be important. Moreover, when phenyl ester was substituted for a methyl ester, no product was observed (Table 2.5, 1h) indicating the reaction conditions were specific to the cross-coupling of aryl-esters. When nicotinoyl chloride was screened in place of phenyl nicotinate 3-phenylpyridine was formed in 13% GC yield (Table 2.5, 1i).
Table 2.5 Scope and limitation of heteroaryl esters

\[
\text{FG} \begin{array}{c} \text{O} \\ \text{Ph} \end{array} + \begin{array}{c} \text{B(OH)}_2 \end{array} \xrightarrow{\text{Ni(cod)}_2 (10 \text{ mol}\%)} \xrightarrow{\text{PCy}_3 (20 \text{ mol}\%)} \xrightarrow{\text{Cs}_2\text{CO}_3 (2 \text{ equiv.})} \text{toluene, reflux, 24 h} \end{array} \text{FG} \begin{array}{c} \text{O} \\ \text{Ph} \end{array}
\]

<table>
<thead>
<tr>
<th>Ester</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1b</td>
<td>2r</td>
<td>n.r.</td>
</tr>
<tr>
<td>1a</td>
<td>2a</td>
<td>51%</td>
</tr>
<tr>
<td>1c</td>
<td>2s</td>
<td>49%</td>
</tr>
<tr>
<td>1d</td>
<td>2t</td>
<td>n.r.</td>
</tr>
<tr>
<td>1e</td>
<td>2a</td>
<td>38% (42%)</td>
</tr>
<tr>
<td>1f</td>
<td>2a</td>
<td>44% (51%)</td>
</tr>
<tr>
<td>1g</td>
<td>2a</td>
<td>n.r.</td>
</tr>
<tr>
<td>1h</td>
<td>2a</td>
<td>n.r.</td>
</tr>
<tr>
<td>1i</td>
<td>2a</td>
<td>(13%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields are reported for isolated products and are an average of two runs

<sup>b</sup> Numbers in parenthesis represent GC yields using n-dodecane as an internal standard
The methodology also accommodates cross-coupling of aryl esters without nitrogen atoms, although two products, a combination of biaryl, and ketone are produced (Table 2.6). The electronics of both aryl ester, and boronic acid were considered. Both electron-rich, and electron-deficient aryl esters were permitted although differences in product selectivity were observed. Aryl esters possessing electron-neutral or -withdrawing substituents showed predominant formation for the biaryl product (Table 2.6, entries 1 and 5-7). Interestingly, electron-rich aryl esters primarily formed the undesired ketone product (Table 2.6, entries 2 and 3). Consistent with the results obtained for heteroaryl esters, electron-deficient boronic acids resulted in lower yields than electron-rich (Table 2.6, entries 3, 4, 6 and 7). At this time a rationale for the differences in biaryl, and ketone product formation is not understood, and requires further investigation.

Table 2.6 Scope and limitation of aryl esters

<table>
<thead>
<tr>
<th>entry</th>
<th>ester</th>
<th>biaryl</th>
<th>yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ketone</th>
<th>yield&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1k</td>
<td>R = H</td>
<td>R' = OMe</td>
<td>3a</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4a</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>1l</td>
<td>R = Me</td>
<td>R' = OMe</td>
<td>3b</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4b</td>
<td>24%</td>
</tr>
<tr>
<td>3</td>
<td>1m</td>
<td>R = OMe</td>
<td>R' = OMe</td>
<td>3c</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4c</td>
<td>33%</td>
</tr>
<tr>
<td>4</td>
<td>1m</td>
<td>R = OMe</td>
<td>R' = CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3d</td>
<td>11%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4d</td>
<td>8%</td>
</tr>
<tr>
<td>5</td>
<td>1n</td>
<td>R = F</td>
<td>R' = OMe</td>
<td>3e</td>
<td>25%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4e</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>1o</td>
<td>R = CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>R' = OMe</td>
<td>3f</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4f</td>
<td>15%</td>
</tr>
<tr>
<td>7</td>
<td>1o</td>
<td>R = CO&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>R' = CF&lt;sub&gt;3&lt;/sub&gt;</td>
<td>3g</td>
<td>34%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4g</td>
<td>0%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields determined by <sup>1</sup>H NMR spectroscopy using acetophenone as the internal standard.
2.2.4 Mechanistic inquiry

Attempts were made to identify relative catalytic species. The first step may involve oxidative addition of an aryl ester CO-OPh bond or Ar-CO bond. Efforts to identify such a species through stoichiometric reactivity were unsuccessful. Over a period of 4 h a tol-$d_8$ solution of Ni(cod)$_2$, PCy$_3$, and phenyl nicotinate was heated to 373 K giving a dark red solution (Scheme 2.1). Analysis by $^{31}$P{$^1$H} NMR spectroscopy showed a predominant signal at $\delta$ 42 (assignable to A) which grew in intensity as the reaction progressed (Figure 2.4). A series of transient phosphine-containing intermediates, which were not characterized, were also observed (Figure 2.4).

![Scheme 2.1 Formation of [Ni(O)PCy$_3$]$_4$](image)
Also over a period of 4 h, a tol-\textit{d}_8 solution of Ni(cod)$_2$, PCy$_3$, phenyl nicotinate, phenyl boronic acid, and cesium carbonate was heated to 373 K resulting in a dark red solution. Interestingly NMR analysis showed a signal of $\delta$ 42 (assignable to A). Transient phosphine intermediates were also observed in the reaction. In 2010, Ogoshi and colleagues encountered aggregate A in a report of nickel-catalyzed aldehyde coupling, where it was determined to be a catalytically ineffective off-cycle species.\textsuperscript{52} The presence of this species is
detrimental to the catalytic functionalization of carbonyl compounds and likely stems from O-atom abstraction of the ester moiety.

Another stoichiometric experiment was performed using 2-pyridinephenyl ester 1b in hope of observing the oxidative addition product (eq. 2). Instead, Ni(CO)$_2$(PCy$_3$)$_2$ B (Figure 2.5) was isolated – the product of ester decarbonylation.$^{53}$ The presence of nitrogen ortho to the ester may play a critical role in facilitating Ni insertion into this bond. This result is consistent with the limitation of 2-pyridinephenyl ester and pyrazinephenyl ester substrates (Table 2.6, 1a and 1d) in the cross-coupling reaction. Such a species is proposed to be an off-cycle Ni(CO)-containing complex and lends support to the production of intermediate CO-containing species in this catalytic cycle.

![Scheme 2.2 Formation of (PCy$_3$)$_2$Ni(CO)$_2$](image)

Scheme 2.2 Formation of (PCy$_3$)$_2$Ni(CO)$_2$
**Figure 2.5** ORTEP depiction of the solid-state molecular structure of Ni(PCy$_3$)$_2$(CO)$_2$ B (displacement ellipsoids are shown at the 50% probability, hydrogen atoms omitted for clarity). Selected bond lengths [Å] and angles [°]. Ni(1)-P(1) 2.2503(8), Ni(1)-P(2) 2.2458(9), Ni(1)-C(1) 1.779(2), Ni(1)-C(2) 1.778(2), C(1)-O(1) 1.149(3), C(2)-O(2) 1.154(3), P(1)-Ni(1)-P(2) 120.35(3), P(1)-Ni(1)-C(1) 105.04(8), P(1)-Ni(1)-C(2) 105.51(8), P(2)-Ni(1)-C(2) 105.99(8).

Based on these results and literature reports$^{47,51,54}$ a possible mechanism for this methodology is presented in Figure 2.6. It is important to note that a detailed kinetic and mechanistic investigation has not yet been completed. The following analysis is based upon C-O (80 kcal/mol)$^{51b}$ cleavage, although C-C (83 kcal/mol)$^{51c}$ cleavage is also plausible and cannot be excluded at this time (Figure 2.7). Following oxidative addition to give I, CO migration would give II, whereupon transmetalation would give III. Confirmation that the aryl fragment bonded to the carbonyl group (ArCO-R) is involved in transmetalation was provided by aryl ester Ig, where 3-phenylpyridine was not detected (Table 2.5). The steps of CO extrusion and transmetalation likely occur at similar rates as evidenced by the products of reaction with aryl esters lacking heteroatoms, where both biaryl and ketone products were obtained (Table 2.6, entries 1, 2, and 4-6). Finally, reductive elimination to afford the desired
product followed by CO extrusion to reform the catalyst concludes the catalytic cycle. Notably, Ni can operate under various oxidation states;\textsuperscript{3} however, the depiction in Figure 2.6 is consistent with the observed product distribution.

\begin{center}
\textbf{Figure 2.6 Possible mechanism}
\end{center}

\begin{center}
\textbf{Figure 2.7 Possible bond cleavages for an aryl ester}
\end{center}
Chapter 3: Summary and Future Work

3.1 Summary and conclusions

The overarching goal of this project was to design a sustainable catalytic reaction using nickel and a carboxylic acid derivative and apply it to the synthesis of a relevant structural motif. A new example of nickel-catalyzed Suzuki-Miyaura-type decarbonylative cross-coupling of aryl esters was developed providing a route to biaryl scaffolds. The method employs a cheap, low toxic catalyst system composed of Ni(cod)$_2$ and PCy$_3$, and is capable of cross-coupling commercially available starting materials. Electronics of the boronic acid influenced reaction yields. Arylboronic acids rich in electron density resulted in the highest isolated yields and electron-deficient arylboronic acids the lowest. Aryl esters having heteroatoms and without nitrogen atoms are accommodated in the reaction. A number of functional groups including methyl ethers, esters, fluorine substituents and acetals are compatible in this reaction. Poor yields or no reaction were also observed when electron-deficient boronic acids were screened e.g. cyano- or halogen substituted boronic acids. We suggest the necessity of high reaction temperature and long reaction time are attributable to CO extrusion being rate limiting.

3.2 Future work

Several aspects of this project present areas for future research. First, an investigation into by-product formation is warranted. GC analysis indicated homocoupling of boronic acid and is a possible reason for the somewhat low yields. Currently, the method is successful
cross-coupling electron-rich boronic acids, it would be useful to identify conditions accommodating electron-deficient boronic acids.

In terms of making the reaction more sustainable, there are several avenues that could be explored. First, it would be beneficial to limit or harvest the by-products to improve upon the reaction’s atom economy. As well identifying conditions that would promote the reaction at lower temperature would address energy efficiency of the reaction. Use of a Ni(II) salt would potentially eliminate use of a glovebox further improving upon the energy requirements of the reaction. Lower catalytic loading of Ni and PCy₃ is also possible.

Extending this methodology to acyl chlorides as the electrophilic cross-coupling partner in the decarboxylative reaction is also a possible avenue of future research (Scheme 3.1, eq. 1). Such a reaction would be appealing as acyl chlorides are easily derived from their mother acids using an appropriate Cl-source such as SOCl₂.

The development of a catalyst system capable of cross-coupling alkyl esters for generation of C(sp²)-C(sp³) or C(sp³)-C(sp³) bonds would be synthetically useful (Scheme 3.1, eq. 2). The formation of C(sp²)-C(sp³) is a challenging task due to potential β-hydrogen elimination.

![Scheme 3.1 Decarboxylative coupling of acyl chlorides and alkyl esters](image)

Scheme 3.1 Decarboxylative coupling of acyl chlorides and alkyl esters
Chapter 4: Experimental Procedures

4.1 General procedures

Organometallic compounds were handled in a glovebox under N\textsubscript{2} atmosphere (O\textsubscript{2} < 2ppm) or using standard Schlenk techniques. All cross-coupling reactions were performed in 50-mL round bottom flasks and heated in an oil bath. All esters were prepared by a published procedure and were purified before use. NMR spectra were recorded on 300, 400 or 600 MHz spectrometers. \textsuperscript{1}H and \textsuperscript{13}C chemical shifts are reported in parts per million and referenced to residual solvent. Coupling constant values were extracted assuming first-order coupling. The multiplicities are abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, br = broad. Mass spectra were recorded on a Kratos MS-50 mass spectrometer. Microwave experiments were performed using a Biotage initiator. The photolysis experiment was performed using a Halogen lamp, Model: PL-2264/#60568 with a Philips 100 W light bulb. Reaction mixtures were concentrated using rotary evaporation methods combined with pumping on the vacuum line.

4.2 Materials and methods

All materials were purchased from chemical suppliers and used as received. Toluene was degassed prior introducing into the glovebox and was used without further purification. 1,4-Dioxane and THF were purified by distillation from benzophenone and sodium. ACN was purified by distillation from CaH\textsubscript{2}. All column chromatography was performed using SiO\textsubscript{2} 70-230 mesh.
4.3 Preparation of aryl esters

Representative Procedure Esters (1a-1f): 

To a 250 mL round bottom flask equipped with a Teflon stir bar was added SOCl₂ (9 mL, 12 mmol, 1.2 equiv.) and nicotinic acid (1.23g, 10 mmol, 1.0 equiv). The mixture was stirred overnight for 18 h after which the solution was concentrated in-vacuo. To the residue was added THF (10 mL), triethylamine (1.7 mL) and phenol (941 mg, 10 mmol, 1.2 equiv). The reaction mixture was stirred for 24 h at room temperature. The solution was concentrated in-vacuo and quenched with 30 mL of H₂O. The reaction mixture was then washed with 3 x 30 mL of ethyl acetate, dried over Na₂SO₄ and concentrated in-vacuo. Subsequent column chromatography (SiO₂) afforded the desired product.

Table 4.1 Aryl ester (1a-1f) synthesis summary

<table>
<thead>
<tr>
<th>1a</th>
<th>1b</th>
<th>1c</th>
<th>1d</th>
<th>1e</th>
<th>1f</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPh</td>
<td>OPh</td>
<td>OPh</td>
<td>OPh</td>
<td>OPh</td>
<td>OMe</td>
</tr>
<tr>
<td>1a: 48%</td>
<td>1b: 70%</td>
<td>1c: 84%</td>
<td>1d: 76%</td>
<td>1e: 40%</td>
<td>1f: 27%</td>
</tr>
</tbody>
</table>

*a Isolated yields*
Representative Procedure Esters (1g, 1l-o):

To a 250 mL round bottom flask was added benzoyl chloride (1.16 mL, 1.4 g, 10 mmol), 3-pyridinol (1.14g, 12 mmol), a spatula tip of DMAP, 3 mL triethylamine and 20 mL of THF. The reaction was stirred for 1 h at room temperature. The solution was filtered through SiO₂ and concentrated in-vacuo. The corresponding ester was purified by column chromatography (hexane/EtOAc = 3:1) to afford a white solid.

Table 4.2 Aryl ester (1g, 1l-o) synthesis summary

![Synthesis diagram](image)

<table>
<thead>
<tr>
<th>FG</th>
<th>3-pyridinecarboxylic acid, phenyl ester (1a) [3468-53-9]</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>FG</td>
<td>1a: 48%</td>
<td></td>
</tr>
</tbody>
</table>

1H NMR (CDCl₃, 600 MHz, 298K): δ 9.41 (s, 1H), 8.87-8.86 (d, J = 3.8 Hz, 1H), 8.47-8.46 (d, J = 8.0 Hz, 1H), 7.49-7.44 (m, 3H), 7.32-7.31 (m, 1H), 7.25-7.23 (d, J = 6.3 Hz, 2H). 13C{¹H} NMR (CDCl₃, 150 MHz, 298K): δ 164.07, 154.14, 151.33, 150.70, 137.85, 129.82, 126.46, 125.84, 123.71, 121.75. HRMS (ESI) m/z calc. for C₁₂H₉NO₂ [M+H]⁺: 200.0633; found: 200.0717.
Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1a as a white solid (812 mg, 48%).

2-pyridinecarboxylic acid, phenyl ester (1b) [26838-86-8]47

\(^1\)H NMR (CDCl\(_3\), 300 MHz, 298K): \(\delta\) 8.86-8.84 (d, \(J = 6.1\) Hz, 1H), 8.29-8.27 (d, \(J = 9.7\) Hz, 1H), 7.89 (td, \(J = 7.7, 1.77\) Hz, 1H), 7.58-7.54 (m, 1H), 7.46-7.41, (m, 2H), 7.28-7.24 (m, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\), 150 MHz, 298K): \(\delta\) 164.10, 151.10, 150.34, 147.72, 137.40, 129.72, 127.61, 126.35, 126.06, 121.88. HRMS (ESI) \(m/z\) calc. for C\(_{12}\)H\(_9\)NO\(_2\) [M+H]: 200.0633; found: 200.0714. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1b as a white solid (1.40 g, 70%).

4-pyridinecarboxylic acid, phenyl ester (1c) [940-00-8]47

\(^1\)H NMR (CDCl\(_3\), 600 MHz, 298K): \(\delta\) 8.89-8.88 (d, \(J = 7.3\) Hz, 2H), 8.03-8.02 (d, \(J = 5.5\) Hz, 2H), 7.48-7.46 (t, \(J = 7.5\) Hz, 2H), 7.34-7.26-7.23 (m, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\), 150 MHz, 298K): \(\delta\) 164.02, 151.01, 150.77, 136.61, 129.87, 126.60, 123.44, 121.60. HRMS (ESI) \(m/z\) calc. for C\(_{12}\)H\(_9\)NO\(_2\) [M+H]: 200.0633; found: 200.0713. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1c as a white solid (1.35 g, 84%).

2-pyrazinecarboxylic acid, phenyl ester (1d) [184592-91-4]47

\(^1\)H NMR (CDCl\(_3\), 600 MHz, 298K): \(\delta\) 9.53-9.52 (d, \(J = 2.2\) Hz, 1H), 8.91-8.87 (dd, \(J = 9.7, 2.6\) Hz, 2H), 7.54-7.49 (t, \(J = 7.6\) Hz, 2H), 7.39-7.31 (m, 3H). \(^{13}\)C\{\(^1\)H\} NMR (CDCl\(_3\), 150 MHz, 298K): \(\delta\) 162.36, 150.64, 148.35, 147.01, 144.86, 143.25, 129.88, 126.71, 121.65. HRMS (ESI) \(m/z\) calc. for C\(_{11}\)H\(_8\)N\(_2\)O\(_2\) [M+H]: 201.0633; found: 201.0499. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1d as a white solid (1.54 g, 76%).
3-pyridinecarboxylic acid, 4-fluorophenyl ester (1e) [109358-39-6]

$^1$H NMR (CDCl$_3$, 600 MHz, 298K): $\delta$ 9.40 (s, 1H), 8.88-8.87 (dd, $J$ = 7.4, 5.0 Hz, 1H), 8.46-8.45 (dt, $J$ = 8.7, 2.6 Hz, 1H), 7.50-7.48 (dd, $J$ = 8.2, 5.7 Hz, 1H), 7.21 (m, 2H), 7.15 (m, 2H). $^{13}$C$^{1}$H NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 164.13, 160.95 (d, $J_{CF}$ = 191.6 Hz), 154.33, 151.60, 146.48, 137.79, 126.69, 123.69, 122.22, 116.58. $^{19}$F$^{1}$H NMR (CDCl$_3$, 282 MHz, 298K): $\delta$ -116.70. HRMS (ESI) m/z calc. for C$_{12}$H$_8$FNO$_2$ [M+H]$^+$: 218.0539; found: 218.0617. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1e as a white solid (382 mg, 40%).

3-pyridinecarboxylic acid, 4-methoxyphenyl ester (1f) [3468-30-2]

$^1$H NMR (CDCl$_3$, 600 MHz, 298K): $\delta$ 9.41 (s, 1H), 8.86 (d, $J$ = 4.0 Hz, 1H), 8.46-8.45 (d, $J$ = 4.0 Hz, 1H), 7.49-7.47 (dd, $J$ = 8.5, 5.0 Hz, 1H), 7.17-7.15, (d, $J$ = 8.7 Hz, 2H), 6.97-6.96 (d, $J$ = 9.1 Hz, 2H), 3.85 (s, 3H). $^{13}$C$^{1}$H NMR (CDCl$_3$, 75 MHz, 298K): $\delta$ 164.46, 157.83, 154.15, 151.58, 144.14, 137.75, 126.12, 123.64, 122.50, 114.80, 55.83. HRMS (ESI) m/z calc. for C$_{13}$H$_{11}$NO$_3$ [M+H]$^+$: 230.0739; found: 230.0817. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1f as a white solid (272 mg, 27%).

3-benzoate, 3-pyridinol (1g) [27039-13-1]

$^1$H NMR (CDCl$_3$, 300 MHz, 298K): $\delta$ 8.57-8.56 (d, $J$ = 2.5 Hz, 1H), 8.53-8.52 (d, $J$ = 4.7 Hz, 1H), 8.21-8.19 (d, $J$ = 6.9 Hz, 2H), 7.68-7.60 (m, 2H), 7.53-7.51 (t, $J$ = 6.4 Hz, 2H), 7.40-7.37 (dd, $J$ = 7.9, 4.9 Hz, 1H). $^{13}$C$^{1}$H NMR (CDCl$_3$, 75 MHz, 298K): $\delta$ 164.71, 147.68, 147.01, 143.57, 134.06, 130.31, 129.46, 128.74, 128.40, 123.98. HRMS (ESI) m/z calc. for C$_{12}$H$_9$NO$_2$ [M+H]$^+$:
Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1g as a white solid (800 mg, 40%).

4-methyl-benzoic acid, phenyl ester (1l) [1900-85-2] 55

\(^1\)H NMR (CDCl\(_3\), 300 MHz, 298K): \(\delta\) 8.11-8.09 (d, \(J = 7.1\) Hz, 2H), 7.45-7.41 (t, \(J = 8.2\) Hz, 2H), 7.32-7.25 (m, 3H), 7.22-7.20 (m, 2H), 2.46 (s, 3H). \(^1^3\)C\(^{\{}^1\)H\} NMR (CDCl\(_3\), 75 MHz, 298K): \(\delta\) 165.29, 151.48, 145.89, 130.25, 129.48, 129.32, 126.86, 125.81, 121.80, 21.95. HRMS (EI) \(m/z\) calc. for C\(_{14}\)H\(_{12}\)O\(_2\) [M\(^+\)]: 212.0837; found: 212.0835. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1l as a white solid (1.32 g, 63%).

4-methoxy-benzoic acid, phenyl ester (1m) [4181-97-9] 55

\(^1\)H NMR (CDCl\(_3\), 400 MHz, 298K): \(\delta\) 8.23-8.19 (d, \(J = 7.6\) Hz, 2H), 7.49-7.45 (m, 2H), 7.33-7.24 (m, 3H), 7.05-7.02 (d, \(J = 8.8\) Hz, 2H), 3.94 (s, 3H). \(^1^3\)C\(^{\{}^1\)H\} NMR (CDCl\(_3\), 100 MHz, 298K): \(\delta\) 164.99, 163.93, 151.10, 132.33, 129.47, 125.76, 121.84, 115.31, 113.87, 55.55. HRMS (EI) \(m/z\) calc. for C\(_{14}\)H\(_{12}\)O\(_3\) [M\(^+\)]: 228.0786; found: 228.0787. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1m as a white solid (1.75 g, 77%).

4-fluoro-benzoic acid, phenyl ester (1n) [2714-90-1] 55

\(^1\)H NMR (CDCl\(_3\), 400 MHz, 298K): \(\delta\) 8.26-8.21 (m, 2H), 7.46-7.41 (m, 2H), 7.30-7.28 (m, 2H), 7.22-7.16 (m, 3H). \(^1^3\)C\(^{\{}^1\)H\} NMR (CDCl\(_3\), 100 MHz, 298K): \(\delta\) 166.17 (d, \(J_{C,F} = 256.5\) Hz), 164.25, 150.92, 132.82 (d, \(J_{C,F} = 9.1\) Hz), 129.55, 126.02, 125.85 (d, \(J_{C,F} = 5.0\) Hz), 121.68, 115.83 (d, \(J_{C,F} = 19.0\) Hz). HRMS (EI) \(m/z\) calc. for C\(_{13}\)H\(_9\)FO\(_2\) [M\(^+\)]: 216.0587; found: 216.0585. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1n as a white solid (1.64 g, 76%).
methyl phenyl benzene-1,4-dicarboxylate (1o) [6725-72-0]\(^{56}\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 8.28 (d, \(J = 8.6\) Hz, 2H), 8.27-8.26 (d, \(J = 8.3\) Hz, 2H), 7.46 (t, \(J = 8.0\) Hz, 2H), 7.30 (t, \(J = 6.9\) Hz, 1H), 7.24-7.22 (m, 2H), 3.98 (s, 3H).

\(^{13}\)C\(^{1}\)H NMR (CDCl\(_3\), 100 MHz, 298K): \(\delta\) 166.21, 164.18, 150.32, 134.59, 133.39, 130.17, 129.75, 129.61, 126.16, 121.60, 52.56. HRMS (EI) \(m/z\) calc. for C\(_{15}\)H\(_{12}\)O\(_4\) [M]\(^+\): 256.0736; found: 256.0736. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 1o as a white solid (1.02 g, 80%).

### 4.4 Experimental procedure for decarbonylative coupling

**General Procedure:** A 50 mL one-necked round bottom flask equipped with a teflon stir bar, was flame dried and brought into the glovebox. To this flask was added Cs\(_2\)CO\(_3\) (325.8 mg, 1 mmol, 2.0 equiv.), phenyl ester derivative (0.5 mmol, 1 equiv.), boronic acid (0.75 mmol, 1.5 equiv.), Ni(cod)\(_2\) (13.5 mg, 0.05 mmol, 10 mol%), PCy\(_3\) (28.0 mg, 0.1 mmol, 20 mol%) and 4 mL of toluene. To the round bottom, was attached a condenser equipped with an adapter for attachment to a Schlenk line. The flask was removed from the glovebox, attached to a Schlenk, and was heated to reflux under a continuous flow of N\(_2\) for 24 h. After cooling the vessel to room temperature, the crude reaction mixture was filtered through a small Celite plug with ethyl acetate and concentrated *in-vacuo*. Column chromatography was performed to afford the desired product. Yields are reported for isolated product and are an average (± 10 %) of two runs.

Isolation of products proved to be difficult, thus yields are reported for an average of two runs (± 10 %). Many troubleshooting strategies were attempted. The first involved aqueous work-up of the crude reaction mixture with 1M HCl to protonate the pyridine
moiety, followed by back extraction with 1M NaOH and drying over MgSO₄. This product was obtained cleanly albeit in low amounts, likely due to solubility of the product in water. Second, a salt method using oxalic acid was attempted. The crude reaction mixture was filtered through a small Celite plug and concentrated in-vacuo. A small amount of acetone was added to the residue. To this residue was added a solution of pre-dissolved oxalic acid in acetone. A white precipitate was formed instantly upon addition of the oxalic acid solution. The precipitate solution was then filtered and the pyridine was back extracted with NaOH. This method yielded the same product yield as the aqueous work-up strategy. The best product yields were obtained when column chromatography was performed with SiO₂ and an eluent of ethyl acetate and hexanes.

3-phenylpyridine (2a) [1008-88-4][57]

![Structure of 3-phenylpyridine (2a)]

1H NMR (CDCl₃, 400 MHz, 298K): δ 8.90 (s, 1H), 8.63 (s, 1H), 7.92 (d, J = 7.9 Hz, 1H), 7.60 (d, J = 6.8 Hz, 2H), 7.49 (m, 4H). 13C{1H} NMR (CDCl₃, 75 MHz, 298K): δ 148.62, 148.49, 138.01, 136.83, 134.51, 129.23, 128.25, 127.32, 123.72. HRMS (ESI) m/z calc. for C₁₁H₉N [M+H]+: 156.0735; found: 156.0813. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2a as a colourless oil (39 mg, 51%).

3-(1-naphthalenyl)pyridine (2b) [189193-21-3][58]

![Structure of 3-(1-naphthalenyl)pyridine (2b)]

1H NMR (CDCl₃, 400 MHz, 298K): δ 8.80 (s, 1H), 8.70 (d, J = 1.50 Hz, 1H), 7.94-7.91 (t, J = 7.0 Hz, 2H), 7.84-7.61 (m, 2H), 7.61-7.42 (m, 5H). 13C{1H} NMR (CDCl₃, 150 MHz, 298K): δ 150.16, 148.15, 136.95,
HRMS (ESI) m/z calc. for C₁₅H₁₁N [M+H]: 206.0891; found: 206.0891. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2b as a white solid (47 mg, 47%).

3-(4-methyl)pyridine (2c) [4423-09-0]⁵⁹

¹H NMR (CDCl₃, 400 MHz, 298K): δ 8.84 (s, 1H), 8.57 (s, 1H), 7.87-7.85 (d, J = 8.4 Hz, 1H), 7.49-7.47 (d, J = 7.6 Hz, 2H), 7.35 (s, 1H), 7.30-7.26 (d, J = 7.63 Hz, 2H), 2.41 (s, 3H). 

¹³C{¹H} NMR (CDCl₃, 75 MHz, 298K): δ 148.04, 138.11, 136.70, 134.87, 134.29, 129.84 (2C), 127.00, 123.63, 21.18.

HRMS (ESI) m/z calc. for C₁₂H₁₁N [M+H]: 170.0891; found: 170.0969. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2c as a colourless oil (33 mg, 39%).

3-[4-(tbutyl)pyridine] (2d) [1110656-20-6]⁶⁰

¹H NMR (CDCl₃, 400 MHz, 298K): δ 8.90 (s, 1H), 8.60 (s, 1H), 7.88-7.86 (d, J = 7.4 Hz, 1H), 7.52-7.50 (m, 4H), 7.35-7.33 (m, 1H), 1.37 (s, 9H). 

¹³C{¹H} NMR (CDCl₃, 150 MHz, 298K): δ 151.47, 148.38, 148.33, 136.71, 135.07, 134.43, 127.01, 126.27, 123.76, 34.82, 31.51. HRMS (ESI) m/z calc. for C₁₅H₁₇N [M+H]: 212.1361; found: 212.1439. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2d as a yellow oil (41 mg, 41%).

3-[1,1′-biphenyl]4-yl-pyridine (2e) [93324-68-6]⁶⁰

¹H NMR (CDCl₃, 400 MHz, 298K): δ 8.92 (s, 1H), 8.62 (m, 1H), 7.94-7.92 (d, J = 7.7 Hz, 1H), 7.75-7.73 (d, J = 7.7 Hz, 2H), 7.68-7.64 (m, 4H), 7.49-7.46 (m, 2H), 7.40-7.36 (m, 2H). 

¹³C{¹H} NMR (CDCl₃, 150 MHz, 298K): δ 148.16, 147.92, 141.42, 140.51, 136.60, 134.91, 129.11, 128.07, 127.85, 127.71, 127.44, 127.29, 123.99. HRMS (ESI) m/z calc. for C₁₇H₁₃N [M+H]: 232.1048; found: 232.1126. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2e as a white solid (38 mg, 33%).
3-(4-methoxyphenyl)pyridine (2f) [5958-02-1]\(^6\)

\(^1\)H NMR (CDCl\(_3\), 400 MHz, 298 K): \(\delta\) 8.82 (s, 1H), 8.55 (s, 1H), 7.84–7.82 (dt, \(J = 8.4\) Hz, 2.11 Hz, 1H), 7.54–7.50 (d, \(J = 8.8\) Hz, 2H), 7.35–7.32 (dd, \(J = 8.1\), 4.0 Hz, 1H), 7.03–7.00 (d, \(J = 7.9\) Hz, 2H), 3.86 (s, 3H). \(^{13}\)C\(^{\{1\}}\)H NMR (CDCl\(_3\), 150 MHz, 298 K): \(\delta\) 160.00, 147.91, 147.78, 136.59, 132.76, 130.30, 128.42, 123.82, 114.77, 55.78. HRMS (ESI) \(m/z\) calc. for C\(_{12}\)H\(_{11}\)NO [M+H]\(^+\): 186.0841; found: 186.0919. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2f as a white solid (42 mg, 45%).

3-(2-methoxyphenyl)pyridine (2g) [5958-01-0]\(^6\)

\(^1\)H NMR (CDCl\(_3\), 300 MHz, 298K): \(\delta\) 8.78 (s, 1H), 8.57 (s, 1H), 7.87–7.84 (d, \(J = 8.0\) Hz, 1H), 7.37–7.31 (m, 3H), 7.08–7.00 (m, 2H), 3.82 (s, 3H). \(^{13}\)C\(^{\{1\}}\)H NMR (CDCl\(_3\), 75 MHz, 298K): \(\delta\) 156.59, 150.30, 147.95, 136.79, 134.79, 130.68, 129.56, 127.09, 122.93, 121.07, 111.29, 55.54. HRMS (ESI) \(m/z\) calc. for C\(_{12}\)H\(_{11}\)NO [M+H]\(^+\): 186.0841; found: 186.0916. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2g as a white solid (25 mg, 27%).

3-[(4-((butyldimethylsilyl)oxy)phenyl)pyridine (2h)

\(^1\)H NMR (CDCl\(_3\), 400 MHz, 298K): \(\delta\) 8.83 (s, 1H), 8.56 (s, 1H), 7.86–7.84 (d, \(J = 8.0\) Hz, 1H), 7.47–7.45 (d, \(J = 8.9\) Hz, 2H), 7.35 (s, 1H), 6.95–6.93 (d, \(J = 8.2\) Hz, 2 H), 1.01 (s, 9H), -0.24 (s, 6H). \(^{13}\)C\(^{\{1\}}\)H NMR (CDCl\(_3\), 75 MHz, 298K): \(\delta\) 156.10, 147.75, 147.57, 134.09, 130.73, 128.21, 123.70, 120.75, 25.70, 18.27, -4.35 (2C). HRMS (ESI) \(m/z\) calc. for C\(_{17}\)H\(_{23}\)NOSi [M+H]\(^+\): 286.1549; found: 286.1627. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2h as a yellow solid (44 mg, 31%).
methyl 4-(3-pyridinyl)benzoate (2i) [90395-47-4] 63

$^1$H NMR (CDCl$_3$, 600 MHz, 298K): $\delta$ 8.91 (s, 1H), 8.66 (s, 1H), 8.15-8.14 (d, $J = 7.3$ Hz, 2H), 7.93-7.92 (d, $J = 7.8$ Hz, 1H), 7.67-7.65 (d, $J = 7.8$ Hz, 2H), 7.42 (s, 1H), 3.95 (s, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 166.93, 149.26, 148.37, 142.33, 134.89, 130.58, 129.99, 127.32, 124.03 (2C), 52.48. HRMS (ESI) m/z calc. for C$_{13}$H$_{11}$NO $[M+H]^+$: 214.0790; found: 214.0868. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2i as a white solid (25 mg, 22%).

3-(4-(trifluoromethyl)phenyl)pyridine (2j) [426823-25-8] 64

$^1$H NMR (CDCl$_3$, 400 MHz, 298K): $\delta$ 8.88 (s, 1H), 8.67 (s, 1H), 7.91-7.89 (d, $J = 8.0$ Hz, 1H), 7.76-7.68 (m, 4H), 7.42 (m, 1H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 148.88, 147.88, 141.26, 135.32, 133.91, 127.73, 126.32 (d, $J_{C,F} = 3.7$ Hz), 124.56 (d, $J_{C,F} = 4.8$ Hz), 124.23 (d, $J_{C,F} = 271.2$ Hz), 124.18. $^{19}$F{$^1$H} NMR (CDCl$_3$, 282 MHz, 298K): $\delta$ -62.49. HRMS (ESI) m/z calc. for C$_{12}$H$_8$F$_3$N [M+H]$^+$: 224.0609; found: 224.0687. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2j as a white solid (30 mg, 27%).

3-(4-fluorophenyl)pyridine (2k) [85589-65-7] 64

$^1$H NMR (CDCl$_3$, 300 MHz, 298K): $\delta$ 8.82 (s, 1H), 8.60 (s, 1H), 7.85-7.83 (d, $J = 6.8$ Hz, 1H), 7.55-7.52 (t, $J = 6.4$ Hz, 2H), 7.37 (s, 1H), 7.20-7.14 (t, $J = 7.9$ Hz, 2H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 75 MHz, 298K): $\delta$ 162.95 (d, $J_{C,F} = 266.24$ Hz), 148.24, 147.91, 135.75, 134.46, 133.84 (d, $J_{C,F} = 5.2$ Hz), 128.82, 123.72, 116.24 (d, $J_{C,F} = 17.6$ Hz). $^{19}$F{$^1$H} NMR (CDCl$_3$, 282 MHz, 298K): $\delta$ -114.64. HRMS (ESI) m/z calc. for C$_{11}$H$_8$FN [M+H]$^+$: 174.0641; found: 174.0720. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2k as a colorless oil (20 mg, 23%).
3-(2,5-difluorophenyl)pyridine (2l) [426823-29-2]  

$^1$H NMR (CDCl$_3$, 400 MHz, 298K): $\delta$ 8.79 (s, 1H), 8.65-8.63 (d, $J$ = 3.4 Hz, 1H), 7.87-7.85 (d, $J$ = 6.0 Hz, 1H), 7.41-7.37 (dd, $J$ = 8.2, 3.4 Hz, 1H), 7.20-7.04 (m, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 158.44 (dd, $J$ C-F = 242.5, 3.3 Hz), 155.38 (dd, $J$ C-F = 243.7, 3.7 Hz), 149.09, 148.88, 135.77 (d, $J$ C-F = 4.1 Hz), 130.50, 126.49 (dd, $J$ C-F = 16.9, 8.0 Hz), 122.95, 117.04 (dd, $J$ C-F = 19.25, 8.42 Hz), 116.27 (dd, $J$ C-F = 24.4, 3.9 Hz), 115.83 (dd, $J$ C-F = 19.9, 7.2 Hz). $^{19}$F{$^1$H} NMR (CDCl$_3$, 282 MHz, 298K): $\delta$ -118.30, -123.97. HRMS (ESI) $m/z$ calc. for C$_{11}$H$_7$F$_2$N$^+$$[M+H]^+$: 192.0547; found: 192.0625. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2l as a colourless oil (30 mg, 23%).

3-benzo[b]thien-2-yl-pyridine (2m) [936734-97-3]$^{65}$  

$^1$H NMR (CDCl$_3$, 400 MHz, 298K): $\delta$ 9.00 (s, 1H), 8.59-8.58 (d, $J$ = 3.4 Hz, 1H), 7.98-7.96 (d, $J$ = 8.0 Hz, 1H), 7.85-7.81 (d, $J$ = 7.7 Hz, 2H), 7.61 (s, 1H), 7.39-7.34 (m, 3H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 148.65, 148.60, 146.95, 139.95, 139.71, 139.23, 133.47, 128.43, 124.48, 124.40, 123.45, 121.94, 120.36. HRMS (ESI) $m/z$ calc. for C$_{13}$H$_9$NS$^+$$[M+H]^+$: 212.0456; found: 212.0534. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2m (10.2 mg, 10%) as a yellow solid.

3-(2-benzofuranyl)pyridine (2n) [7035-06-5]$^{65}$  

$^1$H NMR (CDCl$_3$, 600 MHz, 298K): $\delta$ 9.06 (s, 1H), 8.53 (s, 1H), 8.10-8.09 (d, $J$ = 7.9 Hz, 1H), 7.57-7.55 (d, $J$ = 6.9 Hz, 1H), 7.50-7.48 (d, $J$ = 8.4 Hz, 1H), 7.39 (s, 1H), 7.29-7.26 (t, $J$ = 8.4 Hz, 1H), 7.21-7.17 (m, 1H), 7.08 (s, 1H). $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K): $\delta$ 154.67, 152.33, 148.55, 145.73, 131.66, 129.24 128.29, 124.60, 123.30, 122.87, 120.82, 110.91, 102.46. HRMS
(ESI) m/z calc. for C_{13}H_{9}NO [M+H]^+: 196.0684; found: 196.0762. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2n as a white solid (8 mg, 8%).

3-(1,3-benzodioxol-5-yl)pyridine (2o) [869985-49-9]

1H NMR (CDCl₃, 300 MHz, 298K): δ 8.78 (s, 1H), 8.55 (s, 1H), 7.83-7.80 (d, J = 5.9 Hz, 1H), 7.35 (s, 1H), 7.04 (s, 2H), 6.93 (d, J = 8.5 Hz, 1H), 6.02 (s, 2H). 13C\{1H\} NMR (CDCl₃, 75 MHz, 298K): δ 148.62 (2C), 147.99 (2C), 136.67, 134.34, 132.09, 123.73, 121.05, 109.07, 107.70, 101.53. HRMS (ESI) m/z calc. for C_{12}H_{9}NO [M+H]^+: 200.0633; found: 200.0712. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2o as a white solid (41 mg, 41%).

3-(2,6-dimethylphenyl)pyridine (2p) [157402-43-2]

1H NMR (CDCl₃, 600 MHz, 298K): δ 8.63 (s, 1H), 8.46 (s, 1H), 7.55-7.54 (d, J = 7.7 Hz, 1H), 7.45-7.40 (dd, J = 7.7, 4.4 Hz, 1H), 7.24-7.20 (t, J = 7.3 Hz, 1H), 7.14-7.13 (d, J = 7.3 Hz, 2H), 2.04 (s, 6H). 13C\{1H\} NMR (CDCl₃, 150 MHz, 298K): δ 150.32, 148.68, 138.28, 129.33, 127.20, 121.89. HRMS (ESI) m/z calc. for C_{13}H_{13}N [M+H]^+: 184.1048; found: 184.1126. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2p as a colourless oil (10 mg, 10%).

4-phenylpyridine (2s) [939-23-1]

1H NMR (CDCl₃, 600 MHz, 298K): δ 8.67 (d, J = 3.5 Hz, 2H), 7.65 (m, 2H), 7.50 (m, 4H), 7.45 (m, 1H). 13C\{1H\} NMR (CDCl₃, 150 MHz, 298K): δ 150.32, 148.68, 138.28, 129.33, 129.31 127.20, 121.89. HRMS (ESI) m/z calc. for C_{11}H_{9}N [M+H]^+: 156.0735; found: 156.0813. Purification by column chromatography (hexane/EtOAc = 3:1) afforded 2s (37 mg, 49%) as a white solid.
4.5 Experimental procedure for decarbonylative coupling (2a, large scale)

A 100 mL one-neck round bottom flask equipped with a teflon stir bar, was flame dried and brought into the glovebox. To this flask was added Cs₂CO₃ (3.28 g, 1 mmol, 2.0 equiv.), phenyl nicotinate (1.00 g, 5 mmol, 1 equiv.), phenyl boronic acid (915 mg, 7.5 mmol, 1.5 equiv.), Ni(cod)₂ (137.5 mg, 0.5 mmol, 10 mol%), PCy₃ (280.0 mg, 1 mmol, 20 mol%), and 40 mL of toluene. To the round bottom was attached a condenser equipped with an adapter for attachment to a N₂ line. The flask was removed from the glovebox, attached to a Schlenk line, and heated to reflux under a continuous flow of N₂ for 24 h. After cooling the vessel to room temperature, the crude reaction solution was filtered through a small Celite plug with ethyl acetate, and concentrated in-vacuo. Column chromatography using (hexane/EtOAc = 3:1) was performed to afford 2a (380 mg, 50%) as a colourless oil.

4.6 Stoichiometric experiments

Stoichiometric reaction of Ni(cod)₂, PCy₃ and phenyl nicotinate

In the glovebox, a 20 mL scintillation vial was charged with phenyl nicotinate (24 mg, 0.12 mmol), Ni(cod)₂ (20 mg, 0.07 mmol), and PCy₃ (40 mg, 0.14 mmol). The reagents were then dissolved in approximately 700 µL of toluene-d₈ giving a dark red solution. The solution was transferred to a J-Young NMR tube. The reaction was monitored at 298K, 313K, 333K, 353K, and 373K. Observed $^{31}$P{¹H} NMR spectra are depicted in Figure S2.

Stoichiometric reaction of Ni(cod)₂, PCy₃ and 2-Pyridine carboxylic acid, phenyl ester (1b)

In the glovebox, a 20 mL scintillation vial was charged with 2-pyridinecarboxylic acid phenyl ester (38.5 mg, 0.2 mmol), Ni(cod)₂ (52.7 mg, 0.2 mmol), and PCy₃ (108 mg, 0.4 mmol). The reagents were dissolved in 3 mL of C₆D₆, and stirred for 1 h at room temperature
resulting in a dark blue solution. The dark blue solution was concentrated *in-vacuo* and washed with pentanes. The pentane solution was concentrated affording a green residue that was subsequently re-dissolved in a minimal amount of pentanes and filtered through a glass Celite pipette. The filtrate was placed in the freezer at -35 °C and left to crystallize over the period of one week after which X-ray quality green crystals were obtained. Analysis via x-ray diffraction revealed Ni(PCy₃)₂(CO)₂ to be present (Figure S3).⁶²

4.7 Procedure for ¹H NMR spectroscopy yields (Table 2.7)

A 50 mL one-necked round bottom flask equipped with a teflon stir bar, was flame dried, and brought into the glovebox. To this flask was added Cs₂CO₃ (325.8 mg, 1 mmol, 2.0 equiv.), phenyl ester derivative (0.5 mmol, 1 equiv.), boronic acid (0.75 mmol, 1.5 equiv.), Ni(cod)₂ (13.5 mg, 0.05 mmol, 10 mol%), PCy₃ (28.0 mg, 0.1 mmol, 20 mol%), and 4 mL of toluene. To the round bottom was attached a condenser equipped with an adapter for attachment to a N₂ line. The flask was removed from the glovebox, attached to a Schlenk line, and heated to reflux under a continuous flow of nitrogen for 24 h. After cooling the vessel to room temperature, the crude reaction solution was filtered through a small Celite plug with ethyl acetate, and concentrated *in-vacuo*. Approximately 35 mg of acetophenone was added to the residue. A representative spectrum for biaryl product 3d and ketone 4d is shown below. These products were identified in analogy to previous literature reports (references provided below).
Figure 4.1 Representative $^1$H NMR spectrum for biaryl products 3d and 4d (CDCl₃, 300MHz, 298K)

Figure 4.2 Enhancement of Figure 4.1 from 0.5 to 5 ppm (CDCl₃, 300MHz, 298K)
Products from Table 2.7 (not isolated, spectral data referenced)

4-methoxy-1,1’biphenyl [613-37-6]^{69}

4-methoxy-4’-methyibiphenyl [53040-92-9]^{70}

4,4’-dimethoxybiphenyl [2132-80-1]^{71}

4’-methoxy-4-(trifluoromethyl)biphenyl [10355-12-1]^{72}

4-fluoro-4’-methoxybiphenyl [450-39-5]^{73}
[1,1'-biphenyl]-4-carboxylic acid, 4’-(dimethylamino)-methyl ester [893734-76-4] \(^{73}\)

methyl 3-(4-trifluoromethylphenyl)benzoate [773875-92-6] \(^{73}\)

(4-methoxyphenyl)phenyl-methanone [611-94-9] \(^{74}\)

4-methoxy-4’-methylbenzophenone [23886-71-7] \(^{74}\)

bis(4-methoxyphenyl)-methanone [90-96-0] \(^{75}\)
(4-methoxyphenyl)[4-(trifluoromethyl)phenyl]-methanone [6185-76-8]
Diagnostic signal, OMe at $\delta$ 3.84

4-fluoro-4'-methoxybenzophenone [345-89-1]$	ext{76}$

4-(4-methoxybenzoyl)-methyl ester benzoic acid [71616-84-7]
Diagnostic signal, OMe at $\delta$ 3.86

4-(4-trifluoromethylbenzoyl)-methyl ester benzoic acid

4.8 Description of GC FID study

GC analysis was performed using an Agilent 7890A GC equipped with an autosampler. A HP-5MS column (30 m x .25 mm x .25 µm film thickness) with carrier gas H$_2$ and a temperature ramp from 80°C to 200°C at 20°C/min, followed by 200°C to 325°C at 40°C/min holding for 5 minutes was used. The injection volume was 0.2 µL. A calibration
curve for 3-phenylpyridine was generated using 6 standard solutions corresponding to 0%, 20%, 40%, 60%, 80% and 100% product conversion based on a 0.5 mmol scale. Since the GC column was sensitive to 50-1400 ppm concentrations, dilutions were necessary. The equation (grams of product / grams of solvent) x 10^6 was used to calculate concentrations of the standard solutions in ppm. A 350 ppm internal standard solution of n-dodecane was also prepared. Following this, 6 different GC vials were made, one for each % conversion of 3-phenylpyridine. For example, 100 µL of the 20% conversion standard solution, 100 µL of internal standard, and 1600 µL of ethyl acetate was added to a 2 mL GC vial. The procedure was completed for each standard solution totaling 6 GC vials. Once the GC samples were prepared they were run twice on the GC FID using the optimized method. The data collected from each run was averaged and used to generate a calibration curve. Milligrams of 3-phenylpyridine versus the area ratio of 3-phenylpyridine and internal standard was plotted to generate the corresponding calibration curve (Figure 4.3). Excel was then used to determine product conversion for various reaction conditions.

![Figure 4.3 GC calibration curve for 3-phenylpyridine](image)

\[ y = 5.2715x + 0.1199 \]
\[ R^2 = 0.99654 \]
References


Appendix 1 NMR Spectra

1a, $^1$HNMR (CDCl$_3$, 600 MHz, 298K)

1a, $^{13}$C($^1$H)NMR (CDCl$_3$, 150 MHz, 298 K)
$^{1}b$, $^{1}H$ NMR (CDCl$_3$, 600 MHz, 298 K)

$^{1}b$, $^{13}C$($^{1}H$) NMR (CDCl$_3$, 150 MHz, 298 K)
1c, $^1$H NMR (CDCl$_3$, 600 MHz, 298 K)

$^1$C, $^{13}$C-$^1$H NMR (CDCl$_3$, 150 MHz, 298K)
1d, $^1$H NMR (CDCl$_3$, 600 MHz, 298 K)

1d, $^{13}$C($^1$H)NMR (CDCl$_3$, 150 MHz, 298 K)
1e, $^1$H NMR (CDCl$_3$, 600 MHz, 298 K)

1e, $^{13}$C-$^1$H NMR (CDCl$_3$, 150 MHz, 298 K)
1e, $^{19}$F-$^1$H NMR (CDCl$_3$, 282 MHz, 298K)
1f, $^1$H NMR (CDCl$_3$, 600 MHz, 298K)

1f, $^{13}$C($^1$H) NMR (CDCl$_3$, 150 MHz, 298K)
1g, $^1$H NMR (CDCl$_3$, 300 MHz, 298K)

1g, $^{13}$C{$^1$H} NMR (CDCl$_3$, 75 MHz, 298K)
II, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

II, $^{13}$C($^1$H) NMR (CDCl$_3$, 100 MHz, 298K)
1m, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

1m, $^{13}$C{$^1$H} NMR (CDCl$_3$, 75 MHz, 298K)

1n, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

$^{13}$C\{\textsuperscript{1}$^1$H\} NMR (CDCl$_3$, 100 MHz, 298K)
10, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

10, $^{13}$C-$^1$H NMR (CDCl$_3$, 100 MHz, 298K)
2a, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

2a, $^{13}$C($^1$H) (CDCl$_3$, 75 MHz, 298K)
2b, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

2b, $^{13}$C{${^1}$H} NMR (CDCl$_3$, 150 MHz, 298K)
$2c$, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

$2c$, $^{13}$C $^1$H NMR (CDCl$_3$, 75 MHz, 298K)
2d, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

2d, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)
2e, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

![2e, $^1$H NMR](image)

2e, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)

![2e, $^{13}$C{$^1$H} NMR](image)
2f, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

![NMR spectrum of 2f, 1H](image)

2f, $^{13}$C($^1$H) NMR (CDCl$_3$, 150 MHz, 298K)

![NMR spectrum of 2f, 13C](image)
2g, $^1$H NMR (CDCl$_3$, 300 MHz, 298K)

2g, $^{13}$C{$^1$H} NMR (CDCl$_3$, 75 MHz, 298K)
2h, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

2h, $^{13}$C{$^1$H} NMR (CDCl$_3$, 75 MHz, 298K)
2i, $^1$H NMR (CDCl$_3$, 600 MHz, 298K)

![NMR Spectrum of 2i, $^1$H](image)

2i, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)

![NMR Spectrum of 2i, $^{13}$C{$^1$H}](image)
$2j$, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

$2j$, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)
2j, $^{19}$F ($^1$H) NMR (CDCl$_3$, 282 MHz, 298K)
2k, $^1$H NMR (CDCl$_3$, 300 MHz, 298K)

2k, $^{13}C\{^1H\}$ NMR (CDCl$_3$, 75 MHz, 298K)
$2k$, $^{19}$F-$^1$H NMR (CDCl$_3$, 282 MHz, 298K)
21, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

21, $^{13}$C$_{^1}$H NMR (CDCl$_3$, 150 MHz, 298K)
$^{19}$F-{$^1$H}NMR (CDCl₃, 282 MHz, 298K)
2m, $^1$H NMR (CDCl$_3$, 400 MHz, 298K)

![NMR spectrum of 2m (1H)]

2m, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)

![NMR spectrum of 2m (13C)]
$2n$, $^1$H NMR (CDCl$_3$, 600 MHz, 298K)

$2n$, $^{13}$C{$_1^1$H} NMR (CDCl$_3$, 150 MHz, 298K)
2o, $^1$H NMR (CDCl$_3$, 300 MHz, 298K)

2o, $^{13}$C$_{\{^1\}H}$ NMR (CDCl$_3$, 75 MHz, 298K)
2p, $^1$H NMR (CDCl$_3$, 600MHz, 298K)

![2p, $^1$H NMR (CDCl$_3$, 600MHz, 298K)](image)

2p, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)

![2p, $^{13}$C{$^1$H} NMR (CDCl$_3$, 150 MHz, 298K)](image)
2s, $^1$H NMR (CDCl$_3$, 600MHz, 298K)

![NMR Spectrum](image1)

2s, $^{13}$C($^1$H) NMR (CDCl$_3$, 150 MHz, 298K)

![NMR Spectrum](image2)
**Table A1.1** Crystallographic data for Ni(CO)$_2$(PCy$_3$)$_2$ (B)

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C$<em>{33.00}$H$</em>{78}$NiO$_2$P$_2$</td>
</tr>
<tr>
<td>Formula weight</td>
<td>748.36</td>
</tr>
<tr>
<td>Temperature/K</td>
<td>296.15</td>
</tr>
<tr>
<td>Crystal system</td>
<td>Triclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>P-1</td>
</tr>
<tr>
<td>a/Å</td>
<td>11.784(3)</td>
</tr>
<tr>
<td>b/Å</td>
<td>12.434(4)</td>
</tr>
<tr>
<td>c/Å</td>
<td>16.583(5)</td>
</tr>
<tr>
<td>α/°</td>
<td>76.672(7)</td>
</tr>
<tr>
<td>β/°</td>
<td>76.225(7)</td>
</tr>
<tr>
<td>γ/°</td>
<td>63.041(7)</td>
</tr>
<tr>
<td>Volume/Å$^3$</td>
<td>2082.2(10)</td>
</tr>
<tr>
<td>Z</td>
<td>2</td>
</tr>
<tr>
<td>ρ$_{calc}$/g/cm$^3$</td>
<td>1.194</td>
</tr>
<tr>
<td>μ/mm$^{-1}$</td>
<td>0.576</td>
</tr>
<tr>
<td>F(000)</td>
<td>821.0</td>
</tr>
<tr>
<td>Crystal size/mm$^3$</td>
<td>0.21 × 0.25 × 0.15</td>
</tr>
<tr>
<td>Radiation</td>
<td>MoK$_\alpha$ ($λ = 0.71073$)</td>
</tr>
<tr>
<td>2Θ range for data collection/°</td>
<td>2.554 to 60.222</td>
</tr>
<tr>
<td>Index ranges</td>
<td>-15 ≤ h ≤ 16, -16 ≤ k ≤ 17, 0 ≤ l ≤ 23</td>
</tr>
<tr>
<td>Reflections collected</td>
<td>15348</td>
</tr>
<tr>
<td>Independent reflections</td>
<td>15348 [R$_{sigma}$ = 0.0724]</td>
</tr>
<tr>
<td>Data/restraints/parameters</td>
<td>15348/369/436</td>
</tr>
<tr>
<td>Goodness-of-fit on F$^2$</td>
<td>1.005</td>
</tr>
<tr>
<td>Final R indexes [I&gt;=2σ (I)]</td>
<td>R$_1$ = 0.0439, wR$_2$ = 0.0887</td>
</tr>
<tr>
<td>Final R indexes [all data]</td>
<td>R$_1$ = 0.0634, wR$_2$ = 0.0952</td>
</tr>
<tr>
<td>Largest diff. peak/hole / e Å$^{-3}$</td>
<td>0.51/-0.58</td>
</tr>
</tbody>
</table>

**Table A1.2** Bond lengths for Ni(PCy$_3$)$_2$(CO)$_2$ (B)

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Length/Å</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ni1</td>
<td>P1</td>
<td>2.2504(8)</td>
</tr>
<tr>
<td>Ni1</td>
<td>P2</td>
<td>2.2457(8)</td>
</tr>
<tr>
<td>Ni1</td>
<td>C1</td>
<td>1.780(2)</td>
</tr>
<tr>
<td>Ni1</td>
<td>C2</td>
<td>1.777(2)</td>
</tr>
<tr>
<td>P1</td>
<td>C3</td>
<td>1.870(2)</td>
</tr>
<tr>
<td>P1</td>
<td>C9</td>
<td>1.875(2)</td>
</tr>
<tr>
<td>P1</td>
<td>C15</td>
<td>1.877(2)</td>
</tr>
<tr>
<td>P2</td>
<td>C21</td>
<td>1.860(2)</td>
</tr>
<tr>
<td>C16</td>
<td>C17</td>
<td>1.525(3)</td>
</tr>
<tr>
<td>C17</td>
<td>C18</td>
<td>1.528(3)</td>
</tr>
<tr>
<td>C18</td>
<td>C19</td>
<td>1.526(4)</td>
</tr>
<tr>
<td>C19</td>
<td>C20</td>
<td>1.532(3)</td>
</tr>
<tr>
<td>C20</td>
<td>C21</td>
<td>1.536(3)</td>
</tr>
<tr>
<td>C21</td>
<td>C22</td>
<td>1.537(3)</td>
</tr>
<tr>
<td>C22</td>
<td>C23</td>
<td>1.528(3)</td>
</tr>
<tr>
<td>C23</td>
<td>C24</td>
<td>1.528(3)</td>
</tr>
</tbody>
</table>

100
P2  C27  1.869(2)  C24  C25  1.525(3)
P2  C33  1.889(2)  C25  C26  1.534(3)
O1  C1   1.149(3)  C27  C28  1.539(3)
O2  C2   1.154(3)  C27  C32  1.544(3)
C3  C4   1.539(3)  C28  C29  1.525(3)
C3  C8   1.533(3)  C29  C30  1.530(3)
C4  C5   1.532(3)  C30  C31  1.532(3)
C5  C6   1.523(3)  C31  C32  1.530(3)
C6  C7   1.525(3)  C33  C34  1.538(3)
C7  C8   1.531(3)  C33  C38  1.539(3)
C9  C10  1.542(3)  C34  C35  1.533(3)
C9  C14  1.542(3)  C35  C36  1.523(3)
C10 C11  1.531(3)  C36  C37  1.525(3)
C11 C12  1.529(3)  C37  C38  1.537(3)
C12 C13  1.529(3)  C39  C40  1.502(3)
C13 C14  1.537(3)  C40  C41  1.514(3)
C15 C16  1.541(3)  C41  C42  1.528(3)
C15 C20  1.541(3)  C42  C43  1.521(4)

Table A1.3 Bond angles for Ni(PCy$_3$)$_2$(CO)$_2$(B)

<table>
<thead>
<tr>
<th>Atom</th>
<th>Atom</th>
<th>Atom</th>
<th>Angle/°</th>
<th>Atom</th>
<th>Atom</th>
<th>Atom</th>
<th>Angle/°</th>
</tr>
</thead>
<tbody>
<tr>
<td>P2</td>
<td>Ni1</td>
<td>P1</td>
<td>120.35(3)</td>
<td>C16</td>
<td>C15</td>
<td>P1</td>
<td>116.18(16)</td>
</tr>
<tr>
<td>C1</td>
<td>Ni1</td>
<td>P1</td>
<td>105.04(7)</td>
<td>C20</td>
<td>C15</td>
<td>P1</td>
<td>110.04(15)</td>
</tr>
<tr>
<td>C1</td>
<td>Ni1</td>
<td>P2</td>
<td>106.33(8)</td>
<td>C20</td>
<td>C15</td>
<td>C16</td>
<td>108.40(18)</td>
</tr>
<tr>
<td>C2</td>
<td>Ni1</td>
<td>P1</td>
<td>105.50(7)</td>
<td>C17</td>
<td>C16</td>
<td>C15</td>
<td>110.9(2)</td>
</tr>
<tr>
<td>C2</td>
<td>Ni1</td>
<td>P2</td>
<td>106.00(8)</td>
<td>C16</td>
<td>C17</td>
<td>C18</td>
<td>112.6(2)</td>
</tr>
<tr>
<td>C2</td>
<td>Ni1</td>
<td>C1</td>
<td>113.99(10)</td>
<td>C19</td>
<td>C18</td>
<td>C17</td>
<td>110.9(2)</td>
</tr>
<tr>
<td>C3</td>
<td>P1</td>
<td>Ni1</td>
<td>111.33(7)</td>
<td>C18</td>
<td>C19</td>
<td>C20</td>
<td>110.8(2)</td>
</tr>
<tr>
<td>C3</td>
<td>P1</td>
<td>C9</td>
<td>102.64(10)</td>
<td>C19</td>
<td>C20</td>
<td>C15</td>
<td>111.98(19)</td>
</tr>
<tr>
<td>C3</td>
<td>P1</td>
<td>C15</td>
<td>99.17(10)</td>
<td>C22</td>
<td>C21</td>
<td>P2</td>
<td>110.95(14)</td>
</tr>
<tr>
<td>C9</td>
<td>P1</td>
<td>Ni1</td>
<td>118.36(7)</td>
<td>C22</td>
<td>C21</td>
<td>C26</td>
<td>109.66(18)</td>
</tr>
<tr>
<td>C9</td>
<td>P1</td>
<td>C15</td>
<td>101.62(10)</td>
<td>C26</td>
<td>C21</td>
<td>P2</td>
<td>113.22(15)</td>
</tr>
<tr>
<td>C15</td>
<td>P1</td>
<td>Ni1</td>
<td>120.71(7)</td>
<td>C23</td>
<td>C22</td>
<td>C21</td>
<td>111.26(18)</td>
</tr>
<tr>
<td>C21</td>
<td>P2</td>
<td>Ni1</td>
<td>117.83(7)</td>
<td>C24</td>
<td>C23</td>
<td>C22</td>
<td>111.19(18)</td>
</tr>
<tr>
<td>C21</td>
<td>P2</td>
<td>C27</td>
<td>102.67(10)</td>
<td>C25</td>
<td>C24</td>
<td>C23</td>
<td>111.20(19)</td>
</tr>
<tr>
<td>C21</td>
<td>P2</td>
<td>C33</td>
<td>102.79(10)</td>
<td>C24</td>
<td>C25</td>
<td>C26</td>
<td>111.84(18)</td>
</tr>
<tr>
<td>C27</td>
<td>P2</td>
<td>Ni1</td>
<td>115.17(8)</td>
<td>C25</td>
<td>C26</td>
<td>C21</td>
<td>110.50(18)</td>
</tr>
<tr>
<td>C27</td>
<td>P2</td>
<td>C33</td>
<td>103.21(10)</td>
<td>C28</td>
<td>C27</td>
<td>P2</td>
<td>118.22(15)</td>
</tr>
<tr>
<td>C33</td>
<td>P2</td>
<td>Ni1</td>
<td>113.32(7)</td>
<td>C28</td>
<td>C27</td>
<td>C32</td>
<td>109.29(18)</td>
</tr>
</tbody>
</table>
O1  C1  Ni1  178.5(2)  C32  C27  P2  112.15(14)
O2  C2  Ni1  178.6(2)  C29  C28  C27  110.42(19)
C4  C3  P1  114.39(15)  C28  C29  C30  111.24(19)
C8  C3  P1  112.08(15)  C29  C30  C31  111.18(19)
C8  C3  C4  109.21(17)  C32  C31  C30  111.05(19)
C5  C4  C3  111.35(19)  C31  C32  C27  111.23(18)
C6  C5  C4  111.60(19)  C34  C33  C32  116.42(15)
C5  C6  C7  110.73(18)  C34  C33  C38  109.12(18)
C6  C7  C8  111.49(19)  C38  C33  C32  113.29(15)
C7  C8  C3  111.44(18)  C35  C34  C33  111.53(18)
C10  C9  P1  114.78(14)  C36  C35  C34  111.35(19)
C14  C9  P1  116.46(15)  C35  C36  C37  110.29(19)
C14  C9  C10  109.39(18)  C36  C37  C38  111.90(19)
C11  C10  C9  110.09(18)  C37  C38  C33  111.73(18)
C12  C11  C10  111.73(19)  C39  C40  C41  112.4(2)
C13  C12  C11  111.55(19)  C40  C41  C42  113.4(2)
C12  C13  C14  111.89(19)  C43  C42  C41  113.0(2)
C13  C14  C9  110.66(18)