ACRYLATE SYNTHESIS FROM
CARBON DIOXIDE – ETHYLENE COUPLING
CATALYZED BY FIRST-ROW TRANSITION METAL COMPLEXES

A Dissertation presented to
the Faculty of the Chemistry Department
at the University of Missouri-Columbia

In Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

by

KATHERINE UTTLEY

Dr. Wesley Bernskoetter, Dissertation Supervisor

JULY 2021
The undersigned, appointed by the dean of the Graduate School, have examined the
dissertation entitled

ACRYLATE SYNTHESIS FROM

CARBON DIOXIDE – ETHYLENE COUPLING

CATALYZED BY FIRST-ROW TRANSITION METAL COMPLEXES

presented by Katherine Uttley

a candidate for the degree of doctor of philosophy of chemistry

and hereby certify that, in their opinion, it was worth of acceptance.

________________________________________
Professor Wesley Bernskoetter

________________________________________
Professor Justin Walensky

________________________________________
Professor Michael Harmata

________________________________________
Professor Caixia Wan
DEDICATION

In loving memory of my father, Cliff Ryan Uttley, who passed away in 2011 at the age of 55. As I complete my graduate studies and prepare for commencement, I am reminded of his absence from both my high school and undergraduate graduation ceremonies. Although there will be many more milestones to come, I know he would be proud of my accomplishments and excited for my future.

I would also like to acknowledge my mother, Michele Meeth Uttley, who has been a loving parent, role model, mentor, and friend. I truly would not be the woman I am today without her. Thank you for everything you have done and continue to do for me and my brothers.

Lastly, I would like to acknowledge my brothers, Mathew Ryan Uttley and Lyle Benjamin Uttley. While we may have had our arguments – as siblings often do – our relationships became more meaningful than I could have imagined following the death of our father. You both have been equal parts brother, father, and friend in my eyes. I know I can always count on you for advice, support, or just a laugh. Thank you and I love you.
ACKNOWLEDGEMENTS

I would like to thank Dr. Bernskoetter – Wes – for introducing me to the challenging and (often) colorful world of air-free inorganic chemistry. Thank you for only making me TA once, except for the second time (which I am still mad at you about). Thank you for not getting mad when I break then Schlenk line or other expensive equipment. More importantly, thank you for being my mentor and role model. I have always felt that I can come to you with any question or concerns I may have and trust that you will give me sound advice, albeit with a healthy dose of sarcasm.

Thank you Dr. Walensky and Dr. Harmata for your mentorship over the years. You both have been an invaluable source of knowledge and wisdom that I am greatly appreciative of. Thank you Dr. Wan for graciously joining my committee in the 11th hour. It is not often that one must find a replacement doctoral committee member during the last 6 months of their studies, and I appreciate your willingness to serve in that capacity.

I would also like to thank the faculty and staff of the University of Missouri Chemistry Department that continuously work to maintain and improve the facilities that are so vital to my work as well as the work of my colleagues. Finally, I would like to specifically thank the custodial staff, without whom the department could not operate. You arrive early, stay late, and are often under-appreciated. Thank you for all that you do both publicly and behind the scenes.
# TABLE OF CONTENTS

ACKNOWLEDGEMENTS........................................................................ ii

LIST OF FIGURES AND SCHEMES................................................... vii

LIST OF TABLES............................................................................. xii

ABSTRACT.................................................................................... xiv

Chapter 1: Transition Metal-Catalyzed Reactions with Carbon Dioxide

1.1 Introduction: Carbon Dioxide as a Renewable C\textsubscript{1} Source ........................................................................... 1

1.1.1 Metal-Catalyzed CO\textsubscript{2} Functionalization and Substrate Scope.................................................. 4

1.2 Carbon-Carbon Bond Formation from Organometallics ................................................................. 6

1.2.1 Stille-Type Cross-Coupling: Organotin .................................................................................. 7

1.2.2 Suzuki-Type Cross-Coupling: Organoboron ..................................................................... 8

1.2.3 Negishi-Type Cross-Coupling: Organozinc ...................................................................... 11

1.3 Carbon-Carbon Bond Formation from C-X Electrophiles .......................................................... 12

1.4 Carbon-Carbon Bond Formation from Unsaturated Hydrocarbons ................................................. 16

1.4.1 Catalytic Coupling of CO\textsubscript{2} with Alkynes .................................................................. 16

1.4.2 Catalytic Coupling of CO\textsubscript{2} with Polyunsaturated Substrates ..................................... 20

1.4.3 Catalytic Coupling of CO\textsubscript{2} with Olefins .................................................................. 25

1.5 Transition-Metal Mediated Coupling of CO\textsubscript{2} and Ethylene .................................................. 27

1.5.1 Molybdenum and Tungsten Mediated Reactions .................................................................. 27

1.5.2 Catalytic Acrylate Production .................................................................................. 29

1.6 Perspective and Relevance of Current Studies ........................................................................... 30

1.7 References ............................................................................. 32
Chapter 2: Catalytic Acrylate Formation Catalyzed by Nickel(0) Complexes Bearing Bidentate Phosphine Ligands

2.1 Introduction: Acrylate Production from Ethylene–CO₂ Coupling.................................................41

2.1.1 Stoichiometric Ethylene-CO₂ Coupling and Nickelolactone Reactivity......................................41

2.1.2 Catalytic Acrylate Production from Ethylene and CO₂.................................................................46

2.1.3 Effect of Additives on Acrylate Formation: Lewis Acid...............................................................50

2.1.4 Effect of Additives on Acrylate Formation: Zinc ............................................................................51

2.1.5 Effect of Additives on Acrylate Formation: Phenoxide Base.........................................................54

2.2 Results and Discussion......................................................................................................................59

2.2.1 Synthesis of BenzP and Derivatives...............................................................................................59

2.2.2 Catalytic Trials

2.2.2.1 Catalytic Trials: Catalyst Comparison.........................................................................................61

2.2.2.2 Catalytic Trials: Base Comparison..............................................................................................64

2.2.2.3 Catalytic Trials: Lewis Acid Survey............................................................................................65

2.2.2.4 Catalytic Trials: iPr₄BenzP Studies..............................................................................................66

2.2.3 Stereoelectronic Influences Between Catalyst and Base..............................................................69

2.2.4 Catalytic Reaction Profile and Carbonate Formation.................................................................70

2.3 Concluding Remarks.......................................................................................................................73

2.4 Experimental.....................................................................................................................................75

2.4.1 General Considerations.................................................................................................................75

2.4.2 Preparation and Characterization of Ligands...............................................................................76

2.4.3 Preparation and Characterization of Nickel Complexes...............................................................77

2.4.4 Preparation of Sodium Phenoxide bases.....................................................................................82

2.4.5 General Procedure for Catalytic Acrylate Production Experiments...........................................82

2.5 References.........................................................................................................................................84
Chapter 3: Development of Low Valent Iron Complexes for Oxidative Coupling of Ethylene and Carbon Dioxide

3.1 Introduction: The Basis for Iron-Mediated Acrylate Production......................................................87

3.1.1 Meet in the Middle – A Case for CO$_2$-Olefin Coupling at Group VIII Metals ..................87

3.1.2 Iron-Mediated Oxidative Coupling of CO$_2$ and Olefins..........................................................89

3.2 Results and Discussion ..................................................................................................................94

3.2.1 Development of an Alkylated Tridentate Ligand ........................................................................94

3.2.2 Synthesis and Reactivity of P$_3$Fe Complexes.............................................................................96

3.2.3 Investigations of Ethylene-CO$_2$ Coupling Mediated by Complex 2a.................................100

3.2.4 Prevention of Double CO$_2$ Insertion

3.2.4.1 Prevention of Double CO$_2$ Insertion: Modification of Tridentate Sterics ...................102

3.2.4.2 Prevention of Double CO$_2$ Insertion: Mono-Dentate Ligand Addition ......................105

3.2.4.3 Prevention of Double CO$_2$ Insertion: Base-Mediated Lactone Deprotonation..........110

3.2.4.4 Prevention of Double CO$_2$ Insertion: P$_3$Fe(C$_5$H$_4$)(N$_2$) Oxidation.................................112

3.2.5 Quantification of Carboxylate Products Resulting from Iron-Mediated Coupling........114

3.3 Concluding remarks.........................................................................................................................116

3.4 Experimental ..................................................................................................................................119

3.4.1 General Considerations ..............................................................................................................119

3.4.2 Preparation and Characterization of P$_3$..................................................................................119

3.4.3 Preparation and Characterization of Iron Complexes .................................................................121

3.4.4 General Procedure for CO$_2$-Ethylene Coupling Experiments...........................................124

3.5 References ......................................................................................................................................125

Chapter 4: Iron-Catalyzed Amide Formation from the Dehydrogenative Coupling of Alcohols and Secondary Amines

4.1 Introduction: The Significance of Carbon-Nitrogen Bonds...........................................................129
4.2 Catalytic Dehydrogenative Coupling of Alcohols and Amines ................................................. 130
  4.2.1 Precious Metal Catalysts ........................................................................................................ 131
  4.2.2 Base Metal Catalysts ................................................................................................................ 139

4.3 Results and Discussion .................................................................................................................. 142
  4.3.1 Catalytic Trials: Optimizations ............................................................................................... 143
  4.3.2 Catalytic Trials: Amine Screening ........................................................................................... 146
  4.3.3 Catalytic Trials: Alcohol Screening ........................................................................................ 149

4.4 Mechanistic Considerations ......................................................................................................... 152
  4.4.1 Mechanistic Investigations into 1-catalyzed Dehydrogenative Amidation ....................... 153
  4.4.2 Additional Experiments ........................................................................................................... 154

4.5 Concluding Remarks .................................................................................................................... 160

4.6 Experimental Details .................................................................................................................... 160
  4.6.1 General Considerations ........................................................................................................... 160
  4.6.2 General Procedure for the Formation of Complex 2 ............................................................. 161
  4.6.3 General Methods for Catalytic Alcohol Dehydrogenation in the Presence of Amines .... 162
  4.6.4 General Procedure for H2 Collection Studies ......................................................................... 162

4.7 References .................................................................................................................................... 164

VITA .................................................................................................................................................. 169
LIST OF FIGURES AND SCHEMES

Chapter 1: Transition Metal-Catalyzed Reactions with Carbon Dioxide

Figure 1. Commodity chemicals currently made using CO₂……………………………………..5

Scheme 1. Palladium-catalyzed coupling of CO₂ and organotin reagents……………………..7

Scheme 2. Aryl organoboron catalytic carboxylation in the presence of CsF…………………8

Scheme 3. Aryl organoboron catalytic carboxylation in the presence of KOtBu……………..9

Scheme 4. Catalytic carboxylation of vinyl boronic esters………………………………………10

Scheme 5. Carboxylation of boronic ester derivatives………………………………………..11

Scheme 6. Catalytic coupling of organozinc reagents with CO₂...............................12

Scheme 7. Catalytic carboxylation of aryl halides……………………………………………13

Scheme 8. Catalytic coupling of primary benzyl chlorides with CO₂...............................14

Scheme 9. Nickel-catalyzed carboxylation of benzyl bromides……………………………..14

Scheme 10. Nickel-catalyzed carboxylation of alkyl halides…………………………………15

Scheme 11. Nickel-catalyzed coupling of alkynes with CO₂…………………………………16

Scheme 12. Telomerization of 1,3-butadiene with CO₂………………………………………20

Scheme 13. Palladium-catalyzed isoprene dimerization………………………………………21

Scheme 14. Nickel-catalyzed cycloisomerization of bis-dienes……………………………21

Scheme 15. Catalytic coupling of CO₂ with allenes…………………………………………23

Scheme 16. Carboxylation of L-tryptophan for the synthesis of (-)-corynantheidine………24
Scheme 17. Carboxylative cyclization of enynes and diynes .................................24

Scheme 18. Catalytic carboxylation of styrenes ......................................................25

Scheme 19. Catalytic carboxylation of substituted olefins ........................................26

Scheme 20. Reactivity of Mo⁰ and W⁰ ethylene-complexes with CO₂ ..........................28

Chapter 2: Catalytic Acrylate Formation Catalyzed by Nickel(0) Complexes Bearing Bidentate Phosphine Ligands

Scheme 1. Synthesis and reactivity of the Hoberg complex ....................................42

Figure 1. Proposed catalytic cycle ........................................................................47

Scheme 2. Lewis acid-induced Ni-lactone cleavage and γ- to β-lactone isomerization ..51

Scheme 3. Synthesis of BenzP and derivatives .......................................................60

Figure 2. Quadrant sterics for BenzP derivatives ...................................................63

Scheme 4. (iPr₄BenzP)Ni(COD) Reactivity ...............................................................67

Figure 3. iPr₄BenzP-acrylate crystal structure ......................................................68

Figure 4. (BenzP)Ni(COD) reaction profile and carbonate formation ........................71

Chapter 3: Development of Low Valent Iron Complexes for Oxidative Coupling of Ethylene and Carbon Dioxide

Figure 1. Proposed catalytic cycle for acrylate production from CO₂-ethylene coupling ......88

Scheme 1. First iron-mediated CO₂-olefin coupling .................................................89

Scheme 2. First CO₂-ethylene coupling by an iron complex .....................................90

Scheme 3. Proposed mechanism for dicarboxylate formation from CO₂-ethylene coupling ........91
Scheme 4. Carboxylate formation mediated by (iPrPDI)Fe(N$_2$)$_2$..............................92

Scheme 5. Sodium acrylate production by (depe)$_2$Fe(C$_2$H$_4$)...........................................93

Scheme 6. Synthesis of alkylated tridentate phosphine ligands..............................................95

Figure 2. Qualitative d-orbital splitting diagram for complex 1a..............................................97

Figure 3. Structure of 2a........................................................................................................97

Scheme 7. Synthesis of complexes 2a and 3 .................................................................98

Figure 4. Comparison of the $^{13}$C NMR spectra for complexes 2a and 3* .........................99

Figure 5. Hooke’s Law and the prediction of IR stretching frequencies.................................100

Scheme 8. Proposed mechanism for the formation of complex 4 .........................................102

Scheme 9. Synthesis of iPr and Cy variants of P$_3$, 1a, and 2a..............................................103

Figure 6. Structure of complexes 2b (left) and 2c (right).......................................................103

Figure 7. Topographic steric maps of complexes 2a-c.........................................................104

Scheme 10. Reactivity of complexes 2a-c with ethylene and CO$_2$........................................106

Scheme 11. Summary of the reactivity of 2a-c and 5a-c with ethylene and CO$_2$...............110

Figure 8. Cyclic voltammetry of 2a.......................................................................................113

Scheme 12. Summary of the reactivity of P$_3$Fe complexes...............................................118

Chapter 4: Iron-Catalyzed Amide Formation from the Dehydrogenative Coupling of Alcohols and Secondary Amines

Scheme 1. Transition metal-mediated dehydrogenation of alcohols in the presence of amines to form amides and dihydrogen.........................................................130
Scheme 2. Ruthenium-catalyzed coupling of amino alcohols .................................................. 131

Scheme 3. Intermolecular amidation catalyzed by Milstein’s PNN-Ru complex .............. 131

Scheme 4. Catalytic amide production mediated by Ru/dppb complex in the presence of base and a hydrogen acceptor ................................................................. 132

Scheme 5. Ru-diamine-diphosphine complexes for the catalytic dehydrogenative coupling of alcohols and amines ................................................................................. 134

Scheme 6. Ru-PNN catalysts for tertiary amide formation ........................................ 135

Scheme 7. Ru-Macho catalyzed amide and urea production ........................................ 136

Scheme 8. Chelating hydrazine-based Ru catalysts for alcohol-amine coupling .......... 137

Scheme 9. Ru catalysts featuring bidentate phosphine-amine ligands .................... 138

Scheme 10. Dehydrogenative amidation of alcohols catalyzed by Rh and Re complexes .... 139

Scheme 11. Copper/ABNO-catalyzed aerobic coupling of alcohols and amines ............. 140

Scheme 12. Cobalt-catalyzed dehydrogenative coupling of alcohols and amines .......... 141

Scheme 13. Manganese-catalyzed amide production from alcohols and amines ............ 141

Figure 1. Complex 1 ............................................................................................................. 142

Figure 2. Reaction Duration ............................................................................................... 143

Figure 3. Proposed Mechanism for the Dehydrogenative Amidation of Alcohols ....... 152

Figure 4. Iron-Catalyzed Coupling of Benzaldehyde and Methyl Formate with Morpholine ................................................................................................................. 154

Figure 5. NMR Experiments: MeOH Addition ............................................................... 155

Figure 6. Variable Temperature $^{31}$P NMR Spectra of 1 in the Presence of MeOH .......... 156
Figure 7. Low Temperature NMR Experiments in the Presence of $^{13}$CH$_3$OH………………157

Figure 8. DFT Calculated Pathways for Dehydrogenation of MeOH by Five-Coordinate Iron Complex………………………………………………………………………………………………………159
LIST OF TABLES

Chapter 1: Transition Metal-Catalyzed Reactions with Carbon Dioxide

Table 1. Nickel-Catalyzed Alkyne-\(\text{CO}_2\) Coupling ..................................................... 17
Table 2. Alkyne Carboxylations Catalyzed by Other Metals ................................................. 19
Table 3. Catalytic Carboxylation of Dienes ............................................................................. 22
Table 4. Acrylate Production Catalyzed by Pd and Ru Complexes ....................................... 29

Chapter 2: Catalytic Acrylate Formation Catalyzed by Nickel(0) Complexes Bearing Bidentate Phosphine Ligands

Table 1. Ligand Scope Utilized in Studies Between 1982 and 2004 ........................................ 42
Table 2. Ligand Survey and Their Effect on Ni-Lactone Reactivity ........................................ 44
Table 3. Reaction of Ni-lactone with Methyl Iodide ................................................................. 46
Table 4. Effect of Tether Length on Ni-Lactone Formation ..................................................... 48
Table 5. Combined Effects of Lewis Acid, Base, and Zinc on Catalysis ................................... 52
Table 6. Effect of Tether Length, Phosphine Substituent, and Gas Ratios on TON .................. 54
Table 7. Ligand Survey Conducted by Limbach et al .............................................................. 55
Table 8. Base Survey Conducted by Limbach et al ................................................................. 58
Table 9. Catalytic Trials – Optimization, Base Screen, and Lewis Acid Screen ...................... 62
Table 10. Phenoxide Bases Surveyed and Their Relative Basicity ........................................... 64
Table 11. Catalyst-Base Pairing ............................................................................................. 69
Chapter 3: Development of Low Valent Iron Complexes for Oxidative Coupling of Ethylene and Carbon Dioxide

Table 1. Selected Structural Data for Complexes 2a-c .............................................104

Table 2. Precent Buried Volume for Complexes 2a-c .............................................104

Table 3. Reactivity of Mono-Dentate Ligands with Complex 2a .............................107

Table 4. Quantification of Carboxylate Products from CO₂-Ethylene Coupling ......115

Chapter 4: Iron-Catalyzed Amide Formation from the Dehydrogenative Coupling of Alcohols and Secondary Amines

Table 1. Ru-NHC Catalysts for Alcohol Amidation in the Presence of Base ...........133

Table 2. Ru-NHC Catalysts with Extended π-Systems .........................................135

Table 3. Solvent Screening .................................................................................143

Table 4. Temperature Screen ............................................................................144

Table 5. Alcohol/Amine Ratio ...........................................................................145

Table 6. Catalyst Control Experiments ...............................................................146

Table 7. Amide Substrate Screen ......................................................................147

Table 8. Alcohol Substrate Screen ....................................................................150
Acrylate Synthesis from Carbon Dioxide – Ethylene Coupling Catalyzed by First-Row Transition Metal Complexes

Katherine Uttley

Dr. Wesley Bernskoetter, Dissertation Supervisor

ABSTRACT

Carbon dioxide (CO$_2$) is an abundant and renewable carbon source than can be used as feedstock for the synthesis of value-added materials. One such material is acrylic acid, and acrylate derivatives, which can be used in the production of super absorbent polymers, adhesives, and coatings. The oxidative coupling of CO$_2$ and ethylene offers a more atom-economical and sustainable approach acrylic acid formation relative to the petroleum-based synthesis currently in use. This dissertation examines the ability of the first-row transition metals Nickel (Ni) and Iron (Fe) to yield acrylate from CO$_2$ and ethylene.

A wealth of research on Ni-mediated CO$_2$-ethylene coupling reactions laid the groundwork for a variety of in-depth investigations into ancillary ligand effects and the role of additives in the multi-component system. Moderate improvements to catalytic activity were observed but ultimately the progress of this system has stalled, and investigations turned to the development of novel Fe complexes.

A family of low valent Fe complexes were found to facilitate CO$_2$-ethylene coupling. However, the insertion of two CO$_2$ units was observed, resulting in the formation of the dicarboxylate product methylmalonic acid (MMA). A one electron oxidation was found to slow the rate of second CO$_2$ insertion and mixtures of propionic acid (PA) and MMA were obtained.
CHAPTER 1

Transition Metal-Catalyzed Reactions with Carbon Dioxide

1.1 Introduction: Carbon Dioxide as a Renewable C₁ Source

Global fossil fuel consumption has grown by more than 1400% relative to pre-industrial levels, most of which occurred in the last 50 years.¹,² As a result, there has been a sharp increase in the emission of greenhouse gases (GHG).³ Specifically, the amount of carbon dioxide (CO₂) in the atmosphere has surged from pre-industrial levels of 278 ppm to more than 417 ppm as of March 2021.³ Recent reports from the Intergovernmental Panel on Climate Change (IPCC) highlight the relationship between anthropogenic CO₂ emissions, global mean surface temperature (GMST), and the predicted impacts on human and natural systems.²,⁴ As of 2017, the GMST was measured to be 0.87°C above pre-industrial levels (~407 ppm CO₂) with a total increase of less than 2.0°C (or 500 ppm CO₂) by the end of the century necessary to avoid the most severe impacts to natural and human systems.²,⁴ However, without mitigation strategies in place to substantially reduce emissions, it is predicted the CO₂ concentrations will exceed 450 ppm by 2030 and range between 750 and 1300 ppm by 2100, resulting in a GMST increase of 3.7°C and 4.8°C and catastrophic impacts on human health, economic productivity, biodiversity, and ecological stability.²,⁴

Numerous strategies have been proposed to address this problem with an emphasis on reducing future emissions by revolutionizing the energy and transportation sectors.²,⁴,⁵
However, the sources of CO$_2$ emissions are ubiquitous and will require developments across all sectors of the economy. For example, the chemical sector alone is responsible for 5.5% of global CO$_2$ emissions and 7% of total GHG emissions, as well as consuming the largest amount of energy of any industrial sector: 42.5 exajoules (EJ) or about 10% of global energy consumption in 2013.$^5,6$ An analysis from Levi and Cullen found that, in order to achieve the targeted emission reductions needed to limit warming to 2°C – and without disproportionate reductions in other sectors – the chemical sector would have to achieve a 75% reduction in emissions *per unit of production* by 2050 to keep up with projected growth in demand over the same time period.$^5$ It is without question that a considerable decrease in emissions could be achieved by transitioning away from fossil fuel-based energy sources. However, the chemical sector’s reliance on coal, oil, and natural gas goes beyond the need for fuel.

Approximately 95% of the organic chemical commodities were generated from fossil fuel-based carbon sources in 2013.$^7$ This means that even if the energy demand for production was met using 100% renewable sources, the chemical sector would still be reliant on fossil fuels as feedstock. To achieve a more environmentally benign chemical industry, alternative feedstocks must be examined and incorporated into large-scale production. The use of biomass for the production of commodity and specialty chemicals is one such alternative that has been extensively reviewed.$^7,8$ Enormous quantities of biomass (mostly carbohydrates) are produced from photosynthesis each year, making them the most abundant renewable resource and an attractive feedstock.$^7$ However, utilization of carbohydrates as a feedstock can limit the variety of end-products readily obtained due
to the more complex chemical structure (i.e. multiple carbons and functional groups) and the means by which chemical and microbial transformations are achieved.\textsuperscript{8,9}

Carbon dioxide, in addition to being a potent GHG, is another alternative carbon source that has received significant attention due to its abundance, recyclability, and relative nontoxicity.\textsuperscript{10-16} The utilization of CO\textsubscript{2} can be described as either physical or chemical with the end products resulting in either direct or indirect use.\textsuperscript{17,18} The distinction between physical and chemical utilization is characterized by whether the CO\textsubscript{2} molecule is used “as is” or if it undergoes a chemical transformation; whereas direct versus indirect use refers to whether the CO\textsubscript{2} molecule is directly incorporated into the product or if it simply enhances a process that results in product formation.\textsuperscript{18}

For example, dry ice is a direct physical method of CO\textsubscript{2} utilization because the molecule is not altered chemically and the final product contains (or in this case, consists entirely of) CO\textsubscript{2}.\textsuperscript{16} Other examples of direct physical CO\textsubscript{2} utilization include fire extinguishers, carbonated beverages, solvent (supercritical CO\textsubscript{2}) and welding medium.\textsuperscript{17,18} Indirect physical methods of CO\textsubscript{2} utilization include enhanced oil/gas recovery from depleted reservoirs and accelerated cement curing.\textsuperscript{9,19,20} The scope of physical CO\textsubscript{2} utilization, however, is severely limited and the end products do not result in long-term emission reductions as the CO\textsubscript{2} is often released into the atmosphere in relatively short order.

The chemical utilization of CO\textsubscript{2} on the other hand can, in theory, be used to produce a wide variety of commodity and specialty chemicals through both direct and indirect means.\textsuperscript{9-24} Large-scale utilization has been limited, however, due to the thermodynamic stability ($\Delta H^0_f = -393.5$ kJ mol\textsuperscript{-1}) and kinetic inertness of CO\textsubscript{2}. One of the main strategies
employed to overcome the stability of CO$_2$ has been to react it with high-energy, nucleophilic substrates such as epoxides or amines, which makes product formation more thermodynamically favorable. Such methods have allowed for the large-scale production of urea, salicylic acid, and carbonates from CO$_2$.\textsuperscript{10-24} The use of transition metal catalysts has also been vital for lowering the kinetic barrier to CO$_2$ activation and innumerable transition metal complexes have been developed for such purposes.

1.1.1 Metal-Catalyzed CO$_2$ Functionalization and Substrate Scope

There are two separate but distinct classes of catalysts – heterogeneous and homogeneous – with different advantages and drawbacks. Heterogeneous catalysts are almost exclusively used in large-scale industrial applications because of the ease with which they can be separated from products or incorporated into flow reactors.\textsuperscript{25, 26} However, the ability to gain mechanistic insight from these systems is incredibly difficult and modifying the reactivity of heterogeneous systems (either structurally or conditionally) can be arduous.\textsuperscript{26} Homogeneous catalysts on the other hand, are more difficult to separate from reaction mixtures and are therefore not often utilized in large-scale production.\textsuperscript{25, 26} From a catalyst development perspective however, homogeneous complexes are ideal because the molecular structure can be fine-tuned to optimize reactivity and/or selectivity and mechanistic investigations can be more easily conducted.\textsuperscript{25, 26} For these reasons, an in-depth analysis of heterogeneous catalysts is beyond the scope of this discussion, but several excellent reviews are available.\textsuperscript{27, 28} Our discussion, and the studies that follow in this dissertation, will focus on the use of homogeneous catalysts to transform CO$_2$.

A comprehensive review of homogeneous CO$_2$ functionalization reactions is impractical and unnecessary for our purposes. However, a more general overview of the
current state of CO₂ functionalization reactions is warranted. Numerous commodity chemicals have been produced using CO₂ as a C₁ synthon (Figure 1). The products of these reactions can be generally characterized as either building up CO₂ or breaking it down. For example, the hydrogenation of CO₂ to methanol (MeOH) and the reduction of CO₂ to CO require the cleavage of a C=O bond, effectively breaking it down.¹¹⁻²² The hydrogenation of CO₂ to formic acid (FA) represents a gray area, so to speak, between these two categories. Although production of FA does not involve the cleavage of C=O bonds, subsequent reactions needed to drive the thermodynamics of this reaction typically target reduced products such as MeOH.⁹⁻¹²⁻¹⁴⁻¹⁷⁻²⁰⁻²²⁻²⁴ In general, the development of CO₂ functionalization reactions which break CO₂ down has been the more active domain of catalysis research over the past two decades.

Methods of building up CO₂ have received considerably less investigation despite their need in the production of larger and more complex structures. In many cases, these

---

**Figure 1. Commodity chemicals currently made using CO₂**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Products</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₂</td>
<td>O</td>
<td>11-14, 17-20, 22-24</td>
</tr>
<tr>
<td>H₂</td>
<td>$</td>
<td>9, 12-22, 24</td>
</tr>
<tr>
<td>ROH</td>
<td>$</td>
<td>9, 10, 15-18, 21, 22, 29-34</td>
</tr>
<tr>
<td>$</td>
<td>$</td>
<td>9-11, 14, 16, 20-23</td>
</tr>
<tr>
<td>$</td>
<td>$</td>
<td>10, 11, 14, 16, 18, 20, 22-24, 35-38</td>
</tr>
<tr>
<td>NH₂R + ROH</td>
<td>$</td>
<td>9, 12-16, 18, 20-24, 39-42</td>
</tr>
<tr>
<td>NH₂R</td>
<td>$</td>
<td>10-18, 20-24</td>
</tr>
<tr>
<td>$</td>
<td>$</td>
<td>11, 21-23</td>
</tr>
<tr>
<td>$</td>
<td>$</td>
<td>10-12, 18, 20-22, 24, 43</td>
</tr>
</tbody>
</table>

*Industrialized processes indicated with $
elaborated CO₂ functionalized products may be utilized further with existing technologies to yield industrially important materials. Take the reaction of CO₂ with epoxides or amines to yield carbonates or carbamates; these products may then be used in subsequent reactions to produce value-added materials such as polycarbonates, polycarbamates, or ureas.¹⁰, ¹¹, ¹⁴-¹⁸, ²⁰-²⁴, ²⁹-⁴³ While this manner of forming C-E (E = O, N) bonds is an excellent way to incorporate renewable carbon sources into the production of value added materials, the scope is restricted to materials that also contain C-E bonds. A more diverse group of materials could be produced from targeted C-C bond formation from CO₂, however unactivated C-C bonds are much weaker nucleophiles than their nitrogen- or oxygen-containing counterparts. Therefore, much of C-C bond forming reactions catalyzed by transition metal complexes have utilized pre-activated substrates such as organolithium or Grignard reagents.

1.2 Carbon-Carbon Bond Formation from Organometallics

The use of highly reactive substrates such as organolithium or Grignard reagents to facilitate C-C bond formation with CO₂ is a practice that dates back more than 80 years.⁴⁴ However, the poor chemoselectivity and sensitive nature of these reagents has restricted their use as a tool for organic synthesis. Rapid advancements in the field of catalytic cross-coupling and investigations into CO₂ activation by transition metal complexes spurred a flurry of developments that opened the door for less nucleophilic substrates to be coupled with CO₂.⁴⁵ Relative to Grignard and organolithium reagents, organometallic complexes containing tin, boron, and zinc are more air and water stable and are compatible with a wider variety of functional groups. For this reason, extensive research has been done on the coupling of these substrates with CO₂.⁴⁶
1.2.1 *Stille-Type Cross-Coupling: Organotin*

In a traditional Stille reaction, an organotin (or stannane) reagent is cross-coupled with an alkyl or aryl halide in a palladium-catalyzed reaction to yield a tin-halide and the organic coupled product. Unlike a typical Stille cross-coupling reaction, the coupling of CO\(_2\) with stannanes affords a single carboxylated stannane product (Scheme 1). The first report of catalytic CO\(_2\) coupling with an organotin substrate was published in 1997 by Shi and Nicholas.\(^{47}\) Carboxylic acids were obtained in high yields from allyl stannanes in the presence of catalytic amounts of Pd(PPh\(_3\))\(_4\), although partial isomerization from the \(\alpha,\beta\)- to \(\beta,\gamma\)-unsaturated products was observed (Scheme 1, top). However, this catalytic system was plagued by a narrow substrate scope and the need for high CO\(_2\) pressures and catalyst loading. Similarly high yields were obtained at significantly lower pressure of CO\(_2\) and catalyst loading when the pincer Pd complex Pd-1 was employed (Scheme 1, top).\(^{48}\)

**Scheme 1. Palladium-catalyzed coupling of CO\(_2\) and organotin reagents**

Reports from Hazari and co-workers expanded the scope of organotin reagents to include substituted stannanes (Scheme 1, bottom).\(^{49,50}\) The \(\eta^3\)-allyl Pd complex Pd-2 and
the bridging allyl dimer Pd-3, both of which feature the N-heterocyclic carbene IPr (1,3-bis(2,6-di-iso-propylphenyl)-1,3-dihydro-2H-imidazol-2-ylidene), facilitated carboxylation reactions under notably mild conditions (1 atm CO₂, 25°C) (Scheme 1, bottom).

1.2.2 Suzuki-Type Cross-Coupling: Organoboron

The use of organoboron reagents in cross-coupling reactions has been the focus of considerable research due, in part, to their availability and relative stability. The first account of organoboron carboxylation was reported by Iwasawa et al. in 2006. A variety of aryl-substituted neopentyl glycol boronic (BNpG) esters were carboxylated under 1 atm CO₂ in the presence of [Rh(COD)(OH)]₂ with the bidentate phosphine ligand 1,3-bis(diphenylphosphino)propane (dppp) (Scheme 2, top). A high degree of functional group tolerance was observed, and high yields of the corresponding carboxylic acid were obtained, although an excess of cesium fluoride (CsF) was required. Cheaper, copper-based catalysts were reported in 2008 that achieved similarly high yields and exhibited exceptional functional group tolerance.

Scheme 2. Aryl organoboron catalytic carboxylation in the presence of CsF

![Scheme 2 Diagram]
Near quantitative yields of the respective carboxylate products were obtained from reactions catalyzed by CuI with bisoxazoline (L1) and an excess of CsF (Scheme 2, bottom). However, the N-heterocyclic carbene (NHC) supported copper complex Cu(IPr)(Cl) was found to be a more robust catalyst, operating at lower catalyst loading and without the need for excess base (Scheme 3, top). This same ligand scaffold was later modified to create a pH-sensitive NHC-Cu complex that was employed as a method of catalyst recycling for homogeneous carboxylation of aryl boronic esters.\(^5^4\)

**Scheme 3. Aryl organoboron catalytic carboxylation in the presence of KOtBu**

In addition to Rh- and Cu-catalyzed cross-coupling, Ag and Ni complexes have been reported to be highly active for the carboxylation of organoboron substrates.\(^5^5,5^6\) The combination of Ag(OAc), PPh\(_3\), and 2.2 eq. KOtBu proved to be an especially robust catalytic system operating at low catalyst loadings and obtaining high yields in the presence of a wide variety of functional groups (Scheme 3, middle).\(^5^5\) The first nickel-catalyzed
reaction was reported in 2014 by Nolan et al. and utilized Ni(IPr*)(allyl)(Cl) (Ni-1), which featured the phenyl-substituted NHC variant IPr* (1,3-bis[2,6-bis(diphenylmethyl)-4-methylphenyl]-1,3-dihydro-2H-imidazol-2-ylidene) (Scheme 3, bottom). In the presence of 1 eq. KOrBu and 1 atm CO₂, Ni-1 successfully converted aryl substrates to the corresponding carboxylic acids in high yields. These catalysts were also capable of coupling CO₂ with vinyl-substituted boronic esters (Scheme 4), although the substrate scope was considerably more limited than the aryl-substituted boronic esters.

**Scheme 4. Catalytic carboxylation of vinyl boronic esters**

![Scheme 4. Catalytic carboxylation of vinyl boronic esters](image)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Conditions</th>
<th>Examples</th>
<th>Yield/TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>[Rh(nbd)Cl]₂ (5 mol%)</td>
<td>dppp (10 mol%)</td>
<td>5</td>
<td>Up to 94% yield</td>
</tr>
<tr>
<td></td>
<td>CO₂ (1 atm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsF (3 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dioxane 60°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CuI (5 mol%)</td>
<td>L₁ (6 mol%)</td>
<td>5</td>
<td>Up to 76% yield</td>
</tr>
<tr>
<td></td>
<td>CO₂ (1 atm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>CsF (3 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DMF, 90°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cu(IPr)Cl (1 mol%)</td>
<td>CO₂ (1 atm)</td>
<td>3</td>
<td>Up to 92% yield</td>
</tr>
<tr>
<td></td>
<td>KOrBu (1.05 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>THF, reflux</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ag(OAc) (1 mol%)</td>
<td>PPh₃ (1.5 mol%)</td>
<td>TON = 80</td>
<td>80% yield</td>
</tr>
<tr>
<td></td>
<td>CO₂ (20 atm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>KOrBu (2.2 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dioxane, 100°C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ni-1 (5 mol%)</td>
<td>CO₂ (1 atm)</td>
<td>3</td>
<td>Up to 92% yield</td>
</tr>
<tr>
<td></td>
<td>KOrBu (2.2 eq.)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Toluene, 100°C</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Boronic esters featuring neopentyl glycol backbones have been the primary substrate class of organoboron reagents used for CO\textsubscript{2} functionalization (Scheme 5, top). However, allyl pinacol boronic (Bpin) esters have also been utilized substrate for reactions catalyzed by Pd-2, Pd-3, and Cu(IPr)Cl, confirming that the NpG-motif is not required for carboxylation (Scheme 5, bottom).\textsuperscript{49, 50, 52} In fact, the Pd-2 complex reported by Hazari facilitated reactions with numerous boronic esters (Scheme 5, left).\textsuperscript{50} Organoboron reagents generated in situ have also been shown to trigger CO\textsubscript{2} insertion reactions (Scheme 5, right).\textsuperscript{57-59}

1.2.3 Negishi-Type Cross-Coupling: Organozinc

Despite the popularity of organozinc reagents in Negishi cross-coupling reactions, there has been comparatively little research done into the reaction of such substrates with CO\textsubscript{2} (Scheme 6). Motivated by the lack of catalytic CO\textsubscript{2} functionalization reactions reported for Aresta’s complex,\textsuperscript{60} – the first metal-CO\textsubscript{2} complex isolated and characterized – Yeung and Dong investigated the ability of Aresta’s Ni(η\textsuperscript{2}-CO\textsubscript{2})(PCy\textsubscript{3})\textsubscript{2} complex (Ni-2) and its precursor [Ni(PCy\textsubscript{3})\textsubscript{2}]\textsubscript{2}(N\textsubscript{2}) (Ni-3) to facilitate catalytic carboxylation of arylzinc reagents (Scheme 6, top).\textsuperscript{61} Both nickel complexes as well as the combination of Pd(OAc)\textsubscript{2} and PCy\textsubscript{3} afforded high yields under mild conditions, although the Pd(OAc)\textsubscript{2}/PCy\textsubscript{3} system demonstrated a greater substrate scope (Scheme 6, bottom).\textsuperscript{61} When this ligand was paired
with Ni(acac)₂, it effectively catalyzed the carboxylation of alkylzinc reagents as well as Ni-3 (Scheme 6, bottom). For all Ni-catalyzed carboxylation reactions, the presence of lithium chloride (LiCl) was found to be essential, the role of which is believed to increase the nucleophilicity of the organozinc substrate.

**Scheme 6. Catalytic coupling of organozinc reagents and CO₂**

1.3 Carbon-Carbon Bond Formation from C-X Electrophiles

The use of organometallic reagents as substrates for C-C bond forming reactions with CO₂ allowed for a wide variety of product types and functional group tolerance. However, the use of stoichiometric amounts of these materials is inefficient, costly, and hazardous in the case of highly reactive compounds like diethyl zinc. Alternative methods of C-C bond formation include the direct carboxylation of halogenated or otherwise
electron-poor carbon atoms. However, this manner of cross-electrophile coupling of CO₂ with an electrophilic carbon substrate requires the addition of a reductant to close the catalytic cycle and balance the redox properties of the system. Therefore, the choice of substrate and the corresponding reducing agent must be carefully considered to avoid deleterious or unproductive side reactions.

The first catalytic carboxylation of aryl bromides was reported in 2009 and detailed the use of Pd(OAc)₂ with the bulky phosphine ligand tBuXPhos (L₂) and Et₂Zn (Scheme 7, top). This system displayed remarkable functional group tolerance and achieved high yields of the corresponding benzoic acids. However, the substrate scope was limited to aryl bromides and the need for high pressures of CO₂ and pyrophoric Et₂Zn as the reducing agent were significant drawbacks to this system. A Ni catalyst was reported in 2012 that was capable of coupling both aryl and vinyl chlorides at atmospheric pressures of CO₂ (Scheme 7, middle). This system utilized the more benign yet expensive reducing agent.

### Scheme 7. Catalytic carboxylation of aryl halides

- **Br**
  - Pd(OAc)₂ (5 mol%)
  - L₂ (10 mol%)
  - CO₂ (10 atm)
  - Et₂Zn (2 eq.)
  - NiBr₂(bpy) (5 mol%)
  - bpy (15 mol%)
  - Et₂NI (10 mol%)
  - CO₂ (1 atm)
  - Mn (3 eq.)
  - CuI (3 mol%)
  - DMEDA or TMEDA (3 mol%)
  - CO₂ (1 atm)
  - Et₂Zn (2.5 eq.)
  - 19 examples
  - Up to 82% yield
  - Max TON = 16.4

- **Cl**
  - 14 examples
  - Up to 90% yield
  - Max TON = 18.0

- **I**
  - 19 examples
  - Up to 88% yield
  - Max TON = 29.3
catalytic amounts of Et₄NI in order to achieve high yields of carboxylic acids. Aryl iodides have also been used as substrates for CO₂ coupling reactions catalyzed by CuI with chelating amine ligands (Scheme 7, bottom).

Scheme 8. Catalytic coupling of primary benzyl chlorides with CO₂

Carboxylation of benzyl halides have been successfully coupled by Pd- and Ni-complexes in the presence of mild reducing agents such as magnesium and zinc (Scheme 8, top). The Pd catalyst reported by He et al. utilized the SPhos ligand (L₃) and MgCl₂ to achieve near quantitative yields of benzoic acid. The Martin group reported a Ni catalyst with electron-rich phosphine ligands that facilitated the coupling of both benzyl chlorides and benzyl bromides (Scheme 8, bottom and Scheme 9, top). Although higher catalyst loading was required compared to the Pd-system, benzoic acids were obtained in moderate to high yields. The presence of MgCl₂ was found to be essential to product formation.

Scheme 9. Nickel-catalyzed carboxylation of benzyl bromides
although its role in the catalytic cycle is speculative. Secondary and tertiary benzyl bromides were catalyzed using a similar Ni catalyst in the presence of tetrabutylammonium iodide (TBAI) (Scheme 9, bottom).

Alkyl bromides and chlorides have also been used as substrates for CO₂ functionalization (Scheme 10). A series of Ni catalysts were reported that utilize modified 1,10-phenanthroline ligands to achieve high yields of carboxylic acid products. The ethyl-substituted L₄ and methyl-substituted L₅ were shown to catalyze the coupling of primary alkyl bromides, with the L₄-system demonstrating exceptional functional group tolerance (Scheme 10, top). The catalytic reaction carried out with the di-substituted L₆ were capable of coupling primary, secondary, and tertiary alkyl chlorides in the presence of either TBAB or LiCl (Scheme 10, bottom).

**Scheme 10. Nickel-catalyzed carboxylation of alkyl halides**

![Scheme 10](image-url)
1.4 Carbon-Carbon Bond Formation from Unsaturated Hydrocarbons

1.4.1 Catalytic Coupling of CO₂ with Alkynes

In 1978, Inoue and co-workers reported the catalytic formation of substituted α-pyrones from the reaction of alkynes with CO₂ in the presence of a Ni(0) catalyst and chelating phosphine ligand (Scheme 1). Although low yields were obtained with terminal alkynes, the use of internal alkynes resulted in yields of up to 60% and a maximum TON of 12.5. Spectroscopic data collected by Walther et al. suggested that the mechanism of this transformation results in the formation of an intermediate 5-membered oxanickelacyclopentene following the oxidative coupling of CO₂ and alkyne (Scheme 1). These findings were corroborated by the isolation of this intermediate by Hoberg and co-workers. Around this time, Aresta reported a rhodium complex that was capable of catalyzing the coupling of alkynes and CO₂ but yields of the resulting pyrone were <10%.

Scheme 11. Nickel-catalyzed coupling of alkynes and CO₂

Given the success of these initial investigations, as well as concomitant breakthroughs in the field of Ni-mediated olefin-CO₂ coupling (vide infra), the surge of reports on Ni-catalyzed coupling of alkynes and CO₂ that followed comes as no surprise (Table 1). Many of the Ni-systems achieved near-quantitative yields of the corresponding carboxylate products with high degrees of regio- and stereoselectivity as well as
exceptional functional group tolerance. However, these systems were plagued by the need for stoichiometric amounts of Lewis acid and reducing agents as well as an excess of secondary reagents in the form of organozinc or alcohols.

The carboxylation of aryl alkynes, propargyl alcohol, and silane-substituted alkynes were selective for Markovnikov products in the presence of alkylzinc reagents (Table 1, entries 1-4),\textsuperscript{78-81} whereas the use of alcohols afforded anti-Markovnikov products (Table 1, entry 5).\textsuperscript{82} Water was also used as a secondary reagents for the coupling of aliphatic alkynes as well as ynamides (Table 1, entries 6).\textsuperscript{83} Double carboxylation reactions were observed when no secondary reagent was present, affording maleic anhydrides in high yields (Table 1, entry 7).\textsuperscript{84}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Ligand</th>
<th>Conditions</th>
<th>Product</th>
<th>Max TON</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(COD)\textsubscript{2}</td>
<td>1-3 mol%</td>
<td>ZnEt\textsubscript{2} (3 eq.) CsF (1 eq.) CH\textsubscript{3}CN, 60°C</td>
<td>H[\text{COOH}] R[\text{Ar}] 11 examples Up to 91% yield</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Ni(COD)\textsubscript{2}</td>
<td>1-3 mol%</td>
<td>ZnEt\textsubscript{2} (3 eq.) CsF (1 eq.) DMSO, 25°C</td>
<td>R[\text{H}] [\text{COOH}] NHTs 5 examples Up to 96% yield</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Ni(COD)\textsubscript{2}</td>
<td>1 mol%</td>
<td>ZnMe\textsubscript{2} (3 eq.) CsF (1.5 eq.) CH\textsubscript{3}CN, 50°C</td>
<td>Me[\text{O}] R[\text{O}] 18 examples Up to 97% yield</td>
<td>90</td>
</tr>
</tbody>
</table>
In addition to nickel, the coupling of alkynes and CO$_2$ has been carried out by iron, cobalt, and copper catalysts (Table 2). The iron complex FeCl$_2$ (Table 2, entry 1)$^{85}$ and cobalt complex (IMes)CuF (Table 2, entry 2)$^{86}$ were found to catalyze the coupling of aryl-substituted alkynes and CO$_2$ with similar yields and selectivity to that of Ni-catalyzed reactions (Table 1, entries 1, 2, and 4b). As in the Ni systems, the addition of secondary reagents was required for catalytic activity. Similar copper complexes were shown to catalyze the carboxylation of ynamides (Table 2, entry 3)$^{87}$ as well as alkyne-substituted...
boron and silicon substrates (Table 2, entries 4 and 5). In 2016, a cobalt-catalyzed multi-component system was developed for the production of tetrasubstituted acrylic acids (Table 2, entry 6). Following Co-catalyzed carboxy-zincation, the resulting alkenyl zinc moiety undergoes Negishi-type cross coupling with an electron deficient alkene.

Table 2. Alkyne Carboxylations Catalyzed by Other Metals

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Ligand</th>
<th>Conditions</th>
<th>Product</th>
<th>Max TON</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>FeCl₂</td>
<td>5 mol%</td>
<td>EtMgBr (2 eq.) Et₂O</td>
<td>H COOH</td>
<td>18.085</td>
</tr>
<tr>
<td>2</td>
<td>(IMes)CuF</td>
<td>1-2.5 mol%</td>
<td>HSi(OEt)₃ (2 eq.) Dioxane, 100°C</td>
<td>H COOH</td>
<td>78.086</td>
</tr>
<tr>
<td>3</td>
<td>(IPr)CuCl</td>
<td>5 mol%</td>
<td>Zn(R')₂ (1.5 eq.) THF, 50°C</td>
<td>H COOHMe</td>
<td>19.4.087</td>
</tr>
<tr>
<td>4</td>
<td>(SIMes)CuCl</td>
<td>5 mol%</td>
<td>LiOtBu (1.1 eq.) Bpin₂ (1 eq.) THF, 80°C</td>
<td>N COOH</td>
<td>18.8.088</td>
</tr>
<tr>
<td>5</td>
<td>[CuCl(PCy₃)₂]</td>
<td>2.5 mol%</td>
<td>NaOtBu (12 mol%) Me₂PhSi-Bpin (1.2 eq.) Octane, 100°C</td>
<td>O COOH</td>
<td>39.6.089</td>
</tr>
<tr>
<td>6</td>
<td>(dppf)CoI₂</td>
<td>10 mol%</td>
<td>1. Zn(OAc)₂ (10 mol%) Et₂NI (10 mol%) Zn (1.5 eq.) CH₃CN/DMF, 40°C 2. Electrophile</td>
<td>E COOH</td>
<td>8.2.090</td>
</tr>
</tbody>
</table>
1.4.2 Catalytic Coupling of CO₂ with Polyunsaturated Substrates

The coupling of CO₂ with polyunsaturated substrates is an attractive method of synthesizing carboxylate products that could be further functionalized. Specifically, 1,3-butadiene has received a considerable amount of attention as a substrate for CO₂ functionalization dating back to the mid-1970s. Inoue and Musco were among the first to report the Pd-catalyzed telomerization (or dimerization) of 1,3-butadiene with CO₂ to yield 5- and 6-memebered lactones. Shortly thereafter, Behr et al. reported varying degrees of catalytic activity for Pd, Rh, and Ni complexes in the presence of tri-iso-propyl phosphine (Scheme 12, top). Of these catalysts, Pd was found to be considerably more active than either Rh or Ni, achieving a TON of 686 for the 6-membered δ-lactone.

### Scheme 12. Telomerization of 1,3-butadiene with CO₂

The choice of ligand has been shown to affect both the selectivity and overall reactivity of Pd-catalyzed reactions, with the use of chelating ligands affording the respective 5-memebered γ-lactone in much lower yields than with mono-dentate phosphines (Scheme 12, bottom). The selectivity of Ni-mediated reactions was also affected by choice of ligand, although catalytic activity remained low (Scheme 12,
Similar dimerization was observed for the Pd-catalyzed reaction of isoprene with CO$_2$ in the presence of DBU and tributyltin ethoxide (Scheme 13).$^{95}$ In 2002, Mori reported the intramolecular cyclization of bis-diienes catalyzed by a Ni complex in the presence of alkylzinc reagents (Scheme 14).$^{96}$ Racemic mixtures were obtained when the mono-dentate PPh$_3$ was selected as the ligand, but the use of L9 as the ligand resulted in a dramatic improvement in the enantioselectivity. Quantitative yields of the cyclic products were obtained in what constitutes the first enantioselective coupling of CO$_2$ by a metal complex.$^{97}$ More recently, Limbach and co-workers reported the Pd-catalyzed coupling of CO$_2$ with 1,3-butadiene and 1,3-pentadiene using a system similar to that developed for Ni-catalyzed ethylene-CO$_2$ coupling (Table 3, entries 1a and 1b).$^{98}$

**Scheme 13. Palladium-catalyzed isoprene dimerization**

![Scheme 13](image)

**Scheme 14. Nickel-catalyzed cycloisomerization of bis-diienes**

![Scheme 14](image)
In the presence of the weak phenoxide base sodium 2-fluorophenoxide (2-FPhONa) and zinc, modest TONs of 24 and 50 were achieved for the carboxylation of 1,3-butadiene and 1,3-pentadiene, respectively (Table 3, entries 1a and 1b). A pincer-type Pd(II) complex developed by Iwasawa et al. was capable of much higher catalytic activity, achieving a TON of more than 500 for the carboxylation of substituted dienes (Table 3, entry 2). This system demonstrated excellent functional group tolerance and afforded yields of up to 97%. A site-selective Ni catalyst has also been reported that utilizes a modified 1,10-phenanthroline ligand (L10) to achieve selectivity for 1,4-dicarboxylation. Despite the tendency for 1,3-dienes to undergo telomerization (or dimerization) reactions, no such products were observed among the Pd- and Ni-catalyzed reactions described in Table 3.

### Table 3. Catalytic Carboxylation of Dienes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst/Ligand</th>
<th>Conditions</th>
<th>Product</th>
<th>Max TON</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Pd(COD)Cl2 dcpe</td>
<td>0.1 mmol 1.1 eq. 2-FPhONa (300 eq.) Zn (100 eq.) CO2 (20 atm) THF, 145°C</td>
<td></td>
<td>24</td>
<td>98</td>
</tr>
<tr>
<td>1b</td>
<td>Pd-1</td>
<td>0.025 – 5 mol% AlR3 (0.25 – 1.5 eq.) CO2 (1 atm) DMF or THF 18 examples Up to 97% yield</td>
<td></td>
<td>50</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>NiBr4(TBA)2</td>
<td>5 – 10 mol% Mn CO2 (1 atm) DMA, 50°C</td>
<td></td>
<td>17.8</td>
<td>100</td>
</tr>
</tbody>
</table>

In the presence of the weak phenoxide base sodium 2-fluorophenoxide (2-FPhONa) and zinc, modest TONs of 24 and 50 were achieved for the carboxylation of 1,3-butadiene and 1,3-pentadiene, respectively (Table 3, entries 1a and 1b). A pincer-type Pd(II) complex developed by Iwasawa et al. was capable of much higher catalytic activity, achieving a TON of more than 500 for the carboxylation of substituted dienes (Table 3, entry 2). This system demonstrated excellent functional group tolerance and afforded yields of up to 97%. A site-selective Ni catalyst has also been reported that utilizes a modified 1,10-phenanthroline ligand (L10) to achieve selectivity for 1,4-dicarboxylation. Despite the tendency for 1,3-dienes to undergo telomerization (or dimerization) reactions, no such products were observed among the Pd- and Ni-catalyzed reactions described in Table 3.
Dicarboxylation reactions have also been carried out using allenes (1,2-dienes) as substrates (Scheme 15, top). In 2005, Mori et al. reported the Ni-catalyzed functionalization of silyl-substituted allenes in the presence of an excess of DBU and Me₂Zn. A base-free mono-carboxylation reaction was reported by Iwasawa and coworkers in 2004 catalyzed by their previously reported Pd-I complex (Scheme 15, middle). Although stoichiometric amounts of the reducing agent Et₃Al were required, quantitative yields were achieved with low catalyst loading. The use of aryl-substituted allenes as substrates resulted in intramolecular cyclization reactions catalyzed by Pd complexes in the presence of diethyl zinc (Scheme 15, bottom).

**Scheme 15. Catalytic coupling of CO₂ and allenes**

![Scheme 15 Diagram](image)
Similar intramolecular cyclization reactions were observed from the Ni-catalyzed coupling of CO$_2$ with enynes. In 2011, Sato et al. reported the total synthesis of (-)-corynantheidine from the carboxylation of L-tryptophan in the presence of Ni(COD)$_2$ and an excess of DBU and Et$_2$Zn (Scheme 16).$^{104}$ Related Ni systems have been reported to facilitate the cyclization of similar enynes with remarkable functional group tolerance (Scheme 17, top).$^{105,106}$ This methodology was also applied to the carboxylative cyclization of diynes with high regio- and stereoselectivity (Scheme 17, bottom).$^{107}$ However, all of these Ni systems required the presence of stoichiometric additives such as diethyl zinc, which is an extremely reactive reagent and that would be impractical for use in large-scale syntheses.

**Scheme 16. Carboxylation of L-tryptophan for the synthesis of (-)-corynantheidine**

**Scheme 17. Carboxylative cyclization of enynes and diynes**
1.4.3 Catalytic Coupling of CO$_2$ with Olefins

The catalytic coupling of CO$_2$ with olefins, specifically ethylene, has been the focus of many investigations over the last 50 years.$^{108,109}$ Production of acrylic acid or acrylate derivatives from CO$_2$ is considered to be a “dream reaction” due to the industrial significance of these materials.$^{23,24}$ However, the catalytic coupling of CO$_2$ and ethylene has proven to be a considerable challenge (vide infra). Substituted alkenes on the other hand have been successfully coupled with CO$_2$ in reactions mediated by numerous transition metal complexes.

In 2008, Rovis et al. reported the Ni-mediated carboxylation of styrenes aided by the addition of Et$_2$Zn (Scheme 18, top).$^{110}$ Mechanistic and DFT calculations revealed that Et$_2$Zn was acting as both a hydride hydrogen source as well as a Lewis acid that assists the reaction of the intermediate Ni-benzyl species with CO$_2$.$^{111}$ A similar Ni catalyst was later

Scheme 18. Catalytic carboxylation of styrenes

- Ni(acac)$_2$ (10 mol%)
- CsCO$_3$ (20 mol%)
- CO$_2$ (1 atm)
- Et$_2$Zn (2.5 eq.)
- THF, 25°C

- NiCl$_2$ H$_2$O (5 mol%)
- L12 (5 mol%)
- CO$_2$ (1 atm)
- Mn, H$_2$O (9 eq.)
- DMA

1) FeCl$_2$ (1 mol%)
- L13 (1 mol%)
- EtMgBr (1.2 eq.)
- THF, 25°C

2) CO$_2$ (1 atm)

13 examples
Up to 92% yield
Max TON = 9.2

23 examples
Up to 91% yield
Max TON = 18.2

15 examples
Up to 93% yield
Max TON = 93

13 examples
Up to 92% yield
Max TON = 18.4
reported by Martin et al. that utilized water as a hydrogen source (Scheme 18, middle).\textsuperscript{112} Using a modified 1,10-phenanthroline ligand (L\textsubscript{12}) and Mn as a reductant, high yields of carboxylic acids were obtained with an improved substrate scope from the Et\textsubscript{2}Zn-mediated system. Grignard reagents have also been used to promote the reaction of CO\textsubscript{2} and styrene in the presence of Fe and Ti complexes.\textsuperscript{113, 114} The two-step reaction of styrene and Grignard followed by exposure to CO\textsubscript{2} resulted in the formation of phenyl acetic acids in high yields (Scheme 18, bottom). Relatively low catalyst loading was employed in the Fe-system, allowing for higher overall TONs.

This same titanium system was found to be effective for carboxylation reactions with terminal alkenes, although the substrate scope was somewhat decreased (Scheme 19, top).\textsuperscript{114} Olefins substituted with electron withdrawing groups have been coupled with CO\textsubscript{2} in the presence of a cobalt catalyst and Et\textsubscript{2}Zn in a mechanism similar to the that proposed for Ni/Et\textsubscript{2}Zn styrene carboxylation (Scheme 19, bottom).\textsuperscript{115, 116} However, the incorporation of stoichiometric additives in these reactions is undesirable. The direct coupling of CO\textsubscript{2} with olefins to yield acrylic acid or similar \(\alpha,\beta\)-unsaturated carboxylic acids is more atom efficient and straightforward approach that would avoid the potential for side reactions or similar complications that could arise with the incorporation of additives. As the above discussion has demonstrated, the insertion of CO\textsubscript{2} into unactivated carbon bonds is not trivial.

\textbf{Scheme 19. Catalytic carboxylation of substituted olefins}

1) Cp\textsubscript{2}TiCl\textsubscript{2} (5 mol\%)
2) LiBr (1.1 eq.)
3) iPrMgCl (1.1 eq.)
4) Et\textsubscript{2}O, 30°C
5) CO\textsubscript{2} (1 atm)

10 examples
Max TON = 17.4

\textbf{FWG = CN}
17 examples
Up to 99% yield
Max TON = 19.8

\textbf{EWG = C(O)NR\textsubscript{2}}
37 examples
Up to 99% yield
Max TON = 19.8
1.5 Transition-Metal Mediated Coupling of CO$_2$ and Ethylene

Decades of research has been conducted in pursuit of coupling CO$_2$ and ethylene to produce acrylic acid (or its derivatives). The first instance of CO$_2$-ethylene coupling by a homogeneous transition metal complex was reported by Hoberg in 1983 with the isolation of the 5-membered nickel-lactone, now known as the Hoberg complex.$^{117}$ In the nearly 40 years since, a wealth of information has been gathered on nickel-mediated reactions between CO$_2$ and ethylene as well as investigations into the reactivity of Ni-lactones (see Chapter 2).

However, nickel is by no means the only metal that has been reported to facilitate this reaction. The early transition metals titanium and zirconium have also demonstrated the ability to form metallocycles with ethylene and CO$_2$.\textsuperscript{118,119} However there have been no noteworthy developments for the production of acrylate with these metals, likely due to their extreme oxophilicity. Later transition metals such as molybdenum and tungsten have attracted more attention relative to their earlier d-block counterparts.

1.5.1 Molybdenum and Tungsten Mediated Reactions

Seminal reports from Carmona \textit{et al.} revealed the formation of bimetallic complexes featuring a bridging acrylate group from the reaction of Mo$^0$ and W$^0$ complexes with ethylene and CO$_2$ (Scheme 20, left).\textsuperscript{120,121} The same dimerization was observed when the Mo complexes featuring the chelating Triphos ligand were examined (Scheme 20, left).\textsuperscript{122} However, trimethylphosphite-ligated complexes were found to yield monomeric acrylate complexes upon addition of CO$_2$ (Scheme 20, right).\textsuperscript{123} Wolfe and Bernskoetter reported the rapid isomerization of the W-acrylate complex, whereas the Mo-acrylate complex reported by Galindo \textit{et al.} did not undergo isomerization.\textsuperscript{123,124}
Although the reactivity of dimeric Mo and W complexes was found to vary slightly, both yielded propionate monomers upon the addition of donor ligand in the presence of H₂ or acrylate monomers in the absence of H₂. Subsequent investigations from Bernskoetter et al. revealed that tris-ethylene Mo complexes featuring tridentate ligands are also capable of producing Mo-propionate species without observed dimerization (Scheme 20, bottom). Free methyl acrylate was obtained from (P(OMe)₃)₄W-acrylate complexes following the addition of excess methyl iodide (MeI) (Scheme 20, right).
1.5.2 Catalytic Acrylate Production

Despite the advances in Mo- and W-mediated coupling of CO$_2$ and acrylate, there have yet to be reports of catalytic activity using these metals. In fact, the only homogeneous metal catalysts that have been reported for CO$_2$-ethylene coupling to yield acrylates have been Ni, Pd, or Ru complexes. In 2015, Limbach et al. reported the first palladium-catalyzed acrylate production using Pd(COD)Cl$_2$ with dcpe (Table 4, entry 1).$^{126}$ A TON of 29 was achieved in the presence of a weak sodium phenoxide base and zinc. This Pd-system was later improved upon to achieve a max TON of 106 under similar conditions (Table 4, entry 2).$^{98}$ The only report of ruthenium-catalyzed acrylate production was reported by Iwasawa et al. in 2019.$^{127}$ The tetra-dentate phosphine complex Ru(PP$_3$)(C$_2$H$_4$) managed a modest TON of 6 in the presence of KOrBu (Table 4, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Ligand</th>
<th>Additives</th>
<th>Conditions</th>
<th>TON</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(COD)Cl$_2$ 0.1 mmol</td>
<td>dcpe (1.1 eq.)</td>
<td>ONa (100 eq.)</td>
<td>10 bar C$_2$H$_4$ 20 bar CO$_2$ THF, 145°C, 20 h</td>
<td>29</td>
<td>$^{126}$</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh$_3$)$_4$ 0.01 mmol</td>
<td>dcpe (1.1 eq.)</td>
<td>–</td>
<td>10 bar C$_2$H$_4$ 20 bar CO$_2$ Anisole, 145°C, 20 h</td>
<td>106</td>
<td>$^{98}$</td>
</tr>
<tr>
<td>3</td>
<td>Ru(PP$_3$)(C$_2$H$_4$)$_2$ 0.01 mmol</td>
<td>–</td>
<td>KOrBu (250 eq.)</td>
<td>1.5 MPa C$_2$H$_4$ 1.5 MPa CO$_2$ DMA, 140°C, 20 h</td>
<td>6</td>
<td>$^{127}$</td>
</tr>
</tbody>
</table>
1.6 Perspective and Relevance of Current Studies

Apart from these few examples, all the reported catalysts for CO$_2$–ethylene coupling are Ni-based complexes (see Chapter 2). Following the first reports of nickel-catalyzed acrylate production in 2012,$^{128}$ several investigations were carried out with the aim of improving catalytic activity. From these, a complex multi-component catalytic system was developed that utilized numerous additives to achieve TONs of approximately 100 (see Chapter 2). Specifically, the use of Ni$^0$ complexes featuring stereogenic phosphine ligands with rigid backbones were found to be particularly effective catalysts when the reactions were carried out in the presence of a weak sodium phenoxide base, Lewis acid, and zinc. However, an in-depth understanding of the relative roles of the various reaction components was lacking.

The investigations detailed in Chapter 2 address the need for a more complete understanding of the roles of these additives within Ni-mediated CO$_2$-ethylene coupling reactions. Through systematic modifications to the steric environment of bidentate phosphine ligands, as well as a thorough investigation into the effect of base steric and electronics, subtle relationships were observed that had previously gone unnoticed. Additional insight was gained into the role of Lewis acid with respect to cation/anion pairing and reaction intermediates never previously isolated were characterized and examined for catalytic viability.

Ultimately, the results discussed within Chapter 2 highlighted the need to develop novel, non-nickel complexes for CO$_2$ – ethylene coupling. The slowed rate of progress within nickel-based systems and the increasing use of additives are problematic for larger scale application. Iron mediated CO$_2$ – ethylene coupling has been largely unexplored
despite the potential that Group VIII metals have in overcoming the challenges faced by Group VI and Group X metals. The handful of accounts that have probed Fe-mediated CO$_2$-ethylene coupling have achieved mixed results, with most failing to yield acrylate products. Chapter 3 provides much needed insight into the reactivity of iron complexes towards CO$_2$ and ethylene. The results discussed in Chapter 3 may serve as a building block for future investigations toward the aim of iron-catalyzed acrylate production.

Chapter 4 details the iron-catalyzed dehydrogenative coupling of alcohols and secondary amine to yield amines. The field of catalytic amide production from alcohols and amines has been dominated by precious metal catalysts, which are toxic and expensive. A previously reported five-coordinate iron(II) compound was found to be the most active base metal catalyst for this reaction upon publication. The investigations discussed in Chapter 4 examine the substrate scope and mechanism of this transformation.
1.7 References


120. Alvarez, R.; Carmona, E.; Cole-Hamilton, D. J.; Galindo, A.; Gutiérrez-Puebla, E.; Monge, A.; Poveda, M. L.; Ruiz, C., Formation of Acrylic Acid Derivatives from


CHAPTER 2

Catalytic Acrylate Formation Catalyzed by Nickel(0) Complexes Bearing Bidentate Phosphine Ligands

2.1 Introduction: Acrylate Production from Ethylene–CO\textsubscript{2} Coupling

Acrylic acid and its derivatives comprise a group of highly valuable commodity chemicals used for the production of a wide variety of materials including superabsorbent polymers, adhesives, coatings, detergents, and fabrics.\textsuperscript{1} The estimated global market in 2020 was 8.7 million tons, valued at 22.55 billion USD.\textsuperscript{2} Large-scale production of acrylic acid currently employs a two-step oxidation process wherein propene is oxidized to form acrolein – a highly toxic and unstable intermediate – and then subsequently oxidized to acrylic acid in a separate reactor.\textsuperscript{3} Whereas fossil fuels are the primary carbon source in propylene oxidation, the production of acrylic acid via the coupling of ethylene (which can be derived from biomass) with carbon dioxide (CO\textsubscript{2}) represents a more environmentally friendly alternative.

2.1.1 Stoichiometric Ethylene-CO\textsubscript{2} Coupling and Nickelalactone Reactivity

The first demonstration of the successful nickel-mediated coupling of ethylene and carbon dioxide was reported by Hoberg \textit{et al.} in 1983.\textsuperscript{4} The resulting five-membered nickelalactone (Ni-lactone), or “Hoberg complex,” was found to be notably stable, undergoing subsequent reactions only in the presence of harsh or coordinating reagents such as hydrochloric acid, methanol, or carbon monoxide to yield the corresponding
organic products (Scheme 1). For many decades, nickel studies utilized a small group of bidentate nitrogen- and phosphorous-containing ligands: bipyridine (bpy; Table 1, entries 1-6), tetra-methylethylenediamine (TMEDA; Table 1, entry 7-9), bis(diphenylphosphino)ethane) (dppe; Table 1, entry 10 and 11), and its congener bis(dicyclohexylphosphino)ethane (dcpe; Table 1, entry 12 and 13).

### Scheme 1. Synthesis and reactivity of the Hoberg complex

![Chemical structure for Scheme 1.]

**Table 1. Ligand Scope Utilized in Studies Between 1982 and 2004**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Reagents</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>bpy</td>
<td>CO₂</td>
<td>[Ni]</td>
<td>85</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>[Ni]</td>
<td>60</td>
<td>8</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>R−R−CO₂</td>
<td>[Ni]</td>
<td>R = Me: 87</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>R−R−CO₂</td>
<td>[Ni]</td>
<td>R = Ph: 48</td>
<td>5</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>H-X, R-X</td>
<td>[Ni]</td>
<td>COOH</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>H-X, R-X</td>
<td>[Ni]</td>
<td>COOH</td>
<td>76</td>
</tr>
</tbody>
</table>
The broad variety of reagents employed in these early studies make direct ligand comparisons difficult, although monodentate phosphine ligands were demonstrated to be ineffective for CO$_2$ functionalization. Historically, the conversion of Ni-lactones into organic products was limited to sub-stoichiometric yields and relied on similarly harsh conditions to those reported by Hoberg.\textsuperscript{4-9} Computational investigations eventually confirmed the stability of the Hoberg complex, with a $\Delta G = -36.2$ kcal mol$^{-1}$ relative to the parent nickel complex + CO$_2$ + ethylene.\textsuperscript{13} However, shortly after this computational work by Aresta \textit{et al.}, a more broad ligand survey was carried out that demonstrated the profound effect of ligand selection on the reactivity of Ni-lactones.\textsuperscript{14}

Walther \textit{et al.} reported a small library of chelating nitrogen- and phosphorous-containing ligands that varied in “tether length” (the number of bonds between coordinating atoms) as well as their steric and electronic environments (Table 2).\textsuperscript{14} A

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Reagents</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>MeNMe</td>
<td>R==R CO$_2$</td>
<td>R = Me: 58</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>MeNMe</td>
<td>R==R CO$_2$</td>
<td>R = Ph: 42</td>
<td></td>
<td>9</td>
</tr>
<tr>
<td>9</td>
<td>[Ni]</td>
<td>O=O H-X, R-X</td>
<td>R = COOH</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>dppe</td>
<td>R = Ph</td>
<td>O==O</td>
<td>33</td>
<td>8</td>
</tr>
<tr>
<td>11</td>
<td>dppe</td>
<td>R = Ph</td>
<td>R = CO$_2$</td>
<td>50</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>dcpe</td>
<td>R = Cy</td>
<td>R == R CO$_2$</td>
<td>R = Me: 89</td>
<td>5</td>
</tr>
<tr>
<td>13</td>
<td>dcpe</td>
<td>R = Cy</td>
<td>R == R CO$_2$</td>
<td>R = H: 60</td>
<td>5</td>
</tr>
</tbody>
</table>

\textsuperscript{a} In addition to the ligands listed above, there were single reports of similar nitrogen- or phosphorous-containing ligands such as DBU\textsuperscript{10} and dcpe-pyridine.\textsuperscript{11}
majority of surveyed ligands underwent simple ligand substitution reactions to yield the corresponding Ni-lactone (Table 2, entries 1-5) and a small subset resulted in the reductive disproportionation of CO$_2$ and ethylene (Table 2, entries 6-7b). However, reactions carried out in the presence of bis(diphenylphosphino)methane (dppm) resulted in the first
instance of β-hydride elimination from an ethylene-derived Ni-lactone,* resulting in the formation of a bimetallic acrylate-hydride nickel complex (Table 2, entry 7c).¹⁴ Although this complex was ultimately unable to yield free acrylate, and catalytically incompetent due to concomitant ligand activation, these findings remain significant because they represent the first ligand-directed change in reactivity of the otherwise-stable Ni-lactone.

Liberation of free carboxylate-containing products from Ni-lactones has historically been achieve in one of four ways: protonolysis via a strong acid to yield the corresponding carboxylic acid (Scheme 1, top),⁴, ⁶, ⁷, ¹⁵ alcoholyis via methanol or ethanol and hydrochloric acid to yield the corresponding ester (Scheme 1, middle),⁴, ⁵, ¹¹, ¹⁶ carbonylation in the presence of CO to yield cyclic anhydrides (Scheme 1, bottom),⁴, ⁵, ⁸, ¹¹ and reaction with alkyl electrophiles to yield the corresponding alkylated ester.⁹, ¹⁶-¹⁸ However, these reactions were conducted with little to no deviation from the small group of commonly used ligands (Table 1). Not until a 2011 report from Kühn and co-workers was the choice of ligand demonstrated to play a substantial role in the liberation of free acrylate products from isolated Ni-lactones (Table 3).¹⁹

Cleavage of Ni-lactones was achieved in the presence of an excess of methyl iodide (MeI), resulting in the formation of free methyl acrylate.¹⁹ The ethyl-linked TMEDA- and dppe-complexes were the most effective, achieving respective yields of 56% and 48% (Table 3, entries 1 and 2). The yield of methyl acrylate decreased with each successive carbon that was added to the ligand backbone, with the propyl-linked dppp achieving 29% yield and the butyl-linked dppb producing no methyl acrylate (Table 3, entries 3 and 4).

* Thermolysis of a styrene-derived Ni-lactone was reported in 1986 to result in β-hydride elimination.⁶
The monodentate pyridine ligand was also found to be unproductive for methyl acrylate, although a lesser amount of MeI was used (Table 3, entry 5). The authors concluded that ligands containing sp$^2$-donor atoms such as pyridine are unfavorable for the reaction of Ni-lactones with MeI, as they bind more closely with the metal center and limit rotation of the ligand about the nickel center.\textsuperscript{19} The variation in reactivity among the sp$^3$-hybridized ligands was attributed to their respective bite angles, with larger bite angles resulting in a more crowded Ni center and impeding β-hydride elimination.\textsuperscript{19} Despite the unfavorable thermodynamics computed by Aresta et al., the results presented by Walther and Kühn demonstrate that conversion of Ni-lactones is in fact possible given the right set of circumstances.\textsuperscript{13,14,19}

2.1.2 Catalytic Acrylate Production from Ethylene and CO$_2$

There have been limited reports of palladium\textsuperscript{20} and ruthenium\textsuperscript{21} catalysts that were able to achieve catalytic turnover, however these catalysts were far inferior to the nickel-based system and will not be part of the discussion here (see Chapter 1). Following the publication of our work, there were a small number of reports that investigated nickel catalysts featuring N-heterocyclic carbene (NHC) ligands. The most active of these catalysts managed a TON of 450 but required an extreme excess of base (1200 eq.) and Lewis acid in order to reach levels of catalytic activity that were comparable to those we

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TMEDA</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>dppe</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>dppp</td>
<td>29</td>
</tr>
<tr>
<td>4</td>
<td>dppb</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Py</td>
<td>0$^c$</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 0.2 mmol nickelalactone, 0.6 mL CD$_2$Cl$_2$.  
$^b$ Determined by $^1$H NMR analysis with an internal standard.  
$^c$ Conditions: as in [a] 10 eq. CH$_3$I.
reported in 2018 (*vide infra*).\textsuperscript{22} More recently, a nickel complex featuring a NHC-pyridine ligand was published, although a max TON of 8 was reported for this system.\textsuperscript{23}

The first account of catalytic acrylate production from the coupling of CO\textsubscript{2} and ethylene was published by Limbach *et al.* in 2012, though their use of the term “catalytic” has been criticized by many in the field.\textsuperscript{24} Initial investigations focused on optimization of each step in a proposed catalytic cycle (Figure 1): oxidative coupling of ethylene and CO\textsubscript{2} to yield a Ni-lactone, cleavage of the Ni-lactone to form an $\eta^2$-acrylate complex, and ligand substitution of acrylate with ethylene. A small family of diphenyl- and di-tert-butyl-substituted phosphine ligands with varying tether lengths were surveyed for their ability to form Ni-lactones in the presence of Ni(COD)$_2$ (COD = 1,5-cyclooctadiene), ethylene, and CO\textsubscript{2} (Table 4).\textsuperscript{24} Variation of the steric parameters and tether length of the ligand was found to have a considerable effect on product formation.

Phenyl-substituted diphosphines were found to be ineffective for lactone formation, yielding instead nickel aggregates in the case of dppm (Table 4, entry 1) and bis-ligated
nickel complexes in the case of dppe and dppp (Table 4, entries 2 and 3), the formation of which render the Ni complex impotent due to the inability of ethylene and CO$_2$ to coordinate to the metal center. Increasing the steric bulk of the phosphine substituents from phenyl to tert-butyl successfully prevented the formation of bis-ligated complexes (Table 4, entries 4-6). Additionally, tether length was found to directly affect reactivity, in agreement with the findings from Walther’s 2006 ligand survey (Table 2) and Kühn’s MeI studies (Table 3). The methyl- and propyl-linked ligands dtbpm and dtbpp resulted in selective formation of the Ni-lactone and Ni-ethylene complex respectively (Table 4, entries 4 and 6); whereas the ethyl-linked dtbpe resulted in a mixture of the two (Table 4, entry 5). Although the authors did not offer insight into the possible mechanism underlying these variations in reactivity, it can be inferred that the increased bite angle of the propyl-linked relative to the methyl-linked diphosphine impedes the formation of the Ni-lactone.

Given that the (dtbpm)Ni-lactone was found to decompose upon release of ethylene and CO$_2$, the (dtbpe)Ni-lactone was used for subsequent investigations, as it proved to be isolable and stable for several months. Following the initial ligand survey, efforts turned to

### Table 4. Effect of Tether Length on Ni-Lactone Formation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>n</th>
<th>Yield (%) $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppm</td>
<td>Ph</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>dppe</td>
<td>Ph</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>dppp</td>
<td>Ph</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>dtbpm</td>
<td>tBu</td>
<td>1</td>
<td>60 $^c$</td>
</tr>
<tr>
<td>5</td>
<td>dtbpe</td>
<td>tBu</td>
<td>2</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>dtbpp</td>
<td>tBu</td>
<td>3</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$Conditions: 65 μmol Ni(COD)$_2$, 1 eq. ligand, 2 bar C$_2$H$_4$, 6 bar CO$_2$, THF-d$_8$, 50°C, 72 h. $^b$Yield determined by $^{31}$P NMR spectroscopy. $^c$Conditions: as in [a] 25 C, 19 h.
optimization of what is widely believed to be the most challenging step in the catalytic cycle – cleavage of the Ni-lactone. Inspired by computational work by Buntine et al.\textsuperscript{25} that investigated base-mediated deprotonation of a Ni-lactone, the authors screened a variety of bases for their effectiveness to convert the isolated (d/tbpe)Ni-lactone into the corresponding $\eta^2$-acrylate complex. The strong alkoxide base sodium tert-butoxide (NaOtBu) was found to induce such a transformation readily under ambient conditions, resulting in 90\% yield of (d/tbpe)Ni($\eta^2$-CH$_2$CHCOONa). Density functional theory (DFT) calculations found that the incorporation of a sodium base lowered the kinetic barrier for Ni-lactone cleavage from +105 to +98 kJ mol$^{-1}$, an observation that was attributed to the ability of the Lewis acidic Na$^+$ to stabilize carboxylate intermediates. Additionally, these calculations revealed that the overall Gibbs free energy for the formation of sodium acrylate from ethylene and CO$_2$ was exothermic ($\Delta$G = -59 kJ mol$^{-1}$), a substantial finding given that acrylic acid production from ethylene and CO$_2$ is calculated to be mildly endothermic ($\Delta$G = +42. kJ mol$^{-1}$) in gas phase.\textsuperscript{26}

The final step in the proposed catalytic cycle, exchange of the $\eta^2$-acrylate with ethylene, was found to occur readily when isolated samples of (d/tbpe)Ni($\eta^2$-CH$_2$CHCOONa) were exposed to elevated pressures of ethylene (<30 bar). Having completed the optimization of each individual step, efforts turned to assembling the catalytic cycle. Due to the irreversible reaction of NaOtBu with CO$_2$ to form carbonate, the catalytic cycle was split into two steps: a CO$_2$-rich step, and a CO$_2$-poor step. However, this resulted in an arduous set of conditions that required multiple pressurization/depressurization steps repeated over numerous cycles in order to achieve catalytic activity. Although this seminal report represents a considerable breakthrough after decades of
stalled efforts, catalytic activity was disappointingly low, achieving a turnover number (TON) of 10. Furthermore, the conditions required to accomplish this low-level catalysis were cumbersome and impractical for use.

2.1.3 Effect of Additives on Acrylate Formation: Lewis Acid

In the case of Limbach’s 2012 report, the incorporation of NaO\textsubscript{t}Bu proved to be of substantial importance from both a thermodynamic and kinetic standpoint by (a) shifting the overall reaction energy to one that is thermodynamically favorable ($\Delta G = -59$ kJ mol\textsuperscript{-1}) and (b) lowering the kinetic barrier for Ni-lactone cleavage via stabilization of intermediates by the Lewis acidic sodium cation. Similar stabilizing effects were observed in the reaction of Ni-lactones with methyl iodide wherein the Lewis acidic Me\textsuperscript{+} was found to assist in Ni-O bond cleavage, as demonstrated by Rieger \textit{et al.} The theory that Lewis acids stabilize and assist in ring-opening reactions was reinforced in subsequent reports from our laboratories.

The neutral Lewis acid tris(pentafluorophenyl)borane (BAr\textsubscript{3}F) was found to facilitate reversible $\beta$-hydride elimination from the diphosphine-ligated five-membered $\gamma$-lactone (dppf)Ni(CH\textsubscript{2}CH\textsubscript{2}COO) (dppf = bis(diphenylphosphino)ferrocene), eventually giving way to the formation of a four-membered $\beta$-lactone resulting from 2,1-insertion of a transient nickel hydride (Scheme 2). The reactivity of the newly formed $\beta$-lactone was such that mild organic bases such as DBU (DBU = 1,8-diaza-bicyclo(5.4.0)undec-7-ene) or BTPP (BTPP = \textit{tert}-butyliminotri(pyrrolidino)phosphorane) were sufficient for deprotonation and subsequent release of acrylate, whereas the parent five-membered $\gamma$-lactone can only be deprotonated by strong bases that are incompatible with CO\textsubscript{2}. 


Although the dppf-ligated nickel complex utilized in these investigations proved to be ineffective for ethylene-CO$_2$ coupling, successive studies performed on Ni-lactones produced from ethylene and CO$_2$ were found to undergo similar β-hydride elimination and ring isomerization.$^{28}$ The reaction of tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (NaBAr$_4^+$) with (dcpe)Ni(CH$_2$CH$_2$COO) resulted in the coordination of the Na$^+$ cation, elongation of the Ni-O bond, and γ- to β-lactone isomerization at elevated temperatures. DFT calculations revealed the isomerization pathway was nearly 40 kJ mol$^{-1}$ lower in energy in the presence of sodium and the resulting β-lactone was found to be <9 kJ mol$^{-1}$ more stable than the parent γ-lactone.$^{28}$ These findings, supplemented by the results from the methyl iodide$^{19, 26}$ and sodium tert-butoxide studies,$^{24}$ established the importance of Lewis acids in improving the reactivity of Ni-lactones.

2.1.4 Effect of Additives on Acrylate Formation: Zinc

In 2014, Vogt et al. demonstrated the cumulative effects of incorporating both Lewis acid and base into the catalytic coupling of ethylene and CO$_2$ to form acrylate.$^{29}$ Preliminary DFT studies found that the energy barrier for β-hydride elimination from a lithium-stabilized Ni-lactone was 20 kJ mol$^{-1}$ lower in energy than the sodium congener and 42 kJ mol$^{-1}$ lower in energy than the non-stabilized reaction.$^{29}$ Experimental investigations were carried out wherein the isolated Ni-lactone (dppe)Ni(CH$_2$CH$_2$COO) was treated with various Lewis acids. In agreement with the DFT calculations, lithium
iodide (LiI) was found to result in considerably higher yields of free acrylate than its sodium analogue (73% and 4%, respectively). Additionally, the use of non-iodide containing salts afforded limited acrylate with lithium bromide and lithium chloride achieving 8% and 3% yields, respectively. When the weak base triethylamine (Et₃N) was used in tandem with LiI, a near quantitative yield of lithium acrylate was observed. This increase in conversion was attributed to the suppression of by-product formation such as HI and lithium propionate. Additionally, the parent lactone (dppe)Ni(CH₂CH₂COO) was found to be completely converted into (dppe)NiI₂, a species believed to be catalytically inactive; therefore, zinc dust (Zn) was included as a reducing agent.\(^{29}\)

Having confirmed the effectiveness of LiI to cleave isolated Ni-lactones and identified the need to reduce off-cycle Ni(II) species, the authors set out to optimize the catalytic formation of lithium acrylate (Table 5). While LiI and Et₃N were found to be incapable of producing catalytic TON independently, their concurrent use resulted in a TON of 1 (Table 5, entries 2-4a). However, when LiI, Et₃N, and Zn were all incorporated into the reaction mixture, a TON of 8 was achieved (Table 5, entry 4b). Interestingly, the combination of LiI and Zn was alone

### Table 5. Combined Effects of Lewis Acid, Base, and Zinc on Catalysis \(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>MX</th>
<th>Base</th>
<th>Red.</th>
<th>TON (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>LiI</td>
<td>–</td>
<td>–</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>Et₃N</td>
<td>–</td>
<td>0</td>
</tr>
<tr>
<td>4a</td>
<td>LiI</td>
<td>–</td>
<td>–</td>
<td>1</td>
</tr>
<tr>
<td>4b</td>
<td>LiI</td>
<td>Et₃N</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>4c</td>
<td>LiI</td>
<td>–</td>
<td>Zn</td>
<td>2</td>
</tr>
<tr>
<td>4d</td>
<td>–</td>
<td>Et₃N</td>
<td>Zn</td>
<td>0</td>
</tr>
<tr>
<td>5a</td>
<td>NaI</td>
<td>Et₃N</td>
<td>Zn</td>
<td>&lt;1</td>
</tr>
<tr>
<td>5b</td>
<td>LiBr</td>
<td>Et₃N</td>
<td>Zn</td>
<td>1</td>
</tr>
<tr>
<td>5c</td>
<td>LiCl</td>
<td>Et₃N</td>
<td>Zn</td>
<td>&lt;1</td>
</tr>
<tr>
<td>6a</td>
<td>LiI</td>
<td>DIPEA</td>
<td>Zn</td>
<td>1</td>
</tr>
<tr>
<td>6b</td>
<td>LiI</td>
<td>K₂CO₃</td>
<td>Zn</td>
<td>2</td>
</tr>
<tr>
<td>6c</td>
<td>LiI</td>
<td>Cs₂CO₃</td>
<td>Zn</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 50 μmol Ni(COD)₂, 50 μmol depe, 1.5 mmol MX, 2.5 mmol base, 2.5 mmol Zn, 2 mL PhCl, 10 bar CH₄, 20 bar CO₂, 72 h, 50°C. \(^b\) Determined by \(^1\)H NMR spectroscopy.
enough to produce a TON of 2; whereas the combination of Et$_3$N and Zn failed to achieve catalytic turnover (Table 5, entries 4c and 4d). These findings confirm the importance of both a Lewis acid and a reductant in the catalytic cycle. In agreement with their initial findings, other Lewis acids proved to be less effective for acrylate production even in the presence of Et$_3$N and Zn (Table 5, entries 5a-c). Finally, a small variety of bases were screened but none resulted in a TON greater than 2 (Table 5, entries 6a-c).

In addition to the presence of these additives, the identity of the ligand and the ratio of ethylene/CO$_2$ were found to significantly affect catalytic activity (Table 6).$^{29}$ A ligand screen was conducted wherein the tether length and phosphine substituent were systematically varied, and, in agreement with the findings from the 2012 report from Limbach et al.$^{24}$ the methyl-linked dcpm was found to be insufficient for acrylate production even in the presence of LiI, Et$_3$N, and Zn (Table 6, entries 1a and 1b). Dicyclohexyl-substituted phosphines linked by 2-, 3- and 4-carbon bridges were all capable of achieving catalytic turnover in the presence of LiI and Et$_3$N, but TON was enhanced in upon the addition of Zn (Table 6, entries 2a-4b). Of these, dcpe and dcpp resulted in the highest TONs of 8 and 9 respectively (Table 6, entries 2b and 3) and were therefore selected to examine the effect varying the ethylene/CO$_2$ ratio on catalytic activity.

Increasing the partial pressure of ethylene had a favorable effect on TON with the optimized pressures of ethylene : CO$_2$ found to be 25:5 bar (Table 6, entries 5a-6c). Finally, the phenyl-substituted dppe was found to result in a lower TON than its cyclohexyl-substituted counterpart (Table 6, entries 7a and 7b). This brief examination of ligand sterics is in agreement with previous findings that reported a preference for bulky, bidentate ligands linked by a two carbon bridge.$^{19,24}$ A maximum TON of 21 was ultimately achieved
by increasing the equivalents of LiI, Et$_3$N, and Zn relative to nickel (Table 6, entry 6c).

These results represent one of (vide infra) the first one-pot production of acrylate from CO$_2$ and ethylene.

Table 6. Effect of Tether Length, Phosphine Substituent, and Gas Ratios on TON $^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>$n$</th>
<th>R</th>
<th>Red.</th>
<th>$C_2H_4$ (bar)</th>
<th>$CO_2$ (bar)</th>
<th>TON$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>dcpm</td>
<td>1</td>
<td>Cy</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>&lt;1</td>
</tr>
<tr>
<td>1b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>10</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>2a</td>
<td>dcpe</td>
<td>2</td>
<td>Cy</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>10</td>
<td>20</td>
<td>4</td>
</tr>
<tr>
<td>3a</td>
<td>dcpp</td>
<td>3</td>
<td>Cy</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>9</td>
</tr>
<tr>
<td>3b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>10</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>4a</td>
<td>dcpb</td>
<td>4</td>
<td>Cy</td>
<td>–</td>
<td>10</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>4b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>10</td>
<td>20</td>
<td>6</td>
</tr>
<tr>
<td>5a</td>
<td>dcpe</td>
<td>2</td>
<td>Cy</td>
<td>–</td>
<td>30</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>5b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>30</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>6a</td>
<td>dcpp</td>
<td>3</td>
<td>Cy</td>
<td>–</td>
<td>25</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>6b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>25</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>6c</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>25</td>
<td>5</td>
<td>21c</td>
</tr>
<tr>
<td>7a</td>
<td>dppe</td>
<td>2</td>
<td>Ph</td>
<td>–</td>
<td>25</td>
<td>5</td>
<td>&lt;1</td>
</tr>
<tr>
<td>7b</td>
<td></td>
<td></td>
<td></td>
<td>Zn</td>
<td>25</td>
<td>5</td>
<td>8</td>
</tr>
</tbody>
</table>

$^a$ Conditions: 50 $\mu$mol Ni(COD)$_2$, 50 $\mu$mol ligand, 1.25 mmol LiI, 2.5 mmol Et$_3$N, 2.5 mmol Zn, 2 mL PhCl, 72 h, 50$^\circ$C. $^b$ Determined by $^1$H NMR spectroscopy. $^c$ Conditions: 25 $\mu$mol Ni(COD)$_2$, 25 $\mu$mol ligand, 1.25 mmol LiI, 2.5 mmol Et$_3$N, 2.5 mmol Zn, 2 mL PhCl, 72 h, 50$^\circ$C.

2.1.5 Effect of Additives on Acrylate Formation: Phenoxide Base

While Vogt and coworkers were investigating the effects of LiI with Et$_3$N and Zn on nickel-mediated acrylate production, Limbach et al. were simultaneously probing the effects of various bases on catalytic activity.$^{30}$ To overcome the challenges imposed by utilizing strong alkoxide bases, which react irreversibly with CO$_2$, weaker phenoxide bases were investigated for their ability to assist in acrylate production. Sodium 2-fluorophenoxide (2FPhONa) was found to be a weak enough base to tolerate CO$_2$ but strong enough to deprotonate their previously reported (d/bpe)Ni-lactone to yield the
corresponding $\eta^2$-acrylate complex. With this base in hand, a wide variety of ligands were examined for their propensity to facilitate catalytic acrylate formation from CO$_2$ and ethylene (Table 7).

**Table 7. Ligand Survey Conducted by Limbach et al.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>$n$</th>
<th>$R$</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>[dppe][BF$_4$]$_2$</td>
<td>2</td>
<td>Cy; P = [PH]BF$_4$</td>
<td>2</td>
</tr>
<tr>
<td>1b</td>
<td>dppe</td>
<td>2</td>
<td>Cy</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>dbpe</td>
<td>2</td>
<td>tBu</td>
<td>9</td>
</tr>
<tr>
<td>3a</td>
<td>dippe</td>
<td>2</td>
<td>iPr</td>
<td>6</td>
</tr>
<tr>
<td>3b</td>
<td>dipp</td>
<td>3</td>
<td>iPr</td>
<td>5</td>
</tr>
<tr>
<td>3c</td>
<td>dippb</td>
<td>4</td>
<td>iPr</td>
<td>2</td>
</tr>
<tr>
<td>4a</td>
<td>dcpf</td>
<td></td>
<td>PCy$_2$</td>
<td>1</td>
</tr>
<tr>
<td>4b</td>
<td>HiersoPHOS-1</td>
<td></td>
<td>PPh$_2$</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-Me-DuPhos</td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-QuinoxP*</td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>7</td>
<td>(S)-BINAPINE</td>
<td></td>
<td></td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>(S,S,R,R)-TangPhos</td>
<td></td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>

*a Conditions: 0.2 mmol Ni(COD)$_2$, 0.22 mmol ligand, 10 mmol 3-FPhONa, 5 bar C$_2$H$_4$, 10 bar CO$_2$, 30 mL THF unless otherwise noted, 20 h, 80°C.
The ligand screen that was carried out examined ligands connected by both sp$^3$- and sp$^2$-hybridized carbons as well as alkyl and cyclic phosphines. Additionally, the phosphine substituents were varied to include a range of steric environments. Among the sp$^3$-linked diphosphines, the steric of the substituents was observed to have a direct effect on TON, with a more sterically bulky ligand resulting in a higher TON (Table 7, entries 1-3c). Increasing the steric from cyclohexyl to iso-propyl was found to increase TON from 3 to 6 for ethyl-linked diphosphines (Table 7, entries 1b and 3a). The cumbersome tert-butyl substituted dbphe was the highest performing of the sp$^3$-linked diphosphines, achieving a TON of 9 (Table 7, entry 2). The preference for C$_2$-linked ligands – reported numerous times prior to this investigation$^{19,24,29}$ – was again reinforced, with the C$_3$- and C$_4$-linked diphosphines performing worse than their C$_2$-linked analogue (Table 7, entries 3a-c).

More complex ligands were also surveyed with varying success. The ferrocene-based dcpf and HiersoPHOS-1 resulted in TONs of 1 and 4 respectively (Table 7, entries 4a and 4b). The chiral ligands (R,R)-Me-DuPhos and (R,R)-QuinoxP* afforded similarly low TONs of 2 and 4 respectively (Table 7, entries 5 and 6). However, the chiral ligands (S)-BINAPINE, (S,S,R,R)-TangPhos, (R,R,S,S)-DuanPhos and (R,R)-BenzP* were the

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>n</th>
<th>R</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>(R,R,S,S)-DuanPhos</td>
<td></td>
<td></td>
<td>16</td>
</tr>
<tr>
<td>10a</td>
<td>(R,R)-BenzP*</td>
<td></td>
<td></td>
<td>2 (DMF)</td>
</tr>
<tr>
<td>10b</td>
<td></td>
<td></td>
<td></td>
<td>10 (PhCl, THF)</td>
</tr>
<tr>
<td>10c</td>
<td></td>
<td></td>
<td></td>
<td>13 (dioxane)</td>
</tr>
<tr>
<td>10d</td>
<td></td>
<td></td>
<td></td>
<td>17 (toluene)</td>
</tr>
</tbody>
</table>

*Conditions: 0.2 mmol Ni(COD)$_2$, 0.22 mmol ligand, 10 mmol 3-FPhONa, 5 bar C$_2$H$_4$, 10 bar CO$_2$, 30 mL THF unless otherwise noted, 20 h, 80°C.
highest performing within the ligand survey, achieving TONs between 10 and 16 (Table 7, entries 7-9 and 10b). In addition to the ligand, solvent selection was found to have a considerable effect on TON with BenzP* affording TONs between 2 and 17 in various solvents (Table 7, entries 10a-d). Although DuanPhos performed better than BenzP* under the initial ligand survey conditions, it proved to be less active at elevated temperatures whereas BenzP* demonstrated a marked improvement in catalytic activity (Table 8, entries 6 and 7a-e).

Following the ligand screen, a small family of sodium phenoxide bases with varying steric and electronic environments were surveyed in the presence of Ni(COD)2 and BenzP* (Table 8). The addition of the electron-donating methyl substituent did little to improve the TON relative to the unsubstituted sodium phenoxide (PhONa) with TONs of 4 and 3, respectively (Table 8, entries 1-3). The presence of the electron-withdrawing fluorine substituent was shown to improve the TON; however, only when located in the ortho- or meta-positions (Table 8, entries 4-7a). The highest performing base was found to be 2-FPhONa, achieving a TON of 10 under the initial reaction conditions (Table 8, entry 7a). The degree to which a base was able to facilitate catalytic turnover was broadly attributed to their relative pKₐ value in H₂O, although there was little discussion regarding the role of sterics.³⁰

Optimization of the reaction temperature resulted in an increase in TON from 10 to 35 at 100°C, with a slight decrease to 31 observed at 120°C (Table 8, entries 7a-c). Increasing the amount of 2-FPhONa from 50 eq. to 100 eq. relative to nickel also afforded an increase in TON from 35 to 39 (Table 8, entries 7b and 7d). However, TON was
observed to nearly double from 39 to 69 upon the addition of zinc dust (Table 8, entries 7d and 7c), in agreement with the findings from Vogt et al. that the addition of a reductant improves nickel-catalyzed acrylate production.\textsuperscript{29,30} Finally, a maximum TON of 107 was achieved following an increase in base loading to 300 eq. (Table 8, entry 7g).\textsuperscript{29} The vast improvement in TON for nickel-based catalysts described in these 2014 reports

\begin{table}[h]
\centering
\caption{Base Survey Conducted by Limbach et al.\textsuperscript{a}}
\begin{tabular}{|c|c|c|c|c|c|c|c|}
\hline
Entry & Base & Base (eq.) & Temp. (°C) & C\textsubscript{2}H\textsubscript{4} (bar) & CO\textsubscript{2} (bar) & Zn (eq.) & TON (DuanPhos) \\
\hline
1 & PhONa & 50 & 80 & 5 & 10 & 0 & 3 \\
\hline
2 & 2-MePhONa & 50 & 80 & 5 & 10 & 0 & 4 \\
\hline
3 & 2,6-Me\textsubscript{2}PhONa & 50 & 80 & 5 & 10 & 0 & 4 \\
\hline
4 & 2,6-F\textsubscript{2}PhONa & 50 & 80 & 5 & 10 & 0 & 2 \\
\hline
5 & 4-FPhONa & 50 & 80 & 5 & 10 & 0 & 2 \\
\hline
6 & 3-FPhONa & 50 & 80 & 5 & 10 & 0 & 8 (16) \\
\hline
7a &  & 50 & 80 & 5 & 10 & 0 & 10 (21) \\
\hline
7b &  & 50 & 100 & 5 & 10 & 0 & 35 (24) \\
\hline
7c &  & 50 & 120 & 5 & 10 & 0 & 31 (21) \\
\hline
7d &  & 100 & 100 & 5 & 10 & 0 & 39 (31) \\
\hline
7e &  & 100 & 100 & 10 & 20 & 100 & 69 (28) \\
\hline
7f &  & 200 & 100 & 10 & 20 & 100 & 80 \\
\hline
7g &  & 300 & 100 & 10 & 20 & 100 & 107 \\
\hline
\end{tabular}
\\textsuperscript{a}Conditions: 0.2 mmol Ni(COD)\textsubscript{2}, 0.22 mmol ligand, 10 mmol sodium phenoxide, 30 mL THF, 20 h.
demonstrated the significance of including a base, Lewis acid, and reductant for the
catalytic production of acrylate from ethylene and CO₂.

2.2 Results and Discussion

Ligand structure has been demonstrated to have a direct and marked effect on
catalytic acrylate production from CO₂ and ethylene. However, systematic
investigations of ligand structure have largely been limited to variation of tether length and,
to a lesser extent, ligand substituents (vide supra). Furthermore, these reports relied on
in situ catalyst generation by mixing the selected ligand with the nickel(0) precursor
Ni(COD)₂. While this method of catalyst loading is common, there are many potentially
deleterious side reactions that could occur including the formation of bis-ligated nickel
species and thermal decomposition of Ni(COD)₂. Therefore, investigations within our lab
focused on the systematic variation of the steric environment about the BenzP phosphorous
and use of only those nickel complexes that were isolable for catalytic trials.

2.2.1 Synthesis of BenzP and Derivatives

As previous reports have demonstrated, ligands featuring non-rotating backbones
and electron-donating substituents are advantageous for the coupling of CO₂ and
ethylene. Of these, the (R,R)-(+)1,2-bis(tert-butylmethylphosphino)benzene (BenzP)
ligand has been particularly effective, resulting in the highest TON previously reported.
Given this prior art, efforts in our lab focused on conducting an in-depth structure-activity
analysis of this ligand platform. A family of BenzP derivatives were synthesized by
modification of the previously reported synthesis (Scheme 3) wherein 1,2-bis(dichloro-
phosphino)benzene was treated with 2 equivalents (eq.) of tert-butylmagnesium chloride
followed by an excess of magnesium(0) to yield 7,8-diphosphabicyclo-[4.2.0]octa-1,3,5-triene, 7,8-bis(1,1-dimethyl) \((tBu\text{-phosphacycle})\). Subsequent addition of methyl triflate to \(tBu\text{-phosphacycle}\) gave rise to the un-isolated triflate salt, which was then alkylated in the presence of various Grignard reagents to yield racemic mixtures of the corresponding BenzP derivatives.

**Scheme 3. Synthesis of BenzP and derivatives**

Using this method, two new BenzP derivatives were ultimately prepared featuring iso-propyl \((1\text{-}(\text{tert-butyl)methylphosphino})\text{-}2\text{-}(\text{tert-butyl-iso-propylphosphino})\text{benzene}; \text{iPrBenzP})\) and cyclohexyl \((1\text{-}(\text{tert-butyl)methylphosphino})\text{-}2\text{-}(\text{tert-butylcyclohexylphosphino})\text{benzene}; \text{CyBenzP})\). Although attempts to isolate other alkylated variants of the phosphacycle were unsuccessful in our hands, a third BenzP derivative was prepared via direct alkylation of 1,2-bis(dichlorophosphino)benzene with 4 eq. of iso-propylmagnesium chloride to yield 1,2-bis(di-iso-propylphosphino)benzene \((\text{iPr}_4\text{BenzP})\). Nickel(0) complexes featuring these ligands were prepared by dropwise addition of a THF/ligand solution to a THF solution of Ni(COD)\(_2\), resulting in isolable samples suitable for use in catalytic trials. New BenzP derivatives and the respective Ni-complexes were
characterized, and their purity determined by $^{31}$P and $^1$H NMR analysis. With these new complexes in hand, efforts turned to investigating their catalytic viability.

2.2.2.1 Catalytic Trails: Catalyst Comparison

Initial reaction conditions were modified from those previously reported by adjusting the ratio of ethylene : CO$_2$ in order to minimize reductive disproportionation of CO$_2$, a reaction known to occur at low valent metals.$^{24, 29, 30}$ Further optimization was carried out in the presence of (BenzP)Ni(COD), 3-FPhONa, and zinc dust (Table 9, entry 1a). The addition of 50 eq. LiI resulted in an appreciable increase in TON from 65 to 82 (Table 9, entry 1b). However, increasing the loading of LiI or zinc further resulted in no additional enhancement of TON (Table 9, entries 1c-e). Therefore, subsequent trials were carried out in the presence of 100 eq. Zn and 50 eq. LiI.

Examination of the catalytic activity of BenzP variants was conducted in reference to isolated samples of (dcpp)- and (dcpe)Ni(COD), as these ligands have been previously reported to facilitate catalytic acrylate formation.$^{29, 30}$ Under the previously optimized reaction conditions, the C$_3$-linked dcpp-Ni complex was found to be slightly more active than the C$_2$-linked analogue, achieving TONs of 22 and 6, respectively (Table 9, entries 2c and 2e). Prior studies that have examined the C$_2$- vs C$_3$-linked ligands report mixed results with respect to lactone formation and catalytic activity.$^{24, 29, 30}$ Taken together, variation of the ligand substituents is indicated to have an equal or greater effect on reactivity, with alkyl-substituted diphosphines achieving higher TONs when linked by a C$_2$ bridge (Table 4, entries 4 and 5; Table 7, entries 2 and 3a)$^{24, 30}$ and cyclic-substituted diphosphines preforming better when linked by a C$_3$ bridge (Table 6, entry 3b and 6c).$^{29}$
Table 9. Catalytic Trials – Optimization, Base Screen, and Lewis Acid Screen \(^a\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>L-Ni(COD) (mmol)</th>
<th>Additives (eq.)</th>
<th>Base (p(K_a)) (^b)</th>
<th>(C_2H_4) (bar)</th>
<th>(CO_2) (bar)</th>
<th>TON (^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>BenZP 0.1</td>
<td>Zinc 100</td>
<td>– –</td>
<td>3-F</td>
<td>10 15</td>
<td>65 (± 7.4)</td>
</tr>
<tr>
<td>1b</td>
<td>BenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>86 (± 10.3)</td>
</tr>
<tr>
<td>1c</td>
<td>BenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 100</td>
<td>3-F</td>
<td>10 15</td>
<td>84</td>
</tr>
<tr>
<td>1d</td>
<td>BenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 200</td>
<td>3-F</td>
<td>10 15</td>
<td>86</td>
</tr>
<tr>
<td>1e</td>
<td>BenZP 0.1</td>
<td>Zinc 200</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>86</td>
</tr>
<tr>
<td>2a</td>
<td>CyBenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>65 (± 7.2)</td>
</tr>
<tr>
<td>2b</td>
<td>pPrBenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>64 (± 13.7)</td>
</tr>
<tr>
<td>2c</td>
<td>dcpp 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>22 (± 9.1)</td>
</tr>
<tr>
<td>2d</td>
<td>pPrBenZP 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>12 (± 2.6)</td>
</tr>
<tr>
<td>2e</td>
<td>dcepe 0.1</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>10 15</td>
<td>6 (± 3.3)</td>
</tr>
<tr>
<td>3a</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>2,6-iPr(_2)</td>
<td>11.10</td>
<td>20 10</td>
</tr>
<tr>
<td>3b</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>2-Cl</td>
<td>8.56</td>
<td>20 10</td>
</tr>
<tr>
<td>3c</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>2-Cl-6-Me</td>
<td>9.71</td>
<td>20 10</td>
</tr>
<tr>
<td>3d</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>3-F</td>
<td>9.29</td>
<td>20 10</td>
</tr>
<tr>
<td>3e</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>2,6-iBu(_2)</td>
<td>12.20</td>
<td>20 10</td>
</tr>
<tr>
<td>3f</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>2,6-CI(_2)</td>
<td>6.79</td>
<td>20 10</td>
</tr>
<tr>
<td>3g</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>NaOrBu</td>
<td>19.20</td>
<td>20 10</td>
</tr>
<tr>
<td>3h</td>
<td>BenZP 0.05</td>
<td>Zinc 100</td>
<td>LiL 50</td>
<td>NaHMDS</td>
<td>26</td>
<td>20 10</td>
</tr>
<tr>
<td>4a</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>– –</td>
<td>2-Cl</td>
<td>20 10</td>
<td>135 (± 6.2)</td>
</tr>
<tr>
<td>4b</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>NaI 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>404 (± 6.2)</td>
</tr>
<tr>
<td>4c</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>LiL 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>344 (± 7.3)</td>
</tr>
<tr>
<td>4d</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>NH(_2)I 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>248 (± 6.2)</td>
</tr>
<tr>
<td>4e</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>NEt(_3)I 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>204 (± 6.2)</td>
</tr>
<tr>
<td>4f</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>KI 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>152 (± 6.2)</td>
</tr>
<tr>
<td>4g</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>LiClO(_4) 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>141 (± 6.2)</td>
</tr>
<tr>
<td>4h</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>LiBF(_4) 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>71 (± 6.2)</td>
</tr>
<tr>
<td>5a</td>
<td>pPr(_2) lactone 0.01</td>
<td>– –</td>
<td>– –</td>
<td>3-F</td>
<td>20 10</td>
<td>55 (± 6.2)</td>
</tr>
<tr>
<td>5b</td>
<td>pPr(_2)BenZP 0.01</td>
<td>– –</td>
<td>– –</td>
<td>3-F</td>
<td>20 10</td>
<td>45 (± 6.2)</td>
</tr>
<tr>
<td>5c</td>
<td>pPr(_2)BenZP 0.01</td>
<td>Zinc 200</td>
<td>–</td>
<td>3-F</td>
<td>20 10</td>
<td>84 (± 6.2)</td>
</tr>
<tr>
<td>5d</td>
<td>pPr(_2)BenZP 0.01</td>
<td>Zinc 200</td>
<td>LiL 100</td>
<td>3-F</td>
<td>20 10</td>
<td>30 (± 6.2)</td>
</tr>
<tr>
<td>5e</td>
<td>pPr(_2)BenZP 0.01</td>
<td>Zinc 200</td>
<td>NaI 100</td>
<td>3-F</td>
<td>20 10</td>
<td>35 (± 6.2)</td>
</tr>
<tr>
<td>5f</td>
<td>BenZP 0.01</td>
<td>Zinc 200</td>
<td>NaI 100</td>
<td>3-F</td>
<td>20 10</td>
<td>64 (± 6.2)</td>
</tr>
<tr>
<td>5g</td>
<td>pPr(_2)BenZP 0.01</td>
<td>Zinc 200</td>
<td>NaI 100</td>
<td>2-Cl</td>
<td>20 10</td>
<td>30 (± 6.2)</td>
</tr>
<tr>
<td>5h</td>
<td>pPr(_2)BenZP 0.01</td>
<td>Zinc 200</td>
<td>– –</td>
<td>2-Cl</td>
<td>20 10</td>
<td>21 (± 6.2)</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 400 eq. base, 20 mL THF, 110°C, 20 h. All TONs are an average of two or more trials unless no standard deviation is listed. \(^b\) p\(K_a\) listed for the conjugate acid. \(^c\) Determined by \(^1\)H NMR analysis with an internal standard. \(^d\) Conditions: as in [a] 800 eq. base.
In agreement with the findings from Limbach *et al.*, the BenzP-ligated complex was found to be significantly more effective than the dcpp- or dcpe-Ni complexes, resulting in a TON of 82 (Table 9, entry 1b). The cyclohexyl and *iso*-propyl variants, CyBenzP and *i*PrBenzP, were slightly less active, affording TONs of 65 and 64 respectively (Table 9, entries 2a and 2b). Finally, the tetra-*iso*-propyl variant, *i*Pr₄BenzP, was found to result in a markedly lower TON than other BenzP derivatives, affording a TON of 12 (Table 9, entry 2d). While the net steric environment of BenzP is comparable to that of *i*Pr₄BenzP (two P-*t*Bu and two P-Me versus four P-*i*Pr), the considerable decrease in TON observed upon switching from BenzP to *i*Pr₄BenzP indicates that the underlying structure-activity relationship is more complex than net sterics. In the case of *i*Pr₄BenzP, the four “quadrants” about the phosphorous atoms have been filled by moderately bulky *i*Pr substituents; whereas BenzP, CyBenzP, and *i*PrBenzP share at least one sterically accessible quadrant occupied by P-Me. It is likely that the presence of this sterically open quadrant gives rise to the improved performance of CyBenzP and *i*PrBenzP relative to *i*Pr₄BenzP. Furthermore, the superior performance of BenzP can be attributed to the presence of two open quadrants (Figure 2).

---

**Figure 2. Quadrant sterics for BenzP derivatives**

![Diagram showing the sterics for BenzP derivatives](image-url)
2.2.2.2 Catalytic Trials: Base Comparison

The incorporation of an exogenous base into the catalytic cycle has been demonstrated to have drastic effects on TON.\textsuperscript{24, 29, 30} Sodium phenoxide bases have been particularly effective in promoting acrylate formation, but there have been limited systematic investigations into the steric and electronic influences of these bases.\textsuperscript{30} Therefore, a collection of phenoxide bases was prepared to further probe this relationship (Table 10). The (BenzP)Ni(COD) catalyst was utilized in these studies, as it was the most active catalyst of those previously screened, and reaction conditions were reoptimized to minimize the mass of base required for each trial.

The new reaction conditions resulted in a slight increase in the TON from 82 to 104 (Table 9, entries 1b and 3d) in the presence of 3-F. The strong bases NaHMDS and NaO\textsubscript{t}Bu afforded little to no catalytic activity (Table 9, entries 3g and 3h), likely due to their propensity to irreversibly form carbonates in the presence of CO\textsubscript{2}. Of the mono-substituted phenoxides, 2-Cl was found to be more effective than 3-F in the presence of (BenzP)Ni(COD), resulting in a TON of 160 (Table 9, entry 3b). Disubstituted

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Structure</th>
<th>pK\textsubscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,6-Cl\textsubscript{2}</td>
<td><img src="image" alt="" /></td>
<td>6.79</td>
</tr>
<tr>
<td>2-Cl</td>
<td><img src="image" alt="" /></td>
<td>8.56</td>
</tr>
<tr>
<td>3-F</td>
<td><img src="image" alt="" /></td>
<td>9.29</td>
</tr>
<tr>
<td>2-Cl-6-Me</td>
<td><img src="image" alt="" /></td>
<td>9.71</td>
</tr>
<tr>
<td>2,6-iPr</td>
<td><img src="image" alt="" /></td>
<td>11.10</td>
</tr>
<tr>
<td>2,6-iBu\textsubscript{2}</td>
<td><img src="image" alt="" /></td>
<td>12.20</td>
</tr>
<tr>
<td>NaO\textsubscript{t}Bu</td>
<td><img src="image" alt="" /></td>
<td>19.20</td>
</tr>
<tr>
<td>NaHMDS</td>
<td><img src="image" alt="" /></td>
<td>26</td>
</tr>
</tbody>
</table>

\textsuperscript{a}pK\textsubscript{a} listed for the conjugate acid.\textsuperscript{31}
phenoxides were found to have a much more varied set of TONs however (Table 9, entries 3a, 3c, 3e, and 3f). Similar to the findings of the catalyst comparison, the results of the base survey do not indicate a direct relationship between TON and the steric environment or strength of a given base; rather, the interplay of these two parameters likely contribute to the observed TONs.

Comparison of the sterically similar but electronically distinct 2-Cl-6-Me and 2,6-Cl₂ reveals a drastic increase in TON from 32 to 111 for the more basic 2-Cl-6-Me (Table 9, entries 3c and 3f). These electronic influences are outweighed, however, when there is sufficient steric hindrance about the site of basicity, as was demonstrated by the moderate TON of 89 achieved by 2,6-ᵢBu₂ (Table 9, entry 3e). The slightly less bulky 2,6-ᵢPr₂ proved to be the most effective base for acrylate production, achieving a TON of 174 (Table 9, entry 3a). It would appear this base exhibits an ideal balance between electronic and steric parameters – basic enough to deprotonate the Ni-lactone and sterically protected to limit reaction with CO₂. The similar degree of catalytic activity observed in the presence of 2-Cl is attributed to the limited ability of this less nucleophilic base to react with CO₂ to form carbonate.

2.2.2.3 Catalytic Trials: Lewis Acid Survey

As demonstrated by our lab, the presence of a Lewis acid assists with the cleavage of the Ni-O bond of nickelalactones but the effect of Lewis acids on catalytic acrylate production has only briefly been explored.²⁷⁻²⁹ Therefore, a systematic survey of Lewis acids was carried out wherein the cation and anion were independently varied (Table 9, entries 4a-h). The mono-substituted 2-Cl was selected for use in these trials rather than 2,6-ᵢPr₂ due to the ease of purification and comparable TONs achieved. To reduce the mass of
additives required, the reaction conditions were again reoptimized. Under these new reaction conditions, an increase in TON from 106 to 344 was observed in the presence of LiI (Table 9, entries 3b and 4c). A moderate increase in TON was observed upon switching from LiI to NaI, achieving a TON of 404 (Table 9, entry 4b).

The use of ammonium iodide (NH₄I) and tetraethylammonium iodide (NEt₄I) resulted in markedly lower TONs of 248 and 204, respectively (Table 9, entries 4d and 4e). However, TON was considerably impaired in the presence of LiClO₄ and LiBF₄, achieving TONs of 141 and 71, respectively (Table 9, entries 4g and 4h). Interestingly, the TON observed when LiBF₄ was used is considerably lower than the TON of 135 observed is no Lewis acid is present (Table 9, entry 4a). Analysis of the trends found within this survey indicate a “hard-soft” ion pairing of Lewis acid is beneficial for acrylate production, with hard cations such as Li⁺ and Na⁺ paired with soft anions such as I⁻ achieving the best TONs. Notably, the “hard-soft” Lewis acid KI resulted in a surprisingly low TON of 152, which is considerably lower than those observed in the presence of the “soft-soft” NH₄I or NEt₄I. This suggests that the relationship between cation-anion pairing is more complex, possibly predicated on the combination of ionic radius and ion hardness / softness.

2.2.2.4 Catalytic Trials: iPr₄BenzP Studies

A parallel study of acrylate production mediated by the iPr₄BenzP-ligated Ni complex was carried out to further probe the reactivity of proposed catalytic intermediates. Upon treatment of an isolated sample of \((\text{iPr}_4\text{BenzP})\text{Ni(COD)}\) with a 1:1 mixture of ethylene and CO₂, it was rapidly converted into a new complex with spectroscopically distinct \(^{31}\text{P}\) and \(^{1}\text{H}\) NMR resonances. The same peaks were observed following treatment of \((\text{iPr}_4\text{BenzP})\text{Ni(COD)}\) with ethylene alone, confirming the identity of this species as that
of the respective ethylene complex \((i\text{Pr}_4\text{BenzP}-C_2\text{H}_4)\) (Scheme 4, left). Unfortunately, characterization of this species was limited to in situ NMR spectroscopy, as the removal of the ethylene atmosphere converted \(i\text{Pr}_4\text{BenzP}-C_2\text{H}_4\) back into \((i\text{Pr}_4\text{BenzP})\text{Ni}(\text{COD})\). Exposure of \(i\text{Pr}_4\text{BenzP}-C_2\text{H}_4\) to a mixture of ethylene and \(\text{CO}_2\) at 60°C did result in the generation of detectable amount of the respective lactone \((i\text{Pr}_4\text{BenzP}-\text{lactone})\) over the course of 2 days, although conversion did not exceed 20% and prolonged reaction times or further heating resulted in sample decomposition.

Isolated samples of \(i\text{Pr}_4\text{BenzP}-\text{lactone}\) were successfully synthesized, however, via ligand substitution with the previously reported \((\text{bpy})\text{Ni-lactone}\) complex, allowing for further investigation of the reactivity of \(i\text{Pr}_4\text{BenzP}-\text{lactone}\) (Scheme 4, top). Upon treatment of a \(i\text{Pr}_4\text{BenzP}-\text{lactone}\) solution with \(\text{NaHMDS}\), an immediate color change from yellow-orange to pale green was observed and new resonances were observed in the \(^{31}\text{P}\) NMR spectra. Crystals suitable for X-ray diffraction were grown over several days from a pentane solution at -35°C and the structure was confirmed to be that of an \(\eta^2\)-acrylate
complex ($iPr_4BenzP$-acrylate) (Figure 3). This is the first crystallographically characterized $\eta^2$-coordinated nickel acrylate complex, although similar acrylic acid complexes have been previously reported. Further studies of the reactivity of $iPr_4BenzP$-acrylate revealed that this complex readily converts into $iPr_4BenzP$-$C_2H_4$ in the presence of as little as 0.25 atm ethylene.

**Figure 3. $iPr_4BenzP$-acrylate crystal structure**

Catalytic trials were carried out to examine the effects of various additives on TON in the presence of $iPr_4BenzP$ and base (Table 9, entries 5a-i). Initial reactions were carried out without additives to establish a baseline of reactivity, resulting in a TON of 45 for $iPr_4BenzP$ with 3-F (Table 9, entry 5b). An identical reaction carried out in the presence of $iPr_4BenzP$-lactone yielded comparable TON of 55, indicating that these two complexes produce acrylate via the same reaction pathway. The addition of zinc was found to increase TON to 84, in agreement with previous reports that demonstrated the beneficial role of reductants in reducing off-cycle Ni species. Unexpectedly, the presence of both zinc and LiI resulted in a markedly lower TON of 30 (Table 9, entry 5d), a result that is inconsistent
with the BenzP-mediated reaction (*vide supra*). It is possible that this loss of catalytic activity is reflective of variations in base purity rather than the presence of Lewis acid, as empirical evidence has suggested elsewhere.

In agreement with our prior findings, the identity of the Lewis acid was found to affect catalytic activity, with a slight increase in TON from 30 to 35 observed upon switching from LiI to NaI (Table 9, entries 5d and 5e). Nonetheless, (BenzP)Ni(COD) was more active under these reaction conditions, achieving a TON of 64 (Table 9, entry 5f). In light of the above results, it is unsurprising that the choice of base was observed to affect TON, with 2-Cl resulting in a slightly lower TON of 30 relative to 3-F in the presence of NaI (Table 9, entry 5g). Additional studies with 2-Cl revealed no loss of activity when Lewis acid was omitted from the reaction, however a measurable decrease in TON from 30 to 21 was observed when zinc was omitted (Table 9, entries 5h and 5i).

### 2.2.3 Stereoelectronic Influences Between Catalyst and Base

Comparison of the trends observed in the catalyst comparison and base survey demonstrate a complex relationship between steric and electronic parameters of both the ligand and the base reaction components. To further examine this relationship, a series of experiments was conducted that paired sterically distinct catalysts with different bases (Table 11). When (BenzP)Ni(COD) and (CyBenzP)Ni(COD) were compared in the presence of 3-F, the BenzP-ligated complex was found to achieve a slightly higher TON of 82 relative to the 65 observed for the CyBenzP variant (Table 11).

<table>
<thead>
<tr>
<th>Entry</th>
<th>L-Ni(COD)</th>
<th>Base</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>BenzP</td>
<td>3-F</td>
<td>82 (± 7.4)</td>
</tr>
<tr>
<td>1b</td>
<td>CyBenzP</td>
<td>3-F</td>
<td>65 (± 7.2)</td>
</tr>
<tr>
<td>2a</td>
<td>BenzP</td>
<td>2,6-tBu₂</td>
<td>33 (± 4.2)</td>
</tr>
<tr>
<td>2b</td>
<td>CyBenzP</td>
<td>2,6-tBu₂</td>
<td>49 (± 4.2)</td>
</tr>
</tbody>
</table>

*Table 11. Catalyst-Base Pairing*

*Conditions: 0.1 mmol catalyst, 40 mmol base, 10 mmol zinc, 5 mmol LiI, 10 bar C₂H₄, 15 bar CO₂, 20 mL THF, 20 h, 110°C. * Determined by ¹H NMR integration with an internal standard.*
11, entries 1a and 1b). However, \((\text{CyBenzP})\text{Ni(COD)}\) managed a higher TON than \((\text{BenzP})\text{Ni(COD)}\) (49 and 33, respectively) when the more sterically bulky 2,6-\(t\)Bu\(_2\) base was utilized (Table 11, entries 2a and 2b).

The basis of this relationship may originate from any number of factors previously discussed (\textit{vide supra}). While the increased rate of carbonate formation in the case of the more basic 2,6-\(t\)Bu\(_2\) may explain the overall decrease in catalytic activity between both \textbf{BenzP} and \textbf{CyBenzP} Ni complexes, it does not explain the inversion of their relative catalytic activities. It is possible that the origins of this catalyst-base pairing relationship are linked to the difference in sterics within the various quadrants about the nickel center. However, interactions arising from the presence of zinc or Lewis acid cannot be ruled out.

\textbf{2.2.4 Catalytic Reaction Profile and Carbonate Formation}

In order to construct a more complete picture of the activity and possible deactivation of \((\text{BenzP})\text{Ni(COD)}\), turnover was measured at multiple time points in the presence of various bases (Figure 4a). All examined bases displayed saturation kinetics, with TON tapering off after 20 hours. While the relative activity of the bases remained unchanged from the base comparison trials, the rate of saturation varied - with the more nucleophilic 2,6-\(Cl\)\(_2\) achieving little to no increase in TON between 8 and 20 hours whereas the less nucleophilic 2-\(Cl\) and 2,6-\(iPr\)\(_2\) bases continued to facilitate catalytic turnover between these time points. To test whether this loss of catalytic activity was due to catalyst deactivation, a reaction was carried out in the presence of 400 eq. 2-\(Cl\) and allowed to react under the conditions described in Table 9. After 20 hours, an additional 200 eq. of base were added, and the reaction resumed for an additional 20 hours.
Figure 4. (BenzP)Ni(COD) reaction profile and carbonate formation

a) 

b) 

0.1 mmol (BenzP)Ni(COD) 
100 eq. Zn, 50 eq. LiI, 
+ 400 eq. NaOD 
10 bar 25 mL THF, 110°C, 20 h 
15 bar 

$\text{TON}$ vs. Time (h) 

Carbonylation, Base, TON vs. Time (h) 

Carbonate, Base, TON vs. Time (h)
The addition of supplementary base resulted in a TON of 243, which represents a considerable increase from the 160 (Table 9, entry 3b) observed under the same conditions. This confirms that the catalyst is still active at 20 hours and the observed loss of catalytic activity is more likely due to the consumption of base via the formation of its conjugate acid or the carbonate. To further probe the reaction profile, carbonate formation was measured at various time points and quantified via NMR analysis (Figure 4b). The use of 3-F allowed for the identity of the phenoxide-derived products to be confirmed via $^{19}\text{F}$ NMR analysis and their quantities determined via integration of the $^1\text{H}$ spectra in the presence of an internal standard. The formation of carbonate was found to correspond with the consumption of base and eventually tapered off with TON after 8 hours. These findings, in combination with the supplementary base addition, confirm that the loss of catalytic activity is due to the consumption of base, an integral component required for catalysis.

Consideration of the series of experiments described above offer valuable insight into the complex interactions of this multi-component nickel-based system for acrylate production. At the time of publication, these results contained the highest reported TON for acrylate from ethylene and CO$_2$ although comparable TONs have been achieved in the years since.\textsuperscript{22} Despite these promising improvements, catalytic efficacy must increase by many orders of magnitude in order to compete with the current rate of industrial production. The necessity for an extreme excess of additives also diminishes the attractiveness of this system for large-scale use. Efforts are currently underway in our lab to develop novel, non-nickel-based catalysts for ethylene-CO$_2$ coupling that do not require exorbitant additives in order to achieve catalytic activity (see Chapter 3).
2.3 Concluding Remarks

The coupling of CO₂ and ethylene to produce acrylic acid – a multi-billion-dollar commodity chemical used in a variety of goods such as superabsorbent polymers and adhesives – has been a long sought-after reaction for synthetic chemists. Development of a viable catalyst for this transformation has been in the works for many decades, but nickel-mediated coupling of olefins and CO₂ began to pick up in the 1980’s with a flurry of reports from Hoberg \(^\text{4-7, 11, 15}\) and Walther \(^\text{9, 16, 17, 32-35}\). The metaphorical jabs traded by these two scientists laid the foundation for this field, although progress stalled throughout much of the 1990s and into the 2000s. Eventually, DFT calculations offered valuable insight into potential pathways for this transformation and the energetic sinkhole that results from Ni-lactone formation. \(^\text{13}\)

Following this computational work, a trickle of reports began to emerge that specifically investigated the reactivity of Ni-lactones with promising results. \(^\text{14, 19, 26}\) The problematic step of β-hydride elimination was found to be overcome if the “right” ligand is selected \(^\text{14}\) or in the presence of an excess of MeI. \(^\text{19, 26}\) Although these sub-stoichiometric transformations proved to be catalytic dead ends, they conclusively demonstrated that Ni-lactones are not impervious to subsequent reactivity. Catalytic acrylate formation was finally achieved by obviating β-hydride elimination all together via the addition of exogeneous base. \(^\text{24}\) However, this development introduced a new set of constraints given the incompatibility of strong bases with CO₂ due to irreversible carbonate formation.

Our lab demonstrated the ability of Lewis acids to assist in Ni-O bond cleavage of isolated Ni-lactones, resulting in rapid β-hydride elimination and subsequent isomerization to form 4-membered Ni-lactones that were capable of deprotonation in the presence of
weak bases.\textsuperscript{27, 28} These findings were later confirmed in catalytic experiments that incorporated Lewis acid and a weak base with promising results.\textsuperscript{29} Notably, this report also revealed the significance of including a reducing agent, such as zinc, in order to reduce the Ni(II) species that form when Lewis acid is present.\textsuperscript{29} The combination of these three additives—base, Lewis acid, and zinc—resulted in dramatically increased TONs, particularly when weak phenoxide bases were employed.\textsuperscript{30} Despite these improvements, catalytic activity remained low (TON = 107) and there was little known about the interaction of these additives with the metal center or ancillary ligands.

Aggregation of the above studies highlight the complexity of base-assisted acrylate production from ethylene and CO$_2$ in nickel-mediated systems. The efficacy of an individual base depends largely on achieving a Goldilocks-type balance between strength and steric; it must be basic enough to deprotonate a Ni-lactone but not too basic that it irreversibly reacts with CO$_2$ to form carbonate. Likewise, steric protection at the site of basicity can slow the rate of carbonate formation to a degree but cannot be so bulky as to impede the ability of the base to approach and deprotonate the Ni-lactone. Access to the metal center is also impacted by the steric environment of the ancillary ligands. In the case of 3-F-mediated acrylate production, the presence of at least one, but preferably two sterically accessible quadrants around the Ni center are beneficial for catalytic activity.

The relationship between any one nickel catalyst and phenoxide base cannot be broadly defined, however, as variations in the ligand steric can lead to inversions of the previously established catalyst efficacy when different bases are selected. Consideration of the Lewis acid selected for catalysis can also significantly alter turnover. Those Lewis acids with “hard-soft” ion pairings were generally effective in aiding catalysis; although there
may be conflicting factors that confound the role of this additive such as ionic radius or perhaps the base utilized when surveying Lewis acids. Examination of these factors and the broader interaction of additives in ethylene-CO$_2$ coupling reactions should be investigated further. Finally, the characterization of $i$Pr$_4$BenzP-C$_2$H$_4$, -lactone, and -acrylate complexes was illustrative for gaining further mechanistic insight into the proposed catalytic cycle. Crystallographic evidence for $\eta^2$-coordinated sodium acrylate complex was obtained for the first time and the catalytic viability of Ni-lactones – previously examined only in stoichiometric experiment$^{24,27,28}$ – was confirmed in a one-pot system.

**2.4 Experimental**

*2.4.1 General Considerations*

Manipulations were carried out using standard Schlenk, glovebox, cannula, or vacuum techniques. Solvents were deoxygenated and dried according to literature procedures.$^{34}$ Carbon dioxide (laser-grade) and ethylene (dry) were purchased from Airgas and used as received. Other chemicals were purchased from Aldrich, Strem, Fischer, VWR, or Cambridge Isotope Laboratories. Nonvolatile solids were dried under vacuum at 50°C overnight. Previously reported procedures were followed for the synthesis of the ligand precursor 7,8-diposphabicyclo[4.2.0]octa-1,3,5-triene,7,8-bis(1,1-dimethylethyl) (tBu-phosphacycle) and BenzP, which was obtained as a racemic mixture.$^{35}$

NMR spectra were recorded on a Bruker 300 MHz DRX, 500 MHz DRX, and 600 MHz spectrometer at ambient temperatures. Probe temperatures were calibrated using methanol and ethylene glycol as previously described.$^{36}$ An external standard of H$_3$PO$_4$
was used to reference $^{31}\text{P}$ chemical shifts; $^1\text{H}$ and $^{13}\text{C}$ chemical shifts were referenced to residual solvent signals. X-ray crystallographic data were collected on a Bruker CMOS diffractometer with Mo Kα radiation. Samples were collected in an inert oil and quickly transferred to a cold gas stream. The structures were solved from direct methods and Fourier syntheses and refined by full-matrix least-squares procedures with anisotropic thermal parameters for all non-hydrogen atoms. Crystallographic calculations were carried out using SHELX programs. High pressure catalytic coupling reactions were performed using a Parr 5500 Series compact reactor with a 100 mL glass insert.

2.4.2 Preparation and Characterization of Ligands

Preparation of 1,2-Bis(dialkylphosphino)benzene Complexes. A 20 mL scintillation vial was filled with 757 mg (3.00 mmol, 1 mol eq.) 7,8-diphosphabicyclo[4.2.0]octa-1,3,5-triene,7,8-bis(1,1-dimethylethyl) (tBu-phosphacycle), the solids were dissolved in 20 mL of dichloromethane, and the mixture was transferred to a 50 mL sealed glass reaction vessel. The yellow solution was cooled to -196°C, and 3.30 mmol (1.1 mol eq.) of methyl triflate was added via vapor-phase gas addition. The resulting light-yellow solution was stirred at ambient temperature for 4 h. The solvent was removed under vacuum, leaving behind an oil, yellow residue. A 20-30 mL volume of Et₂O was added to the residue and cooled to -35°C, at which point 3.15 mmol of the appropriate alkyl Grignard reagent was added. The resulting dark yellow solution was stirred at ambient temperature overnight. The solution was filtered through Celite in a Pasteur pipet, and the solvent was removed under vacuum. The yellow solid was then dissolved in pentane and filtered again through fresh Celite in a Pasteur pipet. The pentane was removed under vacuum and used without further purification. Description and isolated yields of ligands:
**BenzP**, white solid, 56%; **CyBenzP**, pale yellow oil, 68%; **iPrBenzP**, pale yellow oil, 75%. **iPr4BenzP**, pale yellow oil, 85%.

*Spectral Data for CyBenzP.* \(^{31}\)P\(^{1}\)H NMR (300 MHz, C\(_6\)D\(_6\)): \(\delta \) -24.66 (d, \(J = 152.6\) Hz), 1.19 (d, \(J = 152.6\) Hz). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta \) 1.10 (m, 18 H, PrBu-CH\(_3\)), 1.13 (s, 3 H, P-CH\(_3\)), 1.48 (m, 10 H, Cy-CH\(_2\)), 2.17 (m, 1 H, PCy-CH), 7.13 (m, 2 H, Benz-CH), 7.43 (m, 1 H, Benz-CH), 7.48 (m, 1 H, Benz-CH). \(^{13}\)C\(^{1}\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta \) 6.19 (P-CH\(_3\)), 26.77 (PCy-CH\(_2\)), 27.36 (PCy-CH\(_2\)), 27.72 (PrBu-CH\(_3\)), 29.45 (PrBu-CH\(_3\)), 30.72 (PrBu-C), 30.99 (PCy-CH\(_2\)), 31.17 (PrBu-C), 31.43 (PCy-CH\(_2\)), 31.68 (PCy-CH\(_2\)), 34.23 (PCy-CH), 132.02 (Benz-CH), 132.40 (Benz-CH), 145.64 (Benz-C), 146.95 (Benz-C).

*Spectral Data for iPrBenzP.* \(^{31}\)P\(^{1}\)H NMR (300 MHz, C\(_6\)D\(_6\)): \(\delta \) -25.44 (d, \(J = 151.2\) Hz), 7.66 (d, \(J = 150.8\) Hz). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta \) 0.96 (dd, \(J = 6.9, 13.1\) Hz, 3 H, PriPr-CH\(_3\)), 1.11 (m, 18 H, PriPr-CH\(_3\)), 1.17 (m, 3 H, P-CH\(_3\)), 1.27 (dd, \(J = 6.7, 13.9\) Hz, 3 H, PriPr-CH\(_3\)), 2.25 (m, 1 H, PriPr-CH), 7.12 (m, 2 H, Benz-CH), 7.39 (m, 2 H, Benz-CH). \(^{13}\)C\(^{1}\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta \) 6.11 (P-CH\(_3\)), 21.85 (PriPr-CH\(_3\)), 22.02 (PriPr-CH\(_3\)), 22.78 (PriPr-CH), 27.67 (PrBu-CH\(_3\)), 29.17 (PrBu-CH\(_3\)), 31.00 (PrBu-C), 132.23 (Benz-CH), 146.08 (Benz-C), 146.70 (Benz-C).

2.4.3 Preparation and Characterization of Nickel Complexes

**Preparation of [1,2-bis(dialkylphosphino)benzene]Ni(COD) complexes.** A 20 mL scintillation vial was filled with 196 mg (0.71 mmol, 1.05 mol eq.) Ni(COD)\(_2\), the solid was dissolved in THF, and the mixture stirred for 10 min to fully dissolve the solid. In a separate vial, 0.68 mmol (1.0 mol eq.) of 1,2-bis(dialkylphosphino)benzene ligand was dissolved in 5 mL THF and added dropwise to the stirred nickel solution. The resulting dark brown solution was stirred overnight at ambient temperatures in the case of (BenzP)-
and (iPr₄BenzP)Ni(COD). Solutions containing iPrBenzP or CyBenzP with Ni(COD)₂ were transferred to a 50 mL sealed glass reaction vessel and stirred at 50°C overnight. The THF solvent was the removed under vacuum, and the resulting dark brown oil was dissolved in pentane and filtered through Celite in a Pasteur pipet. The filtrate was dried under vacuum and the dark golden-brown solid was recrystallized in Et₂O at -35°C to afford the catalyst complex as a dark golden brown solid. Isolated yields of catalysts: (BenzP)Ni(COD), 77%; (CyBenzP)Ni(COD), 85%; (iPrBenzP)Ni(COD), 65%; (iPr₄BenzP)Ni(COD), 50%.

Spectral Data for (CyBenzP)Ni(COD). ³¹P{¹H} NMR (300 MHz, C₆D₆): δ 50.97 (d, J = 25.4 Hz), 71.81 (d, J = 25.4 Hz). ¹H NMR (500 MHz, C₆D₆): δ 1.01 (m, 18 H, PrBu-CH₃), 1.24 (m, 7 H, PCy-CH₂), 1.42 (d, J = 4.5 Hz, 3 H, P-CH₃), 1.53 (d, J = 11.0 Hz, 1 H, PCy-CH₂), 1.61 (d, J = 9.5 Hz, 1 H, PCy-CH₂), 1.85 (d, J = 13.0 Hz, 1 H, PCy-CH₂), 2.01 (apparent qt, J = 4.0, 12.8 Hz, 1 H, COD-CH₂), 2.16 (m, 1 H, COD-CH₂), 2.39 (m, 1 H, COD-CH₂), 2.56 (apparent qt, J = 3.8, 11.5 Hz, 1 H, PCy-CH), 2.81 (m, 2 H, COD-CH₂), 2.90 (td, J = 8.0, 4.0 Hz, 1 H, COD-CH₂), 3.13 (m, 1 H, COD-CH₂), 4.29 (m, 1 H, COD-CH), 4.52 (m, 2 H, COD-CH), 4.93 (apparent quintet, 1 H, COD-CH), 7.09 (m, 2 H, Benz-CH), 7.52 (m, 2 H, Benz-CH). ¹³C{¹H} NMR (500 MHz, C₆D₆): δ 8.78 (P-CH₃), 26.69 (PCy-CH₂), 27.66 (PrBu-CH₃), 27.52 (PCy-CH₂), 27.85 (PCy-CH₂), 28.07 (COD-CH₂), 29.03 (PrBu-CH₃), 29.31 (COD-CH₂), 30.06 (PCy-CH₂), 33.24 (PrBu-C), 36.86 (COD-CH₂), 37.59 (COD-CH₂), 38.24 (PCy-CH), 78.98 (COD-CH), 79.73 (COD-CH), 85.20 (COD-CH), 86.15 (COD-CH), 127.37 (Benz-CH), 127.84 (Benz-CH), 129.78 (Benz-CH), 130.66 (Benz-CH), 147.43 (Benz-C), 148.24 (Benz-C).
Spectral Data for (iPr2BenzP)Ni(COD). $^{31}$P$^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 50.87 (d, $J = 25.3$ Hz), 77.66 (d, $J = 25.3$ Hz). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 0.83 (dd, $J = 7.1$, 14.2 Hz, 3 H, PiPr-CH$_3$), 1.00 (m, 18 H, PrBu-CH$_3$), 1.41 (d, $J = 4.8$ Hz, 3 H, P-CH$_3$), 1.48 (dd, $J = 7.0$, 13.0 Hz, 3 H, PiPr-CH$_3$), 2.14 (m, 2 H, COD-CH$_2$), 2.39 (m, 2 H, COD-CH$_2$), 2.67 (apparent ddt, $J = 7.0$, 11.5, 14.0 Hz, 1 H, P-iPr-CH), 2.79 (m, 2H, COD-CH$_2$), 2.86 (apparent td, $J = 8.0$, 15.5 Hz, 1 H, COD-CH$_2$), 4.28 (m, 1 H, Benz-CH), 7.08 (m, 2H, Benz-CH), 7.42 (m, 1H, Benz-CH), 7.50 (m, 1H, Benz-CH). $^{13}$C$^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 8.76 (P-CH$_3$), 20.10 (PiPr-CH$_3$), 21.53 (PiPr-CH$_3$), 26.58 (PrBu-CH$_3$), 27.62 (COD-CH$_2$), 28.06 (PiPr-CH), 28.73 (COD-CH$_2$), 33.24 (P-CH$_3$), 37.46 (COD-CH$_2$), 78.32 (COD-CH), 79.51 (COD-CH), 85.05 (COD-CH), 85.95 (COD-CH), 129.94 (Benz-CH), 130.05 (Benz-CH), 130.50 (Benz-CH), 130.60 (Benz-CH), 147.18 (Benz-C), 148.30 (Benz-C).

Spectral Data for (iPr$_4$BenzP)Ni(COD). $^{31}$P$^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 65.89 (s). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 0.90 (dd, $J = 6.1$, 12 Hz, 12 H, PiPr-CH$_3$), 0.97 (dd, $J = 6.1$, 12 Hz, 12 H, PiPr-CH$_3$), 2.34 (m, 4 H, PiPr-CH$_3$), 2.49 (m, 4 H, COD CH$_2$), 2.65 (m, 4 H, COD-CH$_2$), 4.43 (s, 4 H, COD-CH), 7.09 (m, 2 H, Benz-CH), 7.40 (m, 2 H, Benz-CH). $^{13}$C$^1$H NMR (C$_6$D$_6$): $\delta$ 18.66 (PiPr-CH$_3$), 19.07 (PiPr-CH$_3$), 26.31 (PiPr-CH), 32.81 (COD-CH$_2$), 80.38 (COD-CH), 128.45 (Benz-CH), 130.10 (Benz-CH), 146.91 (Benz-CH).

Preparation and Spectral Data for (iPr$_4$BenzP)Ni(C$_2$H$_4$) [(iPr$_4$BenzP-C$_2$H$_4$)]. A 20 mL scintillation vial was filled with 10 mg (21 µmol) (iPr$_4$BenzP)Ni(COD), dissolved in approximately 500 µL of C$_6$D$_6$ and then transferred into a J. Young NMR tube. The tube was cooled to -196°C, degassed, and 1 atm of ethylene was admitted via calibrated
gas bulb. Near full conversion to \( \text{iPr}_4\text{BenzP-C}_2\text{H}_4 \) occurred immediately upon thawing (as judged by NMR spectroscopy), although the sample’s visual appearance remains unchanged. The product was not stable in the absence of ethylene and quickly reverted to \( (\text{iPr}_4\text{BenzP})\text{Ni(COD)} \) upon removal of the volatiles. \(^{31}\text{P}\{\text{\textsuperscript{1}H}\} \text{NMR (300 MHz, C}_6\text{D}_6\): } \delta \) 71.70 (s). \(^{1}\text{H} \text{NMR (500 MHz, C}_6\text{D}_6\): } \delta \) 0.82 (m, 12 \text{H, PiPr-CH}_3), 1.14 (m, 12 \text{H, PiPr-CH}_3), 2.20 (m, 4 \text{H, PiPr-CH }), 7.12 (m, 2 \text{H, Benz-CH}), 7.43 (m, 2 \text{H, Benz-CH}). The resonance for ethylene was not located due to rapid exchange with free ethylene.

**Preparation and Spectral Data for \( (\text{iPr}_4\text{BenzP})\text{Ni(κC,κO-CH}_2\text{CH}_2\text{COO)} \) (\( \text{iPr}_4\text{BenzP-lactone} \)).** A 20 mL scintillation vial was filled with 176 mg (0.64 mmol, 1 mol eq.) Ni(COD)$_2$ and dissolved in 5 mL THF. In a separate vial, 100 mg (0.64 mmol, 1 mol eq.) 2,2’-bipyridine and 35 mg (0.35 mmol, 0.55 mol eq.) succinic anhydride were dissolved in 5 mL THF. This mixture was then added dropwise to the nickel-THF solution and stirred at ambient temperature for 4 h. The reaction solution was filtered through a fine frit and the remaining red powder ((\text{bpy})Ni-lactone) was washed with pentane and Et$_2$O. Then, 113 mg (0.40 mmol) (\text{bpy})Ni-lactone was combined with 122 mg (0.40 mmol) \( \text{iPr}_4\text{BenzP} \) in a 20 mL scintillation vial, dissolved in 10 mL dichloromethane, and stirred at ambient temperatures for 24 h. The solvent was removed under vacuum, the residue was dissolved in Et$_2$O and filtered through Celite in a Pasteur pipet. The solvent was removed under vacuum and the resulting orange solid was recrystallized in Et$_2$O at -35°C to afford an orange solid. Isolated yield 75%. \(^{31}\text{P}\{\text{\textsuperscript{1}H}\} \text{NMR (300 MHz, C}_6\text{D}_6\): } \delta \) 62.92 (d, \( J = 9.0 \) Hz), 70.53 (d, \( J = 9.0 \) Hz). \(^{1}\text{H} \text{NMR (C}_6\text{D}_6, 500 MHz): } \delta \) 0.78 (dd, \( J = 6.4, 12 \) Hz, 6 \text{H, PiPr-CH}_3), 0.86 (dd, \( J = 6.4, 12 \) Hz 6 \text{H, PiPr-CH}_3), 0.97 (dd, \( J = 6.4, 12 \) Hz, 6 \text{H, PiPr-CH}_3), 1.10 (m, 2 \text{H, α-CH}_2), 1.32 (dd, \( J = 6.4, 12 \) Hz, 6 \text{H, PiPr-CH}_3), 1.92 (m, 2 \text{H, PiPr-CH}_3),
PiPr−CH), 2.18 (m, 2 H, PiPr−CH), 2.84 (m, 2 H, β-CH2), 6.96 (m, 2 H, Benz-CH), 7.01 (m, 1 H, Benz-CH), 7.07 (m, 1 H, Benz-CH).

$^{13}$C{H} NMR (500 MHz, C₆D₆): δ 12.10 (α-CH₂), 18.32 (PiPr-CH₃), 18.71 (PiPr-CH₃), 19.14 (PiPr-CH₃), 25.30 (PiPr-CH), 26.19 (PiPr-CH), 37.11 (β-CH₂), 129.99 (Benz-CH), 130.40 (Benz-CH), 131.31 (Benz-CH), 188.50 (C=O). IR (KBr): νC−O = 1629 cm⁻¹.

Preparation and Spectral Data for (iPr₄BenzNi(η²−CH₂=CHCOONa) (iPr₄BenzP-acrylate). A 20 mL scintillation vial was filled with 45 mg (0.10 mmol, 1 mol eq.) iPr₄BenzP-lactone and 37 mg (0.20 mmol, 2 mol eq.) sodium hexamethyldisilazide and dissolved in 10 mL THF. The reaction was stirred for 30 min at ambient temperature and the volatiles removed under vacuum. The residue was washed with pentane followed by extraction with Et₂O. Concentration of the Et₂O solution and cooling to -35°C for several days afforded yellow-green crystals of iPr₄BenzP-acrylate co-crystallized with NaHMDS, as indicated by X-ray diffraction and NMR analysis. $^{31}$P{¹H} NMR (300 MHz, C₆D₆): δ 67.69 (d, J = 45 Hz), 72.97 (d, J = 45 Hz). $^1$H NMR (300 MHz, C₆D₆): δ 0.81 (m, 6 H, PiPr-CH₃), 1.00 (m, 6 H, PiPr-CH₃), 1.28 (m, 6 H, PiPr-CH₃), 1.38 (m, 6 H, PiPr-CH₃), 1.93 (m, 2 H, PiPr-CH), 2.03 (s, 1 H, acrylate-CH₂), 2.40 (s, 1 H, acrylate-CH₂), 3.16 (1 H, acrylate-CH) 2.51 (m, 2 H, PiPr-CH), 6.82 (m, 1 H, Benz-CH), 7.09 (m, 1 H, Benz-CH), 7.35 (m, 1 H, Benz-CH), 8.93 (m, 1 H, Benz-CH).$^{13}$C{¹H} NMR (500 MHz, C₆D₆): δ 19.42 (PiPr-CH₃), 19.61 (PiPr-CH₃), 24.53 (PiPr-CH), 26.28 (PiPr-CH), 34.00 (O₂CCH=CH₂), 49.70 (O₂CCH=CH₂) 118.14 (Benz-CH), 127.77 (Benz-CH), quaternary carbonyl carbon not located.
2.4.4 Preparation of Sodium Phenoxide bases

A 20 mL scintillation vial was filled with 3.60 g (150 mmol, 1 mol eq.) of NaH and the quantitatively transferred to a 250 mL Schlenk flask via a THF slurry (40 mL). In a separate vial, 158 mmol (1.05 mol eq.) of freshly distilled liquid phenol was weighed out and then taken up into a 20 mL syringe. In the case of solid 2,6-tBu2-6-MePhOH, the phenol was first dissolved in 50 mL THF prior to being taken up in the syringe. The sodium hydride solution was cooled to 0°C and stirred as the phenol was added dropwise under a positive flow of argon. The solution was stirred overnight at ambient temperature at which point the solvent was removed under vacuum and the resulting oily solid triturated with 20-40 mL of Et2O to remove residual THF. The solid product was dissolved in Et2O, filtered through Celite, and the solvent then removed under vacuum. The solid was then washed with cold pentane on a frit and the recrystallized in Et2O with the exception of 2,6-iPr2, which was recrystallized in THF layered with pentane.

2.4.5 General Procedure for Catalytic Acrylate Production Experiments

A stainless-steel autoclave reactor fitted with a glass insert was loaded with the appropriate amount of catalyst (0.1, 0.05, or 0.01 mmol; 1 mol eq.), sodium phenoxide base (400 or 800 mol eq.), zinc dust (100 or 200 mol eq.), Lewis acid (50 or 100 mol eq.), and 25 mL THF. The reactor was sealed under an inert atmosphere and removed from the glovebox. The contents of the reactor were stirred while the reactor was pressurized with ethylene followed by carbon dioxide. The reactor was heated to 110°C for 20 h. Following the reaction period, the vessel was removed from the heating element, cooled in an ice-water bath for 30 min, and slowly vented to ambient pressure. The reaction residue was extracted with D2O, and an internal standard of sodium sorbate was added. The organic-
soluble species were removed by washing with Et₂O. Production of acrylate salt was quantified by integration of the ¹H NMR spectrum.
2.5 References


2. Acrylic Acid Market Analysis, By Product (Acrylate Esters, Glacial Acrylic Acid), By End-Use (Surfactants and Surface Coatings, Organic Chemicals, Adhesives, Textiles, Water Treatment, Personal Care Products), Bio Acrylic Acid Downstream Potential And Segment Forecasts To 2022. 2016.


CHAPTER 3

Development of Low Valent Iron Complexes for Oxidative Coupling of Ethylene and Carbon Dioxide

3.1 Introduction: The Basis for Iron-Mediated Acrylate Production

In the years following the first report of catalytic acrylate production by a nickel-based catalyst, notable improvements were made that allowed for one-pot catalysis with TONs exceeding 400.\(^1\)\(^2\) This modest level of activity was only achieved, however, in the presence of an extreme excess of additives such as Lewis acid and zinc, and using specialty bases such as sodium 2-chlorophenoxide. Such a mixture is impractical for large scale acrylate production and catalytic activity would need to improve by many orders of magnitude to be industrially relevant. The slowed rate of progress within nickel-based systems and the problematic reliance on additives warrants the investigation of alternative approaches to CO\(_2\)-ethylene coupling.

3.1.1 Meet in the Middle – A Case for CO\(_2\)-Olefin Coupling at Group VIII Metals

The precedent for transition metal-mediated coupling of CO\(_2\) and olefins is largely comprised of Group VI metals – such as Mo\(^3\)\(^-\)\(^7\) and W\(^3\)\(^-\)\(^5\)\(^-\)\(^8\) – and Group X metals – namely Ni,\(^1\)\(^2\)\(^-\)\(^9\)\(^-\)\(^26\) although there are a handful of reports featuring Pd\(^16\)\(^-\)\(^27\)\(^-\)\(^31\) and Pt\(^20\) complexes. Unsurprisingly, these two categories exhibit strikingly different reactivity towards CO\(_2\) and ethylene. Group VI metals readily undergo oxidative coupling and \(\beta\)-hydride elimination, the first two steps in the proposed catalytic cycle, but the oxophilicity of these metals result
in strong metal-oxygen bonds that make these complexes resistant to reductive elimination (Figure 1). Conversely, Group X metals are less oxophilic and are therefore more capable of reductive elimination, but are plagued by slow rates of oxidative coupling and the inability to undergo β-hydride elimination due to orbital constraints.\(^{32}\)

Considering the relative strengths and weaknesses of these two Groups, it is reasonable to assume that a balance of these characteristics could be achieved if one were to literally “meet in the middle” and employ the use of a Group VIII metal such as Fe or Ru. The fewer d-electrons present in Group VIII metals relative to Group X would make available orbitals that could allow for β-hydride elimination, and the decreased oxophilicity would make them less resistant to product elimination compared to their Group VI counterparts. Of the Group VIII metals, both Fe and Ru have been demonstrated to be robust catalysts for a wide range of transformations.\(^{33, 34}\) Arguably the most notable of these is the Ru-based olefin metathesis catalyst developed by Robert Grubbs (also known as the Grubbs catalyst), for which he was awarded the Nobel Prize in Chemistry in 2005.\(^{34, 35}\) However, the relative abundance and cost of ruthenium compared to iron (Ru: 0.001 ppm, $11,896 USD/kg; Fe: 56,300 ppm, $0.16 USD/kg),\(^{36, 37}\) makes the development of an iron-
based catalyst a more economically-attractive target than ruthenium. Furthermore, most of the known catalysts for acrylate production contain first row metals.\textsuperscript{1,2,21-23,25,26}

3.1.2 Iron-Mediated Oxidative Coupling of CO\textsubscript{2} and Olefins

Despite the seemingly exhaustive scope of iron-catalyzed reactions, there remains little precedent for the oxidative coupling of CO\textsubscript{2} and ethylene mediated by an Fe complex.\textsuperscript{38-41} The first such report, published by Hoberg \textit{et al.} in 1986, detailed the characterization and reactivity of an \(\eta^3\)-allyl carbonate Fe complex generated from the coupling of CO\textsubscript{2} and 1,4-butadiene (Scheme 1).\textsuperscript{38} Liberation of the CO\textsubscript{2}-functionalized product was achieved via protonolysis with a strong acid to yield a mixture of mono-carboxylic acid isomers.\textsuperscript{38} The formation of dicarboxylic acids was observed following exposure to additional equivalents of CO\textsubscript{2} or as a result of intermolecular C-C coupling of an \(\eta^3\)-allyl ligands upon addition of FeCl\textsubscript{3}.\textsuperscript{38}

\begin{center}
\textbf{Scheme 1. First iron-mediated \(\text{CO}_2\)-olefin coupling}
\end{center}

Shortly after this work, Hoberg and co-workers reported the first evidence for ethylene-CO\textsubscript{2} coupling at an iron center.\textsuperscript{39} Interestingly, the reactivity of the parent iron complex, (PEt\textsubscript{3})\textsubscript{2}Fe(C\textsubscript{2}H\textsubscript{4})\textsubscript{2}, with CO\textsubscript{2} was found to be altered in the presence of various ligands. In the absence of free ligand, reductive disproportionation of CO\textsubscript{2} was observed resulting in the formation of iron-carbonate and -carbonyl complexes; whereas oxidative
coupling of ethylene and CO₂ was observed when the reaction was carried out in the
presence of additional ligands (Scheme 2).³⁹ Two major carboxylate products were
identified by their respective methyl esters following protonolysis by a strong acid in the
presence of methanol: dimethyl succinate (Scheme 2, top) and dimethyl methylmalonate
(Scheme 2, bottom).³⁹ The ratio of these products was found to be influenced by the identity
of the additional ligands present during coupling, with the branched methylmalonate
formed as the major product in the presence of PMe₃ and DMPE (400:1 and 7:1
respectively) and the linear succinate formed as the major product in the presence of DCPE
(10:1).³⁹

**Scheme 2. First CO₂ – ethylene coupling by an iron complex**

The proposed mechanism for the formation of these two dicarboxylic acid products
hinges upon the formation of a transient iron-lactone, although this complex was not
observed experimentally (Scheme 3).³⁹ Insertion of a second equivalent of CO₂ into the
Fe-C bond of the 5-membered iron-lactone is proposed to result in the formation of an iron-
succinate complex (Scheme 3, left); whereas CO₂ insertion into a 4-membered lactone –
arising from β-hydride elimination and subsequent 2,1-insertion – results in the formation
of an iron-methylmalonate complex (Scheme 3, right).\textsuperscript{39} Unfortunately, the authors offered no insight into the variations in reactivity or product ratios observed in the presence of different ligands. These findings from the Hoberg group demonstrate the capacity of iron complexes to facilitate C-C bond formation, although yields of CO\textsubscript{2}-functionalized products were sub-stoichiometric in both cases.\textsuperscript{38, 39}

It was more than 30 years before another example of Fe-mediated ethylene-CO\textsubscript{2} coupling was reported by Chirik \textit{et al.}\textsuperscript{40} Addition of a 10:1 ratio of ethylene and CO\textsubscript{2} to the bis-N\textsubscript{2} iron complex (\textsuperscript{iPr}PDI)Fe(N\textsubscript{2})\textsubscript{2} (PDI: pyridine(diimine)) resulted in the formation of a mixture of various iron-carboxylate compounds, of which the major product was found to be an iron propionate complex (Scheme 4).\textsuperscript{40} Analysis of the CO\textsubscript{2}-functionalized

\textbf{Scheme 3. Proposed mechanism for dicarboxylate formation from CO\textsubscript{2} – ethylene coupling}
products required protonolysis by a strong acid in the presence of ethanol, after which the products were identified by their corresponding ethyl esters. Analysis by GC-MS found a mixture of saturated and unsaturated carboxylate products as well as dicarboxylates containing between one and ten ethylene units incorporated (Scheme 4). The proposed mechanism that gives rise to these various products includes the formation of a transient iron-lactone that undergoes subsequent reactions with ethylene, CO$_2$, or H$_2$ (Scheme 4). Unfortunately, sub-stoichiometric quantities of carboxylate products were obtained, with yields of less than 14% versus iron.

**Scheme 4. Carboxylate formation mediated by (iPrPDI)Fe(N$_2$)$_2$**
A recent report from our lab detailed the successful coupling of ethylene and CO$_2$ using a bis-ligated (diethylphosphino)ethane (depe) iron complex (Scheme 5). Addition of a 2:1 ratio of ethylene and CO$_2$ to an isolated sample of the ethylene complex (depe)$_2$Fe(C$_2$H$_4$) resulted in the formation of an isolable iron-lactone that was characterized crystallographically. However, this electronically saturated complex was unable to undergo β-hydride elimination and would require the dissociation of one or more ligands in order to achieve this transformation. The addition of excess sodium tert-butoxide (NaOttBu) and gentle heating of the Fe-lactone successfully liberated the acrylate moiety. Unfortunately, the CO$_2$-rich environments required for catalysis are incompatible with strong bases due to the competitive formation of organocarbonate products. Weaker sodium phenoxide bases, which react reversibly with CO$_2$, were also capable of producing free acrylate when combined with the Lewis acid lithium triflate (LiOTf). This additive was found to be essential for Fe-lactone cleavage, as no free acrylate was detected from the addition of a phenoxide base alone.

Unfortunately, attempts to use (depe)$_2$Fe(C$_2$H$_4$) for catalytic acrylate production were unsuccessful and sub-stoichiometric levels of acrylate were only produced in the presence of NaOttBu (Scheme 5). There are, however, some notable differences in the reactivity of (depe)$_2$Fe(C$_2$H$_4$) and the previously reported iron complexes capable of CO$_2$-ethylene coupling. Unlike the (PEt$_3$)$_2$Fe(C$_2$H$_4$)$_2$ complex reported by Hoberg, the reaction
of (depe)$_2$Fe(C$_2$H$_4$) with CO$_2$ and ethylene did not result in the insertion of two equivalents of CO$_2$. Additionally, the insertion of multiple ethylene units was not observed, in contrast with the reactivity of Chirik’s (P$_{PDI}$)Fe(N$_2$)$_2$ complex. The formation of (depe)$_2$Fe-lactone affords an 18-electron complex that is unable to undergo β-hydride elimination, effectively marking a dead end en route to developing an iron catalyst for acrylate production. Therefore, efforts in our lab turned to the development of a similar electron-rich Fe complex that would afford a 16-electron species upon CO$_2$-ethylene coupling.

3.2 Results and Discussion

3.2.1 Development of an Alkylated Tridentate Ligand

Initial considerations focused on reviewing previous reports of tridentate Fe(0) complexes containing an ethylene or labile ligand that could be replaced by ethylene. Although no such ethylene complexes had been reported, a bis-N$_2$ iron complex featuring the tridentate ligand tert-butyl-bis-[2-(dicyclohexylphosphino)ethyl]phosphine (CyP$_3$) was published by Mézailles et al. in 2018. Although this complex was used for N$_2$ reduction rather than CO$_2$ reduction, the lability of N$_2$ made this an attractive target for our purposes. In an effort to more closely mimic the depe ligand employed in our previous studies, a slightly modified version of the ligand reported by Mézailles et al. was targeted in which the terminal cyclohexyl substituents were replaced with ethyl groups.

A majority of existing precedent for the synthesis of such phosphine complexes call for a two-step procedure that requires isolation of the volatile divinyl-tert-butylphosphine (tBuP(vinyl)$_2$) intermediate and subsequent radical-initiated hydrophosphinization with a
secondary phosphine (Scheme 6, top). However, this method consistently resulted in disappointingly low yields of \( \textit{tBuP(vinyl)}_2 \) (<15%) and the radical-initiated coupling was unsuccessful in our hands. To overcome these challenges, a “one-pot” procedure was developed that avoided isolation of the divinyl phosphine and employed a base-mediated method of coupling, a commonly used alternative for such hydrophosphination reactions (Scheme 6, bottom).

Dropwise addition of vinyl Grignard to an ether solution of dichloro-tert-butylphosphine (tBuPCl\(_2\)) resulted in the precipitation of magnesium salts. Formation of \( \textit{tBuP(vinyl)}_2 \) was complete within two hours of stirring at ambient temperatures. The reaction solution was then filtered through Celite in a Pasteur pipet into a 250 mL Schlenk flask, to which 1.9 molar equivalents of diethylphosphine (Et\(_2\)PH) were added and the flask sealed with a septa. Published procedures for base-mediated hydrophosphination reactions report product formation upon the addition of catalytic amounts of lithium di-iso-propylamide (LDA). However, for reasons that are unclear, an excess of LDA (5 equivalents) was required for the successful coupling of \( \textit{tBuP(vinyl)}_2 \) and Et\(_2\)PH.

Following the addition of 5 eq. LDA, the reaction solution was observed to change from light-yellow to dark-red in color and reaction progress was monitored via \(^{31}\text{P}\) NMR analysis of reaction aliquots. The reaction was quenched with DI water that had been sparged with Argon following full conversion of the \( \textit{tBuP(vinyl)}_2 \) \(^{31}\text{P}\) signal at 4.43 ppm.
to the product signals located at -17.03 (d, $J = 23.2$ Hz) and 9.12 (t, $J = 23.2$ Hz) ppm. The aqueous layer was extracted with two 20 mL portions of ether and the resulting light-yellow organic layer was cannula transferred into a Schlenk frit packed with sodium sulfate, the filtrate collected in a 250 mL Schlenk flask, and the solvent removed under vacuum. This one-pot synthesis affords tert-butyl-bis[2-(diethylphosphino)ethyl]phosphine (dBuP(depe)$_2$; $P_3$) in high yields and was used without further purification.

3.2.2 Synthesis and Reactivity of $P_3$Fe Complexes

Following isolation of the $P_3$ ligand, investigations were conducted to probe the reactivity of various $P_3$Fe complexes. The Fe(II) complex, $P_3$FeCl$_2$ ($1a$), was generated upon dropwise addition of a THF solution of $P_3$ to a THF solution of FeCl$_2$, resulting in an immediate color change to dark blue. The reaction solution was stirred at ambient temperatures overnight, at which point the solution was filtered through Celite in a Pasteur pipet and the THF removed under vacuum. The resulting dark blue oil was triturated with pentane to yield $1a$ as a fine powder in near quantitative yields. A broad paramagnetic signal was detected in the $^1$H NMR spectrum at approximately 27 ppm in benzene-$d_6$ and the magnetic moment was measured to be 5.5 $\mu_B$ in solution using the Evans method (Eq. 1 and 2). A spin-only value of 4.9 $\mu_B$ is calculated for high spin, $S = 2$ complex,

$$\mu_{eff} = \frac{3k}{N(\mu_0)(\mu_B)^2} \sqrt{(X_M)T}$$

Eq. 1.

$$= 798\sqrt{(X_M)T}$$

$k = $ Boltzmann constant

$N = $ Avogadro’s number

$\mu_0 = $ permeability of vacuum

$\mu_B = $ Bohr magneton

$$X_M = \frac{6(\Delta f)}{1000(c)(f)}$$

Eq. 2.

$c = $ conc. of sample (M)

$\Delta f = $ frequency shift (Hz)

$f = $ spectrometer frequency (Hz)
which is within the range of experimentally determined values reported (5.0 – 5.6 \( \mu_B \)) (Figure 2).

Reduction of 1a by KC\(_8\) was carried out in the presence of 3 atm of ethylene and resulted in the formation of a brown diamagnetic complex (2a) that exhibited a triplet at 124.89 ppm (\( J_{P-P} = 36.5 \) Hz) and a doublet at 86.57 ppm (\( J_{P-P} = 36.5 \) Hz) in the \(^{31}\)PNMR spectrum. The presence of a coordinated ethylene unit was confirmed by \(^1\)H – \(^{13}\)C HSQC NMR analysis, which revealed a single-bond correlation between the \(^{13}\)C resonance at 24.07 ppm and a multiplet at 1.53 ppm in the \(^1\)H NMR spectrum. Consideration of the NMR data, combined with a distinctive N-N stretch (\( \nu_{NN} = 2050 \) cm\(^{-1}\)) observed in the liquid-phase IR, suggest the identity of complex 2a to be the ethylene-N\(_2\) iron complex \( \text{P}_3\text{Fe(C}_2\text{H}_4)(\text{N}_2) \). Samples suitable for XRD were grown from a concentrated pentane solution cooled at \(-45^\circ\)C for several weeks, which confirmed the identity of 2a.

Analysis of the crystallographic data revealed complex 2a to be arranged in a distorted trigonal bipyramidal geometry wherein the central chelate phosphorous atom and N\(_2\) occupy the axial positions and the terminal chelate phosphorous atoms and \( \eta^2\)-coordinated ethylene occupy the equatorial positions (Figure 3). Similar tridentate Fe(0)
complexes reported by Mézailles et al. were found to form bis-dinitrogen species when reduced under a nitrogen atmosphere; however, XRD analysis of those complexes revealed square pyramidal geometries. This discrepancy is likely due to the coordination of the more sterically demanding ethylene group, which forces the central P₃ phosphorous atom from the equatorial position and into the axial position.

Upon the addition of 1 molar equivalent of ethylene to an isolated sample of 2a in benzene-δ6, new peaks were observed in the ³¹P NMR spectrum at 156.87 ppm (t, J = 16.5 Hz) and 74.89 ppm (d, J = 16.5 Hz), indicating the formation of the bis-ethylene complex P₃Fe(C₂H₄)₂ (3) (Scheme 7). Gradual conversion of 2a to 3 was observed via ³¹P NMR analysis, eventually reaching an equilibrium consisting of 35% 2a and 65% 3 after 3 days at ambient temperatures. Increasing the equivalents of ethylene was found to have only small influence on production of 3, with a large excess of ethylene (13 eq.) resulting in only 70% conversion. Attempts to isolate 3 were unsuccessful, however, due to regeneration of complex 2 following the removal of solvent under vacuum and exposure to an N₂ glove box atmosphere. For this reason, further characterization of 3 was limited to in situ NMR analysis.

The addition of ¹³C-labeled ethylene to complex 2a (Figure 4, blue spectrum) resulted in the partial conversion to the isotopically labeled P₃Fe(¹³C₂H₄)₂ (3*) (Figure 4, red spectrum). Analysis of the ¹³C NMR spectrum revealed enhancement of the original
$\eta^2$-ethylene signal at 24.07 ppm as well as a new enhanced signal at 24.62 ppm corresponding to the second ethylene unit. Coordination of $^{13}$C-labeled ethylene \textit{trans} to the P-\textit{t}Bu group resulted in carbon-phosphorous coupling that split the signal into a doublet of doublets. The observed shift of this resonance to a more upfield location is likely due to the strong \textit{trans} influence of ethylene compared to N$_2$. Regeneration of complex 2a was observed following the removal of $^{13}$C$_2$H$_4$ under vacuum and exposure to N$_2$, although the relative intensity of the $\eta^2$-ethylene signal at 24.07 ppm was notably enhanced, indicating incorporation of the labeled ethylene into the N$_2$ complex.

Figure 4. Comparison of the $^{13}$C NMR spectra for complexes 2a and 3* $^a$

$^a$ Characterization of stacked spectra and labeled peaks. Blue spectrum: complex 2a in C$_6$D$_6$, P$t$Bu (27.71 ppm), Fe-$^{13}$C$_2$H$_4$ (24.07 ppm). Red spectrum: complex 2a + 5 eq. $^{13}$C$_2$H$_4$ $\rightarrow$ 3*, P$t$Bu (29.40 ppm), Fe-$^{13}$C$_2$H$_4$ (24.62, 24.07 ppm).
3.2.3 Investigations of Ethylene-CO$_2$ Coupling Mediated by Complex 2a

Having successfully synthesized and characterized 2a, efforts shifted to probing the ability of this complex to facilitate the coupling of ethylene and CO$_2$. Initial investigations were conducted on a NMR-scale (~10 mg of 2a / 500 μL solvent) in the presence of an excess of ethylene and $^{13}$CO$_2$ to allow for unambiguous detection of any CO$_2$-functionalized products. Following the addition of a 3:1 mixture of C$_2$H$_4$ : $^{13}$CO$_2$ to a sample of 2a in C$_6$D$_6$, a fine red precipitate (4*) was observed to form within 15 minutes, the presence of which obscured characterization via NMR analysis. Solid-state IR of complex 4* revealed the presence of a strong C-O stretch ($v_{13CO} = 1549$ cm$^{-1}$), indicating the incorporation of $^{13}$CO$_2$ into the organometallic complex. Comparison of this data to a sample generated with non-labeled CO$_2$ (4) resulted in a shift of the C-O stretch to 1585 cm$^{-1}$, in agreement with the predicted frequency obtained from a Hooke’s Law model of the vibration (Figure 5).

![Figure 5. Hooke’s Law and the prediction of IR stretching frequencies](image)

Further characterization of 4* proved exceedingly difficult due to lack of solubility in numerous solvents including THF, chloroform, methylene chloride, acetone, and isopropanol. Although complex 4* appeared visibly soluble in DMSO-$d_6$ and CD$_5$Cl, no isotopically labeled species were observed in the $^{13}$C NMR spectrum. However, following the addition of CD$_3$CN to a sample of 4* a single $^{13}$C resonance was observed at 178.42
ppm, confirming the formation of a CO$_2$-functionalized species. Attempts to generate 4* in CD$_3$CN were unsuccessful due to the instability of 2a in acetonitrile, therefore coupling reactions were carried out in C$_6$D$_6$ or THF and ensuing characterization was conducted in CD$_3$CN. Conclusive assignment of the $^{31}$P NMR spectrum proved difficult as numerous, complex and overlapping signals were observed, suggesting the reaction is not highly selective. However, major resonances were observed at 102.47 ppm (d, $J = 18.3$ Hz), 97.81 ppm (d, $J = 18.3$ Hz), and 88.13 ppm (broad) and are tentatively attributed to 4*.

Analysis of the $^1$H – $^{13}$C HSQC and HMBC NMR data of 4* in CD$_3$CN revealed a correlation between the carbonyl signal at 178.42 ppm and proton signals at 3.25 ppm and 1.01 ppm, the phasing of which were indicative of methyl/methine groups. Protonolysis of the sample by HCl vapor resulted in the formation of methylmalonic acid (MMA), which was verified by the addition of an authentic MMA to the sample. These findings suggest that the identity of 4* is likely an iron-methylmalonate complex of the formula ($P_3$)Fe(κ$_2$-OOCCH(CH$_3$)COO) ($P_3$Fe-OMM*).

The reactivity of 2a toward CO$_2$ and ethylene appears to resemble that of the complexes previously reported by Hoberg and Chirik (vide supra), where a second equivalent of CO$_2$ is inserted following β-hydride elimination and 2,1-insertion (Scheme 8).$^{39, 40}$ To further examine this theory, an excess of ethylene and exactly 1 eq. of $^{13}$CO$_2$ were added to 2a in C$_6$D$_6$ and the reaction was monitored by NMR spectroscopy. Partial conversion to the bis-ethylene complex 3 was observed within 10 minutes, but the formation of precipitate shortly thereafter required the addition of CD$_3$CN for further NMR analysis. Examination of the $^{13}$C NMR spectra revealed selective formation of the iron-
methylmalonate complex $4^a$, indicating insertion of a second CO$_2$ molecule occurs rapidly even at reduced pressures of CO$_2$. The ability of $2a$ to facilitate oxidative coupling of CO$_2$ and ethylene is a promising first step towards the development of an iron catalyst for acrylate production. However, the insertion of multiple CO$_2$ moieties appears to be a common occurrence among the limited reports of such iron-mediated reactions. Prevention of this double insertion is therefore fundamental to tuning the selectivity of CO$_2$-functionalized products to produce mono-carboxylates such as acrylate.

3.2.4.1 Prevention of Double CO$_2$ Insertion: Modification of Tridentate Sterics

Initial investigations focused on the synthesis of more sterically encumbered variants of the P$_3$ ligand based on the hypothesis that it may restrict access to the metal center and slow the insertion of a second CO$_2$ moiety. The iso-propyl- and cyclohexyl-substituted variants iPrP$_3$ and CyP$_3$ were synthesized using the same one-pot method employed for the ethyl-substituted ligand (Scheme 9). Metalation reactions occurred readily upon addition of a THF solution of the ligand to a THF solution of FeCl$_2$ to yield the iPr- and CyP$_3$FeCl$_2$ complexes 1b and 1c, respectively (Scheme 9). Reduction by
KC$_8$ in the presence of 3 atm ethylene resulted in the isolation of the respective ethylene-N$_2$ complexes 2b and 2c (Scheme 9).

**Scheme 9. Synthesis of iPr and Cy variants of P$_3$, 1a, and 2a**

Crystals suitable for XRD analysis were grown from concentrated pentane solutions of 2b and 2c. Comparison of the crystallographic data collected for the ethylene-N$_2$ complexes 2a-c revealed some notable differences in their structural properties (Figure 6). Elongation of the coordinated ethylene C-C bond (relative to free ethylene; 1.339 Å) was observed for all three complexes, however 2b displayed the longest C-C ethylene bond of 1.418(6) Å, suggesting this complex is slightly more reducing than 2a or 2c (Table 1, entry 2). Analysis of the geometric parameters for these complexes revealed the trigonal bipyramidal geometry of 2a is markedly more distorted than that of 2b and 2c, evidenced by their respective tau ($\tau$) values – a measure of molecular geometry. (Table 1, entry 7). For five-coordinate complexes such as 2a-c, a tau value of 0 corresponds with a square pyramidal geometry and a tau value of 1 corresponds with a trigonal bipyramidal geometry.

**Figure 6. Structure of complex 2b (left) and 2c (right)**
With this data in hand, a comparative analysis of the percent buried volume (%V<sub>Bur</sub>) was conducted to gain further insight into the coordination sphere surrounding the iron center (Figure 7).<sup>47</sup> Of the three ethylene-N<sub>2</sub> complexes, 2a was found to be approximately 5% less encumbered than 2b and 2c, with a total %V<sub>Bur</sub> of 64.8 (Table 2, entry 1). The dinitrogen was found to occupy the most accessible site within the coordination sphere, with a quadrant %V<sub>Bur</sub> of 31.1, 36.7, and 35.2 for complexes 2a, 2b, and 2c, respectively (Table 2, entry 2). The quadrant containing the central P-tBu group was found to be the most sterically crowded region for all three complexes.

<table>
<thead>
<tr>
<th>Entry</th>
<th>%V&lt;sub&gt;Bur&lt;/sub&gt;</th>
<th>PR&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Total</td>
<td>Et (2a)</td>
</tr>
<tr>
<td>2</td>
<td>SW</td>
<td>iPr (2b)</td>
</tr>
<tr>
<td>3</td>
<td>NW</td>
<td>Cy (2c)</td>
</tr>
</tbody>
</table>

*Generated using SambVca 2.1.*

<sup>a</sup> Steric maps for complex 2a (top), 2b (middle), and 2c (bottom).
with \( \%V_{\text{Bur}} \) of 86.2, 88.0, and 88.2 for 2a, 2b, and 2c, respectively (Table 2, entry 4). Next, the reactivity of these complexes with ethylene and CO\(_2\) was examined.

Following the addition of an excess of ethylene to C\(_6\)D\(_6\) solutions of 2b and 2c, no bis-ethylene iron species were observed in the \(^{31}\)P NMR spectra. It would appear the more sterically protected metal centers of these complexes inhibits the coordination of a second ethylene unit, a finding which can be rationalized by consideration of the total \( \%V_{\text{Bur}} \) and \( \%V_{\text{Bur}} \) of the SW dinitrogen quadrant of 2a-c (Table 2, entry 2). These results confirm the ability to affect reactivity at the metal center via ancillary ligand alteration, a promising first step towards tuning the selectivity of CO\(_2\)-coupled products. However, the reactivity of 2b and 2c with ethylene and CO\(_2\) was found to closely resemble that of 2a.

After 18 hours at ambient temperatures, precipitate was observed to have collected in the bottom of the J-Young tubes containing C\(_6\)D\(_6\) solutions of 2b and 2c in the presence of a 3:1 mixture of ethylene : \(^{13}\)CO\(_2\). Protonolysis of the samples by HCl vapor revealed the exclusive production of MMA for both complexes. The incorporation of more sterically demanding ligand substituents appears to have little effect on the propensity for double CO\(_2\) insertion despite effectively preventing the coordination of a second ethylene (Scheme 10). For this reason, alternative methods for inhibiting double CO\(_2\) insertion were explored.

3.2.4.2 Prevention of Double CO\(_2\) Insertion: Mono-Dentate Ligand Addition

Consideration of the precedent for iron-mediated CO\(_2\) – olefin coupling revealed two general conditions that give rise to mono-carboxylate products: incorporation of olefins containing 4 or more carbons (e.g. 1,4-butadiene), and saturation of the
Coordination sphere about the iron center. Clearly, the use of a substrate other than ethylene would not be productive for acrylate formation and can therefore be ruled out. In the case of the (depe)$_2$Fe(C$_2$H$_4$) complex previously reported by our lab, double CO$_2$ insertion was not observed due to electronic saturation of the Fe-lactone that resulted from CO$_2$-ethylene coupling. However, this also prevented β-hydride elimination and catalytic activity, which spurred the investigations that ultimately lead to the development of complex 2a.

Ironically, decreasing the coordination sphere from two bidentate ligands to one tridentate ligand appears to have solved one problem while causing another. The creation of an open coordination site allows for β-hydride elimination to occur – based on selective formation of the MMA isomer – but also opens the door to a second CO$_2$ insertion. It is likely that the presence of chelating ligands in the bis-depe system prevented ligand dissociation that would have been required to undergo β-hydride elimination. Therefore, the addition of a mono-dentate ligand to complex 2a could create a coordination sphere similar to the bis-depe system while introducing a more easily dissociated ligand. To examine this hypothesis, a variety of dative ligands with an assortment of steric environments were surveyed for their coordination sphere about the iron center. Clearly, the use of a substrate other than ethylene would not be productive for acrylate formation and can therefore be ruled out. In the case of the (depe)$_2$Fe(C$_2$H$_4$) complex previously reported by our lab, double CO$_2$ insertion was not observed due to electronic saturation of the Fe-lactone that resulted from CO$_2$-ethylene coupling. However, this also prevented β-hydride elimination and catalytic activity, which spurred the investigations that ultimately lead to the development of complex 2a.

Ironically, decreasing the coordination sphere from two bidentate ligands to one tridentate ligand appears to have solved one problem while causing another. The creation of an open coordination site allows for β-hydride elimination to occur – based on selective formation of the MMA isomer – but also opens the door to a second CO$_2$ insertion. It is likely that the presence of chelating ligands in the bis-depe system prevented ligand dissociation that would have been required to undergo β-hydride elimination. Therefore, the addition of a mono-dentate ligand to complex 2a could create a coordination sphere similar to the bis-depe system while introducing a more easily dissociated ligand. To examine this hypothesis, a variety of dative ligands with an assortment of steric environments were surveyed for their coordination sphere about the iron center. Clearly, the use of a substrate other than ethylene would not be productive for acrylate formation and can therefore be ruled out. In the case of the (depe)$_2$Fe(C$_2$H$_4$) complex previously reported by our lab, double CO$_2$ insertion was not observed due to electronic saturation of the Fe-lactone that resulted from CO$_2$-ethylene coupling. However, this also prevented β-hydride elimination and catalytic activity, which spurred the investigations that ultimately lead to the development of complex 2a.

Ironically, decreasing the coordination sphere from two bidentate ligands to one tridentate ligand appears to have solved one problem while causing another. The creation of an open coordination site allows for β-hydride elimination to occur – based on selective formation of the MMA isomer – but also opens the door to a second CO$_2$ insertion. It is likely that the presence of chelating ligands in the bis-depe system prevented ligand dissociation that would have been required to undergo β-hydride elimination. Therefore, the addition of a mono-dentate ligand to complex 2a could create a coordination sphere similar to the bis-depe system while introducing a more easily dissociated ligand. To examine this hypothesis, a variety of dative ligands with an assortment of steric environments were surveyed for their coordination sphere about the iron center. Clearly, the use of a substrate other than ethylene would not be productive for acrylate formation and can therefore be ruled out. In the case of the (depe)$_2$Fe(C$_2$H$_4$) complex previously reported by our lab, double CO$_2$ insertion was not observed due to electronic saturation of the Fe-lactone that resulted from CO$_2$-ethylene coupling. However, this also prevented β-hydride elimination and catalytic activity, which spurred the investigations that ultimately lead to the development of complex 2a.

Ironically, decreasing the coordination sphere from two bidentate ligands to one tridentate ligand appears to have solved one problem while causing another. The creation of an open coordination site allows for β-hydride elimination to occur – based on selective formation of the MMA isomer – but also opens the door to a second CO$_2$ insertion. It is likely that the presence of chelating ligands in the bis-depe system prevented ligand dissociation that would have been required to undergo β-hydride elimination. Therefore, the addition of a mono-dentate ligand to complex 2a could create a coordination sphere similar to the bis-depe system while introducing a more easily dissociated ligand. To examine this hypothesis, a variety of dative ligands with an assortment of steric environments were surveyed for their coordination sphere about the iron center. Clearly, the use of a substrate other than ethylene would not be productive for acrylate formation and can therefore be ruled out. In the case of the (depe)$_2$Fe(C$_2$H$_4$) complex previously reported by our lab, double CO$_2$ insertion was not observed due to electronic saturation of the Fe-lactone that resulted from CO$_2$-ethylene coupling. However, this also prevented β-hydride elimination and catalytic activity, which spurred the investigations that ultimately lead to the development of complex 2a.

Ironically, decreasing the coordination sphere from two bidentate ligands to one tridentate ligand appears to have solved one problem while causing another. The creation of an open coordination site allows for β-hydride elimination to occur – based on selective formation of the MMA isomer – but also opens the door to a second CO$_2$ insertion. It is likely that the presence of chelating ligands in the bis-depe system prevented ligand dissociation that would have been required to undergo β-hydride elimination. Therefore, the addition of a mono-dentate ligand to complex 2a could create a coordination sphere similar to the bis-depe system while introducing a more easily dissociated ligand. To examine this hypothesis, a variety of dative ligands with an assortment of steric environments were surveyed for their
reactivity with complex \(2a\) (Table 3) and the reactions were monitored via \(^{31}\text{P}\) NMR spectroscopy.

**Table 3. Reactivity of Mono-Dentate Ligands with Complex 2a**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>(R_1)</th>
<th>(R_2)</th>
<th>(R_3)</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PCy(_3)</td>
<td>Cy</td>
<td>Cy</td>
<td>Cy</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>PPh(_3)</td>
<td>Ph</td>
<td>Ph</td>
<td>Ph</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>PMePh(_2)</td>
<td>Me</td>
<td>Ph</td>
<td>Ph</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>PMe(_2)Ph</td>
<td>Me</td>
<td>Me</td>
<td>Ph</td>
<td>5a</td>
</tr>
<tr>
<td>5</td>
<td>PMe(_3)</td>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>5b</td>
</tr>
<tr>
<td>6</td>
<td>tBuNC</td>
<td>N≡C:</td>
<td></td>
<td></td>
<td>5c</td>
</tr>
<tr>
<td>7</td>
<td>Py</td>
<td></td>
<td></td>
<td></td>
<td>–</td>
</tr>
</tbody>
</table>

*a* Conditions: Approximately 10 mg \(2a\) was combined with 1 eq. ligand in 500 \(\mu\)L \(C_6D_6\) and monitored via \(^{31}\text{P}\) NMR analysis.

The results of the mono-dentate ligand survey revealed a limit to the degree of steric encumbrance that could be tolerated for coordination. Phosphine ligands featuring two or more bulky substituents – such as tricyclohexylphosphine (PCy\(_3\)), triphenylphosphine (PPh\(_3\)), and methyldiphenylphosphine (PMePh\(_2\)) – were unable to coordinate to the iron center (Table 3, entries 1-3). However, the smaller dimethylphenylphosphine (PMe\(_2\)Ph), trimethylphosphine (PMe\(_3\)), and tert-butyl isocyanide (tBuNC) were found to undergo immediate reaction with \(2a\) (Table 3, entries 4-6), giving rise to the PMe\(_2\)Ph-, PMe\(_3\)-, and
(tBuNC)P₃Fe(C₂H₄) complexes 5a, 5b, and 5c, respectively. The characterization of these complexes as mono-ethylene species was confirmed by analysis of their respective ¹H – ¹³C HSQC NMR data. The ³¹P NMR spectra of 5a and 5b featured the same series of diagnostic peaks: two doublet of triplets and a doublet of doublets. These splitting patterns are consistent with a coordination sphere occupied by two equivalent phosphorous atoms coupled with two inequivalent phosphorous atoms. The reaction of 2a with tBuNC gave rise to a 5:1 mixture of phosphorous-containing products with distinct ³¹P resonances each consisting of a doublet and triplet. Analysis of the liquid-phase IR of 5c revealed multiple overlapping C-N stretching frequencies at approximately νCN = 1974 cm⁻¹, supporting the characterization of electronically inequivalent (tBuCN)P₃Fe(C₂H₄) complexes – possibly arising from axial- and equatorial-tBuCN isomers.

With complexes 5a-c in hand, reactions were carried out to examine their capacity to facilitate CO₂-ethylene coupling. The reaction of 5a with a 3:1 mixture of ethylene and ¹³CO₂ did not result in the formation of CO₂-functionalized products, as determined by ³¹P and ¹³C NMR spectroscopy. In contrast, 5b displayed strikingly similar reactivity to that of 2a with precipitate formation observed within an hour of the ¹³CO₂-ethylene addition. Examination of the organometallic species in CD₃CN revealed a single resonance in the ¹³C NMR at 178.58 ppm – consistent with that observed for complex 4#. The ³¹P data revealed several notable similarities to that obtained for 4# including a doublet at 102.47 ppm (J = 19.4 Hz), a multiplet 88.06 ppm and a doublet of doublets at 80.06 ppm (J = 24.3, 46.7 Hz). Protonolysis of this sample by HCl vapor confirmed the identity of the ¹³C-labeled species to be MMA, thereby ruling out complex 5b as a viable alternative to prevent double CO₂ insertion.
Despite numerous unsuccessful attempts to purify the tBuNC complex, the mixture of 5c species (5:1) was carried forward and its reactivity in the presence of a 3:1 mixture of ethylene and $^{13}$CO$_2$ was monitored over time via NMR analysis. The $^{13}$C NMR of the reaction mixture revealed the presence of a $^{13}$C-labeled species at 187.68 ppm as well as free $^{13}$CO$_2$ and free ethylene. Disappearance of the $^{31}$P signals assigned to the major 5c isomer tracked with the appearance of a new species characterized by resonances at 102.56 ppm (dd, $J = 19.9$, 36.2 Hz), 91.58 ppm (dd, $J = 4.6$, 36.2 Hz), and 80.52 (ddd, $J = 4.6$, 13.5, 25.5 Hz) in the $^{31}$P spectrum. After 4.5 days at ambient temperatures, the relative intensity of the $^{13}$C-labeled species did not appear to increase and free ethylene and $^{13}$CO$_2$ were still present in the sample, so the reaction was quenched via HCl protonolysis. Subsequent $^{13}$C NMR analysis revealed a mixture of carboxylate products, of which the major was identified as MMA.

Although the “1+3” ligand coordination of 5a-c is strikingly similar to that of the “2+2” bis-depe species previously reported by our lab, the reactivity of these two classes of complexes bear considerable differences. It appears that the combination of a monodentate and tridentate ligand systems is not sufficient for preventing the insertion of a second CO$_2$ moiety into the transient Fe-lactone. Nevertheless, these findings provide useful insight into the broader reactivity of this system (Scheme 11). The inability of 5b and 5c to form bis-ethylene complexes, but still result in MMA production in the presence of ethylene and CO$_2$ is similar to the reactivity observed for complexes 2b and 2c. On the other hand, the failure of 5a to generate any CO$_2$-functionalized products suggests that dissociation of PMe$_2$Ph ligand is likely not occurring and the presence of this sterically
demanding group restricts access to the metal center to the point where CO₂ activation is unable to occur.

Having exhausted the readily available steric change for preventing insertion of a second CO₂ moiety, efforts turned to investigating alternative methods to modify the reactivity of complex 2a. The addition of exogeneous base has proved to be a successful means of acrylate production in numerous Ni systems as well as the bis-depe Fe system.¹ 2, 21-25, 41 In both systems, the base was instrumental in facilitating lactone deprotonation due to the inability of the metal center to undergo β-hydride elimination. Although this transformation is proposed to readily occur for complex 2a, it is possible that the rate of base-mediated lactone deprotonation could outcompete the rate of the second CO₂ insertion. Therefore, a series of experiments were conducted to investigate this hypothesis.

3.2.4.3 Prevention of Double CO₂ Insertion: Base-Mediated Lactone Deprotonation

The effect of base on the coupling of CO₂ and ethylene mediated by complex 2a was examined in the presence of two distinct bases – sodium tert-butoxide (NaOtBu) and
sodium 2-chlorophenoxide (2-ClPhONa). Previous work from our lab has demonstrated the effectiveness with which weak phenoxide bases are able to facilitate acrylate formation within Ni-based systems. Unlike strong alkoxide bases such as NaOtBu, phenoxide bases have been shown to reversibly react with CO₂ making them more compatible with the CO₂-rich conditions required for acrylate production. However, investigations of base-mediated reactions within the bis-depe iron system found that NaOtBu was the only base to result in acrylate formation under CO₂ pressure.

For this reason, both classes of base were examined for their ability to facilitate acrylate formation in the presence of 2a. Addition of 10 equivalents of NaOtBu and 2-ClPhONa to separate samples of 2a in a THF/C₆D₆ solution were exposed to a 3:1 mixture of ethylene and ¹³CO₂ and monitored via ¹³C NMR analysis. After 18 hours at ambient temperatures, no CO₂-functionalized products were observed in either base reaction as determined by ¹³C NMR analysis. However, protonolysis by HCl addition revealed the presence of an enhanced signals in the ¹³C NMR spectrum at 170.6 ppm. The identity of this species was confirmed to be MMA by addition of an authentic sample to each reaction solution.

The production of MMA despite the addition of excess NaOtBu disproves the hypothesis that the rate of base-mediated lactone deprotonation may outcompete the rate of the second CO₂ insertion that is proposed to give rise to methylmalonate products. Considering the nucleophilic nature of the second CO₂ insertion, it is possible that by making the metal less electron-rich, this reaction could be slowed or even prevented. Although this has the potential to adversely affect the initial coupling reaction, all other methods of preventing double CO₂-insertion have proved unsuccessful. Therefore,
investigations were conducted to probe whether a one-electron oxidation of \textbf{2a} would result in selective formation of mono-carboxylate products from CO$_2$-ethylene coupling.

\textit{3.2.4.4 Prevention of Double CO$_2$ Insertion: P$_3$Fe(C$_2$H$_4$)(N$_2$) Oxidation}

Initial oxidation studies were conducted in the presence of ferrocenium tetrafluoroborate (FcBF$_4$), a commonly used chemical oxidizing agent for organometallic complexes. However, this oxidizing agent was not soluble in any of the known solvents compatible with \textbf{2a}. Review of various chemical redox agents and their solubility revealed AgBF$_4$ to be a comparable one-electron oxidizing agent that is soluble in THF.$^{48}$ The addition of 1 equivalent of AgBF$_4$ to \textbf{2a} in THF resulted in the immediate formation of a black precipitate, likely silver particulates. Filtration of the dark brown reaction solution through Celite allowed for NMR analysis of the oxidized species. Examination of the \textsuperscript{31}P NMR spectrum appeared to indicate the complete consumption of the diamagnetic complex \textbf{2a}, although no paramagnetic resonances were observed in the \textsuperscript{1}H NMR spectrum, suggesting an NMR silent species was formed.

Despite the lack of signals in the proton spectrum, the reaction solution was treated with a 3:1 mixture of ethylene and $^{13}$CO$_2$ to examine the reactivity of any oxidized species present. A red precipitate was observed to form after 18 hours at ambient temperatures, after which the solvent was removed under vacuum, the reaction contents dissolved in CD$_3$CN and examined via NMR spectroscopy. Surprisingly, a mixture of two species were present in the $^{13}$C spectrum with resonances at 189.38 and 178.43 ppm. The more upfield and minor of these signals corresponds with that observed for complex \textbf{4*}. However, the more downfield and major signal at 189.38 ppm is significantly shifted and had not been observed in previous reactions. These findings support the assertion that the reaction of \textbf{2a}
with AgBF$_4$ yields an oxidized P$_3$Fe species (6) that is capable of CO$_2$ functionalization. Upon protonolysis by HCl, a mixture of propionic acid (PA) and MMA were observed in the $^{13}$C spectrum, as confirmed by the addition of authentic samples to the reaction solution. Based on their relative integration, the ratio of these two products was determined to be approximately 2:1 (PA:MMA) when the number of representative carbons is accounted for.

The observed reactivity of the oxidized species 6 is markedly distinct to that of complex 2a and confirms that the problematic insertion of two CO$_2$ moieties can, in fact, be attenuated. Attempts to characterize complex 6 via NMR analysis proved unsuccessful as paramagnetic signals were never detected despite numerous synthetic attempts. Cyclic voltammetry (CV) of 2a revealed two oxidation peaks at approximately -0.67 and -1.03 V (vs Fc) (Figure 8), that may be attributed to successive one electron oxidations of a single Fe$^0$ species (Fe$^0$/Fe$^I$ and Fe$^I$/Fe$^{II}$). The observed potentials confirm that the selected chemical oxidizing agent AgBF$_4$ is sufficiently oxidizing to generate an Fe$^I$ species if used in stoichiometric amounts, however there is the potential for over-oxidation if an excess of AgBF$_4$ is used.

Although the formation of the mono-carboxylate product, propionic acid, from the reaction of CO$_2$ and ethylene with 6 is compelling, the quantification of these products is essential to determining the viability of the
P₃Fe system as a potential catalyst for acrylate production. To date, the best reported yield for mono- and dicarboxylate products from iron-mediated CO₂-ethylene coupling is 13.20 and 60% respectively.³⁹,⁴⁰ In order to compare the P₃Fe system to these previous reports, efforts shifted to quantifying yields of CO₂-functionalized products from the P₃Fe system for CO₂-ethylene coupling.

3.2.5 Quantification of Carboxylate Products Resulting from Iron-Mediated Coupling

Of the limited precedent of iron-mediated CO₂-ethylene coupling, there exists even fewer details regarding product quantification. Work from both Hoberg and Chirik report GC-MS methods of analysis following protonolysis of the organometallic species in the presence of an alcohol.³⁹,⁴⁰ To verify the efficacy of this method, a sample of lithium methylmalonate (LiOMM) was subjected the conditions reported by Chirik and quantified by GC-FID.⁴⁰ The measured yield of the respective ethyl ester obtained from this method was found to be 44.73%. Various other conditions were explored to improve the efficacy of ethanolysis including the addition of catalysts such as LiOTf and triethyl orthoformate, extended reaction times, and elevated temperatures; however, the measured yield did not exceed 61.95%.

Due to the low efficacy of ethanolysis reactions in our hands, alternative methods of quantification were subsequently investigated. Ultimately, quantitative ¹³C NMR analysis following protonolysis via HCl vapor addition was found to result in a measured yield of 91.53% for control experiments using LiOMM with an internal standard of naphthalene in CD₃CN. With this method confirmed to be a reliable measure of product yield, the quantification of carboxylate products arising from iron-mediated reactions was then measured. Small, NMR-scale reactions containing 10-15 mg of complex 2a in 500 µL
of C₆D₆ were exposed to a 3:1 ratio of ethylene and CO₂ and allowed to react for 18 hours at ambient temperatures, at which point the solvent was removed under vacuum and the sample re-dissolved in CD₃CN prior to protonolysis. Quantitative ¹³C NMR spectra were obtained using inverse-gated decoupled acquisition parameters with an extended delay time of 60 seconds and product peaks were integrated relative to an internal standard of naphthalene.

Analysis of the products obtained from coupling reactions conducted in the presence of complex 2a revealed a modest 67.42% yield of MMA (per Fe atom) and no observed PA formation (Table 4, entry 1). The selectivity of 2a to yield branched dicarboxylate products in moderate yields suggests that the mechanism likely resembles the mono-metallic pathway proposed by Hoberg and co-workers, rather than the bimetallic pathway proposed by Chirik et al. that afforded considerably lower yields of linear dicarboxylate products. Coupling reactions carried out with the oxidized complex 6 resulted in a slightly decreased overall yield of 46.35%, of which 27.78% was comprised of PA whereas only 18.57% was attributed to MMA (Table 4, entry 2). Shortening the reaction time from 18 hour to 3 hours was found to shift the product ratio towards PA, with yield of 38.39% PA and 11.52% MMA obtained (Table 4, entry 3). These findings suggest that PA and MMA formation occur via the same pathway that contains a 5-memebered Fe-lactone which yields PA upon protonolysis or MMA following a second CO₂ insertion and protonolysis.

Table 4. Quantification of Carboxylate Products from CO₂-Ethylene Coupling

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Fe]</th>
<th>Yield (%)</th>
<th>Ratio</th>
<th>MMA : PA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1ᵇ</td>
<td>2ᵃ</td>
<td>67.98 ± 3.68</td>
<td>67.42</td>
<td>1:0</td>
</tr>
<tr>
<td>2ᶜ</td>
<td>6</td>
<td>18.57 ±2.27</td>
<td>27.78 ± 1.63</td>
<td>46.35</td>
</tr>
<tr>
<td>3ᵈ</td>
<td>6</td>
<td>11.52</td>
<td>38.39</td>
<td>49.92</td>
</tr>
</tbody>
</table>

ᵃ Yield determined via integration of quantitative ¹³C NMR spectrum relative to an internal standard. ᵇ Conditions: 10 mg 2, 500 μL C₆D₆, 6 eq. C₂H₄, 2 eq. ¹³CO₂, 18 hours, 25°C. ᶜ Conditions: 13 mg 2 was reacted with 1 eq. AgBF₄ in 1 mL of 1:1 C₆D₆: THF, filtered through celite, and combined with 6 eq. C₂H₄ and 2 eq. ¹³CO₂ for 18 h. ᵃ Conditions: as with (b) but for 3 h.
The decrease in total carboxylate yield observed when coupling reactions are carried out in the presence of 6 may either be a result of complex degradation due to the instability of the oxidized species or due to decreased ability to functionalize CO$_2$ following the oxidation. However, these reactions were also subjected to filtration following oxidation and prior to ethylene/CO$_2$ addition, which may have resulted in non-quantitative transfer of materials that also contributed to the decreased yield. The considerable shift in MMA : PA production observed between 3 and 18 hours indicates that complex 6 does not entirely prevent the insertion of a second CO$_2$ moiety, but the proposed rate of the second CO$_2$ insertion may be slowed to the point where product selectivity can be obtained.

3.3 Concluding remarks

Investigations into the transition metal-catalyzed oxidative coupling of CO$_2$ and ethylene have largely employed Group VI and X metals such as Mo, W, and Ni.$^{1-26}$ However, the inability of Group X metals to undergo β-hydride elimination and the problematic reductive elimination of acrylate from oxophilic Group VI metals have largely limited catalyst development. There has been one report of a Group VIII metal catalyzing the reaction of CO$_2$ and ethylene to yield acrylate, although the Ru-based catalyst was only capable of achieving low TONs in the presence of large excess of base and Lewis acid.$^{49}$ However, considering that a majority of catalysts for CO$_2$–ethylene coupling utilize first row metals, the development of an iron-based catalyst holds promise and offers a more economical alternative to expensive Ru complexes.

A family of low-valent Fe complexes were synthesized featuring electron-rich tridentate phosphine ligands (2a-c) and their reactivity toward CO$_2$ and ethylene was
examined (Scheme 12). Addition of ethylene to the ethyl substituted \(2a\) resulted in the partial conversion to the bis-ethylene complex \(3\), however the \textit{iso}-propyl substituted \(2b\) and cyclohexyl substituted \(2c\) were incapable of forming bis-ethylene species due to their more sterically protected metal centers (Scheme 12, top). Upon the addition of a 3:1 mixture of ethylene and \(^{13}\)CO\(_2\) to C\(_6\)D\(_6\) solutions of \(2a\)-c, precipitate was observed to form over the course of several minutes. Analysis of the spectroscopic data revealed the formation of a CO\(_2\)-functionalized iron species, the identity which is believed to be the iron-methylmalonate complex \(4\) that yields methylmalonic acid (MMA) following protonolysis by HCl vapor addition.

The proposed mechanism for MMA production involves the formation of a transient P\(_3\)Fe-lactone that undergoes rapid \(\beta\)-hydride elimination and subsequent 2,1-insertion to yield a 4-membered lactone, followed by nucleophilic attack of the iron-alkyl bond by a second CO\(_2\) molecule (Scheme 12, middle). Attempts to prevent the second CO\(_2\) insertion were largely unsuccessful. One approach that did slow the second carboxylation was the use of the one-electron oxidation of \(2a\) by AgBF\(_4\). The oxidized, NMR silent complex \(6\) was found to yield a 2:1 mixture of propionic acid (PA) to methylmalonic acid (MMA) following CO\(_2\)-ethylene coupling and protonolysis (Scheme 12, left). Although \(6\) was still observed to yield MMA, these results confirm that the second CO\(_2\) insertion reaction can be attenuated and that selective CO\(_2\) functionalization may be possible.

Quantification of the CO\(_2\)-functionalized products via quantitative \(^{13}\)C NMR analysis revealed moderate yields of 67.89\% MMA when CO\(_2\)-ethylene coupling is carried out in the presence of \(2a\). The selectivity of this reaction was shifted to favor mono-carboxylate products when coupling reactions were carried out in the presence of \(6\), with a
2:3 ratio of MMA:PA obtained in modest yields. Shorter reaction times further shifted the product ratio to 3:10 MMA:PA, suggesting the intermediacy of a 5-membered Fe-lactone for both products. Investigations into the yield of CO₂-functionalized products obtained from coupling reactions mediated by complexes 2b and 2c as well as additional oxidation studies continue to be a focus of our laboratory.

Scheme 12. Summary of the reactivity of P₃Fe complexes
3.4 Experimental

3.4.1 General Considerations

Manipulations were carried out using standard Schlenk, glovebox, cannula, or vacuum techniques. Nonvolatile solids were dried under vacuum at 50°C overnight. Solvents were deoxygenated and dried according to literature procedures.\textsuperscript{50} Carbon dioxide (laser-grade) and ethylene (dry) were purchased from Airgas and stored in thick-walled reaction vessels on molecular sieves. Other chemicals were purchased from Aldrich, Strem, Fischer, VWR, or Cambridge Isotope Laboratories.

NMR spectra were recorded on a Bruker 300 MHz DRX, 500 MHz DRX, and 600 MHz spectrometer at ambient temperatures. Probe temperatures were calibrated using methanol and ethylene glycol as previously described.\textsuperscript{51} $^{31}$P chemical shifts were referenced to an external standard of H$_3$PO$_4$; $^1$H and $^{13}$C chemical shifts were referenced to residual solvent signals.

X-ray crystallographic data were collected on a Bruker CMOS diffractometer with Mo K$\alpha$ radiation. Samples were collected in an inert oil and quickly transferred to a cold gas stream. The structures were solved from direct methods and Fourier syntheses and refined by full-matrix least-squares procedures with anisotropic thermal parameters for all non-hydrogen atoms. Crystallographic calculations were carried out using SHELX programs.

3.4.2 Preparation and Characterization of P$_3$

A 239 mg (1.50 mmol, 1 mol eq.) sample of dichloro-\textit{tert}-butylphosphine was weighed into a 20 mL scintillation vial and dissolved in 5 mL Et$_2$O. In a separate vial, 6.43
mL (4.50 mmol, 3 mol eq.) vinyl magnesium bromide solution (0.7 M in THF) was dispersed with 10 mL Et₂O. Dropwise addition of the phosphine solution into the Grignard solution resulted in the formation of a pale-yellow precipitate. The reaction solution was stirred at ambient temperatures overnight and then placed in the freezer to further precipitate magnesium salts. Filtration through celite in a Pasture pipet yielded a light-yellow Et₂O solution that was stored at -35°C for future use. Divinyl-tert-butylphosphine is not isolated due to significant loss of product under vacuum.

The Et₂O solution containing divinyl-tert-butylphosphine was added to a 250 mL Schlenk flask with a stir bar. A 2.57 g (2.85 mmol, 1.9 mol eq.) sample of diethyl phosphine (10wt% in hexane) was weighed into a 20 mL scintillation vial and then transferred to the Schlenk flask, which was then sealed with a septa. A 3.75 mL (7.50 mmol, 5 mol eq.) sample of LDA (2.0 M in THF) was added dropwise to the Schlenk flask through the septa while stirring, resulting in a gradual color change from light yellow to dark red. The solution was stirred at ambient temperatures and reaction progress is monitored via NMR analysis of reaction aliquots. Upon full conversion to the triphos product (Bu₃P(depe)₂), the reaction solution was quenched with 20 mL of DI water which had been sparged with Argon for 10 minutes.

The aqueous layer was extracted with two 20 mL portions of Et₂O and the resulting light-yellow organic layer was cannula transferred into a Schlenk frit packed with sodium sulfate and collected in a 250 mL Schlenk flask. The Et₂O was removed under vacuum and the remaining oil was dispersed in pentane and filtered through celite in a Pasture pipet. The pentane solvent was removed under vacuum resulting in a yellow oil. Yield 97.72%.

³¹P{¹H} NMR (300 MHz, C₆D₆): δ -17.03 (d, J = 23.2 Hz), 9.12 (t, J = 23.2 Hz).
3.4.3 Preparation and Characterization of Iron Complexes

Preparation of $\text{P}_3\text{FeCl}_2$ (1a). A 20 mL scintillation vial was filled with 100 mg (0.785 mmol, 1 mol eq.) FeCl$_2$, dispersed in 5 mL THF and stirred for 10 minutes. Into a separate vial, 250 mg (0.785 mmol, 1 mol eq.) $\text{tBuP(dePe)}_2$ was weighed out, dissolved in 5 mL THF, and added dropwise to the FeCl$_2$/THF solution. The reaction solution immediately became dark blue in color and was stirred under ambient temperatures overnight. The crude reaction solution was filtered through celite in a Pasteur pipet and the THF solvent removed under vacuum. The resulting dark blue oil was triturated with pentane to yield a fine powder. Yield = 98.89%

Characterization Data for 1a. $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 0.87 ppm (s), 1.23 (s), 1.77 (bs), 2.02 (bs), 2.16 (bs), 3.20 (bs), 3.55 (bs), 3.87 (bs), 4.97 (bs), 5.78 (bs), 25.35 (bs), 26.32 (bs), 26.71 (bs). $\mu_{\text{eff}}$ (Evans, THF-$d_8$) = 5.5 $\mu_B$. Elemental analysis for $\text{C}_{16}\text{H}_{37}\text{P}_3\text{Cl}_2\text{Fe}$: Found(Calc.) C, 43.30(42.79); H, 7.77(8.30); N, <0.10(0.00).

Preparation of $\text{P}_3\text{Fe(C}_2\text{H}_4)(\text{N}_2)$ (2a). A sample of 225 mg (0.500 mmol, 1 mol eq.) 1a was dissolved in 10 mL THF and transferred into a 50 mL side arm Schlenk flask. The THF was removed under vacuum and 203 mg (1.50 mmol, 3 mol eq.) KC$_8$ was added directly to the reaction flask. The flask was cooled to -78°C and approximately 20 mL THF was vacuum transferred into the vessel followed by the addition of 3 atm ethylene. The reaction solution was stirred under ambient temperatures overnight. The THF was removed under vacuum and the remaining brown oil was dissolved in pentane and filtered through celite on a fine frit. The pentane solvent was removed under vacuum leaving behind an oily brown residue. Crystals suitable for XRD were grown from a concentrated pentane solution cooled at -45°C for several weeks.
Characterization Data for 2a. $^{31}$P{$^{1}$H} NMR (300 MHz, C$_{6}$D$_{6}$): $\delta$ 86.57 (d, $J = 36.5$ Hz), 124.89 (t, $J = 36.5$ Hz). $^1$H NMR (600 MHz, C$_{6}$D$_{6}$): $\delta$ 0.71 (d, $J = 11.0$ Hz, 9 H, PrBu-CH$_{3}$), 0.91 (m, 4 H, PET-CH$_{2}$), 1.06 (dt, $J = 7.4$, 11.0 Hz, 6 H, PET-CH$_{3}$), 1.14 (m, 2 H, PET-CH$_{2}$), 1.27 (dt, $J = 7.4$, 13.3 Hz, 6 H, PET-CH$_{3}$), 1.50 (m, 2 H, dePe-CH$_{2}$), 1.51 (m, 2 H, PET-CH$_{2}$), 1.55 (m, 2 H, Fe-C$_{2}$H$_{4}$), 1.87 (m, 2 H, dePe-CH$_{2}$), 1.94 (m, 2 H, dePe-CH$_{2}$), 2.05 (m, 2 H, dePe-CH$_{2}$), 2.11 (m, 2 H, Fe-C$_{2}$H$_{4}$). $^{13}$C{$^{1}$H} (600 MHz, C$_{6}$D$_{6}$): $\delta$ 8.78 (PET-CH$_{3}$), 8.83 (PET-CH$_{3}$), 23.55 (dePe-CH$_{2}$), 24.06 (Fe-C$_{2}$H$_{4}$) 24.10 (Fe-C$_{2}$H$_{4}$), 25.05 (PET-CH$_{2}$), 25.10 (PET-CH$_{2}$), 27.70 (PrBu-CH$_{3}$), 34.43 (PrBu-C). IR (C$_{5}$H$_{12}$): $\nu$N≡N = 2050 cm$^{-1}$.

Preparation and Characterization of P$_{3}$Fe(C$_{2}$H$_{4}$)$_{2}$ (3). Addition of as little as 1 molar equivalent of ethylene results in the formation of the bis-ethylene species P$_{3}$Fe(C$_{2}$H$_{4}$)$_{2}$ over several days. The initial N$_{2}$ complex is reformed following the removal of solvent under vacuum and re-dissolving the sample in C$_{6}$D$_{6}$. $^{31}$P{$^{1}$H} NMR (300 MHz, C$_{6}$D$_{6}$): $\delta$ 74.89 (d, $J = 16.5$ Hz), 156.87 (t, $J = 16.5$ Hz). $^1$H NMR (600 MHz, C$_{6}$D$_{6}$): $\delta$ 0.59 (PrBu-CH$_{3}$), 1.52 (Fe-C$_{2}$H$_{4}$), 2.12 (Fe-C$_{2}$H$_{4}$). $^{13}$C{$^{1}$H} (600 MHz, C$_{6}$D$_{6}$): $\delta$ 6.95 (PET-CH$_{3}$), 6.96 (PET-CH$_{3}$), 24.07 (Fe-C$_{2}$H$_{4}$), 24.62 (Fe-C$_{2}$H$_{4}$), 29.40 (PrBu-CH$_{3}$), 34.45 (PrBu-C). Unable to assign $^{13}$C and $^1$H signals for dePe-CH$_{2}$ and PET-CH$_{2}$ signals due to the relative intensity of $^{13}$C$_{2}$H$_{4}$-related peaks.

Preparation of (L)P$_{3}$Fe(C$_{2}$H$_{4}$) Complexes 5a-c. A 50 mg (0.115 mmol, 1 mol eq.) sample of 2a was dissolved in 20 mL THF and transferred into a 50 mL side arm Schlenk flask, to which 1 molar equivalent of ligand was added via calibrated gas bulb addition. The reaction solution was stirred at ambient temperatures for 18 hours, at which point the solvent was removed under vacuum leaving behind a brown oil that was stored at -35°C.
Characterization Data for 5a. $^{31}$P{$^1$H} NMR (300 MHz, C$_6$D$_6$): δ 39.28 (dt, $J$ = 43.4, 113.8 Hz), 76.10 (dd, $J$ = 29.1, 43.4 Hz), 125.26 (dt, $J$ = 29.1, 113.8 Hz).

Characterization Data for 5b. $^{31}$P{$^1$H} NMR (300 MHz, C$_6$D$_6$): δ 29.26 (dt, $J$ = 50.9, 114.5 Hz), 77.87 (dd, $J$ = 29.9, 50.9 Hz), 123.48 (dt, $J$ = 29.9, 114.5 Hz). $^1$H NMR (600 MHz, C$_6$D$_6$): δ 0.83 (m, 2H, Fe-C$_2$H$_4$), 0.95 (m, 9H, PMe-CH$_3$), 0.98 (m, 9H, PrBu-CH$_3$), 1.02 (m, 6H, PCH$_3$), 1.02 (m, 2H, dePe-CH$_2$), 1.31 (m, 6H, PCH$_3$), 1.75 (m, 2H, dePe-CH$_2$), 1.77 (m, 2H, dePe-CH$_2$), 1.92 (m, 4H, PCH$_3$), 2.00 (m, 4H, PCH$_3$). $^{13}$C{$^1$H} NMR (600 MHz, C$_6$D$_6$): δ 9.51 (PCH$_3$), 10.19 (PCH$_3$), 20.85 (PCH$_3$), 24.24 (Fe-C$_2$H$_4$), 26.61 (dePe-CH$_2$), 27.16 (PCH$_3$), 28.74 (PrBu-CH$_3$), 35.83 (PrBu-C).

Characterization Data for 5c (major). $^{31}$P{$^1$H} NMR (300 MHz, C$_6$D$_6$): δ 90.53 (d, $J$ = 40.4 Hz), 119.61 (t, $J$ = 40.4 Hz). $^1$H NMR (600 MHz, C$_6$D$_6$): δ 0.86 (d, $J$ = 10.5 Hz, PrBu-CH$_3$), 0.88 (m, CH$_2$), 1.07 (m, CH$_2$), 1.11 (m, PCH$_3$), 1.13 (s, NtBu-CH$_3$), 1.36 (m, CH$_2$), 1.39 (m, PCH$_3$), 1.56 (m, CH$_2$), 1.62 (m, CH$_2$), 1.74 (d, $J$ = 5.8 Hz, Fe-C$_2$H$_4$), 1.99 (m, CH$_2$), 2.04 (m, CH$_2$), 2.15 (m, CH$_2$). $^{13}$C{$^1$H} NMR (600 MHz, C$_6$D$_6$): δ 9.25 (PCH$_3$), 9.35 (PCH$_3$), 20.34 (Fe-C$_2$H$_4$), 20.37 (Fe-C$_2$H$_4$), 24.75 (CH$_2$), 25.00 (CH$_2$), 26.27 (CH$_2$), 26.78 (CH$_2$), 28.01 (PrBu-CH$_3$), 32.58 (NtBu-CH$_3$), 35.06 (PrBu-C), 55.24 (NtBu-C).

Preparation of Oxidized Fe Complex 6. A 5.3 mg (0.027 mmol, 1 mol eq.) sample of AgBF$_4$ was dissolved in 500 μL THF and added to a 10 mg (0.027 mmol, 1 mol eq.) sample of 2a in 500 μL THF resulting in the immediate formation of black precipitate. The reaction solution was briefly mixed, filtered through Celite in a Pasteur pipet, and collected in a J-Young tube for use in subsequent experiments.
3.4.4 General Procedure for CO$_2$-Ethylene Coupling Experiments

A 10 mg sample of the respective iron complex was dissolved in 500 μL C$_6$D$_6$, transferred to a J-Young tube, and connected to a calibrated gas addition bulb. The sample was frozen in a liquid nitrogen bath and 6 equivalents ethylene and 2 equivalents $^{13}$CO$_2$ were added. The sample was warmed to room temperature under a stream of warm water and allowed to react for 18 hours. Upon completion of the allotted reaction time, the solvent was removed under vacuum, the sample was redissolved in 500 μL CD$_3$CN, and analyzed by NMR analysis. The addition of 10 equivalents of HCl vapor resulted in the formation of free carboxylate products that were subjected to quantitative $^{13}$C NMR analysis. An internal standard of naphthalene (~0.04 mmol) was weighed into a 20 mL scintillation vial, dissolved in 300 μL and added to the reaction solution following protonolysis. Product yields were calculated via relative integration of the naphthalene peak to the respective product peak.

Characterization data for P$_3$Fe-OMM* (4*). Significant peaks observed in the $^{31}$P{$_1$H} NMR (300 MHz, CD$_3$CN): δ 83.13 (broad), 97.81 ppm (d, J = 18.3 Hz), 102.47 ppm (d, J = 18.3 Hz). Significant peaks observed in the $^1$H NMR (600 MHz, CD$_3$CN): δ 1.01 ppm (P$_3$FeOMM-CH$_3$), 3.25 (P$_3$FeOMM-CH). Significant peaks observed in the $^{13}$C{$_1$H} NMR (600 MHz, CD$_3$CN): δ 178.42 ppm. IR (KBr): $\nu$$_{13C=O}$ = 1549 cm$^{-1}$; $\nu$$_{C=O}$ = 1585 cm$^{-1}$.)
3.5 References


5. Galindo, A.; Pastor, A.; Pérez, P. J.; Carmona, E., Bis(ethylene) Complexes of Molybdenum and Tungsten and Their Reactivity toward CO₂. New Examples of Acrylate Formation by Coupling of Ethylene and Carbon Dioxide. *Organometallics* 1993, 12, 4443-4451.


CHAPTER 4

Iron-Catalyzed Amide Formation from the Dehydrogenative Coupling of Alcohols and Secondary Amines

4.1 Introduction: The Significance of Carbon-Nitrogen Bonds

The carbon-nitrogen (C-N) bond is one of the most prevalent found throughout synthetic and naturally occurring compounds. This moiety has unique characteristics that lend to wide-ranging utility. For example, primary and secondary amines act as both hydrogen bond donors and acceptors.\(^1\) Additionally, the presence of C-N bonds increases the oral bioavailability of pharmaceutical compounds.\(^1\) Thus, it comes as no surprise that over 93% of new FDA-approved drugs in 2019 contained one or more C-N bonds.\(^2\) Of the C-N bond-containing functional groups, amides are among the most ubiquitous.\(^3, 4\) Their biological significance underlies the emergence of life on Earth with amides forming the backbone of amino acids that make up our DNA. In addition to their role in biochemistry, amides are found in numerous synthetic materials such as diketopyrrolopyrroles, which have been widely used as organic pigments.\(^5\) More recently, amides have garnered interest in the field of organic solar cells.\(^6\) Given their predominance in pharmaceuticals and other synthetic materials, the production of amides is of considerable significance.

Innumerable resources have been devoted to the synthesis of amides. In fact, amidation reactions account for 16% of all reactions used for the synthesis of pharmaceutical drugs, making it one of the most common synthetic approaches toward this
Traditional synthetic methods involve the reaction of amines with acid halides, acid anhydrides, or other derivatives of activated carboxylic acids. Pre-activation of the carboxylic acid is considered necessary to avoid the formation of the thermodynamically favored carboxylate-ammonium salt; however, this required the undesirable use of a stoichiometric coupling reagent.

The need for pre-activated carboxylic acids has been circumvented to a limited extent with the use of direct amide synthesis from carboxylic acids and amines via thermal and radiofrequency heating. Similarly, boronic acid-catalyzed methods of direct amide synthesis have been a topic of considerable research. However, these methods are often regarded as expensive and wasteful, producing stoichiometric amounts of waste and suffering from limited substrate scope. A more atom-economical and environmentally friendly approach to amide synthesis is the catalytic dehydrogenative coupling of alcohols and amines (Scheme 1). Additionally, this approach avoids the use of harsh or toxic reagents such as anhydrides or acid halides.

**Scheme 1. Transition metal-mediated dehydrogenation of alcohols in the presence of amines to form amides and dihydrogen**

4.2 Catalytic Dehydrogenative Coupling of Alcohols and Amines

The scope of dehydrogenative amide synthesis encompasses both heterogeneous and homogeneous catalysts, although reports of heterogeneous systems have been limited to coinage metals such as silver and gold. While these catalysts are effective for
amide synthesis, they typically require harsh conditions, long reaction times, and high catalyst loading to achieve high yields, effectively lowering their turnover numbers (TONs) to <100.\textsuperscript{12-17} In contrast, there are considerably more homogeneous catalysts capable of dehydrogenative amide synthesis that exhibit greater productivity than heterogeneous systems. A majority of reported homogeneous catalysts feature precious metals such as ruthenium,\textsuperscript{3, 4} rhodium,\textsuperscript{3, 4} and rhenium.\textsuperscript{18} Although, there are emerging reports of select base metal catalysts such as manganese, cobalt, and copper.\textsuperscript{19}

4.2.1 Precious Metal Catalysts

The plurality of precious metal catalysts that effectively couple alcohols and amines to form amides are ruthenium-based complexes, the first of which was reported in 1991 by Naota and Murahashi (Scheme 2).\textsuperscript{20} However, the substrate scope was exclusively limited to tethered amino alcohols and required the presence of a hydrogen acceptor as well as a co-catalytic amount of water for product formation.\textsuperscript{20} It wasn’t until 2007 that the first intermolecular coupling was reported by Milstein et al (Scheme 3).\textsuperscript{21} This seminal publication detailed near-quantitative yields of amides and TONs upwards of 1000 using a ruthenium complex featuring a unique PNN-pincer ligand with a dearomatized ring.\textsuperscript{21}

Scheme 2. Ruthenium-catalyzed coupling of amino alcohols

\[
\begin{align*}
\text{CH}_2\text{OH} & \xrightarrow{\text{RuH}(\text{PPh}_3)_4 (5 \text{ mol\%})} \text{NHR} \\
& \text{hydrogen acceptor (2 eq.)} \\
& \text{DME, 140°C, 3 h} \\
\end{align*}
\]

4 examples
Up to 81% yield
TON = 16.2

Scheme 3. Intermolecular amidation catalyzed by Milstein’s PNN-Ru complex

\[
\begin{align*}
\text{ROH + NH}_2\text{R'} & \xrightarrow{0.1 \text{ mol\%}} \text{Reflex, 8 h} \\
& \text{PrBu}_2 \text{ N} \text{Ru} \text{CO} \text{ NEt}_2 \text{ N} \\
\end{align*}
\]

10 examples
Up to 99% yield
TON = 990
This characteristic feature gives rise to metal-ligand cooperation (MLC) wherein both the metal center and the ligand are directly involved in activating the substrate.\textsuperscript{22} In the case of Milstein’s PNN-Ru complex, MLC was achieved by the aromatization and dearomatization of the lutidine ring in order to facilitate $\text{H}_2$ formation, avoiding the need for additives such as hydrogen acceptors.\textsuperscript{21, 22} At the time of its publication, this was the most significant breakthrough in decades and spurred a flurry of activity in ruthenium-catalyzed amidations as a result.

Shortly after Milstein’s 2007 report, Madsen and co-workers described a family of ruthenium complexes featuring $N$-heterocyclic carbene (NHC) ligands, the most active of which combined $\text{Ru(COD)}\text{Cl}_2$ with a NHC and PCy\textsubscript{3} resulting in the quantitative yield of amide (Table 1, entries 1 and 2).\textsuperscript{23, 24} A myriad of similar Ru-NHC complexes with ligand hapticity akin to that of $\text{Ru(COD)}\text{Cl}_2$ were also reported by Hong and co-workers\textsuperscript{25-27} and later by Albrecht \textit{et al} (Table 1, entries 3-7).\textsuperscript{28} However, all of these catalytic systems were limited to low TONs ($\leq 50$) due to high catalyst loading and required the presence of strong bases such as KO\textsubscript{t}Bu or NaH.\textsuperscript{23-28} Around this time, the Williams group began reporting on the effectiveness of a bidentate phosphine-ligated Ru complex for the dehydrogenative coupling of alcohols and amines (Scheme 4).\textsuperscript{29, 30} While this catalyst was able to produce amides in high yields, product formation was dependent upon the utilization of a co-catalytic amount of base as well as an excess of 3-methyl-2-butanone, which acted as a hydrogen acceptor.\textsuperscript{29, 30}

\begin{center}
\textbf{Scheme 4. Catalytic amide production mediated by Ru/dppb complex in the presence of base and a hydrogen acceptor}
\end{center}

\textbf{[Ru($p$-cymene)Cl\textsubscript{2}] (2.5 mol\%)}

\textbf{dppb (5 mol\%)}

\textbf{Cs\textsubscript{2}CO\textsubscript{3} (10 mol\%)}

\textbf{3-methyl-2-butanone (2 eq.)}

\begin{align*}
\text{tBuOH, reflux, 24 h} & \quad \text{R} \quad \text{N} \quad \text{R}' \\
\text{TON = 37.2} & \quad \text{51 examples} \\
\text{Up to 93\% yield} & \quad \text{dppb} = \text{Pb}_2\text{P} \quad \text{PPh}_2
\end{align*}
Table 1. Ru-NHC Catalysts for Alcohol Amidation in the Presence of Base

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ru]</th>
<th>NHC/Ligand</th>
<th>Base</th>
<th>Products</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru(COD)Cl₂ (5 mol%)</td>
<td>IPr-HCl (5 mol%)</td>
<td>KOtBu (20 mol%)</td>
<td>11 examples</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PCyp₂HBF₄ (5 mol%)</td>
<td></td>
<td>Up to 100% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 20</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>[Ru(p-cymene)Cl₂]₂ (2.5 mol%)</td>
<td>IPr-HBr (5 mol%)</td>
<td>NaH (15 mol%)</td>
<td>17 examples</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyridine (5 mol%)</td>
<td></td>
<td>Up to 99% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 19.8</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[Ru(benzene)Cl₂]₂ (2.5 mol%)</td>
<td>IPr-HBr (5 mol%)</td>
<td>KOtBu (15 mol%)</td>
<td>7 examples</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH₃CN (5 mol%)</td>
<td></td>
<td>Up to 100% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 20</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>KOtBu (15 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>KOtBu (15 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>KOtBu (15 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td>KOtBu (15 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>KOtBu (10 mol%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>RuCl₃ (5 mol%)</td>
<td>IPr-HBr (5 mol%)</td>
<td>NaH (40 mol%)</td>
<td>23 examples</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pyridine (5 mol%)</td>
<td></td>
<td>Up to 84% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 16.8</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td>NaH (20 mol%)</td>
<td>22 examples</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Up to 96% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 19.2</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>IPr</td>
<td></td>
<td>2* amines: KOtBu or NaH (15 mol%)</td>
<td>16 examples</td>
<td>34</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td>Up to 97% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 19.4</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Ru(COD)(methylallyl)_2 (2 mol%)</td>
<td>ICy-HCl (4 mol%)</td>
<td>KOtBu (5 mol%)</td>
<td>17 examples</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Up to 99% yield</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TON = 49.5</td>
<td></td>
</tr>
</tbody>
</table>

ROH + NH₂R' → [Ru]/NHC Base, Ligand

NHC = R = iPr (IPr), Me (Me), Bu (Bu), Cy (Cy)
In 2010, Madsen et al. expanded upon the previously reported family of Ru-NHC complexes with variations of Grubbs 2nd-generation catalysts (Table 1, entry 8). Hong and co-workers also published new Ru-NHC complexes in 2010 and beyond, which featured various dative ligands in combination with a di-iso-propyl-NHC (Table 1, entries 9-12). However, TONs did not exceed 20 and base was still required for amide formation in nearly all of these systems. Later that year, Crabtree and colleagues began publishing pyridine-based Ru(diamine)-(diphosphine) complexes that were capable synthesizing amides in moderate yields (Scheme 5). These complexes displayed an extremely limited substrate scope, however, and amide yield was once again contingent upon the presence of base. 

Scheme 5. Ru-diamine-diphosphine complexes for the catalytic dehydrogenative coupling of alcohols and amines

A considerable advancement was made by Milstein et al. in 2013 when they published a bipyridine-based PNN-pincer complex that achieved TONs of up to 495 and near-quantitative yields of amides (Scheme 6). Like their 2007 complex, this Ru-PNN catalyst was capable of MLC due to the dearomatization of the central pyridine ring, allowing for base-free amide formation. Another significant contribution can be attributed to a 2013 report by Glorius et al. wherein amides were produced via the coupling of methanol and amine for the first time (Table 1, entry 13). This unique bis-NHC
A complex was able to achieve yields up to 99%, although the high catalyst loading limited the TON to less than 50 and exogenous base was necessary for amide formation.\textsuperscript{39}

**Scheme 6. Ru-PNN catalysts for tertiary amide formation**

![Scheme 6](image.png)

Around this time, Möller et al. developed a benzimidazolium-NHC complex with an extended π-system, which they believed would increase the electron density at the metal center and lead to higher productivity (Table 2, entry 1).\textsuperscript{40} Similar Ru-NHC complexes were later reported by Huynh et al (Table 2, entry 2).\textsuperscript{41} Although both catalysts proved to be capable of achieving good yields of amides, they were plagued by high catalyst loading, base-dependence, and limited substrate scope.\textsuperscript{40,41} In 2014, Bera et al. reported one of the most efficient Ru-NHC catalysts for dehydrogenative amidation featuring a chelating NHC ligand (Table 2, entry 3).\textsuperscript{42}

**Table 2. Ru-NHC Catalysts with Extended π-Systems**

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ru]</th>
<th>Base</th>
<th>Products</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image.png" alt="Ru" /></td>
<td>KOtBu (15 mol%)</td>
<td>12 examples Up to 95% yield TON = 31.7</td>
<td>40</td>
</tr>
</tbody>
</table>
Table 2 Continued

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ru]</th>
<th>Base</th>
<th>Products</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td><img src="image1" alt="RuBnCl_NaH_12_examples" /></td>
<td>NaH (30 mol%)</td>
<td>12 examples Up to 94% yield TON = 18.8</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td><img src="image2" alt="RuBrOC_NaH_24_examples" /></td>
<td>NaH (5 mol%)</td>
<td>24 examples Up to 92% yield TON = 92</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td><img src="image3" alt="RuPh3E_BuNaH_23_examples" /></td>
<td>E=P, B=PPh3</td>
<td>Up to 96% yield TON = 288</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image4" alt="RuPh3E_BuNaH_23_examples" /></td>
<td>E=As, B=AsPh3</td>
<td>Up to 93% yield TON = 272</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image5" alt="RuPh3E_BuNaH_23_examples" /></td>
<td>E=P, B=Py</td>
<td>Up to 89% yield TON = 332</td>
<td></td>
</tr>
</tbody>
</table>

Despite being limited to primary amines, this catalyst produced amides in high yields and achieved a TON of 92 in the presence of base.\textsuperscript{42} That same year, Guan et al. achieved slightly better TONs of amides using the commercially available Ru-Macho complex with the assistance of base (Scheme 7, top).\textsuperscript{43} This same catalyst was later utilized in the base-free coupling of methanol and primary amines, as reported by Kim and Hong in 2016 (Scheme 7, bottom).\textsuperscript{44} Under these conditions, the Ru-Macho catalyst was capable of producing urea in yields up to 97% and TONs up to 194.\textsuperscript{44}

**Scheme 7. Ru-Macho catalyzed amide and urea production**

\[
\text{ROH} + \text{NHR}_2 \xrightarrow{\text{[Ru] (1 mol\%), KOH (15 mol\%)}} \text{NH}_2 \xrightarrow{\text{[Ru] (0.5 mol\%), BH}_4} \text{NHR}_2
\]

21 examples Up to 95% yield TON = 95

\[
\text{CH}_3\text{OH} + 2 \text{NH}_2\text{R'} \xrightarrow{\text{[Ru] (0.5 mol\%), BH}_4} \text{R''N}_2\text{R''}
\]

21 examples Up to 95% yield TON = 190
In 2016, Viswanathamurthi and co-workers began publishing a series of robust Ru catalysts featuring a variety of polydentate ligands, the first of which utilized an OCO pincer type NHC ligand (Table 2, entries 4-6). This complex achieved moderate yields of amides and was operational with a very low catalyst loading (0.25-1 mol%), resulting in TONs of more than 300 (Table 2, entry 6). Shortly thereafter, the same group reported a new Ru catalyst featuring a conjugated bidentate hydrazine-based ligand that achieved a TON of 1480 (Scheme 8, top). The following year, they published a similar conjugated Ru complex featuring a ONS pincer type ligand that out-performed their previous Ru-complex with a TON of 1520 (Scheme 8, bottom). Although these reports offer no detailed mechanistic investigations, it cannot be ruled out that MLC is a potential explanation for the exceptionally high TONs.

**Scheme 8. Chelating hydrazine-based Ru catalysts for alcohol-amine coupling**

These catalysts are the first to achieve higher TONs than Milstein’s seminal 2007 Ru complex. However, it should be noted that Milstein’s catalyst achieved a TON of 990.
in a base-free manner whereas Viswanathamurthi’s catalysts require the presence of base. A family of Ru catalysts were reported by Mashima et al. in 2017 that featured chelating phosphine-amine ligands which demonstrated a wide substrate scope for both primary and secondary amines as well as alcohols (Scheme 9). However, these catalysts required the presence of base and Lewis acid in order to achieve high yields of amides and high catalyst loading limited the TON to <200.48

**Scheme 9. Ru catalysts featuring bidentate phosphine-amine ligands**

In addition to Ru complexes, there have been few reports of other precious metal catalysts, the first of which was a rhodium complex published in 2009 by Grützmacher et al.49 Their rhodium diolefin amido complex Rh(trop2N)(PPh3) readily facilitated the coupling of primary amines in the presence of a small variety of alcohols, achieving yields up to 94% (TON = 470) after only 4 hours at ambient temperatures (Scheme 10, top).49 These reaction conditions are the mildest reported for amide synthesis from amine/alcohol coupling, however an excess of methyl methacrylate was necessary for catalytic activity.49 Several years later, Klankermayer et al. reported a rhenium-triphos complex that produced amides in near-quantitative yields and achieved a TON of 192 without the need for
additives (Scheme 10, bottom). Unfortunately, the substrate scope was severely limited for this complex with only primary amines and a small number of alcohols proving to be effective substrates for coupling.

Scheme 10. Dehydrogenative amidation of alcohols catalyzed by Rh and Re complexes

4.2.2 Base Metal Catalysts

It is without question that precious metal catalysts have proven effective for the dehydrogenative coupling of alcohols and amines. However, the utilization of these toxic metals in large-scale, industrial synthesis of amides is neither cost-effective nor environmentally benign. The development of Earth-abundant, base metal catalysts is considered a more economical alternative, however progress on this front has been insufficient. Reports of homogeneous base-metal-catalyzed amide synthesis began to emerge in 2016.
A copper/nitroxyl co-catalyzed system was developed by Stahl et al. in which amide yields of up to 98% were achieved (Scheme 11).\textsuperscript{50} This system was capable of forming tertiary amides in good yields, although the presence of molecular sieves was required.\textsuperscript{50} Around this same, Zhang et al. reported a cobalt complex capable of achieving quantitative yields of amides from the coupling primary amines and alcohols (Scheme 12).\textsuperscript{51} However, an excess of base and the hydrogen-abstraction species T-HYDRO (the trademarked name for 70 wt% tert-butyl hydroperoxide solution in water) was necessary for catalysis.\textsuperscript{51}

**Scheme 11. Copper/ABNO-catalyzed aerobic coupling of alcohols and amines**

![Scheme 11](image_url)
In 2017, Milstein and co-workers published the first manganese catalysts for dehydrogenative amide synthesis. One such catalyst was a pyridine-based PNN-pincer complex that managed to produce amides from primary amines in good to moderate yields (Scheme 13, top). Although the additional base and long reaction times decrease the desirability of this system. A concurrent report from Milstein et al. described a similar Mn-PNP pincer catalyst that operated under base-free conditions to couple methanol and secondary amines (Scheme 13, bottom). Despite these advancements, all of these catalytic systems have been limited to low TONs (<50) due to high catalyst loading. Indeed, higher TONs are required if a catalyst is to be considered commercially relevant.

**Scheme 12. Cobalt-catalyzed dehydrogenative coupling of alcohols and amines**

\[
\text{ROH} + \text{NH}_2\text{R}' \xrightarrow{\text{CoL}_2 (2.5 \text{ mol\%}), \text{CaCO}_3 (1.1 \text{ eq.}), T-\text{HYDRO (2.5 eq.)}} \xrightarrow{12 \text{ examples}} \xrightarrow{\text{Up to 97\% yield}} \xrightarrow{\text{TON} = 38.8} \text{R}^+\text{N}^-\text{R'}
\]

**Scheme 13. Manganese-catalyzed amide production from alcohols and amines**

11 examples
Up to 86\% yield
TON = 17.2

14 examples
Up to 86\% yield
TON = 43.0
4.3 Results and Discussion

Of the dozens of precious and base metal catalysts that facilitate the dehydrogenative coupling of alcohols and amines, only a select few do so without the assistance of a base or hydrogen acceptor.\textsuperscript{18, 21, 34, 35, 38, 44, 53} Furthermore, of those that operate under base-free conditions, fewer than half are capable of forming tertiary amides.\textsuperscript{35, 38, 53} Prior to our 2017 publication, only one example of unassisted tertiary amide formation catalyzed by a base metal complex had been reported.\textsuperscript{53} However, the manganese PNP-pincer complex developed by Milstein \textit{et al.} was only able to reach a TON of 43 (Scheme 13, bottom).\textsuperscript{53} The utilization of such pincer catalysts is quite common in dehydrogenative catalysis.

A wide variety of transition metal PNP complexes have been reported for the dehydrogenation of alcohols including ruthenium,\textsuperscript{44, 54, 55} osmium,\textsuperscript{55, 56} rhenium,\textsuperscript{57} iridium,\textsuperscript{58} cobalt,\textsuperscript{59, 60} manganese,\textsuperscript{53, 61} and iron.\textsuperscript{61-63} In 2017, we reported the ability of the five-coordinate iron(II) complex (\textit{iPrPNP})Fe(H)(CO) (1; \textit{iPrPNP} = N[CH\textsubscript{2}CH\textsubscript{2}(\textit{iPr})\textsubscript{2}]\textsubscript{2}) (Figure 1) to facilitate the base-free hydrogenation of amides to alcohols.\textsuperscript{64} Similar Fe complexes have also demonstrated the ability to convert alcohols to dehydrogenated products such as carbon dioxide,\textsuperscript{62, 65} ketones,\textsuperscript{66} and esters.\textsuperscript{66} Given this prior art, and the ability of 1 to readily catalyze the microscopic reverse – carbonyl hydrogenation – investigations were carried out to probe the competence of complex 1 as a catalyst for the dehydrogenative coupling of alcohols and amines to yield amides.
4.3.1 Catalytic Trials: Optimizations

Initial investigations into the dehydrogenative coupling of alcohols and amines by 1 were carried out using morpholine and methanol based on the success of the 4-formylmorpholine hydrogenation observed previously. A 4:1 mixture of morpholine and methanol was combined with 0.1 mol% (3 μmol) 1, dispersed in 10 mL dioxane, and heated for 8 hours at 80°C. Amide formation was determined by $^1$H NMR analysis with mesitylene as an internal standard for integration. Turnover number (TON) was calculated by dividing the amount of amide produced by the catalyst loading (in mmol). This preliminary experiment yielded an auspicious TON 297 for 4-formylmorpholine production and served as a benchmark for further optimizations (Table 3, entry 1).

Following a solvent screen, it was found that the polar solvents acetonitrile and ethyl acetate decreased the TON considerably from 297 to 30 and 49 respectively (Table 3).

**Reaction Optimization Tables for:**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Acetonitrile</td>
<td>30</td>
</tr>
<tr>
<td>2</td>
<td>Ethyl Acetate</td>
<td>49b</td>
</tr>
<tr>
<td>3</td>
<td>Dioxane</td>
<td>297b</td>
</tr>
<tr>
<td>4</td>
<td>Toluene</td>
<td>344b</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>392</td>
</tr>
<tr>
<td>6</td>
<td>THF, 5 mL</td>
<td>503</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3 μmol catalyst 1 (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 10 mL solvent at 80°C for 8 hrs. Each entry is an average of two trials unless otherwise indicated. b Only one trial.

**Figure 2. Reaction Duration**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>176</td>
</tr>
<tr>
<td>5</td>
<td>383</td>
</tr>
<tr>
<td>10</td>
<td>503</td>
</tr>
<tr>
<td>15</td>
<td>553</td>
</tr>
</tbody>
</table>

*Reaction conditions: 3 μmol catalyst 1 (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 5 mL THF at 80°C for Z hrs. Each entry is an average of two trials unless otherwise indicated. Average of three trials.
entries 1-3). Slight improvements in TON were observed when the solvents toluene and THF were used, affording TONs of 344 and 392, respectively (Table 3, entries 4 and 5). Decreasing the volume of THF from 10 mL to 5 mL resulted in a considerably higher TON of 503 (Table 3, entry 6). This result is somewhat unsurprising given that reaction rates are concentration dependent. Therefore, it follows that an increase in the concentration of the reaction solution would produce an increase in productivity.

With the newly optimized solvent conditions in hand, reaction duration was investigated (Figure 2). Time trials revealed a TON of 176 after 1 hour and 383 after 4 hours at 80°C. Reactions carried out for 8 and 16 hours resulted in TONs of 503 and 553, respectively. Given that the longer reaction time afforded only a marginal increase in TON, subsequent reactions were carried out for 8 hours.

Temperature variation revealed a significant thermal dependence for amide production with reactions conducted at ambient temperature resulting in a TON of 10 (Table 4, entry 1). Upon increasing the temperature to 60°C, the productivity improved by more than an order of magnitude, achieving a TON of 172 (Table 4, entry 2). However, when the temperature was increased above 80°C, TONs began to drop from 503 to 328 at 100°C and 341 at 120°C (Table 4, entries 3-5). These findings indicate a kind of “Goldilocks” effect with respect to TON. Increasing the temperature increases the rate of amide formation but it also likely increases the rate of catalyst decomposition. Only when the temperature is “just right” can amide production be maximized.

<table>
<thead>
<tr>
<th>Table 4. Temperature Screen a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
</tbody>
</table>

a Reaction conditions: 3 μmol catalyst 1 (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 5 mL THF at Y°C for 8 hrs. Each entry is an average of two trials unless otherwise indicated.
Finally, with the solvent, reaction time, and temperature optimized, the ratio of alcohol to amine was investigated (Table 5). When the ratios of methanol and morpholine were switched from 1:4 to 4:1, the TON was observed to decrease from 503 to 163, indicating excess alcohol is deleterious to amide production (Table 5, entries 1 and 2). This is supported by the finding that a 1:1 ratio resulted in a slightly better TON of 261 (Table 5, entry 3). However, when the ratio was increased to 1:10 alcohol:amine, a TON of 425 was observed, suggesting amide production is also impaired by a large excess of amine (Table 5, entry 4).

These findings indicate unique roles played by each class of substrate. When an excess of alcohol is present, the formation of esters resulting from alcohol-alcohol coupling is likely favored over amide production. This undesirable ester formation is diminished by the presence of a slight excess (1:4) of amine, as observed by the maximum TON of 503 achieved. Interestingly, there appears to be a limit to the amount of excess amine that is beneficial for amide formation. The moderate decrease in TON observed in the presence of a large excess (1:10) of amine is presumably a result of the decreased concentration of alcohol relative to amine in the reaction mixture. A lower alcohol concentration would likely reduce the rate of alcohol dehydrogenation, the first step in the presumed mechanism for the dehydrogenative coupling of alcohols and amines to form amides.

<table>
<thead>
<tr>
<th>Entry</th>
<th>CH$_3$OH (mmol)</th>
<th>Morpholine (mmol)</th>
<th>CH$_3$OH: Morpholine</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3</td>
<td>12</td>
<td>1:4</td>
<td>503</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>3</td>
<td>4:1</td>
<td>163</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>3</td>
<td>1:1</td>
<td>261</td>
</tr>
<tr>
<td>4</td>
<td>12</td>
<td>3</td>
<td>1:10</td>
<td>425</td>
</tr>
</tbody>
</table>

Table 5. Alcohol/Amine Ratio $^a$

$^a$ Reaction conditions: 3 μmol catalyst 1 (0.1 mol%), A mmol alcohol, B mmol amine in 5 mL THF at 80°C for 8 hrs. Each entry is an average of two trials unless otherwise indicated.
To confirm the production of amide was due to the presence of 1, a series of control experiments were carried out (Table 6). When the reaction was run in the absence of an iron species or in the presence of FeCl₂, no amide formation was observed (Table 6, entries 1 and 2). The previously characterized formate complex of 1 (1-formate) was observed in NMR experiments and was therefore examined for catalytic activity. This complex was found to be an off-cycle iron species that does not contribute to amide production with catalytic trials resulting in a TON of 0 (Table 6, entry 3). Indeed, these control studies confirmed that formamide production is arising purely from complex 1 and not from other iron species (Table 6, entry 4).

### 4.3.2 Catalytic Trials: Amine Screening

Following the optimization of reaction conditions, a range of secondary amines were tested to probe the substrate scope of complex 1 (Table 7). As a class of substrates, secondary amines have previously proven to be resistant to dehydrogenative coupling reactions. With the exception of a small number of outliers, all reports of catalysts that facilitate the coupling of secondary amines with alcohols never exceed TONs greater than 100. Furthermore, of the three base-metal catalysts that have been reported to couple secondary amines and alcohols, TONs have been limited to less than 50.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>FeCl₂</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1-formate</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>503</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 6. Catalyst Control Experiments a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>

#### a Reaction conditions: 3 μmol catalyst (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 5 mL THF at 80°C for 8 hrs. Each entry is an average of two trials unless otherwise indicated. b Only one trial. c Reaction carried out in the presence of 10 mol% LiBF₄ or LiOTf.

Given these prior results, the efficacy of 1 to couple methanol and secondary amines – specifically cyclic amines – cannot be understated. The optimized reaction conditions resulted in a TON of 503 for the formylation of morpholine (Table 7, entry 3).
Table 7. Amine Substrate Screen

CH₃OH + HNR₂ → 0.1 mol% [Fe] → THF, 80°C, 8h → H₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>TON (yield)</th>
<th>Other Reports: TON (yield) Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Base-Free</td>
</tr>
<tr>
<td>1</td>
<td><img src="image1" alt="Amine 1" /></td>
<td>600 (60.0%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8.8 (88%)&lt;sup&gt;35&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td><img src="image2" alt="Amine 2" /></td>
<td>564 (56.4%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>42.5 (85%)&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td><img src="image3" alt="Amine 3" /></td>
<td>503 (50.3%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>24.8 (49.5%)&lt;sup&gt;53&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td><img src="image4" alt="Amine 4" /></td>
<td>213 (21.3%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td><img src="image5" alt="Amine 5" /></td>
<td>126 (12.6%)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image6" alt="Amine 6" /></td>
<td>&lt;10 (&lt;1.0%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td><img src="image7" alt="Amine 7" /></td>
<td>&lt;10 (&lt;1.0%)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td><img src="image8" alt="Amine 8" /></td>
<td>0&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td><img src="image9" alt="Amine 9" /></td>
<td>0&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: 3 μmol catalyst (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 5 mL THF at 80°C for 8 hrs. Each entry is an average of two trials, and the TON was determined by GC analysis of amide production unless otherwise indicated. <sup>b</sup>Determined by <sup>1</sup>H NMR spectroscopy. <sup>c</sup>Only one trial.
A moderate increase was observed with piperidine, achieving a TON of 564 (Table 7, entry 2). Finally, a maximum TON of 600 was observed with the use of 1,2,3,4-tetrahydroisoquinoline (Table 7, entry 1). These results surpass the TONs of all other reported catalysts for the coupling of any secondary amine and alcohol. Furthermore, the coupling of methanol with secondary amines is an even less common reaction. All prior reports of the dehydrogenative coupling of methanol with secondary amines have been limited to TONs of less than 50.\textsuperscript{35,39,53} Despite the ability of 1 to achieve unprecedented TONs with cyclic amines, the catalytic productivity appears to be dramatically affected by the sterics of amine substituents. A considerable decrease in TON was observed upon switching from sterically restricted, cyclic amines to less hindered amines such as diethyl amine and dibenzyl amine, which afforded TONs of 213 and 126, respectively (Table 7, entries 4 and 5).

Although complex 1 is less effective at catalyzing the coupling of methanol with diethyl- or dibenzylamine, these results are nonetheless noteworthy. This is the first report of the formylation of diethylamine. Stahl et al. previously described the coupling of \textit{p}-methyl benzyl alcohol with diethylamine, but TON was limited to less than 10.\textsuperscript{50} The use of other secondary, mostly unsymmetrical, alkyl amines as substrates is not uncommon, although most are catalyzed by ruthenium complexes and have TONs that to not exceed 50.\textsuperscript{26,38,39,50} Additionally, complex 1 is the most effective catalyst for the coupling of dibenzylamine with an alcohol. The best TON previously reported for this substrate was 72 for the ruthenium-mediated coupling of dibenzyl amine with phenethanol.\textsuperscript{45} The only other report of methanol/dibenzyl amine coupling was catalyzed by a ruthenium complex and achieved a TON of 35.\textsuperscript{39} In summary, 1 was the first reported catalyst for the
formylation of diethylamine and achieved the highest TON for the formylation of dibenzylamine at the time of publication.

Additional amines featuring bulky substituents were examined for amide production including diphenyl- and di-iso-propylamine, although only trace amounts of amides were detected (Table 7, entries 6 and 7). These findings confirm the deleterious effect of amine substituent size on TON. Finally, two cyclic amides were investigated as substrates for their viability towards the synthesis of diamides, but these failed to result in product formation (Table 7, entries 8 and 9). However, previous reports from our group have proposed a competing N-H bond 1,2-addition reaction with secondary amides and complex 1 that is likely inhibiting diamide formation.64 Investigations into the coupling of methanol with primary amines have revealed the ability of 1 to produce ureas from the formamides generated in situ, however this work is discussed elsewhere.67

4.3.3 Catalytic Trials: Alcohol Screening

As detailed above, the ability of 1 to catalyze the dehydrogenative coupling of methanol and amines is significant. The limited reports of catalysts capable of utilizing methanol for amide production is reflective of the larger kinetic barrier that small alcohols must overcome for dehydrogenation compared to larger alcohols. For example, the activation energy for methanol dehydrogenation is $+84 \text{ kJ/mol}$ 68 whereas the activation energy for ethanol dehydrogenation is only $+68 \text{ kJ/mol}$.69 Given the success of complex 1 in dehydrogenating a substrate as challenging as methanol, investigations were carried out to probe the compatibility of 1 with other alcohols (Table 8). Primary alcohols were screened under the previously optimized reaction conditions using morpholine as the amine substrate.
Despite the lower activation energy for ethanol dehydrogenation relative to methanol, catalytic trials carried out in the presence of ethanol resulted in a significantly lower TON of 50, decreasing by an order of magnitude relative to methanol (Table 8, entries 1 and 2). Increasing the alcohol chain length further stifled amide production resulting in a TON of 13 for hexanol (Table 8, entry 3). This sterically sensitive relationship mirrors that observed with amines. Indeed, the productivity of complex 1 appears to be directly related to the steric environment of both alcohol and amine substrates.

Table 8. Alcohol Substrate Screen

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>TON (yield)</th>
<th>Other Reports: TON (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(\text{Ref.}^a)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Base Free</td>
<td>Non-Base-Free</td>
</tr>
<tr>
<td>1</td>
<td>CH(_3)OH</td>
<td>503 (50.3%)</td>
<td>24.8 (49.5%) (^{53})</td>
</tr>
<tr>
<td>2</td>
<td>(\text{CH}_2\text{OH})</td>
<td>50 (5.0%)</td>
<td>37 (74%) (^{39})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{C}_2\text{H}_5\text{OH})</td>
<td>13 (1.3%)</td>
<td>(13 (65%)^ {26})</td>
</tr>
<tr>
<td>4</td>
<td>(\text{C}_6\text{H}_5\text{OH})</td>
<td>10 (1.0%)</td>
<td>(36 (90%)^ {25})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(17.4 (86%)^ {27})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(16 (80%)^ {32})</td>
</tr>
<tr>
<td>5</td>
<td>(\text{CF}_3\text{OH})</td>
<td>10 (1.0%)</td>
<td>(460 (92%)^ {47})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(324 (81%)^ {46})</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(86 (86%)^ {43})</td>
</tr>
<tr>
<td>6</td>
<td>(\text{CF}_3\text{OH})</td>
<td>0(^b)</td>
<td>(66 (66%)^ {48})</td>
</tr>
</tbody>
</table>

\(\text{Ref.}^a\) Reaction conditions: 3 \(\mu\)mol catalyst (0.1 mol%), 3 mmol alcohol, 12 mmol amine in 5 mL THF at \(80^\circ\)C for 8 hrs. Each entry is an average of two trials, and the TON was determined by GC analysis of amide production unless otherwise indicated. \(\text{Ref.}^b\) Determined by \(^1\)H NMR spectroscopy.
Aryl-substituted alcohols also proved to be ineffective substrates for dehydrogenation with only trace amounts of amide produced. (Table 8, entries 4 and 5). Although there are numerous reports of ruthenium catalysts achieving higher TONs for dehydrogenative coupling of aryl-substituted alcohols with secondary amines (vide supra), the only base metal-mediated examples of this rely on the presence of base to achieve catalytic activity and are limited to TONs of less than 40.\textsuperscript{50,51} Despite the low TONs achieved by 1, this is the first report of the base-free coupling of aryl-substituted alcohols with a secondary amine catalyzed by a base metal complex. The alcohol substrate screen was concluded with 2,2,2-trifluoroethanol, which resulted in no amide production (Table 8, entry 6). This absence of catalysis is likely a result of the relatively increased acidity of this substrate as well as the presence of the electron withdrawing CF\textsubscript{3} substituent.

The results of the amine and alcohol substrate screens suggest an appreciable steric effect with respect to the C-N bond forming site. Considering the sterics of the pincer ligand with four isopropyl substituents, these results are somewhat unsurprising. It is likely that these bulky pincer substituents interfere with the ability of large, sterically unrestrained substrates to access the metal center and undergo dehydrogenation. Despite the substrate scope of complex 1 being limited sterically, the high TONs observed for small and sterically restrained substrates indicate the iron center is intrinsically active. Therefore, alterations to the environment of the ancillary ligand may likely result in an increased tolerance for larger substrates.
4.4 Mechanistic Considerations

Many reports of the dehydrogenative amidation of alcohols propose the same mechanistic pathway, with only slight variations in metal-coordinated intermediates versus free intermediates (*vide supra*). The general proposed mechanism is depicted in Figure 3, Pathway A and as follows: alcohol dehydrogenation to form an aldehyde, followed by

---

**Figure 3. Proposed Mechanism for the Dehydrogenative Amidation of Alcohols**

---

*a* Proposed mechanism: Pathway A: hemiaminal intermediate dehydrogenated to form amide. Pathway B: hemiacetal intermediate dehydrogenated to form ester, followed by transamidation to yield amide.
aldehyde amidation to yield a hemiaminal intermediate, and subsequent dehydrogenation of the hemiaminal to produce amide. There are a handful of reports that propose an alternative mechanistic pathway wherein, following alcohol dehydrogenation, the aldehyde undergoes esterification in the presence of an additional equivalent of alcohol, resulting in the formation of an intermediate hemiacetal (Figure 3, Pathway B).26, 34, 42, 52

Dehydrogenation of this hemiacetal yields an ester that undergoes subsequent transamidation to produce amide (Figure 3, Pathway B). The exact mechanism is likely dependent upon individual reaction conditions as well as catalyst identity. The role of additives and metal-ligand cooperation likely effect the proposed pathway by assisting in transamidation26 or proton transfer reactions, preventing hemiaminal formation,41 or improving the coordination of alcohols to the metal center.31

4.4.1 Mechanistic Investigations into 1-catalyzed Dehydrogenative Amidation

Previous reports from our lab have established that complex 1 is a highly active catalyst for the esterification of methanol to yield methyl formate, achieving a TON of 107 after 12 minutes under similar conditions to those used for amidation in this work.65 Considering the ability of 1 to facilitate both ester and amide formation, a set of experiments were devised to investigate the viability of each mechanistic pathway. To test Pathway A, catalytic trials were carried out wherein methanol was replaced with benzaldehyde. By removing the presence of an alcohol, Pathway B becomes inaccessible. Under the previously optimized reaction conditions, complex 1 was found to achieve a TON of 460 for the coupling of morpholine and benzaldehyde, indicating that 1 is in fact capable of forming amides via Pathway A (Figure 4, left).
The viability of Pathway B was tested by replacing methanol with methyl formate, effectively testing the ester transamidation step of this proposed mechanism. These catalytic trials resulted in a TON of 790 for the coupling of methyl formate and morpholine, which confirms that Pathway B is also a feasible route to amide production (Figure 4, right). The ability of 1 to facilitate amide formation via both mechanistic pathways is both promising as well as confounding. These findings indicate that amide formation is achievable irrespective of the identity of intermediates, which is in agreement with the results of the alcohol/amine ratio optimization experiments. However, more in depth studies will be required to elucidate the exact mechanism for 1-catalyzed dehydrogenative amidation of alcohol although subsequent research favors the formation of the hemiaminal intermediate.67

4.4.2 Additional Experiments

Throughout the course of the above experiments, the reaction solution was observed to undergo a reversible color change. Upon the addition of alcohol to a solution of 1 and amine at room temperature, the mixture changed from a deep red to yellow orange in color. Heating of the solution during catalysis reversed the observed color change, returning the reaction mixture to its original shade. The origin of this color change and its
implications were studied via NMR spectroscopy of complex 1 in morpholine and methanol (Figure 5).

**Figure 5. NMR Experiments: MeOH Addition**

A

Room temperature NMR spectra of the sequential addition of reagents to 1 in C₆D₆. A: ¹H NMR spectra, hydride region, blue spectrum is a solution of 1, red spectrum is after the addition of morpholine, green spectrum is after the addition of methanol.  B: ³¹P NMR spectra, same sample/addition sequence.
At room temperature, the addition of 6 equivalents of morpholine to a sample of 1 in benzene-$d_6$ was found to produce no changes in the $^1$H (Figure 5A) or $^{31}$P NMR spectra (Figure 5B). However, the observed color change following the addition of 6 equivalents of methanol was found to correspond with new peaks in both the $^1$H and $^{31}$P NMR spectra (Figure 5, green spectrum). This indicates the formation of a new iron complex believed to be the iron-methoxy species ($^{i}$PrPN$^H$P)Fe(H)(OCH$_3$)(CO) (2) arising from the addition of methanol across the Fe-N bond. To further examine the reaction of 1 with methanol, a series of variable temperature NMRs were carried out (Figure 6).

**Figure 6. Variable Temperature $^{31}$P NMR Spectra of 1 in the Presence of MeOH**

![Variable Temperature $^{31}$P NMR Spectra of 1 in the Presence of MeOH](image)

A new sample was prepared wherein 6 equivalents of methanol were added to a sample of 1 in benzene-$d_6$ and the reaction was monitored via $^{31}$P NMR analysis at a range of temperatures between 22°C and 70°C. As the temperature was increased, the doublet observed at approximately 93 ppm began to broaden and shift downfield until eventually becoming sharp once again at approximately 117 ppm – the chemical shift associated with
complex 1. Throughout the course of these experiments, only one $^{31}$P NMR resonance was observed, indicating the presence of an equilibrium that favors complex 1 at high temperatures and complex 2 at ambient temperatures.

To confirm the identity of 2, 6 equivalents of $^{13}$C labeled methanol were added to a NMR sample of 1 in $d_8$-THF (Figure 7). The proton decoupled $^{13}$C NMR ( $^{13}$C{ [$^1$H]}) contained a broad peak at approximately 50 ppm (Figure 7A, blue spectrum). The chemical shift corresponds with free methanol; however, the broad peak shape is indicative of rapid exchange between two separate $^{13}$C-containing species. To resolve this, low-temperature NMR studies were used to slow the exchange rate beyond the NMR time scale. The $^{13}$C, $^{31}$P, and $^1$H NMR spectra were monitored at a range of temperatures between 22°C and -80°C.

**Figure 7. Low Temperature NMR Experiments in the Presence of $^{13}$CH$_3$OH$^a$**

$^a$Conditions: 6 equivalents of $^{13}$CH$_3$OH added to a sample of 1 in $d_8$-THF. A: $^{13}$C{[$^1$H]} NMR (red and blue) and $^{13}$C NMR (green) spectra. B: $^{31}$P{[$^1$H]} spectra. C: $^1$H NMR spectra, hydride region. Hydride peaks for 4 are not observed due to its low concentration.
At -80°C, two distinct peaks were observed at 59.6 ppm and 49.3 ppm in the \(^{13}\text{C}\{^1\text{H}\} \text{NMR}\) (Figure 7A, red spectrum). The proton coupled \(^{13}\text{C}\) NMR revealed that the peak at 59.6 ppm was still attached to three protons, which confirms the presence of an iron-methoxy species (Figure 7A, green spectrum). As the temperature was decreased, new peaks were observed in the \(^{31}\text{P}\) NMR (Figure 7B). The major peak was found to have a
chemical shift of 93.2 ppm and is associated with complex 2. Minor peaks are attributed to the formation of the trans-dihydride complex (PrPNH2)Fe(H)2(CO) (3), with trace formation of the cis-dihydride complex 4 and the dicarbonyl complex 5 observed.

Computational studies previously reported by our lab have found that methanol dehydrogenation in the presence of 1 likely occurs via the concerted transfer of hydrogen atoms from the methanol C-H and O-H across the Fe-N bond (Figure 8, blue pathway). The dehydrogenation of complexes analogous to complex 2 were found to be considerably higher in energy (Figure 8, red pathway). In light of the above NMR studies and our

Figure 8. DFT Calculated Pathways for Dehydrogenation of MeOH by Five-Coordinate Iron Complex

\[ E = \text{PMe}_3 \]
previous computational findings, it is likely that 2 is formed in an off-cycle reaction that competes with catalytic amidation. While complex 2 may have some kinetic relevance, it is unlikely to be directly involved in the catalytic cycle and the high temperature conditions of catalysis serve to further minimize the role of 2 in catalytic amide formation.

### 4.5 Concluding Remarks

The five-coordinate iron-PNP complex 1 displays the highest productivity for the intermolecular dehydrogenative coupling of alcohols and amines to yield amides. This catalyst outperformed all prior catalysts for the production of tertiary amides, achieving TONs of up to 600. However, the substrate scope was demonstrated to be limited to small, sterically constrained substrates. The presence of sterically bulky groups on either the alcohol or amine proved to be detrimental to amide formation. Alternation of the steric environment on ancillary ligands could likely improve the substrate scope for this catalyst. Given the high catalytic productivity demonstrated, further development of this catalyst toward improved substrate scope and mechanistic understanding is warranted.

### 4.6 Experimental Details

#### 4.6.1 General Considerations

All manipulations were carried out under a nitrogen or argon atmosphere using standard glovebox, Schlenk, cannula, or vacuum techniques. Catalysts 1 and ((PrPNH)PF(x)(H)(HCO)(CO) (1-formate) were prepared as previously described. Amide products (for gas chromatography response factors) that were not commercially available were prepared using previously reported procedures. All other chemicals were purchased
from Aldrich, Fisher, Strem, Synthonix, Oakwood Chemicals, VWR, or Cambridge Isotope Laboratories. Liquid amine and alcohol substrates were dried over calcium hydride or sodium hydride, purified by vacuum transfer or distillation, and stored over 3 Å molecular sieves. Solid substrates were purified by sublimation, followed by recrystallization (if necessary).

Bulk solvents were dried and deoxygenated using literature procedures. Deuterated solvents were dried over 3 Å molecular sieves and then used without further manipulation or were dried over sodium and then vacuum-transferred prior to use. Hydrogen and carbon dioxide were purchased from Airgas and were used as received. $^1$H, $^{13}$C, and $^{31}$P NMR spectra were recorded on Bruker 300 MHz Avance II+, 300 MHz DRX, 500 MHz DRX, and 600 MHz spectrometers at ambient temperature, unless otherwise noted. Chemical shifts are reported in ppm; $J$ values are given in Hz. $^1$H and $^{13}$C chemical shifts are referenced to residual solvent signals; $^{31}$P chemical shifts are referenced to an external standard of H$_3$PO$_4$. Probe temperatures were calibrated using ethylene glycol and methanol as previously described. Gas chromatography was performed on a Thermofisher Scientific Trace 1300 Series gas chromatograph with an FID using helium as the carrier gas.

4.6.2 General Procedure for the Formation of Complex 2

In a drybox, 5 mg of complex 1 was dissolved in either C$_6$D$_6$ or d$_8$-THF in a 20 mL scintillation vial and then transferred to a J. Young tube. The tube was then sealed, removed from the glovebox, degassed, and 6 equivalents of methanol or $^{13}$C-labeled methanol were added via calibrated gas bulb. Select NMR data for 2 (at -80°C): $^1$H NMR (d$_8$-THF, 300 MHz): $\delta$ -24.3 (t, 1H, $J = 52$ Hz , Fe-H); $^{13}$C{$^1$H} NMR (d$_8$-THF, 300 MHz): $\delta$ 59.58 (s,
Fe-O-CH$_3$); $^{13}$C NMR ($d_8$-THF, 300 MHz): $\delta$ 59.57 (q, $J = 132$ Hz, Fe-O-CH$_3$); $^{31}$P{$^1$H} NMR ($d_8$-THF, 300 MHz) 93.21 (d, $J = 32$ Hz).

4.6.3 General Methods for Catalytic Alcohol Dehydrogenation in the Presence of Amines

In a drybox, a 100 mL Schlenk tube was loaded with 5 mL of THF, 12 mmol of amine, 3 $\mu$mol catalyst 1, and 3 mmol of alcohol and then sealed. It was immediately placed in an oil bath preheated to 80$^\circ$C, and the contents were stirred for 8 h. It was then cooled in an ice bath for 30 min prior to analysis. For analysis using NMR spectroscopy, 100 $\mu$L of the reaction solution was placed in an NMR tube with 395 $\mu$L of CDCl$_3$ and 5 $\mu$L of mesitylene standard and an NMR delay time of 60 s was used. For analysis by GC, 100 $\mu$L of the reaction solution were diluted to 1 mL with THF and a mesitylene standard (0.024 or 0.0024 M after final dilution) was added.

4.6.4 General Procedure for H$_2$ Collection Studies

In a drybox, a 100 mL Schlenk flask was loaded with 2.5 mL of THF, 6 mmol of morpholine, 1.5 $\mu$L of catalyst 1, and 1.5 mmol of methanol. The flask was fitted with a reflux condenser and an adapter with a stopcock, removed from the glovebox, and connected to a gas burette setup that had been pre-sparged with N$_2$. The connecting hoses/trap were subjected to two evacuation/refill cycles, the trap was cooled in a dry ice/acetone bath, and a small amount of vacuum was used to reset the starting water volume. The Schlenk flask was lowered into an oil bath (preheated to 80$^\circ$C), and the system was allowed to equilibrate for 3.5 min, after which a small amount of vacuum was used to restore the water volume in the burette (with the connection to the reflux setup closed). The stopcock was then opened, the reaction was allowed to proceed for 8 h, and the change in
the water level in the gas burette was used to determine the TON. This procedure for determining TON has been previously reported.\textsuperscript{63}
4.7 References


16. Soulé, J.-F.; Miyamura, H.; Kobayashi, S., Direct Amidation from Alcohols and Amines through a Tandem Oxidation Process Catalyzed by Heterogeneous-Polymer-


47. Selvamurugan, S.; Ramachandran, R.; Prakash, G.; Nirmala, M.; Viswanathamurthi, P.; Fujiwara, S.; Endo, A., Ruthenium(II) complexes encompassing 2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone


VITA

Katherine Uttley was born on June 20th, 1994, in Kansas City, Missouri. She attended Blue Springs South High School where she excelled in Advanced Placement courses as well as vocal music. She graduated with Suma Cum Laude honors in 2012 and received a full ride scholarship to Drury University in Springfield, Missouri where she studied chemistry and behavioral neuroscience. Katie’s passion for vocal music compelled her to audition for and join all three of Drury’s choirs. She performed with these choirs in Turkey and Greece in 2013, as well as the Springfield Symphony in 2015 and 2016.

As a undergraduate, Katie conducted research into the development of green chemistry techniques for allene synthesis under the mentorship of Dr. Madhuri Manpadi. In 2015, she was the recipient of a Steven’s Summer Research Fellowship from the University of Missouri Columbia where she studied the formation of interstrand crosslinks in DNA. In 2016, she graduated from Drury University with Cum Laude honors and was accepted into the chemistry PhD program at the University of Missouri Columbia.

Katie began researching the conversion of CO₂ via organometallic catalysts in the laboratory of Wesley Bernskoetter in 2016. Developing air-free chemistry techniques was a new and exciting challenge that drew her even deeper into the world of organometallic chemistry and catalysis. While in Columbia, Katie’s love for outdoor recreation grew to include rock climbing, kayaking, trail running, and disc golfing. She quickly became involved in numerous organizations that allowed her to become more engaged with preserving and protecting the parks and wildlife in her community.