ASYMMETRIC $\alpha$-ALKYLATION OF ALDEHYDES

VIA

NEW STRATEGIES IN ORGANIC CATALYSIS

Hui-Wen Shih

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Advisor: David W. C. MacMillan

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Abstract

The construction of carbonyl α-alkyl stereocenters is an important and longstanding challenge in organic synthesis. The chiral α-alkyl carbonyl is a common motif found in natural products and medicinal targets. However, general technologies do not exist for a direct asymmetric carbonyl α-alkylation protocol.

The synergistic catalysis strategy, wherein the nucleophile and electrophile are simultaneously activated by separate catalysts, allows access to difficult transformations that are impossible to access via mono-catalysis strategies. The intersection of a chiral amine catalyzed nucleophile activation (enamine catalysis) and a metal-catalyzed electrophile activation has been applied to the development of direct methods for carbonyl α-(sp³)-carbon functionalization. This thesis describes our efforts to develop novel asymmetric aldehyde α-alkylation technologies via the merger of enamine and metal catalysis.

Electron-deficient arenes and heteroarenes are incorporated in pharmaceutical compounds, yet a direct carbonyl α-benzylolation employing electron-deficient benzyl electrophiles has not been achieved. The enantioselective α-benzylolation of aldehydes employing electron-poor arenes and heteroarenes has been achieved via a synergistic enamine/photoredox catalysis strategy (chapter 2).

Methyl stereogenicity is the most common chiral alkyl motif, yet no direct methods exist for asymmetric electrophilic methylation. A synergistic enamine/copper catalysis strategy has been applied towards the development of an asymmetric aldehyde α-methylation via the coupling of a chiral enamine with an electrophilic alkylcopper(III). Progress regarding the development of this novel transformation is detailed in chapter 3.
Acknowledgements

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<th>Definition</th>
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<tr>
<td>Ac</td>
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<td>AcOH</td>
<td>acetic acid</td>
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<td>adamantyl</td>
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<td>butyl</td>
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<td>cat.</td>
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<td>dr</td>
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<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
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<tr>
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<td>-----------</td>
</tr>
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<td>ESI-TOF</td>
<td>electrospray ionization-time of flight</td>
</tr>
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<td>fac</td>
<td>facial (isomer)</td>
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<tr>
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<td>fluorescent light</td>
</tr>
<tr>
<td>GC/GLC</td>
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<td>i-Pr</td>
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<tr>
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<td>Abbreviation</td>
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<tr>
<td>NMR</td>
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<td>SAMP</td>
<td>(S)-1-amino-2-methyl-oxyethyl-pyrrolidine</td>
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<tr>
<td>SCE</td>
<td>standard calomel electrode</td>
</tr>
<tr>
<td>SET</td>
<td>single electron transfer</td>
</tr>
<tr>
<td>SM</td>
<td>starting material</td>
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<tr>
<td>SOMO</td>
<td>singly occupied molecular orbital</td>
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<tr>
<td>( S_{\text{Ar}} )</td>
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<tr>
<td>( S_{\text{RN}} )</td>
<td>substitution radical-nucleophilic unimolecular</td>
</tr>
<tr>
<td>( \tau )</td>
<td>excited state lifetime</td>
</tr>
<tr>
<td>TBA</td>
<td>tribromoacetic acid</td>
</tr>
<tr>
<td>Symbol</td>
<td>Definition</td>
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給

親愛的爸媽
Chapter 1

Introduction: Carbonyl α-Alkyl Stereocenters

I. Introduction

The development of novel technologies for the formation of asymmetric \((\text{sp}^3)\)-carbon-(\(\text{sp}^3\))-carbon bonds is a important and longstanding challenge for synthetic chemists. The value of stereogenic alkyl centers lies fundamentally in nature’s ability to recognize and synthesize discrete enantiomers. Consequently, chiral \((\text{sp}^3)\)-carbon centers are found in many complex natural products and pharmaceutical compounds (Figure 1). Novel chiral bond construction methodologies improve the design and execution of synthetic strategies towards these target molecules.

Figure 1. Famous Compounds Bearing Asymmetric \((\text{sp}^3)\)-Carbon-(\(\text{sp}^3\))-Carbon Bonds

![Strychnine](Strychnine.png)  
**Strychnine**  
toxic alkaloid

![Penicillin](Penicillin.png)  
**Penicillin**  
fungal antibiotic

![Tetrahydrocannabinol](Tetrahydrocannabinol.png)  
**Tetrahydrocannabinol**  
Marijuana psychoactive component

Starting from its basic building blocks, biological systems display a distinct enantiomer preference. The chirality of these building blocks results in the chirality of the corresponding cellular structures. For example, L-amino acids are the standard building blocks encoded by most living organisms (Figure 2). The corresponding D-amino acids are not suitable replacements, and are not recognized by the cell. The enzymes, receptors and other structural proteins that are formed from L-amino acids are
Figure 2. Biological Building Blocks are Chiral: Select Amino Acids

Asymmetric. Because asymmetry is embedded in biological structures, nature is well suited to recognize and synthesize organic molecules that possess chiral (sp$^3$)-carbon centers.

As a result, asymmetric (sp$^3$)-carbon-(sp$^3$)-carbon bonds are ubiquitous in natural products, medicinally important analogues and drug-like molecules. Often, medicinal properties are displayed by only one enantiomer. However, the opposite enantiomer may be recognized by other biological systems, resulting in dangerous toxic side effects. The famous case of Thalidomide highlights the need for enantioselective syntheses. Prescribed in racemic form as a treatment for morning sickness during pregnancy in the 1950s, scientists belatedly realized the (R)-enantiomer of Thalidomide suppressed nausea, while the (S)-enantiomer tragically caused birth defects. The possibility of enantiomer-induced side effects has resulted in the current government regulations, which require clinical compounds to be enantiopure. Consequently, an ongoing demand exists for the improvement and expansion of synthetic methods to form asymmetric sp$^3$-carbon bonds.

Figure 3. Thalidomide: A Classic Example of the Effect of Chirality on Bioactivity
Carbonyls are useful functional handles for complex bond construction. Carbonyls are prevalent in biology, and the mechanism and methods of carbonyl activation are well-understood. While nature is capable of $\alpha$-alkylating carbonyls to form asymmetric (sp$^3$)-carbon-(sp$^3$)-carbon bonds, direct synthetic strategies are rare. Undeniably, the successful realization of the desired transformation would fulfill an unmet need in the synthetic toolbox (Scheme 1).

**Scheme 1. Asymmetric Carbonyl $\alpha$-Alkylation: An Important and Challenging Transformation**

The development of a general method for the direct and asymmetric $\alpha$-alkylation of carbonyls is challenging due to a number of side reactions.$^{1,2}$ Aldehyde substrates can undergo Canizzaro or Tishchenko disproportionation reactions, and self-condense to form aldol products (Scheme 2). Metal enolate or enamine intermediates are susceptible to competing O- or N-alkylation by the electrophilic alkylation reagent.

**Scheme 2. Aldehyde Side Reactions**

General strategies for asymmetric carbonyl α-alkylations are briefly reviewed in the next section. In particular, chiral auxiliary technology is a robust and commonly utilized method to form carbonyl α-alkyl products (Scheme 3). The requirement for stoichiometric chiral auxiliaries and multi-step syntheses is a limitation of this chemistry, and has led to the development of several catalytic strategies.

**Scheme 3. General Chiral Auxiliary Strategy**

Catalytic methods allow access to previously unattainable or challenging reactivity. Consequently, the desired asymmetric carbonyl α-alkyl motif can be accessed in fewer elemental steps. Chiral catalysts are employed to induce enantioselectivity, and catalytic protocols may additionally benefit from milder reaction conditions and reduced waste streams.

However, a catalytic strategy must also overcome challenges. The typical nucleophilic Lewis or Brønsted base catalysts for carbonyl activation are at risk to undergo alkylation with electrophilic alkylation reagents. The possibility exists for the α-alkylated product to undergo dialkylation, since α-alkylated enolates possess enhanced stability and nucleophilicity. Finally, product racemization must be avoided. Phase transfer catalysis, metal-enolate catalysis, and organocatalysis have been applied towards carbonyl α-alkylation.

The development of direct carbonyl (sp³)-carbon-alkylation reactions remains sparsely explored. Notably, the rare reports of direct asymmetric carbonyl α-alkylations employ organocatalysis as the unifying strategy. Undeniably, the successful realization
of the desired transformation would fulfill an unmet need in the synthetic toolbox. Progress towards an organocatalyzed protocol for the direct construction of aldehyde α-alkyl stereocenters is the goal of the research described in this work.

II. General Strategies for Carbonyl α-Alkylation

A number of strategies have evolved to construct asymmetric α-alkyl carbonyl bonds. Methods for alkylation employing generic alkyl electrophiles are presented here; other relevant technologies will be presented in their respective chapters.

Chiral Auxiliaries

The earliest examples of enantioselective carbonyl α-alkylation involve the use of chiral auxiliaries. Chiral auxiliaries are asymmetric compounds that are temporarily incorporated into the desired molecule to induce selectivity. A subsequent step is required after alkylation to remove the chiral auxiliary.

Enders reported the first use of chiral auxiliaries for asymmetric carbonyl α-alkylation in 1977. Chiral α-alkyl aldehydes are constructed from simple aldehydes and alkyl halides using (S)-1-amino-2-methyl-oxyethyl-pyrrolidine (SAMP) as a chiral auxiliary (Scheme 4). The opposite product enantiomer could be formed by using the opposite enantiomer of the chiral auxiliary.

![Scheme 4. Ender’s Chiral Auxiliary-Mediated α-Alkylation](image)

---

A few years later, Evans introduced prolino l amines as chiral auxiliaries for carboxylic acid derivatives.\(^4\) Optimization led to the development of \(N\)-acyl oxazolidone chiral auxiliaries, which afforded excellent yields and selectivities (Scheme 5).\(^5\) Addition of the chiral auxiliary is straightforward, and methods have been developed to generate the aldehyde, ester, acid or amide product upon removal of the chiral auxiliary. The high levels of diastereocontrol, good functional group tolerance, and ease of carbonyl diversification have contributed to widespread use of Evan’s \(N\)-acyl oxazolidones for the formation of chiral \(\alpha\)-carbonyl centers.

\[
\textbf{Scheme 5. Evan’s Chiral Auxiliary for } \alpha\text{-Benzylation}
\]

![Scheme 5](image)

Another chiral auxiliary that is commonly used is Myers’ pseudoephedrine chiral auxiliary (Scheme 6).\(^6\) Similar to Evan’s auxiliary, addition of the pseudoephedrine is straightforward. Excellent yields and selectivities are obtained for \(\alpha\)-alkylation, and the

products are often crystalline, which leads to easy purification and isolation. Removal of the auxiliary yields alcohol, aldehyde, or acid products.

Figure 4. Select Chiral Auxiliaries Employed in Asymmetric $\alpha$-Alkylations

Chiral auxiliary technology is well-developed and often employed in modern synthetic strategies. Other chiral auxiliaries developed for carbonyl $\alpha$-alkylation include but are not limited to Helmchen camphor-derived auxiliaries, Oppolzer camphorsultam auxiliaries as well as Yamaguchi $C_2$-symmetric amine auxiliaries (Figure 4). The reliability, broad substrate tolerance, and high levels of efficiency and selectivity, contribute to the popularity of the auxiliary strategy. Unfortunately, the multiple steps for the incorporation and removal of the chiral auxiliary in the synthesis are inefficient, and stoichiometric amounts of chiral auxiliary required, which is undesirable for large-scale processes. Desire for atom-economical protocols has led to the development of catalytic methods for carbonyl $\alpha$-alkylation.

Phase Transfer Catalysis

Advances in phase transfer catalysis (PTC) have made it an attractive method for $\alpha$-alkylating carbonyl compounds. Asymmetric phase transfer catalysts facilitate transfer of the molecule of interest (substrate $Y^-$, e.g. carbonyl) from one reaction phase to another (Figure 5). Preorganization of the carbonyl substrate with the chiral catalyst is

---

required for the substrate to undergo phase transfer to the phase where the electrophilic alkylating reagent (R–X) resides. The partitioning of the activated substrate minimizes side reactions, and results in an increase in effective concentration of the reactive species. Phase transfer catalysts are commonly chiral quaternary ammonium salts, though phosphonium salts and organometallic complexes have also been employed. 

*Figure 5. Phase Transfer Catalysis Strategy*

**Scheme 7. Merck Process Develops Phase Transfer Catalysis**

Merck Process first pioneered the technology using a cinchonine-derived N-benzylammonium salt in 1984 for the synthesis of the clinical candidate MK-0197 (Scheme 7). Phase transfer catalysis has since been adopted for the synthesis of α-amino acids starting from readily accessible protected glycine esters, where it is commonly applied in the present day. Seminal work conducted by O’Donnell used the cinchona alkaloid scaffold. Improvements from the O’Donnell group in scaffold design and the

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use of organic-soluble Schwesinger bases have resulted in a homogenous system that gives excellent yields and selectivities (Scheme 8).\textsuperscript{10-11}

\textit{Scheme 8. O'Donnell's Synthesis of \(\alpha\)-Alkyl Amino Esters}

\[
\begin{align*}
\text{Ph} & \text{N} \overset{10 \text{ mol% cat.}}{\xrightarrow{\text{CH}_2\text{Cl}_2, -78 ^\circ C}} \text{Ph} \text{N} \\
\text{O} & \text{OtBu}
\end{align*}
\]

Phase transfer catalysis has become a practical and efficient technology for the formation of \(\alpha\)-functionalized amino acids. As demonstrated by work from the Maruoka group, synthetically useful yields and enantioselectivities have been reported for a wide range of alkyl electrophiles (Scheme 9).\textsuperscript{12} Employment of the BINOL-derived \(N\)-spiro \(C_2\)-symmetric quaternary ammonium bromide catalyst affords low catalyst loadings and mild reaction conditions.\textsuperscript{13}

\textit{Scheme 9. Maruoka's Synthesis of \(\alpha\)-Alkyl Amino Esters}

<table>
<thead>
<tr>
<th>Electrophiles:</th>
<th>Me–I</th>
<th>Et–I</th>
<th>Br</th>
<th>Br</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me–I</td>
<td>72–98%, 96–99% ee</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et–I</td>
<td>72–98%, 96–99% ee</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{13} Corey has also done significant work, and technology developed by the Corey group is often used: Corey, E.J.; Xu, F.; Noe, M.C. \textit{J. Am. Chem. Soc.} \textbf{1997}, \textit{119}.
However, because the carbonyl substrates must be enolizable under the aqueous phase transfer conditions, $\alpha$-alkyl amino acids cannot be directly synthesized by phase transfer catalysis technology. Instead, amino acid starting materials are first protected as the glycine imines. The non-generality of the carbonyl substrates, which are restricted to carbonyls possessing relatively acidic $\alpha$-protons, is a severe limitation of phase transfer catalysis.

**Counterion Catalysis**

A strategy to overcome the limitation of generating enolate equivalents *in situ* is the use of preformed enolate equivalents. Counterion catalysis employs chiral metal complexes to active the preformed enolate. Seminal research from Koga and co-workers demonstrate the enantioselective $\alpha$-alkylation of cyclic ketones starting from silyl enol ethers (Scheme 10). A chiral amine imparts selectivity through ligation of the lithium ion of the lithium enolate generated in situ. Useful yields and selectivities are obtained can be obtained, but the inability to overcome substrate limitations has checked development of Koga-type counterion catalysis. In general, enantioselectivity cannot be maintained unless the carbonyl starting materials are limited to structurally rigid systems.

![Scheme 10. An Example of Koga's Chiral Amine Catalysis of Lithium Enolates](image)

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The Tsuji–Trost reaction employs a different strategy, wherein a chiral palladium catalyst is employed to generate an enantiodefined electrophilic palladium π-allyl intermediate. Nucleophilic enolate attacks the catalytic intermediate to arrive at carbonyl α-quaternary centers with high levels of enantioselectivity (Scheme 11).\textsuperscript{16} However, the product derives from the more easily formed enolate. The Stoltz group later reported an enantioselective version of the work done by Tsuji and coworkers,\textsuperscript{17} wherein substrate decarboxylation forms the palladium π-allyl intermediate.\textsuperscript{18} Notably, when decarboxylation occurs from the preformed enolate, good regioselectivity is observed. The transformation works well for the formation of quaternary allylic stereocenters.

\textit{Scheme 11. The Tsuji–Trost Reaction and Stoltz's Modifications}

In 2005, Jacobsen and co-workers reported a general ketone α-alkylation strategy employing catalytic chromium-salen complexes (Scheme 12).\textsuperscript{19} While formation of


methine stereocenters is problematic due to starting material decomposition.\textsuperscript{20} \(\alpha\)-alkylation to form quaternary centers proceeds under mild conditions with very good to excellent selectivities and efficiencies from both cyclic and acyclic tin enolates.\textsuperscript{21} A variety of common alkyl halides, including methyl iodide and benzyl bromide, can participate in this reaction.

\textit{Organocatalytic Aldehyde \(\alpha\)-Alkylation}

An organocatalytic protocol can bypass the need to employ preformed substrates. Condensation of a ketone or aldehyde starting material with a chiral amine organocatalyst generates a nucleophilic enamine intermediate. Reaction with a suitable alkyl electrophile and hydrolysis of the resulting iminium yields the asymmetric \(\alpha\)-alkylated carbonyl directly (Scheme 13).

\textit{Scheme 13. Organocatalysis Strategy}

\textsuperscript{20} Yields of 83\% (53\% ee) were achieved for an \(\alpha\)-benzylaion of cyclohexanone-derived silyl enol ether, see: ref. 19.
List and co-workers first demonstrated the efficacy of chiral secondary amines as catalysts for aldehyde \( \alpha \)-alkylation in an intramolecular reaction. An enamine \( S_N2 \) mechanism is operative, with bromide, iodide and tosylate all functioning as viable leaving groups (Scheme 14).\(^{22}\) The scope of the transformation is limited to cyclopentyl and cyclopropyl products bearing germinal-disubstitution as a result of problematic side reactions.

\[ \text{Scheme 14. Example of List's Intramolecular Aldehyde } \alpha \text{-Alkylation} \]

Recently, the MacMillan group has turned its attention to the challenge of asymmetric carbonyl \( \alpha \)-alkylation. Proceeding via the intermediacy of an activated radical, several novel carbonyl \( \alpha \)-alkylation strategies have been developed.\(^{23}\) These direct, highly enantioselective transformations demonstrate the value of SOMO-catalysis and synergistic catalysis strategies.

Methods that have been developed for the \( \alpha \)-alkylation of a specific alkyl electrophile will be discussed in their relevant chapters. Direct catalytic methods for aldehyde \( \alpha \)-benzylation will be described in chapter 2, and catalytic methods for aldehyde \( \alpha \)-benzylation will be described in chapter 3.

III. Organocatalysis in the MacMillan Group

The MacMillan Group is broadly interested in the discovery and development of general strategies for enantioselective catalysis. Research focuses on the use of organic catalysts for the development of novel transformations for carbonyl compounds, a ubiquitous functional handle in organic chemistry. Compared to their organometallic counterparts, organic catalysts are typically lower molecular weight and less toxic. Organic catalysts are easily accessible from the organic chiral pool.

The field of organocatalysis has grown to encompass hundreds of novel transformations, and is delineated by a few general strategies, which we term modes of activation (Figure 6). Virtually all transformations fall under the umbrella of (1) hydrogen-bonding catalysis, (2) iminium catalysis, (3) enamine catalysis, or (4) SOMO (singly occupied molecular orbital) catalysis.\textsuperscript{24} Extensive work in our group has demonstrated that chiral imidazolidinones, easily synthesized from commercially available amino acids, serve readily as catalysts for aldehydes and ketones. MacMillan catalysts react under the platforms of iminium, enamine or SOMO-catalysis (Figure 6).

In the case of iminium catalysis, condensation of an α,β-unsaturated carbonyl with the secondary amine generates a charged iminium intermediate possessing a lower

energy LUMO relative to the starting material aldehyde, making it more susceptible to nucleophilic attack at the β-position. Enamine catalysis raises the energy of the carbonyl HOMO upon condensation of the same catalyst with a saturated carbonyl to form an enamine intermediate, which is prone to electrophilic addition at the α-position. Finally, SOMO-catalysis is marked by an electrophilic radical species reactive towards π-nucleophiles at the α-position, formed via single electron oxidation of a transient catalyst-condensed enamine.

Product enantioselectivity results from (1) iminium/enamine geometry, and (2) stereoelectronic effects of the 2,5 disubstitution on the imidazolidinone (Figure 7). The catalyst-carbonyl adduct prefers to sit in the trans geometry to minimize A₁,₃ strain. In addition, the enamine prefers to sit away from the bulkier substitution. Shielding of the Re face from the second substituent leaves the Si face open to approach of the coupling partner. In addition to imparting selectivity, catalyst 2,5-disubstitution results in the unfavorable redocking of the product onto the catalyst being due to nonbonding interactions.

![Figure 7. Disubstituted Imidazolidinone Controls Enantioinduction](image)

The SOMO-catalysis strategy has enabled the development of numerous transformations for the formation of carbonyl α-(sp³)-carbon stereocenters. In SOMO catalysis, enamine formed via condensation of the chiral amine catalyst and substrate
aldehyde undergoes single electron oxidation by a metal oxidant to form a transient electrophilic $\alpha$-iminium radical. The radical reacts rapidly with $\pi$-nucleophiles to form useful products. In the context of $\alpha$-alkylations, $\alpha$-allylation, $\alpha$-enolation, and $\alpha$-homobenzylation have been demonstrated (Figure 8).

**Figure 8. SOMO-Catalysis**

The invention of new activation platforms is extremely powerful, since each serves as the genesis for a multitude of novel transformations. Recently, we have become interested in the merger of multiple intersecting catalytic systems in a strategy we define as synergistic catalysis, wherein the nucleophile and electrophile are simultaneously activated by two distinct catalysts to afford a single chemical transformation.\(^{25}\) Challenging or previously unattainable reactivity under single catalysis strategies can be accessed when both reactive partners are activated (Figure 9).

**Figure 9. Synergistic Catalysis Strategy**

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Introduction of a redox active photocatalytic cycle with the organocatalytic enamine cycle has led to several exciting new reactions under an activation mode we term photoredox organocatalysis. The photoredox organocatalytic strategy couples electrophilic radicals, generated by single electron reduction by the photoredox catalyst, with enamine, which behaves as a π-nucleophile (Figure 10).

![Figure 10. Synergistic Catalysis via Photoredox Organocatalysis](image)

A postdoctoral fellow in the group, Dr. David Nicewicz, applied this strategy in the context of coupling to electrophilic α-acyl radicals (Scheme 15). In a seminal work, Dr. Nicewicz demonstrated that the synergistic merger of organocatalysis and photoredox catalysis can be applied successfully to the α-alkylation of aldehydes using α-bromocarboxyls.

![Scheme 15. Photoredox Organocatalysis: The Enantioselective α-Alkylation of Aldehydes](image)

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Ru(bpy)$_3$Cl$_2$ acts as the photocatalyst, which undergoes a Ru(I)/Ru(II) redox cycle in this reaction. Noteably, the low photoredox catalyst loading (0.5 mol% Ru(bpy)$_3$Cl$_2$) reflects its competence in generating radicals in a mild and controlled fashion and highlights the effectiveness of coupling two highly reactive intermediates in a synergistic catalytic strategy.

The productive merger of organocatalysis and transition metal catalysis is another fruitful area of research that has allowed access to previously unattainable asymmetric transformations (Figure 11). Copper participates in oxidative insertion of vinyl- and aryl-iodoniums to form electrophilic Cu(III) intermediates, which interact with catalyst-derived enamine to form carbonyl α-(sp$^2$)-carbon stereocenters.$^{27}$ Most recently, the discovery that Cu(III)-aryl intermediates can also be access from transmetallation with vinyl boronic acids has led to an alternative strategy for asymmetric aldehyde α-vinylation.

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*Figure 11. Synergistic Catalysis Employing an Organic Catalyst and a Metal Catalysis*

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The synergistic catalysis strategy has the potential to uncover novel reactivity. Excitingly, the application of organocatalysis within synergistic catalysis protocols may allow access to direct asymmetric carbonyl α-alkylations. The development of this powerful transformation would be of high value to the synthetic chemistry community.

**IV. Thesis Outline**

The realization of a direct and general asymmetric carbonyl α-alkylation protocol has remained elusive. However, the development of synergistic catalytic systems provides the framework for a novel strategy towards the challenge of asymmetric carbonyl α-alkylation. By harnessing more reactive intermediates, many problems associated with traditional alkylations may be circumvented.

An attempt towards aldehyde α-benzylation utilizing a photoredox organocatalytic strategy is detailed in chapter 2. The reaction proceeds under mild conditions with electron-poor substrates; both carbocyclic and heterocyclic substrates can be employed. Chapter 3 highlights progress towards an asymmetric aldehyde α-methylation via the merger of an imidazolidinone catalyst and copper. Transition metal catalysis enables the use of mild boron methylating reagents.
Chapter 2

The Enantioselective α-Benzylation of Aldehydes

I. Introduction

The carbonyl group has long been utilized as a functional handle to introduce complexity in synthetic strategies. Carbonyl α-benzylation, leading to the formation of homobenzylic stereocenters, is a significant and long-standing challenge due to the prevalence of benzyl groups in natural products and medicinally relevant compounds (Figure 1). The stereogenic α-formyl benzyl motif is found in four of the twenty natural

Figure 1. The Significance of the Carbonyl α-Benzyl Motif

Phenylalanine
amino acid
L-DOPA
neurotransmitter precursor
Thyroxine (T₄)
thyroid hormone
Complanadine A
nerve growth factor inducer
(+)-Lithospermic acid
HIV-integrase inhibitor
(–)-Berkelic acid
cytotoxic Penicillium metabolite

28 The majority of the experimental results from this chapter have been published: Shih, H.-W.; Vander Wal, M. N.; Grange, R. L.; MacMillan, D. W. C. J. Am. Chem. Soc. 2010, 132, 13600. Accounts of this work were also presented at the American Chemical Society’s 241st National Meeting and Exposition in Anaheim, CA (March 27–31, 2011).
amino acids, and appears in their natural product derivatives. Consequently, the motif is incorporated in important biological molecules, including neurotransmitters, hormones, and complex metabolites. The significance of the homobenzylic stereocenter is recognized by medicinal chemists, and has also been assimilated in the design of medicinal agents (Figure 2).

![Figure 2. Drugs Possessing Electron-Deficient Homobenzylic Stereocenter](image)

Access to these targets is limited by the scarcity of direct catalytic technologies for the installation of the homobenzylic stereocenter by alkylation. General carbonyl α-alkylation protocols can be found in chapter 1. The few reports in the literature of direct catalytic methods are reviewed in part II of this chapter, and employ benzylic electrophiles possessing electron-rich and electron-neutral arenes.

The development of complementary carbonyl α-benzylation protocols for the incorporation of electron-deficient aromatic and heteroaromatic compounds would fulfill an unmet need in the design and synthesis of clinical molecules. Electron-deficient aromatics are more stable towards metabolic oxidation, and heteroaromatics containing basic nitrogens can act as hydrogen-bond acceptors. The impact of the electron-deficient

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heteroaromatic subunit is underscored by its prevalence in pharmaceutical research. Of the top five heterocycles in the Comprehensive Medicinal Chemistry Database\textsuperscript{32} – pyridine, imidazole, indole, quinoline and pyrimidine – three are electron-deficient, with electron-deficient pyridine being the most prevalent (Figure 3).\textsuperscript{33}

![Figure 3. Top Five Heterocycles in the Comprehensive Medicinal Chemistry Database (2008)](image)

The following chapter describes work towards a solution for direct carbonyl α-benzylation employing aldehydes and electron-deficient arenes and heteroarenes. A synergistic catalysis strategy merging enamine catalysis with photoredox catalysis is applied to the challenge of a highly enantioselective aldehyde α-benzylation protocol. The realization of the proposed transformation would result in a novel method to rapidly access interesting bioactive molecules.

**II. Enantioselective Aldehyde α-Benzylaion Methods**

In recent years, reports of direct, asymmetric aldehyde α-benzylations have begun to appear in the literature. The methodologies described share a common mechanistic strategy, involving (1) activation of the aldehydic component and induction of enantioselectivity by an organocatalyst, and (2) *in situ* formation of a stabilized benzylic

\textsuperscript{32} Analysis of drugs and natural products MW <500 (excludes steroids, proteins, macromolecules).

carbocation. Coupling between the two activated intermediates and subsequent dissociation from the catalyst yields the desired enantioenriched product (Scheme 1).

**Scheme 1. General Strategy for \(\alpha\)-Benzylation of Electron-Rich Arenes**

Melchiorre and co-workers reported the first examples of this methodology in 2008 as a formal \(\alpha\)-alkylation employing 3-(1-arylsulfonylalkyl)indoles (Scheme 2).\(^\text{34}\) Using L-proline as the catalyst, tolylsulfonyl anion serves as an excellent leaving group under basic conditions to generate the desired carbocation.\(^\text{35}\) Yields and enantioselectivities are synthetically useful (63–92% yield, 75–92% ee, one example with 11% ee) with diastereoselectivities ranging from 1.5:1 d.r. to 12:1 d.r.

**Scheme 2. 2008: Melchiorre’s Formal \(\alpha\)-Alkylation**

The following year, Cozzi and co-workers successfully coupled aldehydes with diarylmethine carbocations generated from the corresponding alcohols (Scheme 3).\(^\text{36}\) A MacMillan imidazolidinone catalyst is employed. Yields are dependent upon carbocation stability (30–95%) with very good to excellent enantioselectivities observed.

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\(^\text{35}\) The carbocationic character of the indolyl intermediate is unclear due to resonance delocalization into the indole; the transformation may be classified as a conjugate addition.

Using the same imidazolidinone organocatalyst to activate the aldehyde starting material, the Cozzi group employed the enamine-carbocation coupling strategy in a subsequent report, which demonstrated that benzylic carbocations can be accessed via in situ DDQ oxidation of the benzylic C–H bond to yield similar aldehyde α-benzyl products.\textsuperscript{37} Finally, stabilized arylmethine carbocations could be added to the reaction mixture directly, albeit with mediocre product enantiopurity.\textsuperscript{38} The scope of this transformation is limited by the scarcity of stabilized benzylic carbocations. Xiao and co-workers have shown that synergistic catalysis systems (diarylprolinol silyl ether/Cu(I) Lewis acid) improve the efficiency of the reaction for diarylmethanol substrates.\textsuperscript{39}

Jacobsen and co-workers have demonstrated chiral thiourea catalysts can be employed for the formation of quaternary homobenzylic stereocenters (Scheme 4). α-Disubstituted aldehydes and symmetrical diarylmethyl bromides can be coupled in good


yields and excellent enantioselectivities. Notably, the bifunctional thiourea catalyst allows coupling of electron neutral and mildly electron-withdrawing arenes, which were previously inaccessible.\textsuperscript{40}

\textit{Scheme 4. Hydrogen-Bonding Catalysts Activate Both Aldehyde and Carbocation}

These advances represent a relatively new transformation under development. The power of organocatalytic strategies to access challenging reactivity is demonstrated by these seminal reports of direct carbonyl α-benzylation. Thus far, the inherent instability of the electrophilic carbocation intermediate has limited the scope of the benzylic coupling partner. The electrophilic coupling partner is restricted to secondary carbocations, and with few exceptions,\textsuperscript{34} both substituents must be aromatic. In general, electron-rich arenes are utilized to improve the stability of the carbocation intermediate. There is one report utilizing an electron-poor arene; however, it exists as part of a captodative diaryl (indole/nitroarene) methine carbocation.\textsuperscript{37} The strategy is not adaptable for very electron-poor arenes, requiring an alternative mechanistic strategy for the direct carbonyl α-benzylation employing electron-poor heteroarenes.

\textit{III. Design Plan}

Recent work in the MacMillan group in the area of SOMO catalysis stimulated us to consider radical chemistry as a method of accessing novel reactivity.\textsuperscript{41} The key

reactive intermediate in the SOMO reaction platform is a chiral enamine radical cation, which is generated from condensation of the secondary amine catalyst with starting material carbonyl followed by single electron oxidation to the enamine radical cation (Scheme 5). The enamine radical cation is electrophilic, and thus enables coupling with \( \pi \)-nucleophiles.

**Scheme 5. Mechanism of Organocatalyzed SOMO Reaction**

While unsubstituted alkyl radicals are generally nucleophilic and unstable, the SOMO enamine radical cation is rendered electrophilic by the conjugated iminium.\(^{42}\) The extended \( \pi \)-system serves additionally to delocalize the radical and improves its stability.

Inspired by SOMO technology, we considered the possibility of applying the enamine activation mode to the coupling of electrophilic radicals. Organocatalytic alkylation via traditional 2-electron closed shell pathways is difficult to access due to the high activation energy (Figure 4). However, as in the carbocation strategy, radical coupling is facilitated by the increased reactivity of the electrophilic partner. As a result, the activation energy of the overall reaction is lowered, and a one-electron open shell pathway can successfully access previously challenging transformations.

Studies from the Kornblum group indicate that substitution of electron-withdrawing groups on the aryl ring renders the resultant benzylic radical electrophilic. The model substrate, \( p \)-nitrobenzyl chloride, reacts with nucleophiles through a \( S^\text{RN}1 \) (substitution radical-nucleophilic unimolecular) mechanism (Scheme 6).\(^{43}\) Initial single electron reduction of the benzyl chloride yields an unstable benzyl halide radical anion, which undergoes fragmentation of the weak benzyl-chloride bond to form a neutral benzyl radical and the chloride anion. In addition to chloride, a variety of leaving groups undergo mesolysis, including \( +\text{NMe}_3 \), Br, I, OTs, COOAr, \( \text{SO}_2\text{Ph} \), NO\(_2\), SCN, \( N_3 \), and \( +\text{SMe}_2 \). The \( S^\text{RN}1 \) mechanism is operative for a variety of nucleophilic partners, including the sodium salt of 2-nitropropane, \( \beta \)-ketoester anions, amines, sulfide anions, sulfoxide anions, malonates, nitriles, cyanides, amides, and phenoxides, under both thermal and photochemical conditions.\(^{44}\)


Russell and co-workers have further demonstrated that $p$-nitrobenzyl chlorides react with enamines in high yields under photostimulation (Scheme 7). No product is obtained in the absence of light, which indicates that the closed-shell $S_{N}2$ mechanism is not operative, and suggests that the reaction proceeds via light-induced homolytic Bn–Cl fragmentation followed by enamine attack on the radical. The work establishes that electron-rich enamines are sufficiently nucleophilic to couple with electrophilic benzyl radicals.

**Scheme 7. Enamines Couple with Electrophilic Benzyl Radicals**

Photoredox Catalysis: A Strategy for Radical Generation

A mild method of generating radicals is through the use of a photoredox catalyst. Photoredox catalysts are compounds that convert light energy to facilitate single electron transfer oxidations and reductions. Upon exposure to light, an electron in the photocatalyst HOMO is excited to the LUMO, leading to two nondegenerate singly occupied molecular orbitals (Figure 5). The lower energy SOMO readily accepts an electron when the photoredox catalyst acts as an oxidant. The higher energy SOMO easily donates its electron when the photocatalyst acts as a reductant.

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Photoredox catalysts can be inorganic, metal-ligand complexes or purely organic compounds, the majority being metal-ligand complexes. Metal-ligand complexes are preferred for organic reactions due to their solubility in organic solvents and improved stability over organic compounds.

Metal-ligand complexed photoredox catalysts typically consist of a transition metal fully chelated by aromatic ligands. Many ligands are bidentate, such as 2,2’-bipyridine (bpy) or 2-phenylpyridine (ppy). Advantageously, the catalyst’s properties can be adjusted through changes in ligand architecture, such that absorbance wavelength, excited state lifetime, and oxidation and reduction potentials may be optimized.

We envision that the photoredox catalyst can generate the desired electrophilic radical by single electron reduction. Substrate mesolysis (fragmentation of radical ions
into radicals and ions) then leads to the desired radical intermediate. The incorporation of a photoredox catalyst foregoes the need for harsh photolytic conditions or stoichiometric chemical reductants.

**Photoredox Organocatalysis**

The productive merger of a photoredox catalytic cycle with an organocatalytic cycle would yield the anticipated asymmetric aldehyde α-benzylation. Dr. David Nicewicz, a former postdoctoral fellow in the group, was the first to apply the photoredox organocatalysis strategy, resulting in a successful aldehyde α-alkylation protocol.\(^\text{47}\)

Mechanistically, the photoredox cycle is initiated by oxidation of a sacrificial amount of enamine (not shown) by photoexcited \(*\text{Ru(bpy)}_3^{2+}\) (1) to form highly reducing \(\text{Ru(bpy)}_3^+\) (2), which transfers a single electron to the alkyl halide (Figure 6). Mesolysis of the resultant radical anion generates a neutral electrophilic radical. Simultaneously, condensation of the chiral amine catalyst with starting material aldehyde forms a stereodefined enamine (3). The catalyst blocks the Re-face of the enamine, leaving the Si-face open for approach of the electrophile. Addition of the radical generates an α-amino radical (4), which is rapidly oxidized by \(*\text{Ru(bpy)}_3^{2+}\) (1) to reform \(\text{Ru(bpy)}_3^+\) (2), and finally hydrolysis of the iminium 5 yields the desired enantioenriched α-alkyl product and reforms the organocatalyst. By coupling photocatalyst regeneration into the organocatalytic cycle, radicals can be generated in a controlled manner, minimizing possible radical side reactions.

Electron-poor benzyl halides are intrinsically suitable electrophile precursors for the photoredox organocatalytic activation platform. Addition of catalytic enamine to electron-poor benzyl radicals would allow access to a direct aldehyde $\alpha$-benzylolation reaction. Progress towards this valuable and challenging transformation is detailed in the following section.

**IV. Enantioselective Aldehyde $\alpha$-Benzylation via Photoredox Organocatalysis**

*Mechanistic Validation*

The viability of the synergistic photoredox organocatalysis activation platform for aldehyde $\alpha$-benzylation was rapidly confirmed in the laboratory using Dr. Nicewicz’s
conditions and p-nitrobenzyl bromide as the benzylating reagent, although the desired radical coupling product is formed in trace amounts (Scheme 8).

**Scheme 8. Validation of α-Benzylation Concept**

Improvements to reactive efficiency are observed when the photoredox catalyst is exchanged for a more reducing anionic iridium catalyst. Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆ (where dF(CF₃)ppy = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine and dtbbpy = 4,4'-di-tert-butyl-2,2’-dipyridyl, ⁰E (*Ir³⁻/Ir⁴⁺) = −1.21 V vs SCE in MeCN) possesses cyclometallating ligands for improved catalyst stability and an improved lifetime over Ru(bpy)₃Cl₂ (2.3 µs vs. 0.6 µs). In addition, both the HOMO and LUMO of the iridium organometallic photocatalyst extend over the ligand framework, resulting in efficient electron transfer. Employing a higher dielectric solvent such as DMSO, which stabilizes charge transfer complexes and radical intermediates, leads to an additional enhancement in product yield.

**Figure 7. Products Generated in Attempts at Radical Benzylation**

Unfortunately, the desired reaction could never be improved (yield < 20%) due to competing side reactions. Radical homodimer, catalyst N-alkylation and reaction with

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DMSO solvent to form benzaldehyde (Kornblum oxidation) and benzyl alcohol are observed under a range of conditions (Figure 7).

*Lessons from the Initial Attempt to Develop an Aldehyde α-Benzylation*

We reasoned that p-nitrobenzyl bromide is difficult to reduce and the resultant radical insufficiently electrophilic to prefer coupling with π-nucleophilic enamine. Unfavorable radical formation results in the increased formation of \( S_n2 \) products, such as alkylated catalyst. The presence of radical homodimer suggests that the benzyl radical is not electrophilic enough to react easily with nucleophilic enamine. Therefore, decreasing the reduction potential of the benzyl radical and increasing the electrophilicity of the benzyl radical should bias the electrophile towards the desired reaction with the enamine.

Coupling between 2,4-dinitrobenzyl radical and enamine proved to be more facile. We sought to understand the impact of the benzylic leaving group in order to render it less reactive towards two electron pathways. Functionalities known to undergo mesolytic cleavage (Cl, SMe\(_2\), SO\(_2\)Ph, Br, SCN) were attempted.\(^{44}\) We discovered that use of thiocyanate (SCN) as a leaving group could minimize unwanted two-electron pathways. Increasing the intensity of light and the surface area of the reaction vessel resulted in a corresponding improvement in reaction efficiency (Table 1). Unfortunately, under a variety of experimental conditions, leaving groups that were less reactive towards closed-shell nucleophilic attack (SCN, SO\(_2\)Ph) also underwent radical fragmentation with more difficulty; thus, while undesired pathways can be eliminated, the desired reaction suffers as well (entries 1 and 6).
By replacing the leaving group with bromide, which fragments to benzyl radical more rapidly, the reaction proceeds with sufficient facility – comparable to thiocyanate – to be competitive with the Kornblum reaction and catalyst alkylation (entry 7). As a general strategy, reaction vessel engineering is undesirable. Therefore, the reaction efficiency was improved to tolerate non-specialized equipment. By decreasing the photoredox catalyst to 0.5 mol% loading, the reaction could be performed in the standard borosilicate reaction vial with good yield and excellent enantioselectivity (78% yield, 93% ee). Isolated enantiomeric excess is slightly depressed compared to the crude mixture due to slight racemization on silica gel.

In summary, the efficacy of the 2,4-dinitrobenzyl radical to couple with catalytic enamine stems from (1) ease of benzylic reduction resulting from additional electron-withdrawing substitution, (2) improved radical stability from the extended π-system, and (3) enhanced electrophilicity of the resultant radical.

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**Table 1. Effect of Light and Surface Area on Radical Generation**

<table>
<thead>
<tr>
<th>entry</th>
<th>LG</th>
<th>light</th>
<th>Rxn Vessel</th>
<th>Vessel Diam. (mm)</th>
<th>Yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>SO₂Ph</td>
<td>26 W CFL</td>
<td>NMR Tube</td>
<td>7</td>
<td>0</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>SCN</td>
<td>26 W CFL</td>
<td>8 ml Vial</td>
<td>17</td>
<td>5</td>
<td>97</td>
</tr>
<tr>
<td>3</td>
<td>SCN</td>
<td>26 W CFL</td>
<td>Test Tube</td>
<td>12</td>
<td>21</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>SCN</td>
<td>26 W CFL</td>
<td>Test Tube</td>
<td>10</td>
<td>28</td>
<td>97</td>
</tr>
<tr>
<td>5</td>
<td>SCN</td>
<td>15 W FL</td>
<td>NMR Tube</td>
<td>7</td>
<td>32</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>SCN</td>
<td>26 W CFL</td>
<td>NMR Tube</td>
<td>7</td>
<td>47</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>Br</td>
<td>26 W CFL</td>
<td>NMR Tube</td>
<td>7</td>
<td>75</td>
<td>97</td>
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<tr>
<td>8</td>
<td>Br</td>
<td>26 W CFL</td>
<td>8 ml Vial</td>
<td>17</td>
<td>69</td>
<td>97</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields are based on ¹H NMR with internal standard. <sup>b</sup>Enantiomeric excess is determined by HPLC analysis.
The scope of the benzylic electrophiles is severely limited to those with substitution that is both electron-withdrawing and possess extended \( \pi \)-systems. Less conjugated radicals are not sufficiently stable to undergo the desired reaction with the transient enamine (Figure 8).

*Figure 8. Limitations of Benzylic Radical Coupling*

We hypothesized that the limitations of the electrophilic benzyl coupling partner could be overcome by catalyst redesign. Russell has demonstrated that \( p \)-nitrobenzyl radical couples efficiently when stoichiometric enamine is employed. By increasing the effective concentration of enamine present, an organocatalyst designed to favor enamine formation should enable coupling with less electrophilic benzyl radicals.

*Catalyst Design*

The 2,5-disubstituted imidazolidinone organocatalysts impart enantioselectivity because (1) the enamine adopts the *trans* geometry to minimize \( A^{1,3} \) strain, and (2) the enamine prefers to sit away from the bulkier substitution, and is shielded from one face by the second substituent. The relationship between the two catalyst substituents may be *cis* or *trans*, and advantages and disadvantages exist for the two catalyst architectures (Figure 9).

*Cis*-2,5-disubstituted imidazolidinones impart selectivity in the following manner. The enamine partitions away from the bulky *tert*-butyl group, which allows the less sterically bulky substituent to shield approach from one face of the enamine. *Cis-*
disubstituted catalysts are less sterically hindered around the nucleophilic nitrogen. Enamine formation is consequently more rapid in comparison to the analogous trans-disubstituted catalyst.

**Figure 9. Chiral Imidazolidinone Catalyst: Structural Advantages**

Enamines formed from aldehyde condensation with trans-2,5-disubstituted imidazolidinone also partition away from the tert-butyl group. However, if the enamine partitions to the side of the tert-butyl group, the pseudo C2-symmetric of the catalyst framework confers the same sense of enantioinduction (Figure 10). In addition, increased nonbonding interactions in trans-2,5-disubstituted imidazolidinones cause product redocking to be more energetically unfavorable, minimizing the possibility of catalyst-mediated product racemization. Therefore, due to more selective bond formation and suppressed post-reaction racemization, a trans-2,5-disubstituted imidazolidinone generally imposes improved stereocontrol at elevated temperatures.

**Figure 10. C2-Symmetric Catalysts Induce High Levels of Enantiocontrol**

A pseudo-C2-symmetric catalyst architecture is necessary to impart high levels of stereocontrol for our room temperature reaction. The (2R,5S)-2-tert-butyl-3,5-
dimethylimidazolidin-4-one catalyst was originally selected as the organocatalyst because it demonstrated high levels of efficiency and enantioselectivity in previous photoredox transformations developed in the MacMillan group. In contrast, when cis-2,5-disubstituted imidazolidinone catalysts were initially employed in the reaction involving p-nitrobenzyl bromide, only very low levels of enantioselectivity are achieved (~10 % ee). However, compared to the less sterically hindered cis-2,5-disubstituted imidazolidinones, enamine formation using the (2R,5S)-2-tert-butyl-3,5-dimethylimidazolidin-4-one catalyst is slow.

We rationalized that decreasing the steric bulk of the trans-2,5-disubstitution should increase rates of enamine formation by making the nucleophilic amine more accessible. Dr. Nicewicz and Dr. Pickworth undertook the development of catalysts wherein the bulky 2-tert-butyl substitution is replaced by less bulky substituents.

Scheme 9. Catalyst Design Results in Improved Reaction Efficiency

The development of pseudo-C₂ symmetric imidazolidinone catalysts led to dramatic improvement in the benzylation project. Catalysts of this type allowed less electrophilic carbocyclic benzyl radicals, which are problematic substrates with the original (2R,5S)-2-tert-butyl-3,5-dimethylimidazolidin-4-one catalyst, to react in synthetically useful yields (Scheme 9). While exchange of tert-butyl for methyl
substitution did not afforded only modest enantioinduction, replacement with a more shielding benzyl substituent resulted in recovery of product enantioselectivity.

α-Benzylaion of Heteroarenes

The development of less sterically hindered pseudo-\( C_2 \) symmetric imidazolidinone catalysts opened up the opportunity to consider benzylic substrates beyond substituted carbocycles. We realized a class of heterocycles fulfilled the requirements for this coupling reaction. Six-membered nitrogen heterocycles contain an embedded electronegative atom, thus possessing an inherently electrophilic conjugated benzyl system (Figure 11).

![Figure 11. Electron-Deficient Heteroaromatics](image)

We began our investigation with (4-pyridinyl)methylbromide (as the hydrobromic acid salt)\(^{49}\) using the conditions that were optimal for carbocyclic benzyl substrates. Gratifyingly, using (2\( R,5S \))-5-benzyl-2,3-dimethylimidazolidin-4-one resulted in product formation with good efficiency and excellent enantioselectivity (Scheme 10).

The significance of the catalyst design is dramatic; using the original (2\( R,5S \))-2-\( tert \)-butyl-3,5-dimethylimidazolidin-4-one catalyst afforded no product formation. In this case, the starting material bromide decomposes in the presence of base. The redesigned

\(^{49}\) The unprotonated (4-pyridinyl)methylbromide is not stable.
catalyst forms enamine more rapidly, resulting in improved rates of the desired \( \alpha \)-alkylation. Starting material decomposition is not observed.

Scheme 10. New Catalyst Design Allows Access to Heteroaromatic Substrates

\[ \text{fac-Ir(ppy)}_3 \] has been identified as a photoredox catalyst that performs comparably to \( \text{Ir(dF(CF}_3\text{ppy})_2(dtbbpy)} \text{PF}_6 \) (Figure 12).\(^{50}\) \( \text{Ir(dF(CF}_3\text{ppy})_2(dtbbpy)} \text{PF}_6 \) is synthesized in a straightforward three-step procedure. In contrast, \( \text{fac-Ir(ppy)}_3 \) is commercially available from Aldrich, which increases the operational ease of the reaction.

Figure 12. Spectroscopic Properties of Iridium Photoredox Catalysts\(^{57}\)

Unfortunately, 2-pyridyl and 3-pyridyl substrates remain ineffective for \( \alpha \)-alkylation (Scheme 11a).\(^{52}\) The importance of the position of the electron-withdrawing


\(^{51}\) Reduction potentials use the standard calomel electrode (SCE) as the reference electrode and are taken in MeCN.

\(^{52}\) Both substrates were tested as the hydrobromic acid salt; neither are stable as the free base.
substituent has previously been observed in the placement of nitro substitution in the \( \alpha \)-benzylation with carbocyclic substrates and remains a common trend for heterocyclic substrates. Therefore, when 2-pyridyl is substituted with a nitro group at the 4-position, reactivity is restored.

**Scheme 11. Effects of Heteroatom Substitution**

The importance of pyridyl ring substitution was investigated (Scheme 11b). Using 4-pyridyl as a model substrate, the effect of substitution at the 3-position was investigated. Surprisingly, substitution with electronegative halides resulted in yield depression. Thinking perhaps the halides destabilized the pyridine ring system by activating it towards nucleophilic attack, substitution was moved to the 2-position. Again, relative to unsubstituted pyridine, the reaction efficiency was reduced. However, increasing the electron density by 3-methyl substitution resulted in excellent conversion to the desired product.
Reaction efficiency is correlated to starting material pK \(_a\) (Figure 13).\(^{53}\) Under the reaction conditions (2,6-lutidine is the base, pK \(_a\) = 6.60), a fraction of the pyridine starting material is protonated. Protonation of the aromatic ring facilitates both the reduction and enhances the electrophilicity of the resultant radical. Credence is added to the protonation mechanism given that the reduction of unsubstituted pyridine is challenging under reaction conditions (E\(_{1/2}\) –1.6 V vs. SCE) and explains the poor reactivity of halide-substituted pyridines, which are not protonated under the reaction conditions.\(^{54}\) Only when substituted with a very electron-withdrawing group such as nitro is does reduction and subsequent radical coupling become facile. Significantly, substrate protonation is a strategy for the activation of basic heteroatoms that are challenging to reduce or not innately electrophilic to couple with the enamine.

![Figure 13. Correlation Between pKa and Reactivity](image)

<table>
<thead>
<tr>
<th>pK (_a)</th>
<th>product yield</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.44</td>
<td>21%</td>
<td>0.90</td>
<td>35%</td>
<td>2.84</td>
<td>23%</td>
</tr>
<tr>
<td>5.14</td>
<td>86%</td>
<td>5.97</td>
<td>75%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In general, five-membered rings are problematic for this chemistry, even when substituted with electron-withdrawing groups (Scheme 12a). In cases for which radical generation and coupling are sluggish, the corresponding benzyl alcohol from reaction with DMSO is observed, as well as radical homodimer product and oftentimes remaining starting material. The strategy of aromatic activation by base protonation allows access to applicable substrates that are difficult to reduce or insufficiently electrophilic. As demonstrated by the benzimidazole substrate, N-alkylation to effect in situ substrate


protonation is more effective than protection with electron-withdrawing groups (Scheme 12b). While protection with electron-withdrawing groups led to substrate decomposition, N-alkylated benzimidazole cleanly undergoes α-benzylation.

**Scheme 12. Five-Membered Heterocycles are Challenging Substrates**

(a) 5-Membered Heterocycles are Problematic Substrates

(b) Protonation Allows Access to Challenging Heterocycles

**Scope of the Reaction**

Along with Dr. Rebecca Grange and Mark Vander Wal, the scope of the photoredox organocatalytic aldehyde α-benzylation was investigated. As revealed in Table 2, these mild redox conditions are compatible with a wide range of functional groups, including ethers, amines, imides, carbamates, and aromatic rings (72–91% yield, 87–90% ee). The reaction does proceed more slowly when aldehydes bearing β-disubstitution are employed, and starting materials such as 4-(bromomethyl)pyridine, which are prone to decomposition, are problematic. However, in general, significant variation in the steric demand of the aldehyde substituent can be accommodated without loss in enantiocontrol (entries 4 and 5, ≥ 73% yield, 90% ee).
We found that a broad range of electron-deficient aryl and heteroaryl methylene bromides participate in this enantioselective benzylation reaction (Table 3). For example, benzyl systems that incorporate a nitro-substituent with other electron-withdrawing groups such as nitriles and esters (entries 1–3) are well tolerated. Moreover the 1,2-nitrofluoro aryl ring can serve to produce a suitably electrophilic radical without the intervention of $S_N$Ar byproducts (entry 3). Perhaps more notable with respect to medicinal agent synthesis, a large range of heteroaryl rings can be successfully employed such as pyridines, quinolines, benzimidazoles, pyrimidines, and triazines. As highlighted in entries 4 and 5, bromomethyl pyridines that have electron-donating substitution (entry 5, 2-methyl, 91% ee), or electron-withdrawing groups (entry 4, 5-nitro, 90% ee) are both competent in this enantioselective coupling. Moreover, fused bicycles such as 4-quinolinyl and 2-benzimidazolyl also perform well (81–90% yield, 82–88% ee, entries 6, 10). Heterocycles containing two nitrogens such as 2-pyrazinyl and 4-pyrimidinyl, and
three nitrogens, such as 2-triazinyl – which all lack a basic nitrogen – also react with good efficiency and excellent enantioselectivity (68–78%, 87–91% ee, entries 7–9). Examples contain substitution on the aryl ring because the parent bromomethyl-heterocycles additional substitution (e.g. 2-(bromomethyl)pyrazine) are unstable.

Table 3. Asymmetric Aldehyde α-Benzylolation: Bromide Scope

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield, ee</th>
<th>Entry</th>
<th>Product</th>
<th>Yield, ee</th>
<th>Entry</th>
<th>Product</th>
<th>Yield, ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Image" /></td>
<td>76% yield, 93% ee</td>
<td>4</td>
<td><img src="image2" alt="Image" /></td>
<td>74% yield, 90% ee</td>
<td>8</td>
<td><img src="image3" alt="Image" /></td>
<td>78% yield, 87% ee</td>
</tr>
<tr>
<td>2</td>
<td><img src="image4" alt="Image" /></td>
<td>83% yield, 90% ee</td>
<td>5</td>
<td><img src="image5" alt="Image" /></td>
<td>75% yield, 91% ee</td>
<td>9</td>
<td><img src="image6" alt="Image" /></td>
<td>68% yield, 91% ee</td>
</tr>
<tr>
<td>3</td>
<td><img src="image7" alt="Image" /></td>
<td>74% yield, 90% ee</td>
<td>6</td>
<td><img src="image8" alt="Image" /></td>
<td>90% yield, 82% ee</td>
<td>10</td>
<td><img src="image9" alt="Image" /></td>
<td>81% yield, 88% ee</td>
</tr>
<tr>
<td>7</td>
<td><img src="image10" alt="Image" /></td>
<td>73% yield, 90% ee</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Stereochemistry assigned by chemical correlation or by analogy. Enantiomeric excess determined by chiral SFC or HPLC. 30 mol% organocatalyst used. 3Performed at 15 C using Ru(bpy)3Cl2 as the photoredox catalyst. 3Substrate added as the hydrobromic acid salt with an additional equivalent of 2,6-lutidine. The free base organocatalyst was used. 3Yield determined by 1H NMR. 3Ir(dF(CF3)ppy)2(dtbbpy)PF6 was employed as the photoredox catalyst. 3Isolated yield of the corresponding alcohol.

V. Mechanistic Insights

Fluorescence Quenching

The Stern-Volmer relationship describes the kinetics of an intermolecular deactivation, or quenching, process in which a second species, Q, accelerates the rate of deactivation (i.e. fluorescence or phosphorescence) of an activated species, A*.

\[ A^* + Q \rightarrow A + Q \]

The efficiency of a given quencher is correlated with the decrease in intensity of the activated species, in this case the photoredox catalyst, in the following relationship

\[ \frac{I_f}{I_f^0} = 1 + k_q \tau_o [Q] \]

where \( k_q \) is the quencher rate coefficient, \( \tau_o \) is the fluorescence lifetime of A, [Q] is the quencher concentration, \( I_f \) is the intensity of fluorescence with the addition of the quencher and \( I_f^0 \) is the intensity of fluorescence in the absence of the quencher. Often \( k_q \tau_o \) is combined into one constant, K. This is the constant cited in work from the MacMillan Group. The quencher rate constant, K, can be calculated by graphing the experimental fluorescence values as a function of concentration and determining the slope; the strength of the quencher is directly proportional to its quencher rate coefficient.

In an effort to provide insight into the mechanistic details in the seminal photoredox organocatalysis transformation, several fluorescence quenching experiments (Stern-Volmer studies) with the Ru(bpy)_3Cl_2 photoredox catalyst were performed.\(^\text{47}\) Fluorescence quenching determined photoexcited Ru(bpy)_3^{2+} is not quenched by the alkyl bromide precursors, which undergo single electron reduction before mesolytic cleavage to the electrophilic radical coupling partner. Since no direct electron transfer occurs
between \(^{13}\text{Ru(bpy)}_{3}^{2+}\) and the species undergoing reduction, a Ru(II)/Ru(III) redox cycle is precluded. Neither did the photocatalyst display fluorescence quenching by the remaining starting materials. However, quenching is observed upon addition of enamine preformed from aldehyde and the imidazolidinone catalyst, suggesting photoexcited Ru(II) is reduced by enamine to Ru(I), a strong reductant (\(E_{1/2} = -1.35\) V vs. SCE in MeCN).\(^{46}\) Fluorescence quenching, however, does not preclude the possibility of photocatalyst acting via energy transfer. Femtosecond absorbance spectroscopy (FAS) in collaboration with the McCusker Group at the University of Michigan, Ann Arbor validated that Ru(bpy)\(_{3}\)Cl\(_{2}\) acts in a Ru(I)/Ru(II) redox fashion by spectroscopic identification of a Ru(I) species.\(^{56}\)

**fac-Ir(ppy)\(_{3}\): A Photoredox Catalyst**

To elucidate the oxidation-reduction mechanism of **fac-Ir(ppy)\(_{3}\)**, we have similarly performed several fluorescence quenching experiments (Stern–Volmer studies) with the **fac-Ir(ppy)\(_{3}\)** photoredox catalyst. The cyclometalated iridium catalyst can undergo single electron oxidation-reduction in either an Ir(III)/Ir(II) or Ir(III)/Ir(IV) cycle (Figure 14).

Photoexcited **fac-Ir(ppy)\(_{3}\)** is quenched by both carbocyclic and heterocyclic substrates, represented by 2,4-dinitrobenzyl bromide and 4-(pyridinyl)methylbromide as the HBr salt (Figure 15). All heterocyclic substrates that are successful in the aldehyde \(\alpha\)-benzylolation reaction quench the photoredox catalyst.\(^{57}\) While energy transfer to activate the aromatic system and facilitate bond homolysis or otherwise activate the

\(^{56}\) Dr. David Nicewicz, Prof. D. W. C. MacMillan, Prof. J. K. McCusker, unpublished result.
\(^{57}\) Please see Supporting Information for quenching data of the remaining substrates.
benzyl substrate cannot be ruled out, these findings, in conjunction with the precedent from our seminal findings, are indicative that \textit{fac}-Ir(ppy)\textsubscript{3} acts as a photoredox catalyst in an Ir(III)/Ir(IV) cycle.

No other starting materials quench the photoredox catalyst. However, it must be noted that upon exposure to preformed enamine derived from (2\textit{R},5\textit{S})-5-benzyl-2,3-dimethylimidazolidin-4-one catalyst and octanal, weak Ir(ppy)\textsubscript{3} fluorescence quenching is observed, which would suggest sacrificial enamine is being reduced to form the anionic
Ir(II) species. This is highly unlikely, as \(^{*}\)Ir(pppy)\(_3\) (\(E_{\text{red}} = -0.3\) V vs. SCE in MeCN) should not be able to oxidize enamine (enamines possess reduction potentials in the range of 0.92 to 1.12 V vs. SCE in CH\(_2\)CN).\(^5\) Instead, it is likely that a trace amount of molecular sieves, used in the formation of enamine, causes the fluorescence quenching. Molecular sieves are known to quench fluorescence for iridium compounds. In any case, reductive quenching of the photoredox catalyst is weak relative to oxidative quenching, indicating that even if enamine oxidation were possible, under the reaction conditions \(^{*}\)Ir(pppy)\(_3\) reduction of the benzyl substrate is greatly favored and the Ir(III)/Ir(IV) cycle is operative.

**The Role of 2,6-Lutidine**

Given the ability of the 4-pyridinyl substrate to protonate and undergo electron transfer, we wondered if 2,6-lutidine, the common base used in photoredox organocatalytic protocol, serves also as an electron-shuttle in its protonated pyridinium form. We hypothesized that \(N\)-methylation of 2,6-lutidine should form a compound that

![Reaction Scheme](image)

**Table 4. 2,6-Lutidine Is Not an Electron Shuttle**

<table>
<thead>
<tr>
<th>entry</th>
<th>Base (equiv)</th>
<th>(N)-methyl lutidinium (equiv)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 equiv 2,6-lutidine</td>
<td>none</td>
<td>86(^a)</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv 2,6-lutidine</td>
<td>2 equiv</td>
<td>79(^b)</td>
</tr>
<tr>
<td>3</td>
<td>1 equiv 2,6-lutidine</td>
<td>none</td>
<td>74(^b)</td>
</tr>
<tr>
<td>4</td>
<td>none</td>
<td>3 equiv</td>
<td>24(^c)</td>
</tr>
<tr>
<td>5</td>
<td>3 equiv NaH(_2)PO(_4)</td>
<td>none</td>
<td>69(^b)</td>
</tr>
</tbody>
</table>

\(^a\)Isolated yield. \(^b\)Yield determined by GC analysis with internal standard. \(^c\)Yields are based on \(^1\)H NMR with internal standard.

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accepts electrons in a comparable fashion to protonated 2,6-lutidinium. If 2,6-lutidine serves as an electron-shuttle, partial replacement of 2,6-lutidine with the \(N\)-methyl analogue should affect the reaction efficiency (Table 4). However, the yield in the presence and absence of \(N\)-methyl-2,6-lutidinium is comparable (entries 2–3). Complete replacement of 2,6-lutidine with the \(N\)-methyl analogue resulted in a dramatic drop in reaction efficiency (entry 4). Therefore, 2,6-lutidine plays a role that is not hindered by its methylated equivalent but cannot be solely replaced by \(N\)-methyl-2,6-lutidinium triflate.

Furthermore, we discovered that the inorganic base \(\text{NaH}_2\text{PO}_4\) proved to be a competent replacement for 2,6-lutidine (entry 5). \(\text{NaH}_2\text{PO}_4\) is incapable of acting as an electron shuttle. Therefore, the role of 2,6-lutidine in the reaction is solely that of a base to facilitate enamine formation.

**Validation of an Activated Protonated Heteroaromatic Species**

Protonation of basic functionality facilitates single electron reduction by (1) lowering the reduction potential of the substrate and (2) increasing the electrophilicity of the resultant radical. Stern–Volmer experiments corroborated the increased ease of reduction. The quenching coefficient of the most electron-neutral substrate, \(N\)-methyl benzimidazolyl methyl bromide, has been determined for \(fac\)-Ir(ppy)\(_3\) as both the salt and free base compound (Figure 16).\(^{59}\) The protonated benzimidazole substrate undergoes reduction preferentially over the unprotonated benzimidazole, accounting for the improved reaction efficiency demonstrated by \(N\)-alkylated benzimidazole compared to its protected analogues (Scheme 12).

\(^{59}\) 4-(pyridinyl)methylbromide was not used because the free base decomposes rapidly.
Mechanism for the Photoredox Organocatalytic α-Benzylation of Aldehydes

The final proposed mechanism for the developed aldehyde α-benzylation transformation is detailed below (Figure 17). The fac-Ir(ppy)_3 photoredox catalyst (6) is
excited by 26W CFL to \(\text{fac-}^*\text{Ir(ppy)}_3\), which transfers an electron to the benzyl bromide substrate. The radical anion undergoes mesolysis of the weak \(\text{Bn}-\text{Br}\) bond to generate a neutral electrophilic benzyl radical (8). Concurrently, aldehyde starting material condenses with \textit{trans}\-2,5-disubstituted imidazolidinone catalyst to form a facially biased enamine (9). DFT calculations show that the enamine prefers to sit under the benzyl group of the catalyst. The radical approaches from the open \textit{Si}-face to forge the key homobenzylic stereocenter, yielding an unstable \(\alpha\)-amino radical intermediate (10) that is rapidly oxidized to the corresponding iminium \((11)\) by \(\text{fac-}\text{Ir(ppy)}_3^+\) (12) to reform the photoredox catalyst. Hydrolysis reforms the organocatalyst and yields the enantioenriched \(\alpha\)-benzyl aldehyde.

\textbf{V. Conclusion}

In conclusion, the first enantioselective aldehyde \(\alpha\)-benzylations using electron-deficient aryl and heteroaryl substrates has been accomplished. The productive merger of a chiral imidazolidinone organocatalyst and a commercially available iridium photoredox catalyst in the presence of household fluorescent light directly affords the desired homobenzylic stereogenicity in good to excellent yield and enantioselectivity.
VI. Supporting Information

I. General Information.

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego. Dimethylsulfoxide (DMSO) and 2,6-lutidine were distilled from CaH₂ prior to use. Octanal and propanal were passed through a short plug of basic alumina and then distilled. All other solvents were purified according to the method of Grubbs. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using force-flow chromatography according to the method of Still on ICN 60 32-64 mesh silica gel. Davisil Grade 643 silica gel or Iatrobeads 6RS-8060 silica gel were used where specified. Thin-layer chromatography (TLC) was performed on Silicycle 250 µm silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or by KMnO₄, anisaldehyde, ceric ammonium molybdate, or ninhydrin stain.

¹H and ¹³C NMR spectra were recorded on a Varian Inova 400 (400 MHz or 100 MHz) or a Bruker Avance 500 (500 MHz or 125 MHz) and are internally referenced to residual protio solvent signals (note: CDCl₃ referenced at δ 7.27 ppm for ¹H and δ 77.0 ppm for ¹³C). Data for ¹H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, hept = heptet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ¹³C NMR are reported in terms of chemical shift. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in terms of frequency of absorption.

(cm$^{-1}$). High Resolution Mass spectra were obtained from the Princeton Mass Spectrometry Laboratory. Supercritical fluid chromatography (SFC) was performed on a Berger Minigram equipped with a diode array UV detector ($\lambda = 214–280$ nm) using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. High Performance Liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series chromatographs using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. Optical rotations were measured on a Jasco P-1010 polarimeter with $[\alpha]_D$ values reported in degrees; concentration (c) is in g/100 mL.

II. Method A. General Procedure for Enantioselective $\alpha$-Benzylation using Non-basic Substrates:

To an oven-dried 8 mL vial equipped with a magnetic stir bar and rubber septum was added (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (0.10 mmol, 0.20 equiv), tris-(2-phenylpyridinato-C$^2$N)iridium(III) ($fac$-Ir(ppy)$_3$) (0.0025 mmol, 0.0050 equiv), 2,6-lutidinium triflate (0.10 mmol, 0.20 equiv), and the benzyl bromide (0.50 mmol, 1.0 equiv). The vial was then degassed by alternative evacuation and back filling with Ar or N$_2$ (1 min x4). Previously degassed DMSO (1.0 mL, 0.5 M), aldehyde (1.0 mmol, 2.0 equiv), and 2,6-lutidine (1.0 mmol, 2.0 equiv) were then added to the vial via syringe addition. The reaction vial was sealed with parafilm and positioned approximately 1 cm in front of two 13W compact fluorescent light bulbs for 6 h. Upon completion, the
reaction mixture was poured into 8 mL of saturated aqueous NH₄Cl or NaHCO₃ and extracted with Et₂O (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ or MgSO₄ and the solvent was removed in vacuo. The resulting crude oil was purified by flash chromatography with the solvent mixture as noted to provide the pure products. Racemic samples were obtained by running the reaction with equal amounts of each enantiomer of the catalyst. The corresponding alcohols were obtained for chiral SFC or HPLC analysis by the following procedure. The aldehyde starting material (1 equiv) was dissolved in a 5:1 mixture of CH₂Cl₂/MeOH (0.1 M) and NaCNBH₃ (10 equiv) was added to the stirring solution at room temperature. Upon consumption of the aldehyde (1-2 hours) the reaction mixture was poured into saturated aqueous NH₄Cl and extracted with CH₂Cl₂ (2 x 5 mL). The combined organic extracts were dried over Na₂SO₄ and concentrated in vacuo. The product alcohol sample was submitted to chiral SFC or HPLC analysis without any further purification.

Method B. General Procedure for Enantioselective α-Benzylation using Basic Substrates:

To an oven-dried 8 mL vial equipped with a magnetic stir bar and rubber septum was added (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (0.10 mmol, 0.20 equiv), tris-(2-phenylpyridinato-C²,N)iridium(III), (fac-Ir(ppy)₃) (0.0025 mmol, 0.0050 equiv), and the methylaryl bromide as the hydrobromic acid salt (0.50 mmol, 1.0 equiv). The vial was then degassed by alternative evacuation and back filling with Ar or N₂ (1 min x 4).
Previously degassed DMSO (1.0 mL, 0.5 M), aldehyde (1.0 mmol, 2.0 equiv), and 2,6-lutidine (1.5 mmol, 3.0 equiv) were then added to the vial via syringe addition. The reaction vial was sealed with parafilm and positioned approximately 1 cm in front of two 13W compact fluorescent light bulbs for 3 h. Upon completion, the reaction mixture was poured into 8 mL of saturated aqueous NaHCO$_3$ and extracted with Et$_2$O (2 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ or MgSO$_4$ and the solvent was removed \textit{in vacuo}. The resulting crude oil was either immediately purified by flash chromatography with the solvent mixture as noted to provide the pure aldehyde products or subjected to the following reduction conditions: The crude oil was dissolved in a 5:1 mixture of CH$_2$Cl$_2$/MeOH (0.1 M), NaBH$_4$ (10 equiv) was added, and the reaction mixture was stirred at room temperature for one hour. Water (10 mL) was added and the mixture was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated \textit{in vacuo}. The crude alcohol product was then purified by flash chromatography with the solvent mixture as noted to provide the pure alcohol product. Racemic samples were obtained by running the reaction with equal amounts of each enantiomer of the catalyst.

(R)-2-(2,4-Dinitrobenzyl)octanal (Table 1, entry 4). General $\alpha$-benzylolation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 1-(bromomethyl)-2,4-dinitrobenzene (0.131 g, 0.50 mmol), octanal (0.128 g, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil
was purified by flash chromatography (20% EtOAc/hexanes) to provide the pure title compound as a light yellow oil (145 mg, 94% yield, 90% ee). IR (thin film): 3100, 2930, 2858, 2731, 1724, 1605, 1532, 1457, 1346, 1276, 1197, 1150, 1065 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 9.63 (d, J = 1.5 Hz, 1H, CH₀), 8.77 (d, J = 2.3 Hz, 1H, ArH), 8.35 (dd, J = 8.5 Hz, 2.4, 1H, ArH), 7.67 (d, J = 8.4 Hz, 1H, ArH), 3.35 (dd, J = 13.7, 9.0 Hz, 1H, ArC₂H₂), 3.10 (dd, J = 13.7, 4.7 Hz, 1H, ArC₂H₂), 2.79 (m, 1H, CHOC₂H₂), 1.79 (m, 1H, CH₂(CH₂)₄CH₃), 1.60 (m, 1H, CH₂(CH₂)₄CH₃), 1.35 (m, 8H, CH₂(CH₂)₄CH₃), 0.86 (m, 3H, CH₂(CH₂)₄CH₃); ¹³C NMR (125 MHz, CDCl₃) δ 202.7, 149.4, 146.8, 142.1, 134.9, 127.0, 120.7, 52.7, 32.0, 31.7, 29.7, 29.5, 26.8, 22.7, 14.2; HRMS (ESI-) exact mass calculated for [M-H]- (C₁₅H₁₉N₂O₅) requires m/z 307.1300, found m/z 307.1300; [α]D³ = +72.1 (c = 1.30, CHCl₃). HPLC analysis (AS, 5% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 92% ee: tᵣ(major) = 19.75 minutes, tᵣ(minor) = 21.51 minutes.

(R)-2-(Pyridin-4-ylmethyl)octanal (Table 2, entry 1). General α-benzylation method B was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)₃ (1.6 mg, 0.0025 mmol), 4-(bromomethyl)pyridinium bromide (0.127 g, 0.50 mmol), octanal (0.128 g, 1.0 mmol), and 2,6-lutidine (0.161 g, 0.174 mL, 1.5 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (Davisil, 40% EtOAc/hexanes) to provide the pure title compound (95 mg, 87% yield, 90% ee) as a light yellow oil. IR (thin film) 3024, 2926, 2856, 2711, 1724, 1601, 1457, 1415 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 9.67 (d, J = 1.2 Hz, 1H, CH₀), 8.51 (d, J = 5.3
Hz, 2H, ArH), 7.10 (d, J = 5.7 Hz, 2H, ArH), 3.05 – 2.93 (m, 1H, ArCH2), 2.73 – 2.59 (m, 2H, ArCH2, ArCH2CH), 1.74 – 1.59 (m, 1H, CHOCHCH2), 1.56 – 1.44 (m, 1H, CHOCHCH2), 1.42 – 1.18 (m, 8H, CH2(CH2)4CH3), 0.87 (t, J = 6.8 Hz, 3H, CH2CH3); 13C NMR (100 MHz, CDCl3) δ: 203.4, 149.7, 148.4, 124.3, 52.4, 33.9, 31.5, 29.2, 28.6, 26.7, 22.5, 14.0; HRMS (ESI-TOF) calculated for C14H22NO [M+H]+ m/z 220.1696, found 220.1699. [α]D23 = +43.6 (c = 0.90, CHCl3). HPLC analysis of the corresponding alcohol (OD, 7% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 90% ee: tR(major) = 12.03 minutes, tR(minor) = 10.83 minutes.

(R)-2-Benzyl-3-(pyridin-4-yl)propan-1-ol (Table 2, entry 2). General α-benzylation method B was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)3 (1.6 mg, 0.0025 mmol), 4-(bromomethyl)pyridinium bromide (0.127 g, 0.50 mmol), hydrocinnamaldehyde (0.134 g, 0.132 mL, 1.0 mmol), and 2,6-lutidine (0.161 g, 0.174 mL, 1.5 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was subjected to the reduction conditions described and purified by flash chromatography (40% EtOAc/hexanes + 0.5% Et3N) to provide the pure title compound (104 mg, 91% yield, 90% ee) as a light yellow oil. IR (thin film) 3296, 2921, 1603, 1418, 1030, 701 cm−1; 1H NMR (500 MHz, CDCl3) δ: 8.34 (d, 1H, J = 5.5 Hz, CHNCH), 7.20 (t, 2H, J = 7.4 Hz, ArH), 7.12 (t, 1H, J = 7.2 Hz, ArH), 7.08 (d, 2H, J = 7.5 Hz, ArH), 7.02 (d, 2H, J = 5.3 Hz, CHCHNCHCH), 3.39 (d, 2H, J = 4.9 Hz, CH2OH), 2.9 (bs, 1H, CH2OH), 2.65 (dt, 2H, J = 15.9, 7.9 Hz, ArCH2), 2.53 (ddd, 2H, J = 13.5, 6.3, 4.3 Hz, ArCH2), 2.06 (m, 1H, ArCH2CH); 13C NMR (125 MHz, CDCl3) δ: 150.4, 149.5, 140.2, 129.3, 128.6, 126.3,
124.9, 63.3, 44.0, 37.5, 36.7; HRMS (ESI-TOF) calculated for C_{15}H_{18}NO [M+H]^+ m/z 228.1383, found 228.1383. $[\alpha]_D^{23} = -3.42$ (c = 1.0, CHCl$_3$). HPLC analysis (AS, 6% EtOH/hexanes, 1.0 mL/min, 254 nm) indicates 90% ee: $t_R$(major) = 16.98 minutes, $t_R$(minor) = 18.67 minutes.

(R)-5-(Benzyloxy)-2-(pyridin-4-ylmethyl)pentanal (Table 2, entry 3). General $\alpha$-benzylation method B was followed using (2$R$S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), $fac$-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 4-(bromomethyl)pyridinium bromide (0.127 g, 0.50 mmol), 5-(benzyloxy)pentanal (0.192 g, 1.0 mmol), and 2,6-lutidine (0.161 g, 0.174 mL, 1.5 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (Davisil, 50% EtOAc/hexanes) to provide the pure title compound (112 mg, 77% yield, 87% ee) as a light yellow oil. IR (thin film) 2931, 2858, 1721, 1607, 1496, 1454, 1417, 1362, 1206, 1102 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.67 (d, $J$ = 1.6 Hz, 1H, CHO), 8.50 (d, $J$ = 5.9 Hz, 2H, PyrH), 7.39 – 7.29 (m, 5H, PhH), 7.11 (d, $J$ = 5.9 Hz, 2H, PyrH), 4.48 (s, 2H, PhCH$_2$), 3.47 (t, $J$ = 5.9 Hz, 2H, BnOCH$_2$), 3.01 (dd, $J$ = 16.2, 9.7 Hz, 1H, PyrCH$_2$), 2.75 – 2.65 (m, 2H, PyrCH$_2$, PyrCH$_2$CH), 1.86 – 1.54 (m, 4H, CHOCH(CH$_2$)$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 203.2, 149.5, 148.5, 138.2, 128.4, 127.7, 127.7, 124.4, 73.0, 69.6, 52.1, 33.9, 26.9, 25.4; HRMS (ESI-TOF) calculated for C$_{18}$H$_{22}$NO$_2$ [M+H]$^+$ m/z 284.1645, found 284.1648. $[\alpha]_D^{23} = +13.4$ (c = 1.04, CHCl$_3$). HPLC analysis of the corresponding alcohol
(OD, 3% EtOH/hexanes, 1.0 mL/min, 254 nm) indicates 87% ee: $t_R$(major) = 91.60 minutes, $t_R$(minor) = 85.47 minutes.

(S)-2-Cyclohexyl-3-(2,4-dinitrophenyl)propanal (Table 2, entry 4). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), $\text{fac-Ir(ppy)}_3$ (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 1-(bromomethyl)-2,4-dinitrobenzene (0.131 g, 0.50 mmol), 2-cyclohexylethanial (0.126 g, 0.137 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (10% EtOAc/hexanes) to provide the pure title compound (113 mg, 73% yield, 90% ee) as a light yellow oil. IR (thin film) 2925, 2853, 1721, 1604, 1530, 1345 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.65 (s, 1H, CHO), 8.76 (d, 1H, $J$ = 2.2 Hz, ArH), 8.33 (dd, 1H, $J$ = 8.5, 2.2 Hz, ArH), 7.71 (d, 1H, $J$ = 8.5 Hz, ArH), 3.31 (dd, 1H, $J$ = 13.4, 10.5 Hz, ArCH$_2$CH), 3.17 (dd, 1H, $J$ = 13.5, 3.0 Hz, ArCH$_2$CH), 2.73 (m, 1H, ArCH$_2$CHCH), 2.02–1.55 (m, 6H, Cy), 1.43–1.06 (m, 5H, Cy); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 203.3, 149.3, 146.6, 142.7, 135.3, 126.9, 120.6, 58.5, 39.2, 30.7, 30.0, 29.2, 26.2; HRMS (ESI-TOF) calculated for C$_{15}$H$_{18}$N$_2$NaO$_5$ [M+Na]$^+$ m/z 329.1108, found 329.1107. $[\alpha]_D^{24}$ = +81.07 (c = 1.0, CHCl$_3$). SFC analysis of the corresponding alcohol (IA, 5–50% MeOH gradient, 1.0 mL/min, 220 nm) indicates 90% ee: $t_R$(major) = 7.90 minutes, $t_R$(minor) = 7.16 minutes.
(S)-tert-Butyl 4-(1-(2,4-dinitrophenyl)-3-oxopropan-2-yl)piperidine-1-carboxylate

(Table 2, entry 5). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 1-(bromomethyl)-2,4-dinitrobenzene (0.131 g, 0.50 mmol), tert-butyl 4-(2-oxoethyl)piperidine-1-carboxylate (0.227 g, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (35% EtOAc/hexanes) to provide the pure title compound (152 mg, 75% yield, 90% ee) as a light yellow oil. IR (thin film) 2937, 2862, 1724, 1685, 1533, 1346, 1167 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ: 9.65 (s, 1H, CHO), 8.77 (d, 1H, $J = 2.2$ Hz, ArH), 8.33 (dd, 1H, $J = 8.5, 2.2$ Hz, ArH), 7.71 (d, 1H, $J = 8.5$ Hz, ArH), 4.12 (bs, 2H, NBocCH$_2$), 3.29 (dd, 1H, $J = 13.1, 10.8$ Hz, ArCH$_2$CH), 3.18 (dd, 1H, $J = 13.4, 2.4$ Hz, ArCH$_2$CH), 2.81 (m, 1H, ArCH$_2$CH), 2.70 (bs, 2H, NBocCH$_2$), 2.05 (m, 1H, CH$_2$CHCH$_2$), 1.74 (d, 1H, $J = 12.6$ Hz, CH$_2$CHCH$_2$), 1.66 (d, 1H, $J = 12.9$ Hz, CH$_2$CHCH$_2$), 1.57–1.34 (m, 11H, CH$_2$CHCH$_2$, and C(CH$_3$)$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) δ: 202.2, 154.5, 148.9, 146.5, 142.0, 135.1, 126.9, 120.4, 79.6, 57.2, 37.3, 29.6, 29.4, 29.0, 28.3; HRMS (ESI-TOF) calculated for C$_{19}$H$_{25}$N$_3$NaO$_7$ [M+Na]$^+$ m/z 430.1585, found 430.1585. [$\alpha$]$^D_{24} = +70.21$ (c = 1.0, CHCl$_3$). SFC analysis of the corresponding alcohol (IA, 5–50% MeOH gradient, 1.0 mL/min, 220 nm) indicates 90% ee: $t_R$(major) = 6.35 minutes, $t_R$(minor) = 5.55 minutes.
(S)-2-(2,4-Dinitrobenzyl)-3-hydroxypropylisoindoline-1,3-dione (Table 2, entry 6). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (10.2 mg, 0.05 mmol), fac-Ir(ppy)₃ (0.8 mg, 0.00125 mmol), 2,6-lutidinium triflate (12.9 mg, 0.05 mmol), 1-(bromomethyl)-2,4-dinitrobenzene (0.065 g, 0.25 mmol), 3-(1,3-dioxoisouindolin-2-yl)propanal (0.102 g, 0.5 mmol), and 2,6-lutidine (0.54 g, 0.68 mL, 1.0 mmol) in DMSO (0.5 mL, 0.5 M). This procedure varies from the general procedure in that it is on half the scale. After 2 h, 5 mL of 4:1 CH₂Cl₂/MeOH was added and the reaction cooled to −78°C. 15 equiv of NaCNBH₃ was added to reduce the aldehyde to the alcohol. The reaction mixture was partitioned between saturated NH₄Cl and CH₂Cl₂ and extracted twice with CH₂Cl₂, dried with MgSO₄ and concentrated. The crude oil was purified by flash chromatography (Iatrobeads, 50% Et₂O/petroleum ether) to provide the pure title compound (69 mg, 72% yield, 90% ee) as a light yellow solid. IR (thin film) 3467, 1771, 1706, 1606, 1533, 1399, 1348 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 8.84 (s, 1H, ArH), 8.41 (d, J = 8.4 Hz, 1H, ArH), 7.91 – 7.86 (m, 2H, ArH), 7.82 – 7.74 (m, 3H, ArH), 3.84 (d, J = 6.7 Hz, 2H, CH₂OH), 3.58 – 3.50 (m, 1H NCH₂), 3.45 – 3.36 (m, 1H, NCH₂), 3.19 (dd, J = 6.2, 13.5 Hz, 1H, ArCH₂), 3.13 (dd, J = 8.4, 13.6 Hz, 1H, ArCH₂), 2.87 (m, 1H, CH₂CHOH), 2.30 (s, 1H, OH); ¹³C NMR (125 MHz, CDCl₃) δ: 169.0, 149.3, 146.6, 142.0, 134.4, 134.3, 131.6, 126.9, 123.6, 120.6, 60.6, 41.1, 38.3, 32.4; HRMS (ESI-TOF) calculated for C₁₈H₂₅N₃O₇ [M+H]⁺ m/z 386.0983, found 386.0983. [α]²⁰D = +16.8 (c = 1.02, CHCl₃). HPLC analysis (OD, 25%
EtOH/hexanes, 1.0 mL/min, 230 nm) indicates 90% ee: \( t_R(\text{major}) = 31.15 \) minutes, \( t_R(\text{minor}) = 26.72 \) minutes.

(R)-Methyl 2-(2-formyloctyl)-5-nitrobenzoate (Table 3, entry 1). General \( \alpha \)-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), \( \text{fac-Ir(ppy)}_3 \) (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), methyl 2-(bromomethyl)-5-nitrobenzoate (0.137 g, 0.50 mmol), octanal (0.128 g, 0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (15% EtOAc/hexanes) to provide the pure title compound (122 mg, 76% yield, 93% ee) as a light yellow oil. IR (thin film) 2928, 2857, 1726, 1524, 1360, 1256, 1129, 1072 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \): 9.64 (d, 1H, \( J = 2.1 \) Hz, CHO), 8.78 (d, 1H, \( J = 2.0 \) Hz, ArH), 8.25 (dd, 1H, \( J = 8.4 \), 2.2 Hz, ArH), 7.47 (d, 1H, \( J = 8.5 \) Hz, ArH), 3.95 (s, 3H, CO\(_2\)CH\(_3\)), 3.44 (dd, 1H, \( J = 13.1 \), 8.4 Hz, ArCH\(_2\)CH), 3.15 (dd, 1H, \( J = 13.2 \), 5.4 Hz, ArCH\(_2\)CH), 2.71 (m, 1H, ArCH\(_2\)CH), 1.73 (m, 1H, CHOCHCH\(_2\)CH\(_2\)), 1.56 (m, 1H, CHOCHCH\(_2\)CH\(_2\)), 1.43–1.17 (m, 8H, CH\(_2\)(CH\(_2\))\(_4\)CH\(_3\)), 0.85 (t, 3H, \( J = 7.0 \) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \): 203.9, 165.8, 149.4, 146.5, 133.5, 130.6, 126.5, 126.4, 53.5, 52.9, 33.6, 31.7, 29.6, 29.5, 26.9, 22.7, 14.2; HRMS (ESI-TOF) calculated for C\(_{17}\)H\(_{23}\)NNaO\(_5\) [M+Na]\(^+\) m/z 344.1468, found 344.1468. \( [\alpha]_D^{22} = +6.01 \) (c = 0.75, CHCl\(_3\)). SFC analysis of the corresponding alcohol (IA, 5–50% MeOH gradient, 1.0 mL/min, 220 nm) indicates 93% ee: \( t_R(\text{major}) = 4.11 \) minutes, \( t_R(\text{minor}) = 3.74 \) minutes.
(R)-2-(2-Formyloctyl)-5-nitrobenzonitrile (Table 3, entry 2). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 2-(bromomethyl)-5-nitrobenzonitrile (0.121 g, 0.50 mmol), octanal (0.128 g, 0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (15% EtOAc/hexanes) to provide the pure title compound (120 mg, 83% yield, 90% ee) as a light yellow oil. IR (thin film) 2932, 2855, 1722, 1529, 1353, 1168 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 9.67 (d, 1H, $J = 1.4$ Hz, CHO), 8.50 (d, 1H, $J = 2.4$ Hz, ArH), 8.36 (dd, 1H, $J = 8.6$, 2.4 Hz, ArH), 7.61 (d, 1H, $J = 8.6$ Hz, ArH), 3.32 (dd, 1H, $J = 14.1$, 8.9 Hz, ArCH$_2$CH), 3.03 (dd, 1H, $J = 14.1$, 5.2 Hz, ArCH$_2$CH), 2.90–2.80 (m, 1H, ArCH$_2$CH), 1.80 (m, 1H, CHOCHCH$_2$CH$_2$), 1.60 (m, 1H, CHOCHCH$_2$CH$_2$), 1.51–1.24 (m, 8H, CH$_2$(CH$_2$)$_2$CH$_3$), 0.89 (t, 3H, $J = 6.8$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 202.2, 150.8, 146.3, 132.0, 127.9, 127.3, 115.9, 114.1, 52.6, 33.0, 31.5, 29.3, 29.2, 26.7, 22.5, 14.0; HRMS (ESI-TOF) calculated for C$_{16}$H$_{20}$N$_2$NaO$_3$ [M+Na]$^+$ m/z 311.1366, found 311.1365. [$\alpha$]$_D^{22}$ = +12.44 (c = 0.75, CHCl$_3$). SFC analysis of the corresponding alcohol (IC, 5–25% MeOH gradient, 1.0 mL/min, 220 nm) indicates 90% ee: $t_R$(major) = 5.95 minutes, $t_R$(minor) = 7.04 minutes.
(R)-2-(3-Fluoro-4-nitrobenzyl)octanal (Table 3, entry 3). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (30.6 mg, 0.15 mmol, 0.30 equiv), fac-Ir(ppy)_3 (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 4-(bromomethyl)-2-fluoro-1-nitrobenzene (0.117 g, 0.50 mmol), octanal (0.128 g, 0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). This procedure differs from the general procedure in that 30 mol% of the organocatalyst is used. The crude oil was purified by flash chromatography (10% EtOAc/hexanes) to provide the pure title compound (103 mg, 74% yield, 90% ee) as a light yellow oil. IR (thin film) 2929, 2857, 1724, 1601, 1524, 1342, 841 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 9.67 (d, 1H, J = 1.8 Hz, CHO), 8.01 (t, 1H, J = 8.0 Hz, ArH), 7.12 (m, 2H, (ArH)₂), 3.09 (dd, 1H, J = 14.1, 7.8 Hz, ArCH₂CH), 2.76 (dd, 1H, J = 14.1, 6.2 Hz, Ar CH₂CH), 2.67 (m, 1H, ArCH₂CH), 1.70 (m, 1H, CHOCHCH₂CH₃), 1.52 (m, 1H, CHOCHCH₂CH₂), 1.42–1.19 (m, 8H, CH₂ (CH₂)₄ CH₃), 0.88 (t, 3H, J = 6.9 Hz, CH₂CH₃); ¹³C NMR (125 MHz, CDCl₃) δ: 202.9, 156.6, 154.4, 149.1 (d, J = 8.1 Hz), 126.3 (d, J = 2.5 Hz), 125.1 (d, J = 3.8 Hz), 118.7 (d, J = 20.7 Hz), 52.8, 34.1, 31.5, 29.2, 28.7, 26.7, 22.5, 14.0; HRMS (ESI-TOF) calculated for C₁₅H₂₁FNO₃ [M+H]^+ m/z 282.1500, found 282.1499. [α]D² = +39.62 (c = 1.0, CHCl₃). HPLC analysis of the corresponding alcohol (OD, 0.5% EtOH/hexanes, 1.0 mL/min, 254 nm) indicates 90% ee: tᵣ(major) = 86.76 minutes, tᵣ(minor) = 80.93 minutes.
(R)-2-((5-Nitropyridin-2-yl)methyl)octanal (Table 3, entry 4). General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.3 mg, 0.10 mmol, 0.32 equiv), tris-(2,2'-bipyridyl)ruthenium (II) chloride hexahydrate (1.9 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol), 2-(bromomethyl)-5-nitropyridine (109 mg, 0.50 mmol), octanal (0.128 g, 0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol) in DMSO (1.0 mL, 0.5 M). The vial was placed in a 17 °C cryocooler in between two 26 W lamps and irradiated for 8 h. The crude oil was purified by flash chromatography (Davisil, 80% EtOAc/petroleum ether) to provide the pure title compound (98 mg, 74% yield, 90% ee). IR (thin film) 2927, 2857, 1724, 1599, 1578, 1520, 1469, 1343, 861, 724 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.75 (d, 1H, $J$ = 1.2 Hz, CHO), 9.31 (d, 1H, $J$ = 2.6 Hz, ArH), 8.37 (dd, 1H, $J$ = 2.6, 8.4 Hz, ArH), 7.39 (d, 1H, $J$ = 8.4 Hz, ArH), 3.30 (dd, 1H, $J$ = 7.8, 14.3 Hz, CH$_2$Ar), 3.09-3.02 (m, 1H, CH$_2$Ar), 3.00 (dd, 1H, $J$ = 5.2, 14.3 Hz, CHCHO), 1.78-1.72 (m, 1H, CH$_2$(CH$_2$)$_3$CH$_3$), 1.55-1.47 (m, 1H, CH$_2$(CH$_2$)$_3$CH$_3$), 1.42-1.27 (m, 8H, CH$_2$(CH$_2$)$_4$CH$_3$), 0.87 (t, 3H, $J$ = 6.8 Hz, CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 203.6, 166.3, 144.7, 142.6, 131.3, 123.8, 50.9, 36.8, 31.5, 29.3, 28.8, 26.8, 22.5, 14.0; HRMS (ESI-TOF) calculated for C$_{14}$H$_{21}$N$_2$O$_3$ [M+H]$^+$ m/z 265.1552, found 265.1550. [$\alpha$]$_D^{23}$ = +41.2 (c = 0.76, CHCl$_3$); HPLC analysis (AS, 3.5% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 90% ee: $t_R$ (minor) = 18.4 minutes, $t_R$ (major) = 23.3 minutes.

$^{(63)}$ The apparatus used to irradiate the vial at a sub-ambient temperature was identical to that described in Nagib, D. A.; Scott, M. E.; MacMillan, D. W. C. J. Am. Chem. Soc. 2009, 131, 10875. The reaction can be conducted without cooling but the yield decreases by ca. 10%.
(R)-2-((2-Methylpyridin-4-yl)methyl)octanal (Table 3, entry 5). General α-benzylolation method B was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (16.3 mg, 0.08 mmol), fac-Ir(ppy)$_3$ (1.3 mg, 0.002 mmol), 4-(bromomethyl)-2-methylpyridinium bromide (0.107 g, 0.40 mmol), octanal (0.103 g, 0.8 mmol), and 2,6-lutidine (0.129 g, 0.140 mL, 1.2 mmol) in DMSO (0.8 mL, 0.5 M). The crude oil was purified by flash chromatography (Davisil, 15% EtOAc/hexanes) to provide the pure title compound (87 mg, 75% yield, 91% ee) as a light yellow oil. IR (thin film) 2955, 2930, 2857, 1726, 1606, 1561, 1457 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$: 9.67 (d, J = 1.7, 1H, CHO), 8.39 (d, J = 5.1, 1H, ArH), 6.97 (s, 1H, ArH), 6.91 (d, J = 5.1, 1H, ArH), 2.96 (dd, J = 9.7, 16.2, 1H, ArCH$_2$), 2.70 – 2.58 (m, J = 6.2, 2H, ArCH$_2$, CHOCH), 2.53 (s, 3H, ArCH$_3$), 1.76 – 1.60 (m, 1H, CHOCHCH$_2$), 1.54 – 1.42 (m, 1H, CHOCHCH$_2$), 1.42 – 1.16 (m, 8H, CH$_2$(CH$_2$)$_4$CH$_3$), 0.88 (t, J = 6.8, 3H, (CH$_2$)$_4$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 203.7, 158.4, 149.1, 148.6, 124.0, 123.9, 121.4, 121.6, 52.5, 33.9, 31.5, 29.2, 28.6, 26.8, 24.3, 22.5, 14.0; HRMS (ESI-TOF) calculated for C$_{15}$H$_{24}$NO [M+H]$^+$ m/z 234.1852, found 234.1852. $[^{[\alpha]}]D^{23}_2 = +16.0$ (c = 1.02, CHCl$_3$). HPLC analysis of the corresponding alcohol (OD, 6% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 91% ee: t$_R$(major) = 11.76 minutes, t$_R$(minor) = 10.30 minutes.

(R)-2-(Quinolin-4-ylmethyl)octanal (Table 3, entry 6). General α-benzylolation method B was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), fac-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 4-(bromomethyl)quinolinium bromide
(0.152 g, 0.50 mmol), octanal (0.128 g, 1.0 mmol), and 2,6-lutidine (0.161 g, 0.174 mL, 1.5 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (Davisil, 15% EtOAc/hexanes) to provide the pure title compound (121 mg, 90% yield, 82% ee) as a light yellow oil. IR (thin film) 2927, 2857, 1724, 1592, 1569, 1509, 1464 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\): 9.72 (d, \(J = 2.2\), 1H, CHO), 8.82 (d, \(J = 8.5\), 1H, ArH), 8.00 (d, \(J = 8.4\), 1H , ArH), 7.73 (dd, \(J = 4.1, 11.2\), 1H, ArH), 7.60 (t, \(J = 7.6\), 1H, ArH), 7.25 (d, \(J = 4.4\), 1H, ArH), 3.10 (dd, \(J = 6.8, 14.4\), 1H, ArCH\(_2\)), 2.90 – 2.77 (m, 1H, ArCH\(_2\)CH), 1.81 – 1.68 (m, 1H, CHOCHCH\(_2\)), 1.66 – 1.55 (m, 1H, CHOCHCH\(_2\)), 1.48 – 1.12 (m, 8H, CH\(_2\)(CH\(_2\))\(_4\)CH\(_3\)), 0.87 (t, \(J = 6.9\), 3H, CH\(_3\)); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\): 203.5, 150.0, 148.4, 145.1, 130.5, 129.3, 127.3, 126.7, 123.1, 121.9, 51.8, 31.5, 30.9, 29.25, 26.8, 22.5, 14.0; HRMS (ESI-TOF) calculated for C\(_{18}\)H\(_{24}\)NO \([M+H]^+\) m/z 270.1852, found 270.1854. \([\alpha]_{D}^{23}\) = +34.8 (c = 1.2, CHCl\(_3\)). HPLC analysis of the corresponding alcohol (OD, 5% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 82% ee: \(t_R\)(major) = 18.79 minutes, \(t_R\)(minor) = 21.82 minutes.

(R)-Methyl 5-(2-formyloctyl)pyrazine-2-carboxylate (Table 3, entry 7). Alternative conditions were employed: an oven-dried 40 mL vial equipped with a Teflon septum and magnetic stir bar was charged with 2,6-lutidinium triflate (7.8 mg, 0.030 mmol), methyl 5-(bromomethyl)pyrazine-2-carboxylate \(^{64}\) (34.7 mg, 0.150 mmol), bis[2-(2,4-

difluorophenyl)-5-trifluoromethylpyridine)\] (4,4’-di-tert-butyl-2,2’-dipyridyl) iridium(III) hexafluorophosphate (Ir(dF(CF₃)ppy)₂(dtbbpy)PF₆) (1.7 mg, 0.0016 µmol, 0.01 equiv.) and (2R, 5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (6.1 mg, 0.030 mmol). The vial was purged with a stream of argon and dry acetonitrile (0.050 mL) followed by octanal (0.047 mL, 0.30 mmol), and dry 2,6-lutidine (0.032 mL, 0.90 mmol, 1.8 equiv.) were added. The mixture was degassed through freeze-pump-thaw at −78°C \(\times 3\) and then the vial was sealed with parafilm. The vial was then placed as close as possible to three 13 W lamps and irradiated for 6 h. Volatiles were removed \textit{in vacuo}. Analysis of the residue by \textsuperscript{1}H NMR spectroscopy using 1,3-benzodioxole as an internal standard indicated a 72% NMR yield of the title compound. The crude oil was purified by flash chromatography (60% EtOAc/petroleum ether) to yield an analytical sample of the title compound. IR (thin film) 2926, 2856 1747, 1723, 1436, 1281, 1157, 1031, 732 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\): 9.75 (d, 1H, \(J = 1.2\) Hz, CHO), 9.17 (d, 1H, \(J = 1.4\) Hz, ArH), 8.60 (d, 1H, \(J = 1.4\) Hz, ArH), 4.01 (s, 3H, OCH\textsubscript{3}), 3.29 (dd, 1H, \(J = 8.0, 14.7\) Hz, CH\textsubscript{2}Ar), 3.08-3.01 (m, 1H, CHO), 2.97 (dd, 1H, \(J = 5.4, 14.7\) Hz, CH\textsubscript{2}Ar), 1.77-1.70 (m, 1H, CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{3}), 1.56-1.48 (m, 1H, CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{3}), 1.41-1.25 (m, 8H, CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{4}CH\textsubscript{3}), 0.86 (t, \(J = 6.0\) Hz, 3H, CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 203.1, 164.5, 158.9, 145.3, 144.5, 140.7, 53.0, 50.5, 33.9, 31.5, 29.2, 28.7, 26.7, 22.5, 14.0; HRMS (ESI-TOF) calculated for C\textsubscript{15}H\textsubscript{23}N\textsubscript{2}O\textsubscript{3} \([M+H]^+\) m/z 279.1703, found 279.1706; \([\alpha]_D^{23}\) = +26.0 (c = 0.51, CHCl\textsubscript{3}); HPLC analysis (AS, 3.5% \textsuperscript{1}PrOH/hexanes, 1.0 mL/min, 254 nm) indicates 87% ee: \(t_R\) (major) = 28.4 minutes, \(t_R\) (minor) = 32.2 minutes.
(R)-2-((2-Chloropyrimidin-4-yl)methyl)octanal (Table 3, entry 8). General α-benzyla-

lotion method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-
one (20.3 mg, 0.10 mmol), fac-Ir(ppy)₃ (1.6 mg, 0.0025 mmol), 2,6-lutidinium triflate
(25.7 mg, 0.10 mmol), 4-(bromomethyl)-2-chloropyrimidine (104 mg, 0.50 mmol),
octanal (0.128 g, 0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 1.0 mmol)
in DMSO (1.0 mL, 0.5 M). After 7 h, the reaction was subject to basic work up
conditions and the crude oil was purified by flash chromatography (Davisil, 30%
EtOAc/petroleum ether) to provide the pure title compound (99 mg, 78% yield, 87% ee)
as a light yellow oil. IR (thin film) 2927, 2858, 1724, 1566, 1539, 1433, 1339, 1184, 722
cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ: 9.72 (s, 1H, CHO), 8.47 (d, 1H, J = 5.2 Hz, ArH),
7.16 (d, 1H, J = 5.2 Hz, ArH), 3.17-3.05 (m, 2H, CH₂Ar, CHCHO), 2.80 (dd, 1H, J = 4.4,
14.0 Hz, CH₂Ar), 1.76-1.70 (m, 1H, CH₂(CH₂)₂CH₃), 1.58-1.49 (m, 1H, CH₂(CH₂)₂CH₃),
1.42-1.26 (m, 8H, CH₂(CH₂)₂CH₃), 0.86 (t, J = 6.8 Hz, 3H, CH₃); ¹³C NMR (125 MHz,
CDCl₃) δ: 203.1, 171.9, 161.2, 159.1, 119.7, 50.2, 35.8, 31.5, 29.2, 28.8, 26.6, 22.5, 14.0;
HRMS (ESI-TOF) calculated for C₁₃H₂₀Cl₂N₂O [M+H]⁺ m/z 255.1264 (³⁵Cl), 257.1235
(³⁷Cl), found 255.1282 (³⁵Cl), 257.1239 (³⁷Cl); [α]D²⁰ = +5.27 (c = 0.86, CHCl₃); HPLC
analysis (AS, 3.5% ¹PrOH/hexanes, 1.0 mL/min, 254 nm) indicates 87% ee: tᵣ (minor) =
13.0 minutes, tᵣ (major) = 15.4 minutes.

(R)-2-((4,6-Dimethyl-1,3,5-triazin-2-yl)methyl)octanal (Table 3, entry 9). General α-
benzyla-

one (20.3 mg, 0.10 mmol), bis[2-(2,4-difluorophenyl)-5-trifluoromethylpyridine)] (4,4’-
di-tert-butyl-2,2’-dipyridyl) iridium(III) hexafluorophosphate (Ir(dF(CF-
3)ppy)2(dtbbpy)PF6) (2.8 mg, 0.0025 mmol), 2,6-lutidinium triflate (25.7 mg, 0.10 mmol),
2-(bromomethyl)-4,6-dimethyl-1,3,5-triazine65 (101 mg, 0.50 mmol), octanal (0.128 g,
0.156 mL, 1.0 mmol), and 2,6-lutidine (0.107 g, 0.116 mL, 0.90 mmol) in DMSO (1.0
mL, 0.5 M). After 3 h, the reaction was subject to basic work up conditions and the
crude oil was purified by flash chromatography (Davisil, 80% EtOAc/petroleum ether) to
provide the pure title compound (85 mg, 68% yield, 87% ee) as a light yellow oil. The
enantiomeric excess was determined on the alcohol, which was prepared by treating a
solution of the aldehyde (30.4 mg, 0.121 mmol) in 10% MeOH/THF (2 mL) with NaBH4
(13.0 mg, 0.342 mmol) at 0 °C. After complete consumption of the aldehyde (10 min., as
judged by TLC) the reaction was quenched with sat. NH4Cl solution (5 mL) and product
was extracted into Et2O (3 x 5 mL). The organic layer was dried (Na2SO4) and
concentrated in vacuo. The residue was purified by flash chromatography using 3%
MeOH/CH2Cl2 to afford the alcohol as a colourless oil (17.9 mg, 58% yield). IR (thin
film) 2927, 2857, 1536, 1433, 1396 cm−1; 1H NMR (400 MHz, CDCl3) δ 9.78 (s, 1H, ,
CHO), 3.21 (dd, 1H, J = 8.4, 15.7 Hz, CH2Ar), 3.08-3.01 (m, 1H, CHCHO), 2.93 (dd, 1H,
J = 5.0, 15.7 Hz, CH2Ar), 2.56 (s, 6H, 2 x ArCH3), 1.79-1.69 (m, 1H, CH2(CH3)2CH3),
1.53-1.46 (m, 1H, CH2(CH3)2CH3), 1.39-1.25 (m, 8H, CH2(CH3)2CH3), 0.86 (t, 3H, J =
6.6 Hz, CH3); 13C NMR (125 MHz, CDCl3) δ 203.7, 176.7, 176.0, 49.1, 37.6, 31.5, 29.2,
28.8, 26.7, 25.5, 22.5, 14.0; HRMS (ESI-TOF) calculated for C14H24N3O [M+H]+ m/z
250.1919, found 250.1920. [α]33D = +25.8 (c = 1.18, CHCl3); HPLC analysis of the

corresponding alcohol (AS, 2% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 91% ee:
\( t_R \) (minor) = 13.7 minutes, \( t_R \) (major) = 15.5 minutes.

(R)-2-((1-Methyl-1H-benzo[d]imidazol-2-yl)methyl)octan-1-ol (Table 3, entry 10).

General \( \alpha \)-benzylation method B was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (20.4 mg, 0.10 mmol), \textit{fac}-Ir(ppy)$_3$ (1.6 mg, 0.0025 mmol), 2-(bromomethyl)-1-methyl-1H-benzo[d]imidazolium bromide (0.153 g, 0.50 mmol), octanal (0.128 g, 1.0 mmol), and 2,6-lutidine (0.161 g, 0.174 mL, 1.5 mmol) in DMSO (1.0 mL, 0.5 M). The crude oil was purified by flash chromatography (Davisil, 20% EtOAc/hexanes) and reduced to the alcohol using NaBH$_4$ (4 equiv) in CH$_2$Cl$_2$/MeOH (4:1) to provide the pure title compound (112 mg, 81% yield, 88% ee) as a light yellow solid. IR (thin film) 3215, 3054, 2925, 2855, 1615, 1508, 1466, 1443, 1400 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$: 7.69 (dd, $J = 2.3, 6.3$ Hz, 1H, ArH), 7.32 (dd, $J = 2.4, 6.4$ Hz, 1H, ArH), 7.29 – 7.22 (m, 2H, ArH), 3.76 (s, 3H, NC$_3$H$_3$), 3.60 (dd, $J = 6.5, 11.5$ Hz, 1H, CH$_2$OH), 3.02 (dd, $J = 3.4, 11.5$ Hz, 1H, ArCH$_2$), 2.95 (dd, $J = 8.6, 15.5$ Hz, 1H, ArCH$_2$), 2.26 – 2.09 (m, 1H,CHCH$_2$OH), 1.52 – 1.44 (m, 1H,CHCH$_2$CH$_2$), 1.39 (m, 3H, CHCH$_2$CH$_2$), 1.29 (m, 6H, (CH$_2$)$_3$CH$_3$), 0.88 (t, $J = 6.8$ Hz, 3H, (CH$_2$)$_4$CH$_3$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$: 154.5, 141.7, 135.5, 123.2, 122.1, 119.0, 109.1, 77.3, 77.0, 76.8, 65.7, 39.5, 32.1, 31.8, 30.7, 29.9, 29.5, 27.2, 22.6, 14.1; HRMS (ESI-TOF) calculated for C$_{17}$H$_{27}$N$_2$O [M+H]$^+$ m/z 275.2118, found 275.2119. $[\alpha]_{D}^{23} = -15.9$ (c = 1.18, CHCl$_3$). HPLC analysis (OD, 8% iPrOH/hexanes, 1.0 mL/min, 254 nm) indicates 88% ee: $t_R$(major) = 14.42 minutes, $t_R$(minor) = 12.12 minutes.
III. Absolute stereochemical proof:

(R)-2-(4-Nitrobenzyl)propanoic acid. General α-benzylation method A was followed using (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one (81.6 mg, 0.40 mmol), fac-Ir(ppy)$_3$ (6.4 mg, 0.010 mmol), 2,6-lutidinium triflate (102.8 mg, 0.40 mmol), 1-(bromomethyl)-4-nitrobenzene (0.121 g, 2.0 mmol), propanal (0.232 g, 0.290 mL, 4.0 mmol), and 2,6-lutidine (0.428 g, 0.464 mL, 4.0 mmol) in DMSO (4.0 mL, 0.5 M). This procedure varies from the general procedure in that it is on four times the scale. The crude aldehyde isolated from the general benzylation workup was then subjected to a Pinnick Oxidation using the following procedure.

The crude aldehyde was dissolved in a 1:1:1 mixture of THF/t-BuOH/2-methyl-2-butene (9 mL), NaH$_2$PO$_4$ (0.56 g, 4.0 mmol) was added, and the mixture was stirred at room temperature. NaClO$_2$ (80% technical grade, 0.30 g, 2.6 mmol) dissolved in water (1 mL) was then added to the reaction mixture, which was left to stir at room temperature for 3 hours. Upon completion, aqueous HCl (1.0 M, 20 mL) was added and the solution was extracted with EtOAc (3x 20 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The crude acid was purified by flash chromatography (25% EtOAc in hexanes) to provide the pure title compound (105 mg, 26% yield over 2 steps,
88% ee) as a white solid. Spectroscopic data matched that reported in the literature.\textsuperscript{66} SFC analysis (IA, 5–10% MeOH gradient, 1.0 mL/min, 220 nm) indicates 88% ee: \( t_R \) (major) = 6.89 minutes, \( t_R \) (minor) = 6.33 minutes. \([\alpha]_{D}^{24} = -32.53 \) (c = 1.14, CHCl\(_3\)). The experimental optical rotation indicates that the compound is indeed \((R)\)-2-(4-nitrobenzyl)propanoic acid when compared to the known data in the literature \([\alpha]_{D}^{25} = -36.9 \) (c = 1.14, CHCl\(_3\)) for the same compound of 97% ee).\textsuperscript{7} All other compounds in this publication were assigned the appropriate stereochemistry by analogy.

IV. Synthesis of \((2R,5S)\)-5-benzyl-2,3-dimethylimidazolidin-4-one organocatalyst.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{C} & \quad \text{O} \\
\text{Cbz-Cl} & \quad \text{NaHCO}_3 & \quad \text{H}_2\text{O}, 1 \text{ h, R.T.} \\
\text{Cbz} & \quad \text{H} & \quad \text{N} \\
\text{CH}_2\text{CHO} & \quad \text{TFA, MgSO}_4 & \quad \text{CH}_2\text{Cl}_2, 3 \text{ d, 40 °C} \\
\text{Me} & \quad \text{N} & \quad \text{Me} \\
\text{H}_2, \text{Pd/C} & \quad \text{EtOAc} & \quad 3 \text{ h, R.T.} \\
\text{Bn} & \quad \text{O} & \quad \text{Me} \\
\end{align*}
\]

To a flask containing L-phenylalanine-N-methylamide\textsuperscript{67} (13.9 g, 78 mmol, 1.0 equiv) was added NaHCO\(_3\) (26 g, 312 mmol, 4.0 equiv), CbzCl (16 g, 13.5 mL, 93.5 mmol, 1.2 equiv), and H\(_2\)O (200 mL). The product immediately began to precipitate and the mixture was allowed to stand with stirring for one hour. The crude solid was then collected on a fritted glass funnel by suction filtration. The solid was rinsed with aqueous HCl (1.0 M, 1 L) to remove excess NaHCO\(_3\) and dried under reduced pressure (~0.1 torr) overnight. To a 1 L flask containing this solid was added MgSO\(_4\) (50 g, 2 wt equiv), acetaldehyde (10.3 g, 13.1 mL, 234 mmol, 3 equiv), TFA (44.5 g, 30 mL, 390 mmol, 5 equiv), and CH\(_2\)Cl\(_2\) (300 mL, 0.25 M). The flask was then equipped with a reflux condenser and heated to 40 °C for three days. The solution was concentrated \textit{in vacuo}


giving a mixture of the cis and trans imidazolidinone products as a dark brown oil. The
pure trans product was isolated by flash chromatography (25% EtOAc in hexanes) as a
light yellow oil (2.77 g, 11% yield). To the Cbz protected catalyst (2.77 g, 8.2 mmol)
dissolved in EtOAc (50 mL, 0.16 M) was added 10% dry Pd/C (0.25 g, 9 wt%) and the
reaction mixture was stirred under an atmosphere of H₂ for 3 hours. The solution was
then passed through a pad of celite eluting with EtOAc (250 mL). The organic solvent
was removed in vacuo yielding the pure title compound (1.6 g, 96% yield, >99% ee) as a
light yellow oil that solidified spontaneously upon standing. IR (thin film) 3308, 2922,
1682, 1399, 1083, 751, 700 cm⁻¹; ¹H NMR (500 HHz, CDCl₃) †: 7.25–7.11 (m, 5H, ArH), 4.00 (q, 1H, J = 5.7 Hz, NMeCHNH), 3.77 (dd, 1H, J = 7.1, 4.2 Hz, COCHNH), 2.98 (dd, 1H, J = 13.8, 4.1 Hz, ArCH₂), 2.84 (dd, 1H, J = 13.8, 7.3 Hz, ArCH₂), 2.65 (s, 3H, NCH₃), 1.90 (bs, 1H, NH), 1.17 (d, 3H, J = 5.8 Hz, CHCH₃); ¹³C NMR (125 MHz, CDCl₃) †: 174.1, 137.5, 129.5, 128.3, 126.6, 70.8, 59.9, 37.7, 26.5, 20.2; HRMS (ESI-TOF) calculated for C₁₂H₁₇N₂O [M+H]⁺ m/z 205.1335, found 205.1336. [α]ₑ²³ = –99.21 (c = 1.0, CHCl₃). SFC analysis (IA, 5% MeOH, 1.0 mL/min, 220 nm) indicates >99% ee:
tᵣ(major) = 4.86 minutes, tᵣ(minor) = 5.70 minutes.

V. Synthesis of Starting Material Bromides.

2-(Bromomethyl)-5-nitropyridine. To a solution of 2-methyl-5-nitropyridine⁶⁸ (1.01 g,
7.29 mmol) in acetic acid (6 mL) was added bromine (185 µL, 3.61 mmol) and the
mixture was refluxed for 30 min. After the solution had cooled to ambient temperature, it

was diluted with H₂O (60 mL) and product was extracted into Et₂O (3 × 60 mL). The combined organic phase was washed with sat. NaHCO₃ solution (3 × 90 mL), dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/petroleum ether) to provide the title compound as an orange solid (325 mg, 21% yield) followed by unreacted 2-methyl-5-nitropyridine (0.521 g). IR (thin film) 1599, 1577, 1519, 1471, 1343, 1294, 1017, 865, 852, 809, 721, 609 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.38 (d, 1H, J = 2.5 Hz, ArH), 8.49 (dd, 1H, J = 2.5, 8.7 Hz, ArH), 7.67 (d, 1H, J = 8.7 Hz, ArH), 4.62 (s, 2H, CH₂); ¹³C NMR (125 MHz, CDCl₃) δ 162.9, 145.0, 143.3, 132.2, 123.7, 31.8; HRMS (ESI-TOF) calculated for C₆H₆BrN₂O₂ [M+H]⁺ m/z 216.9613 (⁷⁹Br), 218.9592 (⁸¹Br), found 216.9607 (⁷⁹Br), 218.9586 (⁸¹Br).

4-(Bromomethyl)-4-chloropyrimidine. N-Bromosuccinimide (7.14 g, 40.1 mmol) and benzoyl peroxide (1.76 g, 7.27 mmol) were added to a solution of 2-chloro-4-methylpyrimidine⁶⁹ (4.44 g, 34.5 mmol) in carbon tetrachloride (110 mL) and the mixture was refluxed for 24 h. The mixture was filtered and the solids washed with carbon tetrachloride. The filtrate was concentrated in vacuo and the residue was purified by flash chromatography (10% Et₂O/petroleum ether) to provide the title compound as a colourless oil (0.945 g, 13% yield). IR (thin film) 1565, 1541, 1427, 1337, 1204, 1182, 913, 718, 680 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ: 8.65 (d, 1H, J = 5.0 Hz, ArH), 7.45 (d, 1H, J = 5.0 Hz, ArH), 4.42 (s, 2H, CH₂Br); ¹³C NMR (125 MHz, CDCl₃) δ: 168.2, 161.2,

160.4, 118.8, 30.4; HRMS (ESI-TOF) calculated for C₅H₅BrClN₂[M+H]+ m/z 206.9325 (³⁵Cl, ⁷⁹Br), 208.9295 (³⁵Cl, ⁸¹Br), 208.9304 (³⁷Cl, ⁷⁹Br), 210.9265 (³⁷Cl, ⁸¹Br), found 206.9319, 208.9298, 210.9269.

VI. Emission Quenching Experiments.

Emission intensities were recorded using a Perkin Elmer LS50 Luminescence spectrometer. All fac-Ir(ppy)₃ solutions were excited at 385 nm and the emission intensity at 520 nm was observed. In a typical experiment, a 0.0656 M solution of fac-Ir(ppy)₃ in DMSO was added to the appropriate amount of quencher in a screw-top 1.0 cm quartz cuvette. After degassing with a stream of argon for 15 minutes, the emission spectrum of the sample was collected. Enamine refers to condensation product between n-octanal and (2R, 5S)-5-benzyl-2,3-dimethylimidazolidin-4-one.

Figure S1: fac-Ir(ppy)₃ Emission Quenching by Imidazolidinone.
Figure S2: *fac-Ir(ppy)_3* Emission Quenching by *n*-Octanal.

![Graph showing emission quenching by *n*-Octanal.]

Figure S3: *fac-Ir(ppy)_3* Emission Quenching by 2,6-Lutidine.

![Graph showing emission quenching by 2,6-Lutidine.]

Figure S4: *fac-Ir(ppy)_3* Emission Quenching by *n*-Bu_4NBr.

![Graph showing emission quenching by *n*-Bu_4NBr.]

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Figure S5: *fac*-Ir(ppy)$_3$, Emission Quenching by Enamine.

Figure S6: *fac*-Ir(ppy)$_3$, Emission Quenching by Carbocyclic Benzyl Bromides.
Figure S7: fac-Ir(ppy)$_3$ Emission Quenching by Basic Heterocyclic Benzyl Bromides.

Figure S8: fac-Ir(ppy)$_3$ Emission Quenching by Non-basic Heterocyclic Benzyl Bromides.
Chapter 3

The Enantioselective $\alpha$-Methylation of Aldehydes

I. Introduction

In biological systems, methylation is the most common form of alkylation. Specialized enzymes called methyltransferases are used to deliver an electrophilic methyl equivalent. The alkylation reaction plays a role in gene regulation, protein regulation, RNA metabolism and modification of heavy metals in enzyme active sites. Unsurprisingly, the methyl group is ubiquitous, and methyl stereogenic centers are a prevalent motif found in biological compounds, as demonstrated by their appearance in molecules ranging from amino acid building blocks, to lipid-derived toxins and steroidal hormones (Figure 1).

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Figure 1. Representative Biological Compounds Bearing Methyl Stereocenters

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Of interest to society, the stereogenic methyl motif is widespread in bioactive natural products, their analogues and other small molecules that have become best-selling drugs (Figure 2). The ever-present demand for enantiopure compounds has made the construction of methyl stereogenicity an important challenge to organic chemists.

**Figure 2. Important Pharmaceutical Compounds Bearing Methyl Stereocenters**

The ubiquitous nature of the carbonyl functionality renders it a useful handle for the synthesis of methyl stereogenicity. Direct catalytic technologies utilizing a nucleophilic methyl source, typically as an organometallic reagent, in the presence of a chiral ligand, are well preceded for the formation of asymmetric methyl bonds. General methods have been developed for both carbonyl ipso methyl addition, traditionally employing an organozinc reagent, as well as conjugate additions into α,β-unsaturated carbonyls, commonly through the use of an organocuprate reagent, to form products in very good yields and enantioselectivities.73-74

Complementary technologies for catalytic carbonyl α-methylation employing an electrophilic alkylation reagent have been much less successful. While many powerful indirect methods have been developed using enolate equivalents and common electrophilic reagents, asymmetric catalytic protocols have proved challenging (see

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chapter 1). In contrast, enzyme catalysis is designed to perform direct asymmetric carbonyl α-methylations.

Nature has evolved families of methyltransferases. Among these, S-adenosylmethionine-dependent enzymes are generally responsible for endogenous methylations, including carbonyl α-methylations. S-adenosylmethionine (SAM) is the electrophilic methylating reagent. Carbonyl deprotonation in the enzyme active site generates a nucleophilic enol, which is positioned strategically to attack the electrophilic SAM reagent. Floss and co-workers have demonstrated using a chiral methyl-labeled SAM that alkylation proceeds via an $S_N2$ mechanism with inversion of stereochemistry, as demonstrated in the biosynthesis of indolmycin (Scheme 1).

\begin{center}
\textbf{Scheme 1.} \textit{S-Adenosylmethionine: Nature’s Electrophilic Methylating Reagent}
\end{center}

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.png}
\end{center}

Phase transfer catalysis remains the sole example of direct carbonyl α-methylation, yet the restrictions to the carbonyl substrate limit its utility. No known direct ketone or aldehyde α-methylations, either racemic or asymmetric, have been published. In addition to the problems that hinder all electrophilic alkylation protocols due to closed-shell processes (see chapter 1), development of a methylation protocol in

\footnotesize

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particular is challenging because alternative activation of the methyl unit as a radical or carbocation is energetically unfavorable and not synthetically viable.\textsuperscript{78}

The successful development of a general enantioselective carbonyl $\alpha$-methylation protocol would be an important advancement for the construction of stereogenic methyl centers. The following chapter details progress towards a direct asymmetric aldehyde $\alpha$-methylation via synergistic enamine and copper catalysis.

\textbf{II. Modern $\alpha$-Methylation Methods}

Typically, chiral auxiliaries are employed in modern syntheses for the introduction of carbonyl $\alpha$-methyl stereocenters. A sole example from the Cozzi group demonstrates an enamine-mediated addition to 1,3-benzodithiolylium, which is proposed to act as a masked methyl group that can be revealed under reductive conditions (Scheme 2).\textsuperscript{79} However, a direct derivatization is not reported.

\begin{scheme}
\textbf{Scheme 2. Cozzi's Indirect Aldehyde $\alpha$-Methylation}
\end{scheme}

\textbf{III. Design Plan}

\textit{Synergistic Catalysis: Merger of Enamine and Copper Catalysis}

Recently, the MacMillan group has begun exploring synergistic catalysis as a means to achieve challenging transformations via the simultaneous activation of the

\textsuperscript{78} The methyl radical is unstable and nucleophilic, see: De Vleeschouwer, F.; Van Speybroeck, V.; Waroquier, M.; Geerlings, P.; De Proft, F. \textit{Org. Lett.} \textbf{2007}, \textit{9}, 2721.

nucleophile and electrophile. The intersection of chiral amine-catalyzed nucleophile activation (enamine catalysis) and transition metal-catalyzed electrophile activation has led to the development of previously difficult or unattainable transformations for asymmetric carbonyl α-(sp²)-carbon functionalization.

Work conducted by Anna Allen, a graduate student in the group, demonstrated a novel carbonyl α-arylation for the formation of α-methine aryl stereocenters using a dual chiral imidazolidinone/Cu(I) catalyst system (Scheme 3). A diaryliodonium salt serves as the aryl reagent. Generally very good yields and excellent enantioselectivities are observed for the transformation.

**Scheme 3. Synergistic Enamine/Cu(I) Catalysis: Direct Aldehyde α-Arylation**

Mechanistic elucidation undertaken by Dr. Jeff Van Humbeck, a former graduate student in the group, demonstrated that the reaction most likely proceeds via an arylcopper(III) intermediate (Figure 3). Cu(I) oxidative insertion into the Ar–I'Ar bond of the diaryliodonium generates a highly electrophilic arylcopper(III) intermediate (15). In the case of an unsymmetrical diaryliodonium bond insertion occurs as the less hindered Ar–I'Ar bond. Condensation of the aldehyde and imidazolidinone catalyst

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82 An analogous aldehyde α-vinylation has been developed, see: Skucas, E.; MacMillan, D. W. C.; J. Am. Chem. Soc. Manuscript accepted for publication.
forms the stereodefined enamine 16. Coordination of the arylcopper(III) on the less hindered Re-face of the electron-rich enamine (17) followed by bond isomerization yields iminium 18. Stereoretentive reductive elimination and subsequent iminium hydrolysis forms the desired enantioenriched α-arylated aldehyde product.

The propensity of a highly electrophilic organocopper(III) to coordinate to the 4π-system of the catalytic enamine and isomerize to the η1-organocopper(III) iminium (18) is the mechanistic linchpin of the copper/enamine synergistic catalysis strategy. Dr. Jay Stevens, a postdoctoral fellow in the group, recognized that the electrophilic (sp²)-carbon-copper(III) species is a proposed intermediate in the Chan–Evans–Lam reaction (Scheme 4). The Chan–Evans–Lam reaction describes the copper(II)-catalyzed cross-coupling of boronic acids with heteroatom nucleophiles. Initial heteroatom coordination to copper(II) and transmetallation with boronic acid forms an organocopper(II) intermediate (19),
which is very slow to undergo the desired reductive elimination. However, air oxidation to organocopper(III) 20 is followed by rapid reductive elimination to form the desired cross-coupled product.

Scheme 4. Chan–Evans–Lam Cross-Coupling Reaction

Dr. Stevens demonstrated that the putative copper(III) intermediate formed under Cham–Evans–Lam conditions successfully reacts with catalytic enamine to form enantioenriched α-vinyl aldehydes (Scheme 5). The desired electrophilic vinylcopper(III) species could be generated from transmetallation of vinylboronic acid with Cu(II) followed by oxidation from ambient O₂ in the air. The presence of methylboronic acid and molecular sieves suggests that the transmetallating species is a

Scheme 5. Synergistic Enamine/Cu(II) Catalysis: Direct Aldehyde α-Vinylation

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mixed boroxine.\textsuperscript{87}

We proposed that \textit{in situ} generation of a highly electrophilic methylcopper(III) intermediate could coordinate enamine in a similar fashion to form asymmetric $\alpha$-methylated aldehydes (Scheme 6). The chiral enamine can be derived from condensation of a chiral imidazolidinone catalyst with starting material aldehyde. The methylcopper(III) species would result from transmetallation with a stable organometallic species followed by oxidation. Reductive elimination from the alkylcopper(III) iminium intermediate produces the desired $\alpha$-methyl aldehyde.

\textbf{Scheme 6. Proposed Strategy for Aldehyde $\alpha$-Methylation}

Organocopper(III) compounds have long been proposed as catalytic intermediates. However, the characterization and mechanistic evaluation of organocopper compounds is a difficult challenge for organic chemists due to the predisposition of organocopper to form diverse structural aggregates.\textsuperscript{88} The first experimental identification of an alkylcopper(III) intermediate occurred in 2007 using rapid-inject NMR spectroscopy at –100 °C.\textsuperscript{89} Since then advances in spectroscopic methods and molecular modeling have begun to allow the characterization and study of alkylcopper(III) species.\textsuperscript{90} Although they are still not well understood, the square-planar alkylcopper(III) species undergo

\textsuperscript{87} It has been speculated that the Chan–Evans–Lam reaction proceeds through boroxines formed \textit{in situ} via molecular sieve-mediated dehydration, see: Kerins, F.; O’Shea, D. F. \textit{J. Org. Chem.} \textbf{2002}, 67, 4968.


\textsuperscript{90} Hickman, A. J.; Sanford, M. S. \textit{Nature} \textbf{2012}, 484, 177.
rapid reductive elimination at room temperature.\textsuperscript{91} Furthermore, mechanistic studies of simple alkylcopper(III) compounds have demonstrated that systems can be biased towards reductive elimination.\textsuperscript{92}

Investigation from the Lam group in the area of alkyl Chan–Evans–Lam reactions suggests that the formation of an electrophilic alkylcopper(III), while challenging, is possible (Scheme 7).\textsuperscript{85} The Cu(II)-catalyzed cross-coupling between alkylboronic acids and nucleophilic aniline forms the desired $N$-alkyl aniline in low yields.\textsuperscript{93} Transmetallation from a methylboron reagent to Cu(II), followed by single electron oxidation, should generate the proposed alkylcopper(III) intermediate required for an enamine/copper-catalyzed aldehyde $\alpha$-methylation protocol.\textsuperscript{94}

**Scheme 7. Alkyl Chan–Evans–Lam Cross-Coupling**

\[
\text{PhNH}_2 + \text{B(OH)}_2 + \text{Cu(OAc)}_2, \text{Et}_3\text{N, DCE, 70 °C, 2 d} \rightarrow \text{PhNHCHBu} \quad 16\%
\]

Key to the success of this challenging transformation is the generation of an alkylcopper(III) intermediate with a predilection for stereobiased coordination to a chiral enamine, consequent $\eta^1$ migration and reductive elimination. The validation of the synergistic enamine/Cu(II) catalysis strategy would lead to the first direct aldehyde $\alpha$-methylation, providing a solution towards an important and yet unsolved problem in


\textsuperscript{93} Since the initiation of this project, an alkyl Chan–Evans–Lam cross-coupling has been reported using trialkylboranes, see: Naya, L; Larrosa, M.; Rodriguez, R.; Cruces, J. \textit{Tetrahedron Lett.} \textbf{2011}, \textit{53}, 769.

\textsuperscript{94} A strategy involving Cu(I) oxidative insertion into alkyliodonium to form the electrophilic alkylcopper(III) species has not been attempted due to the instability of alkyliodonium reagents, see: Zhdankin, V. V. \textit{Top. Curr. Chem.} \textbf{2003}, \textit{224}, 99.
organic synthesis. The following section details progress towards the development of a direct asymmetric α-methylation.

**IV. The Enantioselective α-Methylation of Aldehydes**

We began our investigation employing copper(II) triflate as the transition metal catalyst, hydrocinnamaldehyde as the starting material aldehyde and the soluble tetramethylammonium salt of methyltriphenylborate as the methylating reagent.\(^5\)

**Table 1. Aldehyde α-Methylation: Organocatalyst Evaluation**

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Methyl reagent</th>
<th>20 mol% organocat.</th>
<th>2 equiv Cu(OTf)₂</th>
<th>Na₂CO₃, DMF, 23 ºC</th>
<th>α-methyl aldehyde</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me₄NMePh₃</td>
<td>H₂C=CHPh</td>
<td>1%</td>
<td>2%, 17% ee</td>
<td>3%, 7% ee</td>
<td>5%, 0% ee</td>
</tr>
<tr>
<td>Me₄NMePh₃</td>
<td>H₂C=CHPh</td>
<td>8%, 18% ee</td>
<td>4%, 0% ee</td>
<td>5%, 16% ee</td>
<td>5%, 4% ee</td>
</tr>
<tr>
<td>Me₄NMePh₃</td>
<td>H₂C=CHPh</td>
<td>5%, 0% ee</td>
<td>5%, 0% ee</td>
<td>5%, 0% ee</td>
<td>5%, 0% ee</td>
</tr>
<tr>
<td>Me₄NMePh₃</td>
<td>H₂C=CHPh</td>
<td>8%, 21% ee</td>
<td>4%, 46% ee</td>
<td>8%, 49% ee</td>
<td>no reaction</td>
</tr>
</tbody>
</table>

Borates were selected as the alkylating reagent because they are known undergo Cu(II)-catalyzed transmetallation and reductive elimination.\textsuperscript{96} An evaluation of chiral amine catalyst scaffolds identified that only the newly developed \textit{trans-(2R,5S)-5-alkyl-2,3-dimethylimidazolidin-4-one} catalysts (see chapter 2) gave appreciable levels of enantioinduction (Table 1). The \textit{trans-2-methyl-5-benzyl imidazolidinone} was chosen for further studies because of its availability in comparison to the 1-napthyl analogue.\textsuperscript{97} The Brønsted acid co-catalyst trichloroacetic acid (TCA) improved the yield and enantioselectivity of the \(\alpha\)-methyl aldehyde product (Scheme 8, 8% yield, 62% ee).\textsuperscript{98}

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{Scheme_8.png}
\caption{Scheme 8. Aldehyde \(\alpha\)-Methylation Products}
\end{scheme}

We discovered that biphenyl is the major byproduct of the reaction. The presence of biphenyl suggests that the Cu(II)-catalyzed transmetallation from aryl-boron bonds is preferable to alkyl-boron bonds, resulting in undesirable borate decomposition. Evaluation of the boron reagent revealed that tetrasubstituted borates are not efficient for the desired methylation reaction (Table 2). Changes to the ammonium counterion decreased the reaction efficiency (entries 2–4). Modification of the arene of the borate reagent to favor the desired transmetallation of the boron-methyl bond was likewise

\textsuperscript{97} The synthesis of the \(\textit{2R,5S}-2,3\)-dimethyl-5-(naphthalen-1-ylmethyl)imidazolidin-4-one results in 5% of the desired catalyst over five synthetic steps.
\textsuperscript{98} Unfortunately, the co-catalyst survey was performed under various conditions and is not presented here. The reaction is promoted by TCA and HCl (lower enantioselectivities are observed). See Supporting Information.
unsuccessful (entries 4–5). Transmetallation of the boron-aryl bond is preferred in all cases, which led us to consider an alternative methyl reagent.

Table 2. Effect of Borate Reagent Modification

<table>
<thead>
<tr>
<th>entry</th>
<th>methylating reagent</th>
<th>yield (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NMe(_3)BMePh(_3)</td>
<td>8</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>NBnNMe(_3)BMePh(_3)</td>
<td>2</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>N(p-NO(_2)Bn)Me(_3)BMePh(_3)</td>
<td>2</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>NBu(_3)BMePh(_3)</td>
<td>2</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>NMe(_2)BMe(C(_6)F(_5))(_3)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>6</td>
<td>NMe(_2)BMe(1-Naphthyl)(_3)</td>
<td>0</td>
<td>na</td>
</tr>
</tbody>
</table>

\(^a\) Yields determined by GC analysis with internal standard. \(^b\) Enantioselective excess determined by HPLC analysis of the corresponding alcohol.

Boron reagents that have been successfully employed in Chan–Evans–Lam couplings were evaluated (Table 3). Gratifyingly, employing trimethylboroxine as the methyl source resulted in improved conversion to the \(\alpha\)-methyl aldehyde (entry 4). Neat trimethylboroxine hydrolyzes rapidly when exposed to the ambient moisture and is difficult to handle on the benchtop. Using the more stable trimethylboroxine as a THF

Table 3. Chan–Evans–Lam Type Boron Reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>methylating reagent</th>
<th>yield (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeB(OH)(_2)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>2</td>
<td>MeBF(_3)K</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>3</td>
<td>Me–B(pin)</td>
<td>0</td>
<td>na</td>
</tr>
<tr>
<td>4</td>
<td>(MeBO(_3))</td>
<td>36</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>(MeBO(_3)) (50 wt% in THF)</td>
<td>35</td>
<td>29</td>
</tr>
</tbody>
</table>

\(^a\) Yields determined by GC analysis with internal standard. \(^b\) Enantioselective excess determined by HPLC analysis of the corresponding alcohol.
solution gave comparable results while improving the reproducibility of the transformation (entry 5).

The Suzuki–Miyaura and Chan–Evans–Lam cross-coupling reactions are proposed to proceed through *in situ* formation of the boroxine from dehydration of the corresponding boronic acid. The addition of small amounts of 5 Å molecular sieves slightly enhanced the product enantioselectivity. While molecular sieves prevent *in situ* hydrolysis of the reactive boroxine, in larger quantities they have a deleterious effect on the rate of iminium hydrolysis.

It has been suggested in a Chan–Evans–Lam reaction using vinylboroxines that pyridine coordination to form a tetrahedral borate activates the boroxine towards transmetallation. Disappointingly, lower reaction efficiency is observed upon the addition of amine or phosphorus additives. Rather than coordinate boroxine, the Lewis basic additives complex the more Lewis acidic copper, as noted by a color change of the reaction mixture. The resulting copper complexes are unreactive. The preformed boroxine-pyridine complex is also unreactive. Under the reaction conditions, the complex dissociates and the formation of the bright blue copper-pyridine complex is observed.

The ligand environment of the copper catalyst is highly influential to the reaction efficiency (Table 4). An oxyanionic copper ligand promotes the transformation, likely by facilitating the formation of the alkycopper intermediate. The transmetallation step is enthalpically favored by the large energy difference between the boron-carbon (B–C

---

bond energy: 77 kcal/mol) versus the boron-oxygen bond strengths (B–O bond energy (boric acid): approximately 120 kcal/mol).  

Table 4. Effect of Copper Ligand on Catalytic Efficiency

<table>
<thead>
<tr>
<th>entry</th>
<th>Copper catalyst</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
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<tr>
<td>1</td>
<td>Cu(OTf)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTFA)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>CuO</td>
<td>0</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>CuBr&lt;sub&gt;2&lt;/sub&gt;</td>
<td>&lt; 1</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>Cu(BF&lt;sub&gt;4&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>5</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>Cu(OAc)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OMe)&lt;sub&gt;2&lt;/sub&gt;</td>
<td>9</td>
<td>17</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields determined by GC analysis with internal standard. <sup>b</sup> Enantioselective excess determined by HPLC analysis of the corresponding alcohol.

Copper(II) transmetallation generates an alkylcopper(II) intermediate with concomitant formation of a Lewis acidic boron triflate. The borate has been implicated in the catalysis of undesired side reactions. An investigative time study revealed that consumption of the starting material aldehyde exceeded product formation (Figure 4). Aldol dimerization appears to be the major aldehyde decomposition pathway. While

![Figure 4. α-Methyl Aldehyde Reaction: Time Study](image)
isolation and quantification of the aldol products have not been possible, the existence of homo-aldol and cross-aldol products has been verified indirectly.\textsuperscript{101} We believe that the borate promotes aldolization via the intermediacy of an activated boron enolate (Figure 5).

\textit{Figure 5. Boron Enolate is Complicit in Deleterious Side Reactions}

![Diagram showing the reaction of aldol products and the proposed boron enolate intermediate](image)

The Lewis acidic boron triflate byproduct is complicit in two pathways that lead to the loss of product enantiopurity. (1) Post-reaction product racemization can result from Lewis acid-mediated tautomerization of the enantioenriched aldehyde $\alpha$-methyl product. (2) The boron enolate nucleophile can participate in the $\alpha$-methylation reaction (Figure 5). The formation of racemic $\alpha$-methylated aldehyde in the absence of an organocatalyst suggests that the boron enolate is nucleophilic enough to coordinate to the electrophilic alkylcopper(III) intermediate and undergo the subsequent bond-formation.\textsuperscript{102}

The reactivity of acidic borate byproducts is a complication that must be overcome to successfully develop a synthetically useful asymmetric aldehyde $\alpha$-methylation. We proposed that the undesired aldol reactions as well as racemic product formation could be suppressed by sequestering the Lewis acidic boron triflate. The \textit{in situ} formation of a coordinated complex is not possible because Lewis bases also

\textsuperscript{101} The aldol products are observed in the crude $^1$H NMR reaction mixture and crude reaction mixtures of aldol reactions correlate with compounds in the GC assay.

\textsuperscript{102} Copper(II) does not catalyze the aldehyde $\alpha$-methylation or aldol formation; under conditions where the $\alpha$-methylation is sluggish (and concentrations of borate byproducts are correspondingly low), only trace aldol reaction is observed even in the presence of organocatalyst and copper.
complex and deactivate the copper catalyst. Instead, continuous consumption of the boron triflate in a subsequent transformation would render it unavailable to form reactive boron enolates.

**Scheme 9. Partitioning the Lewis Acidic Boron Triflate Towards an Inert Boroxine**

Boroxines in solution exist in dynamic equilibrium with the corresponding boronic acid. The Lewis acidity of boron is dependent on its substituents. Boron compounds that possess electron-rich substituents, such as borate esters, are not Lewis acidic. Unlike Lewis bases, non-Lewis acidic boron additives should not disrupt the desired transformation. In the presence of boron triflate, the electron-rich boron additives should react to yield mixed boroxines and borate oligomers that are not Lewis acidic (Scheme 9). Gratifying, the addition of boric acid dramatically improved

**Figure 6. α-Methyl Aldehyde Reaction with B(OH)₃: Time Study**

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105 The amount of cinnamaldehyde starting material at 2h is within experimental error. Individual reactions were sacrificed at each time point.
enantioselectivity. The decrease in reaction efficiency results from deactivation of the boron-catalyzed racemic α-methylation pathway. A time study showed conclusively that the undesired side reactions associated with boron enolate formation are stifled. Both the rates of starting material decomposition and the erosion of product enantiopurity are decelerated by the addition of boric acid (Figure 6). The inclusion of borate esters to tune the electronics of the boroxine byproducts was successful. Specifically, addition of triethyl borate improved the reaction efficiency with a slight depression in product enantioselectivity (entry 7, 51% yield, 68% ee). The reaction efficiency could be improved further by adjusting the stoichiometry of boric acid and borate ester (entry 8, 58%, 41% ee). The loss in product enantiomeric excess suggests that the equilibrium of boron triflate lies towards a Lewis acid compound.

Currently, boron enolate-induced reactions cannot be completely inhibited without shutting down the asymmetric aldehyde α-methylation pathway. The development of a useful alkylation protocol hinges on an improved system that does not

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Table 5. The Effect of Boron Additives

<table>
<thead>
<tr>
<th>entry</th>
<th>B(OH)₃ (equiv)</th>
<th>B(OR)₃ (equiv)</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>none</td>
<td>45</td>
<td>23</td>
</tr>
<tr>
<td>2</td>
<td>1 equiv</td>
<td>none</td>
<td>33</td>
<td>61</td>
</tr>
<tr>
<td>3</td>
<td>2 equiv</td>
<td>none</td>
<td>27</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>2 equiv</td>
<td>2 equiv B(OPh)₃</td>
<td>28</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv</td>
<td>2 equiv B(OPr)₃</td>
<td>16</td>
<td>55</td>
</tr>
<tr>
<td>6</td>
<td>2 equiv</td>
<td>2 equiv B(OEt)₃</td>
<td>49</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>2 equiv</td>
<td>3 equiv B(OEt)₃</td>
<td>51</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>1 equiv</td>
<td>3 equiv B(OEt)₃</td>
<td>58</td>
<td>41</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields determined by GC analysis with internal standard. <sup>b</sup> Enantioselective excess determined by HPLC analysis of the corresponding alcohol.
suffer from the formation of a destructive byproduct. Experiments to elucidate the mechanism of the reaction have been initiated to provide insight towards a strategy to overcome byproduct formation.

V. Mechanistic Insights

The key asymmetric (sp³)-carbon-(sp³)-carbon bond formation is proposed to proceed through the formation of an enamine-coordinated alkylcopper(III) intermediate 20 (Figure 7). The putative alkylcopper(III) species 21 is formed from copper(II) transmetallation of trimethylboroxine followed by single electron oxidation. Concurrent condensation of the chiral secondary amine catalyst with aldehyde yields the nucleophilic enamine (22). Electrophilic alkylcopper(III) coordination to the 4π-system of the enamine is followed by isomerization to the η¹-copper(III) iminium intermediate 23. Reductive elimination and iminium hydrolysis releases the asymmetric α-methyl

Figure 7. Proposed Enamine/Copper Catalytic Cycle

![Diagram of proposed enamine/copper catalytic cycle]
aldehyde to reform the organocatalyst and returns copper(I) \( \text{Cu(I)} \). A second single electron oxidation finally regenerates the copper(II) triflate catalyst.

Superstoichiometric addition of Cu(OTf)\(_2\) (2 equiv) is required for optimal reaction efficiency. We believe that, analogous to the Chan–Evans–Lam conditions, Cu(OTf)\(_2\) also serves as the oxidant in this reaction.\(^{85}\) However, a radical mechanism may also be operative, wherein Cu(OTf)\(_2\) acts as a single electron oxidant to form an electrophilic enamine radical cation (Scheme 10).\(^{106}\) The SOMO-species can be trapped by alkylcopper(II) to generate the \( \eta^1 \)-copper(III) iminium intermediate 23.

\[ \text{Scheme 10. Proposed SOMO Mechanism for Aldehyde } \alpha \text{-Methylation} \]

An aldehyde radical clock experiment demonstrated that the enamine radical is formed in the course of the reaction (Scheme 11). \( \beta \)-disubstituted aldehydes form enamine more slowly, and it is possible that radical clock opening occurs via single electron oxidation of the boron enolate intermediate. Regardless, the formation of the SOMO radical is reversible, and may not participate in the aldehyde \( \alpha \)-methylation. The same cyclopropyl isomerization is observed under the enamine/copper catalyzed aldehyde \( \alpha \)-arylation conditions.\(^{107}\) Evidence exists that the copper in the aldehyde \( \alpha \)-arylation transformation proceeds through a Cu(I)/Cu(III) catalytic cycle, which suggests

\(^{106}\) Cu(OTf)\(_2\) is known to oxidize imidazolidinone-derived enamine to the enamine radical cation at room temperature, Dr. Mark Pickworth, unpublished results.

\(^{107}\) Dr. Michael Clift, unpublished results.
that, in the arylation reaction, formation of the SOMO species is reversible and nonproductive.\textsuperscript{83} Neither mechanism can be dismissed at the present time.

**Scheme 11. Evidence for a SOMO Mechanism**

The identification of the boron reagent that undergoes transmetallation has likewise been elusive. \textsuperscript{11}B NMR experiments suggest that trimethylboroxine is not the active methylating reagent. Under the reaction conditions, the consumption of trimethylboroxine exceeds that of \(\alpha\)-methyl aldehyde formation. Furthermore, when the boron additives (boric acid and/or borate ester) are present, the boroxine signal (23.9 ppm) disappears in less than 5 minutes. Transmetallation does not occur from a mixed boroxine intermediate. Preformed mixed boroxines (generated from condensation of methyl boronic acid and the boron additives) do not participate in the desired transformation. Methyl boronic acid is also not a viable methylating reagent, even upon addition of the boron additives. We hypothesize that transmetallation occurs from either a coordinated boroxine (catalyst-coordinated boron –ate complexes have been observed under the reaction conditions) or a boron dimer or oligomer, which would be obfuscated in the \textsuperscript{11}B NMR.

Progress towards the mechanistic elucidation of the asymmetric aldehyde \(\alpha\)-methylation is ongoing. Evidence for the identity of the reactive intermediates should facilitate reaction development. Specifically, an improved understanding of the copper
catalytic cycle and the transmetallation from boron will guide the development of the novel enantioselective \((\text{sp}^3)\)-carbon-\((\text{sp}^3)\)-carbon bond formation.

**VI. Conclusion**

The application of a synergistic enamine/copper catalysis strategy towards a novel enantioselective aldehyde \(\alpha\)-methylation represents the first direct aldehyde \(\alpha\)-methylation. The transformation is still under development; however, synthetically useful yields and good enantioselectivities can be achieved using a commercially available methylating reagent. The coupling of a chiral enamine nucleophile with a highly electrophilic alkylcopper(III) intermediate is proposed. The confirmation of an alkylcopper(III)-mediated mechanism would provide a rare example of an alkylcopper electrophile, and moreover suggests that extension of the powerful enamine/copper catalysis strategy may provide a general solution for the direct asymmetric \(\alpha\)-alkylation of aldehydes.
VII. Supporting Information

I. General Information.

Commercial reagents were purified prior to use following the guidelines of Perrin and Armarego.\(^{108}\) All solvents were purified according to the method of Grubbs or distilled from CaH\(_2\) prior to use.\(^{109}\) Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using force-flow chromatography according to the method of Still\(^{110}\) on ICN 60 32-64 mesh silica gel 63 or on preparatory Silicycle 1000 µm silica gel F-254 plates. Thin-layer chromatography (TLC) was performed on Silicycle 250 µm silica gel F-254 plates. Visualization of the developed plates was performed by fluorescence quenching or by KMnO\(_4\), or ceric ammonium molybdate stain.

\(^1\)H, and \(^13\)C NMR spectra were recorded on a Varian Inova 400 (400 MHz or 100 MHz) or a Bruker Avance 500 (500 MHz or 125 MHz) and are internally referenced to residual protio solvent signals (note: CDCl\(_3\) referenced at \(\delta 7.27\) ppm for \(^1\)H and \(\delta 77.0\) ppm for \(^13\)C). \(^{11}\)B NMR spectra were recorded on a Bruker Avance 300 (96 MHz) or a Varian Inova 500 (160 MHz) and are internally referenced to residual protio solvent signals for DMF by the TopSpin 2.1 software. High Performance Liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series chromatographs using a chiral column (25 cm) and guard column (5 cm) as noted for each compound. Gas liquid chromatography (GLC) was performed on Hewlett-Packard 6850 Series gas


chromatographs equipped with a split-mode capillary injection system and flame ionization detectors using an achiral HP-1 column (30 m x 0.25 mm).

A. Procedure for Enantioselective α-Methylation using Tetrasubstituted Borates.

To an oven-dried 8 mL vial equipped with a magnetic stir bar and rubber septum was added organocatalyst (0.06 mmol, 0.20 equiv), sodium carbonate (0.60 mmol, 2.0 equiv), copper(II) triflate (0.60 mmol, 2.0 equiv), and the tetraalkylammonium methyltriarylborate (0.30 mmol, 1.0 equiv). The vial was degassed by flushing with N₂ under positive pressure (15 min). DMF (4 mL, 0.075 M), and 3-phenylpropanal (0.6 mmol, 2.0 equiv) were then added to the vial via syringe addition. The reaction vial was sealed with parafilm for 24h. Upon completion, the reaction mixture was poured into 8 mL of saturated aqueous NaHCO₃ and extracted with Et₂O (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ or MgSO₄ and the solvent was removed in vacuo. The resulting crude oil was either immediately purified by flash chromatography or benzyl propionate (0.30 mmol, 1.0 equiv) was added as an internal standard and an aliquot submitted for GC analysis under the following conditions: 80 °C isotherm (4 minutes) then ramp 5 °C/min (6 minutes). 3-Phenylpropanal: $t_r = 4.0$ min (burn coefficient: 1.5), 2-methyl-3-phenylpropanal: $t_r = 5.2$ min (burn coefficient: 1.04), benzyl propionate: $t_r = 6.2$ min (burn coefficient: 1.0), biphenyl: $t_r = 9.8$ min (burn coefficient: 0.78). The corresponding alcohol was obtained for chiral HPLC analysis by the following procedure. An aliquot of the crude reaction (2.0 mL) was diluted with EtOH (0.5 mL) and cooled in a dry ice/acetone bath to –78 °C and NaBH₄ (5 equiv) was added.
to the stirring solution. The bath was allowed to room temperature (~1 hour) at which point the aldehyde was completely consumed. The reaction mixture was poured into H$_2$O and extracted with Et$_2$O (2 x 5 mL). The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. The resulting crude oil was purified on a preparatory silicon plate (20% EtOAc/hexanes) to provide the pure alcohol, which was submitted to HPLC analysis under the following conditions: ODH, 4% IPA/hexanes, 1.0 mL/min, 220 nm; $t_r = 14.8$ min, 17.8 min for the two enantiomers. Spectroscopic data for aldehyde and alcohol products are identical to literature values.$^{111}$

**B. Procedure for Enantioselective α-Methylation using Trimethylboroxine.**

![Chemical structure diagram]

To an oven-dried 8 mL vial equipped with a magnetic stir bar and rubber septum was added (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one as the trichloroacetic acid salt (0.06 mmol, 0.20 equiv), sodium carbonate (0.60 mmol, 2.0 equiv), copper(II) triflate (0.60 mmol, 2.0 equiv), and 10 mg of 5 Å molecular sieves if used. The vial was degassed by flushing with N$_2$ under positive pressure (15 min). DMF (4 mL, 0.075 M), 3-phenylpropanal (0.6 mmol, 2.0 equiv), and trimethylboroxine as a 50 wt% THF solution (0.3 mmol, 1.0 equiv) were then added to the vial via syringe addition. The reaction vial was sealed with parafilm for 24h. Upon completion, the reaction mixture was poured into 8 mL of saturated aqueous NaHCO$_3$ and extracted with Et$_2$O (2 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ or MgSO$_4$ and the solvent was

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removed in vacuo. The resulting crude oil was either immediately purified by flash chromatography or benzyl propionate (0.30 mmol, 1.0 equiv) was added as an internal standard and an aliquot submitted for GC analysis under the following conditions: 80 °C isotherm (4 minutes) then ramp 5 °C/min (6 minutes). 3-Phenylpropanal: $t_r = 3.9$ min (burn coefficient: 1.5), 3-Phenylpropanal: $t_r = 4.9$ min (burn coefficient: 1.5), 2-methyl-3-phenylpropanal: $t_r = 6.1$ min (burn coefficient: 1.04), benzyl propionate: $t_r = 6.9$ min (burn coefficient: 1.0). The presence of aldol products can be observed in nonquantitatively: $t_r = 13.5$ min. The corresponding alcohol was obtained for chiral HPLC analysis by the same procedure described above.

C. Procedure for Enantioselective α-Methylation using Trimethylboroxine with Boron Additives.

To an oven-dried 8 mL vial equipped with a magnetic stir bar and rubber septum was added (2R,5S)-5-benzyl-2,3-dimethylimidazolidin-4-one as the trichloroacetic acid salt (0.03 mmol, 0.20 equiv), sodium carbonate (0.30 mmol, 2.0 equiv), copper(II) triflate (0.30 mmol, 2.0 equiv), 5 mg of 5 Å molecular sieves and boric acid. The vial was degassed by flushing with N$_2$ under positive pressure (15 min). DMF (1.5 mL, 0.10 M), (the borate ester, if used), 3-phenylpropanal (0.3 mmol, 2.0 equiv), and trimethylboroxine as a 50 wt% THF solution (0.15 mmol, 1.0 equiv) were then added to the vial via syringe addition. The reaction vial was sealed with parafilm for 24h. Upon completion, the reaction mixture was poured into 8 mL of saturated aqueous NaHCO$_3$ and extracted with
Et₂O (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ or MgSO₄ and the solvent was removed in vacuo. The resulting crude oil was either immediately purified by flash chromatography or benzyl propionate (0.15 mmol, 1.0 equiv) was added as an internal standard and an aliquot submitted for GC analysis under the following conditions: 80 °C isotherm (4 minutes) then ramp 5 °C/min (6 minutes). 3-Phenylpropanal: \( t_r = 4.0 \text{ min} \) (burn coefficient: 1.5), 2-methyl-3-phenylpropanal: \( t_r = 5.2 \text{ min} \) (burn coefficient: 1.04), benzyl propionate: \( t_r = 6.2 \text{ min} \) (burn coefficient: 1.0). The presence of aldol products can be observed in nonquantitatively: \( t_r = 13.5 \text{ min} \). The corresponding alcohol was obtained for chiral HPLC analysis by the same procedure described above.

Table S1. Effect of Concentration Enantioselective \( \alpha \)-Methylation using Trimethylboroxine.

<table>
<thead>
<tr>
<th>entry</th>
<th>DMF [x M]</th>
<th>yield (%)(^a)</th>
<th>ee (%)(^b)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>1.0</td>
<td>6</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>0.50</td>
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</tr>
<tr>
<td>3</td>
<td>0.20</td>
<td>34</td>
<td>34</td>
</tr>
<tr>
<td>4</td>
<td>0.10</td>
<td>36</td>
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<td>5</td>
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<td>19</td>
</tr>
<tr>
<td>7</td>
<td>0.05</td>
<td>21</td>
<td>28</td>
</tr>
<tr>
<td>8</td>
<td>0.025</td>
<td>8</td>
<td>36</td>
</tr>
</tbody>
</table>

\(^a\) Yields determined by GC analysis with internal standard. \(^b\) Enantioselective excess determined by HPLC analysis of the corresponding alcohol. \(^c\) This result appears anomalous.
Table S2: Effect of Co-Catalyst on the Enantioselective α-Methylation using Trimethylboroxine.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>co-catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
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<td>TCA</td>
<td>52</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>TFA</td>
<td>12</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>TBA</td>
<td>4</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>HCl</td>
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</tr>
<tr>
<td>5</td>
<td>HBr</td>
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<td>38</td>
</tr>
<tr>
<td>6</td>
<td>TiOH</td>
<td>25</td>
<td>43</td>
</tr>
<tr>
<td>7</td>
<td>MeSO(_3)H</td>
<td>31</td>
<td>38</td>
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<tr>
<td>8</td>
<td>3,5-(NO(_3))(_2)-Benzoic acid</td>
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</tr>
<tr>
<td>9</td>
<td>AcOH</td>
<td>12</td>
<td>48</td>
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</table>

*Reaction performed in 0.10 M of DMF. *Yields determined by GC analysis with internal standard. *Enantioselective excess determined by HPLC analysis of the corresponding alcohol.

Table S3. Copper(I) Catalyzes the Enantioselective α-Methylation using Trimethylboroxine.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>Copper catalyst</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)(_2)</td>
<td>35</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OTf)·PhMe</td>
<td>29</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>CuPF(_6)·4MeCN</td>
<td>6</td>
<td>58</td>
</tr>
<tr>
<td>4</td>
<td>CuCl</td>
<td>8</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>CuBr</td>
<td>&lt;1</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>CuI</td>
<td>0</td>
<td>nd</td>
</tr>
</tbody>
</table>

* Yields determined by GC analysis with internal standard. *Enantioselective excess determined by HPLC analysis of the corresponding alcohol.
Table S4. Evaluation of Inorganic Bases

<table>
<thead>
<tr>
<th>entry</th>
<th>base</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaOAc</td>
<td>2</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>NaOPent</td>
<td>3</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>NaOC(O)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;</td>
<td>10</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>NaOTFA</td>
<td>0</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>NaF</td>
<td>&lt;1</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>LiCO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8</td>
<td>nd</td>
</tr>
<tr>
<td>7</td>
<td>K&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>28</td>
<td>33</td>
</tr>
<tr>
<td>8</td>
<td>Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>9</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
<td>40</td>
<td>27</td>
</tr>
</tbody>
</table>

<sup>a</sup> Yields determined by GC analysis with internal standard. <sup>b</sup> Enantioselective excess determined by HPLC analysis of the corresponding alcohol. <sup>c</sup>This result appears anomalous.