Enabling Organic Methodology through Photoredox Catalysis

Sean Michael Treacy

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Abstract

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Sean Michael Treacy

Organic methods development has long dictated the molecular scaffolds available to the pharmaceutical and fine chemical synthesis industries. Photoredox catalysis has emerged as a powerful platform to enable novel reactivity with visible light irradiation through triplet sensitization and single-electron transfer. New methods involving radical intermediates are now readily accessible from countless starting materials through the application of these catalysts. Much of my work has utilized established photoredox platforms to enable both nickel catalyzed remote cross-coupling of primary amines via 1,5 hydrogen-atom transfer (HAT) and formal [3+2] synthesis of γ-lactams through triplet sensitization. My further work focuses on the application of ligand-to-metal charge transfer catalysis with cupric chloride and ferric chloride salts towards the alkylation of alkanes through the catalytic generation of chlorine radical to enable HAT. These studies expand photoredox catalysis to inner sphere mechanisms with abundant base-metal salts to enable redox chemistry at reduced electrochemical potentials.
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I would like to thank especially my advisor, Tomislav Rovis, who provided the mentorship I needed to make the most of my graduate training. We spent hours discussing mechanisms for graduate courses or lab results that formed the fondest and most edifying times of my PhD. He motivated and challenged me to work on what I found interesting, making each day at work an opportunity that I treasured. Research has its highs and lows but the guidance of Tom and the camaraderie of my colleagues buffered the gloom that at times plagued life and lab. I would also like to thank the rest of my committee, Professor Norton, Prof. Owen, Prof. Nuckolls, and Prof. Knowles for offering their time and attention to my work over the years and at its completion.

To the Rovis group past and present, I owe so much from whom I have learned and from those I had the pleasure of teaching or mentoring, I learned almost as much. Both my formal mentor my first year, Scott Thullen, and dozens of informal mentors and colleagues, taught me everything from running columns to being more ambitious. To my undergraduate mentees: Sabina, Yi Cheng, and Daniel, I count myself lucky to be a part of your research training and
can’t wait to see what you all do with your scientific careers. For all the friends I have made in the group, I feel so fortunate to have spent time in such an amazing community.

To my friends outside of chemistry, I hope I have not bored you too much with the details when you’ve asked me about work. The trivia team, my fellow runners and climbers, and my friends from high school and college, have made my time in New York City truly special. It was a privilege to be able to spend time with the amazing people I count amongst my closest friends.
Dedication

To Mom, Dad, Siobhan, Margaret, and Patrick
Chapter 1: An Introduction to Photoredox Catalysis

1.1 Photochemistry

Humans have relied on the interactions between light and matter long before these concepts were circumscribed by science. Even in reading this page, light harvesting organic molecules in your eyes are discerning between the light and enabling a signal-transduction pathway to your brain.\(^1\) Whereas we can only view visible light, there exists a broad electromagnetic spectrum (Figure 1.1) from which to produce countless light matter relationships with organic compounds. As chemists, we search for new mechanisms through which we may forge chemical bonds. By utilizing light matter interactions, photochemistry offers a plethora of opportunities in synthetic methods.

Figure 1.1: The Electromagnetic Spectrum

<table>
<thead>
<tr>
<th>Light Matter Interactions</th>
<th>Radio</th>
<th>Microwave</th>
<th>Infrared</th>
<th>Visible Light</th>
<th>Ultraviolet</th>
<th>X-rays</th>
<th>Gamma</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wavelength (10(^\text{8}) m)</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>-1</td>
<td>-2</td>
<td>-3</td>
<td>-4</td>
</tr>
<tr>
<td>Energy (2.9 x 10(^\text{5}) kcal/mol)</td>
<td>-7</td>
<td>-6</td>
<td>-5</td>
<td>-4</td>
<td>-3</td>
<td>-2</td>
<td>-1</td>
</tr>
</tbody>
</table>
Light comes in a wide range of energies which can be used for photochemical transformations. The first step of these reactions involves the absorption of a photon of light which promotes the molecule to an excited state which can then access chemical pathways inaccessible in its ground state. While tuning the energy of irradiation enables well-studied isomerization, electrocyclization and cycloaddition reactions, not all molecules are capable of productive reactivity via irradiation. (Figure 1.2) This is due to two key limitations. First, the molecule must be able to absorb a photon and reach a higher energetic state; Second, this high energy state must access an exothermic pathway for reactivity. (Figure 1.3) Despite these requirements, photochemistry has produced a multitude of useful organic reactions.
**1.2 Light Enabled Catalysis**

The mechanisms of molecular excitations with light have been studied extensively. A compound of interest is able to reach an excited state through the absorption of a photon of sufficient energy to elevate an electron across the HOMO-LUMO gap to a vibrationally and electronically excited state $S_n$. These transitions are readily measured through UV-Visible spectroscopy. After vibrational relaxation, the result is an excited state singlet ($S_1$) which can either fluoresce back to the ground state, undergo intersystem crossing to an excited triplet state ($T_1$) or vibrationally relax to $S_0$ (Figure 1.4). Intersystem crossing is spin forbidden and therefore unfavored. Relaxation from $T_1$ to the ground state is also spin forbidden which enables long lifetimes of $T_1$ relative to $S_1$, up to the order of milliseconds if intramolecular reactivity is disfavored. This property has been widely leveraged for applications in photochemistry, as the rate of phosphorescence is significantly slower than the rate of molecular diffusion, allowing for the energy originating from light to be utilized for intermolecular reactivity.
Photosensitizers are molecules capable of transferring light energy to other molecules for which benzophenone is a representative example (Figure 1.5). Excitation of benzophenone with light forms a singlet excited state. This species then undergoes intersystem crossing (ISC) to generate a long-lived triplet excited state $T_1$, which can undergo Forster or Dexter energy transfer (EnT) to a molecule with sufficiently $T_1$ to accomplish triplet sensitization resulting in an excited state molecule and $S_0$ benzophenone. (Figure 1.5a) This process is efficiently repeated through continuous irradiation and supply of substrate in a process known as photocatalysis. Obviating the need of the substrate to absorb light, one can tune the triplet energies of the photocatalyst to enable reactivity with a wide range of molecules.
An additional mechanism available to benzophenone $T_1$ is electron transfer. The charge separation generated during photoexcitation leaves both a higher lying reducing electron and a low-lying hole which may act as a one electron oxidant. In the presence of sufficient reductants or oxidants single electron transfer (SET) can occur, generating a reduced or oxidized variant of benzophenone.
the starting catalyst which is also capable of SET. Coupling the excited state SET with an opposing ground state SET furnishes catalytic cycles that are driven by light and the chemical reactivity of redox-active substrates. (Figure 1.5b)

1.3 Photoredox Catalysis: Foundation and Renaissance in Synthesis

Photoredox catalysis has become an established platform for organic chemistry due to the demonstrable synthetic utility granted from these photophysical mechanisms.\textsuperscript{10} Inorganic, organometallic, and organic photoredox catalysts have been known for decades; however, it has been only in the last decade that there has been an explosion in their use in synthesis.\textsuperscript{11-12} (Figure 1.6)

**Figure 1.6 Representative Examples of Photoredox Catalysts**

Organometallic photoredox catalysts have received much attention for their historic prevalence in coordination chemistry as well as their inherent facility in tunability. Metal polypyridyl complexes such as Ir\{[(dF\textsubscript{3}ppy)\textsubscript{2}dtbbpy]\}+, represented in Figure 1.7, exemplify the richness of substitution patterns available to organometallic complexes to generate favorable photophysical properties. The mechanism of photoexcitation involves metal-to-ligand charge transfer (MLCT), which involves the reduction of the ligand through population of its \(\pi^*\) orbital as well as oxidation of the metal. Each of these sites is redox active, allowing both oxidation and
reduction to occur from $T_1$. Through manipulation of the structure of the ligands as well as the selection of the metal center, one can tune the HOMO and LUMO of the complex to change the catalyst’s redox properties to enable desired reactivity.

A representative catalytic cycle in photoredox catalysis is shown below. First, excitation with light, thermal relaxation, and intersystem crossing furnish a long-lived triplet excited state. (Figure 1.7a) Then, SET with a substrate of interest gives either the oxidized or reduced ground state catalyst. SET with an appropriate stoichiometric reductant, oxidant, or substrate in the opposite direction closes the catalytic cycle. (Figure 1.7b)

**Figure 1.7 Representative Catalytic Cycle**

![Representative Catalytic Cycle](image)

It is important to note that the redox window, the difference between the oxidizing capacity and reducing capacity of a given reaction, is inherently limited by the wavelength of excitation as well as the efficiency of ISC. Recent work has provided strategies to circumvent this, including two-photon absorption strategies and electro-photoredox chemistry.\textsuperscript{13-15} A number of factors differentiate photoredox catalysts; sufficient excited state and ground state redox potentials do not guarantee that a reaction of interest will be successful. Subtleties including the excited state lifetimes, photocatalyst stability, differential rates of electron
transfer and undesired competing reactions all serve to complicate the simple pictures drawn in catalytic cycles and show the value of having an organic chemist in employment.

Foundational studies in photoredox catalysis for synthetic methods showed a wide range of reactivity, most often relying on stoichiometric oxidants or reductants to enable catalyst turnover. These contributions, presented graphically in Figure 1.8, include olefin reduction from Pac utilizing Ru(bpy)$_3^{2+}$, hydrodehalogenation$^{17}$ and singlet $O_2^{18}$ sensitization from Fukuzumi with Ru(bpy)$_3^{2+}$ and acridinium photocatalysts respectively, as well as the dimerization of benzylic bromides with Cu(dap)$_2^+$ from Kern and Sauvage.$^{19}$ These initial reactions advanced the field mechanistically, but their techniques found limited adoption by the synthetic community. It was not until the 2010s with LED lamp commercialization that organic chemists began to utilize this foundational work towards more complex transformations. Now, photoredox catalysis is a widely field, providing innovations in natural product synthesis, materials science and biocatalysis.

**Figure 1.8 Early Work in Photoredox Catalysis**

During the recent popularization of photoredox catalysis in synthetic methods, Yoon,$^{20}$ MacMillan,$^{21}$ and Stephenson$^{22}$ each provided seminal work utilizing Ru(bpy)$_3^{2+}$ to furnish valuable organic radical intermediates and novel chemistry. Yoon showed that intramolecular
[2+2] cyclizations could be accomplished through reduction of bis-enones through electron transfer from the intermediate reductant, Ru(bpy)$_3^+$. The mild conditions provided by photoredox catalysis enable other catalytic paradigms to be well tolerated in a dual catalysis manifold. The MacMillan group found that their well-studied organocatalysis platform was amenable to combination with photoredox catalysis for the asymmetric alkylation of aldehydes with bromomalonates. Stephenson was able to show the effective hydrodehalogenation of activated carbon-halogen bonds through reduction by a reduced state photocatalyst.

Likewise, MacMillan showed that oxidation of tertiary anilines could promote α-amino radical formation which can attack electron deficient cyano-arenes to generate αarylated products in an overall redox neutral transformation enabled by catalytic SET from a photoredox catalyst.

Our group showed a major innovation in the asymmetric alkylation of aldehydes with bromomalonates. These innovations created a paradigm shift in the formation of organic radicals, which otherwise required the use of excess toxic or pyrophoric reagents to access these highly reactive species. Furthermore, it was the ability to take substrates that are largely inert in their ground state, and through oxidation or reduction, facilitate access to highly energized intermediates poised for further reactivity. Thus began a gold rush to find redox-active functional groups to render them more reactive under photoirradiation for useful chemistry. The orthogonality of this chemistry to other strategies has led to widespread adoption of these techniques in various chemical industries.
This paradigm has similarly exploded in popularity due to proficiency in which transition metal catalysis works in tandem with photoredox catalysis. Initial discoveries by Molander,\textsuperscript{25} as well as Doyle and MacMillan,\textsuperscript{26} showed the ability of organic radicals to couple with aryl halides through nickel-photoredox catalysis through single-electron transmetallation. Building on mechanistic work from Weix in nickel catalyzed reductive cross couplings,\textsuperscript{27} these innovations likewise provided organic acids, alkyl trifluoroborates, and aryl amines as viable radical precursors poised for coupling reactions with organometallic electrophiles generated \textit{in-situ}.

For each, the catalytic cycle begins with excitation of the photocatalyst with visible light to its excited state. Then, oxidation of the radical precursor leads to a reduced state photocatalyst and an organic radical. The reduced state photocatalyst may undergo SET to the nickel catalyst to turn over the catalytic cycle. Meanwhile, the nickel catalyst once reduced undergoes oxidative addition with the aryl halide to generate a Ni\textsuperscript{III} oxidative addition complex. Attack of the organic radical through single electron transmetallation furnishes a Ni\textsuperscript{III} intermediate.

Reductive elimination provides the desired cross coupled product and forms Ni\textsuperscript{I} which is then reduced by the photocatalyst to turn over the Ni catalytic cycle. Since these studies, many more...
examples of metallophotoredox catalysis have been disclosed with a variety of transition metals.\textsuperscript{28,29}

**Figure 1.11 Ni-Metallophotoredox**

\begin{align*}
\text{Molander} &\quad \text{cat. dtbbpyNiCl}_2 \quad \text{cat. Ir}[dF(CF_3)ppy]_2(dtbbpy)PF_6 \\
\text{Doyle and MacMillan} &\quad \text{cat. dtbbpyNiCl}_2 \quad \text{cat. Ir}[dF(CF_3)ppy]_2(dtbbpy)PF_6
\end{align*}

1.5 \textbf{Summary}

Applications of light in organic chemistry have been noted for over a century. Recent developments in photoredox catalysis have provided expansive opportunities for organic chemists to explore open-shell intermediates that are readily accessible under mild conditions. Through the combination of reactive intermediates, dual catalysis offers similarly bountiful opportunities to expand the synthetic toolkit available to organic chemists. The Rovis group is ultimately interested in applying the foundational advantages of photoredox catalysis towards the development of novel synthetic methods.
1.6 References


Chapter 2: Remote Alkylation of Amides through Ni-Photoredox Catalysis

2.1 The Hofmann-Löffler-Freytag (HLF) Reaction

In 1883, Hofmann found that N-Br alkyl amines cyclize to corresponding pyrrolidines at elevated temperatures in sulfuric acid.\(^1\) Subsequent research by Löffler and Freytag further elucidated the reaction that now bears their names.\(^2\) The HLF reaction provides the first example of intramolecular hydrogen atom transfer (HAT). HAT describes the scission of an X-H bond via a hydrogen atom, comprising of a proton and an electron. In the case of the HLF reaction, the intramolecular HAT was enabled through the homolysis of a N-Br bond, forming a highly reactive N-centered ammonium radical which abstracts remote C(sp\(^3\))-H bonds in a regioselective fashion for \(\delta\)-positions. This process proceeds through a six-membered transition state known as 1,5 HAT which maintains enthalpic and entropic preference to 1,4 and 1,6 HAT respectively. Although the 6-endo-tet transition state is formally unfavorable according to Baldwin rules, the six membered transition state accommodates the highly linear transition state between the three atoms directly involved in HAT that would be highly strained in a 1,4 HAT process.\(^3\) 1,6 HAT is correspondingly less common due to the higher contribution of entropic factors as seven membered ring conformations are less favored compared to their six membered analogues. After 1,5 HAT, a remote alkyl radical is generated which either propagates a radical chain with other N-Br bonds to form the corresponding alkyl bromide, or terminates the radical chain with previously extruded Br-radical. Subsequent cyclization upon basic workup furnishes pyrrolidine products.\(^4\) Although discovered in the nineteenth century,
further modifications to this reaction have progressed periodically to provide electrophilic N-centered radicals under more mild conditions without prefunctionalization.

**Scheme 2.1 The HLF Reaction and the Suarez Modification**

*Hofmann-Löffler-Freytag Reaction*

\[
\begin{align*}
\text{H}^+, \Delta &\quad \text{N}^+ \\
\text{H}^+, \Delta &\quad \text{N}^+ \quad \text{-X} \\
\text{H}^+, \Delta &\quad \text{N}^+ \quad \text{-X} \\
\end{align*}
\]

*Suarez Modification*

\[
\begin{align*}
\text{Ph(OAc)}_2, \text{hv}, \text{I}_2 &\quad \text{EWG} \\
\text{PIDA, hv, I}_2 &\quad \text{EWG} = \text{NO}_2, \text{CN, P(O)(OR)}_2, \text{CBz, Boc} \\
\end{align*}
\]

*Radical Polarity and HAT*

\[
\begin{align*}
e^- \text{ rich } \text{C(sp)}_3-H \text{ bond} &\quad 1,5-HAT \text{ Favored when } \\
\text{X-H BDE > C-H BDE} &\quad \text{X is electrophilic} \\
\end{align*}
\]

Suarez and co-workers demonstrated an improvement to the HLF reaction through the appendage of an electron withdrawing functionality at nitrogen which obviates the need for strong acid to generate the reactive ammonium intermediate.\(^5\)\(^6\) Whereas both the neutral and
cationic N-radicals are sufficiently reactive to enable exothermic HAT in the case of the classical HLF reaction, only the ammonium radical is sufficiently electrophilic to enable rapid 1,5 HAT at unactivated positions. Weak and electron rich C(sp\(^3\))-H bonds have shown propensity to undergo 1,5 HAT with neutral N-centered radicals albeit with limited synthetic efficiency.\(^7\) HAT occurs most efficiently when the abstracting radical is of opposite polarity to the X-H bond to be abstracted and the reaction is exothermic. Therefore, efficient HAT tends to proceed via a polarity matched transition state, in which electron rich X-H bonds are readily abstracted by electron deficient X radicals. The Suarez modification shows that electron withdrawing functionality can similarly impart sufficient electrophilicity without protonation. Likewise, this innovation allows for halogenation and N-X bond homolysis to occur in the same vessel unlike in the original HLF reaction in which the N-halogenation cannot be conducted under acidic conditions. Further work by Muñiz, Herrera, and Nagib showed even milder protocols for oxidative HLF reactions.\(^8\)-\(^10\) Likewise, efforts have expanded the scope of the reaction beyond furnishing pyrrolidine products through N-centered radical driven 1,5 HAT.\(^11\)-\(^12\)

### 2.2 Remote Functionalization of Amides via Photoredox Catalysis

The application of photoredox catalysis for N-centered radical formation for 1,5 HAT was introduced by Rovis and Knowles in 2016 using trifluoroacetamides and benzoamides respectively.\(^13\),\(^14\) Both reactions furnish remotely alkylated amides with exquisite regioselectivity for the δ-position with electron deficient olefins. A truly innovative aspect of their strategies was the absence of N-X functionality to enable radical formation as both protocols furnish N-centered radicals from native N-H bonds. In the case of Rovis, the trifluoroacetamide is sufficiently acidic to be deprotonated with K\(_3\)PO\(_4\). The putative amide salt
is then oxidized by the photocatalyst to furnish an unstable N-centered radical rendered electrophilic by the TFA protecting group. This species undergoes 1,5 HAT to furnish a remote alkyl radical which readily adds into electron deficient olefins via a Giese reaction to furnish a more stable electrophilic radical. This is reduced by the reduced state photocatalyst and protonated to enable turnover and give the desired product. (Figure 2.2)

**Figure 2.2 Remote Alkylation of Amides via Photoredox Catalysis**

The primary difference in the protocol disclosed by Knowles lies in the proposed activation for the N-H bond. Benzamides are not sufficiently acidic to be deprotonated with catalytic loading of organophosphate base. Instead, complexation between the excited state
photocatalyst and base enables a ternary transition state with the benzamide in a concerted proton-coupled electron transfer to furnish the N-centered radical. (Figure 2.3)

**Figure 2.3 Comparison of Mechanisms for N-H Activation**

Numerous extensions of N-centered radicals for 1,5 and even 1,6 functionalization have been disclosed using photoredox catalysis as well as other modes of activation including influential work from Roizen, Cook, Nagib, and Zhu.\(^{15-18}\)

### 2.3 Ni-Metallophotoredox: Alkyl Radicals as Nucleophiles in Ni-Cross Coupling

The transformative work of Molander, Doyle, and MacMillan was discussed in Chapter 1. However, following these reports, an entire field of Nickel metallophotoredox evolved to elucidate the various alkyl radical precursors and Ni-activated electrophiles capable of enabling a wide swath of novel cross-couplings. Summarized in Figure 2.4 are the various alkyl radical precursors that have been developed for Ni-metallophotoredox cross couplings.\(^{19-23}\) While most of these protocols enable arylation, reports enabling alkylation, acylation, and vinylation have all been shown through the employment of suitable electrophiles. These are also summarized in figure 2.4.\(^{24-27}\)
Figure 2.4 Cross Coupling Scope of Ni-Photoredox Catalysis

Ni-Photoredox Cross-Coupling

MacMillan, Doyle

Goddard, Ollivier, Fensterbank

Doyle, MacMillan, Martin

Doyle

MacMillan

MacMillan
Key contributions in recent years have enabled alkyl radicals to be generated directly from C(sp³)-H bonds via HAT. Work from the MacMillan group demonstrated that an additional organocatalyst can promote alkyl radical formation at electron rich C(sp³)-H bonds through polarity matched HAT. This enabled the C(sp³)-C(sp³) cross coupling of alkyl halides and C-H bonds through Ni-photoredox catalysis. The mechanism of this reaction, shown in Figure 2.5, begins with absorption of light by the photocatalyst to reach its excited state. This now potent oxidant oxidizes quinuclidine to form the quinuclidinium radical cation. The unstable and electrophilic N-centered radical is polarized to selectively abstract weak electron rich C(sp³)-H bonds to furnish a nucleophilic alkyl radical and protonated quinuclidine. Stoichiometric base enables deprotonation to return the organocatalyst to its starting state. Meanwhile, the reduced state photocatalyst reduces a Ni^{III} species generated via oxidative addition to an alkyl halide to form a stable Ni^{II} electrophilic organometallic complex. Single electron
transmetallation of the electron rich radical generates a Ni\textsuperscript{III} species capable of rapid reductive elimination to furnish product and turn over the catalytic cycle.

Subsequent work demonstrated arylation at unactivated C(sp\textsuperscript{3})-H bonds through Ni-polyoxometalate catalysis and Ni-photoredox catalysis by MacMillan and Doyle respectively\textsuperscript{28,21}. These contributions highlight an attractive opportunity in organic synthesis, namely the ability to functionalize C(sp\textsuperscript{3})-H bonds through selective HAT with complex coupling partners enabled by nickel catalysis.

**Figure 2.6 Selective Activation of C(sp\textsuperscript{3})-H Bonds**

**2.4 Remote Alkylation of Amides through Ni-Photoredox Catalysis**

The selective activation of C(sp\textsuperscript{3})-H bonds remains an intrigue for synthetic chemists due to their ubiquity and relative similarity in organic molecules. Methods involving transition metal C-H activation and HAT have developed in recent years to enable direct functionalization of these traditionally inert bonds\textsuperscript{29}. Whereas much of the success in C-H bond functionalization through transition metal catalysis has focused on C(sp\textsuperscript{2})-H bonds, the weaker bond energies of C(sp\textsuperscript{3})-H bonds render them more amenable to activation via HAT\textsuperscript{30}. This difference in general reactivity is also driven by the relatively stronger C(sp\textsuperscript{2})-M bonds compared to their C(sp\textsuperscript{3})-M congeners\textsuperscript{31,32}.
Concomitant with issues of reactivity due to their high bond enthalpies is achieving selectivity in C(sp³)-H HAT as most efforts thus far have utilized large differences in bond polarity or enthalpies to drive selectivity. In the absence of proximal directing functionalities C(sp³)-H bonds on alkyl chains are chemically indistinguishable. (Figure 2.6) One way to distinguish them is through their relative position to a functional group that may act as a directing group. Directing groups are quite common in transition metal catalysis to enable C-H activation via the relative energies of competing metallocycles. We envisioned that we could utilize 1,5 HAT as a mechanism to distinguish between otherwise chemically identical C(sp³)-H bonds to promote regioselective metalation with a nickel catalyst to furnish remotely cross-coupled products. This would allow for the reactivity of the C(sp³)-H bond to be decoupled from its native polarity or BDE driven reactivity and allow traditionally less reactive bonds to be functionalized in the presence of those that are weaker or more polarized.
Figure 2.7 Optimization and Control Reactions

**Control Reactions and Optimization**

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**Reactions**

- **1a** to **3a**

- **1** to **3**

- **Origin of Diastereoselectivity**

**Diastereoselectivity**

- Reversible or selective metallation
- Reductive elimination

**Major Product**

**Minor Product**
2.5 Reaction Discovery and Scope

Inspired by the ability of our group’s previous disclosure on regioselective remote radical formation, Dr. Scott Thullen posited that we could combine this technology with nickel catalysis to form C-C bonds with protected primary amines. While we were working on this project, a similar strategy was applied towards Ni promoted remote allylation of trifluoroacetamides.\textsuperscript{33} Initial attempts showed promising reactivity which Scott optimized. Control reactions reveal the necessity of light, photocatalyst, base, nickel catalyst, and ligand to enable reactivity. (Figure 2.7a) In evaluating the limitations of the remote cross-coupling protocol we found that reactivity was only seen at methylene sites rather than methyl or methine C(sp\textsuperscript{3})-H bonds. (Figure 2.7b) Together, we demonstrated a wide scope of aliphatic amines amenable to remote cross-coupling as well as a variety of primary alkyl bromides with excellent functional group tolerance. (Figure 2.8) In the case that the remote site is part of a cyclic system, we note high selectivity for the more stable trans diastereomer. We attribute this finding to reversible metalation of the radical at Ni, allowing for preference for the less hindered organonickel intermediate. (Figure 2.7c) In the case of the corresponding Giese reaction on similar substrates, we see no attendant diastereoselectivity.

We also demonstrated a wide array of primary alkyl bromide coupling partners. (Figure 2.9a) We see a notable lack of competitive reactivity in an intramolecular competition between alkyl and aryl halides as in the case of \textbf{3km}. The use of deuterium labeled alkyl bromides permits the synthesis of isotopically distinguished ethyl and d\textsubscript{5}-ethyl groups with ease. (Figure 2.9b) Substrates bearing two separate sites of functionalization allow for sequential transformations permitting access to highly functionalized products. (Figure 2.9c) Finally, the selectivity of this
strategy for methylene sites allows for complementary reactivity with our previously disclosed technologies to generate remote quaternary centers from the sequential Ni-catalyzed alkylation followed by a Giese reaction. (Figure 2.9d)

**Figure 2.8 Amide Substrate Scope**
Figure 2.9 Alkyl Bromide Substrate Scope

**a**

![Chemical structures](image)

3kb 65% 14:1 trans:cis
3kc 42% >20:1 trans:cis
3kd 57% >20:1 trans:cis
3ke 63% >20:1 trans:cis
3kf 48% >20:1 trans:cis
3kg 48% >20:1 trans:cis
3kh 34% 1:1 dr
3ki 61% >20:1 trans:cis
3kj 54% >20:1 trans:cis
3kk 69% >20:1 trans:cis
3kl 56% >20:1 trans:cis
3km 43% >20:1 trans:cis
3kn 61% >20:1 trans:cis
3ko 54% >20:1 trans:cis

**b** Isotopic Incorporation

3ap 42%

**c** Iterative Functionalization:

![Chemical structures and reactions](image)

2a 45% >20:1 dr

**d** Remote Synthesis of 4° centers

![Chemical structures and reactions](image)
2.6 Mechanistic Investigations

Utilizing a N-D labeled starting material and conducting the reaction in d$_3$-MeCN, we note no incorporation of deuterium into the alkyl C-H bonds of the product, demonstrating that 1,5-HAT is presumably irreversible. (Figure 2.10a) The protocol is quite effective at secondary $\delta$-C(sp$^3$)-H bonds, but is unproductive in the case of tertiary or primary congeners, as stated previously. Primary $\delta$-C(sp$^3$)-H bonds were unproductive in our previously reported protocols as well, likely due to the more modestly exothermic 1,5 HAT to furnish the primary alkyl radical. From previous work, we are confident that the tertiary radical would form under the reaction conditions but generates none of the desired product. Instead, we see oxidation of the starting material through a net loss of H$_2$. (Figure 2.10b) We propose that this occurs via metalation of the tertiary alkyl radical to Ni, but that reductive elimination is slow due to the steric bulk of the substrate. Instead, a proposed base mediated elimination of Ni forms the Zaitsev olefin. (Figure 2.10c) This could also proceed through $\beta$-hydride elimination and separate turnover of the Ni-hydride. Preparation of a deuterium labeled substrate at the $\delta$- and $\epsilon$- positions showed complete retention of deuterium in the remote positions, demonstrating that 1,5 HAT is irreversible before cross-coupling. (Figure 2.10e) We attribute the depressed yields of this reaction to a strong kinetic isotope effect (KIE) in the pivotal 1,5 HAT step leading to sluggish reactivity towards the desired product.
The preceding mechanistic work supports the following proposed catalytic cycle.

Oxidation of the amide salt by the excited state photocatalyst generates an amidyl radical. 1,5 HAT furnishes the $\delta$-radical. This attacks a Ni$^{\text{II}}$ organometallic species through single electron transmetallation to form a Ni$^{\text{III}}$ intermediate which undergoes reductive elimination to generate the cross coupled product. Reduction of the nickel catalyst by the reduced state photocatalyst enables the turnover of both catalytic cycles. (Figure 2.10d)

**2.7 Co-Photoredox Catalyzed Remote Acceptorless Dehydrogenation**

Intrigued by the reactivity of $\delta$-tertiary amines from our Ni-Photoredox coupling, we posited that other catalyst platforms may enable remote dehydrogenation due to the bond weakening imparted by our 1,5 system. This presented a host of challenges as directing dehydrogenation towards different positions on the alkyl chain or the resulting geometry of the
formed internal olefin would be quite difficult. Initial results with cobaloxime based catalysts showed some promise and quite good selectivity for methyl-\(\text{C}(\text{sp}^3)-\text{H}\) bonds. However, the catalytic nature of the intramolecular HAT at nitrogen in our trifluoroacetamide protecting group meant that overoxidation would likely prove a continuing issue. Exploration of numerous Co-centered catalysts showed little to no change in regioselectivity and only a small scope of amides was demonstrated despite exhaustive efforts. (Figure 2.11)

**Figure 2.11 Remote Acceptorless Dehydrogenation of Amides through Co-Photoredox Catalysis**

![Co-Photoredox Remote Dehydrogenation of Amides](image)

We propose that the mechanism of this reaction proceeds via oxidation of the amide salt by the excited state photocatalyst which generates then-centered radical. 1,5 HAT produces the \(\delta\)-radical at a tertiary site that weakens the surrounding \(\text{C}(\text{sp}^3)-\text{H}\) bonds considerably to render them as weaker than 40 kcal/mol.\(^{36}\) Meanwhile, our Co\(^{\text{III}}\) catalyst is reduced by the reduced state photocatalyst to Co\(^{\text{II}}\). This species is known to perform HAT on very weak \(\text{C}(\text{sp}^3)-\text{H}\) bonds (<50 kcal/mol)\(^{37}\) Co\(^{\text{II}}\) then intercepts the intermediate radical and abstracts the weaken \(\alpha\)-\(\text{C}(\text{sp}^3)-\text{H}\) bond forming the kinetic product and a Co\(^{\text{III}}\)-\(\text{H}\). Two Co\(^{\text{III}}\)-\(\text{H}\) species can combine to from \(\text{H}_2\) and two equivalents of Co\(^{\text{III}}\) which can reenter the catalytic cycle. (Figure 2.12)
2.8 Summary

Working from the foundation provided by my colleague Dr. Scott Thullen, we were able to present a wide scope of remote cross couplings from readily prepared protected primary amines. Our intramolecular activation paradigm permits unique pathways for the facile generation of synthetic complexity. Metallophotoredox functionalization of C(sp$^3$)-H bonds via 1,5 HAT remains an attractive avenue for synthesis. Remote functionalization is a paradigm shift to the ways we usually think of crafting molecules and photoredox has permitted facile access to the high energy intermediates required for such transformations.

2.9 References


Chapter 3: Cu-Catalyzed C(sp³)-H Alkylation via Photoinduced Ligand to Metal Charge Transfer

3.1 Ligand-to-Metal and Metal-to-Ligand Charge Transfer Bands

To this point, most of my graduate work has focused on the use of organometallic photoredox catalysts. These complexes function via the photoexcitation from a metal centered orbital into a ligand centered orbital resulting in a charge separated excited state giving the excited state its electronic duality, capable of both oxidation and reduction. Photoinduced ligand to metal charge transfer involves electron transfer in the opposite direction, from a ligand centered HOMO to a metal centered LUMO. While the field of coordination chemistry has furnished many examples of complexes exhibiting photoinduced LMCT, some of which have been applied to photoredox catalysis,¹ (Figure 3.1) these have predominantly been stable complexes capable primarily of SET or EnT reactions.

Figure 3.1 Ligand to Metal Charge Transfer vs. Metal to Ligand Charge Transfer
3.2 Extruding Ligand Centered Radicals via Photoinduced LMCT

While much work has been shown in the creation of stable charge separated species via LMCT, an alternative pathway for photoexcited metal-complexes involves the ejection of open shell species concomitant with reduction at the metal center. Foundational work by Kochi disclosed numerous reactions of metal complexes when irradiated that were not possible through alternative means with cerium and copper. In solution, the association of an anionic ligand to the metal center forms a dative bond. The complex is then capable of absorbing a photon to transfer an electron from the dative bond to the metal. This populates the antibonding orbital of the dative bond to cause bond homolysis and extrude a ligand centered radical. In the case of Cerium carboxylates, the extruded carboxy radical undergoes rapid decarboxylation to form an alkyl radical which either abstracts a hydrogen atom from solution or is subsequently oxidized by Ce to a carbocation which then undergoes elimination. In the case of cupric chloride solutions, a chlorine radical is ejected that conducts HAT on the substrate which undergoes chlorination upon radical recombination with CuCl$_3$. (Figure 3.2)

**Figure 3.2 Stoichiometric LMCT towards Reactive Radicals**

![LMCT Enabled Reactivity: General Mechanism](image)

**Ce-LMCT Alkyl Acid Decarboxylation**

**Cu-LMCT C(sp$^3$)-H Chlorination**
Since these initial disclosures in the 1960s, numerous metal complexes have exhibited LMCT to enable useful chemistry including those centered on Mn,\(^4\) Fe,\(^5,6\) Co,\(^7,8\) Ce,\(^2\) and U.\(^9\) Recent advances have provided synthetic applications for LMCT catalysis from Doyle, Wu, Reiser, and our group. We became interested in the photophysical processes that enabled Co-photoredox catalyzed light gated cyclotrimerization of alkynes and nitriles, especially given that reactivity was still present in the absence of the photoredox catalyst.\(^10\) These mechanistic investigations revealed a key LMCT event which enabled reduction of the Co-center without need for a reduced state photocatalyst. Work from Reiser showed that Cu photocatalysts are capable of producing azide radicals via LMCT which can react with vinyl arenes to generate difunctionalized products.\(^11\) Inspiring work from the Doyle and Wu groups showed that LMCT could be leveraged to obviate a separate HAT catalyst in Ni-photoredox cross-couplings. Wu utilized this strategy towards the alkenylation of C(sp\(^3\))-H bonds with alkynes.\(^12\) In Doyle’s work the coupling of aryl halides with C(sp\(^3\))-H bonds was achieved through the photocatalytic oxidation of a Ni\(^{II}\) oxidative addition complex, to form a Ni\(^{III}\) complex. This complex can absorb a photon to reach an excited state and extrude a chlorine radical via photoinduced LMCT. This radical can conduct HAT on an appropriately polarized C(sp\(^3\))-H bond to furnish an alkyl radical which can then recombine with the Ni\(^{II}\) oxidative addition complex and undergo reductive elimination to give the desired cross coupled product.\(^13\) (Figure 3.3)
Figure 3.3 LMCT Catalysis Enabling Synthetic Methods

**Doyle and Wu**

Doyle

Wu

Figure 3.4 LMCT Cerium Catalysis HAT Enabled Amination and Alkylation

**Rovis**

**Reiser**

Active Catalyst
Innovative work from Zuo leveraged photoinduced LMCT on cerium alkoxides to form alkoxy radicals for a wide array of synthetic transformations. This was applied to 1,5 amination of alcohols,\textsuperscript{14} skeletal rearrangement of cycloalkanols to form remotely aminated ketones,\textsuperscript{15} and amination and alkylation of alkanes via intermolecular HAT.\textsuperscript{16,17} First coordination of the alcohol to Ce(IV) forms a photoactive complex. Excitation by light enables LMCT, furnishing an alkoxy radical and a Ce\textsuperscript{III} species. This alkoxy radical is sufficiently unstable and electrophilic to abstract a hydrogen atom forming an alkyl radical or undergo $\beta$-scission to furnish a remote alkyl radical. This alkyl radical rapidly adds to azodicarboxylates forming an electrophilic N-centered radical. This radical is reduced by Ce\textsuperscript{III} and protonated to provide the desired product.

(Figure 3.4) Recent mechanistic investigations have cast doubt on the direct LMCT of alcohols with Ce salts with a competing hypothesis, that formation of chlorine radicals enables complexation with alcohols to modulate reactivity.\textsuperscript{18} We envisioned that other metal
complexes should be capable of photoexcited redox cycles without the employment of other sensitizing agents.

3.3 Reaction Discovery and Scope

Figure 3.5 CuCl₂ Remote Photochlorination of Amines

Investigating the photochlorination of alkanes with CuCl₂ and irradiation we posited that we could intercept the reactive alkyl radical intermediate with another radical electrophile. We first set our attention on utilizing the directing effect of ammonium cations as directing groups remote C(sp³)-H functionalization of amines. We found that these undergo chlorination quite readily with moderate selectivity but proved exceedingly difficult to separate from the reaction mixture. (Figure 3.5) In exploring other coupling partners that would be more synthetically useful, I found initial success in the use of ethyl acrylate and found quickly that the reaction was still efficient even at catalytic loadings of CuCl₂. We saw the C(sp³)-H alkylation of alkanes with electron deficient olefins by employing catalytic CuCl₂ to be a valuable transformation. (Figure 3.6) Although such reactivity has long been characteristic of decatungstate salts, we posited that Cu-LMCT catalysis should offer opportunities for leveraging inner-sphere mechanisms unavailable to polyoxometalate HAT catalysts.
Figure 3.6 Optimization and Control Reactions

Optimizing this reaction, we found that an excess of the alkane was necessary for high yields due to the propensity of the product to undergo HAT when in competitive concentration to the starting materials. Coupling was still efficient at lower equivalents of alkane pronucleophile albeit in decreased yield. Following the example of Kochi, we found that the addition of LiCl led to more homogenous reaction conditions, and for us, more efficient catalysis. Light and Cu are both required for reactivity and the reaction is more efficient at elevated temperatures which were accessible from the residual heat of the lamps.
We found that a wide variety of alkanes undergo the coupling quite efficiently with appropriately polarized C(sp³)-H bonds. (Figure 3.7) Substrates bearing weakened bonds or modestly electron deficient polarity often are less reactive with the acrylate electrophile and require higher catalyst loadings to increase yields. (12-14, 22, 23) Carboxylic acids, which are known to undergo competitive oxidation under the potentials typically required to oxidize chloride to chlorine radical are well tolerated under our protocol. (26-30) Similarly, we are able to selectively abstract the C(sp³)-H bond of aldehydes and the Si-H bond of silanes selectively to produce alkylated products. (24-25)
We also found that a wide variety of electrophiles are also competent coupling partners including variously substituted acrylates, diisopropyl methylene malonate, and acrylic acid. (Figure 3.8, 31-36) Vinyl sulfones and azodicarboxylates are similarly efficient coupling partners. (37-39) When applying our method to endocyclic olefins we were surprised to find that the coupling proceeds with high diastereoselectivity even in cases that had not should selectivity in previously demonstrated decatungstate catalysis. (43-48) This finding invited further work on the mechanism of the reduction side of our reaction.

3.4 Mechanistic Investigations

First, we wanted to explore the mechanism of chlorine radical formation in our protocol. This commenced with an investigation into the photoactive copper species that was enabling LMCT. The first effect that was explored was the effect of additional chloride ion in the form of LiCl which was documented by Kochi to increase the solubility of CuCl₂ in MeCN. This is due to
the formation of different chlorocuprate salts which are more soluble in acetonitrile than the parent CuCl$_2$ complex. Early studies from Manahan found the equilibrium constants for various chlorocuprate salts based on the dissolved chloride in solution using electrochemistry.$^{19}$ Photophysical studies of chlorocuprate solutions in acetonitrile conducted by Tarnovsky and Mereshenko documented the quantum yield of LMCT versus other relaxation pathways for each species as well as their characteristic UV-Vis absorption profiles.$^{20}$ Using protocols from these sources we replicated the conditions to form each of the chlorocuprate salts that were previously characterized and applied them to our catalytic protocol. We found that only CuCl$_3^-$ was a competent catalyst and find that a UV-Vis of our active catalyst matches that characterized by Tarnovsky and Mereshenko. After continuous irradiation with 390 nm light we note a complete bleach of the solution by UV-Vis spectroscopy. (Figure 3.9) The work from Tarnovsky and Mereshenko shows that CuCl$^+$ is also capable of LMCT with a slightly higher quantum yield than CuCl$_3^-$ such that chlorine radical generation and subsequent HAT could be operative but that the intermediate Cu$^+$ species is apparently incapable of delivering a hydrogen atom to the resultant radical following Giese addition.
Figure 3.9 UV-Vis Characterization

Normalized Absorbance

Wavelength (nm)

220 270 320 370 420 470 520 570

6 hrs

Normalized Absorbance

Wavelength (nm)

220 270 320 370 420 470 520 570
We next wished to interrogate the mechanism of HAT. Other protocols have suggested that M-X bond homolysis could be coupled with HAT. To probe this, we conducted an isotopically differentiated competition experiment between cyclohexane and d_{12}-cyclohexane. Running the reaction for 6 hours, we found a KIE of 1.20. (Figure 3.10a) Previous work involving the photolysis of chlorine gas in mixtures of cyclohexane/cyclohexane-d_{12} has demonstrated a KIE of 1.18.\textsuperscript{21} Similarly, the Wu group has shown a KIE of 1.34 through the oxidation of chloride to chlorine radical to enable alkylation with highly electron deficient radicals.\textsuperscript{22} These examples
taken together, as well as the differences in solvent and temperature are sufficiently close to be in agreement for the reported value, implicating free chlorine radical as the HAT reagent.

Then we set to investigating the mechanism of hydrogen atom transfer delivery to the stabilized radical resulting from Giese addition. Previous work has shown the ability of Cu salts to inhibit the polymerization of electron deficient olefins in Giese reactions.\textsuperscript{23} We wished to probe the presumed Cu-enolate intermediate through a number of experiments. Early on we noticed that the addition of base inhibits catalyst turnover. We proposed that our Cu-enolate intermediate may require sufficiently strong acid to undergo proto-demetalation. This would require that the HCl generated via HAT enables catalyst turnover. We set up two experiments to test whether protodemetallation is rate-determining for product formation by adding exogenous deuterated acid. In fact, the addition of 0.5 equivalents of D\textsubscript{2}SO\textsubscript{4}, compared to only a possible 20% generated HCl showed a strong KIE with only 17% deuterium incorporation into the product of the protocol utilizing ethyl acrylate and cyclohexane. The inverse reaction further confirmed this result as the addition of H\textsubscript{2}SO\textsubscript{4} to a reaction between d\textsubscript{12}-cyclohexane showed only 7% incorporation of deuterium at α-position to the ester. (Figure 3.10b)

We were unable to measure the kinetic isotope definitively via these experiments due to our lack of knowledge as far as the relative concentrations of HCl, DCl, H\textsubscript{2}SO\textsubscript{4}, HDSO\textsubscript{4}, and D\textsubscript{2}SO\textsubscript{4} over the course of the reaction. Literature surveys into the KIEs involved in proton transfer reactions provides precedent that bears little similarity to the protonation of a Cu-enolate. However, there are a wide swath of known values for the KIE in proton transfer reactions involving organic molecules that follow an empirical pattern that the strongest effects are seen when ΔG of proton transfer is close to zero with decreasing KIE values as proton
transfer becomes more exothermic. Applying this to our protocol implies that our Cu-enolate intermediate must be very weakly basic to detect a KIE in the presence of such strong acids. This also explains a lack of reactivity when other electrophiles are added such as trimethylsilyl chloride or phenyl chloroformate are added to assess whether the Cu-enolate intermediate is otherwise reactive.

To ensure that deuterium incorporation occurs during the reaction of interest and not from enolization of the ester product, we subjected the product to the reaction conditions with exogenous D₂SO₄ to find no incorporation into the reisolated starting material. (Figure 3.10c)

We propose that the turnover limiting protodemetallation step is the source of diastereoselectivity in the case of endocyclic olefins. These mechanistic investigations support the following catalytic cycle. First, CuCl₂ and LiCl react to form CuCl₃⁻. Then irradiation enables photoinduced LMCT to form CuCl₂⁻ and a chlorine radical. This chlorine radical undergoes HAT with an appropriately polarized C(sp³)-H bond to form a reactive alkyl radical. This radical adds across an electron deficient olefin to form a more stable electrophilic radical, which recombines with CuCl₂⁻ to form a stable Cu-enolate. This species undergoes protodemetallation to form the cross-coupled product and regenerate the photoactive CuCl₂⁻. (Figure 3.11)
3.5 Summary

We have disclosed a new method of generating chlorine radical catalytically through LMCT catalysis using Cu salts. This protocol shows a wide substrate scope with mechanistic work that supports a novel protodemetallation mechanism to enable reoxidation of the photoreduced Cu-species and furnish product with high diastereoselectivity in the case of endocyclic olefins. Without the need for exogenous photosensitizer, this strategy provides a foundation for more complex reactivity through base-metal LMCT catalysis to provide cheaper and more environmentally sustainable catalytic methods.

3.6 References


Chapter 4: FeCl\textsubscript{3} LMCT: Primary Radicals Enable Carbon Skeleton

Rearrangements

4.1 The Dowd-Beckwith Rearrangement

In the late 1980s, Dowd and Beckwith independently reported a radical mediated skeletal rearrangement of carbonyl compounds via the reduction of appropriately situated alkyl-halides.\textsuperscript{1-3} Finding significant synthetic utility in the ring expansion of cyclic ketones, hindering further progress on this reaction is the requirement of prefunctionalization most often through enolization and subsequent alkylation with geminal dihalides.\textsuperscript{4} The mechanism of the reaction involves abstraction by a tributyltin hydride radical, formation of a primary alkyl radical, radical addition to furnish a cyclopropyl alkoxy radical, beta scission of the cyclopropane to form the ring expanded alkyl radical, and finally HAT from another equivalent of tributyltin hydride to deliver product and continue the radical chain. (Figure 4.1)

Figure 4.1: Mechanism of the Dowd-Beckwith Rearrangement

4.2 Reaction Discovery and Scope

Due to the high bond dissociation energy of HCl, chlorine radical is able to abstract methyl C(sp\textsuperscript{3})-H bonds when no other bonds are sufficiently electron rich to be favored for HAT.\textsuperscript{5} Due to the electron withdrawing nature of carbonyl groups, the α-protons are rendered
acidic and are recalcitrant to HAT by electrophilic radicals even with significant thermodynamic driving force. Therefore, we estimated that we would be able to form radicals at appropriately placed methyl groups via HAT to undergo Dowd-Beckwith type rearrangements directly from C(sp$^3$)-H bonds.

For this project, I had the opportunity to work alongside a very talented undergraduate student, Yi Cheng Kang, who discovered this reaction and performed many of the reactions I will discuss. Yi Cheng was working on a reaction where we found that FeCl$_3$ could enable the addition of heteroarenes to substrates bearing weak C(sp$^3$)-H bonds. In probing the mechanism of this transformation, we found that FeCl$_3$ like CuCl$_2$ was capable of generating chlorine radicals when appropriately irradiated under the reaction conditions. This is well preceded in work by both Takehira and Shul’pin who demonstrated the photooxidation of various alkanes through the irradiation of various transition metal chloride salts with molecular oxygen.$^{6-8}$ We then found that the C(sp$^3$)-H alkylation with electron deficient olefins was also productive with FeCl$_3$. During the course of these investigations, we found that pinacolone produced two products arising from a mixture of the rearranged and unrearranged products. Whereas the Dowd-Beckwith type rearrangement was theoretically predictable based on the formation of a primary alkyl radical in the case of pinacolone, what was surprising was that the rate of intramolecular rearrangement would be so competitive with the intermolecular rate of Giese addition to the electron deficient olefin under the reaction conditions.

In conducting control reactions, we found that adjusting the temperature and concentration of the reaction could change the distribution of products obtained to more strongly favor the rearranged product rather than the straightforward radical addition (Figure...
4.2) This is due to the unimolecular nature of the intramolecular rearrangement, which is promoted with additional heat and given more time to rearrange when the concentration of the electrophile is lowered. Since this reaction involves photoexcitation of the catalyst, we are able to sample various temperatures with only slight changes in reactivity, with the differences seen primarily in selectivity. This provides an essential advantage when compared to reactivity with CuCl₂, which showed diminished reactivity at lower temperatures. Also, unlike with the analogous copper catalyzed reaction, we see less efficient reactivity with the addition of LiCl. However, continuous irradiation and FeCl₃ are both necessary for efficient reactivity.

**Figure 4.2: Optimization and Control Reactions**

![Diagram of reaction](image)

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<td>4</td>
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<td>5</td>
<td>0% FeCl₃</td>
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The mechanism of the rearrangement in the case of chlorine radical hydrogen atom abstraction is shown in Figure 4.3. We provided a wide scope of carbonyl compounds, arenes, and heterocycles that all proved capable of Dowd-Beckwith type rearrangements as pronucleophiles. (Figure 4.4) We provide all of the substrates with yields and isomeric ratios under two different sets of reaction conditions to demonstrate the universality of adjusting the isomeric ratio with the presented functional groups and how that relates to the temperature.
and concentration. This scope provides significant data concerning the ability to change the rate of rearrangement through these facile adjustments to the reaction conditions. Some substrates, such as 2,2,5,5-tetramethylcyclopentan-1-one are completely recalcitrant towards alkylation prior to rearrangement, providing a range for the rate of rearrangement given that Giese addition should remain relatively constant in either condition. This was indeed supported by our scope of olefin acceptors as each substrate retained roughly equivalent changes in isomeric ratio through a change in temperature and concentration. Alongside the substrates that undergo rearrangement we also demonstrated a number of substrates which do not undergo rearrangements and are simply alkylated.

Figure 4.3 Mechanism of 1,2 Rearrangement
Figure 4.4 Scope of C-H Pronucleophiles for Alkylation and 1,2 Migration-Alkylation

Pronucleophile

Unrearranged

Rearranged

Conditions A

Conditions B

r.t., 0.33 M

60 °C, 0.1 M

59%, 1:1.4

64%, 1:10

58%, 12:1

44%, 1:6:1

30%, 4:1

N.D.

6a-9a

6b-9b

6  = H  40%, 16:1  25%, 2.4:1

7  = Ac  28%, 1:13  58%, <1:20

8  = CN  30%, 1:8  54%, <1:20

9  = OAc  46%, 20:1  35%, 1:1

8%  19%

37%  41%

20%, 1.4:1  44%, 1:1.6

Trace  34%, <1:20
Figure 4.5 Scope of C-H Pronucleophiles and Electrophiles for Alkylation

EWG

R = Bn, 54%
R = Et, 51%
R = Ph, 52%

R = Bn, 50%
R = Et, 44%

81%
β:γ 2.3:1

R = Ph, 52%

39%
61%
37%
44%
32%
45%

from MeCOCl

40%, after EtOH workup

MeCN

5 equiv.

5 equiv.

37%
68%
61%
32%
45%

9:1 a:b

39%
61%
55%, 2:1 β:γ

37%
68%
Figure 4.6 Scope of Olefin Acceptors for Alkylation and 1,2 Migration-Alkylation

Acceptor

14

Unrearranged

14a

Rearranged

14b

Conditions A

rt, 0.3 M

38%, 1:1

Conditions B

60 °C, 0.1 M

57%, 1:8

15

15a

52%, 1:1.2

51%, 1:8

16

16a

54%, 1:1.4

66%, 1:10

17

17a

35%, 1.2:1

47%, 1:9

18

18a

25%, 1:1

41%, 1:7

19

19a

46%, 1:1.7

61%, 1:10

20

20a

43%, 1:3

62%, 1:15

21

21a

63%, 2:3

73%, 1:14

22

22a

32%, 1:5

50%, 1:18

22b

a:b 6:1

17%, 1:15

63%, <1:20

a:b 5:1

23

24

54%, 1:1.4

66%, <1:20

24a

(X-ray)

24b

57%, 1:9

70%, <1:20
4.3 Mechanistic Investigations

Our wide scope of electrophiles gave us the rare opportunity to benchmark the rates of primary radical addition to various electron deficient olefins. For a given rate constant of the rearrangement at a given temperature, one can utilize the rearrangement as a radical clock to calculate the rates of radical addition to each olefin electrophile. Surprisingly, some of the highest yielding electrophiles in our reaction maintain the slowest rates of addition, showing the importance of subsequent steps in the reaction mechanism to determine the overall yield of the reaction. Given that the electrophile is the limiting reagent, the rates of competitive oligerimization versus protodemetalation could account for this difference. A table of rate constants are provided in Figure 4.7a. Next, we wanted to see how far we could push the isomeric ratio for a given substrate. Diisopropyl ketone showed a switch in the major product between our standard sets of reaction conditions. We showed that we can retain quite high yields and further increase the isomeric ratio to favor either product by further increasing the concentration of the reaction or adding the electrophile portion wise at low concentration and high temperature. (Figure 4.7b) Mirroring the experiments conducted on the CuCl₂ catalyzed reaction, we found that again we see limited incorporation of deuterium in the product when the reaction is conducted with 0.5 equivalents of D₂SO₄. Likewise, a competition experiment between cyclohexane and d₁₂-cyclohexane showed a KIE ratio of 1.41:1. Although this is slightly higher than the KIE value we saw in the case of the copper catalyzed reaction (1.20:1), we can account for this difference due to the higher reaction temperature of the Cu catalyzed reaction, which may lead to less discriminant abstraction between the proteo- and deutero-substrates as expected in an Arrhenius calculated prediction of KIE.
These experiments lead us to the following mechanism. First, solvated FeCl$_3$ is irradiated to extrude a chlorine radical and furnish FeCl$_2$. This chlorine radical conducts HAT on an appropriately polarized C(sp$^3$)-H bond to form a reactive alkyl radical. This radical rapidly adds to an electron deficient olefin to form a more stable electron deficient radical $\alpha$ to the carbonyl. Metalation with FeCl$_2$ forms an Fe$^{\text{III}}$ species which is protonated by HCl to regenerate the active catalyst and form the desired product. (Figure 4.8)
4.4 Accessing Radical Cross-Coupling through LMCT Photocatalysis and Hydrazone Electrophiles

Hydrazones have a rich history in synthetic methods and have found significant utility in the reduction of ketones through the Wolf-Kishner, Caglioti, and Bamford-Stevens reactions. These reactions proceed via extrusion of $N_2$ via proposed anionic or carbene intermediates to generate alkanes. (Figure 4.9) Hydrazones also with react with electrophilic...
radicals to enable useful C-C bond forming reactions. The König group has especially leveraged this reactivity towards the carboxylation and difluoromethylenation of hydrazones.\textsuperscript{13} Similarly, the Baran group has utilized their iron metal hydride chemistry to enable the hydromethylation of unactivated olefins with in-situ generated methylene sulfonyl hydrazide.\textsuperscript{14} This proceeds first through radical addition to form the alkyl hydrazide. Subsequent application of heat and base enables the extrusion of N\textsubscript{2} and the reduced product. Subsequent studies from the Bradshaw group showed the efficiency of similar radical couplings with benzylidene sulfonyl hydrazones.\textsuperscript{15} We envisioned that we could utilize our novel methods to access alkyl radicals and enable traceless C-C bond formations between aldehydes and C(sp\textsuperscript{3})-H bonds. (Figure 4.10)

**Figure 4.10 Radical Couplings with Hydrazones**

Thus far we have leveraged LMCT catalysis for the generation of chlorine radicals for HAT and subsequent alkylation with electron deficient pi-systems. In order to investigate whether we could leverage the Lewis acidity of our metal salts for additional reactivity we attempted to use sulfonyl hydrazones as electrophiles for our alkyl radicals formed via HAT. Initial studies were promising, with the desired hydrazide intermediate forming in moderate yields. Isolation of this intermediate proved challenging and much lower yielding than from \textsuperscript{1}H NMR analysis. Subsequent efforts to enable C-N bond scission though N\textsubscript{2} extrusion were
complicated by the isolation of various products from similar conditions to those used by Bradshaw. We proposed these product mixtures stemmed from the undesired reactivity of carbene intermediates. The combination of these difficulties with the severely diminished yields of the desired product motivated an exploration of substrate scope. Further poor yields with alkyl hydrazones motivated pursuit of other avenues of reactivity. (Figure 4.11)

**Figure 4.11 Radical Cross-Coupling through LMCT Photocatalysis and Hydrazone Electrophiles**

### 4.5 Summary

Together, Yi Cheng and I showed that the mechanisms available to my previously disclosed Cu catalyzed system are available to other base metal salts. In an excellent extension of this reactivity, Yi Cheng discovered that 1,2 rearrangements are available through these cheap and abundant catalysts from C(sp³)-H bonds to enable novel pathways for C-C coupling. Further work is underway to leverage LMCT catalysis towards the formation of other reactive radicals as well as coupling partners.
4.6 References


Chapter 5: γ-Lactam Synthesis through Triplet Sensitized Electron Donor-Acceptor Complexes

5.1 N-Heterocycles: Valuable Scaffolds in Organic Synthesis

Figure 5.1 Abundance of Elements in FDA Approved Drugs and Representative Examples

Nitrogen atoms are highly prevalent in organic molecules including both pharmaceuticals and natural products with biological activity. A survey of small-molecule drugs approved by the FDA in 2018 found that 84% maintain at least one nitrogen atom.\(^1\) For small-molecule drugs approved through 2012 we find N to be fourth only to oxygen, carbon, and hydrogen in terms of abundance. The cause for this prevalence is manifold, as nitrogen increases water solubility reversibly through its ease in protonation, its ability to donate and receive hydrogen bonds depending on its substitution, and its propensity to enrich scaffolds with secondary and ternary structures.\(^1-3\) All of these characteristics render compounds containing nitrogen to bind efficiently to biological targets.
Among FDA approved pharmaceuticals containing nitrogen, 59% of them contain a nitrogen heterocycle. While innumerable methods exist for the synthesis of various N-heterocycles, there is continued interest in generating scaffolds built around these valuable motifs to increase the chemical space available for pharmaceutical development. Among the most common N-heterocycles in FDA-approved drugs are pyrrolidines. These five membered heterocycles are synthesized through a wide variety of methods. One common strategy to craft highly substituted pyrrolidines is through protected γ-lactams. Protected γ-lactams provide two facile sites of functionalization. First, nucleophiles such as Grignard reagents add readily to the carbonyl group within the ring with the carbamate behaving like a Weinreb amide such that monoaddition can be controlled. Subsequent intramolecular reductive amination can be conducted with high diastereoselectivity to give pyrrolidine products. Similarly, enolizable protons on the ring are capable of reacting with various electrophiles. Finally, direct reduction of the protected γ-lactam to the aminal or the pyrrolidine is also well preceded. All of these transformations demonstrate the synthetic utility of protected γ-lactams and their ease in subsequent substitution to furnish highly substituted pyrrolidine products.
γ-Lactams themselves are widely distributed in pharmaceuticals and biologically active natural products. There are numerous methods for their direct synthesis with some common strategies outlined including intramolecular amide bond formation, intramolecular S_N2 reactions, orthogonal C-C bond formations about amides, 4+1 couplings of acrylelectrophiles.
with amines, 3+2 reactions of enolates and α-halo-amides, and 3+2 couplings between iminium ylides and electron deficient olefins.\textsuperscript{11,12} While these strategies have been gainfully employed towards the synthesis of γ-lactams, they require tailored starting materials and limit the substitution patterns available for the final product.

**Figure 5.5 Substituted γ-Lactams in Pharmaceuticals and Natural Products**

![Natural Products](image)

![Small-Molecule Pharmaceuticals](image)

**Figure 5.6 Common Strategies for the Synthesis of γ-Lactams**

Due to continued interest in furnishing γ-lactams with more complex substituents, significant advances have been made with more specific reagents as well as tailored catalytic reactions. This includes valuable work from Lin applying Ellman-imines towards the enantioselective construction of 2-methylene, 4,5-substituted γ-lactams from tailored acrylates.\textsuperscript{13} Likewise, work from Tiwari has enabled the diastereoselective alkylation of tosyl-aziridines with malonate nucleophiles using copper catalysis.\textsuperscript{14} Organometallic methods include
work from Onitsuka applying asymmetric ruthenium catalysis for the 3+2 coupling of α-halo-imides with allylic chlorides. Complementary work from Nishimura demonstrated the iridium catalyzed asymmetric carboamination of 2-oxo-imides with 1,3 dienes. Organocatalytic approaches from our group have enabled the 3+2 coupling of acrolein derivatives with aza-dienes through N-heterocyclic carbene catalysis.

**Figure 5.7 Representative Recent Developments in γ-Lactam Synthesis**

![Diagram of Representative Recent Developments in γ-Lactam Synthesis](image-url)
Routes to substituted γ-lactams have benefitted greatly from open-shell chemistry as well. Through continuous radical initiation, Renaud enabled the three-component coupling of α-Br-esters, tosyl azide, and unactivated olefins in a three-step protocol involving first alkylazidation of the olefin followed by reduction and cyclization to the γ-lactam. A similar three component strategy was shown by the Hull group to enable the copper catalyzed alkylimination of styrenes, which upon liberation of the free amine from benzophenonimine, cyclizes to the desired γ-lactam. Our group provided a significant advance in the formal [3+2] synthesis of γ-lactams from acrylates and primary amines through α-amino HAT and subsequent cyclization onto various acrylates utilizing CO₂ as a transient activating and protecting group.

5.2 Radical Addition Reactions of α-Halo-amides

One strategy that has long attracted synthetic chemists is a [3+2] synthesis from amides and olefins through radical intermediates. Whereas addition of α-carbonyl radicals to unactivated olefins is facile in the case of esters and ketones, α-amido radicals are much less reactive without additional electron withdrawing functionality or scope limiting formation of an organometallic intermediate. Within this paradigm, numerous methods have been furnished in recent years utilizing copper or photoredox catalysis that achieve the formal [3+2] synthesis of γ-lactams from α-halo-amides and activated olefins.

Photoredox catalysis has been gainfully applied in this area by Zhu, who demonstrated that BrCF₂-amides are capable of undergoing a formal [3+2] coupling with styrenes utilizing an iridium photocatalyst. Key to this method is the addition of iodide salts which form the more reactive ICF₂-amide in-situ which is then reducible by the reduced state photocatalyst. The
corresponding electrophilic radical adds rapidly to styrenes and the resulting benzylic radical can be oxidized to the carbocation to generate the desired lactam. Likewise, Cu catalysis has been employed for the [3+2] synthesis of γ-lactams with activated olefins by Nishikata although with requisite tertiary substitution at the α-Br-amide coupling partner to enable efficient reactivity.\textsuperscript{22} In order to enable reactivity with unactivated α-olefins, Lv and Zhang utilized BrCF\textsubscript{2}-amides as electrophiles for a [3+2] lactam synthesis.\textsuperscript{23}

One often overlooked limitation to both of these classes of methods is the requirement of N-aryl substitution. This is due to the competitive nucleophilicity of oxygen and nitrogen in secondary and primary amides for which the aryl substituent renders N-more nucleophilic when the electrophilic component, such as a carbocation or an electron deficient organocuprate, is driving the reactivity.\textsuperscript{24,25} A recent study from Tiefenbacher showed that the addition of silver salts greatly favors the formation of an iminolactone rather than the more synthetically valuable lactam.\textsuperscript{26} This is presumably due to the enabling of \textit{S\textsubscript{N}1} chemistry which favors O-alkylation rather than N-alkylation. A survey of the literature on intramolecular amide alkylations shows that N-alkylation is most often favored when the amide is deprotonated with base before nucleophilic attack and works most effectively with more stable electrophiles.\textsuperscript{27}
5.3 α-Halo-imides: Facile Atom-Transfer Radical Addition with Unactivated Olefins

We envisioned that we could circumvent many of the limitations presented by current methodology for the synthesis of γ-lactams from α-halo-amides by increasing the electrophilicity of the intermediate radical via an electron withdrawing protecting group. This should not only enable radical addition to unactivated olefins, but should also promote N-alkylation under mild conditions due to the relatively acidic N-H bond of the imide.

Initial surveys of the literature found examples of intramolecular atom-transfer radical addition reactivity driven by a protecting group strategy. Work in our own department, from Stork, showed that the appendage of a trifluoroacetyl group onto an α-Br-amide promotes intramolecular hydroalkylation which gives only the des-bromination product otherwise. We decided to synthesize a trifluoroacetyl-α-Br-imide to see if it would undergo atom-transfer radical addition (ATRA) with unactivated olefins under photoredox conditions. However, efforts to cyclize the resulting γ-bromo-imide showed limited product formation even with a large
screen of bases. We theorized that the imide may be too acidic, and that the resulting anion is only weakly nucleophilic such that the desired intramolecular cyclization is slow.

**Figure 5.9 Atom-Transfer Radical Addition with α-Br-Imides**

We then explored whether carbamate protecting groups would offer sufficient electrophilicity of the ATRA while being sufficiently nucleophilic when deprotonated. Initial studies showed the necessity of sufficiently strong base to enable reactivity with Boc-imides. Further optimization showed that only a catalytic amount of diisopropyl ethylamine (DIPEA) was required for quantitative reactivity with Boc imides. Control reactions revealed that the reaction could be conducted under 390 nm irradiation without photocatalyst and still lead to good yields of the desired ATRA product. We ascribe this reactivity to the formation of an electron donor-acceptor complex which can enable electron transfer through irradiation with appropriately energetic light. This interaction can also be sensitized under visible light with the excited state of the photocatalyst via triplet sensitization. Further work on this front is currently under investigation by my talented undergraduate student, Daniel Vaz.
5.4 Electron Donor-Acceptor Complexes in Synthesis

Due to the unexpected nature of this mechanistic finding, I will now introduce some of the nuances of Electron Donor-Acceptor (EDA) complex chemistry. The fundamental framework underlying EDA complexes involves molecular orbitals in separate molecules interacting in solution such as that a high-lying electron from one species may be excited into a low-lying orbital of another through excitation with light. EDA complexes have been studied extensively since the 1970s. Groundbreaking work from Cantacuzene\textsuperscript{30} and Bunnett\textsuperscript{31} showed the ability of enolates and enamines to react with perfluoroalkyl and aryl iodides through an EDA complex; reactivity that does not proceed through classical nucleophile-electrophile couplings. Kornblum\textsuperscript{32} and Russell\textsuperscript{33} similarly showed the ability of enamines and highly nucleophilic amines to undergo EDA excitation with electron-deficient benzyl chlorides towards substitution reactions. Kochi also made seminal contributions in this field through the nitration of electron-rich arenes with tetraniitromethane through EDA complex formation.\textsuperscript{34} His group likewise
demonstrated that EDA complexes form between tetracyano ethylene and tin hydrides to undergo hydrostannylation of the highly electron-deficient olefin.$^{35}$

**Figure 5.12 Seminal Examples of EDA Complex Photochemistry**

Recent applications of photochemistry in organic synthesis have furnished additional examples of EDA complexes. The popularization of photoredox catalysis has led to the discovery of numerous EDA complexes through control reactions showing that the photocatalyst is not essential for reactivity. Such serendipitous discoveries were disclosed by Chatani$^{36}$ and Melchiorre$^{37}$ in 2013 towards the coupling of electron-rich heteroarenes with aryl-iodonium species and organocatalyzed enantioselective alkylation of aldehydes with electron deficient benzylic halides respectively.

Since these disclosures numerous reactive EDA complexes have been disclosed enabling a variety of useful organic transformations. Electron rich moieties such as Hantzsch ester have been shown by Chen$^{38}$ and Aggarwal$^{39}$ to form EDA complexes with alkyl hydroxyphthalimides and Katritzky salts respectively. A significant contribution was further made by Aggarwal in the find that diboron species can become donors for N-hydroxyphthalimide esters,$^{39}$ Katritzky salts,$^{40}$ and 2-iodophenyl-thionocarbonates,$^{41}$ to enable radical formation from carboxylic acids,
primary amines, and alcohols respectively for further functionalization. Electron-rich amines have likewise found significant utility as electron donors and have been shown by Yu, Leonori, and in a catalytic fashion by Bosque and Bach.⁴³ One challenge in the formation of EDA complexes in a catalytic fashion is in promoting special proximity of the donor and acceptor in solution. Melchiorre disclosed an enantioselective organocatalytic protocol which enabled the umpolung radical alkylation of enones driven by in-situ formation of an iminium that undergoes charge transfer from a pendant carbazole.⁴⁴ Innovative work from the Hyster group showed the ability of evolved keto-reductases to asymmetrically reduce halo-lactones through an in-situ EDA complex between the NADH and the substrate formed in the active site.⁴⁵ Further work from the Hyster group enabled the asymmetric intramolecular radical cyclization of α-halo amides with evolved ene-reductases.⁴⁶
5.5 Formal [3+2] γ-Lactam Synthesis from α-Halo-amides and Olefins

Attaining a quantitative yield of the ATRA product, we next worked to see if a more nucleophilic N-anion would be able to undergo the intramolecular cyclization. Optimization of the cyclization showed the reaction proceeds most efficiently under basic conditions in polar...
aprotic solvents. Complicating the cyclization is the propensity for the anionic intermediate to attack via oxygen to form the iminolactone instead of nitrogen to form the desired protected lactam. While some iminolactones are sufficiently stable to be isolated,\(^\text{26}\) ours are readily hydrolyzed by adventitious water and are instead isolated as the corresponding lactone. Finding the optimal solvent and base to be MeCN and K\(_3\)PO\(_4\) respectively, we conducted the reaction in a one-pot procedure by irradiating the reaction mixture overnight, diluting the solution with MeCN, adding excess K\(_3\)PO\(_4\), and then stirring at room temperature for three hours. (Figure 5.14)

**Figure 5.14 Optimization and Control Reactions**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from Standard Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>no light</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>no PC</td>
<td>33</td>
</tr>
<tr>
<td>4</td>
<td>no base</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>2 equiv. olefin, 1 equiv. imide</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>1 equiv. olefin, 1 equiv. imide</td>
<td>29</td>
</tr>
</tbody>
</table>
Exploring the scope of the reaction we found that numerous α-olefins are efficient coupling partners with good functional group tolerance. (Figure 5.15) We also found a variety of carbamate and sulfonamide protected amides are competent at reacting with unactivated olefins. (3ba, 3ca, 3da, 3ea) Secondary alkyl bromides were found to undergo the coupling also but with less efficiency and no diastereoselectivity. (3fa) The reactivity was completely shut down when utilizing a tertiary alkyl bromide for two plausible explanations: the intermediate radical is insufficiently electrophilic to react with unactivated olefins or the substrate may be unable to undergo propagation through a radical chain mechanism by virtue of being a less
reactive bromine atom donor. (3ga) In order to regain this reactivity, we surmised that the addition of a Lewis acid would impart greater electrophilicity to overcome all of these issues.

In order to prevent undesired deprotection of Boc-protected imides, we instead utilized methoxycarbonyl protected imides which proved more robust in the presence of Lewis acids. Screening of Lewis acids revealed that fully substituted α-Br-imides can be rendered reactive towards ATRA and cyclization through the addition stoichiometric La(OTf)$_3$. Evaluation of a scope of tertiary alkyl bromides showed varying substitution patterns to furnish various spirocyclic ring systems. (Figure 5.16) Furthermore, reactivity of primary alkyl bromides was shown to be highly limited with internal olefins, with yields of the ATRA product below 10%. With the addition of La(OTf)$_3$ this reactivity was recovered and enables the synthesis of 2,3-disubstituted γ-lactams in moderate yields albeit with limited diastereoselectivity. This result shows that even when initial reduction of the α-Br-imide is facile and the radical formed is nearly identical to our previously established reactivity, that La(OTf)$_3$ must be enhancing the electrophilicity of the intermediate radical to promote radical addition to the olefin to facilitate the reaction.
5.6 Mechanistic Studies

With an expansive scope in hand, we then set to explore the mechanism of the reaction. First, in order to establish whether the reaction is merely initiated and proceeds via a radical chain we conducted in-situ LED NMR experiment to confirm that productive reactivity halts without continuous irradiation. However, in measuring the quantum yield of the reaction we found a quantum yield $\Phi = 14$ showing that a radical chain is quite efficient early on in the reaction but must proceed through relatively short radical chains. Cyclic voltammetry of the starting materials shows that even the reduced state of the photocatalyst is insufficiently reducing to efficiently undergo SET to furnish the desired electrophilic alkyl radical. Instead, we propose that the formation of an EDA complex is sensitized by the triplet state of the photocatalyst. (Figure 5.18A) This explains more efficient reactivity with 440 nm irradiation only with the use of a photocatalyst. UV-Vis characterization of the Boc-\(\alpha\)-Br-imide as well as mixtures of the imide and DIPEA reveal a new signal at (344 nm) we ascribe to the EDA complex enabling our observed reactivity. (Figure 5.17)
To ensure that halogen-atom transfer from α-amino radicals does not enable the reaction, we also conducted the reaction with photocatalyst and 1,4-diazabicyclo[2.2.2]octane (DABCO). (Figure 5.18B) The C(sp³)-H bonds α-to nitrogen in DABCO are geometrically locked out of hyperconjugation with the nitrogen lone pair, disfavoring their deprotonation when the N-centered radical is formed, in contrast to DIPEA. When utilizing DABCO we note similar yields compared to reactions employing DIPEA illustrating that XAT is not the operative mechanism.

In order to probe the rate of intermolecular XAT between the intermediate alkyl radical and the starting material, α-ω-dienes were employed as substrates capable of intramolecular radical cyclization prior to XAT. While both 1,5-hexadiene and 1,7-octadiene give primarily the monofunctionalized olefin, 1,6-heptadiene undergoes rapid intramolecular radical cyclization and subsequent XAT. This shows that halogen atom transfer must occur at a rate approximately
between $5.5 \times 10^3$ and $2.3 \times 10^5$ based on literature precedent of kinetic data for analogous radical cyclizations under the reaction conditions. (Figure 5.18C)

**Figure 5.18 Mechanistic Investigations**

<table>
<thead>
<tr>
<th>A) Direct Photosensitization of EDA Complex</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram of A) Direct Photosensitization of EDA Complex" /></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>B) Excluding a-Amino Radical Mediated XAT Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram of B) Excluding a-Amino Radical Mediated XAT Mechanism" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C) $\alpha$-$\omega$-Dienes as In-Situ Radical Clocks for XAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Diagram of C) $\alpha$-$\omega$-Dienes as In-Situ Radical Clocks for XAT" /></td>
</tr>
</tbody>
</table>

These mechanistic data lead to the proposal of the following catalytic cycle. First, formation of an EDA complex enables either direct excitation through irradiation or triplet sensitization by the excited state photocatalyst to form an electrophilic $\alpha$-imido radical. Then rapid radical addition leads to an electron-rich alkyl radical. This abstracts a bromine-atom from another equivalent of starting material to furnish ATRA product and another equivalent of electrophilic radical. (Figure 5.19)
5.7 Summary

Herein we have disclosed a novel method for the [3+2] synthesis of γ-lactams from α-Br-imides and unactivated olefins. This complements previous syntheses through the use of novel electrophilic radical precursors that do not require additional activating functionality that limits the possible substitution patterns of the γ-lactam product. Mechanistic investigations reveal a novel activation pathway for α-halo-carbonyl compounds through triplet sensitization or direct photoinduced electron transfer through an in-situ formed EDA complex. Further investigations into enabling olefin difunctionalizations by leveraging this facile radical addition are underway.

5.8 References


Appendix A

SUPPLEMENTARY DATA FOR CHAPTER 2

Regioselective Alkylation Cross-Coupling of Remote Unactivated C(sp3)–H Bonds

Author: Scott M. Thullen, Sean M. Treacy, Tomislav Rovis
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Publisher: American Chemical Society
Date: Sep 1, 2019

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Supporting Information

Regioselective Alkylation of Remote Unactivated Csp³-H Bonds
Scott M. Thullen, Sean M. Treacy, and Tomislav Rovis*
Department of Chemistry, Columbia University
*tr2504@columbia.edu

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CHARACTERIZATION DATA OF PRODUCTS: ............................................. 103
NMR SPECTRA: .................................................................................. 119
Materials and Methods:

Unless otherwise noted, all reactions were performed in oven-dried glassware and carried out under an atmosphere of argon or nitrogen with magnetic stirring. All photochemical reactions were run in 1.0 dram vials fitted with Teflon caps under irradiation from a Blue H150 Kessil 35W LED lamp with Teflon stir-bars under vigorous magnetic stirring. All photochemical reactions were set-up in a nitrogen glovebox, though can also be performed with suitable All column chromatography was performed using a Teledyne Isco CombiFlash using CombiFlash gold pre-packed columns outfitted with an ELSD detector. As most of the compounds listed do not exhibit an UV trace, ELSD was integral to the separation of product while thin layer chromatography was performed on SiliCycle® 250 µm 60 Å plates. Visualization was accomplished with 254 nm UV light, Seebach’s stain, or I2.

1H NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers at ambient temperature. Chemical shift is reported in parts per million (ppm) from CDCl3 (7.26 ppm) with multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet) and coupling constants (Hz). 13C NMR was recorded on Bruker 500 MHz spectrometers (125 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl3 (77.2 ppm). Mass spectra were recorded on an Agilent 7890B GC System 5977B MSD GCMS with an EI ionization method. Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer.

Unless otherwise mentioned, all starting materials were obtained from commercial sources including Sigma-Aldrich, TCI, Matrix, Alfa-Aesar, and Oakwood Scientific. Anhydrous Ni(glyme)Cl2, 4,4'-di-methyl-2,2'-dipyridyl, anhydrous acetonitrile, and anhydrous K3PO4 were obtained from Millipore-Sigma. Ni(COD)2 was obtained through Strem. Photocatalysts used in this studied were either synthesized through known methods or bought from commercial sources. [Ir(dF-CF3ppy)(dtbbpy)]PF6, in particular, was synthesized according to a reported literature procedure or purchased from Aspira Scientific.
Extended Optimization Studies:

Table S1: Photocatalyst optimization

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} & \quad \text{Br} & \quad \text{Ni(cod)\textsubscript{2}}, \text{dtbbpy} & \quad \text{Photocatalyst} & \quad \text{K}_3\text{PO}_4, \text{MeCN}, 36 \text{ h} & \quad \text{F}_3\text{C} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} & \quad \text{Ph} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Photocatalyst (1 mol%)</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ir(dF-CF\textsubscript{3}ppy)\textsubscript{2}dtbbpy]PF\textsubscript{6}\textsuperscript{−}</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>4Cz-IPN (5 mol%):</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>4Cz-TPN (5 mol%):</td>
<td>52%</td>
</tr>
<tr>
<td>4</td>
<td>[Ir(ppy)\textsubscript{2}dtbbpy]PF\textsubscript{6}\textsuperscript{−}</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>[Ir((dF-Me)ppy)\textsubscript{2}dtbbpy]PF\textsubscript{6}\textsuperscript{−}</td>
<td>54%</td>
</tr>
<tr>
<td>6</td>
<td>[Ir((dF-CF\textsubscript{3})ppy)\textsubscript{2}(5,5′-dCF\textsubscript{3}bpy)]PF\textsubscript{6}\textsuperscript{−}</td>
<td>61%</td>
</tr>
<tr>
<td>7</td>
<td>Ru(bpy\textsubscript{3})Cl\textsubscript{2}\textsuperscript{−}</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>Ir(ppy)\textsubscript{2}</td>
<td>0%</td>
</tr>
</tbody>
</table>

Table S2: Nickel Precatalyst Optimization

\[
\begin{align*}
\text{F}_3\text{C} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} & \quad \text{Br} & \quad \text{Ni Source}, \text{dtbbpy} & \quad [\text{Ir(dF-CF\textsubscript{3}ppy)\textsubscript{2}dtbbpy}]PF\textsubscript{6}\textsuperscript{−} & \quad \text{K}_3\text{PO}_4, \text{MeCN}, 36 \text{ h} & \quad \text{F}_3\text{C} & \quad \text{N} & \quad \text{Me} & \quad \text{Me} & \quad \text{Ph} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nickel Source (10 mol%)</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Ni(cod)\textsubscript{2}</td>
<td>63%</td>
</tr>
<tr>
<td>2</td>
<td>Ni(glyme)\textsubscript{2}Cl\textsubscript{2}</td>
<td>78%</td>
</tr>
<tr>
<td>3</td>
<td>Ni(acac)\textsubscript{2}</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>NiBr\textsubscript{2}</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Ni(OAc)\textsubscript{2}4H\textsubscript{2}O</td>
<td>43%</td>
</tr>
<tr>
<td>6</td>
<td>Ni(PPh\textsubscript{3})\textsubscript{2}Cl\textsubscript{2}</td>
<td>20%</td>
</tr>
</tbody>
</table>
Table S3: Ligand Optimization

\[
\begin{array}{ccc}
\text{F}_3\text{C} & \text{O} & \text{N} \\
\text{Me} & \text{H} & \text{Me} \\
\hline
\text{Ph} & \text{Br} & \text{Ni(glyme)Cl}_2, \text{Ligand} \\
\text{[Ir(dF-CF}_3\text{ppy)}_2\text{dtbbpy}]PF_6} & \text{K}_3\text{PO}_4, \text{MeCN, 36 h} & \text{F}_3\text{C} \\
\text{O} & \text{N} & \text{Me} \\
\text{Me} & \text{H} & \text{Me} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>bpy</td>
<td>62%</td>
</tr>
<tr>
<td>2</td>
<td>dtbbpy</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>(4,4′-dMe)bpy</td>
<td>76%</td>
</tr>
<tr>
<td>4</td>
<td>(6, 6′-dMe)bpy</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>acridine</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>2, 9-neocuproin</td>
<td>0%</td>
</tr>
<tr>
<td>7</td>
<td>Bathocuproin</td>
<td>0%</td>
</tr>
<tr>
<td>8</td>
<td>(diBn-BOX)</td>
<td>0%</td>
</tr>
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</table>

Table S4: Relative Equivalents

\[
\begin{array}{ccc}
\text{F}_3\text{C} & \text{O} & \text{N} \\
\text{Me} & \text{H} & \text{Me} \\
\hline
\text{Ph} & \text{Br} & \text{Ni(glyme)Cl}_2, (4,4′\text{dMe})bpy \\
\text{[Ir(dF-CF}_3\text{ppy)}_2\text{dtbbpy}]PF_6} & \text{K}_3\text{PO}_4, \text{MeCN, 36 h} & \text{F}_3\text{C} \\
\text{O} & \text{N} & \text{Me} \\
\text{Me} & \text{H} & \text{Me} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equivalents of alkyl bromide</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>30%</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>55%</td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>15%</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>12%</td>
</tr>
<tr>
<td>6</td>
<td>2 (2 aliquots, start, 18 h)</td>
<td>36%</td>
</tr>
<tr>
<td>7</td>
<td>2 (4 aliquots, start, 6 h, 12 h, 18 h, 24 h)</td>
<td>32%</td>
</tr>
</tbody>
</table>
Starting Material Synthesis and characterization Data:

Procedure A: To a stirring solution of amine (5 mmol) in dichloromethane (50 mL, 0.1 M), triethylamine (10 mmol, 2.0 equiv) was added under N₂. The resulting solution was cooled with an ice bath and trifluoroacetic anhydride (5.5 mmol, 1.1 equiv) was added dropwise. After complete addition, the reaction was warmed to room temperature and the solution was allowed to stir for 12 hours. The reaction was quenched with slow addition of 1 M HCl and extracted with dichloromethane (3 x 10 mL). The organic layer was then washed with concentrated NaHCO₃ (50 mL) before being passed through a short silica plug and concentrated to afford the intended trifluoroacetamide without need for further chromatography.

1a - 2,2,2-trifluoro-N-(heptan-2-yl)acetamide
Prepared using procedure A from commercially available heptan-2-amine.
Yield 82%

1H NMR (500 MHz, Chloroform-d) δ 6.01 (s, 1H), 4.02 (dq, J = 8.5, 6.6 Hz, 1H), 1.63 – 1.43 (m, 2H), 1.37 – 1.25 (m, 6H), 1.21 (d, J = 6.6 Hz, 3H), 0.96 – 0.82 (m, 3H).

13C NMR (126 MHz, Chloroform-d) δ 156.65 (q, J = 36.7 Hz), 116.08 (q, J = 288.2 Hz), 46.71, 36.51, 31.64, 25.65, 22.66, 20.57, 14.13.

19F NMR (471 MHz, Chloroform-d) δ -75.12.

IR (film) νmax 3293, 3099, 2960, 2932, 2862, 1696, 1556, 1156, 1182, 724
LRMS (EI) m/z calculated 211.12, found 211.2

1b - 2,2,2-trifluoro-N-hexylacetamide
Prepared using procedure A from commercially available hexylamine. Structure previously reported by Xu et al.²
Yield 90%

1c - 2,2,2-trifluoro-N-pentylacetamide
Prepared using procedure A from commercially available pentylamine. Structure previously reported by Milan et al.¹
Yield 92%

1d - 2,2,2-trifluoro-N-(2-methylhexan-2-yl)acetamide
Prepared according to previously published procedure from Chu et al.³
Yield 17% (3 steps)
1e - 2,2,2-trifluoro-N-octylacetamide
Prepared using procedure A from commercially available octylamine. Structure previously reported by Xu et al. Yield 88%

1f - N-(2-ethylhexyl)-2,2,2-trifluoroacetamide
Prepared using procedure A from commercially available 2-ethylhexan-1-amine. Yield 83%

1g - ethyl 3-(2,2,2-trifluoroacetamido)heptanoate
Prepared using procedure A from commercially available ethyl 3-aminoheptanoate. Yield 72%

1h - N-(1-((tert-butyldimethylsilyl)oxy)hexan-2-yl)-2,2,2-trifluoroacetamide
From commercially available 2-aminohexan-1-ol (1.00 g, 8.53 mmol) 1-((tert-butyldimethylsilyl)oxy)hexan-2-amine was prepared by the portionwise addition of 1.5 equivalents (1.93 g) tert-Butyldimethylsilyl Chloride to a stirring solution of amino alcohol in dichloromethane (1 M) at room temperature. After stirring for two hours, the reaction mixture was quenched with H2O and extracted three times with dichloromethane. The organic layers were combined and washed with H2O and brine and dried over Na2SO4. The solution was concentrated en vacuo to give 1-((tert-butyldimethylsilyl)oxy)hexan-2-amine which was carried through without further purification. 2h was prepared using procedure A from 1-((tert-butyldimethylsilyl)oxy)hexan-2-amine. Yield 63%
\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 6.52 (d, \(J = 9.1\) Hz, 1H), 3.98 (ddt, \(J = 10.5, 6.9, 3.2\) Hz, 1H), 3.78 – 3.57 (m, 2H), 1.65 – 1.53 (m, 2H), 1.34 (dddd, \(J = 17.2, 13.9, 6.9, 5.0\) Hz, 4H), 0.91 (s, 7H), 0.08 (d, \(J = 2.5\) Hz, 6H).

\(^13\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 156.63 (q, \(J = 36.5\) Hz), 115.97 (q, \(J = 287.8\) Hz), 63.48, 51.28, 30.75, 27.95, 25.73, 22.46, 18.18, 13.89, -5.62 (d, \(J = 7.2\) Hz).

\(^19\)F NMR (471 MHz, Chloroform-\(d\)) \(\delta\) -75.21.

IR (film) \(\nu_{\text{max}}\) 3305, 3104, 2932, 2859, 1702, 1557, 1161, 833, 774

LRMS (EI) \([\text{C}_{14}\text{H}_{28}\text{F}_3\text{NO}_2\text{Si}]\) m/z calculated 327.18 found 327.0

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 6.75 (s, 1H), 3.83 – 3.30 (m, 7H), 1.24 (t, \(J = 7.0\) Hz, 3H).

\(^13\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 157.21 (q, \(J = 37.0\) Hz), 115.64 (q, \(J = 287.6\) Hz), 67.80, 66.69, 39.75, 14.99.

\(^19\)F NMR (471 MHz, Chloroform-\(d\)) \(\delta\) -75.09.

IR (film) \(\nu_{\text{max}}\) 3308, 3100, 2980, 2939, 2875, 1706, 1556, 1153, 1117, 723

LRMS (ESI+APCI) \([\text{C}_{6}\text{H}_{10}\text{F}_3\text{NO}_2\text{]}\) m/z ([M+H]+) calculated 185.15 found 185.9

\(^1\)H NMR (500 MHz, Chloroform-\(d\)) \(\delta\) 6.21 (s, 1H), 3.43 – 3.33 (m, 2H), 1.75 – 1.63 (m, 3H), 1.52 – 1.43 (m, 2H), 1.35 – 1.10 (m, 3H), 1.00 – 0.87 (m, 2H).

\(^13\)C NMR (126 MHz, Chloroform-\(d\)) \(\delta\) 157.27 (q, \(J = 38.6, 37.6\) Hz), 116.05 (q, \(J = 287.8\) Hz), 38.07, 36.57, 35.42, 33.20, 26.55, 26.27.

\(^19\)F NMR (471 MHz, Chloroform-\(d\)) \(\delta\) -75.08.
IR (film) $\nu_{\text{max}}$ 3303, 3106, 2924, 2853, 1700, 1560, 1449, 1157, 723
LRMS (EI) [C$_{10}$H$_{16}$F$_3$NO] m/z calculated 223.12 found 223.1

1k-N(d) - $N$-(2-cyclohexylethyl)-2,2,2-trifluoroacetamide-d
Prepared through portion wise addition of KH (40.1 mg, 1.0 equiv.) to 10 mL THF solution of 223 mg (1mmol) 1k. The solution was allowed to stir for 6 hours under nitrogen atmosphere. The reaction was quenched via dropwise addition of DCl (1.0 M, Et$_2$O). The solvent was removed under reduced pressure to afford the N-deuterated product which was verified by the absence of the N-H signal in the $^1$H NMR spectrum.
Yield 96%
$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 3.43 – 3.33 (m, 2H), 1.75 – 1.63 (m, 3H), 1.52 – 1.43 (m, 2H), 1.35 – 1.10 (m, 3H), 1.00 – 0.87 (m, 2H).

1l - 2,2,2-trifluoro-$N$-(2-(tetrahydro-2H-pyran-4-yl)ethyl)acetamide
Prepared using procedure A from commercially available 2-(tetrahydro-2H-pyran-4-yl)ethan-1-amine.
Yield 88%
$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 6.73 (s, 1H), 3.96 – 3.90 (m, 2H), 3.42 – 3.31 (m, 4H), 1.67 – 1.48 (m, 5H), 1.29 (ddt, $J = 16.8, 10.7, 4.6$ Hz, 2H).
$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 157.47 (q, $J = 36.8$ Hz), 116.01 (q, $J = 287.8$ Hz), 67.91, 37.44, 36.06, 32.84, 32.66.
$^{19}$F NMR (471 MHz, Chloroform-d) $\delta$ -75.05.
IR (film) $\nu_{\text{max}}$ 3295, 3095, 2924, 2849, 1706, 1560, 1181, 1149, 1091, 722
LRMS (EI) [C$_{9}$H$_{14}$F$_3$NO$_2$] m/z calculated 223.12 found 223.1

1m - $N$-(2-cyclopentylethyl)-2,2,2-trifluoroacetamide
Prepared using procedure A from commercially available 2-cyclopentylethan-1-amine.
Yield 87%
$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 3.38 (dt, $J = 7.8, 6.0$ Hz, 2H), 1.85 – 1.75 (m, 3H), 1.67 – 1.49 (m, 6H), 1.18 – 1.04 (m, 2H).
$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 157.28 (q, $J = 36.6$ Hz), 116.06 (q, $J = 287.8$ Hz), 39.66, 37.73, 35.36, 32.71, 25.23.
$^{19}$F NMR (471 MHz, Chloroform-d) $\delta$ -75.09.
IR (film) $\nu_{\text{max}}$ 3304, 3102, 2950, 2868, 1700, 1559, 1181, 1152, 720, 691
LRMS (EI) [C$_{9}$H$_{14}$F$_3$NO] m/z calculated 209.10 found 209.2
**1n** - N-(2-cyclopentyl-2-phenylethyl)-2,2,2-trifluoroacetamide
Prepared using procedure A from commercially available 2-cyclopentyl-2-phenylethan-1-amine.
Yield 78%

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.34 (t, $J = 7.4$ Hz, 2H), 7.29 – 7.22 (m, 1H), 7.21 – 7.09 (m, 2H), 6.01 (s, 1H), 3.93 (ddd, $J = 13.5$, 7.2, 4.4 Hz, 1H), 3.31 (ddd, $J = 13.5$, 10.5, 4.6 Hz, 1H), 2.57 (td, $J = 10.4$, 4.5 Hz, 1H), 2.15 – 1.92 (m, 2H), 1.75 – 1.65 (m, 1H), 1.65 – 1.28 (m, 3H), 1.09 – 0.94 (m, 1H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 157.10 (q, $J = 36.7$ Hz), 141.71, 129.08, 128.04, 127.37, 115.89 (q, $J = 288.0$ Hz), 51.56, 44.57, 43.90, 31.80, 31.47, 25.53, 24.82.

$^{19}$F NMR (471 MHz, Chloroform-$d$) $\delta$ -75.28.

IR (film) $\nu_{\text{max}}$ 3310, 3105, 3030, 2952, 2869, 1703, 1556, 1452, 1160, 724, 700

LRMS (EI) [C$_{15}$H$_{18}$F$_3$NO] $m/z$ calculated 285.13 found 285.1

**1o** - (Z)-2,2,2-trifluoro-N-(octadec-9-en-1-yl)acetamide
Prepared using procedure A from commercially available (Z)-octadec-9-en-1-amine.
Yield 66%

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.30 (s, 1H), 5.39 – 5.30 (m, 2H), 3.35 (q, $J = 6.8$ Hz, 2H), 2.06 – 1.92 (m, 3H), 1.58 (p, $J = 7.2$ Hz, 2H), 1.41 – 1.18 (m, 23H), 0.88 (t, $J = 6.9$ Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 157.33 (q, $J = 36.6$ Hz), 130.22, 129.90, 116.07 (q, $J = 287.8$ Hz), 40.18, 32.09, 29.95, 29.88, 29.84, 29.71, 29.51, 29.50, 29.34, 29.29, 29.14, 27.40, 27.34, 26.84, 22.86, 14.28.

$^{19}$F NMR (471 MHz, Chloroform-$d$) $\delta$ -75.07.

IR (film) $\nu_{\text{max}}$ 3305, 3107, 2924, 2855, 1703, 1557, 1464, 1182, 1163, 722

LRMS (EI) [C$_{20}$H$_{36}$F$_3$NO] $m/z$ calculated 363.27, found 363.3

**1p** - 2,2,2-trifluoro-N-(5-methylhexan-2-yl)acetamide
Prepared using procedure A from commercially available 5-methylhexan-2-amine. Prepared according to previously published procedure from Chu et al.³
Yield 75%

101
Standard Reaction Conditions:

To an oven-dried vial, [Ir(dF-CF$_3$ppy)$_2$dtbbpy]PF$_6$ (0.001 mmol, 0.01 equiv.), 4, 4'-dimethyl-2, 2'-bipyridine (0.012 mmol, 0.12 equiv.), trifluoroacetamide (0.1 mmol, 1 equiv.), and K$_3$PO$_4$ (0.4 mmol, 4 equiv) were added sequentially. The vial was charged with a stir bar and transferred to a glovebox, where the solids were backfilled with an inert atmosphere. In the glovebox, Ni(glyme)Cl$_2$ (0.01 mmol, 0.1 equiv) was added followed by anhydrous acetonitrile (0.75 mL, 0.13 M) and the reaction was stirred for roughly 5 minutes to insure complexation between nickel and the ligand. Subsequently add alkyl bromide (0.11 mmol, 1.1 equiv.) and seal tightly. Place ~2-6 inches from a blue Kessil lamp and irradiate and stir for 36 hours at room temperature. Upon completion, reactions were run through a short silica plug and concentrated in vacuo. Products were purified using flash column chromatography using EtOAc:Hexanes as an eluent.
Characterization Data of Products:

### 3aa - ethyl 5-ethyl-8-(2,2,2-trifluoroacetamido)nonanoate
Prepared using procedure B from compound 2c.
Yield 65% 1:1 dr
Mix of diastereomers ~2:1 Maj:Min, 1H peaks unresolved. $^{13}$C Major diastereomer selected

**$^1$H NMR (500 MHz, Chloroform-**$d$**): $\delta$ 6.20 (d, $J$ = 8.6 Hz, 1H), 4.20 – 3.90 (m, 3H), 2.30 – 2.22 (m, 2H), 1.62 – 1.52 (m, 2H), 1.50 – 1.43 (m, 1H), 1.41 – 1.18 (m, 14H), 0.89 – 0.80 (m, 3H).

**$^{13}$C NMR (126 MHz, Chloroform-**$d$**): $\delta$ 173.88, 156.62 (q, $J$ = 36.6 Hz), 116.05 (q, $J$ = 288.2 Hz), 60.44, 44.72, 40.99, 35.67, 34.62, 34.17, 32.91, 21.81, 20.95, 19.59, 14.46, 14.38.

**$^{19}$F NMR (471 MHz, Chloroform-**$d$**): $\delta$ -75.13.

**IR (film)** $\nu_{max}$ 3309, 3096, 2960, 2932, 2873, 1700, 1553, 1155, 724

**LRMS (EI)** [C$_{15}$H$_{26}$F$_3$NO$_3$] m/z calculated 325.19, found 325.2

### 3ba - ethyl 5-ethyl-8-(2,2,2-trifluoroacetamido)octanoate
Prepared using procedure B from compound 2b.
Yield 46%

**$^1$H NMR (500 MHz, Chloroform-**$d$**): $\delta$ 6.46 (s, 1H), 4.12 (q, $J$ = 7.1 Hz, 2H), 3.34 (q, $J$ = 6.8 Hz, 2H), 2.28 (t, $J$ = 7.3 Hz, 2H), 1.57 (ddt, $J$ = 14.5, 11.9, 7.3 Hz, 3H), 1.31 – 1.22 (m, 92H), 0.86 – 0.81 (m, 3H).

**$^{13}$C NMR (126 MHz, Chloroform-**$d$**): $\delta$ 174.01, 157.38 (q, $J$ = 36.9 Hz), 116.07 (q, $J$ = 287.9 Hz), 60.46, 40.48, 38.41, 34.68, 32.45, 29.95, 26.18, 22.04, 14.41, 10.92.

**$^{19}$F NMR (471 MHz, Chloroform-**$d$**): $\delta$ -75.05.

**IR (film)** $\nu_{max}$ 3322, 3102, 2919, 2854, 1705, 1554, 1155, 1035, 724

**LRMS (EI)** [C$_{14}$H$_{24}$F$_3$NO$_3$] m/z calculated 311.17, found 311.1

### 3ca - ethyl 5-methyl-8-(2,2,2-trifluoroacetamido)octanoate
Prepared using procedure B from compound 2a.
Yield 55%

**$^1$H NMR (500 MHz, Chloroform-**$d$**): $\delta$ 6.51 (s, 1H), 4.11 (q, $J$ = 7.1 Hz, 2H), 3.38 – 3.28 (m, 2H), 2.27 (ddd, $J$ = 7.8, 7.1, 2.3 Hz, 2H), 1.66 – 1.51 (m, 4H), 1.48 – 1.40 (m, 1H), 1.39 – 1.21 (m, 6H), 1.21 – 1.08 (m, 2H), 0.88 (d, $J$ = 6.6 Hz, 3H).

**$^{13}$C NMR (126 MHz, Chloroform-**$d$**): $\delta$ 174.00, 157.38 (q, $J$ = 36.8 Hz), 116.06 (q, $J$ = 287.8 Hz), 60.43, 40.39, 36.27, 34.63, 33.72, 32.34, 26.55, 22.45, 19.52, 14.40.
19F NMR (471 MHz, Chloroform-d) δ -75.05.  
IR (film) $\nu_{\text{max}}$ 3324, 3102, 2935, 2873, 1706, 1554, 1156, 1034, 722  
LRMS (EI) $[\text{C}_{13}\text{H}_{22}\text{F}_{3}\text{NO}_{3}]$ m/z calculated 297.16, found 297.1

\[
\text{3da} - \text{ethyl 5,8-dimethyl-8-(2,2,2-trifluoroacetamido)nonanoate}
\]
Prepared using procedure B from compound 2d.  
Yield 71%  
$^1$H NMR (500 MHz, Chloroform-d) δ 5.99 (s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.27 (t, $J = 7.4$ Hz, 2H), 1.70 – 1.57 (m, 4H), 1.40 (dz, 6H), 1.35 – 1.21 (m, 8H), 0.85 (t, $J = 7.1$ Hz, 3H).  
$^{13}$C NMR (126 MHz, Chloroform-d) δ 173.77, 156.17 (q, $J = 35.7$ Hz), 115.79 (q, $J = 35.7$ Hz), 60.45, 56.04, 43.60, 35.15, 34.64, 34.42, 27.46, 27.07, 26.94, 22.18, 14.42, 10.77.  
$^{19}$F NMR (471 MHz, Chloroform-d) δ -75.35.  
IR (film) $\nu_{\text{max}}$ 3330, 3086, 2966, 2936, 2876, 1711, 1551, 1179, 1152, 723  
LRMS (EI) $[\text{C}_{15}\text{H}_{26}\text{F}_{3}\text{NO}_{3}]$ m/z calculated 325.19, found 325.3

\[
\text{3ea} - \text{ethyl 5-(3-(2,2,2-trifluoroacetamido)propyl)nonanoate}
\]
Prepared using procedure B from compound 2e.  
Yield 51%  
$^1$H NMR (500 MHz, Chloroform-d) δ 6.46 (s, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.37 (q, $J = 6.8$ Hz, 2H), 2.30 (t, $J = 7.3$ Hz, 2H), 2.25 – 1.90 (m, 1H), 1.64 – 1.51 (m, 3H), 1.44 – 1.16 (m, 14H), 0.91 (t, $J = 7.0$ Hz, 3H).  
$^{13}$C NMR (126 MHz, Chloroform-d) δ 174.03, 157.38 (q, $J = 36.5$ Hz), 116.08 (q, $J = 288.1$ Hz), 60.47, 40.50, 36.98, 34.69, 33.20, 32.93, 30.40, 29.01, 26.15, 23.20, 22.02, 14.42, 14.27.  
$^{19}$F NMR (471 MHz, Chloroform-d) δ -75.04.  
IR (film) $\nu_{\text{max}}$ 3321, 3102, 2929, 2861, 1705, 1554, 1156, 722  
LRMS (EI) $[\text{C}_{16}\text{H}_{30}\text{F}_{3}\text{NO}_{3}]$ m/z calculated 339.20, found 339.2

\[
\text{3fa} - \text{ethyl 5-ethyl-7-((2,2,2-trifluoroacetamido)methyl)nonanoate}
\]
Prepared using procedure B from compound 2f.  
Yield 63% 1:1 dr  
$^1$H NMR (500 MHz, Chloroform-d) δ 6.42 (s, 1H), 4.12 (qd, $J = 7.2$, 1.4 Hz, 2H), 3.41 – 3.12 (m, 2H), 2.36 – 2.21 (m, 2H), 1.68 – 1.47 (m, 3H), 1.40 – 1.08 (m, 12H), 0.99 – 0.78 (m, 6H).
$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.90, 157.69 (q, $J = 18.6$ Hz), 116.13 (q, $J = 287.9$ Hz), 60.51, 43.26, 41.79, 38.09, 35.88, 34.56, 32.90, 26.00, 24.72, 21.68, 20.98, 14.38, 10.77.
$^{19}$F NMR (471 MHz, Chloroform-$d$) $\delta$ -74.92, -75.01.
IR (film) $\nu_{\text{max}}$ 3321, 3104, 2961, 2932, 2875, 1705, 1554, 1156, 1032, 723
LRMS (EI) [C$_{16}$H$_{28}$F$_{3}$NO$_{3}$] m/z calculated 339.20, found 339.2

3ga - diethyl 6-methyl-3-(2,2,2-trifluoroacetamido)decanedioate
Prepared using procedure B from compound 2g.
Yield 67% 1:1 dr

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.19 (s, 1H), 4.33 (m, 1H), 4.26 – 3.97 (m, 4H), 2.67 – 2.52 (m, 2H), 2.28 (tt, $J = 7.4$, 2.3 Hz, 4H), 1.68 – 1.50 (m, 4H), 1.48 – 1.39 (m, 1H), 1.39 – 1.30 (m, 2H), 1.30 – 1.21 (m, 8H), 0.88 – 0.77 (m, 3H).

13C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.81, 171.72, 156.74 (q, $J = 36.8$ Hz), 116.03 (q, $J = 288.0$ Hz), 61.27, 60.44, 45.02, 37.93, 37.48, 35.69, 34.57, 32.59, 32.14, 25.71, 21.78, 14.27, 10.57.
$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -76.09, -76.12.
IR (film) $\nu_{\text{max}}$ 3317, 2932, 2860, 1708, 1553, 1158, 911, 729, 648
LRMS (EI) [C$_{17}$H$_{38}$F$_{3}$NO$_{5}$Si] m/z calculated 383.19, found 383.2

3ha - ethyl 9-((tert-butyldimethylsilyl)oxy)-5-methyl-8-(2,2,2-trifluoroacetamido)nonanoate
Prepared using procedure B from compound 2h.
Yield 49% 1:1 dr
3:1 mix of diastereomers isolated

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 6.46 (d, $J = 8.8$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 4.08 (td, $J = 7.4$, 6.5, 3.5 Hz, 1H), 3.74 – 3.58 (m, 2H), 2.33 – 2.26 (m, 2H), 1.68 – 1.49 (m, 4H), 1.45 – 1.31 (m, 5H), 1.27 (t, $J = 7.1$ Hz, 3H), 0.96 – 0.82 (m, 12H), 0.08 (d, $J = 1.7$ Hz, 6H).

13C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.65, 156.55 (q, $J = 36.7$ Hz), 115.94 (q, $J = 288.2$ Hz), 63.74, 60.24, 49.29, 35.29, 34.72, 34.50, 32.56, 32.28, 25.74, 21.73, 18.18, 14.25, 10.43, -5.59 (d, $J = 12.2$ Hz).
$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -76.09, -76.12.
IR (film) $\nu_{\text{max}}$ 3317, 2932, 2860, 1708, 1553, 1162, 838, 778, 726
LRMS (EI) [C$_{20}$H$_{38}$F$_{3}$NO$_{5}$Si] m/z calculated 441.61, found 442.3
3ia - ethyl 5-(2,2,2-trifluoroacetamido)ethoxy)hexanoate
Prepared using procedure B from compound 2i.
Yield 62%
$^1$H NMR (500 MHz, Chloroform-$d$) δ 6.93 (s, 1H), 4.16 (q, $J = 7.1$ Hz, 2H), 3.66 (ddd, $J = 9.3$, 5.9, 3.4 Hz, 1H), 3.57 (m, 2H), 3.52 – 3.43 (m, 2H), 2.34 (td, $J = 7.3$, 3.0 Hz, 2H), 1.78 – 1.66 (m, 2H), 1.60 – 1.45 (m, 2H), 1.28 (t, $J = 7.1$ Hz, 3H), 1.17 (d, $J = 6.1$ Hz, 3H).
$^{13}$C NMR (126 MHz, Chloroform-$d$) δ 173.64, 157.21 (q, $J = 37.0$ Hz), 115.89 (q, $J = 287.6$ Hz), 75.63, 65.71, 60.38, 40.07, 34.07, 20.82, 19.41, 14.22.
$^{19}$F NMR (471 MHz, Chloroform-$d$) δ -75.09.
IR (film) $\nu_{\text{max}}$ 3327, 3099, 2930, 2861, 1709, 1555, 1178, 1151, 722, 654, 549
LRMS (EI) $[\text{C}_{13}\text{H}_{22}\text{F}_{3}\text{NO}_{4}]$ m/z calculated 299.13, found 299.1

3ja - ethyl 5-((4-methylphenyl)sulfonamido)ethyl)-8-(2,2,2-trifluoroacetamido)octanoate
Prepared using procedure B from compound 2j.
Yield 49%
$^1$H NMR (500 MHz, Chloroform-$d$) δ 7.68 – 7.64 (m, 2H), 7.32 – 7.28 (m, 2H), 6.61 (s, 1H), 6.42 (s, 1H), 4.12 (q, $J = 7.1$ Hz, 2H), 3.37 (p, $J = 6.5$ Hz, 2H), 3.11 (p, 2H), 2.42 (s, 2H), 2.34 (t, $J = 7.2$ Hz, 2H), 1.89 – 1.76 (m, 2H), 1.63 – 1.53 (m, 4H), 1.36 (m, 5H), 1.25 (t, $J = 7.2$ Hz, 4H).
$^{13}$C NMR (101 MHz, Chloroform-$d$) δ 173.09, 157.26 (q, $J = 36.8$ Hz), 143.25, 136.56, 129.70, 127.09, 115.91 (q, $J = 287.9$ Hz), 60.54, 48.38, 47.85, 39.54, 31.10, 28.58, 28.25, 25.67, 25.57, 24.15, 21.48, 14.19.
$^{19}$F NMR (471 MHz, Chloroform-$d$) δ -74.99.
IR (film) $\nu_{\text{max}}$ 3327, 3101, 2924, 2856, 1706, 1554, 1159, 863, 722
LRMS (ESI+APCI) $[\text{C}_{21}\text{H}_{31}\text{F}_{3}\text{N}_{2}\text{O}_{5}]$ m/z ([M+H]$^+$) calculated 481.19 found 481.1

3ka - ethyl 4-((1S,2S)-2-(2,2,2-trifluoroacetamido)ethyl)cyclohexyl)butanoate
Prepared using procedure B from compound 1k.
Yield 68% >20:1 dr
$^1$H NMR (400 MHz, Chloroform-$d$) δ 6.67 (s, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.46 – 3.21 (m, 2H), 2.41 – 2.09 (m, 2H), 1.88 – 1.61 (m, 6H), 1.59 – 1.28 (m, 4H), 1.24 (t, $J = 7.2$ Hz, 3H), 1.22 – 1.15 (m, 2H), 1.14 – 0.91 (m, 4H).
$^1$C NMR (101 MHz, Chloroform-$d$) $\delta$ 174.15, 157.38 (q, $J = 36.5$ Hz), 116.09 (q, $J = 287.9$ Hz), 60.47, 41.06, 38.89, 37.96, 34.54, 32.66, 32.44, 31.85, 31.56, 26.16, 26.12, 21.30, 14.37.

$^1$F NMR (376 MHz, Chloroform-$d$) $\delta$ -75.95.

IR (film) $\nu_{\text{max}}$ 3320, 3101, 2924, 2856, 1706, 1554, 1159, 722

LRMS (EI) $[\text{C}_{16}\text{H}_{26}\text{F}_{3}\text{NO}_{3}]^{-}$ m/z calculated 337.19, found 337.2

$^{3}\text{la}$ - ethyl 4-((3S,4R)-4-(2,2,2-trifluoroacetamido)ethyl)tetrahydro-2H-pyran-3-yl)butanoate

Prepared using procedure B from compound 2l.

Yield 52% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.56 (s, 1H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.94 (qd, $J = 11.7$, 4.1 Hz, 2H), 3.43 – 3.31 (m, 3H), 3.12 – 3.03 (m, 1H), 2.37 – 2.21 (m, 2H), 2.02 – 1.88 (m, 2H), 1.75 – 1.65 (m, 2H), 1.58 – 1.42 (m, 3H), 1.41 – 1.31 (m, 3H), 1.26 (t, $J = 7.1$ Hz, 3H), 1.21 – 1.10 (m, 1H).

$^1$C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.81, 157.49 (q, $J = 36.8$ Hz), 116.06 (q, $J = 288.3$, 287.0 Hz), 71.91, 68.00, 60.64, 40.37, 37.53, 36.82, 34.35, 32.13, 31.45, 28.84, 21.68, 14.40.

$^1$F NMR (471 MHz, Chloroform-$d$) $\delta$ -74.99.

IR (film) $\nu_{\text{max}}$ 3307, 3092, 2928, 2854, 1709, 1555, 1153, 1096, 723

LRMS (EI) $[\text{C}_{15}\text{H}_{24}\text{F}_{3}\text{NO}_{4}]^{-}$ m/z calculated 480.19, found 481.1

$^{3}\text{ma}$ - ethyl 4-(2-(2,2,2-trifluoroacetamido)ethyl)cyclopentyl)butanoate

Prepared using procedure B from compound 2m.

Yield 58% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.32 (s, 1H), 4.13 (qd, $J = 7.1$, 4.0 Hz, 2H), 3.39 (dddt, $J = 36.6$, 20.2, 13.3, 6.6 Hz, 2H), 2.39 – 2.20 (m, 3H), 1.92 – 1.44 (m, 9H), 1.38 (p, $J = 9.4$, 8.8 Hz, 2H), 1.26 (td, $J = 7.1$, 3.7 Hz, 3H), 1.17 (dddd, $J = 21.3$, 19.3, 10.5, 6.2 Hz, 2H).

$^1$C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.94, 130.75, 130.29, 60.54, 38.10, 37.00, 35.15, 34.52, 33.45, 33.42, 32.84, 32.80, 32.76, 32.74, 32.09, 29.84, 29.68, 29.51, 29.38, 22.87, 21.93 (d, $J = 1.7$ Hz), 14.43, 14.30.

$^1$F NMR (471 MHz, Chloroform-$d$) $\delta$ -75.06.

IR (film) $\nu_{\text{max}}$ 3322, 3102, 2943, 2868, 1708, 1556, 1180, 1161, 723

LRMS (EI) $[\text{C}_{15}\text{H}_{24}\text{F}_{3}\text{NO}_{3}]^{-}$ m/z calculated 337.19, found 337.2

$^{3}\text{na}$ - ethyl 4-(2-(1-phenyl-2-(2,2,2-trifluoroacetamido)ethyl)cyclopentyl)butanoate

Prepared using procedure B from compound 2n.

Yield 37% >20:1:1:1 dr

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$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 7.35 (dd, $J$ = 8.1, 6.5 Hz, 2H), 7.32 – 7.25 (m, 1H), 7.18 – 7.12 (m, 2H), 6.07 (s, 1H), 4.17 (q, $J$ = 7.2 Hz, 2H), 3.96 (ddd, $J$ = 13.4, 10.7, 4.5 Hz, 1H), 2.79 (ddd, $J$ = 10.6, 8.2, 4.8 Hz, 1H), 2.35 (td, $J$ = 7.3, 5.3 Hz, 2H), 1.84 – 1.37 (m, 10H), 1.31 – 1.27 (m, 5H), 1.19 – 1.11 (m, 1H), 0.95 – 0.79 (m, 1H).

$^{13}$C NMR (101 MHz, Chloroform-$d$) $\delta$ 173.73, 156.97 (q, $J$ = 36.3, 35.8 Hz), 140.18, 128.79, 128.44, 127.24, 120.28 – 111.15 (q, $J$ = 287.7 Hz), 60.30, 49.14, 48.56, 43.91, 42.48, 35.67, 34.41, 31.81, 29.93, 24.06, 23.64, 14.26.

$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -76.13.

IR (film) $\nu_{\text{max}}$ 3324, 3088, 3029, 2938, 2868, 1711, 1554, 1177, 1160, 703

LRMS (EI) [C$_{21}$H$_{28}$F$_3$NO$_3$] m/z calculated 339.17, found 339.2

3oa - ethyl (Z)-5-(3-(2,2,2-trifluoroacetamido)propyl)nonadec-10-enoate
Prepared using procedure B from compound 2o.
Yield 35%

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.39 (s, 1H), 5.43 – 5.25 (m, 1H), 4.13 (qd, $J$ = 7.1, 1.7 Hz, 2H), 3.36 (dq, $J$ = 13.5, 6.8 Hz, 2H), 2.35 – 2.19 (m, 2H), 2.07 – 1.90 (m, 4H), 1.65 – 1.46 (m, 7H), 1.46 – 1.36 (m, 1H), 1.45 – 1.36 (m, 1H), 1.30 – 1.13 (m, 1H), 1.30 – 1.13 (m, 1H), 1.08 – 0.93 (m, 3H), 0.88 (t, $J$ = 6.8 Hz, 5H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 173.94, 130.75, 130.29, 60.54, 38.79, 37.00, 35.15, 34.52, 33.45, 32.84, 32.80, 32.76, 32.74, 32.09, 29.84, 29.68, 29.51, 29.38, 22.87, 21.93, 21.92, 14.43, 14.30.

$^{19}$F NMR (471 MHz, Chloroform-$d$) $\delta$ -75.04.

IR (film) $\nu_{\text{max}}$ 3320, 3106, 2923, 2854, 1700, 1557, 1161, 722

LRMS (ESI+APCI) [C$_{26}$H$_{46}$F$_3$NO$_3$] m/z ([M+H$^+$]) calculated 478.34 found 478.3

3kb - N-(2-(2-ethylcyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available bromoethane.
Yield 65% 14:1 trans:cis dr
Mix of diastereomers (1.6:1 isolated)

$^1$H NMR (400 MHz, Chloroform-$d$) $\delta$ 6.30 (s, 1H), 3.52 – 3.26 (m, 2H), 1.89 – 1.68 (m, 5H), 1.63 – 1.46 (m, 2H), 1.46 – 1.36 (m, 1H), 1.30 – 1.13 (m, 4H), 1.08 – 0.93 (m, 3H), 0.86 (t, $J$ = 7.5 Hz, 3H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 157.08 (q, $J$ = 36.4 Hz), 115.87 (q, $J$ = 287.9 Hz), 42.48, 38.79, 37.89, 33.02, 32.55, 31.68, 30.84, 26.07, 26.02, 25.58, 10.44.

$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -75.99, -76.01.

IR (film) $\nu_{\text{max}}$ 3302, 3106, 2923, 2855, 1700, 1557, 1179, 1157, 722

LRMS (EI) [C$_{12}$H$_{30}$F$_3$NO] m/z calculated 225.13, found 225.2
3kc - N-(2-(2-(cyclobutylmethyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available (Bromomethyl)cyclobutane.
Yield 42% >20:1 dr
1H NMR (500 MHz, Chloroform-d) δ 6.24 (s, 1H), 3.43 (ddt, J = 15.2, 10.6, 5.2 Hz, 1H), 3.30 (ddt, J = 13.0, 9.6, 6.3 Hz, 1H), 2.34 (qd, J = 8.3, 6.2 Hz, 1H), 2.01 (ddq, J = 22.6, 11.3, 3.9 Hz, 2H), 1.87 – 1.71 (m, 5H), 1.70 – 1.49 (m, 5H), 1.36 (dtt, J = 16.9, 8.3, 4.2 Hz, 1H), 1.17 (m, 3H), 1.01 (m, 3H), 0.89 (qd, J = 11.4, 10.8, 5.3 Hz, 1H).
13C NMR (101 MHz, Chloroform-d) δ 157.06 (q, J = 36.7 Hz), 115.88 (q, J = 287.9 Hz), 40.92, 39.97, 39.58, 37.95, 33.91, 32.75, 31.65, 29.71, 28.71, 25.92, 25.89, 18.64.
19F NMR (471 MHz, Chloroform-d) δ -75.05.
IR (film) νmax 3300, 3106, 2924, 2854, 1700, 1557, 1157, 1178, 722
LRMS (EI) [C15H24F3NO] m/z calculated 291.18, found 291.1

3kd - 2,2,2-trifluoro-N-(2-(4,4,4-trifluorobutyl)cyclohexyl)ethyl)acetamide
Prepared using procedure B from compound 1k and commercially available 4-bromo-1,1,1-trifluorobutane.
Yield 57% >20:1 dr
1H NMR (500 MHz, Chloroform-d) δ 6.24 (s, 1H), 3.44 (ddt, J = 13.6, 9.8, 5.5 Hz, 1H), 3.30 (ddt, J = 13.3, 9.2, 6.2 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.87 – 1.74 (m, 3H), 1.74 – 1.67 (m, 2H), 1.67 – 1.51 (m, 3H), 1.51 – 1.31 (m, 2H), 1.26 – 1.14 (m, 3H), 1.12 – 0.92 (m, 3H).
13C NMR (126 MHz, Chloroform-d) δ 157.31 (q, J = 36.9 Hz), 127.35 (d, J = 276.5 Hz), 116.02 (q, J = 287.9 Hz), 41.11, 39.37, 38.00, 34.24 (q, J = 28.3 Hz), 32.78, 32.46, 31.71, 31.36, 26.00 (d, J = 3.2 Hz), 19.00 (q, J = 3.0 Hz).
19F NMR (471 MHz, Chloroform-d) δ -65.43 (t, J = 10.9 Hz), -75.08.
IR (film) νmax 3450, 3305, 3106, 2926, 2858, 1701, 1557, 1253, 1180, 1151, 722, 658
LRMS (EI) [C14H21F6NO] m/z calculated 333.15, found 333.2

3ke - 2,2,2-trifluoro-N-(2-((2-octylcyclohexyl)ethyl)acetamide
Prepared using procedure B from compound 1k and commercially available 1-bromo-octane.
Yield 63% >20:1 dr
1H NMR (500 MHz, Chloroform-d) δ 6.21 (s, 1H), 3.43 (ddt, J = 15.3, 10.8, 5.5 Hz, 1H), 3.30 (ddt, J = 13.0, 9.6, 6.2 Hz, 1H), 1.83 – 1.72 (m, 2H), 1.68 (d, J = 7.9 Hz, 2H), 1.62 – 1.40 (m, 4H), 1.42 – 1.33 (m, 2H), 1.34 – 1.16 (m, 12H), 1.13 – 0.92 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H).
13C NMR (126 MHz, Chloroform-d) δ 157.24 (q, J = 36.5 Hz), 116.06 (d, J = 288.0 Hz), 41.44, 39.52, 38.12, 33.50, 32.83, 32.10, 31.87, 31.68, 30.33, 29.87, 29.53, 26.50, 26.19, 26.19, 22.87, 14.29.
19F NMR (471 MHz, Chloroform-d) δ -75.07.
IR (film) νmax 3300, 3106, 2922, 2854, 1700, 1558, 1161, 1180, 722
LRMS (EI) [C18H32F3NO] m/z calculated 335.24, found 335.3

3kf - N-(2-(2-(6-(tert-butyldimethylsilyl)oxy)hexyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available ((6-bromohexyl)oxy)(tert-butyldimethylsilyl)dimethylsiline.
Yield 48% >20:1 dr

1H NMR (500 MHz, Chloroform-d) δ 6.24 (s, 1H), 3.59 (t, J = 6.6 Hz, 2H), 3.47 – 3.38 (m, 1H), 3.30 (ddt, J = 13.0, 9.5, 6.3 Hz, 1H), 1.79 (ddt, J = 23.3, 13.4, 2.9 Hz, 3H), 1.72 – 1.64 (m, 2H), 1.54 – 1.42 (m, 3H), 1.41 – 1.15 (m, 9H), 1.15 – 0.91 (m, 5H), 0.89 (s, 9H), 0.04 (s, 5H).
13C NMR (126 MHz, Chloroform-d) δ 157.24 (q, J = 36.6 Hz), 116.05 (q, J = 288.0 Hz), 63.50, 41.41, 39.50, 38.10, 33.40, 33.04, 32.80, 31.84, 31.66, 30.07, 26.44, 26.17, 26.03, 18.57, -5.08.
19F NMR (471 MHz, Chloroform-d) δ -75.05.
IR (film) νmax 3307, 3105, 2928, 2856, 1703, 1207, 1164, 908, 834, 776, 731
LRMS (ESI+APCI) [C22H42F3N2O2Si] m/z ([M+H]+) calculated 438.29 found 438.3

3kg - N-(2-(2-(6-cyanohexyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available 7-bromoheptanenitrile.
Yield 48% >20:1 dr

1H NMR (500 MHz, Chloroform-d) δ 6.48 (s, 1H), 3.41 (ddt, J = 13.5, 10.4, 5.5 Hz, 1H), 3.28 (ddt, J = 13.0, 9.7, 6.2 Hz, 1H), 2.34 (t, J = 7.0 Hz, 2H), 1.85 – 1.61 (m, 7H), 1.51 – 1.27 (m, 4H), 1.19 (dddd, J = 10.4, 8.5, 4.6, 2.3 Hz, 2H), 1.11 – 0.91 (m, 2H).
13C NMR (126 MHz, Chloroform-d) δ 157.05 (q, J = 36.7 Hz), 119.96, 115.94 (q, J = 287.9 Hz), 41.37, 39.56, 38.14, 33.19, 32.89, 31.98, 31.81, 29.23, 28.73, 26.31, 26.02, 26.03, 25.49, 17.46.
19F NMR (471 MHz, Chloroform-d) δ -75.05.
IR (film) νmax 3318, 3104, 2923, 2854, 2252, 1707, 1556, 1179, 1159, 909, 729, 648
LRMS (EI) [C17H22F3N2O] m/z calculated 332.21, found 332.2
**3kh** - N-(2-(2-(3,7-dimethyl-6-en-1-yl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available (S)-8-bromo-2,6-dimethylcyclohexyl-2-ene. Yield 34% 20:1 trans:cis, 1:1 dr.

1H NMR (500 MHz, Chloroform-d) δ 6.22 (s, 1H), 5.10 (dddd, J = 7.1, 5.6, 2.9, 1.5 Hz, 1H), 3.54 – 3.36 (m, 1H), 3.30 (ddt, J = 13.1, 9.3, 6.3 Hz, 1H), 2.03 – 1.88 (m, 2H), 1.86 – 1.72 (m, 2H), 1.68 (d, J = 1.3 Hz, 2H), 1.60 (d, J = 1.3 Hz, 2H), 1.41 – 1.28 (m, 2H), 1.20 (ddt, J = 10.3, 6.2, 2.1 Hz, 1H), 1.12 (dtdd, J = 11.2, 7.5, 4.9, 3.1 Hz, 1H), 1.04 – 0.92 (m, 2H), 0.86 (dd, J = 8.6, 6.4 Hz, 3H).

13C NMR (126 MHz, Chloroform-d) δ 157.79 – 156.49 (m), 131.24, 125.16 (d, J = 1.6 Hz), 116.05 (d, J = 288.1 Hz), 41.76, 41.60, 39.46, 38.11, 37.58, 36.91, 33.71, 33.03, 32.92, 32.81, 30.64, 26.18, 25.90, 20.01, 19.64, 17.81.

19F NMR (471 MHz, Chloroform-d) δ -75.04.

IR (film) νmax 3302, 3105, 2921, 2854, 1702, 1562, 1161, 1180, 723.

LRMS (EI) [C20H34F3NO] m/z calculated 361.26, found 361.3.

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**3ki** - N-(2-(2-(1,3-dioxolan-2-yl)ethyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available 2-(2-bromoethyl)-1,3-dioxolane. Due to coelution with homocoupled bromide product with desired product, the integrations for some 1H NMR peaks have inflated integrations. The yield was adjusted according to normalized integrations.

Yield 61% >20:1 dr.

1H NMR (400 MHz, Chloroform-d) δ 6.37 (s, 1H), 5.10 – 4.69 (m, 2H), 4.00 – 3.90 (m, 4H), 3.90 – 3.78 (m, 4H), 3.48 – 3.23 (m, 2H), 1.89 – 1.75 (m, 2H), 1.68 (dddd, J = 12.1, 8.8, 5.2, 3.1 Hz, 6H), 1.46 (dddd, J = 7.6, 4.7, 3.4 Hz, 3H), 1.40 – 1.31 (m, 1H), 1.25 – 1.15 (m, 2H), 1.11 (ddd, J = 8.8, 6.1, 3.1 Hz, 1H), 0.98 (t, J = 11.0 Hz, 1H).

13C NMR (101 MHz, Chloroform-d) δ 157.26 (d, J = 36.7 Hz), 116.06 (d, J = 287.6 Hz), 104.68, 65.00, 40.99, 39.19, 38.01, 33.99, 32.62, 31.72, 31.45, 30.51, 26.07, 26.04, 24.17.

19F NMR (376 MHz, Chloroform-d) δ -75.94.

IR (film) νmax 3312, 3097, 2920, 2853, 1708, 1559, 1153, 1178, 1035, 721.

LRMS (EI) [C15H24F3NO3] m/z calculated 323.17, found 323.1.

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111
3kj - 2,2,2-trifluoro-N-(2-(4-phenylbutyl)cyclohexyl)ethyl)acetamide
Prepared using procedure B from compound 1k and commercially available (4-bromobutyl)benzene.
Yield 54% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-d) $\delta$ 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 6.27 (s, 1H), 3.40 (ddt, $J = 14.9, 9.9, 5.0$ Hz, 1H), 3.28 (ddt, $J = 13.1, 9.5, 6.3$ Hz, 1H), 2.62 (ddd, $J = 8.6, 6.7, 4.7$ Hz, 2H), 1.72-1.83 (m, 3H), 1.72 – 1.45

$^{13}$C NMR (126 MHz, Chloroform-d) $\delta$ 157.24 (q, $J = 36.6$ Hz), 142.89, 128.58, 128.41, 125.77, 116.04 (q, $J = 287.9$ Hz), 41.35, 39.45, 38.07, 36.07, 32.75, 31.95, 31.81, 31.67, 26.15, 26.14, 26.02.

$^{19}$F NMR (471 MHz, Chloroform-d) $\delta$ -75.02.
IR (film) $\nu_{max}$ 3304, 3087, 3063, 3027, 2923, 2854, 1701, 1559, 1159, 739, 724, 698
LRMS (EI) [C$_{20}$H$_{28}$F$_3$NO] m/z calculated 355.21, found 355.2

3kk - N-(2-((1S,2S)-2-(3-(1,3-dioxoisindolin-2-yl)propyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available 2-(3-bromopropyl)isoindoline-1,3-dione.
Yield 69% >20:1 dr

$^1$H NMR (400 MHz, Chloroform-d) $\delta$ 7.83 (dd, $J = 5.3, 3.1$ Hz, 2H), 7.71 (dd, $J = 5.4, 3.1$ Hz, 2H), 6.54 (s, 1H), 3.65 (t, $J = 6.7$ Hz, 2H), 3.36 (ddh, $J = 13.6, 7.5, 7.1$ Hz, 2H), 1.81 – 1.49 (m, 8H), 1.37 (dq, $J = 13.7, 8.0$ Hz, 1H), 1.25 – 1.06 (m, 5H), 0.98 (p, $J = 10.0$ Hz, 2H).

$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 168.74, 157.29 (q, $J = 36.7$ Hz), 134.14, 132.26, 123.36, 116.09 (q, $J = 288.0$ Hz), 40.57, 39.11, 38.44, 37.94, 32.58, 31.54, 31.37, 30.28, 25.94, 25.92, 25.25.

$^{19}$F NMR (376 MHz, Chloroform-d) $\delta$ -75.87.
IR (film) $\nu_{max}$ 3339, 3091, 2922, 2852, 2256, 1772, 1704, 1552, 1397, 1156, 909, 718, 529
LRMS (ESI+APCI) [C$_{21}$H$_{25}$F$_3$N$_2$O$_3$] m/z ([M+H]$^+$) calculated 411.18 found 411.2
3kl - N-(2-(2-(3-(1H-pyrrol-1-yl)propyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available 1-(3-bromopropyl)-1H-pyrole.
Yield 56% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 6.66 (t, $J = 2.1$ Hz, 2H), 6.20 (s, 1H), 6.13 (t, $J = 2.1$ Hz, 2H), 3.90 (ddd, $J = 13.4$, 7.0, 6.2 Hz, 1H), 3.81 (dt, $J = 13.8$, 7.1 Hz, 1H), 3.32 (ddt, $J = 13.3$, 10.5, 5.4 Hz, 1H), 3.21 (ddt, $J = 13.0$, 9.7, 6.3 Hz, 1H), 1.80 – 1.62 (m, 7H), 1.56 (ddt, $J = 13.0$, 6.6, 2.8 Hz, 1H), 1.43 (dddt, $J = 13.5$, 11.1, 5.5, 2.5 Hz, 1H), 1.31 – 0.93 (m, 9H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 157.20 (q, $J = 36.6$ Hz), 120.83, 116.05 (q, $J = 36.6$ Hz), 107.97, 49.99, 41.05, 39.13, 37.85, 32.55, 31.80, 31.69, 29.98, 28.19, 26.16, 26.16.

$^{19}$F NMR (471 MHz, Chloroform-$d$) $\delta$ -74.99.

IR (film) $\nu_{max}$ 3315, 3102, 2922, 2855, 1702, 1551, 1158, 1088, 721, 518
LRMS (EI) [C$_{17}$H$_{25}$F$_3$N$_2$O] m/z calculated 330.19, found 330.2

3km - N-(2-((1S,2S)-2-(4-bromophenethyl)cyclohexyl)ethyl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1k and commercially available 1-bromo-4-(2-bromoethyl)benzene.
Yield 43% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-$d$) $\delta$ 7.50 – 7.39 (m, 2H), 7.11 – 7.02 (m, 2H), 6.21 (s, 1H), 3.43 (ddt, $J = 15.3$, 10.5, 5.3 Hz, 1H), 3.30 (ddt, $J = 13.1$, 9.6, 6.3 Hz, 1H), 2.66 (dddt, $J = 13.8$, 10.7, 5.2 Hz, 1H), 2.46 (dddt, $J = 13.8$, 10.6, 6.2 Hz, 1H), 1.94 – 1.66 (m, 5H), 1.47 – 1.34 (m, 2H), 1.30 – 1.20 (m, 2H), 1.19 – 1.00 (m, 4H), 0.90 (h, $J = 6.9$, 5.4 Hz, 1H).

$^{13}$C NMR (126 MHz, Chloroform-$d$) $\delta$ 157.08 (q, $J = 36.6$ Hz), 141.75, 131.40, 130.09, 119.40, 115.84 (q, $J = 36.6$ Hz), 40.77, 39.26, 37.84, 35.13, 32.58, 32.15, 31.49, 31.30, 25.85, 25.82.

$^{19}$F NMR (376 MHz, Chloroform-$d$) $\delta$ -75.95.

IR (film) $\nu_{max}$ 3303, 3104, 2923, 2855, 1701, 1553, 1487, 1160, 1180, 1072, 1011, 802, 722
LRMS (EI) [C$_{18}$H$_{23}$BrF$_3$NO] m/z calculated 405.09/407.09, found 405.1/407.1
3kn - 2,2,2-trifluoro-N-(2-((2-methoxyphenethyl)cyclohexyl)ethyl)acetamide
Prepared using procedure B from compound 1k and commercially available 1-(2-bromoethyl)-2-methoxybenzene.
Yield 61% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-d) δ 7.21 – 7.15 (m, 1H), 7.12 (dd, $J = 7.4, 1.8$ Hz, 1H), 6.88 (td, $J = 7.4, 1.1$ Hz, 1H), 6.84 (dd, $J = 8.2, 1.2$ Hz, 1H), 6.19 (s, 1H), 3.81 (s, 3H), 3.42 – 3.27 (m, 2H), 2.67 (ddd, $J = 13.4, 11.2, 5.1$ Hz, 1H), 2.47 (ddd, $J = 13.4, 11.0, 5.7$ Hz, 1H), 1.92 – 1.67 (m, 6H), 1.49 – 1.33 (m, 2H), 1.27 – 1.09 (m, 5H), 1.06 – 0.96 (m, 1H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 157.53, 157.20 (q, $J = 36.7$ Hz), 131.47, 129.84, 127.12, 120.63, 116.05 (q, $J = 288.1$ Hz), 110.45, 55.40, 41.38, 39.15, 37.99, 33.71, 32.59, 31.81, 31.68, 27.08, 26.20, 26.18.

$^{19}$F NMR (471 MHz, Chloroform-d) δ -75.06.

IR (film) $\nu_{\text{max}}$ 3307, 3104, 2922, 2854, 1702, 1553, 1493, 1461, 1205, 1158, 1031, 750, 724

LRMS (EI) [C$_{19}$H$_{26}$F$_3$NO$_2$] $m/z$ calculated 357.19, found 357.2

3ko - 2,2,2-trifluoro-N-(2-((3-phenoxypropyl)cyclohexyl)ethyl)acetamide
Prepared using procedure B from compound 1k and commercially available (3-bromopropoxy)benzene.
Yield 54% >20:1 dr

$^1$H NMR (500 MHz, Chloroform-d) δ 7.28 (dd, $J = 8.7, 7.4$ Hz, 2H), 6.95 – 6.91 (m, 1H), 6.89 (dd, $J = 8.8, 1.1$ Hz, 2H), 6.21 (s, 1H), 4.02 – 3.88 (m, 2H), 3.42 (ddt, $J = 13.4, 10.2, 5.4$ Hz, 1H), 3.30 (ddt, $J = 13.1, 9.6, 6.4$ Hz, 1H), 1.75-1.91 (m, 4H), 1.62-1.74 (m, 4H), 1.46 – 1.18 (m, 4H), 1.18 – 0.91 (m, 4H).

$^{13}$C NMR (126 MHz, Chloroform-d) δ 159.14, 157.25 (q, $J = 36.8$ Hz), 129.62, 120.75, 117.18 (q, $J = 287.9$ Hz), 114.67, 68.19, 41.12, 39.42, 38.05, 32.71, 31.79, 31.64, 29.60, 26.14, 26.13, 26.08.

$^{19}$F NMR (471 MHz, Chloroform-d) δ -75.02.

IR (film) $\nu_{\text{max}}$ 3306, 3100, 3040, 2920, 2853, 1701, 1600, 1552, 1496, 1205, 1158, 1035, 753, 691, 512

LRMS (EI) [C$_{19}$H$_{26}$F$_3$NO$_2$] $m/z$ calculated 357.19, found 357.2
**3c** - N-(5-ethylhept-2-yl-6,6,7,7-d5)-2,2,2-trifluoroacetamide

Prepared using procedure B from compound 2c and commercially available bromoethane-d5.

Yield 42% 1:1 dr

**1H NMR** (400 MHz, Chloroform-d) δ 6.01 (s, 1H), 4.10 (hept, \( J = 6.6 \) Hz, 1H), 1.51 – 1.16 (m, 11H), 0.89 (t, \( J = 6.9 \) Hz, 3H).

**13C NMR** (101 MHz, Chloroform-d) δ 156.62 (q, \( J = 36.7 \) Hz), 116.09 (q, \( J = 288.1 \) Hz), 44.87, 40.85, 35.44, 29.89, 21.11, 20.54, 19.74, 14.53, 11.23 – 10.87 (m).

**19F NMR** (376 MHz, Chloroform-d) δ -76.08.

**IR (film)** \( \nu_{max} \) 3295, 3100, 2959, 2921, 2852, 2220, 2097, 2073, 1698, 1556, 1185, 1162, 725

**LRMS (EI)** [C\(_{11}\)H\(_{15}\)D\(_5\)F\(_3\)NO] m/z calculated 244.18, found 244.3

**4a** - ethyl 4-(3-(3-(1,3-dioxoisindolin-2-yl)propyl)-2-(2,2,2-trifluoroacetamido)ethyl)cyclohexyl)butanoate

Prepared using procedure B from compound 3kk and commercially available ethyl 4-bromobutanoate.

Yield 45% >20:1:1:1 dr

**1H NMR** (400 MHz, Chloroform-d) δ 7.85 (dd, \( J = 5.4, 3.0 \) Hz, 2H), 7.80 – 7.68 (m, 2H), 6.73 (s, 1H), 4.14 (q, \( J = 7.1 \) Hz, 2H), 3.79 – 3.64 (m, 2H), 3.31 (dtd, \( J = 23.6, 13.0, 6.4 \) Hz, 1H), 2.41 – 2.23 (m, 2H), 1.89 – 1.46 (m, 12H), 1.27 (t, \( J = 7.1 \) Hz, 4H), 1.24 – 1.11 (m, 3H), 1.02 – 0.83 (m, 3H).

**13C NMR** (101 MHz, Chloroform-d) δ 173.85, 168.66, 157.07 (q, \( J = 288.0 \) Hz), 133.97, 132.09, 123.19, 115.93 (q, \( J = 288.0 \) Hz), 60.27, 43.74, 39.88, 39.67, 38.18, 37.18, 34.43, 32.85, 31.90, 31.81, 30.69, 28.29, 25.69, 25.38, 21.57, 14.23.

**19F NMR** (376 MHz, Chloroform-d) δ -75.90.

**IR (film)** \( \nu_{max} \) 3339, 3090, 2927, 2858, 1771, 1705, 1553, 1397, 1370, 1177, 1155, 720

**LRMS (ESI+APCI)** [C\(_{27}\)H\(_{35}\)F\(_3\)N\(_2\)O\(_5\)] m/z ([M+H\(^+\)]) calculated 525.25, found 525.2
3cj - N-(5-ethyl-9-phenylnonan-2-yl)-2,2,2-trifluoroacetamide
Prepared using procedure B from compound 1c and commercially available (4-bromobutyl)benzene.
Yield 68% 1:1 dr
10:1 mixture of diastereomers isolated
\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 7.37 – 7.22 (m, 3H), 7.18 (d, \(J = 7.8\) Hz, 4H), 5.96 (s, 1H), 4.10 (p, \(J = 7.0\) Hz, 1H), 2.74 – 2.52 (m, 2H), 1.69 – 1.53 (m, 2H), 1.52 – 1.10 (m, 14H), 0.96 – 0.80 (m, 3H).
\(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 156.40 (q, \(J = 36.5\) Hz), 142.67, 128.39, 128.25, 125.62, 115.90 (q, \(J = 288.1\) Hz), 44.69, 41.14, 35.86, 35.73, 34.17, 33.30, 31.68, 25.93, 20.86, 19.49, 14.35.
\(^{19}\)F NMR (376 MHz, Chloroform-d) \(\delta\) -76.04.
IR (film) \(\nu_{max}\) 3294, 3088, 3027, 2929, 2858, 1696, 1556, 1455, 1158, 1182, 744, 725, 697
LRMS (EI) \([\text{C}_{19}\text{H}_{28}\text{F}_3\text{NO}]\) m/z calculated 343.21, found 344.2

4b - ethyl 4-ethyl-8-phenyl-4-(3-(2,2,2-trifluoroacetamido)butyl)octanoate
Synthesized according to conditions reported by Chu et al.,\(^3\) compound 3cj was reacted with commercially available ethyl acrylate.
Yield 61% 1:1 dr
\(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 7.19 (s, 1H), 4.33 (m, 1H), 4.26 – 3.97 (m, 4H), 2.67 – 2.52 (m, 2H), 2.28 (tt, \(J = 7.4, 2.3\) Hz, 4H), 1.68 – 1.50 (m, 4H), 1.48 – 1.39 (m, 1H), 1.39 – 1.30 (m, 2H), 1.30 – 1.21 (m, 8H), 0.88 – 0.77 (m, 3H).
\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 173.81, 171.72, 156.74 (q, \(J = 36.8\) Hz), 116.03 (q, \(J = 288.0\) Hz), 61.27, 60.44, 45.02, 37.93, 37.48, 35.69, 34.57, 32.59, 32.14, 25.71, 21.78, 14.27, 10.57.
\(^{19}\)F NMR (471 MHz, Chloroform-d) \(\delta\) -75.17, -75.22.
IR (film) \(\nu_{max}\) 3311, 3089, 2930, 2862, 1701, 1552, 1155, 1177, 724, 699
LRMS (EI) \([\text{C}_{24}\text{H}_{36}\text{F}_3\text{NO}_3]\) m/z calculated 443.26, found 443.3

5a - 2,2,2-trifluoro-N-(5-methylhex-5-en-2-yl)acetamide
Prepared using procedure B from compound 1p utilizing ethyl 4-bromobutanoate as an oxidant.
Yield 40%
\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 6.05 (s, 1H), 4.76 (s, 1H), 4.70 (s, 1H), 4.11 – 3.98 (m, 1H), 2.15 – 2.00 (m, \(J = 7.6\) Hz, 2H), 1.80 – 1.60 (m, 5H), 1.25 (d, \(J = 6.7\) Hz, 3H).
\(^{13}\)C NMR (101 MHz, Chloroform-d) \(\delta\) 156.66 (q, \(J = 37.0\) Hz), 144.66, 116.06 (q, \(J = 288.1\) Hz), 111.04, 46.53, 34.18, 34.05, 22.51, 20.45.
\(^{19}\)F NMR (376 MHz, Chloroform-d) \(\delta\) -76.05.
LRMS (EI) \([\text{C}_{9}\text{H}_{14}\text{F}_3\text{NO}]\) m/z calculated 209.10, found 209.1
1q - 2,2,2-trifluoro-N-(pentyl-4,4,5,5-d-)acetamide
Prepared from the commercially available 2-(pent-4-yn-1-yl)isoindoline-1,3-dione, (5.00 g, 23.4 mmol) which was subjected to ten percent Pd/C (2.5 grams, 2.34 mmol) in MeOH (0.05M) under an atmosphere of D₂ overnight at room temperature to form the corresponding alkane. The product was dried under vacuum and used for the subsequent step without further purification. The phthalimide alkane was then subjected to 3.5 equivalents (1.18 g, 23.4 mmol) hydrazine monohydrate in 150 mL EtOH at room temperature. The mixture was then refluxed overnight. Three equivalents (8.00 g, 70.2 mmol) of trifluoroacetic acid was then added. EtOH was then removed en vacuo and to the resulting white solid was added 50 mL 1 M NaOH in H₂O slowly. The mixture was then extracted with DCM three times, washed with brine and dried over Na₂SO₄. The solvent was removed by careful evaporation and the product was subjected to procedure A without further purification to form 1q.
Yield 15% (3 steps)

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta 6.20 (s, 1H), 3.36 (q, J = 6.8 Hz, 2H), 1.59 (tt, J = 8.4, 6.6 Hz, 2H), 1.32 (q, J = 9.4, 8.0 Hz, 2H), 0.88 (t, J = 7.4 Hz, 1H).

\(^2\)H NMR (61 MHz, Chloroform-d) \(\delta 1.30 (s, 2H), 0.88 (s, 2H).

3qa - ethyl 5-(methyl-d)-8-(2,2,2-trifluoroacetamido)octanoate-4,5,6,7-d4
Prepared using procedure B from compound 1q.

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta 6.39 (s, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.37 (td, J = 8.2, 2.8 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 1.68 – 1.48 (m, 6H), 1.37 – 1.18 (m, 7H), 0.93 – 0.75 (m, 1H).

\(^2\)H NMR (61 MHz, Chloroform-d) \(\delta 1.33 (s, 1H), 0.84 (s, 2H).
References:


NMR Spectra:

$^1$H-NMR
CDCl$_3$
500 MHz

$^1$a

$^{13}$C-NMR
CDCl$_3$
126 MHz

$^1$a
$^{13}$C-NMR
CDCl$_3$
126 MHz

$^{19}$F-NMR
CDCl$_3$
471 MHz
\( ^{19}\text{F-NMR} \)
\( \text{CDCl}_3 \)
\( 471 \text{ MHz} \)
\( 1\text{g} \)

\( ^{1}\text{H-NMR} \)
\( \text{CDCl}_3 \)
\( 500 \text{ MHz} \)
\( 1\text{h} \)
$^1$H-NMR
CDCl$_3$
500 MHz

1i

$^{13}$C-NMR
CDCl$_3$
126 MHz

1i
$^{13}$C-NMR
CDCl$_3$
101 MHz
$^1j$

$^{19}$F-NMR
CDCl$_3$
376 MHz
$^1j$
$^{1}H$-NMR
CDCl$_3$
500 MHz

$^{13}$C-NMR
CDCl$_3$
126 MHz
$^{19}$F-NMR
CDCl$_3$
471 MHz
1k

$^1$H-NMR
CDCl$_3$
500 MHz
1l
**13C-NMR**

CDCl$_3$

126 MHz

1I

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**19F-NMR**

CDCl$_3$

471 MHz

1I
$^1$H-NMR
CDCl$_3$
500 MHz

1m

$^{13}$C-NMR
CDCl$_3$
126 MHz

1m
13C-NMR
CDCl₃
126 MHz

19F-NMR
CDCl₃
471 MHz

1n
\[ 1^1H-NMR \]

\[ CDCl_3 \]

\[ 500 \text{ MHz} \]

\textbf{3da}
$^{1} \text{H-NMR}$
CDCl$_3$
500 MHz
$^{3} \text{ga}$

$^{13} \text{C-NMR}$
CDCl$_3$
126 MHz
$^{3} \text{ga}$
$^1$H-NMR
CDCl$_3$
400 MHz

3ka

$^{13}$C-NMR
CDCl$_3$
101 MHz

3ka
$^{19}$F-NMR
CDCl$_3$
376 MHz
3ka

$^1$H-NMR
CDCl$_3$
500 MHz
3la
19F-NMR
CDCl₃
471 MHz
3ma

1H-NMR
CDCl₃
400 MHz
3na
$^{13}$C-NMR
CDCl$_3$
101 MHz

3na

$^{19}$F-NMR
CDCl$_3$
376 MHz

3na
$^{13}$C-NMR
CDCl$_3$
126 MHz
3kb

$^{19}$F-NMR
CDCl$_3$
376 MHz
3kb


**1H-NMR**

CDCl$_3$

500 MHz

3kc

---

**13C-NMR**

CDCl$_3$

101 MHz

3kc
$^{19}$F-NMR
CDCl$_3$
471 MHz
3kc
$^{1}H$-NMR
CDCl$_3$
500 MHz
3kf

$^{13}$C-NMR
CDCl$_3$
126 MHz
3kf
**19F-NMR**

CDCl₃

471 MHz

3kh

---

**1H-NMR**

CDCl₃

400 MHz

3ki
$^{13}$C-NMR
CDCl$_3$
101 MHz
3ki

$^{19}$F-NMR
CDCl$_3$
376 MHz
3ki
\text{1H-NMR} \\
\text{CDCl}_3 \\
500 \text{ MHz} \\
3\text{kJ} \\
\text{13C-NMR} \\
\text{CDCl}_3 \\
126 \text{ MHz} \\
3\text{kJ}
$^{19}\text{F-NMR}$

CDCl$_3$

$471$ MHz

$3kl$

---

$^{1}\text{H-NMR}$

CDCl$_3$

$500$ MHz

$3km$

---

175
**1H-NMR**
**CDCl₃**
**400 MHz**

3ap

**13C-NMR**
**CDCl₃**
**101 MHz**

3ap
$^{19}$F-NMR
CDCl$_3$
376 MHz
3ap

$^2$H-NMR
CDCl$_3$
61 MHz
3cp
$^{19}$F-NMR
CDCl$_3$
376 MHz

4a

$^{1}$H-NMR
CDCl$_3$
400 MHz

3aj
$^{13}$C-NMR
CDCl$_3$
101 MHz
3aj

$^{19}$F-NMR
CDCl$_3$
376 MHz
3aj
$^{19}$F-NMR
CDCl$_3$
471 MHz
4b

$^1$H-NMR
CDCl$_3$
400 MHz
5a
$^{13}$C-NMR
CDCl$_3$
101 MHz
5a
$^1$H NMR
CDCl$_3$
400 MHz
1c-d$_4$

$^2$H NMR
CDCl$_3$
61 MHz
1c-d$_4$
$^1$H NMR
CDCl$_3$
400 MHz
3ca-d$_3$

$^2$H NMR
CDCl$_3$
3ca-d$_3$
61 MHz
Appendix B

SUPPLEMENTARY DATA FOR CHAPTER 3

Copper Catalyzed C(sp3)--H Bond Alkylation via Photoinduced Ligand-to-Metal Charge Transfer

Author: Sean M. Treacy, Tomislav Rovis
Publication: Journal of the American Chemical Society
Publisher: American Chemical Society
Date: Feb 1, 2021

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Supporting Information

Copper Catalyzed C(sp\(^3\))-H Bond Alkylation via Photoinduced Ligand to Metal Charge Transfer

Sean M. Treacy, and Tomislav Rovis*

Department of Chemistry, Columbia University

*tr2504@columbia.edu

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NMR SPECTRA: ........................................................................................................................................... 210
Materials and Methods:

Unless otherwise noted, all reactions were performed in oven-dried glassware and carried out under an atmosphere of nitrogen with magnetic stirring. All photochemical reactions were run in 1.0 dram vials fitted with Teflon caps under irradiation from a PR-160 Kessil 40W LED lamp with Teflon stir-bars under vigorous magnetic stirring. All photochemical reactions were set-up in a nitrogen glovebox, though can also be performed with suitable Schlenk-line techniques. All column chromatography was performed using a Teledyne Isco CombiFlash using CombiFlash pre-packed columns outfitted with an ELSD detector. As most of the compounds listed do not exhibit an UV trace, ELSD was integral to the separation of product while thin layer chromatography was performed on SiliCycle® 250 µm 60 Å plates. Visualization was accomplished with 254 nm UV light, Seebach’s stain, or I₂.

¹H NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers at ambient temperature. Chemical shift is reported in parts per million (ppm) from CDCl₃ (7.26 ppm) with multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet) and coupling constants (Hz). ¹³C NMR was recorded on Bruker 500 or 400 MHz spectrometers (126 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl₃ (77.2 ppm). Mass spectra were recorded on an Agilent 7890B GC System 5977B MSD GCMS with an EI ionization method. High resolution mass spectra (HRMS) were obtained from the Columbia University Chemistry Department Mass Spectrometry Facility on a Waters XEVO G2XS QToF mass spectrometer equipped with a UPC2 SFC inlet and a LockSpray source with one of the following three probes: electrospray ionization (ESI) probe, atmospheric pressure chemical ionization (APCI) probe, or atmospheric pressure solids analysis probe (ASAP). Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer.

Unless otherwise mentioned, all starting materials were obtained from commercial sources including Millipore-Sigma, TCI, and Alfa-Aesar. Anhydrous CuCl₂, anhydrous LiCl, and anhydrous acetonitrile were obtained from Millipore-Sigma.
Table S1. Extended Optimization Studies:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from Standard Conditions</th>
<th>Yield 3 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>93</td>
</tr>
<tr>
<td>2</td>
<td>3 equiv. cyclooctane</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>0% CuCl₂</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0% LiCl</td>
<td>79</td>
</tr>
<tr>
<td>5</td>
<td>in the dark</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>440 nm LED</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>30°C</td>
<td>45</td>
</tr>
<tr>
<td>8</td>
<td>under air</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>with 10% Cs₂CO₃</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>Irradiated 1 hour, then in the dark</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>3 mmol scale (10x)</td>
<td>86</td>
</tr>
<tr>
<td>12</td>
<td>1 equiv. cyclooctane</td>
<td>44</td>
</tr>
</tbody>
</table>

Table S2. Identifying the Catalytically Active Species: Conditions correspond to experiments conducted by Mereshchenko et. al.¹ Photochemical studies conducted by these authors reveal that both CuCl⁺ and CuCl₃⁻ are capable of photoreduction at varying wavelengths with quantum yields of ~6.0% and ~1.5 % respectively.

<table>
<thead>
<tr>
<th>Entry</th>
<th>% TBACI</th>
<th>Catalyst Formed In-situ</th>
<th>Yield 3da (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>CuCl⁺</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>60</td>
<td>CuCl₃⁻</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>200</td>
<td>CuCl₄²⁻</td>
<td>0</td>
</tr>
</tbody>
</table>
**Figure S1.** Absorbance spectrum of 60 μM CuCl₂ and 150 μM solution of LiCl in MeCN. This is 1000x dilution from catalytic conditions. The spectrum matches the spectrum produced by Mereshchenko *et. al.*

**Figure S2.** Absorbance spectrum of 60 μM CuCl₂ in MeCN. This is 1000x dilution from catalytic conditions.
**Figure S3.** Absorbance spectrum of 60 μM CuCl$_2$ and 150 μM solution of LiCl in MeCN after 2 hours of irradiation under 390 nm LED.

**Figure S4.** Absorbance spectrum of reaction mixture after 6 hours irradiation at 1000x dilution under N$_2$. 
Figure S5. Absorbance spectrum of reaction mixture after stirring open to air for 2 hours at 1000x dilution.

Figure S6. Image of Chlorocuprate solutions:

Left: 60 mM CuCl₂ in MeCN

Right: 60 mM CuCl₂ and 150 mM solution of LiCl
Figure S7. Image of Photoreactor:
Starting Material Synthesis and characterization Data:

Procedure adapted from reference 2.
To a solution of 7-hydroxy-4-methyl-2H-chromen-2-one (1.00 mmol) in DMF (5.0 mL) was added NEt₃ (180 uL, 1.30 mmol. The mixture was cooled in an ice bath after which acryloyl chloride (117 uL, 1.30 mmol) in DMF (1.0 mL) was added dropwise. The solution was allowed to warm to room temperature and stirred vigorously for 12 hours. Aq. NH₄Cl (5 mL) was then added followed by 10 mL of ethyl acetate. The organic layer was separated and the aqueous layer was extracted twice with ethyl acetate. (10 mL) The combined organic extractions were dried with MgSO₄ filtered and concentrated by rotary evaporation. The product was isolated by column chromatography using hexanes:ethyl acetate as the eluent.

1 - 4-methyl-2-oxo-2H-chromen-7-yl acrylate

Yield 90%

¹H NMR (400 MHz, Chloroform-d) δ 7.62 (d, J = 8.6 Hz, 1H), 7.17 (d, J = 2.2 Hz, 1H), 7.13 (dd, J = 8.6, 2.3 Hz, 1H), 6.65 (dd, J = 17.3, 1.1 Hz, 1H), 6.33 (dd, J = 17.3, 10.5 Hz, 1H), 6.27 (d, J = 1.3 Hz, 1H), 6.08 (dd, J = 10.5, 1.2 Hz, 1H), 2.44 (d, J = 1.2 Hz, 3H).

¹³C NMR (101 MHz, Chloroform-d) δ 163.94, 160.60, 154.36, 153.14, 152.00, 133.75, 127.49, 125.53, 118.17, 118.05, 114.73, 110.59, 18.86.

HRMS (ASAP+) [C₁₃H₁₁O₄] m/z calculated [M+H] 231.07, found 231.0680
Standard Reaction Conditions:

A) To an oven-dried 1-dram vial, CuCl$_2$ and LiCl were added. The vial was charged with a stir bar and transferred to a glovebox, where the solids were backfilled with an inert atmosphere. In the glovebox anhydrous acetonitrile was added (1 mL, 0.3 M) followed by the alkane (5 equiv.) and electron deficient olefin and sealed tightly. The vial was then placed ~3 inches from a 390 nm Kessil lamp to be irradiated and stirred for 36 hours at 60°C. Upon completion, silica was added to the reaction and then concentrated in vacuo. Products were purified using flash column chromatography using EtOAc:Hexanes as an eluent.

B) Identical to standard reaction conditions A but with 50% CuCl$_2$ and 1.25 equiv. of LiCl.

C) Identical to standard reaction conditions A but with only 3 equivalents of alkane.
Characterization Data of Products:

4 -ethyl 3-cyclopentylpropanoate
Prepared using standard reaction conditions A from cyclopentane.
Yield 90%
$^1$H (500 MHz, Chloroform-d) δ 4.12 (q, $J = 7.1$ Hz, 2H), 2.30 (t, $J = 7.8$ Hz, 2H), 1.82 – 1.70 (m, 3H), 1.67 – 1.56 (m, 4H), 1.55 – 1.46 (m, 2H), 1.25 (t, $J = 7.1$ Hz, 3H), 1.15 – 1.03 (m, 2H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 174.23, 60.35, 39.89, 33.92, 32.58, 31.36, 25.30, 14.44.
LRMS (EI) [C$_{10}$H$_{18}$O$_{2}$] m/z calculated 170.13, found 170.1
IR (film) $\nu$max 2948, 2866, 1735, 1178, 1036

5 -ethyl 3-cyclohexylpropanoate
Prepared using standard reaction conditions A from cyclohexane.
Yield 92%
$^1$H NMR (400 MHz, CDCl$_3$) δ 4.12 (q, $J = 7.1$ Hz, 2H), 2.29 (t, $J = 7.9$ Hz, 2H), 1.77 – 1.44 (m, 7H), 1.34 – 1.07 (m, 7H), 0.89 (q, $J = 11.2, 10.6$ Hz, 2H).
$^{13}$C NMR (101 MHz, Chloroform-d) δ 174.42, 60.35, 37.43, 33.15, 32.55, 32.16, 26.72, 26.41, 14.43.
LRMS (EI) [C$_{11}$H$_{20}$O$_{2}$] m/z calculated 184.15, found 184.1
IR (film) $\nu$max 2922, 2851, 1734, 1449, 1176, 1162, 943

6 -ethyl 3-cycloheptylpropanoate
Prepared using standard reaction conditions A from cycloheptane.
Yield 89%
$^1$H NMR (400 MHz, Chloroform-d) δ 4.12 (q, $J = 7.1$ Hz, 2H), 2.29 (t, $J = 7.9$ Hz, 2H), 1.78 – 1.32 (m, 13H), 1.33 – 1.06 (m, 5H).
$^{13}$C NMR (101 MHz, Chloroform-d) δ 174.38, 60.34, 38.97, 34.38, 33.18, 32.67, 28.66, 26.51, 14.43.
LRMS (EI) [C$_{12}$H$_{22}$O$_{2}$] m/z calculated 198.16, found 198.2
IR (film) $\nu$max 2920, 2853, 1735, 1458, 1177, 1035, 824

3 -ethyl 3-cyclooctylpropanoate
Prepared using standard reaction conditions A from cyclooctane.
Yield 93%
$^1$H NMR (400 MHz, Chloroform-d) δ 4.12 (q, $J = 7.1$ Hz, 2H), 2.29 (t, $J = 7.9$ Hz, 2H), 1.74 – 1.35 (m, 15H), 1.31 – 1.18 (m, 5H).
$^{13}$C NMR (101 MHz, Chloroform-d) δ 174.37, 60.33, 37.01, 33.24, 32.74, 27.40, 26.46, 25.57, 14.44.
LRMS (EI) [C$_{13}$H$_{24}$O$_{2}$] m/z calculated 212.18, found 212.2
IR (film) $\nu$max 2917, 2854, 1735, 1447, 1158, 1030, 857

7 -ethyl 4-methylheptanoate (major isomer)
Prepared using standard reaction conditions A from n-pentane.
Mix of regioisomers: 1:1.7:1 (a:b:c)
Yield 95%
$^1$H NMR (500 MHz, Chloroform-d) δ 4.11 (qd, $J = 7.1, 0.8$ Hz, 2H), 2.36 – 2.18 (m, 2H), 1.73 – 1.04 (m, 11H), 0.95 – 0.76 (m, 5H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 174.35, 60.34, 39.12, 32.34, 32.09, 25.26, 20.18, 19.42, 14.42, 10.94.
LRMS (EI) [C$_{10}$H$_{18}$O$_{2}$] m/z calculated 172.15, found 172.1
IR (film) $\nu$max 2924, 2854, 1738, 1461, 718

8 -ethyl 4-ethoxypentanoate
Prepared using standard reaction conditions A from diethyl ether.
Yield 71%
$^1$H NMR (500 MHz, Chloroform-d) δ 4.12 (q, $J = 7.1$ Hz, 2H), 3.54 (dq, $J = 9.0, 7.0$ Hz, 1H), 3.48 – 3.27 (m, 2H), 2.50 – 2.28 (m, 2H), 1.87 – 1.70 (m, 2H), 1.25 (t, $J = 7.2$ Hz, 3H), 1.20 – 1.12 (m, 6H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 174.01, 74.21, 63.90, 60.39, 31.82, 30.61, 19.82, 15.70, 14.41.
LRMS (EI) [C$_{9}$H$_{16}$O$_{3}$] m/z calculated 174.13, found 174.1
IR (film) $\nu$max 2923, 2854, 1733, 1461, 1273, 1123, 961, 742
9 -ethyl 3-(tetrahydrofuran-2-yl)propanoate
Prepared using standard reaction conditions A from tetrahydrofuran.
Yield 77%
$^1$H NMR (500 MHz, Chloroform-d) δ 4.12 (q, J = 7.1 Hz, 2H), 3.83 (dddd, J = 10.9, 7.2, 5.5, 2.4 Hz, 2H), 3.70 (td, J = 7.9, 6.2 Hz, 1H), 2.50 – 2.31 (m, 2H), 1.98 (dddd, J = 11.7, 8.5, 6.5, 5.0 Hz, 1H), 1.94 – 1.77 (m, 3H), 1.46 (ddt, J = 12.0, 8.7, 7.4 Hz, 1H), 1.24 (t, J = 7.1 Hz, 3H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 173.77, 78.36, 67.86, 60.46, 31.35, 30.90, 25.88, 14.39.
LRMS (EI) [C$_9$H$_{16}$O$_3$] m/z calculated 172.11, found 172.1
IR (film) $\nu_{max}$ 3388, 2930, 2854, 1730, 1712, 1172, 1025, 754

10 -ethyl 3-(tetrahydro-2H-pyran-2-yl)propanoate
Prepared using standard reaction conditions A from tetrahydropyran.
Yield 61%
$^1$H NMR (500 MHz, Chloroform-d) δ 4.12 (q, J = 7.1 Hz, 2H), 3.95 (ddt, J = 11.5, 4.1, 1.8 Hz, 1H), 3.38 (td, J = 11.6, 2.5 Hz, 1H), 3.24 (dddd, J = 10.9, 7.3, 5.1, 2.1 Hz, 1H), 2.52 – 2.30 (m, 2H), 1.87 – 1.70 (m, 3H), 1.62 – 1.44 (m, 4H), 1.31 – 1.22 (m, 4H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 174.01, 68.63, 60.39, 31.99, 31.70, 30.60, 26.27, 23.64, 14.42.
LRMS (EI) [C$_{10}$H$_{18}$O$_3$] m/z calculated 186.13, found 186.1
IR (film) $\nu_{max}$ 3454, 2930, 2872, 1728, 1664, 1183, 1157, 1080, 1027

11 -ethyl 3-(1,4-dioxan-2-yl)propanoate
Prepared using standard reaction conditions A from 1,4 dioxane.
Yield 83%
$^1$H NMR (500 MHz, Chloroform-d) δ 4.13 (q, J = 7.1 Hz, 2H), 3.81 – 3.63 (m, 4H), 3.63 – 3.51 (m, 2H), 3.28 (dd, J = 11.5, 9.9 Hz, 1H), 2.55 – 2.31 (m, 2H), 1.78 – 1.62 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 173.47, 74.54, 71.24, 66.93, 66.67, 60.60, 30.02, 26.82, 14.40.
LRMS (EI) [C$_9$H$_{16}$O$_4$] m/z calculated 188.10, found 188.1
IR (film) $\nu_{max}$ 2921, 2958, 2853, 1731, 1174, 1119, 898, 875, 621

12 -ethyl 4-phenylbutanoate
Prepared using reaction conditions B from toluene.
Yield 69%
$^1$H NMR (500 MHz, Chloroform-d) δ 7.32 – 7.26 (m, 2H), 7.19 (td, J = 7.3, 6.8, 1.5 Hz, 3H), 4.12 (q, J = 7.1 Hz, 2H), 2.71 – 2.60 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.96 (p, J = 7.6 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 173.71, 141.64, 128.69, 128.57, 126.15, 60.46, 35.34, 33.88, 26.74, 14.45.
LRMS (EI) [C$_{12}$H$_{16}$O$_2$] m/z calculated 192.12, found 192.1
IR (film) $\nu_{max}$ 2921, 2958, 2853, 1731, 1174, 1119, 898, 875, 621

13 -ethyl 3-(2,3-dihydro-1H-inden-1-yl)propanoate
Prepared using standard reaction conditions A from indane.
Yield 72%
$^1$H NMR (400 MHz, Chloroform-d) δ 7.25 – 7.10 (m, 4H), 7.19 (td, J = 7.3, 6.8, 1.5 Hz, 3H), 4.12 (q, J = 7.1 Hz, 2H), 2.71 – 2.60 (m, 2H), 2.32 (t, J = 7.5 Hz, 2H), 1.96 (p, J = 7.6 Hz, 2H), 1.25 (t, J = 7.1 Hz, 3H).
$^{13}$C NMR (126 MHz, Chloroform-d) δ 173.92, 146.69, 144.15, 128.69, 128.57, 126.15, 60.46, 35.34, 33.88, 26.74, 14.45.
LRMS (EI) [C$_{14}$H$_{18}$O$_2$] m/z calculated 218.13, found 218.1
IR (film) $\nu_{max}$ 2959, 2929, 2870, 1733, 1453, 1163, 700

14 -ethyl 4-phenylpentanoate
Prepared using standard reaction conditions A from ethylbenzene.
Mix of regioisomers 5:1 (2:1 isolated) $^1$H NMR shifts are not resolved. In the cases in which the signals overlap, the minor signal integrations are subtracted from overlapping signals for reported shifts. $^{13}$C NMR shifts completely resolve allowing for major regioisomer to be selected.
Yield 68%
\[ ^1H\text{ NMR (major regioisomer) (500 MHz, Chloroform-\text{d})} \delta 7.33 - 7.25 (m, 2H), 7.22 - 7.15 (m, 3H), 4.21 - 4.00 (m, 2H), 2.71 (dq, J = 15.6, 6.9 Hz, 1H), 2.26 - 2.11 (m, 2H), 1.99 - 1.83 (m, 2H), 1.36 - 1.18 (m, 6H).
\]
\[ ^13C\text{ NMR (major regioisomer) (126 MHz, Chloroform-\text{d})} \delta 173.90, 146.49, 128.63, 127.21, 126.36, 60.40, 39.62, 33.41, 32.78, 22.33, 14.40.
\]
LRMS (EI) \[ [\text{C}_{13}\text{H}_{18}\text{O}_2] m/z \text{ calculated 206.13, found 206.1} \]
IR (film) \( \nu_{\text{max}} \text{ calculated 2979, 2930, 1731, 1453, 1177, 1142, 1030, 745, 699} \]

15 -ethyl 4-(3,5-dimethylphenyl)butanoate
Prepared using standard reaction conditions B from mesitylene.
Yield 69%
\[ ^1H\text{ NMR (500 MHz, Chloroform-\text{d})} \delta 6.84 (s, 1H), 6.81 (s, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.64 - 2.52 (m, 2H), 2.39 - 2.26 (m, 8H), 1.94 (p, J = 7.6 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).
\]
\[ ^13C\text{ NMR (126 MHz, Chloroform-\text{d})} \delta 173.77, 141.55, 138.00, 127.75, 126.51, 60.40, 35.18, 33.95, 26.77, 21.43, 14.43.
\]
LRMS (EI) \[ [\text{C}_{14}\text{H}_{20}\text{O}_2] m/z \text{ calculated 220.15, found 220.1} \]
IR (film) \( \nu_{\text{max}} \text{ calculated 2920, 1733, 1606, 1459, 1373, 1241, 1178, 1144, 842, 703} \]

16 -ethyl 4-phenoxybutanoate
Prepared using standard reaction conditions B from anisole.
Yield 58%
\[ ^1H\text{ NMR (500 MHz, Chloroform-\text{d})} \delta 7.32 - 7.26 (m, 2H), 6.94 (tt, J = 7.3, 1.1 Hz, 1H), 6.89 (dt, J = 7.9, 1.0 Hz, 2H), 4.15 (q, J = 7.1 Hz, 2H), 4.01 (t, J = 6.1 Hz, 2H), 2.52 (t, J = 7.3 Hz, 2H), 2.11 (tt, J = 7.4, 6.1 Hz, 2H), 1.26 (t, J = 7.1 Hz, 3H).
\]
\[ ^13C\text{ NMR (126 MHz, Chloroform-\text{d})} \delta 173.45, 159.00, 129.63, 120.89, 114.65, 66.77, 60.62, 31.02, 24.85, 14.42.
\]
LRMS (EI) \[ [\text{C}_{12}\text{H}_{16}\text{O}_3] m/z \text{ calculated 208.11, found 208.1} \]
IR (film) \( \nu_{\text{max}} \text{ calculated 2925, 2856, 1732, 1496, 1243, 1172, 753, 691} \]

17 -ethyl 3-(3-oxocyclohexyl)propanoate
Prepared using standard reaction conditions A from cyclohexanone.
Yield 72%
7:1 regioselectivity, major regioisomer selected (isolated fraction 11:1 rr)
\[ ^1H\text{ NMR (500 MHz, Chloroform-\text{d})} \delta 4.12 (qd, J = 7.1, 1.5 Hz, 2H), 2.42 (ddd, J = 13.8, 4.0, 2.0 Hz, 1H), 2.39 - 2.26 (m, 4H), 2.10 - 2.20 (m, 2H), 1.95 - 1.88 (m, 1H), 1.85 - 1.58 (m, 4H), 1.41 - 1.29 (m, 1H), 1.25 (td, J = 7.2, 1.5 Hz, 3H).
\]
\[ ^13C\text{ NMR (126 MHz, Chloroform-\text{d})} \delta 211.36, 173.51, 60.62, 47.91, 41.53, 38.67, 31.80, 31.64, 31.17, 25.26, 14.40.
\]
LRMS (EI) \[ [\text{C}_{11}\text{H}_{18}\text{O}_3] m/z \text{ calculated 198.13, found 198.1} \]
IR (film) \( \nu_{\text{max}} \text{ calculated 2931, 2865, 1729, 1710, 1176, 1155, 1033, 863} \]

18 -ethyl 4-methyl-6-oxononanoate
Prepared using standard reaction conditions A from 4-heptanone.
Yield 78%
6:1 regioselectivity, major regioisomer selected
\[ ^1H\text{ NMR (400 MHz, Chloroform-\text{d})} \delta 4.11 (q, J = 7.2 Hz, 2H), 2.43 - 2.18 (m, 7H), 2.10 - 1.95 (m, 1H), 1.71 - 1.42 (m, 5H), 1.24 (t, J = 7.1 Hz, 3H), 0.98 - 0.83 (m, 6H).
\]
\[ ^13C\text{ NMR (101 MHz, Chloroform-\text{d})} \delta 210.72, 173.81, 60.50, 50.02, 45.47, 32.22, 31.95, 28.84, 19.64, 17.37, 14.40, 13.91.
\]
LRMS (EI) \[ [\text{C}_{12}\text{H}_{22}\text{O}_3] m/z \text{ calculated 214.16, found 214.2} \]
IR (film) \( \nu_{\text{max}} \text{ calculated 2960, 2934, 2875, 1732, 1711, 1372, 1176, 1032} \]

19 -1-ethyl 7-methyl 4-(2-methoxy-2-oxoethyl)heptanedioate
Prepared using standard reaction conditions A from dimethyl adipate.
Yield 65%
6:1 regioselectivity, major regioisomer selected
\[ ^1H\text{ NMR (500 MHz, Chloroform-\text{d})} \delta 4.12 (q, J = 7.1 Hz, 2H), 3.67 (d, J = 2.3 Hz, 6H), 2.44 - 2.22 (m, 6H), 2.03 - 1.84 (m, 1H), 1.77 - 1.56 (m, 4H), 1.25 (t, J = 7.1 Hz, 3H).
\]
\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 173.92, 173.47, 173.12, 60.61, 51.81 (d, \(J = 2.8\) Hz), 38.33, 34.20, 31.66, 31.42, 28.75, 14.39.

HRMS (ESI+) \([\text{C}_{13}\text{H}_{22}\text{O}_6]\) m/z calculated [M+Na] 297.13, found 297.1329

IR (film) \(\nu_{\text{max}}\) 2952, 1729, 1436, 1253, 1151, 1018

\(\textbf{20}\) -ethyl 4-acetoxypentanoate
Prepared using standard reaction conditions A from ethyl acetate.
Yield 58%

\(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 4.92 (h, \(J = 6.3\) Hz, 1H), 4.13 (q, \(J = 7.1\) Hz, 2H), 2.47 – 2.23 (m, 2H), 2.03 (s, 3H), 1.96 – 1.81 (m, 2H), 1.95 – 1.81 (m, 2H).

\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 173.23, 170.82, 70.21, 60.67, 31.11, 30.58, 20.07, 14.40.

LRMS (ESI+) \([\text{C}_9\text{H}_{16}\text{O}_4]\) m/z calculated [M+Na] 211.09, found 211.0972

IR (film) \(\nu_{\text{max}}\) 2981, 2934, 1734, 1373, 1241, 1180

\(\textbf{21}\) -ethyl 3-(4-oxotetrahydro-2H-pyran-2-yl)propanoate
Prepared using standard reaction conditions A from tetrahydro-4H-pyran-4-one.
Yield 58%

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 4.27 (ddd, \(J = 11.5, 7.4, 1.5\) Hz, 1H), 4.14 (q, \(J = 7.1\) Hz, 2H), 3.73 – 3.56 (m, 2H), 2.64 – 2.24 (m, 6H), 1.99 – 1.80 (m, 2H), 1.26 (t, \(J = 7.2\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 206.69, 173.29, 66.67, 60.66, 48.39, 42.33, 31.47, 30.30, 14.41.

LRMS (EI) \([\text{C}_{10}\text{H}_{16}\text{O}_4]\) m/z calculated 200.10, found 200.0

IR (film) \(\nu_{\text{max}}\) 2975, 2931, 2857, 1719, 1276, 1174, 1156, 1087, 862

\(\textbf{22}\) -ethyl 4-(N-methylformamido)butanoate
Prepared using standard reaction conditions B from dimethylformamide.
Yield 42%

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 8.05 (s, 1H), 4.14 (qd, \(J = 7.1, 3.2\) Hz, 2H), 3.33 (dt, \(J = 31.0, 7.1\) Hz, 2H), 2.90 (d, \(J = 32.6\) Hz, 3H), 2.31 (dt, \(J = 9.8, 7.3\) Hz, 2Hz), 1.88 (h, \(J = 7.2\) Hz, 2H), 1.26 (td, \(J = 7.1, 2.5\) Hz).

\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 172.94 (d, \(J = 51.2\) Hz), 162.78 (d, \(J = 3.3\) Hz), 60.77 (d, \(J = 25.9\) Hz), 48.88, 43.67, 31.76, 30.83, 29.62, 23.33, 22.13, 14.38.

LRMS (EI) \([\text{C}_8\text{H}_{15}\text{NO}_3]\) m/z calculated 173.11, found 173.1

IR (film) \(\nu_{\text{max}}\) 2927, 1775, 1730, 1162, 1069, 1026, 917

\(\textbf{23}\) -ethyl 4-(N-methylacetamido)butanoate
Prepared using standard reaction conditions B from dimethylacetamide.
Yield 59%

\(^1\)H NMR (400 MHz, Chloroform-d) \(\delta\) 4.14 (dq, \(J = 9.1, 7.1\) Hz, 2H), 3.36 (ddd, \(J = 29.1, 8.1, 6.5\) Hz, 2H), 2.95 (d, \(J = 30.4\) Hz, 3H), 2.32 (q, \(J = 7.1\) Hz, 2H), 2.08 (d, \(J = 12.6\) Hz, 3H), 2.01 – 1.79 (m, 2H), 1.26 (td, \(J = 7.2, 5.4\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 173.13 (d, \(J = 70.3\) Hz), 170.75 (d, \(J = 16.0\) Hz), 60.73 (d, \(J = 34.7\) Hz), 50.06, 46.90, 36.29, 33.32, 31.67, 31.05, 23.55, 22.71, 22.04, 21.35, 14.40.

LRMS (EI) \([\text{C}_9\text{H}_{17}\text{NO}_3]\) m/z calculated 187.12, found 187.1

IR (film) \(\nu_{\text{max}}\) 2966, 2856, 1719, 1372, 1254, 1174, 1156, 1087

24 -ethyl 4-oxo-4-phenylbutanoate
Prepared using standard reaction conditions C from benzaldehyde.
Yield 94%

\(^1\)H NMR (500 MHz, Chloroform-d) \(\delta\) 8.02 – 7.96 (m, 2H), 7.61 – 7.54 (m, 1H), 7.51 – 7.43 (m, 2H), 4.16 (q, \(J = 7.2\) Hz, 2H), 3.32 (t, \(J = 6.7\) Hz, 2H), 2.76 (t, \(J = 6.7\) Hz, 2H), 1.27 (t, \(J = 7.1\) Hz, 3H).

\(^{13}\)C NMR (126 MHz, Chloroform-d) \(\delta\) 198.34, 173.11, 136.78, 133.39, 128.80, 128.23, 60.85, 33.58, 28.48, 14.39.

LRMS (EI) \([\text{C}_{12}\text{H}_{14}\text{O}_3]\) m/z calculated 206.09, found 206.1

IR (film) \(\nu_{\text{max}}\) 2926, 2855, 1731, 1689, 1243, 1172, 754, 691

\(\textbf{25}\) -ethyl 3-(triphenylsilyl)propanoate
Prepared using standard reaction conditions C from triphenylsilane.

203
Yield 82%

1H NMR (500 MHz, Chloroform-d) δ 7.56 – 7.49 (m, 5H), 7.45 – 7.39 (m, 3H), 7.37 (ddt, J = 8.3, 6.7, 1.3 Hz, 5H), 4.05 (q, J = 7.1 Hz, 2H), 2.48 – 2.36 (m, 2H), 1.77 – 1.66 (m, 2H), 1.20 (t, J = 7.1 Hz, 3H).

13C NMR (126 MHz, Chloroform-d) δ 174.84, 135.78, 134.35, 129.83, 128.18, 60.65, 29.11, 14.37, 8.44.

LRMS (EI) [C13H18O3Si] m/z calculated 360.15, found 360.1
IR (film) νmax 3068, 2924, 2853, 2360, 1735, 1428, 1112, 701

26 3-methyl-6-oxo-6-phenoxhexanoic acid
Prepared using standard reaction conditions A from butanoic acid and ethyl acrylate.
Yield 60%, 2:1 rr

1H NMR (400 MHz, Chloroform-d) δ 4.22 – 4.03 (m, 2H), 2.45 – 2.12 (m, 4H), 2.00 (dq, J = 13.7, 6.8 Hz, 1H), 1.80 – 1.49 (m, 3H), 1.47 – 1.34 (m, 1H), 1.25 (t, J = 7.1, 1.2 Hz, 3H), 0.99 (d, J = 6.7 Hz, 3H).

13C NMR (101 MHz, Chloroform-d) δ 178.33, 173.71, 60.60, 41.24, 34.28, 32.15, 31.65, 29.88, 19.50, 14.40.

HRMS (ASAP-)[C6H13O2] m/z calculated [M-H] 187.0970, found 187.0966
IR (film) νmax 2935, 1734, 1708, 1375, 1182, 1094, 1032

27 7-ethoxy-3-methyl-7-oxoheptanoic acid
Prepared using standard reaction conditions A from 3-methylbutanoic acid and ethyl acrylate.
Yield 73%, 3:1 rr

1H NMR (400 MHz, Chloroform-d, major selected) δ 4.13 (q, J = 7.1 Hz, 2H), 2.44 – 2.12 (m, 4H), 1.99 (dt, J = 13.5, 6.7 Hz, 1H), 1.78 – 1.54 (m, 2H), 1.39 (ddt, J = 13.4, 11.0, 5.6 Hz, 1H), 1.31 – 1.18 (m, 5H), 0.99 (d, J = 6.6 Hz, 3H).

13C NMR (101 MHz, Chloroform-d) δ 178.26, 173.80, 60.47, 36.15, 34.52, 30.10, 27.07, 22.51, 19.73, 14.43.

HRMS (ASAP-)[C11H17O2] m/z calculated [M-H] 201.112, found 201.1126
IR (film) νmax 2963, 1733, 1706, 1371, 1265, 1186, 935, 738

28 7-ethoxy-3,3-dimethyl-7-oxoheptanoic acid
Prepared using standard reaction conditions A from 3,3-dimethylbutanoic acid and ethyl acrylate.
Yield 59%

1H NMR (400 MHz, Chloroform-d) δ 4.13 (q, J = 7.1 Hz, 2H), 2.28 (t, J = 7.4 Hz, 2H), 2.24 (s, 2H), 1.68 – 1.57 (m, 2H), 1.41 – 1.30 (m, 2H), 1.25 (t, J = 7.1 Hz, 3H), 1.03 (s, 6H).

13C NMR (101 MHz, Chloroform-d) δ 177.88, 173.87, 60.47, 45.73, 41.60, 34.98, 33.31, 27.33, 19.92, 14.43.

HRMS (ASAP-)[C11H19O3] m/z calculated [M-H] 215.1283, found 214.128
IR (film) νmax 2924, 2855, 1704, 1191, 1162, 1133, 690

29 3-(3-ethoxy-3-oxopropyl)cyclopentane-1-carboxylic acid
Prepared using standard reaction conditions A from cyclopentane carboxylic acid and ethyl acrylate.
Yield 57%, 1:1 dr

1H NMR (500 MHz, Chloroform-d) δ 4.12 (q, J = 7.1 Hz, 2H), 2.95 – 2.73 (m, 1H), 2.31 (td, J = 7.7, 3.9 Hz, 2H), 2.19 – 2.06 (m, 1H), 2.05 – 1.77 (m, 4H), 1.77 – 1.58 (m, 2H), 1.55 – 1.38 (m, 1H), 1.25 (td, J = 7.1, 2.2 Hz, 4H).

13C NMR (126 MHz, Chloroform-d, major selected) δ 182.55, 173.90, 60.51, 42.82, 39.30, 35.74, 33.62, 32.77, 30.78, 29.70, 14.42.

HRMS (ASAP-)[C11H19O3] m/z calculated [M-H] 213.1127, found 213.1127
IR (film) νmax 2945, 1733, 1701, 1450, 1374, 1181, 940

30 6-ethoxy-2,2,3-trimethyl-6-oxohexanoic acid
Prepared using standard reaction conditions A from 2,2-dimethylbutanoic acid and ethyl acrylate.
Yield 62%, 2:1 rr

1H NMR (400 MHz, Chloroform-d, major selected) δ 4.12 (qd, J = 7.1, 2.4 Hz, 2H), 2.48 – 2.14 (m, 2H), 1.88 – 1.73 (m, 1H), 1.68 – 1.44 (m, 2H), 1.25 (td, J = 7.2, 2.9 Hz, 3H), 1.14 (d, J = 8.5 Hz, 6H), 0.89 (d, J = 6.9 Hz, 3H).

13C NMR (101 MHz, Chloroform-d) δ 184.17, 173.84, 60.54, 46.15, 39.48, 33.20, 25.13, 21.88, 21.64, 14.42.

HRMS (ASAP-)[C13H23O3] m/z calculated [M-H] 215.1283, found 215.1285
IR (film) νmax 2976, 2939, 1734, 1697, 1463, 1372, 1180, 937, 857

31 -methyl 3-cyclooctylpropanoate
Prepared using standard reaction conditions A from methyl acrylate and cyclooctane.
Yield 96%

1H NMR (400 MHz, CDCl3) δ 3.66 (s, 3H), 2.34 – 2.28 (m, 2H), 1.71 – 1.35 (m, 15H), 1.32 – 1.20 (m, 2H).

13C NMR (101 MHz, CDCl3) δ 174.79, 51.64, 37.05, 33.20, 32.47, 32.17, 27.43, 26.46, 25.56.

LRMS (EI) [C12H22O2] m/z calculated 198.16, found 198.1

IR (film) νmax 2918, 2853, 1736, 1446, 1032, 857

32 -phenyl 3-cyclooctylpropanoate
Prepared using standard reaction conditions A from phenyl acrylate and cyclooctane.
Yield 90%

1H NMR (400 MHz, CDCl3) δ 7.42 – 7.33 (m, 2H), 7.25 – 7.19 (m, 1H), 7.12 – 7.05 (m, 2H), 2.61 – 2.52 (m, 2H), 1.75 – 1.27 (m, 6H).

13C NMR (101 MHz, CDCl3) δ 172.73, 150.99, 129.55, 125.84, 121.74, 37.04, 33.19, 32.78, 32.24, 27.40, 26.48, 25.59.

LRMS (EI) [C17H24O2] m/z calculated 260.18, found 260.1

IR (film) νmax 2918, 2854, 1758, 1492, 1193, 1134, 749, 689

33 -methyl 3-cyclooctyl-2-methylpropanoate
Prepared using standard reaction conditions A from methyl methacrylate and cyclooctane.
Yield 64%

1H NMR (500 MHz, CDCl3) δ 3.66 (s, 3H), 2.52 (dq, J = 13.6, 7.0 Hz, 1H), 1.67 – 1.36 (m, 14H), 1.29 – 1.17 (m, 3H), 1.12 (d, J = 6.9 Hz, 3H).

13C NMR (126 MHz, CDCl3) δ 172.73, 150.99, 129.55, 125.84, 121.74, 37.04, 33.19, 32.78, 32.24, 27.40, 26.48, 25.59.

LRMS (EI) [C13H24O2] m/z calculated 212.18, found 212.2

IR (film) νmax 2921, 2853, 1738, 1460, 1196, 1164

34 -diisopropyl 2-(cyclooctylmethyl)malonate
Prepared using standard reaction conditions A from diisopropyl 2-methylenemalonate and cyclooctane.
Yield 48%

1H NMR (500 MHz, CDCl3) δ 5.05 (hept, J = 6.2 Hz, 2H), 3.35 (t, J = 7.7 Hz, 1H), 1.77 (t, J = 7.4 Hz, 2H), 1.67 – 1.37 (m, 13H), 1.32 – 1.26 (m, 2H), 1.23 (dd, J = 6.3, 3.2 Hz, 12H).

13C NMR (126 MHz, CDCl3) δ 169.57, 68.75, 50.79, 36.70, 35.08, 32.14, 27.32, 26.47, 25.46, 21.85, 21.78.

LRMS (EI) [C18H32O4] m/z calculated 312.23, found 312.0

IR (film) νmax 2980, 2921, 2856, 1728, 1246, 1100

35 -3-cyclooctylpropanoic acid
Prepared using standard reaction conditions B from acrylic acid and cyclooctane with 3.0 equiv. trifluoroacetic acid as an additive.
Yield 83%

1H NMR (500 MHz, CDCl3) δ 2.47 – 2.23 (m, 2H), 1.70 – 1.37 (m, 15H), 1.33 – 1.21 (m, 2H).

13C NMR (126 MHz, CDCl3) δ 180.45, 36.96, 32.88, 32.37, 32.13, 27.41, 26.43, 25.52.

LRMS (EI) [C11H20O2] m/z calculated 184.15, found 184.1

IR (film) νmax 2919, 2853, 1708, 1446, 1272, 933

36-4-methyl-2-oxo-2H-chromen-6-yl 3-cyclooctylpropanoate
Prepared using standard reaction conditions A from 4-methyl-2-oxo-2H-chromen-6-yl acrylate and cyclooctane.
Yield 86%

1H NMR (500 MHz, CDCl3) δ 7.60 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 2.2 Hz, 1H), 7.06 (dd, J = 8.6, 2.3 Hz, 1H), 6.27 (q, J = 1.3 Hz, 1H), 2.67 – 2.54 (m, 2H), 2.43 (d, J = 1.3 Hz, 3H), 1.74 – 1.65 (m, 8H), 1.53 – 1.42 (m, 5H), 1.36 – 1.23 (m, 4H).

13C NMR (126 MHz, CDCl3) δ 172.15, 160.75, 154.39, 153.41, 152.12, 125.52, 118.32, 117.95, 114.66, 110.65, 37.03, 33.02, 32.75, 32.21, 27.39, 26.47, 25.57, 18.92.

LRMS (EI) [C21H26O2] m/z calculated 342.18, found 342.2

IR (film) νmax 2917, 2853, 1757, 1729, 1612, 1261, 1127, 855
37 - (2-(phenylsulfonyl)ethyl)cyclooctane
Prepared using standard reaction conditions B from phenyl vinyl sulfone and cyclooctane.
Yield 77%

\[ ^{1}H \text{NMR (500 MHz, CDCl}_3\] \( \delta \) 7.90 (dd, \( J = 8.4, 1.3 \text{ Hz, 2H} \)), 7.68 – 7.62 (m, 1H), 7.59 – 7.53 (m, 2H), 3.15 – 3.02 (m, 2H), 1.65 – 1.48 (m, 10H), 1.46 – 1.32 (m, 5H), 1.28 – 1.17 (m, 2H).

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3\] \( \delta \) 139.45, 133.76, 129.42, 128.20, 55.02, 36.46, 32.14, 30.45, 27.16, 26.31, 25.38.

LRMS (EI) \( [C_{19}H_{22}O_2S] m/z \) calculated 280.15 found 280.1

IR (film) \( \nu_{\text{max}} \) 2919, 2855, 1495, 1335, 1145, 762, 687

38 - 5-((2-cyclooctetyl)sulfonyl)-1-phenyl-1H-tetrazole
Prepared using standard reaction conditions B from diisopropyl 1-phenyl-5-(vinylsulfonyl)-1H-tetrazole and cyclooctane.
Yield 73%

\[ ^{1}H \text{NMR (500 MHz, CDCl}_3\] \( \delta \) 7.71 – 7.66 (m, 2H), 7.64 – 7.57 (m, 3H), 3.77 – 3.71 (m, 2H), 1.88 – 1.79 (m, 2H), 1.71 – 1.54 (m, 8H), 1.47 (d, \( J = 8.4 \text{ Hz, 5H} \)), 1.39 – 1.29 (m, 2H).

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3\] \( \delta \) 153.66, 133.22, 131.62, 129.88, 125.25, 54.82, 36.54, 31.99, 29.58, 27.18, 26.29, 25.34.

HRMS (ASAP+) \( [C_{11}H_{24}N_4S] m/z \) calculated [M+H] 349.17, found 349.1698

IR (film) \( \nu_{\text{max}} \) 2917, 2852, 1497, 1336, 1148, 761, 688

39 - diisopropyl 1-cyclooctylhydrazine-1,2-dicarboxylate
Prepared using standard reaction conditions B from diisopropyl azodicarboxylate and cyclooctane.
Yield 72%

\[ ^{1}H \text{NMR (400 MHz, CDCl}_3\] \( \delta \) 6.10 (d, \( J = 56.3 \text{ Hz, 1H} \)), 4.93 (dp, \( J = 12.6, 6.3 \text{ Hz, 2H} \)), 4.22 (s, 1H), 1.89 – 1.41 (m, 15H), 1.24 (t, \( J = 6.8 \text{ Hz, 12H} \)).

\[ ^{13}C \text{NMR (126 MHz, CDCl}_3\] \( \delta \) 156.00 (d, \( J = 185.4 \text{ Hz} \)), 69.82 (d, \( J = 33.3 \text{ Hz} \)), 57.78, 31.13, 26.81, 26.21, 24.67, 22.22 (d, \( J = 18.0 \text{ Hz} \)).

LRMS (EI) \( [C_{16}H_{28}N_2O_4] m/z \) calculated 314.22, found 314.2

IR (film) \( \nu_{\text{max}} \) 3291, 2979, 2922, 2855, 1729, 1702, 1682, 1107, 760

40 - cyclooctylcyclopentan-1-one
Prepared using standard reaction conditions A from cyclopent-2-en-1-one and cyclooctane.
Yield 65%

\[ ^{1}H \text{NMR (400 MHz, CDCl}_3\] \( \delta \) 2.42 – 2.23 (m, 2H), 2.23 – 2.07 (m, 2H), 2.05 – 1.92 (m, 1H), 1.89 – 1.76 (m, 1H), 1.77 – 1.58 (m, 7H), 1.54 – 1.40 (m, 7H), 1.38 – 1.24 (m, 2H).

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3\] \( \delta \) 220.18, 44.15, 43.73, 42.98, 39.31, 30.89, 29.95, 28.12, 27.52, 27.44, 26.54, 25.70, 25.59.

LRMS (EI) \( [C_{19}H_{12}O] m/z \) calculated 194.17, found 194.2

IR (film) \( \nu_{\text{max}} \) 2915, 2854, 1740, 1470, 1446, 1162, 503

41 - cyclooctylidihydrofuran-2,5-dione
Prepared using standard reaction conditions A from furan-2,5-dione and cyclooctane.
Yield 76%

\[ ^{1}H \text{NMR (400 MHz, CDCl}_3, \text{major selected}\] \( \delta \) 3.11 (dd, \( J = 10.3, 6.2, 4.3 \text{ Hz, 1H} \)), 2.96 (dd, \( J = 18.9, 10.0 \text{ Hz, 1H} \)), 2.73 (dd, \( J = 18.9, 6.2 \text{ Hz, 1H} \)), 2.27 (dd, \( J = 11.3, 7.5, 3.9 \text{ Hz, 1H} \)), 1.77 – 1.31 (m, 14H).

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3\] \( \delta \) 173.38, 170.60, 48.18, 38.07, 32.04, 31.21, 29.42, 26.55, 26.46, 25.36, 25.36.

LRMS (EI) \( [C_{15}H_{10}O_2] m/z \) calculated 210.13, found 210.1

IR (film) \( \nu_{\text{max}} \) 2919, 2853, 1860, 1777, 1470, 1220, 1061, 917, 640, 422

42 - cyclooctyl-1-methylpyrrolidine-2,5-dione
Prepared using standard reaction conditions A from 1-methyl-1H-pyrrole-2,5-dione and cyclooctane.
Yield 87%

\[ ^{1}H \text{NMR (400 MHz, CDCl}_3, \text{major selected}\] \( \delta \) 2.97 (s, 3H), 2.81 (dt, \( J = 8.9, 4.3 \text{ Hz, 1H} \)), 2.67 (dd, \( J = 18.2, 9.2 \text{ Hz, 1H} \)), 2.44 (dd, \( J = 18.3, 4.7 \text{ Hz, 1H} \)), 2.33 – 2.22 (m, 1H), 1.72 – 1.24 (m, 14H).

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3\] \( \delta \) 179.86, 177.40, 47.40, 37.58, 32.35, 31.13, 28.68, 26.62, 26.54, 26.13, 25.54, 24.86.

LRMS (EI) \( [C_{16}H_{22}NO_2] m/z \) calculated 223.16, found 223.2
33 -3-cyclooctyl-2-methylcyclopentan-1-one
Prepared using standard reaction conditions A from 2-methylcyclopent-2-en-1-one and cyclooctane.
Yield 83% >20:1 dr
Major diastereomer assigned by literature precedent.  

\( ^1 \)H NMR (400 MHz, CDCl3) \( \delta \) 2.40 – 2.00 (m, 2H), 2.00 – 1.83 (m, 2H), 1.80 – 1.24 (m, 17H), 1.08 (d, J = 6.9 Hz, 3H).
\( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta \) 221.93, 51.79, 47.37, 38.32, 37.43, 32.87, 27.87, 27.16, 27.05, 26.89, 26.59, 25.90, 22.86, 13.85.
LRMS (EI) [C\(_{14}\)H\(_{24}\)O] m/z calculated 208.18, found 208.2

34 -endo-3-(cyclooctylmethyl)bicyclo[2.2.1]heptan-2-one
Prepared using standard reaction conditions A from 3-methylenebicyclo[2.2.1]heptan-2-one and cyclooctane.
Yield 72% 10:1 dr
Major diastereomer assigned by similarity to literature precedent.

\( ^1 \)H NMR (400 MHz, CDCl3, major selected) \( \delta \) 2.59 (d, J = 4.7 Hz, 2H), 2.06 (dd, J = 10.4, 4.5 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.68 – 1.36 (m, 19H), 1.33 – 1.18 (m, 2H), 1.15 – 1.05 (m, 1H).
\( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta \) 220.97, 51.93, 50.77, 38.71, 37.31, 35.50, 34.32, 33.59, 30.60, 27.61, 27.46, 26.43, 25.55, 25.53, 25.47, 21.51.
LRMS (EI) [C\(_{16}\)H\(_{26}\)O] m/z calculated 234.20, found 234.2

35 -endo-3-phenethylbicyclo[2.2.1]heptan-2-one
Prepared using standard reaction conditions A from 3-methylenebicyclo[2.2.1]heptan-2-one and toluene.
Yield 70% 20:1 dr
Major diastereomer assigned by literature precedent.

\( ^1 \)H NMR (400 MHz, CDCl3, major selected) \( \delta \) 7.27 (d, J = 7.6 Hz, 2H), 7.20 (d, J = 7.4 Hz, 3H), 2.80 – 2.51 (m, 4H), 2.15 – 1.95 (m, 2H), 1.89 – 1.75 (m, 1H), 1.73 – 1.48 (m, 5H), 1.48 – 1.36 (m, 1H).
\( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta \) 220.00, 141.78, 128.58, 126.14, 52.95, 50.75, 38.48, 37.19, 34.24, 28.26, 25.51, 21.38.
LRMS (EI) [C\(_{15}\)H\(_{18}\)O] m/z calculated 214.14, found 214.1
IR (film) \( \nu_{\text{max}} \) 3026, 2958, 2875, 1740, 1454, 914, 750, 700, 487

46 -1-(2-cyclooctycyclohexyl)ethan-1-one
Prepared using standard reaction conditions B from 1-cyclohexylethan-1-one and cyclooctane.
Yield 57% 15:1 dr
Major diastereomer assigned by similarity to literature precedent.

\( ^1 \)H NMR (400 MHz, CDCl3, major selected) \( \delta \) 2.44 (td, J = 11.3, 3.4 Hz, 1H), 2.12 (s, 3H), 1.85 – 1.59 (m, 7H), 1.54 – 1.12 (m, 16H), 1.01 (qd, J = 12.5, 3.1 Hz, 1H).
\( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta \) 213.76, 55.28, 47.08, 38.92, 33.93, 30.36, 28.90, 27.49, 27.08, 27.04, 26.74, 26.57, 26.46, 26.34, 26.12, 25.02.
LRMS (EI) [C\(_{16}\)H\(_{28}\)O] m/z calculated 236.21, found 236.2
IR (film) \( \nu_{\text{max}} \) 2919, 2853, 1707, 1446, 1352, 1159, 606, 561

47 -2-cyclooctycyclopentanone-1-carboxylic acid
Prepared using standard reaction conditions A from cyclopent-1-ene-1-carboxylic acid and cyclooctane.
Yield 54% >20:1 dr
Major diastereomer assigned by analogy.

\( ^1 \)H NMR (500 MHz, CDCl3, major selected) \( \delta \) 2.93 (td, J = 11.3, 3.4 Hz, 1H), 2.12 (s, 3H), 1.85 – 1.59 (m, 7H), 1.54 – 1.12 (m, 16H), 1.01 (qd, J = 12.5, 3.1 Hz, 1H).
\( ^{13} \)C NMR (101 MHz, CDCl3) \( \delta \) 213.76, 55.28, 47.08, 38.92, 33.93, 30.36, 28.90, 27.49, 27.08, 27.04, 26.74, 26.57, 26.46, 26.34, 26.12, 25.02.
HRMS (ASAP) [C\(_{14}\)H\(_{20}\)O\(_2\)] m/z calculated 223.1698, found 223.17
IR (film) \( \nu_{\text{max}} \) 3026, 2958, 1740, 1446, 1352, 1159, 606, 561
48 -3-cyclooctyl-3,4-dimethylidihydrofuran-2,5-dione
Prepared using standard reaction conditions A from 3,4-dimethylfuran-2,5-dione and cyclooctane.
Yield 67%
Major diastereomer assigned by analogy.

^1H NMR (400 MHz, CDCl3, major selected) δ 2.86 (q, J = 7.3 Hz, 1H), 1.85 (t, J = 9.2 Hz, 1H), 1.79 – 1.67 (m, 3H), 1.61 – 1.39 (m, 13H), 1.33 (d, J = 7.3 Hz, 4H).

^13C NMR (101 MHz, CDCl3) δ 173.71, 52.86, 46.57, 42.00, 29.61, 28.59, 27.08, 26.41, 25.66, 21.93, 8.56.LRMS
LRMS (EI) [C_{13}H_{22}O] m/z (-CO_2) calculated 194.17, found 194.2
IR (film) ν max 2921, 2853, 1842, 1775, 1461, 1220, 948, 922, 755, 540
References:


NMR Spectra:

$^1\text{H}, \text{CDCl}_3, 500 \text{ MHz}$

$^{13}\text{C}, \text{CDCl}_3, 126 \text{ MHz}$
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
ST-516-9-iso.1.7d
Proton

Me  γ  β  Me

7, 1:1.7:1 (α:β:γ)

$^1\text{H}, \text{CDCl}_3, 500 \text{ MHz}$

ST-516-9-iso.2.7d
Carbon 13

$^{13}\text{C}, \text{CDCl}_3, 126 \text{ MHz}$
8

$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$, CDCl$_3$, 126 MHz
1H, CDCl₃, 500 MHz

13C, CDCl₃, 126 MHz
$\text{Me} - \text{15}$

$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$, CDCl$_3$, 126 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
$^{13}$C, CDCl$_3$, 126 MHz
$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
Ph₃Si

O

25

OEt

¹H, CDCl₃, 500 MHz

¹³C, CDCl₃, 126 MHz
O
HO
OEt
Me

26, 2:1 rr

$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
27, 3:1 rr

$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{1}H$, CDCl$_3$, 400 MHz
$^{13}$C, CDCl$_3$, 101 MHz
$^{13}$C, CDCl$_3$, 101 MHz
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$, CDCl$_3$, 126 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
$\text{H, CDCl}_3, 500 \text{ MHz}$

$\text{C, CDCl}_3, 126 \text{ MHz}$
$^{1}H$, CDCl$_3$, 500 MHz

$^{13}C$, CDCl$_3$, 126 MHz
$\text{H, CDCl}_3$, 500 MHz

$\text{C, CDCl}_3$, 126 MHz
$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
$^{1}H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
Me \ O

46

$^1H$, CDCl$_3$, 400 MHz

$^{13}C$, CDCl$_3$, 101 MHz
$^1$H, CDCl$_3$, 500 MHz

$^{13}$C, CDCl$_3$, 126 MHz
$^1$H, CDCl$_3$, 400 MHz

$^{13}$C, CDCl$_3$, 101 MHz
17% D incorporation

${^1}H$, CDCl$_3$, 400 MHz

7% D incorporation

${^1}H$, CDCl$_3$, 400 MHz
Appendix C

SUPPLEMENTARY DATA FOR CHAPTER 4

Iron-Catalyzed Photoinduced LMCT: A 1° C–H Abstraction Enables Skeletal Rearrangements and C(sp3)–H Alkylation

Author: Yi Cheng Kang, Sean M. Treacy, Tomislav Rovis
Publication: ACS Catalysis
Publisher: American Chemical Society
Date: Jun 1, 2021

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Supporting Information

Iron-Catalyzed C(sp\(^3\))–H Alkylation via Photoinduced Ligand to Metal Charge Transfer

Yi Cheng Kang, Sean M. Treacy, and Tomislav Rovis*

Department of Chemistry, Columbia University

*tr2504@columbia.edu

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Materials and Methods

Unless otherwise noted, all reactions were performed in oven-dried glassware and carried out under an atmosphere of nitrogen with magnetic stirring. All photochemical reactions were run in 1.5 dram vials fitted with Teflon caps under irradiation from a PR-160 Kessil 40W LED lamp with Teflon stir-bars under vigorous magnetic stirring. All photochemical reactions were set up in a nitrogen glovebox, although optimization experiments showed that the reactions could also be set up on the benchtop without significant loss of yield. Thin layer chromatography was performed on SiliCycle® 250 μm 60 Å plates. Visualization was accomplished with 254 nm ultraviolet light, 2,4-dinitrophenylhydrazine, iodine or potassium permanganate stains.

$^1$H NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers at ambient temperature. Chemical shift is reported in parts per million (ppm) from CDCl$_3$ (7.26 ppm) with multiplicity ($s$ = singlet, $bs$ = broad singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, and $m$ = multiplet) and coupling constants (Hz). $^{13}$C NMR was recorded on Bruker 500 or 400 MHz spectrometers (126 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl$_3$ (77.15 ppm). Mass spectra were recorded on an Agilent 7890B GC System 5977B MSD GCMS with an EI ionization method. High resolution mass spectra (HRMS) were obtained from the Columbia University Chemistry Department Mass Spectrometry Facility on a Waters XEVO G2XS QTof mass spectrometer equipped with a UPC2 SFC inlet and a LockSpray source with one of the following three probes: electrospray ionization (ESI) probe, atmospheric pressure chemical ionization (APCI) probe, or atmospheric pressure solids analysis probe (ASAP). Infrared spectra were collected on a Perkin Elmer Spectrum Two FT-IR Spectrometer. UV-vis spectra were recorded on a Beckman-Coulter DU720 General Purpose UV/Vis Spectrophotometer.

Unless otherwise mentioned, all starting materials were obtained from commercial sources including Millipore-Sigma, TCI, and Alfa-Aesar. Anhydrous FeCl$_3$ and anhydrous acetonitrile were obtained from Millipore-Sigma.
Extended Optimization Studies

Optimization experiments

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from Standard Conditions</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>56%</td>
</tr>
<tr>
<td>2</td>
<td>with LiCl (50 mol%)</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>60 °C</td>
<td>48%</td>
</tr>
<tr>
<td>4</td>
<td>FeCl₃ (0 mol%)</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>in the dark</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>Irritate at 390 nm for 1 h, then dark.</td>
<td>7%</td>
</tr>
<tr>
<td>7</td>
<td>427 nm LEDs</td>
<td>15%</td>
</tr>
<tr>
<td>8</td>
<td>under air</td>
<td>51%</td>
</tr>
<tr>
<td>9</td>
<td>10 µL H₂O added</td>
<td>45%</td>
</tr>
<tr>
<td>10</td>
<td>FeCl₃ (10 mol%)</td>
<td>46%</td>
</tr>
<tr>
<td>11</td>
<td>FeCl₃ (50 mol%)</td>
<td>60%</td>
</tr>
</tbody>
</table>

*Optimizations were performed on a 0.3 mmol scale using 5 equiv. of 3-pentanone and 1 equiv. of benzyl acrylate. *Yields were determined by NMR with 1,3,5-trimethoxybenzene as internal standard.

To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.33 M) was then added, followed by 3-pentanone (5 equiv.) and benzyl acrylate (1 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 36 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the reaction yield determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

Experiments at 60 °C were carried out with the fan turned off.

Deuteration experiment

To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.33 M) was then added, followed by 3-pentanone (5 equiv.), benzyl acrylate (1 equiv.) and D₂SO₄ (0.5 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 36 hours, the reaction mixture was concentrated in vacuo and purified using silica gel flash column chromatography, using ethyl acetate/hexanes as the eluent. A 40% yield was obtained, and the deuterium incorporation was determined from the difference between the expected integral (6.00) and the actual integral (5.85) of the peak at 2.38 ppm (m, 6H).
Deuterium KIE experiment

To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.33 M) was then added, followed by cyclohexane (2.5 equiv.), cyclohexane-d₁₂ (2.5 equiv.), and benzyl acrylate (1 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 36 hours, an aliquot was taken from the reaction mixture and analyzed by GC/MS. The yields of the hydrogenated and deuterated products were determined from the respective calibration curves. A secondary KIE of 1.41 was found.
UV-vis studies

Sample preparation (75 μM FeCl₃ in MeCN)
FeCl₃ (12.1 mg, 0.075 mmol) was dissolved in 1.0 mL of acetonitrile. The resultant solution was stirred for 15 minutes, and a 3.0 μL aliquot was drawn and added to 3.0 mL of acetonitrile in a quartz cuvette.

Sample preparation (75 μM FeCl₃, 187.5 μM LiCl in MeCN)
FeCl₃ (12.1 mg, 0.075 mmol) and LiCl (7.9 mg, 0.1875 mmol, 2.5 equiv.) were dissolved in 1.0 mL of acetonitrile. The resultant solution was stirred for 15 minutes, and a 3.0 μL aliquot was drawn and added to 3.0 mL of acetonitrile in a quartz cuvette.
Sample preparation (75 μM FeCl₃ in 3-pentanone/MeCN)
FeCl₃ (12.1 mg, 0.075 mmol) was dissolved in 1.0 mL of acetonitrile. The resultant solution was stirred for 15 minutes, and a 3.0 μL aliquot was drawn and added to a solution containing 414 μL of 3-pentanone and 2586 μL of acetonitrile in a quartz cuvette. This solution contains the same ratio of 3-pentanone and acetonitrile as the reaction mixture under standard reaction conditions.

![Absorbance vs Wavelength](image1)

Note: The peaks at 240 nm and 313 nm are hidden below the ultraviolet absorbance of the carbonyl C=O.

Sample preparation (75 μM FeCl₃ in 3-pentanone)
FeCl₃ (12.1 mg, 0.075 mmol) was dissolved in 1.0 mL of acetonitrile. The resultant solution was stirred for 15 minutes, and a 3.0 μL aliquot was drawn and added to 3.0 mL of 3-pentanone in a quartz cuvette.

![Absorbance vs Wavelength](image2)

Note: The peaks at 240 nm and 313 nm are hidden below the ultraviolet absorbance of the carbonyl C=O.
Studies of the 1,2-Rearrangement

Relationship between acrylate concentration and RM

To oven-dried 1.5 dram vials were added FeCl₃ (25 mol%). Magnetic stir bars were added and the vials were transferred to a glovebox. Anhydrous acetonitrile (0.4 – 4.0 mL) was then added, followed by pinacolone (5 equiv., 1.0 mmol) and benzyl acrylate (1 equiv., 0.2 mmol). The initial concentration of benzyl acrylate was therefore varied from 0.05M to 0.50 M. The vials were sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. No fan was used, allowing the temperature to reach 60 °C. After 36 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the ratio of unrearranged over rearranged product, RM, was determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

On the basis of the observed linear dependence of RM on [benzyl acrylate]₀, we propose the following model of the 1,2-rearrangement kinetics.

\[
R_M = \frac{[\text{Unrearranged pdt.}]}{[\text{Rearranged pdt.}]} = \frac{k_1[A][B]}{k_2[A]} = \frac{k_1}{k_2} \frac{[B]}{[A]} \approx \frac{k_1}{k_2} [B]_0
\]

Abstraction of a C-H bond from pinacolone yields a primary radical A, which can be consumed by two possible reaction pathways. Direct addition to benzyl acrylate (k₁) yields the unrearranged product. Rearrangement via a cyclopropyl intermediate to the more stable tertiary radical A’ (k₂) may also occur. A’ may then be trapped by benzyl acrylate to yield the rearranged product.

The strong dependence of RM on the concentration of acrylate suggests against a Curtin-Hammett type situation wherein A and A’ are in rapid equilibrium and the ratio of products depends mainly on the barrier to radical addition to the acrylate. We would expect concentration to have little to no effect on RM in a Curtin-Hammett scenario, since both radical additions (of either the primary or tertiary radical) to benzyl acrylate would be bimolecular.
Determining $k_1$ via initial rate experiments

To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (3 mL) was then added, followed by di-tert-butyl ketone (5 equiv.) and benzyl acrylate (2 equiv., 0.20 M). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 3 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the reaction yield and $R_M$ determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

From the earlier equation, we can find $k_1$, the rate constant for addition of the primary radical to benzyl acrylate. The value of $k_2$ for di-tert-butylketone is known to be $1.7 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$ at 25 °C in CCl₄.¹

$$R_M = \frac{k_1}{k_2}[B]_0$$

We found a $R_M$ value of 0.272. This gave $k_1 = 2.3 \times 10^5 \text{ M}^{-1} \text{s}^{-1}$ under our reaction conditions (28°C in MeCN). Given the similar structure of the primary radical formed from initial HAT, we assumed an equivalent $k_1$ value for the addition of the pinacolone primary radical to benzyl acrylate.

The experiment was then repeated with pinacolone as the substrate in place of di-tert-butyl ketone. We found a $R_M$ value of 1.6. Using the same equation above, we obtained a value for the rate constant of 1,2-migration for pinacolone, $k_2 = 2.9 \times 10^4 \text{ s}^{-1}$. This value could then be used to calculate the values of $k_1$ for acceptors other than benzyl acrylate.

Initial rate experiments with other acceptors

To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%) and the appropriate acceptor (if solid) (2 equiv., 0.20 M). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (3 mL) was then added, followed by pinacolone (5 equiv.) and the appropriate acceptor (if liquid) (2 equiv., 0.20 M). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 1-3 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the reaction yield and $R_M$ determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

Reaction time used:
- Maleic anhydride, N-methylmaleimide (4a-b): 1 hour
- Benzyl acrylate, ethyl methacrylate, fumaronitrile, benzylidenemalonitrile (4c-f): 3 hours

The reaction yields were generally below 20% within the time frame, and the effective concentration of the acceptor was assumed to be equal to the initial concentration of acceptor (i.e. 0.20 M).
Other variations of reaction conditions and effect on $R_M$

A. Increased acrylate equiv., reduced reaction time

To an oven-dried 1.5 dram vial was added FeCl$_3$ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.33 M) was then added, followed by pinacolone (5 equiv.) and benzyl acrylate (1.5 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 12 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the reaction yield and $R_M$ determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.

B. Portionwise addition of acrylate, extended reaction time

To an oven-dried 1.5 dram vial was added FeCl$_3$ (25 mol%). A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.10 M) was then added, followed by pinacolone (5 equiv.) and benzyl acrylate (0.33 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. No fan was used, allowing the temperature to reach 60 °C. After 24 hours, the vial was transferred into a glovebox and another portion of benzyl acrylate (0.33 equiv.) was added. This was repeated again after another 24 hours. After 72 hours, the reaction mixture was concentrated in vacuo and flushed through a silica plug using dichloromethane as the eluent. The solvent was removed again in vacuo and the reaction yield and $R_M$ determined by NMR using 1,3,5-trimethoxybenzene as the internal standard.
Starting Material Preparation

4-(tert-butyl)phenyl acetate

Prepared in accordance to reported methods.\(^2\)

\[
\text{Ac}_2\text{O} \\ \\
\begin{array}{c}
\text{OH} \\
\text{tBu}
\end{array} \\ \\
\begin{array}{c}
\text{neat} \\
\text{3 drops conc. H}_2\text{SO}_4
\end{array} \\ \\
\begin{array}{c}
\text{OAc} \\
\text{tBu}
\end{array}
\]

To a mixture of 4-tertbutylphenol (3.00 g, 20 mmol) and acetic anhydride (1.89 mL, 20 mmol) was added three drops of concentrated H\(_2\)SO\(_4\) at room temperature. The reaction mixture was stirred for 30 min and poured into water (10 mL), then extracted with ethyl acetate (3 x 20 mL), dried with MgSO\(_4\) and concentrated under reduced pressure to yield the product as a pale yellow oil (3.71g, 96% yield). The NMR spectrum of the product was in agreement with literature precedent.\(^3,4\)

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.41 – 7.35 (m, 2H), 7.03 – 6.98 (m, 2H), 2.29 (s, 3H), 1.32 (s, 9H).

\(^1\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 169.84, 148.74, 148.45, 126.45, 120.98, 34.60, 31.54, 21.29.

\(2,2,5,5\)-tetramethylcyclopentanone

Prepared in accordance to reported methods.\(^5\)

\[
\begin{array}{c}
\text{O} \\
\text{DMSO, 50 °C}
\end{array} \\ \\
\begin{array}{c}
\text{KOH (20 equiv.)} \\
\text{Mel (8 equiv.)}
\end{array}
\]

In a round-bottomed flask equipped with a reflux condenser, dimethyl sulfoxide (20 mL) was heated to 50 °C. Cyclopentanone (0.846 g, 10 mmol), methyl iodide (5.0 mL, 80 mmol) and potassium hydroxide (11.2 g, 200 mmol) were then added and the resultant mixture stirred for 1 h. The mixture was extracted with pentane (3x10mL). The combined organic phases were washed with distilled water (3x10 mL), dried with MgSO\(_4\) and concentrated under reduced pressure. The resultant crude product was then passed through a short plug of silica (5% ethyl acetate/hexanes) to obtain the product as a colorless oil (726 mg, 52% yield). The NMR spectrum of the product was in agreement with literature precedent.\(^5\)

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 1.76 (s, 3H), 1.04 (s, 12H).

\(^1\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 227.22, 45.44, 35.01, 25.06.
3-methyl-3-phenylbutan-2-one

Prepared in accordance to reported methods.\textsuperscript{6,7}

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

To a solution of 2-phenylisobutyric acid (1.23 g, 7.5 mmol) in diethyl ether (50 mL, 0.15M) at −30 °C was added a solution of methyllithium (1.6 M in diethyl ether, 14.0 mL, 3.0 equiv.) dropwise. The resulting solution was allowed to warm to room temperature and kept stirring for 1.5 h. The reaction was then cooled to 0 °C and poured into iced hydrogen chloride solution, extracted with hexanes (3×20 mL). The organic phase was combined, dried with MgSO\textsubscript{4}, concentrated under reduced pressure and purified with column chromatography on silica gel (5\% ethyl acetate/hexanes) to afford the product as a colorless oil (702 mg, 58\% yield). The NMR spectrum of the product was in agreement with literature precedent.\textsuperscript{8}

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) $\delta$ 7.39 – 7.31 (m, 2H), 7.26 (m, 3H), 1.92 (s, 3H), 1.48 (s, 6H).

\textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}) $\delta$ 211.31, 144.22, 128.89, 126.99, 126.07, 52.61, 25.66, 25.26.
Standard Reaction Conditions

![Chemical Reaction Diagram](image)

A) To an oven-dried 1.5 dram vial was added FeCl₃ (25 mol%). Any solid reactants were also added at this stage. A magnetic stir bar was added and the vial was transferred to a glovebox. Anhydrous acetonitrile (1 mL, 0.33 M) was then added, followed by the C-H substrate (5 equiv.) and the electron-deficient alkene (1 equiv.). The vial was sealed and then placed on a stir plate 2-3 inches away from a 390 nm Kessil lamp. Ambient temperature was maintained with the use of a fan above the set-up. After 36 hours, the reaction mixture was concentrated in vacuo and purified using silica gel flash column chromatography, using ethyl acetate/hexanes as the eluent.

B) Identical to standard reaction conditions A, but using 3 mL of anhydrous acetonitrile instead (0.1 M) and without a fan (allowing the reaction to reach a temperature of 60 °C due to the heat dissipated by the LED lamps).

C) [For acyl chlorides] Identical to standard reaction conditions A, but upon completion of the reaction, K₂PO₄ (1 equiv.) and ethanol (1 mL) were added. The solution was then stirred overnight to ensure complete ethanolysis, then concentrated in vacuo and purified via silica gel flash column chromatography.
Characterization of Products

C-H Scope

3a Benzyl 6-oxooctanoate

\[
\text{O} \quad \text{CO}_2\text{Bn}
\]

Prepared using standard reaction conditions A from 3-pentanone.

Yield = 54%, colorless oil. R\(_f\) = 0.4 (5:1 hexanes : ethyl acetate).

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.62 – 7.12 (m, 5H), 5.11 (s, 2H), 2.54 – 2.25 (m, 6H), 1.72 – 1.51 (m, 4H), 1.04 (t, \(J = 7.4\) Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 211.12, 173.26, 136.14, 128.63, 128.38, 128.28, 66.24, 41.92, 35.95, 34.13, 24.56, 23.34, 7.90.

IR, film (cm\(^{-1}\)): 2939, 1732, 1712, 1497, 1455, 1414, 1377, 1211, 1113, 1084, 976, 739, 697.

LRMS m/z (EI): calculated for C\(_{14}\)H\(_{18}\)O\(_3\) [M\(^+\)] 248.14, found 248.1.

3b Ethyl 6-oxooctanoate

\[
\text{O} \quad \text{CO}_2\text{Et}
\]

Prepared using standard reaction conditions A from 3-pentanone.

Yield = 51%, colorless oil. R\(_f\) = 0.3 (5:1 hexanes : ethyl acetate).

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 4.09 (q, \(J = 7.1\) Hz, 2H), 2.39 (m, 4H), 2.34 – 2.19 (m, 2H), 1.69 – 1.52 (m, \(J = 4.9\) Hz, 4H), 1.22 (t, \(J = 7.1\) Hz, 3H), 1.02 (t, \(J = 7.3\) Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 211.28, 172.51, 60.35, 41.98, 35.98, 34.17, 24.58, 23.35, 14.31, 7.89.

IR, film (cm\(^{-1}\)): 2939, 1731, 1713, 1459, 1415, 1372, 1247, 1178, 1113, 1032.

LRMS m/z (EI): calculated for C\(_{14}\)H\(_{18}\)O\(_3\) [M\(^+\)] 248.14, found 248.1.

3c Phenyl 6-oxooctanoate

\[
\text{O} \quad \text{CO}_2\text{Ph}
\]

Yield = 52%, colorless oil. R\(_f\) = 0.4 (5:1 hexanes : ethyl acetate).

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta\) 7.44 – 7.34 (m, 2H), 7.27 – 7.20 (m, 1H), 7.09 (m, 2H), 2.60 (t, \(J = 7.1\) Hz, 2H), 2.50 (t, \(J = 6.9\) Hz, 2H), 2.46 (q, \(J = 7.3\) Hz, 2H), 1.82 – 1.62 (m, 4H), 1.08 (t, \(J = 7.4\) Hz, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta\) 211.25, 172.02, 150.76, 129.50, 125.87, 121.65, 41.93, 36.04, 34.25, 24.54, 23.26, 7.93.

IR, film (cm\(^{-1}\)): 2938, 1755, 1710, 1593, 1491, 1456, 1413, 1372, 1192, 1162, 1130, 749, 690, 500.

LRMS m/z (EI): calculated for C\(_{14}\)H\(_{18}\)O\(_3\) [M\(^+\)] 234.13, found 234.1.

3d Benzyl 6-oxoheptanoate

\[
\text{O} \quad \text{CO}_2\text{Bn}
\]

Prepared using standard reaction conditions A from 2-butanone.

Yield = 50%, colorless oil. R\(_f\) = 0.4 (5:1 hexanes : ethyl acetate).
1H NMR (500 MHz, CDCl3) δ 7.39 – 7.27 (m, 5H), 5.11 (s, 2H), 2.43 (t, J = 6.9 Hz, 2H), 2.37 (t, J = 7.0 Hz, 2H), 2.11 (s, 3H), 1.73 – 1.51 (m, 4H).

13C NMR (126 MHz, CDCl3) δ 208.49, 173.26, 136.12, 128.65, 128.30, 66.27, 43.30, 34.11, 29.94, 24.46, 23.26.

IR, film (cm⁻¹): 2938, 1731, 1713, 1497, 1454, 1416, 1358, 1213, 1143, 1080, 968, 739, 698.

LRMS m/z (EI): calculated for C14H18O3 [M⁺] 234.13, found 234.1.

3e Ethyl 6-oxoheptanoate

Prepared using standard reaction conditions A from 2-butanone.

Yield = 44%, colorless oil. Rf = 0.35 (5:1 hexanes : ethyl acetate).

1H NMR (500 MHz, CDCl3) δ 4.10 (q, J = 7.1 Hz, 2H), 2.48 – 2.38 (m, 2H), 2.36 – 2.25 (m, 2H), 2.12 (s, 3H), 1.71 – 1.53 (m, 4H), 1.23 (t, J = 7.1 Hz, 3H).

13C NMR (126 MHz, CDCl3) δ 208.65, 173.51, 60.40, 43.38, 34.17, 29.99, 24.50, 23.28, 14.34.

IR, film (cm⁻¹): 2939, 1729, 1714, 1418, 1370, 1176, 1092, 1030.

LRMS m/z (EI): calculated for C14H18O3 [M⁺] 234.13, found 234.1.

3f Ethyl 4-methyl-6-oxononanoate – major (β-alkylated)

Prepared using standard reaction conditions A from 4-heptanone.

Yield = 81%, 2.3:1 mixture of β:γ alkylated products. Colorless oil. Rf = 0.4 (5:1 hexanes : ethyl acetate).

1H NMR (500 MHz, CDCl3) δ 4.08 (q, J = 7.1 Hz, 2H), 2.37 – 2.18 (m, 6H), 2.00 (tdt, J = 7.9, 6.8, 5.6 Hz, 1H), 1.65 – 1.52 (m, 4H), 1.49 – 1.41 (m, 1H), 1.31 – 1.25 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 1.49 – 1.41 (m, 1H), 1.31 – 1.25 (m, 1H), 1.21 (t, J = 7.1 Hz, 3H), 1.08 – 0.85 (overlapping triplet and doublet, 6H).

13C NMR (126 MHz, CDCl3) δ 210.48, 173.59, 60.28, 49.81, 45.26, 32.02, 31.75, 28.64, 19.44, 17.17, 14.20, 13.71.

IR (neat): cm⁻¹: 2960, 2874, 1732, 1711, 1459, 1412, 1371, 1253, 1176, 1097, 1032.

LRMS m/z (EI): calculated for C12H22O3 [M⁺] 214.16, found 214.2. (Retention time = 4.780 min)

Ethyl 7-oxodecanoate – minor (γ-alkylated)

1H NMR (500 MHz, CDCl3) δ 4.08 (q, J = 7.1 Hz, 2H), 2.37 – 2.18 (m, 6H), 1.65 – 1.52 (m, 8H), 1.21 (t, J = 7.1 Hz, 3H), 0.89 – 0.85 (t, 3H).

13C NMR (126 MHz, CDCl3) δ 211.09, 173.62, 60.18, 44.70, 42.45, 34.10, 28.66 (overlaps with major isomer peak), 24.69, 23.35, 17.26, 14.21, 13.73.

IR (neat): cm⁻¹

LRMS m/z (EI): calculated for C12H22O3 [M⁺] 214.16, found 214.2. (Retention time = 5.003 min)

Regioselectivity based on the integration of the characteristic peaks of the major isomer at 2.00 ppm (tdt, 1H) against the integration of the ester CH₂ and CH₃ peaks (which contain the peaks from both isomers). Setting the integral of the ester CH₂ to 2.00, an integral of 0.69 was obtained for the characteristic peak at 2.00 ppm, which corresponds to a 70:30 ratio of isomers (2.3:1).
3g Benzyl 6-oxo-4-phenylheptanoate

\[
\text{\includegraphics[width=0.1\textwidth]{benzyl_6-oxo-4-phenylheptanoate.png}}
\]

Prepared using standard reaction conditions A from 4-phenyl-2-butanoic acid.

**Yield** = 28%, yellow oil. Rf = 0.3 (9:1 hexanes : ethyl acetate).

**\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.23 (m, 7H), 7.24 – 7.17 (m, 1H), 7.18 – 7.12 (m, 2H), 5.10 – 4.97 (m, 2H), 3.19 – 3.07 (m, 1H), 2.82 – 2.68 (m, 2H), 2.32 – 2.11 (m, 2H), 2.10 – 1.95 (4H; s, 3H overlapping with m, 1H), 1.93 – 1.82 (m, 1H).

**\(^13C\) NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 207.29, 173.13, 143.06, 135.92, 128.70, 128.56, 128.28, 128.24, 127.55, 126.78, 66.23, 50.66, 40.50, 32.24, 31.18, 30.57.

**IR**, film (cm\(^{-1}\)): 3029, 2932, 1729, 1717, 1602, 1494, 1453, 1417, 1357, 1253, 1214, 1150, 752, 699.

**LRMS** m/z (EI): calculated for C\(_{20}\)H\(_{22}\)O\(_3\) [M\(^+\)] 310.16, found 310.2.

3h Diethyl 2-methylhexanedioate

\[
\text{\includegraphics[width=0.1\textwidth]{diethyl_2-methylhexanedioate.png}}
\]

Prepared using reaction conditions C from isobutyryl chloride.

**Yield** = Colorless oil. Rf = 0.5 (5:1 hexanes : ethyl acetate).

**\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 4.12 (overlapping quartets, 4H), 2.43 (m, 1H), 2.29 (t, \(J = 7.3\) Hz, 2H), 1.79 – 1.54 (m, 3H), 1.49 – 1.38 (m, 1H), 1.25 (overlapping triplets, 6H), 1.15 (d, \(J = 7.0\) Hz, 3H).

**\(^13C\) NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 176.50, 173.41, 60.30, 60.25, 39.30, 34.16, 33.10, 22.67, 17.06, 14.26, 14.25.

**IR**, film (cm\(^{-1}\)): 2978, 1730, 1461, 1373, 1348, 1249, 1158, 1113, 1029.

**HRMS** m/z (ESI): calculated for C\(_{11}\)H\(_{20}\)O\(_4\) [M+Na\(^+\)] 217.1440, found 217.1431.

3i Benzyl 5-cyanopentanoate

\[
\text{\includegraphics[width=0.1\textwidth]{benzyl_5-cyanopentanoate.png}}
\]

Prepared using standard reaction conditions A from propionitrile.

**Yield** = 32%, colorless oil. Rf = 0.25 (5:1 hexanes : ethyl acetate).

**\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 7.36 (m, 5H), 5.12 (s, 2H), 2.42 (t, \(J = 7.1\) Hz, 2H), 2.36 (t, \(J = 7.0\) Hz, 2H), 1.84 – 1.78 (m, 2H), 1.74 – 1.64 (m, 2H).

**\(^13C\) NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 172.68, 135.89, 128.74, 128.47, 128.41, 119.42, 66.54, 33.39, 24.90, 24.00, 17.10.

**IR**, film (cm\(^{-1}\)): 2948, 2246, 1731, 1497, 1455, 1421, 1385, 1353, 1149, 742, 698.

**HRMS** m/z (ESI): calculated for C\(_{13}\)H\(_{15}\)NO\(_2\) [M+Na\(^+\)] 240.1001, found 240.1014.

3j Ethyl 5-cyanoheptanoate

\[
\text{\includegraphics[width=0.1\textwidth]{ethyl_5-cyanoheptanoate.png}}
\]

Prepared using standard reaction conditions A from isobutyronitrile.

**Yield** = 45%, colorless oil. Rf = 0.2 (5:1 hexanes : ethyl acetate).

**\(^1H\) NMR** (500 MHz, CDCl\(_3\)) \(\delta\) 4.13 (q, \(J = 7.2\) Hz, 2H), 2.62 (dqd, \(J = 8.4, 7.1, 5.9\) Hz, 1H), 2.35 (t, \(J = 7.2\) Hz, 2H), 1.92 – 1.70 (m, 2H), 1.69 – 1.56 (m, 2H), 1.33 (d, \(J = 7.1\) Hz, 3H), 1.25 (t, \(J = 7.1\) Hz, 3H).

**\(^13C\) NMR** (126 MHz, CDCl\(_3\)) \(\delta\) 172.97, 122.79, 60.62, 33.64, 33.45, 25.49, 22.48, 18.04, 14.34.

**IR**, film (cm\(^{-1}\)): 2979, 2939, 2238, 1730, 1458, 1374, 1347, 1296, 1248, 1165, 1095, 1030.
LRMS m/z (EI): calculated for C₉H₁₅NO₂ [M⁺] 169.11, found 169.1.

3k Ethyl 5-cyano-5-methylhexanoate

\[
\text{CO}_2\text{Et} \quad \text{NC}
\]

Prepared using standard reaction conditions A from pivalonitrile.

**Yield** = 44%, colorless oil. Rf = 0.25 (5:1 hexanes : ethyl acetate).

\[\text{H NMR} \ \text{(400 MHz, CDCl}_3\text{)} \ \delta 4.13 \ (q, J = 7.1 \text{ Hz}, 2\text{H}), \ 2.35 \ (t, J = 7.2 \text{ Hz}, 2\text{H}), \ 1.88 \text{–} 1.73 \ (m, 2\text{H}), \ 1.63 \text{–} 1.51 \ (m, 2\text{H}), \ 1.35 \ (s, 6\text{H}), \ 1.25 \ (t, J = 7.1 \text{ Hz}, 3\text{H}).\]

\[\text{C NMR} \ \text{(101 MHz, CDCl}_3\text{)} \ \delta 172.97, \ 124.93, \ 60.55, \ 40.44, \ 34.05, \ 32.35, \ 26.68, \ 20.81, \ 14.34.\]

IR, film (cm⁻¹): 2979, 2234, 1730, 1460, 1371, 1346, 1256, 1187, 1130, 1095, 1050, 1029, 752.

LRMS m/z (EI): calculated for C₁₀H₁₇NO₂ [M⁺] 183.13, found 183.1.

3l Ethyl 3-(3-oxocyclobutyl)propanoate

\[
\text{CO}_2\text{Et}
\]

Prepared using standard reaction conditions A from cyclobutanone.

**Yield** = 39%, yellow oil. Rf = 0.3 (5:1 hexanes : ethyl acetate).

\[\text{H NMR} \ \text{(500 MHz, CDCl}_3\text{)} \ \delta 4.13 \ (q, J = 7.1 \text{ Hz}, 2\text{H}), \ 3.24 \text{–} 3.08 \ (m, 1\text{H}), \ 2.78 \text{–} 2.63 \ (m, 1\text{H}), \ 2.37 \ (s, 0\text{H}), \ 2.34 \ (t, J = 7.5 \text{ Hz}, 1\text{H}), \ 1.92 \ (q, J = 7.6 \text{ Hz}, 2\text{H}), \ 1.26 \ (t, J = 7.1 \text{ Hz}, 3\text{H}).\]

\[\text{C NMR} \ \text{(126 MHz, CDCl}_3\text{)} \ \delta 207.51, \ 173.06, \ 60.64, \ 52.48, \ 33.18, \ 31.45, \ 23.58, \ 14.34.\]

IR, film (cm⁻¹): 2979, 1780, 1728, 1448, 1374, 1342, 1251, 1179, 1099, 1028.

HRMS m/z (ASAP): calculated for C₉H₁₄O₃ [M+H]⁺ 171.1021, found 171.1012.

3m Ethyl 3-(3-oxocyclopentyl)propanoate

\[
\text{CO}_2\text{Et}
\]

Prepared using standard reaction conditions A from cyclopentanone.

**Yield** = 61%, yellow oil. Rf = 0.25 (5:1 hexanes : ethyl acetate).

\[\text{H NMR} \ \text{(500 MHz, CDCl}_3\text{)} \ \delta 4.12 \ (q, J = 7.2 \text{ Hz}, 2\text{H}), \ 2.45 \text{–} 2.22 \ (m, 4\text{H}), \ 2.23 \text{–} 1.97 \ (m, 3\text{H}), \ 1.89 \text{–} 1.66 \ (m, 3\text{H}), \ 1.59 \text{–} 1.40 \ (m, 1\text{H}), \ 1.24 \ (t, J = 7.2 \text{ Hz}, 3\text{H}).\]

\[\text{C NMR} \ \text{(126 MHz, CDCl}_3\text{)} \ \delta 218.74, \ 173.18, \ 60.42, \ 44.83, \ 38.42, \ 36.66, \ 32.67, \ 30.59, \ 29.24, \ 14.21.\]

IR, film (cm⁻¹): 2933, 1729, 1453, 1404, 1371, 1349, 1303, 1241, 1179, 1158, 1033.

HRMS m/z (ASAP): calculated for C₁₀H₁₆O₃ [M+H]⁺ 185.1178, found 185.1167.

3n Benzyl 3-(1,1-dioxidotetrahydrothiophen-3-yl)propanoate

\[
\text{CO}_2\text{Bn}
\]

Prepared using standard reaction conditions A from sulfolane.

**Yield** = 58%, colorless viscous oil. Rf = 0.3 (1:1 hexanes : ethyl acetate).

\[\text{H NMR} \ \text{(500 MHz, CDCl}_3\text{)} \ \delta 7.62 \text{–} 6.99 \ (m, 5\text{H}), \ 5.12 \ (s, 2\text{H}), \ 3.19 \ (tdd, J = 13.2, 7.8, 2.1 \text{ Hz}, 2\text{H}), \ 2.99 \ (ddd, J = 13.2, 11.3, 7.7 \text{ Hz}, 1\text{H}), \ 2.64 \ (dd, J = 13.0, 10.8 \text{ Hz}, 1\text{H}), \ 2.41 \ (t, J = 7.5 \text{ Hz}, 2\text{H}), \ 2.31 \ (ddd, J = 14.9, 7.7, 3.5, 1.6 \text{ Hz}, 1\text{H}), \ 1.93 \text{–} 1.75 \ (m, 3\text{H}).\]
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 172.31, 135.67, 128.73, 128.54, 128.46, 77.40, 77.15, 76.90, 66.69, 56.61, 52.26, 36.16, 31.99, 29.50, 28.94.
IR, film (cm$^{-1}$): 2940, 1728, 1497, 1454, 1414, 1388, 1354, 1301, 1268, 1168, 1117, 749, 698, 570, 460.
LRMS m/z (EI): calculated for C$_{14}$H$_{18}$O$_4$S [M$^+$] 282.09, found 282.1.

3o Ethyl 3-(5-oxobicyclo[2.2.1]heptan-2-yl)propanoate

Prepared using standard reaction conditions A from norcamphor.
Yield = 37%, yellow oil. Rf = 0.2 (5:1 hexanes : ethyl acetate).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.11 (q, J = 7.1 Hz, 2H), 2.55 (d, J = 4.7 Hz, 1H), 2.39 (d, J = 3.3 Hz, 1H), 2.34 – 2.26 (m, 2H), 2.06 (dd, J = 17.7, 4.7 Hz, 1H), 1.79 (dd, J = 17.7, 4.1 Hz, 1H), 1.76 – 1.54 (m, 6H), 1.32 (dt, J = 13.0, 4.5 Hz, 1H), 1.24 (t, J = 7.0 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 217.87, 173.47, 60.51, 50.25, 45.65, 39.97, 39.84, 34.76, 32.91, 31.68, 31.52, 14.33.
IR, film (cm$^{-1}$): 2957, 1730, 1448, 1410, 1372, 1350, 1298, 1256, 1095, 1027, 960, 928, 860, 779, 570, 467
LRMS m/z (EI): calculated for C$_{12}$H$_{18}$O$_3$ [M$^+$] 210.13, found 210.1.
*See NMR Spectra section for 2D NMR spectra and proton/carbon assignments.

Acceptor Scope

4a Ethyl 2-methyl-6-oxooctanoate

Prepared using reaction conditions A from ethyl methacrylate.
Yield = 41%, yellow oil. Rf = 0.45 (5:1 hexanes : ethyl acetate).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.11 (q, J = 7.1 Hz, 2H), 2.40 (m, 5H), 1.68 – 1.48 (m, 3H), 1.44 – 1.34 (m, 1H), 1.24 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.04 (t, J = 7.3 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 211.40, 176.68, 60.34, 42.21, 39.53, 36.00, 33.31, 21.63, 17.20, 14.37, 7.93.
IR, film (cm$^{-1}$): 2976, 2938, 1728, 1716, 1459, 1414, 1374, 1251, 1160, 1029.
HRMS m/z (ASAP): calculated for C$_{11}$H$_{20}$O$_3$ [M+H]$^+$ 201.1491, found 201.1486.

4b 2-methyl-6-oxooctanenitrile

Prepared using reaction conditions A from methacrylonitrile.
Yield = 63%, colorless oil. Rf = 0.35 (5:1 hexanes : ethyl acetate).
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 2.64 – 2.55 (m, 1H), 2.45 (t, J = 7.1 Hz, 2H), 2.40 (t, J = 7.3 Hz, 2H), 1.82 – 1.65 (m, 2H), 1.62 – 1.50 (m, 2H), 1.30 (d, J = 7.1 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H).
$^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 210.67, 122.89, 41.34, 36.01, 33.47, 25.56, 21.22, 17.98, 7.85.
IR, film (cm$^{-1}$): 2976, 2939, 2237, 1711, 1457, 1413, 1376, 1115, 1031.
HRMS m/z (ASAP): calculated for C$_{9}$H$_{15}$NO [M+H]$^+$ 154.1232, found 154.1228.
4c 7-(phenylsulfonyl)heptan-3-one

\[
\begin{align*}
\text{SO}_2\text{Ph} & \\
\end{align*}
\]

Prepared using reaction conditions A from phenyl vinyl sulfone.

**Yield** = 51%, yellow oil. Rf = 0.3 (1:1 hexanes : ethyl acetate).

**^1H NMR** (500 MHz, CDCl₃) δ 7.94 – 7.83 (m, 1H), 7.68 – 7.61 (m, 0H), 7.56 (dd, J = 8.4, 6.9 Hz, 1H), 3.46 – 2.86 (m, 2H), 2.38 (p, J = 7.1 Hz, 2H), 1.82 – 1.48 (m, 2H), 1.01 (t, J = 7.3 Hz, 1H).

**^13C NMR** (126 MHz, CDCl₃) δ 210.51, 139.18, 133.82, 129.41, 128.11, 56.15, 41.45, 36.06, 22.38, 22.36, 7.86.

**IR**, film (cm⁻¹): 2938, 1709, 1446, 1410, 1374, 1291, 1113, 1085, 731, 689, 592, 563, 533.

**LRMS** m/z (EI): calculated for C₁₃H₁₈O₃S [M⁺] 254.10, found 254.1.

4d 3-(3-oxopentyl)dihydrofuran-2,5-dione

\[
\begin{align*}
\end{align*}
\]

Prepared using reaction conditions B from maleic anhydride.

**Yield** = 68%, yellow oil. Rf = 0.3 (3:1 hexanes : ethyl acetate, 1% acetic acid).

**^1H NMR** (400 MHz, CDCl₃) δ 3.24 – 3.06 (m, 2H), 2.76 – 2.56 (m, 3H), 2.45 (q, J = 7.3 Hz, 2H), 2.12 – 1.93 (m, 2H), 1.05 (t, J = 7.3 Hz, 3H).

**^13C NMR** (101 MHz, CDCl₃) δ 209.91, 173.51, 169.85, 39.61, 38.56, 36.15, 34.66, 25.00, 7.82.

**IR**, film (cm⁻¹): 2940, 1858, 1774, 1708, 1457, 1412, 1376, 1226, 1093, 1018, 963, 909, 721, 572, 410

**LRMS** m/z (EI): calculated for C₉H₁₂O₄ [M⁺] 184.07, found 184.1.

4e 1-methyl-3-(3-oxopentyl)pyrrolidine-2,5-dione

\[
\begin{align*}
\end{align*}
\]

Prepared using reaction conditions A from N-methyl maleimide.

**Yield** = 57%, yellow oil. Rf = 0.2 (1:1 hexanes : ethyl acetate).

**^1H NMR** (500 MHz, CDCl₃) δ 2.94 (s, 3H), 2.89 – 2.75 (m, 2H), 2.71 – 2.55 (m, 2H), 2.43 (q, J = 7.3 Hz, 2H), 2.33 (dd, J = 17.3, 3.7 Hz, 1H), 2.05 – 1.95 (m, 1H), 1.93 – 1.83 (m, 1H), 1.04 (t, J = 7.3 Hz, 3H).

**^13C NMR** (126 MHz, CDCl₃) δ 210.16, 179.70, 176.39, 39.04, 38.84, 36.11, 34.86, 25.64, 24.85, 7.84.

**IR**, film (cm⁻¹): 2938, 1774, 1691, 1434, 1379, 1278, 1117, 954, 698.

**HRMS** m/z (ASAP): calculated for C₁₀H₁₅N₂O₃ [M+H⁺] 198.1130, found 198.1127.

4f 2-(3-oxopentyl)succinonitrile

\[
\begin{align*}
\end{align*}
\]

Prepared using reaction conditions B from fumaronitrile.

**Yield** = 79%, yellow oil. Rf = 0.3 (1:1 hexanes : ethyl acetate).

**^1H NMR** (500 MHz, CDCl₃) δ 3.11 (dtd, J = 10.4, 6.5, 5.0 Hz, 1H), 2.89 – 2.75 (m, 2H), 2.71 – 2.55 (m, 2H), 2.43 (q, J = 7.3 Hz, 2H), 2.06 (dddt, J = 13.9, 8.1, 6.9, 5.0 Hz, 1H), 1.90 (ddddd, J = 13.9, 10.4, 6.4, 5.6 Hz, 1H), 1.04 (t, J = 7.3 Hz, 3H).

**^13C NMR** (126 MHz, CDCl₃) δ 209.21, 118.72, 115.70, 38.29, 36.03, 27.69, 25.51, 21.22, 7.71.

**IR**, film (cm⁻¹): 2939, 2360, 2340, 2248, 1711, 1418, 1375, 1117.

**HRMS** m/z (ASAP): calculated for C₁₀H₁₂N₂O [M+H⁺] 165.1028, found 165.1035.
**4g 2-(4-oxo-1-phenylhexyl)malononitrile**

![Structural formula of 2-(4-oxo-1-phenylhexyl)malononitrile]

Prepared using reaction conditions B from benzylidenemalonitrile.  
**Yield = 54%, yellow oil. Rf = 0.3 (3:1 hexanes : ethyl acetate).**

**¹H NMR** (500 MHz, CDCl₃) δ 7.48 – 7.35 (m, 3H), 7.34 – 7.25 (m, 2H), 3.95 (d, J = 6.4 Hz, 1H), 3.32 (ddd, J = 11.4, 6.3, 3.5 Hz, 1H), 2.42 – 1.98 (m, 6H), 0.99 (t, J = 7.3 Hz, 3H).

**¹³C NMR** (126 MHz, CDCl₃) δ 209.80, 135.94, 129.59, 129.29, 128.05, 111.83, 45.54, 38.89, 36.10, 30.41, 26.12, 7.82.

**IR**, film (cm⁻¹): 3468 (weak, broad), 2977, 2903, 2254, 1710, 1603, 1496, 1455, 1411, 1376, 1115, 763, 703.

**HRMS m/z (ASAP):** calculated for C₁₅H₁₆N₂O [M+H]^+ 241.1341, found 241.1344.

**4h 2-ethyl-2-hydroxy-5-phenylcyclopentane-1,1-dicarbonitrile (minor component)**

![Structural formula of 2-ethyl-2-hydroxy-5-phenylcyclopentane-1,1-dicarbonitrile]

**¹H NMR** (500 MHz, CDCl₃) Characteristic peaks: δ 7.52 – 7.48 (m, 2H), 4.12 (dd, J = 11.0, 8.7 Hz, 1H, benzylic C-H), 1.62 (broad s, 1H, -OH), 1.16 (t, J = 7.5 Hz, 3H, -CH₂CH₃).

Ratio of acyclic product to cyclic product (4i:4ia) determined by comparison of the integral of the peak at 3.32 ppm to the peak at 4.12 ppm (1.0 to 0.11 = 9:1).

**¹³C NMR** (126 MHz, CDCl₃) δ 134.91, 129.03, 128.98, 128.47, 114.54, 113.41, 88.14, 54.30, 52.63, 35.06, 31.31, 26.38, 8.10.
**Rearrangement Scope**

\[ R_M = \text{the ratio of unrearranged to rearranged product.} \]

**5a**

Conditions A: Yield = 59%, \( R_M = 1:1.4 \)
Conditions B: Yield = 64%, \( R_M = 1:10 \)

From pinacolone

Benzyl 5,5-dimethyl-6-oxoheptanoate (unrearranged product) – minor

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Bn} \\
\end{align*}
\]

\(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) Characteristic peaks: \( \delta \) 2.09 (s, 3H, \( \text{CH}_3\text{CO}^-\)), 1.10 (s, 6H, dimethyl).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\textsubscript{3}) \( \delta \) 213.77, 176.45, 60.33, 47.66, 39.98, 37.35, 28.85, 25.08, 24.39, 24.31, 17.29, 14.37.

Using Conditions B: We were able to separate 40.1 mg of product from mixed fractions containing both isomers as well as 10.4 mg containing only the rearranged product.

\( R_M \) for the mixed fractions determined by comparing the integral of the peaks at 2.12 ppm (s, 3H, \( \text{CH}_3\text{CO}^-\)) and 0.99 ppm (s, 6H, dimethyl) to those of the characteristic peaks. \( R_M = 1:7.4 \)

Taking into account the 10.4 mg of rearranged product isolated separately gives an overall \( R_M = 1:10 \).

Benzyl 4,4-dimethyl-6-oxoheptanoate (rearranged product) – major

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Bn} \\
\end{align*}
\]

Colorless oil. \( R_f = 0.40 \) (5:1 hexanes : ethyl acetate).

\(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.41 – 7.29 (m, 5H), 5.11 (s, 2H), 2.40 – 2.26 (m, 4H), 2.12 (s, 3H), 1.77 – 1.63 (m, 2H), 0.99 (s, 6H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\textsubscript{3}) \( \delta \) 208.37, 173.77, 135.97, 128.59, 128.30, 128.26, 66.32, 53.55, 36.69, 33.08, 32.52, 29.62, 26.80.

\( \text{IR, film (cm}^{-1}\)\): 2956, 1732, 1715, 1497, 1454, 1361, 1298, 1211, 971, 747, 698.

\( \text{LRMS m/z (EI)}\) calculated for C\textsubscript{16}H\textsubscript{22}O\textsubscript{3} [M\textsuperscript{+}] 262.16, found 262.1.

**5b**

Conditions A: Yield = 65%, \( R_M = 3:1 \)
Conditions B: Yield = 63%, \( R_M = 1:3 \) (NMR yield)

From 2,4-dimethyl-3-pentanone

Benzyl 5,7-dimethyl-6-oxooctanoate (unrearranged product) – major

\[
\begin{align*}
\text{O} & \quad \text{CO}_2\text{Bn} \\
\end{align*}
\]

\( \text{Yield} = 65\% \), yellow oil. \( R_r = 0.40 \) (5:1 hexanes : ethyl acetate).

\(^1\text{H NMR}\) (400 MHz, CDCl\textsubscript{3}) \( \delta \) 7.41 – 7.24 (m, 5H), 5.11 (s, 2H), 2.69 (m, 2H), 2.45 – 2.22 (m, 2H), 1.74 – 1.46 (m, 3H), 1.38 – 1.18 (m, 1H), 1.15 – 0.97 (m, 9H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\textsubscript{3}) \( \delta \) 217.90, 173.15, 136.08, 128.57, 128.23, 66.19, 44.11, 39.62, 34.28, 32.39, 22.86, 18.34, 16.81.
IR, film (cm⁻¹): 2966, 2933, 2873, 1734, 1708, 1497, 1456, 1381, 1242, 1212, 1159, 1027, 1001, 738, 697.
LRMS m/z (EI): calculated for C₁₇H₂₄O₃ [M⁺] 276.17, found 276.2.

Benzyl 4,7-dimethyl-6-oxooctanoate (rearranged product)

\[
\begin{align*}
\text{O} & & \text{CO₂Bn} \\
\end{align*}
\]

\(^1\)H NMR (400 MHz, CDCl₃) Characteristic peaks: \(\delta 2.54\) (sept, \(J = 6.9\) Hz, 1H, \((\text{CH₃})₂\text{CHC(O)-CH₂-CHMe-})\), \(2.05\) (tdt, \(J = 8.0, 6.9, 5.6\) Hz, 1H, Me₂CHC(O)-CH₂-CHMe-), \(0.89\) (d, \(J = 6.7\) Hz, 3H, Me₂CHC(O)-CH₂-CHMe-).

\(R_M\) determined by comparing the integral of the peak at 2.69 ppm (overlapping sept., 2H, Me₂CHC(O)-CH₂-CHMe-) to the sum of the characteristic peaks at 2.54 ppm (sept.) and 2.05 ppm (m).

5c
Conditions A: Yield = 54%, \(R_M = 11:1\)
Conditions B: Yield = 45%, \(R_M = 1.6:1\) (NMR yield)
From 3-methyl-2-butanone

Benzyl 5-methyl-6-oxoheptanoate (unrearranged product) – major

\[
\begin{align*}
\text{O} & & \text{CO₂Bn} \\
\end{align*}
\]

Yellow oil. \(R_f = 0.45\) (5:1 hexanes : ethyl acetate).
\(^1\)H NMR (500 MHz, CDCl₃) \(\delta 7.39 – 7.31\) (m, 5H), \(5.11\) (s, 2H), \(2.49\) (h, \(J = 6.8\) Hz, 1H), \(2.36\) (td, \(J = 7.1, 1.2\) Hz, 2H), \(2.11\) (s, 3H), \(1.76 – 1.53\) (m, 3H), \(1.42 – 1.30\) (m, 1H), \(1.08\) (d, \(J = 7.0\) Hz, 3H).
\(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta 212.21, 173.18, 136.12, 128.66, 128.33, 66.29, 46.95, 34.25, 32.13, 28.07, 22.67, 16.27\).
IR, film (cm⁻¹): 2935, 1732, 1709, 1497, 1455, 1355, 1212, 1151, 1111, 747, 697.
LRMS m/z (EI): calculated for C₁₅H₂₀O₃ [M⁺] 248.14, found 248.1.

Ethyl 4-methyl-6-oxoheptanoate (rearranged product) – minor

\[
\begin{align*}
\text{O} & & \text{CO₂Et} \\
\end{align*}
\]

\(^1\)H NMR (500 MHz, CDCl₃) Characteristic peaks: \(\delta 0.90\) (d, 3H, MeC(O)-CH₂-CHMe-).
\(R_M\) determined by comparing the integral of the peak at 1.08 ppm (MeC(O)-CHMe-CH₂-) to the characteristic peak at 0.90 ppm.

5d
Conditions A: Yield = 54%, \(R_M = 11:1\)
Conditions B: Yield = 44%, \(R_M = 1.3:1\) (NMR yield)
From 3-methyl-2-butanone

Ethyl 5-methyl-6-oxoheptanoate (unrearranged product)
Colorless oil. \( R_f = 0.40 \) (5:1 hexanes : ethyl acetate).

\(^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \): 4.10 (q, \( J = 7.1 \) Hz, 2H), 2.50 (h, \( J = 6.9 \) Hz, 1H), 2.28 (td, \( J = 7.3, 2.0 \) Hz, 2H), 2.12 (s, 3H), 1.72 – 1.47 (m, 3H), 2.28 (td, \( J = 7.3, 2.0 \) Hz, 2H), 1.41 – 1.31 (m, 1H), 1.23 (t, \( J = 7.1 \) Hz, 3H), 1.08 (d, \( J = 7.0 \) Hz, 3H).

\(^{13}\text{C} \text{NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \): 212.41, 173.43, 60.40, 46.99, 34.29, 32.17, 28.14, 22.68, 16.30, 14.34.

\( \text{IR, film (cm}^{-1})\): 2972, 2939, 1731, 1711, 1459, 1370, 1246, 1178, 1156, 1097, 1031.

\( \text{LRMS} \ m/z \ (EI): \) calculated for C\(_{10}\)H\(_{18}\)O\(_3\) [M\(^+\)] 186.13, found 186.2.

Ethyl 4-methyl-6-oxoheptanoate (rearranged product)

\( \text{IR, film (cm}^{-1})\): 2972, 2939, 1731, 1711, 1459, 1370, 1246, 1178, 1156, 1097, 1031.

\( \text{LRMS} \ m/z \ (EI): \) calculated for C\(_{10}\)H\(_{18}\)O\(_3\) [M\(^+\)] 186.13, found 186.2.

Ethyl 4-methyl-6-oxoheptanoate (rearranged product)

\( \text{IR, film (cm}^{-1})\): 2972, 2939, 1731, 1711, 1459, 1370, 1246, 1178, 1156, 1097, 1031.

\( \text{LRMS} \ m/z \ (EI): \) calculated for C\(_{10}\)H\(_{18}\)O\(_3\) [M\(^+\)] 186.13, found 186.2.

Benzyl 5,5,7,7-tetramethyl-6-oxooctanoate (unrearranged product) – minor

\( \text{IR, film (cm}^{-1})\): 2957, 1734, 1705, 1456, 1385, 1365, 1297, 1153, 1067, 1004, 975, 915, 844, 746, 697, 579, 501.

\( \text{LRMS} \ m/z \ (EI): \) calculated for C\(_{10}\)H\(_{18}\)O\(_3\) [M\(^+\)] 304.20, found 304.2.

Benzyl 4,4,7,7-tetramethyl-6-oxooctanoate (rearranged product) – major

\( \text{IR, film (cm}^{-1})\): 2957, 1734, 1705, 1456, 1385, 1365, 1297, 1153, 1067, 1004, 975, 915, 844, 746, 697, 579, 501.

\( \text{LRMS} \ m/z \ (EI): \) calculated for C\(_{10}\)H\(_{18}\)O\(_3\) [M\(^+\)] 304.20, found 304.2.

5e
Conditions A: Yield = 69%, \( R_m = 1:7 \)
Conditions B: Yield = 60%, \( R_m = 1:20 \)
From di-tert-butyl ketone

5f
Conditions C: Yield = 30%, \( R_m = 4:1 \)
(Identical to Conditions A, but with additional workup in alkaline ethanol after completion)
From pivaloyl chloride
Diethyl 2,2-dimethylhexanedioate (unrearranged product) – major

\[
\text{CH}_2\text{C(OEt)}_2
\]

Colorless oil. \(R_f = 0.50\) (5:1 hexanes : ethyl acetate).

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta 4.12\) (d, \(J = 7.1\), 4H), 2.27 (m, 2H), 1.61 – 1.48 (m, 4H), 1.25 (t, \(J = 7.1\), 6H), 1.17 (s, 6H).

\(\text{^13C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta 177.87, 173.55, 60.45, 60.39, 42.17, 40.08, 34.78, 27.12, 25.19, 20.65, 14.38, 14.36.

\(\text{IR, film (cm}^{-1}\)): 2977, 1729, 1472, 1370, 1248, 1175, 1030.

\(\text{HRMS m/z (ASAP)}\): calculated for C\(_{12}\)H\(_{22}\)O\(_4\) [M+H]\(^+\) 231.1596, found 231.1588.

Diethyl 2,2-dimethylhexanedioate (rearranged product) – minor

\[
\text{CH}_2\text{C(OEt)}_2
\]

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\)) Characteristic peaks 2.33 – 2.29 (m, 2H), 2.18 (s, 2H, EtO\(_2\)C-CH\(_2\)-Me\(_2\)-), 1.73 – 1.64 (m, 2H), 1.01 (s, 6H, EtO\(_2\)C-CH\(_2\)-Me\(_2\)-).

\(R_M\) determined by comparing the integral of the peak at 1.17 ppm (s, 6H, EtO\(_2\)C-CHMe\(_2\)-) to the characteristic peak at 1.01 ppm.

5g

Conditions A: Yield = 42%, \(R_M = 16:1\)
Conditions B: Yield = 25%, \(R_M = 2.4:1\) (NMR yield)
From tert-butylbenzene

Ethyl 5-methyl-5-phenylhexanoate (unrearranged product) – major

\[
\text{CH}_2\text{C(OEt)}_2
\]

Yellow oil. \(R_f = 0.3\) (9:1 hexanes : ethyl acetate).

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta 7.36 – 7.28\) (m, 4H), 7.20 – 7.15 (m, 1H), 4.10 (q, \(J = 7.1\) Hz, 2H), 2.20 (t, \(J = 7.4\) Hz, 2H), 1.75 – 1.55 (m, 2H), 1.44 – 1.36 (m, 2H), 1.32 (s, 6H), 1.23 (t, \(J = 7.1\) Hz, 3H).

\(\text{^13C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta 173.65, 149.10, 128.10, 125.78, 125.50, 60.17, 43.94, 37.61, 34.82, 28.88, 20.41, 14.26.

\(\text{IR, film (cm}^{-1}\)): 2962, 1732, 1496, 1446, 1369, 1263, 1184, 1159, 1029, 932, 859, 764, 699, 566, 547

\(\text{LRMS m/z (EI)}\): calculated for C\(_{15}\)H\(_{22}\)O\(_2\) [M+] 234.16, found 234.1.

Ethyl 4,4-dimethyl-5-phenylpentanoate (rearranged product) – minor

\[
\text{CH}_2\text{C(OEt)}_2
\]

\(\text{^1H NMR}\) (500 MHz, CDCl\(_3\)) 2.52 (s, 2H), 2.38 – 2.31 (m, 2H), 0.87 (s, 6H).

\(R_M\) determined by comparing the integral of the peak at 1.32 ppm (s, 6H, Ar-CMe\(_2\)-CH\(_2\)-) to the characteristic peak at 0.87 ppm (s, 6H, Ar-CH\(_2\)-CMe\(_2\)-).

5h

Conditions A: Yield = 28%, \(R_M = 1:13\)
Conditions B: Yield = 58%, \(R_M = <1:20\) (NMR yield)
From 4’-tert-butylacetophenone
Ethyl 5-(4-acetylphenyl)-5-methylhexanoate (unrearranged product) – minor

\[
\text{Ac} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{Et}
\]

\[^1\text{H NMR}\ (400\ \text{MHz, CDCl}_3)\] Characteristic peaks $\delta$ 2.19 (t, $J = 7.4$ Hz, 2H, -CH$_2$-CO$_2$Et), 1.33 (s, 6H, Ar-CMe$_2$-)

$R_M$ determined by comparing the integrals of the peak at 0.85 ppm (s, 6H, Ar-CH$_2$-CMe$_2$-) to the characteristic peak at 1.33 ppm.

Ethyl 5-(4-acetylphenyl)-4,4-dimethylpentanoate (rearranged product) – major

\[
\text{Ac} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{Et}
\]

Yellow oil. $R_f = 0.3$ (9:1 hexanes : ethyl acetate).

\[^1\text{H NMR}\ (500\ \text{MHz, CDCl}_3)\] $\delta$ 7.88 – 7.82 (m, 2H), 7.23 – 7.17 (m, 2H), 4.11 (q, $J = 7.1$ Hz, 2H), 2.56 (overlapping singlets, 5H, CH$_3$C(O) + benzylic CH$_2$), 2.35 – 2.28 (m, 2H), 1.62 – 1.55 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.85 (s, 6H).

\[^{13}\text{C NMR}\ (126\ \text{MHz, CDCl}_3)\] $\delta$ 197.96, 174.14, 144.76, 135.24, 130.81, 127.96, 60.45, 48.32, 36.81, 34.19, 29.80, 26.63, 26.38, 14.31.

\[^{\text{IR}}\], film (cm$^{-1}$): 2961, 1730, 1681, 1506, 1414, 1358, 1266, 1182, 1125, 1021, 956, 826, 780, 689, 601, 585

\[^{\text{LRMS}}\] m/z (EI): calculated for C$_{17}$H$_{24}$O$_3$ [M$^+$] 276.17, found 276.1.

5i

Conditions A: Yield = 30%, $R_M$ = 1:8

Conditions B: Yield = 54%, $R_M$ = <1:20

From 4-tert-butylbenzonitrile

Ethyl 5-(4-cyanophenyl)-5-methylhexanoate (unrearranged product) – minor

\[
\text{NC} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{Et}
\]

\[^1\text{H NMR}\ (400\ \text{MHz, CDCl}_3)\] Characteristic peaks $\delta$ 2.20 (t, $J = 7.3$ Hz, 2H, -CH$_2$-CO$_2$Et), 1.31 (s, 6H, Ar-CMe$_2$-)

$R_M$ determined by comparing the integrals of the peak at 0.86 ppm (s, 6H, Ar-CH$_2$-CMe$_2$-) to the characteristic peak at 1.31 ppm.

Ethyl 5-(4-cyanophenyl)-4,4-dimethylpentanoate (rearranged product) – major

\[
\text{NC} \quad \text{Me} \quad \text{Me} \quad \text{CO}_2\text{Et}
\]

Yellow oil. $R_f = 0.2$ (9:1 hexanes : ethyl acetate).

\[^1\text{H NMR}\ (400\ \text{MHz, CDCl}_3)\] $\delta$ 7.59 – 7.51 (m, 2H), 7.25 – 7.18 (m, 2H), 4.12 (q, $J = 7.1$ Hz, 2H), 2.56 (s, 2H), 2.36 – 2.27 (m, 2H), 1.62 – 1.53 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H), 0.85 (s, 6H).

\[^{13}\text{C NMR}\ (101\ \text{MHz, CDCl}_3)\] $\delta$ 173.97, 144.62, 131.65, 131.32, 119.10, 110.11, 60.50, 48.50, 36.78, 34.25, 29.75, 26.30, 14.30.

\[^{\text{IR}}\], film (cm$^{-1}$): 2961, 2871, 2227, 1729, 1607, 1505, 1469, 1416, 1370, 1297, 1263, 1177, 1127, 1024, 853, 826, 781, 566, 533

283
**LRMS** m/z (EI): calculated for C$_{16}$H$_{21}$NO$_2$ [M$^+$] 259.16, found 259.1.

5j
Conditions A: Yield = 46%, R$_M$ = >20:1
Conditions B: Yield = 35%, R$_M$ = 1:1
From 4-(tert-butyl)phenyl acetate

Ethyl 5-(4-acetoxyphenyl)-5-methylhexanoate (unrearranged product) – major

Yellow oil. Rf = 0.3 (9:1 hexanes : ethyl acetate).

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.35 – 7.28 (m, 2H), 7.04 – 6.90 (m, 2H), 4.09 (q, $J$ = 7.1 Hz, 2H), 2.29 (s, 3H), 2.20 (t, $J$ = 7.3 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.41 (m, 2H), 1.30 (s, 6H), 1.23 (t, $J$ = 7.1 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.71, 169.72, 148.55, 146.78, 126.93, 121.04, 60.32, 44.06, 37.55, 34.89, 29.04, 21.30, 20.47, 14.37.

IR, film (cm$^{-1}$): 2961, 1761, 1731, 1605, 1506, 1467, 1368, 1299, 1193, 1168, 1099, 1016, 911, 847, 662, 594, 564

**LRMS** m/z (EI): calculated for C$_{17}$H$_{24}$O$_4$ [M$^+$] 292.17, found 292.1.

Ethyl 5-(4-acetoxyphenyl)-4,4-dimethylpentanoate (rearranged product) – minor

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.15 – 7.08 (m, 2H), 6.99 – 6.96 (m, 2H), 4.13 (q, $J$ = 7.1 Hz, 2H), 2.50 (s, 2H), 2.37 – 2.30 (m, 2H), 1.61 – 1.55 (m, 2H), 1.26 (t, $J$ = 7.1 Hz, 3H), 0.86 (s, 6H).

R$_M$ determined by comparing the integral of the peak at 1.30 ppm (s, 6H, Ar-$\text{CH}_2$-$\text{CMe}_2$-) to the characteristic peak at 0.86 ppm (s, 6H, Ar-$\text{CH}_2$-$\text{CMe}_2$-).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.36, 169.75, 149.10, 136.46, 131.53, 120.88, 60.47, 47.77, 36.78, 34.00, 29.90, 26.33, 21.30, 14.36.

**LRMS** m/z (EI): calculated for C$_{17}$H$_{24}$O$_4$ [M$^+$] 292.17, found 292.1.

[Peaks assigned from the 1:1 mixture with the unrearranged product]

5k
Conditions A: Yield = 37%, R$_M$ = <1:20
Conditions B: Yield = 41%, R$_M$ = <1:20
From 2,2,5,5-tetramethylcyclopentanone

Benzyl 4-(1,3,3-trimethyl-2-oxocyclopentyl)butanoate (unrearranged product) – N.D.

Benzyl 3-(1,4,4-trimethyl-3-oxocyclohexyl)propanoate (rearranged product) – exclusive
Colorless oil. R$_f$ = 0.35 (9:1 hexanes : ethyl acetate).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.29 (m, 5H), 5.11 (s, 2H), 2.38 – 2.27 (m, 3H), 2.11 (dd, J = 13.8, 1.7 Hz, 1H), 1.72 – 1.61 (m, 5H), 1.54 – 1.46 (m, 1H), 1.10 (s, 3H), 1.08 (s, 3H), 0.87 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 215.63, 173.62, 135.97, 128.70, 128.43, 128.41, 66.51, 49.66, 44.33, 38.80, 36.67, 36.42, 32.46, 29.05, 25.28, 25.17, 24.36.

IR, film (cm$^{-1}$): 2960, 2929, 2867, 1733, 1703, 1497, 1455, 1422, 1384, 1365, 1303, 1214, 1161, 1079, 1028, 967, 910, 747, 698, 507

LRMS m/z (EI): calculated for C$_{19}$H$_{26}$O$_3$ [M$^+$] 302.19, found 302.2.

5ka
Benzyl 3-(2,2,4,4-tetramethyl-3-oxocyclopentyl)propanoate – side product (alkylation at methylene positions)

Conditions A: Yield = 15%
Conditions B: Yield = 20%

Colorless oil. R$_f$ = 0.4 (9:1 hexanes : ethyl acetate).

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.40 – 7.29 (m, 5H), 5.14 (d, J = 1.7 Hz, 2H), 2.48 (ddd, J = 15.2, 9.2, 5.8 Hz, 1H), 2.39 (ddd, J = 15.8, 8.9, 6.9 Hz, 1H), 1.87 (dd, J = 12.5, 6.1 Hz, 1H), 1.79 (ddd, J = 12.2, 10.2, 6.1, 4.1 Hz, 1H), 1.54 (ddd, J = 13.3, 10.2, 8.9, 5.8 Hz, 1H), 1.42 – 1.31 (m, 1H), 1.09 (s, 3H), 1.04 (s, 3H), 0.95 (s, 3H), 0.82 (s, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 226.94, 173.42, 136.05, 128.71, 128.49, 128.45, 66.44, 48.46, 44.88, 43.25, 41.26, 32.80, 25.85, 25.35, 25.06, 23.99, 18.79.

IR, film (cm$^{-1}$): 2961, 2868, 1733, 1497, 1457, 1362, 1215, 1166, 1133, 1063, 1028, 903, 750, 698, 580, 487

LRMS m/z (EI): calculated for C$_{19}$H$_{26}$O$_3$ [M$^+$] 302.19, found 302.2.

5l
Conditions A: Yield = 8%, R$_M$ = <1:20
Conditions B: Yield = 19%, R$_M$ = <1:20

From 3-methyl-3-phenylbutan-2-one

Ethyl 5-methyl-6-oxo-5-phenylheptanoate (unrearranged product) – N.D.

Ethyl 4-methyl-6-oxo-4-phenylheptanoate (rearranged product) – exclusive

Pale yellow oil. R$_f$ = 0.3 (5:1 hexanes : ethyl acetate).
\textbf{\textsuperscript{1}H NMR} (500 MHz, CDCl\textsubscript{3}) \(\delta\) 7.36 – 7.29 (m, 4H), 7.20 (m, 1H), 4.05 (qd, \(J = 7.1, 2.1\) Hz, 2H), 2.92 (d, \(J = 14.5\) Hz, 1H), 2.61 (d, \(J = 14.5\) Hz, 1H), 2.25 – 2.10 (m, 2H), 2.03 – 1.87 (m, 2H), 1.79 (s, 3H, CH\textsubscript{3}C(O)-, confirmed by HMBC), 1.45 (s, 3H), 1.20 (t, \(J = 7.1\) Hz, 3H).

\textbf{\textsuperscript{13}C NMR} (126 MHz, CDCl\textsubscript{3}) \(\delta\) 207.65, 173.77, 145.24, 128.64, 126.45, 126.19, 60.49, 56.24, 40.14, 37.72, 32.09, 29.59, 23.33, 14.29.

\textbf{IR}, film (cm\textsuperscript{-1}): 2978, 1731, 1446, 1376, 1299, 1180, 1031, 765, 702, 547

\textbf{LRMS} m/z (EI): calculated for C\textsubscript{15}H\textsubscript{22}O\textsubscript{2} [M]\textsuperscript{+} 262.16, found 262.1.
Rearrangement Electrophile Scope

\( \text{RM} = \text{the ratio of unrearranged to rearranged product.} \)

6a
Conditions A: Yield = 38%, \( \text{RM} = 1:1 \)
Conditions B: Yield = 57%, \( \text{RM} = 1:8 \) (NMR yield)
From maleic anhydride

3-(2,2-dimethyl-3-oxobutyl)dihydrofuran-2,5-dione (unrearranged product) – minor

\[
\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 3.15 – 3.05 \ (m, 1H), 3.05 – 2.94 \ (m, 1H), 2.70 \ (dd, J = 18.3, 7.0 \text{ Hz}, 1H), 2.30 \ (dd, J = 14.4, 3.7 \text{ Hz}, 1H), 2.15 \ (s, 3H), 1.82 \ (dd, J = 14.4, 8.9 \text{ Hz}, 1H), 1.23 \ (s, 3H), 1.21 \ (s, 3H).
\]

\( \text{C NMR} \ (126 \text{ MHz, CDCl}_3) \ \delta \ 212.85, 174.26, 169.78, 47.27, 40.54, 38.19, 36.31, 25.40, 25.22, 24.71. \)

\( \text{LRMS} \ m/z \ (EI): \text{calculated for } \text{C}_{10}\text{H}_{14}\text{O}_4 [M^+ ] 198.09, \text{found} 198.1. \)

3-(2-ethyl-4-oxopentan-2-yl)dihydrofuran-2,5-dione (rearranged product) – major

\[
\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 3.88 \ (dd, J = 10.2, 6.5 \text{ Hz}, 1H), 3.11 – 2.87 \ (m, 2H), 2.78 \ (dd, J = 18.9, 6.7 \text{ Hz}, 1H), 2.45 \ (d, J = 17.9 \text{ Hz}, 1H), 2.15 \ (s, 3H), 1.11 \ (s, 3H), 1.04 \ (s, 3H).
\]

\( \text{C NMR} \ (126 \text{ MHz, CDCl}_3) \ \delta \ 207.92, 172.53, 170.10, 51.49, 46.73, 34.84, 31.76, 31.06, 25.50, 24.24. \)

\( \text{IR, film } (\text{cm}^{-1}): 2967, 1859, 1775, 1707, 1471, 1413, 1366, 1294, 1219, 1159, 1074, 1054, 915, 722. \)

\( \text{LRMS} \ m/z \ (EI): \text{calculated for } \text{C}_{10}\text{H}_{14}\text{O}_4 [M^+ ] 198.09, \text{found} 198.1. \)

6b
Conditions A: Yield = 86%, \( \text{RM} = 1:1.2 \)
Conditions B: Yield = 51%, \( \text{RM} = 1:8 \) (NMR yield)
From N-methylmaleimide

3-(2,2-dimethyl-3-oxobutyl)-1-methylpyrrolidine-2,5-dione (unrearranged product)

\[
\text{H NMR} \ (500 \text{ MHz, CDCl}_3) \ \delta \ 2.95 \ (s, 3H), 2.84 \ (dd, J = 18.2, 8.9 \text{ Hz}, 1H), 2.65 \ (ddd, J = 9.1, 5.2, 3.5 \text{ Hz}, 1H), 2.42 – 2.28 \ (m, 2H), 2.18 \ (s, 3H), 1.62 \ (dd, J = 14.3, 9.7 \text{ Hz}, 1H), 1.19 \ (overlapping singlets, J = 4.3Hz, 6H).
\]

\( \text{C NMR} \ (126 \text{ MHz, CDCl}_3) \ \delta \ 213.02, 180.07, 176.43, 47.44, 41.30, 37.32, 36.75, 25.43, 25.11, 25.07, 24.79. \)

\( \text{IR, film } (\text{cm}^{-1}): 2969, 1775, 1690, 1435, 1383, 1358, 1280, 1124, 877. \)
LRMS m/z (EI): calculated for C_{11}H_{17}NO_{3} [M^+] 211.11, found 211.1.

1-methyl-3-(2-methyl-4-oxopentan-2-yl)pyrrolidine-2,5-dione (rearranged product)

1H NMR (500 MHz, CDCl₃) δ 3.43 (dd, J = 9.3, 5.0 Hz, 1H), 3.04 (d, J = 17.5 Hz, 1H), 2.93 (s, 3H), 2.70 (dd, J = 18.5, 9.3 Hz, 1H), 2.54 – 2.40 (m, 2H), 2.15 (s, 3H), 1.08 (s, 3H), 0.93 (s, 3H).

13C NMR (126 MHz, CDCl₃) δ 208.20, 179.02, 176.63, 52.05, 45.79, 34.85, 31.89, 31.23, 25.63, 24.68, 23.82.

IR, film (cm⁻¹): 2961, 1770, 1688, 1434, 1382, 1366, 1280, 1157, 1122, 952, 697.

LRMS m/z (EI): calculated for C_{11}H_{17}NO_{3} [M^+] 211.11, found 211.1.

The two isomers could be isolated separately. R_M for Conditions A was determined on the basis of the mass of the two isolated products.

For Conditions B, R_M was determined by comparing the combined integrals of the methyl peaks at 1.19 (overlapping singlets, 6H) to that of the methyl peaks at 1.08 (s, 3H) and 0.93 (s, 3H).

Ratio found = 1:7.7

NMR yield = 6%:45% (combined = 51%) using 1,3,5-trimethoxybenzene as internal standard.

6c (cf. compound 3a)

6d

Conditions A: Yield = 35%, R_M = 1.2:1
Conditions B: Yield = 47%, R_M = 1:9

From ethyl methacrylate

Ethyl 2,5,5-trimethyl-6-oxoheptanoate (unrearranged product) – minor

1H NMR (500 MHz, CDCl₃) Characteristic peaks: δ 1.08 (overlapping singlets, J = 5.3 Hz, 6H, MeC(O)-CMe₂-CH₂-)

13C NMR (126 MHz, CDCl₃) δ 213.77, 176.45, 60.33, 47.66, 39.98, 37.35, 28.85, 25.08, 24.39, 24.31, 17.29, 14.37.

R_M was determined by the relative integral of the characteristic peak at 1.08 ppm against the peak at 0.95 ppm (MeC(O)-CH₂-CMe₂-).

Ethyl 2,4,4-trimethyl-6-oxoheptanoate (rearranged product) – major

Colorless oil. Rf = 0.45 (5:1 hexanes : ethyl acetate).

1H NMR (500 MHz, CDCl₃) δ 4.09 (q, J = 7.1, 2H), 2.45 (dqd, J = 9.8, 7.0, 2.8 Hz, 1H), 2.37 – 2.26 (m, 2H), 2.09 (s, 3H), 1.92 (dd, J = 14.2, 9.4 Hz, 1H), 1.35 (dd, J = 14.2, 2.8 Hz, 1H), 1.23 (t, J = 7.2 Hz, 3H), 1.13 (d, J = 7.0 Hz, 3H), 0.95 (overlapping singlets, J = 2.5 Hz, 6H).

13C NMR (126 MHz, CDCl₃) δ 208.56, 177.74, 60.39, 53.92, 45.88, 36.04, 33.83, 32.56, 27.31, 27.08, 20.43, 14.23.

IR, film (cm⁻¹): 2972, 1729, 1705, 1463, 1363, 1249, 1155, 1096, 1054, 1025.
LRMS m/z (EI): calculated for C₁₂H₂₂O₃ [M⁺] 214.16, found 214.2.

6e
Conditions A: Yield = 63%, Rₘ = 1:2.3
Conditions B: Yield = 73%, Rₘ = 1:14
From fumaronitrile

2-(2,2-dimethyl-3-oxobutyl)succinonitrile (unrearranged product) – minor

\[ \begin{array}{c}
\text{O} \\
\text{CN} \\
\text{CN}
\end{array} \]

\(^1\)H NMR Characteristic peaks: δ 2.91 (dtd, J = 8.1, 6.3, 5.0 Hz, 1H, methine CH), 1.32 (s, 3H), 1.23 (s, 3H) (MeC(O)-CMe₂-CH₂-)
\(^{13}\)C NMR (126 MHz, CDCl₃) δ 212.47, 119.84, 115.77, 47.35, 40.38, 25.76, 25.18, 24.80, 23.91, 22.65.
Rₘ was determined by the relative integral of the characteristic peak at 1.32 ppm (s, 3H) against half the integral of the peak at 1.14 ppm (overlapping singlets, 6H, MeC(O)-CH₂-CMe₂-).

2-(2-methyl-4-oxopentan-2-yl)succinonitrile (rearranged product) – major

\[ \begin{array}{c}
\text{O} \\
\text{CN} \\
\text{CN}
\end{array} \]

Colorless oil. Rf = 0.40 (3:1 hexanes : ethyl acetate).
\(^1\)H NMR (500 MHz, CDCl₃) δ 3.68 (dd, J = 8.7, 5.9 Hz, 1H), 2.71 – 2.57 (m, 3H), 2.49 (d, J = 18.0 Hz, 1H), 2.14 (s, 3H), 1.14 (overlapping singlets, J = 7.2 Hz, 6H)
\(^{13}\)C NMR (126 MHz, CDCl₃) δ 207.01, 118.32, 116.63, 51.29, 36.67, 35.46, 31.70, 25.18, 24.09, 16.69.
IR, film (cm⁻¹): 2971, 2243, 1708, 1470, 1421, 1364, 1181, 1157, 1055, 1033, 1005, 626, 554.
LRMS m/z (EI): calculated for C₁₀H₁₄N₂O [M⁺] 178.11, found 178.1.

6f
Conditions A: Yield = 57%, Rₘ = 1:8.6
Conditions B: Yield = 70%, Rₘ = <1:20
From benzylidenemalonitrile

2-hydroxy-2,3,3-trimethyl-5-phenylcyclopentane-1,1-dicarbonitrile (unrearranged product) – minor

\[ \begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{OH} \\
\text{Me}
\end{array} \]

\(^1\)H NMR Characteristic peaks: δ 2.55 (broad s, 1H, -C(OH)Me-) 1.62 (s, 3H, -C(OH)Me-), 1.35 (s, 3H, -CMe₂-), 1.18 (s, 3H, -CMe₂-)
Rₘ was determined by the relative integral of the characteristic peak at 1.35 ppm against the integral of the peak at 1.06 ppm (s, 3H).

2-hydroxy-2,4,4-trimethyl-5-phenylcyclopentane-1,1-dicarbonitrile (rearranged product) – major
\( ^1H \text{ NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 7.63 – 7.54 (m, 2H), 7.46 – 7.35 (m, 3H), 3.90 (s, 1H), 2.73 (broad d, \( J = 2.0 \) Hz, 1H), 2.21 – 2.08 (m, 2H), 1.74 (s, 3H), 1.21 (s, 3H), 1.06 (s, 3H).

\( ^{13}C \text{ NMR} \) (126 MHz, CDCl\(_3\)) \( \delta \) 133.28, 130.00, 128.74, 128.63, 115.82, 114.30, 83.69, 61.15, 52.57, 52.06, 40.88, 31.64, 27.87, 24.39.

\( \text{IR, film \( (cm^{-1}) \):} \) 3482 (broad), 2968, 2932, 2252, 1498, 1453, 1389, 1367, 1220, 1194, 1172, 1121, 1070, 1052, 951, 935, 853, 732, 700, 528.

\( \text{LRMS m/z (EI):} \) calculated for C\(_{16}\)H\(_{18}\)N\(_2\)O [M\(^+\)] 254.14, found 254.1.
References


NMR Spectra
Proton assignments

4.11 q
1.24 t
2.30
1.64 m
1.75, 1.60, m
2.39 d
1.75 m
1.31 dt
1.79 dd
1.68-1.63 m
2.55 d
2.06 dd

13 12 11 10 9 8 7 6 5 4 3 2 1 0 -1
fl (ppm)
-2000 -1800 -1600 -1400 -1200 -1000 -800 -600 -400 -200 0 200 400 600 800 1000 1200 1400 1600 1800 2000 22000
J (Hz)
Carbon assignments
Key COSY correlations
Key HMBC correlations (1)
Key HMBC correlations (2)
Supporting Information

Electron Donor Acceptor Complexation Enables [3+2] g-Lactam Synthesis via a-Olefin Difunctionalization

Sean M. Treacy, Daniel R. Vaz, and Tomislav Rovis*

Department of Chemistry, Columbia University, New York, New York, 10027 United States

*tr2504@columbia.edu

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CHARACTERIZATION DATA OF PRODUCTS: .............................................................. 363
REFERENCES: ...................................................................................................... 373
NMR SPECTRA ...................................................................................................... 374
Materials and Methods:

Unless otherwise noted, all reactions were performed in oven-dried glassware and carried out under an atmosphere of Argon with magnetic stirring. All photochemical reactions were run in 8 mL reaction tubes fitted with Teflon caps under irradiation from a PR-160 Kessil 40W LED lamp with Teflon stir-bars under vigorous magnetic stirring. All photochemical reactions were set-up in an Argon glovebox, though can also be performed with suitable Schlenk-line techniques. Chromatographic purification was accomplished by flash chromatography on SiliCycle® Silica Flash® 40-63 μm, 60 Å or Teledyne ISCO CombiFlash®Rf+ LumenTM instrument. As most of the compounds listed do not exhibit a strong UV trace, ELSD was integral to the separation of product while thin layer chromatography was performed on SiliCycle® 250 μm 60 Å plates. Visualization was accomplished with 254 nm UV light, Seebach’s stain, potassium permanganate or I₂.

1H NMR spectra were recorded on Bruker 400 or 500 MHz spectrometers at ambient temperature. Chemical shift is reported in parts per million (ppm) from CDCl₃ (7.26 ppm) with multiplicity (s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet) and coupling constants (Hz). 13C NMR was recorded on Bruker 500 or 400 MHz spectrometers (126 MHz) at ambient temperature. Chemical shifts are reported in ppm from CDCl₃ (77.2 ppm). Mass spectra were recorded on an Agilent 7890B GC System 5977B MSD GCMS with an EI ionization method. High resolution mass spectra (HRMS) were obtained from the Columbia University Chemistry Department Mass Spectrometry Facility on a Waters XEVO G2XS QToF mass spectrometer equipped with a UPC2 SFC inlet and a LockSpray source with one of the electrospray ionization (ESI) probe.

Unless otherwise mentioned, all starting materials were obtained from commercial sources including Millipore-Sigma, TCI, and Alfa-Aesar.
### Table S1. Photocatalyst Screen

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<td>3</td>
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### Table S2. Base Screen

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**Table S4. DIPEA Loading Screen**

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Table S5. Other Amide Substituents

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<td>4</td>
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Figure S1. UV-Vis Absorption Spectrum of 1

![UV-Vis 1a spectrum with λ_max = 344 nm]

Figure S2. Cyclic Voltammetry of 1a

![Cyclic Voltammetry 1a with E_p/2 = -1.90 and λ_max = 344 nm]
Figure S3. UV-Vis of DIPEA-1a Mixtures in DCE
**Figure S4. On-Off Study**

Quantum yield calculation

Quantum yield was calculated according to reported literature.¹

The measurement of the combined photon flux of two Kessil PR160s at maximum intensity (45W maximum, 440 nm), 11 cm away from each light source, was determined by standard ferrioxalate actinometry following already reported procedures.

Photon flux = $1.15 \times 10^{-9}$ E/s

A cuvette was filled with standard reaction solution and placed 11 cm away from each light source. Under these conditions, the fraction of light absorbed by the photocatalyst was $f = 0.9998$. The sample was irradiated for 30 min (1800 s). Product was detected by $^1$H NMR in 10% yield. The quantum yield was calculated as 14.

$$\Phi = \frac{\text{mol of Product}}{\text{photon flux } \times t \times f} = \frac{0.1 \times 0.3 \times 10^{-3} \text{ mol}}{\left(1.15 \times 10^{-9} \text{ E/s}\right) \times 1800 \text{ s} \times 0.9998} \approx 14$$
Starting Material Synthesis and Characterization Data:

α-Br-imides 1a-b\textsuperscript{2} and 1e\textsuperscript{3} and 1g\textsuperscript{4} were synthesized according to known literature procedures. α-Br-imides 1c-d f-g, \textsuperscript{2} 1h-k, \textsuperscript{5,6} and 1l\textsuperscript{6,7} were synthesized via adapted literature procedures. Olefins 2k,\textsuperscript{9} 2n,\textsuperscript{9} 2o,\textsuperscript{10} 2p,\textsuperscript{11} and 2r\textsuperscript{12} were synthesized according to a known literature procedure. Olefins 2q and 2s were synthesized via an adapted literature procedure.\textsuperscript{11}

All remaining olefins were purchased from Aldrich or Fisher and used as received.

Synthesis of imide 1c.

![Chemical Structure](image)

To a dry 100 mL flask was added 2-bromoacetamide (20 mmol, 2.56 g) and affixed a reflux condenser. The flask was evacuated and refilled with N\textsubscript{2} three times after which 40 mL dry and degassed DCE was added. The solution was cooled to 0 °C with an ice bath and placed under slight positive pressure of N\textsubscript{2} with an outlet needle due to gas evolution during the reaction. 30 mmol (2.54 g, 1.72 mL) of oxalyl chloride was added dropwise via syringe. The mixture was stirred at 0 °C, warmed to room temperature, and then refluxed at 80 °C for 3 hours. The solution was again brought to 0 °C, warmed to room temperature, and then refluxed at 80 °C for 3 hours. The solution was then poured into 100 mL 0 °C solution of NaHCO\textsubscript{3} and extracted with DCM x1 and EtOAc x2. The organic layers were combined and dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated by rotary evaporation, and subjected to flash silica gel column chromatography (eluent 0-20% EtOAc in Hexanes) to furnish 1.5 g (4.6 mmol, 23%) of desired imide 1c.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 8.17 (s, 1H), 4.82 (s, 2H), 4.31 (s, 2H).
\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 166.67, 149.88, 94.25, 75.24, 28.42.

HRMS (ESI+) [C\textsubscript{3}H\textsubscript{3}BrCl\textsubscript{3}NaO\textsubscript{2}+] m/z calculated 335.8391, found 335.8395

Synthesis of imide 1d.

![Chemical Structure](image)

To a dry 100 mL flask was added 2-bromoacetamide (20 mmol, 2.56 g) and affixed a reflux condenser. The flask was evacuated and refilled with N\textsubscript{2} three times after which 40 mL dry and degassed DCE was added. The solution was cooled to 0 °C with an ice bath and placed under slight positive pressure of N\textsubscript{2} with an outlet needle due to gas evolution during the reaction. 30 mmol (2.54 g, 1.72 mL) of oxalyl chloride was added dropwise via syringe. The mixture was stirred at 0 °C, warmed to room temperature, and then refluxed at 80 °C for 3 hours. The solution was again brought to 0 °C, warmed to room temperature, and then refluxed at 80 °C for 3 hours. The solution was then poured into 100 mL 0 °C solution of NaHCO\textsubscript{3} and extracted with DCM x1 and EtOAc x2. The organic layers were combined and dried over Na\textsubscript{2}SO\textsubscript{4}, concentrated by rotary evaporation, and subjected to flash silica gel column chromatography (eluent 0-20% EtOAc in Hexanes) to furnish 3.1 g (11 mmol, 55%) of desired imide 1d.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.70 (s, 1H), 4.33 (s, 2H), 4.32 – 4.24 (m, 4H), 1.16 – 0.90 (m, 2H), 0.06 (s, 9H).
\textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 167.04, 151.49, 65.77, 28.81, 17.68, -1.36.

HRMS (ESI+) [C\textsubscript{6}H\textsubscript{16}BrNaO\textsubscript{2}+] m/z calculated 305.9955, found 305.9989
Synthesis of imide 1h.

To a dry 100 mL flask was added methyl carbamate (40 mmol, 3.0 g) and affixed a reflux condenser. The flask was evacuated and refilled with N₂ three times after which 40 mL dry and degassed toluene was added. To the resulting solution was slowly added 2-bromo-2-methylpropanoyl bromide (20 mmol, 4.6 g, 2.5 mL) at 0 °C. The solution was heated at 80 °C overnight under a stream of N₂. The solution was then poured into 100 mL 0 °C solution of NaHCO₃ and extracted with DCM x1 and EtOAc x2. The organic layers were combined and dried over Na₂SO₄, concentrated by rotary evaporation, and subjected to flash silica gel column chromatography (eluent 0-10% EtOAc in Hexanes) to furnish 3.0 g (14 mmol, 68%) of desired imide 1h.

¹H NMR (400 MHz, CDCl₃) δ 8.50 (s, 1H), 3.82 (s, 3H), 1.95 (s, 6H).

¹³C NMR (101 MHz, CDCl₃) δ 169.33, 151.21, 60.63, 53.41, 31.77.

HRMS (ESI+) [C₆H₁₀BrNNaO₃+] m/z calculated 247.9716, found 247.9767

Synthesis of imides 1i-k.

To a dry 100 mL flask fitted with a reflux condenser and an addition funnel was added cyclohexanecarboxylic acid (23.5 mmol, 3.0 g). The flask was sparged with N₂ for 20 minutes and then PBr₃ (7.1 mmol, 0.670 mL) was added via syringe. The solution was heated to 110 °C for 1 hour. Then Br₂ (58.6 mmol, 3.0 mL) was added dropwise. The reaction was stirred overnight and then allowed to cool to room temperature. The reaction was then sparged with N₂ into a saturated solution of sodium thiosulfate. To the resulting crude a-Br-acid bromide was added methyl carbamate (40 mmol, 3.0 g) followed by 40 mL dry degassed toluene. The resulting mixture was heated to 80 °C overnight under a stream of N₂. The solution was then poured into 100 mL 0 °C solution of NaHCO₃ and extracted with DCM x1 and EtOAc x2. The organic layers were combined and dried over Na₂SO₄, concentrated by rotary evaporation, and subjected to flash silica gel column chromatography (eluent 0-10% EtOAc in Hexanes) to furnish 1.6 g (6 mmol, 26%) of desired imide 1i.

¹H NMR (400 MHz, CDCl₃) δ 8.37 (s, 1H), 3.82 (s, 3H), 2.38 – 1.88 (m, 4H), 1.70 (dtt, J = 21.0, 13.2, 4.1 Hz, 5H), 1.41 – 1.20 (m, 1H).

¹³C NMR (101 MHz, CDCl₃) δ 168.99, 151.41, 69.34, 53.39, 37.80, 24.78, 22.85.

HRMS (ESI+) [C₉H₁₄BrNNaO₃+] m/z calculated 286.0049, found 286.0078

The above procedure provided 1j in 23% yield from cyclopentanecarboxylic acid.

¹H NMR (400 MHz, CDCl₃) δ 8.49 (s, 1H), 3.84 (s, 3H), 2.45 (ddddd, J = 15.3, 8.5, 5.5, 1.5 Hz, 2H), 2.36 – 2.17 (m, 2H), 2.08 – 1.81 (m, 4H).

¹³C NMR (101 MHz, CDCl₃) δ 168.52, 151.18, 71.34, 53.43, 41.99, 23.81.

HRMS (ESI+) [C₈H₁₂BrNNaO₃+] m/z calculated 271.9893, found 271.9924

The above procedure provided 1k in 44% yield from cyclobutane carboxylic acid.

¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 1.96 (s, 6H), 1.52 (s, 9H).

¹³C NMR (101 MHz, CDCl₃) δ 169.62, 149.24, 83.32, 61.14, 31.93, 28.14.

HRMS (ESI+) [C₇H₁₀BrNNaO₃+] m/z calculated 257.9736, found
Synthesis of imide 11.

From commercially available methyl tetrahydro-2H-pyran-4-carboxylate was synthesized methyl 4-
bromotetrahydro-2H-pyran-4-carboxylate via a known literature procedure in an 87% isolated yield.\(^6\) The isolated material was then added to a 250 mL flask and dissolved in 150 mL THF. LiOH monohydrate 950 mg (1.3 equiv.) was dissolved in 75 mL of deionized water and added dropwise to the organic solution and allowed to stir at room temperature until disappearance of the starting material was seen by TLC. The reaction was quenched via the addition of 1M HCl, diluted with EtOAc and the organic layer separated. The aqueous layer was extracted twice more with EtOAc, dried with sodium sulfate, and concentrated. Analysis by \(^1\)H NMR showed complete conversion to the acid. The crude acid was dissolved in dry DCM (35 mL, 0.5 M) with two drops of DMF. The solution was cooled to 0 °C and oxalyl chloride (4.42 mL, 2 equiv.) was added dropwise. After complete conversion of starting material by TLC the solution was concentrated under reduced pressure. The flask was fitted with a reflux condenser and dry degassed toluene was added under a N\(_2\) atmosphere. Methyl carbamate (2.61 g, 2 equiv.) was then added quickly and the solution heated at 80 °C overnight under a stream of N\(_2\). The solution was then poured into 100 mL 0 °C solution of NaHCO\(_3\) and extracted with DCM x1 and EtOAc x2. The organic layers were combined and dried over Na\(_2\)SO\(_4\), concentrated by rotary evaporation, and subjected to flash silica gel column chromatography (eluent 0-40% EtOAc in Hexanes) to furnish 600 mg (5.2 mmol, 26%) of desired imide 11.

\[^1\]H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.28 (s, 1H), 3.92 (dd, \(J = 9.9, 6.0\) Hz, 2H), 3.87 – 3.77 (m, 5H), 2.35 (ddd, \(J = 14.6, 10.1, 4.4\) Hz, 2H), 2.03 (dd, \(J = 14.6, 3.0\) Hz, 2H).

\[^13\]C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 167.76, 151.25, 64.09, 53.58, 37.11.

HRMS (ESI\(^+\)) [\(\text{C}_{23}\text{H}_{24}\text{BrN}_{2}\text{O}_3\text{Na}^+\)] m/z calculated 287.9842, found 287.9870

Synthesis of olefins 2q and 2s

To a solution of amine (1 equiv., 10 mmol) and triethylamine (2 equiv., 20 mmol) in DCM (0.1 M) was added undec-10-enoic chloride (1.2 equiv. 12 mmol) dropwise at 0 °C. The solution was allowed to warm to room temperature and stir overnight (16 hours). The reaction was quenched with saturated aqueous sodium bicarbonate and extracted with DCM twice. The organic phases were combined and dried over sodium sulfate and concentrated under reduced pressure. The crude material was then purified via silica column chromatography.

2q - N-cyclohexylundec-10-enamide
Yield 86%

\[^1\]H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.80 (ddt, \(J = 16.8, 10.0, 6.6\) Hz, 1H), 5.32 – 5.19 (m, 1H), 5.16 – 4.75 (m, 1H), 4.02 – 3.55 (m, 1H), 2.19 – 2.07 (m, 1H), 2.07 – 1.96 (m, 2H), 1.90 (dd, \(J = 12.7, 4.0\) Hz, 2H), 1.65 (ddt, \(J = 32.4, 10.7, 3.5\) Hz, 5H), 1.44 – 1.22 (m, 13H), 1.13 (dddt, \(J = 23.2, 15.5, 9.4, 3.5\) Hz, 2H).

\[^13\]C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.37, 139.37, 114.32, 48.19, 37.30, 33.96, 33.47, 29.50, 29.48, 29.45, 29.42, 29.26, 29.24, 29.07, 26.06, 25.74, 25.06.

HRMS (ESI\(^+\)) [\(\text{C}_{17}\text{H}_{32}\text{NO}_3\text{Na}^+\)] m/z calculated 266.2478, found 266.2549

2s - tert-butyl 4-(undec-10-enoypiperazine-1-carboxylate
Yield 92%

\[^1\]H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.79 (ddt, \(J = 16.9, 10.1, 6.7\) Hz, 1H), 5.10 – 4.84 (m, 1H), 3.58 (t, \(J = 5.2\) Hz, 2H), 3.40 (d, \(J = 15.7\) Hz, 5H), 2.38 – 2.22 (m, 2H), 2.11 – 1.93 (m, 2H), 1.68 – 1.54 (m, 2H), 1.46 (s, 7H), 1.40 – 1.13 (m, 10H).

\[^13\]C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 172.08, 154.76, 139.32, 114.30, 80.44, 45.59, 41.49, 33.93, 33.53, 29.60, 29.52, 29.48, 29.22, 29.05, 28.53, 25.46.

360
HRMS (ESI+) [C_{20}H_{36}N_{2}NaO_{3}] m/z calculated 375.2618, found 375.2646
Standard Reaction Conditions:

A) To an oven-dried 8 mL test tube vial, was added 1% [Ir(dFCF₃ppy)₂dtbbpy]PF₆ and α-bromoimide (0.6 mmol, 2 equiv.) electrophile. The vial was charged with a stir bar and transferred to a glovebox, where the solids were backfilled with an inert atmosphere. In the glovebox anhydrous degassed 1,2-dichloroethane was added (750 μL, 0.4 M) followed by the olefin nucleophile (0.3 mmol, 1 equiv.) and diisopropylethylamine (0.06 mmol, .2 equiv.) and sealed tightly. The vial was then placed ~3 inches from a 440 nm Kessil lamp to be irradiated and stirred for 16 hours at room temperature. The vial was then removed from the light box and K₃PO₄ (5 equiv. 1.5 mmol) was added along with 2.25 mL MeCN and sufficient H₂O to render the K₃PO₄ soluble. After stirring at room temperature for 3 hours, the vial was rinsed with EtOAc into a flask and then concentrated onto silica gel in vacuo. Products were purified using flash column chromatography using EtOAc:Hexanes as an eluent.

B) Identical to standard reaction conditions A but using 50% loading of N-isopropyl-N,2-dimethylpropan-2-amine instead of diisopropylethylamine.

C) To an oven-dried 8 mL test tube vial, was added 2% [Ir(dFCF₃ppy)₂dtbbpy]PF₆, 0.3 mmol (1 equiv.), of α-bromoimide, 0.3 mmol (1 equiv.) La(OTf)₃ and 750 μL of MeCN. This solution was allowed to stir at room temperature for at least 30 minutes. Then 3 equiv. (0.9 mmol) of the olefin nucleophile and 0.33 mmol diisopropylethylamine are added and the vial was placed ~3 inches from a 440 nm Kessil lamp to be irradiated and stirred for 36 hours at room temperature. In some cases, noted specifically, the intramolecular cyclization does not occur and so the vial was removed from the light box and K₃PO₄ (5 equiv. 1.5 mmol) was added along with 2.25 mL MeCN and sufficient H₂O to render the K₃PO₄ soluble. After stirring at room temperature for 3 hours or directly from the photoreactor the vial was rinsed with EtOAc and saturated aqueous ammonium chloride into a separatory funnel and extracted 3x with EtOAc. This was then dried with sodium sulfate and and concentrated onto silica gel in vacuo. Products were purified using flash column chromatography using EtOAc:Hexanes as an eluent.

Helpful Tips:

Sufficiently wet MeCN also works well for the cyclization as we found through control studies. Excess H₂O does not appear deleterious but does start to enable phase separation if too much is added. Sufficient mixing was found to be essential in these cases.

Depending on the structure of the a-bromoimide, complexation with the Lewis acid often results in an insoluble complex. The mixture typically becomes homogeneous after a few minutes of stirring under irradiation.
Characterization Data of Products:

3aa - tert-butyl 2-butyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2a.
Yield 77%
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.09 (dddd, J = 9.5, 8.3, 3.4, 1.9 Hz, 1H), 2.57 (ddd, J = 17.7, 11.0, 9.2 Hz, 1H), 2.41 (ddd, J = 17.7, 9.5, 2.7 Hz, 1H), 2.16 – 2.01 (m, 1H), 1.83 – 1.71 (m, 2H), 1.52 (s, 9H), 0.91 (t, J = 7.0 Hz, 3H).
$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 174.62, 150.21, 82.83, 58.25, 33.55, 31.60, 28.24, 27.96, 27.96, 22.71, 22.67, 14.20.
HRMS (ESI+) $[\text{C}_{13}\text{H}_{23}\text{NNaO}_3]^+$ m/z calculated 264.1570, found 264.1606

3ab - tert-butyl 2-hexyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2b.
Yield 69%
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.09 (dddd, J = 9.3, 8.2, 3.4, 1.9 Hz, 1H), 2.57 (ddd, J = 17.7, 11.0, 9.1 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.15 – 2.00 (m, 1H), 1.76 (dddd, J = 12.8, 9.2, 2.7, 2.0 Hz, 2H), 1.53 (s, 9H), 1.34 – 1.24 (m, 12H), 0.92 – 0.84 (m, 3H).
$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 174.62, 150.21, 82.83, 58.28, 33.90, 32.00, 31.61, 29.70, 29.65, 28.24, 25.83, 22.82, 22.69, 14.26.
HRMS (ESI+) $[\text{C}_{15}\text{H}_{27}\text{NNaO}_3]^+$ m/z calculated 320.2196, found 320.2223

3ac - tert-butyl 2-isobutyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2c.
Yield 50%
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 4.28 – 4.06 (m, 1H), 2.58 (ddd, J = 17.6, 11.4, 9.0 Hz, 1H), 2.41 (ddd, J = 17.7, 9.4, 2.3 Hz, 1H), 2.15 – 2.02 (m, 1H), 1.76 (ddt, J = 12.9, 9.0, 2.0 Hz, 1H), 1.67 – 1.57 (m, 2H), 1.53 (s, 9H), 1.40 (ddd, J = 12.4, 10.6, 3.4 Hz, 1H), 0.98 – 0.84 (m, 6H).
$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 174.38, 60.34, 38.97, 34.38, 33.18, 32.67, 28.66, 26.51, 14.43.
HRMS (ESI+) $[\text{C}_{13}\text{H}_{23}\text{NNaO}_3]^+$ m/z calculated 264.1570, found 264.1606

3ad - tert-butyl 2-(((3r,5r,7r)-adamantan-1-yl)methyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A 1a and 2d.
Yield 59%
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.11 (dddd, J = 11.1, 8.1, 3.2, 1.6 Hz, 1H), 2.59 (ddd, J = 17.6, 11.5, 9.0 Hz, 1H), 2.47 – 2.35 (m, 1H), 2.15 – 2.00 (m, 2H), 1.98 – 1.76 (m, 6H), 1.53 (s, 10H), 1.37 (ddd, J = 13.4, 10.7, 4.1 Hz, 1H).
$^{13}$C NMR (101 MHz, Chloroform-d) $\delta$ 174.37, 60.33, 37.01, 33.24, 32.74, 32.19, 27.40, 26.46, 25.57, 14.44.
HRMS (ESI+) [C_{20}H_{31}NNaO_{3}] m/z calculated 356.2196, found 356.2227

3ae - tert-butyl 2-(cyclohexylmethyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2e.
Yield 62%

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \delta 4.27 - 4.07 (m, 1H), 2.58 (dd, d = 17.7, 11.4, 9.0 Hz, 1H), 2.40 (dd, d = 17.7, 9.3, 2.3 Hz, 1H), 2.08 (dd, d = 12.6, 11.4, 9.3, 8.1, 1.1 Hz, 1H), 1.85 - 1.57 (m, 7H), 1.53 (s, 9H), 1.41 - 1.09 (m, 5H), 1.07 - 0.87 (m, 2H). \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \delta 174.68, 150.05, 82.85, 56.33, 41.36, 35.06, 34.60, 32.69, 31.36, 28.28, 26.59, 26.49, 26.28, 23.02. \]

HRMS (ESI+) [C_{16}H_{27}NNaO_{3}] m/z calculated 304.1883, found 304.1916

3af - tert-butyl 2-oxo-5-phenethylpyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2f.
Yield 84%

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \delta 7.33 - 7.27 (m, 2H), 7.23 - 7.15 (m, 3H), 4.15 (dddd, d = 9.7, 8.3, 3.4, 1.5 Hz, 1H), 2.79 - 2.52 (m, 3H), 2.44 (dd, d = 17.7, 9.5, 2.8 Hz, 1H), 2.22 - 2.05 (m, 2H), 1.93 - 1.75 (m, 2H), 1.50 (s, 9H). \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \delta 174.47, 150.09, 141.03, 128.75, 128.45, 126.36, 83.00, 57.82, 35.50, 32.26, 31.51, 28.21, 22.57. \]

HRMS (ESI+) [C_{17}H_{23}NNaO_{4}] m/z calculated 312.1570, found 312.1610

3ag - tert-butyl 2-(4-methoxybenzyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A 1a and 2g.
Yield 50%

\[ ^1H \text{NMR (400 MHz, CDCl}_3 \delta 7.17 - 7.05 (m, 2H), 6.89 - 6.81 (m, 2H), 4.32 (tdd, d = 8.6, 3.4, 1.5 Hz, 1H), 3.79 (s, 3H), 3.09 - 2.95 (m, 1H), 2.71 (dd, d = 13.5, 8.8 Hz, 1H), 2.49 - 2.16 (m, 2H), 1.96 (dd, d = 13.0, 10.4, 8.4 Hz, 1H), 1.80 (dd, d = 13.0, 7.7, 3.6, 1.5 Hz, 1H), 1.58 (s, 9H). \]

\[ ^{13}C \text{NMR (101 MHz, CDCl}_3 \delta 174.61, 158.77, 150.15, 130.55, 129.17, 114.36, 83.11, 59.27, 55.44, 38.79, 31.33, 28.32, 21.78. \]

HRMS (ESI+) [C_{17}H_{23}NNaO_{4}] m/z calculated 328.1519, found 328.1557

3ah - tert-butyl 2-(3-ethoxy-3-oxopropyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2h.
Yield 72%

1H NMR (400 MHz, CDCl₃) δ 4.27 – 4.02 (m, 3H), 2.59 (ddd, J = 17.8, 11.0, 9.1 Hz, 1H), 2.43 (ddd, J = 17.8, 9.5, 2.8 Hz, 1H), 2.34 (ddd, J = 8.5, 7.0, 2.0 Hz, 2H), 2.20 – 2.03 (m, 2H), 1.93 – 1.80 (m, 1H), 1.75 (dddd, J = 13.0, 9.1, 2.8, 2.0 Hz, 1H), 1.53 (s, 9H), 1.26 (t, J = 7.1 Hz, 3H).

13C NMR (101 MHz, CDCl₃) δ 174.14, 172.75, 150.12, 83.25, 60.85, 57.38, 31.48, 30.79, 29.22, 28.21, 22.72, 14.37.

HRMS (ESI+) [C₁₄H₂₃NNaO₅⁺] m/z calculated 308.1468, found

3ai - tert-butyl 2-(acetoxymethyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2i.

Yield 54%

1H NMR (400 MHz, CDCl₃) δ 4.43 – 4.33 (m, 2H), 4.25 – 4.11 (m, 1H), 2.65 (ddd, J = 17.7, 11.1, 9.6 Hz, 1H), 2.45 (ddd, J = 17.7, 9.9, 2.3 Hz, 1H), 2.26 – 2.13 (m, 1H), 2.07 (s, 3H), 1.94 (ddt, J = 13.3, 9.6, 1.9 Hz, 1H), 1.54 (s, 9H).

13C NMR (101 MHz, CDCl₃) δ 174.25, 170.79, 149.85, 83.64, 65.07, 56.31, 31.93, 28.21, 21.19, 21.03.

HRMS (ESI+) [C₁₂H₁₉NNaO₅⁺] m/z calculated 280.1155, found 280.1195

3aj - tert-butyl 2-(5-bromopentyl)-5-oxopyrrolidine-1-carboxylate
Prepared using reaction conditions A from 1a and 2j.

Yield 68%

1H NMR (400 MHz, CDCl₃) δ 4.15 – 4.05 (m, 1H), 3.41 (t, J = 6.7 Hz, 2H), 2.57 (ddd, J = 17.7, 11.0, 9.1 Hz, 1H), 2.42 (ddd, J = 17.7, 9.5, 2.8 Hz, 1H), 2.10 (tt, J = 10.9, 9.1 Hz, 1H), 1.95 – 1.70 (m, 4H), 1.53 (s, 10H), 1.47 – 1.23 (m, 4H).

13C NMR (101 MHz, CDCl₃) δ 174.39, 150.23, 144.81, 133.40, 129.97, 128.05, 82.84, 70.83, 58.23, 33.87, 31.61, 29.58, 29.44, 29.06, 29.00, 28.23, 25.80, 25.50, 22.67, 21.82.

HRMS (ESI+) [C₁₄H₁₉BrNaO₅⁺] m/z calculated 356.0832, found 356.0859

3ak - tert-butyl 2-oxo-5-(9-(tosyloxy)nonyl)pyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2k.

Yield 86%

1H NMR (500 MHz, CDCl₃) δ 7.81 – 7.75 (m, 2H), 7.34 (d, J = 8.1 Hz, 2H), 4.08 (dddd, J = 9.5, 8.2, 3.4, 1.9 Hz, 1H), 4.01 (t, J = 6.5 Hz, 2H), 2.62 – 2.49 (m, 1H), 2.48 – 2.33 (m, 4H), 2.09 (tt, J = 12.1, 9.1 Hz, 1H), 1.75 (dddd, J = 14.7, 10.4, 6.3, 4.0 Hz, 2H), 1.67 – 1.57 (m, 2H), 1.52 (s, 9H), 1.38 – 1.15 (m, 13H).

13C NMR (126 MHz, CDCl₃) δ 174.62, 150.20, 144.81, 133.40, 129.97, 128.05, 82.84, 70.83, 58.23, 33.87, 31.61, 29.58, 29.44, 29.06, 29.00, 28.23, 25.80, 25.50, 22.67, 21.82.

HRMS (ESI+) [C₂₅H₃₉NNaO₆S⁺] m/z calculated 504.2390, found 504.2431
3al - tert-butyl 2-((tert-butylidiphenylsilyl)oxy)pentyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2l.
Yield 78%

1H NMR (400 MHz, CDCl3) δ 7.70 – 7.62 (m, 4H), 7.43 – 7.33 (m, 6H), 4.07 (ddq, J = 9.4, 5.3, 1.9 Hz, 1H), 3.67 (t, J = 6.3 Hz, 2H), 2.55 (dd, J = 17.7, 11.0, 9.1 Hz, 1H), 2.41 (dd, J = 17.7, 9.5, 2.7 Hz, 1H), 2.08 (tt, J = 12.4, 9.3 Hz, 1H), 1.74 (ddt, J = 11.0, 6.4, 2.3 Hz, 2H), 1.63 – 1.35 (m, 15H), 1.05 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 174.51, 150.17, 135.72, 134.12, 129.77, 127.80, 82.84, 63.72, 58.19, 33.59, 32.51, 31.56, 28.23, 27.04, 22.61, 22.15, 19.39.

HRMS (ESI+) [C29H41NNaO4Si+] m/z calculated 518.2697, found 518.2708

3am - tert-butyl 2-((tert-butylidiphenylsilyl)oxy)butyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2m.
Yield 71%

1H NMR (400 MHz, CDCl3) δ 4.15 (tdd, J = 8.3, 4.5, 2.0 Hz, 1H), 2.70 – 2.25 (m, 4H), 2.17 (s, 3H), 2.11 – 1.95 (m, 2H), 1.83 (dtd, J = 13.7, 8.3, 6.6 Hz, 1H), 1.75 – 1.67 (m, 1H), 1.54 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 207.32, 174.09, 150.38, 83.26, 57.30, 39.76, 31.55, 30.14, 28.24, 27.93, 23.02.

HRMS (ESI+) [C13H21NNaO+] m/z calculated 278.1363, found 278.1386

3an - tert-butyl 2-oxo-5-(2,4,6-trimethylphenethyl)pyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2n.
Yield 88%

1H NMR (400 MHz, CDCl3) δ 6.84 (s, 2H), 4.28 – 4.18 (m, 1H), 2.71 – 2.42 (m, 4H), 2.26 (d, J = 16.7 Hz, 10H), 1.98 – 1.84 (m, 2H), 1.69 (ddd, J = 13.7, 11.4, 9.0, 5.9 Hz, 1H), 1.51 (s, 9H).

13C NMR (101 MHz, CDCl3) δ 174.38, 150.13, 135.83, 135.62, 134.77, 129.26, 83.02, 58.26, 33.18, 31.69, 28.22, 25.36, 22.75, 20.95, 19.85.

HRMS (ESI+) [C20H29NNaO3+] m/z calculated 354.2040, found 354.2063

3ao - tert-butyl 2-((1,3-dioxoisindolin-2-yl)pentyl)-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2o.
Yield 60%

1H NMR (400 MHz, CDCl3) δ 7.84 (dd, J = 5.4, 3.0 Hz, 2H), 7.76 – 7.67 (m, 2H), 4.08 (dddd, J = 9.7, 8.2, 3.4, 1.9 Hz, 1H), 3.70 (t, J = 7.1 Hz, 2H), 2.64 – 2.47 (m, 1H), 2.40 (ddd, J = 17.8, 9.4, 2.6 Hz, 1H), 2.08 (tt, J = 12.6, 9.3 Hz, 1H), 1.90 – 1.62 (m, 5H), 1.51 (m, 11H), 1.45 – 1.28 (m, 2H).
\[^1\text{H}\text{ NMR (400 MHz, CDCl}_3\text{)} \delta 7.52 (d, J = 7.9 Hz, 2H), 7.37 – 7.24 (m, 1H), 7.09 (t, J = 7.4 Hz, 1H), 4.14 – 4.04 (m, 1H), 2.57 (ddd, J = 17.7, 11.0, 9.2 Hz, 1H), 2.46 – 2.30 (m, 3H), 2.17 – 1.99 (m, 1H), 1.81 – 1.66 (m, 4H), 1.52 (s, 9H), 1.32 (s, 11H). \]

\[^1\text{C}\text{ NMR (101 MHz, CDCl}_3\text{)} \delta 174.63, 171.46, 150.23, 138.18, 129.17, 124.33, 119.89, 82.88, 58.23, 37.93, 33.87, 31.64, 29.52, 29.46, 29.33, 29.29, 28.26, 28.25, 25.67, 22.69. \]

HRMS (ESI+) [C\text{24}H\text{36}N\text{2}NaO\text{4}+] \text{m/z calculated 439.3037, found 439.3127}
3as - tert-butyl 4-([1-(tert-butoxycarbonyl)-5-oxopyrrolidin-2-yl]nonanoyl)piperazine-1-carboxylate
Prepared using standard reaction conditions A from 1a and 2s.
Yield 82%
$^1$H NMR (400 MHz, CDCl$_3$) δ 4.12 – 4.02 (m, 1H), 3.58 (s, 2H), 3.43 (s, 6H), 2.56 (ddd, $J$ = 17.7, 11.0, 9.1 Hz, 1H), 2.40 (ddd, $J$ = 17.8, 9.5, 2.7 Hz, 1H), 2.31 (t, $J$ = 7.6 Hz, 2H), 2.20 – 1.97 (m, 1H), 1.82 – 1.69 (m, 2H), 1.61 (d, $J$ = 7.4 Hz, 2H), 1.52 (s, 9H), 1.46 (s, 9H), 1.30 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.39, 171.92, 154.60, 150.13, 82.66, 80.30, 58.06, 45.42, 43.65, 41.33, 33.72, 33.34, 31.53, 29.44, 29.42, 29.34, 28.37, 28.34, 28.07, 25.63, 25.24, 22.51.

HRMS (ESI+) [C$_{2}$7H$_{47}$N$_{3}$NaO$_{6}$+] m/z calculated 532.3357, found 532.3441

3ba - methyl 2-butyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1b and 2a.
Yield 72%
$^1$H NMR (400 MHz, CDCl$_3$) δ 4.18 (dddd, $J$ = 9.5, 8.3, 3.4, 1.9 Hz, 1H), 3.86 (s, 3H), 2.62 (ddd, $J$ = 17.9, 11.0, 9.2 Hz, 1H), 2.45 (ddd, $J$ = 17.9, 9.4, 2.7 Hz, 1H), 2.13 (ddd, $J$ = 20.2, 12.0, 9.0 Hz, 1H), 1.87 – 1.76 (m, 2H), 1.56 – 1.46 (m, 2H), 0.92 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.19, 152.50, 58.42, 53.62, 33.24, 32.49, 31.61, 27.78, 22.75, 22.68, 14.14.

HRMS (ESI+) [C$_{10}$H$_{17}$NNaO$_{3}$+] m/z calculated 222.1101, found 222.1163

3ca - 2,2,2-trichloroethyl 2-butyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1c and 2a.
Yield 55%
$^1$H NMR (400 MHz, CDCl$_3$) δ 4.94 (d, $J$ = 11.9 Hz, 1H), 4.78 (d, $J$ = 11.9 Hz, 1H), 4.25 (ddd, $J$ = 9.8, 8.3, 3.2, 1.7 Hz, 1H), 2.64 (ddd, $J$ = 18.0, 11.3, 9.1 Hz, 1H), 2.49 (ddd, $J$ = 18.0, 9.5, 2.5 Hz, 1H), 2.25 – 2.10 (m, 1H), 1.96 – 1.83 (m, 2H), 1.58 (ddd, $J$ = 11.3, 9.6, 5.3, 3.3 Hz, 1H), 1.44 – 1.18 (m, 4H), 0.91 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.36, 149.68, 94.71, 75.21, 58.56, 33.48, 31.18, 27.91, 22.80, 22.71, 14.20.

HRMS (ESI+) [Cl$_{2}$H$_{10}$ClNaO$_{3}$+] m/z calculated 338.0088, found 338.0118

3da - (trimethylsilyl)methyl 2-butyl-5-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions A from 1d and 2a.
Yield 90%
$^1$H NMR (400 MHz, CDCl$_3$) δ 4.40 – 4.24 (m, 2H), 4.16 (ddd, $J$ = 9.4, 8.2, 3.4, 2.0 Hz, 1H), 2.60 (ddd, $J$ = 17.8, 11.0, 9.2 Hz, 1H), 2.43 (ddd, $J$ = 17.8, 9.5, 2.7 Hz, 1H), 2.18 – 2.03 (m, 1H), 1.87 – 1.74 (m, 2H), 1.57 – 1.42 (m, 1H), 1.40 – 1.24 (m, 4H), 1.17 – 1.05 (m, 2H), 0.91 (t, $J$ = 7.0 Hz, 3H), 0.05 (s, 9H).
$^{13}$C NMR (101 MHz, CDCl$_3$) δ 174.19, 152.02, 65.26, 58.28, 33.32, 31.64, 27.81, 22.73, 22.69, 17.82, 14.15, -1.40. HRMS (ESI+) $[\text{C}_{13}H_{25}\text{NaO}_3\text{Si}^+]$ m/z calculated 308.1652, found 308.1703

3ea - 5-butyl-1-tosylpyrrolidin-2-one
Prepared using standard reaction conditions C from 1e and 2a.
Yield 35%

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.95 (d, $J = 8.4$ Hz, 2H), 7.32 (m, 2H), 4.39 (dddd, $J = 9.3$, 8.4, 3.1, 1.7 Hz, 1H), 2.52 (ddd, $J = 1.7$, 11.2, 9.2 Hz, 1H), 2.43 (s, 3H), 2.34 (ddd, $J = 13.7$, 11.0, 5.3, 3.1 Hz, 1H), 1.85 (dtt, $J = 13.0$, 9.2, 2.0 Hz, 1H), 1.70 – 1.59 (m, 1H), 1.43 – 1.15 (m, 4H), 0.90 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.69, 145.05, 136.26, 129.60, 128.48, 60.58, 34.44, 30.97, 27.37, 23.72, 22.62, 21.81, 14.10.
HRMS (ESI+) $[\text{C}_{15}H_{21}\text{NaO}_3^+]$ m/z calculated 318.1134, found 318.1170

3fa - tert-butyl 5-butyl-3-methyl-2-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions B from 1f and 2a.
Yield 56%

$^1$H NMR (400 MHz, CDCl$_3$) δ 4.00 (td, $J = 8.9$, 3.3 Hz, 1H), 3.92 (dtd, $J = 10.1$, 7.4, 2.9 Hz, 1H), 2.74 (q, $J = 7.4$ Hz, 1H), 2.69 – 2.57 (m, 1H), 2.55 – 2.45 (m, 1H), 2.36 (ddd, $J = 12.8$, 9.7, 7.6 Hz, 1H), 2.10 – 1.93 (m, 2H), 1.53 (d, $J = 1.9$ Hz, 17H), 1.40 – 1.16 (m, 11H), 0.91 (t, $J = 7.0$ Hz, 6H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 177.34, 176.76, 150.67, 150.38, 82.87, 82.70, 56.34, 56.06, 37.68, 36.63, 34.89, 33.16, 31.84, 28.44, 28.24, 28.18, 27.00, 22.74, 22.71, 16.73, 15.65, 14.22, 14.20.
HRMS (ESI+) $[\text{C}_{14}H_{25}\text{NaO}_3^+]$ m/z calculated 278.1727, found 278.1751

3ha - methyl 5-butyl-3,3-dimethyl-2-oxopyrrolidine-1-carboxylate
Prepared using standard reaction conditions C from 1h and 2a.
Yield 59%

$^1$H NMR (400 MHz, CDCl$_3$) δ 3.99 (dddd, $J = 9.4$, 8.1, 6.0, 3.1 Hz, 1H), 3.86 (s, 3H), 2.12 – 1.99 (m, 2H), 1.63 (dd, $J = 13.1$, 6.0 Hz, 1H), 1.49 – 1.19 (m, 8H), 1.18 (s, 3H), 0.91 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 179.57, 153.01, 54.98, 53.61, 41.64, 38.52, 34.35, 27.32, 26.50, 26.13, 22.67, 14.16.
HRMS (ESI+) $[\text{C}_{12}H_{21}\text{NaO}_3^+]$ m/z calculated 250.1414, found 250.1526

3ia - methyl 3-butyl-1-oxo-2-azaspiro[4.5]decane-2-carboxylate
Prepared using standard reaction conditions C from 1i and 2a.
Yield 80%
$^{1}$H NMR (400 MHz, CDCl$_{3}$) δ 3.99 (dddd, $J$ = 9.7, 8.7, 5.6, 3.1 Hz, 1H), 3.86 (s, 3H), 2.10 (dd, $J$ = 13.3, 8.5 Hz, 1H), 2.02 (dddd, $J$ = 12.5, 9.4, 6.0, 3.1 Hz, 1H), 1.83 – 1.55 (m, 5H), 1.54 – 1.20 (m, 8H), 0.91 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_{3}$) δ 179.27, 153.02, 55.25, 53.59, 46.14, 34.74, 34.40, 34.32, 34.26, 27.38, 25.43, 22.68, 22.13, 22.01, 14.17.

HRMS (ESI+) [C$_{15}$H$_{25}$NNaO$_3$+] m/z calculated 290.1727, found 290.1839

3ja - methyl 3-butyl-1-oxo-2-azaspiro[4.4]nonane-2-carboxylate
Prepared using standard reaction conditions C from 1j and 2a.
Yield 46%

$^{1}$H NMR (400 MHz, CDCl$_{3}$) δ 4.10 – 3.93 (m, 1H), 3.86 (s, 3H), 2.16 – 1.93 (m, 4H), 1.83 (td, $J$ = 8.1, 4.3 Hz, 2H), 1.78 – 1.51 (m, 6H), 1.47 – 1.22 (m, 6H), 0.91 (t, $J$ = 7.0 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_{3}$) δ 179.92, 152.90, 55.83, 53.59, 51.83, 39.11, 39.00, 38.14, 34.05, 27.70, 25.96, 25.55, 22.68, 14.17.

HRMS (ESI+) [C$_{14}$H$_{23}$NNaO$_3$+] m/z calculated 276.1570, found 276.1608

3ka - methyl 7-butyl-5-oxo-6-azaspiro[3.4]octane-6-carboxylate
Prepared using standard reaction conditions C from 1k and 2a and was subjected to extra base for 3 hours.
Yield 63%

$^{1}$H NMR (400 MHz, CDCl$_{3}$) δ 4.09 – 3.93 (m, 1H), 3.85 (s, 3H), 2.58 – 2.40 (m, 2H), 2.24 – 1.79 (m, 7H), 1.44 – 1.20 (m, 5H), 0.99 – 0.81 (m, 3H).

$^{13}$C NMR (101 MHz, CDCl$_{3}$) δ 178.22, 152.76, 56.15, 53.59, 46.14, 36.99, 34.26, 33.92, 33.57, 30.54, 27.98, 25.96, 16.53, 14.12.

HRMS (ESI+) [C$_{13}$H$_{21}$NNaO$_3$+] m/z calculated 262.1414, found 262.1535

3la - methyl 3-butyl-1-oxo-8-oxa-2-azaspiro[4.5]decane-2-carboxylate
Prepared using standard reaction conditions C from 3l and 2a.
Yield 68%

$^{1}$H NMR (400 MHz, CDCl$_{3}$) δ 4.09 – 3.92 (m, 3H), 3.87 (s, 3H), 3.55 (ddt, $J$ = 12.4, 9.5, 2.3 Hz, 2H), 2.19 (dd, $J$ = 13.3, 8.4 Hz, 1H), 2.07 (dt, $J$ = 14.1, 3.9 Hz, 2H), 1.95 (ddt, $J$ = 13.8, 9.9, 4.1 Hz, 1H), 1.75 (dd, $J$ = 13.3, 5.5 Hz, 1H), 1.53 – 1.17 (m, 7H), 0.92 (t, $J$ = 6.9 Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_{3}$) δ (101 MHz, CDCl$_{3}$) δ 177.62, 152.84, 63.97, 63.86, 55.16, 53.74, 43.29, 35.04, 34.74, 34.57, 34.35, 27.37, 22.65, 14.15.

HRMS (ESI+) [C$_{14}$H$_{23}$NNaO$_4$+] m/z calculated 292.1519, found 292.1562

2:1 dr
**3bt - methyl 5-oxo-2,3-dipropylpyrrolidine-1-carboxylate**  
Prepared using standard reaction conditions C from 1b and 2t and was subjected to extra base for 3 hours.  
Yield 48% 2:1 dr  
1H NMR (400 MHz, CDCl₃) δ 4.26 (q, J = 6.4 Hz, 1H), 3.86 (s, 1H), 3.85 (s, 3H), 2.86 (dd, J = 18.0, 8.5 Hz, 0H), 2.78 (dd, J = 17.9, 8.5 Hz, 1H), 2.55 – 2.36 (m, 2H), 2.35 – 2.13 (m, 2H), 1.84 – 1.61 (m, 1H), 1.53 – 1.25 (m, 13H), 1.02 – 0.81 (m, 1H).  
13C NMR (101 MHz, CDCl₃) δ 173.85, 152.71, 63.79, 62.91, 60.58, 53.63, 53.59, 38.37, 38.02, 38.00, 37.44, 37.34, 37.23, 35.79, 35.76, 34.86, 34.54, 37.44, 37.34, 37.23, 35.79, 35.76, 34.86, 34.54, 32.03, 31.73, 21.24, 20.21, 20.15, 19.68, 18.99, 14.51, 14.31, 14.16, 14.10.  
HRMS (ESI+) [C₁₂H₂₁NNaO₃+] m/z calculated 250.1414, found 250.1475

**3bu - methyl 2,3-diethyl-5-oxopyrrolidine-1-carboxylate**  
Prepared using standard reaction conditions C from 1b and 2t and was subjected to extra base for 3 hours.  
Yield 55% 2:1 dr  
1H NMR (400 MHz, CDCl₃) δ 4.24 (dt, J = 7.2, 5.8 Hz, 1H), 3.86 (s, 4H), 3.85 (s, 3H), 3.81 (ddd, J = 9.1, 3.4, 1.3 Hz, 1H), 2.77 (dd, J = 18.0, 8.6 Hz, 1H), 2.55 – 2.44 (m, 1H), 2.40 – 2.11 (m, 3H), 1.97 – 1.87 (m, 1H), 1.88 – 1.71 (m, 2H), 1.65 – 1.32 (m, 8H), 1.09 – 0.82 (m, 13H).  
13C NMR (101 MHz, CDCl₃) δ 173.87, 173.81, 152.71, 152.65, 64.82, 61.56, 53.64, 53.60, 39.09, 37.95, 37.81, 36.16, 28.06, 26.41, 22.53, 22.45, 12.57, 11.49, 10.84, 9.82.  
HRMS (ESI+) [C₁₀H₁₇NNaO₃+] m/z calculated 222.1101, found 222.1133

**3aw - tert-butyl 2-(but-3-en-1-yl)-5-oxopyrrolidine-1-carboxylate**  
Prepared using standard reaction conditions A from 1a and 2w.  
Yield 67%  
1H NMR (400 MHz, CDCl₃) δ 5.81 (ddt, J = 17.0, 10.1, 6.6 Hz, 1H), 5.11 – 4.97 (m, 2H), 4.13 (dddd, J = 9.9, 8.3, 3.2, 2.0 Hz, 1H), 2.58 (ddd, J = 17.7, 11.0, 9.1 Hz, 1H), 2.43 (ddd, J = 17.7, 9.5, 2.7 Hz, 1H), 2.22 – 1.99 (m, 2H), 1.90 (dddt, J = 12.9, 9.8, 7.1, 3.1 Hz, 1H), 1.78 (ddtt, J = 12.8, 9.1, 2.3 Hz, 1H), 1.53 (s, 1H).  
13C NMR (101 MHz, CDCl₃) δ 174.48, 150.15, 137.40, 115.66, 82.99, 57.68, 32.91, 31.52, 30.12, 28.25, 22.50.  
HRMS (ESI+) [C₁₄H₂₅NNaO₃+] m/z calculated 278.1727, found 278.1751

**3ay - tert-butyl 2-(hex-5-en-1-yl)-5-oxopyrrolidine-1-carboxylate**  
Prepared using standard reaction conditions A from 1a and 2y.  
Yield 40%  
1H NMR (400 MHz, CDCl₃) δ 5.79 (dddt, J = 16.9, 10.2, 6.7 Hz, 1H), 5.10 – 4.84 (m, 2H), 4.15 – 4.05 (m, 1H), 2.57 (ddd, J = 17.7, 11.0, 9.1 Hz, 1H), 2.41 (ddd, J = 17.7, 9.5, 2.7 Hz, 1H), 2.17 – 2.02 (m, 3H), 1.77 (tdd, J = 12.2, 7.0, 3.1 Hz, 2H), 1.61 – 1.21 (m, 15H).  
13C NMR (101 MHz, CDCl₃) δ 174.55, 150.22, 138.67, 114.89, 82.89, 58.19, 33.78, 33.74, 31.60, 28.83, 28.26, 25.25, 22.71.  
HRMS (ESI+) [C₁₃H₂₁NNaO₃+] m/z calculated 262.1414, found 262.1443
4aa - tert-butyl (4-bromooctanoyl)carbamate
Prepared using standard reaction conditions A from 1a and 2a without the addition of base and MeCN.
Yield 92%

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.33 (s, 1H), 4.18 – 3.95 (m, 1H), 3.13 – 2.75 (m, 2H), 2.23 (dddd, $J = 15.1, 8.2, 7.0, 3.5$ Hz, 1H), 2.05 (dddd, $J = 15.1, 9.6, 7.9, 5.8$ Hz, 1H), 1.93 – 1.76 (m, 2H), 1.49 (s, 13H), 0.91 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 173.91, 150.54, 82.83, 57.66, 39.25, 34.51, 33.43, 29.88, 28.19, 22.29, 14.12.

LRMS (EI) [C$_{13}$H$_{24}$BrNO$_3$] m/z calculated 321.1, found
References:


NMR Spectra

1c

1H NMR

13C NMR
$^{1}H$ NMR

$^{13}C$ NMR
3aa

$^1$H NMR

3aa

$^{13}$C NMR
3af
$^1$H NMR

3af
$^{13}$C NMR
3ai
$^1$H NMR

3ai
$^{13}$C NMR
3ak

1H NMR

3ak

13C NMR
$^{1}H$ NMR

$^{13}C$ NMR
3da
$^1$H NMR

3da
$^{13}$C NMR
3ea
$^1$H NMR

3ea
$^{13}$C NMR
MeO

3bt
2:1 dr
\(^1\)H NMR

\[
\begin{align*}
  &\text{MeO} \\
  &\text{nPr} \quad \text{nPr} \\
  &\text{3bt} \\
  &2:1 \text{ dr}
\end{align*}
\]

\(\text{C NMR}\)

\[
\begin{align*}
  &\text{MeO} \\
  &\text{nPr} \quad \text{nPr} \\
  &\text{3bt} \\
  &2:1 \text{ dr}
\end{align*}
\]

\(\text{13C NMR}\)
MeO

\[ \text{Et} \quad 3bu \quad 2:1 \, dr \]

\[^1\text{H NMR}\]

\[ \text{Et} \quad \text{Et} \]

\[ \text{MeO} \quad \text{O} \quad \text{O} \]

\[ \text{Et} \quad \text{Et} \]

\[^{13}\text{C NMR}\]

413
$^{1}$H NMR

$^{13}$C NMR