Asymmetric Synthesis of Lactones and Lactams: Rhodium Catalysis in the Hydroacylation of Ketones and the Hydrogenation of Cyclic Dehydropeptides

Hasan Azam Khan

A thesis submitted in conformity with the requirements for the degree of Doctor of Philosophy

Department of Chemistry
University of Toronto

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Asymmetric Synthesis of Lactones and Lactams: Rhodium Catalysis in the Hydroacylation of Ketones and the Hydrogenation of Cyclic Dehydropeptides

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Abstract

Organic synthesis allows access complex materials in the context of fine chemicals, pharmaceuticals, and natural products, but many contemporary methods are wasteful – the focus is on the target rather than the process. Stoichiometric reagents, protecting groups, and multi-step processes are often involved to synthesize moieties such as chiral lactones and lactams, which are prevalent in biologically-relevant molecules like antibiotics (for example, the macrolides, typified by erythromycin) and cyclic peptides (such as cyclosporin and gramicidin). We have developed a rhodium-catalyzed lactonization of prochiral keto-aldehydes to access chiral lactones in a mild and atom-economical fashion, and a synthesis of cyclic peptides from achiral dehydropeptides using asymmetric rhodium-catalyzed hydrogenation to set the chirality in the peptide. In this fashion, we avoid using expensive and wasteful activating agents, protecting groups, and a host of other drawbacks endemic in lactonizations and peptide synthesis. This dissertation details: 1) the development of asymmetric rhodium-catalyzed hydroacylation, elucidation of the mechanism of this transformation through experimental and theoretical analyses, and the synthesis of chiral benzoxazecinones using this method, and 2) the synthesis of prochiral linear dehydropeptides, efficient cyclization of these molecules, and asymmetric reduction of multiple enamides in a highly enantio- and diastereoselective manner to access cyclic peptides.
Acknowledgements

I’ll start from the start – by thanking my family. I have been blessed with an outrageously overprotective mother, a stern but moral and endearing father, and an older brother who finds every reason to make me happier. They never miss a chance to tell me that they love me and that they’re proud of me. The constant stream of well-wishes, prayers, FOOD, gifts, rides, FOOD, and everything else made my day-to-day living much less stressful and complicated. They mean the world to me and I love them dearly.

When I moved to Toronto, I was looking for a distraction from the trials and tribulations of research. Instead, what I found was Samba Elegua (SE). SE is a community of folk from around Toronto that meet up every Sunday to practice the percussion stylings of Brazilian samba, and then perform at various venues. It’s hard to describe SE and accurately convey the sense of belonging and community I felt during practices and meetings. Thanks to Jon Medow and J.R., the head honchos, the grand poobahs, for bringing me in to the group. I really cherish knowing you guys and playing music with you. I’ve met so many incredible people and had many enjoyable experiences through the group. If you’re reading this and you’re in Toronto, join the group or go to a gig. You’ll never meet so many vivid souls in a single place.

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Vy and Wilmer. I have no idea what to say. “Thank you” is thoroughly insufficient. They took a chance on a student with little training or confidence but a great deal of passion. They built me from the ground up. They were there at my best and at my worst. They created a group culture wherein I didn’t know where I ended and the group began, and vice versa. I think more as “we” and “us” than I do as “I.” They fed us, even clothed us (they’re really nice scarves!) and they treated us like family. Vy and Wilmer worked hard and dealt with all manner of problems behind the scenes to keep us happy and focused on our research. If you were to ask me which group I’d join if I had to do my PhD again, heck, if I had to do another PhD, I’d answer the Dong group in a heartbeat. It was an incredible experience and I feel the most profound sense of gratitude that you let me experience it. I hope I’ve done well by you and I’ll work hard to continue doing well by you. I really miss my second family and I hope to visit soon and often.
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List of Publications

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<thead>
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<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>°C</td>
<td>Degrees Celsius</td>
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<tr>
<td>2-MeTHF</td>
<td>2-Methylenetetrahydrofuran</td>
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<tr>
<td>Ac₂O</td>
<td>Acetic anhydride</td>
</tr>
<tr>
<td>Alloc</td>
<td>Allyloxy carbonyl</td>
</tr>
<tr>
<td>BDPP</td>
<td>2,4-Bis(diphenylphosphino)pentane</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-Butyloxy carbonyl</td>
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<td>BOP</td>
<td>(Benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate</td>
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<td>Bz</td>
<td>Benzoyl</td>
</tr>
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<td>Cbz</td>
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<td>DIPEA</td>
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<td>4-(N,N-dimethylamino)pyridine</td>
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<td>N,N-Dimethylformamide</td>
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<tr>
<td>Dppm</td>
<td>1,1-Bis(diphenylphosphino)methane</td>
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<td>Dppp</td>
<td>1,3-Bis(diphenylphosphino)propane</td>
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<td>ee</td>
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<td>HRMS</td>
<td>High resolution mass spectrometry</td>
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<td>iBCF</td>
<td><em>iso</em>-butylchloroformate</td>
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<td>Abbreviation</td>
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<td>-----------</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
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<tr>
<td>Nsc</td>
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<tr>
<td>RRSPS</td>
<td>Repetitive Rapid Solid Phase Synthesis</td>
</tr>
<tr>
<td>SPPS</td>
<td>Solid phase peptide synthesis</td>
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<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
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<td>TLC</td>
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Chapter 1: The Synthesis of Chiral Lactones – Asymmetric Ketone Hydroacylation

1.1 Methods for the Synthesis of Chiral Lactones

The lactone is an important functional group in materials and therapeutics. Lactones find use in polyesters, as the ring-opening polymerization of lactones is an effective method for the synthesis of polylactic acid and polycaprolactone.\(^1\) Many antibiotics, namely the macrolides such as erythromycin, are macrolactones, which operate via the inhibition of bacterial protein synthesis.\(^2\) Conventional synthesis of chiral lactones is accomplished using a few established methods: the Corey-Nicolaou method,\(^3\) the Yamaguchi method,\(^4\) or the halolactonization method.\(^5\) Asymmetric variants of halolactonization have been developed only recently.\(^6\) While these methods are known for their mild conditions and applications in total synthesis, they suffer from similar drawbacks: the use of stoichiometric reagents, issues of chemoselectivity, and the need to install chirality before the lactonization.

Scheme 1.1 - Contemporary (left) and catalytic (right) strategies for the synthesis of chiral lactones
As of yet, no prevalent catalytic method has been developed for the synthesis of chiral lactones. To address this challenge, we envisioned a catalytic lactonization from an achiral keto-aldehyde involving concomitant oxidation of the aldehyde C–H bond and asymmetric reduction of the ketone. This transformation could potentially solve many drawbacks with established lactonizations through the use of a transition metal to catalyze this atom-economical reaction, which could promote a chemoselective reaction and induce enantioselectivity simultaneously.

At the onset of our studies on ketone hydroacylation, the asymmetric hydroacylation of alkenes and alkynes was well-established (vide infra) but the corresponding hydroacylation of prochiral ketones had been virtually unexplored. To provide perspective for the development of our proposed ketone hydroacylation, the development of olefin hydroacylation needs to be discussed.
1.2 A Short History of Rhodium-catalyzed Olefin Hydroacylation

Scheme 1.3 - A general mechanism for the hydroacylation of 4-pentenals

Hydroacylation, the formal addition of an acyl C–H bond across a π-system (olefin, alkyne, carbonyl, etc.), originated from a different transformation that is typically considered a side-reaction in hydroacylation: decarbonylation. In 1965, Tsuji reported the use of Wilkinson’s complex (Rh(PPh₃)₃Cl) in the decarbonylation of simple aldehydes at room temperature.⁷

Scheme 1.4 - Tsuji’s decarbonylation of benzaldehyde with Wilkinson’s complex

This transformation was thought to proceed through a Rh(III) intermediate via oxidative addition into the aldehyde C–H bond followed by insertion into the C–C bond. Aldehyde C–H
bonds could be activated using a variety of catalyst archetypes — aldehydes and organic carbenes can form Breslow intermediates \(^8\) and undergo benzoin condensations \(^9\) and metal alkoxides could mediate the dimerization of aldehydes into esters \(^10\) — but the oxidation of the C–H bond of an aldehyde using a Rh(I) catalyst had been unexplored. Sakai was the first to observe the hydroacylation of pentenals in the presence of Rh(I) in the synthesis of prostanoids. \(^11\) James observed the first example of an asymmetric hydroacylation in the form of a kinetic resolution of chiral racemic pentenals. \(^12\) Sakai later reported the first asymmetric hydroacylation of prochiral alkenes using Rh(I) catalysts and chiral diphosphine ligands (such as DIPMC, Scheme 1.5). \(^13\)

![Scheme 1.5](image)

**Scheme 1.5** - An example of Sakai’s asymmetric olefin hydroacylation

Since then, the mechanism of olefin hydroacylation has been studied by Bosnich \(^14\) and Sargent \(^15\) and many asymmetric examples have been reported. \(^14d,16\) Importantly, Bosnich observed that the dimeric complex [Rh(dppe)\(_2\)]\(^{2+}\) could be monomerized to form an efficient catalyst for the hydroacylation of 4-pentenals. \(^14a,17\) Dissociation could be accomplished using a coordinating solvent (such as acetone) or in the presence of the pentenal substrates. Using a deuterium-labelled pentenal, Bosnich observed a wide distribution of deuterated compounds resulting from scrambling of the deuterium atom, suggesting that the elemental steps in the hydroacylation of pentenals leading up to reductive elimination are fast and reversible.
Directing groups were used to stabilize catalytic intermediates in Suggs’ pioneering hydroacylation chemistry. When 8-quinolinecarboxaldehyde was taken in a CH$_2$Cl$_2$ solution of Wilkinson’s complex, a yellow precipitate formed which was characterized as the corresponding acyl-Rh$^{III}$ hydride complex.$^{18}$ Following this study, Suggs reported that the condensation of simple aryl aldehydes with 2-amino-3-picoline resulted in compounds capable of undergoing hydroacylation as the pyridinyl moiety could stabilize the Rh$^{III}$ intermediate.$^{19}$ Jun developed a research program based on the use of 2-amino-3-picoline as a catalytic directing group, taking advantage of the reversible nature of imine formation via condensation.$^{20}$ Miura was successful in applying this concept of β-directing groups in the use of salicylaldehydes as substrates for hydroacylation.$^{21}$

Observations relevant to our work in ketone hydroacylation have been summarized briefly above. At the onset of my studies in ketone hydroacylation, there were no asymmetric catalytic methods to accomplish this transformation. For a thorough literature review on olefin hydroacylation, please refer to the introduction of Matthew Coulter’s doctoral thesis.$^{22}$ At the end of this chapter, I will discuss the continuing work on carbonyl hydroacylation from the Dong group and others. The work presented above culminated in a thorough understanding of the types of catalysts that are capable of inserting into the aldehyde C–H bond, adding across a prochiral π-system in an enantioselective manner, and undergoing reductive elimination to restore the catalyst and allowing further turnover. The work of Suggs, Jun, Miura, and many others$^{23}$ indicated that substrates bearing directing groups would facilitate our desired hydroacylation. We were interested in using cationic Rh(I) precursors with chiral diphosphine ligands for the purpose of ketone hydroacylation, wherein the π-system would be a ketone instead of an olefin.$^{14a}$ With a model catalyst in mind, we conducted our initial study.
1.3 Rhodium-Catalyzed Hydroacylation of Ketones

1.3.1 Initial Report and Optimization$^{24}$

We chose readily available keto-aldehyde 1a as the test substrate. Keto-aldehydes of this type were synthesized from protected or reduced salicylaldehyde derivatives and α-halo ketones (2-bromoacetophenone in the case of 1a) and we thought the β-ether oxygen would be beneficial as a directing group.

Intramolecular hydroacylation of 1a could yield a seven-membered lactone 2a and/or the six-membered chromanone 3a.$^{25}$ The Rh-catalyzed decarbonylation of 1a to form phenolic ether 4a is a possible competitive pathway, particularly since decarbonylation is known to inactivate the catalyst towards hydroacylation. The protons α to the ketone would also be more acidic due to the adjacent phenolic oxygen, so the aldol pathway is another possible side reaction. Based on previous studies,$^{26}$ we considered that the coordinating ability of the ether-oxygen in 1a could help suppress decarbonylation and facilitate hydroacylation. Mechanistic studies (vide infra) revealed the nature of this coordinating heteroatom and how it was crucial to the desired reactivity. Much of the initial optimization was performed by Zengming Shen and I joined soon
after the initial proof-of-principle was achieved. We collaborated closely to optimize the reaction, synthesize keto-aldehyde substrates, and perform the titular transformation.

We initially investigated a number of transition metal catalysts known to undergo oxidative addition to aldehyde C–H bonds (Table 1.1). Over the course of these studies, chromanones of the type 4a were not isolated; benzoin-type cyclizations were not observed. In the absence of any catalyst, an aldol cyclization occurred to provide dihydrobenzofuran 6a in low yield and starting material was isolated otherwise (8%, Table 1.1, entry 1). The use of Wilkinson’s complex, Ru3(CO)12, and Pd(PPh3)4 resulted in decarbonylation to phenolic ether 3a and aldol products 5a and 6a (entries 2–4). However, studies with [Rh(COD)2]BF4 (COD = cyclooctadiene) and dppp resulted in the desired lactone 2a in 17% yield (entry 5). We reasoned that the low reactivity of [Rh(COD)2]BF4 and dppp (entry 2) resulted from competitive binding of COD to Rh. The use of [Rh(dppp)]2(BF4)2, prepared via the hydrogenation of [Rh(NBD)2]BF4 (NBD = norbornadiene) in the presence of dppp, resulted in complete conversion to 2a with no by-products resulting from decarbonylation or aldol side reactions (96% yield, entry 6).
Table 1.1 - Catalyst screening for hydroacylation of ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>2a</td>
</tr>
<tr>
<td>1</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Rh(PPh₃)₂Cl</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Ru₂CO₁₂</td>
<td>0</td>
</tr>
<tr>
<td>4ᵇ</td>
<td>Pd(PPh₃)₄</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>Rh(COD)₂BF₄ + dppp</td>
<td>17</td>
</tr>
<tr>
<td>6ᶜ</td>
<td>[Rh(dpnp)₂BF₄]₂</td>
<td>96ᵈ</td>
</tr>
</tbody>
</table>

ᵃ NMR yield. ᵇ This reaction was performed in toluene at 110 °C for 3d. ᵇ 2 h, rt. ᵇ Isolated yield.

We found that dichloroethane (DCE) also provided good reactivity and our next set of test reactions were conducted in DCE at 120 °C. We screened a series of chiral diphosphine ligands using Rh(NBD)₂BF₄ as the cationic rhodium source (Table 1.2). The catalysts were formed by dissolving the Rh salt and the ligand in DCE in a Schlenk vial and exposing this solution to hydrogen. Aldol products were absent from these reactions. Six chiral diphosphine ligands are shown in Table 2. These ligands are listed in order of increasing basicity to highlight a trend between phosphine-basicity and catalyst selectivity. (R)-Ph-MeOBIPHEP (7), the least basic phosphine in this series, was ineffective at promoting hydroacylation. Use of 7 resulted in complete decarbonylation (98% yield 3a, entry 1). (R)-DTBM-MeOBIPHEP 8 is a larger and more Lewis basic variant of 7. [Rh(8)]BF₄ transformed 1a into lactone 2a in 63% yield and 95%
ee. Decarbonylated product 3a was formed in 31% yield (entry 2). \((R)-\text{DTBM-SEGPHOS 9,}\)
more basic than 8, promoted hydroacylation further without compromising enantioselectivity
(76% yield 1a, 96% ee, and 22% yield 3a, entry 3). We studied several alkyl-substituted
phosphine ligands, which were expected to improve reaction efficiency due to their increased
electron density. Achiral ligand 1,3-bis(diphenylphosphino)propane (dppp) enabled Rh(I)-
catalyzed hydroacylation of 1a to yield 2a exclusively in 96% yield, as above. However, \((S,S)-\text{BDPP 10}\) gave only 4% ee and 67% yield of 2a (entry 4). This was unexpected in light of the
fact that 10 is a close chiral analogue of dppp. \((R,R)-\text{Me-DuPhos 11}\) also afforded lactone 2a
efficiently (95% yield) albeit in 82% ee (entry 5). \((R,R)-\text{Me-BPE 12},\) the most basic ligand in
this series, appeared to be either too electron-rich or not bulky enough, affording sluggish
reactivity (46% yield 2a, 6% yield 3a) and moderate enantioselectivity (76% ee) (entry 6).

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ligand</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
</tr>
<tr>
<td>Yield 3a</td>
<td>98%</td>
<td>31%</td>
<td>22%</td>
<td>33%</td>
<td>&lt;5%</td>
<td>6%</td>
</tr>
<tr>
<td>Yield 2a</td>
<td>&lt;2%</td>
<td>63%</td>
<td>76%</td>
<td>67%</td>
<td>95%</td>
<td>46%</td>
</tr>
<tr>
<td>ee 2a</td>
<td>ND</td>
<td>95%</td>
<td>96%</td>
<td>4%</td>
<td>82%</td>
<td>76%</td>
</tr>
</tbody>
</table>

Table 1.2 - Ligand effect on catalyst efficiency and enantioselectivity for hydroacylation of 1a.

General conditions: 5 mol% \([\text{Rh(Ligand)}]BF_4\), dichloroethane, 120 °C, 3 d in a sealed tube. Yields based on integration by \(^1\text{H}\) NMR. Enantiomeric excess determined by chiral HPLC.

On the basis of the results from Table 1.2, we chose catalyst \([\text{Rh)((R)-(9)}]BF_4\) for further
studies. We examined the scope of the reaction by varying substituents on the prochiral ketone
Changing from DCE to CH\textsubscript{2}Cl\textsubscript{2} improved asymmetric hydroacylation efficiency considerably. Under these conditions, lactone 2a was formed in 83\% yield and 99\% ee at 90 °C with a 15\% yield of the decarbonylated product. The yield of 2a increased to 92\% at rt due to the suppression of decarbonylation (7\% yield) while maintaining high enantioselectivity (99\% ee Table 1.3, entry 1). Other aromatic ketones (e.g. R = 4-Cl-Ph and 2-naphthyl) underwent hydroacylation to form the corresponding lactones in high yields and enantioselectivities (entries 2 and 3). Aliphatic ketones also demonstrated excellent reactivity. The methyl-substituted ketone 1d formed lactone 2d in 91\% yield and 99\% ee (entry 4). n-Butyl, benzyl, i-Pr, and t-butyl substituted lactones were isolated in high yields and enantioselectivities (≥ 93\%, >99\% ee, entries 5-8). Single crystal X-ray analysis of chloro-substituted lactone 2b revealed the absolute configuration to be the S enantiomer as drawn.

Table 1.3 - Enantioselective Rh(I)-catalyzed hydroacylation of aromatic and aliphatic prochiral ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Lactone</th>
<th>Time (d)</th>
<th>% Yield 2a</th>
<th>% ee 2b</th>
<th>% Yield 3c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>2a</td>
<td>3</td>
<td>92</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>2</td>
<td>4-Cl-Ph</td>
<td>2b</td>
<td>2</td>
<td>89</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>2-naphthyl</td>
<td>2c</td>
<td>2</td>
<td>85</td>
<td>99</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>2d</td>
<td>2</td>
<td>91</td>
<td>99</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>n-Bu</td>
<td>2e</td>
<td>2</td>
<td>99</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Bn</td>
<td>2f</td>
<td>3.5</td>
<td>93</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>i-Pr</td>
<td>2g</td>
<td>1.5</td>
<td>98</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>t-Bu</td>
<td>2h</td>
<td>1.5</td>
<td>94</td>
<td>&gt;99</td>
<td>0</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Isolated yield. \textsuperscript{b} Determined by chiral HPLC. \textsuperscript{c} Decarbonylated product yield based on \textsuperscript{1}H NMR integration relative to product peaks.
This work represented the first example of asymmetric rhodium-catalyzed ketone hydroacylation.\textsuperscript{24} It garnered a great deal of attention.\textsuperscript{28} We were interested in the mechanism of this transformation and, in particular, how it was distinct from olefin hydroacylation. We observed a few trends: the basicity of the phosphine ligand plays a critical role in promoting hydroacylation over competitive decarbonylation and intramolecular hydroacylation of ketoaldehydes \textbf{1} occurs with complete regioselectivity to produce formal Tishchenko lactones in large enantiomeric excess. There were three main questions that we sought to answer: what is the model for enantioselectivity? What is the precise role of the phenolic oxygen in \textbf{1}? What are the intermediates in the catalytic cycle? To address these questions, we embarked on a mechanistic study combining both experimental and theoretical methods. At this time, Peter Dornan joined the lab, bringing with him computational expertise that he had acquired in the Woo group at the University of Ottawa. Peter conducted the computational studies and kinetics modeling, and Zengming Shen performed most of the NMR studies and rate experiments. I performed the catalytic experiments, substrate syntheses and scope studies, ligand screens, and collaborated with Zengming Shen on the rate experiments. We collaborated with Professor Tom Woo to conduct this study.

1.3.2 Mechanistic Study\textsuperscript{29}

**Hydroacylation with [Rh(dppp)BF\textsubscript{4}]\textsubscript{2}**

In the previous study, we had identified two catalysts that effectively promote hydroacylation: achiral catalyst [Rh(dppp)BF\textsubscript{4}]\textsubscript{2} and chiral catalyst Rh((R)-DTBM-SEGPHOS)BF\textsubscript{4}. We began our mechanistic study by first studying the characteristics of [Rh(dppp)BF\textsubscript{4}]\textsubscript{2} in hydroacylation. We studied a series of diphosphine ligands that have similar
electronic properties to dppp but differ in their bite angles (Table 1.4).\textsuperscript{30} The literature and calculated values for related metal bisphosphine complexes for Rh(diphosphine)\textsuperscript{+} are listed in Table 1.4. Dppm (1,1-bis(diphenylphosphino)methane) forms the smallest bite angle with Rh, followed by dppe (1,2-bis(diphenylphosphino)ethane), dppp, and, dppb (1,4-bis(diphenylphosphino)butane). As summarized in Table 1.4, dppp provided optimal reactivity: complete conversion was observed after 4 hours. Dppb was also effective, promoting 98% conversion after 24 hours. However, the reaction efficiency decreased with smaller bite angles: with dppe, only 58% conversion to lactone 2a was achieved with a small amount of decarbonylation (15%) and with dppm, neither hydroacylation nor decarbonylation was observed. In the reaction with dppb (entry 4), good reactivity was observed with minimal decarbonylation. Dppf (1,1’-bis(diphenylphosphino)ferrocene) was ineffective at promoting hydroacylation or decarbonylation of 1a under these conditions. The results of Table 1.4 provide support for the trends we observed in Table 1.2: while there is a strong electronic trend in the ligands that promote hydroacylation, sterics play a large role as well. Sterically encumbered ligands will promote reductive elimination. Sterics also influence decarbonylation. Decarbonylation requires dissociation of a ligand to open a coordination site and the steric properties of the ligand are expected to affect this process. The exact mechanism by which bite angle influences these two processes is difficult to elucidate, considering that the bite angle is known to impart both steric and electronic influences on metal catalysts.\textsuperscript{31}
**Table 1.4** - Screening of diphosphine ligands with varying bite angles

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield 2a (%)</th>
<th>Yield 3a (%)</th>
<th>Bite Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>dppm</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>75.4°</td>
</tr>
<tr>
<td>2</td>
<td>dppe</td>
<td>58</td>
<td>15</td>
<td>86.3°</td>
</tr>
<tr>
<td>3</td>
<td>dppp</td>
<td>&gt;99</td>
<td>&lt;1</td>
<td>95.5°</td>
</tr>
<tr>
<td>4</td>
<td>dppb</td>
<td>98</td>
<td>2</td>
<td>98.6°</td>
</tr>
<tr>
<td>5</td>
<td>dppf</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>100.3°</td>
</tr>
</tbody>
</table>

* Yield by $^1$H-NMR after 24 hours. $^b$ Calculated at the B3LYP/LACV3P** level, see Supporting Information for details. $^c$ Literature bite angles for square-planar Pd(diphosphine)(1,1-dimethylallyl) complexes from X-ray crystallography. $^d$ Complete conversion after 4 hours. $^e$ Reported bite angle for Pd(diphosphine)(1-methylallyl) calculated at the PM3 level.

Keto-aldehydes bearing both alkyl and aryl substituents underwent hydroacylation (Table 1.5) in high yields (89-99%) and with short reaction times (1.2–12 h) (entries 1-13), with the exception of furyl- and thienyl-substituted ketones (78% and 37% respectively) (entries 14 and 15). With these heteroaromatic ketones, benzofuran side-products (analogous to 5a, Table 1.1) could be observed due to competitive intramolecular aldol condensation.
Table 1.5 - Hydroaclylation of substituted keto-aldehydes using $[\text{Rh(dppp)}\text{BF}_4]_2$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Yield 2 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph (1a)</td>
<td>4 h</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>4-CF&lt;sub&gt;3&lt;/sub&gt;-Ph (1i)</td>
<td>1.2 h</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>4-CO&lt;sub&gt;2&lt;/sub&gt;Me-Ph (1j)</td>
<td>1.5 h</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-Ph (1b)</td>
<td>3.5 h</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>4-F-Ph (1k)</td>
<td>1.2 h</td>
<td>96</td>
</tr>
<tr>
<td>6</td>
<td>4-Me-Ph (1l)</td>
<td>5 h</td>
<td>&gt;99</td>
</tr>
<tr>
<td>7</td>
<td>4-OMe-Ph (1m)</td>
<td>12 h</td>
<td>89</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl (1c)</td>
<td>4.5 h</td>
<td>91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>Yield 2 (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>n-Bu (1e)</td>
<td>9 h</td>
<td>94</td>
</tr>
<tr>
<td>10</td>
<td>i-Pr (1g)</td>
<td>3.7 h</td>
<td>95</td>
</tr>
<tr>
<td>11</td>
<td>t-Bu (1h)</td>
<td>3.5 h</td>
<td>94</td>
</tr>
<tr>
<td>12</td>
<td>Bn (1f)</td>
<td>9 h</td>
<td>92</td>
</tr>
<tr>
<td>13</td>
<td>Mo (1d)</td>
<td>10 h</td>
<td>&gt;99</td>
</tr>
<tr>
<td>14</td>
<td>2-furyl (1n)</td>
<td>20 h</td>
<td>78</td>
</tr>
<tr>
<td>15</td>
<td>2-thienyl (1o)</td>
<td>28 h</td>
<td>37</td>
</tr>
</tbody>
</table>

Conditions: substrate (0.2 mmol), $[\text{Rh(dppp)}\text{BF}_4]_2$ (2.5 mol%) in degassed CH<sub>2</sub>Cl<sub>2</sub> (2 mL) at rt. <sup>b</sup> Isolated yield.

The hydroaclylation of racemic α-substituted keto-aldehydes 1p and 1q resulted in high yields (86-89%) of the corresponding lactones 2p and 2q with excellent diastereocontrol (Scheme 1.8). By <sup>1</sup>H NMR analysis, we observed that only the cis diastereomer of lactone 2p was formed. The cis isomer was confirmed upon obtaining the molecular structure of 2q from single crystal X-ray crystallography. These transformations exhibit a remarkable level of substrate control. These examples highlight the potential of using diastereoselective ketone hydroacylation using catalysts like $[\text{Rh(dppp)}]_2(\text{BF}_4)_2$ as a strategy in complex molecule synthesis.
On the basis of our experimental observations (discussed below) and literature precedence, we propose the mechanism shown in Scheme 1.9 below. Substrate 1a mediates slow dissociation of the dimeric precatalyst 13 to give a substrate-bound catalyst monomer 14. Based on rate experiments, the concentration of active catalyst 14 increases over the course of the reaction after an initial induction period, wherein dimer 13 is monomerized by substrate 1. Complex 14 undergoes a fast and reversible oxidative addition to the C─H bond of the aldehyde. Based on the observed kinetic isotope effect and Hammett plot, we can suggest that the turn-over limiting step is insertion of the ketone carbonyl into the Rh-hydride 15 to provide acyl Rh-alkoxide 16. The irreversible reductive elimination of 16 forms the lactone-Rh complex 17. To turn over the catalytic cycle, another molecule of the substrate can displace the product from complex 17 to form the substrate-bound complex 14. Both dimer dissociation and catalyst turnover influence the overall rate.
Crossover Experiment. In accord with known Rh(I) catalyzed hydroacylation reactions,\textsuperscript{14a,34} we hypothesized that ketone hydroacylation is an intramolecular process with no intermolecular hydride transfer. To support this hypothesis, we performed a crossover experiment using a mixture of the deuterium-labeled substrate 1a-D and the protio substrate 1h and observed formation of the corresponding lactone products 2a-D and 2h (Scheme 1.10). We chose substrates 1a and 1h due to their similar reactivity. The absence of the crossover products 2a and 2h-D supports a mechanism where hydride transfer occurs intramolecularly. These results
disfavor alternative intermolecular mechanisms (e.g., the Rh–H derived from one substrate reducing the ketone-carbonyl of another substrate).

\[
\text{Scheme 1.10 - Crossover experiment with 1a-D and 1h}
\]

**NMR Studies.** Zengming Shen conducted the majority of the NMR studies described below. The results will be summarized and details can be found in the full article.\textsuperscript{29} Initial studies focused on monitoring the stoichiometric reaction of [Rh(dppp)]\(_2\)(BF\(_4\))\(_2\) \text{13} with substrate 1a by both \(^1\text{H}\) and \(^{31}\text{P}\) NMR at low temperature. Bosnich previously reported that [Rh(dppp)]\(^+\) exists as a diastereomeric mixture of arene-bridged dimers in non-coordinating solvents such as CH\(_2\)Cl\(_2\) or CH\(_3\)NO\(_2\).\textsuperscript{14a} As Bosnich observed, we detected a 1:1 mixture of complexes by \(^{31}\text{P}\) NMR that can be attributed to a meso and a chiral dimeric form of [Rh(dppp)]\(_2\)^{2+} in CH\(_2\)Cl\(_2\). While the analogous dimer of [Rh(dppe)]\(^+\) has been confirmed in the solid state,\textsuperscript{35} the dimeric forms of [Rh(dppp)]\(^+\) were characterized in solution by \(^{31}\text{P}\) NMR studies.\textsuperscript{14a} We postulate that dimer \text{13} must dissociate to the catalytically active monomer. Bosnich has suggested a similar dimer-splitting step in his mechanistic study on the hydroacylation of 4-pentenal by [Rh(dppe)]\(_2\)^{2+}.\textsuperscript{14a} Bosnich noted the dimer is a coordinatively saturated 18-electron species and therefore, most likely a pre-catalyst. Plotting \(k_{\text{obs}}\) versus catalyst concentration revealed a fractional order fit of
0.67 (Figure 1.1). A half-order kinetic dependence would be expected in a reaction involving slow dissociation of a dimeric precatalyst to an active monomer, whereas a first-order kinetic dependence would be expected if both the ground state and the transition structure are derived from monomeric catalyst species.\textsuperscript{36} Thus, the rates of dimer dissociation and catalyst turnover are both important in controlling the reaction rate; the rate attrition could be attributed to product inhibition.

![Graph showing Observed rate of hydroacylation of 1a versus catalyst concentration](image)

**Figure 1.1** - Observed rate of hydroacylation of 1a (measured after the initial induction period) versus catalyst concentration. The curve describes a non-linear fit to the power function $k_{\text{obs}} = a[Rh(dppp)]_2(BF_4)_2^b$ ($a = 0.0095 \pm 0.0003; b = 0.67 \pm 0.03$).

To further support that substrate 1a can facilitate the dissociation of the dimeric pre-catalyst, we prepared diketone analogue 1r (see SI for details). We proposed that diketone 1r would bind to dimer 13 in a similar manner to the substrate 1a, but the resulting complex should be spectroscopically detectable as it is incapable of undergoing oxidative addition. Indeed, when 40 equivalents of diketone 1r were added to a 0.001 M solution of [Rh(dppp)]$_2$(BF$_4$)$_2$ in CD$_2$Cl$_2$, the $^{31}$P NMR signals corresponding to 13a and 13b were observed to slowly disappear at room
temperature (19% conversion after 30 min). After heating at 90 °C for 2 hours, the dimer signals for 13a and 13b were completely absent and a new set of resonances was observed. We attribute these new signals to a mixture of three monomeric Rh species bound to 1r with various modes of coordination.

Scheme 1.10 - Dimer 13 in the presence of diketone 1r results in decomplexation of the dimer to a mixture of monomers 18

**Substrate and Product Dependence on Rate.** After studying the resting states of the catalyst in solution, we turned our attention to the effect of substrate and product concentrations on the rate of reaction with [Rh(dppp)]_{2}(BF_{4})_{2}. To determine the kinetic order in substrate 1a, we measured the rate of reaction (after an apparent induction period) with various concentrations of the substrate. We were able to observe a first order dependence of the rate on substrate concentration (Figure 1.2). Addition of two equivalents of 2a resulted in a 40% decrease in the rate of the reaction, as measured after the induction period. Our observation of product inhibition is consistent with the accumulation of product-bound complex 17 by NMR analysis as discussed above. However, the observed rate of product formation remains constant until much higher conversion than would be expected given a typical first order rate law. The kinetic profile shows a pronounced sigmoidal curve (Figure 1.2). An induction phase followed by a relatively long interval where rate of product formation appears constant (up to ca. 60% conversion) is observed. This sigmoidal curve suggests that the concentration of active catalyst must increase
over the course of the reaction. Importantly, this mechanistic scenario (Scheme 2) was modeled using the kinetics modeling software package Copasi. As illustrated in Figure 5, our proposed mechanism is consistent with the observed kinetic profile.

**Figure 1.2** – (Left) Plot of \( k_{\text{obs}} \) vs [1a] concentration with [Rh(dppp)]$_2$(BF$_4$)$_2$ (0.0025M). The trend line describes a linear least-squares fit to \( k_{\text{obs}} = m \cdot [1a] \) \( (m = 0.0247 \pm 0.0005) \). (Right) Reaction profile for the hydroacylation of 1a with [Rh(dppp)]$_2$(BF$_4$)$_2$ monitored by $^1$H NMR (dotted line) and Copasi model fit (solid line) show sigmoidal curve.

**Support for Turnover-Limiting Step.** The rate of a catalytic process is influenced by a number of factors. In this study, for example, dimer dissociation affects the rate by controlling the concentration of active catalyst in solution. To determine the turnover-limiting step in this hydroacylation (i.e., the step with the highest energy transition state within the catalyst cycle) the H/D kinetic isotope effect (KIE) for substrate 1a was examined with [Rh(dppp)]$_2$(BF$_4$)$_2$. As mentioned above, the rate constants were obtained from the slope of the linear region of the curve after an apparent induction period. The \( k_H/k_D \) was determined to be 1.79 \( \pm \) 0.06. Since the H/D atom is relatively far from the forming C─O bond, a negligible H/D KIE would be expected.
if reductive elimination were the turnover-limiting step.\textsuperscript{38} Thus, the observed kinetic isotope effect suggests that reductive elimination is not the turnover-limiting step.\textsuperscript{39}

\begin{center}
\begin{tikzpicture}
\node (A) at (0,0) {\textbf{Scheme 1.11} - Observation of a kinetic isotope effect during the hydroacylation of 1a-H and 1a-D};
\end{tikzpicture}
\end{center}

A Hammett plot was constructed in order to determine the rate dependence on the electronic character of the ketone (Figure 1.3). The intramolecular hydroacylation of seven arylketones (1a, 1b, 1i-m) in the presence of 1.25 mol\% [Rh(dppp)]\textsubscript{2}(BF\textsubscript{4})\textsubscript{2} was monitored by \textsuperscript{1}H NMR to obtain reaction rates (after the induction period). By plotting these rates versus $\sigma^+$,\textsuperscript{40} a clear trend was observed with relatively electron poor aryl ketones undergoing hydroacylation more rapidly. Linear regression of the Hammett plot yielded $\rho = +0.29 \pm 0.04$ with good correlation ($R^2 = 0.91$). However, the electronic character of the ketone affects not only the rate of the catalytic turnover but also the rate of dissociation of the dimer to produce the active catalyst. Since more electron-rich aryl ketones possess a more basic lone pair on the ketone, they are also more effective promoting dissociation of the dimeric form of the catalyst. Indeed, we can see this effect by examining the reaction profiles of the substrates in the Hammett plot. For example, as shown in Figure 1.3, substrate 1j ($p$-OMe) does not show an induction period and initially reacts faster than substrate 1m ($p$-COOMe). However, substrate 1j does demonstrate a significant induction period and reacts much faster than 1m after the induction period. This trend suggests that electron-rich substituents facilitate the dissociation of the dimer more effectively.
than electron-poor substituents, but electron-poor substituents preferentially accelerate the turnover-limiting step. The slope of the Hammett plot results from the combination of these two factors. Both the observed kinetic isotope effect and the Hammett study support insertion of the ketone into the rhodium hydride as the turnover-limiting step. This result represents a significant difference between the mechanism of our ketone hydroacylation and the related olefin hydroacylation; for olefin hydroacylation it is well established that reductive elimination is rate-determining.\textsuperscript{13a,13b}

![Chemical structure and Hammett Plot](image)

**Figure 1.3** – (Left) Hammett Plot for the hydroacylation of keto-aldehyde substrates 1a, 1b, and 1i-m. The trend line describes a linear least squares fit to log $k_{obs} = m\sigma^+ + b$ ($m = 0.29 \pm 0.04; b = 0.23 \pm 0.02; R^2 = 0.91$). (Right) Product formation as a function of time for substrates 1j and 1m.
Hydroacylation with Rh((R)-DTBM-SEGPHOS)BF₄

For enantioselective hydroacylation, treating the keto-aldehydes with catalyst [Rh((R)-DTBM-SEGPHOS)]BF₄ at room temperature in CH₂Cl₂ provided optimal results (92% yield of 2a, 99% ee, Table 1.6, entry 1). Under these conditions, a wide variety of substrates with arene- and alkyl-substituted ketones were tolerated. Ketones bearing electron-poor arene substituents were transformed to their corresponding lactones in excellent yield and enantiomeric excess (97-98% yield, 99% ee) with little decarbonylation side-product (1-1.5%) (entries 2 and 3). In comparison, electron-rich arene-substituted substrates underwent hydroacylation more slowly (entries 6 and 7): the p-tolyl-substituted substrate 1l was converted to the corresponding lactone selectively (99% ee) albeit in moderate yield (50%) (entry 6), and the p-methoxyphenyl-substituted substrate 1m underwent hydroacylation with poor efficiency and low enantioselectivity (14% yield and 32% ee) (entry 7). Compared to the arene-substituted ketones, asymmetric hydroacylation of aliphatic ketones occurred in relatively higher yields, higher enantioselectivities, and shorter reaction times (entries 9-13). With the exception of the methyl-substituted ketone 1d case (entry 13), no competing decarbonylation was observed, and essentially one enantiomer of the corresponding lactones were formed (>99% ee) (entries 9-12). Heteroarene-substituted ketones were not well-tolerated; a furyl substituted substrate (entry 14) was transformed in a very poor yield (7%) with a significant amount of the decarbonylation byproduct (41%), while a thiophene substituted ketone (entry 15) formed only the decarbonylated byproduct in 73% yield.
Table 1.6 – Extended scope of the hydroacylation of substituted keto-aldehydes using [Rh((R)-DTBM-SEGPHOS)]BF₄. Some examples are repeated from Table 1.3 in order to highlight trends.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time</th>
<th>2 (%)a</th>
<th>ee (%)b</th>
<th>3 (%)c</th>
</tr>
</thead>
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<td>92</td>
<td>99</td>
<td>7</td>
</tr>
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<td>2</td>
<td>4-CF₂-Ph (1l)</td>
<td>2 d</td>
<td>97</td>
<td>99</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>4-CO₂Me-Ph (1j)</td>
<td>2 d</td>
<td>98</td>
<td>99</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>4-Cl-Ph (1b)</td>
<td>2 d</td>
<td>89</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>4-F-Ph (1k)</td>
<td>3 d</td>
<td>84</td>
<td>99</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>4-Me-Ph (1l)</td>
<td>6 d</td>
<td>50</td>
<td>99</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>4-OMe-Ph (1m)</td>
<td>6 d</td>
<td>14</td>
<td>32</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>2-naphthyl (1c)</td>
<td>2 d</td>
<td>85</td>
<td>99</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Time</th>
<th>2 (%)a</th>
<th>ee (%)b</th>
<th>3 (%)c</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<td>i-Pr (1g)</td>
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<td>98</td>
<td>&gt;99</td>
<td>0</td>
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<td>11</td>
<td>i-Pri (1h)</td>
<td>1.5 d</td>
<td>94</td>
<td>&gt;99</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>Bn (1f)</td>
<td>3.5 d</td>
<td>93</td>
<td>&gt;99</td>
<td>2</td>
</tr>
<tr>
<td>13</td>
<td>Me (1d)</td>
<td>2 d</td>
<td>91</td>
<td>99</td>
<td>6</td>
</tr>
<tr>
<td>14d</td>
<td>2-furyl (1n)</td>
<td>5 d</td>
<td>7</td>
<td>ND⁵</td>
<td>41</td>
</tr>
<tr>
<td>15d</td>
<td>2-thiophenyl (1o)</td>
<td>4 d</td>
<td>-</td>
<td>ND⁵</td>
<td>73</td>
</tr>
</tbody>
</table>

⁴ Isolated yield. ⁵ Determined by chiral HPLC. ⁶ The yield of decarbonylated product is based on ¹H NMR integration relative to product and starting material peaks. ⁷ 90 °C in sealed tube. ⁸ Not determined.

Mechanism of Hydroacylation with [Rh((R)-DTBM-SEGPHOS)]BF₄. As stated above, Zengming Shen conducted most of the NMR experiments and Peter Dornan conducted the computational study. Details on these two aspects of this study can be found in the manuscript and will only be described here in summary. On the basis of kinetic studies, NMR experiments, and computational modeling, we proposed the mechanism shown in Scheme 1.12 for the hydroacylation of 1a with [Rh((R)-DTBM-SEGPHOS)]BF₄. In contrast to the mechanism proposed for dppp, the resting state of the catalyst is a monomeric Rh-complex 20 coordinated to two molecules of substrate 1a. In order to undergo catalysis, one molecule of 1a dissociates to form a three-coordinate complex 21. In support of this mechanism, the substrate is observed to
inhibit the reaction rate. While 21 can be observed by NMR, computational modeling suggests that the intermediate prior to oxidative insertion is a square planar, four coordinate Rh(I) complex 21’ (in which the ether oxygen is coordinated to Rh). Reversible C–H bond activation occurs to form 22 which undergoes turnover-limiting insertion. Reductive elimination forms complex 24 from which another substrate molecule 1a can displace the bound product 2a and regenerate 21’. In this catalytic system, decarbonylation is a kinetically competitive process that occurs subsequent to oxidative addition, and ultimately leads to the formation of a Rh–CO complex 26 that is not an active catalyst.\textsuperscript{14a} This mechanistic proposal is consistent with the experimental data and supported by computational studies. Rate experiments, which show competitive product inhibition as well as competitive substrate decarbonylation, support the proposed substrate-bound complex 21 and product-bound complex 24 as resting states in the catalytic cycle. The calculated free energy profile indicated that the putative transition state for decarbonylation was 3 kcal/mol higher in energy than that of hydride insertion. NMR studies showed the nature of the resting states. Notably, in the presence of 25 eq. of keto-aldehyde 1a, a mixture of complexes 20 and 21 was observed. Precatalyst 19 in solution with varying amounts of diketone 1r resulted in varying amounts of corresponding complexes of the type 20 and 21, suggesting that this pre-equilibrium is sensitive to the concentration of the substrate. The implied conclusion from this observation is that there is some substrate inhibition at high substrate concentration, consistent with Bosnich’s observations.\textsuperscript{14a,17}
Scheme 1.12 – Based on our studies, we proposed this mechanism for [Rh((R)-DTBM-SEGPHOS)]BF₄-catalyzed hydroacylation of 1a.

**Chelation effect.** As thioethers are well known to be ligands in chelation assisted hydroacylation, we also investigated thio-based substrates.²³ᵃ,⁴¹ Substrate 1s was allowed to react in the presence of [Rh(dppp)]₂(BF₄)₂ and [Rh((R)-DTBM-SEGPHOS)]BF₄ (Scheme 13). The thioether substrate was converted efficiently into chiral lactone 2s with both ligands. Excellent enantioselectivity (>99% ee) was observed in the case with (R)-DTBM-SEGPHOS. No decarbonylation was observed with use of either ligand.
Furthermore, we found that the keto-aldehyde derivative 1u bearing a methylene unit in place of a chelating oxygen or sulfur atom shows no desired reactivity with [Rh(dppp)]_{2}(BF_{4})_{2} or [Rh((R)-DTBM-SEGPHOS)]BF_{4}, (Scheme 14). These results support our hypothesis that a heteroatom plays a crucial role in the catalytic cycle by coordinating to the rhodium center. However, the precise role of the chelating atom during catalysis cannot be determined easily by experiment because this understanding requires structural knowledge of inobservable intermediates. Our calculations^{29} determined that the chelating atom remains bound to the metal centre throughout the catalytic cycle, suppressing decarbonylation by occupying an empty coordination site as well as orienting the ketone π-bond to facilitate hydride insertion.
Rhodium Hydride Intermediates. Dichloro-substituted keto-aldehyde 1t was inadvertently synthesized during the Swern oxidation of the keto-alcohol of 1s (See experimental section for details). To our surprise, 1t did not undergo hydroacylation with either [Rh(dppp)]$_2$(BF$_4$)$_2$ or [Rh((R)-DTBM-SEGPHOS)]BF$_4$, even at elevated temperatures. Presumably, the chloro substituents cause significant steric and electronic perturbations that prevent hydroacylation. To investigate this lack of reactivity, we treated 1t with stoichiometric [Rh((R)-DTBM-SEGPHOS)]BF$_4$ in CD$_2$Cl$_2$ and monitored the resulting transformation. By $^1$H NMR, we observed a pair of high field signals with coupling constants characteristic of rhodium hydrides (Figure 12). These two resonances appeared as doublet of triplets: one at $-15.17$ ppm, ($J$(Rh, H) = 22.8 Hz, $J$(P, H) = 13.6 Hz) and the other at $-15.63$ ppm, ($J$(Rh, H) = 23.6 Hz, $J$(P, H) = 15.2 Hz). Notably, the P–H couplings observed are completely consistent with literature data for rhodium hydrides oriented cis to phosphine ligands.$^{42}$ We proposed that there are two isomeric octahedral Rh complexes present, each featuring a hydride cis to both phosphorous atoms in the ligand. Due to their geometry, we believe these observable configurational isomers cannot adopt a conformation to allow carbonyl insertion into the Rh–H via a four-membered transition state.

**Scheme 1.14** - Loss of reactivity with the removal of the catalyst-binding heteroatom

\[
\begin{align*}
A: [\text{Rh(dppp)}]_2(\text{BF}_4)_2 & (2.5 \text{ mol%}, \text{CH}_2\text{Cl}_2, 90 \degree \text{C}, 3 \text{ d}) & 0\% & 4\% \text{ yield} \\
B: [\text{Rh((R)-DTBM-SEGPHOS)})](\text{BF}_4), & (5 \text{ mol%}) \text{CH}_2\text{Cl}_2, 90 \degree \text{C}, 3 \text{ d} & 0\% & 5\% \text{ yield}
\end{align*}
\]
Since it is also possible that isomerization to a more reactive geometry could precede insertion, an alternative explanation is that the chlorine substituents prevent insertion for steric reasons.

Our mechanistic study resulted in a thorough understanding of how two catalysts, Rh-dppp dimer 13 and chiral precatalyst 19, promote the hydroacylation of prochiral keto-aldehydes. Through ligand studies, we observed both steric and electronic effects on the efficiency of hydroacylation with respect to the catalyst. We measured the orders in substrate, catalyst, and product, observed a kinetic isotope effect, and constructed a Hammett plot. These pieces of information allowed us to elucidate the nature of the resting states and determine the rate-limiting and enantiodetermining step in ketone hydroacylation: hydride insertion into the ketone.

The coordinating heteroatom, either an ether as in 1a or a thioether as in 1s, is necessary for catalysis as determined experimentally through the study of 1u, and the role of this heteroatom was elucidated computationally. Finally, we were able to observe a stable acyl Rh-hydride by placing precatalyst 19 in the presence of dichlorosubstituted keto-aldehyde 1t.

**Scheme 1.15** - Attempted hydroacylation of dichlorinated keto-aldehyde 1t results in stable Rh-hydride 27 as an isomeric mixture. Right: $^1$H NMR spectrum of stable rhodium hydride intermediates 27 formed with substrate 1t and [Rh((R)-DTBM-SEGPHOS)]BF$_4$. 

Our mechanistic study resulted in a thorough understanding of how two catalysts, Rh-dppp dimer 13 and chiral precatalyst 19, promote the hydroacylation of prochiral keto-aldehydes.
Following the mechanistic study, we were interested in expanding the scope of ketone hydroacylation, particularly synthesizing lactones of varying sizes. In 2009, Diem Phan and Byoungmoo Kim from the Dong group published an excellent study on the synthesis of chiral phthalides. Notably, Phan and Kim observed a potent counterion effect on the efficiency of catalysis – different counterions, namely nitrates, mesylates, and triflates, would promote highly enantioselective hydroacylations of keto-aldehydes with different electronic properties. I engaged in a study that would expand the lactone size to 8-membered rings and would use nitrogen as the coordinating heteroatom. Kevin Kou, a new student in the Dong group at the time, collaborated with me on this study.

1.3.3 Synthesis of Chiral Nitrogen-Containing Lactones

The majority of biologically relevant targets and pharmaceutical agents contain nitrogen-heterocycles. The above studies have shown that oxygen and sulfur both act as effective chelating groups in ketone hydroacylation but the analogous synthesis of N-heterocycles by this methodology remains an unmet challenge. By substituting oxygen and sulfur for nitrogen, we were able to demonstrate a ketone hydroacylation that takes advantage of the inherent Lewis basicity of amines to produce novel benzoazepinones and benzoazecinones with excellent enantioselectivity.

Initial studies

Considering the importance of nitrogen-containing motifs, we investigated the ability of amine to direct a Rh-catalyzed intramolecular hydroacylation as proposed in Scheme 1.6. Bolm and co-workers recently reported that 2-formylaniline derivatives can undergo
intermolecular hydroacylation with norbornadiene to produce chiral ketones in good yield, albeit with low enantioselectivity.\textsuperscript{46}

Our proposed \(N\)-directed \(C–H\) bond functionalization would occur via a rhodabicycle to generate seven- and eight-membered nitrogen-heterocycles. Our initial studies focused on the hydroacylation of substrates 1\textsubscript{v–x}, derived from commercially available methyl anthranilate, using our reported hydroacylation catalyst: \([\text{Rh}((R)-\text{DTBM-SEGPHOS})]\text{BF}_4\). With this model system, we were able to tune the basicity of the amine to achieve the desired transformation (Table 7). Strongly electron-withdrawing substituents (e.g., Ts or Ms) on the nitrogen atom led to no reactivity (entries 1 and 2). However, substrate 1\textsubscript{x} bearing a more Lewis basic \(N\)-Me group underwent cyclization smoothly to produce enantioenriched benzo[\textit{e}][1,4]oxazepinone \textit{2c} in 86% yield and 72% ee.

Next, we compared the reactivity of substrate 1\textsubscript{x} to the analogous O- or S-containing keto-aldehydes (Table 7, entries 4 and 5). By measuring conversion over time in the presence of 2 mol\% \([\text{Rh}((R)-\text{DTBM-SEGPHOS})]\text{BF}_4\), we observed a marked difference in the relative

\begin{align*}
\text{Scheme 1.16} & - \text{Proposed } N\text{-directed ketone hydroacylation towards chiral benzoazepinones } (n = 1) \text{ and benzoazacinones } (n = 2)
\end{align*}
rates of hydroacylation. The $O$-bearing substrate achieved 36% conversion after 48h, while the $S$-bearing keto-aldehyde underwent complete conversion to the desired lactone after 2h. $N$-bearing substrate 1w achieved >99% conversion in less than 5 min at room temperature. Hence, we were able to use amines in intramolecular ketone hydroacylation via Rh$^1$ catalysis. Throughout these studies, no decarbonylation was observed by $^1$H-NMR in the $N$-directed hydroacylation reactions. Thus, the presence of a nitrogen atom not only promotes faster reactivity but also suppresses decarbonylation completely.

**Table 1.7**—Comparison of different moieties on the nitrogen atom in 1 and a comparison between nitrogen, oxygen, and sulfur as coordinating groups for hydroacylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Time (min)</th>
<th>Conv. (%) $^a$</th>
<th>%ee 2 $^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1u $X = N$-Ts</td>
<td>/</td>
<td>0$^c$</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1v $X = N$-Ms</td>
<td>/</td>
<td>0$^c$</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>1w $X = N$-Me</td>
<td>&lt;5</td>
<td>&gt;99</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>1a $X = O$</td>
<td>2880</td>
<td>36</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>1s $X = S$</td>
<td>120</td>
<td>&gt;99</td>
<td>99</td>
</tr>
</tbody>
</table>

Conditions: 2 mol% [Rh((R)-DTBM-SEGPHOS)]BF$_4$, 0.2 mmol substrate (1), room temperature (rt), CH$_2$Cl$_2$. $^a$ Conversion determined by $^1$H-NMR. $^b$ Determined by chiral HPLC. $^c$ Starting material was recovered quantitatively.

**Benzoazepinone synthesis**

To improve the enantioselectivity, numerous chiral bidentate phosphine ligands were examined and 3,4,5-OMe-MeOBIPHEP was found to offer a modest increase in ee. At $-35$ $^\circ$C,
the desired hydroacylation of keto-aldehyde 1w proceeded in the presence of 2 mol% [Rh(R)-3,4,5-OMe-MeOBIPHEP]BF₄ in 85% ee and 91% yield (Table 1.8, entry 2). Under our optimized conditions, alkyl- and aryl-substituted keto-aldehydes undergo hydroacylation at low catalyst loading to produce the corresponding benzo[e][1,4]oxazepinones in high yields and moderate to high enantiomeric excesses (50-93% ee).

**Table 1.8** - Scope of ketone hydroacylation to produce chiral benzo[e][1,4]oxazepinones.

<table>
<thead>
<tr>
<th>Entry</th>
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<th>Temp (°C)</th>
<th>Yield 2 (%)</th>
<th>%ee 2</th>
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<td>91</td>
<td>77</td>
</tr>
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<td>1z t-Bu</td>
<td>-35</td>
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<td>50</td>
</tr>
</tbody>
</table>

* a Isolated yield  b Determined by chiral HPLC

**Extending the ring size**

Kevin Kou synthesized compounds 30, 31, and 32, and conducted these studies. Having synthesized chiral benzoazepinones via hydroacylation, we next investigated the preparation of larger-ring lactones using the same strategy. Our previous mechanistic studies have pointed to a [5.5.0]rhodabicycle intermediate prior to lactonization in the preparation of 7-membered ring lactones. We thus rationalized that substrates 28a and 30 that could potentially proceed through a [3.4.0]- and [4.3.0]rhodabicycle intermediate, respectively, in the catalytic cycle could give rise to benzoazecinone products containing an 8-membered ring lactone.
Scheme 1.17- Efforts towards the synthesis of benzoxazicinones and benzoxazinones and the corresponding proposed intermediates
moiety (Scheme 1.17). Indeed, aniline derivative 28a underwent intramolecular ketone hydroacylation in the presence of 2 mol% [Rh((R)-DTBM-SEGPHOS)]BF$_4$ to give the corresponding benzoazecinone 29a in 95% isolated yield and 96% ee, whereas benzylamine derivative 30 gave no reactivity even at higher catalyst loadings (up to 10 mol%) and elevated temperatures (up to 60 °C). Similarly, keto-aldehyde 31, which would theoretically proceed via a [4.4.0]rhodabicycle to furnish a 9-membered ring benzoazacinone, gave no reactivity. These results suggest that not only is a basic heteroatom necessary for ketone hydroacylation to occur, but both the electronics and the position of the heteroatom are also significant. Since it appeared that the 5-membered amino-acyl rhodacycle is critical for the current transformation, we envisioned substrates that would form [3.5.0]rhodacycle intermediates could provide chiral benzoazacinone macrocycles following reductive elimination. However, subjecting substrate 32 to our ketone hydroacylation conditions also resulted in no reactivity.

Scope of benzoazecinone synthesis

While structural analogues of benzo[e][1,4]oxazepinones are reported to have potent medicinal activity, 47 8-membered benzoazecinones are unprecedented organic frameworks. We prepared a series of keto-aldehydes of the type 28 from commercially available N-methyl methylanthraniolate. In the presence of [Rh((R)-DTBM-SEGPHOS)]BF$_4$, these homologated keto-aldehydes underwent hydroacylation smoothly to provide the corresponding substituted benzo[c][1,5]oxazecinones 29 in high yields and enantioselectivities (Table 3, 84-99%, 88-99% ee). In contrast to the keto-aldehyes we presented in our earlier work with O directing groups, 3c both electron-donating and electron-withdrawing groups were accommodated. Notably, substrate 28c bearing an electron-rich arene substituent underwent hydroacylation to afford the
corresponding 8-membered lactone 29c in 84% yield and 95% ee. As with the 7-membered lactones, no decarbonylation was observed. An X-ray crystal structure of lactone 29i allowed us to unambiguously determine the absolute configuration of the benzo[c][1,5]oxazecinones.

Table 1.9 - Scope of ketone hydroacylation to produce chiral benzo[c][1,5]oxazecinones.

| Reactions performed with 0.2 mmol substrate in 1 mL CH$_2$Cl$_2$; $^a$ Enantiomeric excesses determined by chiral HPLC; $^1$ 1 mol% catalyst; $^2$ 2 mol% catalyst; $^3$ 5 mol% catalyst | ![Diagram of lactones] |

Table 1.9 - Scope of ketone hydroacylation to produce chiral benzo[c][1,5]oxazecinones.
Conclusions and Future Directions

Our initial study on the asymmetric Rh-catalyzed hydroacylation of ketones was the first report on hydroacylation from the Dong group (and the first publication from the group as well).\textsuperscript{24} Our mechanistic study provided unexpected insights into the nature of the catalytic resting states and intermediates and established a model for enantioselectivity and further method development.\textsuperscript{29} Using this methodology, we were able to construct a new class of chiral lactones known as benzoxazecinones, 8-membered nitrogen-containing heterocycles.\textsuperscript{44} Phan and Kim have developed an efficient and clever strategy for the asymmetric lactonization of γ-keto-aldehydes\textsuperscript{43} and, more recently, Stephen Murphy has studied the use of Ru-based asymmetric transfer hydrogenation catalysts for the lactonization of γ-keto-alcohols.\textsuperscript{48} Kou, experienced in ketone hydroacylation after our collaboration, has developed a method for the asymmetric intermolecular hydroacylation of activated ketones, and is currently optimizing that transformation.

Several methods reported in recent years were directly inspired by the work presented above. The Lu group reported the intermolecular hydroacylation of isatins with simple aldehydes via \textit{N}-heterocyclic carbene catalysis.\textsuperscript{49} The Fu group accomplished the stereoconvergent Suzuki coupling of secondary alkyl chlorides with simple alkyl boronates.\textsuperscript{50} The key to this transformation was the use of arylamines as directing groups, much like in our benzoxazecinone synthesis. In this report, Fu also notes that the \textit{N}-directed ketone hydroacylation we reported was the only example of an asymmetric metal-catalyzed transformation directed by a tertiary arylamine. Finally, the Bendorf group used amine directing groups in the intramolecular hydroacylation of olefins to give 7- and 8-membered cyclic ketones.\textsuperscript{51} As of yet, no reports of asymmetric intermolecular ketone hydroacylation have been reported and efforts towards
addressing this challenge are ongoing in the Dong group. Application of ketone hydroacylation in the synthesis of complex natural products was demonstrated in the lactonization of a keto-aldehyde formed \textit{en route} to Salvileucalin B in a report from the Reisman group.\textsuperscript{52} The natural product was isolated as a mixture of epimers, but this work highlights the use of ketone hydroacylation in the transformation of keto-aldehydes to medicinally useful and complex molecules.

I did not study olefin hydroacylation, but I would be remiss if I did not comment on the fruitful olefin hydroacylation program ongoing in the Dong group. Matthew Coulter and Peter Dornan published our first report on intramolecular asymmetric olefin hydroacylation to form medium-sized cyclic ketones.\textsuperscript{53} Coulter and Phan independently reported methods for the intermolecular asymmetric hydroacylation of homoallylic sulfides and cyclopropenes respectively.\textsuperscript{54} It should be noted that intermolecular hydroacylation is an ongoing challenge, and these two methods are remarkably selective for single isomers (enantio-, diastereo-, regio-). Stephen has accomplished an impressive feat in the hydroacylation of allylic and homoallylic alcohols.\textsuperscript{55} Alcohols tend to make poor directing groups for hydroacylation, so scaffolding phosphinates were used as catalytic directing groups to effect the transformation. Finally, Max von Delius’ exquisite protocol for the hydroacylation of simple olefins using an unusual chiral rhodium catalyst allowed access to numerous natural products and derivates in an efficient manner. Novel hydroacylation methods are being developed in our group on a regular basis, with a focus on reducing our reliance on directing groups to stabilize catalytic intermediates and accessing more complex targets with more robust catalysts. Hydroacylation, as an atom-economical method that has the potential to promote a great degree of regio-, enantio-, and diastereocontrol, is a promising solution for many contemporary synthetic challenges.
1.5 Notes and References


(22) Coulter, M. M. Doctoral dissertation, University of Toronto, **2011**.


(34) Barnhart, R. W.; Bosnich, B. Organometallics 1995, 14, 4343.


(38) It is also possible that reversible insertion steps could lead to a pre-equilibrium isotope effect which would translate to different rates of rate-limiting reductive elimination based on different concentrations of the intermediate prior to reductive elimination. However we believe this is unlikely since the observed kH/kD = 1.8 is large for a thermodynamic isotope effect: Kogut, E., Zeller, A., Warren, T.H., Strassner, T. J. Am. Chem. Soc., 2004, J26, 11984. It should be noted that in our mechanistic study (ref. 29), we found a marked difference in the observed kH/kD of hydroacylation with (Rh(dppe)BF_4)_2 and [Rh(DTBM-SEGPHOS)]BF_4 (1.8 and 3.3 respectively). This difference could arise as a result of the differing electronic character at the rhodium centre, which would certainly play a role in determining the nature of the transition state of the Rh–H insertion step.


(48) Murphy, S. K., Dong, V. M. Submitted for publication 2012.


1.6 Experimental Section

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I. General procedures

Commercial reagents were purchased from Sigma Aldrich or Alfa Aesar and were purified prior to use following the guidelines of Perrin and Armarego. All reactions were carried out under nitrogen or argon atmosphere unless otherwise indicated. Reactions were monitored using thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 plates. Visualization of the developed chromatogram was performed by fluorescence quenching or KMnO4 stain. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. 1H and 13C NMR spectra were recorded on any of three instruments: a Varian Mercury 300 and a Varian Mercury 400, both equipped with automatic sample loaders, and a Varian NMR 400. NMR spectra were internally referenced to residual protio solvent signals. Data for 1H NMR data are reported as follows: chemical shift (δ shift), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for 13C NMR are reported in terms of chemical shift (δ ppm).

Mass spectra (MS) were recorded on a Sciex QStar Mass Spectrometer. Infrared (IR) spectra were obtained on a Perkin-Elmer Spectrum 1000 FT-IR Systems and are reported in terms of frequency of absorption (cm\(^{-1}\)). Melting point ranges were determined on a Fisher-Johns Melting Point Apparatus. Enantiomeric excesses were ascertained on an Agilent 1100 Series HPLC. Optical rotations were measured on a Rudolph Research Analytical Autopol IV Automatic Polarimeter. Column chromatography was performed using Silicycle Silia-P Flash Silica Gel, using either glass columns or a Biotage SP1 system. All salts were purchased from Aldrich and used without purification. Solvents were purchased from Caledon and were purified according to standard procedures. Chiral diphosphine ligands were purchased from Strem.

II. Methods for the synthesis of substrates

Synthesis of the substrates was accomplished using by two general routes from precursor 18. Acetal 18 was prepared according to Gopinath.\(^2\)

General Method A

According to a modified procedure of Cheung,\(^3\) to a suspension of K\(_2\)CO\(_3\) (1.38 g, 10 mmol) and KI (1.00 g, 6 mmol) in acetone (30 mL) was added halo-ketone (6 mmol, 1.2 eq) and acetal 33 (0.90 g, 5 mmol). The resulting mixture was heated to reflux in open atmosphere until complete consumption of the starting material occurred as monitored by TLC. The reaction mixture was then cooled to rt and the solvent removed under reduced pressure. The resulting residue was dissolved in EtOAc (10 mL) and added to 30 mL of H\(_2\)O, then was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried (Na\(_2\)SO\(_4\)) and concentrated. The resulting residue was used without further purification. The above residue was dissolved in THF (12 mL) and cooled to 0\(^\circ\)C in an ice bath. To the cooled solution was added HCl (2M in H\(_2\)O, 5 mL, 10 mmol) and the reaction mixture was allowed to stir until the starting material was consumed completely (ca. 6-12 hr). The reaction mixture was then quenched with sat. NaHCO\(_3\) (aq.) and the solvent removed under reduced pressure. The resulting residue was extracted with EtOAc (3 x 15 mL), and the combined organic extracts were dried (Na\(_2\)SO\(_4\)) then concentrated. The

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crude residue was then separated by silica-gel column chromatography (EtOAc:Hex = 4:1) to furnish the corresponding keto-aldehyde.

2-(2-oxo-2-phenylethoxy)benzaldehyde (1a). Prepared using General Method A from 2-bromo-acetophenone to provide 1a as a white solid (0.37 g, 1.55 mmol) in 31% yield. $^1$H and $^{13}$C NMR data for 1a matched those reported in the literature.4

2-(2-(4-chlorophenyl)-2-oxoethoxy)benzaldehyde (1b). Prepared using General Method A from 2-chloro-4'-chloro-acetophenone to provide 1b as pale yellow crystals (0.23, 0.89 mmol) in 17% yield after recrystallization in EtOAc and hexanes; mp 145.0-148.5 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.55 (s, 1H, CHO), 7.93-7.95 (m, 2H, Ar), 7.86-7.88 (m, 1H, Ar), 7.48-7.53 (m, 3H, Ar), 7.06-7.10 (m, 1H, Ar), 6.86 (d, $J$ = 8.4 Hz, 1H, Ar), 5.38 (s, 2H, O-CH$_2$-CO); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 192.6, 189.4, 160.1, 140.8, 135.8, 132.5, 129.5, 129.4, 128.9, 125.4, 121.9, 112.7, 70.9; IR (KBr) 3084, 2867, 1702, 1681, 1601, 1485, 1287, 1230, 1091, 986, 832, 763 cm$^{-1}$; LRMS (ESI+) m/z 297 (MNa)$^+$, 275 (MH)$^+$; HRMS (ESI+) exact mass calc'd for (C$_{15}$H$_{11}$ClO$_3$Na)$^+$ requires m/z 297.0288, found m/z 297.0290.

2-(2-(naphthalen-2-yl)-2-oxoethoxy)benzaldehyde (1c). Prepared using General Method A from 2-bromo-2'-aceto-naphthone (1.49 g, 6 mmol) to provide 1c as an orange solid (0.48 g, 1.65 mmol) in 33% yield; mp 142.0-145.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.62 (s, 1H, CHO), 8.55 (s, 1H, Ar), 7.87-8.05 (m, 5H, Ar), 7.58-7.67 (m, 2H, Ar), 7.50-7.54 (m, 1H, Ar), 7.06-7.10 (m, 1H, Ar), 6.93 (d, $J$ = 8.4 Hz, 1H, Ar), 5.56 (s, 2H, O-CH$_2$-CO); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 193.5, 189.6, 160.3, 136.0, 135.8, 132.4, 131.6, 130.0, 129.6, 129.1, 129.0, 128.8, 127.9, 127.2, 125.4, 123.4, 121.7, 112.8, 71.0; IR (KBr) 3053, 2916, 2364, 1703, 1687, 1598, 1484, 1288, 1246, 946, 748 cm$^{-1}$; LRMS (ESI+) m/z 313 (MNa)$^+$, 291 (MH)$^+$; HRMS (ESI+) exact mass calc'd for (C$_{19}$H$_{14}$O$_3$Na)$^+$ requires m/z 313.0835, found m/z 313.0844

2-(2-oxopropoxy)benzaldehyde (1d). Prepared using General Method A from 2-chloro-acetone to provide 1d as a white solid (0.63 g, 3.55 mmol) in 71% yield. $^1$H and $^{13}$C NMR data for 1d matched those reported in the literature.4

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4 Takikawa, H. and Suzuki, K. *Org. Lett.* 2007, 9, 2713
2-(3,3-dimethyl-2-oxobutoxy)benzaldehyde (1h). Prepared using General Method A from 2-chloropinacolone (0.80 g, 6 mmol) to provide 1h as a white solid (0.26 g, 1.18 mmol) in 24% yield; mp 49.5-52.5 ºC; ¹H NMR (400 MHz, CDCl₃) δ 10.58 (s, 1H, CHO), 7.85-7.88 (m, 1H, Ar), 7.47-7.51 (m, 1H, Ar), 7.06-7.07 (m, 1H, Ar), 6.74 (d, J = 8.4 Hz, 1H, Ar), 5.03 (s, 1H, O-CH₂-CO), 1.27 (s, 9H, C(CH₃)₃); ¹³C NMR (100 MHz, CDCl₃) δ 208.6, 189.6, 160.4, 135.6, 128.6, 125.4, 121.5, 112.5, 69.0, 43.2, 26.3; IR (film) 2969, 2871, 1721, 1687, 1599, 1480, 1461, 1300, 1229, 1048, 992, 757 cm⁻¹; LRMS (ESI+) m/z 243 (MNa)⁺, 221 (MH)⁺; HRMS (ESI+) exact mass calc’d for (C₁₃H₁₆O₃H)⁺ requires m/z 221.1172, found m/z 221.1183

2-(2-(4-Trifluoromethylphenyl)-2-oxoethoxy)benzaldehyde (1i). 42% yield; white solid, mp 160-162 ºC; ¹H NMR (400 MHz, CDCl₃) δ 5.43 (s, 2H), 6.89 (d, J = 8.4 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.51-7.55 (m, 1H), 7.80 (d, J = 8.2 Hz, 2H), 7.89 (dd, J = 1.7, 7.7 Hz, 1H), 8.12 (d, J = 8.2 Hz, 2H), 10.56 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 71.0, 112.6, 122.0, 125.4, 126.0 (q, J = 27.2 Hz, 1C), 126.1 (q, J = 3.7 Hz, 1C), 128.5, 129.0, 129.5 (q, J = 173 Hz, 1C), 135.8, 135.4 (q, J = 32.8 Hz, 1C), 159.9, 189.3, 192.9; IR (neat): 1704, 1686, 1600, 1584, 1404, 1313, 1160, 1112, 752 cm⁻¹; MS (EI) m/z: 308 (M⁺), 309 (M+1)⁺, 291, 290, 262, 221, 173, 145; HRMS (EI) Calcd for C₁₆H₁₁F₃O₃: 308.0663, found: 308.0660;

Methyl 4-(2-(2-formylphenoxyl)acetyl) benzoate (1j). 49% yield; white solid, mp 148-150 ºC; ¹H NMR (400 MHz, CDCl₃) δ 3.97 (s, 3H), 5.44 (s, 3H), 6.88 (d, J = 8.3 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.50-7.54 (m, 1H), 7.88 (dd, J = 1.8, 7.7 Hz, 1H), 8.05 (d, J = 8.6 Hz, 2H), 8.21 (d, J = 8.6 Hz, 2H), 10.56 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 52.6, 71.0, 112.7, 121.9, 125.4, 128.0, 128.9, 130.1, 134.8, 135.7, 137.4, 160.0, 165.9, 189.4, 193.3; IR (neat): 702, 1692, 1600, 1487, 1432, 1292, 1226, 1116, 983, 750 cm⁻¹; MS (EI) m/z: 298 (M⁺), 280, 249, 221, 165, 163, 145; HRMS (EI) Calcd for C₁₇H₁₄O₅: 298.0841, found: 298.0840;

2-(2-(4-Fluorophenyl)-2-oxoethoxy)benzaldehyde (1k). 95% yield; white solid, mp 117-118 ºC; ¹H NMR (400 MHz, CDCl₃) δ 5.38 (s, 2H), 6.87 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.5 Hz, 1H), 7.18 (t, J = 8.6 Hz, 2H), 7.48-7.52 (m, 1H), 7.86 (dd, J = 1.8, 7.7 Hz, 1H), 8.02-8.05 (m, 2H), 10.56 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 70.8, 112.7, 116.2 (d, J = 22.1 Hz), 121.8, 125.3, 128.8, 130.7 (d, J = 3.0 Hz), 130.8 (d, J = 9.5 Hz), 135.7, 166.2 (d, J = 258.9 Hz), 167.5, 189.4, 192.1; IR (neat): 1699, 1683, 1484, 1432, 1403, 1232, 986, 839, 756 cm⁻¹; MS (EI) m/z: 258 (M⁺), 241, 240, 239, 212, 183, 145, 123, 121, 95; HRMS (EI) Calcd for C₁₅H₁₄FO: 258.0692, found: 258.0705;
2-(2-(4-Methylphenyl)-2-oxoethoxy)benzaldehyde (1l). 100% yield; white solid, mp 152-153 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.44 (s, 3H), 5.39 (s, 2H), 6.86 (d, \(J = 8.4\) Hz, 1H), 7.06 (t, \(J = 7.5\) Hz, 1H), 7.31 (d, \(J = 7.9\) Hz, 2H), 7.49 (t, \(J = 8.1\) Hz, 1H), 7.87-7.90 (m, 3H), 10.58 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 21.6, 70.8, 112.7, 121.6, 125.3, 128.1, 128.6, 129.6, 131.7, 135.7, 145.2, 160.3, 189.6, 193.1; IR (neat): 1699, 1679, 1666, 1600, 1401, 1190, 980, 760 cm\(^{-1}\); MS (EI) \(m/z\): 254 (M\(^+\)), 255 (M+1), 237, 236, 221, 145, 131, 119, 118, 89; HRMS (EI) Calcd for C\(_{16}\)H\(_{14}\)O\(_3\): 254.0943, found: 254.0942;

2-(2-(4-Methoxyphenyl)-2-oxoethoxy)benzaldehyde (1m). 96% yield; white solid, mp 131-133 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.89 (s, 3H), 5.36 (s, 2H), 6.87 (d, \(J = 8.4\) Hz, 1H), 6.97 (d, \(J = 8.6\) Hz, 2H), 7.05 (t, \(J = 7.9\) Hz, 1H), 7.47-7.51 (m, 1H), 7.85 (dd, \(J = 1.7, 7.7\) Hz, 1H), 7.98 (d, \(J = 8.6\) Hz, 2H), 10.58 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 55.5, 70.7, 112.8, 114.2, 121.6, 125.3, 127.2, 128.6, 130.4, 135.7, 160.4, 164.3, 189.6, 192.0; IR (neat): 1680, 1597, 1457, 1265, 1223, 1164, 832, 756 cm\(^{-1}\); MS (EI) \(m/z\): 270 (M\(^+\)), 252, 253, 252, 221, 152, 135; HRMS (EI) Calcd for C\(_{16}\)H\(_{14}\)O\(_4\): 270.0892, found: 270.0890;

2-(3-Oxobutan-2-yloxy)benzaldehyde (1p). Prepared using the General Method A from 3-chloro-2-butanone. Clear, colorless oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 1.58 (d, \(J = 9.1\) Hz, 3H), 2.29 (s, 3H), 4.76 (q, \(J = 9.1\) Hz, 1H), 6.78 (d, \(J = 11.2\) Hz, 1H), 7.08 (t, \(J = 9.9\) Hz, 1H), 7.48-7.53 (m, 1H), 7.88 (dd, \(J = 10.3\) Hz, 2.6 Hz, 1H), 10.58 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 17.6, 25.0, 79.9, 113.0, 121.9, 125.5, 129.2, 136.2, 159.8, 189.5; IR (neat): 2864, 1721, 1687, 1598, 1240, 1041, 759 cm\(^{-1}\); MS (EI) \(m/z\): 191 (M-H), 173 (M-H\(_2\)O); HRMS (EI) Calcd for C\(_{11}\)H\(_{11}\)O\(_3\) (M-H): 191.0701, found: 191.0702.

General Method B
Weinreb amide 35 was prepared using a modified version of the procedure reported by Takikawa.\textsuperscript{4,5} To form acetamide 34, chloroacetyl chloride (4.06 g, 36 mmol) was dissolved in dichloromethane (20 mL) and this solution was added to a solution of the hydrochloride salt of N,O-dimethylhydroxylamine (2.93 g, 30 mmol) in water (20 mL) and stirred at 0ºC. To the resulting biphasic solution was slowly added K$_2$CO$_3$ (4.97 g, 36 mmol) and the reaction mixture was allowed to stir for 12 hr. The solution was then extracted with dichloromethane (3 x 20mL), and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated to furnish 2-chloro-N-methoxy-N-methylacetamide 34 quantitatively.

To a suspension of K$_2$CO$_3$ (1.38 g, 10 mmol) and KI (1.00 g, 6 mmol) in acetone (30 mL) was added acetamide 34 (0.84 g, 6 mmol) and acetal 33 (0.90 g, 5 mmol). The resulting mixture was heated to reflux in open atmosphere until complete consumption of the starting material occurred as indicated by TLC. The reaction mixture was allowed to cool to rt and the solvent was evaporated under reduced pressure. The resulting residue was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were dried (Na$_2$SO$_4$) and concentrated to afford Weinreb amide 35 quantitatively as a spectroscopically pure white solid that was used without further purification.

Grignard reagents were made from the corresponding alkylbromides using magnesium granules. Magnesium granules (0.20 g, 8.25 mmol) and alkylbromide (7.5 mmol, 2.5 eq) were suspended in anhydrous and degassed THF (20 mL) in an oven-dried 3-neck flask under Ar(g). The suspension was heated (40 ºC) until the magnesium granules were consumed (ca. 30 min), then cooled to 0ºC. To the cooled solution was added dropwise Weinreb amide 35 (0.84 g, 3 mmol in 3 mL of THF). The reaction flask was then equipped with an Ar(g) balloon and the reaction mixture was allowed to stir at rt until the starting material was consumed (ca. 8 hr). The resulting crude mixture was extracted with EtOAc (3 x 20mL) and the combined organic extracts were dried (Na$_2$SO$_4$) then concentrated. The resulting residue was dissolved in THF (8 mL) and cooled to 0ºC. HCl (2M in H$_2$O, 3 mL, 6 mmol) was added slowly to the cooled solution. The reaction mixture was then stirred for 12 hr and quenched with sat. NaHCO$_3$ (aq.) and concentrated under reduced pressure. The residue was extracted with EtOAc (3 x 20 mL) and the combined organic extracts were dried (Na$_2$SO$_4$) then concentrated. The crude product was purified by silica-gel column (EtOAc:Hex = 4:1) to afford the corresponding keto-aldehyde.

\begin{center}
\textbf{2-(2-oxo-3-phenylpropoxy)benzaldehyde (1f).} Prepared using General Method B and benzyl bromide to produce 1f as a white solid (0.46 g, 1.81 mmol) in 60% yield. $^1$H and $^{13}$C NMR data for 1f matched those reported in the literature.\textsuperscript{4}
\end{center}

2-(3-methyl-2-oxobutoxy)benzaldehyde (1g). Prepared using General Method B from 2-bromopropane to produce 1g as a white solid (0.27 g, 1.30 mmol) in 43% yield: mp 39.0-41.5 ºC; 1H NMR (400 MHz, CDCl3) δ 10.58 (s, 1H, CHO), 7.87-7.89 (m, 1H, Ar), 7.53-7.54 (m, 1H, Ar), 7.09-7.11 (m, 1H, Ar), 6.81 (d, J = 8.4, 1H, Ar), 4.78 (s, 2H, O-CH2-CO), 2.95-2.98 (m, 1H, CO-C(CH3)2) 1.19 (d, J = 6.9 Hz, 6H, CH(CH3)2); 13C NMR (100 MHz, CDCl3) δ 209.4, 189.3, 160.0, 135.9, 129.0, 125.2, 121.7, 112.3, 71.5, 37.3, 17.8; IR (film) 2974, 2867, 1720, 1682, 1599, 1483, 1461, 1300, 1231, 1191, 834, 761 cm⁻¹; LRMS (ESI+) m/z 229.1 (MNa)⁺; HRMS (ESI+) exact mass calc’d for (C12H14O3Na)⁺ requires m/z 229.0835, found m/z 229.0844

Synthesis of 2-(2-oxohexyloxy)benzaldehyde (1e)

1e was prepared using a variation of General Method B. To a solution of amide 35 (0.80 g, 2.84 mmol) in anhydrous and degassed THF (20 mL) was added n-BuLi (2.62 M in hexanes, 2.1 mL, 5.68 mmol) at -40 ºC and the resulting solution was stirred for 50 min. The reaction mixture was then quenched with sat. NH4Cl (aq.) and extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried (Na2SO4) and concentrated under reduced pressure. The resulting residue was dissolved in THF (7 mL), to which was added HCl (2 M in H2O, 0.8 mL, 5.7 mmol) at 0ºC. The reaction mixture was allowed to stir for ca. 12 hr at rt then quenched with sat. NaHCO3 (aq) and concentrated under reduced pressure. The resulting residue was extracted with EtOAc (3 x 10 mL), dried (Na2SO4) and concentrated. The product was separated by silica gel column chromatography (EtOAc:Hex = 1:3) to afford the title compound (0.48 g, 2.19 mmol) in a 77% yield as a clear, colorless oil; 1H NMR (400 MHz, CDCl3) δ 10.58 (s, 1H, CHO), 7.86-7.89 (m, 1H, Ar), 7.51-7.56 (m, 1H, Ar), 7.10-7.11 (m, 1H, Ar), 6.81 (d, J = 8.4 Hz, Ar), 4.68 (s, 2H, O-CH2-CO), 2.62 (t, J = 7.4 Hz, 2H, CO-CH2-CH2-CH2-CH3), 1.60-1.65 (m, 2H, CO-CH2-CH2-CH2-CH3), 1.33-1.38 (m, 2H, CO-CH2-CH2-CH2-CH3); 13C NMR (100 MHz, CDCl3) δ 206.4, 189.2, 159.9, 135.9, 129.0, 125.2, 121.8, 112.3, 72.8, 38.9 25.1, 22.3, 13.8; IR (film) 3076, 2958, 2932, 2872, 1731, 1687, 1600, 1483, 1460, 1397, 1288, 992, 757 cm⁻¹; LRMS (ESI+) m/z 243.0 (MNa)⁺; HRMS (ESI+) exact mass calc’d for (C13H16O3Na)⁺ requires m/z 243.0991, found m/z 243.1001
Preparation of 2-lithiofuran:

To a well-stirred solution of furan (0.41 mL, 5.68 mmol) in THF (19 mL) cooled to -55 °C was added butyllithium dropwise (2.1 mL, 5.68 mmol) and the resulting solution was stirred at 0 °C for 4 h. The resulting solution of 2-lithiofuran in THF was used for the next step.

To a solution of amide 35 (800 mg, 2.84 mmol) in THF (15 mL) was added crude 2-lithiofuran dropwise at -40 °C. After stirring for 50 min, the reaction was quenched with sat. NH₄Cl (aq.). The product was extracted with EtOAc (3 x 15 mL). The combined organic extracts were dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The residue was dissolved in THF (7 mL) and 2 M HCl (2.8 mL, 5.7 mmol) was added dropwise at 0 °C. After stirring overnight at rt, the reaction mixture was quenched with sat. NaHCO₃ (aq.) and the solvent removed under reduced pressure. The resulting residue was extracted with EtOAc (3 x 15 mL), and the combined organic extracts were dried (Na₂SO₄) then concentrated. The crude residue was recrystallized with EtOAc/Hexanes to furnish the corresponding keto-aldehyde.

2-(2-(Furyl)-2-oxoethoxy)benzaldehyde (1n). 84% yield; white solid, mp 87-88 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.27 (s, 2H), 6.65 (dd, J = 1.6, 3.6 Hz, 1H), 6.89 (d, J = 8.4 Hz, 1H), 7.07 (t, J = 7.6 Hz, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.49-7.53 (m, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.86 (dd, J = 1.8, 7.6 Hz, 1H), 10.60 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 70.3, 112.7, 112.8, 118.7, 121.7, 125.3, 128.7, 135.8, 147.1, 150.5, 160.2, 182.6, 189.5; IR (neat): 1682, 1599, 1458, 1297, 1219, 761 cm⁻¹; MS (EI) m/z: 212 (M-H₂O)+, 213, 185, 184, 145, 121, 95; HRMS (EI) Calcd for (C₁₃H₁₀O₄Br): 212.0473, found: 212.0475;

2-(2-(Thiophenyl)-2-oxoethoxy)benzaldehyde (1o). Prepared using the same method as 1n from Weinreb 33 and 2-lithiothiophene. 64% yield; white solid, mp 95-96 °C; ¹H NMR (400 MHz, CDCl₃) δ 5.26 (s, 2H), 6.91 (d, J = 8.4 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.19 (dd, J = 3.9, 4.9 Hz, 1H), 7.50-7.54 (m, 1H), 7.74 (dd, J = 1.0, 4.9 Hz, 1H), 7.88 (dd, J = 1.8, 7.7 Hz, 1H), 7.93 (dd, J = 1.0, 3.9 Hz, 1H), 10.60 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 71.3, 112.7, 121.9, 125.3, 128.4, 128.9, 133.0, 134.9, 135.9, 140.2, 160.1, 187.0, 189.4; IR (neat): 1682, 1667, 1597, 1476, 1411, 1215, 1194, 1056, 765, 736 cm⁻¹; MS (EI) m/z: 246 (M⁺), 247 (M+1)⁺, 228, 200, 121, 111, 84; HRMS (EI) Calcd for C₁₃H₁₀O₃S: 246.0351, found: 246.0356;

Synthesis of 2-(2-oxo-1,2-diphenylethoxy)benzaldehyde 1q
To a slurry of lithium aluminum hydride (380.0 mg, 10.0 mmol) in THF (20 mL) at 0 ºC was added a solution of methyl 2-hydroxybenzoate (1 g, 6.6 mmol) in THF (5 mL). The reaction was warmed to rt and stirred for 3 h then quenched at 0 ºC with EtOAc. 1 M HCl (15 mL) was added and the resulting mixture was extracted with EtOAc (3 x 30 mL) and the combined organic extracts were dried (anhydrous Na₂SO₄) and concentrated. 2-(hydroxymethyl)phenol 36 was afforded quantitatively as a spectrally pure white solid which was used in the following step without further purification.

To a solution of 2-(hydroxymethyl)phenol 36 (496 mg, 4.0 mmol) in DMF (20 mL) was added desyl chloride (920 mg, 4.0 mmol) and K₂CO₃ (1.1 g, 8.0 mmol) at rt. After stirring for 3 h at rt, 20 mL of EtOAc and 20 mL of H₂O were added to the resulting mixture, which was then extracted with EtOAc (2 x 15 mL), washed with brine (2 x 10 mL), and dried (MgSO₄). The crude mixture was then concentrated under reduced pressure and the residue was purified by silica gel chromatography (EtOAc:Hexanes = 1:3) to afford 2-(2-(hydroxymethyl)phenoxy)-1,2-diphenylethanone 37 as a clear, colorless oil (865 mg, 2.7 mmol) in 68% yield. ¹H NMR (300 MHz, CDCl₃) δ 3.10-3.32 (br, 1H), 4.65 (d, J = 12.6 Hz, 1H), 4.91 (d, J = 12.6 Hz, 1H), 6.60 (s, 1H), 6.88 (d, J = 12.5 Hz, 1H), 6.95 (t, J = 7.4 Hz, 1H), 7.17 (dt, J = 1.6, 8.0 Hz, 1H), 7.30-7.46 (m, 6 H), 7.53 (d, J = 7.3 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 7.2 Hz, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 62.2, 81.8, 112.5, 121.9, 127.7, 128.7, 128.9, 129.0, 129.1, 129.2, 129.6, 130.4, 133.8, 134.5, 134.9, 155.4, 195.8; IR (neat): 3411 (br), 1684, 1596, 1489, 1449, 1222, 750, 694 cm⁻¹; MS (EI) m/z: 318 (M)+, 317 (M+1)+, 213, 196, 167, 165, 105, 84, 77; HRMS (EI) Calcd for C₂₁H₁₈O₃: 318.1256, found: 318.1255;

To a solution of oxalyl chloride (214 mg, 1.7 mmol) in CH₂Cl₂ (7 mL) was added DMSO (265 mg, 3.4 mmol) at -78 °C over 10 min. After 1 h, a solution of 2-(2-(hydroxymethyl)phenoxy)-1,2-diphenylethanone 37 (318 mg, 1 mmol) in CH₂Cl₂ (7 mL) was added dropwise to the reaction and the resulting solution was allowed to stir at -78 °C for 2 h. Et₃N (0.51 mL, 5 mmol) was added over 10 min to the mixture which was stirred overnight prior to the addition of HCl (1M, 5 mL) at -78 °C. The crude mixture was extracted with CH₂Cl₂ (3 x 15 mL), washed with brine (2 x 15 mL) and dried (Na₂SO₄). The combined organic extracts were concentrated under reduced pressure to furnish 2-(2-oxo-1,2-diphenylethoxy)benzaldehyde 1q as a spectrally pure colorless oil in 82% yield. ¹H NMR (400 MHz, CDCl₃) δ 6.49 (s, 1H), 6.90 (d, J = 6.9 Hz, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.35-7.47 (m, 6H), 7.51-7.61 (m, 3H), 7.86 (dd, J = 1.8, 7.7 Hz, 1H), 8.01 (d, J = 7.3 Hz, 2H), 10.58 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 195.1, 189.8, 160.0, 136.0, 134.7, 134.5, 134.1, 129.5, 129.4, 129.3, 129.1, 129.0, 127.6, 125.9, 122.1, 114.1, 83.3; IR
(neat): 1687, 1598, 842, 732 cm$^{-1}$; MS (ESI) $m/z$: 317 (M+H)$^+$, 339 (M+Na)$^+$; HRMS (ESI) Calcd for C$_{21}$H$_{16}$O$_3$H$^+$: 317.1180, found: 317.1172.

**Synthesis of 2-(2-oxo-2-phenylethoxy)-benzaldehyde-D (1a-D):**

![Chemical Diagram]

To a slurry of lithium aluminum deuteride (554.4 mg, 13.2 mmol) in THF (25 mL) at 0 °C was added a solution of methyl 2-hydroxybenzoate (1 g, 6.6 mmol) in THF (5 mL). The reaction was warmed to rt, stirred for 1 h, then quenched with wet EtOAc. 1 M HCl (15 mL) was then added and the resulting mixture was extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried (Na$_2$SO$_4$) and then concentrated to afford 2-(hydroxylideuterium-methyl)phenol 37 as a spectrally pure white solid (91% yield).

2-(hydroxylideuterium-methyl) phenol 38 (495 mg, 3.9 mmol), 2-bromo-acetophenone (1.16 g, 5.85 mmol) and K$_2$CO$_3$ (808 mg, 5.85 mmol) were dissolved in acetone (50 mL). The reaction was stirred at rt for 2 hours. After filtration to remove any salts, the filtrate was concentrated under reduced pressure and the residue was purified by column chromatography (EtOAc/hexanes = 45/55) to furnish 2-(hydroxylideuterium-methyl)phenoxy-1-phenylethanone 39 quantitatively as a white solid. mp 82-84 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.11-3.60 (br, 1H), 5.40 (s, 2H), 6.86 (d, $J$ = 8.2 Hz, 1H), 6.98 (dt, $J$ = 0.9, 7.4 Hz, 1H), 7.24 (dt, $J$ = 2.2, 8.0 Hz, 1H), 7.30 (dd, $J$ = 1.7, 7.4 Hz, 1H), 7.51 (t, $J$ = 7.7 Hz, 2 H), 7.61-7.65 (m, 1H), 7.96-7.98 (m, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 61.3 (quintet, $J$ = 22.4 Hz, 1C), 70.4, 111.7, 121.7, 127.8, 128.78, 128.82, 129.4, 130.1, 134.0, 134.1, 156.2, 194.5; IR (neat): 3549, 1696, 1452, 1228, 980, 749 cm$^{-1}$; MS (EI) $m/z$: 244 (M$^+$), 228, 226, 197, 169, 122, 120, 105, 77; HRMS (EI) Calcd for C$_{15}$H$_{12}$D$_2$O$_3$: 244.1068, found: 244.1064;

To a solution of oxalyl chloride (0.2 mL, 2.4 mmol) in CH$_2$Cl$_2$ (7 mL) was added DMSO (0.34 mL, 4.8 mmol) at $-78$ °C over 5-10 min. After 1 h, a solution of 2-(2-(hydroxylideuterium-methyl)phenoxy)-1-phenylethanone 39 (340 mg, 1.4 mmol) in CH$_2$Cl$_2$ (7 mL) was added dropwise to the reaction and the resulting solution was allowed to stir at $-78$ °C for 2 h. Et$_3$N (0.85 mL, 6.1 mmol) was then added over 10 min. The mixture was stirred overnight prior to the addition of HCl (1M, 5 mL) at $-78$ °C. The crude mixture was extracted with CH$_2$Cl$_2$ (3 x 15 mL), washed with brine (2 x 15 mL) and dried (anhydrous Na$_2$SO$_4$). The combined organic extracts were concentrated under reduced pressure to furnish pure product 1a-D as a white solid (97% yield). mp 87-88 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.43 (s, 2H), 6.86 (d, $J$ = 8.4 Hz, 1H), 7.06 (t, $J$ = 7.5 Hz, 1H), 7.47-7.53 (m, 3H), 7.62-7.65 (m, 1H), 7.86 (dd, $J$ = 1.7, 7.6 Hz, 1H), 7.99 (d, $J$ = 7.6 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 70.8, 112.7, 121.7, 125.2, 128.0, 129.0, 134.1, 134.2, 135.7, 160.3, 189.2 (t, $J$ = 27.6 Hz), 193.5; IR (neat): 1729, 1599, 1476, 1449, 1291, 1218, 1109, 983 cm$^{-1}$; MS (EI) $m/z$: 241 (M$^+$), 242 (M+1)$^+$, 223, 195, 146, 122, 105, 77; HRMS (EI) Calcd for C$_{15}$H$_{13}$D$_3$O: 241.0849, found: 241.0859;
Synthesis of 2-(2-oxo-2-phenylethylthio)benzaldehyde (1s)

To a slurry of lithium aluminum hydride (380.0 mg, 10.0 mmol) in THF (20 mL) at 0 °C was added a solution of methyl thiosalicylate (840 mg, 5 mmol) in THF (5 mL). The reaction was warmed to rt and stirred for 3 h, then quenched at 0 °C with EtOAc. 1 M HCl (15 mL) was then added and the resulting mixture was extracted with EtOAc (3 x 30 mL), and the combined organic extracts were dried (MgSO₄) then concentrated. 2-(hydroxymethyl)thiophenol 40 was afforded quantitatively as a spectrally pure white solid and was used in the following step without purification.

To a solution of 2-(hydroxymethyl)thiophenol 40 (560 mg, 4.0 mmol) in DMF (20 mL) was added 2-bromoacetophenone (800 mg, 4.0 mmol) and K₂CO₃ (1.1 g, 8.0 mmol). The resulting mixture was stirred at rt for 3 h. 20 mL of EtOAc and 20 mL of H₂O were then added to the mixture, which was further extracted with EtOAc (2 x 15 mL), washed with brine (2 x 10 mL) and dried (MgSO₄). The residue was then concentrated under reduced pressure and purified by silica gel chromatography (EtOAc/Hexanes = 1/3) to afford 2-(2-(hydroxymethyl)phenylthio)-1-phenylethanone 41 as a yellow solid (830 mg, 3.2 mmol) in 81% yield. mp: 72-74 ºC; ¹H NMR (400 MHz, CDCl₃) δ 2.65-2.74 (br, 1H), 4.32 (s, 2H), 4.78 (d, J = 5.1 Hz, 2H), 7.24 (dt, J = 1.7, 7.4 Hz, 1H), 7.28 (dt, J = 1.7, 7.4 Hz, 1H), 7.40-7.48 (m, 4H), 7.59 (tt, J = 1.3, 7.4 Hz, 1H), 7.91-7.94 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 41.8, 63.4, 128.0, 128.4, 128.5, 128.8, 128.8, 128.8, 132.3, 132.8, 133.1, 135.2, 135.3, 142.2, 194.2; IR (neat): 3529, 1670, 1445, 1187, 741 cm⁻¹; MS (EI) m/z: 258 (M)⁺, 238, 207, 161, 135, 105, 84, 77, 49; HRMS (EI) Calcd for C₁₅H₁₄O₂S: 258.0715 found: 258.0723

To a solution of 2-(2-(hydroxymethyl)phenylthio)-1-phenylethanone 41 (130 mg, 0.5 mmol) in CH₂Cl₂ (2 mL) was added DMP (320 mg, 0.75 mmol) at rt. After 1 h, the reaction was quenched with 5% Na₂S₂O₃ in sat. NaHCO₃ (3 mL). The resulting mixture was extracted with CH₂Cl₂ (3 x 10 mL). The combined organic extracts were concentrated under reduced pressure. The crude product was recrystallized from EtOAc/hexanes to furnish 2-(2-oxo-2-phenylethylthio)benzaldehyde 1s (73 mg, 57% yield) as a spectrally pure pale orange solid. mp 92-94 ºC; ¹H NMR (400 MHz, CDCl₃) δ 4.33 (s, 2H), 7.36 (m, 1H), 7.48 (m, 2H), 7.55 (m, 2H), 7.60 (m, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 8.6 Hz, 2H), 10.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 40.4, 126.7, 129.0, 129.1, 129.9, 132.5, 134.0, 134.4, 135.4, 139.8, 191.7, 193.8; IR (neat): 2741, 1674, 1458, 1444, 1013, 757 cm⁻¹; MS (ESI) m/z: 279 (M+Na)⁺; HRMS (ESI) Calcd for C₁₅H₁₂O₂SNa⁺: 279.0445, found: 279.0440;
To a solution of oxalyl chloride (214 mg, 1.7 mmol) in CH₂Cl₂ (7 mL) was added DMSO (265 mg, 3.4 mmol) at -78 ºC over 10 min. After 1 h, a solution of 2-(2-(hydroxymethyl)phenylthio)-1-phenylethanone 41 (258 mg, 1 mmol) in CH₂Cl₂ (7 mL) was added dropwise to the reaction and the resulting solution was allowed to stir at –78 ºC for 2 h. Et₃N (505 mg, 5 mmol) was added over 10 min to the above mixture which was stirred overnight prior to the addition of HCl (1M, 5 mL) at -78 ºC. The crude mixture was extracted with CH₂Cl₂ (3 x 15 mL), washed with brine (2 x 15 mL) and dried (Na₂SO₄). The combined organic extracts were concentrated under reduced pressure to furnish 2-(1,1-dichloro-2-oxo-2-phenylethylthio)benzaldehyde 1t as a spectral ly pure yellow solid in 43% yield. mp: 76-79 ºC; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (t, J = 7.9 Hz, 2H), 7.62-7.72 (m, 3H), 7.81-7.85 (m, 1H), 8.11-8.15 (m, 1H), 8.29-8.32 (m, 2H), 10.60 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 128.4, 129.1, 130.7, 131.4, 131.7, 131.8, 133.9, 134.3, 139.5, 139.8, 185.1, 191.7; IR (neat): 2860, 1698, 1676, 1230, 755 cm⁻¹; MS (ESI) m/z: 347 (M+Na)⁺; HRMS (ESI) Calcd for C₁₅H₁₀O₂SCl₂Na⁺: 346.9676, found: 346.9670

Synthesis of 2-(2-acetylphenoxy)-1-phenylethanone (1r): 2'-hydroxyacetophenone (500 mg, 3.68 mmol), 2-bromoacetophenone (1.46 g, 7.36 mmol) and K₂CO₃ (508 mg, 3.68 mmol) were dissolved in acetone (20 mL). The reaction mixture was stirred at 50 ºC for 5 h. After filtration to remove salts, the filtrate was concentrated under reduced pressure and the residue was purified by column (EtOAc/hexanes = 35/85) and then recrystallized (EtOAc/hexanes) to give white needle-like crystals 1r (204 mg) in 21% yield. mp 107-109 ºC; ¹H NMR (400 MHz, CDCl₃) δ 2.70 (s, 3H), 5.41 (s, 2H), 6.87 (d, J = 8.3 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.40-7.44 (m, 1H), 7.50-7.54 (m, 2H), 7.62-7.66 (m, 1H), 7.76 (dd, J = 1.8, 7.7Hz, 1H), 7.97-8.00 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 32.0, 70.7, 112.4, 121.6, 128.0, 128.9, 129.0, 130.7, 133.4, 134.1, 134.3, 157.1, 193.3, 200.0; IR (neat): 1709, 1661, 1595, 1487, 1297, 1230, 979, 757 cm⁻¹; MS (EI) m/z: 254 (M)⁺, 255 (M+1)⁺, 236, 235, 219, 207, 149, 132, 105, 77; HRMS (EI) Calcd for C₁₆H₁₄O₃: 254.0943, found: 254.0949;

Synthesis of 2-(3-oxobutyl)benzaldehyde (1u). The procedure is based on the procedure of Enders and Niemeier.⁷ ¹H NMR (400 MHz, CDCl₃) δ 2.15 (s, 3H), 2.76 (t, J = 7.5 Hz, 2H), 3.28 (t, J = 7.5 Hz, 2H), 7.32 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.51(t, J = 7.5 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 10.20 (s, 1H).

Substrates 1w-z were synthesized from common precursor 44 via General Method

C. Substrates 1u and 1v were synthesized via Method D. Substrates 29a-i were synthesized from commercially available N-methyl methyl anthranilate via General Method C.8

**General Method C**

*Synthesis of 2-iodo-N-methoxy-N-methylacetamide (42)*

To a round-bottom flask equipped with a magnetic stirbar was added a solution of chloroacetyl chloride (3.38g, 30 mmol) in 30 mL of CH₂Cl₂ and a solution of N,O-dimethylhydroxylamine hydrochloride salt (3.0 g, 30 mmol) in 30 mL of H₂O. 20 mL of CH₂Cl₂ and H₂O were added to the biphasic mixture. The mixture was stirred vigorously and cooled in an ice bath, and then K₂CO₃ (4.28 g, 31 mmol) was added slowly. Gas evolved rapidly. The biphasic mixture was then stirred at rt for 4 h before being separated through an ISOLUTE™ Phase Separator. The organic layer was evaporated under reduced pressure, and the organic residue was reconstituted in 300 mL of acetone. To this solution was added 15 g of potassium iodide (90 mmol, 3 eq). The reaction vessel was equipped with a reflux condenser and the reaction mixture was heated to 70 °C and maintained at this temperature overnight (12 h). The solvent was removed from the resulting dark red reaction mixture under reduced pressure, and then reconstituted in 40 mL of EtOAc, which was subsequently added to a separatory funnel. This solution was mixed with 20 mL of sat. Na₂SO₃, which rendered the organic layer light yellow. The aqueous layer was extracted with 3x30 mL EtOAc, and the combined organic extracts were washed with brine. Upon concentration under reduced pressure, 6.87 g of the title compound 42 was recovered as a light yellow oil of sufficient purity for further transformations.

*Synthesis of 2-((2-(hydroxymethyl)phenyl)(methyl)amino)-N-methoxy-N-methylacetamide (43)*

To a flame-dried round bottom flask equipped with a magnetic stirbar and charged with 300 mL of THF cooled via ice bath was added 2g of LiAlH₄ (52.5 mmol, 1.05 eq). To this chilled suspension was added

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8 For the synthesis of substrates 1d and 1e: Shen, Z.; Dornan, P. K.; Khan, H. A.; Woo, T. K.; Dong, V. M. J. Am. Chem. Soc. 2009, 131, 1077
dropwise a solution of N-methyl methylantranilate (8.25g, 50 mmol in 30 mL of THF) over 1h. The reaction mixture was then removed from the ice bath and stirred at rt for 2h. The reaction was quenched by slow addition of EtOAc on ice. After further addition of EtOAc showed no visible reaction, 2 mL of distilled H₂O was added dropwise with stirring, followed by 2 mL of 10% NaOH (aq.) and then another 6 mL of distilled H₂O. This resulted in the formation of a grey suspension that was then filtered through a medium-porosity glass frit. The filtered solids were washed with EtOAc. The clear, slightly yellow solution was concentrated under reduced pressure to afford 6.8g (quant.) of a clear, yellow oil that was determined by ¹H-NMR to be pure enough for further elaboration.

To a round-bottom flask equipped with a magnetic stir bar was added 1.37 g of 2-(methylamino)benzyl alcohol (10 mmol), 2.5 g of 42 (11 mmol, 1.1 eq) and 30 mL of DMF. To this solution was added 1.66 g (12 mmol, 1.2 eq) of K₂CO₃. The reaction vessel was then equipped with a water-cooled reflux condenser and the reaction mixture was stirred at a temperature of 70 °C for 10 h (TLC conditions: 40% EtOAc in hexanes). The reaction vessel was then cooled to rt and the dark brown reaction mixture was added to a separatory funnel with 50 mL of EtOAc and 50 mL of H₂O. The aqueous phase was extracted with 3x15 mL of EtOAc, and the combined organic extracts were washed repeatedly (4x20 mL) with H₂O and then twice with brine in order to remove DMF. After drying (MgSO₄) and concentration under reduced pressure, a dark brown oil was produced (2.5 g) which was then purified by column chromatography (30% EtOAc in CH₂Cl₂) to afford 43 as a light yellow oil (1.5 g, 62%). ¹H NMR (400 MHz, CDCl₃) δ 7.27-7.21 (m, 3H, Ar), 7.07 (td, 1H, J = 7.72, 1.52 Hz, Ar), 5.38 (br, 1H, OH), 4.73 (s, 2H, Ar-CH₂-OH), 3.96 (s, 2H, N-C₃H₃-C(O)), 3.68 (s, 3H, N-O-CH₃), 3.18 (s, 3H, N-C₃H₃), 2.81 (s, 3H, C(O)-N-C₃H₃); ¹³C NMR (100 MHz, CDCl₃) δ 171.5, 151.6, 136.9, 129.7, 128.5, 124.8, 121.9, 64.2, 61.4, 56.8, 43.7, 32.4; IR (neat) 3391, 2938, 1743, 1658, 1492, 1179, 983, 759 cm⁻¹; LRMS (ESI⁺) m/z 239 (MH⁺); HRMS (ESI⁺) exact mass calc’d for (C₁₂H₁₈N₂O₃H)⁺ requires m/z 239.1392, found m/z 239.1390.

Synthesis of 2-((2-(1,3-dioxan-2-yl)phenyl)(methyl)amino)-N-methoxy-N-methylacetamide (44)

To a solution of Weinreb amide 43 (1.5 g, 6.2 mmol) in DMSO (40 mL) in a round-bottom flask equipped with a magnetic stir bar was added IBX (1.96 g, 7 mmol, 1.1 eq) and the resulting suspension was stirred at rt for 3 h. The IBX eventually dissolved completely and the reaction mixture turned from light yellow to dark brown. Upon complete conversion (monitored by thin-layer chromatography, 40% EtOAc in hexanes), the reaction mixture was added to a separatory funnel with 50 mL of EtOAc and water. The aqueous layer was extracted with 3x10 mL of
EtOAc and the combined organic extracts were washed once with water and once with brine, and then dried (MgSO₄) and concentrated under reduced pressure. The resulting brown oil was used without further purification. To the crude aldehyde was added 1,3-propanediol (5 mL), triethylorthoformate (5 mL) and tetrabutylammonium tribromide (70 mg, 0.02 eq). The reaction mixture was stirred at rt for 1 d then added to a separatory funnel with 30 mL of EtOAc and water. The aqueous layer was extracted with 3x10 mL EtOAc and the combined organic extracts washed with 5x10 mL water and once with brine, then dried (MgSO₄) and concentrated under reduced pressure. The resulting brown oil was then purified by silica gel chromatography (30% EtOAc in CH₂Cl₂) to provide 44 as a thick orange oil in 63% yield over 2 steps. 

1H NMR (400 MHz, CDCl₃) δ 7.64 (m, 1H, Ar), 7.28 (m, 1H, Ar), 7.18 (m, 1H, Ar), 7.09 (m, 1H, Ar), 5.93 (s, 1H, Ar-CH(O)(OR)), 4.20 (dd, 2H, J = 11.12, 4.88 Hz, O-CH₂), 3.98 (s, 2H, NMe-CH₂-C(O)), 3.98 (m, 2H, O-CH₂), 3.61 (s, 3H, C(O)N-CH₃), 3.19 (s, 3H, C(O)N-CH₃), 2.90 (s, 3H, Ar-N-CH₃), 2.24 (m, 1H, O-CH₂-CH(H)), 1.41 (m, 1H, O-CH₂-CH(H)); 

13C NMR (100 MHz, CDCl₃) δ 161.3, 151.1, 132.8, 129.3, 127.4, 123.4, 120.2, 96.4, 67.6, 61.0, 59.0, 41.4, 32.3, 25.9; 

IR (neat) 2961, 2852, 1720, 1674 cm⁻¹; 

LRMS (ESI+) m/z 295.2 (MH+); HRMS (ESI+) exact mass calc’d for (C₁₅H₂₂N₂O₄H)⁺ requires m/z 295.1652, found m/z 295.1644.

In a flame-dried Schlenk flask equipped with a magnetic stirbar and purged with argon, Weinreb amide acetal 44 (450 mg, 1.5 mmol) was dissolved in THF (10 mL) and the solution was cooled to -78 °C (CO₂/acetone). To this cooled solution was added organolithium (2 mmol, 1.3 eq) dropwise over a period of 10 min. The solution turned from light to dark yellow. The reaction was monitored by TLC. The reaction was quenched with water, and extracted 3x10 mL with EtOAc, washed with brine, dried (MgSO₄) and concentrated to produce a crude yellow oil. This oil was redissolved in THF (5 mL) and to this solution was added 2 mL of 2M HCl (aq.) (4 mmol, 2.7 eq) and the reaction mixture was allowed to stir at rt overnight. The reaction mixture was then poured into a separatory funnel with 20 mL EtOAc and water. The aqueous phase was neutralized with 10 mL of sat. NaHCO₃, then extracted with 3x10 mL of EtOAc. The combined organic extracts were washed with brine, then dried and concentrated to afford a yellow oil which was then purified by column chromatography (10% EtOAc in hexanes) to produce the keto-aldehydes as bright yellow oils.
2-(methyl(2-oxo-2-phenylethyl)amino)benzaldehyde (1w) Prepared via General Method C from 7 and phenyllithium to produce 1w as a yellow oil (163 mg, 0.64 mmol) in 43% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.12 (s, 1H, CHO), 7.92 (m, 2H, Ar), 7.73 (m, 1H, Ar), 7.50 (m, 4H, Ar), 7.17 (m, 1H, Ar), 7.05 (m, 1H, Ar), 4.69 (s, 2H, N-CH$_2$-C(O)), 3.09 (s, 3H, N-C$_3$H$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 196.2, 191.3, 154.4, 135.6, 135.0, 133.8, 132.7, 129.0, 128.1, 127.2, 121.4, 119.5, 63.8, 43.0; IR (neat) 2865, 2740, 1696, 1674, 1485, 1222, 1162, 944, 750 cm$^{-1}$; LRMS (ESI+) $m/z$ 254 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{16}$H$_{15}$NO$_2$H)$^+$ requires $m/z$ 254.1164, found $m/z$ 254.1175.

2-(methyl(2-oxohexyl)amino)benzaldehyde (1x) Prepared via General Method C from 44 and n-butyllithium to produce 1x as a yellow oil (220 mg, 0.94 mmol) in 63% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.14 (s, 1H, CHO), 7.73 (m, 1H, Ar), 7.49 (m, 4H, Ar), 7.05 (m, 2H, Ar), 3.99 (s, 2H, N-CH$_2$-C(O)), 2.99 (s, 3H, N-C$_3$H$_3$), 2.39 (t, 2H, $J$ = 7.4 Hz, C(O)-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 1.55 (m, 2H, C(O)-CH$_2$-CH$_2$-CH$_2$-CH$_2$-CH$_3$), 1.30 (m, 2H, C(O)-CH$_2$-CH$_2$-CH$_2$-C$_3$H$_3$), 0.90 (t, 3H, $J$ = 7.32 Hz, C(O)-CH$_2$-CH$_2$-CH$_2$-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 207.9, 191.1, 154.0, 134.8, 132.5, 126.9, 121.3, 118.9, 66.7, 42.8, 39.7, 25.7, 22.4, 13.8; IR (neat) 2957, 2871, 1723, 1682, 1597, 1485, 1284, 1188, 1042, 759 cm$^{-1}$; LRMS (ESI+) $m/z$ 233 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{14}$H$_{19}$NO$_2$H)$^+$ requires $m/z$ 234.1493, found $m/z$ 234.1488.

2-methyl((2-oxopropyl)amino)benzaldehyde (1y) Prepared via General Method C from 44 and methyllithium to produce 1y as a pale yellow oil (152 mg, 0.93 mmol) in 52% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.13 (s, 1H, CHO), 7.74 (dd, 1H, $J$ = 6.8, 1.6 Hz, Ar), 7.48 (m, 1H, Ar), 7.06 (m, 2H, Ar), 3.98 (s, 2H, N-CH$_2$-C(O)), 2.99 (s, 3H, N-C$_3$H$_3$), 2.15 (s, 3H, C(O)C$_3$H$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 205.6, 191.0, 153.9, 134.9, 132.9, 126.9, 121.3, 118.8, 67.2, 42.7, 27.2; IR (neat) cm$^{-1}$ 2856, 1727, 1679, 1596, 1485, 1269, 1213, 1188, 66.7, 42.8, 39.7, 25.7, 22.4, 13.8; IR (neat) cm$^{-1}$ 2963, 1715, 1682, 1597, 1482; LRMS (EI) $m/z$ 192.1 (M$^+$); HRMS (EI) exact mass calc’d for (C$_{11}$H$_{13}$NO$_2$H)$^+$ requires $m/z$ 192.1025, found $m/z$ 192.1023.

2-(((3,3-dimethyl-2-oxobutyl)(methyl)amino)benzaldehyde (1z) Prepared via General Method C from 44 and $t$-butyllithium to produce 1z as a pale yellow oil (218 mg, 0.93 mmol) in 61% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.08 (s, 1H, CHO), 7.71 (dd, 1H, $J$ = 7.68, 1.68 Hz, Ar), 7.46 (m, 1H, Ar), 7.09 (d, 1H, $J$ = 8.2 Hz, Ar), 7.01 (t, 1H, $J$ = 7.52 Hz, Ar), 4.25 (s, 2H, N-CH$_2$-C(O)), 2.96 (s, 3H, N-C$_3$H$_3$), 1.15 (s, 9H, C(C$_3$H$_3$)$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 211.8, 191.2, 154.5, 134.7, 132.3, 126.7, 120.9, 119.1, 62.3, 43.4, 41.7, 26.4; IR (neat) cm$^{-1}$ 2963, 2865, 1715, 1682, 1597, 1482; LRMS (EI) $m/z$ 233 (M$^+$); HRMS (EI) exact mass calc’d for (C$_{14}$H$_{19}$NO$_2$H)$^+$ requires $m/z$ 233.1420, found $m/z$ 233.1416.
Method D

To a round-bottom flask equipped with a magnetic stir bar was added 2-aminobenzyl alcohol\(^9\) (1.37 g, 10 mmol) and CH\(_2\)Cl\(_2\) (100 mL). To the resulting solution was added sulfonyl chloride (methyl or tolyl, 1.1 eq) and triethylamine (4 mL, 30 mmol, 3 eq) was added dropwise. The reaction mixture was stirred at rt overnight (12 h) and then added to a large separatory funnel with 50 mL of water. The biphasic mixture was extracted (2x20 mL CH\(_2\)Cl\(_2\)), washed with dilute acid (1x20 mL 1M HCl), water (1x20 mL) then brine (1x20 mL). The combined organic phases were collected, dried (MgSO\(_4\)) and then concentrated to afford the N-protected 2-aminobenzyl alcohol quantitatively as an off-white solid of sufficient purity for further elaboration.

The crude N-protected 2-aminobenzyl alcohol (10 mmol) was dissolved in DMF (40 mL) and to this mixture was added K\(_2\)CO\(_3\) (1.66 g, 12 mmol, 1.2 eq) and 2-bromoacetophenone (2.1 g, 10.5 mmol, 1.05 eq). The resulting suspension was stirred at rt for 4h. Upon completion (judged by TLC, 20% EtOAc in hexanes, KMnO\(_4\)), the reaction mixture was added to a separatory funnel with 40 mL of EtOAc and 50 mL of water. The aqueous phase was extracted (3x15 mL EtOAc) and the combined organic phases were washed repeatedly with water (5x15 mL) and twice with brine (2x15 mL). The organic phase was dried (MgSO\(_4\)) and concentrated to afford the keto-alcohol quantitatively as brown solids of sufficient purity for the oxidation.

The crude keto-alcohol (2 mmol) was dissolved in CH\(_2\)Cl\(_2\) (10 mL). To this mixture was added MnO\(_2\) (90% tech. grade, 2.8 g, 15 eq.) and the resulting suspension was stirred at rt for 2h (TLC conditions: 10% EtOAc in hexanes). After the oxidation was complete, Celite (2 g) was added to the reaction mixture and stirred. The suspension was filtered through a pad of Celite on a sintered glass frit of medium porosity. The solvent was removed under reduced pressure, and the crude keto-aldehyde was recrystallized from EtOAc/hexanes to give the product as white, free-flowing crystals (46-50% yield).

N-(2-formylphenyl)-4-methyl-N-(2-oxo-2-phenylethyl)-benzenesulfonamide \(^{\text{1u}}\), white powder. Mp: 171 – 173 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.44 (s, 1H, CHO), 7.97 (m, 1H, Ar), 7.87 (m, 2H, Ar), 7.58 (m, 2H, Ar), 7.46 (m, 5H, Ar), 7.29 (d, 2H, J = 8.1 Hz, Ar), 6.91 (m, 1H, Ar), 5.04 (br s, 2H, Ar-NTs-CH\(_2\)-O), 2.45 (s, 3H, SO\(_2\)-C\(_6\)H\(_4\)-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 193.0, 190.7, 144.7, 141.5, 136.0, 134.9, 134.5, 134.2, 134.1, 129.9, 129.6, 128.3, 127.6, 57.5, 21.9 \(\delta\); IR (neat) 3072, 2920, 1694, 1682, 1596 cm\(^{-1}\).

\(^9\) Made using the same procedure as 2-N-methylaminobenzyl alcohol, starting instead from methyl anthranilate.
N-(2-formylphenyl)-N-(2-oxo-2-phenylethyl)-methanesulfonamide, (1v) white crystals.

Mp: 126 – 128 ºC; ¹H NMR (400 MHz, CDCl₃) δ 10.46 (s, 1H, CHO), 8.00 (m, 1H, Ar), 7.91 (m, 2H, Ar), 7.79 (m, 1H, Ar), 7.63 (m, 2H, Ar), 7.53 (m, 1H, Ar), 7.48 (m, 2H, Ar), 5.24 (br s, 2H, Ar-NMs-CH₂-C(O)); ¹³C NMR (100 MHz, CDCl₃) δ 194.5, 190.5, 141.7, 135.3, 135.1, 134.5, 134.4, 130.7, 130.6, 129.8, 129.2, 128.2, 59.1, 40.4; IR (neat) 2933, 1704, 1695, 1595, 1329 cm⁻¹; LRMS (ESI+) m/z 318 (MH⁺), 340 (MNa⁺); HRMS (ESI+) exact mass calc’d for (C₁₆H₁₅NO₄SH)+ requires m/z 318.0780, found m/z 318.0770.

**General Method E**¹⁰

Note: While efforts were made to isolate certain intermediates, many seemed to decompose when various purification methods were attempted. Many compounds underwent retro-aza-Michael on silica. As a result, only the final keto-aldehydes were isolated and characterized.

To a flame-dry round-bottom flask charged with a magnetic stirbar and 70 mL of CH₂Cl₂ cooled via ice bath was added AlCl₃ (1.6 g, 12 mmol, 1.2 eq.) then arene (10 mmol, 1 eq.) dropwise. The initial suspension becomes a clear, slightly brown solution over the course of 30 min of stirring. 3-chloropropionyl chloride (1.15 mL, 12 mmol, 1.2 eq) was then added dropwise to the solution. The reaction was monitored by thin-layer chromatography (5 - 10% EtOAc in hexanes) and, once observed to be complete, the reaction mixture was added to a separatory funnel containing ice. The aqueous phase was extracted 3x15 mL with CH₂Cl₂, then the combined organic extracts were washed once with 30 mL of sat. NaCl (aq.), dried with MgSO₄ and concentrated under reduced pressure to afford a yellow oil (or, in the case of bromobenzene, a brown solid) in crude yields ranging from 85 – 92%. The crude material was used in the next step without further purification. Many of the materials synthesized in this fashion are commercially available, but this method is sufficiently operationally simple and scalable that it is more cost and time efficient to synthesize them rather than purchase them.

¹⁰ For the synthesis of compounds 30, 31, and 32, please refer to the SI of ref. 45.
To a Teflon-capped vial equipped with a magnetic stir bar was charged the crude 3-chloroketone in 15 mL of absolute EtOH. To this solution was added NaOAc (2.46 g, 45 mmol, 3 eq.). The resulting suspension was stirred at 70 °C for 20 min (monitored by TLC, 2.5 – 5% EtOAc in hexanes) then cooled to room temperature in an ice bath. The reaction mixture was added to a separatory funnel containing 30 mL of EtOAc then washed with 30 mL of distilled H₂O. The aqueous phase was extracted with 3x10 mL EtOAc, the combined organic phases were washed with brine (15 mL), then dried (MgSO₄) and concentrated under reduced pressure to afford a yellow oil which was used in the next step without further purification.

According to a modified procedure of Srivastava and Banik, 11 2-methylaminobenzyl alcohol (410 mg, 3 mmol) was added to a concentrated solution (1M) of crude α, β-unsaturated ketone in CH₂Cl₂ in a scintillation vial equipped with a magnetic stirbar. To this solution was added Bi(NO₃)₃ (290 mg, 0.6 mmol, 0.2 eq.), and the resulting suspension was stirred overnight (12 h). In the cases of methyl and ethyl vinyl ketone, no Bismuth salt was added. After complete consumption of the starting materials, the reaction mixture was filtered through a glass frit, washed with CH₂Cl₂ and then concentrated. The crude mixture was then dissolved in DMSO (10 mL) and to this solution was added IBX (925 mg, 3.3 mmol, 1.1 eq). The reaction was stirred at rt for 4h, over which time the IBX dissolved completely and the reaction mixture turned from a yellow suspension to a dark brown homogeneous solution. The reaction mixture was added to a separatory funnel with 20 mL of EtOAc and 20 mL of H₂O, and the aqueous phase was extracted with 3x10 mL of EtOAc. The combined organic phases were washed with brine, then dried (MgSO₄) and concentrated under reduced pressure to give approx. 1g of a crude, dark brown oil. The crude keto-aldehydes were purified via flash chromatography (20% EtOAc in hexanes) to furnish the pure keto-aldehydes as bright yellow oils.

2-(Methyl(3-oxobutyl)amino)benzaldehyde (28e). Prepared using General Method E from methyl vinyl ketone to provide 28e as a yellow oil (256 mg, 1.24 mmol) in 42% yield. ¹H NMR (400 MHz, CDCl₃) δ 10.23 (s, 1H, CHO), 7.78 (dd, 2H, J = 7.72, 1.72 Hz, Ar), 7.49 (m, 1H, Ar), 7.08 (m, 2H, Ar), 3.41 (t, 2H, J = 7.32 Hz, N-C₃H₂-CH₂-C(O)), 2.85 (s, 3H, N-C₃H₃), 2.72 (t, 2H, J = 7.32 Hz, N-C₃H₂-CH₂-C(O)), 2.13 (s, 3H, C(O)-C₃H₃); ¹³C NMR (100 MHz, CDCl₃) δ 207.1, 191.3, 155.1, 134.7, 130.5, 128.9, 122.2, 119.7, 51.9, 43.6, 41.4, 30.2; IR (neat) 2850, 1711, 1682, 1594, 1483, 1162, 768 cm⁻¹; LRMS (EI) m/z 205 (M+); HRMS (EI) exact mass calc’d for (C₁₂H₁₅NO₂)⁺ requires m/z 205.1103, found m/z 205.1107.

2-(Methyl(3-oxopentyl)amino)benzaldehyde (28d). Prepared using General Method E from ethyl vinyl ketone to provide 28d as a yellow oil (290 mg, 1.32 mmol) in 44% yield. ¹H NMR (400 MHz, CDCl₃) δ 10.23 (s, 1H, CHO), 7.78 (dd, 2H, J = 7.72, 1.72 Hz, Ar), 7.49 (m, 1H, Ar), 7.08 (m, 2H, Ar), 3.43 (t, 2H, J = 7.16 Hz, N-CH₂-CH₂-C(O)), 2.85 (s, 3H, N-CH₃), 2.69 (t, 2H, J = 7.32, N-CH₂-CH₂-C(O)), 2.40 (q, 2H, J = 7.32 Hz C(O)-

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CH$_2$-CH$_3$), 1.02 (t, 3H, $J = 7.32$, C(O)-CH$_2$-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 209.7, 191.2, 155.1, 134.6, 130.5, 128.9, 122.1, 119.7, 52.0, 43.6, 40.1, 36.3, 7.7; IR (neat) 2938, 1710, 1682, 1594, 1483, 1110, 766 cm$^{-1}$; LRMS (EI) m/z 219.1 (M+); HRMS (EI) exact mass calc’d for (C$_{19}$H$_{17}$NO$_2$)$^+$ requires m/z 219.1263, found m/z 219.1259.

2-((3-(4-methoxyphenyl)-3-oxopropyl)-(methyl)amino)benzaldehyde (28c). Prepared using General Method E from anisole and 3-chloropropionyl chloride to provide 28c as a yellow oil (303 mg, 1.01 mmol) in 34% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.23 (s, 1H, CHO), 7.86 (m, 2H, Ar), 7.77 (dd, 1H, $J = 7.72, 1.72$ Hz, Ar), 7.47 (m, 1H, Ar), 7.15 (m, 1H, Ar), 7.07 (m, 1H, Ar), 6.90 (m, 2H, Ar), 3.85 (s, 3H, Ar-O-C$_2$H$_3$), 3.57 (t, 2H, $J = 7.04$ Hz, N-CH$_2$-CH$_2$-C(O)), 3.20 (t, 2H, $J = 7.6$, N-CH$_2$-CH$_2$-C(O)), 2.91 (s, 3H, N-C$_3$H$_7$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 197.2, 191.3, 163.7, 155.2, 134.7, 130.5, 130.3, 129.9, 128.9, 122.1, 119.7, 113.8, 55.5, 52.9, 43.7, 36.0; IR (neat) 2389, 1669, 1596, 1256, 1169 cm$^{-1}$; LRMS (ESI+) m/z 298 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{18}$H$_{19}$NO$_3$H)$^+$ requires m/z 298.1452, found m/z 298.1437.

2-(methyl(3-oxo-3-(p-tolyl)propyl)amino)benzaldehyde (28d). Prepared using General Method E from toluene and 3-chloropropionyl chloride to provide 28d as a yellow oil (261 mg, 0.93 mmol) in 32% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.23 (s, 1H, CHO), 7.78 (m, 3H, Ar), 7.49 (m, 1H, Ar), 7.23 (m, 2H, Ar), 7.15 (m, 1H, Ar), 7.07 (m, 1H, Ar), 3.60 (t, 2H, $J = 7.52$ Hz, N-CH$_2$-CH$_2$-C(O)), 3.23 (t, 2H, $J = 6.96$, N-CH$_2$-CH$_2$-C(O)), 2.91 (s, 3H, N-CH$_3$), 2.40 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.3, 191.3, 155.1, 144.1, 134.7, 134.3, 130.5, 129.4, 128.9, 128.1, 122.1, 119.7, 52.7, 43.7, 36.3, 21.7; IR (neat) 2836, 1681, 1595, 1483, 1180, 770 cm$^{-1}$; LRMS (ESI+) m/z 288 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{18}$H$_{19}$NO$_2$H)$^+$ requires m/z 282.1480, found m/z 282.1488.

2-(methyl(3-oxo-3-phenylpropyl)amino)benzaldehyde (28a). Prepared using General Method E from benzene and 3-chloropropionyl chloride to provide 28a as a yellow oil (192 mg, 0.75 mmol) in 25% yield. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.23 (s, 1H, CHO), 7.89 (m, 2H, Ar), 7.77 (dd, 1H, $J = 7.72, 1.72$ Hz, Ar), 7.55 (m, 1H, Ar), 7.49 (m, 1H, Ar), 7.43 (m, 2H, Ar), 7.15 (m, 1H, Ar), 7.08 (m, 1H, Ar), 3.61 (t, 2H, $J = 7.48$ Hz, N-CH$_2$-CH$_2$-C(O)), 3.26 (t, 2H, $J = 7.32$, N-CH$_2$-CH$_2$-C(O)), 2.91 (s, 3H, N-CH$_3$), 2.40 (s, 3H, Ar-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.7, 191.3, 155.1, 136.8, 134.7, 133.3, 130.5, 128.9, 128.7, 128.0, 122.1, 119.7, 52.6, 43.7, 36.4; IR (neat) 3063, 2973, 1674, 1594, 1448, 1159, 945, 740, 689 cm$^{-1}$; LRMS (ESI+) m/z 268 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{17}$H$_{15}$NO$_2$H)$^+$ requires m/z 268.1339, found m/z 268.1332.
2-((3-(4-chlorophenyl)-3-oxopropyl)(methyl)amino)-benzaldehyde (28f). Prepared using General Method E from 1-methylnaphthalene and 3-chloropropionyl chloride to provide 28f as a yellow oil (926 mg, 2.7 mmol) in 93% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.22 (s, 1H, CHO), 8.63 (m, 1H, Ar), 8.05 (m, 1H, Ar), 7.75 (dd, 1H, \(J = 7.68, 1.64\) Hz, Ar), 7.72 (m, 1H, Ar), 7.57 (m, 2H, Ar), 7.48 (m, 1H), 7.30 (d, 1H, \(J = 7.36\) Hz, Ar), 7.15 (d, 1H, \(J = 8.2\) Hz, Ar), 7.07 (t, 1H, \(J = 7.48\) Hz, Ar), 3.67 (t, 2H, \(J = 7.16\) Hz, N-CH\(_2\)-CH\(_2\)-C(O)), 3.33 (t, 2H, \(J = 7.0\) Hz, N-CH\(_2\)-CH\(_2\)-C(O)), 2.92 (s, 3H, N-C\(_3\)H\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 202.3, 191.3, 155.1, 140.2, 134.7, 133.9, 133.1, 130.5, 130.2, 128.8, 127.9, 127.7, 126.4, 126.3, 125.2, 124.4, 122.1, 119.7, 52.9, 43.9, 39.6, 20.1; IR (neat) 2858, 1732, 1679, 1593, 1456, cm\(^{-1}\); LRMS (ESI+) \(m/z\) 332.2 (MH\(^+\)); HRMS (ESI+) exact mass calc’d for (C\(_{22}\)H\(_{21}\)NO\(_2\)H)\(^+\) requires \(m/z\) 332.1645, found \(m/z\) 332.1658.

2-((3-(4-fluorophenyl)-3-oxopropyl)(methyl)amino)-benzaldehyde (28g). Prepared using General Method C from fluorobenzene and 3-chloropropionyl chloride to provide 28g as a yellow oil (303 mg, 1.06 mmol) in 35% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.23 (s, 1H, CHO), 7.93 (m, 2H, Ar), 7.79 (m, 1H, Ar), 7.49 (m, 1H, Ar), 7.14 (m, 4H, Ar), 3.60 (t, 2H, \(J = 7.52\) Hz, N-CH\(_2\)-CH\(_2\)-C(O)), 3.24 (t, 2H, \(J = 7.24\) Hz, N-CH\(_2\)-CH\(_2\)-C(O)), 2.92 (s, 3H, N-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 197.0, 191.2, 167.1, 164.6, 154.9, 134.7, 133.1 (d, \(J = 3.03\) Hz), 130.7 (d, \(J = 9.4\) Hz), 129.0, 122.2, 119.7, 115.7 (d, \(J = 21.6\) Hz), 52.6, 43.7, 36.3; IR (neat) 3355, 2928, 1682, 1596, 1504, 1316, 1226, 808, 743 cm\(^{-1}\); LRMS (ESI+) \(m/z\) 286 (MH\(^+\)); HRMS (ESI+) exact mass calc’d for (C\(_{17}\)H\(_{16}\)FNO\(_2\)H)\(^+\) requires \(m/z\) 286.1239, found \(m/z\) 286.1226.

2-((3-(4-chlorophenyl)-3-oxopropyl)(methyl)amino)-benzaldehyde (28h). Prepared using General Method E from chlorobenzene and 3-chloropropionyl chloride to provide 28h as a yellow oil (362 mg, 1.2 mmol) in 40% yield. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.23 (s, 1H, CHO), 7.83 (m, 2H, Ar), 7.78 (m, 1H, Ar), 7.50 (m, 1H, Ar), 7.15 (d, 1H, \(J = 8.2\) Hz, Ar), 7.09 (t, 1H, \(J = 7.4\) Hz, Ar), 3.59 (t, 2H, \(J = 6.6\) Hz, N-CH\(_2\)-CH\(_2\)-C(O)), 2.91 (s, 3H, N-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 197.4, 191.3, 154.9, 139.8, 135.0, 134.7, 130.8, 129.4, 129.0, 128.9, 122.2, 119.7, 52.5, 43.7, 36.4; IR (neat) 3331, 2852, 1735, 1673, 1585, 1083, cm\(^{-1}\); LRMS (ESI+) \(m/z\) 302.1 (MH\(^+\)); HRMS (ESI+) exact mass calc’d for (C\(_{17}\)H\(_{16}\)ClNO\(_2\)H)\(^+\) requires \(m/z\) 302.0964, found \(m/z\) 302.0955.
2-((3-(4-bromophenyl)-3-oxopropyl)(methyl)amino)-benzaldehyde (28i). Prepared using General Method E from bromobenzene and 3-chloropropionyl chloride to provide 28i as a yellow oil (410 mg, 1.19 mmol) in 40% yield. 1H NMR (400 MHz, CDCl₃) δ 10.22 (s, 1H, CHO), 7.77 (m, 3H, Ar), 7.57 (m, 2H, Ar), 7.49 (m, 1H, Ar), 7.12 (m, 2H, Ar), 3.58 (t, 2H, J = 7.04 Hz, N-CH₃CH₂C(O)), 3.22 (t, 2H, J = 7.6, N-CH₂C₃H₇C(O)), 2.91 (s, 3H, N-CH₃); 13C NMR (100 MHz, CDCl₃) δ 197.6, 191.1, 154.9, 135.4, 134.7, 132.0, 130.7, 129.5, 128.9, 128.5, 122.2, 119.7, 52.5, 43.6, 36.4; IR (neat) 3439, 2839, 1662, 1582, 1501, 1198, 1064, 998, 730 cm⁻¹; LRMS (ESI+) m/z 346 (MH⁺); HRMS (ESI+) exact mass calc’d for (C₁₇H₁₆BrNO₂H)+ requires m/z 346.0437, found m/z 346.0437.

III. Representative procedure for enantioselective rhodium-catalyzed hydroacylation of ketones (Table 1.6, entry 1)

Inside the glove box, to a dry 25 mL Schlenk-sealed tube containing a magnetic stir bar was added a solution of [Rh(NBD)₂]BF₄ (5 mol%, 3.7 mg) and (R)-DTBM-Segphos (5.5 mol%, 13 mg) dissolved in dry and degassed CH₂Cl₂ (1 mL). The resulting solution was stirred for 2-5 min then H₂ (g) was passed through the solution for 30 min. During this time the solution changed color from orange red to deep red. The resulting solution was then degassed by freeze-pump-thaw three times and filled with Ar (g). The substrate 1a (48 mg, 0.2 mmol) was dissolved in dry and degassed CH₂Cl₂ (1 mL) and added to the above catalyst solution via syringe under Ar (g). The reaction vessel was sealed and stirred at rt for 3 days. The reaction mixture was then concentrated in vacuo and purified by flash column chromatography (10% EtOAc in hexanes) to afford the product (S)-2a as a viscous oil (40 mg) in 92% yield.

(S)-2a (Table 1.3, entry 1); 1H NMR (400 MHz, CDCl₃) δ 7.90 (dd, J = 2.0, 8.0 Hz, 1H, Ar), 7.53-7.58 (m, 1H, Ar), 7.38-7.43 (m, 5H, Ar), 7.18-7.23 (m, 1H, Ar), 7.09 (dd, J = 8.4, 1.2 Hz, 1H, Ar), 5.57 (dd, J = 2.4, 9.2 Hz, 1H, O-CH), 4.58 (dd, J = 9.2, 12.4 Hz, 1H, O-CH₂), 4.42 (dd, J = 2.4, 12.4 Hz, 1H, O-CH₂); 13C NMR (100 MHz, C₆D₆) δ 167.4, 155.7, 135.6, 134.9, 134.1, 129.17, 129.16, 127.0, 123.6, 122.0, 121.4, 77.9, 76.6; IR (film): 1730, 1603, 1479, 1295, 1116, 755, 699 cm⁻¹; LRMS (EI) m/z: 240 (M)⁺, 241 (MH⁺); HRMS exact mass calc’d for C₁₅H₁₂O₃ requires m/z 240.0786, found m/z 240.0786; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 60/40, flow rate 1.0 mL/min, detection 225 nm, tₖ₁: 12.7 min and tₖ₂: 19.9 min); [α]D²⁷ = +159.1° (c = 0.93, CHCl₃).
(S)-2b (Table 1.3, entry 2): 86% yield, white solid; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.88 (dd, $J = 1.2$, 5.7 Hz, 1H, Ar), 7.52-7.57 (m, 1H, Ar), 7.37 (s, 4H, Ar), 7.17-7.22 (m, 1H, Ar), 7.08 (dd, $J = 6.3$, 0.6 Hz, 1H, Ar), 5.54 (dd, $J = 2.0$, 7.2 Hz, 1H, COO-CH), 4.52 (dd, $J = 7.2$, 9.3 Hz, 1H, O-CH$_2$), 4.39 (dd, $J = 2.0$, 9.3 Hz, 1H, O-CH$_2$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 167.7, 154.7, 135.05, 135.02, 133.1, 132.8, 129.1, 127.9, 123.6, 121.1, 121.2, 121.0, 77.1, 76.2; IR (film): 2918, 1732, 1603, 1479, 1295, 1109, 814, 752 cm$^{-1}$; LRMS (EI) $m/z$ 274 ($^{35}$M)$^+$, 276 ($^{37}$M)$^+$; HRMS exact mass calc’d for C$_{15}$H$_{11}$ClO$_3$ requires $m/z$ 274.0397, found $m/z$ 274.0393; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 80/20, flow rate 2.0 mL/min, detection 225 nm, $t_R1$: 8.8 min and $t_R2$: 11.3 min); $\left[\alpha\right]^{25}_{D} = +160.4^\circ$ (c = 1.0, CHCl$_3$).

(S)-2c (Table 1.3, entry 3): 80% yield, yellow solid; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (m, 5H, Ar), 7.49-7.59 (m, 4H, Ar), 7.22 (t, $J = 8.0$ Hz, 1H, Ar), 7.12 (d, $J = 8.4$ Hz, 1H, Ar), 5.74 (dd, $J = 2.4$, 9.2 Hz, COO-CH), 4.66 (dd, $J = 9.2$, 12.4 Hz, 1H, O-CH$_2$), 4.51 (dd, $J = 2.4$, 12.4 Hz, 1H, O-CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.1, 154.9, 135.0, 133.4, 133.1, 131.5, 128.8, 128.1, 127.7, 126.71, 126.66, 126.0, 123.6, 123.5, 121.2, 121.1, 77.9, 76.4; IR (film): 1717, 1603, 1478, 1295, 1109, 756 cm$^{-1}$; LRMS (EI) $m/z$ 290 (M)$^+$, 291 (MH)$^+$; HRMS exact mass calc’d for C$_{19}$H$_{14}$O$_3$ requires $m/z$ 290.0943, found $m/z$ 290.0937; HPLC analysis: 97% ee (DAICEL CHIRALCEL AD, eluent, hexane/2-propanol = 90/10, flow rate 1.0 mL/min, detection 225 nm, $t_{R1}$: 18.5 min and $t_{R2}$: 24.1 min); $\left[\alpha\right]^{27}_{D} = +168.9^\circ$ (c = 0.81, CHCl$_3$).

(S)-2d (Table 1.3, entry 4): 85% yield, oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.86 (dd, $J = 1.5$, 6.0 Hz, 1H, Ar), 7.45-7.50 (m, 1H, Ar), 7.47-7.14 (m, 1H, Ar), 7.00 (dd, $J = 0.9$, 6.3 Hz, 1H, Ar), 4.68-4.78 (m, 1H, COO-CH), 4.32 (dd, $J = 12.3$, 21.6 Hz, 1H, O-CH$_2$), 4.30 (dd, $J = 12.3$, 16.5 Hz, 1H, O-CH$_2$), 1.41 (d, $J = 4.8$ Hz, 3H, CH$_3$); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 168.5, 155.1, 134.7, 133.3, 122.9, 120.9, 120.4, 75.6, 72.4, 16.3; IR (film) 2936, 1722, 1604, 1480, 1295, 1115, 755, 706 cm$^{-1}$; LRMS (EI) $m/z$ 178 (M)$^+$, 179 (MH)$^+$; HRMS exact mass calc’d for C$_{10}$H$_{10}$O$_3$ requires
m/z 178.0630, found m/z 178.0625; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 92/8, flow rate 1.0 mL/min, detection 225 nm, t_R1: 19.5 min and t_R2: 23.2 min); [α]^{25}_D = +87.7° (c = 1.5, CHCl_3).

(S)-2e (Table 1.3, entry 5): 97% yield, oil; ^1H NMR (400 MHz, CDCl_3) δ 7.89 (dd, J = 2.0, 9.6 Hz, 1H, Ar), 7.46-7.51 (m, 1H, Ar), 7.12 (t, J = 7.2 Hz, 1H, Ar), 7.00 (d, J = 8.0 Hz, 1H, Ar), 4.49-4.53 (m, 1H, COO-CH), 4.29-4.38 (m, 2H, O-CH_2), 1.25-1.82 (m, 6H, (CH_2)_3), 0.91 (t, J = 7.2 Hz, 3H, CH_3); ^13C NMR (100 MHz, CDCl_3) δ 168.6, 155.2, 134.7, 133.4, 122.8, 120.8, 120.2, 76.2, 74.7, 30.4, 27.3, 22.4, 13.8; IR (film): 2956, 1726, 1605, 1480, 1295, 1116, 755, 706 cm^{-1}; LRMS (EI) m/z 220 (M)^+, 221 (MH)^+; HRMS exact mass calc’d for C_{13}H_{16}O_3 requires m/z 220.1099, found m/z 220.1093; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 93/7, flow rate 1.0 mL/min, detection 225 nm, t_R1: 12.1 min and t_R2: 14.7 min); [α]^{25}_D = +66.3° (c = 1.64, CHCl_3).

(S)-2f (Table 1.3, entry 6): 100% yield, oil; ^1H NMR (400 MHz, CDCl_3) δ 7.83-7.85 (m, 1H, Ar), 7.41-7.45 (m, 1H, Ar), 7.20-7.30 (m, 5H, Ar), 7.07 (t, J = 7.2 Hz, 1H, Ar), 6.93 (d, J = 8.0 Hz, 1H, Ar), 4.67-4.73 (m, 1H, COO-CH), 4.31 (d, J = 5.2 Hz, 2H, CH_2-Ph), 3.11 (dd, J = 14.4, 7.0 Hz, 1H, O-CH_2), 2.88 (dd, J = 14.4, 7.0 Hz, 1H, O-CH_2); ^13C NMR (100 MHz, CDCl_3) δ 168.1, 155.2, 135.6, 134.8, 133.5, 129.4, 128.8, 127.2, 122.8, 120.8, 119.9, 76.9, 73.8, 37.2; IR (film): 2925, 1721, 1604, 1480, 1450, 1294, 1238, 1120, 754, 701 cm^{-1}; LRMS (EI) m/z 254 (M)^+, 255 (MH)^+; HRMS exact mass calc’d for C_{16}H_{14}O_3 requires m/z 254.0943, found m/z 254.0940; HPLC analysis: >99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 90/10, flow rate 1.5 mL/min, detection 225 nm, t_R1: 21.3 min and t_R2: 23.3 min); [α]^{27}_D = +41.4° (c = 0.72, CHCl_3).

(S)-2g (Table 1.3, entry 7): 96% yield, oil; ^1H NMR (400 MHz, CDCl_3) δ 7.91 (dd, J = 1.6, 8.0 Hz, 1H, Ar), 7.46-7.50 (m, 1H, Ar), 7.11 (d, J = 8.4 Hz, 1H, Ar), 7.00 (d, J = 8.4 Hz, 1H, Ar), 4.34-4.43 (m, 2H, O-CH_2), 4.26-4.30 (m, 1H, COO-CH), 2.00-2.09 (m, 1H, CH(CH_2)_2), 1.07 (d, J = 6.8 Hz, 3H, CH_3), 1.04 (d, J = 6.8 Hz, 3H, CH_3); ^13C NMR (100 MHz, CDCl_3) δ 168.6, 155.3, 134.7, 133.6, 122.5, 120.6, 119.6, 80.6, 73.2, 30.0, 18.4, 17.7; IR (film):
2966, 1713, 1605, 1480, 1295, 1116, 754 cm\(^{-1}\); LRMS (EI) \text{m/z} 206 (M\(^{+}\)), 207 (MH\(^{+}\)); HRMS exact mass calc’d for C\(_{12}\)H\(_{14}\)O\(_3\) requires \text{m/z} 206.0943, found \text{m/z} 206.0940; HPLC analysis: >99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 93/7, flow rate 1.0 mL/min, detection 225 nm, \(t\text{R1: 11.1 min and } t\text{R2: 13.9 min}\); \([\alpha]^{27}_{D} = +67.7^o\) (c = 1.4, CHCl\(_3\)).

\[\text{(S)-2h (Table 1.3, entry 8): 90% yield; oil; } \text{\`H NMR (400 MHz, CDCl}\(_3\}) \delta 7.90 (dd, J = 1.6, 7.6 Hz, 1H, Ar), 7.46-7.50 (m, 1H, Ar), 7.08-7.12 (m, 1H, Ar), 6.99 (d, J = 8.4 Hz, 1H, Ar), 4.50 (dd, J = 1.6, 12.8 Hz, 1H, O-CH\(_2\)), 4.30 (dd, J = 7.6, 12.8 Hz, 1H, COO-CH\(_2\)), 4.14 (dd, J = 1.6, 7.6 Hz, 1H, O-CH), 1.06 (s, 9H, C(CH\(_3\)_3)); \text{\`C NMR (100 MHz, CDCl}\(_3\}) \delta 168.7, 155.3, 134.7, 133.6, 122.4, 120.6, 119.4, 83.2, 72.1, 33.6, 25.7; \text{IR (film): 2960, 1711, 1606, 1481, 1296, 1122, 752 cm}\(^{-1}\); LRMS (EI) \text{m/z} 220 (M\(^{+}\)), 221 (MH\(^{+}\)); HRMS exact mass calc’d for C\(_{13}\)H\(_{16}\)O\(_3\) requires \text{m/z} 220.1099, found \text{m/z} 220.1094; HPLC analysis: >99% ee (DAICEL CHIRALCEL OJ, eluent, hexane/2-propanol = 95/5, flow rate 1.0 mL/min, detection 225 nm, \(t\text{R1: 9.0 min and } t\text{R2: 11.7 min}\); \([\alpha]^{27}_{D} = +61.4^o\) (c = 0.93, CHCl\(_3\)).

\[\text{(S)-2i (Table 1.6, entry 2) white solid, mp 91-93 \degree C; } \text{\`H NMR (400 MHz, CDCl}\(_3\}) \delta 4.44 (dd, J = 2.4, 12.4 Hz, 1H), 4.55 (dd, J = 9.3, 12.4 Hz, 1H), 5.64 (dd, J = 2.4, 9.3 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.55-7.59 (m, 3H), 7.68 (d, J = 8.3 Hz, 2H), 7.91 (dd, J = 1.7, 7.8Hz, 1H); \text{\`C NMR (100 MHz, CDCl}\(_3\}) \delta 168.7, 155.3, 134.7, 133.6, 122.4, 120.6, 119.4, 83.2, 72.1, 33.6, 25.7; \text{IR (neat): 1683, 1606, 1484, 1309, 1121, 1112, 825, 754 cm}\(^{-1}\); MS (EI) \text{m/z}: 308 (M\(^{+}\)), 173, 134, 105, 92, 76, 69; HRMS (EI) Calcd for C\(_{16}\)H\(_{11}\)F\(_3\)O\(_3\): 308.0660, found: 308.0657; HPLC analysis: 99% ee (DAICEL CHIRALCEL AD, eluent, hexane/2-propanol = 90:10, flow rate 1.0 ml/min, detection 235 nm light, \(t\text{R1: 13.2 min and } t\text{R2: 16.4 min}\); \([\alpha]^{25}_{D} = +135.1^o\) (c = 1.08, CHCl\(_3\)).

\[\text{(S)-2j (Table 1.6, entry 3) white solid, mp 139-142 \degree C; } \text{\`H NMR (400 MHz, CDCl}\(_3\}) \delta 3.92 (s, 3H), 4.44 (dd, J = 2.5, 12.4 Hz, 1H), 4.55 (dd, J = 9.3, 12.4 Hz, 1H), 5.63 (dd, J = 2.4, 9.3 Hz, 1H), 7.09 (d, J = 8.2 Hz, 1H), 7.21 (dt, J =
0.8, 7.6 Hz, 1H), 7.51-7.58 (m, 3H), 7.90 (dd, J = 1.7, 7.9 Hz, 1H), 8.07 (dd, J = 8.3 Hz, 2H); $^{13}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 52.3, 76.1, 77.3, 120.9, 121.2, 123.6, 126.4, 130.1, 130.8, 133.1, 135.1, 139.1, 154.8, 166.4, 167.7; IR (neat): 1717, 1602, 1279, 1113, 767 cm$^{-1}$; MS (EI) m/z: 298 (M$^+$), 299 (M+1)$^+$, 267, 149, 134, 133, 105, 77; HRMS (EI) Calcd for C$_{17}$H$_{14}$O$_5$: 298.0841, found: 298.0846; HPLC analysis: 99% ee (DAICEL CHIRALCEL OJ, eluent, hexane:2-propanol = 70:30, flow rate 1.0 ml/min, detection 235 nm light, $t_{R1}$: 20.3 min and $t_{R2}$: 30.4 min); $[\alpha]^{25}_D = +109.2^\circ$ (c = 0.87, CHCl$_3$).

(S)-2k (Table 1.6, entry 5) white solid, mp 99-101 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 4.39 (dd, J = 2.4, 12.3 Hz, 1H), 4.55 (dd, J = 9.6, 12.3 Hz, 1H), 5.55 (dd, J = 2.4, 9.6 Hz, 1H), 7.07-7.11 (m, 3H), 7.20 (t, J = 7.6 Hz, 1H), 7.39-7.43 (m, 2H), 7.53-7.57 (m, 1H), 7.88 (dd, J = 1.5, 7.8 Hz, 1H); $^{13}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 76.3 (d, J = 1.1 Hz), 77.2, 115.9 (d, J = 22.1 Hz), 121.1, 121.2, 123.6, 128.4 (d, J = 8.4 Hz), 130.1 (d, J = 3.3 Hz), 133.0, 135.0, 154.8, 163.0 (d, J = 245.2 Hz), 167.8; IR (neat): 1719, 1602, 1293, 1221, 1088, 762 cm$^{-1}$; MS (EI) m/z: 258 (M$^+$), 259 (M+1)$^+$, 239, 183, 149, 134, 105; HRMS (EI) Calcd for C$_{15}$H$_{13}$FO$_3$: 258.0692, found: 258.0692; HPLC analysis: 99% ee (DAICEL CHIRALCEL AD, eluent, hexane:2-propanol = 90:10, flow rate 1.0 ml/min, detection 235 nm light, $t_{R1}$: 13.7 min and $t_{R2}$: 17.7 min); $[\alpha]^{25}_D = +161.0^\circ$ (c = 0.62, CHCl$_3$).

(S)-2l (Table 1.6, entry 6) colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.36 (s, 3H), 4.39 (dd, J = 2.4, 12.3 Hz, 1H), 4.57 (dd, J = 9.6, 12.3Hz, 1H), 5.53 (dd, J = 2.4, 9.6 Hz, 1H), 7.08 (dd, J = 1.0, 8.2 Hz, 1H), 7.18-7.22 (m, 3H), 7.31 (d, J = 8.1 Hz, 2H), 7.52-7.57 (m, 1H), 7.89 (dd, J = 1.8, 7.9 Hz, 1H); $^{13}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 21.2, 76.4, 77.7, 121.2, 121.3, 123.5, 126.5, 129.5, 131.2, 132.9, 134.9, 139.0, 154.8, 168.1; IR (neat): 1724, 1604, 1480, 1449, 1291, 1114 cm$^{-1}$; MS (EI) m/z: 254 (M$^+$), 255 (M+1)$^+$, 235, 221, 149, 134, 121, 120, 105, 92; HRMS (EI) Calcd for C$_{16}$H$_{14}$O$_5$: 254.0943, found: 254.0938; HPLC analysis: 99% ee (DAICEL CHIRALCEL AD, eluent, hexane:2-propanol = 90:10, flow rate 1.0 ml/min, detection 235 nm light, $t_{R1}$: 12.1 min and $t_{R2}$: 16.1 min); $[\alpha]^{25}_D = +162.3^\circ$ (c = 0.61, CHCl$_3$).
(S)-2m (Table 1.6, entry 7) white solid, mp 98 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.82 (s, 3H), 4.37 (dd, $J$ = 2.4, 12.3 Hz, 1H), 4.58 (dd, $J$ = 9.7, 12.3Hz, 1H), 5.51 (dd, $J$ = 2.4, 9.7 Hz, 1H), 6.92 (d, $J$ = 8.7 Hz, 2H), 7.08 (d, $J$ = 8.3 Hz, 1H), 7.20 (t, $J$ = 7.6 Hz, 1H), 7.34 (d, $J$ = 8.8 Hz, 2H), 7.52-7.57 (m, 1H), 7.88 (dd, $J$ = 1.7, 7.8 Hz, 1H); $^{12}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 55.3, 76.4, 77.6, 114.3, 121.2, 121.4, 123.5, 126.2, 128.0, 132.9, 134.9, 154.8, 160.2, 168.2; IR (neat): 1716, 1602, 1515, 1456, 1287, 1237, 1110, 1027, 772 cm$^{-1}$; MS (EI) $m/z$: 270 (M$^+$), 149, 136, 135, 121, 91, 86, 84, 77; HRMS (EI) Calcd for C$_{16}$H$_{14}$O$_4$: 270.0892, found: 270.0896; HPLC analysis: 32% ee (DAICEL CHIRALCEL AD, eluent, hexane:2-propanol = 90:10, flow rate 1.0 ml/min, detection 225 nm light, $t_{R1}$: 18.5 min and $t_{R2}$: 25.3 min); $[^2]D$ = +15.8° (c = 0.215, CHCl$_3$).

(S)-2n (Table 1.6, entry 14) Colorless, cloudy oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$4.52 (dd, $J$ = 2.6, 12.2 Hz, 1H), 4.80 (dd, $J$ = 9.7, 12.2 Hz, 1H), 5.60 (dd, $J$ = 2.6, 9.7 Hz, 1H), 6.40 (dd, $J$ = 3.0, 9.0 Hz, 1H), 6.48 (d, $J$ = 3.0 Hz, 1H), 7.03 (dd, $J$ = 1.0, 9.0 Hz, 1H), 7.21(dt, $J$ = 1.1, 7.6 Hz, 1H), 7.52-7.58 (m, 1H), 7.89 (dd, $J$ = 1.7, 7.9 Hz, 1H); $^{12}$C NMR (100 MHz, CDCl$_3$) $\delta$ 71.7, 73.4, 110.4, 110.9, 121.5, 121.6, 124.0, 133.2, 143.1, 147.1, 155.0, 167.8; IR (neat): 3242, 1726, 1289, 1112, 703 cm$^{-1}$; MS (ESI) $m/z$: 231 (M+H)$^+$, 253 (M+Na)$^+$, 269 (M+K)$^+$; HRMS (ESI) Calcd for (C$_{13}$H$_{10}$O$_3$+H)$^+$: 231.0657, found: 231.0651.

(S)-2o (Table 1.6, entry 15) Colorless, cloudy oil; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 4.50 (dd, $J$ = 2.5, 12.2 Hz, 1H), 4.70 (dd, $J$ = 9.6, 12.2 Hz, 1H), 5.83 (dd, $J$ = 2.5, 9.6 Hz, 1H), 7.03 (dd, $J$ = 3.6, 5.0 Hz, 1H), 7.08-7.13 (m, 2H), 7.21 (dt, $J$ = 1.0, 7.6 Hz, 1H), 7.37 (dd, $J$ = 1.1, 5.0 Hz, 1H), 7.53-7.58 (m, 1H), 7.88 (dd, $J$ = 1.7, 7.8 Hz, 1H); $^{12}$C NMR (100 MHz, CDCl$_3$) $\delta$ 73.9, 75.8, 121.3, 121.4, 123.8, 126.6, 126.7, 127.0, 133.0, 135.0, 135.9, 154.7, 167.4; IR (neat): 3241, 1726, 1289, 1112, 703 cm$^{-1}$; MS (ESI) $m/z$: 247 (M+H)$^+$, 269 (M+Na)$^+$; HRMS (ESI) Calcd for (C$_{13}$H$_{10}$O$_3$+S+H)$^+$: 247.0429, found: 247.0423.
5o (Table 1.6, entry 15) white solid, mp 65-67 °C; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.24-7.27 (m, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.48-7.54 (m, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.73-7.78 (m, 3H), 8.34 (dd, J = 1.0, 3.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 112.4, 114.6, 123.2, 124.0, 127.0, 128.1, 128.4, 134.6, 142.3, 152.6, 155.8, 175.1; IR (neat): 1608, 1550, 1410, 1292, 1236, 826, 726 cm$^{-1}$; MS (EI) m/z: 228 (M)$^+$, 229 (M+1)$^+$, 200, 111; HRMS (EI) Calcd for C$_{13}$H$_8$O$_2$S: 228.0245, found: 228.0245.

2p (Scheme 1.8) Pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 1.35 (d, J = 6.7 Hz, 3H), 1.43 (d, J = 6.6 Hz, 3H), 4.39 (qd, J = 6.6, 2.2 Hz, 1H), 4.70 (qd, J = 6.7, 2.2 Hz, 1H), 7.01 (dd, J = 8.2, 0.8 Hz, 1H), 7.13 (m, 1H), 7.49 (m, 1H), 7.83 (dd, J = 7.9, 1.8 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 14.7, 15.8, 74.4, 80.4, 121.5, 121.7, 123.4, 132.9, 135.0, 154.8, 168.9; IR (neat) 2988, 1720, 1291, 1115, 766 cm$^{-1}$; MS (EI) m/z: 192 (M)$^+$, 141; HRMS (EI) Calcd for C$_{11}$H$_{12}$O$_3$: 192.0786, found: 192.0781.

2q (Scheme 1.8) Clear, colorless crystals; mp: 140-142 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.40 (d, J = 3.4 Hz, 1H), 5.89 (d, J = 3.4 Hz, 1H), 6.96-6.99 (m, 2H), 7.05-7.07 (m, 2H), 7.16-7.30 (m, 6H), 7.32 (dt, J = 1.1, 7.6 Hz, 2H), 7.61-7.66 (m, 1H), 7.87 (dd, J = 1.7, 7.7 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 79.5, 88.2, 122.0, 123.5, 124.8, 126.7, 127.8, 128.1, 128.25, 128.31, 128.7, 132.0, 133.6, 134.5, 135.0, 154.4, 168.4; IR (neat) 2924, 1738, 1600, 766, 701 cm$^{-1}$; MS (ESI) m/z: 339 (M+Na)$^+$; HRMS (ESI) Calcd for (C$_{21}$H$_{16}$O$_3$+Na)$^+$: 339.1002, found: 339.0991.

2a-D (Scheme 1.10) colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.41 (d, J = 12.4 Hz, 1H), 4.58 (d, J = 12.4Hz, 1H), 7.09 (dd, J = 1.1, 8.2 Hz, 1H), 7.18-7.23 (m, 1H), 7.37-7.44 (m, 5H), 7.53-7.57 (m, 1H), 7.89 (dd, J = 1.1, 8.2
Hz, 1H); $^{13}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 77.7 (t, $J = 22.8$ Hz), 121.48, 121.53, 123.8, 126.8, 129.1, 129.2, 129.3, 133.2, 134.4, 135.2, 155.1, 168.3; IR (neat): 1729, 1599, 1476, 1449, 1291, 1217, 1109 cm$^{-1}$; MS (EI) m/z: 241 (M)$^+$, 242 (M+1)$^+$, 222, 149, 134, 121, 105, 92; HRMS (EI) Calcd for C$_{15}$H$_{11}$DO$_3$: 241.0849, found: 241.0848;

(+)-2s (Scheme 1.13) white solid, mp 137-140 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 3.25 (t, $J = 11.9$ Hz, 1H), 3.40 (dd, $J = 12.5$ Hz, 3.5 Hz, 1H), 5.14 (dd, $J = 11.8$ Hz, 3.5 Hz, 1H), 7.33-7.40 (m, 5H), 7.47-7.53 (m, 2H), 7.57-7.60 (m, 1H), 7.68-7.70 (m, 1H); $^{13}$C NMR (100 M Hz, CDCl$_3$) $\delta$ 40.0, 78.7, 126.5, 129.0, 129.1, 129.3, 129.5, 131.0, 133.0, 134.1, 137.1, 169.5; IR (neat): 2917, 1724, 1440, 1101, 724 cm$^{-1}$; MS (EI) m/z: 256 (M)$^+$, 238; HRMS (EI) Calcd for C$_{15}$H$_{12}$O$_2$: 256.0558, found: 256.0558; HPLC analysis: 99% ee (DAICEL CHIRALCEL AD, eluent, hexane:2-propanol = 90:10, flow rate 1.0 ml/min, detection 235 nm light, $t_R1$: 16.8 min and $t_R2$: 22.6 min); [a]$^\lambda$ D = +342.9° (c = 0.59, CHCl$_3$).

IV. Representative procedure for enantioselective rhodium-catalyzed hydroacylation of ketones to form benzo[e][1,4]oxazepinones

Inside the glove box, to a dry 25 mL Schlenk-sealed tube containing a magnetic stir bar was added a solution of [Rh(NBD)$_2$]BF$_4$ (5 mol%, 3.7 mg) and (R)-DTBM-Segphos (5.5 mol%, 13 mg) dissolved in dry and degassed CH$_2$Cl$_2$ (1 mL). On a Schlenk manifold, the reaction vessel was cooled in a N$_2$(g) bath, evacuated then refilled with H$_2$(g). The solution was thawed and then stirred under an atmosphere of H$_2$(g) for 30 min. During this time the solution changed color from orange red to deep red. The resulting solution was then degassed by freeze-pump-thaw three times and finally filled with Ar(g). Substrate 1w (52 mg, 0.2 mmol) was dissolved in dry and degassed CH$_2$Cl$_2$ (0.2 mL). Both the catalyst and substrate solutions were cooled in the glovebox freezer (temperature: −35 °C) for 30 minutes before the substrate solution was added to the catalyst solution. The reaction vessel was sealed and left to stand in the glovebox freezer. The reaction mixture was then concentrated in vacuo and purified by flash column chromatography (20% EtOAc in hexanes) to afford the product 2c as a light yellow oil (47 mg) in 91% yield.

(S)-1-methyl-3-phenyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (2w). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (dd, 1H, $J = 7.6$, 1.6 Hz, Ar), 7.51 (m, 2H, Ar), 7.44 (m, 2H, Ar), 7.37 (m, 3H, Ar), 7.03 (m, 1H, Ar), 6.92 (d, 1H, $J = 8.0$ Hz, Ar), 5.47 (dd, 1H, $J = 11.6$, 2.8 Hz, C(O)-O-CH-Ph), 3.79 (t, 1H, $J = 11.6$ Hz, N-CH$_3$H$_b$), 3.20 (dd, 1H, $J = 12.0$, 3.2, N-CH$_2$H$_b$), 2.88 (s, 3H, N-CH$_3$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.5, 147.7, 136.1, 133.9, 132.1, 128.7,
128.6, 126.5, 123.4, 121.0, 117.2, 78.1, 63.7, 39.8; IR (neat) 2859, 1715, 1681, 1600, 1303 cm\(^{-1}\); LRMS (ESI+) \(m/z\) 254.1 (MH\(^+\)), 276.1 (MNa\(^+\)); HRMS (ESI+) exact mass calc’d for \((C_{16}H_{25}NO_{2})^+\) requires \(m/z\) 254.1175, found \(m/z\) 254.1163; HPLC analysis: 85% ee (DAICEL CHIRALPAK ADH, eluted in 1:9 iPrOH:hexanes, flow rate 1 mL/min, detection: 254 nm, \(t_{R1}: 11.69\) min, \(t_{R2}: 18.78\) min); \([\alpha]^{25}_{D} = -163.2^\circ\) (c = 0.60, CHCl\(_3\)).

**>(S)-1,3-dimethyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (2x)** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.61 (dd, 1H, J = 7.6, 1.2 Hz, Ar), 7.38 (m, 1H, Ar), 6.94 (d, 1H, J = 7.6 Hz, Ar), 6.83 (m, 1H, Ar), 4.59 (s, 1H, C(O)-O-CH-CH\(_3\)), 3.51 (t, 1H, J = 11.2 Hz, N-CH\(_3\)H\(_b\)), 3.02 (dd, 1H, J = 11.6, 2.8, N-CH\(_3\)H\(_b\)), 2.85 (s, 3H, N-CH\(_3\)), 1.41 (d, 3H, J = 6.4 Hz, C(O)-O-CH-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.1, 147.9, 133.7, 132.0, 123.6, 120.8, 117.2, 72.4, 64.1, 39.9, 17.8; IR (neat) 2939, 1712, 1692, 1600, 1306 cm\(^{-1}\); LRMS (ESI+) \(m/z\) 192.1 (MH\(^+\)), 214 (MNa+); HRMS (ESI+) exact mass calc’d for \((C_{11}H_{23}NO_{2})^+\) requires \(m/z\) 192.1019, found \(m/z\) 192.1024; HPLC analysis: 75% ee (DAICEL CHIRALPAK ADH, eluted in 1:9 iPrOH:hexanes, flow rate 1 mL/min, detection: 254 nm, \(t_{R1}: 28.93\) min, \(t_{R2}: 33.60\) min); \([\alpha]^{25}_{D} = -145.7^\circ\) (c = 0.65, CHCl\(_3\)).

**>(S)-1,3-dimethyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (2y)** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64 (dd, 1H, J = 7.6, 1.2 Hz, Ar), 7.41 (m, 1H, Ar), 6.94 (m, 1H, Ar), 6.83 (m, 1H, Ar), 4.37 (m, 1H, C(O)-O-CH-\(n\)-Bu), 3.48 (t, 1H, J = 11.2 Hz, N-CH\(_3\)H\(_b\)), 3.00 (dd, 1H, J = 11.6, 2.4, N-CH\(_3\)H\(_b\)), 2.83 (s, 3H, N-CH\(_3\)), 1.74 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_3\)), 1.59 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_3\)), 1.32 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_3\)), 0.89 (t, 3H, J = 7 Hz, CH\(_2\)-CH\(_2\)-CH\(_2\)-CH\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 167.6, 148.1, 133.9, 132.2, 123.8, 120.9, 117.3, 62.0, 40.2, 32.1, 27.8, 22.7, 14.1; IR (neat) 2926, 1721, 1443, 1365 cm\(^{-1}\); LRMS (ESI+) \(m/z\) 234.1 (MH\(^+\)), 256.1 (MNa+); HRMS (ESI+) exact mass calc’d for \((C_{15}H_{25}NO_{2})^+\) requires \(m/z\) 234.1488, found \(m/z\) 234.1493; HPLC analysis: 93% ee (DAICEL CHIRALPAK ADH, eluted in 1:9 iPrOH:hexanes, flow rate 1 mL/min, detection: 254 nm, \(t_{R1}: 7.056\) min, \(t_{R2}: 8.526\) min); \([\alpha]^{25}_{D} = -164.25^\circ\) (c = 1.2, CHCl\(_3\)).

**>(S)-1,3-dimethyl-2,3-dihydrobenzo[e][1,4]oxazepin-5(1H)-one (2z)** \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.66 (dd, 1H, J = 7.6, 1.6 Hz, Ar), 7.42 (m, 1H, Ar), 6.94 (m, 1H, Ar), 6.83 (d, 1H, J = 8.4 Hz, Ar), 4.04 (dd, 1H, J = 11.2, 2.8 Hz, C(O)-O-CH-\(t\)-Bu), 3.54 (t, 1H, J = 11.6 Hz, N-CH\(_3\)H\(_b\)), 3.06 (dd, 1H, J = 11.6, 2.8, N-CH\(_3\)H\(_b\)), 2.86 (s, 3H, N-CH\(_3\)), 1.02 (s, 9H, -C(CH\(_3\))\(_3\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 171.3, 147.9, 133.7, 132.1, 123.4, 120.6, 117.2, 83.4, 57.6, 40.4, 33.7, 26.1; IR (neat) 2957, 1715, 1600, 1453, 1307, 1118, 758 cm\(^{-1}\); LRMS (ESI+) \(m/z\) 234.1 (MH\(^+\)), 256.1 (MNa+); HRMS (ESI+) exact mass calc’d for \((C_{14}H_{19}NO_{2})^+\) requires \(m/z\) 234.1488, found \(m/z\) 234.1488; HPLC analysis: 50% ee (DAICEL CHIRALPAK ADH, eluted in 1:9 iPrOH:hexanes, flow rate 1 mL/min, detection: 254 nm, \(t_{R1}: 5.78\) min, \(t_{R2}: 6.79\) min); \([\alpha]^{25}_{D} = -115.6^\circ\) (c = 0.8, CHCl\(_3\)).
V. Representative procedure for enantioselective rhodium-catalyzed hydroacylation of ketones to form 8-membered lactones

Inside the glove box, to a dry 25 mL Schlenk-sealed tube containing a magnetic stir bar was added a solution of [Rh(NBD)₂]BF₄ (5 mol%, 3.7 mg) and (R)-DTBM-Segphos (5.5 mol%, 13 mg) dissolved in dry and degassed CH₂Cl₂ (1 mL). On a Schlenk manifold, the reaction vessel was cooled in a liq N₂ bath, evacuated then refilled with H₂ (g). The solution was thawed and then stirred under an atmosphere of H₂ (g) for 30 min. During this time the solution changed color from orange red to deep red. The resulting solution was then degassed by freeze-pump-thaw three times and filled with Ar (g). The substrate 28e (60 mg, 0.2 mmol) was dissolved in dry and degassed CH₂Cl₂ (1 mL) and added to the above catalyst solution via syringe under Ar (g) in the glove box. The reaction vessel was sealed and stirred at rt for 30 h. The reaction mixture was then concentrated in vacuo and purified by flash column chromatography (20% EtOAc in hexanes) to afford the product 4e as a light yellow oil (50.5 mg) in 84% yield. (Author’s note: The 2-aminoarylester functional group fluoresces brightly compared to typical aromatic organic compounds. Presence of the lactone products of the type 2 and 4 can be determined by holding a UV lamp up to a reaction vessel and observing by eye the level of fluorescence. This is by no means quantifiable, but it is an interesting sidenote.)

(S)-1-methyl-4-phenyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (29a) White solid, mp: 151 – 155 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.50 (m, 1H, Ar), 7.34 (m, 1H, Ar), 7.28 (m, 2H, Ar), 7.16 (m, 1H, Ar), 6.72 (m, 2H, Ar), 5.34 (dd, 1H, J = 15.40, 3.88 Hz, C(O)-O-CH-Ar), 3.78 (ddd, 1H, J = 21.16, 15.56, 3.44, N-CH₂H₆), 3.33 (ddd, 1H, J = 21.32, 5.36, 3.40, N-CH₂H₆), 3.11 (s, 3H, N(CH₃)₂), 2.52 (s, 3H, Ph-CH₃), 2.22 (m, 1H, N-CH₂-CH₂H₆-CH₂-), 2.10 (m, 1H, N-CH₂-CH₂H₆-CH₂-); ¹³C NMR (100 MHz, CDCl₃) δ 173.3, 148.1, 139.0, 134.3, 132.5, 128.6, 128.2, 126.0, 116.4, 115.3, 112.6, 49.4, 39.6, 36.5; IR (neat) 2923, 1687, 1505, 1228, 1087, 808, 742 cm⁻¹; LRMS (ESI+) m/z 282 (MH+); HRMS (EI) exact mass calc’d for (C₁₇H₁₇NO₃)⁺ requires m/z 267.1259, found m/z 267.1257; HPLC analysis: 96% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, tᵣ₁: 5.19 min, tᵣ₂: 6.63 min); [α]°D = -117.1° (c = 1.10, CHCl₃).

(R)-4-ethyl-1-methyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (29b). ¹H NMR (400 MHz, CDCl₃) δ 7.48 (dd, 1H, J = 7.8, 1.76 Hz, Ar), 7.29 (m, 1H, Ar), 6.67 (m, 2H, Ar), 4.24 (m, 1H, C(O)-O-CH-Et), 3.63 (ddd, 1H, J = 15.92, 11.92, 2.36, N-CH₂H₆), 3.24 (ddd, 1H, J = 15.96, 4.24, 2.64, N-CH₂H₆), 3.03 (s, 3H, N-CH₃), 2.00 (m, 1H, N-CH₂-CH₂H₆-CH₂-), 1.73 (m, 2H, C(O)-CH₂CH₂-CH₂-), 1.63 (m, 1H, N-CH₂-CH₂H₆-CH₂-); ¹³C NMR (100 MHz, CDCl₃) δ 174.1, 148.0, 134.0, 132.2, 116.1, 115.6, 112.4, 77.4, 49.0, 39.5, 33.7, 27.8, 9.9; IR (neat) 2939, 1690, 1500, 745 cm⁻¹; LRMS (ESI+) m/z 220.1 (MH+), 242.1 (MNa+); HRMS (ESI+) exact mass calc’d for (C₁₃H₁₇NO₃)⁺ requires m/z 220.1328, found m/z 220.1332; HPLC analysis: 96% ee (DAICEL
CHIRALPAK ODH, eluted in 1:99 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, $t_{R1}$: 7.07 min, $t_{R2}$: 9.81 min; $[\alpha]^2_{D} = -49.11^\circ$ (c = 0.90, CHCl$_3$).

(S)-4-(4-methoxyphenyl)-1-methyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4c). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.51 (m, 1H, Ar), 7.34 (m, 3H, Ar), 6.86 (m, 2H, Ar), 6.73 (m, 2H, Ar), 5.33 (dd, 1H, $J = 15.16, 4.2$ Hz, C(O)-O-CH-Ar), 3.80 (s, 3H, Ar-OMe), 3.78 (m, 1H, N-CH$_3$H$_6$), 3.33 (ddd, 1H, $J = 21.04, 16.3, 3.84$, N-CH$_3$H$_6$), 3.11 (s, 3H, N-CH$_3$), 2.15 (m, 2H, N-CH$_2$-CH$_2$-CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.6, 159.8, 148.3, 134.5, 132.6, 131.2, 127.8, 116.5, 115.5, 114.1, 112.8, 77.4, 55.5, 49.6, 39.8, 36.5; IR (neat) 2917, 1693, 1600, 1501, 1222, 746 cm$^{-1}$; LRMS (ESI+) m/z 298 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{13}$H$_{17}$NO$_3$H)$^+$ requires m/z 298.1439, found m/z 298.1437; HPLC analysis: 95% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, $t_{R1}$: 5.95 min, $t_{R2}$: 7.33 min; $[\alpha]^2_{D} = -64.3^\circ$ (c = 0.90, CHCl$_3$).

(S)-1-methyl-4-(p-tolyl)-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4d) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.50 (m, 1H, Ar), 7.34 (m, 1H, Ar), 7.28 (m, 2H, Ar), 7.16 (m, 1H, Ar), 6.72 (m, 2H, Ar), 5.34 (dd, 1H, $J = 15.40, 3.88$ Hz, C(O)-O-CH-Ar), 3.78 (ddd, 1H, $J = 21.16, 15.56, 3.44$, N-CH$_3$H$_6$), 3.33 (ddd, 1H, $J = 21.32, 5.36, 3.40$, N-CH$_3$H$_6$), 3.11 (s, 3H, N-CH$_3$), 2.32 (s, 3H, Ph-CH$_3$), 2.22 (m, 1H, N-CH$_2$-CH$_2$H$_6$-CH), 2.10 (m, 1H, N-CH$_2$-CH$_2$H$_6$-CH); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.6, 148.3, 138.2, 136.2, 134.4, 132.6, 129.4, 126.2, 116.5, 115.5, 112.8, 77.5, 49.6, 39.8, 36.6, 21.4; IR (neat) 2923, 1687, 1505, 1228, 1087, 808, 742 cm$^{-1}$; LRMS (ESI+) m/z 282 (MH$^+$); HRMS (ESI+) exact mass calc’d for (C$_{13}$H$_{17}$NO$_3$H)$^+$ requires m/z 282.1484, found m/z 282.1488; HPLC analysis: 99% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, $t_{R1}$: 5.19 min, $t_{R2}$: 6.63 min; $[\alpha]^2_{D} = -113.6^\circ$(c = 1.10, CHCl$_3$).

(R)-1,4-dimethyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4e) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.49 (ddd, 1H, $J = 7.8, 1.72$ Hz, Ar), 7.30 (m, 1H, Ar), 6.70 (m, 2H, Ar), 4.50 (m, 1H, C(O)-O-CH$_2$-CH$_3$), 3.64 (ddd, 1H, $J = 15.88, 12.04, 2.36$, N-CH$_3$H$_6$), 3.24 (ddd, 1H, $J = 15.96, 4.28, 2.40$, N-CH$_3$H$_6$), 3.04 (s, 3H, N-CH$_3$), 2.00 (m, 1H, N-CH$_2$-CH$_2$H$_6$-CH), 1.76 (m, 1H, N-CH$_2$-CH$_2$H$_6$-CH), 1.36 (d, 3H, $J = 6.2$ Hz); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 173.8, 147.9, 134.1, 132.2, 116.1, 115.5, 112.4, 72.7, 49.0, 39.5, 36.0, 20.6; IR (neat) 2936, 1688, 1600, 1500, 1219, 746 cm$^{-1}$; LRMS (ESI+) m/z 206.1 (MH$^+$), 228.1 (MNa$^+$); HRMS (ESI+) exact mass calc’d for (C$_{13}$H$_{17}$NO$_3$H)$^+$ requires m/z 205.1175, found m/z 206.1172; HPLC analysis: 98% ee (DAICEL CHIRALPAK
ODH, eluted in 1:99 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, t_R1: 7.30 min, t_R2: 9.89 min; [\alpha]_{D}^{25} = -80.34° (c = 0.85, CHCl₃).

(S)-1-methyl-4-(4-methylnaphthalen-1-yl)-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4f) White solid, mp: 181 – 183 °C; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 8.02 (d, 1H, J = 8.04 Hz, Ar), 7.68 (t, 2H, J = 7.4 Hz, Ar), 7.58 (dd, 1H, J = 7.8, 1.64 Hz, Ar), 7.33-7.52 (m, 5H, Ar), 6.78 (m, 2H, Ar), 6.14 (dd, 1H, J = 11.64, 2.28 Hz, C(0)-O-CH-Naph), 3.88 (ddd, 1H, J = 15.76, 11.68, 2.36, N-CH₃H₅b), 3.44 (ddd, 1H, J = 15.96, 3.96, 2.76, N-CH₃H₅a), 3.19 (s, 3H, N-CH₃), 2.69 (s, 3H, Naph-CH₃), 2.45 (m, 1H, N-CH₂-CH₃H₅a-CH), 2.29 (m, 1H, N-CH₂-CH₃H₅b-CH); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 173.4, 148.3, 135.1, 134.2, 132.9, 132.6, 132.5, 130.2, 126.3, 126.1, 125.8, 125.1, 123.4, 122.9, 116.6, 115.5, 112.7, 74.2, 49.6, 39.6, 35.2, 19.6; IR (neat) 2919, 1693, 1599, 1500, 1219, 908, 742 cm\(^{-1}\); LRMS (ESI+) m/z 332.2 (MH⁺); HRMS (ESI+) exact mass calc’d for (C\(_{17}\)H\(_{14}\)ClNO\(_2\)H)\(^{+}\) requires m/z 332.1645, found m/z 332.1657; HPLC analysis: 97% ee (DAICEL CHIRALPAK ADH, eluted in 1:24 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, t_R1: 19.28 min, t_R2: 20.75 min); [\alpha]_{D}^{25} = -65.6° (c = 0.80, CHCl₃).

(S)-4-(4-fluorophenyl)-1-methyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4g). Mp: 110 – 113 °C; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.50 (dd, 1H, J = 10.76, 2.48 Hz, Ar), 7.33 (m, 3H, Ar), 7.02 (m, 2H, Ar), 6.72 (m, 2H, Ar), 5.36 (dd, 1H, J = 15.52, 3.8 Hz, C(O)-O-CH-Ar), 3.76 (dddd, 1H, J = 21.32, 15.36, 3.6, N-CH₃H₅b), 3.35 (dddd, 1H, J = 21.36, 5.44, 3.76, N-CH₃H₅a), 3.10 (s, 3H, N-CH₃), 2.20 (m, 1H, N-CH₂-CH₃H₅b-CH), 2.06 (m, 1H, N-CH₂-CH₃H₅a-CH); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 173.3, 164.3, 161.1, 148.3, 135.0 (d, J = 4 Hz), 132.7, 128.1 (d, J = 10.88 Hz) 116.6, 115.8, 115.5, 115.3, 112.8, 49.6, 39.8, 36.7; IR (neat) 2940, 1681, 1600, 1504, 1210, 742 cm\(^{-1}\); LRMS (ESI+) m/z 305 (MNa⁺); HRMS (ESI+) exact mass calc’d for (C\(_{17}\)H\(_{14}\)NO\(_2\)FNa)\(^{+}\) requires m/z 286.1238, found m/z 286.1237; HPLC analysis: 88% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, t_R1: 5.74 min, t_R2: 6.62 min); [\alpha]_{D}^{25} = -90.8° (c = 1.15, CHCl₃).

(S)-4-(4-chlorophenyl)-1-methyl-3,4-dihydro-1H-benzo[c][1,5]oxazocin-6(2H)-one (4h) White solid, mp: 160 – 162 °C; \(^1\)H NMR (400 MHz, CDCl₃) \(\delta\) 7.51 (d, 1H, J = 8.08, 1.84 Hz, Ar), 7.34 (m, 1H, Ar), 7.32 (m, 4H, Ar), 6.73 (m, 2H, Ar), 5.36 (dd, 1H, J = 11.8, 2.84 Hz, C(O)-O-CH-Ar), 3.76 (dd, 1H, J = 16.04, 11.64, 2.76, N-CH₃H₅b), 3.36 (dd, 1H, J = 16.04, 4.08, 2.76, N-CH₃H₅a), 3.11 (s, 3H, N-CH₃), 2.22 (m, 1H, N-CH₂-CH₃H₅b-CH), 2.05 (m, 1H, N-CH₂-CH₃H₅a-CH); \(^{13}\)C NMR (100 MHz, CDCl₃) \(\delta\) 173.3, 148.3, 137.7, 134.5, 134.2, 132.8, 129.0, 127.6, 116.7, 115.2, 112.9, 76.8, 49.6, 39.8, 36.7; IR (neat) 2929, 1683, 1505, 1492, 1089, 811, 742 cm\(^{-1}\); LRMS (ESI+) m/z 302.1 (MH⁺); HRMS (ESI+) exact mass calc’d for (C\(_{17}\)H\(_{14}\)ClNO\(_2\)H)\(^{+}\) requires m/z 302.0942, found m/z
302.0946; HPLC analysis: 97% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, tᵣ₁: 5.55 min, tᵣ₂: 6.43 min); [α]²⁵_D = -133.2° (c = 0.9, CHCl₃).

((S)-4-(4-bromophenyl)-1-methyl-3,4-dihydro-1H-benzo[c][1,5] oxazocin-6(2H)-one (4i) mp: 162 – 164 °C; ¹H NMR (400 MHz, CDCl₃) δ 7.52 (dd, 1H, J = 10.76, 2.48 Hz, Ar), 7.34 (m, 3H, Ar), 7.04 (m, 2H, Ar), 6.74 (m, 2H, Ar), 5.37 (dd, 1H, J = 15.64, 3.76 Hz, C(O)-O-CH-Ar), 3.76 (ddd, 1H, J = 21.40, 5.40, 3.44, N-CH₃H₅), 3.11 (s, 3H, N-CH₃), 2.22 (m, 1H, N-CH₂-CH₃H₅-CH), 2.04 (m, 1H, N-CH₂-CH₃H₅-CH); ¹³C NMR (100 MHz, CDCl₃) δ 173.2, 148.3, 138.3, 134.5, 132.8, 131.9, 127.9, 122.3, 116.7, 115.2, 112.9, 76.8, 49.6, 39.8, 36.7; IR (neat) 2926, 1684, 1600, 1504, 1427, 1010, 807, 730 cm⁻¹; LRMS (ESI+) m/z 346 (MH+);

HRMS (ESI+) exact mass calc’d for (C₁₇H₁₆BrNO₂H)⁺ requires m/z 346.0423, found m/z 346.0413; HPLC analysis: 99% ee (DAICEL CHIRALPAK ADH, eluted in 1:1 iPrOH:hexanes, flow rate 1 mL/min, detection: 225 nm, tᵣ₁: 5.05 min, tᵣ₂: 5.72 min); [α]²⁵_D = -132.0° (c = 1.20, CHCl₃).
VI. The X-ray crystal structure of (S)-2b and associated data

![Chemical structure of (S)-2b](image)

Table 1. Crystal data and structure refinement for k07298a.

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<td>$b = 12.2672(2)$ Å</td>
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c = 17.4319(10) Å     \( \phi = 90^\circ \).

Volume
1262.45(15) Å\(^3\)

Z
4

Density (calculated)
1.445 Mg/m\(^3\)

Absorption coefficient
0.303 mm\(^{-1}\)

F(000)
568

Crystal size
0.30 x 0.22 x 0.12 mm\(^3\)

Theta range for data collection
2.87 to 27.47°.

Index ranges
-7 \( \leq \) h \( \leq \) 7, -15 \( \leq \) k \( \leq \) 12, -22 \( \leq \) l \( \leq \) 22

Reflections collected
7916

Independent reflections
2855 [R(int) = 0.0414]

Completeness to theta = 27.47°
99.8 %

Absorption correction
Semi-empirical from equivalents

Max. and min. transmission
0.965 and 0.890

Refinement method
Full-matrix least-squares on F\(^2\)

Data / restraints / parameters
2855 / 0 / 173

Goodness-of-fit on F\(^2\)
1.045

Final R indices [I>2\sigma(I)]
R1 = 0.0400, wR2 = 0.0904

R indices (all data)
R1 = 0.0620, wR2 = 0.1021

Absolute structure parameter
-0.01(7)

Extinction coefficient
0.007(2)

Largest diff. peak and hole
0.248 and -0.217 e.Å\(^{-3}\)
Table 2. Atomic coordinates \((x \times 10^4)\) and equivalent isotropic displacement parameters \((\AA^2 \times 10^3)\) for k07298a. \(U(eq)\) is defined as one third of the trace of the orthogonalized \(U_{ij}\) tensor.

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Table 3. Bond lengths [Å] and angles [°] for k07298a.

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C(12)-C(11)-C(10)  120.5(2)
C(13)-C(12)-C(11)  119.0(2)
C(14)-C(13)-C(12)  121.5(2)
C(14)-C(13)-Cl(1)  119.80(18)
C(12)-C(13)-Cl(1)  118.67(18)
C(13)-C(14)-C(15)  119.1(2)
C(10)-C(15)-C(14)  120.6(2)

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for k07298a. The anisotropic displacement factor exponent takes the form: $-2\sum h^2 a^* U^{11} + \ldots + 2 h k a^* b^* U^{12}$

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Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^2 x 10^{-3}) for k07298a.

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VII. The X-ray crystal structure of (S)-29i and associated data
Table 1. Crystal data and structure refinement for k09242a.

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<td>Independent reflections</td>
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Absorption correction  Semi-empirical from equivalents
Max. and min. transmission  0.720 and 0.620
Refinement method  Full-matrix least-squares on $F^2$
Data / restraints / parameters  3332 / 0 / 192
Goodness-of-fit on $F^2$  1.022
Final R indices [I>2sigma(I)]  R1 = 0.0363, wR2 = 0.0771
R indices (all data)  R1 = 0.0544, wR2 = 0.0842
Absolute structure parameter  -0.028(11)
Extinction coefficient  0.0055(8)
Largest diff. peak and hole  0.566 and -0.501 e.Å$^{-3}$
Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for k09242a. U(eq) is defined as one third of the trace of the orthogonalized U_ij tensor.

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Table 3. Bond lengths [Å] and angles [°] for k09242a.

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C(7)-N(1)-C(11)  120.0(3)
C(8)-N(1)-C(11)  116.1(3)
O(2)-C(1)-O(1)  115.7(3)
O(2)-C(1)-C(2)  120.9(3)
O(1)-C(1)-C(2)  123.1(3)
C(3)-C(2)-C(7)  119.5(3)
C(3)-C(2)-C(1)  111.2(3)
C(7)-C(2)-C(1)  129.2(3)
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C(5)-C(4)-C(3)  118.2(3)
C(6)-C(5)-C(4)  121.0(3)
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N(1)-C(7)-C(6)  119.0(3)
N(1)-C(7)-C(2)  124.4(3)
C(6)-C(7)-C(2)  116.6(3)
N(1)-C(8)-C(9)  112.1(3)
C(10)-C(9)-C(8)  110.4(3)
O(1)-C(10)-C(12)  107.0(2)
O(1)-C(10)-C(9)  107.2(2)
C(12)-C(10)-C(9)  111.7(2)
C(13)-C(12)-C(17)  118.5(3)
C(13)-C(12)-C(10)  120.1(3)
C(17)-C(12)-C(10)  121.3(3)
C(12)-C(13)-C(14)  121.8(3)
C(15)-C(14)-C(13)  118.0(3)
C(16)-C(15)-C(14)  121.4(3)
C(16)-C(15)-Br(1)  118.7(2)
C(14)-C(15)-Br(1)  119.9(2)
C(15)-C(16)-C(17)  119.8(3)
C(16)-C(17)-C(12)  120.5(3)

_____________________________________________________________

Symmetry transformations used to generate equivalent atoms:
Table 4. Anisotropic displacement parameters (Å² x 10³) for k09242a. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^* U^{11} + \ldots + 2hk a^* b^* U^{12}]$

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Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{Å}^2 \times 10^3$) for k09242a.

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<td>H(5A)</td>
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<td>H(6A)</td>
<td>3010</td>
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VIII. Rate experiments

Determination of the reaction order in catalyst for [Rh(dppp)]$_2$(BF$_4$)$_2$-catalyzed hydroacylation: In a glove box, a solution of [Rh(dppp)]$_2$(BF$_4$)$_2$ (0.015 M of Rh) in CD$_2$Cl$_2$ (5 mL) was prepared in a volumetric flask (5 mL). The [Rh] catalyst (9 mol% Rh, 600 μL) was added to a J. Young NMR tube containing a solution of substrate 1a (24 mg, 0.1 mmol) in CD$_2$Cl$_2$ (400 μL) using a Hamilton microliter syringe. The J. Young NMR tube was taken out of the glove box and immediately cooled in liquid N$_2$. Before the NMR sample was placed in the NMR probe (25 ± 0.1 °C), the sample was warmed to rt in a water bath. The consumption of substrate 1a and the appearance of the product 2a were monitored by $^1$H NMR. The rate ($k_{obs}$) (after the induction period) of each catalyst concentration was obtained (table S1). According to the graph of $k_{obs}$ vs catalyst concentration, a fractional order (0.67) in catalyst was determined (Figure S1). This experiment was repeated and a similar result was obtained.

Table S1. Observed rate versus catalyst concentration for [Rh(dppp)]$_2$(BF$_4$)$_2$-catalyzed hydroacylation.$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>1</th>
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<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td>[Rh] (M of Rh)</td>
<td>0.009</td>
<td>0.00705</td>
<td>0.005</td>
<td>0.003</td>
<td>0.0015</td>
<td>0.0005</td>
</tr>
<tr>
<td>$k_{obs} \times 10^{-3}$ (M/sec)</td>
<td>0.0261</td>
<td>0.0225</td>
<td>0.018</td>
<td>0.0131</td>
<td>0.0077</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

$^a$ Conditions: substrate (0.1 mmol, 0.1 M), [Rh(dppp)]$_2$(BF$_4$)$_2$ (variable amount), CD$_2$Cl$_2$ (1.0 mL), 25 ± 0.1 °C.

Figure S1. Observed rate (measured after the initial induction period) versus catalyst concentration for [Rh(dppp)]$_2$(BF$_4$)$_2$.
Representative data:

**Figure S2.** (a) Progress of reaction for the hydroacylation of 1a with 2.5 mol% [Rh(dppp)]$_2$(BF$_4$)$_2$.

**Determination of the reaction order in substrate for [Rh(dppp)]$_2$(BF$_4$)$_2$-catalyzed hydroacylation:** In a glove box, a solution of [Rh(dppp)]$_2$(BF$_4$)$_2$ (0.0125 M) in CH$_2$Cl$_2$ (1 mL) was prepared in volumetric flask (1 mL). The [Rh(dppp)]$_2$(BF$_4$)$_2$ solution (200 μL) was added to a solution of model substrate 1a (12 variable amount) in CH$_2$Cl$_2$ (800 μL) using a Hamilton microliter syringe. Aliquots (80 μL) of the reaction were taken every 5 min for the first 20 minutes, and then every 10 minutes until the conversion for substrate had reached ~90% as indicated by $^1$H NMR. All samples were quenched with CH$_3$CN and removed from the glove box immediately. Notably, no catalysis occurred either in CH$_3$CN or open air. The disappearance of substrate 1a and the appearance of the product 2a were monitored by $^1$H NMR. The rate ($k_{obs}$) (after the induction period) of each substrate concentration was obtained (table S2). According to the graph of the $k_{obs}$ vs [1a], a first order dependence in substrate was determined (Figure S2).
Table S2. Observed rate versus substrate concentration for [Rh(dppp)]2(BF4)2-catalyzed hydroacylation.\textsuperscript{a}

![Diagram](image)

<table>
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<tbody>
<tr>
<td>[1a] (M)</td>
<td>0.05</td>
<td>0.1</td>
<td>0.2</td>
<td>0.3</td>
</tr>
<tr>
<td>(k_{\text{obs}}) (M/min)</td>
<td>0.0014</td>
<td>0.0027</td>
<td>0.0051</td>
<td>0.0072</td>
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\(\text{ Conditions: substrate (variable amount), [Rh(dppp)]2(BF4)2 (200 \mu L, 0.0025 mmol), CH2Cl2 (1.0 mL), rt.}\)

Figure S3. Plot of \(k_{\text{obs}}\) vs substrate concentration with [Rh(dppp)]2(BF4)2.

\textbf{KIE experiments for [Rh(dppp)]2(BF4)2-catalyzed hydroacylation:} (refer to the procedure of determining the substrate order for [Rh(dppp)]2(BF4)2-catalyzed hydroacylation).
Table S3. KIE studies for [Rh(dppp)]$_2$(BF$_4$)$_2$.\textsuperscript{a}

<table>
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<tr>
<th></th>
<th>Concentration</th>
<th>$k_{\text{obs}}$ (min$^{-1}$)</th>
<th>$k_{\text{obsH}}$/$k_{\text{obsD}}$</th>
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<tr>
<td>1a-H</td>
<td>0.2 M</td>
<td>1.7861</td>
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<tr>
<td>1aa-D</td>
<td>0.2 M</td>
<td>1.0047</td>
<td>1.8</td>
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\textsuperscript{a} Conditions: substrate (0.2 mmol), [Rh(dppp)]$_2$(BF$_4$)$_2$ (2.502 mol%), CH$_2$Cl$_2$ (2.0 mL), rt.

Figure S4. H/D kinetic isotope effect for dppp. The curve for H describes a linear least squares fit to Conversion = m (time) + b (m = 1.79 ± 0.02; b = -0.89 ± 0.5). The curve for D describes a linear least squares fit to Conversion = m (time) + b (m = 1.00 ± 0.02; b = -0.3 ± 0.3). The kinetic isotope is $k_{\text{H}}/k_{\text{D}} = 1.79 ± 0.06$.

General procedure for the Hammett study with \textit{para}-substituted phenyl substrates: In a glove box, a solution containing [Rh(dppp)]$_2$(BF$_4$)$_2$ (0.00625 M) in CH$_2$Cl$_2$ (2 mL) was prepared in a volumetric flask (2 mL). The [Rh(dppp)]$_2$(BF$_4$)$_2$ solution (200 μL) was added into a solution of substrate (1a-1g) (0.1 mmol) in CH$_2$Cl$_2$ (0.8 mL) using a Hamilton microliter syringe respectively. Seven reactions were set up in parallel in the glove box. Aliquots (80 μL) were then taken every 5 min for the first 20 minutes, and then every 10 minutes until the conversion for substrate had reached ~90% (as indicated by $^1$H NMR). All samples were quenched with CH$_3$CN and removed from the glove box immediately. The consumption of substrate 1 and the appearance of the product 2 were monitored by $^1$H NMR. The log($k_{\text{obs}}$) of each substrate (table S8) was obtained.
Table S4. Observed rate versus standard σ+ for [Rh(dppp)]\(_2\)(BF\(_4\))\(_2\)-catalyzed hydroacylation.\(^a\)

![Chemical structure](image)

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<td>COOMe</td>
<td>Cl</td>
<td>H</td>
<td>F</td>
<td>Me</td>
<td>OMe</td>
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<tr>
<td>σ(^+)(^b)</td>
<td>0.61</td>
<td>0.49</td>
<td>0.11</td>
<td>0</td>
<td>-0.07</td>
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<td>-0.78</td>
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<tr>
<td>logk(_{obs})</td>
<td>0.367</td>
<td>0.353</td>
<td>0.323</td>
<td>0.271</td>
<td>0.238</td>
<td>0.092</td>
<td>-0.008</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: substrate (0.1 mmol), [Rh(dppp)]\(_2\)(BF\(_4\))\(_2\) (200 μL, 0.00125 mmol), CH\(_2\)Cl\(_2\) (1.0 mL), rt. \(^b\) σ\(^+\) values were chosen as they provided a better fit compared to σ and σ\(^-\) values.

![Hammett study graph](image)

Figure S5. Hammett study.
Chapter 2: The Synthesis of Cyclic Peptides –

Stereodivergent Hydrogenation of Cyclic Dehydropeptides

2.1 An Overview of Peptide Synthesis

2.1.1 Conventional Synthesis of Peptides

The complex machinery of the ribosome is able to translate the coded messenger RNA into a sequence of amino acids with complete fidelity and selectivity for a particular functional group among several, and without racemizing a single stereocentre. Synthetic chemists tasked with achieving this type of efficiency in peptide synthesis will readily admit that we are poorly equipped, which is why we resort to biosynthetic methods to produce commercial proteins that are coded by the ribosome (ex. Human insulin). For most nonribosomal peptides such as cyclic peptides, we turn to total chemical synthesis.¹

![Scheme 2.1 - Synthesis of Bz(Gly)_3 via the azide method by Theodor Curtius in 1904](image)

For perspective on the synthesis of cyclic peptides, it is crucial to understand that the chemical synthesis of peptides, as it is today, has been evolving as an art for over 100 years, since Emil Fischer and Theodor Curtius independently developed the first methods for coupling two amino
acids through an amide bond-forming reaction in the early 1900s – the acid chloride method and the azide method, respectively. There are challenges to address when considering the synthesis of peptides: 1) chemoselectivity – ensuring that one particular amino group is going to couple with one particular carboxylic acid to form the correct amide bond, 2) fidelity of chirality – suppressing racemization such that one furnishes the desired diastereomer upon completion of the synthesis, and 3) molecular shape – performing the synthesis such that the peptide product adopts the correct conformation. Landmark technologies have been developed in order to address these challenges and these will be described further below.

The advent of solid-phase peptide synthesis (SPPS), developed by Bruce Merrifield in 1963, is arguably the most significant advance in peptide synthesis, and earned the Nobel Prize in chemistry in 1984. Up until this development, peptide synthesis had been performed only in the solution phase, which has its benefits but is invariably time-consuming and labour intensive. In SPPS, a growing peptide is anchored to an insoluble resin, typically at the C-terminus, and amino acids are iteratively added in the C→N direction using a large excess of reagents to ensure complete conversion. As the peptide remains bound to the resin, by-products can be washed off at each step. The directionality of SPPS comes partly from the ease of synthesis of resins linked to the C-terminus through ester or ether linkages, and partly because some side reactions are avoided, as discussed in 2.1.3. Due to the efficiency and repetitiveness of the process, the majority of a synthesis performed by SPPS can be completely automated by making stock solutions of the necessary reagents and programming an automatic reactor. This enables non-experts in chemical synthesis to access peptides in a simple manner. After the peptide is complete, it needs to be cleaved from the resin and then characterized to ensure that each amino acid was added in a chemoselective and stereoretentive manner.
Scheme 2.2 – A generic illustration of Fmoc-based solid phase peptide synthesis using the rink amide resin and HBTU as coupling agent to form a tripeptide.
2.1.2 The Advent and Development of Protecting Groups

The synthesis of complex peptides necessitated a means for ensuring chemoselective transformations – one amine should couple with one carboxylic acid, and all other functional groups should be unreactive. To this end, protecting groups were developed to block the undesired reaction of functional groups. In 1932, the first amino protecting group was developed by Max Bergmann – the carbobenzylxylo group (Cbz), which is removed under catalytic hydrogenation. The advent of protecting group chemistry enabled the synthesis of numerous peptides, culminating in Vincent du Vigneaud’s synthesis of Oxytocin, which earned the Nobel Prize in chemistry in 1955. In 1957, McKay and Albertson introduced the strong acid-labile tert-butyloxycarbonyl (Boc) protecting group. Stable to hydrogenation and strong alkali bases, the Boc group was orthogonal to the Cbz group, allowing the protection of reactive side chain functional groups during the chain extension of a peptide. In 1970, Carpino developed the 9-fluorenlymethyloxycarbonyl (Fmoc) protecting group, which is base-labile but stable to acids and hydrogenation. The allyloxycarbonyl (Alloc) protecting group is removed by allyl transfer to a scavenger, typically catalyzed by palladium (specifically, Pd(PPh₃)₄). These four amino protecting groups (Cbz, Boc, Fmoc, and Alloc) are the most common in contemporary peptide synthesis and allow for the selective functionalization of the α-amino group in the presence of highly reactive side chain functional groups. They are designed to promote chemoselective transformations, and careful selection of the protecting groups is necessary to provide an orthogonal deprotecting strategy that reveals the correct functional group at the correct time. As the demands of peptide synthesis increase due to the greater size and complexity of the targets, new protecting group classes are being developed. The para-nitrobenzyloxy carbonyl (pNZ) protecting group, developed in 1952 by Carpenter and Gish is more stable than the Cbz group.
and is deprotected orthogonally to the Alloc, Boc, and Fmoc groups – reduction using tin (II) is used to remove the pNZ group. Because it is deprotected orthogonally to three other protecting groups, it enabled the synthesis of a complex cyclic peptide Oxathiocoraline.\textsuperscript{10} The 2-(4-nitrophenylsulfonyl)-ethyloxycarbonyl (Nsc) protecting group\textsuperscript{11} offers some advantages over the Fmoc group – Nsc-protected amino acids are typically more crystalline and more soluble in organic solvents than the corresponding Fmoc-protected amino acids. Additionally, racemization does not occur as often with Nsc-protected amino acids as with their Fmoc-protected counterparts. Carboxy-terminal protecting groups are less common in contemporary peptide synthesis. The C-terminus is usually bound covalently to the resin as the C$\rightarrow$N directionality of peptide synthesis is more common. In situations where the N-terminus or the side chain is bound to the resin, the carboxyl-terminus can be protected to ensure chemoselective transformations. Common protecting groups include methyl/ethyl esters (removed by saponification), tert-butyl esters (removed in strong acid), and benzyl and \textit{para}-nitrobenzyl esters (removed by catalytic hydrogenation, or with tin(II) for the latter).

\textbf{Scheme 2.3} - Some representative amine protecting groups and their respective deprotections
2.1.3 Amide Coupling Reagents in Peptide Synthesis

The development of carbodiimides provided a powerful alternative to the acid chloride and the azide methods of peptide coupling. Sheehan and Hess introduced dicyclohexylcarbodiimide (DCC) as a coupling agent to peptide chemists in 1955. DCC reacts with carboxylic acids to form O-acylisoureas, a highly activated ester, but reacts slowly with nitrogen-based nucleophiles. Thus, the carboxylic acid of an N-protected amino acid can be activated in the presence of an unprotected amine on a growing peptide and, once activated, can undergo a condensation to form an amide bond. Drawbacks of DCC include potent toxicity and the formation of an intractable by-product: dicyclohexylurea (DCU). DCU is insoluble in many organic solvents and creates complications in SPPS. Nonetheless, this proved to be a powerful method for peptide coupling, as it allowed a one-pot activation and substitution reaction. Derivatives such as N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (EDCI) have been developed to provide the same reactivity while producing less toxic and more water-soluble by-products. Since then, other methods have been developed to address the various issues associated with the use of DCC. Activation of the carboxylic acid using ethyl or iso-butyl chloroformates (ECF and iBCF, respectively) results in the formation of a mixed anhydride, which can then undergo substitution with a nucleophile to furnish the peptide bond. Carbonyldiimidazole (CDI) functions in much the same way, although a nucleophilic base (typically an imidazole) intercepts the intermediate to form a transient acylimidazolium species.
The phosphonium coupling reagents, like benzotriazole-1-yl-oxy-tris-(dimethylamino)-phosphonium hexafluorophosphate (BOP) (Scheme 2.4),\textsuperscript{14} offer advantages in chemoselectivity as they do not react with amino groups, making them well-suited for cyclization reactions where the substrate and the reagents are present in equimolar amounts. BOP releases hydroxybenzotriazole, which can then transesterify with the intermediate; the effects of this process are discussed below. The byproduct of this transformation, hexamethylphosphoramide (HMPA), is toxic and carcinogenic, so a related reagent, benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate (PyBOP),\textsuperscript{15} is used instead – the dimethylamine groups on BOP are replaced with pyrrolidines, resulting in a less hazardous byproduct. Other classes of coupling agents exist such as the aminium/uronium class, each with their own advantages and disadvantages.
While these reagents enable highly chemoselective activation of carboxylic acids in the presence of reactive functional groups like amines, they all form highly electrophilic esters, which give rise to numerous undesired side reactions. Activated esters at the terminus of a peptide can undergo intramolecular cyclization to form oxazolones or diketopiperazines. The pKa of the α-proton decreases precipitously (from ~20 in a peptide to 9) when the oxazolone forms as dissociation of that proton creates an aromatic ring. Diketopiperazines are stable cyclic structures that act as thermodynamic sinks, resulting in lower yields of the desired products. N-Carboxyanhydrides are formed in another off-pathway reaction, typically from N-acyl or N-carbamoyl peptides. In the context of SPPS, it is for this reason that the directionality becomes a critical issue. In the N→C direction, the C-terminus on the growing resin-bound peptide would be activated and, thus, susceptible to the aforementioned side reactions. This would result in a large number of errors (such as epimerization) and incomplete peptides bound to the resin, which would complicate purification at the end of the synthesis. In the C→N direction, the incoming residue is activated rather than the resin-bound peptide, so any products of undesired reactivity are washed off after each step. This is one method of circumventing problematic side reactions. Even in the C→N direction, errors occur as a result of having a highly activated ester and, in the solution phase, the problem becomes more significant.\textsuperscript{16} To alleviate this effect, nucleophilic additives in the form of hydroxytriazoles can be used to transacylate with esters activated by carbodiimides and other reagents. 1-Hydroxybenzotriazole (HOBt) can attack an activated ester to form an HOBt-ester, which promotes fast reactivity with an incoming amine nucleophile and reduces epimerization.\textsuperscript{17} These hydroxylamine additives can be derivatized to offer more functionality in peptide couplings; as the pyridinyl nitrogen of 1-hydroxy-7-azabenzotriazole (HOAt)\textsuperscript{18} acts as a hydrogen bond acceptor with an amine while the hydroxylamine component
activates an ester, thereby inducing temporary intramolecularity\textsuperscript{19} between both components of a peptide coupling.

\textbf{Scheme 2.5} - Off-pathway reactions resulting in the formation of undesired by-products

The synthesis of peptides is challenging. The activation of a carboxylic acid in the presence of the plethora of polar functional groups present in peptides requires sophisticated methods, and the above strategies are innovative and effective methods for promoting the required chemoselectivity in peptide synthesis. Activating agents, transacylating agents, and protecting groups are engineered to provide chemoselective routes towards challenging peptide targets. Unfortunately, these engineered reagents generate a great deal of waste; an amide bond formation is a simple condensation, ideally requiring nothing more than extrusion of water, but a reagent like EDCI or BOP will generate a large amount of waste material. This problem is magnified in the synthesis of small cyclic peptides, and this will be discussed next.
2.2 Cyclic Peptides

2.2.1 A Short History of Interest in Cyclic Peptides

The use of cyclic peptides in medicine dates back to the 1944, when Russian microbiologists Georgyi Fransevitch Gause and Maria Brazhnikova reported the discovery and use of peptide derived from a bacterial extract in treating infections arising from bullet wounds. From the work of Dubos, the bacterial strain *Bacillus brevia* was known to produce antibacterial peptides known as the gramicidins, but the structure of the peptide that Gause and Brazhnikova had discovered, dubbed gramicidin S (Figure 2.1), could not be determined by conventional techniques. The discovery of gramicidin S and the associated supporting information were published in the British journal *Nature* in an effort to foment collaboration between scientific communities in order to ascertain the structure of this peptide. Over 30 years later, E. J. Dodson and coworkers provided the solved crystal structure of gramicidin S, based on the predictions of Nobel laureate Dorothy Hodgkin. Through the work of these scientists, gramicidin S was determined to be a cyclic peptide. The potent activity of cyclic peptides such as the antibacterial agent gramicidin S and the immunosuppressant cyclosporine is recognized even in the present day, as these two molecules find common use in contemporary medicine.
Since the 1970s, numerous bioactive small cyclic peptides have been isolated and studied, typically derived from fungi and bacteria.\(^{24}\) The diversity present in small cyclic peptides is staggering – nonproteinogenic amino acids are common as well as peptides containing a mixture of D- and L-amino acids. In addition, they are prohibitively difficult to synthesize as head-to-tail cyclization of short peptide sequences often result in a large degree of oligomerization unless high dilution conditions are employed, often in the submillimolar range.\(^{25}\) In addition, reactions conducted at low concentrations require more time to achieve complete conversion, increasing the likelihood of C-terminal epimerization. Creative solutions exist to address the difficulty of cyclizing short linear peptides, but these often require particular backbone residues such as pseudoprolines\(^ {26}\) and β-amino acids.\(^ {27}\) The Yudin group has developed a strategy to cyclize linear peptide sequences using ambiphilic aziridine aldehydes in an Ugi-type multicomponent transformation, resulting in peptide-like macrocycles that can be further functionalized at the aziridine moiety.\(^ {28}\) Notably, Yudin can conduct this macrocyclization at concentrations as high as 0.2M with no competing dimerization, a remarkable improvement over the high dilution conditions typically required. The Hackenberger
group has applied the Staudinger ligation to peptide cyclization and they have observed remarkable functional group tolerance and reactivity in aqueous reaction conditions. Some of the most well-established transformations in organic synthesis have been employed to cyclize peptides, including native chemical ligation and the azide-alkyne click reaction. In a total synthesis of the anti-malarial cyclic peptide (Mahafacyclin B), Robinson applied an olefin tether to orient a heptapeptide towards cyclization (55% yield). In the absence of this olefin tether, the cyclization occurred in 6% yield. These methods are innovative and, especially in the case of the Yudin protocol, efficient methods for cyclizing linear peptide sequences. However, these methods are not well-suited to address the issues of incorporating unnatural residues and other challenges in conventional peptide synthesis, because the linear peptidic segments are constructed using conventional peptide synthesis.

Head-to-tail cyclization of short and homochiral (all L or all D) linear peptide sequences is rendered difficult due to the propensity of these sequences to adopt linear conformations in solution. As a result, these peptide sequences often oligomerize under cyclization conditions performed at conventional reaction concentrations (> 0.1M). High dilution conditions (< 10 mM) can be employed to disfavor this side reaction but, even still, dimers and oligomers are observed. This proclivity towards oligomerization arises from the thermodynamic drive to minimize $A_{1,3}$ strain in linear peptides.
The side chains of adjacent amino acids suffer from steric strain in certain conformations, but the linear conformation staggers the side chains to reduce this effect. Incorporating specific amino acids that can promote bent conformations, such as proline and pseudoproline, as mentioned above, and \( N \)-methylated amino acids,\(^{35} \) facilitates ring closing. Peptide segments that contain a mixture of D- and L-amino acids are also turn-inducing.\(^{36} \) Alternating D,L-peptides cyclize much more efficiently than their homochiral counterparts and these peptides have been found to have interesting medicinal properties.\(^{37} \)
2.3 Condensation and Reduction Approach to the Synthesis of Cyclic Peptides

2.3.1 Proposal

Small cyclic peptides exhibit potent biological activity but the head-to-tail cyclization of linear peptides of 4-8 amino acid residues is prohibitively difficult to accomplish due to competing oligomerization. A unifying synthetic strategy that allows access to small cyclic peptides with both proteinogenic and non-proteinogenic residues has yet to be developed. Herein, we describe a synthetic strategy that uses dehydroamino acids in place of chiral amino acids to favour cyclization over oligomerization, and subsequent reduction of these cyclic dehydropeptides via transition metal-catalyzed hydrogenation to access cyclic peptides with high enantio- and diastereoselectivity (Scheme 2.7). The use of dehydroamino acids both provides a handle for various asymmetric transformations (hydrogenation, hydroformylation, conjugate addition, etc.) and induces turns in the linear peptide to accelerate cyclization. Both proteinogenic and non-proteinogenic residues are accessible using this strategy, allowing for the synthesis of a number of functionalized small cyclic peptides. We show evidence of complete catalyst-controlled and substrate-controlled hydrogenations, as well as hydrogenations that are influenced by both catalyst and substrate, providing selective access to a variety of diastereomers. This strategy complements conventional peptide synthesis and provides a new route towards a variety of natural and unnatural cyclic peptides. Our proposed strategy can be integrated into solid phase synthesis through judicious selection of the proper resin – our purpose in this work was to provide additional tools that are fully integrable with established techniques in peptide synthesis. By moving away from chiral amino acids, we can use simpler reagents to replace engineered coupling reagents and protecting groups, allowing us to construct peptides
more efficiently and generating benign waste products. We hope to provide a fresh perspective that would allow the synthetic chemist to approach the synthesis of small cyclic peptides with the assurance that unnatural residues and various diastereomers can be accessed in a selective and efficient manner.

2.3.2 Enamides as Turn Inducers

Dehydroamino acids (ΔAAs) are residues wherein the α-centre is sp²-hybridized. Chauhan and coworkers have shown via NMR and X-ray crystallographic studies that short linear peptide sequences bearing ΔAAs exhibit a β-turn, wherein a 1,4 hydrogen bond is observed in the crystal structure. Importantly, they observed a small temperature dependency of certain amide N–H chemical shifts in DMSO, suggesting that these are participating in an intramolecular hydrogen bond that is shielded from the solvent. This hydrogen-bond is more pronounced in apolar solvents; CD spectra of peptides bearing different ΔAAs showed rigid conformations in CDCl₃ as compared to in DMSO-d₆. A number of naturally-derived peptides bear ΔAAs, and the abnormal behavior of ΔAAs to induce rigid secondary structure has been a topic of intense study. A body of work from the Rzeszotarska group in Poland has focused on detailing the properties of ΔAAs using both theoretical and experimental methods. This work is

Scheme 2.7 - An enantioselective, catalytic, and green approach to cyclic peptides.
extensive, spanning two decades in a series of studies. On the basis of NMR studies focusing on N–H solvent shifts, nuclear Overhauser effects (NOEs), and cis/trans isomerism of amide bonds, Rzeszotarska found that ΔAAs resembled peptides with D- and L-amino acids, while peptides with only L-amino acids were in a different class.\textsuperscript{40} Importantly, the unsaturated and mixed-chirality peptides took distinct β-turn conformations in solution, whereas the homochiral peptides took a variety of conformations.\textsuperscript{41} Subsequent X-ray diffraction and DFT studies placed the torsion angles of unsaturated peptides in the high energy region of the Ramachandran plot typically less accessible to saturated peptides.\textsuperscript{40d} Singh have identified a strong turn in the solid-state structure of BocAlaΔPheΔPhePheOMe (Figure 2.3) that brings the N- and the C-termini in close proximity. The Chauhan and Rzeszotarska studies suggest that ΔAAs can induce turns in peptides, particularly in non-polar media, and that this effect is more pronounced when multiple ΔAAs are in a sequence. However, this effect has not been exploited in the context of peptide cyclization – it can be proposed that the turns induced by ΔAAs can bring the two termini of a peptide in close proximity, favoring head-to-tail cyclization over dimerization.
2.3.3 Diastereoselective Hydrogenation of Enamides

Since the pioneering work of Kagan (Wolf Prize 2001), Knowles, Noyori, and Sharpless (Nobel Prize 2001), great advances have been made in asymmetric catalysis, especially in the area of hydrogenation. Following the first commercial application of hydrogenation to the synthesis of L-DOPA, thousands of chiral ligands have been developed. The asymmetric hydrogenation of ΔAAs, specifically ΔPhe and ΔAla, is a benchmark for catalyst development. Thus, the scope of this enantioselective process is wide, including ΔAAs bearing both alkyl and aryl substituents. Moreover, the Rh catalysts, particularly with chiral bisphosphine ligands, have broad functional group compatibility. For these reasons, we thought to apply asymmetric hydrogenation to the synthesis of cyclic peptides – we expected that, in light
of the breadth and versatility of chiral hydrogenation catalysts in the literature, we would be able to perform these hydrogenations in a highly diastereoselective and chemoselective manner.

Pioneering studies on the diastereoselective hydrogenation of peptides bearing two ΔAAs were conducted by Henri Kagan. He showed that two enamides, in the presence of a chiral rhodium catalyst, could be hydrogenated to afford a highly enantio- and diastereoenriched dipeptide. In concurrent studies, Ojima showed that hydrogenation of a peptide bearing both ΔAAs and α-amino acids could result in selectivity for different diastereomers, based on judicious screening of chiral catalysts. These studies together indicate that our approach is viable, but no study had extended this concept beyond two ΔAAs.
2.4 Synthesis of a Cyclic Peptide via Condensation and Reduction

2.4.1 Iterative Condensation and Aminolysis – Substrate Design

To test the validity of this proposal, I sought to synthesize a linear dehydropeptide of the type 1 (Figure 2.4). The N-terminal protecting group had to be chosen so as to be orthogonal to basic aminolyses and also maintain the integrity of the existing functional groups (i.e. the enamides). This precluded the use of Fmoc (unstable to nucleophilic amine bases) and the Cbz group (removed under catalytic hydrogenation, which would reduce the enamides). We chose an N-terminal Boc group, which could be removed using trifluoroacetic acid under anhydrous conditions. Glycine was chosen as the N-terminal residue to provide an achiral starting point for the peptide. The N-terminus of glycine would also act as an unhindered nucleophile during the peptide cyclization, facilitating the head-to-tail nucleophilic attack. The C-terminal activated ester would be an oxazolone, which can be rapidly aminolyzed by an amino acid in the presence of nucleophilic catalysts such as DMAP.50

These structures are also much more soluble in non-polar media than the corresponding carboxylic acids, which would favour the desired pre-cyclization conformation, as detailed above.

The ΔAAs could come from a number of different precursors. The simplest sequence that would arrive at the desired ΔAA, however, was via dehydration of serine derivatives. The synthesis of serine derivatives and ΔAAs is antiquated and robust but narrow in scope – few
reports exist of large-scale synthesis of serine derivatives. These typically include an aldol reaction between glycine and an aldehyde. Often, two or more equivalents of the aldehyde are required as one equivalent will form an imine with glycine first, rendering the α-proton more acidic. A number of metal-mediated methods (involving Cu most often) exist to accomplish the same goal. Modern methods for the synthesis of serine derivatives are often highly controlled systems that afford the amino acids in high enantioselectivity and diastereoselectivity; Keiji Maruoka’s phase transfer salts are the catalysts of choice for this transformation. However, these reactions are typically performed on small scale, and we desired a scalable synthesis using simple reagents that did not induce enantioselectivity. β-PhSerOH (3) was accessible at large scale (>100 g) from benzaldehyde, glycine, and NaOH. Other arylserine derivatives were accessible using similar conditions.

The carboxyl of BocGlyOH (2) was activated using ethyl chloroformate, and β-PhSerOH (3) was added as a solution in 1M NaOH (Scheme 2.9). After work-up and condensation with acetic anhydride and sodium acetate, the crude oxazolone was repeatedly washed with saturated sodium bicarbonate solution in order to decompose all of the remaining acetic anhydride and quench the resulting acetic acid. The crude oxazolone, often a yellow solid, could be precipitated from dichloromethane using hexanes to afford the product (5).

Aminolysis of 5 proved intractable for a remarkably long period of time. Max Bergmann had established a protocol using the amino acid free base in acetone and 1M NaOH, and this protocol was well-cited by other chemists for the synthesis of dehydropeptides. In my hands, however, this protocol resulted exclusively in hydrolysis of the oxazolone. Numerous permutations, adjusting addition order and other parameters, were attempted but all resulted in hydrolysis. I was able to successfully aminolyze the oxazolone with using an as of yet uncited
procedure from 2002, using an alkyamine base instead of sodium hydroxide and THF instead of acetone. This procedure resulted in complete aminolysis of 5 with only traces of hydrolysis observed by LCMS. Condensation provided the tripeptide oxazolone as a yellow solid precipitated as above in high yield (~90%). With efficient aminolysis conditions established, another iteration of the aminolysis/condensation procedure was performed to furnish the tetrapeptide oxazolone. This tetrapeptide exhibited different properties than the tripeptide. Primarily, it dissolved much less readily than the tripeptide, although the tetrapeptide still dissolved completely at 0.05M in THF. It did not readily dissolve in chloroform, and \(^1\)H-NMR analysis of the tetrapeptide oxazolone resulted in some broad peaks. Importantly, the aminolysis of the tetrapeptide oxazolone using 3 as the nucleophile required more than a day to achieve complete conversion. However, once complete conversion was achieved, the pentapeptide oxazolone 1 could be readily precipitated as above in high yields.

The Boc group was removed by addition of TFA to a solution of the pentapeptide in dichloromethane. Trace TFA was removed under vacuum or via precipitation from diethyl ether. It was difficult to determine a set of conditions from the literature for the desired head-to-tail cyclization, as this was the first of its type. Rather, a simple set of reaction conditions was chosen at the outset. Fortunately, little optimization was necessary.
DMF was chosen as the solvent to ensure all of the reagents remained soluble. Triethylamine was chosen as the stoichiometric base as it had proven effective in the aminolyses described above. The concentration was maintained at 0.01M for the first attempt in order to

Scheme 2.9 – Forward synthesis of a linear dehydropentapeptide 1.

Scheme 2.10 – Cyclization of linear dehydropentapeptide using a nucleophilic transacylating catalyst furnishes the desired cyclic dehydropentapeptide in high yield.
favor cyclization. Finally, DMAP was added as a nucleophilic catalyst. An aliquot taken of the reaction mixture at 10 minutes was analyzed by LCMS and only a single peak was observed with the same mass as the starting material but a significantly different retention time; the peak eluted much later in the run. As well, this new peak ionized much weaker than the starting material by ESI+. In the context of this cyclization, this offered support that the observed peak represented the cyclized product as this particular cyclic peptide would have no readily ionizable functional groups, whereas the starting material has a free amine that ionizes very well by ESI+. At first, I assumed that the trace amount of DMF in the sample was causing the large shift in retention time, and there was no ready method for determining the truth of that without working up the reaction. I diluted the reaction mixture with ethyl acetate then washed the organic layer repeatedly with 1M HCl and finished by washing twice with brine. The first clue that the cyclization had succeeded was that I was able to recover 63% of the mass even after repeated acidic aqueous washes, which would have hydrolyzed the oxazolone and rendered the peptide water soluble. The $^1$H-NMR spectrum of the crude material, which was only soluble in DMSO-d$_6$, was uncomplicated but exhibited broad peaks (see spectral data). It was clear, however, that the oxazolone was no longer intact. All of the evidence suggested that the product I had isolated was the cyclic pentapeptide. Importantly, by LCMS, it was the only product I could observe, with no hydrolysis or higher order peptides (decapeptides or larger oligomers). In optimizing the cyclization conditions, I discovered that the use of dichloromethane as solvent enhanced reactivity (faster, and absolutely no traces of any other product by LCMS) and offered a simplified method of isolation – simply add hexanes to the reaction mixture in order to precipitate the product, and the cyclic dehydropentapeptide can be isolated as a white solid in
excellent yield (93%) at higher concentration (0.1M). This is consistent with the observations that more apolar solvents promote stronger intramolecular hydrogen-bonding (*vide infra*).

Attempts at cyclizing shorter peptides resulted only in cyclic dimers, even in high dilution conditions. Although monocyclization was not observed, it may be possible to take advantage of this selectivity. By installing the correct number of ΔAAs in a small peptide fragment, it may be possible to selectively oligomerize to a predetermined length and then cyclize, based on the conformation of the linear oligomer. There are numerous natural trimeric and tetrameric cyclic peptides,\textsuperscript{57} and this could prove an effective strategy for accessing these products.

### 2.4.2 Hydrogenation of Cyclic Dehydropeptides

With a cyclic pentapeptide bearing 4 enamides in hand, I looked to the next challenge – the diastereoselective reduction of all 4 enamides using asymmetric homogeneous hydrogenation. As described above, Kagan and Ojima observed that 2 enamides could be reduced with high selectivity using a variety of rhodium catalysts bearing chiral diphosphine ligands. Burk’s DuPhos ligands had long been known to effect the asymmetric hydrogenation of enamides\textsuperscript{47,58} and, more recently, Xumu Zhang had developed a set of chiral bisphosphine ligands known as TangPhos\textsuperscript{59} and DuanPhos\textsuperscript{60} based on Burk’s DuPhos ligands. Zhang’s ligands proved to be particularly effective in the asymmetric hydrogenation of various enamides, accessing grams of chiral amino acids using low catalyst loadings.

Based on these reports, I chose a handful of ligands to screen for efficacy in the asymmetric hydrogenation of 10: dppp, DIPAMP, iPr-DuPhos, RRSS-DuanPhos, iPr-BPE, and
MeO-BIPHEP (Figure 2.5). These ligands were chosen based on their use in the literature in the hydrogenation of enamides.

![Ligands](image)

**Figure 2.5 - Ligands screened in the hydrogenation of 10**

Initial conditions for the hydrogenations, which were conducted in 25 mL Schlenk vials, were as follows: 0.1M in MeOH, 20% catalyst loading, under 3 atm of hydrogen pressure at room temperature, and the reaction was quenched after one day. Analysis by LCMS indicated that most of the hydrogenations had not proceeded to complete conversion. However, the hydrogenation catalyzed by Rh-DuanPhos had completely converted to the fully-hydrogenated product and, while the reaction mixtures after 2 days were homogeneous in the other vials, I observed a white precipitate in this particular vial. Filtration of the solid (86% yield) and analysis by $^1$H-NMR in DMSO-$d_6$ showed a remarkably well-resolved and uncomplicated spectrum. The $^{13}$C-NMR spectrum of this compound was also relatively simple – it seemed that there was a single diastereomer present. Confirmation of the stereochemical structure of this cyclic pentapeptide could not be immediately provided by spectroscopic methods, however.
To ascertain which diastereomer I had created, Byoungmoo constructed cyclo(GlyL-PheL-PheL-PheL-Phe) using conventional peptide synthesis (via EDCI/HOBt couplings with L-PheOH, obtaining only a 12% yield of the material from the cyclization reaction). NMR- and chiral SFC-analysis indicated that we had indeed made a single diastereomer of the cyclic GFFFF after cyclization of the linear dehydropeptide and asymmetric hydrogenation. As well, using the (RRSS) enantiomer of DuanPhos, we had produced the all-D enantiomer in > 99:1 er. The sense of enantioinduction is in agreement with the literature. Analysis of the 1H-NMR spectrum of a 24h aliquot of the hydrogenation reaction shows that the process is diastereoselective, and the diastereopurity of the product does not necessarily arise due to purification of the crude material (Figure 2.6).
Figure 2.6 - $^1$H-NMR spectra of a 24h crude aliquot (above) and the triturated product (below), showing that the hydrogenation is diastereoselective and purification does not significantly increase the diastereopurity of the product.
It was fortunate that the first ligand screen yielded an asymmetric hydrogenation catalyst that provided the target in high diastereo- and enantioselectivity. We had shown that a single stereoisomer out of a possible 16 \((2^4)\) was obtained in excellent yield. Analysis of the crude reaction mixture showed that the purity of the product did not arise from the method of isolation – the catalyst was highly selective. Thus, each enamide was being reduced under complete catalyst control. Installation of a fluorinated residue (Scheme 2.11) allowed for straightforward determination of diastereoselectivity, and the fluorinated cyclic peptide also exhibited high diastereopurity. Optimization of the reaction conditions allowed us to decrease the catalyst loading down to 4 mol\% (1% per enamide). Subsequent experiments showed that the first three hydrogenations proceeded rapidly but the fourth would be sluggish. It was presumed that this is due to the difference in solubility in polar solvents of the starting material and various intermediates; after 3 enamides are reduced, the peptide becomes much less soluble in MeOH, and so the fourth reduction is much slower. To partially alleviate this, DMF can be added as a co-solvent in a ratio of 4:1 MeOH:DMF. I tried adding DMSO as a co-solvent, but DMSO arrested catalysis. With DMF, reactions proceeded to completion more rapidly and reliably and catalysis did not seem to be negatively affected.

Using the optimized conditions, I studied the effects of different modes of catalytic hydrogenation on the fluorinated cyclic dehydropeptide (10-F). Hydrogenation of this cyclic dehydropeptide under heterogeneous conditions using palladium on carbon resulted in a complicated mixture of diastereomers – 7 distinct peaks were visible in the \(^{19}\text{F}-\text{NMR}\) spectrum. This was expected with any achiral catalyst, so we were thoroughly surprised to see that hydrogenation under homogeneous conditions using dppp as the ligand produced a cyclic peptide with high diastereoselectivity (19:1:1). However, this diastereomer was different than (11-F) and
the structure of this molecule eluded us for some time. We hypothesized that this peptide would be racemic but could have alternating chirality. In order to test this hypothesis, I synthesized the cyclic pentapeptide bearing alternating chirality from D-Phe and L-Phe. As we hypothesized, the $^1$H-NMR data for the cyclic peptide in question and this alternating cyclic peptide matched; hydrogenation of the cyclic dehydropeptide with Rh-dppp results in alternating D,L stereocentres. This is an exciting result; Reza Ghadiri has made use of peptides with alternating chirality to combat Methicillin-resistant *Staphylococcus aureus*. These peptides form nanotubes with the R-groups of the amino acids project outwards, thus allowing a strong hydrogen-bond network between the amides of adjacent peptides. These self-assembling nanotubes form ion channels that will disrupt the organism’s cellular functions and cause it to die. However, the basis of our observed selectivity was difficult to grasp. As of yet, it is still unclear as to why a simple, achiral ligand like dppp can offer such high diastereoselectivity for such an unusual diastereomer. Studies on this aspect of the hydrogenation are currently underway.

**Scheme 2.12** - Hydrogenation of 10-F using achiral catalyst [Rh(dppp)(COD)]BF$_4$ delivers 12-F, a cyclic pentapeptide with alternating chirality, with high diastereoselectivity.

Finally, to highlight the use of this strategy with other residues, we synthesized a number of serine derivatives (Figure 2.7). We constructed another cyclic dehydropentapeptide containing
different aryl- and alkyl-substituents (18, Scheme 2.13). The synthesis for 18 was similarly efficient as the above synthesis of 1. This cyclic dehydropeptide was reduced at rt using 10 mol% Rh[(SSRR)-DuanPhos](COD)]BF₄ to produce the substituted cyclic pentapeptide 19. The product was precipitated with hexanes to produce 19 as a single diastereomer, as observed by ¹H- and ¹⁹F-NMR, in 50% yield. The condensation and reduction approach can access cyclic peptides with amino acid sequences that differ greatly in their properties in a high yielding and stereoselective manner.

**Figure 2.7** – Selected examples of other serine derivatives

**Scheme 2.13** – Synthesis of substituted cyclic pentapeptide 19.
These preliminary studies suggest that we can access small cyclic peptides efficiently via iterative condensations to construct linear dehydropeptides, cyclize them under standard reaction concentrations without any oligomerization, and then reduce them via homogeneous rhodium catalysis to form different diastereomers using different ligands in a highly selective manner. With this proof-of-principle, we turned to the synthesis of biologically-relevant cyclic peptides to demonstrate the practicality of this strategy.

These homogeneous hydrogenation conditions will hydrogenate a linear dehydropeptide in high diastereoselectivity as well. What is perhaps surprising is that a dehydro-oxazolone will not be reduced under these conditions. Thus, linear hexapeptide 20 under the same hydrogenation conditions, will undergo reduction at the 4 dehydroresidues but not at the terminal oxazolone to provide 21.

Scheme 2.14 – Hydrogenation of linear dehydrohexapeptide 20 reduces the 4 dehydroresidues, but not the dehydro-oxazolone. Stereochemistry assigned in analogy to 11 and to ref. 60.
2.5 Mahafacyclin B

2.5.1 Prior Syntheses of Mahafacyclin B

As initial benchmarking for this synthesis, I targeted two natural products: Mahafacyclin B and Clausenain B. These two cyclic peptides were well-suited for our synthesis, each bearing four phenylalanine residues. I was successful in applying the condensation-and-reduction strategy to the synthesis of both molecules. I will describe the synthesis of Mahafacyclin first then Clausenain, as this was the order in which I synthesized them.

![Figure 2.8 - Mahafacyclin B](image)

**Mahafacyclin B** was isolated from the latex of *Jatropha mahafalensis*, a bottle tree from Madagascar, as a minor peptide component. The latex has been traditionally used as a topical treatment for wounds. Mahafacyclin B (Figure 2.8) was characterized as cyclo(TFFGFFG) by repetitive preparative HPLC followed by tests to determine the nature of the compound and numerous 1D- and 2D-NMR experiments. Preliminary biological assays demonstrate a moderate antimalarial activity ($IC_{50} = 2.2 \mu M$; cf. 16 µM in Mahafacyclin A). These two cyclic peptides display a β-bulge, a disruption of H-bonding in a peptide that can allow for extra amino acid incorporation without affecting the secondary structure of the rest of the peptide. The
significance of this in the biological activity of the Mahafacyclin and related cyclic peptides is unknown. Irrespective of the unknown mechanism of action and the moderate biological activity, Mahafacyclin B has been a popular target in peptide synthesis.

The Phe-Phe-Gly repeat is a common motif in most of the known syntheses of Mahafacyclin B. In addition to its isolation, the group of Catherine Auvin-Guette also accomplished the synthesis of the cyclic heptapeptide in order to confirm its structure. Figure 2.7 highlights the use of the aforementioned tripeptide motif – they build the tripeptide then dimerize it to form Boc-Phe-Phe-Gly-Phe-Phe-Gly-OMe. Deprotection and addition of Thr completes the linear heptapeptide. Deprotection of the C- and N-termini and cyclization under high dilution (<1 mM) conditions afforded the cyclic peptide in 30% cyclization yield, 10% yield overall. This synthesis provided enough material to confirm the structure they had elucidated.

**Figure 2.9 -** Auvin-Guette's synthesis of Mahafacyclin B
The group of Katrina Jolliffe has developed the use of pseudoprolines as turn-inducers that also function as masked Thr and Ser residues. Mahafacyclin B provided a promising platform upon which to benchmark this method, but a different disconnection was proposed in order to place the Thr (and, hence, the pseudoproline) in the middle of the linear heptapeptide (Figure 3). As such, they were unable to take advantage of the repeated tripeptide, making their synthesis less convergent. However, the cyclization yield of the linear heptapeptide (23) bearing a pseudoproline (63%) was twice that of the yield obtained by Auvin-Guette at over 5 times the concentration (5 mM).

![Scheme 2.15](image)

**Scheme 2.15** – Replacing Thr with Jolliffe’s pseudoproline results in an increase in efficiency in peptide cyclization. Acidic hydrolysis removes the auxiliary, revealing Thr and delivering Mahafacyclin B.

In 2009, the group of Andrea Robinson published their strategy for the synthesis of cyclic peptides making use of olefin metathesis. They targeted Mahafacyclin B and achieved the synthesis of an analogue thereof. The Phe-Phe-Gly tripeptide was modified, replacing the first phenylalanine of each tripeptide with L-allylglycine (Scheme 2.16). The linear heptapeptide contained allyl groups at residues 2 and 6. Submitting this bis-allyl peptide to ring-closing metathesis using Grubbs G2 catalyst, peptide macrocycle 25 was formed in high yield. Head-to-
tail cyclization of the peptide provided an impressive 55% yield of the bicyclic peptide 26. Direct ring-opening metathesis of this product with styrene did not proceed, so the olefin tether had to be opened via ring-opening olefin metathesis with butene, and then these were replaced, again using metathesis, with styrenyl groups. Overall, this synthesis was not efficient or step-economical, nor did it provide the natural product, but it did highlight the use of a tether to help favor cyclization over competing pathways.

**Scheme 2.16** – Robinson’s synthesis of Mahafacyclin B. The linear peptide is constructed using SPPS. Phe-2 and Phe-6 are replaced with L-allylglycine. Olefin metathesis tethers these two olefins together, bringing the N- and C- termini in proximity and facilitating peptide cyclization.

Most recently comes the work of Laurent Trembleau in what was dubbed “rapid repetitive solution phase synthesis” or RRSPS. The crux of this strategy is the use of Boc-amino pentafluorophenyl (Pfp) esters, which are in turn synthesized from the corresponding N-protected amino acids and pentafluorophenol using EDCI. These amino-Pfp esters are significantly less polar than the corresponding amino acids, so the products of coupling reactions can be rapidly purified by extraction from acidic aqueous solution with ethyl acetate then precipitating the
product in a nonpolar solvent (typically petroleum ether) via ultrasonic extraction. In this fashion, Mahafacyclin B was synthesized in 12 steps in an overall yield of 24%. While this strategy runs closely parallel to conventional peptide synthesis, including the implied use of coupling reagents at each step as well as protecting groups, the manipulations required to accomplish each step are significantly streamlined. Despite the streamlined synthesis, each step still requires the use of pentafluorophenol, coupling reagents, and protecting groups, generating a great deal of waste. The Pfp-esters can be compared to oxazolones in the sense that they are isolable activated esters that render the peptide more non-polar, but Pfp-esters are made using EDCI couplings, whereas oxazolones are simple condensations, eliminating only acetic acid.

2.5.2 Condensation and Reduction Approach to Mahafacyclin B

We set out to synthesize Mahafacyclin B with the purpose of developing a convergent synthesis while minimizing \( N \)-protecting group manipulations and peptide couplings, and simplifying purifications. Since we had observed excellent results using glycine at the \( N \)-terminus of our cyclizations, we chose the disconnections shown in Scheme 2.17.

![Scheme 2.17 - Our retrosynthetic strategy for the synthesis of Mahafacyclin B](image-url)
BocGlyΔPheβPhSerOH (31) was an intermediate in the synthesis of 10 (see experimental section). In the synthesis of tetrapeptide oxazolone 30, we anticipated that the β-OH of the Thr residue would be acetylated during the condensation cyclization. What we did not anticipate was the effect this would have during the subsequent aminolysis. Normally, opening an aminolysis of an oxazolone adjacent to a chiral amino acid requires precise stoichiometry to avoid epimerization of that chiral centre. However, this acetate rendered the chiral centre much more sensitive. Upon deprotonation, instead of simply racemizing the chiral centre, the acetate would eliminate and generate a dehydro-ethylglycine residue 33 as shown in Scheme 2.18.

scheme 2.18 - The aminolysis conditions from oxazolone 32 need to be milder to avoid elimination of the acetate.

This by-product was difficult to remove via chromatography. However, we could very easily observe this process by LCMS during the course of the reaction. As a result, we could quickly optimize conditions that would avoid deprotonating the Thr α-proton by cooling the reaction in an ice bath and further modifying the stoichiometry of the amino acid nucleophile and base. Submitting the tetrapeptide acid to condensation conditions (Ac₂O and NaOAc) resulted in the rapid formation of the tetrapeptide oxazolone, which would precipitate from the reaction mixture.
within 2 hours. Mild basic extraction followed by precipitation from dichloromethane using hexanes provided tetrapeptide oxazolone 30 in 84% yield, which was used without further purification.

The coupling of the tetrapeptide oxazolone 30 and the tripeptide free acid 31 proceeded sluggishly when compared to other aminolyses, but there were few by-products during the reaction. The coupling was accomplished by deprotecting 31 using TFA, removing all of the volatile compounds, and then adding a solution of the deprotected tripeptide in CH₂Cl₂ and NEt₃ (3 eq.) to a solution 30 in CH₂Cl₂. Catalytic DMAP was then added to accelerate the aminolysis. Even with the catalyst, the reaction still required 20h to achieve complete conversion by LCMS. Condensation of this heptapeptide and subsequent isolation by column chromatography afforded the heptapeptide oxazolone in 76% yield over two steps. Cyclization of this heptapeptide oxazolone was accomplished much the same as above – deprotection of the Boc group in TFA followed by dissolution in CH₂Cl₂ and addition of NEt₃ and DMAP. These conditions afforded the cyclic dehydropeptide in 73% yield originally. Further optimization provided conditions that were more concentrated and used a more benign solvent. The optimized cyclization was performed at a concentration of 0.1M in 2-MeTHF with NEt₃ and DMAP. After purification by passing through a plug of silica eluting with ethyl acetate, 88% of the cyclic dehydropeptide was isolated as an off-white solid.
Scheme 2.19 - Forward synthesis of Mahafacyclin B. Synthesis of cyclization precursor was high-yielding and convergent. See experimental data for reaction conditions.

Hydrogenation of the cyclic dehydroheptapeptide proceeded slower than previous hydrogenations. While the starting material was readily soluble in dichloromethane or methanol, the partially hydrogenated peptide was decidedly insoluble in these solvents. In order to reduce the amount of partially hydrogenated peptide, the starting material was dissolved in enough DMF such that the final reaction solvent was 4:1 MeOH:DMF. Even still, 20% catalyst loading and 4 days of reaction time were required to achieve complete conversion. In this case, switching to a MeOH:CH$_2$Cl$_2$ (1:1) mixture rendered the reaction mixture homogeneous throughout the reduction. This allowed us to drop the catalyst loading to 5%, and the reduction was complete after two days at rt. Deprotection of the acetate was accomplished in a straightforward manner – addition of 10 eq. of potassium carbonate directly to the crude solution from the hydrogenation and stirring at rt for 20 min resulted in complete deprotection.
Completion of Mahafacyclin B. Cyclization of linear heptapeptide proceeded efficiently. Hydrogenation and deacetylation of the cyclic dehydroheptapeptide provided Mahafacyclin B in a moderately high yield.

Mahafacyclin B was purified via reverse phase chromatography (see experimental section for details) to provide the natural product as a white solid in 74% over the two steps (hydrogenation and deacetylation).

The overall yield of our synthesis, 37%, is higher than Trembleau’s 24%. However, our synthesis provides the advantages of significantly reducing N-protecting groups (2 Boc groups vs. 7 Boc groups) and conventional peptide couplings (1 EDCI coupling vs. 4 EDCI/HBTU couplings). These parameters can be quantified using industrial green metrics, which will be discussed below. Further work will be focused on optimizing purification procedures to offer better yields.
2.5.3 Analysis of the Synthesis of Mahafacyclin B Using Green Metrics

The strength of the condensation and reduction approach to cyclic peptide synthesis does not lie in comparatively higher yields or step economy,\textsuperscript{64} although fewer steps are required as a result of obviating the need for \textit{N}-protecting groups in each iteration. SPPS is designed to offer a reliable synthesis of peptides in high yields, and the typical Fmoc-based synthesis on rink amide resin does exactly that. Cyclization, as discussed above, requires high dilution, but high yields can still be achieved. The conventional synthesis of peptides is, however, quite wasteful. Forcing conditions are required to ensure complete conversion of starting material. Many equivalents of coupling agents, transacylating agents, and bases are used in each step. Toxic solvents (namely DMF) are used to bring the peptide component of the peptide-resin complex into solution, and this solvent is difficult to process for disposal because of its high boiling point and the inherent toxicity of its vapors. And, finally, the high dilution conditions required for cyclization are prohibitive towards scaling of this process.

These are issues that need to be addressed in order to provide a general synthesis of small cyclic peptides that can be industrialized. For an example of a process that creates small cyclic peptidic structures in an efficient manner, one can refer to Yudin’s Ugi multicomponent cyclization of short peptides.\textsuperscript{28b} Where the head-to-tail cyclizations of many short peptide sequences occur at 0.1\,-\,10\,mM and often at low temperatures to control epimerizations, the optimized conditions in the Yudin method were 0.2M at room temperature. The only drawback of this method is that the synthesis of the linear peptide sequence is unchanged from the conventional paradigm, using EDCI/HOBt or HATU to accomplish the linear solid phase synthesis, with all of the waste that that entails. This is still a massive improvement over the
convention, and this can be quantitatively measured using a parameter designed to describe the net amount of material required to create a certain amount of desired product: process mass intensity.65

Process mass intensity is defined as the amount of material (solvents, reagents, reactants, catalysts, etc.) required to produce a unit of the desired product, typically measured in kg/kg. Process mass intensity (PMI) has recently been chosen by the American Chemical Society Green Chemistry Institute’s Pharmaceutical Roundtable as the key benchmarking parameter for an industrial process, and this is for good reason.66 PMI takes into account almost every physical aspect of a process (exceptions being time, temperature, etc.) to produce a straightforward measure of the amount of waste produced, which can then be translated easily into a mass efficiency by calculating the reciprocal. Atom economy, concentration, the presence of catalysts, and stoichiometry are all taken into account. Process safety, toxicity of the components, and ecological impact are not accounted for, however. Other previously-used parameters such as carbon efficiency are less comprehensive than PMI. Carbon efficiency, for example, does not take into account solvent use.

Solvent volume (i.e. reaction concentration) and density, as one might expect, contribute significantly to the PMI of a particular process. There is also a bias towards higher molecular weight products, as PMI is calculated based on mass and not molecular weight. Stoichiometry, atom economy, and other factors contribute as well, but as lesser components. In comparing our synthesis of Mahafacyclin B to the next best (Trembleau’s RRSPS strategy), we can see the strengths of our synthesis. This is important – comparing yields directly shows little advantage in the condensation and reduction approach because, as mentioned above, the conventional synthesis of peptides is optimized to deliver high yields.
I calculated the PMI of two separate steps in the synthesis of Mahafacyclin B, comparing our condensation and reduction approach to Trembleau’s RRSPS approach (see experimental section for details). These calculations should be taken with a grain of salt – some conditions were not specified in the Trembleau work, and in order to provide an accurate comparison, I omitted materials required for work-up and purification conditions. I looked specifically at the process of taking a protected C-activated (an oxazolone in our case or a Pfp ester in Trembleau’s case) tripeptide through to an activated tetrapeptide. This represents an iteration in adding an amino acid to a growing peptide. The calculated PMIs show that the condensation and reduction approach requires 27.7 kg of material to make 1 kg of activated tetrapeptide, whereas the RRSPS approach requires 40.2 kg. The difference of almost one third is significant – the condensation and reduction approach does not require protecting groups and large, engineered coupling reagents. In analyzing the nature of the reagents required, the condensation and reduction approach uses only simple and inexpensive reagents that are not hazardous to human health or the environment. The RRSPS approach as well as conventional peptide synthesis use expensive reagents and toxic solvents such as CH$_2$Cl$_2$ and DMF. It should be noted that Trembleau’s approach was not optimized for PMI but for yield. As a result, a comparison such as this is not completely fair; it is only included to highlight an area of improvement in current technologies for peptide synthesis and where our method can offer some advantages.

Calculating the PMI of our cyclization to cyclic dehydropeptide 29 delivers a value of 12.0 kg per kg of product. Trembleau’s cyclization reaction results in a PMI of 2276 kg per kg of product. This is a vast difference and underscores the importance of reaction concentration in evaluating the efficiency of a process; Trembleau’s cyclization is conducted at 0.1 mM, 1000 times more dilute than ours. Admittedly, these quantities do not include purification processes
and they are not directly comparable because the products are different, but they do offer an indication of the value of dehydroresidues in a cyclization reaction. The use of a benign solvent (2-MeTHF) is also valuable – it is simple to dispose of and made from renewable feedstocks. Our process has a long way to go to become industrially viable, but is, so far, showing signs that it can be optimized to become an efficient and inexpensive protocol to deliver a variety of both natural and unnatural cyclic peptides.

2.6 Clausenain B

2.6.1 Isolation of Clausenain B

Clausenain B is a cyclic octapeptide isolated from the aerial components of *Clausena anisum-olens*, a shrub that grows in the Hekou County of the Yunnan province of China. This cyclic octapeptide is unusually rich in phenylalanine residues and takes the structure of \( \text{cyclo} (\text{LeuSerPhePheLeuGlyPhePhe}) \).\(^{67}\) As of yet, this cyclic peptide has not been synthesized nor has any biological activity been determined. I thought this would be an interesting target to see how the bulky leucine residues might influence the diastereoselectivity of the hydrogenation.

2.6.2 Condensation and Reduction Approach to Clausenain B

As with Mahafacyclin B (see Scheme 2.17), I chose to disconnect the peptide into two halves at positions where coupling the halves would open an oxazolone and the cyclization would also occur at an oxazolone. The resulting segments would both start with leucine, followed by serine in segment A and glycine in segment B, and then addition of two \( \beta \)-PhSerOH residues (3) as described above would complete both segments. I anticipated that the \( \beta \)OH in tetrapeptide 36 would be acetylated much like threonine in 30.
The synthesis of segments A and B proceeded as follows (Scheme 2.22). BocLeuOH was coupled to HCl•SerOMe (segment A) or HCl•GlyOEt (segment B) via EDCI coupling, and the esters were then hydrolyzed with LiOH. Both peptides were then coupled to HCl•β-PhSerOMe. The tripeptides were hydrolyzed as above, and then condensed using acetic anhydride. Both tripeptides were washed repeatedly with sat. sodium bicarbonate (aq.) to yield crude solids, which were precipitated from dichloromethane with hexanes to produce excellent yields of the tripeptide oxazolones 38 and 39 as white solids that were analytically pure by NMR and HPLC analysis.

Scheme 2.21 – Retrosynthetic strategy targeting Clausenain B (33)

Scheme 2.22 - Synthesis of Clausenain fragments 34 and 35. No chromatography was necessary in the synthesis of these tetrapeptides.
During the condensation, the βOH of the serine residue in 38 was acetylated, as expected. Aminolysis of the 38 with βPhSerOH (3) had to be performed much more carefully than that of 39 due to the presence of a chiral centre adjacent to the oxazolone, much like in Mahafacyclin B. Slightly substoichiometric base and an excess of 3 were used, and the reaction was kept in an ice bath to avoid racemizing the chiral centre or eliminating the acetate group. Aminolysis of 39 could be performed at room temperature using excess base and nucleophile, to give 37, which was then deprotected using TFA. Condensation of 38 yielded tetrapeptide oxazolone 36, and, thus, I was ready for the coupling of both tetrapeptides.

The coupling of 36 and 37-TFA was considerably slower than the corresponding coupling of 30 and 31-TFA in the synthesis of Mahafacyclin B, only achieving complete conversion after 36h. As a result, the LC/MS trace was more complicated, with small amounts of numerous by-products arising from hydrolysis of oxazolone 36 and other, less tractable side reactions. After acidic work-up, the crude reaction mixture was submitted to condensation using acetic anhydride and NaOAc. The desired mass was easily distinguishable by LC/MS and was indeed the major product, but there were still numerous by-products. Unfortunately, the linear octapeptide was difficult to purify. Nonetheless, the linear octapeptide was deprotected and submitted to cyclization conditions, and the cyclic dehydro-octapeptide 39 was isolable by silica gel chromatography, providing spectroscopically pure material (albeit in a very modest 36% yield from 36 and 37-TFA) upon which to perform the asymmetric hydrogenation. The low yield is attributed to the inefficient coupling reaction; we are engaged in a second generation synthesis of Clausenain B, which provides an alternative disconnection pattern.
I was excited to observe that the above hydrogenation conditions and de-acetylation procedure using (SSRR)-DuanPhos and K$_2$CO$_3$/MeOH provided Clausenain B (35) with high diastereoselectivity for the correct (natural) diastereomer even in the crude mixture (Figure 2.10) after removal of the acetate. This also shows that these deacetylation conditions do not epimerize the peptide. The natural product was isolated by filtering through a plug of C18-silica, to remove the catalyst. Concentration of the filtrate to dryness provided Clausenain B as a white solid in 60% yield from 41. Although the overall yield of the synthesis was low due to the difficulties in coupling fragments 36 and 37, it shows an example of highly diastereoselective hydrogenation of a cyclic dehydropeptide bearing chiral centres.
2.7 Thoughts, Conclusions, and Future Directions

We were able to take advantage of the nature of dehydropeptides to favor cyclization, accessing small cyclic dehydropentapeptides in very high yields with no observed side reactions. We were able to apply asymmetric hydrogenation, a well-established methodology, to set all of the stereochemistry in the peptide in a highly stereoselective manner, creating one stereoisomer out of a possible sixteen. We can access unusual diastereomers by simply changing one ligand for another, and because of the robustness of asymmetric hydrogenation catalysts, we can
hydrogenate a peptide bearing substituents with differing chemical properties, including both steric and electronic, in a similarly highly selective manner. And finally, I was able to apply this strategy in the synthesis of two natural products, Mahafacyclin B and Clausenain B. Altogether, these preliminary results suggest that this approach could provide stereoselective access to new cyclic peptides and enable the synthesis of these compounds in an efficient and scalable manner.

There are many avenues to explore from here. First, we would like to integrate our approach to peptide synthesis to solid phase synthesis. Our goal in this work is not to replace any current methodologies, but to offer peptide chemists a new way of thinking when approaching the synthesis of peptide targets. To this end, our synthesis should be amenable to on-resin synthesis with judicious resin selection. Since our synthesis is in the N→C direction, which is opposite of conventional SPPS, the choice of resins is limited, but the commercially-available imidazole carboxylate resin shown in Figure 2.11 is well-suited for our strategy. It is electrophilic and designed to anchor the N-terminus to the resin, and the peptide can be cleaved from the linker using TFA, using similar conditions to the Boc deprotection in our peptide synthesis.

![Figure 2.11 - The imidazole carboxylate resin is an electrophilic peptide resin that can be cleaved with TFA](image)

One area of immediate improvement is in the scope of this synthesis. The challenge does not lie in incorporating different residues into our synthesis but rather the synthesis of the serine
derivatives themselves. As indicated in section 2.4.1, the synthesis of serine derivatives is typically accomplished in a stereoselective manner at a small scale. We would need to develop a general and scalable method that is not necessarily stereoselective, as that chiral information would be deleted over the course of the synthesis. Aldol additions of glycine into aryl aldehydes work well only for this class of electrophile, but work needs to be done to access a wider variety of serine derivatives. Using a copper-mediated aldol,\textsuperscript{51a} we were able to access βiPrSerOH (15), and similar serine derivatives can be made the same way – the report also indicates that βOH-Asp is accessible using this method. Unfortunately, this method necessitates purification using ion exchange chromatography, which is unfeasible for a simple, scalable process.

Once we have developed the condensation and reduction approach to the point where we can access a wide variety of peptides in both the solution and solid phase, we can think about collaborations with other academics and with industrial partners. If we are able to access a variety of small cyclic peptides and, importantly, the various diastereomers thereof in high stereopurity, we would have an incredibly valuable small molecule library that exists in a chemical space that industry has not yet been able to explore. Professor Stuart Schreiber, director of the Broad Institute, has expressed interest in screening the cyclic peptides we have made for various disease types, which could be a promising collaboration. The compounds we have made thus far, even the achiral cyclic dehydropeptides, are unique in the literature, and the biological activity of these molecules has never been ascertained.

Moving away from typical peptide scaffolds is a promising research path as well. There are numerous asymmetric transformations of enamides, including conjugate addition,\textsuperscript{68} hydroacylation,\textsuperscript{69} and hydroformylation,\textsuperscript{70} which could be optimized for transforming our cyclic dehydropeptides to chiral peptidic molecules with unique properties. Appending an alkyne or an
azide, which should be straightforward from a halogenated phenylalanine residue, will allow for numerous functional small molecules to be added to our cyclic peptides via Huisgen cycloaddition. This strategy is attractive because of its efficiency, its simplicity, and for its versatility in accessing natural and unnatural peptide structures, and we hope that it finds general use in the synthetic community. We can apply the concept of installing ΔAAs to facilitate the synthesis of cyclic natural products and pharmaceuticals and then applying a substrate- or catalyst-controlled asymmetric transformation in order to set chirality after the cyclization.
2.8 References


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2.9  Experimental Data

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I.  General procedures

Commercial reagents were purchased from Sigma Aldrich or Alfa Aesar and were purified prior to use following the guidelines of Perrin and Armarego. Amino acids and peptide coupling agents were purchased from Anaspec and Chem-Impex and used as is. All reactions were carried out under nitrogen or argon atmosphere unless otherwise indicated. Reactions were monitored using thin-layer chromatography (TLC) on EMD Silica Gel 60 F254 plates (visualization of the developed chromatogram was performed by fluorescence quenching or KMnO4 stain) or via analysis on a Waters 2795 Separations Module equipped with a Waters 2996 Photodiode Array and a Waters Micromass ZQ mass spectrometer. Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. 1H and 13C NMR spectra were recorded on any of three instruments: a Varian Mercury 300 and a Varian Mercury 400, both equipped with automatic sample loaders, and a Varian NMR 400. NMR spectra were internally referenced to residual protio solvent signals. Data for 1H NMR data are reported as follows: chemical shift (δ shift), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for 13C NMR are reported in terms of chemical shift (δ ppm).

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Mass spectra (MS) were recorded on a Sciex QStar Mass Spectrometer. Infrared (IR) spectra were obtained on a Thermo-Scientific Nicolet iS5 equipped with an iD5 Diamond ATR and are reported in terms of frequency of absorption (cm$^{-1}$). Melting point ranges were determined on a Fisher-Johns Melting Point Apparatus. Chiral analysis was performed on an Agilent 1200 series HPLC equipped with an Aurora SFC module. Optical rotations were measured on a Rudolph Research Analytical Autopol III Automatic Polarimeter. Column chromatography was performed using Silicycle Silia-P Flash Silica Gel, using either glass columns, a Biotage SP1 system, or a Biotage Isolera system. All salts were purchased from Aldrich and used without purification. Solvents were purchased from Caledon and were purified according to standard procedures. Chiral diphosphine ligands were purchased from Strem.

**Note:** It is difficult to obtain clean $^{13}$C-NMR spectra of dehydropeptides due to slow tumbling and rotation at the NMR timescale, and possibly due to aggregation. Byoungmoo has recently found that heating NMR samples to high temperatures (on the order of 75 °C) can offer high resolution $^1$H-NMR spectra, and we are currently investigating similar NMR experiments studying $^{13}$C and 2D experiments. However, the hydrogenated peptides tend to provide well-resolved spectra, and those are shown below.

## II. Methods for the synthesis of serine derivatives

### Phenylserine

\[
\begin{align*}
\text{H}_2\text{N-} & \text{COOH} + \text{H-} & \text{COPh} \xrightarrow{\text{NaOH (aq.)}} \text{HO-} & \text{PhCOOH}
\end{align*}
\]

To a 2L beaker equipped with a large stirbar was added 250 mL of water. 60g of NaOH was added slowly with stirring. To this solution was added 75g of glycine and 206 mL of benzaldehyde in one portion. The biphasic reaction mixture was stirred vigorously at rt for 3h. During this time, the reaction mixture homogenized, turned from colorless to light yellow and then a precipitate formed. After 3h, the entire reaction mixture solidifies. This white solid was broken to the consistency of a paste using a glass rod, a pestle and/or manually using heavy-duty gloves. 130 mL of conc. HCl (aq.) was then added in one portion (caution: evolution of heat) and the reaction mixture was stirred for 2h. Once the mixture had cooled to rt, a precipitate began to form. The reaction vessel was then cooled in a refrigerator for 6h and copious amounts of a white solid precipitated. This precipitate was filtered and washed with 6x50 mL of absolute ethanol and then dried overnight. By this method, 122g (67%) of phenylserine was isolated. Spectral data matches the literature.
**β(4-halophenyl)serine derivatives**

To a 250 mL Erlenmeyer flask equipped with a magnetic stirbar was added EtOH (200 mL) and KOH (5.6 g, 100 mmol, 2 eq.) and this mixture was stirred at rt until complete dissolution of the KOH was observed. Glycine (3.75 g, 50 mmol, 1 eq.) was then added, and this mixture was again stirred until homogeneous. 100 mmol of the corresponding haloarylaldehyde was then added with stirring. After 2-4h of stirring at rt, precipitate formed until the entire reaction mixture became a white solid. This solid was then broken up mechanically (note: addition of 25 mL of EtOH on top of the solid and letting it rest overnight facilitated this step substantially) and 9 mL of 12M HCl (aq.) was added with stirring. Any remaining large clumps were crushed using a glass rod. The precipitate (likely to be KCl) was filtered off, and the filtrate was concentrated under reduced pressure. To the crude concentrate was added 50 mL of dichloromethane (note: often, a precipitate forms after addition of dichloromethane, which is the desired product - however, much of it remains dissolved in the crude mixture, so it is best to continue with the extraction) and 80 mL of water. The phases were separated and the aqueous phase was washed twice more with dichloromethane (2x50 mL) then concentrated under reduced pressure to afford the arylserine derivative as an off-white or white solid (note: evaporation of water under reduced pressure is rendered much less problematic by adding a small amount of 2-propanol to the mixture prior to concentration).

Isolated as a white solid in 78% yield (8.4 g) in a 5:1 mixture of diastereomers.  

$^1$H-NMR (MeOD, 400 MHz): δ 7.44 (m, 4H), 5.29 (d, 1H, $J = 5.28$), 3.97 (d, 1H, $J = 5.24$);  $^{13}$C-NMR (MeOD, 100MHz) δ 169.6, 139.1, 128.6, 127.8, 70.2, 59.8, 40.2; LRMS (ESI+) m/z 216.0; HRMS (ESI+) m/z calc’d for C$_9$H$_{10}$ClNO$_3^+$ (MH$^+$): 216.0433, found: 216.04275

Isolated as a white foam which, upon further drying, crumbled as a white solid in 42% yield (4.2g) in a 4:1 mixture of diastereomers. $^1$H-NMR (MeOD, 400 MHz): δ 7.49 (dd, 2H, $J = 11.44, 7.24$), 7.14 (m, 2H), 5.30 (d, 1H, $J = 5.52$), 4.08 (d, 1H, $J = 5.68$); $^{13}$C-NMR (MeOD, 100MHz) δ 169.6, 164.5, 161.3, 135.9, 128.2 (d, $J = 11.0$ Hz), 115.3 (d, $J = 28.9$ Hz), 70.4, 59.7, 40.1; LRMS (ESI+) m/z 200.1; HRMS (ESI+) m/z calc’d for C$_9$H$_{10}$FNO$_3^+$ (MH$^+$): 200.0725, found: 200.0717
**β(4-nitrophenyl)serine**

To a 250 mL recovery flask equipped with a stirbar was added 150 mL of dichloromethane, 170 mg of tetrabutylammonium hydrogensulfate (0.5 mmol, 0.01 eq.) and 15 g of 4-nitrobenzaldehyde (100 mmol, 2 eq.). This suspension was cooled in an ice bath and stirred. Separately, a solution of 3.75 g of glycine (50 mmol, 1 eq.) and 2.2 g of NaOH (55 mmol, 1.1 eq.) in 30 mL of water was prepared and stirred until homogeneous. This aqueous solution was added dropwise over 2 h via addition funnel to the organic suspension with vigorous stirring. After the addition was complete, an off-white solid began to precipitate from the biphasic reaction mixture. Once 6 h had passed, 9 mL of conc. HCl (aq.) was added to the reaction mixture, and the water bath was heated to 40 °C for 30 min. Over this period of time, the precipitate dissolved completely and the aqueous phase became yellow. The aqueous phase was diluted with 50 mL of additional water, then was washed with dichloromethane (3 x 50 mL). The aqueous phase was concentrated under reduced vacuum and the crude residue was reconstituted in ethanol, precipitating a white crystalline solid. This solid was removed by filtration, and the filtrate was concentrated under reduced pressure to afford the desired product as a light yellow-to-red fluffy solid.

Isolated as a yellow powder in 67% yield as a single diastereomer. $^1$H NMR (500 MHz, MeOD-D$_4$) δ 8.32 (d, $J = 8.7$ Hz, 2H), 7.80 (d, $J = 8.6$ Hz, 2H), 5.49 (d, $J = 3.8$ Hz, 1H), 4.34 (d, $J = 3.8$ Hz, 1H). $^{13}$C NMR (126 MHz, MeOD-D$_4$) δ 168.19, 148.02, 146.91, 127.23, 123.43, 69.79, 58.55.; LRMS (ESI+) m/z 227.2; HRMS (ESI+) m/z calc’d for C$_9$H$_{10}$N$_2$O$_5$ (MH$^+$): 227.06680, found: 227.06754

Synthesized as per the Otani protocol. Characterization data matches the literature.$^2$

![Structure 14]

Made as per the Bolhofer protocol.$^3$ Isolated as a white powder in 72% yield as a 1:1 mixture of diastereomers. $^1$H NMR (500 MHz, MeOD-D$_4$) δ 7.39 (ddd, $J = 30.7, 18.1, 5.4$ Hz, 285H), 7.02 (dd, $J = 17.4, 8.8$ Hz, 78H), 5.27 (d, $J = 4.5$ Hz, 36H), 5.12 (d, $J = 7.9$ Hz, 76H), 4.63 (s, 2H), 3.88 (d, $J = 4.4$ Hz, 12H), 3.67 (d, $J = 3.6$ Hz, 11H).

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$^2$ Otani, T. T.; Winitz, M. Arch. Biochem. Biophys. 1963, 102, 464

III. Synthesis of Cyclic Pentapeptide

*BocGly∆Phe∆PheOx*

To a flame dry flask was added 30 mL of dry THF followed by 3.03 g (10 mmol) of BocGly∆PheAz. In a separate flask, 2.2 g (12 mmol, 1.2 eq) of phenylserine was added to a solution of 10 mL of THF and 4 mL of water. 2.1 mL (15 mmol, 1.5 eq) of triethylamine was added to the phenylserine suspension, and this mixture was sonicated for 5 minutes. This homogeneous mixture was then added to the BocGly∆PheAz solution in one portion, followed. If the reaction mixture is not homogeneous, more water can be added. The homogeneous reaction mixture was stirred at rt until the reaction was judged complete by LC/MS. Upon completion, the reaction mixture was acidified to pH 2-3 with 5% KHSO4 (aq.). The aqueous phase was extracted with EtOAc (3x30 mL) and the combined organic phases were washed with brine (1x20 mL), dried (MgSO4) and then concentrated under reduced pressure to afford a crude, viscous oil. This oil was dissolved in EtOAc (25 mL) and Ac2O (10 mL). To this solution was added 1.6 g (20 mmol, 2 eq) of NaOAc, and this suspension was stirred at rt. Upon completion, as determined by LC/MS, the reaction was quenched by addition of 30 mL of sat. aqueous NaHCO3 (caution – gas evolution) The aqueous phase was extracted with EtOAc (3x30 mL) and the combined organic phases were washed with brine (20 mL), washed again with sat. aqueous NaHCO3 (20 mL, caution – gas evolution), dried (MgSO4) and then concentrated under reduced pressure to afford a crude yellow solid. The crude material was purified by precipitation from dichloromethane using hexanes to afford 3.6 g (82% over 2 steps) of a yellow solid.

This two-step procedure was repeated for the synthesis of BocGly∆Phe∆Phe∆PheAz and BocGly∆Phe∆Phe∆Phe∆PheOx. mp: 129-133 °C; 1H-NMR (CDCl3, 400 MHz): δ 8.10 (dd, 2H, J = 7.8, 2.3), 7.87 (br s, 1H), 7.58 (d, 2H, J = 5.8 Hz), 7.54 (s, 1H), 7.38-7.50 (m, 7H), 7.22 (s, 1H), 5.25 (br, 1H), 4.04 (d, 2H, J = 3.68 Hz), 1.46 (s, 9H); IR (neat) 3268, 1784, 1689, 1650; LRMS (ESI+) m/z 448; HRMS (ESI+) calc’d for C25H26N3O5+: 448.1866, found: 448.1851
**BocGly∆Phe∆Phe∆Phe∆PheOx**

mp: 138-143 °C; $^1$H-NMR (CDCl$_3$, 400 MHz): δ 8.24 (s, 1H), 8.12 (m, 2H), 7.75 (s, 1H), 7.72 (d, 2H, $J = 7.48$ Hz), 7.55 (s, 1H), 7.34-7.52 (m, 12H), 7.20 (s, 1H), 5.18 (br, 1H), 3.91 (d, 2H, $J = 5.6$ Hz), 1.36 (s, 9H); IR (neat): 3372, 3237, 2989, 1806, 1778, 1686, 1660; LRMS (ESI+) $m/z$ 593; HRMS (ESI+) calc’d for C$_{34}$H$_{33}$N$_4$O$_6^+$: 593.2394, found: 593.2368

**BocGly∆Phe∆Phe∆Phe∆PheOx**

mp: 151-154 °C; $^1$H-NMR (CDCl$_3$, 400 MHz): δ: 8.98 (br s, 1H), 8.35 (br s, 1H), 8.12 (d, 2H, $J = 6.68$ Hz), 8.00 (br s, 1H), 7.74 (d, 2H, $J = 7.56$ Hz), 7.27-7.58 (m, 20H), 7.10 (s, 1H), 5.10 (m, 1H), 3.62 (d, 2H, $J = 5.16$ Hz), 1.27 (s, 9H); IR (neat): 3253, 1779, 1640-1670; LRMS (ESI+) $m/z$ 738; HRMS (ESI+) Calc’d for C$_{43}$H$_{40}$N$_5$O$_7^+$: 738.2922, found: 738.2886

**Cyclo(Gly∆Phe∆Phe∆Phe∆Phe), 10**

To a flame dry flask purged with argon and equipped with a stir bar was added 740 mg (1 mmol) of BocGly∆Phe∆Phe∆Phe∆PheOx and 5 mL of CH$_2$Cl$_2$. 5 mL of trifluoroacetic acid (TFA) was then added, and the color of the solution deepened from light yellow to orange. This solution was stirred at rt for 1h. Upon complete deprotection as determined by LC/MS, the reaction mixture was concentrated under reduced pressure and then placed under high vacuum. An additional 10 mL of CH$_2$Cl$_2$ was added and then evaporated under reduced pressure to remove remaining traces of TFA. The deep yellow solid
was dissolved in 10 mL of CH$_2$Cl$_2$ and to this yellow solution was added 280 μL of NEt$_3$ (2 mmol, 2 eq.) 12 mg of DMAP (0.1 mmol). The reaction mixture was stirred at rt until the reaction achieved completion as determined by LC/MS (30 min). The solution was then diluted by addition of 50 mL of CH$_2$Cl$_2$. The organic phase was washed twice with 30 mL 1M HCl, then three times with 30 mL of brine. The organic phase was then dried (MgSO$_4$) and concentrated under reduced pressure to afford a deep yellow solid. This solid was then suspended in CH$_2$Cl$_2$ and hexanes were added to precipitate the product, which was filtered off to produce 594 mg (93%) of a light yellow solid.

Cyclo(GlyΔPheΔPheΔPheΔPhe) mp: 209-212 °C (decomp.); $^1$H-NMR (MeOD-D$_4$, 400 MHz) δ 6.87 – 7.61 (br m, 24H), 4.16 (s, 2H); IR (neat): 3263, 1620-1650; LRMS (ESI+) m/z 638; HRMS: ESI+ calc’d for C$_{38}$H$_{32}$N$_5$O$_5$: 638.2397, found: 638.2379

IV. Methods for the Hydrogenation of Cyclic Dehydropetptides

**Cyclo(Gly$^\alpha$Phe$^\alpha$Phe$^\alpha$Phe$^\alpha$Phe), 11**

Hydrogenation Procedure A: Schlenk Vial

In a nitrogen box, 3 mg (0.0079 mmol) of (RRSS)-DuanPhos was added to 3 mg (0.0075 mmol) of Rh(COD)$_2$BF$_4$ in 2 mL of dry and degassed MeOH in a Schlenk vial equipped with a stirbar. This mixture was stirred at rt for 5 min, then 128 mg (0.2 mmol) of (cyclo)G$\Delta$Phe$\Delta$Phe$\Delta$Phe$\Delta$Phe in 4 mL of MeOH was added to this mixture. The Schlenk vial was capped and removed from the nitrogen box. On a Schlenk line, the vial was frozen (liq. N$_2$) and purged 3 times with H$_2$ gas. On the last cycle, the Schlenk vial was sealed while frozen and thawed to pressurize the vial. The reaction mixture was stirred at rt for
48h, over which an off-white solid precipitated from the solution. After 48 hours, the heterogeneous mixture was collected into a scintillation vial and concentrated under reduced pressure. The resulting crude solid was triturated in CH$_2$Cl$_2$ and MeOH and then filtered to afford an off-white solid (108 mg, 86%).

(Cyclo(Gly$^\Delta$Phe$^\Delta$Phe$^\Delta$Phe$^\Delta$Phe), 11) Mp: 246 (decomp.); $^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.53 (t, $J = 5.6$ Hz, 1H), 8.33 (d, $J = 7.6$ Hz, 2H), 8.22 (d, $J = 7.9$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.35 – 7.00 (m, 20H), 4.35 (dd, $J = 14.2$, 8.7 Hz, 1H), 4.24 (dd, $J = 15.4$, 7.2 Hz, 2H), 4.12 – 3.97 (m, 1H), 3.92 (dd, $J = 14.6$, 5.9 Hz, 1H), 3.28 (dd, $J = 14.5$, 5.1 Hz, 1H), 3.17 (d, $J = 5.3$ Hz, 1H), 3.11 (dd, $J = 13.7$, 5.6 Hz, 1H), 2.95 (dt, $J = 19.4$, 13.8, 7.1 Hz, 5H), 2.75 (dd, $J = 13.8$, 9.4 Hz, 1H); $^{13}$C NMR (100 MHz, DMSO-$d_6$) δ 171.50, 171.07, 170.69, 170.56, 169.14, 138.03, 137.66, 137.51, 137.41, 129.09, 129.07, 128.98, 128.82, 128.19, 128.17, 126.31, 57.37, 55.99, 55.75, 54.58, 43.34, 40.15, 39.94, 39.73, 39.52, 39.31, 39.10, 38.89, 36.85, 36.77, 36.58, 36.48.; LRMS (ESI+) m/z 646.3; HRMS (ESI+) calc’d for C$_{43}$H$_{40}$N$_5$O$_7$+: 646.3020, found: 646.3023

Cyclo(Gly$^\Delta$Phe$^\Delta$Phe$^\Delta$Phe$^\Delta$(pF)Phe), 10-F

Made analogously to 10, replacing the final βPhSerOH residue with β(4-fluorophenyl)serine. Synthetic protocols and yields were identical.

Cyclo(Gly$^\Delta$Phe$^\Delta$Phe$^\Delta$Phe$^\Delta$(pF)Phe): light yellow solid; mp: 210 (decomp.); $^1$H-NMR (DMSO-$d_6$, 400 MHz): δ 9.63 (m, 4H), 8.42 (br s, 1H), 7.83 – 6.95 (m, 20H), 4.06 (s, 2H); 1R (neat) 2964, 2769, 1651, 1626, 1506; LRMS (ESI+) m/z 656.2; HRMS (ESI+) m/z calc’d for C$_{38}$H$_{31}$N$_5$O$_5$+ (MH+): 656.2278, found: 656.2303

Hydrogenation Procedure B: Biotage Endeavour™ Catalyst Screening System

In a nitrogen box, 0.005 mmol of ligand (dppp or (RRSS)-DuanPhos) suspended in 2 mL of MeOH (dried and distilled over CaH$_2$, then degassed) was added to 0.005 mmol Rh(COD)$_2$BF$_4$ in 2 mL of MeOH and the resulting yellow solution was allowed to sit at rt for 20 min. The cyclic peptide (30 mg, 0.05 mmol) was dissolved in this catalyst solution, and the resulting solution was added to an Endeavour vial and
capped with a 19/24 rubber septum before being removed from the glovebox. The vial was placed in the Endeavour chamber, and the Endeavour was programmed to hydrogenate at 100 psi of hydrogen and at 40 °C for 24h. After 24h, the vials were removed from the Endeavour and their respective contents transferred to scintillation vials. The volatiles were removed under reduced pressure, and the crude hydrogenated material was reconstituted and triturated in MeOH. Filtration of the triturated peptide resulted in isolation of 23 mg (76%) of a light brown solid.

**Hydrogenation Procedure C: HEL CATalyst Block**

As above, except a total volume of 2 mL of solvent was used. The 2 mL of MeOH containing the catalyst and the substrate were added to a screw-thread 0.5 dr. vial equipped with a stirbar. The vial was capped using a screwcap that has a slitted rubber septum. The vial was removed from the nitrogen box, placed in the CATalyst block, and the head was screwed into place. The block was filled then purged three times with hydrogen, and then the block was pressurized with hydrogen to 100 psi. The reactions were typically stopped after two or three days, and then worked up as above.

*Cyclo(Gly)^{D}Phe^{D}Phe^{D}Phe^{D}(pF)Phe, 10-F*

(Cyclo(Gly)^{D}Phe^{D}Phe^{D}Phe^{D}(pF)Phe, 11-F) Via hydrogenation of 10-F with RRSS-Duanphos as the ligand in via hydrogenation procedure B: 76% yield as an off-white solid; ^{1}H-NMR (DMSO-d6, 400 MHz) δ 8.53 (t, J = 5.4 Hz, 1H), 8.36 (dd, J = 14.5, 7.7 Hz, 2H), 8.26 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.35 – 7.00 (m, 19H), 4.42 – 4.29 (m, 1H), 4.30 – 4.18 (m, 2H), 4.04 (dd, J = 15.1, 7.7 Hz, 1H), 3.93 (dd, J = 14.4, 6.0 Hz, 1H), 3.36 – 3.25 (m, 1H), 3.18 – 2.69 (m, 8H); ^{13}C NMR (DMSO, 100 MHz) δ 172.09, 171.63, 171.41, 170.65, 169.11, 138.11, 138.08, 137.55, 131.26, 131.18, 129.38, 129.08, 129.03, 128.53, 128.44, 126.69, 126.51, 126.45, 115.43, 115.22, 55.90, 54.71, 53.86, 53.56, 38.09, 36.64, 35.19; IR (neat) 3287, 1650, 1636, 1531, 1598; LRMS (ESI+) m/z 664.3; HRMS (ESI+) m/z calc'd for C_{38}H_{39}N_{5}O_{5}^{+} (MH+): 664.2952, found: 664.2929

((+/-)Cyclo(Gly)^{D}Phe^{D}Phe^{D}(pF)Phe, 12-F): Via hydrogenation of 10-F with dpdp as the ligand using hydrogenation procedure C, off-white solid, 83% yield; ^{1}H NMR (400 MHz, DMSO-d6) δ 8.76 (d, J = 7.0 Hz, 1H), 8.56 (d, J = 8.4 Hz, 1H), 8.39 (t, J = 5.7 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 7.3 Hz, 1H), 7.31 – 6.93 (m, 19H), 4.69 – 4.56 (m, 1H), 4.50 (td, J = 8.7, 5.5 Hz, 1H), 4.38 (dd, J = 13.9, 7.6 Hz,
1H), 4.24 (dd, J = 15.1, 6.7 Hz, 1H), 3.73 (dd, J = 16.0, 6.4 Hz, 1H), 3.49 (dd, J = 16.0, 5.2 Hz, 1H), 3.01 – 2.62 (m, 8H); 13C NMR (101 MHz, DMSO-d6) δ 172.09, 171.63, 171.41, 170.65, 169.11, 160.21, 138.11, 138.08, 137.55, 134.03, 131.26, 131.18, 129.38, 129.08, 129.03, 128.53, 126.69, 126.51, 126.45, 115.43, 115.90, 55.90, 54.71, 53.86, 53.56, 43.42, 40.59, 38.09, 36.64, 35.50, 35.19; LRMS (ESI+) m/z 664.3; HRMS (ESI+) m/z calc’d for C38H39N5O5+ (MH+): 664.2914, found: 664.2929

(Cyclo)-GΔ(pF)PheΔ(pNO2)PheΔLeuΔ(pOBn)Phe (18)

Made analogously to 10, adding serine derivatives 14, 15, 16, and 17 in that order to BocGly. Synthetic protocols were identical and yields were in the same range (80-85% per iteration).

Isolated as a deep orange solid by precipitation from CH2Cl2 and hexanes in 81% yield: 1H NMR (600 MHz, CDCl3) δ 8.30 (d, J = 5.5 Hz, 3H), 8.00 (s, 1H), 7.60 (d, J = 40.0 Hz, 2H), 7.25 – 7.02 (m, 3H), 5.31 (s, 1H), 4.04 (s, 2H), 1.47 (s, 9H). IR (neat, cm⁻¹): 3244, 2980, 2932, 1813, 1792, 1674, 1506

Isolated as a light yellow powder by precipitation from CH2Cl2 and hexanes in 84% yield, 1H NMR (600 MHz, CDCl3) δ 8.50 (s, 1H), 8.30 (d, J = 8.8 Hz, 2H), 7.87 – 7.76 (m, 3H), 7.56 – 7.51 (m, 2H), 7.46 (s, 2H), 7.15 (t, J = 8.5 Hz, 2H), 6.63 (d, J = 10.0 Hz, 1H), 5.27 (s, 1H), 3.96 (d, J = 5.5 Hz, 2H), 3.30 (dd, J = 6.7, 3.3 Hz, 1H), 1.43 (s, 9H), 1.20 (dd, J = 20.4, 6.7 Hz, 7H). IR (neat, cm⁻¹): 3378, 3337, 3232, 2979, 1808, 1683

Cyclo(GlyΔ(pF)PheΔ(pNO2)PheΔLeuΔ(pOBn)Phe), 18. Isolated as an off-white solid by precipitation from CH2Cl2 and hexanes in 73% yield; 1H-NMR (DMSO-d6, 400 MHz): δ 9.63 (m, 4H), 8.42 (br s, 1H), 7.83 – 6.95 (m, 20H), 4.06 (s, 2H); IR (neat) 3269, 2929, 1600, 1507, 1310; LRMS (ESI+) m/z 795.3; HRMS (ESI+) m/z calc’d for C38H31N5O5+ (MH+): 793.2554, found: 793.2556
Cyclo(Gly\(^{1}(pF)\)Phe\(^{1}(pNO_{2})\)Phe\(^{1}\)Leu\(^{1}(pOBn)\)Phe), 19. From 18 using (SSRR)-DuanPhos as the ligand at 0.05 mmol scale using hydrogenation procedure C, isolated in 50% yield as a white solid. [\(\alpha\)] (295.2 K, 589 nm) in DMF = -106.7°. \(^1\)H NMR (600 MHz, DMSO-\(d_6\)) \(\delta\) 8.63 (s, 1H), 8.31 (d, \(J = 16.8\) Hz, 1H), 8.23 (s, 1H), 8.16 (t, \(J = 8.1\) Hz, 3H), 8.03 (s, 1H), 7.50 (d, \(J = 8.0\) Hz, 2H), 7.44 (d, \(J = 7.7\) Hz, 2H), 7.40 (t, \(J = 7.6\) Hz, 2H), 7.33 (t, \(J = 7.9\) Hz, 1H), 7.18 (s, 2H), 7.10 (d, \(J = 8.6\) Hz, 2H), 7.05 (t, \(J = 8.5\) Hz, 2H), 6.91 (d, \(J = 8.1\) Hz, 2H), 4.39 (q, \(J = 7.9\) Hz, 1H), 4.32 (t, \(J = 11.8\) Hz, 1H), 4.26 (dd, \(J = 15.1, 8.4\) Hz, 1H), 3.91 (d, \(J = 8.6\) Hz, 1H), 3.82 (d, \(J = 7.1\) Hz, 1H), 3.26 (d, \(J = 15.5\) Hz, 1H), 3.20 (d, \(J = 7.4\) Hz, 2H), 3.00 (dd, \(J = 13.1, 5.9\) Hz, 1H), 2.90 (dd, \(J = 14.2, 6.0\) Hz, 1H), 2.83 (dd, \(J = 13.6, 8.3\) Hz, 1H), 2.78 (dd, \(J = 14.2, 9.4\) Hz, 1H), 1.65 (t, \(J = 13.0\) Hz, 1H), 1.42 – 1.35 (m, 1H), 1.21 – 1.12 (m, 1H), 0.78 (d, \(J = 6.7\) Hz, 3H), 0.72 (d, \(J = 6.2\) Hz, 3H). \(^{13}\)C NMR (126 MHz, DMSO-\(d_6\)) \(\delta\) 172.33, 172.04, 171.02, 170.51, 169.59, 160.46, 157.40, 146.71, 146.30, 137.69, 134.24, 131.20, 131.13, 130.95, 130.65, 130.40, 128.90, 128.26, 128.10, 123.74, 115.42, 115.25, 114.84, 110.00, 109.99, 79.72, 79.45, 79.19, 69.60, 69.09, 56.10, 55.85, 54.83, 54.74, 43.74, 24.67, 23.09, 22.05. IR (neat, cm\(^{-1}\)): 3338, 3303, 2921, 1652, 1510, 1342, LRMS (ESI+) m/z 803.4 (MNa+); HRMS (ESI+) m/z calc’d for C\(_{42}\)H\(_{46}\)FN\(_{6}\)O\(_{8}\)\(^{+}\) (MNa+): 803.3183, found: 803.3195.
BocGlyΔPheΔPheΔPheΔPheΔPheOx, 20 (from aminolysis and condensation of BocGlyΔPheΔPheΔPheΔPheOx): light yellow solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 10.02 (d, \(J = 14.0\) Hz, 2H), 9.65 (d, \(J = 7.0\) Hz, 2H), 8.36 – 8.21 (m, 2H), 7.97 (d, \(J = 7.5\) Hz, 2H), 7.64 (dd, \(J = 17.5, 17.0, 5.4\) Hz, 8H), 7.50 – 7.25 (m, 18H), 7.08 (d, \(J = 7.2\) Hz, 2H), 3.79 (d, \(J = 5.4\) Hz, 2H), 1.32 (s, 9H). IR (neat, cm\(^{-1}\)): 3245, 1809, 1789, 1658, 1505; LRMS (ESI+) \(m/z\) 883.3; HRMS (ESI+) \(m/z\) calc’d for \(C_{52}H_{46}N_6O_8^+\) (MH\(^+\)): 883.3499, found: 883.3423

BocGly\(^D\)Phe\(^D\)Phe\(^D\)Phe\(^D\)Phe\(^Ox\), 21: from 20 in 0.05 mmol scale using hydrogenation procedure C, isolated in 95% yield as a grey solid, \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) \(\delta\) 8.82 (d, \(J = 7.7\) Hz, 1H), 8.20 (dd, \(J = 7.7, 1.7\) Hz, 2H), 8.14 (d, \(J = 9.0\) Hz, 1H), 7.80 (d, \(J = 8.1\) Hz, 1H), 7.55 – 7.08 (m, 23H), 6.87 (t, \(J = 5.7\) Hz, 1H), 5.07 (dd, \(J = 14.3, 8.0\) Hz, 1H), 4.62 (dt, \(J = 18.6, 9.2\) Hz, 1H), 4.51 (dd, \(J = 7.9, 3.8\) Hz, 2H), 3.47 (ddd, \(J = 37.0, 16.8, 5.9\) Hz, 2H), 3.29 (dd, \(J = 14.1, 6.1\) Hz, 1H), 3.22 – 3.01 (m, 2H), 3.01 – 2.80 (m, 3H), 2.81 – 2.64 (m, 2H), 1.37 (s, 9H). \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)) \(\delta\) 171.66, 171.32, 169.60, 167.97, 167.43, 138.26, 137.98, 137.37, 133.53, 132.99, 132.61, 132.47, 132.17, 129.85, 129.56, 129.01, 128.70, 128.66, 128.58, 127.35, 127.02, 126.85, 78.71, 54.36, 49.99, 38.24, 37.17, 28.84. IR (neat, cm\(^{-1}\)): 3270, 1796, 1781, 1638, 1537 LRMS (ESI+) \(m/z\) 891.4; HRMS (ESI+) \(m/z\) calc’d for \(C_{38}H_{31}N_5O_5^+\) (MH\(^+\)): 891.4075, found: 891.4051;
V. Total Synthesis of Mahafacyclin B

**BocGly(Ac)ThrΔPhe**<sub>ox</sub>. In a round-bottom flask, 3.5g (20 mmol) of Boc-Gly-OH was dissolved in 120 mL of THF and stirred. The reaction vessel was immersed in an ice bath. To the stirring colorless solution was added 3 mL (21 mmol, 1.05 eq.) of triethylamine followed by 2 mL (21 mmol, 1.05 eq) of ethylchloroformate. Over the course of 10 min, copious amounts of a white precipitate formed. After 30 min, a solution of threonine (2.4g, 22 mmol, 1.1 eq) in 1M NaOH (25 mL) was added to the stirring suspension. Upon addition of the threonine solution, the solution homogenized and turned pale yellow. After 2h, the reaction was quenched by addition of 40 mL of 10% KHSO₄ (aq.). THF was removed under reduced pressure and to the crude mixture was added 80 mL of EtOAc. The biphasic mixture was added to a separatory funnel and the aqueous phase was separated and washed twice with 30 mL of EtOAc. The combined organic phases were washed with water (30 mL) then brine (30 mL) then dried over MgSO₄ and concentrated under reduced pressure.

The crude material was dissolved in dichloromethane (250 mL) in a round-bottom flask. The flask was immersed in an ice bath and the solution was stirred at this temperature. Sequentially, β-phenylserine methyl ester hydrochloride (5g, 20 mmol), HOBt hydrate (3.3g, 22 mmol), EDCI hydrochloride (4g, 21 mmol) and DIPEA (10 mL, 57 mmol) were added to the stirring solution and the resulting reaction mixture was allowed to warm to room temperature over 20h. At this time, the reaction mixture was added to a separatory funnel and the organic phase was washed with 10% KHSO₄ (aq., 70 mL), 0.5M HCl (70 mL), water (80 mL) then finally brine (40 mL). The organic phase was dried over MgSO₄ then concentrated under reduced pressure. The crude residue was dissolved in 100 mL of THF and to this solution was added 30 mL of 1M LiOH (aq.) and 100 mL of water. Once the reaction mixture achieved homogeneity (25 min or sooner), the reaction was quenched by addition of 50 mL of 10% KHSO₄ (aq.). The quenched reaction mixture was added to a separatory funnel, and 150 mL of EtOAc was added. The aqueous phase was separated and washed twice with 70 mL of EtOAc. The combined organic phases were washed with water (70 mL) then brine (80 mL) then dried over MgSO₄ and concentrated under reduced pressure.

The crude N-Boc tripeptide was dissolved in 40 mL of EtOAc and stirred at rt. To this colorless stirring solution was added 10 mL of acetic anhydride and 5g (61 mmol, 3 eq.) of NaOAc. The reaction suspension was allowed to stir at rt for 16h. After this time, the reaction mixture was diluted with another
70 mL of EtOAc and quenched with 50 mL of sat. NaHCO$_3$ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 20 mL of EtOAc. The combined organic phases were washed twice with 40 mL of sat. NaHCO$_3$ (aq.) and once with brine (50 mL). The organic phase was then dried over MgSO$_4$ and concentrated under reduced pressure to afford a crude light yellow solid. This crude material was passed through silica gel, eluting with 1:4 EtOAc:Hexanes, to provide 7.1 g (81% yield) of a light yellow solid. Purification of this material is difficult, and often the crude material would be passed through to the next step.

**BocGly(Ac)ThrΔPhe**: $^1$H NMR (300 MHz, CDCl$_3$) δ 8.08 (s, 2H), 7.52 – 7.40 (m, 3H), 6.92 (d, $J = 11.8$ Hz, 1H), 5.52 (dd, $J = 6.4$, 3.2 Hz, 1H), 5.29 – 5.06 (m, 2H), 3.91 (dd, $J = 13.3$, 5.9 Hz, 2H), 2.01 (s, 3H), 1.46 (s, 9H), 1.36 (d, $J = 6.5$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.46, 169.76, 133.95, 132.58, 131.67, 128.94, 69.45, 51.58, 28.25, 20.84, 16.95.

A stirring solution of the above tripeptide oxazolone (2.2 g, 5 mmol) in THF (15 mL) in a round-bottom flask was cooled in an ice bath. In a separate flask, β-PhSerOH (1 g, 1.4 eq.) was added to a mixture of 15 mL THF, 10 mL water and 645 uL of NEt$_3$ (0.92 eq.). A small amount of β-PhSerOH remained undissolved. This solution was added to the aforementioned cooled tripeptide solution in one portion. Upon addition, the colorless solution turned pale yellow. The reaction was allowed to warm to room temperature and was stirred for 14h. At this time, the reaction was quenched by addition of 10 mL of 10% KHSO$_4$ (aq.). To this biphasic mixture was added 25 mL of EtOAc. The aqueous phase was separated and washed twice with 20 mL of EtOAc. The combined organic phases were washed with brine (10 mL) then dried over MgSO$_4$ and concentrated under reduced pressure. The residue was dissolved in 15 mL of EtOAc. To this colorless stirring solution was added 4 mL of acetic anhydride and 1.2g (15 mmol, 3 eq.) of NaOAc. After 2h, a bright yellow solid precipitated from the solution. The reaction suspension was allowed to stir at rt for 16h. After this time, the reaction mixture was diluted with another 25 mL of EtOAc and quenched with 20 mL of sat. NaHCO$_3$ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 20 mL of EtOAc. The combined organic phases were washed twice with 10 mL of sat. NaHCO$_3$ (aq.) and once with 10 mL of brine. The organic phase was then dried over MgSO$_4$ and concentrated under reduced pressure to afford a crude light yellow solid. This solid was dissolved in minimal dichloromethane, and addition of a small
amount of hexanes resulted in the precipitation of a bright yellow solid. The solid was separated by filtration and washed with hexanes. More solid precipitated from the mother liquor and was also collected similarly. From these two batches, 2.5g (83%) of a granular yellow solid were collected and proved to be sufficiently pure for characterization.

**BocGly(Ac)ThrΔPheΔPheox:** Yellow granules, [α] (296.7 K, 589 nm) in CHCl₃ = -16.3°; ¹H NMR (399 MHz, CDCl₃) δ 8.49 (brs, 1H), 8.11 – 8.01 (m, 2H), 7.50 (dd, J = 12.2, 6.7 Hz, 3H), 7.44 – 7.38 (m, 3H), 7.35 – 7.30 (m, 3H), 7.23 – 7.11 (m, 2H), 5.52 – 5.41 (t, J = 4.0 Hz 1H), 5.26 (s, 1H), 4.94 – 4.88 (dd, J = 7.2 Hz, 5.6 Hz, 1H), 3.82 (ddd, J = 42.3, 16.9, 5.6 Hz, 2H), 2.03 (s, 3H), 1.38 (s, 9H), 1.37 (d, J = 6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.39, 169.98, 168.15, 166.83, 161.86, 135.50, 133.25, 133.18, 132.89, 132.47, 132.27, 131.40, 130.36, 130.27, 128.85, 128.77, 128.73, 119.60, 80.66, 69.54, 56.86, 44.58, 28.27, 28.18, 21.10, 16.65. IR (neat) cm⁻¹ 3247, 2979, 1803, 1786, 1732, 1649, 1520; LRMS M(C₃₁H₃₄N₄O₈H⁺): 591.2, HRMS calc’d for M(C₃₁H₃₄N₄O₈H⁺): 591.2468, found: 591.2449

To a solution of Boc-Gly-ΔPhe-PhSerOH (600 mg, 1.2 mmol) in dichloromethane (20 mL) in a round bottom flask was added 2 mL of trifluoroacetic acid. The reaction mixture was stirred at rt for 3h. The volatiles were then removed under reduced pressure. The crude residue was repeatedly redissolved in dichloromethane and concentrated to remove traces of trifluoroacetic acid, resulting in a dark yellow solid. This solid was dissolved in 40 mL of dichloromethane. 850 μL (6 mmol, 5 eq.) of triethylamine were added (vapor evolution was observed) followed by 10 mg of DMAP and 590 mg of the above tetrapeptide oxazolone. The reaction mixture was stirred at rt for 16h, then washed with 10% KHSO₄ (aq.), 0.5M HCl, brine, then dried over MgSO₄ and concentrated under reduced pressure. The condensation procedure to form the heptapeptide oxazolone is analogous to those above. Purification of the oxazolone was accomplished by silica gel chromatography, eluting with a 1:1 mixture of dichloromethane:EtOAc.

**BocGly(Ala)ThrΔPheΔPheox:** Bright yellow solid, [α] (296.7 K, 589 nm) in CHCl₃ = -39.1°; ¹H NMR (600 MHz, CDCl₃) δ 8.83 (s, 1H), 8.54 (s, 1H), 8.13 (d, J = 7.8 Hz, 2H), 8.00 (s, 1H), 7.71 (d, J = 8.0 Hz, 2H), 7.53 (dd, J = 26.7, 13.0 Hz, 5H), 7.48 – 7.39 (m, 4H), 7.39 – 7.09 (m, 25H), 7.07 (d, J = 12.8 Hz, 1H), 5.44 (s, 1H), 5.16 (s, 1H), 4.46 (d, J = 27.3 Hz, 2H), 4.15 (d, J = 17.5 Hz, 1H), 3.62 (d, J = 11.9 Hz, 1H), 3.47 (d, J = 11.9 Hz, 1H), 3.04 (d, J = 17.5 Hz, 1H), 2.84 (d, J = 11.9 Hz, 1H), 2.68 (d, J = 17.5 Hz, 1H), 1.99 (s, 3H), 1.01 (s, 9H), 0.99 (d, J = 6 Hz, 3H).
Hz, 1H), 1.92 (d, $J = 7.4$ Hz, 3H), 1.34 (d, $J = 6.3$ Hz, 3H), 1.27 (s, 9H). IR (neat) cm$^{-1}$ 3273, 2979, 1803, 1782, 1731, 1658, 1508; LRMS M(C$_{51}$H$_{51}$N$_7$O$_{11}$H$^+$): 938.4, HRMS calc’d for M(C$_{51}$H$_{51}$N$_7$O$_{11}$H$^+$): 938.3719, found: 938.3744

**Method A:** To a solution of heptapeptide oxazolone (500 mg, 0.54 mmol) in CH$_2$Cl$_2$ (30 mL) in a round-bottom flask was added 2 mL of trifluoroacetic acid. This dark yellow solution was stirred at rt for 3h. The reaction mixture was repeatedly concentrated and redissolved in CH$_2$Cl$_2$ to remove traces of trifluoroacetic acid. The solid residue was then dissolved in 30 mL of CH$_2$Cl$_2$. 200 uL of diisopropylethylamine (1.1 mmol, 2 eq.) and 20 mg of DMAP (0.3 eq.) were then added and the reaction was stirred at rt. By LCMS, the cyclization was complete after 30 min. Upon completion, the reaction was diluted with 50 mL of CH$_2$Cl$_2$ and the organic phase was washed twice with 1M HCl (20 mL each), once with water (30 mL) then once with brine (20 mL). The organic phase was dried over MgSO$_4$ then concentrated under reduced pressure. The produce was isolated by dissolution in minimal CH$_2$Cl$_2$ and precipitation with hexanes. Filtration of the precipitate afforded 380 mg (85% yield) of a light white solid.

**Method B (in 2-MeTHF):** To a solution of heptapeptide oxazolone (100 mg, 0.107 mmol) in CH$_2$Cl$_2$ (2 mL) in a round-bottom flask was added 2 mL of trifluoroacetic acid. This dark yellow solution was stirred at rt for 1h. The reaction mixture was repeatedly concentrated and redissolved in CH$_2$Cl$_2$ to remove traces of trifluoroacetic acid. The solid residue was then dissolved in 1 mL of 2-MeTHF. 39 uL of diisopropylethylamine (0.22 mmol, 2 eq.) and 1.2 mg of DMAP (0.01 mmol) were then added and the reaction was stirred at rt. By LCMS, the cyclization was complete after 80 min. Upon completion, the reaction was loaded directly onto a plug of silica (the reaction vessel was washed with 2 mL of 2-MeTHF, and this was added to the plug). The product was eluted with EtOAc, affording 82 mg (93%) of an off-white solid.

$^1$H NMR (400 MHz, DMSO) $\delta$ 10.16 – 9.54 (m, 4H), 8.52 – 7.95 (m, 3H), 7.78 – 6.78 (m, 24H), 5.27 (d, $J = 35.8$ Hz, 1H), 4.69 (dd, $J = 17.2$, 9.3 Hz, 1H), 3.95 (d, $J = 68.9$ Hz, 3H), 3.55 (d, $J = 12.4$ Hz, 1H), 1.91 (d, $J = 5.2$ Hz, 3H), 1.18 (t, $J = 7.3$ Hz, 3H); IR (neat) cm$^{-1}$ 3233, 3057, 1740, 1653, 1514; LRMS M(C$_{46}$H$_{43}$N$_7$O$_9$H$^+$): 838.3, HRMS calc’d for M(C$_{46}$H$_{43}$N$_7$O$_9$H$^+$): 838.3195, found: 838.3166
Made following hydrogenation procedure A using 1 mg of [Rh(COD)$_2$BF$_4$] and 1 mg of (SSRR)DuanPhos (5 mol% wrt to substrate) in 1:1 MeOH:CH$_2$Cl$_2$ with 46 mg of the cyclic dehydroheptapeptide (34). The reaction was kept at rt, pressurized to 3 atm of hydrogen gas, and stirred under these conditions for 2 days. At this time, the vessel was vented and the contents of the vial (the peptide had precipitated) were analyzed by LCMS then transferred to a scintillation vial. 3 mL of MeOH and 30 mg of potassium carbonate were added to the scintillation vial, and this suspension was stirred at rt for 20 min. Volatiles were removed under reduced pressure. This material was loaded directly onto a Biotage SP1 C18 cartridge and purified via reverse phase silica gel chromatography assisted by a Biotage SP1 (gradient: 15% to 90% MeOH over 100 column volumes, monitored at 214 nm). The pooled fractions containing the product peak were concentrated under reduced pressure to provide Mahafacyclin B (30 mg, 74% yield) as a white solid.

Water was added to the crude mixture, which dissolved the potassium carbonate and precipitated the peptide. The peptide was isolated as a pale yellow solid by filtration. The peptide was then dissolved in minimal DMSO and HFIP and passed through C18 silica (eluant – H$_2$O:MeCN:TFA gradient from 20:80:1 to 40:60:1) to isolated 10 mg (40% yield) of the product as a white translucent solid.

$^1$H NMR (400 MHz, DMSO-$d_6$) δ 8.69 (d, $J = 5.7$ Hz, 1H), 8.31 (d, $J = 10.0$ Hz, 1H), 8.26 (t, $J = 5.7$ Hz, 1H), 8.00 (t, $J = 5.9$ Hz, 1H), 7.86 (d, $J = 8.0$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 1H), 7.42 (d, $J = 7.7$ Hz, 1H), 7.31 – 7.07 (m, 20H), 5.11 (s, 1H), 4.50 – 4.32 (m, 2H), 4.30 – 4.20 (m, 2H), 4.07 (dd, $J = 12.5, 5.6$ Hz, 1H), 3.83 (dd, $J = 16.5, 5.6$ Hz, 2H), 3.51 (dd, $J = 16.7, 6.0$ Hz, 2H), 3.12 (dd, $J = 15.3, 7.0$ Hz, 2H), 3.05 – 2.87 (m, 3H), 2.82 (dd, $J = 13.6, 8.7$ Hz, 3H), 2.76 – 2.59 (m, 4H), 0.92 (d, $J = 6.3$ Hz, 3H); $^{13}$C NMR (126 MHz, DMSO-$d_6$) δ 172.74, 171.54, 171.44,
171.35, 170.83, 169.39, 169.30, 138.35, 138.19, 138.15, 137.66, 129.66, 129.55, 129.51, 129.27, 128.72, 128.67, 126.91, 126.84, 68.3, 58.61, 55.79, 55.25, 55.00, 54.53, 45.88, 42.99, 37.85, 37.54, 36.68, 36.41, 19.70. **LRMS** M(C_{44}H_{49}N_{7}O_{8}H)^+: 804.3, **HRMS** calc’d for M(C_{44}H_{49}N_{7}O_{8}H)^+: 804.3656, found: 804.3688. Data matches the literature.

**VI. Process Mass Intensity Calculations**

**Green chemistry metrics – PMI Calculations for 2 Steps in the Synthesis of Mahafacyclin B**

Admittedly, these calculations do not account for purifications. It should be pointed out that many of the purifications described above are simple precipitations, which means that our purifications are significantly more efficient than chromatographic purifications, especially HPLC. Still, these calculations are presented to show conceptually where the advantages lie in our strategy.

1. One amide bond forming and carboxylate activation step

**Condensation and Reduction:**

A stirring solution of the above tripeptide oxazolone (2.2 g, 5 mmol) in THF (15 mL) in a round-bottom flask was cooled in an ice bath. In a separate flask, β-PhSerOH (1 g, 1.4 eq.) was added to a mixture of 15 mL THF, 10 mL water and 645 uL of NEt$_3$ (0.92 eq.). A small amount of β-PhSerOH remained undissolved. This solution was added to the aforementioned cooled tripeptide solution in one portion. Upon addition, the colorless solution turned pale yellow. The reaction was allowed to warm to room temperature and was stirred for 14h. At this time, the reaction was quenched by addition of 10 mL of 10% KHSO$_4$ (aq.). To this biphasic mixture was added 25 mL of EtOAc. The aqueous phase was separated and washed twice with 20 mL of EtOAc. The combined organic phases were washed with brine (10 mL) then dried over MgSO$_4$ and concentrated under reduced pressure. The residue was dissolved in 15 mL of EtOAc. To this colorless stirring solution was added 4 mL of acetic anhydride and 1.2 g (15

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mmol, 3 eq.) of NaOAc. After 2h, a bright yellow solid precipitated from the solution. The reaction suspension was allowed to stir at rt for 16h. After this time, the reaction mixture was diluted with another 25 mL of EtOAc and quenched with 20 mL of sat. NaHCO₃ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 20 mL of EtOAc. The combined organic phases were washed twice with 10 mL of sat. NaHCO₃ (aq.) and once with 10 mL of brine. The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to afford a crude light yellow solid. This solid was dissolved in minimal dichloromethane, and addition of a small amount of hexanes resulted in the precipitation of a bright yellow solid. The solid was separated by filtration and washed with hexanes. More solid precipitated from the mother liquor and was also collected similarly. From these two batches, 2.5g (83%) of a granular yellow solid were collected and proved to be sufficiently pure for characterization.

Sum of materials (Note: I will omit the material needed for extractions in the first calculation for a more direct comparison to Trembleau, as they do not describe work-up procedures in their SI)

2.2g of starting material, 40 mL of THF, 10 mL aqueous solution, 1g β-PhSerOH, 0.65 mL NEt₃, 15 mL EtOAc, 4 mL of Ac₂O, 1.2 g NaOAc

Forms 2.5 g of product

Process mass intensity  = (2.2 + 35.56 + 10 + 1 + 0.5 + 13.46 + 4.32 + 1.2)/2.5

= 27.3 kg/kg

(With work-up procedures: 92.12 kg/kg)

None of the reagents are hazardous nor have any ecological impact according to their MSDS.

The most expensive reagent, β-PhSerOH, can be made at a cost of $228/kg.

Trembleau’s RRSPS Approach to BocThrPhePheGlyPfp
(Copied from the SI) Peptide 8 was Boc-deprotected (procedure C), and the resulting peptide ammonium chloride salt 7 (0.35 mmol, 183 mg, 1 eq), coupled to Boc-L-Thr-OPfp (1.5 eq, 202 mg) following procedure D (a petroleum ether/ethyl acetate mixture was used for USE). The desired peptide 9 was obtained after 5h reaction as a white powder (710 mg, 76% yield) – the mass yield is impossible at this scale, so we will extrapolate from the % yield

**Boc deprotection (procedure C):** Removal of the Boc group was performed by acidolysis in the presence of HCl/dioxane (4M). Boc-peptide (1.2 mmol) was added to a cooled solution of HCl/dioxane (10 mL), under an inert atmosphere of argon. The solution was then allowed to warm to room temperature and the mixture stirred for 2h, the solvent was removed under reduced pressure, the resulting solid was washed with dry diethyl ether (3 x 20mL) and finally collected by filtration.

**Coupling protocol (procedure D):** Couplings were carried out using 1 equivalent of the peptide to be elongated, with 1.1-1.5 equivalent of the amino acid/peptide fragment pentafluorophenyl ester in presence of 2-2.1 equivalents of DIEA: DIEA was added to an aqueous solution of the peptide (0.2 M), and the solution stirred for 10 minutes (pH=8.5-9). A solution of the Boc-protected amino acid/peptide fragment pentafluorophenyl ester in THF (0.1M) was then added. Once the reaction had reached completion (TLC) the THF was removed under reduced pressure, the aqueous mixture acidified to pH=3 using a 10% solution of citric acid (the Boc-protected peptide often precipitates) and extracted with ethyl acetate. The combined organic extracts were dried over MgSO4 and the solvent evaporated under reduce pressure. The crude was subjected to USE (3 times) with petroleum ether or diethyl ether for 5 minutes to give the desired Boc-protected peptide acid.

**Synthesis of pentafluorophenyl esters (procedure A):** PfpOH (1 eq) was added to a stirred solution of Boc-amino acid/peptide in dichloromethane (0.2M) followed by EDC.HCl (1.2 eq). After two hours silica (10 times the mass of EDC.HCl used) was added to the solution and the resulting suspension filtered over a bed of silica and celite. The solvent was removed under reduced pressure and the crude pentafluorophenyl ester used directly in the next step.

**Sum of materials**

0.183 g substrate, 0.35 mL 4M HCl/dioxane, 0.202 g BocThrPfp, 0.09 g DIPEA, 1.8 mL water, 3.5 mL THF, 1.8 mL CH₂Cl₂, 0.064 g PfpOH, 0.081 g EDCI
Yields 0.196 g of BocThrPhePheGlyPfp (76%)

Process mass intensity  = \frac{(0.183 + 0.35 + 0.09 + 1.8 + 2.96 + 2.34 + 0.064 + 0.081)}{0.196}

= 40.2 kg/kg

(with the ether washes and the silica gel work-up, the PMI increases to 107.8 kg/kg)

Pentafluorophenol (PfpOH): 1kg costs $3600. MSDS indicates mild toxicity.

EDCI-HCl: 1kg costs $3505, MSDS indicates mild toxicity.

CH\textsubscript{2}Cl\textsubscript{2} is listed as a carcinogen and a significant ecological hazard

2. Macrocyclization in the synthesis of Mahafacyclin B, without deprotection

**Condensation and Reduction Approach**

**Method B (in 2-MeTHF):** The deprotected linear hexapeptide (100 mg, 0.107 mmol) was dissolved in 1 mL of 2-MeTHF. 39 uL of diisopropylethylamine (0.22 mmol, 2 eq.) and 1.2 mg of DMAP (0.01 mmol) were then added and the reaction was stirred at rt. By LCMS, the cyclization was complete after 80 min. Upon completion, the reaction was loaded directly onto a plug of silica (washed with 2 mL of 2-MeTHF). The product was eluted with EtOAc, affording 82 mg (93%) of an off-white solid.

**Sum of materials**

0.1g of starting material, 1 mL of 2-MeTHF, 0.029 g DIPEA, 0.0012 g DMAP

Forms 0.082 g of product
Trembleau’s RRSPS Approach to the Cyclization of Mahafacyclin B

Peptide 11 (0.054 mmol, 50 mg, 1 eq) was deprotected give peptide ammonium chloride salt 12, which was cyclised by addition of triethylamine (0.11 mmol, 15 μl, 2 eq) followed by HBTU (0.085 mmol, 33 mg, 1.6 eq) in DMF (65 ml). The reaction was left to proceed at room temperature and under an inert atmosphere of argon for 70h, after which the DMF was removed under reduced pressure. The resulting residue was then re-dissolved in CHCl₃/i-PrOH (3:1 v/v; 30 mL) and washed with a saturated aqueous solution of NaHCO₃ (20 ml). The aqueous phase was extracted with CHCl₃/i-PrOH (3:1 v/v; 2 x 30 ml), the combined organic phases washed with brine, dried over MgSO₄ and concentrated under reduced pressure. The product was finally purified by semi-preparative reversed-phase HPLC (water/MeOH : 22/78, \( t_r \) 34 min) yielding pure mahafacyclin B (27 mg, cyclization yield 63%, global yield 24%)

Sum of materials

0.05 g of starting material, 0.011 g NEt₃, 0.032 g HBTU, 61.36 g DMF

Forms 0.027 g of product

Process mass intensity \( = \frac{(0.05 + 0.011 + 0.032 + 61.36)}{0.027} \)

\( = 2276 \text{ kg/kg} \)
VII. Total Synthesis of Clausenain B

**Synthesis of BocLeu(Ac)SerΔPheex (38):** To a round-bottom flask equipped with a stirbar was added Boc-Leu-OH (2.5g, 10 mmol) and 150 mL of dichloromethane. The flask was immersed in an ice bath and the solution was stirred at this temperature. Sequentially, serine methyl ester hydrochloride (1.4g, 10 mmol), HOBt hydrate (1.6g, 10.6 mmol), EDCI hydrochloride (2g, 10.4 mmol) and DIPEA (5.25 mL, 30 mmol) were added to the stirring solution and the resulting reaction mixture was allowed to warm to room temperature over 20h. At this time, the reaction mixture was added to a separatory funnel and the organic phase was washed with 10% KHSO₄ (aq., 50 mL), 0.5M HCl (60 mL), water (50 mL) then finally brine (20 mL). The organic phase was dried over MgSO₄ then concentrated under reduced pressure. The crude residue was dissolved in 40 mL of THF and to this solution was added 15 mL of 1M LiOH (aq.) and 40 mL of water. Once the reaction mixture achieved homogeneity (25 min or sooner), the reaction was quenched by addition of 20 mL of 10% KHSO₄ (aq.). The quenched reaction mixture was added to a separatory funnel, and 100 mL of EtOAc was added. The aqueous phase was separated and washed twice with 25 mL of EtOAc. The combined organic phases were washed with water (50 mL) then brine (50 mL) then dried over MgSO₄ and concentrated under reduced pressure.

The crude Boc-Leu-Ser-OH was dissolved in 150 mL of dichloromethane. The flask was immersed in an ice bath and the solution was stirred at this temperature. Sequentially, β-phenylserine methyl ester hydrochloride (2.6g, 10 mmol), HOBt hydrate (1.6g, 10.6 mmol), EDCI hydrochloride (2g, 10.4 mmol) and DIPEA (5.25 mL, 30 mmol) were added to the stirring solution and the resulting reaction mixture was allowed to warm to room temperature over 20h. The same work-up and ester cleavage procedures were followed as above. The crude Boc-protected tripeptide was dissolved in 50 mL of EtOAc and stirred at rt. To this colorless stirring solution was added 5 mL of acetic anhydride and 4g (50 mmol, 5 eq.) of NaOAc. The reaction suspension was allowed to stir at rt for 16h. After this time, the reaction mixture was diluted with another 50 mL of EtOAc and quenched with 50 mL of sat. NaHCO₃ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 20 mL of EtOAc. The combined organic phases were washed twice with 30 mL of sat. NaHCO₃ (aq.) and once with brine (50 mL). The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to afford a crude light yellow solid. The crude ¹H-NMR of this material was fairly clean, but
contained minor impurities and a significant amount of acetic acid. The material was dissolved in a minimal amount of dichloromethane and precipitated with hexanes and cooling in a fridge. The precipitated solid was filtered and washed with hexanes to afford 3.4 g (70% yield) of a light yellow solid, which was sufficiently pure for characterization purposes.

**Synthesis of BocLeu(\text{Ac})\text{SerΔPhe}_\text{ox} (38):** Light yellow powder, [\alpha] (CHCl₃, 296.7 °C, 589 nm) -41.1; \text{^1H NMR (400 MHz, CDCl₃)} δ 8.08 (dd, J = 6.5, 2.8 Hz, 2H), 7.48 – 7.43 (m, 3H), 7.24 (s, 1H), 7.05 (d, J = 8.1 Hz, 1H), 5.32 (dt, J = 8.3, 4.2 Hz, 1H), 4.92 (d, J = 6.7 Hz, 1H), 4.60 – 4.41 (m, 2H), 4.22 (s, 1H), 2.06 (s, 3H), 1.74 (m, 2H), 1.54 (m, 1H), 1.44 (s, 9H) 0.99 (d, J = 6.3 Hz, 3H), 0.97 (d, J = 6.1 Hz, 3H). \text{^13C NMR (100 MHz, CDCl₃)} δ 172.56, 170.55, 166.61, 164.68, 133.98, 132.82, 132.63, 131.77, 128.99, 63.07, 52.98, 47.71, 40.96, 28.30, 24.76, 22.91, 22.10, 20.65. \text{IR (neat)} cm⁻¹: 3327, 2959, 1808, 1790, 1744, 1659, 1514; \text{LRMS M(C}_{25}\text{H}_{33}\text{N}_{3}\text{O}_{7}\text{H}^+) : 488.2, \text{HRMS calc'd for M(C}_{25}\text{H}_{33}\text{N}_{3}\text{O}_{7}\text{H}^+) : 488.23967, found: 488.23787

**Synthesis of BocLeu(\text{Ac})\text{SerΔPheΔPhe}_\text{ox} (36):** A stirring solution of 38 (730 mg, 1.5 mmol) in THF (40 mL) in a round-bottom flask was cooled in an ice bath. In a separate flask, β-\text{PhSerOH} (400 mg, 1.5 eq.) was added to a mixture of 20 mL THF, 10 mL water and 190 uL of NEt₃ (0.92 eq.). A small amount of β-\text{PhSerOH} remained undissolved. The β-\text{PhSerOH} solution was added to the aforementioned cooled solution of 38 in one portion. Upon addition, the colorless solution turned pale yellow. The reaction was allowed to warm to room temperature and was stirred for 14h. At this time, the reaction was quenched by addition of 10 mL of 10% KHSO₄ (aq.). To this biphasic mixture was added 30 mL of EtOAc. The aqueous phase was separated and washed twice with 20 mL of EtOAc. The combined organic phases were washed with brine (25 mL) then dried over MgSO₄ and concentrated under reduced pressure. The residue was dissolved in 15 mL of EtOAc. To this colorless stirring solution was added 2 mL of acetic anhydride and 500 mg (6 mmol, 4 eq.) of NaOAc. The reaction suspension was allowed to stir at rt for 16h. After this time, the reaction mixture was diluted with another 30 mL of EtOAc and quenched with 20 mL of sat. NaHCO₃ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 15 mL of EtOAc. The combined organic phases were washed twice with 15 mL of sat. NaHCO₃
(aq.) and once with brine (20 mL). The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to afford a crude light yellow solid. This solid was dissolved in minimal dichloromethane, and addition of a small amount of hexanes resulted in the precipitation of a filmy solid. The solid was separated by filtration and washed with hexanes. More solid precipitated from the mother liquor and was also collected similarly. From these two batches, 680 mg (72%) of a flaky yellow solid were collected and proved to be sufficiently pure for characterization.

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\text{BocLeu(Ac)SerΔPheΔPhe} \quad (36): \quad \text{Bright yellow solid, } [\alpha] \quad (\text{CHCl}_3, 296.7 \degree \text{C, 589 nm}) -86.3; \quad ^1H \text{ NMR (300 MHz, CDCl}_3) \delta 8.52 (s, 1H), 8.12 (dd, J = 7.7, 1.7 Hz, 2H), 7.60 (dd, J = 10.7, 4.5 Hz, 3H), 7.51 – 7.34 (m, 7H), 7.18 (s, 1H), 4.97 (dd, J = 7.8, 6.1, 3.9 Hz, 1H), 4.88 (d, J = 4.9 Hz, 1H), 4.76 – 4.61 (m, 1H), 4.43 (dd, J = 11.6, 3.8 Hz, 1H), 4.04 (dt, J = 9.8, 4.8 Hz, 1H), 2.11 (s, 3H), 1.67 (dd, J = 13.8, 7.4 Hz, 2H), 1.51 (d, J = 9.4 Hz, 1H), 1.35 (d, J = 10.7 Hz, 9H), 0.93 (d, J = 6.1 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H). ^{13}C \text{ NMR (75 MHz, CDCl}_3) \delta 172.88, 171.62, 168.32, 167.05, 166.37, 161.96, 135.73, 133.37, 133.13, 132.53, 132.09, 131.31, 130.50, 130.35, 128.91, 128.73, 119.79, 81.04, 63.86, 54.20, 53.30, 40.51, 28.14, 24.83, 22.96, 22.16, 21.58, 20.83. \text{ IR (neat) } \text{cm}^{-1} \quad 3271, 2954, 1811, 1784, 1739, 1690, 1510; \quad \text{LRMS M(C}_{34}\text{H}_{46}\text{N}_{4}\text{O}_{8}\text{H}^+) : 633.3, \quad \text{HRMS calc’d for M(C}_{34}\text{H}_{46}\text{N}_{4}\text{O}_{8}\text{H}^+) : 633.2918, \quad \text{found: 633.2901}
\]

\[
\text{Synthesis of BocLeuGlyΔPhe} \quad (39): \quad \text{(The same procedure was followed as above for 38, replacing serine methyl ester hydrochloride with glycine ethyl ester hydrochloride. Otherwise, every reaction parameter was kept the same. Yield of the precipitate was 2.8g (72%) and was pure enough for characterization purposes, as shown below.}
\]

Light yellow powder, [\alpha] \quad (23.7C, 589 nm) -39.1; \quad ^1H \text{ NMR (400 MHz, CDCl}_3) \delta 8.17 – 7.93 (m, 2H), 7.47 – 7.38 (m, 3H), 7.16 (s, 1H), 5.16 (s, 1H), 4.53 (dd, J = 18.1, 4.5 Hz, 1H), 4.33 (d, J = 23.3 Hz, 2H), 1.83 – 1.65 (m, 2H), 1.65 – 1.49 (m, 1H), 1.41 (s, 9H), 0.97 (d, J = 6.2 Hz, 3H), 0.94 (d, J = 6.1 Hz, 3H).
^{13}C \text{ NMR (100 MHz, CDCl}_3) \delta 173.29, 166.92, 164.87, 156.01, 133.07, 132.89, 132.48, 131.50, 128.90, 80.33, 52.95, 41.23, 37.48, 28.31, 24.76, 22.98, 22.03. \text{ IR (neat) } \text{cm}^{-1} \quad 3331, 2953, 1817, 1785, 1689, 1658, 1163; \quad \text{LRMS M(C}_{22}\text{H}_{29}\text{N}_{3}\text{O}_{5}\text{H}^+) : 416.2, \quad \text{HRMS calc’d for M(C}_{22}\text{H}_{29}\text{N}_{3}\text{O}_{5}\text{H}^+) : 416.21855, \quad \text{found: 416.21966}
\]
Synthesis of BocLeuGlyΔPhePhSerOH (37): To a stirring solution of 39 (600 mg, 1.4 mmol) in THF (20 mL) in a round-bottom flask was added a solution of β-PhSerOH (400 mg, 1.5 eq.) in THF/H₂O/NEt₃ (10:10:1 mL) at rt. Upon addition, the colorless solution turned pale yellow. The reaction was allowed to stir at rt for 5h. At this time, the reaction was quenched by addition of 10 mL of 10% KHSO₄ (aq.). To this biphasic mixture was added 30 mL of EtOAc. The aqueous phase was separated and washed twice with 20 mL of EtOAc. The combined organic phases were washed with brine (25 mL) then dried over MgSO₄ and concentrated under reduced pressure. The crude pale yellow oil was dissolved in minimal CH₂Cl₂, and the product was precipitated with the addition of Et₂O. The product was isolated as a white powder via filtration (621 mg, 72% yield). This precipitate was used without further purification.

Synthesis of Cyclo(Leu(Ac)SerΔPheΔPheLeuGlyΔPheΔPhe) (41): Tetrapeptide 37 (200 mg, 0.33 mmol) was deprotected in TFA/CH₂Cl₂ as above. 41-TFA was dissolved in 25 mL of CH₂Cl₂ and to this solution was added 175 μL of DIPEA (1 mmol, 3 eq.). 36 (210 mg, 0.33 mmol, 1 eq.) was added, followed by 10 mg of DMAP (0.2 eq.). The progress of the addition was followed by LCMS, and the reaction achieved complete conversion after 36h. At this time, the reaction was quenched by addition of 10 mL of 1M HCl (aq.). To this biphasic mixture was added 30 mL of CH₂Cl₂. The aqueous phase was separated and washed twice with 20 mL of CH₂Cl₂. The combined organic phases were washed with brine (25 mL) then dried over MgSO₄ and concentrated under reduced pressure. The crude yellow residue was dissolved in EtOAc (5 mL) and 1 mL of Ac₂O and 400 mg of NaOAc were added. The reaction mixture was stirred at rt for 8h. After this time, the reaction mixture was diluted with another 30 mL of EtOAc and quenched with 20 mL of sat. NaHCO₃ (aq.), after which the reaction mixture effervesced for 15 min. After the evolution of gas had subsided, the biphasic mixture was added to a separatory funnel. The aqueous phase was separated and extracted twice with 15 mL of EtOAc. The combined organic phases...
were washed twice with 15 mL of sat. NaHCO₃ (aq.) and once with brine (20 mL). The organic phase was then dried over MgSO₄ and concentrated under reduced pressure to afford a crude light yellow solid.

Linear octapeptide 40 was difficult to purify, and, thus, was carried through to the next step. The yellow residue was deprotected with TFA/CH₂Cl₂. 40-TFA was dissolved in 7 mL of CH₂Cl₂ and to this solution was added 175 μL of DIPEA (1 mmol, 3 eq.). 36 (210 mg, 0.33 mmol, 1 eq.) was added, followed by 10 mg of DMAP (0.2 eq.). The cyclization was complete after stirring for 12h at rt. At this time, the reaction was quenched by addition of 2 mL of 1M HCl (aq.). To this biphasic mixture was added 20 mL of CH₂Cl₂. The aqueous phase was separated and washed twice with 20 mL of CH₂Cl₂. The combined organic phases were washed with brine (25 mL) then dried over MgSO₄ and concentrated under reduced pressure. The product was isolated via silica gel chromatography (eluting with 80% EtOAc/hexanes), affording 110 mg of a yellow powder (36% yield).

Light yellow powder, ¹H NMR (600 MHz, DMF) δ 10.16 (s, 1H), 9.91 (2, 3H), 8.29 (s, 2H), 7.69 (dd, J = 28.7, 19.3, 7.7 Hz, 8H), 7.54 – 7.31 (m, 14H), 7.09 (s, 1H), 4.89 (dd, J = 12.9, 6.2 Hz, 1H), 4.70 – 4.48 (m, 3H), 4.31 (dd, J = 17.2, 5.5 Hz, 1H), 4.06 (dd, J = 16.8, 5.1 Hz, 1H), 2.06 (s, 3H), 2.01 (dd, J = 26.4, 12.4 Hz, 2H), 1.85 (s, 2H), 1.82 – 1.67 (m, 2H), 1.06 – 0.79 (m, 12H). LRMS M(C₅₅H₆₀N₈O₁₀H⁺): 993.4, HRMS calc’d for M(C₅₅H₆₀N₈O₁₀H⁺): 993.4505, found: 993.4501
Clausenain B (35): Made via hydrogenation procedure C, at a 10 mg scale. Isolated 5 mg via reversed phase column chromatography as a white powder. $^1$H NMR (400 MHz, DMSO-d$_6$) NMR data acquired at 315K, as per Wang et al. 2009$^5$ δ 8.38 (s, 2H), 8.17 (s, 1H), 8.04 (d, $J = 6.0$ Hz, 1H), 7.90 (d, $J = 8.7$ Hz, 1H), 7.81 (dd, $J = 12.6$, 6.5 Hz, 2H), 7.48 (d, $J = 7.0$ Hz, 1H), 7.38 – 7.05 (m, 20H), 5.43 (t, $J = 5.2$ Hz, 1H), 4.40 (dt, $J = 17.9$, 10.6 Hz, 3H), 4.32 – 4.16 (m, 2H), 4.11 (dd, $J = 14.2$, 5.8 Hz, 6H), 3.94 (s, 5H), 3.78 (dd, $J = 17.1$, 14.2, 6.4 Hz, 2H), 3.62 (dd, $J = 10.5$, 4.9 Hz, 1H), 3.39 (dd, $J = 16.5$, 4.3 Hz, 1H), 3.12 (dd, $J = 14.2$, 5.1 Hz, 1H), 3.08 – 2.64 (m, 8H), 1.76 – 1.40 (m, 6H), 0.98 – 0.77 (m, 12H). LRMS M(C$_{53}$H$_{66}$N$_8$O$_9$H$^+$): 959.5, HRMS calc’d for M(C$_{53}$H$_{60}$N$_8$O$_9$H$^+$): 959.5025, found: 959.5063. Data matches the literature.

Spectral Data

Chapter 1.
The image contains a chemical structure diagram and a plot. The structure diagram represents a molecular compound with labeled peaks at various positions. The plot likely corresponds to a spectroscopic analysis, such as an NMR spectrum, with the vertical axis representing frequency (in ppm) and the horizontal axis representing intensity or signal strength. Key peaks are marked with their corresponding frequencies, such as 193.310, 189.369, 165.871, 160.030, 137.348, 135.741, 134.823, 130.105, 128.854, 128.005, 125.388, 121.897, 112.678, 77.316, 76.997, 76.679, 71.032, and 52.573.
Selected HPLC traces

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Chapter 2
SFC Traces –

Conditions

Column: IC, 40% MeOH isocratic, thermostat set to 44 °C, sample prepared in 1:1 DCM/MeOH

1. Cyclo(Gly\textsuperscript{L}Phe\textsuperscript{L}Phe\textsuperscript{L}Phe\textsuperscript{L}Phe) (enantio-11) made from \textsuperscript{L}Phe-OH and 11

2. Enantio-11 made from hydrogenation of 10 with (SSRR)-DuanPhos as the ligand

3. 11