Accessing Medicinally-Relevant Scaffolds Via Organocatalyzed Cascade Reactions

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ABSTRACT

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By Joshua Hadley Jones

Advisor: Professor Stacey Brenner-Moyer

Abstract: The field of asymmetric catalysis embodies the efforts of chemists to mimic the stereoselectivity routinely achieved by biological systems. Asymmetric organocatalysis, a sub-field of asymmetric catalysis, is broadly based on the catalytic activity of non-transition metal, small molecules that transmit chirality to substrates. This dissertation describes experimental work towards the construction of versatile, medicinally-relevant molecular scaffolds using chiral, diarylprolinol silyl ether organocatalysts. Specifically, these catalysts were used in 1-pot, iminium-enamine catalyzed cascade reactions to functionalize $\alpha,\beta$-unsaturated aldehydes. A comprehensive review of iminium and enamine organocatalysis is provided, including its development towards iminium-enamine cascade reactions. This review provides background for the original research recounted herein, which are 1) Accessing Medicinally-Relevant Cyclohexene Scaffolds via a Michael-Michael Organocascade, 2) One-Pot Preparation of Enantiopure Fluorinated $\beta$-Amino Acid Precursors, and 3) Accessing Medicinally-Relevant Tetrahydrofuran Scaffolds via Organocascade Reactions.
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And since the most important is saved for last, I wish to express my sincere gratitude and also my humble apologies to my Family. They have all shared this load with me - both triumphs and sacrifices. They all have my enduring commitment to utilize whatever knowledge and skill gained from the practice of science to serve our future together.
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LIST OF SYMBOLS AND ABBREVIATIONS

$2^0$ secondary
$3^0$ tertiary
$[\alpha]_D$ optical rotation
Ar aryl
Bn benzyl
Boc $\text{tert}$-butoxycarbonyl
br broad
Bu butyl
c concentration
$^\circ\text{C}$ degree Celsius
$^{13}\text{C NMR}$ carbon-13 nuclear magnetic resonance
calcd calculated
Cbz carboxybenzyl
CDCl$_3$ deuterated chloroform
Conv Conversion
$\delta$ nuclear magnetic shift
d doublet
DABCO 1,4-diazabicyclo[2.2.2]octane
DBU 1,8-Diazabicyclo[5.4.0]undec-7-ene
DCM dichloromethane
DIBAL-H Diisobutyaluminum hydride
DIPEA $N,N$-diisopropylethylamine
DMAP 4-dimethylaminopyridine
DMF  dimethylformamide
DMSO  dimethylsulfoxide
dr  diastereomeric ratio
E+  electrophile
ee  enantiomeric excess
epi  epimer
equiv  equivalents
er  enantiomeric ratio
ESI  electrospray ionization
Et  ethyl
EtOAc  ethyl acetate
EtOH  ethanol
Et₂O  diethyl ether
Et₃N  triethylamine
EWG  electron withdrawing group
FT-IR  Fourier transform infrared spectroscopy
g  gram
h  hour
¹H NMR  proton nuclear magnetic resonance
HPLC  high performance liquid chromatography
HRMS  high resonance mass spectrometry
Hz  Hertz
iPr  iso-propyl
iPrOH  iso-propyl alcohol
IR  infrared
$J$  coupling constant

kcal  kilocalorie

m  multiplet

M  molar

M+  positively charged mass

M-  negatively charged mass

mM  millimolar

MBH  Morita–Baylis–Hillman

Me  methyl

MeCN  acetonitrile

MeO  methoxy

MeOH  methanol

mg  milligram

MHz  megahertz

min  minutes

mL  milliliter

mmol  millimole

mol  mole

mol%  mole percent

$n$BuLi  $n$-butyl lithium

NFSI  $N$-fluorobenzenesulfonimide

NMO  $N$-Methylmorpholine-$N$-oxide

Nu-  nucleophile

obsd  observed

PCC  pyridinium chlorochromate
PG  protecting group
Ph  phenyl
pH  potential of hydrogen
PhCO₂H  benzoic acid
PKa  ionization constant
rac  racemic
rt  room temperature
s  singlet
t  triplet
TBAF  tetra-N-butylammonium fluoride
TBS  tert-butyldimethylsilyl
TBSCI  tert-butyldimethylsilyl chloride
tBu  tert-butyl
tBuLi  tert-butyl lithium
Temp.  temperature
TES  triethylsilyl
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TLC  thin layer chromatography
TMS  trimethylsilyl
Ts  tosyl
UV  ultraviolet
µL  microliter
wt.%  weight percent
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Chapter 1.

Introduction To Combining Organocatalyzed Reactions

As Cascade Reactions And With Photoredox Catalysis

1.1 Organocatalysis

Beginning in the early 1970's, but accelerating from the late 1990's, a steady stream of robust, versatile organocatalysts have been introduced, many possessing the versatility and durability sought in previously established asymmetric methods (e.g., compared to inefficient resolution of racemates, or stoichiometric use of chiral auxiliaries). Some merits of these catalysts include access to novel reaction manifolds, low sensitivity to water and oxygen, reduced toxicity of catalyst residues, and a potentially reduced environmental impact of catalyst preparation. This introductory chapter offers an abbreviated narrative of this development, with special attention paid to those innovations most relevant to the original research presented in later chapters.

Two of the earliest publications describing the use of amino acids for enantioselective bond formation date to the early 1970's, an era in synthetic chemistry fueled by the tremendous commercial success of steroidal contraceptives (e.g., norethindrone). Efforts to access steroidal derivatives resulted in two industrial groups independently reporting (S)-proline in synthesizing a valuable steroid intermediate, the Wieland-Miescher Ketone, the absolute configuration of which is vital for downstream targets. The first of these publications demonstrated an
enantioselective Robinson Annulation, soon to be known by the authors’ namesake as the Hajos–Parrish–Eder–Sauer–Wiechert reaction (Scheme 1.1).

The authors experimented with a range of conditions and amino catalysts, including the primary amino acids (S)-alanine and (S)-phenylalanine. However, (S)-proline (10 - 100 mol%) was reported to be most effective, with good yields (87%) and optical yield (84% ee), albeit with extended reaction times (72 hrs.)

Shortly thereafter (1974), a similar (S)-proline catalyzed Aldol condensation achieved excellent yields (up to 100%) and enantioselectivity (up to 93% ee) while using lower catalyst loadings (3 mol%) (Scheme 1.1). The authors’ meticulous reaction optimization and verification of absolute configuration (by x-ray crystallography) provided valuable mechanistic insight into proline's mode of substrate activation and stereoinduction (Scheme 1.2).
Condensation of proline’s pyrrolidine nitrogen with a carbonyl carbon of triketone 1.5 gave iminium intermediate 1.5i, whose equilibrium with enamine 1.5e drove the enantioselective aldol addition via combined enamine-Brønsted Acid activation and hydrogen-bonding stereoinduction to give chiral ketol 1.7. Subsequent acid-catalyzed elimination of water gave condensation adduct 1.9.

The authors went on to comment on the *bifunctional* nature of proline as catalyst, describing both nucleophilic pyrrolidine and Brønsted Acid carboxylate. They demonstrated that proline's pyrrolidine core imparts sufficient nucleophilicity for rapid iminium formation with carbonyl carbons (compared to the less capable oxetane or piperidine equivalents), and that subsequent iminium-enamine equilibrium was a driving force for new C-C bond formation. They went on to describe proline's carboxylate moiety to act as a multi-faceted Brønsted Acid 'co-catalyst', facilitating increased catalytic turnover, as well as promoting carbonyl activation and providing hydrogen-bonding stereoinduction.\[8\] Although this early mechanistic proposal would be revised into a more broadly accepted mechanism (via a Zimmerman-Traxler, 6-membered transition state), the authors' general insight into proline's bi-functional mode of catalysis has been repeatedly confirmed.\[9\]
Interestingly, the authors' experience with semi-synthetic chemistry (contraceptives were made using a precursor isolated from Mexican Wild Yams\(^2\)) enabled them to frame the significance of their study in terms of chemical biology, noting:

"We believe that our results may be considered an example of a simplified model of a biological system in which (S)-proline plays the role of an enzyme."

This statement embodied a long-standing aspiration in chemical synthesis: to understand and harness the catalytic activity of enzymes.\(^{10}\) In retrospect, this foretold a renaissance in asymmetric catalysis, with an increased knowledge of bio-catalysis providing inspiration for new enzyme catalysts, as well as biomimetic organocatalysts.\(^{11}\)

Excepting a few notable uses of proline, and the other chiral, small-molecules as chiral catalysts, a ‘re-discovery’ of proline-catalysis began in the late 1990’s, leading to an accelerated
development of new organocatalysts in the coming decade.\textsuperscript{[12]} This increased interest in proline facilitated further details of proline’s interaction with carbonyls, affording researchers greater confidence to explore proline’s compatibility across diverse reaction manifolds.\textsuperscript{[13]} These studies showed proline to be compatible with a range of asymmetric reactions, including aldol-type, conjugate additions to enones, Mannich reactions, \(\alpha\)-amination of aldehydes, and \(\alpha\)-oxidation of aldehydes, to name a few (Figure 1.1).\textsuperscript{[14]}

Collectively, these experiments represented an increased acceptance and maturation of proline-catalysis, more clearly drawing its boundaries, and providing criteria for the development of new organocatalysts. These criteria encouraged more deliberate modifications to reactions
conditions and to proline itself (or other chiral sources), thereby streamlining development of new organocatalysts.[15]

1.2 Types of Organocatalysts - Beyond Proline:

In 2008, Melchiorre, et. al. remarked on the rapid development of organocatalysis:

"A large number of challenging concepts were developed independently (and almost simultaneously) by different research groups. This developed into tremendous scientific competition which has guided asymmetric aminocatalysis…and opened up new synthetic opportunities that were considered inaccessible only a few years before.[16]

Indeed, the coming structural innovations in aminocatalysis would naturally utilize the collective experience and mechanistic knowledge gained from the maturation of proline-catalysis. Specifically, proline-catalysis evolved into three distinct types of organocatalysts, with three respective modes of activation and stereoinduction: 1) hydrogen-bonding catalysis, 2) iminium catalysis, and 3) enamine catalysis.[16] While a union of these modes in proline facilitated effective chiral induction in select reactions, limitations arose due to the complexity of these interactions, as well as proline’s poor solubility.[17] Introducing structural changes to proline’s pyrrolidine and carboxylate moieties became a prominent motif for discovering new proline-derived catalysts.[18]
1.3 Hydrogen-Bonding Organocatalysis

Proline’s Zwitterionic character, although effective for stereoisoduction, unfortunately results in poor solubility (i.e., ‘like brick dust’) in all but the most polar solvents (e.g., DMF, DMSO). This obvious difficulty became the first for which solutions were devised. Modifications to proline's carboxylic acid moiety improved proline's solubility in common solvents while maintaining good levels of hydrogen-bonding stereoisoduction (Figure 1.2). One notable modification was the conversion of proline’s carboxylate to a tetrazole (Figure 1.2, #1.18). This both improved solubility in useful solvents (e.g., DCM, THF, MeCN), and maintained a hydrogen-bonding mode of asymmetric induction. These catalysts proved effective in asymmetric aldol, Mannich, and nitro-Michael reactions, among others.
1.4 Enamine & Iminium Organocatalysis

Organocatalysts with complementary, non-hydrogen bonding modes of stereoinduction were also (and continue to be) extensively pursued. Many (but not all) of these catalysts are proline-based, with enamine / iminium varieties typically retaining a five-membered, nucleophilic heterocycle and integrate bulky, inert components designed to transmit chirality by steric influence.\cite{22}
One of the most widely employed organocatalysts is the MacMillan-type, based on a versatile and easily accessible imidazolidinone skeleton derived from chiral amino acids (e.g., L-phenylalanine and L-tryptamine) (Figure 1.3).\textsuperscript{[23]}

These catalysts were developed with a focus on cycloaddition reactions, such as Diels-Alder reactions and nitrone cycloadditions.\textsuperscript{[24]} Aspects of Frontier Molecular Orbital Theory, such as LUMO-lowering (i.e., iminium-activation) and HOMO-raising (i.e., enamine activation) have been useful in their design and rationalization of stereochemical outcomes.\textsuperscript{[25]} Due to their versatility across many iminium- and enamine-activated reactions, these catalysts have met with remarkable success (Figure 1.4).\textsuperscript{[26]}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{Figure1.3.png}
\caption{MacMillan-Type Organocatalysts}
\end{figure}
1.4.1 Jørgensen–Hayashi Organocatalysts

Another useful proline-derived secondary amine organocatalyst is the diarylprolinol silyl ether variety. Development of these catalysts was influenced by the parent, unsilylated diphenyl prolinol derivative, employed in the Corey-Bakshi-Shibata (CBS) system for catalytic asymmetric reductions. These catalysts, commonly known by their inventors’ namesakes as
the Jørgensen-Hayashi organocatalysts, along with the MacMillan-type organocatalysts, have been widely employed in the activation of aldehydes via iminium-enamine pathways (vide infra). Iminium-activated, conjugate additions have been particularly valuable in delivering enantioselectivity to widely available enal substrates (Scheme 1.3).[29]

A general mechanism for these conjugate additions begins with activation of enal substrate 1.33 by condensation of organocatalyst 1.32 to form the reactive iminium species 1.33i. Conjugate addition (i.e., Michael Addition) of a nucleophile to the less hindered face of the substrate gives enantioenriched enamine intermediate 1.33e, followed by catalyst turnover to give the enantioenriched product aldehyde 1.34.

Jørgensen-Hayashi organocatalysts have been broadly explored in the iminium-enamine activation of α,β-unsaturated aldehyde (enal) substrates towards organocascade reactions.[30] The general mechanism for these organocascades is illustrated below (Scheme 1.4).[31]
Progression through the first Michael addition occurs with iminium activation of starting enal 1.33, as in Scheme 2. But instead of catalyst turnover to provide product 1.34, alternative reactivity is achieved in the presence of an electrophile capable of adding to the \( \alpha \)-position of enamine 1.33e. Enantioselective addition of the electrophile is from the sterically less-hindered face of 1.33e, as was the conjugate addition of the nucleophile to iminium 1.33i. The only remaining reactivity for iminium intermediate is hydrolytic catalyst turnover to give enantioenriched aldehyde product 1.36.

1.5 Photoredox Catalysis:

As asymmetric organocatalysis matured from a niche application into a more commonplace methodology, a wealth of associated reaction data helped to identify conditions where organocatalysis might be cross-compatible with other, achiral catalytic methods, such as certain
transition metal catalysis. For example, the use of chiral organocatalysts under the radical-generating conditions of photoredox catalysis has recently become a topic of considerable interest. Methods for radical generation and propagation are numerous, but visible-light photosensitizers (based both on transition-metals and organic dyes) do not require UV light to operate, thus reducing the likelihood for significant, undesirable side-reactions. This combination of organocatalysis with photoredox catalysis (i.e., Organophotoredox Catalysis) is thereby becoming a source of valuable asymmetric reactivity and mechanistic insight. In order to appreciate the current state of the art, a brief review of photoredox catalysis is provided, with special attention paid to organophotoredox catalysis.

The prototypical photoredox catalyst, and one commonly used in combination with organocatalysts, is a polypyridyl complex of ruthenium, tris(2,2′-bipyridine) ruthenium(II), Ru(bpy)$_3^{2+}$ (Figure 1.5). This catalyst has a long history in inorganic and physical chemistry, with applications broadly inspired by biological electron transfers, e.g., in water-splitting, photovoltaic cells, energy storage and some notable polymerization applications. Of interest to synthetic organic chemists are both the visible-light excitation of Ru(bpy)$_3^{2+}$ (~ 450 nm), which avoids higher-energy UV irradiation typical of much synthetic photochemistry, and the relatively long, excited-state lifetime (~650-1100 ns, solvent dependent) exhibited by this and related complexes. When incorporated into organic reactions, these long-lived excited-states can greatly increase reaction rates and allow for low catalyst loadings, typically 0.5 mol% - 5 mol%.
Since approximately 2008, increased research activity in photoredox catalysis has uncovered new and valuable reactivities.\[39]\) A crucial component for harnessing the redox potential of excited-state photosensitizers is a supply of electrons to be relayed between the excited-state photocatalyst and a desired substrate (e.g., photoelectron transfer - PET).\[40]\) Such electron-donors are often provided as sacrificial additives to a photoredox system. Only in the presence of such additives can a photoredox catalyst act \textit{catalytically}, instead of being consumed in uncontrolled redox processes.\[41]\)

Still, a productive photoredox system capable of converting the electrical potential of an excited-state photocatalyst into a desired transformation depends upon the matching of redox potentials between photocatalyst, additives, and substrate(s).\[42]\) For this purpose, detailed redox studies have been preformed on available photoredox sensitizers, including Ru(bpy)$_3^{2+}$ (Figure
As indicated in Figure 1.5, irradiation of ground-state Ru(bpy)$_3^{2+}$ generates excited-state Ru$^\ast$(bpy)$_3^{2+}$, which has the capacity for either oxidative or reductive transformations, depending on reaction conditions$^{[44]}$. Oxidative conditions require an electron acceptor (A) to abstract an electron from excited-state Ru$^\ast$(bpy)$_3^{2+}$, generating Ru(bpy)$_3^{3+}$ (-0.81 V), which, in the presence of a suitable electron-donor substrate (D), can subsequently be reduced (+1.29 V) back to Ru(bpy)$_3^{2+}$, allowing re-entry into the catalytic cycle.$^{[45]}$ The complementary reductive pathway requires inclusion of an electron donor (D) to generate Ru(bpy)$_3^{1+}$ (+0.88 V), a powerful reductant (-1.31 V) capable of single-electron reduction of an electron-acceptor substrate (A).

### 1.5.1 Additives in Photoredox Catalysis:

Primary among the additives used to supply electrons to a (reductive) photoredox system are hindered, tertiary amines, e.g., triethylamine or Hünig’s base (diisopropylethylamine). An important criterion for selecting sacrificial electron donors is their vulnerability to side-reactions. Factors effecting the reactivity of tertiary aminium radical cation intermediates include the degree of steric hindrance proximal to the radical (thus discouraging unwanted radical couplings), as well as redox potentials of radical intermediates relative to photoredox catalyst.$^{[46]}$

Apart from tertiary-amine additives, acidic additives have been used for substrate activation, more closely aligning the redox potentials between photocatalyst and substrate. Both Brønsted and Lewis acids have been broadly employed for this purpose, as well as for tailoring reaction pathways (Scheme 1.5).$^{[47]}$
Given the multi-component nature of photoredox catalysis, an important aspect of reaction optimization is identifying interactions (either synergistic or detrimental) between components in a reaction mixture.\[48\] For example, PET-generated radicals exhibit reactivities influenced by their vicinal electronic environment (e.g., heteroatoms, pi-systems, etc.), especially their ionic character (cationic or anionic).\[49\] Moreover, the introduction of co-catalysts (e.g., chiral organocatalysts; \textit{vide infra}) as additives in photoredox systems can further complicate optimization efforts, not only in terms of reactivities but also conceptually. For instance, the reactivity of radical couplings may not be well-described using the nomenclature of iminium-enamine organocatalysis (e.g., nucleo- and electrophilicities, HOMO / LUMO activation).\[50\] As a result, alternate terminology has been conceived to better describe and understand the ‘singly-occupied molecular orbitals’ (SOMO) that radicals can possess, such that ‘SOMO-philic’ describes a moiety’s preference for radical couplings.\[51\]
1.6 Organophotoredox Catalysis

Although diastereoselectivity is commonly observed in photoredox catalysis due to stereo-electronic factors, and improved selectivities have been seen using acidic additives (vide supra), enantioselective induction often requires a chiral co-catalyst, such as organocatalysts (i.e., organophotoredox catalysis).^{52}

1.6.1 Iminium-Enamine Activation in Organophotoredox Catalysis

Although organophotoredox catalysis is still in its infancy, initial successes have focused on the α-functionalization of aldehydes via SOMO-activation of enamine intermediates (Scheme 1.6).^{53} MacMillan’s mechanistic proposal involves generation of electron-deficient radical 1.47 by PET from reductant Ru(bpy)$_3^{+}$, followed by coupling of 1.47 with SOMO-philic enamine 1.48 to give stabilized radical 1.49. Loss of an electron by 1.49 to generate iminium intermediate 1.50, which is hydrolyzed to give the free organocatalyst 1.45 and enantioenriched aldehyde product 1.51.
Currently missing from organophotocatalytic methodologies is the iminium activation of an aldehyde or enal using a chiral, secondary amino-catalyst. The goal of such a reaction manifold would be the asymmetric radical-coupling between two electronically mismatched electrophiles analogous to Michael acceptors. Although asymmetric conjugate addition to enones has been achieved using radical coupling, known methods are achieved using α-amino radicals, instead of the more distant (γ-amino) radical possibly compatible with currently known organophotoredox catalysis.\(^{[54]}\)
1.6.2 Hydrogen-Bonding Activation in Organophotoredox Catalysis

Hydrogen-Bonding organocatalysts have also been successfully applied to organophotoredox catalysis. Although a detailed review of these studies is not crucial for understanding the research contained herein, notable references are provided for the interested reader.\textsuperscript{[55]}

1.7 Organocascade Reactions Applied to Organophotoredox Catalysis

Organocascade reactions can streamline synthetic protocols by increasing step- and atom-economy.\textsuperscript{[56]} Although combining organocascades with photoredox catalysis has the potential to greatly expand the utility of organophotoredox catalysis, few methodologies have been communicated (Scheme 1.7).\textsuperscript{[57]} Following this precedent, an expanded integration of iminium-activated, organocascade reactions with photoredox catalysis will surely be soon to follow.

![Scheme 1.7: Organocascade Reaction Combined With Photoredox Catalysis](image-url)
1.8 References


[8] Control experiments using the methyl ester of proline all but eliminated catalytic activity.


(c) For a discussion of ‘synergistic catalysis’, see: Allen, A. E., MacMillan, D. W., *Chem


(b) For a recent review of combining photoredox catalysis with organocatalysis, see: Hopkinson, M. N., Sahoo, B., Li, J. L., Glorius, F., Chemistry 2014, 20, 3874-3886.


(c) For extensive coverage of radical ions: Vlad Todres, Z., *Ion-Radical Organic Chemistry* 2008 CRC Press.

[50] (a) See Ref. 49a.

(b) However, the nucleophilicity of chiral, radical-stabilizing NHC organocatalysts utilize radicals: Maji, B., Breugst, M., Mayr, H., *Angew Chem Int Ed Engl* 2011, 50, 6915-6919.


(c) For reviews of enantioselective photoredox catalysis, see: Wessig, P., *Angew Chem Int Ed Engl* 2006, 45, 2168-2171.


[56] (a) For a general review describing advantages of organocascade reactions, see: Jones, S. B., Simmons, B., Mastracchio, A., MacMillan, D. W., Nature 2011, 475, 183-188.


2.1 Carbocyclic Scaffolds via Iminium-Enamine Organocascades

Organocascade reactions can increase the efficiency of chemical synthesis by forming multiple, chiral bonds in 1-pot procedures\(^1\). As such, the availability of organocascade methodologies are welcome complements to multi-step routes towards valuable core structures. An important application of iminium-enamine organocascades is in the synthesis of medicinally-relevant carbocycles by the functionalization of activated alkenes (e.g., Scheme 2.1)\(^3\).

![Scheme 2.1: Example of Organocascade Reaction With Activated Alkenes](image)

A notable example of organocascades’ utility for access to medicinally-relevant carbocycles is Hayashi’s synthesis of the anti-influenza drug (-)-oseltamivir (i.e., Tamiflu) using organocascade reactions (Scheme 2.2)\(^3\).
Development of related, iminium-enamine organocatalytic methodologies has facilitated (or expedited) the synthesis of valuable, medicinally-relevant scaffolds, especially chiral carbocycles (including heterocycles), as evidenced by the variety of therapeutic targets integrating these scaffolds (Figure 2.1).⁴,⁵

A key synthetic step frequently used to initiate iminium-enamine organocascades is the β-functionalization of enals by Michael addition of nucleophiles.⁶ Given the inclusion of a
suitable electrophile, this initial step can be rapidly followed by electrophilic α-functionalization of the same substrate.[7]

2.2 Michael-Initiated Organocascades For Accessing Carbocycles

Organocatalyzed Michael reactions can provide high yields and enantioselectivities and are useful not only for access to valuable β-amino acid analogues, but more generally as the initial step towards generating greater molecular complexity in iminium-enamine organocascade reactions. Many reaction pathways exist for extending organocatalyzed Michael reactions to encompass α,β-functionalization of the same substrate in 1-pot procedures. A number of these methods are discussed below, especially those relevant to the reports contained in the following, experimental chapters (Ch. 3-5).

2.2.1 Cyclopentanes and Cyclohexenes via Michael-Michael Organocascades

Among potential nucleophiles for initiating iminium-activated organocascade reactions of α,β-unsaturated aldehydes are 1,3-dicarbonyl compounds.[8] For example, 1,3-dicarbonyl compounds have been useful as Michael-donors for the creation of functionalized 5-membered carbocycles (Scheme 2.3). The mechanism of this reaction proceeds first by activation of α,β-unsaturated aldehyde 1.33 by catalyst 1.32 towards nucleophilic attack by 1,3-dicarbonyl 2.3. Approach of enol 2.3e from the re-face of iminium-activated aldehyde 1.33i allows for the first
Michael addition. Intermediate enamine 2.4e then undergoes an *intramolecular* Michael addition, providing the 5-membered ring product 2.5.

![Scheme 2.3: Access to Cyclopentanes via Michael-Michael Organocascades](image)

In the interest of producing functionalized, chiral cyclohexenes via a similar, Michael-Michael organocascade methodology, it was found that repositioning the Michael acceptor relative to the 1,3-dicarbonyl unit (*Figure 2.2, 2.3 vs. 2.6*) provided a template for accessing the desired, highly-functionalized, enantioenriched cyclohexenes (*Scheme 2.4*).[^9]
An overview of the accepted mechanism for forming these cyclohexenes is depicted below (Scheme 2.4). Organocatalyst 1.32 reacts with α,β-unsaturated aldehyde 1.33 to form iminium intermediate 1.33i, which is subsequently attacked by enol 2.6e to give the 1st Michael intermediate 2.7e. A second, intramolecular Michael addition occurs when the enamine, Michael donor moiety of 2.7e attacks the adjacent 4-position of the enone, Michael acceptor moiety, thereby providing iminium carbocycle 2.8, which is readily hydrolyzed to give 6-membered product 2.9.
2.2.2 Cyclohexenes via Michael—Morita-Baylis-Hillman Organocascades

Another possibility mode of reactivity for completion of Michael-initiated organocascades is the Morita-Baylis-Hillman (MBH) reaction (Scheme 2.5). Activated Michael acceptor, iminium 1.33i, reacts stereoselectively with nucleophilic Michael donor 2.10e to give chiral intermediate enamine 2.11. Catalyst release is followed by an intermolecular conjugate addition of the free organocatalyst to intermediate 2.12. This forms 2.13e, which, rather than undergoing a second Michael addition, is transformed by an intramolecular Morita-Baylis-Hillman reaction. Notably, the MBH pathway requires a proton at the α-position of Michael acceptor 2.12, because removal of this proton is necessary to liberate the catalyst and form products 2.15.

Scheme 2.5: Cyclohexenes via Michael-MBH Organocascades

2.2.3 Cyclohexenes via Michael-Acetalization Organocascades

Yet another viable pathway for Michael-initiated organocascades is the Michael-Acetalization pathway, valuable for introducing oxygen into cyclic structures (Scheme 2.6).
Mechanistically, the enol of $\beta$-ketoester $2.6e$ attacks iminium-activated Michael acceptor $1.33i$ to give intermediate enamine $2.7e$. A potential intramolecular second Michael addition to give Michael-Michael product $2.9$ (as in Scheme 2.4) is precluded (due to functionalization of the $\beta$-ketoester by $R^1=aryl$), instead permitting equilibration of keto-enamine $2.7e$ with enol-iminium $2.7i$ to facilitate the *intramolecular* acetalization reaction to give intermediate acetal $2.16$, which, with assistance from acid additive (4-nitrobenzoic acid), is hydrolyzed to furnish heterocyclic product $2.17$.[12]

![Scheme 2.6: Michael-Acetalization Organocascade](image)

### 2.3 Organocatalytic Olefin Amino-Fluorinations

Organic molecules containing fluorine are rare in nature as a consequence of fluorine’s high electronegativity and reactivity.[13] Fortunately, this reactivity has lent the synthetic chemist a useful hand in forming carbon-fluorine bonds. From the 1950s, the inclusion of fluorine into organic chemistry has represented a major synthetic effort, with products that are ubiquitous in
daily life (e.g., fluorinated polymers, refrigerants, solvents, surfactants, anesthetics, pharmaceuticals). The development of safe and efficient fluorination reagents and protocols has revealed the profound changes fluorine can impart to the physical, chemical and biological properties of a molecule. As a result (and more recently), an increased demand for regio-, chemo-, and enantioselective inclusion of fluorine into medicinal targets has driven the expanded availability of bench-stable, mild, chemoselective fluorinating reagents.

The formation of carbon-fluorine bonds for the fine-chemicals’ markets is accomplished by both electrophilic and nucleophilic fluorinating reagents (Figure 2.3).

**Figure 2.3: Some Common Fluorinating Reagents**

![Fluorinating Reagents Diagram]

These reagents have been devised in order to avoid working directly with F2 (and other highly reactive fluorinating agents such as HF), whose extreme reactivity is a danger to valuable substrates and invaluable chemists alike. Nucleophilic fluorinating reagents (NFR) provide an electron-rich environment to increase the nucleophilicity of the attached fluorine atom(s), a
challenge (even with electrochemical methods) due to fluorine’s high electronegativity. Electrophilic fluorinating reagents (EFRs) typically possess a fluorine-nitrogen bond, with vicinal electron-withdrawing groups (e.g., R-SO2) allowing fluorine to act as electrophile. Notably, the development of EFRs has provided important complementary reactivity to NFRs, and has stimulated enantioselective fluorinations mediated by 2º amino organocatalysis.\[17\]

These technologies have not only provided new synthetic knowledge regarding the safe and effective formation of carbon-fluorine bonds, but also have revealed how those carbon-fluorine bonds can radically alter in vivo characteristics of drugs compared to their non-fluorinated counterparts.\[18\] Specifically, the basicity of neighboring amines is decreased, the electrophilicity of carbonyls is increased and the lipophilicity of proximal groups can be modified with the inclusion of fluorine. These and other effects have allowed medicinal chemists to tailor properties related to solubility, CNS penetration, metabolic stability and binding-site affinity.\[19\]

Accessing enantiopure difluoroamines has largely been achieved using racemic methods, which may necessitate inefficient separation of enantiomers and are typically less atom-economical than stereoselective methods (vide infra). In order to appreciate the optimization necessary for developing these organocascades, it is helpful to examine the individual cascade components: first, the organocatalyzed aza-Michael reaction.

### 2.3.1 Aza-Michael Reactions
Nitrogen-containing organic molecules are vital to biological systems and are therefore a dominant functionality in medicinal chemistry. Organocatalyzed Aza-Michael reactions offer access to a variety of highly enantio-enriched β-Amino carbonyl compounds and derivatives, among many other valuable scaffolds. However, the introduction of nucleophilic nitrogen as a Michael-donor, especially in the presence of another nucleophilic heterocyclic amino organocatalyst, can be challenging due to the potential for racemization. Racemization can occur either as a result of competition for iminium formation with the desired enal substrate, or as a result of adventitious nucleophilicity towards the 4-position of the enal substrate before being activated by the chiral catalyst. An example of a successful Aza-Michael design can be seen in Scheme 2.7.

![Scheme 2.7: Aza-Michael Example](image)

2.3.2 α-Fluorination of Aldehydes

Fluorine’s high electronegativity creates a challenge for the stereoselective α-fluorination of aldehydes, largely due to the higher enol (enamine) tendency of the product, which results in an increased potential for racemization, as well as difluorination side-reactions. These difficulties have been largely overcome by the judicious optimization of reaction conditions (e.g., via choice
of solvents and work-up protocols) to achieve the desired organocatalytic, enantioselective mono-fluorinations of aldehydes (Scheme 2.8).\textsuperscript{[25]}

![Scheme 2.8: Organocatalytic α-Fluorination of Aldehydes](image)

2.3.3 Accessing β-fluoroamines Using Enal Substrates

Following reports of the aforementioned, organocatalytic β-aminations and α-fluorinations, several groups took the opportunity to combine these motifs for accessing chiral β-fluoroamines (Scheme 2.9).\textsuperscript{[26]} Mechanistically, enal 1.33 (Scheme 2.9), in the presence of iminium-enamine organocatalyst 1.32 (20 mol%), forms activated iminium intermediate 1.33i, a highly reactive Michael acceptor. This intermediate rapidly undergoes enantioselective conjugate addition by nucleophilic, CBz-protected methoxyamine 2.18 to give intermediate amino-enamine 2.22e.
Addition of electrophilic fluorinating reagent NFSI to the reaction mixture promotes subsequent, stereoselective $\alpha$-fluorination of **2.22e**, followed by hydrolytic catalyst turnover to give enantio-enriched $\alpha$-fluoro-$\beta$-amino aldehyde **2.23**. Reduction to alcohol **2.24** (to avoid racemization of the highly enolizable $\alpha$-fluoro aldehyde **2.23**) provides the more stable alcohol product, $\beta$-fluoroamine **2.24**.

**Scheme 2.9: Organocatalytic Access to Aliphatic $\beta$-Fluoroamines**

![Scheme 2.9](image_url)

2.3.4 Organocascade Access to $\beta,\beta$-difluoroamine Scaffolds

Following this accomplishment, pursuit of an optimized, organocatalytic route to another useful (but less utilized) functionality, the chiral $\beta,\beta$-difluoroamine moiety, ensued. The $\beta,\beta$-difluoroamine functionality is seen in several drugs and drug candidates (Figure 2.4).[^27]
Although methods for the synthesis of $\beta,\beta$-difluoroamines have existed prior to the latest, enantioselective versions, their poor atom-economy and narrow scope has hindered greater utilization of this functionality (Scheme 2.10).
Method (A) is catalytic, highly enantioselective and high yielding but fails to incorporate R=alkyl into its scope. Method (B) is not stereoselective in the reductive amination, which may necessitate low-yielding separation of diastereomers. Method (C) is not catalytic, and requires use of chiral starting materials, and is furthermore prone to racemization during synthesis. Although each of these methods is valuable, none provides chiral products from aliphatic enals, a class of common and inexpensive precursors. Despite the availability of these methods, the need for chiral, aliphatic β,β-difluoroamines in medicinal chemistry successfully motivated the
extension of β-fluoroamine syntheses towards a catalytic, enantioselective method for β,β-difluoroamines, especially for incorporating aliphatic enals as synthons (Scheme 2.11).[29]

Mechanistically, following enantioselective aza-Michael addition of nucleophilic CBz-protected methoxyamine 2.18 to enal 1.33 (as in Scheme 2.9), addition of racemic, proline-derived organocatalyst 1.32r (20 mol% of starting enal), as well as electrophilic fluorinating reagent NFSI (2 equiv.) drove the difluorination component of the cascade reaction to completion. Reductive work-up gave good conversion to enantio-enriched, aliphatic, α,α-difluoro-β-amino alcohol products 2.34, with good to excellent ee values.

2.4 Accessing Enantioenriched Tetrahydrofuran Scaffolds

Substituted tetrahydrofurans (THFs) are common structural cores in natural products, and consequently have some importance in medicinal chemistry.[30] Given the prevalence of these
structural cores, synthetic methods for accessing them are continually being improved, especially for stereoselective functionalization.\[31\] Methods providing diastereoselectivity include the photoredox catalyzed cyclizations of enones (Scheme 2.12).\[32\]

![Scheme 2.12: THFs via Photoredox-Catalyzed Reductive Cyclizations of Enones](image)

Enantiospecific and enantioselective methods are also known, but they often use methods with poor atom-economy, such as with chiral auxiliaries, or ligand-based, transition-metal catalyzed processes.\[33\] An enantioselective organocatalytic method is also known, but despite excellent ee-values, yields were only fair to good (Scheme 2.13).\[34\]

![Scheme 2.13: Organocatalytic Access to Substituted THFs](image)

Despite the myriad of methods for constructing functionalized tetrahydrofurans, opportunities persist for improved yields and enantioselectivities. Future successes may involve
the catalytic formation of two or more bonds in one-pot reactions, especially those with high chemo-, regio-, and stereoselectivities. In this vein, methods arising from recent advances in organophotoredox catalysis may be contenders for providing such needed routes.

2.5 References

[10] (a) See [8](a).


   (b) Regarding the impressive oxidative reactivity of diatomic fluorine, see: Jaccaud, M., Faron, R., Devilliers, D. and Romano, R. *2000*. *Fluorine. Ullmann's Encyclopedia of Industrial Chemistry*.


   (c) Enzymes have also been developed for fluorinations: O'Hagan, D.; Deng, H. *Chem. Rev.* **2015**, *115*, 765–825.


(c) For a non-organocatalyzed example, see: Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A.; McCarthy, T. D. *Synlett* 2004, 0791–0794.


Chapter 3.

Accessing Medicinally-Relevant Cyclohexene Scaffolds

via a Michael-Michael Organocascade

3.1 Introduction

Chapter 2 introduced aspects of organocatalyzed cascade reactions, specifically those involving iminium-enamine activation of $\alpha,\beta$-unsaturated aldehydes (enals) catalyzed by the diphenyl prolinol silyl ether catalysts (Jørgensen-Hayashi catalysts). Among potential building blocks compatible with these reaction manifolds are readily accessible 1,3-dicarbonyl compounds (also discussed in Ch.2), which have been used as nucleophilic Michael donors in conjugate addition reactions.$^{[1]}$ Certain 1,3-dicarboxyls, namely $\beta$-ketoesters with $\alpha,\beta$-unsaturation, possess Michael donor as well as Michael acceptor functionalities. This combination of functionality is useful for cascade reactions as multiple, complementary reactive sites are made available within the same substrate. However, the synthetic potential for this type of $\beta$-ketoester has been less realized with Jørgensen-Hayashi organocatalysts in Michael-Michael cascade reactions for the construction of functionalized, chiral 5- and 6-membered carbocycles (Schemes 2.3 and 2.5)$^{[2]}$. In the interest of expanding the potential of these substrates in organocascade reactions, a reaction manifold was designed for the formation of functionalized cyclohexenes using Jørgensen-Hayashi organocatalysts to activate $\beta$-ketoesters for the Michael-Michael organocascade reactions described below.
In the course of development of the aforementioned Michael-Michael organocascade reactions, an interesting aspect of substrate modification was explored that involved the placement of the Michael acceptor moiety at different positions of the β-ketoester substrate (as in Figure 2.2 and Figure 3.1, structures 2.3 vs. 2.6).\textsuperscript{[2c],[3]}

However, structure 2.6, otherwise known as a Nazarov reagent, although allowing for the initial Michael addition to occur, rather than facilitating a second Michael addition, saw the organocatalyst act as an adventitious Michael donor, attacking the conjugate position of the β-ketoester and initiating an unexpected Morita-Baylis-Hillman reaction (Scheme 3.1).
Scheme 3.1 displays an *intramolecular* Morita-Baylis-Hillman (MBH) reaction, initiated by a stereoselective reaction between organocatalyst 1.32 and conjugate position of intermediate β-ketoester 3.2. Following this organocatalyzed MBH reaction, catalyst release provides product carbocycle 3.3. Interestingly, this Michael-MBH pathway requires a proton at the α-position of β-ketoester 3.4 (Scheme 3.2), because removal of this proton is necessary to liberate the catalyst and form stable, isolable products 3.5e.

Building on this observation, when aryl-substituted β-ketoester Michael donor 2.6 was subjected to similar conditions, a Michael-acetalization cascade was observed (Scheme 3.3). The authors provided a rationale for the acetalization pathway, noting that aryl-substitution of β-ketoester substrate 2.6 afforded extended conjugation, and associated thermodynamic stabilization, to hemi-acetal product 2.17.
Although an iminium-catalyzed Michael-Michael route to cyclohexenes via β-ketoester substrates had not, thus far, been realized, clues contributed by optimization of the aforementioned Michael-initiated organocascades sufficed for development of an analogous Michael-Michael route to the desired cyclohexene scaffolds (Scheme 3.4). Instrumental to this methodology was replacement of the proton necessary for the Michael-MBH reaction (Scheme 3.2) with cyclic alkyl member extending between the α- and β-positions of β-ketoester substrate 3.6. This substrate modification completely precluded the MBH pathway previously reported, thereby leaving open the Michael-Michael manifold and providing the desired bicycles 3.7e in good yields and excellent diastereomeric ratios and enantiomeric excesses.

Mechanistically (Scheme 3.5), catalyst 1.32 reacted with cyclic enal substrate 3.8 to form iminium 1.33i, which was subsequently attacked by Michael donor 3.8e to give activated-
enamine 3.9e. Due to the absence of a proton alpha to the ketone functionality in 3.9e, the MBH pathway was suppressed and no Michael-MBH product (3.10) was reported. Additionally, the undesired acetalization reaction was discouraged, possibly due to absence of extended conjugation of the aryl moiety present in the Michael-Acetalization studies. Indeed, a second Michael addition was favored, providing carbocyclic iminium species 3.11i, which was readily hydrolyzed to give bicyclic product 3.12.
Furthermore, the use of trifluoroethanol as solvent was crucial for the Michael-Michael cascade. This highly polar, protic solvent provided strong hydrogen-bonding interaction with the \( \beta \)-ketoester, activating it toward the second conjugate addition (Scheme 3.6).

While a cyclic olefin (as in Scheme 3.5, #3.8), had been shown to participate in a Michael-Michael cascade to form 6-membered carbocycles, it had yet to be determined whether acyclic olefins (as in Scheme 3.8, #2.6) could also form 6-membered rings via the Michael-Michael cascade pathway (Scheme 3.7).
3.2 Results And Discussion

3.2.1 Initial Cascade Reaction

From the studies previously described (e.g. Michael-Michael cascades for 5-membered rings, Michael-MBH and Michael-acetalization cascades for 6-membered rings), it was known that multiple pathways for organocatalyzed cascades were possible. But the question was whether the Michael-MBH reaction could be avoided with acyclic \( \beta \)-ketoesters by choosing the right reaction conditions (Scheme 3.8). Studies were undertaken to explore this possibility.

![Scheme 3.8: Can conditions be tailored to favor 2nd Michael addition?](image)

Initial conditions (Entry 1, Table 3.1) revealed a good conversion to the desired Michael-Michael products (87%), with low yields of MBH by-products (13%). Enantioselectivity of the major desired diastereomer was 93%. Additional conditions were explored that might further suppress the MBH reaction, i.e., by suppression of the intermolecular reaction between catalyst 1.32 and intermediate 3.2 (Scheme 3.1). These conditions included dilution and reduced catalyst loading (Entries 1-3, Table 1). Next, the influence of additives known to affect catalyst turnover
(such as molecular sieves, and an acid additive) was explored (compare Entry 1 vs. 4-6).

Exploration of these variables revealed that our original reaction conditions were optimal (Entries 2-6, **Table 3.1**).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Additive</th>
<th>Conc.</th>
<th>Conversion(^b): 3.18 (3.19)</th>
<th>% ee B (C, D)(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2d</td>
<td>(none)</td>
<td>0.30 M</td>
<td>87% (13%)</td>
<td>93 (82, 94)</td>
</tr>
<tr>
<td>2</td>
<td>1d</td>
<td>(none)</td>
<td>0.15 M</td>
<td>79% (21%)</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>5% catalyst</td>
<td>0.30 M</td>
<td>84% (16%)</td>
<td>nd</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>4Å MS, pellets</td>
<td>0.30 M</td>
<td>77% (9%)</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>4d</td>
<td>4Å MS, powdered</td>
<td>0.30 M</td>
<td>51% (0%)</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>2d</td>
<td>Benzoic Acid, 10%</td>
<td>0.30 M</td>
<td>78% (22%)</td>
<td>nd</td>
</tr>
</tbody>
</table>

\(^a\) Reaction Conditions: 3.16 (1 equiv), 3.17 (1 equiv), cat. 1.32 (10 mol %), CF$_3$CH$_2$OH (0.3 M), rt. \(^b\) determined by \(^1\)H NMR of crude reaction mixture. \(^c\) determined by chiral HPLC.

With this data in hand, alternate means of suppressing the MBH reaction were sought. Reducing the nucleophilicity of the catalyst could potentially suppress conjugate addition of the catalyst to Michael acceptor 3.2, thereby discouraging the MBH reaction (**Scheme 15**). Thus, we tried an electron deficient catalyst. This reduced the activity of the catalyst; after 8 days the reaction showed almost no conversion to the desired products (compare Entries 1 vs. 2, **Table 3.2**). As an alternate means of reducing catalyst nucleophilicity, catalysts with larger silyl protecting groups (e.g., TBDMS, TES, TIPS) were tried. This resulted in lowered ee of the desired products (compare entries 1 with 3-5, **Table 3.2**). Thus, it was decided that the initial conditions (Entry 1, **Tables 3.1, 3.2**) were, in fact, optimal.
3.16

3.17

3.20, 10 mol %

CF$_3$CH$_2$OH

3.18 (B+C+D) Michael-Michael Products

3.19 (A) Morita-Baylis-Hillman Products

<table>
<thead>
<tr>
<th>Entry</th>
<th>Time</th>
<th>Catalyst (R$^1$, R$^2$, mol%)</th>
<th>Conc.</th>
<th>Conversion$^b$: all (3.18 + 3.19)</th>
<th>% ee (B, C)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2d</td>
<td>H, TMS, 10%</td>
<td>0.30 M</td>
<td>100% (87% + 13%)</td>
<td>93, 82</td>
</tr>
<tr>
<td>2</td>
<td>8d</td>
<td>CF$_3$, TMS, 10%</td>
<td>0.30 M</td>
<td>(poor)</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>2d</td>
<td>H, TBS, 10%</td>
<td>0.30 M</td>
<td>97% (89% + 8%)</td>
<td>84, 84</td>
</tr>
<tr>
<td>4</td>
<td>2d</td>
<td>H, TES, 10%</td>
<td>0.30 M</td>
<td>100% (89% + 11%)</td>
<td>90, 91</td>
</tr>
<tr>
<td>5</td>
<td>2d</td>
<td>H, TIPS</td>
<td>0.30 M</td>
<td>98% (91% + 7%)</td>
<td>85, 88</td>
</tr>
</tbody>
</table>

$^a$ Reaction Conditions: 3.16 (1 equiv), 3.17 (1 equiv), 3.20 (10 mol %), CF$_3$CH$_2$OH (0.3 M), rt. 
$^b$ determined by $^1$H NMR of crude reaction mixture. 
$^c$ determined by chiral HPLC

3.2.2 Separation of Diastereomers and NMR Interpretation

Separation of the desired Michael-Michael products from the MBH side product required silylation of the desired product enol followed by chromatography (Scheme 3.9). The MBH product (3.19A) was not silylated at the enol, possibly due to steric hindrance of the adjacent alkyl group. This allowed for facile separation of the silylated, desired Michael-Michael products (B’, C’, D’) from the unsilylated, undesired MBH product. Desilylation of the isolated desired products using TBAF provided the desired diastereomers. The major diastereomers (B and its epimer, C) were separable in some, but not all, cases from the minor diastereomers (D and D’) by careful chromatography.
Products were identified by NMR spectroscopy. Specifically, the aldehyde and enol regions of the spectrum were useful in confirming the presence of the desired products in the crude reaction mixture (3.18B, C, D and D in Figure 3.2). Careful chromatography and silylation allowed for isolation of each product, and identification of each peak in the enol region with a corresponding enol peak. The side product with an enol peak (~ 12.9ppm) that lacked a corresponding aldehyde peak was confirmed to be the Morita-Baylis-Hillman product (3.19A in Figure 3.2).
Figure 3.2: NMR Interpretation

3.18D (minor) + 3.18D_T (epimer of 3.18D) + 3.18C (epimer of B) + 3.18B (major)

3.19 (A)
Morita-Baylis-Hillman Product
It was determined that C was the epimer of B by re-subjecting pure C to the catalyst and CF₃CH₂OH, which gave a mixture of C and B. When D was subjected to the same conditions, a mixture of D and DT was not obtained. However, upon prolonged storage (3-4 weeks) at -30°C, pure D did become a mixture of D and DT. We speculate that D and DT are related as tautomers, and are diastereomers of B/C at the second Michael addition. In one case (Table 3.3, Entry 6), D was the major diastereomer, so decomposition, or products other than the desired Michael-Michael cascade products, could be ruled out.

3.2.3 Substrate Scope

With optimal reaction conditions in hand, an investigation of substrate scope was undertaken (Table 3.3).

<table>
<thead>
<tr>
<th>entry</th>
<th>3.18</th>
<th>time</th>
<th>R¹</th>
<th>R²</th>
<th>conv (yield)</th>
<th>ee (B)</th>
<th>d.r.</th>
<th>α:β</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>2d</td>
<td>n-butyl</td>
<td>p-NO₂-Ph</td>
<td>87</td>
<td>94</td>
<td>4:1</td>
<td>1:8</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>1d</td>
<td>methyl</td>
<td>p-NO₂-Ph</td>
<td>61</td>
<td>98</td>
<td>5:1</td>
<td>1:5</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>1d</td>
<td>ethyl</td>
<td>p-NO₂-Ph</td>
<td>66</td>
<td>95</td>
<td>4:1</td>
<td>1:8</td>
</tr>
<tr>
<td>4</td>
<td>d</td>
<td>2d</td>
<td>i-propyl</td>
<td>p-NO₂-Ph</td>
<td>82</td>
<td>&gt;99</td>
<td>6:1</td>
<td>1:17</td>
</tr>
<tr>
<td>5</td>
<td>e</td>
<td>1d</td>
<td>phenyl</td>
<td>p-NO₂-Ph</td>
<td>100 (93)</td>
<td>97</td>
<td>5:1</td>
<td>1:3</td>
</tr>
<tr>
<td>6</td>
<td>f</td>
<td>1d</td>
<td>phenyl</td>
<td>phenyl</td>
<td>100 (91)</td>
<td>99</td>
<td>7:1</td>
<td>1:11</td>
</tr>
<tr>
<td>7</td>
<td>g</td>
<td>1d</td>
<td>phenyl</td>
<td>p-toluyl</td>
<td>100 (96)</td>
<td>99</td>
<td>9:1</td>
<td>1:2</td>
</tr>
<tr>
<td>8</td>
<td>h</td>
<td>2d</td>
<td>phenyl</td>
<td>o-F-Ph</td>
<td>100 (97)</td>
<td>98</td>
<td>10:1</td>
<td>1:5</td>
</tr>
<tr>
<td>9</td>
<td>i</td>
<td>2d</td>
<td>phenyl</td>
<td>furyl</td>
<td>100 (95)</td>
<td>98</td>
<td>5:1</td>
<td>2:1</td>
</tr>
<tr>
<td>10</td>
<td>j</td>
<td>1d</td>
<td>phenyl</td>
<td>ethyl ester</td>
<td>98 (71)</td>
<td>91</td>
<td>7:1</td>
<td>(No α)</td>
</tr>
</tbody>
</table>

Table 3.3: Substrate Scope
This substrate scope revealed this reaction to work well with alkyl substituted \( \beta \)-ketoesters, and electron deficient and electron neutral aryl substituted \( \alpha,\beta \)-unsaturated aldehydes (Entries 1 & 2, Table 3.3). Shockingly, when the same aryl substituted \( \beta \)-ketoester that exhibited Michael-acetalization cascade reactions\[4\] were subjected to our reaction conditions, only the Michael-Michael product was observed (Entry 5, Table 3.3; Scheme 3.10).

<table>
<thead>
<tr>
<th></th>
<th>k</th>
<th>l</th>
<th>m</th>
<th>n</th>
<th>o</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td></td>
<td>1d</td>
<td>phenyl</td>
<td>n-butyl</td>
<td></td>
<td>89</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>l</td>
<td>3d</td>
<td>( p )-MeO-Ph</td>
<td>furyl</td>
<td>(78)</td>
<td>97c</td>
<td>2:1</td>
</tr>
<tr>
<td>13</td>
<td>m</td>
<td>1d</td>
<td>( p )-Br-Phenyl</td>
<td>( p )-Br-Phenyl</td>
<td>(73)</td>
<td>99</td>
<td>6:1</td>
</tr>
<tr>
<td>14</td>
<td>n</td>
<td>2d</td>
<td>( o )-F-phenyl</td>
<td>furyl</td>
<td>(87)</td>
<td>93c</td>
<td>2:1</td>
</tr>
<tr>
<td>15</td>
<td>o</td>
<td>2d</td>
<td>furyl</td>
<td>furyl</td>
<td>(39)</td>
<td>95</td>
<td>1:2</td>
</tr>
</tbody>
</table>

\[ a \] Reaction Conditions: 1.33 (1 equiv), 3.21 (1 equiv), 1.32 (10 mol %), CF\(_3\)CH\(_2\)OH (0.3 M), rt. \[ b \] Yield = isolated yield of B+C+D. Conversion, dr, and ratio of \( \alpha:\beta \) determined by \(^1\)H NMR. ee determined by chiral phase HPLC. dr = ratio of MAJOR:MINOR. \[ c \] C is the major epimer. \[ d \] D is the major epimer.

With this realization, further substrates were explored with aryl-substituted \( \beta \)-ketoesters (Entries 4-11, Table 3.3). Due to the complete absence of MBH and acetalization products, the reaction favors aryl over aliphatic substituted \( \beta \)-ketoesters. The aromatic groups provide extensive conjugation within the \( \beta \)-ketoester system, thereby lowering the LUMO of the \( \beta \)-

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### Scheme 3.10: Different Conditions Give Different Products

![Scheme 3.10](image-url)
ketoesters as Michael acceptors for the second Michael addition. Due to the absence of side-products (i.e., MBH and acetalization), aryl substituents greatly simplified purification and allowed for yield determination. Moderate yields for an ortho-fluoro-phenyl substituted β-ketoester (Entry 9) showed the reaction’s tolerance for ortho substituents. Using the electronically neutral phenyl substituted β-ketoester, various groups were tolerated at the aldehyde (entries 4-9). Substituting an aryl for an ester group at the aldehyde (entry 6) was also well tolerated. An unsubstituted β-ketoester performed poorly (Entry 12), however, giving only 12% conversion after 3 days. An electron rich aryl-substituted aldehyde, combined with the original alkyl substituted β-ketoester, was not well-tolerated giving 50% conversion after 7 days (entry 13).

3.3 Conclusions

The key result from this work has been the observation that a simple change in solvent (CF₃CH₂OH vs. CH₂Cl₂) can have a dramatic effect on the outcome of these cascade reactions. On the one hand, it was shown by Gong[4] that use of CH₂Cl₂ provides a Michael-acetalization cascade in moderate yield (up to 78%) and excellent enantioselectivity (up to 99%) (3.21 \rightarrow 3.23, Scheme 3.10). On the other hand, our research has shown that use of CF₃CH₂OH with the same substrates and the same catalyst led to Michael-Michael cascade products with good to excellent yield and excellent enantioselectivity (3.21 \rightarrow 3.18, Scheme 3.10). The use of trifluoroethanol as solvent was critical for the prevention of acetalization side-reactions. This was due to suppressing keto-enol tautomerization of the single-Michael intermediate (3.24 \rightleftharpoons 3.25, Scheme 3.11), which was a driving force for the acetalization pathway in studies by Gong.[4]
A further significant result of this research is the fact that while the Brenner-Moyer lab has previously reported the formation of 6-membered carbocycles using cyclic β-ketoesters[^5], we have extended this methodology to a general Michael-Michael cascade tolerating cyclic, acyclic, aryl and alkyl substituted β-ketoesters.
3.4 References


Chapter 4.

One-Pot Preparation of Enantiopure Fluorinated β-Amino Acid Precursors

4.1 Introduction

As introduced in Ch.2, methods for synthesizing chiral β,β-difluoramines often hinge on the availability of enantiomerically pure precursors or, in their absence, expensive chiral auxiliaries for diastereoselective bond-formation.\(^1\) Lacking these options, racemic mixtures can be resolved to attain the desired enantiomer, typically resulting in a material loss of at least 50%.\(^2\) None of these options is ideal, especially considering the recently available options for the enantioselective fluorination of aldehydes and amino-fluorination of alkenes.\(^3\) Following reports of organocatalytic β-aminations and α-fluorinations\(^4\), the Brenner-Moyer group combined these motifs to report an organocascade reaction for the α-fluoro-β-amino functionalization of α,β-unsaturated aldehydes to give β-fluoroamines (Scheme 4.1).\(^5\) Furthering this line of research, our group pursued the chiral β,β-difluoroamine moiety (\textit{vide infra}) (Scheme 4.1).
Although enantioselective methods exist for attaining the same (see Ch.2, section 3.4), none provides chiral products from achiral, aliphatic enals, a class of common and inexpensive precursors. The aim of this project has been to modify our organocascade β-fluoroamine synthesis to produce an enantioselective olefin amino-difluorination compatible with a broad range of aliphatic substrates.

4.2 Results And Discussion

4.2.1 Initial Results

Initially, a general synthetic method was proposed for the desired amino-difluorination organocascade based on the Brenner-Moyer lab’s prior amino-fluorinations\(^5\) (Scheme 4.2). It was imagined that aliphatic enal substrate 1.33, activated by secondary amine catalyst 1.32 to
give iminium \(1.33i\), would undergo conjugate addition by amine nucleophile \(2.18\) to give \(\beta\)-amino enamine \(2.22e\), which, in the presence of electrophilic fluorinating reagent NFSI, was known to give mono-fluorinated enamine intermediate \(2.33e\). In the presence of a second equivalent of NFSI, mono-fluoro enamine \(2.33e\) was reasonably expected to convert to amino-difluoro iminium intermediate \(4.3i\), which could then be hydrolyzed prior to reductive work-up to provide \(\beta,\beta\)-difluoroamino-alcohols \(2.34\).

Scheme 4.2: Proposed Organocascade Access to \(\alpha,\alpha\)-Difluoro-\(\beta\)-amino Alcohols

Due to previous experience in the Brenner lab with this type of reaction, we expected the optimization would be relatively straightforward. We were optimistic specifically because, due of fluorine’s strong inductive effect, the \(\alpha\)-proton of the mono-fluorinated intermediate is more acidic than the non-fluorinated counterpart. This has previously led to either racemization of the
C-F bond, or to di-fluorinated by-products when only mono-fluorination was intended.\(^6\) We anticipated that adding 2 equivalents of NFSI would encourage the desired amino-difluorination.

Initial investigations began by modifying our conditions for the \(\beta\)-fluoroamine analogues;\(^5\) adding 2 equivalents of NFSI instead of 1 equivalent provided 17\% yield of the \(\beta,\beta\) -difluoroamine, reduced to the alcohol for characterization (Table 4.1).

![Table 4.1: Initial Attempts at Enantioselective Amino-difluorinations](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>temp.(^b)</th>
<th>time(^b)</th>
<th>yield(^c) of 4.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt/rt</td>
<td>1d/2d</td>
<td>17</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: (1) \(t\)-BuOMe (0.4 mL, 0.625 M), 2.18 (1.2 equiv), catalyst 1.32 (0.05 mmol, 20 mol %), 4.4 (0.25 mmol, 1 equiv), rt, time; (2) \(t\)-BuOMe (0.6 mL, 0.25 M), NFSI (0.50 mmol, 2 equiv), temp, time. (3) NaBH\(_4\).

\(^b\)Amination/fluorination. \(^c\)4.5, after chromatography.

### 4.2.2 Solvent Screening

Aiming to improve this modest yield, solvent screens were undertaken for both the amination and fluorination steps individually. Although our \(\beta\)-fluoroamine organocascade necessitated \(t\)-BuOMe as solvent for high enantioselectivity in the \(\alpha\)-fluorination step, this was no longer a concern for the \(\alpha,\alpha\)-difluorination. We therefore felt a range of solvents should be explored, first
for the amination component of the cascade (Table 4.2), followed by the difluorination component (Table 4.3).

Table 4.2: Amination Solvent Screen

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temp. (°C)</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CHCl₃</td>
<td>rt</td>
<td>6h</td>
<td>67</td>
</tr>
<tr>
<td>2</td>
<td>CHCl₃</td>
<td>0</td>
<td>6h</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>CHCl₃</td>
<td>rt</td>
<td>1d</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>t-BuOMe</td>
<td>rt</td>
<td>1d</td>
<td>56</td>
</tr>
<tr>
<td>5</td>
<td>t-BuOMe</td>
<td>rt</td>
<td>2d</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>rt</td>
<td>4d</td>
<td>40</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: 1) 0.25 mmol scale with 4.4 (1 equiv), 2.18 (1.2 equiv), solvent (0.625 M), catalyst 1.32 (20 mol %), time, temp; (2) NaBH₄. *b* consumption of 4.4 (monitored by ¹H NMR). *c* 4.6, after chromatography.
These experiments revealed that although the amination was faster in CHCl₃ (Table 4.2, entries 1-3), the fluorination step did not tolerate chlorinated solvents (Table 4.3, entries 1-2). A variety of solvents and solvent combinations revealed that only ethers enabled difluorination in appreciable yields (entries 3, 4, 6, 12), with t-BuOMe proving the best (entry 12, 59%). Since the amination gave moderate to good yields in t-BuOMe (Table 4.2, entries 4, 5), albeit with longer
reaction times, (1-2d vs. 6h for CHCl₃), t-BuOMe was chosen as the best solvent to optimize the organocascade.

### 4.2.3 Catalyst Screen for Difluorination

A few key observations were then made while ¹H NMR monitoring of the individual components of the cascade reaction. First, a monitoring of the aza-Michael component of the cascade revealed what should have been a singlet TMS-ether signal of the catalyst being split into multiple peaks. Second, an intermediate aminal species was seen to appear during the aza-Michael step, but was not being fully consumed during the difluorination step of the cascade, possibly indicating a ‘resting’ state of the catalyst. However, no such aminal species was observed during difluorination of the isolated β-amino aldehyde. Together, these observations suggested that either, (1) the TMS-ether was being cleaved from the catalyst, thereby deactivating the catalyst, or (2) the catalyst was being otherwise deactivated, possibly by an off-cycle species (e.g., aminal) hypothesized to be causing the multitude of silyl-ether peaks.

Hoping to rectify this problem, two observations were utilized for the following optimization: first, that the amination was favored in chloroform (Table 4.2), and second, that the difluorination need not be enantioselective (no stereocenter is formed). These clues led to a screen of racemic catalysts in chlorinated solvents, and solvent mixtures, for the fluorination step (Table 4.4). Since the MacMillan imidazolidinone organocatalysts were known to effect both β-amination and (mono)-α-fluorination of aldehydes in chlorinated solvents, a variety of these catalysts were screened (entries 2-9). However, these catalysts were not effective for the
difluorination, giving lower yields (entries 2,6,8), or gave only the mono-fluorinated intermediate (entries 3-5, 7, 9). Pyrrolidine and DL-proline were also screened (entries 10-14), but no fluorinated product was observed. However, the racemic Hayashi-Jørgensen catalyst 1.32r appeared optimal (entry 1, 78% yield), at least for the isolated difluorination.

**Table 4.4: Racemic Catalysts for Difluorination**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>temp (°C)</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.32r</td>
<td>t-BuOMe</td>
<td>rt</td>
<td>2d</td>
<td>78</td>
</tr>
<tr>
<td>2b</td>
<td>4.6r/TFA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>rt</td>
<td>5d</td>
<td>51</td>
</tr>
<tr>
<td>3b</td>
<td>4.6r/TFA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>0</td>
<td>8d</td>
<td>0</td>
</tr>
<tr>
<td>4b</td>
<td>4.6r/pTSA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>rt</td>
<td>3d</td>
<td>0</td>
</tr>
<tr>
<td>5b</td>
<td>4.6r/pTSA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>0</td>
<td>4d</td>
<td>0</td>
</tr>
<tr>
<td>6b</td>
<td>4.7r/DCA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>rt</td>
<td>3.5d</td>
<td>48</td>
</tr>
<tr>
<td>7b</td>
<td>4.7r/DCA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>0</td>
<td>5d</td>
<td>0</td>
</tr>
<tr>
<td>8b</td>
<td>4.8r/TFA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>rt</td>
<td>2d</td>
<td>67</td>
</tr>
<tr>
<td>9b</td>
<td>4.8r/TFA</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>0</td>
<td>3d</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>4.10</td>
<td>t-BuOMe</td>
<td>rt</td>
<td>2d</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>4.10 (1 equiv)</td>
<td>CHCl₃</td>
<td>rt</td>
<td>2d</td>
<td>0</td>
</tr>
</tbody>
</table>
Pleased with the good yield achieved for the difluorination using racemic catalyst 1.32r, but puzzled about why both pyrrolidine and racemic D,L-proline failed in the difluorination step, we reflected on the putative, enamine-catalyzed mechanism of the difluorination. In order to test the general hypothesis that the desired difluorination was indeed operating via enamine-catalysis (as opposed to transfer fluorination, or via base-catalyzed enol intermediates), 2-fluorotridecanal was subjected to difluorination conditions, but in the absence of an enamine catalyst. After 20h, this reaction showed no evidence of difluorination. Additionally, in the presence of DBU (1 equiv), the same 2-fluorotridecanal showed only traces of difluorinated product (again, after 20h.) Together, these results indicate that the desired, gem-difluorination likely proceeds via sequential enamine-catalyzed α-fluorinations, not by base-catalysis or transfer fluorination (as would have been indicated by DBU-facilitated gem-difluorinations.)

Additionally, concerning the steric bulk of catalyst 1.32 and how it might affect the difluorination, we considered the possibility that mono-fluoro enamine intermediate 2.33e was mismatched with chiral catalyst 1.32, causing an unproductive resting state of the catalyst. To test this hypothesis, the corresponding α-fluoro-β-amino aldehyde was purified (as a 2:1 syn/anti diastereomeric mixture) and resubmitted to the second fluorination using chiral catalyst 1.32. Interestingly (and confirming the ‘matched/mismatched’ hypothesis), approximately 60% of the

<table>
<thead>
<tr>
<th>12</th>
<th>4.10</th>
<th>CHCl₃</th>
<th>rt</th>
<th>2d</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>4.11r</td>
<td>CHCl₃</td>
<td>rt</td>
<td>4d</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>4.11r</td>
<td>CHCl₃:i-PrOH (9:1)</td>
<td>rt</td>
<td>5d</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1) i. 0.25 mmol scale with solvent (1.0 mL, 0.25 M), 4.6 (0.25 mmol, 1 equiv); ii. NFSI (2 equiv), catalyst, time; \(^b\) (0.20 M) \(^c\) Monitored by \(^1\)H-NMR for consumption of both SM and mono-fluoro intermediate. \(^d\) yield of ‘0’ indicates no difluorinated product, but observation of only starting β-amino aldehyde 4.6, or mono-fluorinated intermediates by \(^1\)H NMR. \(^e\) 4.5, after chromatography.
minor diastereomer (i.e., ‘matched’ for catalyst 1.32) was transformed into the corresponding difluorinated aldehyde within 2 min, while none of the major diastereomer (i.e., ‘mismatched’ for 1.32) was transformed (as indicated by $^1$H NMR spectroscopy.) At the same time, the ($R$)-enantiomer of catalyst 1.32 (i.e., derived from $D$-proline) converted ~25% of the major diastereomer, but none of the minor diastereomer. This trend continued throughout monitoring by $^1$H NMR spectroscopy over 24 h. In the light of these results, racemic 1.32r (10 mol%) was used in place of 1.32 for the fluorination step, further improving yield (Table 4.5, entry 6). Increasing the amount of 1.32r (up to 20 mol%) increased the yield of desired product 4.(#) (Table 4.5, entry 7). These results provided confirmation that the mono-fluoro product of the first $\alpha$-fluorination was mismatched for a second enamine-formation with catalyst 1.32. As such, the simple addition of racemic 1.32r during the difluorination understandably provided superior yields over other methods assessed.

As a result of independently optimizing both amination and difluorination steps, and of identifying $t$-BuOMe as the best solvent among those tested, optimization of the one-pot reaction was undertaken (Table 4.5). Since the combined best yields for the amination and fluorination (63% x 78% = 49%) was higher than for the overall cascade yield (17%), improvement of the cascade yield should be possible. Further optimization of the cascade was therefore undertaken, using $t$-BuOMe as solvent. Reaction concentration was considered a simple factor affecting the difluorination step, especially since NFSI (and the sulfonimide by-product) was poorly solvated in $t$-BuOMe. However, only marginal improvements over the initial yield were seen with concentrations ranging from 0.625 M – 0.100 M (Table 4.5, entries 1 vs. 2, 3). Next, due to the (aforementioned) possible inactivation of the organocatalyst during the amination step, adding
fresh catalyst after the amination was investigated. This modification demonstrated considerable improvement in overall yield (entries 1 vs. 4, 5). A still larger improvement was seen when racemic 1.32r was added during the fluorination step (entry 6, 39%). The most sterically hindered Hayashi-Jørgensen catalyst, 4.12, gave a much-reduced yield (entry 7).

### Table 4.5: Fresh Catalyst Addition

<table>
<thead>
<tr>
<th>entry</th>
<th>2nd catalyst</th>
<th>temp</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>--</td>
<td>rt</td>
<td>1d/2d</td>
<td>17</td>
</tr>
<tr>
<td>2a</td>
<td>--</td>
<td>rt</td>
<td>1d/2d</td>
<td>22</td>
</tr>
<tr>
<td>3f</td>
<td>--</td>
<td>rt</td>
<td>18h/3d</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>1.32 (10 mol%)</td>
<td>rt</td>
<td>1d/2d</td>
<td>30</td>
</tr>
<tr>
<td>5g</td>
<td>1.32 (20 mol%)</td>
<td>rt</td>
<td>1d/2d</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>1.32r (10 mol%)</td>
<td>rt</td>
<td>1d/2d</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>4.12 (10 mol%)</td>
<td>rt</td>
<td>1d/14h</td>
<td>18</td>
</tr>
</tbody>
</table>

*a* Reaction conditions: *(i)* 0.25 mmol scale with t-BuOMe (0.4 mL, 0.625 M), 2.18 (1.2 equiv), 1.32 (20 mol %), 4.4 (0.25 mmol, 1 equiv), rt, time; *(ii)* t-BuOMe (0.6 mL, 0.25 M), NFSI (2 equiv), 2nd cat. (20 mol %), temp, time; b temp for fluorination. *c* reaction time for amination/fluorination. *d* yield for isolated 4.5 after chromatography. *e* 0.1 M. *f* 0.625M. *g* 2-step addition (24h apart) of both NFSI (2 x 1 equiv) and 1.32 (10 mol% x 2) during difluorination step.
4.2.4 Optimization of Temperature, NFSI Equivalents, Additives

With improved, although still modest, overall yields (39%, albeit over 3 steps), a range of small adjustments to reaction time, temperature, and equivalents of both amination reagent (2.18) and NFSI were assessed, all-the-while using increased amounts of catalyst 1.32r (20 mol %) for the difluorination (Table 4.6, all entries). Low temperature fluorination was investigated in an effort to suppress any potential, unwanted side-reactions. This resulted in longer reaction time, but failed to improve yield (Table 4.6, entry 2). Varying the equivalents of NFSI, also in an effort to inhibit possible side-reactions, was not productive (entries 4, 5). Finally, using 2 equivalents of amine nucleophile 2.18, 2 equivalents of NFSI, and three days total reaction time gave an optimal yield of 54% (entry 8).
Table 4.6: Cascade Optimization - NFSi, Temperature, Time\(^a\)

<table>
<thead>
<tr>
<th>entry</th>
<th>NFSI (equiv)</th>
<th>time(^b)</th>
<th>yield(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>1d/1d</td>
<td>35</td>
</tr>
<tr>
<td>2(^d)</td>
<td>2</td>
<td>2d/3d</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>2d/2d</td>
<td>20</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>2d/1d</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>1.5</td>
<td>1d/2d</td>
<td>31</td>
</tr>
<tr>
<td>6(^e)</td>
<td>1.5</td>
<td>1d/2d</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>2d/2d</td>
<td>52</td>
</tr>
<tr>
<td>8(^e)</td>
<td>2</td>
<td>1d/2d</td>
<td>54</td>
</tr>
</tbody>
</table>

\(^a\) Reaction conditions: 1) (i) t-BuOMe, \((1.32, 20 \text{ mol \%})\), \(n\)-BuOH, (1.32, \(20 \text{ mol \%}\)), ii. t-BuOMe, NFSi, \(1.32\) (20 mol %), rt, time; (ii) t-BuOMe (0.6 mL, 0.25M), NFSi (equiv.), \(1.32\) (20 mol %), rt, time;  
\(^b\) amination/fluorination. \(^c\) \(4.5\), after chromatography. \(^d\) \(0^\circ\)C fluorination. \(^e\) \(2.18\) (2 equiv).

With an eye still on improving the overall yield, a final optimization was undertaken to study the effect of additives (Table 4.7). The addition of water (0.5 equiv) during the fluorination was evaluated based on the suspicion that hydrates of the \(\alpha,\alpha\)-difluoro aldehyde were forming.\(^8\) Since water is part of the catalytic cycle (e.g., via reversible iminium formation) we felt that additional water might help to sequester the product difluor醛dehyde as the hydrate, leaving the
stoichiometric amount of water to participate in the catalytic cycle, thereby improving overall yield. This however provided no benefit (Table 4.7, entry 1). The addition of Brønsted acids (benzoic and acetic acid), additives known to increase the rate of catalyst turnover, were evaluated, and showed increased speed of amination but had no effect on fluorination, nor did they improve the overall yield (Table 4.7, entries 2-7).

**Table 4.7: Optimization - Effect of Additives on Cascade**

<table>
<thead>
<tr>
<th>entry</th>
<th>additives, conditions</th>
<th>time</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(ii) H&lt;sub&gt;2&lt;/sub&gt;O (0.5 eq)</td>
<td>1d/2d</td>
<td>36</td>
</tr>
<tr>
<td>2&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.625M, BzOH (20 mol%)</td>
<td>2.5h/1d</td>
<td>24</td>
</tr>
<tr>
<td>3&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.625M, BzOH (20 mol%)</td>
<td>2.5h/2d</td>
<td>24</td>
</tr>
<tr>
<td>4&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.25M, BzOH (20 mol%)</td>
<td>1d/1d</td>
<td>20</td>
</tr>
<tr>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.625M, AcOH (20 mol%)</td>
<td>4h/1d</td>
<td>45</td>
</tr>
<tr>
<td>6&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.625M, AcOH (20 mol%)</td>
<td>4h/2d</td>
<td>44</td>
</tr>
<tr>
<td>7&lt;sup&gt;e&lt;/sup&gt;</td>
<td>0.25M, AcOH (20 mol%)</td>
<td>1d/2d</td>
<td>39</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction conditions: (1) (i) 0.25 mmol scale with t-BuOMe (0.4 mL, 0.625 M), 2.18 (2 equiv), c1 (20 mol %), 4.4 (0.25 mmol, 1 equiv), rt, time; (ii) t-BuOMe (0.6 mL, 0.25 M), NFSI (equiv), 1.32 (20 mol %), rt, time; (2) NaBH₄.  
<sup>b</sup> amination/fluorination, monitored by <sup>1</sup>H NMR;  
<sup>c</sup> 4.5, after chromatography;  
<sup>d</sup> water added in (ii);  
<sup>e</sup>  acid added in step-i.
4.2.5 Substrate Scope

With optimized conditions in hand (Table 4.6, entry 8), a substrate scope was performed to demonstrate the cascade’s compatibility with a range of aliphatic enals. Aromatic and alkenyl groups spaced at least two carbons from the reactive enal functionality were compatible (Table 4.8).

Table 4.8: Substrate Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>2.34</th>
<th>R</th>
<th>yield 13 (%)</th>
<th>ee 13 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.34a</td>
<td>n-Bu</td>
<td>54 (81)</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>2.34b</td>
<td>Et</td>
<td>57 (83)</td>
<td>90</td>
</tr>
<tr>
<td>3</td>
<td>2.34c</td>
<td>n-Pr</td>
<td>52 (80)</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>2.34d</td>
<td>C9H19</td>
<td>49 (79)</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>2.34d</td>
<td>C9H19</td>
<td>49 (79)</td>
<td>92</td>
</tr>
<tr>
<td>6</td>
<td>2.34e</td>
<td>CH2Bn</td>
<td>43 (75)</td>
<td>93</td>
</tr>
<tr>
<td>7</td>
<td>2.34f</td>
<td>i-Bu</td>
<td>49 (79)</td>
<td>88</td>
</tr>
<tr>
<td>8</td>
<td>2.34g</td>
<td>i-Pr</td>
<td>40 (73)</td>
<td>90</td>
</tr>
<tr>
<td>9</td>
<td>2.34h</td>
<td>(CH2)3CHCH2</td>
<td>47 (78)</td>
<td>91</td>
</tr>
<tr>
<td>10</td>
<td>2.34i</td>
<td>CH2OBn</td>
<td>44 (76)</td>
<td>92</td>
</tr>
<tr>
<td>11</td>
<td>2.34j</td>
<td>(CH2)7CO2Me</td>
<td>47 (78)</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>2.34k</td>
<td>C9H19</td>
<td>54 (81)</td>
<td>89</td>
</tr>
</tbody>
</table>
\(^{a}\) Reaction conditions: (1) (i) 1.33 (0.25 mmol), 2.18 (0.5 mmol), 1.32 (0.05 mmol), r-BuOMe (0.4 mL), room temp., 1d; (ii) NFSI (0.5 mmol), 1.32r (0.05 mmol), r-BuOMe (0.6 mL), room temp., 2–3 d; (2) NaBH\(_4\) (2.5 equiv.), CH\(_3\)Cl/EtOH (2:1), room temp. \(^{b}\) Isolated yield. \(^{c}\) The number in parentheses corresponds to the average yield per step in the three-step sequence. \(^{d}\) Determined by chiral-phase HPLC of the alcohol. \(^{e}\) Reaction run on a 2.5 mmol scale. \(^{f}\) BnONHCbz used instead of 2.18. \(^{g}\) Yield determined by \(^1\)H NMR spectroscopy using an internal standard. \(^{h}\) ee of ester 4.13 (Scheme 4.3).

### 4.2.6 Synthesis of Rhodopeptin Analogue Precursor

With a substrate scope providing yields (40-57\%) and ee values (88-98\% ee) roughly corresponding to those from reaction optimization (54\% yield, 91\% ee), a capstone substrate was pursued to demonstrate the utility of the organocascade. An anti-fungal candidate containing an aliphatic difluoroamine moiety was chosen for its prospective compatibility with this new reaction manifold (Figure 2.4, Rhodopeptin analogue). Attaining this material has been plagued by a low-yielding, non-catalytic racemic method necessitating chromatographic separation of diastereomer 13-steps into the full synthesis.\(^{[2]}\) Demonstrating a catalytic, highly enantioselective approach to provide precursor 4.14 in fewer steps than the current 8-step method would be a useful application of the methods described herein (Scheme 4.3).
Conditions were found to oxidize the organocascade product alcohol 2.34d to an intermediate carboxylic acid (TPAP/NMO/H₂O, quantitative)\(^9\) followed by esterification (AcCl/MeOH, 98%)\(^{10}\) to give the protected amino acid methyl ester 4.13. Difficulties arose, however, with attempts to deprotect the amine to give the β-amino acid methyl ester 4.14. While CBz removal proved routine (hydrogenation over Pd/C), cleavage of the N-O bond was known to be challenging from prior unsuccessful attempts with a similar, mono-fluorinated substrate.\(^{11}\)

Attempts at one-step cleavage of both N-CBz and N-OMe under various hydrogenation conditions were not successful. Further efforts at reductive N-O bond cleavage, including Mo(CO)₆,\(^{12}\) Zn/AcOH,\(^{12}\) TiCl₃/H₂O,\(^{13}\) and SmI₂\(^{14}\) were unfruitful. Literature reports of N-O cleavage using SmI₂ seemed promising,\(^{14}\) particularly a mention that N-TFA derivatives were more responsive to N-O cleavage. To our great satisfaction, exchanging the N-CBz protecting group for N-TFA\(^{15}\), followed by treatment with SmI₂\(^{14}\) rapidly cleaved the N-O bond in quantitative yield (4.13b → 4.13c). However, subsequent attempts to remove the N-TFA,
including K$_2$CO$_3$/MeOH,$^{[16]}$ NaOMe/MeOH (reflux),$^{[17]}$ and MeOH/HCl (reflux)$^{[18]}$ were all surprisingly unsuccessful (Scheme 4.4).

At this point, we considered using a different nucleophile for the cascade that might ease the N-O cleavage, preferably without needing N-TFA protection. To this end, the organocascade was run using a nucleophile with N-OBn instead of N-OMe (Scheme 4.5)$^{[19]}$ followed by preparation of the methyl ester derivative (as in Scheme 4.3).
We especially hoped that both the N-CBz and N-OBn groups would be sensitive to hydrogenation for simultaneous cleavage. To our delight, hydrogenation conditions were found that provided the target free amine 4.14 from the N-OBn derivative in good yield (91%) (Scheme 4.6).

### 4.3 Conclusions

In conclusion, the key result from this work has been the development of a novel, organocatalyzed cascade reaction for the enantioselective amino-\(\text{di}\)fluorination of aliphatic enals, providing aliphatic \(\beta,\beta\)-difluoroamines in good yields with excellent enantioselectivities. To demonstrate the utility of this reaction, an improved method was devised to furnish an important synthetic intermediate towards a potent anti-fungal drug containing the \(\beta,\beta\)-difluoroamine.
moiety. Generally, this research underscores the utility and versatility of the Hayashi-Jørgensen organocatalysts.

4.4 References


Chapter 5.

Accessing Medicinally-Relevant Tetrahydrofuran Scaffolds via Organocascade Reactions

5.1 Introduction

Transition-metal photoredox catalysis and iminium organocatalysis are two important and mechanistically distinct fields of chemical technology (as reviewed in Chapter 2.) For example, the stereoselective $\alpha,\beta$-functionalization of enones has been achieved using both organocatalysis\textsuperscript{[1a]} (via iminium/enamine catalysis), or photoredox catalysis (via SOMO activation)\textsuperscript{[1b]} (Scheme 5.1).
Under the proper conditions, combining organocatalysis with photoredox catalysis (organophotoredox catalysis) has also been shown capable of α,β-functionalization of enals in good yields and enantioselectivities (Scheme 5.2).\textsuperscript{[2]}

\begin{align*}
\textbf{Scheme 5.2: Organophotoredox} & \alpha,\beta\text{-Functionalization of Enals} \\
\begin{array}{c}
\text{H} \text{C} = \text{C} & \quad \text{OTMS} \\
\text{R} & \quad \text{Ph} \\
\text{H} & \quad \text{E} = \text{CO}_2\text{R}
\end{array} \\
\begin{array}{c}
\text{H} \text{C} = \text{C} & \quad \text{OTMS} \\
\text{R} & \quad \text{Ph} \\
\text{H} & \quad \text{E} = \text{CO}_2\text{R}
\end{array}
\end{align*}

\textit{Scheme 5.2:} Organophotoredox α,β-Functionalization of Enals

\textit{1.32} Ru\textsuperscript{II}/TiO\textsubscript{2}, TEMPO, CH\textsubscript{2}(CO\textsubscript{2}Et)\textsubscript{2}, MeCN, visible light, rt

\begin{align*}
\text{H} \text{C} = \text{C} & \quad \text{OTMS} \\
\text{R} & \quad \text{Ph} \\
\text{H} & \quad \text{E} = \text{CO}_2\text{R}
\end{align*}

Thus far, however, organophotocatalytic reactions have largely focused on the SOMO activation of \textit{enamine} intermediates (see Ch.1, Scheme 1.6 for mechanism, reaction summarized in Scheme 5.3.).\textsuperscript{[3]}

\begin{align*}
\textbf{Scheme 5.3: Organophotocatalytic Enamine-SOMO Activation} \\
\begin{array}{c}
\text{H} \text{C} = \text{C} & \quad \text{OTMS} \\
\text{R} & \quad \text{Ph} \\
\text{H} & \quad \text{E} = \text{CO}_2\text{R}
\end{array} \\
\begin{array}{c}
\text{H} \text{C} = \text{C} & \quad \text{OTMS} \\
\text{R} & \quad \text{Ph} \\
\text{H} & \quad \text{E} = \text{CO}_2\text{R}
\end{array}
\end{align*}

\textit{Scheme 5.3:} Organophotocatalytic Enamine-SOMO Activation

\textit{1.43} Racemic bromocarbonyl

\textit{1.44} Ru(bpy)\textsubscript{3}Cl\textsubscript{2}, 2,6-lutidine, DMF r.t.

Currently missing from the organophotocatalytic methodology is iminium-activation of an enal, followed by photoredox-generated β-enamine neutral radical. Such an intermediate, given an appropriate SOMO-philic partner, may allow access to β-functionalized aldehydes by radical coupling at the β-position. Precedent for a similar, enol-derived neutral radicals exists, albeit only via Brønsted acid activation (Scheme 5.4).\textsuperscript{[4] These conditions provide good yields and
diastereoselectivity for the 5-exo-trig cyclized products, but enantioselectivity was not reported. Interestingly, Lewis acid additives provided different products, through a [2+2] cyclization mechanism (Scheme 5.4, path A vs path B).

If it can be shown that iminium-activation of an enal (as opposed to Brønsted or Lewis acid activation) provides similar β-SOMO reactivity, a new precedent would be set for expanding the utility of organophotocatalytic reactions, including the possibility for enantioselectivity. In this line of inquiry, a corresponding starting enal was constructed (Scheme 5.5, structure 5.6) to
potentiate iminium-activation using an appropriate $2^\circ$ amino-catalyst in conjunction with photoredox catalysis.

Prior to discussing experimental design and optimization, the following mechanistic pathway (Scheme 5.6) is hypothesized for the iminium-activated (here using pyrrolidine), photoredox-catalyzed, reductive cyclization (Scheme 5.5) to be presented herein. Starting enal (5.5), together with $2^\circ$ amine promotor (pyrrolidine, 5.10), may combine to form reactive iminium intermediate 5.5i.
Scheme 5.6: Hypothetical Organophotoredox Catalytic Cycle

a) Red arrows indicate single-electron transfers

Single-electron transfer from active reductant Ru(bpy)$_3^{2+}$ to the β-position of iminium 5.5i can give rise to neutral, stabilized enamine radical 5.5e, which would then be poised to undergo intramolecular 5-exo-trig radical cyclization with the β-position of neighboring ethyl enone. Cyclized radical intermediate 5.5c may then be quenched by hydrogen atom transfer from the DIPEA radical cation 5.7c, followed by hydrolysis of pyrrolidine to give final product aldehyde 5.6. As pyrrolidine has no chiral center, this hypothetical mechanism represents a racemic process, but is expected to exhibit some diastereoselectivity.[4b]
5.2 Results And Discussion

Reaction design and optimization began by adapting Yoon’s conditions (Scheme 5.4, Path B) to enal substrate 5.5 and a range of additives chosen to probe iminium-activation under photoredox conditions (Tables 5.1, 5.2, 5.3). These additives included Bronsted acids, hydrogen-bond donors, and various 2° amines as iminium-promotors. Initially, an excess of iminium-promotors (5 equiv) was used. This was due to Yoon using large excesses of DIPEA (10 equiv), and HCO₂H (5 equiv) relative to starting enone (1.40). This, and the high dilution of the conditions ([0.05] in MeCN, before liquid additives) meant the intermolecular reactions required for iminium-formation would be favored by an excess of 2° amine. Furthermore, unsure if the 2° amine would be consumed in the photoredox cycle (e.g., as is DIPEA: Scheme 5.6, Structures 5.7 --> 5.8 + 5.9), its excess would maximize the likelihood of iminium-activation and subsequent product formation.

5.2.1 Initial Results

Results from initial experiments using pyrrolidine as iminium-promotor (Table 5.1) showed freshly distilled pyrrolidine to give better yields (up to 34%) of cyclized product 5.6 (entries 5-8) than pyrrolidine that was not distilled immediately prior to use. This was possibly due to the presence of water in the highly hygroscopic pyrrolidine. However, it was unclear how water might have such a strong effect on the reaction, especially when the Ru(bpy)₃Cl₂ photocatalyst is supplied as a hydrated (hexahydrate) complex. Higher loadings of pyrrolidine gave higher yields
in lesser time (entries 5-8). However, higher concentrations of pyrrolidine led to significant, unidentified by-product formation. Less pyrrolidine (0.5 equiv, entries 7-8) gave almost no by-products, but yields were lower and reaction times were longer. Reactions run in the absence of pyrrolidine (entry 1) gave no product, which may indicate the necessity of an iminium-promotor. Curious to know if a Brønsted acid would also promote the cyclization, formic acid was used (entry 2, 22%) in place of pyrrolidine, which produced a yield similar to that using pyrrolidine (entry 2, 24%).

\[
\text{Table 5.1: Control Reactions}^a
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Promoter (equiv)</th>
<th>Time</th>
<th>Yield$^b$</th>
<th>unreacted SM$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(none)</td>
<td>-</td>
<td>3h</td>
<td>0</td>
<td>(100% by NMR)</td>
</tr>
<tr>
<td>2</td>
<td>formic acid</td>
<td>5</td>
<td>2.5h</td>
<td>22%</td>
<td>53%</td>
</tr>
<tr>
<td>3</td>
<td>pyrrolidine</td>
<td>5</td>
<td>2.5h</td>
<td>24%</td>
<td>5%</td>
</tr>
<tr>
<td>4</td>
<td>pyrrolidine</td>
<td>5</td>
<td>5h</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>pyrrolidine</td>
<td>5</td>
<td>2.5h</td>
<td>18%</td>
<td>6%</td>
</tr>
<tr>
<td>6</td>
<td>pyrrolidine</td>
<td>5</td>
<td>5h</td>
<td>34%</td>
<td>4%</td>
</tr>
<tr>
<td>7</td>
<td>pyrrolidine</td>
<td>0.5</td>
<td>2.5h</td>
<td>6%</td>
<td>25%</td>
</tr>
<tr>
<td>8</td>
<td>pyrrolidine</td>
<td>0.5</td>
<td>5h</td>
<td>14%</td>
<td>37%</td>
</tr>
</tbody>
</table>

$^a$ Reactions conducted using starting enal **5.5** (0.25 mmol, 1 equiv), Ru(bpy)$_2$Cl$_2$ (2.5 mol%), additive (equiv) and DIPEA (10 equiv) in MeCN (0.05M) and irradiated for the time indicated using a 1400 lumen CFL bulb, followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. $^b$ Yields (and unreacted SM) were determined on crude reaction mixtures using $^1$H NMR with cyclohexene (1 equiv) as internal standard.

From these data, it was apparent that at least two distinct methods of activation were possible: either by Brønsted acid or by iminium formation. Wanting to rule out activation by
other means (e.g., hydrogen-bonding), known hydrogen-bond donors (diisopropylamine, and pyrrolidinone) were used in place of pyrrolidine (Table 5.2, entries 1, 2). As no desired product was observed with the inclusion of these hydrogen-bond donors, hydrogen-bonding activation appeared not to be a productive pathway. Additionally, in order to probe the reactivity of the suspected iminium-activation, a competitive nucleophile, dimethylmalonate, (1 equiv) was used in conjunction with pyrrolidine as iminium-promotor (Table 5.2, entry 3). If iminium-activation was indeed occurring, then the presence of dimethylmalonate, along with excess amine base (DIPEA, 10 equiv), could reasonably be predicted to interrupt the desired reductive cyclization, most likely via iminium-activated conjugate addition reactions.[5] Indeed, when this reaction was run (entry 3) a complex mixture of by-products was observed. Without significant cyclized product observed, this seemed to indicate some iminium-activation.

![Table 5.2: Probing Iminium-Activation](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Promotor equiv</th>
<th>Yield</th>
<th>Unreacted SM</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>diisopropylamine</td>
<td>5 equiv</td>
<td>0</td>
<td>98%</td>
<td>DIPA and DIPEA being consumed</td>
</tr>
<tr>
<td>2</td>
<td>pyrrolidinone</td>
<td>5 equiv</td>
<td>0</td>
<td>100%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>pyrrolidine + dimethylmalonate</td>
<td>5 equiv + 1 equiv</td>
<td>0</td>
<td>-</td>
<td>multiple products</td>
</tr>
</tbody>
</table>

*Reactions conducted using starting enal 5.5 (0.25 mmol, 1 equiv), Ru(bpy)_2Cl_2 (2.5 mol%), additive (equiv), and DIPEA (10 equiv) in MeCN (0.05M) and irradiated for 2.5h using a 1400 lumen CFL bulb, followed by filtering.*
through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. * Yields (and unreacted SM)
were determined on crude reaction mixtures using ¹H NMR with cyclohexene (1 equiv) as internal standard.

Although no single experiment in Table 5.2 decisively indicated iminium-activation, the combination of 1) failed hydrogen-bonding activation, 2) successful reactions using pyrrolidine as additive, 3) the complete lack of reactivity in the absence of pyrrolidine, and 4) the multiple by-products observed with the malonate competitive nucleophile, together allows for increased confidence in concluding this process was likely an iminium-activated, photocatalytic, reductive cyclization.

With these encouraging results, we were next curious to explore the possibility of using enantioselective organocatalysts for iminium-activation (Table 5.3). To our great surprise, none of the typical catalysts used for iminium organocatalysis gave observable cyclized product (entries 1-6), even when 5 equivalents of the chiral organocatalysts were used. Not surprisingly, however, those organocatalysts used as their ammonium salts, did provide yields of cyclized product, an observation that can be rationalized by the alternative Brønsted acid activation modes (compare entry 8 vs 9 thru 11) observed by Yoon, et. al.⁴
### Table 5.3: Probing Enantioselectivity via Iminium-Activation\(^a\)

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iminium-Promotor</th>
<th>Promotor equiv</th>
<th>Time</th>
<th>Yield</th>
<th>SM Recovered</th>
<th>Observations</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>5</td>
<td>17h</td>
<td>0</td>
<td>0</td>
<td>polymerized products</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>5</td>
<td>2.5h</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Ph-NH-OH</td>
<td>5</td>
<td>2.5h</td>
<td>0</td>
<td>100% (by NMR)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Ph-NH-OTMS</td>
<td>5</td>
<td>2.5h</td>
<td>0</td>
<td>0</td>
<td>catalyst stuck on product</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>0.5</td>
<td>14d</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>5</td>
<td>30min</td>
<td>0</td>
<td>62%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>3,5-CF(_3) phenyl-NH-OTMS</td>
<td>5</td>
<td>2.5h</td>
<td>0</td>
<td>100% (by NMR)</td>
<td>catalyst remained intact</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>5</td>
<td>2.5h</td>
<td>0</td>
<td>84%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>5</td>
<td>2.5h</td>
<td>12%</td>
<td>10%</td>
<td>no CHO observed during 1H NMR</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>5</td>
<td>2.5h</td>
<td>11%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>5</td>
<td>5h</td>
<td>38%</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Reactions were conducted on 0.125 mmol scale in MeCN [0.05], with iminium promoter (equiv), DIPEA (10 equiv), Ru(bpy)\(_3\)Cl\(_2\) (2.5 mol%) and irradiated (time), followed by filtering through 3" of silica (100% EtOAc,
125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using 1H NMR with cyclohexene (1 equiv) as internal standard.

Although these results provided some initial discouragement for achieving an enantioselective, organophotoredox-catalyzed reaction manifold, these studies nevertheless seem to indicate control over a racemic process, which could yet strengthen the case for pursuing a chiral version of the same. Specifically, if a racemic version can be well-understood, it may help to clarify factors currently limiting the development of enantioselective iminium organophotoredox catalysts. Of particular interest for future, prochiral substrates would be the construction of chiral, medicinally-relevant, tetrahydrofuran and tetrahydropyran scaffolds, valuable components of bio-active small molecules.[6]

5.2.2 Optimization of Racemic Conditions

Chief among the suspected background reactions targeted for reaction optimization was the mechanistic fate of the hydrogen-atom donor, N,N-diisopropylethylamine (DIPEA.) It had previously been observed during 1H NMR monitoring of similar photoredox chemistries that as DIPEA was consumed, acetaldehyde arises in a dependent manner.[7] The generation of such a reactive aldehyde in the presence of 20 amines intended for iminium activation of enals was a concern during our initial reaction planning. Specifically, our concerns were that if acetaldehyde were to build up to significant amounts (even greater than enal substrate 5.5), its reactivity would likely result in one of several in either the consumption of those 20 amines intended for enal substrate activation. With this concern, a literature survey of alternative hydrogen-transfer
reagents revealed the possibility of constructing a similar, but more hindered, 3\textsuperscript{o} amine for the purpose: N,N-diisopropylisobutylamine (DiPiBA) (Scheme 5.7)[8]

We hypothesized this increased steric bulk would reduce rates of two suspected (and unwanted) decomposition pathways that are known for DIPEA (e.g., Scheme 5.6, structures 5.7 --> 5.10 + 5.9).[8b] These decomposition pathways, hydrolysis of iminium 5.7i (Figure 5.1) into diisopropylamine (5.10) and acetaldehyde (5.9), would be mirrored for DiPiBA, generating the corresponding (and less reactive) aldehyde, isobutyraldehyde, instead of acetaldehyde, thereby reducing the likelihood of interacting with the 2\textsuperscript{o} amine via unwanted background reactions.
Figure 5.1: Decomposition of Hindered 3° Amines

However, while this newly synthesized DiPiBA was soon to be used in place of DIPEA, it was concurrently determined that iminium-promotor pyrrolidine was causing problems with yield reproducibility, likely due to its high nucleophilicity.⁹ Therefore, before an evaluation of DiPiBA as a hydrogen donor, we first investigated alternative iminium-promotors (Table 5.4), revealing morpholine to be best among the secondary amines evaluated (entry 2), with significantly less background reactivity than pyrrolidine (entry 1.) In order to acquire some confidence that morpholine was not activating starting enal 5.5 via hydrogen-bonding (but instead via iminium formation), a control reaction was performed using surrogate hydrogen-bond donor 3-morpholinone instead of morpholine (entry 3). Indeed, this reaction gave only 7% yield after extended reaction (irradiation) time (20 hours.)
**Table 5.4: Choosing an Iminium Promotor**

<table>
<thead>
<tr>
<th>entry</th>
<th>iminium-promotor</th>
<th>time</th>
<th>yield</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>pyrrolidine</td>
<td>2.5h</td>
<td>14</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>morpholine</td>
<td>2.5h</td>
<td>34</td>
<td>43</td>
</tr>
<tr>
<td>3</td>
<td>3-morpholinone</td>
<td>20h</td>
<td>7</td>
<td>65</td>
</tr>
<tr>
<td>4</td>
<td>piperidine</td>
<td>2.5h</td>
<td>21</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>hexamethyleneimine</td>
<td>2.5h</td>
<td>10</td>
<td>27</td>
</tr>
<tr>
<td>6</td>
<td>piperazine</td>
<td>16h</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>perhydro-isoquinoline</td>
<td>2.5h</td>
<td>(trace)</td>
<td>79</td>
</tr>
<tr>
<td>8</td>
<td>diethanolamine</td>
<td>2.5h</td>
<td>20</td>
<td>27</td>
</tr>
</tbody>
</table>
Reactions were conducted on 0.125 mmol scale in MeCN [0.05], with iminium promoter (1 equiv), DIPiBA (10 equiv), Ru(bpy)$_3$Cl$_2$ (2.5 mol%) and irradiated (time), followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using $^1$H NMR with cyclohexene (1 equiv) as internal standard.

Pleased by reliably higher yields using morpholine in place of pyrrolidine, an evaluation of hydrogen donors was then performed, revealing the more sterically hindered DiPiBA to provide cleaner overall reactions, with less by-products and a higher yield (34%) of desired, cyclized product 5.6 (Table 5.5, entry 3). DABCO was also evaluated, but it higher nucleophilicity was likely the cause of minimal cyclized product formation (6%, entry 2).

<table>
<thead>
<tr>
<th>entry</th>
<th>Hydrogen donor</th>
<th>time</th>
<th>yield$^b$</th>
<th>SM$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DIPEA</td>
<td>8h</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>2</td>
<td>DABCO</td>
<td>2.5h</td>
<td>6</td>
<td>68</td>
</tr>
<tr>
<td>3</td>
<td>DiPiBA</td>
<td>2.5h</td>
<td>34</td>
<td>43</td>
</tr>
</tbody>
</table>

Table 5.5: Comparing Hydrogen Donors$^a$

---

$^a$Reactions were conducted on 0.125 mmol scale in MeCN [0.05], with iminium promoter (1 equiv), DIPiBA (10 equiv), Ru(bpy)$_3$Cl$_2$ (2.5 mol%) and irradiated (time), followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using $^1$H NMR with cyclohexene (1 equiv) as internal standard.

$^b$Yields (and unreacted SM)

$^c$SM
Reactions were conducted on 0.125 mmol scale in MeCN [0.05], with morpholine (1 equiv), H-atom donor (10 equiv), Ru(bpy)₃Cl₂ (2.5 mol%) and irradiated (time), followed by filtering through 3" of silica (100% EtOAc, 125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using ¹H NMR with cyclohexene (1 equiv) as internal standard.

Given an optimized choice of both hydrogen donor (DiPiBA) and amine iminium-promotor (morpholine), a more extensive investigation of reaction conditions was undertaken. A solvent screen was performed (Table 5.6), revealing MeCN to be much preferred over DMSO, DMF, THF and dioxane, all highly polar, aprotic solvents with some precedent in photoredox chemistry.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>morph (equiv)</th>
<th>yield</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>0.5</td>
<td>39</td>
<td>46</td>
</tr>
<tr>
<td>2</td>
<td>DMSO</td>
<td>0.5</td>
<td>13</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>DMF</td>
<td>0.5</td>
<td>14</td>
<td>46</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>0.5</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>dioxane</td>
<td>0.5</td>
<td>0</td>
<td>52</td>
</tr>
</tbody>
</table>

Unless noted otherwise, reactions were conducted on 0.125 mmol scale at [0.1] in (solvent), DiPiBA (5 equiv), Ru(bpy)₃Cl₂ (2.5 mol%), with morpholine (0.5 equiv added via syringe-pump over 4h, irradiated for 6h, followed by filtering through 3" of silica (100% EtOAc, 125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using ¹H NMR with cyclohexene (1 equiv) as internal standard.

Continuing with MeCN as solvent, and curious whether an excess of hydrogen donor was necessary, a survey of different equivalents of DiPiBA was performed (Table 5.7.) This study demonstrated a correlation between equivalents of DiPiBA and increases in yield, with 10 equivalents being optimal (36% yield, entry 5.)
Table 5.7: Hydrogen-Atom Donor Equivalents

<table>
<thead>
<tr>
<th>entry</th>
<th>DiPiBA (equiv)</th>
<th>time (h)</th>
<th>yield</th>
<th>SM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>4</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>4</td>
<td>28</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>4</td>
<td>27</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>6</td>
<td>27</td>
<td>54</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>6</td>
<td>36</td>
<td>36</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>6</td>
<td>29</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>6</td>
<td>39</td>
<td>38</td>
</tr>
</tbody>
</table>

* Reactions were conducted on 0.125 mmol scale (in enal 5.5) in MeCN [0.1], with morpholine (0.5 equiv), DiPiBA (equiv), Ru(bpy)\(_3\)Cl\(_2\) (2.5 mol%) and irradiated (time), followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. Yields (and unreacted SM) were determined on crude reaction mixtures using \(^1\)H NMR with cyclohexene (1 equiv) as internal standard.

Next, an investigation into reaction concentration (Table 5.8) showed more dilute conditions to give the best overall results, despite the intermolecular iminium formation required for our hypothesized reaction mechanism (Scheme 5..... Interestingly, although much reduced concentration ([0.025], entry 1) gave a superior yield of desired cyclization product (52%), background reactivity resulted in 40% by-products, observed as a complex mixture by \(^1\)H NMR. A comparable 37% yield was achieved using [0.05] MeCN, and irradiating for longer periods (5hrs, entry 4.)
Next, equivalents of morpholine was investigated at different reaction (irradiation) times, showing a clear correlation between increased yields and stoichiometric amounts of morpholine, with 2 equivalents of morpholine and irradiation for 16h giving the best yields (Table 5.9, entries 9, 10.)
Interestingly, when lesser equivalents of morpholine were irradiated for longer times, yields did not universally increase but plateaued (entries 2-4 & 5-7). This seemed to indicate the reaction was stalling when <1 equiv morpholine was used, with little conversion occurring past 5hrs of irradiation. However, this data also showed that more than 2 equivalents of morpholine caused excessive background reactions, with 4 equivalents morpholine consuming 55% of starting enal, while providing only 32% desired product (entry 11.)

In continuing efforts to identify the suspected background reactivity responsible for consuming (valuable) starting enal 5.5 by unwanted pathways, reactions were conducted at both elevated and reduced temperature, and in the absence of light (Table 5.10.)

<table>
<thead>
<tr>
<th>entry</th>
<th>morpholine (equiv)</th>
<th>time</th>
<th>yield</th>
<th>SM</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.25</td>
<td>24h</td>
<td>16</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>5h</td>
<td>24</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>15h</td>
<td>27</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>0.5</td>
<td>24h</td>
<td>23</td>
<td>57</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>2.5h</td>
<td>34</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>5h</td>
<td>42</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>16h</td>
<td>40</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>8c</td>
<td>2</td>
<td>2.5h</td>
<td>30</td>
<td>39</td>
<td>5 equiv DIPIBA</td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>6h</td>
<td>51</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>10d</td>
<td>2</td>
<td>16h</td>
<td>64</td>
<td>11</td>
<td>(+1eq neat at 8hrs)</td>
</tr>
<tr>
<td>11c</td>
<td>4</td>
<td>2.5h</td>
<td>32</td>
<td>13</td>
<td>5 equiv DIPIBA</td>
</tr>
</tbody>
</table>

a Reactions were conducted on 0.125 mmol scale in MeCN [0.05], with morpholine (equiv), DiPiBA (10 equiv), Ru(bpy)\(_2\)Cl\(_2\) (2.5 mol%) and irradiated (time), followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. b Yields (and unreacted SM) were determined on crude reaction mixtures using \(^1\)H NMR with cyclohexene (1 equiv) as internal standard.
Unfortunately, neither temperature changes (entries 2, 3) showed any improvement over the so-far best conditions (Table 5.9, entry 10; 64%). Interestingly, when the reaction was irradiated for 1h, then placed in the dark for the remaining time (15h), over half of starting enal 5.5 was consumed via pathways not giving rise to desired cyclized product 5.5. This data revealed that background reactivity was likely occurring both under irradiation as well as in the dark, as a similar reaction (Table 5.9, entry 8) showed more starting enal remaining (39%) after 2.5h than did this dark reaction after 16h. Due to this suspicion that morpholine was being consumed during the reaction (i.e., not acting catalytically), we decided to finish optimizing for the stoichiometric (as opposed to catalytic) process, with an intention that future research might still benefit from the nevertheless high-yielding process.

A final investigation was made into the slow-addition of morpholine into the reaction (Table 5.11.)
Table 5.11: Slow-Addition of Morpholine$^a$

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>morpholine addition time</th>
<th>yield$^b$</th>
<th>SM$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>8h</td>
<td>68</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>12h</td>
<td>70</td>
<td>0</td>
</tr>
<tr>
<td>3$^c$</td>
<td>(1+1 equiv added neat at t=0h and t=12h)</td>
<td>75 (65)</td>
<td>0</td>
</tr>
</tbody>
</table>

$^a$ Reactions conducted on 0.125 mmol scale (enal 5.5) in (degassed) MeCN [0.05], with DiPiBA (10 equiv), Ru(bpy)$_3$Cl$_2$ (2.5 mol%), morpholine (2 equiv) added slowly via syringe-pump (add time), and irradiated for 16h, followed by filtering through 3” of silica (100% EtOAc, 125mL) and concentrating for yield determination. $^b$ Yields (isolated) (and % unreacted SM) were determined on crude reaction mixtures using $^1$H NMR with internal standard. $^c$ Morpholine (2 equiv) was added in two parts: 1 equiv at t = 0, and 1 equiv at t=12h.

This final optimization study revealed that a simple addition of extra morpholine at 12h (for a total of 2 equiv morpholine) gave slightly better results (entry 3, 75%; 65% isolated yield after chromatography) than did syringe-pump addition over the same time (entry 2, 70%), or addition over 8h (entry 1, 68%). Overall, this reaction optimization, although not yet facilitating a catalytic or enantioselective protocol, has increased the yield of the racemic products dramatically from an initial 18% (Table 5.1, entry 5) to 75% (65% isolated, Table 5.11, entry 3.)

5.2.3 Substrate Scope

With optimized conditions in hand, a substrate scope was undertaken to survey the versatility of the racemic reaction manifold (Table 5.12).
Table 5.12: Substrate Scope

<table>
<thead>
<tr>
<th>entry</th>
<th>5.14</th>
<th>R</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>X</th>
<th>n</th>
<th>yield (isol.)</th>
<th>d.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5.14a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-OEt</td>
<td>C</td>
<td>3</td>
<td>87 (73)</td>
<td>3:2</td>
</tr>
<tr>
<td>2</td>
<td>5.14b</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-OMe</td>
<td>C</td>
<td>3</td>
<td>76 (69)</td>
<td>3:2</td>
</tr>
<tr>
<td>3</td>
<td>5.14c</td>
<td>H</td>
<td>-CH₃</td>
<td>-CH₃</td>
<td>-OEt</td>
<td>C</td>
<td>3</td>
<td>82 (64)</td>
<td>3:2</td>
</tr>
<tr>
<td>4</td>
<td>5.14d</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-CH₃</td>
<td>C</td>
<td>3</td>
<td>60 (57)</td>
<td>6:1</td>
</tr>
<tr>
<td>5</td>
<td>5.14e</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-Ph</td>
<td>C</td>
<td>3</td>
<td>75 (63)</td>
<td>13:1</td>
</tr>
<tr>
<td>6</td>
<td>5.14f</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-NET₂</td>
<td>C</td>
<td>3</td>
<td>75 (68)</td>
<td>1:4:1</td>
</tr>
<tr>
<td>7</td>
<td>5.14g</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-OEt</td>
<td>O</td>
<td>3</td>
<td>83 (73)</td>
<td>1:1</td>
</tr>
<tr>
<td>8</td>
<td>5.14h</td>
<td>-CH₃</td>
<td>H</td>
<td>H</td>
<td>-OEt</td>
<td>C</td>
<td>3</td>
<td>54 (42)</td>
<td>3:7</td>
</tr>
<tr>
<td>9</td>
<td>5.14i</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>-OEt</td>
<td>C</td>
<td>4</td>
<td>85 (75)</td>
<td>7:3</td>
</tr>
</tbody>
</table>

*Reactions conducted on 0.125 mmol scale (enal 5.5), with morpholine (2 equiv) added at t=0h (1 equiv) and t=12h (1 equiv), before filtering through 3” of silica (100% EtOAc, 125mL) and concentrating.  

yield (1H NMR) determined on crude reaction mixtures using an internal standard. Isolated yields determined after silica gel chromatography.  

d.r. (diastereomeric ratio) determined by 1H NMR.

This substrate scope shows good overall yields (42-73%, isolated), and good diastereoselectivity (d.r. from 1:1 to 13:1), for what appears to be a novel iminium-activated, photoredox-catalyzed process for accessing potentially medicinally-relevant functionalized carbocycles and tetrahydrofurans. Interestingly, after this substrate scope was finished, out of curiosity for any differences in reactivity possessed by the only aromatic substrate (5.14e, with R³ = phenyl) was again synthesized using the same process as in Table 5.12, only this time without the addition of morpholine as iminium-promotor. To our surprise, full conversion to cyclized product 5.14e was observed by 1H NMR spectra of the crude reaction mixture. One
explanation of this reactivity is that this substrate’s extended aromatic systems allow for greater stabilization of radical ions generated during the photoredox catalytic cycle. In order to know if this is indeed happening, it may be useful to subject aromatic substrate 5.15e to cyclic voltammetry studies, comparing its redox potentials with those for aliphatic substrates (any or all substrates 5.14, excepting 5.14e), and with attention paid to any significant differences.

### 5.3 Conclusions

Although the studies described herein appeared to indicate a novel, iminium-activated, photoredox-catalyzed, reductive cyclization of enals, it was subsequently determined, via additional control studies in the Brenner-Moyer lab (in the absence of this author), that unidentified background reactions not involving visible-light photoredox catalysis may have been responsible for the observed reductive cyclizations occurring under the conditions described herein.

Should any future understanding and/or minimization of the background reactivity reported herein be achieved, this author believes that any future optimizations could benefit from consolidating reagents commonly being used in this type of multi-component reaction.\[10\] For example, exploration of alternative hydrogen-atom transfer agents, especially those with the potential for dual-reactivity (e.g., as hydrogen-atom transfer agent and as iminium-activator in a single molecule), could consolidate (2 or more) reaction components. Additionally, if this (hypothetical) multi-purpose additive were chiral, still another function (enantioselectivity)
might be fulfilled by a single reaction component. Yet another approach to consolidation might be to explore alternative charge-transfer ligands for the metal-based photoredox catalyst (in place of 2,2’-bipyridyl ligands in Ru(bpy)$_2$Cl$_2$), notably those with potential to transfer chirality via their excited-state redox reactivity, might potentiate enantioselectivity without the need for additional, chiral iminium-promotors.$^{[1][1]}$

### 5.4 References


    (b) For one (of many) studies taking advantage the ‘decomposition pathways’ of hindered, tertiary amines via photoredox catalysis, see: Pandey, G.; Jadhav, D.; Tiwari, S. K.;
[9] (a) $^1$H NMR monitoring showed unidentified by-products as a mixture of polymer material and a homo-alkene, something we speculated result from a reductive amination process, whereby iminium species were reduced onto their corresponding carbonyl. Attempts at purification and $^{15}$N NMR studies did not lead to conclusive identification of by-products.


(b) Although enantioselective, organophotoredox catalysis has been achieved, no such chirality transfer has so-far been observed using only a functionalized photoredox catalyst. For a discussion, see: Zeitler, K. Angew. Chem. Int. Ed. 2009, 48, 9785–9789.
Chapter 6.
Experimental And Characterization

6.1 General Information

All chemicals used were ACS Reagent grade and used as received unless otherwise noted. $^1$H and $^{13}$C NMR spectra were acquired using a Bruker 400 MHz Biospin instrument (400 MHz for $^1$H, 101 MHz for $^{13}$C), using CDCl$_3$ as solvent and internal reference ($\delta =$ 7.26 for $^1$H, 77.0 for $^{13}$C). The NMR data herein use the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublets, td = triplet of doublets, dt = doublet of triplets, ddt = doublet of doublet of triplets, br = broad signal. Enantiomeric excesses were determined using a Perkin Elmer Series 200 HPLC with Daicel Chiralpak AD-H (0.46 x 25 cm), Chiralpak OD-H (0.46 x 25 cm), and Chiralpak AS-H (0.46 x 25 cm) columns. Optical rotations were acquired using a Jasco P-1020 polarimeter. IR spectra were collected using a Nicolet 6700 FT-IR. High resolution mass spectra were collected using an Agilent 6520 Q-TOF. Silica gel flash chromatography was carried out using Silicycle F60, 40-63 μm 60Å silica gel and with EMD silica 60 F$_{254}$ glass TLC plates. Solvents were dried and kept air free in a solvent purification unit. Solvents were evaporated using a standard rotovapor and a high vacuum. All reactions were carried out in oven dried glassware and conducted under an argon atmosphere.

6.2 Experimental and Characterization for Chapter 3

Determination of relative and absolute configurations

The relative and absolute configuration of Michael-Michael product 3.18m was determined via X-ray crystallography.
It was established that 3.18a(α-epimer) was the C4 epimer of 3.18a(β-epimer) by subjecting pure 3.18a (as a single epimer) to catalyst 1.32 (10 mol%) in CF₃CH₂OH (0.3 M), which produced a mixture of 3.18a(α-epimer) and 3.18a(β-epimer). The configurations of other Michael-Michael products were assigned by analogy.

Preparation of catalysts (1.32, 3.20), enals (1.33m, 1.33g, 1.33h), and β-ketoesters (7, 25)

Catalysts 1.32 and 3.20[1] were prepared from the corresponding diarylprolinols[2] using known procedures. Enals 1.33g and 1.33h were prepared using a known procedure.[3] β-ketoesters of type 3.21 (except 3.21n, 3.21i and 3.21l, whose preparation and characterization are described below) were prepared according to a known literature procedure.[4]

Preparation and characterization of starting enals (1.33m, 1.33g, 1.33h)

Enal 1.33m was prepared by adapting a known procedure.[5]

\[
\begin{align*}
\begin{array}{c}
\text{Br} \\
\text{O}
\end{array}
\end{align*} \xrightarrow{\text{Ph}_3\text{P} = \text{O}} 
\begin{align*}
\begin{array}{c}
\text{Br} \\
\text{O}
\end{array}
\end{align*} \text{1.33m}
\]

A solution of 4-bromobenzaldehyde (2.41 g, 13.0 mmol) and triphenylphosphoranylidene acetaldehyde (4.75 g, 15.6 mmol) in toluene (103 ml) was heated at 80°C for 16 h. To the reaction mixture was added triphenylphosphoranylidene acetaldehyde (250 mg, 0.06 mmol) again and the reaction mixture was further refluxed for 19 h. After the reaction mixture was concentrated in vacuo, the crude residue was chromatographed on silica gel eluting with Et₂O/pet.ether (7.5:9.25) to give 1.33m (1.82 g, 66%) as a yellow solid. Characterization of 1.33m was in agreement with literature.

\[
\begin{align*}
\text{Br} \\
\end{align*} \xrightarrow{\text{Ph}_3\text{P} = \text{O}} 
\begin{align*}
\text{Br}
\end{align*} \text{1.33m}
\]

(E)-3-(4-bromophenyl)acrylaldehyde, Yellow solid; m.p.: 78-79°C; \(^1\)H NMR (400 MHz, CDCl₃) δ 9.71 (d, \(J = 7.6\) Hz, 1H), 7.57 (m, 2H), 7.43 (m, 3H), 6.70 (dd, \(J = 16.0, 7.6\) Hz, 1H); \(^13\)C NMR (101 MHz, CDCl₃) δ 193.3, 151.1, 132.9, 132.4, 129.8, 129.1, 125.7 ppm.
Enals 1.33g and 1.33h were prepared using a known procedure.\(^5\)

\[
\begin{align*}
1.33g & \quad \text{Enal (1.33g)} \\
1.33h & \quad \text{Enal (1.33h)}
\end{align*}
\]

**Preparation and characterization of β-ketoesters:**

Most β-ketoesters were prepared according to a known literature procedure.\(^{[6]}\) β-ketoester 3.21n was prepared by adapting this procedure.

\[
\begin{align*}
\text{1.33h} & \quad \text{Enal (1.33h)} \\
\text{1.33h} & \quad \text{Enal (1.33h)} \\
\end{align*}
\]

1) To a round-bottom flask was added THF (22 mL) and diisopropylamine (844 \(\mu\)L, 6.6 mmol) and cooled to -78°C. n-BuLi (2.5M in hexanes, 6.6 mmol) was added slowly and stirred for 15 minutes. Ethyl acetate (586 \(\mu\)L, 6.0 mmol) was then added dropwise and the solution stirred for 50 minutes. Enal 1.33h (6.0 mmol) was added dropwise and stirred for 10 minutes. The reaction was quenched by the addition of sat. aq. NH\(_4\)Cl (1.7 ml), followed by immediate transfer to a separatory funnel containing diethyl ether (25 ml). The mixture was extracted with diethyl ether (25 mL), washed with brine (2 x 25 ml) and water (2 x 25 mL), and dried over MgSO\(_4\). Removal of solvent yielded the hydroxyester in >99% yield. No further purification was needed before the oxidation with Jones’ Reagent.

2) Jones’ Reagent was prepared by the addition of concentrated H\(_2\)SO\(_4\) (1.8 mL) to CrO\(_3\) (2.0 g) followed by careful dilution with water to give a total volume of 15 mL. Then, Jones’ Reagent (9.0 mL, 9.0 mmol) was added dropwise to a stirred solution of the β-hydroxyester (6.0 mmol) in acetone (24 mL) at 0°C. After complete addition of the oxidizing agent, the reaction was stirred for 10 minutes, when the absence of starting material was determined by thin-layer chromatography. Methanol (1.5 mL) was added slowly to quench excess Jones’ Reagent. The reaction mixture was poured into a separatory funnel and extracted with diethyl ether (30 mL). The organic extracts were washed with water (3 x 20 mL) and then brine (2 x 20 mL). The organic layer was dried (MgSO\(_4\)) and filtered and the solvent removed under reduced pressure. Purification of the crude product mixture was achieved by flash chromatography (silica gel, 2.5% Et\(_2\)O), which gave a white crystalline solid (338 mg, 24% yield).
3.21n:

\[ \text{3.21n-keto} \quad + \quad \text{3.21n-enol} \]

\((E)-\text{ethyl 5-(2-fluorophenyl)-3-oxopent-4-enoate},\) white solid. m.p.: 57-58°C; IR (thin film, KBr): 2983, 1741, 1596, 1486, 1458, 1422, 1235, 1148, 1094, 1039, 969, 799, 755 cm\(^{-1}\); \^H NMR (400 MHz, CDCl\(_3\)) (1:2 ratio of keto : enol) \(\delta\) 11.99 – 11.94 (d, \(J = 1.3\) Hz, 1H, enol), 7.81 – 6.81 (m, 10H), 6.59 – 6.50 (dd, \(J = 16.1, 1.5\) Hz, 2H), 5.21 – 5.16 (s, 1H, enol), 4.29 – 4.17 (qd, \(J = 7.1, 4.6\) Hz, 4H), 3.73 – 3.68 (s, 2H, keto), 1.36 – 1.24 (m, 6H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 192.1, 172.8, 168.9, 167.3, 162.9, 162.4, 159.9, 137.0, 136.9, 132.4, 132.3, 130.7, 130.6, 129.5, 129.4, 129.2, 129.1, 128.7, 128.6, 127.4, 127.4, 124.6, 124.6, 124.5, 124.4, 124.4, 124.3, 123.5, 123.4, 116.4, 116.2, 116.2, 116.0, 92.5, 61.5, 60.3, 47.6, 14.3, 14.1 ppm; HRMS (ESI) calcd for C\(_{13}\)H\(_{13}\)FO\(_3\) [M]+ 236.0849, found 236.0860.
β-ketoesters 3.21i and 3.21l were prepared by a modification of the same procedure.

1) To a round-bottom flask was added THF (22 mL) and diisopropylamine (844 μL 6.6 mmol). The reaction was cooled to -78°C. n-BuLi (2.5M in hexanes, 6.6 mmol) was added slowly and stirred for 15 minutes. Ethyl acetate (586 μL, 6.0 mmol) was then added dropwise and the solution was stirred for 50 minutes. Enal 1.33 (6.0 mmol) was added dropwise and stirred for 10 minutes. The reaction was quenched by the addition of sat. aq. NH₄Cl (1.7 ml), followed by immediate transfer to a separatory funnel containing diethyl ether (25 ml). The mixture was extracted with diethyl ether (25 mL), washed with brine (2 x 25 ml) and water (2 x 25 mL), then dried over MgSO₄. Removal of solvent yielded the hydroxyester in 98-100% yield. No further purification was typically needed before the oxidation with DMP. However, purification could be achieved on silica gel with 15%-25% Et₂O in petroleum ether.

2) To a solution of the hydroxyester (2.0 mmol) corresponding to 9 in CH₂Cl₂ (55.5 mL) and MeCN (77.1 mL) at r.t. was added NaHCO₃ (330.6 mg, 3.9 mmol) mmol). The mixture was cooled to 0°C and Dess-Martin Periodinane (1 equiv) was added. The reaction mixture was stirred at 0°C for 1 hr. TLC (10% EtOAc in pet. ether) indicated ~10% SM remaining, so the reaction mixture was warmed to room temperature and stirred for an additional 30 minutes. TLC at this point indicated all SM had been consumed. The reaction was quenched with a 1:1 solution (110 mL) of saturated NaHCO₃ and saturated Na₂S₂O₃ and was stirred vigorously until the organic layer was no longer cloudy. The quenched reaction mixture was then poured into a separatory funnel. The aqueous layer was extracted with CH₂Cl₂ (2 x 40 mL). The organic layers were combined, dried over Na₂SO₄, filtered and concentrated. Purification by column chromatography (silica gel, 5% Et₂O/petroleum ether) provided yellow solids in 53-55% yield.

Characterization for 3.21l and 3.21i was in agreement with that in the literature.

**Characterization of 3.21i[7]**

(E)-ethyl 5-(furan-2-yl)-3-oxopent-4-enoate, Yellow solid. ¹H NMR (400 MHz, CDCl₃) (1.4:1 ratio of keto to enol) δ 11.92 (s, 1H, enol), 7.35 (m, 4H), 6.50 (m, 6H), 5.12 (s, 1H, enol), 4.20 (qd, J = 7.1, 4.3 Hz, 4H), 3.62 (s, 2H, keto), 1.27 (dt, J = 10.7, 7.1 Hz, 6H); ¹³C NMR (101 MHz, CDCl₃) (1.4:1 ratio of keto to enol) δ 191.4, 172.8, 168.9, 167.4, 151.8, 150.8, 145.4, 143.9,
143.6, 130.3, 126.9, 124.6, 123.6, 122.3, 121.2, 119.9, 116.7, 113.0, 112.7, 112.2, 112.1, 91.9, 61.4, 60.2, 48.0, 14.3, 14.1 ppm.
Characterization of 3.21[8]

\[ \text{3.21-keto} + \text{3.21-enol} \]

*(E)-ethyl 5-(4-methoxyphenyl)-3-oxopent-4-enoate*, Yellow solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)) (1:3.6 ratio of keto to enol) \(\delta\) 12.07 – 11.98 (s, 1H, enol), 7.61 – 7.34 (m, 8H), 7.00 – 6.21 (m, 4H), 5.15 – 5.10 (s, 1H, enol), 4.30 – 4.13 (m, 4H), 3.87 – 3.80 (s, 6H), 3.70 – 3.65 (s, 2H, keto), 1.35 – 1.24 (m, 6H) ppm.

General Procedure for synthesis of carbocycles (3.18)

To an oven-dried flask was added catalyst 1.32 (13.0 mg, 0.04 mmol), CF\(_3\)CH\(_2\)OH (1.33 mL), \(\beta\)-ketoester 3.21 (0.4 mmol), and enal 1.33 (0.4 mmol). The reaction was allowed to stir for the indicated time at room temperature. The reaction mixture was concentrated and filtered through a plug of silica, followed by concentration again. The percent conversion of the crude reaction mixture was determined using an internal standard (allyl alcohol). The diastereomeric ratio was determined through comparison of the relative integrations of the aldehyde peaks in this \(^1\)H NMR spectrum. The diastereomeric mixture was then purified via column chromatography (silica gel, 95/5, petroleum ether/Et\(_2\)O, unless noted otherwise) and an isolated yield of the diastereomeric
mixture was determined. Purified samples of the major diastereomer and minor diastereomers were obtained through further flash chromatography. In certain cases (3.18c, 3.19f 3.18g), the major epimer of the major diastereomer was inseparable from the minor epimer of the major diastereomer and the epimers were characterized as a mixture. Racemic samples of the Michael-Michael products 3.18 were prepared in a similar manner using racemic catalyst 1.32r.

Characterization of Carbocycles

3.18a (β epimer):

\[
\begin{align*}
\text{OH} & \\
\text{CO}_2\text{Et} & \\
\text{CHO} & \\
\text{NO}_2 & \\
\end{align*}
\]

\((1S,5S,6S)\text{-ethyl-5-butyl-6-formyl-3-hydroxy-4'-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, Clear oil. } [\alpha)_D^{26} = +80.4 (c=0.60, \text{CHCl}_3, 93\% \text{ ee}); \text{ IR (thin film, KBr): } 2957, 2928, 2858, 1721, 1653, 1519, 1347, 1277, 1230, 1094, 1044, 854 \text{ cm}^{-1}; \text{ } ^1\text{H NMR (400 MHz, CDCl}_3\text{) } \delta 12.56 (s, 1H), 9.83 (s, 1H), 8.17 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.7 Hz, 2H), 4.40 (d, J = 2.7 Hz, 1H), 4.02 (qd, J = 7.1, 1.7 Hz, 2H), 2.60 (m, 2H), 2.32 (dd, J = 18.8, 10.8 Hz, 1H), 1.95 (dd, J = 16.3, 6.2 Hz, 1H), 1.49 (m, 2H), 1.21 (m, 4H), 0.96 (t, J = 7.1 Hz, 3H), 0.83 (dd, J = 9.1, 4.6 Hz, 3H); \text{ } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{) } \delta 201.5, 173.2, 171.4, 152.1, 146.7, 128.6, 123.7, 97.2, 60.7, 56.6, 38.9, 33.0, 31.9, 30.1, 29.4, 22.5, 13.9, 13.8 ppm; \text{ the enantiomeric excess was determined by HPLC with an AD-H column (}n\text{-hexane: } i\text{-PrOH = 99:1), 0.1 mL/min; major enantiomer } t_R = 22.9 \text{ min, minor enantiomer } t_R = 20.3 \text{ min; HRMS (ESI) calcd for C}_{20}H_{25}NO_6 \text{ [M]}^+ 375.1682, \text{ found 375.1687.}\end{align*}
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3.18a (α epimer):

(IS,5S,6R)-ethyl-5-butyl-6-formyl-3-hydroxy-4'-nitro-1,4,5,6-tetrahydro-[1,1'-biphenyl]-2-carboxylate, Clear oil. $[\alpha]_D^{23} = +26.2$ (c=0.59, CHCl$_3$, 94% ee); IR (thin film, KBr): 2957, 2930, 2860, 1722, 1655, 1621, 1520, 1347, 1278, 1221, 1156, 1109, 854, 705 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.47 (s, 1H), 9.12 (d, $J = 4.4$ Hz, 1H), 8.18 (d, $J = 8.7$ Hz, 2H), 7.31 (d, $J = 8.7$ Hz, 2H), 4.33 (d, $J = 5.6$ Hz, 1H), 4.02 (dd, $J = 12.5, 7.1$ Hz, 2H), 2.82 (dd, $J = 18.6, 5.7$ Hz, 1H), 2.53 (m, 1H), 2.25 (m, 2H), 1.26 (m, 6H), 1.00 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 204.3, 172.5, 170.9, 148.0, 147.1, 129.9, 123.5, 99.0, 60.7, 54.9, 41.2, 33.9, 33.7, 28.2, 27.9, 22.7, 13.9, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (n-hexane: i-PrOH = 90:10), 0.5 mL/min; major enantiomer $t_R = 20.2$ min, minor enantiomer $t_R = 37.8$ min. HRMS (ESI) calcd for C$_{20}$H$_{25}$NO$_6$ [M]$^+$ 375.1682, found 375.1690.
3.18b:

(IS,5S,6S)-ethyl-6-formyl-3-hydroxy-5-methyl-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, Clear oil. \([\alpha]_D^{25} = +59.8\) (c=0.45, CHCl₃, 98% ee); IR (thin film, KBr): 2962, 2925, 1722, 1651, 1519, 1348, 1277, 1225, 1099, 853, 736, 700 cm⁻¹; \(^1H\) NMR (400 MHz, CDCl₃) \(\delta\) 12.56 (s, 1H), 9.81 (d, \(J = 0.6\) Hz, 1H), 8.16 (m, 2H), 7.36 (m, 2H), 4.40 (d, \(J = 3.8\) Hz, 1H), 4.01 (qd, \(J = 7.1, 2.9\) Hz, 2H), 2.62 (dd, \(J = 18.5, 5.6\) Hz, 1H), 2.53 (t, \(J = 3.4\) Hz, 1H), 2.33 (dd, \(J = 18.1, 10.0\) Hz, 1H), 2.22 (dd, \(J = 6.8, 3.4\) Hz, 1H), 1.13 (d, \(J = 6.9\) Hz, 3H), 0.95 (t, \(J = 7.1\) Hz, 3H); \(^13C\) NMR (101 MHz, CDCl₃) \(\delta\) 201.2, 172.9, 171.4, 152.3, 146.7, 128.6, 123.6, 97.2, 60.7, 57.9, 38.5, 34.9, 24.9, 17.4, 13.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (n-hexane: i-PrOH = 99:1), 0.2 mL/min; major enantiomer \(t_R = 38.4\) min, minor enantiomer \(t_R = 43.8\) min. HRMS (ESI) calcd for C₁₇H₁₉NO₆ [M-H] 332.1139, found 332.1121.
(1S,5S,6S)-ethyl-5-ethyl-6-formyl-3-hydroxy-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, Clear oil. [α]_D^23 = +62.9 (c=1.67, CHCl₃, 95% ee); IR (thin film, KBr): 2965, 2933, 2877, 1721, 1652, 1519, 1348, 1275, 1222, 853, 756, 737, 701 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 12.57 (s, 1H), 9.83 (s, 1H), 8.17 (d, J = 8.8 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 4.41 (d, J = 2.7 Hz, 1H), 4.02 (qd, J = 7.1, 1.7 Hz, 2H), 2.62 (m, 2H), 2.31 (dd, J = 18.8, 10.9 Hz, 1H), 1.87 (m, 1H), 1.54 (ddd, J = 29.7, 14.3, 6.9 Hz, 2H), 0.97 (t, J = 7.1 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.5, 173.2, 171.4, 152.1, 146.7, 128.6, 123.7, 97.2, 60.7, 56.5, 38.9, 32.6, 31.8, 25.2, 13.8, 11.8 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (n-hexane: i-PrOH = 97:3), 0.5 mL/min; major enantiomer t_R = 25.8 min, minor enantiomer t_R = 32.7 min. HRMS (ESI) calcd for C₁₈H₂₁NO₆ [M]+ 347.1369, found 347.1360.
(1S,5R,6S)-ethyl-6-formyl-3-hydroxy-5-isopropyl-4′-nitro-1,4,5,6-tetrahydro-[1,1′-biphenyl]-2-carboxylate, Clear oil. \( [\alpha]_{D}^{24} = +71.7 \) (c=1.71, CHCl\(_3\), >99% ee); IR (thin film, KBr): 2962, 2927, 2872, 1720, 1655, 1519, 1348, 1301, 1281, 1264, 1223, 1096, 1033, 854, 832 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 12.55 (s, 1H), 9.85 (s, 1H), 8.18 (d, \( J = 8.8 \) Hz, 2H), 7.34 (d, \( J = 8.5 \) Hz, 2H), 4.42 (s, 1H), 4.04 (qd, \( J = 7.1, 0.8 \) Hz, 2H), 2.76 (s, 1H), 2.66 (dd, \( J = 19.1, 6.1 \) Hz, 1H), 2.31 (dd, \( J = 19.0, 12.1 \) Hz, 1H), 1.86 (m, 1H), 1.42 (m, 1H), 0.96 (m, 6H), 0.78 (d, \( J = 6.6 \) Hz, 3H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 201.7, 173.7, 171.3, 151.6, 146.8, 128.4, 123.7, 96.6, 60.8, 54.0, 39.4, 36.9, 31.7, 31.6, 29.7, 21.1, 20.6, 13.9 ppm. the enantiomeric excess was determined by HPLC with an AS-H column (\( n\)-hexane: \( i\)-PrOH = 99:1), 0.3 mL/min; major enantiomer \( t_R = 31.6 \) min, minor enantiomer \( t_R = 50.4 \) min. HRMS (ESI) calcd for C\(_{19}\)H\(_{22}\)NO\(_6\) [M-H] 360.1447, found 360.1448.
3.18e:

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\begin{align*}
\text{(1'S,2'S,3'S)-ethyl-2'-formyl-5'-hydroxy-4''-nitro-1',2',3',6'-tetrahydro-[1,1':3',1''-}
\text{terphenyl]-4'-carboxylate, White amorphous solid. } & [\alpha]_D^{23} = +247.5 \text{ (c=0.93, CHCl}_3, \text{ 99% ee (18), >99% ee (epi-18)); IR (thin film, KBr): 2983, 1722, 1653, 1618, 1596, 1518, 1403, 1347, 1259, 1217, 1065, 853, 829, 753, 700 cm}^{-1} \text{H NMR (400 MHz, CDCl}_3 \text{) (10:1 mixture of 18 to its C4 epimer) } \delta 12.69 \text{ (s, 1H, 18), 12.55 (s, 1H, epi-18), 9.68 (s, 1H, 18), 8.88 (d, J = 3.8 Hz, 1H, epi-18), 8.28 - 8.17 \text{ (m, 4H, 18+epi-18), 7.50 - 7.04 \text{ (m, 14H, 18+epi-18), 4.66 - 4.49 \text{ (m, 2H, 18+epi-18), 4.07 (m, 4H, 18+epi-18), 3.55 - 3.26 \text{ (m, 2H, 18+epi-18), 3.12 (m, 1H, epi-18), 3.05 - 2.75 \text{ (m, 4H, 18+epi-18), 2.66 (dd, J = 19.0, 11.4 Hz, 1H, epi-18), 1.06 - 0.93 \text{ (m, 6H, 18+epi-18); } }^{13}C \text{ NMR (101 MHz, CDCl}_3 \text{) (10:1 mixture of 18 to its C4 epimer) } \delta 203.4 \text{ (epi-18), 200.8, 172.5, 172.2 \text{ (epi-18), 172.1 \text{ (epi-18), 171.4, 152.1, 146.9, 140.5 \text{ (epi-18), 139.2, 130.2 \text{ (epi-18), 129.3 \text{ (epi-18), 128.9, 128.6, 127.7 \text{ (epi-18), 127.6 \text{ (epi-18), 127.4, 127.3, 123.9, 123.6 \text{ (epi-18), 97.1, 60.8, 58.5, 54.3 \text{ (epi-18), 41.4 \text{ (epi-18), 38.8, 37.5 \text{ (epi-18), 35.3 \text{ (epi-18), 34.3, 31.0, 30.9 \text{ (epi-18), 13.8 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (n-hexane: i-PrOH = 95:5), 1.0 mL/min; major diastereomer: major enantiomer } t_R = 27.9 \text{ min., minor enantiomer } t_R = 35.9 \text{ min.; minor diastereomer: major enantiomer } t_R = 48.7 \text{ min., minor enantiomer } t_R = 56.1 \text{ min. HRMS (ESI) caled for C}_{22}H_{21}NO_6 \text{ [M-H] 394.1291, found: 394.1271. Purification on silica gel was best achieved using 60/40 CH}_2Cl_2/petroleum ether.}
\end{align*}
\]
(1'S,2'S,3'S)-ethyl-2'-formyl-5'-hydroxy-1',2',3',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate. Clear oil. $[\alpha]_D^{26} = +86.2$ (c=2.0, CHCl$_3$, 99% ee); IR (thin film, KBr): 3060, 3027, 2907, 2829, 2732, 1722, 1652, 1621, 1495, 1452, 1403, 1370, 1351, 1292, 1259, 1216, 1066, 1032, 831, 756, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) (5:1 mixture of 19 to its C4 epimer) $\delta$ 12.68 (s, 1H, 19), 12.53 (s, 1H, epi-19), 9.72 (s, 1H, 19), 8.84 (d, $J = 4.4$ Hz, 1H, epi-19), 7.28 (m, 20H, 19 + epi-19), 4.44 (m, 2H, 19 + epi-19.), 4.08 (m, 4H, 19 + epi-19.), 3.58 (td, $J = 11.9$, 6.2 Hz, 1H, epi-19), 3.43 (m, 1H, 19), 2.93 (m, 6H, 19 + epi-19), 1.01 (t, $J = 7.1$ Hz, 6H, 19 + epi-19); $^{13}$C NMR (101 MHz, CDCl$_3$) (5:1 ratio of major 19 to its C4 epimer) $\delta$ 204.7 (epi-19), 201.9, 171.9, 171.9, 171.4 (epi-19), 144.0, 141.2 (epi-19), 140.2, 139.5 (epi-19), 129.3 (epi-19), 129.1 (epi-19), 128.7, 128.5, 128.4 (epi-19), 127.7 (epi-19), 127.6, 127.4 (epi-19), 127.4, 127.1 (epi-19), 127.0, 126.6, 99.9 (epi-19), 97.9, 60.5, 59.0, 54.6 (epi-19), 41.7 (epi-19), 38.9, 37.5 (epi-19), 35.2 (epi-19), 34.1, 31.1, 13.8 ppm; the enantiomeric excess of a mixture of 19 and epi-19 was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 97:3), 0.5 mL/min; major diastereomer: major enantiomer $t_R = 14.8$ min., minor enantiomer $t_R = 17.8$ min.; minor diastereomer: major enantiomer $t_R = 59.6$ min., minor enantiomer $t_R = 28.5$ min. HRMS (ESI) calcd for C$_{22}$H$_{22}$O$_4$ [M]$^+$ 350.1518, found 350.1505.
(1'S,2'S,3'S)-ethyl 2'-formyl-5'-hydroxy-4''-methyl-1',2',3',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate, Clear oil. $[\alpha]_{D}^{23} = +101.3$ (c=2.0, CHCl$_3$, 99% ee (20) 95% ee (epi-20)); IR (thin film, KBr): 2979, 2922, 2730, 1723, 1652, 1619, 1510, 1497, 1454, 1403, 1365, 1259, 1215, 1096, 1065, 821, 759, 699; $^1$H NMR (400 MHz, CDCl$_3$) (2.5:1 ratio of 20 to its C4 epimer) $\delta$ 12.63 (s, 1H, 20), 12.48 (s, 1H, epi-20), 9.69 (d, $J = 0.6$ Hz, 1H, 20), 8.80 (d, $J = 4.4$ Hz, 1H, epi-20), 7.19 (m, 18H, 20 + epi-20), 4.37 (m, 2H, 20 + epi-20), 4.05 (m, 4H, 20 + epi-20), 3.46 (m, 2H, 20 + epi-20), 2.79 (m, 6H, 20 + epi-20), 2.34 (m, 6H, 20 + epi-20), 1.02 (td, $J = 7.1, 1.1$ Hz, 6H, 20 + epi-20); $^{13}$C NMR (101 MHz, CDCl$_3$) (2.5:1 ratio of 20 to its C4 epimer) $\delta$ 204.9 (epi-20), 202.1, 172.0, 171.8, 171.5 (epi-20), 171.2 (epi-20), 141.3 (epi-20), 140.9, 140.3, 136.6 (epi-20), 136.4 (epi-20), 136.0, 129.2, 129.1 (epi-20), 129.0 (epi-20), 128.7, 127.7 (epi-20), 127.5, 127.4, 127.0 (epi-20), 100.1 (epi-20), 98.1, 60.5, 59.1, 54.6 (epi-20), 41.2 (epi-20), 38.5, 37.5 (epi-20), 35.2 (epi-20), 34.1, 31.1, 21.0, 13.8 ppm; the enantiomeric excess of a mixture of 20 and epi-20 was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 97:3), 0.5 mL/min; major enantiomer of major diastereomer $t_R = 14.3$ min, minor enantiomer $t_R = 17.9$ min; major enantiomer of minor diastereomer $t_R = 47.3$ min., minor enantiomer $t_R = 27.3$ min. HRMS (ESI) calcd for C$_{23}$H$_{24}$O$_4$ [M]$^+$ 364.1675, found 364.1675.
(1'S,2'S,3'R)-ethyl-2''-fluoro-2'-formyl-5'-hydroxy-1',2',3',6'-tetrahydro-[1,1':3',1''-terphenyl]-4'-carboxylate, Clear oil. [α]D23 = +82.5 (c=2.0, CHCl3, 98% ee); IR (thin film, KBr): 2982, 2929, 2734, 1724, 1620, 1654, 1486, 1454, 1404, 1259, 1216, 1094, 1066, 1034, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 12.68 (s, 1H), 9.71 (s, 1H), 7.22 (m, 9H), 4.80 (s, 1H), 4.09 (tdd, J = 10.8, 7.1, 3.6 Hz, 2H), 3.35 (m, 1H), 3.02 (dd, J = 18.3, 12.4 Hz, 2H), 2.79 (dd, J = 18.4, 5.5 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl3) δ 201.6, 172.9, 171.9, 161.8, 159.3, 140.3, 129.5, 129.0, 127.7, 127.4, 124.2, 124.2, 115.9, 115.7, 97.2, 60.9, 56.9, 34.9, 32.3, 32.3, 31.2, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AD-H column (n-hexane: i-PrOH = 97:3), 0.5 mL/min; major enantiomer tR = 27.1 min, minor enantiomer tR = 18.8 min. HRMS (ESI) calcd for C22H21FO4 [M]+ 368.1424, found 368.1426.
(1S,2S,3R)-ethyl-2-formyl-3-(furan-2-yl)-5-hydroxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-carboxylate, Yellow amorphous solid. $[\alpha]_D^{23} = +123.4$ (c=1.7, CHCl$_3$, 98% ee); IR (thin film, KBr): 2926, 2851, 2731, 1724, 1654, 1620, 1498, 1277, 1239, 1218, 1096, 1060, 828, 761, 741, 701 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.49 (s, 1H), 9.07 (d, $J = 4.0$ Hz, 1H), 7.25 (m, 6H), 6.31 (d, $J = 1.9$ Hz, 1H), 6.08 (d, $J = 3.0$ Hz, 1H), 4.43 (d, $J = 4.9$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.55 (td, $J = 11.8$, 6.2 Hz, 1H), 2.93 (dt, $J = 12.4$, 4.5 Hz, 1H), 2.81 (dd, $J = 18.9$, 6.2 Hz, 1H), 2.52 (dd, $J = 18.9$, 11.3 Hz, 1H), 1.15 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 203.1, 171.9, 171.4, 153.9, 141.9, 141.2, 129.1, 127.7, 127.4, 110.3, 108.5, 97.9, 60.7, 54.4, 37.5, 36.4, 35.1, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 97:3), 0.5 mL/min; major enantiomer $t_R = 32.7$ min, minor enantiomer $t_R = 36.5$ min. HRMS (ESI) calcd for C$_{20}$H$_{20}$O$_4$ [M]$^+$ 340.1311, found: 340.1311.
3.18j

(IS,2S,3R)-diethyl 2-formyl-5-hydroxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-3,4-dicarboxylate, Clear oil. $[\alpha]_{D}^{23} = +18.5$ (c=1.1, CHCl$_3$, 91% ee); IR (thin film, KBr): 2982, 2936, 2736, 1724, 1660, 1624, 1406, 1371, 1264, 1218, 1183, 1069, 1032, 830, 758, 737, 699 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.44 (s, 1H), 9.54 (s, 1H), 7.34 (dt, $J = 12.5, 7.8$ Hz, 5H), 4.25 (m, 4H), 4.01 (d, $J = 12.9, 7.1$ Hz, 6H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 200.2, 173.6, 171.7, 171.5, 139.3, 128.9, 127.4, 95.5, 61.4, 60.8, 53.5, 39.4, 36.4, 30.7, 14.4, 14.1 ppm; the enantiomeric excess was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 97:3), 0.5 mL/min; major enantiomer $t_R = 21.2$ min, minor enantiomer $t_R = 32.3$ min; HRMS (ESI) calcd for C$_{19}$H$_{22}$O$_6$ [M-H] 345.1338, found 345.1345.
(1S,2S,3R)-ethyl-3-butyl-2-formyl-5-hydroxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-carboxylate, Clear oil. [α]D^23 = -44.5 (c=2.23, CHCl₃, 98% ee); IR (thin film, KBr): 2956, 2930, 2871, 1722, 1617, 1403, 1261, 1064, 831, 698 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 12.45 (s, 1H), 9.60 (s, 1H), 7.32 (ddd, J = 17.9, 12.8, 5.6 Hz, 5H), 4.27 (ddddd, J = 25.1, 10.8, 7.1, 3.7 Hz, 2H), 3.45 (m, 1H), 3.00 (m, 2H), 2.89 (d, J = 1.7 Hz, 1H), 2.64 (dd, J = 18.5, 5.8 Hz, 1H), 1.78 (m, 1H), 1.40 (m, 8H), 0.96 (dd, J = 9.7, 3.9 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 202.8, 172.2, 170.8, 140.9, 128.8, 127.5, 127.0, 100.6, 60.6, 53.2, 34.6, 34.2, 32.8, 31.0, 30.1, 22.4, 14.2, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (n-hexane: i-PrOH = 99:1), 0.3 mL/min; major enantiomer t_R = 26.3 min, minor enantiomer t_R = 29.5 min. HRMS (ESI) calcd for C₂₀H₂₆O₄ [M+H]^+ 331.1904, found 331.1904.
(1S,2S,3R)-ethyl 2-formyl-3-(furan-2-yl)-5-hydroxy-4'-methoxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-carboxylate, Clear oil. $[\alpha]_D^{23} = +106.1$ (c=0.47, CHCl$_3$, 97% ee); IR (thin film, KBr): 2927, 2837, 1723, 1653, 1513, 1306, 1278, 1250, 1214, 1179, 1062, 1035, 1012, 831, 737 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.47 (s, 1H), 9.04 (d, $J = 4.2$ Hz, 1H), 7.33 (m, 1H), 7.08 (d, $J = 8.6$ Hz, 2H), 6.83 (d, $J = 8.6$ Hz, 2H), 6.30 (dd, $J = 2.9$, 1.9 Hz, 1H), 6.07 (d, $J = 3.2$ Hz, 1H), 4.40 (d, $J = 5.0$ Hz, 1H), 4.14 (q, $J = 7.1$ Hz, 2H), 3.76 (s, 3H), 3.50 (td, $J = 11.7$, 6.1 Hz, 1H), 2.83 (m, 2H), 2.48 (dd, $J = 18.9$, 11.3 Hz, 1H), 1.15 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 203.4, 172.0, 171.4, 158.8, 153.9, 141.8, 133.1, 128.7, 114.5, 110.3, 108.4, 97.9, 60.7, 55.2, 54.6, 37.7, 35.6, 35.2, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 90:10), 0.5 mL/min; major enantiomer $t_R = 33.7$ min, minor enantiomer $t_R = 54.0$ min. HRMS (ESI) calcd for C$_{21}$H$_{22}$O$_6$ [M+H]$^+$ 371.1489, found 371.1481.
(1'S,2'S,3'S)-ethyl 4,4''-dibromo-2'-formyl-5'-hydroxy-1',2',3',6'-tetrahydro-[1,1':3',1'"-terphenyl]-4'-carboxylate, Colorless crystals. m.p.: 118-120°C; [α]₀̊²⁴ = +81.6 (c=0.53, CHCl₃, 99% ee); IR (thin film, KBr): 2924, 2853, 1723, 1653, 1488, 1406, 1287, 1258, 1215, 1095, 1072, 1009, 821 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 12.63 (s, 1H), 9.64 (s, 1H), 7.44 (dd, J = 22.2, 8.5 Hz, 4H), 7.12 (d, J = 8.3 Hz, 2H), 6.99 (d, J = 8.3 Hz, 2H), 4.38 (d, J = 1.7 Hz, 1H), 4.06 (tt, J = 7.1, 3.5 Hz, 2H), 3.27 (m, 1H), 2.90 (m, 2H), 2.74 (dd, J = 18.4, 5.4 Hz, 1H), 1.02 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 200.9, 171.9, 171.6, 142.9, 138.9, 131.8, 131.7, 129.3, 129.1, 121.1, 120.6, 97.5, 60.8, 58.7, 38.4, 33.7, 30.9, 13.9 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (n-hexane: i-PrOH = 97:3), 0.5 mL/min; major enantiomer tᵣ = 22.0 min, minor enantiomer tᵣ = 31.0 min. HRMS (ESI) calcd for C₂₂H₂₀Br₂O₄ [M-H] - 504.9650, found 504.9665.
(1S,2S,3R)-ethyl-2'-fluoro-2-formyl-3-(furan-2-yl)-5-hydroxy-1,2,3,6-tetrahydro-[1,1'-biphenyl]-4-carboxylate, Clear oil. $[\alpha]_{D}^{26} = +120.3$ (c=0.71, CHCl$_3$, 93% ee); IR (thin film, KBr): 2983, 2930, 2826, 2731, 1725, 1654, 1622, 1491, 1406, 1307, 1232, 1217, 1097, 1061, 1038, 758 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 12.48 (s, 1H), 9.14 (d, $J = 3.6$ Hz, 1H), 7.33 (dd, $J = 1.8$, 0.8 Hz, 1H), 7.11 (m, 4H), 6.30 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.09 (d, $J = 3.2$ Hz, 1H), 4.46 (d, $J = 5.0$ Hz, 1H), 4.15 (q, $J = 7.1$ Hz, 2H), 3.84 (td, $J = 11.8$, 6.3 Hz, 1H), 3.07 (m, 1H), 2.81 (dd, $J = 18.8$, 6.3 Hz, 1H), 2.59 (dd, $J = 18.8$, 11.3 Hz, 1H), 1.16 (t, $J = 7.1$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 202.5, 171.7, 171.4, 162.0, 159.6, 153.7, 141.9, 129.1, 129.1, 129.0, 128.9, 128.1, 127.9, 124.8, 124.7, 116.1, 115.9, 110.4, 108.5, 97.9, 97.8, 60.7, 53.6, 53.5, 35.4, 34.8, 30.3, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column ($n$-hexane: $i$-PrOH = 97:3), 0.5 mL/min; major enantiomer $t_R = 31.3$ min, minor enantiomer $t_R = 18.5$ min. HRMS (ESI) calcd for C$_{20}$H$_{19}$FO$_5$ [M]$^+$ 358.1217, found 358.1218.
(4S,5S,6R)-ethyl-5-formyl-4,6-di(furan-2-yl)-2-hydroxycyclohex-1-enecarboxylate, Yellow oil. [α]_D^{26} = +65.3 (c=0.58, CHCl₃, 95% ee); IR (thin film, KBr): 2925, 2853, 1723, 1654, 1407, 1276, 1217, 1094, 1067, 1012, 812, 736 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 12.57 (s, 1H), 9.69 (s, 1H), 7.35 (m, 2H), 6.31 (ddd, J = 19.6, 3.2, 1.8 Hz, 2H), 6.13 (m, 1H), 6.00 (dt, J = 3.2, 0.8 Hz, 1H), 4.49 (s, 1H), 4.16 (m, 2H), 3.50 (m, 1H), 3.32 (m, 1H), 2.74 (m, 2H), 1.16 (t, J = 7.1 Hz, 3H); ¹³C NMR (101 MHz, CDCl₃) δ 201.2, 171.7, 171.0, 156.1, 154.1, 141.8, 141.7, 110.4, 110.2, 107.0, 106.1, 96.9, 60.7, 52.3, 32.6, 30.1, 30.0, 14.0 ppm; the enantiomeric excess was determined by HPLC with an AS-H column (n-hexane: i-PrOH = 95:5), 1.0 mL/min; major enantiomer t_R = 17.9 min, minor enantiomer t_R = 25.2 min. HRMS (ESI) calcd for C₁₈H₁₈O₆ [M +Na]^+ 353.1000, found 353.0992.
Ratio of major epimer of major diastereomer to its C4 epimer
6.2.1 References for 6.2


6.3 Experimental and Characterization for Chapter 4

Assignment of Stereochemistry

Stereochemistry was assigned based on the accepted model of stereochemical induction of catalyst 1.32,[1] and the prior determination of stereochemistry for β-amination of substrate 1.33f using catalyst 1.32.[2]

Preparation of catalysts (1.32, 1.32r), starting enals (1.33e-j), and amine nucleophiles (2.18, 4.18)

Catalysts 1.32 and 1.32r were prepared according to literature procedures from the corresponding diarylprolinols.[3] Non-commercially available enals 1.33e,[4a] 1.33f,[4b] 1.33g,[4c] 1.33h,[4d] 1.33i,[4e] and 1.33j[4f] and were prepared according to known procedures. Amine nucleophiles (2.18, 4.18) were prepared according to known literature procedures.[5]

General Procedure for amino-difluorination

To a solution of catalyst 1.32 (0.05 mmol, 0.2 equiv) and amine (0.5 mmol, 2 equiv) in MTBE (0.4 mL) was added enal 1.33a (0.25 mmol, 1 equiv). After ≥95% consumption of enal 1.33a (1d, 1H NMR), the reaction was diluted with MTBE (0.6 mL), followed by addition of NFSI (0.5 mmol, 2 equiv), then catalyst 1.32r (0.05 mmol, 0.2 equiv). The mixture was stirred vigorously until >85% (or, in some cases, complete) consumption of intermediate β-aminoaldehyde and α-fluoro-β-aminoaldehyde (2d, 1H NMR). The reaction mixture was then diluted with Et2O (2 mL), cooled to -8°C and filtered through silica gel (2” in a pipette), eluting with a cold (-50°C) solution of 9:1 Et2O:DCM (30 mL). Me2S (0.2 mL) was added to the eluent at rt and the mixture stirred for 15 minutes, then transferred to a separatory funnel and washed with sat. NaHCO3 (2 x 50 mL) and brine. The combined extracts were dried over MgSO4 and concentrated. The resulting residue was dissolved in 2:1 DCM : EtOH (2 mL), followed by the addition of NaBH4 (0.625 mmol, 2.5 equiv) in one portion. After stirring for 30 min the reaction was cooled to 0°C and quenched by the slow addition of sat. NH4Cl (5 mL). The mixture was then warmed to rt and stirred vigorously for 30 min. The mixture was extracted with DCM (2 x 50 mL), the organics washed with brine and dried over MgSO4, then concentrated. Purification on silica gel was achieved (unless otherwise noted) using 19:1 DCM : pet. ether until the excess unreacted amine nucleophile was free of the column, then switching to 19:1 DCM : Et2O to elute difluoroaminoalcohols in the reported yields.

2.34a:
(R)-benzyl-(2,2-difluoro-1-hydroxyheptan-3 yl)(methoxy)carbamate: pale yellow liquid (44.3 mg, 54% yield, 91% ee). \([\alpha]^{23}_D = +2.8\ (c\ 1.8,\ \text{CHCl}_3);\) IR (thin film, KBr): 3454, 2959, 292, 2859, 113, 145, 1403, 1320, 1286, 1219, 1139, 109, 100, 912, 58, 36 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 0.44 – 0.31 (m, 5H), 5.26 (q, \(J = 12.2\) Hz, 2H), 4.52 – 4.39 (m, 1H), 3.89 – 3.65 (m, 5H), 3.10 (s, 1H), 2.05 – 1.88 (m, 1H), 1.81 – 1.64 (m, 1H), 1.44 – 1.14 (m, 4H), 0.88 (t, \(J = 6.1\) Hz, 3H); \(^1\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.4, 135.5, 128. (2C), 128.5, 128.1 (2C), 121.4 (t, \(J = 249.3\) Hz, 1C), 68.6, 63.5, 62.9 – 61.8 (m, 1C), 59.8, 28.0, 22., 22.3, 13.8; \(^1^9\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) = -113.4 (d, \(J_{F.F} = 258.6\) Hz, 1F), -118.9 (d, \(J = 262.6\) Hz, 1F); ee (HPLC, AD-H column) (n-hexane/i-PrOH = 95:5), 0.3 mL/min; major \(t_R = 42.4\) min, minor \(t_R = 56.1\) min. HRMS (ESI) [M + H]^+ calcd for [C\(_{16}\)H\(_{23}\)F\(_2\)NO\(_4\)]: 331.1595, found: 331.1595.
1H NMR in CDCl3

13C NMR in CDCl3
2.34b:

(R)-benzyl-(2,2-difluoro-1-hydroxypentan-3-yl)(methoxy)carbamate: colorless liquid (43.3 mg, 57% yield, 90% ee). \([\alpha]^{23}_D = +10.9 \ (c \ 2.1, \ \text{CHCl}_3)\); IR (thin film, KBr): 3453, 295, 2944, 112, 145, 1402, 1359, 1314, 1263, 1214, 1143, 10, 1028, 56 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3 (h, \(J = 4.9 \ \text{Hz}, \ 5\)H), 5.26 (q, \(J = 12.2 \ \text{Hz}, \ 2\)H), 4.46 – 4.31 (m, 1H), 3.92 – 3.62 (m, 5H), 3.0 (s, 1H), 1.9 (ddt, \(J = 18., \ 14.4, \ .3 \ \text{Hz}, \ 1\)H), 1.88 – 1.3 (m, 1H), 0.96 (t, \(J = .3 \ \text{Hz}, \ 3\)H); \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.6, 135.5, 128. (2C), 128.5, 128.1 (2C), 121.4 (t, \(J = 249.3 \ \text{Hz}, \ 1\)C), 68.6, 63.6, 62.8 – 61.9 (m, 1C), 61.9 – 61.0 (m, 1C), 16.5, 10.6; \(^{19}\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) = -113.5 (d, \(J_{\text{F-F}} = 25.6 \ \text{Hz}, \ 1\)F), -118. (d, \(J_{\text{F-F}} = 263.3 \ \text{Hz}, \ 1\)F) ppm; ee (HPLC, AS-H column) (n-hexane/i-PrOH = 95:5), 0.3 mL/min; major \(t_R = 34.2 \ \text{min}, \ \)minor \(t_R = 31.5 \ \text{min}. \) HRMS (ESI) [M + H]\(^+\) calcd for \([\text{C}_{14}\text{H}_{19}\text{F}_2\text{NO}_4]\): 303.1282, found: 303.129.
(R)-benzyl-(2,2-difluoro-1-hydroxyhexan-3-yl)(methoxy)carbamate: pale yellow liquid (40.9 mg, 52% yield, 98% ee); [α]\textsubscript{D}\textsuperscript{23} = +3.8 (c 1.2, CHCl\textsubscript{3}); IR (thin film, KBr): 3462, 2962, 285, 112, 145, 1402, 1299, 1239, 1139, 108, 1016, 914, 5 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ .43 – .29 (m, 5H), 5.25 (q, J = 12.2 Hz, 2H), 4.55 – 4.41 (m, 1H), 3.90 – 3.63 (m, 5H), 3.08 (s, 1H), 2.05 – 1.90 (m, 1H), 1.3 – 1.62 (m, 1H), 1.52 – 1.3 (m, 1H), 1.34 – 1.20 (m, 1H), 0.92 (t, J = .4 Hz, 3H); \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}) δ 158.4, 135.5, 128. (2C), 128.5, 128.1(2C), 121.4 (t, J = 249.3 Hz, 1C) 68.6, 63.6, 62.8 – 61.9 (m, 1C), 59.5 (t, J = 26. Hz, 1C), 25.0, 19.1, 13.6; \textsuperscript{19}F NMR (188 MHz, CDCl\textsubscript{3}) δ = -113.4 (d, J\textsubscript{F-F} = 25.8 Hz, 1F), -118.8 (d, J\textsubscript{F-F} = 28.3 Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 95:5), 0.3 mL/min; major t\textsubscript{R} = 42.4 min, minor t\textsubscript{R} = 62.9 min. HRMS (ESI) [M + H]\textsuperscript{+} calcd for [C\textsubscript{15}H\textsubscript{21}F\textsubscript{2}NO\textsubscript{4}]: 31.1439, found: 31.1438.
2.34d:

(R)-benzyl-(2,2-difluoro-1-hydroxydodecan-3-yl)(methoxy)carbamate: Chromatography (3% acetone in pet. ether) gave a yellow liquid (49.5 mg, 49% yield, 92% ee). $[\alpha]_{D}^{23} = +5$ (c 2.6, CHCl$_3$); IR (thin film, KBr) 3462, 292, 2855, 113, 145, 1401, 1304, 1085, 911, 56 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ .42 – .31 (m, 5H), 5.26 (q, $J = 12.2$ Hz, 2H), 4.55 – 4.3 (m, 1H), 3.90 – 3.62 (m, 5H), 3.10 (s, 1H), 2.05 – 1.8 (m, 1H), 1.9 – 1.60 (m, 1H), 1.41 – 1.20 (m, 14H), 0.88 (t, $J = 6.9$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.6, 135.6, 128. (2C), 128.6, 128.2 (2C), 121.6 (t, $J = 249.2$ Hz, 1C), 68.6, 63.6, 62.9 – 62.0 (m, 1C), 59.9 (t, $J = 23.9$ Hz, 1C), 32.0, 29.6, 29.5, 29.4, 29.3, 26.0, 23.2, 22.8, 14.2; $^{19}$F NMR (188 MHz, CDCl$_3$) $\delta = -113.4$ (d, $J_{F,F} = 261.0$ Hz, 1F), -118.9 (d, $J_{F,F} = 266.2$ Hz, 1F) ppm; ee (HPLC, AD-H column) ($n$-hexane/i-PrOH = 9:3), 0.3 mL/min; major $t_R = 41.6$ min, minor $t_R = 48.6$ min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{21}$H$_{33}$F$_2$NO$_4$]: 401.238, found: 401.236.
(R)-benzyl-(2,2-difluoro-1-hydroxy-5-phenylpentan-3-yl)(methoxy) carbamate: colorless liquid (41.1 mg, 43% yield, 93% ee); [α]$_{23}^D$ = +13.8 (c 1.0, CHCl$_3$); IR (thin film, KBr): 3461, 3029, 2944, 112, 149, 1455, 1402, 1309, 1214, 110, 1102, 10, 1018, 913, 52 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.2 – 10 (m, 10H), 5.38 – 5.1 (m, 2H), 4.53 – 4.39 (m, 1H), 3.88 – 3.60 (m, 5H), 3.14 (s, 1H), 2.8 (ddd, J = 14.0, 9.0, 4.5 Hz, 1H), 2.54 (dt, J = 13.8, 8.3 Hz, 1H), 2.39 – 2.24 (m, 1H), 2.13 – 2.01 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.4, 140.5, 135.5, 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.3 (2C), 126.4, 121.50 (t, J = 249.6 Hz, 1C), 68.8, 63.8, 63.2 – 61.3 (m, 1C), 59.3 (t, J = 28.5 Hz, 1C), 32.1, 25.0; $^{19}$F NMR (188 MHz, CDCl$_3$) δ = -113.4 (d, J$_{F,F}$ = 263.1 Hz, 1F), -119.1 (d, J$_{F,F}$ = 20.0 Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 95:5), 0.5 mL/min; major t$_R$ = 42.4 min, minor t$_R$ = 50.9 min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{20}$H$_{23}$F$_2$NO$_4$]: 39.1595, found: 39.1595.
2.34f:

(R)-benzyl-(2,2-difluoro-1-hydroxy-5-methylhexan-3-yl)(methoxy) carbamate: colorless liquid (40.8 mg, 49% yield, 88% ee). [α]$_D^{23}$ = +3 (c 1.2, CHCl$_3$); IR (thin film, KBr) 3460, 2959, 282, 112, 1456, 1402, 1305, 1244, 1085, 1002, 912, 55 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 4.36 – 4.30 (m, 5H), 5.26 (q, $J$ = 12.2 Hz, 2H), 4.64 – 4.49 (m, 1H), 3.89 – 3.66 (m, 5H), 3.20 (s, 1H), 2.01 (ddd, $J$ = 14.1, 11.6, 3.4 Hz, 1H), 1.6 – 1.55 (m, 1H), 1.41 (t, $J$ = 12.4 Hz, 1H), 0.95 (d, $J$ = 6.6 Hz, 3H), 0.86 (d, $J$ = 6.5 Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.3, 135.4, 128.6 (2C), 128.5, 128.1 (2C), 121.6 (t, $J$ = 249.4 Hz, 1C), 68.6, 63.6, 62.8 – 61.6 (m, 1C), 5.31, 24.4, 23.5, 21.1; $^{19}$F NMR (188 MHz, CDCl$_3$) δ = -113.2 (d, $J_{F,F}$ = 25.4 Hz, 1F), -119.0 (d, $J_{F,F}$ = 260.1 Hz, 1F) ppm; ee (HPLC, AD-H column) ($n$-hexane/i-ProOH = 95:5), 0.3 mL/min; major $t_R$ = 31.6 min, minor $t_R$ = 4.8 min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{16}$H$_{23}$F$_2$NO$_4$]: 331.1595, found: 331.1594.
2.34g:

(R)-benzyl-(2,2-difluoro-1-hydroxy-4-methylpentan-3-yl)(methoxy) carbamate: colorless liquid (31.4 mg, 40% yield, 90% ee). $[\alpha]^2_D = +1.0$ (c 0.9, CHCl$_3$); IR (thin film, KBr) 3480, 2968, 2946, 289, 112, 145, 1394, 1350, 1305, 12, 1213, 1148, 105, 1004, 912, 56 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 44 – .31 (m, 5H), 5.32 – 5.18 (m, 2H), 4.21 (d, $J = 1.4$ Hz, 1H), 3.9 – 3.64 (m, 5H), 2.92 (s, 1H), 2.39 (d, $J = 6.9$ Hz, 1H), 1.11 (dd, $J = 6.3, 3.1$ Hz, 3H), 1.04 (d, $J = 6.$ Hz, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.5, 135.5, 128. (2C), 128.5, 128.1 (2C), 122.4 (t, $J = 251.0$ Hz, 1C), 68.6, 64.6, 63.8 – 63.1 (m, 1C), 63.1, 26.1, 20.6, 19.8 (d, $J = 6.2$ Hz, 1C) ppm; $^{19}$F NMR (188 MHz, CDCl$_3$) $\delta$ = -105.3 – -11.1 (m, 2F) ppm; ee (HPLC, AS-H column) (n-hexane/i-PrOH = 9:3), 0.3 mL/min; major $t_R = 35.4$ min, minor $t_R = 50.9$ min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{15}$H$_{21}$F$_2$NO$_4$]: 31.1439, found: 31.1440.
2.34h:

(R)-benzyl-(2,2-difluoro-1-hydroxyoct-en-3-yl)(methoxy)carbamate: yellow liquid (40.8 mg, 4% yield, 91% ee). [α]$_D^23$ = +8.4 (c 1., CHCl$_3$); IR (thin film, KBr) 3458, 2942, 112, 1456, 1401, 1316, 1213, 1165, 1080, 1016, 913, 55 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 42 – .32 (m, 5H), 5.5 (ddt, $J = 16.9, 10.2, 6.$ Hz, 1H), 5.26 (q, $J = 12.2$ Hz, 2H), 5.05 – 4.93 (m, 2H), 4.54 – 4.40 (m, 1H), 3.88 – 3.6 (m, 5H), 3.05 (s, 1H), 2.13 – 1.90 (m, 3H), 1.81 – 1.6 (m, 1H), 1.5 – 1.44 (m, 1H), 1.43 – 1.28 (m, 1H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 158.3, 13.9, 135.4, 128. (2C), 128.5, 128.1 (2C), 121.4 (t, $J = 249.4$ Hz, 1C), 115.1, 68.6, 63.6, 62.4 (dd, $J = 32.8, 30.1$ Hz, 1C), 60.8 – 58.6 (m, 1C), 33.2, 25.1, 22.5; $^{19}$F NMR (188 MHz, CDCl$_3$) δ = -113.4 (d, $J_{F,F} = 25.4$ Hz, 1F), -118. (d, $J_{F,F} = 246.6$ Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 95:5), 0.3 mL/min; major $t_R = 42.2$ min, minor $t_R = 60.0$ min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{13}$H$_{23}$F$_2$NO$_4$]: 343.1595, found: 343.1594.
2.34i:

\[ \text{(R)-benzyl-(1-(benzyloxy)-3,3-difluoro-4-hydroxybutan-2-yl)(methoxy) carbamate:} \]

Chromatography (12.5% to 20% EtOAc in pet. ether) gave a colorless liquid (43.6 mg, 44% yield, 92% ee). \([\alpha]^{23}_D = +6.9 \ (c \ 1.8, \ \text{CHCl}_3)\); IR (thin film, KBr) 3461, 2926, 116, 1455, 1396, 1303, 1120, 106, 1028, 910, 3 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 4.42 – 2.8 (m, 10H), 5.32 – 5.20 (m, 2H), 4.86 (dd, \(J = 1.8, 9.3, 4.3\) Hz, 1H), 4.56 (s, 2H), 4.04 (t, \(J = 9.8\) Hz, 1H), 3.90 – 3.1 (m, 6H), 2.90 (s, 1H); \(^1^3\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 158.3, 13.5, 135.5, 128.6 (2C), 128.4 (2C), 128.1 (2C), 128.2 (2C), 121.1 (t, \(J = 249.6\) Hz, 1C), 3.3, 68.6, 63., 63.3, 62.6 (t, \(J = 31.1\) Hz, 1C), 59.5 (t, \(J = 25.8\) Hz, 1C); \(^1^9\)F NMR (188 MHz, CDCl\(_3\)) \(\delta\) = -113.0 (d, \(J_{F,F} = 253.9\) Hz, 1F), -115.8 (d, \(J_{F,F} = 23.0\) Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 90:10), 1.0 mL/min; major \(t_R = 1.6\) min, minor \(t_R = 20.0\) min. HRMS (ESI) [M + H]\(^+\) calcd for \([\text{C}_{20}\text{H}_{24}\text{F}_{2}\text{NO}_5]\): 395.1544, found: 395.1545.
(R)-methyl-9-(((benzyloxy)carbonyl)(methoxy)amino)-10,10-difluoro-11-hydroxyundecanoate: Chromatography (12.5% to 20% EtOAc in pet. ether) gave a colorless liquid (50.5 mg, 47% yield, 90% ee). $[\alpha]_{D}^{23} = +3.2$ (c 2.8, CHCl$_3$); IR (thin film, KBr) 3999, 2941, 2858, 13, 1456, 1399, 1303, 1213, 111, 1115, 109, 1015, 912, 56 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 1.41 – 1.31 (m, 5H), 5.25 (q, J = 12.2, 11.4 Hz, 2H), 4.53 – 4.38 (m, 1H), 3.91 – 3.64 (m, 8H), 2.29 (t, J = 5 Hz, 2H), 2.01 – 1.90 (m, 1H), 1.69 (s, 1H), 1.63 – 1.56 (m, 2H), 1.45 – 1.16 (m, 8H); $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 14.6, 158.8, 135.8, 129.0 (2C), 128.9, 128.5 (2C), 121.8 (t, J = 249.3 Hz, 1C), 68.9, 63.9, 63.2 – 62.2 (m, 1C), 60.9 – 60.0 (m, 1C), 51.8, 34.4, 29.3, 29.3, 26.1, 25.2, 23.2; $^{19}$F NMR (188 MHz, CDCl$_3$) $\delta$ = -113.4 (d, $J_{F,F}$ = 258.3 Hz, 1F), -118.8 (d, $J_{F,F}$ = 259.9 Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 90:10), 1.0 mL/min; major $t_R$ = 12.8 min, minor $t_R$ = 15.6 min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{21}$H$_{31}$F$_2$NO$_6$]: 431.2119, found: 431.2119.
2.34k:

(R)-benzyl-benzzyloxy(2,2-difluoro-1-hydroxydodecan-3-yl)carbamate: prepared according to the general procedure (3.0 mmol scale), using the N-OBn protected amine nucleophile (4.18). Chromatography (5-15% EtOAc in pet. ether) of the crude cascade product gave an inseparable mixture of alcohol 2.34k and unreacted amine nucleophile in an approximate 2:3 ratio, respectively. Yield was determined by NMR, using cyclohexene as internal standard (54% yield). Full characterization of the corresponding methyl ester (4.19) was achieved and is described below.

4.19:

(R)-methyl-3((benzyloxy)((benzyloxy)carbonyl)amino)-2,2-difluorododecanoate: Prepared from adapted literature procedures. To an inseperable mixture of difluoroaminoalcohol 2.34k (0.53 mmol, as determined by NMR with internal standard) and the amine nucleophile (1.4 mmol) in MeCN (10 mL, 0.2 M) was added NMO (2.34 g, 10 equiv), H2O (360 µL, 10 equiv) and TPAP (0.3 mg, 0.10 equiv) and stirred at rt for 1.5 hrs, followed by quenching with i-PrOH (5 mL) and stirring for 30 min. The crude mixture was filtered through silica gel (4” plug) with 9 : 1 DCM : MeOH (150 mL), and the eluent concentrated. The resulting crude residue was dissolved (Et2O, 50 mL) and washed with sat. KHSO4 (2 x 50 mL) to remove the excess NMO, and the aqueous layer again extracted (Et2O, 2 x 20 mL). The combined organic extracts were washed with brine, dried over Na2SO4 and concentrated. Column chromatography (8:2 EtOAc : PE to 9:1 EtOAc : MeOH) afforded the carboxylic acid (yellow oil) in nearly quantitative yield (260 mg, 0.53 mmol).

To this acid intermediate (260 mg, 0.53 mmol) in methanol (4.0 mL) at 0° C, was added dropwise AcCl (3 µL, 10 equiv). The mixture was warmed to rt, stirred for 2 hrs (when the starting material was confirmed consumed by TLC) then concentrated. This crude residue was dissolved (EtOAc, 50 mL), neutralized with sat. NaHCO3 (50 mL), washed with brine (50 mL), then dried over MgSO4. Concentration provided the pure methyl ester (4.19) as a colorless liquid (261 mg, 98% yield, 89% ee). [α]D23 = +50.4 (c 3.5, CHCl3); IR (thin film, KBr) 3066, 3034, 2956, 2926, 2855, 16, 119, 1498, 1456, 1389, 1285, 1215, 1066, 51 cm-1; 1H NMR (400 MHz, CDCl3) δ .4 – .
28 (m, 10H), 5.24 (s, 2H), 4.99 – 4.81 (m, 2H), 4.82 – 4.58 (m, 1H), 3.6 (s, 3H), 2.1 – 1.91 (m, 1H), 1.3 – 1.52 (m, 1H), 1.40 – 1.11 (m, 14H), 0.94 – 0.81 (m, 3H); $^{13}$C NMR (101 MHz, CDCl$_3$) δ 163.9 (t, $J = 32.2$ Hz, 1C), 15.8, 135.6, 135.0, 129.4 (2C), 128.6 (2C), 128.5, 128.4, 128.4 (2C), 128.2 (2C), 114. (t, $J = 256.3$ Hz, 1C), 9, 68.5, 61.3 (t, $J = 25.8$ Hz, 1C), 53.4, 31.9, 29.4, 29.3, 29.3, 29.1, 25.3, 23.5, 22.1, 14.1; $^{19}$F NMR (188 MHz, CDCl$_3$) δ = -109.9 (dd, $J_{F,F} = 259.4$ Hz, 1F), -115.3 (d, $J_{F,F} = 256.6$ Hz, 1F) ppm; ee (HPLC, AD-H column) (n-hexane/i-PrOH = 99:1), 0.3 mL/min; major $t_R = 26.6$ min, minor $t_R = 59.2$ min. HRMS (ESI) [M + H]$^+$ calcd for [C$_{28}$H$_3$F$_2$NO$_5$]: 505.2640, found: 505.2643.
(R)-methyl-3-amino-2,2-difluorododecanoate: Difluoroaminoester 4.19 (5 mg, 0.11 mmol) in MeOH (5 mL) was slowly added to a slurry of 5% Pd/C (4 mg, 20% Pd) in EtOH (0.5 mL) and hydrogenated (50 psi) at rt for 20 hrs. This crude mixture was filtered through cotton (EtOAc, 30 mL) and concentrated to give the pure free amino ester (4.14), as a yellow oil (2.3 mg, 91% yield); [α]_D^23 = +19.6 (c 0.5, CHCl_3); IR (thin film, KBr) 340, 2956, 2926, 2856, 164, 1459, 1441, 138, 1316, 1196, 109, 812, 23 cm⁻¹; 'H NMR (400 MHz, CDCl₃) δ 3.89 (s, 3H), 3.28 – 3.11 (m, 1H), 1.66 – 1.50 (m, 2H), 1.34 – 1.21 (m, 14H), 0.88 (t, J = 6.6 Hz, 3H); 'C NMR (101 MHz, CDCl₃) δ 164.2 (t, J = 32.9 Hz, 1C), 116.35 (t, J = 253.3 Hz, 1C), 54.32 (t, J = 24.1 Hz, 1C), 53.2, 31.9, 29. (t, J = 2.5 Hz, 1C), 29.5, 29.4, 29.4, 29.3, 25.8, 22., 14.1; 'F NMR (188 MHz, CDCl₃) δ = -115.3 (dd, J_F-F = 256.4, J_F-H = 11.3 Hz, 1F), -118.4 (dd, J_F-F = 256.5, J_F-H = 14.2 Hz, 1F); HRMS: [M+H]^+ calcd [C₁₃H₂₃F₂NO₂]: 265.1853, found: 265.1853.
6.3.1 References for Ch. 6.3


6.4 Experimental and Characterization for Chapter 5

Determination of Diastereomeric Ratios for Products 5.14a-5.14i

As products 5.14a-5.14i were isolated as inseparable mixtures of diastereomers, diastereomeric ratios (dr) were determined using $^1$H NMR spectroscopy to compare integral ratios for the major : minor diastereomers. Spectral peaks of individual diastereomers were chosen based on the best separation of diastereomer peaks. Typically, these peaks were in one of two regions: the aldehyde region (9-10ppm), or the alkyl region (2-3ppm.) Inserts into the $^1$H NMR spectra are provided to demonstrate determination of dr.

General Procedure B, for Reductive Cyclization

To an oven-dried, 10 mL round bottom flask (fitted with rubber septum and magnetic stir bar) was added DiPiBA (N,N-diisopropyl-N-isobutylamine) (256 µL, 10 equiv), morpholine (11 µL 1 equiv), MeCN (1.5mL) (followed by wrapping the flask with aluminum foil to minimize light exposure), and a stock solution of MeCN containing tris(2,2’-bipyridyl)ruthenium(II) dichloride hexahydrate (1.0 mL, 2.5 mg per mL, 2.5 mol%) for a total of 2.5 mL MeCN. The solution was then bubbled though with Argon for 15 min (equivalent results were achieved with 3X degassing by freeze-pump-thaw.) The starting enal (0.125 mmol, 1 equiv) was then added, the aluminum foil removed, and the flask sealed with a yellow cap and parafilm. The reaction was stirred rapidly (DiPiBA was poorly soluble in MeCN) and irradiated overnight (12 hrs) using a 1600 lumen (23 Watt) broad spectrum fluorescent bulb, placed approximately 10cm from the reaction flask. After 12 hrs, morpholine was again added (11 µL, 1 equiv) (with careful argon purging through an attached rubber septum, and re-sealing with cap and parafilm after morpholine addition), followed by an additional 4 hours of irradiation (16 hrs total reaction time.)

Work-up consisted of diluting the reaction mixture with EtOAc (~1 mL) and filtering through a 4” plug of silica, flushing with additional (EtOAc, 120 mL.) The resulting filtrate was concentrated at the rotovap (40°C, 125mbar), followed by high vacuum (15-30 min), before a crude NMR yield was attained using cyclohexene (1 equiv) as internal standard, or equivalently using the ester -CH$_2$ quartet at 4.21 ppm as standard from which the product aldehyde conversion could be calibrated. Isolated yields were obtained by silica chromatography, as indicated for the individual substrates.
Preparation of amines (A1-A2)

A1:

\[
\begin{array}{c}
\text{N} \\
\text{H} \\
\text{O} \\
\text{O}
\end{array}
\]

A known compound, tertiary amine \(N,N\)-diisopropyl-N-isobutylamine (i.e., DiPiBA) \(\text{(A1)}\) was prepared according to literature.\(^1\)

A2:

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{C} \\
\text{O}
\end{array}
\]

A known compound, morpholin-3-one \(\text{(A2)}\) was prepared according to literature.\(^2\)

Preparation of starting enals (5.13a-i):

Unless otherwise noted, enal substrates were synthesized using adapted literature procedures, referenced in General Procedure A, which describes a representative procedure for enal 5.13a. This was used, in part or in whole, with any changes noted under the characterization for individual enal substrates.

General Procedure A:

Representative Procedure for starting enal 5.13a

1) 5-hexen-1-ol (2.93 mL, 24.4 mmol) was added dropwise to a suspension of pyridinium chlorochromate (PCC, 7.90 g, 1.5 equiv) and celite (7.90 g) in DCM (66 mL), with cooling over an ice/water bath. After 10 minutes, the cooling bath was removed and the solution stirred vigorously for 2 h, when the alcohol was observed consumed (TLC, 5% EtOAc/PE; alcohol \(R_f = 0.1\)) \(\text{(Note: the reaction could be left overnight before workup with little loss in yield.)}\) The dark slurry was then diluted with Et\(_2\)O (50 mL) and filtered through a pad of silica gel (4” x 3.0”), rinsing with 9:1 pentane : Et\(_2\)O. The filtrate was concentrated (40°C, 500mbar) to give a crude mixture of the \(\text{(volatile)}\) desired aldehyde and DCM (~1:1), along with trace PCC impurities. Attempts at further purification (chromatography, distillation) were not useful and this crude intermediate could be submitted to the following Wittig olefination without detriment.

2) To a solution of stabilized ylide (carbethoxymethylene)triphenylphosphorane (10.2 g, 1.2 equiv) in THF (150 mL) was added a solution of the product aldehyde from the previous step
(assumed full conversion of 24.4 mmol) in THF (50 mL). After 5 h, the reaction was concentrated (40°C, 250 mbar), until most of the THF had been removed. The white sludge was then dissolved in Et₂O (50 mL), and stirred rapidly for 10 min (precipitation of white OPPh₃ occurred). Petroleum ether (150 mL) was then added and the precipitated OPPh₃ filtered off through a plug of packed celite (3” x 2.5”), rinsing with the same 25% Et₂O/PE solution (100 mL). The filtrate was concentrated (40°C, 500 mbar), washed with brine (2 x 100 mL) and dried over MgSO₄. Concentration (40°C, up to 300 mbar) gave 3.10 g (76% yield over 2-steps; 99% E-isomer) of the desired ethyl ester as volatile, colorless oil, with purity sufficient for the following metathesis step.⁴

3) To a solution of the terminal alkene from step 2 (3.10 g, 18.43 mmol) in anhydrous toluene (140 mL), was added crotonaldehyde (97% E-isomer) (15.3 mL, 10 equiv) followed by Grubb’s II catalyst (782 mg, 5 mol %). The brown mixture was heated to 65°C and stirred for 5-15 h (time depending upon the age of the Grubbs’ catalyst, which seemed to loose activity after a period of weeks from opening, despite storing at -20°C under argon) until the starting alkene was consumed, as monitored by ¹H NMR. After cooling to room temperature, the solvent was removed at the rotovap (40°C, 50 mbar.) Special care was then taken to remove the ruthenium residues from the Grubbs catalyst, as these were found to promote decomposition of the enal product on extended storage.⁵ Initials filtration through silica (6”, 20% EtOAc / PE), followed by a slower purification on silica (7.5% EtOAc / PE) was typically sufficient to remove Grubbs’ residues and stabilize the product for storage. After this procedure, the desired enal (I) was attained as a clear oil (2.68 g, 74% yield, >95% E-isomer).⁶

Characterization of Starting Enals (5.13a-i)

5.13a:

ethyl (2E,7E)-9-oxonona-2,7-dienoate: Prepared exactly as described in General Procedure A, to give 2.68 g (13.6 mmol) as a yellow oil; 56% overall yield from 5-hexen-1-ol; ¹H NMR (400 MHz, CDCl₃): δ 9.52 (dd, J = 7.8, 0.7 Hz, 1H), 6.93 (dt, J = 15.6, 7.0 Hz, 1H), 6.82 (dt, J = 15.6, 6.8 Hz, 1H), 6.13 (ddt, J = 15.6, 7.8, 1.1 Hz, 1H), 5.87-5.82 (m, 1H), 4.19 (qd, J = 7.1, 0.7 Hz, 2H), 2.40-2.35 (m, 2H), 2.30-2.22 (m, 2H), 1.70 (quintet, J = 7.5 Hz, 2H), 1.31-1.26 (m, 3H); ¹³C NMR (101 MHz, CDCl₃): δ 193.9, 166.4, 157.5, 147.7, 133.3, 122.2, 60.2, 31.9, 31.4, 26.1, 14.3 ppm; IR: 2982, 2937, 2736, 1717, 1691, 1654, 1446, 1368, 1269, 1187, 1128, 1095, 1043, 975 cm⁻¹.
5.13b:

**methyl (2E,7E)-9-oxonona-2,7-dienoate**: Prepared according to **General Procedure A**, starting from hex-5-enal (7.0 mmol) using ylide carbmethoxymethylene)triphenylphosphorane (1.2 equiv), which, after Grubbs’ metathesis and purification on silica gel (10% EtOAc / PE), afforded 926mg (5.57 mmol) as a yellow oil; 80% overall yield from hex-5-enal; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.50 (d, $J$ = 7.8 Hz, 1H), 6.93 (dt, $J$ = 15.2, 7.4 Hz, 1H), 6.81 (dt, $J$ = 15.1, 7.3 Hz, 1H), 6.12 (dd, $J$ = 15.6, 7.8 Hz, 1H), 5.84 (d, $J$ = 15.7 Hz, 1H), 3.72 (s, 3H), 2.36 (q, $J$ = 7.3 Hz, 2H), 2.26 (q, $J$ = 7.2 Hz, 2H), 1.69 (quintet, $J$ = 7.4 Hz, 2H) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 193.9, 167.0, 157.4, 148.1, 133.5, 121.9, 51.6, 32.0, 31.5, 26.3 ppm; IR: 2992, 2948, 2854, 2731, 1722, 1689, 1657, 1436, 1315, 1273, 1201, 1128, 1096, 1041, 974 cm$^{-1}$. 

![Chemical Structure]

1) PCC, DCM
2) Wittig
3) Grubbs II, Crotonaldehyde
**5.13c:**

**ethyl (2E,7E)-5,5-dimethyl-9-oxonona-2,7-dienoate:** Prepared by adopting step (3) of **General Procedure A** for use with known starting alkene ethyl (E)-5,5-dimethylocta-2,7-dienoate (874 mg, 4.45 mmol).\(^7\) Purification on silica gel (5% EtOAc / PE) afforded 668 mg as a clear oil; 67% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.52 (d, \(J = 7.9\) Hz, 1H), 6.94 (dt, \(J = 15.5, 7.8\) Hz, 1H), 6.82 (dt, \(J = 15.5, 7.8\) Hz, 1H), 6.15-6.08 (m, 1H), 5.83 (dt, \(J = 15.5, 1.3\) Hz, 1H), 4.18 (q, \(J = 7.1\) Hz, 2H), 2.25 (dd, \(J = 7.8, 1.1\) Hz, 2H), 2.14 (dd, \(J = 7.9, 1.3\) Hz, 2H), 1.28 (t, \(J = 7.1\) Hz, 3H), 0.98 (d, \(J = 7.2\) Hz, 6H) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 193.7, 166.3, 154.8, 145.0, 135.7, 124.4, 60.4, 45.2, 44.9, 35.0, 27.1 (2C), 14.4 ppm; IR: 2957, 2924, 2853, 1718, 1692, 1653, 1465, 1368, 1265, 1190, 1109, 1043, 978 cm\(^{-1}\).
5.13d:

(2E,7E)-9-oxodeca-2,7-dienal: A known compound, prepared according to **General Procedure A** starting from hex-5-enal (10.0 mmol) using ylide (triphenylphosphoranylidene)acetone. Following Grubbs’ metathesis, purification on silica gel (10-15% EtOAC / PE) afforded 252mg as a yellow oil; 19% yield; 1H NMR (400 MHz, CDCl3): δ 9.51 (dd, J = 7.8, 2.4 Hz, 1H), 6.86-6.73 (m, 2H), 6.15-6.07 (m, 2H), 2.42-2.34 (m, 2H), 2.31-2.24 (m, 5H), 1.77-1.66 (m, 2H). ppm; 13C NMR (101 MHz, CDCl3): δ 198.4, 193.9, 193.8, 157.3, 156.9, 146.7, 133.7, 133.6, 132.0, 32.1, 32.1, 31.8, 27.2, 26.3, 26.1 ppm; IR: 2933, 2862, 2740, 1689, 1627, 1429, 1362, 1255, 1165, 1130, 975 cm⁻¹.
(2E,7E)-9-oxo-9-phenylnona-2,7-dienal: A known compound, prepared according to General Procedure A starting from hex-5-enal (8.56 mmol) and using ylide (phenylacylidene)triphenylphosphorane. Following Grubbs’ metathesis, purification on silica gel (5% EtOAc / PE) afforded 1.08mg as a yellow oil; 63% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.49 (t, $J = 6.2$ Hz, 1H), 7.91-7.88 (m, 2H), 7.55-7.50 (m, 1H), 7.45-7.41 (m, 2H), 7.00 (dt, $J = 15.4$, 6.8 Hz, 1H), 6.91-6.78 (m, 2H), 6.11 (ddt, $J = 15.6$, 7.8, 1.5 Hz, 1H), 2.40-2.26 (m, 4H), 1.73 (quintet, $J = 7.5$ Hz, 2H) ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 194.0, 190.6, 157.4, 148.2, 137.9, 133.6, 132.9, 128.7, 128.6, 126.7, 77.5, 77.2, 76.8, 32.2, 26.5 ppm; IR: 3058, 2933, 2860, 2737, 1689, 1670, 1620, 1597, 1578, 1447, 1342, 1288, 1234, 1179, 1165, 1130, 1098, 973, 771, 696 cm$^{-1}$. 
(E)-N,N-diethylocta-2,7-dienamide: As an intermediate to enal 5.13f, terminal alkene (5.13f-int) was prepared according to General Procedure A, starting from hex-5-enal (8.0 mmol) and ylide [(diethylcarbamoyl)methyl]triphenylphosphonium chloride.\textsuperscript{11} Purification on silica gel (15% to 25% EtOAc in PE) afforded 875 mg (5.13f-int) as a yellow oil, as the exclusive E-isomer (56% yield); (although the Z-isomer was formed in approximately 14% of the crude product mixture, it was separable by chromatography); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 6.88 (dt, J = 14.8, 7.3 Hz, 1H), 6.18 (dt, J = 15.0, 1.5 Hz, 1H), 5.82-5.73 (m, 1H), 5.03-4.94 (m, 2H), 3.38 (dq, J = 23.9, 7.2 Hz, 4H), 2.24-2.18 (m, 2H), 2.08 (q, J = 7.2 Hz, 2H), 1.55 (quintet, J = 7.4 Hz, 2H), 1.21-1.11 (m, 6H) ppm; \textsuperscript{13}C NMR (101 MHz, CDCl\textsubscript{3}): δ 165.9, 145.8, 138.4, 120.8, 115.0, 42.2, 40.9, 33.3, 32.0, 27.7, 15.0, 13.3 ppm; IR: 3076, 2974, 2931, 1660, 1618, 1480, 1428, 1378, 1361, 1274, 1248, 1220, 1142, 1096, 973, 910 cm\textsuperscript{-1}.\textsuperscript{1}
(2E,7E)-N,N-diethyl-9-oxonona-2,7-dienamide: Prepared according to step (3) of General Procedure A using (6i) (875 mg, 4.48 mmol). Purification on silica gel (20% – 100% EtOAc / PE) afforded 450 mg 5.13f as a yellow oil; 45% yield; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.49 (d, $J = 7.8$ Hz, 1H), 6.89-6.77 (m, 2H), 6.19 (dt, $J = 15.0$, 1.5 Hz, 1H), 6.10 (ddt, $J = 15.6$, 7.9, 1.5 Hz, 1H), 3.36 (dquintet, $J = 23.3$, 7.4 Hz, 4H), 2.39-2.33 (m, 2H), 2.25 (qd, $J = 7.3$, 1.4 Hz, 2H), 1.67 (quintet, $J = 7.4$ Hz, 2H), 1.14 (dt, $J = 20.3$, 7.1 Hz, 6H). ppm; $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta$ 194.0, 165.6, 157.8, 144.6, 133.5, 121.5, 42.2, 41.0, 32.2, 31.9, 26.7, 15.0, 13.3 ppm; IR: 2973, 2931, 2736, 1689, 1659, 1615, 1481, 1446, 1430, 1379, 1361, 1276, 1219, 1127, 1096, 973 cm$^{-1}$.
**5.13g:**

**ethyl (E)-4-(((E)-4-oxobut-2-en-1-yl)oxy)but-2-enoate:** Prepared according to **General Procedure A** (step 3, Grubbs’ metathesis only), from known starting alkene (ethyl (E)-4-(allyloxy)but-2-enoate) (970 mg, 5.7 mmol). Purification on silica gel (15% - 20% EtOAc / PE) afforded 477 mg **5.13g** as a clear oil; 42% yield; "H NMR (400 MHz, CDCl₃): δ 9.59 (d, J = 7.9 Hz, 1H), 6.94 (dt, J = 15.8, 4.2 Hz, 1H), 6.82 (dt, J = 15.8, 4.0 Hz, 1H), 6.38 (ddd, J = 15.8, 7.8, 1.8 Hz, 1H), 6.09 (dd, J = 15.8, 1.8 Hz, 1H), 4.30 (dd, J = 3.9, 1.9 Hz, 2H), 4.23-4.18 (m, 4H), 1.27 (dt, J = 16.6, 7.9 Hz, 3H). ppm; "C NMR (101 MHz, CDCl₃): δ 193.2, 166.2, 152.2, 143.2, 132.0, 121.9, 69.6, 69.3, 60.7, 14.4 ppm; IR: 2983, 2906, 2850, 2728, 1720, 1692, 1447, 1368, 1303, 1274, 1179, 1122, 1038, 971 cm⁻¹.
5.13h:

**ethyl (2E,7E)-2-methyl-9-oxonona-2,7-dienoate**: Prepared according to **General Procedure A**, starting from hex-5-enal (824 mg, 8.4 mmol) and using ylide (carbethoxyethylidene) triphenylphosphorane (1.2 equiv), which, after Grubbs metathesis and purification on silica gel (5 - 8% EtOAc / PE), afforded 758 g 5.13h as a clear oil; 43% overall yield from hex-5-enal; **H NMR** (400 MHz, CDCl₃): δ 9.49 (d, J = 7.8 Hz, 1H), 6.82 (dt, J = 15.6, 6.7 Hz, 1H), 6.73-6.68 (m, 1H), 6.11 (ddt, J = 15.6, 7.8, 1.5 Hz, 1H), 4.17 (q, J = 7.1 Hz, 2H), 2.39-2.33 (m, 2H), 2.22 (qd, J = 7.4, 0.7 Hz, 2H), 1.81 (q, J = 1.1 Hz, 3H), 1.68 (q, J = 7.5 Hz, 2H), 1.27 (t, J = 7.1 Hz, 3H). ppm; **C NMR** (101 MHz, CDCl₃): δ 194.0, 168.1, 157.8, 140.6, 133.4, 128.9, 60.6, 32.3, 28.1, 26.8, 14.4, 12.6 ppm; **IR**: 2923, 2850, 2734, 1692, 1462, 1367, 1261, 1172, 1109, 1022, 975, 866, 799, 745 cm⁻¹.
5.13i:

ethyl (2E,8E)-10-oxodeca-2,8-dienoate: Prepared according to step (3) of General Procedure A from known alkene (ethyl (E)-nona-2,8-dienoate) (7.24 mmol).<sup>13</sup> Purification on silica gel (7.5% EtOAc / PE) afforded 1.32 g 5.13i as a pale yellow oil; 81% yield; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 9.50 (d, J = 7.9 Hz, 1H), 6.93 (dt, J = 15.6, 7.0 Hz, 1H), 6.82 (dt, J = 15.6, 6.8 Hz, 1H), 6.11 (ddd, J = 15.6, 7.8, 1.3 Hz, 1H), 5.82 (dd, J = 15.6, 1.5 Hz, 1H), 4.18 (qd, J = 7.1, 2.0 Hz, 2H), 2.35 (q, J = 6.3 Hz, 2H), 2.23 (q, J = 6.5 Hz, 2H), 1.55 (td, J = 7.2, 3.0 Hz, 4H), 1.28 (td, J = 7.1, 2.0 Hz, 3H) ppm; <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 194.1, 166.7, 158.1, 148.5, 133.3, 121.9, 60.4, 32.6, 31.9, 27.6, 27.4, 14.4 ppm; IR: 2982, 2934, 2859, 2733, 1717, 1690, 1654, 1461, 1367, 1308, 1268, 1183, 1128, 1096, 1042, 978 cm<sup>-1</sup>.
Characterization of Cyclized Products (5.14a-i)

5.14a:

ethyl 2-(2-(2-oxoethyl)cyclopentyl)acetate: Prepared according to General Procedure B from 5.13a to give, after chromatography (10% EtOAc / PE), 18mg as a clear oil, 73% yield, d.r. = 3:2; ¹H NMR (400 MHz, CDCl₃): δ 9.75 (ddd, J = 5.0, 2.4, 1.6 Hz, 1H), 4.12 (qd, J = 7.2, 2.4 Hz, 2H), 2.64-2.12 (m, 5H), 2.00-1.79 (m, 3H), 1.75-1.55 (m, 2H), 1.38-1.21 (m, 5H); ¹³C NMR (101 MHz, CDCl₃): δ 202.4, 173.2, 173.1, 60.5, 60.4, 49.1, 44.7, 42.2, 39.7, 39.4, 39.0, 36.3, 35.6, 32.4, 32.1, 30.7, 30.7, 23.7, 22.4, 14.4, 14.4 ppm; IR: 2926, 2855, 2715, 1729, 1448, 1374, 1294, 1241, 1163, 1116, 1028 cm⁻¹.
methyl 2-(2-(2-oxoethyl)cyclopentyl)acetate: Prepared according to General Procedure B from 5.13b to give, after chromatography (15% EtOAc / PE), 16 mg as a clear oil, 69% yield, d.r. = 3:2; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.77 (ddd, \(J = 5.0, 2.4, 1.6\) Hz, 1H), 3.68 (d, \(J = 2.1\) Hz, 3H), 2.65-2.15 (m, 5H), 2.02-1.81 (m, 3H), 1.75-1.59 (m, 2H), 1.39-1.22 (m, 2H) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 202.3, 173.63, 173.56, 51.74, 51.64, 49.1, 44.7, 42.1, 39.6, 39.06, 38.90, 36.3, 35.3, 32.4, 32.1, 30.67, 30.65, 23.6, 22.4 ppm; IR: 2952, 2872, 2718, 1735, 1436, 1258, 1194, 1171 cm\(^{-1}\).
5.14c:

![Chemical Structure](image)

**ethyl 2-(4,4-dimethyl-2-(2-oxoethyl)cyclopentyl)acetate:** Prepared according to **General Procedure B** from 5.13c to give, after chromatography (6% EtOAc / PE), 18 mg as a clear oil, 64% yield, d.r. = 3:2; **1H NMR** (400 MHz, CDCl3): δ 9.75 (dt, J = 7.6, 1.8 Hz, 1H), 4.14 (qd, J = 7.1, 2.4 Hz, 2H), 2.77-2.03 (m, 6H), 1.85-1.15 (m, 2H), 1.09-1.03 (m, 6H) ppm; **13C NMR** (101 MHz, CDCl3): δ 202.36, 202.26, 173.17, 173.11, 60.53, 60.47, 49.0, 48.0, 47.6, 46.93, 46.86, 45.7, 42.1, 39.6, 39.2, 37.9, 37.6, 37.4, 36.4, 35.3, 31.27, 31.13, 31.10, 30.2, 14.4 ppm; **IR:** 2952, 2929, 2865, 2718, 1730, 1463, 1366, 1301, 1259, 1178, 1152, 1031 cm⁻¹.
5.14d:

![Structure](image)

2-(2-(2-oxopropyl)cyclopentyl)acetaldehyde: Prepared according to General Procedure B from 5.13d to give, after chromatography (15 - 20% EtOAc / PE), 12 mg as a clear oil, 57% yield, d.r. = 6:1; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.88-9.78 (m, 1H), 2.66-2.59 (m, 2H), 2.43-2.35 (m, 2H), 2.15 (d, \(J = 4.4\) Hz, 3H), 2.01-1.88 (m, 4H), 1.69-1.57 (m, 2H), 1.32-1.17 (m, 2H) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 208.7, 202.5, 49.2, 49.0, 41.0, 39.8, 32.32, 32.29, 30.5, 23.7 ppm; IR: 2948, 2870, 2722, 1788, 1450, 1406, 1359, 1228, 1168, 1129, 1031 cm\(^{-1}\).
5.14e:

![Chemical structure](attachment:image.png)

2-(2-(2-oxo-2-phenylethyl)cyclopentyl)acetaldehyde: Prepared according to General Procedure B from 5.13e to give, after chromatography (10% EtOAc / PE), 18 mg as a clear oil, 63% yield, as a mixture of diastereomers; d.r. = 13:1; \( ^1H \) NMR (400 MHz, CDCl3): \( \delta \) 9.78 (t, \( J = 1.9 \) Hz, 1H), 7.96-7.93 (m, 2H), 7.58-7.54 (m, 1H), 7.49-7.44 (m, 2H), 3.13 (dd, \( J = 16.5, 5.1 \) Hz, 1H), 2.92 (dd, \( J = 16.5, 8.3 \) Hz, 1H), 2.68 (dddd, \( J = 16.7, 4.7, 1.6 \) Hz, 1H), 2.40 (dddd, \( J = 16.7, 8.4, 2.2 \) Hz, 1H), 2.15-1.94 (m, 4H), 1.68-1.61 (m, 2H), 1.27 (dtt, \( J = 16.2, 8.1, 3.9 \) Hz, 2H). ppm; \( ^{13}C \) NMR (101 MHz, CDCl3): \( \delta \) 202.6, 200.0, 137.2, 133.2, 128.8 (2C, major + minor), 128.2 (2C, major + minor), 49.4, 43.9, 41.5, 40.0, 32.47, 32.38, 23.8 ppm; IR: 3060, 2926, 2869, 2720, 1721, 1684, 1597, 1580, 1448, 1405, 1287, 1210, 1001, 983 cm\(^{-1}\).
5.14f:

\[
\begin{array}{c}
\text{O} \\
\text{H} \\
\text{N} \\
\text{N} \\
\text{N} \\
\text{-diethyl-2-(2-oxoethyl)cyclopentyl} \\
\text{acetamide: Prepared according to General} \\
\text{Procedure B from 5.13f to give, after chromatography (40 - 60% EtOAc / PE), 19 mg as a clear} \\
oil, 68\% yield, d.r. = 1.3:1; } ^1\text{H NMR (400 MHz, CDCl}_3\text{): } \delta 9.77-9.72 \text{ (m, 1H), 3.41-3.26 (m, 4H), 2.71-2.15 (m, 5H), 2.07-1.82 (m, 3H), 1.71-1.57 (m, 2H), 1.36-1.22 (m, 3H), 1.17 (t, J = 7.1} \\
\text{Hz, 3H), 1.10 (t, J = 7.1 Hz, 3H) ppm; } ^{13}\text{C NMR (101 MHz, CDCl}_3\text{): } \delta 203.08, 202.91, 171.48, \\
171.34, 49.4, 45.1, 42.29, 42.16, 40.3, 39.8, 39.1, 38.2, 36.3, 33.9, 32.60, 32.52, 30.98, 30.87, \\
23.8, 22.6, 14.6, 13.2 ppm; IR: 2929, 2871, 2718, 1722, 1637, 1458, 1430, 1383, 1260, 1222, \\
1096, 1021 \text{ cm}^{-1}. \\
\end{array}
\]
5.14g:

ethyl 2-(4-(2-oxoethyl)tetrahydrofuran-3-yl)acetate: Prepared according to General Procedure B from 5.13g to give, after chromatography (20-30% EtOAc / PE), 18 mg as a clear oil, 73% yield, d.r. = 1:1; $^1$H NMR (400 MHz, CDCl3): $\delta$ 9.78 (d, J = 8.0 Hz, 1H), 4.13 (qd, J = 7.1, 3.5 Hz, 2H), 4.10-3.97 (m, 2H), 3.54-3.39 (m, 2H), 2.85-2.24 (m, 6H), 1.26 (t, J = 7.1 Hz, 3H) ppm; $^{13}$C NMR (101 MHz, CDCl3): $\delta$ 200.9, 200.6, 172.33, 172.28, 73.15, 73.04, 72.56, 72.50, 60.89, 60.78, 47.8, 42.7, 41.4, 39.0, 37.81, 37.71, 35.6, 33.3, 29.9, 14.3 ppm; IR: 2924, 2853, 2727, 1726, 1465, 1372, 1256, 1175, 1063, 1028, 923 cm$^{-1}$.
**5.14h:**

![Structure of ethyl 2-(2-(2-oxoethyl)cyclopentyl)propanoate](image)

**ethyl 2-(2-(2-oxoethyl)cyclopentyl)propanoate:** Prepared according to **General Procedure B** from **5.13h** to give, after chromatography (7% EtOAc / PE), 9 mg as a clear oil, 42% yield, d.r. = 3:7 (3:7 represents 30% of a single major diastereomer, to 70% of a mixture of minor diastereomers); ^1^H NMR (400 MHz, CDCl3): δ 9.78-9.55 (m, 1H), 4.19-4.09 (m, 2H), 2.63-2.00 (m, 4H), 1.95-1.39 (m, 5H), 1.37-1.22 (m, 5H), 1.21-1.11 (m, 3H) ppm; ^13^C NMR (101 MHz, CDCl3): δ 203.4, 202.8, 202.56, 202.47, 176.5, 77.5, 77.2, 76.8, 60.51, 60.46, 60.42, 60.32, 55.2, 50.1, 48.5, 47.1, 46.9, 43.9, 43.37, 43.33, 43.1, 42.69, 42.56, 41.37, 41.27, 36.6, 35.4, 34.3, 32.83, 32.68, 31.24, 31.06, 30.7, 29.5, 29.0, 27.74, 27.69, 27.67, 25.4, 24.17, 24.11, 21.72, 21.65, 17.3, 16.8, 15.86, 15.77, 14.49, 14.46, 14.40 ppm; IR: 2926, 2854, 2714, 1730, 1457, 1384, 1178, 1158, 1045 cm⁻¹.
5.14i:

**Ethyl 2-(2-oxoethyl)cyclohexylacetate:** Prepared according to **General Procedure B** from 5.13i to give, after chromatography (10% EtOAc / PE), 20 mg as a clear oil, 75% yield, d.r. = 7:3; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 9.76-9.73 (m, 1H), 4.14-4.09 (m, 2H), 2.59-2.08 (m, 4H), 1.78-1.07 (m, 13H) ppm; \(^{13}\)C NMR (101 MHz, CDCl\(_3\)): \(\delta\) 202.7, 202.4, 173.13, 173.08, 60.51, 60.48, 48.6, 44.5, 39.5, 39.1, 36.9, 36.23, 36.10, 33.0, 32.6, 29.20, 29.09, 25.91, 25.86, 23.4, 22.9, 14.4 ppm; IR: 2926, 2855, 2716, 1727, 1448, 1372, 1347, 1293, 1240, 1162, 1117, 1028 cm\(^{-1}\).
References for Ch. 6.4

Chapter 1


[8] Control experiments using the methyl ester of proline all but eliminated catalytic activity.


Soc. 2000, 122, 9874-9875.


(b) For a review of common Ruthenium- and Iridium-based catalysts, see: Koike, T., Akita,


(b) For a recent review of combining photoredox catalysis with organocatalysis, see: Hopkinson, M. N., Sahoo, B., Li, J. L., Glorius, F., *Chemistry 2014*, *20*, 3874-3886.


(c) For extensive coverage of radical ions: Vlad Todres, Z., *Ion-Radical Organic Chemistry* 2008 CRC Press.

[50] (a) See Ref. 49a.

(b) However, the nucleophilicity of chiral, radical-stabilizing NHC organocatalysts utilize radicals: Maji, B., Breugst, M., Mayr, H., *Angew Chem Int Ed Engl* 2011, 50,


For reviews of enantioselective photoredox catalysis, see: Wessig, P., Angew Chem Int Ed Engl 2006, 45, 2168-2171.


Chapter 2


(a) See [8](a).


(b) Regarding the impressive oxidative reactivity of diatomic fluorine, see: Jaccaud, M., Faron, R., Devilliers, D. and Romano, R. 2000. Fluorine. *Ullmann's Encyclopedia of Industrial Chemistry*.


(c) Enzymes have also been developed for fluorinations: O'Hagan, D.; Deng, H. *Chem. Rev.* 2015, 115, 634–649.


In 2012, for example, all but one of FDA approved drugs contained nitrogen: Ding, H. X.; Leverett, C. A.; Kyne, R. E.; Liu, K. K.-C.; Sakya, S. M.; Flick, A. C.; O'Donnell, C. J. Bioorganic & Medicinal Chemistry 2014, 22, 2005–2032.


Although not the only examples, these were seminal works in the field: (a) α-Fluorination of aldehydes: (a) Jørgensen: Marigo, M.; Fielenbach, D.; Brauton, A.; Kjærgaard, A.; Jørgensen, K. A. Angew. Chem. Int. Ed. 2005, 44, 3703–3706.


(c) For a non-organocatalyzed example, see: Andrews, P. C.; Bhaskar, V.; Bromfield, K. M.; Dodd, A. M.; Duggan, P. J.; Duggan, S. A.; McCarthy, T. D. Synlett 2004, 0791–0794.


**Chapter 3**


**Chapter 4**


Chapter 5

   


   


[7] (a) For the first observation and mechanistic study of acetaldehyde generated from tertiary amine hydrogen-transfer agents used with ruthenium-based polypyridyl complexes, see:


[9] (a) ¹H NMR monitoring showed unidentified by-products as a mixture of polymer material and a homo-alkene, something we speculated result from a reductive amination process, whereby iminium species were reduced onto their corresponding carbonyl. Attempts at purification and ¹⁵N NMR studies did not lead to conclusive identification of by-products.


(b) Although enantioselective, organophotoredox catalysis has been achieved, no such chirality transfer has so-far been observed using only a functionalized photoredox catalyst. For a discussion, see: Zeitler, K. *Angew. Chem. Int. Ed.* **2009**, *48*, 9785–9789.

**Chapter 6.2**


**Chapter 6.3**


**Chapter 6.4**


