Development of New Ruthenium-Catalyzed Carbonylation Reactions for Organic Synthesis
and
RDC Investigation for Structural Analysis of Polychlorinated Molecules

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Publications


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New Developments in the Ruthenium-catalyzed Hydroesterification of Olefins. *Awardee Oral Presentation*
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Abstract

Carbonylation chemistry allows a functionalized C\textsubscript{1}-unit to be introduced onto an organic molecule in convenient ways. This has been extensively studied in the context of hydroformylation reactions and as such, successfully applied in bulk industrial processes. While this reaction presents useful solutions in industrial setting, the requirement for the use of highly toxic and hazardous carbon monoxide in pressurized vessels hampers its broader use in academic and discovery chemistry applications. A conceptually related reaction which can be seen as alternative to hydroformylation is the hydroesterification, which utilizes formate esters as convenient C\textsubscript{1} building blocks for the synthetic process. This transformation has been subject to only limited research which disclosed ruthenium carbonyl clusters as most promising catalysts.

The potential utility of this process in fine-chemical applications prompted us to investigate it more closely. General limitations with respect to harsh reaction conditions and restricted substrate scope led us to explore its general applicability in more complex settings.

In a first instance, we developed a catalytic cascade that involves olefin isomerization and intermolecular coupling to a formate ester I by hydroesterification of the resulting alkene (Scheme I). Both steps in this tandem process are promoted by a single catalyst precursor. By exploiting the inherent selectivity of the catalytic system and tuning its reactivity, we were able to achieve C–C bond formation at a remote position of substituted allylic amides and protected allylic alcohols II. The obtained products III, which are not easily accessed otherwise, were then further developed into lactone and lactam building-blocks IV.

Scheme I: Tandem isomerization-hydroesterification of alkenes.

Key to the success of this reaction is the use of substoichiometric acetic acid in combination with halide additives. Mechanistic probing suggests that generation of an active ruthenium
hydride, formed by addition of acetic acid accelerates the isomerization process and allows both reactions to take place under mild conditions in a cascading fashion. Despite the fast isomerization equilibrium, the stereochemical information of the starting material II is retained and therefore allows preparation of enantiomerically enriched products.

In a second part of this work, we applied the catalyst system formed by ruthenium carbonyl and halide additives to the intramolecular hydrocarbamoylation of allylic formamides V (Scheme II). The reaction allowed rapid access to 2-pyrrolidones VI without the need for directing or protecting groups, in a reaction that showcases complete atom economy. The obtained heterocycles displayed complete retention of stereochemical information at C(5) and good control of the stereochemistry at C(4).

Mechanistic investigations of the reaction point to a key role of the amide N–H bond by enabling the formation of an active ruthenium hydride. This is then suggested to be involved in the alkene hydroruthenation process, enabling the reaction.

In general, the scope of both processes was expanded from previous literature and milder reaction conditions were achieved. Combined with the operational convenience of circumventing the need for pressurized carbon monoxide atmospheres, these features demonstrate the synthetic utility of the current catalytic systems for routine research applications.

Finally, in a collaborative effort, we have explored the use of residual dipolar coupling constants to the stereochemical elucidation of polychlorinated molecules. These intriguing, cytotoxic natural products, which have been associated with seafood poisoning, display a complex stereochemical array of secondary chlorides and alcohols that poses a formidable
challenge to structural analysis. Here we describe our efforts thus far in obtaining structural information from model trichlorinated hexanediols VII and VIII (Figure I) by means of NMR spectroscopy of samples in partially aligned media. While the compounds display good accordance between measured and calculated residual dipolar coupling constants, the RDC data alone does not allow unambiguous assignment of relative stereochemistry. We suggest that the difficulties originate from the flexible nature of these molecules which cannot be easily represented by calculated rigid structures.

Figure I: Model compounds studied for their RDC properties for structural elucidation.
Zusammenfassung


Die potentielle Nützlichkeit der Reaktion im Rahmen von Laborsynthesen veranlasste uns zu ihrer genaueren Untersuchung, besonders auch in der Anwendung auf komplexe und empfindliche Substrate.

Zunächst entwickelten wir eine Kaskadenreaktion, die eine Olefinisomerisierung im Substrat II mit einer intermolekularen Hydroesterifizierung mit dem Ameisensäureester I vereint (Schema I). Beide Teilschritte dieser Reaktionskaskade werden von dem identischen Katalysator katalysiert und ermöglichen in der Summe die Knüpfung einer neuen C-C-Bindung am Terminus von substituierten Allylamiden und geschützten Allylalkoholen. Die so erhaltenen Verbindungen (III) können auf anderem Wege nur schwierig dargestellt werden und lassen sich zudem problemlos in Lacton- und Lactambausteine (IV) umsetzen.

Als Schlüssel zum Erfolg dieser Reaktion erwiesen sich der Einsatz von Essigsäure und Tetrabutylammoniumiodid als substöchiometrische Additive. Mechanistische Untersuchungen konnten zeigen, dass die Anwesenheit von Essigsäure zur Bildung eines
Rutheniumhydrids führt, welches die Olefinisomerisierung beschleunigt und gleichermaßen die anschließende Hydroesterifizierung katalysiert. Unter den milden Reaktionsbedingungen bleibt das im Substrat II vorhandene Stereozentrum im Reaktionsverlauf erhalten und erlaubt so die Darstellung von enantiomerenreinen Produkten.

Im zweiten Teil dieser Arbeit übertrugen wir das entwickelte Katalysatorsystem aus Trirutheniumdodecacarbonyl und Tetrabutylammoniumiodid auf die intramolekulare Hydrocarbamoylierung von allylischen Formamiden V (Schema II). Diese Reaktion erlaubt einen schnellen Zugang zu 2-Pyrrolidonen VI ohne den Einsatz von dirigierenden Gruppen oder Schutzgruppen und besticht damit durch seine Atomökonomie. Die Produkte konnten unter vollständiger Retention der Stereoinformation an C(5) und mit guter Diastereokontrolle am neu aufgebauten Stereozentrum C(4) erhalten werden.

**Schema II: Intramolekulare Hydrocarbamoylierung von allylischen Formamiden.**

Mechanistische Untersuchungen weisen auf eine Schlüsselrolle der amidischen N-H-Bindung hin, indem diese die Bildung eines katalytisch kompetenten Rutheniumhydrids ermöglicht. Dieses wiederum erlaubt schließlich die Aktivierung des Olefins durch eine Hydoruthenierungsreaktion.

In beiden Reaktionen konnten wir im Vergleich zur Literatur sowohl ein deutlich breiteres Substratspektrum umsetzen als auch die Reaktionsbedingungen erheblich mildern. Im Zusammenspiel mit der apparativ einfachen Umsetzbarkeit ohne die Notwendigkeit von Kohlenmonoxid unter Druck, konnten wir die Nützlichkeit dieser Reaktionen im Kontext von Laborsynthesen demonstrieren.

Schließlich haben wir im Rahmen einer Kollaboration die Anwendung dipolarer Restkopplungskonstanten (RDC, residual dipolar couplings) zur Strukturaufklärung

Abbildung I: Modellverbindungen zur Messung ihrer dipolaren Restkopplungskonstanten zur Strukturaufklärung.
**List of Abbreviations**

δ  chemical shift in ppm
Ac  acetyl
Ad  adamantyl
Ar  aryl
atm atmosphere
Bn  benzyl
Boc  *tert*-Butyl carbonyl
brsm based on recovered starting material
Bu  butyl
Bz  benzoyl
calcd calculated
cat. catalyst
COD  cycloocta-1,5-diene
conc. concentrated
Cy  cyclohexyl
DABCO 1,4-diazabicyclo[2.2.2]octane
dba  dibenzylideneacetone
DCM  dichloromethane
dcpp  bis(dicyclohexylphosphino)propane
DIAD  diisopropyl azodicarboxylate
DIBAL  diisobutylaluminum hydride
DIPEA  N,N-diisopropylethylamine
DMAP  4-dimethylaminopyridine
DMF  N,N-dimethylformamide
DMP  *Dess–Martin* periodinane
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>DMSO</td>
<td>dimethylsulfoxide</td>
</tr>
<tr>
<td>dppp</td>
<td>bis(diphenylphosphino)propane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact ionization</td>
</tr>
<tr>
<td>eq.</td>
<td>equivalents</td>
</tr>
<tr>
<td>ESI</td>
<td>electron-spray ionization</td>
</tr>
<tr>
<td>Et</td>
<td>ethyl</td>
</tr>
<tr>
<td>FAA</td>
<td>formic acetic anhydride</td>
</tr>
<tr>
<td>h</td>
<td>hour</td>
</tr>
<tr>
<td>Hex</td>
<td>hexyl</td>
</tr>
<tr>
<td>Imid.</td>
<td>imidazole</td>
</tr>
<tr>
<td>IR</td>
<td>infrared</td>
</tr>
<tr>
<td>l/b</td>
<td>linear to branched ratio</td>
</tr>
<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
</tr>
<tr>
<td>Lit.</td>
<td>literature</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>MALDI</td>
<td>matrix-assisted laser desorption ionization</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectrometry</td>
</tr>
<tr>
<td>NMO</td>
<td>N-methylmorpholine-N-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>o</td>
<td>ortho</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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Abbreviations

PG  protecting group
Ph  phenyl
Phth Phthaloyl
Piv  pivaloyl
PKR  Pausson–Khand reaction
PMP  para-methoxyphenyl
ppm  parts per million
PPN  bis(triphenylphosphine)iminium
PPTS  pyridinium para-toluenesulfonate
Pr  propyl
Py  2-pyridyl
quant.  quantitative
r.t.  room temperature
sat.  saturated
SFC  supercritical fluid chromatography
SPO  secondary phosphine oxide
$t$  tert
TBS  tert-butyldimethylsilyl
TES  triethylsilyl
TFA  trifluoroacetic acid
TFAA  trifluoroacetic anhydride
TFAc  trifluoroacetyl
THF  tetrahydrofuran
TLC  thin-layer chromatography
Ts  para-toluenesulfonyl
UV  ultraviolet
1 Introduction


1.1 Carbonylation Chemistry

The rich chemistry of carbon monoxide and its derivatives is of essential importance in organic chemistry. Its relevance spans a broad range, from essential biological transformations\(^1\) to the large-scale bulk-chemical manufacturing.\(^2\) Most synthetically important applications of CO are in the domain of industrial chemistry, where it is used directly as a gas in various catalytic carbonylation processes.\(^3\) The formal introduction of a carbon monoxide unit, however, is a powerful strategy for adding functionality to an organic substrate in synthetic processes that goes beyond bulk chemical production. In principle, it allows the convenient introduction of a C\(_1\)-unit into a more complex molecule by forming a new C–C bond. Moreover, the newly introduced functionality displays a versatile synthetic handle in the form of a carbonyl unit. It is therefore surprising that most fine-chemical-applications of the carbonylation chemistry are still largely restricted to hydroformylation reactions.

The main reason for limited use of carbon monoxide chemistry in research environment is related to the intrinsic properties of this molecule (Figure 1). Carbon monoxide (1) is a stable colorless and odorless gas with a boiling point of 82 K. The carbon-oxygen bond has a length of 112.8 pm,\(^4\) which corresponds to a typical triple bond (e.g. 120.3 pm in acetylene) and is polarized towards the carbon with a relatively small dipole moment of 0.122 D.\(^5\) CO can bind to low valent metals to form stable metal carbonyl complexes. As a ligand, it displays a strong π-accepting effect inducing back-donation of electron density from the metal d-orbitals into the carbonyl π* orbital, enhancing the ligand binding strength by synergistic effect.\(^6\) Carbon monoxide can also bind to the heme site in hemoglobin with an affinity higher than that of oxygen, resulting in formation of carboxyhemoglobin (schematic metal binding depicted by 2).\(^7\) For this reason, it is highly toxic and estimated to be responsible for over 50% of fatal poisonings in industrialized countries.\(^8\)
In addition to its toxicity, many reactions with carbon monoxide often require the use of pressurized atmospheres, placing an additional hurdle for its routine employment. In recent years, a few alternative sources of this reagent have emerged, which aim at overcoming the difficulties in handling and storing large quantities of gaseous CO.\textsuperscript{9}

Morimoto\textsuperscript{10} and Shibata\textsuperscript{11} independently reported the use of aldehydes for the \textit{in situ} generation of carbon monoxide (Scheme 1). In those reactions, inexpensive perfluorobenzaldehyde (3) or cinnamic aldehyde 6 could be used and combined with enynes 4 and 7 in rhodium catalyzed Pauson–Khand-type reactions (PKR) to give the cyclopentenones 5 and 8 respectively. Moreover, these reaction sequences could be rendered asymmetric by the use of chiral bisphosphine ligands for the rhodium catalyst.\textsuperscript{12}

\textit{Morimoto (2002)}

\[ \text{C}_6\text{F}_{5}CH} \]

\[ \text{PhC} \equiv \text{CH} \]

\[ \text{[Rh(COD)Cl]}_2 (5 \text{~mol\%}) \quad \text{dppp (11 \text{~mol\%})} \]

\[ \text{xylene, 130°C, 60 h, constant N}_2 \text{~purge, 97\%} \]

\[ \text{Ph} \]

\[ \text{EtOC} \]

\[ \text{O} \]

\[ \text{EtOC} \]

\[ \text{O} \]

\[ \text{Morimoto (2002)} \]

\textit{Shibata (2002)}

\[ \text{BrO} \equiv \text{CH} \]

\[ \text{[Rh(dppp)Cl]}_2 (5 \text{~mol\%}) \]

\[ \text{neat, 120°C, 8 h, 63\%} \]

Scheme 1: Use of aldehydes as CO-source in PKRs.
The inherent reactivity of the rhodium catalyst, which is capable of inserting into aldehyde C–H bonds, is the key feature for the success of this reaction (Scheme 2). The sequence is suggested to begin with insertion of the rhodium catalyst into the aldehyde C–H bond (9) to give acyl-rhodium 10. Extrusion of CO can then take place to furnish complex 11 which suffers reductive elimination to yield rhodium carbonyl 12. Complex 12 can then efficiently transfer the carbon monoxide unit to oxidatively cyclized compound 14 followed by migratory insertion into metal-bound CO to give 15. Reductive elimination from this complex then furnishes the PKR product 16. Similar systems have also been developed to employ formaldehyde as a source of both carbon monoxide and hydrogen (syngas). In this way, it was employed in Pauson–Khand-type\textsuperscript{13} and hydroformylation reactions.\textsuperscript{14}

![Scheme 2: Proposed mechanism of the PKR with in situ generated CO.](image)

Other sources of carbon monoxide that have been used to circumvent the need for gaseous CO are metal carbonyls. In this respect, molybdenum hexacarbonyl Mo(CO)\textsubscript{6} has been employed as CO-source for the aminocarbonylation of aryl halides (Scheme 3). In his report, Larhed\textsuperscript{15} demonstrated the compatibility of the palladium catalyzed carbonylation of aryl iodide 17 with subsequent trapping by aniline 18, employed in excess. The reaction was shown to benefit from microwave irradiation and gave the product in good yield. More recently, the group of Roberts\textsuperscript{16} has shown that iodobenzene 20, as well as other aryl iodides can engage in aminocarbonylation with excess pyrrolidine 21 in absence of palladium catalyst by employing stoichiometric Mo(CO)\textsubscript{5}ClEt\textsubscript{4}N. This can be obtained by simple heating of Mo(CO)\textsubscript{6} and Et\textsubscript{4}NCl and is suggested to serve both as promoter for the activation of the C–I bond as well as source of CO in the reaction.
While the methods exposed above obviate the need for handling gaseous CO, they are limited with respect to their applications by the *in situ* generation method chosen. CO-consuming catalytic systems that are envisioned to be coupled with such methods must also be robust enough to be compatible with the CO-producing pathways. Modern strategies of “on demand” CO-generation have therefore focused on the *ex situ* release of carbon monoxide gas in physically separated chambers. The group of *Skrydstrup* has disclosed new reagents for the generation of CO in two chamber setups. In 2011 they reported the use of fluorene-derived reagent 23, capable of undergoing palladium-catalyzed decarbonylation to give free carbon monoxide along with non-volatile methylene-fluorene 24 (Scheme 4).<sup>9b</sup> The reaction vessel containing the generated CO was connected through its headspace to a second chamber where the CO-consuming palladium-catalyzed aminocarbonylation of *p*-Iodoanisol 25 with *n*-hexylamine 26 to amide 27 was performed.

Scheme 3: Reports of carbonylations using Mo(CO)<sub>6</sub> as CO source.
An additional advantage of the two-chamber system was the possibility of controlling the exact stoichiometry of the generated CO, since the first reaction was shown to take place nearly quantitatively. This also allowed the employment of this strategy for the introduction of isotopically labeled carbonyl units into different substrates, given that labeled 23 could be used as the limiting reagent in the reaction, obviating the need for expensive gaseous labeled CO (typically $^{13}$CO), normally used in excess. In that respect, the same group was also able to expand their methodology to carbonylative \textit{Heck} reactions for the preparation of isotopically labeled compounds\textsuperscript{17} as well as alkoxy carbonylations of aryl-halides.\textsuperscript{18}

Later in 2011 \textit{Skrydstrup} disclosed a revised system for \textit{ex situ} CO-generation utilizing silacarboxylic acid 28.\textsuperscript{19} By treatment with a slight excess of potassium fluoride, 28 was shown to quantitatively release carbon monoxide in a variety of solvents at mild temperatures (Scheme 5). By use of a two-chamber system, the harnessed gas was then employed in slight excess in a range of palladium-catalyzed transformations. Amide 31 could be prepared by aminocarbonylation of aryl iodide 29 with amine 30. Ester 34 was obtained by alkoxy carbonylation of tosylate 32 with alcohol 33. Aryl iodide 25 could be converted to enone 36 or ynone 38 by carbonylative \textit{Heck} reaction with alkene 35 or carbonylative \textit{Sonogashira} reaction with alkyne 37 respectively. Moreover, the same group was also able to employ this reagent (28) to prepare $^{13}$C isotopically labeled compounds of clinical importance.
Scheme 5: Carboxylative reactions utilizing CO generated from reagent 28.

Recently, an alternative strategy for in situ generation of carbon monoxide was disclosed by Manabe (Scheme 6). The process involves the observed ability of 2,4,6-trichlorophenyl formate (39) to undergo base-promoted decarbonylative decomposition into carbon monoxide and the corresponding phenol 40. This reactivity was harnessed in an alkoxy-carbonylation reaction of aryl halides 41 to the corresponding esters 42 – 45. The product esters could then be functionalized into a variety of products by nucleophilic substitution of the electron-poor trichlorophenol moiety.
1.2 Hydroesterification

While the search for ways of generating carbon monoxide, either in situ or ex situ for various reactions has been pursued as an alternative to handling large amounts of CO gas, other surrogates of this reagent have also been considered. A transformation that is conceptually related to industrially ubiquitous hydroformylation but that circumvents the direct use of carbon monoxide is the hydroesterification of alkenes (Scheme 7). This reaction relies on the use of formate esters (46) as CO-equivalents, formally resulting in the addition of the formyl C–H bond across an alkene substrate 47 to give the C1-homologated product ester 48.

Scheme 7: General scheme of the alkene hydroesterification.
1.2.1 **Early developments in Hydroesterification**

Catalytic hydroesterification was first described by Reppe working at BASF in 1953, along with a range of other carbonylation processes. Nickel salts, in particular nickel bromide, were shown to efficiently promote the hydroesterification of alkynes. In these studies, however, a combination of carbon monoxide and aliphatic alcohols was employed to effect the esterification, for example, employing methanol in the preparation of methyl acrylate (50) from acetylene (49) (Scheme 8).

\[
\text{Reppe (1953)}
\]

\[
\text{H} + \text{CO} + \text{MeOH} \rightarrow \text{MeO} \quad \text{30 bar, 150–180 °C, 100 h, 36% conv.}
\]

**Scheme 8: Reppe’s seminal hydroesterification.**

Developments in the industrial application of this process were undertaken in the 1970’s, particularly focused on the use of methanol as the source of the C\textsubscript{1}-unit to be incorporated. It was shown that methanol could act as both the source of the carbonyl unit and the alkoxide incorporated in the product, under ruthenium catalysis. In those cases, however, along with formation of a range of byproducts, the sacrificial use of an excess olefin was required to effect the formal oxidation of methanol to carbon monoxide (Scheme 9, top).

\[
\text{Shell Oil Co. (1972)}
\]

\[
3 + 2 \text{MeOH} \rightarrow \text{MeO} + 2 \text{C}_2\text{H}_4
\]

\[
\text{Sneeden and Cognion (1983)}
\]

\[
\text{H} + \text{MeO} \rightarrow \text{MeO} \quad \text{190 °C, 20 bar, 18 h, TON = 400}
\]

**Scheme 9: Ethylene hydroesterification.**
In 1983, Sneeden and Cognion showed that methyl formate could be employed in the hydroesterification of ethylene under ruthenium catalysis (Scheme 9, bottom). Decarbonylative decomposition of the methyl formate to methanol and carbon monoxide was also observed as a main competing pathway. In contrast to the system developed using only methanol, however, no sacrificial olefin was required and ethane byproduct was limited to 1%. In their report, Sneeden and Cognion also observed that formates of higher alcohols failed to react and underwent extensive decomposition.

The use of ruthenium carbonyl complexes as catalysts for alkene hydroesterification with formate esters was reported by Keim and Becker in 1989 (Scheme 10, top).24 They showed that under high pressure and temperature in toluene, triruthenium dodecacarbonyl (Ru3(CO)12) is a highly efficient catalyst for the 1:1 reaction of ethylene and methyl formate, yielding methyl propionate. Other olefins screened, however, showed lower reactivity.

In the same year, Watanabe reported that a catalytic system formed by Ru3(CO)12 and trimethylamine oxide as additive was active in the hydroesterification of cyclohexene (51) with benzyl- (52), pentyl- (53) and ethyl- (54) formates to give the corresponding product esters 55, 56 and 57 respectively (Scheme 10, bottom).25 The promoting effect of the amine oxide was attributed to oxidative removal of carbonyl ligands from the ligand sphere of the ruthenium pre-catalyst, leading to formation of a coordinatively unsaturated active species. In their studies they found that high pressures of CO were necessary to promote the reaction and that was explained by dynamic equilibrium of the formate ester with its decarbonylated form, a process that was studied independently.26 Based on this observation, and in accordance with
$^{13}$C label scrambling studies in their previously reported Ru$_3$(CO)$_{12}$-catalyzed hydroacylation reaction, a mechanism was proposed (Figure 2). In this pathway, active catalyst 58 would undergo oxidative addition of the C–H bond of formate ester 59 to give intermediate 60. This would then suffer decarbonylation to give complex 61, which is in equilibrium with complex 62 by ligand loss. It was therefore proposed that this equilibrium can be kept on the side of carbonyl complex 61 by use of high pressures of CO in the reaction mixture. Alkene insertion of the olefin 63 onto complex 61 then generates alkyl-ruthenium 64, which can undergo re-insertion of its carbonyl ligand, either onto the alkoxy ligand to give acyl complex 65 or onto the alkyl chain to give intermediate 66. Finally, reductive elimination would yield the product 67 and regenerate the active catalyst 58.

![Figure 2: Mechanism of the hydroesterification proposed by Watanabe.](image)

The use of ruthenium clusters for the hydroesterification with formate esters was later expanded to include $\alpha,\beta$-unsaturated esters and norbornene (68) as substrates. In the latter case, reported by Kondo and Mitsudo, the use of a catalyst system comprised of [PPN][Ru$_3$H(CO)$_{11}$] with added PCy$_3$ was shown to yield the desired products 71–73 without the need for carbon monoxide atmosphere (Scheme 11) (PPN: bis(triphenylphosphine)-imminium). The reaction conditions, however, remained harsh, with a reaction temperature of 170 °C in pressurized vessels, utilizing two-fold excess of the alkene component 52, 69 or 70.
Kondo and Mitsudo (1999)

Scheme 11: Hydroesterification of norbornene using [PPN][Ru3H(CO)11].

1.2.2 Directing-group assisted Hydroesterification

The harsh conditions required for the intermolecular hydroesterification can, in general, be traced back to the need to prevent or reverse formate ester decarbonylation. This problem has also been of major importance in the development of intermolecular hydroacylation chemistry. To date, only a restricted number of strategies exist to prevent this decomposition process in hydroacylation. Most notably, this is achieved by the use of chelating groups such as phenols, thioethers and pyridines that stabilize the acyl-metal intermediates, preventing decarbonylation.

The chelation strategy developed for intermolecular hydroacylation was successfully employed by Chang in hydroesterification chemistry (Scheme 12). In his studies, he reported that formate ester reagent derived from 2-pyridylmethanol, could efficiently transfer the carbonyl unit to simple olefins using Ru3(CO)12 as catalysis. The use of reagent presented a significant improvement as reactions could be conducted at lower temperature (135 °C) and without the need for pressurized vessels. The products of the reaction were obtained in good yields and modest to good linear-to-branched ratios depending primarily on the steric bulk of the substrate alkene. The study was mainly limited to terminal olefins and the substrates had to be employed in large excess for efficient reactivity. The method was also later expanded to include simple alkynes and dienes as substrates.
The same group was later able to show that reagent 74 is also a competent substitute for carbon monoxide in the alkoxy carbonylation of aryl halides (Scheme 13). In their study, they employed a dual catalytic system involving ruthenium carbonyl for activation of the formate C–H bond and palladium catalyst for the oxidative addition into the aryl-halide. It was suggested that the ruthenium catalyst 84 promotes the decarbonylation of reagent 75 to 2-pyridyl-methanol (86) and carbon monoxide by activation of the C–H bond via intermediate 85. The released compounds would then enter the palladium catalyzed cycle in converting aryl halide 89 into ester 90. With this system, aryl iodides and bromides, used in excess, were successfully carbonylated in good yields.
Chang’s strategy was employed by Floreancig in the one-pot preparation of lactones from terminal alkenes bearing alcohol groups (Scheme 14, top). In this study, the authors employed NMO as an activating agent to promote the reaction, in analogy to the activation reported by Watanabe in 1989 with trimethylamine oxide. The one-pot procedure was made possible by treating the reaction mixture with aqueous acid after the reaction to promote intramolecular displacement of the pyridyl auxiliary. While the study provided useful observations with regard to substrate compatibility of the reaction, it was limited to only a few examples. Additionally, isomerization of the alkene towards the more stable, internal position was observed in a few cases, hampering the application of this strategy to more complex systems.
The first synthetic application of reagent 75 was reported by the same group in their synthetic studies towards Integramycin (99) (Scheme 14, bottom). The method was employed at an early stage onto alkene 96 which was obtained by Duthaler–Hafner crotylation of a suitable aldehyde precursor which set the required stereocenters. The one-step homologation-lactonization then allowed for quick access to the acetal portion (98) of Integramycin (99).

An analogous strategy was applied by Forsyth in the total synthesis of GEX1A (102) (Scheme 15). Here, again, the required stereocenters were set by asymmetric crotylation of a lactate derivative to give alkene 100. This was then homologated by hydroesterification of the alkene using Chang’s auxiliary approach, yielding directly the cyclized product, lactone 101 in modest yield. This was then further developed into the target product GEX1A (102).
The group of Chang reported on an improved version of their auxiliary-mediated hydroesterification by the addition of halide ions. The study was driven by previous investigations by Lavigne on the promoting effect of chloride ions in ruthenium-cluster catalyzed ethylene hydroesterification. In a broad screen for additives, they found that tetrabutylammonium iodide (Bu₄NI) significantly accelerated the hydroesterification of simple alkenes, allowing the reaction to take place at lower temperatures. In the case of terminal monosubstituted olefins, the catalytic system formed by Ru₃(CO)₁₂ and Bu₄NI (1:3 ratio) was able to perform the hydroesterification with reagent 75 at temperatures as low as 70 °C in DMF.

In summary, recent developments in the hydroesterification reaction have allowed this process to be applied under increasingly mild conditions. In particular, the use of ruthenium carbonyl clusters and the chelation approach have provided significant improvements. The reaction presents a viable alternative to the use of carbon monoxide gas for the integration of C₁-units into organic substrates, circumventing the need for hazardous high-pressure operations. Finally, while the substrate scope investigated under the current catalytic systems is modest, it provides the ideal starting point for uncovering the applicability of this transformation in more complex synthetic settings.
1.3 Hydrocarbamoylation

Another alternative strategy that potentially circumvents the need for carbon monoxide in a carbonylation reaction is the hydrocarbamoylation of olefins (Scheme 16). This reaction involves the use of formamides as surrogates for carbon monoxide, and allows molecules to be functionalized with an amide, while adding the desired C1-unit to the carbon framework. Because it is closely related to the hydroesterification, these processes have often been studied in parallel, although each one presents a unique set of challenges. To date, however, only two main catalyst systems have been disclosed for effecting this transformation; ruthenium-carbonyl clusters or low valent nickel catalysts in combination with Lewis acids.

![Scheme 16: General scheme of the alkene hydrocarbamoylation.](image)

1.3.1 Ruthenium-Catalyzed Hydrocarbamoylation

The first incorporation of a formamide into an alkene substrate to be catalyzed by a ruthenium carbonyl cluster was reported by Watanabe in 1987 (Scheme 17). The use of cluster catalysts presented a major improvement over previous systems and allowed efficient coupling of amide with an excess of alkene. In the study, Ru3(CO)12 was the only competent catalyst in a number of surveyed complexes and could be used in as low as 1 mol% loading. The reaction efficiently delivered desired amides although poor linear to branched ratios were observed (typically 1.5:1). In these studies, the authors observed the need for pressurized carbon monoxide atmosphere although further increased pressures inhibited the process, potentially by saturation of the coordination sphere of the catalyst.
The mechanism of the reaction is believed to proceed via oxidative addition of catalyst \( \text{Ru}_3(\text{CO})_{12} \) into the C–H bond of formamide \( \text{HCONH}^+ \) to give hydrido-carbamoyl species \( \text{Ru}(\text{CO})_8 \) (Figure 3). Migratory insertion of olefin \( \text{R}^1\text{R}^2\text{C} = \text{O} \) into the Ru–H bond affords intermediate \( \text{Ru}(\text{CO})_9 \) and subsequent reductive elimination gives amide product \( \text{R}^1\text{R}^2\text{CONH}^+ \) and regenerated catalyst \( \text{Ru}_3(\text{CO})_{11} \).

Figure 3: Proposed catalytic cycle for the hydrocarbamoylation.

A significant improvement over the previous work was reported by Mitsudo in 1999 (Scheme 18). In particular, the group was able to show that alkene hydrocarbamoylation using formamides did not require pressurized carbon monoxide atmosphere. In their study, they employed a combination of \([\text{PPN}]\text{Ru}_3(\text{CO})_{11}\) and \(\text{PCy}_3\) to effect the reaction of norbornene (68) with a range of formamides 116–119, obtaining the products 120–123 in good yields. The authors suggest that the marked improvement in the reaction is caused by the anionic,
electron-rich nature of the catalyst. The increased electron density at the metal center was proposed to accelerate the C–H oxidation step, although no mechanistic investigation was undertaken. Further improvement of the reaction by the use of ionic liquids was later reported.

Scheme 18: Hydrocarbamoylation of norbornene (68).

An improvement in the intermolecular hydrocarbamoylation reaction could be obtained by applying the chelation approach previously reported for the hydroesterification reaction by Chang (Scheme 19). The use of reagent 124, bearing a pyridyl chelating group, allowed the reaction to take place at significantly lower temperatures than previously achieved, while using cheap, commercially available Ru₃(CO)₁₂ as catalyst. Alkenes 125–128 were used in excess but products 129–132 were obtained in good linear to branched selectivity.

Scheme 19: Auxiliary-assisted hydrocarbamoylation.
1.3.2 Nickel/Lewis Acid-Catalyzed Hydrocarbamoylation

In addition to ruthenium carbonyl-catalyzed processes, the hydrocarbamoylation of unsaturated molecules with formamides has been recently disclosed by Nakao and Hiyama under nickel/Lewis acid-catalysis. The method development was based on a previous report that pyridine, when coordinated to a suitable Lewis acid, could be activated at the 2-position and transferred to an alkyne substrate, under low valent nickel catalysis. This type of reaction was then studied for activation of the C–H bond of formamides. The authors showed that a suitable choice of Lewis acid could allow tertiary formamides to be coupled with excess alkynes (Scheme 20). A combination of Ni(COD)$_2$, bulky electron-rich phosphine P(t-Bu)$_3$ as ligand and AlMe$_3$ as Lewis acid was found to promote the hydrocarbamoylation efficiently at 80 °C. Secondary or primary formamides and terminal alkynes were reported to be incompatible with the reaction conditions.

The same group recently reported on an extension of their strategy to allow the intermolecular hydrocarbamoylation of terminal, monosubstituted alkenes (Scheme 21). The use of an N-heterocyclic carbene ligand for the nickel catalyst proved essential for efficient catalytic activity, although the active complex could be formed in situ. Under their optimized conditions, simple terminal alkenes (used in excess) could be hydrocarbamoylated with tertiary alkyl-substituted formamides to give the desired products in good yields and complete linear (i.e. anti-Markovnikov) selectivity.
The reaction is suggested to proceed via Lewis acid activation of formamide 145, which facilitates oxidative addition of low-valent nickel catalyst 147 into the formamide C–H bond to give acyl-nickel 148 (Figure 4).\textsuperscript{52} Complexation of the olefin to give intermediate 149 followed by hydronickelation would then furnish alkyl-nickel intermediate 150. Finally, reductive elimination would form product amide 151 and regenerate the nickel catalyst 147.

Figure 4: Proposed mechanism of nickel-catalyzed hydrocarbamoylation.
The intramolecular hydrocarbamoylation with formamides was initially reported by Nakao and Hiyama for two isolated substrates. Concurrently to our work, this strategy was recently expanded by Cramer and rendered asymmetric by the use of chiral secondary phosphine oxide (SPO) ligands (Scheme 22). Under these conditions, suitably protected terminal homoallylic formamides could be subjected to exo-cyclization to give methyl-substituted pyrrolidones with good degree of stereocontrol. In the case of bis-allylated formamides, the catalyst was capable of discriminating between the two enantiotopic alkenes to give lactam products in good diastereo- and enantioselectivities.

Scheme 22: Asymmetric nickel-catalyzed hydrocarbamoylation.

In their work, the group of Cramer suggests a mode of formamide C–H activation carried out by a hetero-bimetallic catalyst formed in situ (Figure 5). The SPO ligand, in its phosphinous acid tautomer form, is suggested to act as tether for both the nickel and the aluminum Lewis acid entities, leading to formation of intermediate. The chelation of both metals is suggested to aid in the C–H activation process by placing the low-valent nickel metal center in close proximity to the formamide. The tight geometry of the intermediate is then further believed to enable good enantiodiscrimination in the hydrometallation step.
Related carbonylation processes for the installation of amide functionality into an olefin substrate by C–C bond formation have been reported in the literature. Most notably, hydroformylation conditions have been applied to accomplish this task using palladium\textsuperscript{53} or rhodium\textsuperscript{54} catalysts (Scheme 23). In those cases, an amine nucleophile has been used to capture acyl-metal species 160 formed by hydroformylation of olefin 159, leading to formation of amides 162. These transformations, however, require high pressures of syngas (CO/H\textsubscript{2}) in carefully controlled ratios to proceed effectively, given that this is the primary source of the C\textsubscript{1}-unit to be incorporated into the substrate. Moreover, most applications of this strategy have so far been limited to alkynes as substrates and using anilines as nucleophiles.\textsuperscript{55}

\[ \text{Scheme 23: General scheme for hydroaminocarbonylation under hydroformylation conditions.} \]

The hydrocarbamoylation of olefins with formamides has also been reported to proceed via free-radical cascade (Scheme 24). Originally described by Friedman and Shechter,\textsuperscript{56} this reaction is proposed to proceed by homolytic bond cleavage of the formamide C–H bond of formamide 163 by a suitable radical initiator to give radical species 164. Radical addition across the olefin substrate 165 would then furnish intermediate 166 which would terminate the sequence by hydrogen abstraction from a suitable donor to give product amide 167. In

\[ \text{Scheme 24: Proposed mechanism for hydoro-carbamoylation of olefins.} \]
their original system, the authors employed tert-butylperoxide at 130 °C to perform the activation of \(N,N\)-dimethylformamide, and tert-butylformamide which were incorporated into simple aliphatic terminal alkanes. In this initial report, however, unselective initiation by hydrogen abstraction from the alkyl substituents on amide 163 resulted in varying selectivity. A further improvement on the selectivity of the radical species formation was later reported using iron salts in combination with tert-butylperoxide as initiator.\(^{57}\) Recently, the reaction of formamides with olefins bearing an electron-withdrawing group has been achieved by using photocatalyzed radical generation.\(^{58}\) In this case, tetrabutylammonium decatungstate \((\text{Bu}_4\text{N})_4\text{W}_{10}\text{O}_{32}\) was activated photochemically and used to promote the hydrogen abstraction from the substrate 163. Termination of the reaction cycle would then regenerate the photocatalyst in its resting state through hydrogen abstraction by intermediate 166.

![Scheme 24: Free-radical pathway for hydrocarbamoylation.](image)

In conclusion, while significant recent advances have been reported in the literature, the hydrocarbamoylation remains a difficult process of limited application in preparative synthetic chemistry. In the case of the ruthenium carbonyl cluster-catalyzed reaction, the harsh nature of the reaction conditions precludes its broader applicability. Additionally, the difficulties in elucidating precise catalyst structures further hampers rational catalyst design for this process and developments remain largely empirical.\(^{59}\) In the case of the nickel-Lewis acid catalyzed reaction, applications are restricted to tertiary formamides. The current limitations in the applicability of the hydrocarbamoylation reaction and the poor understanding of the species involved in the ruthenium-catalyzed process have, therefore, propelled us to investigate them.
2 Development of a Tandem
Isomerization-
Hydroesterification Cascade
2.1 Concept and Initial Observations

At the outset of our investigations, we recognized the potential of carbonylation and particularly hydroesterification chemistry within fine chemical preparation. To our surprise, however, we found the field largely underexplored, particularly regarding applications in the complex settings we contemplated. Given the several practical advantages of the hydroesterification reaction for the incorporation of C₁-units into molecular scaffolds, we set out to explore the applicability of this transformation in molecules bearing functionality that would allow for their further development into useful building blocks within chemical synthesis.

Initial experiments relied on the assumption that more complex substrates could only be tolerated if the reaction conditions were mild. For this reason, the auxiliary-mediated esterification protocol of Chang was chosen as the ideal starting point.³⁵ In particular, when halide additives were employed, the reaction could be performed under remarkably mild conditions (Ru₂(CO)₁₂ as catalyst, Bu₄NI additive, 75 °C in DMF).⁴² However, when we attempted Chang’s hydroesterification with formate reagent 75 on even very simple substrate 4-phenyl-1-butene (168), we observed, alongside with the expected homologated products 169 and 170, the formation of two unexpected products 171 and 172 arising from olefin isomerization (Scheme 25).

![Scheme 25: Alkene isomerizations observed in initial experiments.](image-url)
This observation revealed that the C–C bond forming reaction was competing with preferential olefin isomerization towards the thermodynamically more stable internal and conjugated alkenes. Indeed, the transposition of olefins is a process commonly observed in certain metal-catalyzed reactions, particularly in those involving reversible olefin hydrometalation such as hydroformylation.60

While the observation that Chang’s hydroesterification system was capable of isomerizing alkenes was interesting, it immediately cast doubt upon its applicability to more complex systems. This isomerization also explained the narrow scope of previously reported applications, where the reaction was only applied to alkenes for which transposition of the olefin is blocked at the alpha position (quaternary or aromatic carbon centers), greatly hampered (bridgeheads) or inconsequential to product formation (simple linear alkenes).42 A more peculiar observation, however, was that the C–C bond forming reaction only took place in two out of the four possible positions to give products 169 and 170, while hypothetical esters 173 and 174 resulting from hydroesterification of isomerized alkenes 171 or 172 were not detected. Additionally, it was observed that the process has a large overall preference for the linear product 169, which is in line with previous reports. This overall selectivity can be traced back to exclusive functionalization of the terminal olefin, which must occur prior to isomerization and is thus in competition with the C–C bond forming process.

The observation that terminal alkenes react exclusively, added to the fact that olefin transposition can be effected under these conditions, led us to set our goal of exploring these two reactions in a combined fashion. In line with observations made in industrial processes that exploit tandem isomerization-functionalization cascades,61 we speculated that the hydroesterification system reported by Chang could be tailored for this same purpose. If we could reverse the alkene transposition and thus obtain an equilibrating mixture of olefins, this mixture would then be subject to selective functionalization of the terminal alkene (Figure 6). If the alkene pre-equilibrium between isomers 175 and 176 can be rendered fast by means of the metal catalyst, we proposed that the resulting system would behave analogously to a Curtin–Hammett type regime.62 In this, the thermodynamically less stable alkene isomer 176 would undergo fast hydroesterification to give desired linear ester 177 along with branched byproduct 178. In contrast, the functionalization of alkene 175 to give undesired esters 178 and 179 is a slow process and would be out-competed by the hydroesterification of the
terminal position. Ultimately, this would allow us to obtain the product of a C–C bond formation with a C₁-unit into an unfunctionalized position of the substrate.

![Curtin–Hammett model](image)

Figure 6: Curtin–Hammett model for functionalization of the terminal position of 175.

### 2.2 Choice of Substrate Class

Our long-standing interest in the synthesis of small ring heterocycles\(^{63}\) led us to explore the present transformation as a platform for their preparation. These molecules are useful building blocks for synthetic and early discovery chemistry applications and are present in a range of biologically active compounds.\(^{64}\) Therefore, new methods for their preparation are of high interest. We reasoned that if the substrates used in this cascade contained a nucleophile, this could later be induced to attack the formed ester in intramolecular fashion. This would then result in the formation of the desired heterocycle. In this respect, we chose to study the present strategy for the preparation of 6-membered lactams, which one could envision arising from the selective functionalization of allylic amines (Scheme 26). The required starting materials can be accessed by a range of methods and, moreover, can be obtained in enantiomerically enriched form by direct asymmetric synthesis,\(^{65}\) by a chiral pool approach or by kinetic resolution of racemic mixtures.\(^{66}\)
2.3 Initial Optimization

Based on reports from the literature,\textsuperscript{35,42} it was far from clear if the substrates proposed would be compatible with the reaction conditions for the carbonylation. Initial attempts at employing free allylic amines \textbf{185} failed and no conversion was observed, which was attributed to catalyst poisoning by the substrate. Our initial studies therefore involved the use of model substrate \textbf{186} which features a phthalimide protected amine. This protecting group was expected to effectively deactivate the amine towards undesired reactivity by masking both the nitrogen lone pair and the N–H bonds (Scheme 27).

We applied the optimized conditions reported for the auxiliary catalyzed hydroesterification to substrate \textbf{186}, taking advantage of the reported halide additive effect (Ru\textsubscript{3}(CO)\textsubscript{12} as catalyst, Bu\textsubscript{4}NI additive, 75 °C in DMF).\textsuperscript{38,42} We chose, however, to utilize the olefin component as the limiting reagent as this was more valuable (Table 1, entry 1). This departure from the originally reported conditions for simple hydroesterification presents an additional challenge since formate reagent \textbf{182} might require an excess of olefins to prevent its decarbonylation (Scheme 28). Upon activation by the metal catalyst through oxidative

\begin{align*}
\text{Scheme 26: Concept for the synthesis of lactams from allylic amines.}
\end{align*}
addition into the C–H bond, the species 187 is presumably formed. In the presence of sufficient olefin substrate 188, this can then react to give hydroesterification product 189. In the absence of an alkene, however, the species 187 can alternatively undergo decarbonylation to give 190 and ultimately, through ligand loss, yield complex 191. This decarbonylative pathway consumes the active reagent 182 and prevents it from entering the productive hydroesterification pathway. In anticipation of this problem, we chose to use this reagent in two-fold excess while employing more valuable alkene 188 as the limiting reagent.

Scheme 28: Potential reaction pathways of formate ester 182.

In initial experiments only trace conversion to the desired product was observed (Table 1, entry 1). Fortunately, by increasing the temperature of the reaction to 100 °C, a conversion of 26% was achieved, which corroborated our cascade hypothesis and provided a reasonable entry point for further optimization (entry 2). We then set out to screen a range of catalysts and conditions reported for related transformations.

During this survey we found that only ruthenium carbonyl cluster was competent in this transformation (entry 2). Other metal catalysts based on iridium, rhodium and palladium, showed no reactivity in this case and both starting materials and reagents were re-isolated quantitatively (entries 7–12). It is noteworthy that cluster complexes analogous to ruthenium carbonyl such as Fe₂(CO)₉, Fe₃(CO)₁₂ and Os₃(CO)₁₂ showed some form of activity. More specifically, the iron complexes resulted in complete decarbonylation of reagent 75 with no change to substrate 186, when the reaction was carried out in DMF at 135 °C (entries 3 and 4). Triosmium dodecacarbonyl (Os₃(CO)₁₂) on the other hand, showed some conversion of the substrate 186 to product 192 under these conditions (entry 13). This observation led us to conclude that the multinuclear nature of the catalyst is of key importance.
for reactivity and can be explained by the higher stability of these catalysts under heat which is a common feature of metal clusters, when compared to their mononuclear counterparts.\(^{59}\)

**Table 1: Initial observation and selected screened catalysts.\(^{[a]}\)**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Solvent</th>
<th>T [°C]</th>
<th>Conversion of 186(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ru(<em>3)(CO)(</em>{12})(^{[c]})</td>
<td>DMF</td>
<td>75</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>Ru(<em>3)(CO)(</em>{12})(^{[c]})</td>
<td>DMF</td>
<td>100</td>
<td>26%</td>
</tr>
<tr>
<td>3</td>
<td>Fe(_2)(CO)(_9)(^{[c]})</td>
<td>DMF</td>
<td>135</td>
<td>-(^{[d]})</td>
</tr>
<tr>
<td>4</td>
<td>Fe(<em>3)(CO)(</em>{12})(^{[c]})</td>
<td>DMF</td>
<td>135</td>
<td>-(^{[d]})</td>
</tr>
<tr>
<td>5</td>
<td>Fe(_2)(CO)(_9)(^{[c]})</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>Fe(<em>3)(CO)(</em>{12})(^{[c]})</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>[Ir(CO)(_3)Cl]</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>[Ni(COD)(_2)]</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>[Rh(C(_2)H(_4)(_2)Cl)(_2)]</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>[Rh(COD)(_2)]BF(_4)</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Pd(_2)(dba)(_3)</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>Pd(OAc)(_2)</td>
<td>Toluene</td>
<td>100</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>Os(<em>3)(CO)(</em>{12})(^{[c]})</td>
<td>DMF</td>
<td>135</td>
<td>trace</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Conditions: substrate \textbf{186} (0.40 mmol), reagent \textbf{75} (2.0 eq.) and catalyst (10 mol\%) were suspended in the appropriate solvent (0.60 M) under argon in a septum-capped vial and stirred at the indicated temperature for 16 h. \(^{[b]}\) Conversion was determined by integration of the crude \(^1\)H-NMR against an added standard (1,4-dimethoxybenzene). \(^{[c]}\) Reaction was carried out using Bu\(_4\)N\(_I\) (15 mol\%) as an additive. \(^{[d]}\) complete reagent decarbonylation was observed. COD = 1,5-cyclooctadiene, dba = dibenzylideneacetone, Py = 2-pyridyl.

Recognizing the unique performance of ruthenium carbonyl in this process, we turned our attention to screening for solvents and additives that could improve the reaction outcome (Table 2). In our preliminary search for suitable conditions to promote the reaction we
observed that polar solvents such as DMF and DMSO (entries 1 and 2) yielded superior results over apolar toluene (entry 3). Omitting the halide source, tetrabutylammonium iodide, lead to a completely inactive system and only starting materials could be isolated (entry 4). We also chose to study the effect of other potential ligands for the ruthenium catalyst.

### Table 2: Selected additive and solvent screen for phthalimide substrate.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Solvent</th>
<th>Conversion of 186[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bu(_4)NI</td>
<td>DMF</td>
<td>26%</td>
</tr>
<tr>
<td>2</td>
<td>Bu(_4)NI</td>
<td>DMSO</td>
<td>23%</td>
</tr>
<tr>
<td>3</td>
<td>Bu(_4)NI</td>
<td>Toluene</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Bu(_4)NI, IPrHCl</td>
<td>DMF</td>
<td>33%</td>
</tr>
<tr>
<td>6</td>
<td>Bu(_4)NI, IPr</td>
<td>DMF</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Bu(_4)NI, LiCl</td>
<td>DMF</td>
<td>33%</td>
</tr>
<tr>
<td>8</td>
<td>Bu(_4)NI, water</td>
<td>DMF</td>
<td>37%</td>
</tr>
<tr>
<td>9</td>
<td>Bu(_4)NI, water</td>
<td>DMSO</td>
<td>32%</td>
</tr>
<tr>
<td>10</td>
<td>Bu(_4)NI</td>
<td>water</td>
<td>17%</td>
</tr>
<tr>
<td>11</td>
<td>Bu(_4)NI, IPrHCl, water</td>
<td>DMF</td>
<td>58%[d]</td>
</tr>
<tr>
<td>12</td>
<td>Bu(_4)NI</td>
<td>DMF</td>
<td>90%</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate 186 (0.40 mmol), reagent 75 (2.0 eq.), Ru\(_3\)(CO)\(_{12}\) (10 mol%) and the additive (15 mol%) were suspended in the appropriate solvent (0.60 M) under argon in a septum-capped vial and stirred at 100 °C for 16 h. [b] Conversion was determined by integration of the crude \(^1\)H-NMR against an added standard (1,4-dimethoxybenzene). In all cases, the branched regioisomer was observed in less than 10% relative to the linear product. [c] IPr was obtained by suspending IPrHCl in THF and treating it with NaH, filtering off the salts and evaporating the solvent prior to addition of all other reaction components. [d] Significant formation of the branched product was observed. Ratio of linear/branched 3:1. [e] Reaction carried out at 135 °C. IPrHCl = 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride; Py = 2-pyridyl.
The use of Arduengo-type NHC-carbene ligands\textsuperscript{70} had been reported and extensively studied by Cabeza in reactions of ruthenium carbonyl clusters.\textsuperscript{71} These ligands show stronger binding to ruthenium clusters than the parent carbonyl ligand, while displaying increased steric demand. We speculated that such ligands could increase the selectivity of the reaction due to the increased steric demand around the metal center which would result in enhanced steric discrimination between linear and branched positions of the substrate alkene \textsuperscript{186}. We were pleased to observe that when we employed the prototypical IPrHCl salt as a ligand precursor in the reaction, a slight increase in conversion could be obtained (Table 2, entry 5). To our dismay, however, control experiments utilizing the \textit{in situ} generated free carbene IPr showed no activity (entry 6). Moreover, when the reaction was conducted in the presence of LiCl instead of the carbene salt (entry 7), the same increase in conversion was observed, which suggests that the halide counter-ion (chloride) promotes the reaction, rather than the NHC ligand.

We were also interested in studying the effect of added water to the reaction mixture for its potential to engage in a ruthenium-catalyzed water-gas shift reaction\textsuperscript{72} and generate a reactive ruthenium hydride ate-complex (Scheme 29). Indeed, the use of catalytic amount of water (15 mol\%) resulted in improved conversion in both DMF and DMSO solvents (Table 2, entries 8 and 9) while performing the reaction purely in water resulted in diminished conversion (entry 10).

\begin{center}
\begin{tikzpicture}
  \node (a1) at (0,0) {[Ru]\textsubscript{2}CO};
  \node (a2) at (1.5,0) {OH\textsuperscript{-}};
  \node (a3) at (3,0) {H\textsuperscript{+}};
  \node (a4) at (4.5,0) {[Ru]};
  \node (a5) at (6,0) {CO\textsubscript{2}};
  \node (a6) at (7.5,0) {H\textsuperscript{+}};
  \node (a7) at (9,0) {[Ru\textsubscript{4}]};

  \draw [->] (a1) to (a2);
  \draw [->] (a2) to (a3);
  \draw [->] (a3) to (a4);
  \draw [->] (a4) to (a5);
  \draw [->] (a5) to (a6);
  \draw [->] (a6) to (a7);
\end{tikzpicture}
\end{center}

\textbf{Scheme 29: Proposed activation of the ruthenium catalyst by water.}

Interestingly, when all additives were combined (Bu\textsubscript{4}NI, IPrHCl and water, 15 mol\% each), an overall higher conversion of the starting material \textsuperscript{186} was observed (entry 11). Unfortunately, in this case, the appearance of the regioisomeric, branched product as a major side-product of the reaction (linear/branched ratio 3:1) undermined its further development. Finally, by increasing the temperature from 100 °C to 135 °C in DMF, we were able to obtain good conversion (90\%) for the desired cascade on allylic phthalimide \textsuperscript{186} without the need for additives other than Bu\textsubscript{4}NI (entry 12).
2.4 Note on the Additive Effect on Regioselectivity

To assess the effects of water and IPrHCl on regioselectivity of the C–C bond-forming step, these additives were studied in the hydroesterification of styrene (193), reported in the literature (Table 3). This simple system allowed us to quickly identify the NHC ligand as problematic for the selectivity of the reaction. For instance, in cases where NHC ligand (15 mol%) was added to the reaction mixture, the linear-to-branched ratio was eroded to 1:1 (entries 2 and 4). In contrast, the addition of water, alone or in combination with IPrHCl, to the mixture (15 mol%) had no effect on the regioisomeric ratio (entries 2 and 3) and the ratio of products 194 and 195 was identical to that of the reactions in absence of water.

Table 3: Additive effect on regioselectivity in styrene.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Yield [b]</th>
<th>l/b ratio [c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>96%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>2</td>
<td>IPrHCl, water</td>
<td>94%</td>
<td>1 : 1</td>
</tr>
<tr>
<td>3</td>
<td>water</td>
<td>88%</td>
<td>3 : 1</td>
</tr>
<tr>
<td>4</td>
<td>IPrHCl</td>
<td>94%</td>
<td>1 : 1</td>
</tr>
</tbody>
</table>

[a] Conditions: styrene (193) (0.40 mmol), reagent 75 (2.0 eq.), Ru3(CO)12 (10 mol%), Bu4NI (15 mol%) and additive (15 mol%) were suspended in DMF (0.60 M) under argon in a septum-capped vial and stirred at 135 °C for 16 h. [b] Yield determined by 1H-NMR against an added standard (1,4-dimethoxybenzene). [c] Regioisomeric ratio determined by integration of the 1H-NMR signals of the crude mixture. IPrHCl = 1,3-bis(2,6-diisopropylphenyl)-1H-imidazol-3-ium chloride; Py = 2-pyridyl.

This seemingly unexpected result is surprising, because the increased steric demand of the metal center, bearing the bulky ligand IPr, would be expected to increase steric discrimination of the olefin position during hydrometalation. We can speculate, however, that the increased steric demand can accelerate reductive elimination from the more hindered, branched
position, which would lead to decreased selectivity. Finally, for this to be true, the hydoruthenation step must be fast and reversible, which is also a requirement for a fast alkene isomerization process and thus fits our Curtin–Hammett model for this cascade.

2.5 Screening of Protecting Groups

While the search for suitable additives to promote this reaction at temperatures lower than 135 °C yielded valuable information about the catalytic system, it failed to yield conditions that globally improved the reaction outcome (Table 2, entry 12). We therefore turned our attention to the substrate class, attempting to improve and expand the range of molecules that can undergo this transformation. The key structural element we were interested in varying was the nitrogen protecting group. Although the phthalimide group had been selected in the beginning for its stability, we were now interested in identifying alternative groups that would allow for more selective removal under preferably milder and/or orthogonal conditions. Along these lines, a variety of protecting groups were installed into a common motif and the resulting substrates were subjected to the hydroesterification reaction (Scheme 30).
Yields of the isolated products after flash chromatography. n.p. = no product observed. [a] contains 10% of inseparable branched regioisomer. [b] sluggish reaction; yield of a mixture of regioisomers determined by $^1$H-NMR. [c] yield given is of the pure linear regioisomer; yield of the isolated branched product is given in parenthesis.

**Scheme 30: Protecting group compatibility assessment.**

In these experiments we found that substrates 196b–d bearing toluenesulfonyl group, as well as labile carbamates prone to reductive cleavage such as Fmoc and Cbz were not compatible with the reaction conditions and yielded complex mixtures of compounds. Moreover, substrate 196e bearing a Troc-group (2,2,2-trichloroethoxy carbamate) was also incompatible with the reaction, possibly due to reductive cleavage by oxidative addition of the low-valent ruthenium into its C–Cl bond, giving the free amine. This is analogous to the standard mode of cleavage for this protecting group, which utilizes low-valent zinc.\[^{73}\] In contrast, substrates 196f and 196g with more stable carbamates Boc and methoxy carbamate respectively, both yielded the desired products and were compatible with the reaction conditions. Finally, we observed that substrates with amide groups such as benzamide 196h, acetamide 196i and trifluoroacetamide 196j provided the best results, yielding products in clean transformations and the best yields observed thus far. The latter was chosen for further optimization, given its ease of installation and deprotection under mild conditions. This group also provides a useful
handle for monitoring the reaction due to the presence of fluorine. Therefore it can be conveniently monitored by $^{19}$F-NMR which, given its high resolution, allows one to easily follow consumption of the starting material and product formation.

We next optimized the catalyst loading under the previously established conditions with olefin 196j (Table 4, entry 1). We found that reducing the loading of ruthenium carbonyl (Ru$_5$(CO)$_{12}$) from 10% to 5% resulted in no significant erosion of conversion (entry 2). Further reduction of the catalyst loading to 3% or lower, however, led to significantly reduced conversion of the starting material 196j (entries 5–7), while still resulting in complete decarbonylation of the remaining excess formate reagent 75. Also noteworthy is that reducing the amount of added halide salt tetrabutylammonium iodide below 15 mol% resulted in sluggish conversion (entry 3). Increasing it above this amount, however, resulted in slightly eroded conversion (entry 4). The decrease of activity observed at lower ruthenium loadings can be attributed to a turnover limitation of the active catalyst. The observation that in all cases the excess formate reagent 75 was consumed by decarbonylation suggests that this process can be promoted by a species that is inactive in catalyzing the desired reaction pathway.
### Table 4: Catalyst loading screen.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat. Loading</th>
<th>Conversion [b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 mol%</td>
<td>&gt; 95 %</td>
</tr>
<tr>
<td>2</td>
<td>5 mol%</td>
<td>&gt; 95 %</td>
</tr>
<tr>
<td>3</td>
<td>5 mol% [c]</td>
<td>67%</td>
</tr>
<tr>
<td>4</td>
<td>5 mol% [d]</td>
<td>90 %</td>
</tr>
<tr>
<td>5</td>
<td>3 mol%</td>
<td>60 %</td>
</tr>
<tr>
<td>6</td>
<td>2 mol%</td>
<td>52 %</td>
</tr>
<tr>
<td>7</td>
<td>1 mol%</td>
<td>31 %</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate \textbf{196j} (0.40 mmol), reagent \textbf{75} (2.0 eq.), \textit{Ru}_3(CO)_{12} (indicated amount) and Bu$_4$NI (15 mol%) were suspended in DMF (0.60 M) under argon in a septum-capped vial and stirred at 135 °C for 16 h. [b] Conversion determined by $^{19}$F-NMR against an added standard (trifluoromethylbenzene). [c] Reaction conducted using only 5 mol% Bu$_4$NI. [d] Reaction conducted using 30 mol% Bu$_4$NI. Py = 2-pyridyl.

## 2.6 Substrate Preparation

Driven by our interest in the resulting products of the cascade, we selected allylic amides as substrates. In particular, their potential in the synthesis of heterocycles by cyclization to the lactams was appealing. Their use, however, is only advantageous if efficient strategies for their preparation can be employed. In the course of our studies, we explored a variety of routes for the synthesis of allylic amides with the substitution pattern required for the hydroesterification cascade. We were particularly interested in the use of methods that would allow for asymmetric preparation of allylic amines. In that regard, a vast collection of methods for the synthesis of these important scaffolds in optically enriched form exists.\textsuperscript{65a,b}

During optimization of the reaction conditions, we found it useful to access the phthalimide protected allylic amine derived from racemic valinol (\textbf{198}) by a short sequence from this commercially available amino alcohol (Scheme 31). Thus, valinol (\textbf{198}) could be directly
protected by condensation with phthalic anhydride in the melt to yield alcohol 199. Oxidation under Swern conditions\textsuperscript{74} gave aldehyde 200 followed by Wittig olefination to yield the desired allylic amide substrate 186. Other oxidation procedures (Ley oxidation\textsuperscript{75} and Dess-Martin oxidation\textsuperscript{76}) were also successful but the convenience of the Swern protocol for large-scale preparation was ultimately preferred. Valinol (198) can be commercially obtained as either enantiomer and therefore this route enables the preparation of both optically pure enantiomers of the substrate.

\begin{center}
\textbf{Scheme 31: Preparation of olefin 186 from valinol.}
\end{center}

In cases where the substrate could not be derived from an amino alcohol, an alternative route was used for its preparation from an aldehyde precursor (Scheme 32). Hexanal (201) was treated with propynyl lithium to give racemic propargyl alcohol 202. Under Mitsunobu conditions,\textsuperscript{77} the phthalimide unit could be introduced to give propargyl phthalimide 203. Conversion into olefin 196a was achieved by semi-hydrogenation of the alkyne using Lindlar catalyst (5\% palladium on CaCO\textsubscript{3}, lead-poisoned) under an atmosphere of hydrogen.\textsuperscript{78}

\begin{center}
\textbf{Scheme 32: Preparation of olefin 196a.}
\end{center}

The Mitsunobu route described above allowed us to prepare a range of protected allylic amines (Scheme 33). While at first, direct deprotection of the allylic pthalimide 196a under standard conditions using hydrazine\textsuperscript{79} proceeded sluggishly,\textsuperscript{80,81} we found that propargyl phthalimide 203 could be conveniently cleaved under these conditions. The resulting
propargyl amine 204 was then reprotected with a range of different groups and subjected to Lindlar hydrogenation to give the desired substrates.

![Scheme 33: Substrate preparation for protecting group screen.]

Although the route described provided rapid access to gram-quantities of substrates to ascertain the functional group compatibility of the reaction, we turned to alternative routes that would allow us to modify the backbone of the substrate more easily. To this end, we chose Ellman’s strategy for the synthesis of amines by performing a series of [1,2]-additions of organometallic compounds to α,β-unsaturated sulfinyl aldimine 208 (Scheme 34). This was prepared by condensation of crotonaldehyde 206 with racemic Ellman’s tert-butyl sulfinamine 207 as previously reported. A broad range of organometallic nucleophiles have been reported to undergo this addition and allowed us to access a range of products in a short sequence without the need for tedious purification as for the Mitsunobu route. Products 210–215, resulting from the addition of methyllithium, tert-butyllithium, cyclopropylmagnesium bromide, deprotonated acetonitrile (obtained by treatment of MeCN with LDA at –78 °C), vinylmagnesium bromide and phenyllithium were obtained in this short sequence. In addition, this also allowed us to selectively access the substrates bearing an E-alkene, as opposed to the Z-alkene obtained selectively, or preferentially, under either Lindlar or Wittig conditions respectively.
A limitation of Ellman’s strategy is reflected by the poor reactivity of ketimines compared to the related aldimines. While additions to selected ketimines have been reported, they still present a considerable synthetic challenge for the synthesis of α,α-dibranched amines (tertiary carbinamines, i.e. amines placed on a fully substituted carbon center). Preparation of substrates with that structure was therefore achieved from the amino alcohol by protection of the amine as the trifluoroacetamide followed by oxidation and subsequent Wittig reaction (Scheme 35). Aminoalcohol 216, obtained from commercially available TRIS hydrochloride by a reported procedure was treated with ethyl trifluoroacetate in acetonitrile to give trifluoroacetamide 217. Dess–Martin oxidation to give aldehyde 218 followed by Wittig reaction with ethyl-triphenylphosphonium bromide yielded desired olefin 219. Similarly, known trifluoroacetamido-alcohol 220 was subjected to Dess–Martin oxidation to give aldehyde 221. Subsequent Wittig olefination furnished allylic amide 222. This strategy was also used for the synthesis of trisubstituted olefin 225. PCC oxidation of known alcohol to the ketone 224, followed by Wittig reaction afforded olefin 225 along with recovered ketone starting material.
Finally, substrates displaying an oxygen in α-position to the amide were prepared by diversifying alkene 227 obtained from commercially available Garner’s aldehyde 226, through Wittig olefination (Scheme 36). Deprotection and reprotction of the nitrogen in intermediate 227 yielded alcohol 228, which was then protected as the TBS ether 229. Similarly, heterocyclic substrates were obtained. Deprotection of intermediate 227 was followed by acylation with chloroacetyl chloride to give alcohol 230 which was then cyclized by treatment with sodium hydride, leading to intramolecular displacement of the chloride by the alkoxide to give olefin 231. Lastly, deprotection of intermediate 227 was followed by condensation with diethylcarbonate to give oxazolidinone 232.
Scheme 36: Substrates derived from Garner’s aldehyde.

2.7 Brønsted Acid Activation

While the conditions optimized above (Table 4, entry 2) allowed us to obtain the product of the desired cascade in good yield and selectivity it still required relatively high temperature (135 °C) to proceed efficiently. Attempts at lowering this temperature were met with incomplete conversions and sluggish reactions (see below). In our cascade, the hydroesterification step is proposed to take place at the terminal position of the substrate after alkene isomerization. This process, by itself, has been reported to take place at much lower temperatures, from 110 °C to as low as 70 °C. We reasoned that the requirement for higher temperature (135 °C) for the isomerization-hydroesterification cascade in our case was due to a slow isomerization process of the alkene at lower temperatures, a process that must preclude the C–C bond forming step in the overall sequence. We recognized that if this isomerization, which can be viewed as a pre-equilibrium in this cascade, was not taking place at a high enough rate, our proposed Curtin–Hamnett model (Figure 6) would not be operational. We therefore turned our attention to searching for ways to promote this isomerization process under milder conditions.
Ruthenium(II) complexes such as HRuCl(PPh₃)₃, as well as ruthenium(0) cluster compounds such as triruthenium dodecacarbonyl, Ru₃(CO)₁₂, have been shown to promote olefin isomerization.⁹² In the case of ruthenium clusters, two main mechanistic manifolds have been proposed for this transformation (Figure 7).⁶⁷a, ⁹³ The first (pathway A) relies on allylic mechanism, whereby the η₂-olefin-coordinated ruthenium cluster 233 abstracts the allylic proton. The resulting π-allyl complex 234 then undergoes formal reductive elimination of the hydride at the opposite side of the allyl system to yield the formally transposed system 235. The second mechanistic proposal (pathway B) relies on the active role of a ruthenium hydride that performs hydrometalation of the olefin 236 to give alkyl complex 237 and subsequent β-hydride elimination on the adjacent position to yield the isomerized product 238.

![Figure 7: Proposed mechanistic pathways for ruthenium catalyzed alkene isomerization.](image)

It has been suggested that each pathway occurs under different circumstances. While pathway A has been the preferred rationale in photochemically induced, ruthenium catalyzed isomerizations,⁹⁴ pathway B has been proposed when ruthenium hydride clusters were used as catalysts. In the latter case, the contributions of Vaglio played an important role in understanding this process.⁹³d In all cases the reactions are ultimately driven by the stability of the resulting product, namely the more substituted or conjugated alkene.

With the aim of accelerating the isomerization step of our cascade, we initially attempted photochemical activation of the catalyst in the reaction mixture. This was initially preferred because we anticipated that exogenous formation of a ruthenium hydride species could interfere with the activation of esterification reagent 75. Unfortunately, in preliminary experiments under a variety of conditions attempted, including several solvents (e.g. Benzene, Toluene, MeCN, DMF, THF), temperatures (25 °C to 100 °C) and two different light sources (50W sunlight lamp and 150W UV photoreactor lamp), no product formation was observed.
and starting material remained unreacted in all cases. While the sunlight lamp had no apparent
effect in the system, the stronger UV lamp resulted in decomposition of the catalyst, as
evidenced by the deposition of a metallic ruthenium mirror on the surface of the reaction
vessel. It was clear that photochemical activation was not compatible with our system,
therefore we turned our attention to an alternative isomerization strategy.

The observation that our system was capable of isomerizing alkenes at higher temperatures
(135 °C) led us to propose a working model for this process. It was suggested that olefin
transposition is performed by a ruthenium hydride species via reversible hydrometalation
(Figure 7, pathway B). Under these conditions, the ruthenium-hydride species responsible for
the isomerization would arise from the C–H activation of the formate reagent 75. Formation
of this species can occur at low temperature evidenced by the fact that hydroesterification can
take place on terminal alkenes under such conditions. At lower temperatures, however,
isomerization seems to be hampered and cannot effectively compete with decarbonylation
(Figure 8). To promote alkene transposition independently of formate-ester activation, we
began searching for alternative ways of obtaining catalytically active ruthenium hydride
clusters.

A literature survey showed that ruthenium cluster compounds can be protonated at the metal
center by Brønsted acids to furnish the corresponding metal hydrides. It was also reported
that acetic acid and even acidic silica gel could accelerate the ruthenium-carbonyl cluster-
catalyzed isomerization of 1-pentene to 2-pentene. Although in those cases no mechanistic
rationale was provided, we speculated that this could take place by action of a metal hydride formed by protonation.

The process of ruthenium-carbonyl-cluster protonation at the metal has been shown to benefit from the effect of electron rich ligands such as phosphines, anionic ligands (e.g. amides) and in particular halides, which have been subject of extensive studies. It can be speculated that such ligands allow the formation of a low valent “ate-complex” cluster that is susceptible to protonation at the metal. With tetrabutylammonium iodide as an additive in the reaction, this protonation could be facilitated as depicted in Scheme 37.

Our efforts to promote the process started with a lowering of the reaction temperature to 70 °C (Table 5). With DMF as solvent only 15 % of the starting material was converted, although the desired product was formed cleanly (entry 1), while the remainder of the starting material remained unchanged. A significant improvement could be observed when the solvent was switched to THF, which can better solubilize the ruthenium cluster at this lower temperature. Under these conditions 40 % conversion could be achieved (entry 2). We were pleased to observe that when catalytic amounts of a Brønsted acid additive were added, a dramatic improvement in conversion of the starting material could be observed. We found that in particular, acetic acid could be used for optimal conversion. While addition of 5 % acetic acid resulted in 90 % conversion (entry 3), increasing this amount to 10 % resulted in full consumption of the starting material and formation of the desired product (entry 4). A further increase of the amount of AcOH to 15 % had no beneficial effect (entry 5), while a further increase to one equivalent resulted in deteriorated conversion and formation of unidentified byproducts (entry 6). The use of other acids such as pivalic acid (entry 7) and p-toluenesulfonic acid (entry 8) had similar effects. Employing pyridinium p-toluensulfonate (PPTS, entry 9) had deleterious effect, likely due to catalyst poisoning by the pyridine.
Table 5: Promotion of the reaction by Brønsted acids.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Additive (loading)</th>
<th>Conversion of 196j[c]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMF</td>
<td>-</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>-</td>
<td>40%</td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>AcOH (5 mol%)</td>
<td>90%</td>
</tr>
<tr>
<td>4</td>
<td>THF</td>
<td>AcOH (10 mol%)</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>AcOH (15 mol%)</td>
<td>&gt;95%</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>AcOH (100 mol%)</td>
<td>90% [c]</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>PivOH (10 mol%)</td>
<td>94%</td>
</tr>
<tr>
<td>8</td>
<td>THF</td>
<td>TsOH (10 mol%)</td>
<td>89%</td>
</tr>
<tr>
<td>9</td>
<td>THF</td>
<td>PPTS (10 mol%)</td>
<td>ca. 15% [c]</td>
</tr>
<tr>
<td>10</td>
<td>THF</td>
<td>Bu₄NOAc (10 mol%)</td>
<td>35%</td>
</tr>
<tr>
<td>11</td>
<td>THF</td>
<td>AcOH (10 mol%), no Bu₄NI [d]</td>
<td>&lt;5%</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate 196j (0.40 mmol), reagent 75 (2.0 eq.), Ru₃(CO)₁₂ (5 mol%), Bu₄NI (15 mol%) and the indicated additive were suspended in the appropriate solvent (0.60 M) under argon in a septum-capped vial and stirred at 75 °C for 40 h. [b] Conversion determined by ¹⁹F-NMR against an added standard (trifluoromethylbenzene). [c] Sluggish reaction with formation of an unidentified byproduct. [d] control reaction, carried out without Bu₄NI. Py = 2-pyridyl; PivOH = pivalic acid; PPTS = pyridinium p-toluenesulfonate.

As a control reaction, the cascade was undertaken with tetrabutylammonium acetate in place of acetic acid (entry 10). In this case, we observed a conversion similar to that obtained without any acid additive. This observation points out the relevance of the proton in the promotion of the reaction, as opposed to an effect of the acetate anion as ligand or counterion. In line with our expectations, when tetrabutylammonium iodide was omitted from the reaction no conversion was observed, therefore showing that acetic acid alone was not competent in promoting the reaction.
2.8 Scope of the Isomerization-Hydroesterification Cascade: Allylic Amides

Having identified optimal conditions for conversion of the model substrate 196j into the desired product, we set out to explore the scope of the transformation. We were particularly interested in investigating the range of functional groups that were compatible with the reaction conditions, as this had been a long-standing problem for hydroesterification chemistry in general. Moreover, a broad substrate scope would demonstrate the usefulness of this cascade in fine chemical applications and in particular within the synthesis of advanced building blocks for discovery chemistry.

Under our optimized conditions, we found a wide variety of substrates could be successfully employed in the cascade (Table 6). Pleasingly, both aryl (entry 2) and alkyl groups (entries 3 to 7) of varying steric bulk were compatible with the reaction. A general trend for alkyl substituents was observed where increasing steric demand in the series from methyl (entry 3) to 2-phenylethyl (entry 4) to iso-propyl (entry 5) to tert-butyl (entry 6) to gem-dimethyl (entry 7) led progressively to more selective functionalization of the terminal position of the alkene. It is noteworthy that in all cases, except one (entry 10), the branched byproducts could be conveniently removed by flash chromatography and were obtained as ca. 1:1 mixtures of both diastereomers,\textsuperscript{101} a fact that supports the practicality of the present strategy.

Both (E) and (Z) alkenes could be employed in the reaction and showed indistinguishable reactivity and selectivity. This observation is consistent with our working model where alkene transposition, and therefore isomerization via hydrometalation, is proposed to be a fast pre-equilibrium process (Figure 6). The alkene geometry therefore has no impact in the product formation since both (E) and (Z) substrates are in quick equilibrium with the terminal olefin which then undergoes rate- and product-determining hydroesterification.
Table 6: Scope of the tandem isomerization-hydroesterification of allylic amides.\[^{[a]}\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product (major)</th>
<th>Yield[^{[b]}] (major)</th>
<th>Yield[^{[c]}] (minor)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>81 %</td>
<td>15 %</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>81 %</td>
<td>19 %</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>73 %</td>
<td>21 %</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>71 %</td>
<td>16 %</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>76 %</td>
<td>15 %</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>75 %</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>89 %</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>82 %</td>
<td>11 %</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td>O-CN_{3}H_{7}CF_{3}</td>
<td>66 %</td>
<td>28 %</td>
</tr>
<tr>
<td>No.</td>
<td>Structure</td>
<td>Product</td>
<td>Yield %</td>
<td>Ratio (linear:branched)</td>
</tr>
<tr>
<td>-----</td>
<td>-----------</td>
<td>---------</td>
<td>---------</td>
<td>-------------------------</td>
</tr>
<tr>
<td>10</td>
<td><img src="image" alt="Structure 10" /></td>
<td><img src="image" alt="Structure 11" /></td>
<td>82 % (4:1)</td>
<td>[d,e]</td>
</tr>
<tr>
<td>11</td>
<td><img src="image" alt="Structure 12" /></td>
<td><img src="image" alt="Structure 13" /></td>
<td>76 %</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td><img src="image" alt="Structure 14" /></td>
<td><img src="image" alt="Structure 15" /></td>
<td>85 %</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td><img src="image" alt="Structure 16" /></td>
<td><img src="image" alt="Structure 17" /></td>
<td>68 %</td>
<td>21 %</td>
</tr>
<tr>
<td>14</td>
<td><img src="image" alt="Structure 18" /></td>
<td><img src="image" alt="Structure 19" /></td>
<td>82 %</td>
<td>15 %</td>
</tr>
<tr>
<td>15</td>
<td><img src="image" alt="Structure 20" /></td>
<td><img src="image" alt="Structure 21" /></td>
<td>81 % [d]</td>
<td>-</td>
</tr>
<tr>
<td>16</td>
<td><img src="image" alt="Structure 22" /></td>
<td><img src="image" alt="Structure 23" /></td>
<td>81 %</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td><img src="image" alt="Structure 24" /></td>
<td><img src="image" alt="Structure 25" /></td>
<td>78 %</td>
<td>11 %</td>
</tr>
<tr>
<td>18</td>
<td><img src="image" alt="Structure 26" /></td>
<td><img src="image" alt="Structure 27" /></td>
<td>53 %</td>
<td>-</td>
</tr>
</tbody>
</table>

[a] Conditions: substrate 242 (1.0 eq.), reagent 75 (2.0 eq.), Ru₃(CO)₁₂ (5 mol%), Bu₃NI (15 mol%) and acetic acid (10 mol%) were suspended in THF (0.67 M) under argon in a septum-capped vial and stirred at 75 °C for 48 h. [b] Isolated yield of the pure compound after flash chromatography. [c] Isolated yield of the branched byproduct as a mixture of diastereomers after flash chromatography. [d] Reaction carried out in DMF (0.67 M) at 135 °C. [e] linear and branched products could not be separated by flash chromatography; the isolated yield given is for a mixture with ratio given in parenthesis. See experimental section for details. R = -CH₂Py; Py = 2-pyridyl.
In addition to the trifluoroacetamides, a range of other amides were suitable substrates: benzamide (entry 8), acetamide (entry 9), phthalimide (entry 10) as well as Boc-protected hemiaminal ether (entry 11) and a cyclic carbamate (entry 12). In two isolated cases (entries 8 and 15), we were faced with low conversion under the standard conditions, even at extended reaction times (up to 7 days). Fortunately, when we resorted to higher temperature (135 °C in DMF), we were able to accomplish full conversion and obtain the product in good yield. At lower reaction temperatures, unproductive decarbonylation of reagent 75 was the only observed byproduct. We speculate that over an extended reaction time, this eventually leads to catalyst deactivation, as has been shown for other catalytic systems.31a, 35

A wide variety of functional groups were compatible with the reaction conditions, including cyclopropanes (entry 13), nitriles (entry 14), acetals and hemiaminals (entries 15 and 11), ethers and silyl ethers (entries 16 and 17). This is in stark contrast to the limited compatibility of previously reported methods for this class of transformation and is a testament to the mild nature of the reaction conditions. We were also pleased to observe that trisubstituted olefin 225 was also a competent substrate (entry 18) and led to exclusive formation of the desired, linear product. No product arising from functionalization of the internal methyl group was observed as could be expected if isomerization towards that position was taking place (Scheme 38). We hypothesize that the steric bulk of the ruthenium catalyst directs the metal to take a distal position to the methyl group (i.e. to occupy a secondary rather than a tertiary carbon) during hydoruthenation. This ultimately prevents isomerization of the olefin towards that position.

Scheme 38: proposed regioselectivity of hydoruthenation on trisubstituted olefin substrate.
In the substrates screened, the amide functionality was located on either a tri- or tetra-substituted carbon atom. While the latter presented no reason for concern, we were apprehensive due to the possibility that trisubstituted carbon atoms would allow isomerization of the olefin towards the inner position and result in racemization of optically enriched starting materials. It has been reported that isomerization towards conjugation with heteroatoms is a thermodynamically favored process. To probe this, we prepared substrates in enantioenriched form and subjected them to the reaction conditions (Scheme 39). We were pleased to observe that in all cases, no erosion of stereochemical information took place and the products were isolated with the same degree of enantioenrichment as the starting materials as evidenced by chiral SFC analysis. Enantiopure allylic amide (S)-247, prepared from commercial L-valine was cleanly converted to ester (R)-248 and olefin (R)-227 obtained from (S)-Garner’s aldehyde ((S)-226) was converted under the same conditions to the respective ester (R)-249 both retaining full optical purity.

Scheme 39: Hydroesterification cascade on enantioenriched substrates.

The conservation of optical purity is in line with our previous assumptions (Scheme 40). There seems to be a strong kinetic preference for placing the ruthenium distal to the amide in the initial hydroruthenation step. From this position, it can only lead to isomerization to give the terminal alkene. Alternative placement of the ruthenium in the proximal position, which would lead to isomerization to give enamide 250 does not occur, presumably because of steric constraints.
When allylic amide 214, bearing both a terminal and 1,2-disubstituted alkene, was employed in the reaction the homologation occurred preferentially on the sterically more accessible terminal olefin to give ester 251, albeit in modest yield (Scheme 41). To prevent over-functionalization in this case, only a small excess of the formate reagent 75 was used. Under these conditions no functionalization of the internal olefin was observed. This is consistent with the proposed Curtin–Hammett-type regime for this cascade, where the terminal alkene is readily available to undergo homologation, while the internal alkene is only accessible if it undergoes the isomerization equilibrium.

The strong steric bias and selectivity of the C–C bond forming step for terminal olefins allowed us to perform a more remote functionalization by taking advantage of multiple isomerizations (Scheme 42). When olefin 252 was employed, selective homologation of the terminal position was observed by virtue of the transposition strategy. This observation also suggests that the isomerization process required in this cascade can take place multiple times and is independent from the C–C bond forming process.
2.9 Scope of the reaction: Allylic Ethers

As a logical extension of the employed strategy, we turned our attention to protected allylic alcohols as a similar substrate class. After suitable deprotection and cyclization, these were expected to furnish lactone building-blocks for fine-chemical applications (Scheme 43).

Initial investigations focused on optimization of existing conditions for the amide series (Table 7). Under the conditions described previously, a substrate bearing a free allylic hydroxyl group led to complex reaction mixtures, most likely due to alkene isomerization towards conjugation (entry 1). When a substrate bearing a MOM group was employed, some conversion could be obtained (entry 2), while protection of the hydroxyl group as a benzoate significantly hampered the reaction (entry 3). Finally, when a TBS ether was used, the starting material cleanly converted to desired product 259 (R = TBS), although significant amount of starting material could still be observed in the mixture even after 48 h (entry 4). In an effort to promote the process, the reaction was performed at higher temperature and improved conversion was observed (entry 5). Screening for the required amount of acetic acid at this stage revealed that the use of 15 mol% of this additive resulted in the best results (entries 5 to 9).
Having optimal conditions in hand, we applied this transformation to a range of substrates bearing a silyl protected allylic alcohol functionality (Table 8). We found that both alkyl and aryl groups were tolerated in the reaction and furnished the desired product in good yields (entries 1 and 2). Additionally, a benzothiophene substituent was compatible with the reaction conditions, despite its potential catalyst-poisoning effect (entry 3). Protected diols could be employed (entry 4), including a ketal protected substrate (entry 5) and furnished products in good yields. This is surprising since we expected that the acetic acid present would lead to deprotection of labile protecting groups.
Table 8: Scope of allylic ether substrates.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{n-C}_4\text{H}_9) (\text{OTBS}) (\text{Me})</td>
<td>(\text{n-C}_4\text{H}_9) (\text{OTBS}) (\text{CO}_2\text{CH}_2\text{Py})</td>
<td>66% [c]</td>
</tr>
<tr>
<td>2</td>
<td>(\text{OTBS})</td>
<td>(\text{OTBS}) (\text{Me})</td>
<td>64%</td>
</tr>
<tr>
<td>3</td>
<td>(\text{OTBS})</td>
<td>(\text{OTBS}) (\text{Me})</td>
<td>65%</td>
</tr>
<tr>
<td>4</td>
<td>(\text{TBSO})</td>
<td>(\text{TBSO}) (\text{Me})</td>
<td>73%</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>88%</td>
</tr>
<tr>
<td>6[d]</td>
<td></td>
<td></td>
<td>72%</td>
</tr>
<tr>
<td>7[d]</td>
<td></td>
<td></td>
<td>85%</td>
</tr>
<tr>
<td>8</td>
<td>(\text{OTBS})</td>
<td>(\text{OTBS})</td>
<td></td>
</tr>
</tbody>
</table>

[a] Conditions: the substrate 260 (1.0 eq.), reagent 75 (2.0 eq.), \(\text{Ru}_3(\text{CO})_{12}\) (5 mol%), \(\text{Bu}_4\text{NI}\) (15 mol%) and acetic acid (15 mol%) were suspended in DMF (0.67 M) under argon in a septum-capped vial and stirred at 120 °C for 12 h. [b] Isolated yields of the pure compound after flash chromatography. [c] the branched product was also observed and could be isolated in 14% yield. [d] Reaction conducted at 150 °C. [e] No conversion observed even at more elevated temperatures; starting material re-isolated. Py = 2-pyridyl.

We were also interested in exploiting the potential of this cascade in the synthesis of products displaying four-membered heterocycle building blocks. These scaffolds have shown a variety of interesting chemical properties and have been the subject of studies as bioisosters for ketone and geminal dimethyl-groups.63b To this end, we prepared starting materials bearing
oxetane, thietane and protected azetidine moieties and subjected them to the cascade. While initially showing slow reactivity under the optimized reaction conditions, we were pleased to observe that upon more vigorous thermal activation (150 °C), oxetane and Boc-protected azetidine substrates showed excellent reactivity resulting in the formation of the desired products in good yields (Table 8, entries 6 and 7). In the latter case, it is remarkable that the Boc-protecting group was stable under conditions that would lead to thermal or acid-mediated cleavage. It is noteworthy that the analogous thietane was not a competent substrate in the reaction, yielding exclusively starting material, even at higher temperatures and after extended reaction times (entry 8). We propose that the exposed electron pairs of the thietane moiety must act as ligands and effectively poison the catalyst.

In analogy to the allylic amides, we selected an ether substrate to probe for potential racemization of the allylic position in the ether series (Scheme 44). Gratifyingly, when the reaction was conducted with enantiomerically pure substrate 262, the desired product of the reaction 263 could be isolated with the same level of enantiomeric excess as the starting material, as determined by chiral analytical SFC.

![Scheme 44: Retention of stereochemistry in silyl ether substrate.](image)

While the isolated yields were generally lower than in the case of allylic amides, it was observed that in the series of allylic ether substrates tested, only trace amounts of the branched products were observed by $^1$H-NMR of the crude reaction mixtures. In fact, only in one case was the branched product formed in sufficient amounts to be cleanly isolated (Table 8, entry 1). This seems to indicate that the steric bias from the TBS-protected allylic alcohol substrates has a stronger influence than that of the trifluoroacetamides. It also raises the question whether the amide acts as directing group for the catalyst (Scheme 45). This would ultimately reduce the linear-to-branched selectivity by stabilizing smaller-ring ruthenacycles, e.g. 266 instead of 267 favoring the formation of branched ester 268 instead of linear product 269. This might also explain why substrates bearing the silyl-protected alcohols require higher
temperatures for the cascade to take place. Chelation of the amide would allow the metal catalyst to engage the substrate in hydroruthenation more easily, thus lowering the required thermal activation. This favorable effect, would be absent in the case of the protected alcohols.

\[
\begin{align*}
\text{CF}_3 \quad \text{N}^- \quad \text{CH} = \text{CHR}^2 \quad \text{Me} & \quad [\text{Ru}] \quad \text{CF}_3 \quad \text{N}^- \quad \text{CH} = \text{CHR}^2 \quad \text{Me} \quad \text{isomerization} \quad \text{CF}_3 \quad \text{N}^- \quad \text{CH} = \text{CHR}^2 \quad \text{Me} \quad \text{CF}_3 \quad \text{N}^- \quad \text{CH} = \text{CHR}^2 \quad \text{Me} \quad \text{hydroesterification} \quad \text{CF}_3 \quad \text{N}^- \quad \text{CH} = \text{CHR}^2 \quad \text{Me} \quad \text{CO}_2\text{R}^* \\
\end{align*}
\]

Scheme 45: Possible direct effect of the amide.

Another observation was the more pronounced beneficial effect of acetic acid in the reaction, as 15 mol% was required as opposed to 10 mol% in the amide series. We can speculate that substrates bearing a trifluoroacetamide provide a convenient source of both the proton required for the formation of a ruthenium hydride and a suitable chelating group (Scheme 45). The absence of those in the allylic ethers results in the need for higher temperature and the need for acidic additive to promote the reaction.

These preliminary rationalizations, while here only used to explain minor observed effects, added to our knowledge about this catalytic system and helped in elucidating its mode of action. While of only limited importance here, they played a key role in the development of the intramolecular hydrocarbamoylation reaction (chapter 3.7).

2.10 Cyclization of the Obtained Products

We had now successfully prepared a range of compounds by applying our new isomerization-hydroesterification methodology to both amides and protected alcohols. Hence, we were
interested in exploring their potential reactivity. Of particular allure was their further elaboration into lactams and lactones from these amides and ethers respectively. To achieve this, we would require selective deprotection of the amine or alcohol and their subsequent attack onto the ester moiety, ideally accomplished in a single step.

A previous report on the selective hydrolysis of trifluoroacetamides under mild conditions in the presence of methyl esters set the basis for our initial cyclization experiments. Caution was needed, however, given that premature hydrolysis of the ester would disable any cyclization attempts by formation of the unreactive carboxylate. With acetamide substrate in hand, we set out to investigate conditions under which the cyclization could be effected (Table 9).

Table 9: Screen for cyclization conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Observed Result[a]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>K₂CO₃, MeOH/water (3:1)</td>
<td>Amino acid formation</td>
</tr>
<tr>
<td>2</td>
<td>LiOH, THF/MeOH/water (2:2:1), 12h</td>
<td>Amino acid formation</td>
</tr>
<tr>
<td>3</td>
<td>HCl, MeOH (dry), reflux 12h</td>
<td>Methyl ester formation</td>
</tr>
<tr>
<td>4</td>
<td>Ti(OEt)₄, EtOH, reflux</td>
<td>Ethyl ester formation</td>
</tr>
<tr>
<td>5</td>
<td>Et₃O⁺ BF₄⁻, DCM, then aq. NaHCO₃</td>
<td>Alkylation of the pyridine</td>
</tr>
<tr>
<td>6</td>
<td>Amberlyst A-26 (basic), MeOH</td>
<td>Decomposition</td>
</tr>
<tr>
<td>7</td>
<td>NaBH₄, EtOH, r.t. to reflux</td>
<td>Formation of ethyl ester</td>
</tr>
<tr>
<td>8</td>
<td>NaH (1 eq.), MeOH, r.t., 5 days</td>
<td>Formation of the methyl ester</td>
</tr>
<tr>
<td>9</td>
<td>NaH (1 eq.), MeOH, reflux, 5 days</td>
<td>ca. 20% product observed</td>
</tr>
<tr>
<td>10</td>
<td>NaH (1 eq.), n-BuOH, reflux, 12h</td>
<td>ca. 20% product observed</td>
</tr>
<tr>
<td>11</td>
<td>NaH (10 eq.), CaSO₄, n-BuOH, reflux, 12h</td>
<td>60% product observed</td>
</tr>
<tr>
<td>12</td>
<td>NaH (10 eq.), CaSO₄, MeOH, reflux, 12h</td>
<td>86% product isolated[b]</td>
</tr>
</tbody>
</table>

[a] Reaction outcome determined by analysis of the crude ¹H- and ¹⁹F-NMR spectra of the reaction mixture. [b] Product isolated by flash chromatography.
Originally reported conditions for the selective deprotection,\textsuperscript{103b} employing a methanol-water (3:1) mixture as solvent and carbonate base (K$_2$CO$_3$) resulted in unselective deprotection and ultimately formation of the amino acid product at all attempted temperatures (entry 1). The alternative use of lithium hydroxide in a THF-methanol-water (2:2:1) mixture\textsuperscript{104} yielded the same result (entry 2). Although we considered the possibility of cyclizing the resulting amino acids in a separate step making use of peptide coupling reagents,\textsuperscript{105} we deemed this strategy dissatisfactory. In that respect, the need for an additional step, the need for handling and purification of polar amino acid intermediates and the wasteful use of coupling reagents led us to attempt a direct cyclization. It seemed formation of the carboxylate was hampering the cyclization reaction so anhydrous conditions were attempted. The use of \textit{Bronsted-} or \textit{Lewis-}acid activation in dry alcohol solvents led to transesterification without any observed cyclization (entries 3 and 4). Unsurprisingly, an attempt at forcibly alkylating the amide with \textit{Meerwein’s salt} (Et$_3$O$^+$BF$_4^-$) resulted in exclusive N-alkylation of the pyridine moiety to give the ethyl pyridinium salt, even when excess reagent was employed (entry 5). The cyclization also failed to yield the desired product when either Amberlyst A-26 resin or sodium borohydride\textsuperscript{106} were used in dry alcoholic media (entries 6 and 7). When sodium methoxide (generated from sodium hydride in methanol) was used, only transesterification was observed at room temperature (entry 8). In an attempt to drive the reaction forward by increasing the temperature, we observed formation of some desired product when refluxing the reaction mixture in methanol (entry 9). A switch to refluxing \textit{n}-butanol, which allowed a further increase in temperature did not yield any improved results (entry 10). Finally, use of a large excess of alkoxide and with added drying agent (calcium sulfate) led to reliable and selective formation of the desired lactam product \textbf{271} in a single operation (entries 11 and 12 and Scheme 46).

Compared to the allylic amine substrate, cyclization of the TBS-protected ester \textbf{272} presented less difficulty. The cyclization could be easily carried out through acidic hydrolysis of the TBS-ether, followed by acid-catalyzed cyclization to the lactone \textbf{273} (Scheme 46).
Our initial mechanistic proposal followed from the assumed role of the formate ester reagent $75$ as promoting both the isomerization and hydroesterification of the alkene in the substrate and supplying the hydride and the carbonyl portions that are ultimately incorporated into the product. Under this hypothesis, we postulate a catalytic cycle that explains our observations (Figure 9).

In the proposed cycle, the mixture composed of triruthenium dodecacarbonyl ($\text{Ru}_3(\text{CO})_{12}$) and halide additive tetrabutylammonium iodide ($\text{Bu}_4\text{NI}$) are combined to give the active catalyst $274$ where the iodide is believed to act as a ligand for the ruthenium cluster, increasing the electron density of the complex. $100$ Next, oxidative addition of the highly electron rich low valent ruthenium cluster into the formate C–H bond occurs to give compound $275$. $29, 46, 107$ The resulting ruthenium hydride species coordinates to the olefin of the substrate, possibly assisted by the chelating effect of the heteroatom on the allylic position. This olefin $\eta_2$ complex can thus undergo migratory alkene insertion during which there is a strong steric bias to place the bulky ruthenium cluster distal to the branched position, giving complex $276$. At this point, the complex can either suffer reductive elimination to give the undesired branched isomer of the product, regenerating the catalyst $274$ or perform $\beta$-hydride abstraction of the terminal position to give complex $277$. Finally hydroruthenation of the terminal olefin placing the cluster on the sterically less demanding position to give $278$ and subsequent reductive elimination would give the desired product and regenerate the active catalyst $274$. 

Scheme 46: one-pot deprotection-cyclization of cascade products.

2.11Mechanistic Considerations
Figure 9: Tentative catalytic cycle operating at high temperature.

This cycle is consistent with the observed reactivity that takes place under high temperature regime (135 °C). We believe that under these conditions, the initial hydrometalation of the internal olefin can take place easily from the reagent-bound catalyst 275. When the temperature is reduced, however, the initial attack onto the internal olefin is hampered and without the use of acidic additives, an erosion of the conversion is observed.

At this point it is interesting to notice the role of the pyridine directing group of the formate ester 75. This auxiliary had been initially developed by Chang with the aim of facilitating oxidative addition onto the formate by chelation of ruthenium to the pyridine. To test for this hypothesis under our reaction conditions, we performed a control experiment under both temperature regimes explored during our optimizations (75 °C and 135 °C). In these reactions we replaced the reagent 75 that contains the directing group with its analogous counterpart benzyl formate (279) lacking the chelating group but expected to behave similarly otherwise (Scheme 47). When the reaction was performed at high temperature (135 °C), decarbonylation of the benzyl formate (279) occurred to give benzyl alcohol (280). In
contrast, undertaking the reaction at low temperature (75 °C) resulted in no conversion and the reagent 279 could be re-isolated in unaltered form from the reaction mixture. These observations suggest a dual role of the pyridine directing group. At lower temperatures (75 °C), the pyridine is proposed to be involved in reducing the activation barrier for C–H activation through a chelate effect, given that this process did not occur when benzyl formate was employed. At higher temperatures, however, lowering of the activation barrier becomes unnecessary, which is shown by benzyl formate (279) undergoing decarbonylation. At higher temperatures, the pyridine is suggested to act as a stabilizing group that prevents decarbonylation by limiting decomplexation of the corresponding alcohol from the metal-carbonyl species (Scheme 28, intermediate 190).31a

![Scheme 47: Behavior of a reagent lacking the pyridyl directing group.](image)

We were also interested in the mechanistic role of the Brønsted acid additives. In particular, the possibility that a ruthenium hydride was formed independently of C–H activation of the formate ester was of special interest, since such species might be applied in the development of other reaction cascades. To gain more insight about the specific role of acetic acid we conducted a series of experiments aimed at unraveling its reactivity by monitoring the catalytically relevant mixtures by 1H-NMR. Thus, we conducted two separate experiments; the reaction of a catalyst mixture composed of ruthenium carbonyl (Ru3(CO)12) and tetrabutylammonium iodide (Bu4NI) in 1:3 ratio with the reagent 75 and with acetic acid in d8-THF (Figure 10). Addition of formate 75 to the catalyst mixture at 70 °C resulted in slow formation of two main hydride resonances at δ = −12.5 ppm and δ = −15.5 ppm over the course of several hours. These species can be assigned to hydrides formed by oxidative addition into the C–H bond in formate 75. In a separate experiment acetic acid (2 eq. relative
to Ru$_3$(CO)$_{12}$ was added to the catalyst mixture (Ru$_3$(CO)$_{12}$/Bu$_4$NI) in d$_8$-THF at 70 °C and monitored by $^1$H-NMR. This mixture showed initial formation of multiple hydride species that quickly resolved to a single dominant singlet resonance at $\delta = -17.0$ ppm. Interestingly, when acetic acid was added to the catalyst mixture in conjunction with reagent 75, two dominant hydride resonances at $\delta = -12.5$ ppm and $\delta = -17.0$ ppm were formed readily. All of these signals are in line with previously observed hydrides of ruthenium clusters.

![Figure 10: Observed hydride species in the catalyst mixture at 70 °C in d$_8$-THF.](image)

The formation of metal hydrides by acetic acid had been expected and was also proposed as a pathway to promote faster isomerization. Moreover, in control experiments when Bu$_4$NI was omitted from the NMR experiments (Figure 10), these signals were not observed. This indicates the expected effect of halide additives in facilitating metal protonation by formation of the electron-rich ate-complex. To further confirm our hypothesis that the ruthenium hydride generated from acetic acid was capable of isomerizing alkenes, we subjected the model alkene 4-phenyl-1-butene (168) to the catalyst mixture containing acetic acid and observed isomerization of the alkene towards conjugation to give alkenes 172 and 171 in 8:1 ratio (Scheme 48). The results clearly show that acetic acid can promote the isomerization of alkenes even in absence of formate reagent 75, and therefore is involved in the formation of the active ruthenium hydride species.

![Scheme 48: Alkene isomerization with acetic acid.](image)
The dramatic improvement in the reaction conversion caused by the addition of
substoichiometric acetic acid led us to propose an alternative mechanistic rationale (Figure
11). In this catalytic cycle, the combination of ruthenium carbonyl (Ru$_5$(CO)$_{12}$), halide
additive (Bu$_4$NI) and acetic acid result in the formation of a ruthenium hydride species 281,
which is catalytically competent. This is proposed in conjunction with the observation by $^1$H-
NMR spectroscopy that such species are indeed formed in solution, added to the fact that they
are active in the isomerization of olefins (vide supra). This species is then proposed to
perform hydoruthenation of the alkene substrate to give alkyl-ruthenium species 282. Here,
again, the directing effect of the amide might be responsible for enhanced reactivity by
bringing the olefin of the substrate into position for complexation and subsequent migratory
alkene insertion. This species can then undergo β-hydride elimination from the terminal
position to give the terminal olefin bound to a new ruthenium cluster hydride 283. Next,
another migratory alkene insertion, this time placing the ruthenium cluster on the terminal
position leads to alkyl ruthenium cluster 284. This species can now activate the formate
reagent by oxidative addition onto the C-H bond to give 285 which ultimately suffers
reductive elimination to yield the desired product and regenerating the ruthenium hydride
species 281.

Figure 11: Tentative catalytic cycle accounting for the role of acetic acid.
Complex 285 presents two possible pathways for reductive elimination. In the first, an alkyl–acyl bond is formed to yield the desired product. Alternatively, the formation of the alkyl–hydrogen bond can be envisioned to give the saturated alkane. Interestingly, this type of product was never observed under our reaction conditions. We speculate that reductive elimination of the hydride to give the alkane is hampered by the reported observation that such ligands tend to occupy bridging positions in ruthenium clusters, in the form of μ$_2$- or even μ$_3$-hydrides.\textsuperscript{59} In contrast, acyl ligands tend to occupy apical (μ$_1$) positions of the cluster and are therefore more prone to engage in reductive elimination. Regarding the reductive elimination step, a stepwise mechanism can be drawn (Scheme 49). In this step, the alkyl group engages in migratory insertion of one of the carbonyl ligands of the ruthenium cluster 285 to give acyl complex 286. The free coordination space provided in 286 can then be filled by decarbonylation of the formate reagent to give cluster 287 where the alkoxide ligand from decarbonylated reagent 75 is expected to occupy a bridging μ$_2$-position as previously observed by Chang.\textsuperscript{37} Finally, the acyl ligand can be captured by the 2-pyridyl-methanol in either an inner-sphere process or by outer-sphere attack of previously decarbonylated reagent. In fact, this stepwise mechanistic process is analogous to what has been determined for other important carbonylation reactions such as the Monsanto and Cativa processes.\textsuperscript{108}

![Scheme 49: Proposed mechanism for the C–C coupling.](image_url)

The catalytic cycle described in Figure 11 is likely to be operating at lower temperatures (75 °C), given that only under these conditions is the addition of acetic acid advantageous. In contrast, at high temperatures (135 °C), high conversions can be observed even without acetic acid and therefore the cycle described in Figure 9 is proposed. At low temperatures, in absence of this additive, the transformation still takes place albeit in poor conversion. It is therefore likely that both of the proposed catalytic pathways are operating simultaneously. For instance, several species proposed in both cycles can interconvert into one-another by simple
processes of metal protonation or deprotonation (e.g. 278 and 285). We can also speculate that the cycle in Figure 11 is only responsible for supplying terminal olefin substrates to the main catalytic cycle (i.e. the cycle depicted in Figure 9). In that respect, decomplexation of the terminal alkene substrate from complex 282 would regenerate the catalyst 281 which is competent in the isomerization process. The terminal alkene would then enter the esterification cycle (Figure 9) by complexation to 275 to give 277. The parallel existence of these two cycles would explain the existence of two main hydride signals observed by ¹H-NMR of the catalyst mixture when both acetic acid and reagent 75 are added. These could be assigned to structures of type 275 and 281 respectively.

The multinuclear nature of the catalytic species, the reversible nature of the isomerization process and the potential existence of multiple interconverting catalytic cycles complicate analyses of this system. It is, however, remarkable that such a complex set of catalytic processes can be tamed in the design of a selective cascade, where the order of events is controlled by the inherent selectivity of the catalyst.

2.12 Conclusions

In this chapter, we have described the development process of a ruthenium-catalyzed tandem isomerization-hydroesterification reaction. The method is valuable, as it allows a seemingly unfunctionalized position of the substrate to be coupled with a C₁-unit by C–C bond formation. The unique reactivity of the ruthenium carbonyl cluster, which is able to promote both the isomerization and C–H activation processes, was exploited to allow the transformation to take place. In that respect, we found the remarkable promoting effect of added acid to the catalytic system, which allowed the overall process to take place efficiently.

The reaction process was investigated for a wide range of substrates bearing allylic amide and allylic alcohol functionality and furnished products that are not easily prepared otherwise. Additionally, we demonstrated that the products obtained enables quick access to lactones and lactams by simple cyclization protocols.

Finally, we discussed the effect of the additives used and conducted investigations aimed at unraveling their promoting effect. This information has allowed us to propose a catalytically active ruthenium hydride as key intermediate required for promoting the isomerization
process. While the exact nature of the catalyst still remains elusive, we believe that the observations made in this work will allow a clearer understanding of its reactivity.
3 Intramolecular Hydrocarbamoylation of Allylic Formamides
3.1 Concept Development

In the previous chapter, the development of a cascading sequence of reactions that can take place in an auto-tandem fashion was described. In that case, a single catalyst precursor was employed that was added at the outset of the reaction and performed both steps of the cascade \textit{e.g.} isomerization and hydroesterification, and did not require operator intervention for switching between each transformation. The cascade sequence was applied to allylic amides and then extended to protected alcohols. Its synthetic utility was demonstrated in the preparation of lactams and lactones. Critical inspection of the overall strategy, however, reveals certain conceptual shortcomings with regard to both step and atom economy, if the ultimate goal of the sequence is the preparation of the cyclized products.

During the development of the isomerization-hydroesterification cascade, it was found that free allylic amines could not be tolerated by the catalyst and consequently, the use of a suitable protecting group, in most cases trifluoroacetamide (288), was necessary (Figure 12, top). The reaction also relied on the use of \textit{Chang’s} reagent (75)\textsuperscript{35} in which a pyridyl group not only directs the C–H activation process but also stabilizes the formed acyl-metal species. These two features allow homologation to occur under mild conditions to yield ester 289. In the final cyclization, however, both the amine protecting group and the directing pyridyl group of the parent formate reagent 75 must be removed as they are not present in the product, lactam 290. The use of both protecting and directing groups, while useful for controlling reactivity, presents a drawback with regard to the atom economy of the overall process, since these groups are not integrated into the final lactam product.\textsuperscript{109}
Conceptually, an alternative system that overcomes these limitations can be envisioned for the synthesis of lactams by C–C bond formation. Instead of relying on an intermolecular, auxiliary assisted homologation step followed by deprotection and cyclization in an additional step, the overall process could be performed in intramolecular fashion (Figure 12, bottom). The process would require incorporation of the C₁-unit (highlighted) into the substrate (291) prior to C–C coupling. Ideally, the C₁-unit would be placed on the nitrogen atom as a formamide where it would also prevent catalyst poisoning by masking the free amine. Cyclization would then be effected by cleaving the C–H bond of the formamide in 291 and subsequent intramolecular C–C bond formation to give lactam 292. To yield terminally functionalized product 292, the internal alkene in 291 would have to undergo isomerization to the terminal position prior to trapping (Scheme 50). Moreover, the C–C bond forming step would have to take place selectively at the terminal position of this isomerized alkene. The development of this cascade, thus, depended on the individual success of each step involved i.e. isomerization and C–C bond formation. Given the very limited precedence for the activation of formamide C–H bonds by ruthenium carbonyl cluster complexes, it was preferable to study this process independently, prior to its implementation as part of a cascade. To this end, the intramolecular hydrocarbamoylation of allylic formamides bearing a terminal olefin (294) to give the corresponding 2-pyrrolidones (295) was investigated so olefin isomerization would not be required.
Given the range of amide protecting groups that were tolerated by the reaction conditions for our ruthenium catalyzed hydroesterification, it was speculated that formamides would be equally compatible and could, therefore, serve as the source of the C$_1$-unit to be incorporated in a similar fashion. The success of the intramolecular hydrocarbamoylation would require the development of conditions under which the C–H bond of the formamide could be activated and added across the olefin substrate (Scheme 51). It was, therefore, proposed that the active catalyst species would perform oxidative addition into the C–H bond of the formamide in 296 to give acyl-metal hydride species 297. This would then undergo intramolecular migratory insertion of the alkene portion of the substrate to give alkyl-acyl-metal species 298. Finally, reductive elimination of the metal catalyst would lead to formation of the desired pyrrolidone, 299, and regenerate the active catalyst species.

3.2 Background and Motivation

While initially not seeming as complex as the cascading sequence of reactions involving isomerization and C–C bond formation, the proposed intramolecular hydrocarbamoylation for
the formation of pyrrolidones presents a novel alternative for the preparation of these useful heterocycles. Pyrrolidones, and the related pyrrolidines, are common motifs in a variety of biologically active chemical compounds (Figure 13) ranging from natural alkaloids\textsuperscript{64b, 110} to top-selling drugs such as Keppra\textsuperscript{TM} (UCB Pharmaceuticals), Relpax\textsuperscript{TM} (Pfizer) and Enablex\textsuperscript{TM} (Warner Chilcott)\textsuperscript{111} and other clinically important molecules. Of particular interest are analogues of nicotine, which have been studied as agents against Alzheimer’s and Parkinson’s diseases, among others.\textsuperscript{112} These scaffolds are also present in other useful compounds such as ligands for catalysis,\textsuperscript{113} organocatalysts, in particular the ones derived from proline,\textsuperscript{114} and other industrially relevant functional molecules, such as FDA-approved polyvinylpyrrolidone, which is present in various consumer products.\textsuperscript{115} In light of their broad relevance in multifold applications, there is great value in the development of new methods for accessing these scaffolds.

![Figure 13: Useful compounds containing the pyrrolidine or pyrrolidone skeleton.](image)

### 3.3 Synthesis of Substrates

The development of this project required the use of different allylic formamides that contained a terminal alkene (\textit{300} and \textit{303}). It was clear from the outset that these could be
readily obtained from the corresponding amines (301 and 304) by protection as the formamide (Scheme 52). In most cases this was accomplished with the use of formic acetic anhydride (FAA), which is a convenient formylation reagent because it can be prepared from acetic anhydride and formic acid and is relatively stable for several hours at room temperature. In cases where FAA was incompatible, however, the use of stable ester equivalents were preferred e.g. ethyl and benzyl formate. The synthesis of the allylic amines (301 and 304) was accomplished by employing two alternative routes. Secondary allylic carbinamines 301 (i.e. allylic amines with the nitrogen placed on a secondary carbon atom) were accessed through direct iridium-catalyzed allylic amination of allylic alcohol 302. Tertiary carbinamines 304, on the other hand, were obtained from the appropriate Ellman sulfinyl ketimine 305 by organometallic [1,2]-addition.

Scheme 52: Strategies used in the synthesis of substrates.

Direct allylic amination is of great advantage since it allows easily accessible allylic alcohols to be used as substrates without need for prior activation e.g. as carbonates or acetates. The reaction makes use of cheap sulfamic acid, which is proposed to act both as a promoter for the displacement of the hydroxyl group and as the source of the amino group to be incorporated into the substrate. Moreover, it has been shown to be completely branched-selective, yielding the appropriate allylic amine bearing the terminal olefin. During our investigations, it was found that the obtained allylic amines (301), which have been suggested to be difficult to isolate due to polarity and potential instability, could be directly converted to the formamides in the same reaction mixture by treatment with FAA after allylic amination. Employing an excess (4 eq.) of FAA was necessary to efficiently accomplish the protection due to its inherent instability. In all cases we observed high selectivity for formylation and no acetamide byproduct was observed, indicating that the steric discrimination between acetylation and formylation provided by FAA is sufficient for these substrates. By this
method a range of allylic formamides was quickly accessed (Table 10). Both alkyl- (entries 1 to 3) and aryl-substituted (entries 4 to 7) formamides could be prepared in modest to good yields in a one-pot operation.

**Table 10: Synthesis of secondary cabinamides.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me&lt;sub&gt;2&lt;/sub&gt;CH&lt;sub&gt;2&lt;/sub&gt;</td>
<td>65%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>74%</td>
</tr>
<tr>
<td>3</td>
<td>PhMe&lt;sub&gt;2&lt;/sub&gt;</td>
<td>61%</td>
</tr>
<tr>
<td>4</td>
<td>Ph</td>
<td>35%&lt;sup&gt;[c]&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>53%</td>
</tr>
<tr>
<td>6</td>
<td>Ph</td>
<td>62%</td>
</tr>
<tr>
<td>7</td>
<td>Ph&lt;sub&gt;2&lt;/sub&gt;Me</td>
<td>49%</td>
</tr>
</tbody>
</table>

[a] Conditions: Allylic alcohol 302 (2.63 mmol) was added to a solution of [Ir(cod)Cl]<sub>2</sub> (2.5 mol%), Ligand 307 (5 mol%) and sulfamic acid 306 (1.2 eq.) in THF (8.8 mL) and DMF (1.0 mL) and stirred for 16 h at r.t.. This was then treated with NaHCO<sub>3</sub> (2.0 eq.) and a solution of FAA (4.0 eq.) in acetic acid/formic acid (1:1 ca. 2 mL) at 0 °C and stirred for 3 h at r.t.. [b] Yields are of the pure products after flash chromatography. [c] Allylic amimation was carried out at 60 °C for 25 min and the formamide formation performed by addition of ethyl formate (20 eq.) and triethylamine (3.0 eq.) at 50 °C for 48 h.
The synthesis of tertiary carbinamides was accomplished by the use of Ellman’s sulfinylimine strategy (Scheme 53). In this instance, a range of ketones 308 were condensed with tert-butylsulfinamine in the presence of an excess (2.0 eq.) titanium tetraethoxide, which served as the activator and dehydrating agent to give the corresponding imines (305). These imines were then treated with vinylmagnesium bromide to furnish sulfinamines 309. Removal of the auxiliary with anhydrous hydrogen chloride in methanol provided the amine hydrochloride that was directly subjected to protection with FAA giving desired formamides 303. Using this strategy, allylic formamides obtained from pentan-2-one (310), cyclohexanone (311), cycloheptanone (312) and adamantone (313) were obtained in varying yields.

![Scheme 53: Synthesis of tertiary carbinamides.](image)

The relatively poor overall yields observed in this strategy can be traced back to sluggish organometallic addition of vinylmagnesium bromide to the enolizable sulfinyl ketimines. When enolization of the imine was not possible, as was the case of the adamantone-derived imine, the desired product 313 could be obtained in good yield. In the case of the imine 315, derived from menthone (314) by condensation with Ellman’s auxiliary (R)-207, steric bulk and enolizability prevented the direct addition of vinylmagnesium bromide from taking place (Scheme 54). Attempts with vinyllithium (generated from vinyl bromide and t-BuLi in THF at –78 °C), with or without addition of trimethylalumimum to promote addition, also failed to yield the desired compound 317, and only reduction product 318 was observed, along with recovered starting material. We speculated that the diastereomer 315 presented a “mismatch” situation where the menthone backbone and the sulfinylimine would hamper attack to opposing diastereofaces of the imine. We, therefore, turned our attention to the alternative diastereomer 316, which arose from the condensation of (–)-menthone (314) with the opposite
enantiomer of Ellman’s auxiliary (S)-207. In this case, while the direct use of vinylmagnesium bromide was unsuccessful, we found that formation of the dimethyl-vinylzincate salt prepared in situ by combination of vinylmagnesium bromide with dimethylzinc, allowed the vinyl group to be transferred to the substrate imine 316 smoothly to give olefin 319. The product was then easily converted into the desired allylic formamide 320 by deprotection of the sulfonamine auxiliary with hydrogen chloride in methanol, followed by protection with formic acetic anhydride.

![Scheme 54: Synthesis of allylic formamide 320.](image)

Determination of the relative stereochemistry in compound 320, particularly for the fully substituted carbon atom, was obtained by NOE experiments where the proximity of an axial hydrogen atom in the carbon skeleton and the alkene was established (Figure 14). The relative stereochemistry was unambiguously confirmed by single crystal X–Ray analysis of 320.

![Figure 14: NOE contact and crystal structure of 320 (ellipsoids at 50% probability shown).](image)
The synthesis of additional substrates bearing variations on the alkene was accomplished from a common precursor by, again, employing the sulfonamine strategy (Scheme 55). Aldehyde 321 was condensed with racemic sulfonamine (±)-207 to give imine 322, which was subjected to addition of various organometallic nucleophiles. Treatment with propynyllithium, followed by deprotection of the auxiliary and formamide formation gave alkyne 323, which then underwent semi-hydrogenation with Lindlar’s catalyst (Pd on CaCO₃, Pb poisoned) and catalytic quinolone under an atmosphere of hydrogen to give Z-alkene 324. Addition of allylmagnesium bromide or homoallylmagnesium bromide, followed in both cases by the same deprotection-formamide formation sequence gave the desired homoallylic and bis-homoallylic formamides, 325 and 326, respectively. Imine 322 could also be functionalized by addition of iso-propenylmagnesium bromide or oct-1-en-2-yllithium, followed by a deprotection-protection sequence to give the 1,1-disubstituted alkene substrates, 327 and 328, respectively. All additions proceeded in excellent yields and the products could be directly subjected, without purification, to the removal of the auxiliary and formamide installation.
Scheme 55: Synthesis of additional substrates from imine 322.

3.4 Optimization

The development of our hydrocarbamoylation strategy relied on the observations of Watanabe, who reported that ruthenium carbonyl cluster complex, $\text{Ru}_3(\text{CO})_{12}$, was competent in the addition of simple formamides to olefins, albeit under forcing conditions. Therefore, we speculated that our previously developed catalytic ruthenium system for the intermolecular isomerization-hydroesterification of olefins (chapter 2) would provide the ideal starting point for investigating the intramolecular hydrocarbamoylation. Our investigations
began with attempting ruthenium-catalyzed cyclization of allylic formamide 329 to the corresponding 2-pyrrolidone 330 using triruthenium dodecacarbonyl (5 mol%) as catalyst in combination with tetrabutylammonium iodide (15 mol%) and acetic acid (10 mol%) (Table 11). Under the conditions developed previously, carrying out the reaction in THF at 75 °C resulted in no conversion and the starting material 329 was the only observable species after the reaction (entry 1). We speculated that the absence of a directing group for the oxidative addition on the C–H bond in this reaction would hamper this process from occurring at low temperatures (e.g. 75 °C). This stands in contrast to the corresponding reaction of formate reagent 75, displaying a pyridyl directing group, that had been shown to promote insertion of the metal catalyst (Scheme 47). We speculated that increasing the temperature to 100 °C might result in improved reactivity. However, cyclization attempts with 329 in 1,4-dioxane (entry 2), toluene (entry 3) and DMF (entry 4) showed no conversion at this temperature. Finally, increasing the reaction temperature to 150 °C in DMF (entry 5) resulted in moderate conversion.

Table 11: Initial screening of conditions for hydrocarbamoylation.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>Conversion[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td>75 °C</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>1,4-dioxane</td>
<td>100 °C</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>Toluene</td>
<td>100 °C</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>DMF</td>
<td>100 °C</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>DMF</td>
<td>150 °C[c]</td>
<td>42%</td>
</tr>
</tbody>
</table>

[a] Conditions: In a screw-capped vial, substrate 329 (0.08 mmol), Ru\(_3(CO)_{12}\) (5 mol%), Bu$_4$NI (15 mol%) and acetic acid (10 mol%) were suspended in the appropriate solvent (0.32 M) and the mixture purged with argon. The vial was sealed and heated to the indicated temperature for 40 h. [b] Conversion determined by $^1$H-NMR integration against an added standard 1,4-dimethoxybenzene. [c] Reaction time: 16 h.
With this initial result in hand, we re-examined the need for tetrabutylammonium iodide and acetic acid additives under those conditions (Table 12). Interestingly, without any added halide source some residual conversion was observed (entry 1). Progressively increasing the amount of Bu$_4$NI while maintaining a constant amount of acetic acid (20 mol%), resulted in an increase in conversion, reaching an optimal value of 32% at a loading of 15 mol% of the halide (entries 2 to 4). Increasing the amount of this additive to 30 mol% resulted in erosion of the observed conversion (entry 5). We were pleased to observe that omitting acetic acid from the reaction mixture resulted in an increase in conversion of the allylic formamide substrate, 329, to the desired product, 330 (entry 6). Not surprisingly, increasing the amount of acetic acid resulted in consistently lower catalytic efficiencies (entries 7 to 11).

Table 12: Screening of additive loading.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Bu$_4$NI loading (mol%)</th>
<th>AcOH loading (mol%)</th>
<th>Conversion[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>20</td>
<td>5%</td>
</tr>
<tr>
<td>2</td>
<td>5</td>
<td>20</td>
<td>8%</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>20</td>
<td>28%</td>
</tr>
<tr>
<td>4</td>
<td>15</td>
<td>20</td>
<td>32%</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>20</td>
<td>21%</td>
</tr>
<tr>
<td>6</td>
<td>15</td>
<td>0</td>
<td>55%</td>
</tr>
<tr>
<td>7</td>
<td>15</td>
<td>5</td>
<td>50%</td>
</tr>
<tr>
<td>8</td>
<td>15</td>
<td>10</td>
<td>42%</td>
</tr>
<tr>
<td>9</td>
<td>15</td>
<td>15</td>
<td>37%</td>
</tr>
<tr>
<td>10</td>
<td>15</td>
<td>30</td>
<td>16%</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>100</td>
<td>5%</td>
</tr>
</tbody>
</table>

[a] Conditions: In a screw-capped vial, substrate 329 (0.08 mmol), Ru$_3$(CO)$_{12}$ (5 mol%), Bu$_4$NI (indicated amount) and acetic acid (indicated amount) were suspended in DMF (0.32 M) and the mixture purged with argon. The vial was sealed and heated to 150 °C for 16 h. [b] Conversion determined by $^1$H-NMR integration against an added standard 1,4-dimethoxybenzene.
Screening different solvents and temperatures, in the absence of acetic acid, was undertaken in an effort to disclose milder reaction conditions. Unfortunately, this screen failed to yield any significant improvement from the conditions developed above. Finally, we observed that the reaction yielded consistently cleaner product formation when it was purged with carbon monoxide gas (1 atm, from a balloon) prior to heating (Table 13, entry 1). This was particularly important when reactions were conducted at scales larger than 0.1 mmol. We attribute this to catalyst decomposition by loss of carbonyl ligands under the temperatures required for this transformation, a process that is minimized by conducting the reaction under a CO atmosphere. Deviation from these optimal conditions led to lower conversions and, therefore, reduced observed yields. A control reaction where Ru₃(CO)₁₂ was omitted showed no conversion (entry 2). Reducing the amount of iodide additive to lower than 15% also resulted in lower conversion and yield (entries 3 to 5). Interestingly, sodium iodide, an alternative halide source, was also a competent additive and could be used instead of Bu₄NI (entry 6). CO atmosphere proved critical for obtaining consistently high conversions in the process and alternative purging of the reaction mixture with argon resulted in a sluggish reaction (entry 7). Additionally, conducting the reaction open to air further deteriorated the reaction and no conversion was observed (entry 8). Lowering the catalyst loading (3 mol% Ru₃(CO)₁₂) or lowering the reaction temperature (120 °C) resulted in lower yields of the desired product, despite full conversion of the starting material, and formation of volatile decomposition products (entries 9 and 10).
Table 13: Optimized conditions for intramolecular hydrocarbamoylation.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Deviation from the “standard conditions”</th>
<th>conversion</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>“Standard conditions”[a]</td>
<td>&gt;99%</td>
<td>92%</td>
</tr>
<tr>
<td>2</td>
<td>no Ru₃(CO)₁₂</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>0% Bu₄NI</td>
<td>15%</td>
<td>Trace</td>
</tr>
<tr>
<td>4</td>
<td>5% Bu₄NI</td>
<td>40%</td>
<td>36%</td>
</tr>
<tr>
<td>5</td>
<td>10% Bu₄NI</td>
<td>84%</td>
<td>78%</td>
</tr>
<tr>
<td>6</td>
<td>NaI instead of Bu₄NI</td>
<td>&gt;99%</td>
<td>92%</td>
</tr>
<tr>
<td>7</td>
<td>no CO (under Ar)</td>
<td>53%</td>
<td>10%</td>
</tr>
<tr>
<td>8</td>
<td>no CO (under air)</td>
<td>0%</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>only 3% Ru₃(CO)₁₂</td>
<td>&gt;99%</td>
<td>87%</td>
</tr>
<tr>
<td>10</td>
<td>Reaction at 120 °C</td>
<td>&gt;99%</td>
<td>77%</td>
</tr>
</tbody>
</table>

[a] Conditions: In a vial, substrate 329 (0.08 mmol), Ru₃(CO)₁₂ (5 mol%), Bu₄NI (indicated amount) and acetic acid (indicated amount) were suspended in DMF (0.32 M) and the mixture purged with argon. The vial was sealed and heated to 150 °C for 4 h. [b] Conversion and yield determined by ¹H-NMR integration against an added standard 1,4-dimethoxybenzene.

3.5 Substrate Scope: Terminal Alkenes

After developing the optimized conditions for the intramolecular hydrocarbamoylation on the model substrate 329, the scope of the transformation was investigated. Initial studies were focused on terminal monosubstituted alkenes 331 with secondary carbinamides (formamide placed on a trisubstituted carbon atom) (Table 14). We were pleased to observe that under the optimized conditions both alkyl (entries 1 to 3) and aryl (entries 4 to 7) groups were tolerated. Functional groups such as esters (entry 3), electron poor (entry 6) and electron rich (entry 7) aryl groups were compatible with the reaction conditions. In all cases, the desired 2-pyrrolidones 332 were obtained in good yields.
Table 14: Scope of monosubstituted alkenes with tertiary carbinamides.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1" alt="Substrate 1" /></td>
<td><img src="image2" alt="Product 1" /></td>
<td>87%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="Substrate 2" /></td>
<td><img src="image4" alt="Product 2" /></td>
<td>81%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5" alt="Substrate 3" /></td>
<td><img src="image6" alt="Product 3" /></td>
<td>74%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="Substrate 4" /></td>
<td><img src="image8" alt="Product 4" /></td>
<td>77%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="Substrate 5" /></td>
<td><img src="image10" alt="Product 5" /></td>
<td>74%</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="Substrate 6" /></td>
<td><img src="image12" alt="Product 6" /></td>
<td>77%</td>
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<tr>
<td>7</td>
<td><img src="image13" alt="Substrate 7" /></td>
<td><img src="image14" alt="Product 7" /></td>
<td>75%</td>
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</tbody>
</table>

[a] Conditions: In a vial, substrate 331 (1.0 eq.), Ru$_3$(CO)$_{12}$ (5 mol%) and Bu$_4$NI (15 mol%) were suspended in DMF (0.32 M) and the mixture purged with CO (balloon). The vial was sealed and heated to 150 °C for 4 h. [b] Isolated yield of the pure compound after flash chromatography.
We were pleased to observe that the corresponding tertiary carbinamides were also competent substrates in the cyclization (Table 15). In all cases, the substrate allylic formamides 333 could be cyclized to the desired 2-pyrrolidones 334, bearing a fully substituted carbon center, in good yields and allowed the synthesis of various spirocycles (entries 2 to 5) of varying structural complexity.

Table 15: Intramolecular hydrocarbamoylation with tertiary carbinamides.\[a\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Substrate 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>90%</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Substrate 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>87%</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Substrate 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>70%</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Substrate 4" /></td>
<td><img src="image" alt="Product 4" /></td>
<td>87%</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Substrate 5" /></td>
<td><img src="image" alt="Product 5" /></td>
<td>79%</td>
</tr>
</tbody>
</table>

[a] Conditions: In a vial, substrate 333 (1.0 eq.), Ru$_3$(CO)$_{12}$ (5 mol%) and Bu$_4$NI (15 mol%) were suspended in DMF (0.32 M) and the mixture purged with CO (balloon). The vial was sealed and heated to 150 °C for 4 h. [b] Isolated yield of the pure compound after flash chromatography.
The application of this methodology for the preparation of enantioenriched 2-pyrrolidones was next investigated. In this respect, the potential for olefin transposition under the reaction conditions, and, therefore, possible racemization of the substrate (e.g. as described in Scheme 40) was of concern. During optimization with 329, the formation of volatile byproducts was observed (Table 13), but these could not be isolated. To identify these byproducts, substrate 335 was employed in the cyclization reaction under the unoptimized conditions (i.e. with acetic acid additive and under argon atmosphere). In this experiment, we observed the formation of isomerized products 337 and 338 along with desired pyrrolidone 336 (Scheme 56). We speculated, however, that similarly to the hydroesterification cascade, stereochemical information would be conserved, given that formation of these byproducts was suppressed under the optimal conditions.

Scheme 56: Byproducts formed from 335 under unoptimized conditions.

To probe for potential racemization, we prepared substrate (S)-341 in enantioenriched form using an asymmetric allylic amination protocol (Scheme 57). Addition of racemic allylic alcohol (±)-340 to a mixture of catalytic [Ir(COD)Cl]₂, chiral phosphoramidite-olefin ligand (S)-339, and excess sulfamic acid in a THF/DMF mixture gave the free allylic amine, which was protected as the formamide (S)-341 by treatment of the reaction mixture with base (NaHCO₃) and FAA in acetic acid. After chromatographic purification, determination of optical purity of (S)-341 by chiral SFC analysis revealed enantiomeric excess of 88% and the absolute configuration was assigned by comparison with the literature. Subjection of this enantioenriched allylic formamide to our optimized reaction conditions for the intramolecular hydrocarbamoylation gave the desired 2-pyrrolidone (S)-342 in 77% yield which displayed fully conserved enantioenrichment from the substrate (88% ee), as determined by chiral SFC analysis of the chromatographed product by comparison with a racemic sample.
Scheme 57: Preparation of enantioenriched pyrrolidone (S)-342.

The conservation of optical purity is synthetically relevant because it demonstrates the power of the intramolecular hydrocarbamoylation for the preparation of chiral pyrrolidones. In particular, the strategic advantage of combining this cyclization methodology with the enantioselective allylic amination allows optically enriched 2-pyrrolidones to be prepared in three steps from the corresponding aldehydes. The other portions of the pyrrolidone scaffold can also be traced back to cheap, readily available reagents (formic acid, sulfamic acid, vinylmagnesium bromide) (Figure 15).

Figure 15: Disconnection strategy for preparation of chiral pyrrolidones.

3.6 Substrate Scope: Substituted Alkenes

The use of more substituted alkenes was next explored in the intramolecular hydrocarbamoylation methodology. Initially, it was expected that 1,2-disubstituted alkenes would undergo isomerization as had been observed in the case of the hydroesterification (chapter 2), leading ultimately to formation of the larger ring system in a cascading sequence.
of isomerization and hydrocarbamoylation (e.g. formation of piperidone 292 from 291, Scheme 50). To test this hypothesis, 1,2-disubstituted alkene 324 was subjected to the optimized hydrocarbamoylation conditions (Scheme 58). Contrary to our initial expectations, we observed exclusive formation of the corresponding pyrrolidone product 343 from the direct cyclization of the alkene at the internal position. While this observation does not exclude possible alkene transposition, it demonstrates a strong bias for the system towards five-membered ring formation. Next, the cyclization of homoallylic formamide 325 was reacted under the same conditions and formation of the same pyrrolidone 343 was observed. The formation of product 343 from formamide 325 likely arises from an \textit{exo}-cyclization of the olefin, which confirms the observed preference for pyrrolidone (as opposed to piperidone) formation. Finally, in an attempt to access larger ring systems, the cyclization conditions were applied to bis-homoallylic formamide 326, resulting, however, in formation of the five-membered ring product 344. In this case, formation of the pyrrolidone arises presumably from an alkene isomerization process followed by C–C bond formation.

\begin{center}
\includegraphics[width=\textwidth]{s58.pdf}
\end{center}

\textbf{Scheme 58: Cyclization of formamides 324–326.}

In the cyclizations described above, the products were obtained in 1:1 diastereomeric ratio, an observation for which two potential reasons can be contemplated: either the cyclization process is unselective with respect to the configuration at C(3) in the product, or this center might suffer epimerization under the reaction conditions. To probe for the latter option, a
sample of diastereomically enriched trans-343, obtained by careful chromatographic separation of the diastereomeric mixture, was subjected to the reaction conditions (Scheme 59). In this reaction, no epimerization of the C(3) center was observed, indicating that the lack of diastereoselectivity with respect to the C(3) center in the cyclization arises from a non-selective cyclization event.

Next, the cyclization of 1,1-disubstituted alkenes was investigated (Scheme 60). When methyl-substituted allylic formamide 327 was subjected to intramolecular hydrocarbamoylation, the expected C(4)-substituted product 345 was obtained in good yield. Most surprisingly, in contrast to the unselective cyclization of C(3)-substituted pyrrolidones, formation of the trans-product took place with a high degree of diastereoselection and the cis-product was only observed in minute amounts. Analogously, when 1,1-disubstituted alkene substrate 328 was employed in the reaction, trans-product pyrrolidone 346 was formed with good selectivity.

Scheme 59: Epimerization attempt on trans-343.

Scheme 60: Diastereoselective cyclization of 1,1-disubstituted alkenes.
The high degree of trans-selectivity observed in the cyclization of 1,1-disubstituted alkenes 327 and 328 stands in contrast to the cis-selectivity observed by Sakai for the analogous hydroacylation of substituted pentenals (Figure 16). In this Wilkinson’s catalyst-promoted hydroacylation, cis-selectivity is proposed to arise from a selective hydrometallation step. Thus, the acyl-rhodium species is suggested to adopt conformation 349 instead of 350 by minimizing the A1,2-interaction between R1 and R2, which ultimately places them in a cis-relationship after reductive elimination.

In our case, however, formation of the presumably thermodynamically more stable trans-product was observed. We attribute this to a fast, reversible hydoruthenation step that allows access to both cis- and trans-precursors in equilibrium, leading to formation of the more stable product during ring closure.

Finally, model 1,1,2- and 1,2,2-trisubstituted alkenes 351 and 352 were attempted as substrates in the intramolecular hydrocarbamoylation (Figure 17). Unfortunately, under the optimized conditions, no product formation was observed from these substrates and starting materials were re-isolated quantitatively. Attempts to conduct the reaction at a more elevated temperature (180 °C) also failed to yield the desired products. Presumably, the steric demand of these substrates inhibits functionalization of the alkene by the metal catalyst, and, therefore, no product is obtained. Additionally, no decarbonylation of the formamide was observed in either case, which indicates that olefin hydrometallation must occur prior to activation of the formamide C–H bond, which must be hampered in this case.
In general, the pyrrolidones obtained in this reaction feature a convenient synthetic handle in the form of a free amide N–H bond for further functionalization. This stands in contrast to the Nickel/Lewis-acid catalyzed \textit{exo}-selective hydrocarbamoylation reactions developed by Hiyama\cite{1},\textsuperscript{49,51} and rendered asymmetric by Cramer\cite{2},\textsuperscript{45} which require this rather acidic position to be masked by an appropriate protecting group. Under our conditions, however, employing Ru\textsubscript{3}(CO)\textsubscript{12} as catalyst, we found that this free N–H bond was required for the success of the cyclization (Figure 18). Attempts at cyclizing substrates where this position was blocked by alkyl (353), acyl (354) or sulfonyl (355) groups resulted in no conversion and only starting materials were observed in the reaction mixtures.

![Figure 17: Trisubstituted olefins attempted in the cyclization.](image)

3.7 Mechanistic Considerations

Our initially proposed mechanism is based on the observations made by Watanabe for the ruthenium carbonyl cluster-catalyzed intermolecular hydrocarbamoylation of simple olefins\cite{3,4}. In those studies, initial formamide C–H activation is suggested to occur prior to olefin functionalization. An analogous mechanistic pathway was also suggested by Chang in his auxiliary directed intermolecular hydrocarbamoylation\cite{5}. When translated to our intramolecular system (Figure 19) this would proceed by insertion of the active metal catalyst 356, presumably generated by the combination of Ru\textsubscript{3}(CO)\textsubscript{12} and Bu\textsubscript{4}NI, into the substrate.

![Figure 18: Tertiary formamides attempted in the cyclization.](image)
allylic formamide 357 by C–H oxidative addition to generate acyl-ruthenium intermediate 358. Because of the proximity of the olefin to the metal center, this intermediate would be poised to undergo intramolecular alkene insertion into the Ru–H bond to give alkyl-ruthenium species 359. Finally, reductive elimination from this intermediate would lead to product formation (360) and regeneration of the catalytically active species 356. This mechanism also parallels what has been suggested for the intramolecular rhodium-catalyzed hydroacylation reaction in the course of numerous mechanistic studies.31a, 120-121 Based on this pathway, a potential side reaction involving decarbonylation can be speculated from this mechanism. Acyl-ruthenium intermediate 358 can undergo extrusion of CO to give carbonyl complex 361, which, through ligand loss, results in formation of free allylic amine 362.

While the mechanistic pathway presented above is feasible, it shows inconsistencies with respect to observations made during the reaction development, especially regarding substrate limitations. We were particularly intrigued by the fact that tertiary formamides, where the free N–H bond is not present, were not competent in the cyclization reaction. This led us to propose that this amide N–H bond might play an important role in the catalytic cycle. Moreover, we observed that more hindered tertiary alkenes did not display any reactivity. Functionalization of the alkene could be excluded on steric grounds. These substrates, however, could be expected to undergo catalyst oxidative addition into the formamide C–H bond, which, in the absence of an accessible olefin, would lead to decarbonylation. The fact that this process was not observed suggests that alkene metalation precedes oxidative addition into the formamide C–H bond.
Based on these observations, an alternative, revised mechanism can be suggested (Figure 20). In the first step, the active ruthenium catalyst (356) generated by Ru₃(CO)₁₂ and Bu₄NI complexes the substrate 357 by oxidative addition on the N–H bond to give the ruthenium hydride intermediate 363. This process of N–H insertion can be alternatively viewed as a sequence of metal protonation, followed by coordination of the amide ligand. As observed during the development of the hydroesterification cascade (chapter 2.11), the complex formed by the mixture of triruthenium dodecacarbonyl and tetrabutylammonium iodide can easily suffer protonation at the metal cluster to give active ruthenium hydrides.¹⁰⁰ Ruthenium hydride 363 can then undergo migratory insertion of the alkene into the Ru–H bond to give alkyl complex 364. From this stage, β-hydride elimination would furnish alkyl ruthenium hydride 365, which would be poised to undergo nucleophilic attack of the alkyl-metal moiety onto the electrophilic carbonyl carbon to give intermediate 366. Finally, ligand dissociation and deprotonation of the ruthenium hydride would yield the desired pyrrolidone product 360 and regenerate the active catalyst, 356.

Figure 20: Hydrocarbamoylation mechanism involving N–H insertion.

This alternative mechanism is consistent with the observations made during the development of this reaction, since it involves a key role of the amide N–H bond in the mechanistic cycle. Moreover, it accounts for the lack of decarbonylation from hindered alkene substrates, since hydoruthenation of the olefin precedes cleavage of the formamide C–H bond.
To gain additional insight into the mechanism and corroborate our proposal, we conducted a number of experiments with deuterium-labeled substrates (Scheme 61). A substrate, labeled at the formamide C–H bond (370) could be conveniently accessed by using deuterated formic acid in the preparation of FAA. Labeling of the N–H bond (367) could be effected by repeated rounds of exchange with D₂O. When N–D labeled substrate 367 was subjected to cyclization conditions (experiment A), the product 368 was obtained showing significant deuterium incorporation (45%) into the carbon backbone of the pyrrolidone. This observation suggests that olefin hydroruthenation is reversible and nonselective, leading to scrambling of the deuterium label. Consistent with this result, when the reaction with 367 was interrupted at 50% conversion (experiment B), the alkene in the recovered starting material 369 was shown to incorporate 31% deuterium label. Next, the same experiments were repeated with substrate 370, bearing the label at the formamide C–H bond. With this substrate, when the cyclization reaction was stopped at 50% conversion (experiment C), recovered starting material 372 showed no deuterium loss from the formyl position. This indicates that breaking of the formyl C–H bond is irreversible in the catalytic cycle. When the reaction of 370 was carried out to completion (experiment D), the product pyrrolidone 371 was obtained showing only very minor incorporation of the label at the C(3) position and not at all at the C(4) position. The appearance of residual incorporation of the label at C(3) in 371 is consistent with the fact that deuterium in the product’s N–H position would be susceptible to exchange with the same position of still unreacted starting material. An additional potential cause for this incorporation would be reversible α-hydride elimination from intermediate 365 (Figure 20), leading to scrambling of the label at that position. This process has been described and extensively studied for osmium carbonyl clusters, but not reported for the present catalyst system. In summary, the observations made in the labeling experiments provide additional support for a mechanistic scheme involving initial activation of the N–H bond and subsequent irreversible cleavage of the formamide C–H bond.
Scheme 61: Deuterium labeling experiments.

An additional interesting observation was made when employing allylic acetamide 373 as substrate under the cyclization conditions (Scheme 62). In this experiment, the formation of ca. 20% N-acetyl pyrrolidone product 374 was observed, while the rest of the mass balance was comprised of various unidentified decomposition or isomerization products.

Scheme 62: cyclization attempt with allylic acetamide 373.

The observation that the acetamide is capable of undergoing cyclization, though not efficiently, points to yet another mechanistic nuance. The experiment suggests that carbonylation of the substrate can take place directly from the carbonyl ligands bound to the ruthenium cluster and, vicariously, from the carbon monoxide atmosphere of the reaction. This possibility allows us to extend the proposed mechanism to include this process (Figure 21). From alkyl-ruthenium species 364, carbonylation of the alkyl ligand would lead to formation of complex 375. This could then undergo reductive elimination to furnish formylated pyrrolidone 376 and regenerate the active catalyst. Decarbonylation of 376, in a separate process, through oxidative addition of the ruthenium catalyst into the formamide C–
H bond would give 377. Extrusion of carbon monoxide to give ruthenium hydride 378 followed by decomplexation would provide the desired product 360, and regeneration of the active catalyst, 356.

![Mechanistic scheme](image)

**Figure 21:** Extended mechanistic scheme.

### 3.8 Conclusions

In this chapter we have described the application of a catalytic system based on ruthenium carbonyl clusters for the intramolecular hydrocarbamoylation of allylic formamides. The obtained product pyrrolidones are useful building blocks for the preparation of fine chemicals as this scaffold is present in a wide range of commercially relevant compounds.

The overall transformation proceeds by formal cleavage of the formamide C–H bond of the allylic amide substrate and formation of a new C–C bond in a reaction that is characterized by complete atom economy. Owing to the ample selection of methods for the asymmetric preparation of the corresponding starting materials, the present strategy comprises a convenient route for the preparation of optically enriched chiral pyrrolidones. In this respect, the use of iridium-catalyzed allylic amination or Ellman’s strategy of organometallic additions to sulfinimines was described, demonstrating that the obtained heterocycles can be traced back to the corresponding aldehydes and ketones in a few simple steps.
The cyclization reaction was shown to be selective for the formation of five-membered heterocycles and attempts to obtain larger rings resulted in alkene isomerization prior to cyclization. The preparation of 2-pyrrolidones bearing a substituent in the C(3) position was achieved but without any control of the relative stereochemistry between C(5) and C(3). We could also show, however, that 2-pyrrolidones bearing alkyl substituents on the C(4) position could be accessed and displayed a good degree of diastereospecificity in the cyclization.

With the observations made, in particular regarding the need for a free N–H bond in the substrate, a mechanistic rationale was suggested for the process. In it, the key role of the N–H bond is described, where it serves to generate the active ruthenium hydride that undergoes migratory insertion of the alkene. This was further supported by labeling studies on model substrates. Finally, the procedure presents an attractive and unprecedented strategy for the synthesis of these small saturated nitrogen-containing heterocycles and should find use in preparative applications.
4 Conclusion and Outlook
In this work, we investigated the catalyst system formed by ruthenium carbonyl and an iodide additive in synthetically relevant settings. Their activity in carbonylation reactions was studied, with special focus on reactions that overcome the need for handling highly toxic and hazardous carbon monoxide in pressurized vessels. This was achieved by employing suitable CO surrogates such as formate esters in hydroesterification and formamides in hydrocarbamoylation reactions.

In a first instance, a tandem sequence of olefin isomerization and hydroesterification was developed for allylic amides and alcohols bearing internal alkenes. We devised a way to tune the reactivity of the catalyst so as to promote alkene isomerization prior to C–C bond formation and effect the overall process in a cascading fashion. In that regard, the reaction can be characterized as an auto-tandem catalytic reaction, i.e. where a single catalyst precursor performs multiple distinct catalytic steps in a cascading fashion without the need for operator intervention. Interestingly, the cascade profits from the additive effect of acetic acid which accelerates isomerization by promoting metal-hydride formation. The spectroscopic observation that an active ruthenium hydride is obtained by the use of acetic acid additive provided additional support for its intriguing promoting effect.

In a second part of the project, in an effort to improve the efficiency of the reaction for nitrogen-containing heterocycle preparation, we explored the intramolecular hydrocarbamoylation of allylic formamides. This allowed straightforward access to 2-pyrrolidones from easily prepared allylic amines in a reaction that displays complete atom economy. Mechanistic probing of the reaction showed key involvement of the free amide N–H bond in the reaction, suggesting formation of an active ruthenium hydride.

In general, the scope of substrates that can undergo these transformations has seen a significant improvement, vis a vis the scope previously reported for similar reactions. We attribute this to the comparably mild nature of the reaction conditions that can be achieved when employing the present ruthenium/iodide system. The present work also makes use of accessible experimental setups and reaction conditions, most notably by circumventing the need for pressurized carbon monoxide. The benchtop-friendly protocols and broader scope demonstrate the synthetic utility of the current catalytic systems for routine research applications and is expected to find use in this context.
In the course of our investigations, we have gained valuable insights into the reactivity of the catalytic system used in these transformations. The lessons learned in this process have allowed us to adapt the reaction conditions so as to poise the catalyst towards desired reactivity. Further research in this area can focus on several aspects. The effect of ligands on the reactivity of metal clusters could be used to enhance linear-to-branched selectivity in carbonylation reactions. Chiral ligands that can stabilize the low-valent metal complexes could potentially lead to enantioselective carbonylations of internal alkenes. Finally, the multifold reactivity of ruthenium clusters could be exploited in cascades that involve reactions other than carbonylation and isomerization. In that respect, their rich chemistry includes processes such as conjugate reductions, reductions of carbonyls and nitro groups, activation of alkynes, oxidative additions to carbon–halogen bonds and aryl C–H activation, among others.59, 123

Metal clusters have long been considered to dwell in the space between homogenous catalysis, with well-defined easily tunable catalysts of restricted activity, and surface catalysis, with ill-defined, highly active catalytic entities.67a This is reflected by a formidable challenge in their structural and mechanistic elucidation but also results in highly desirable and often surprising reactivity. As it stands, the exact nature of the active species in the reactions developed here, have yet to be uncovered. We expect that the present work will stimulate further research into understanding these unique metal complexes and unravel their full catalytic potential.
5 Investigation of Residual Dipolar Coupling Constants of Polychlorinated Molecules as a Tool for Structural Analysis
5.1 Introduction*

Chlorinated sulfolipids were first isolated in minute quantities from extracts of the chrysophyte *Ochromonas danica* and later found in a variety of marine organisms (Figure 22). They comprise a class of intriguing naturally occurring compounds (379–383) that have increasingly gained the attention of the scientific community. Most notably, chlorosulfolipids 381–383 were isolated from the digestive glands of mussels contaminated with microorganisms and are associated with seafood poisoning and show moderate cytotoxic activity. The precise mode of action for this activity still remains unknown. Studies aimed at further understanding the role of these halogenated lipids in membranes require a deep understanding of their structural and conformational properties, as those are intimately related to their activity.

![Figure 22: Docosane, Tetracosane and Pentadecane chlorosulfolipids isolated from microalgae.](image)

A striking feature of the chlorosulfolipids is the remarkable complexity of their structure. The intricate stereochemical array of secondary chlorides and alcohols poses a major challenge to both structural elucidation and chemical synthesis of these natural products. In that respect, radioactive labeling with $^{36}\text{Cl}$ has been used to determine the correct connectivity in danicalipin A (379), one of the first of its family to be characterized. Labeled samples,

* This work was carried out in close collaboration with Dr. Marc-Olivier Ebert and MSc Deborah Meyer. All NMR experiments were carried out by these collaborators with substances prepared in our group.
obtained from *O. danica* cultures in an isotopically enriched medium were subjected to a series of laborious degradation studies, including mass-spectrometric analyses of the degradation products. These studies allowed the connectivity of danicalipin A to be correctly identified, albeit devoid of stereochemical details. Efforts towards the structural elucidation of further members of this family have focused on NMR studies, as well as *Mosher’s* ester analysis.\(^{126,129}\)

Confirmation of the correct stereochemistry could, in theory, be achieved by total synthesis of each member of this family of natural products.\(^{130}\) In addition to allowing unambiguous confirmation of structure, it would also supply the scientific community with samples of these often-times rare substances for biological evaluation. To this end, syntheses of various members of the chlorosulfolipid family have been successfully completed,\(^{131}\) including hexachlorosulfolipid (381),\(^{132}\) danicalipin A (379)\(^{133}\) and malhamensilipin (380).\(^{134}\) Recent efforts have also led to the synthesis of the nominal structure of undecachlorosulfolipid A (382),\(^{135}\) prompting a re-evaluation of its stereochemical assignment. Despite significant advances in synthetic strategies, the total synthesis of these polychlorinated natural products still remains a formidable challenge, in particular when limited structural information is available. In this respect, the synthesis of the nominal undecachlorosulfolipid (382) illustrates both the importance of synthetic confirmation for stereochemical assignment as well as the challenges associated with this approach.

Spectroscopic methods for the characterization of chlorosulfolipids have focused heavily on the use of *Murata’s* J-based configuration analysis (JBCA).\(^{136}\) The method is based on the assumption that these acyclic molecules adopt a staggered conformation in solution. In atoms bearing electronegative substituents, the size of the coupling constants \(2J_{\text{CH}}\) and \(3J_{\text{HH}}\) displays a dependence on the torsion angle along the corresponding bonds, described by the *Karplus* relationship.\(^{137}\) If enough coupling constants are known, along with suitable NOE data, the relative stereochemistry of each center can be assigned. To that end, a previous report from our group has provided calibration parameters for applying JBCA to chlorinated natural products.\(^{138}\)

While characterization methods developed thus far have allowed many chlorosulfolipid structures to be correctly assigned, recent synthetic efforts towards undecachlorosulfolipid (382) have demonstrated that characterization of these compounds still presents a considerable challenge. The search for alternative strategies to elucidate the intriguing polychlorinated scaffold of these natural products is therefore essential.
5.2 Hypothesis

An alternative NMR-spectroscopic method that has been used for structural elucidation, as well as conformational refinement in particular for molecules displaying a rigid structure is the measurement of residual dipolar couplings (RDCs). RDCs can be observed when molecules are subjected to partial alignment by interaction with an oriented medium such as liquid crystals or stretched gels. Under these conditions, molecules can freely rotate as in a conventional, isotropic, liquid phase. In contrast to solid phase, where broad lines are observed, free tumbling and diffusion takes place in the partially oriented medium and lead to averaging of intermolecular dipolar couplings. On the other hand, partial orientation of the molecules causes the intramolecular dipolar couplings to have a non-zero average, allowing the measurement of residual dipolar couplings (RDCs). Relaxation times in partially oriented media are also in line with those observed for measurements in liquid phase, since the timescale of molecular motion is similar in both cases. This leads to spectral linewidths that are in the order of 1 Hz, leading to well-resolved spectra.

Unlike other NMR parameters, RDC is not a local phenomenon, having the magnetic field as external reference. In this respect, it is complementary to the local $J$-couplings and provides additional information about the molecular structure. So far, RDC measurements have mostly been used to characterize conformationally restricted molecules, in particular ring systems. In contrast, the study of dynamic, flexible systems has rarely been undertaken. Given our general interest in the chemistry of the chlorosulfolipids as well as the constant need for better analytical strategies for their structural elucidation, we chose to study the applicability of RDC measurements for the stereochemical assignment of these compounds.

The measured residual dipolar coupling $D$ between two nuclei I and J in partially aligned media can be described by Equation (1). This involves matrix multiplication with $\mathbf{P}$ representing the probability tensor and with $\mathbf{r}$ representing the internuclear unit vector between nuclei I and J, in an arbitrarily chosen molecular frame with Cartesian components $(x,y,z)$. In isotropic solution, this term would average to zero.

$$D = \frac{3}{2} D_{\text{max}} \left( \mathbf{r}^T \mathbf{P} \mathbf{r} - \frac{1}{3} \right)$$ (1)
$D_{\text{max}}$ is the largest possible RDC obtainable between the two nuclei I and J in a rigidly aligned sample. It is defined by Equation (2) and depends only on the known gyromagnetic ratios $\gamma_i$ and $\gamma_j$ of the respective nuclei and the distance $r_{ij}$ between them.

$$D_{\text{max}} = \frac{\mu_0 h \gamma_i \gamma_j}{4\pi^2 r_{ij}^3} \quad (2)$$

For a given molecule, the probability tensor $P$ has to be determined experimentally. It can be represented by a symmetric 3x3 matrix with trace = 1. Given the symmetry and trace constraint, this represents a set of five degrees of freedom, i.e. five variables. The probability tensor can therefore be solved by measuring at least five different, independent RDC constants (i.e. with different $r_i$) and solving the resulting set of linear equations (1). Independent RDC values can be obtained when no pair of $r_i$ is collinear and no more than two $r_i$ lie in the same plane. In practice, it is customary to record as many RDC constants as possible and then solve the resulting overdetermined system of linear equations, which is comprised of five variables (the unique elements of $P$) and $N$ equations (where $N$ is the number of measured RDCs) by singular value decomposition (SVD). This numerical solving can be performed by the program PALES (Prediction of Alignment from Structure) which therefore furnishes the probability tensor for which the back-calculated RDC constants have the least-squares deviation from the observed ones.

A good fit between back-calculated and measured RDCs will ultimately depend on the ability to correctly assign a suitable $r_i$ to each measured residual dipolar coupling constant $D$ (i.e. each pair of nuclei I and J). The internuclear unit vector $\mathbf{r}$ is derived from the three-dimensional structure of the molecule being studied. While this is a straightforward process for rigid molecules, in particular ring systems, the prediction of $\mathbf{r}$ for flexible, linear molecules is more challenging. A poor prediction of the internuclear unit vector, i.e. one that does not correspond to the solution structure of the studied molecule, will lead to a poor fit during SVD prediction of $P$. Conversely, a correct estimation of $\mathbf{r}$ is expected to lead to a good accordance between calculated and measured RDCs.

In the case of the chlorosulfolipids, we expect the relative stereochemistry of the secondary chlorides and alcohols to be the major contributing factor determining their solution structure (Figure 23). This structure can be calculated using computational methods and then translated to correctly predict $\mathbf{r}$. This vector can finally be used in the least-square fitting prediction of
the probability tensor $\mathbf{P}$, using the measured RDC data. We hypothesize that the quality of the fit will depend on the accuracy of the predicted $\mathbf{r}$. Under the assumption that $\mathbf{r}$ is highly dependent on the relative stereochemistry of the studied compound, we expect the back-calculated RDCs from the solved $\mathbf{P}$ will only display good correlation with the measured values for $\mathbf{r}$ obtained from the correct stereochemical assignment. Conversely, alternative diastereomeric forms computed for the molecule are expected to result in poor fitting between the calculated and measured RDC data. In summary, a systematic analysis of data fits between calculated and measured RDCs for all diastereomers of a compound, is expected to yield the best correlation for the correct structure.

![Diagram of structural elucidation using RDC measurements](image)

**Figure 23: Suggested procedure for structural elucidation using RDC measurements.**

As a model system for the complex stereochemical array in the chlorosulfolipids, we chose to study the residual dipolar couplings of trichlorinated hexanediols. These compounds have been used in our previous report on the JBCA study and allowed good prediction of relative stereochemistry. Moreover, these substances have been characterized unambiguously by single crystal X-Ray diffraction and provide the ideal model to test our hypothesis. We therefore carried out RDC measurements on compounds 384 and 385, which differ by a single
stereocenter at C(2). Unambiguous assignment of this stereocenter to each of these compounds would demonstrate the power of this proposed method.

\[ \text{Figure 24: Selected structures for the present study.} \]

5.3 Results and Discussion

The residual dipolar couplings of diastereomers 384 and 385 were measured in an alignment medium comprised of PMMA crosslinked with 0.136 mol% EGDMA. Solutions of the compounds in CDCl\textsubscript{3} were added to dry polymer rods in NMR tubes. The polymers were then allowed to swell at r.t. for at least 3 weeks. The obtained gels were then analyzed by NMR and compared to corresponding samples prepared in liquid (isotropic) CDCl\textsubscript{3} phase. Dipolar coupling constants were obtained from HSQC without t2 decoupling, INADEQUATE and INEPT experiments. Dipolar couplings over multiple bonds could be obtained from HSQC-HECADE experiments. The obtained residual dipolar coupling data can be found in Table 16.
Table 16: Measured RDC constants for substances 384 and 385.

<table>
<thead>
<tr>
<th>Nucleus I</th>
<th>Nucleus J</th>
<th>RDC in 384 [Hz]</th>
<th>RDC in 385 [Hz]</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(2)</td>
<td>H(2)</td>
<td>59.6</td>
<td>42.0</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(3)</td>
<td>42.3</td>
<td>38.0</td>
</tr>
<tr>
<td>C(4)</td>
<td>H(4)</td>
<td>33.5</td>
<td>24.0</td>
</tr>
<tr>
<td>C(5)</td>
<td>H(5)</td>
<td>64.7</td>
<td>22.0</td>
</tr>
<tr>
<td>C(6)</td>
<td>H(6) (average)(^a)</td>
<td>13.5</td>
<td>0.0</td>
</tr>
<tr>
<td>C(1)</td>
<td>C(2)</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>C(2)</td>
<td>C(3)</td>
<td>-11.0</td>
<td>-7.0</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>-10.0</td>
<td>-6.0</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>C(6)</td>
<td>H(5)</td>
<td>8.0</td>
<td>n.d.</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(4)</td>
<td>5.0</td>
<td>n.d.</td>
</tr>
<tr>
<td>C(4)</td>
<td>H(2)</td>
<td>n.d.</td>
<td>-5.0</td>
</tr>
<tr>
<td>C(3)</td>
<td>H(4)</td>
<td>n.d.</td>
<td>4.0</td>
</tr>
</tbody>
</table>

\(^a\) Value displayed is the adjusted RDC constant for a virtual, averaged methyl CH. See discussion in text below and equation (3).

With this data in hand, we turned our attention to the determination of the probability tensor. In an initial analysis step, all the possible diastereomers of the trichlorinated hexanediols (Table 17) were systematically analyzed to disclose their solution structure and allow for the calculation of the internuclear unit vectors \( \vec{r} \). To this end, the conformer distribution for each diastereomer was determined by molecular mechanics, using the MMFF force field. All the conformers within a range of 2.5 kcal/mol from the predicted lowest energy conformation were analyzed by the Hartree–Fock method with basis set 6–31G* to determine the Boltzmann distribution in this reduced ensemble. The lowest energy conformation (the one with the highest Boltzmann population) was then further refined by energy minimization by DFT (B3LYP, basis set: 6–31G*). Through this systematic analysis, the lowest-energy conformation for each diastereomer was determined, along with its Boltzmann population.
Table 17: All possible diastereomers of 384 and 385 and corresponding calculated minimized conformations.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Diastereomer</th>
<th>Stereochemical descriptors\textsuperscript{[b]}</th>
<th>preferred conformer (calcd.)</th>
<th>Boltzmann population (calcd.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>384</td>
<td>SRRS</td>
<td>( g^+ g^- t g^- )</td>
<td>88%</td>
</tr>
<tr>
<td>385</td>
<td>RRRS</td>
<td>( g^+ g^- t g^+ )</td>
<td>63%</td>
</tr>
<tr>
<td>386</td>
<td>SSRS</td>
<td>( g^+ t g^- t )</td>
<td>56%</td>
</tr>
<tr>
<td>387</td>
<td>SRSS</td>
<td>( g^+ g^+ g^+ g^+ )</td>
<td>34%</td>
</tr>
<tr>
<td>388</td>
<td>SRRR</td>
<td>( g^+ g^- t g^+ )</td>
<td>95%</td>
</tr>
<tr>
<td>389</td>
<td>RSRS</td>
<td>( g^- g^- g^- t )</td>
<td>91%</td>
</tr>
<tr>
<td>390</td>
<td>RRSS</td>
<td>( t g^+ g^- g^- )</td>
<td>65%</td>
</tr>
<tr>
<td>391</td>
<td>SSSS</td>
<td>( g^+ g^- t g^- )</td>
<td>52%</td>
</tr>
</tbody>
</table>

\textsuperscript{[a]} Energy minimization was performed by molecular mechanics using MMFF, followed by HF minimization (6–31G*) and DFT (B3LYP; 6–31G*). \textsuperscript{[b]} Descriptors of carbons 2, 3, 4 and 5.

To account for fast rotation of the methyl group at C(6) relative to the measurement time-scale, the computed structure was complemented by an additional H-atom. This was
artificially inserted along the methyl-group’s rotation axis, with a bond length equaling that of the other methyl C–H bonds. By using the approximation that the methyl group is perfectly tetrahedral, the time-averaged, measured residual dipolar coupling $D_{C\text{H}_3}$ can be related to the calculated RDC between the methyl-group’s carbon and the virtual Hydrogen by the following equation (3).147

$$D_{C\text{H}_{\text{virt}}} = -3D_{C\text{H}_3} \quad (3)$$

The obtained structural information was then used to determine the alignment tensor and back-calculate the RDC values. This procedure was accomplished using the PALES program, which provides the fit between the observed and calculated RDC constants. The fit of substances 384 and 385 obtained using their respective minimized structures for the determination of $\vec{r}$ is shown in Figure 25.

![Fitting of 384 and 385](image)

**Figure 25:** Fitting of observed (Dobs) and back-calculated (Dcalc) residual dipolar constants for substances 384 and 385, using their respective minimized structures.

The fit of the observed and back-calculated RDC constants for substances 384 and 385 with their respective calculated structures shows a good degree of correlation. In particular for
diastereomer 384, the value of $\chi^2 = 14.6$ is in accordance with the limit of the experimental resolution (1.0 Hz for the measured RDCs). In the case of substance 385, the value of $\chi^2 = 82.1$ is somewhat above the value expected for a perfect fit and likely reflects contributions from alternative conformers of the molecule to the probability tensor. In that respect, it is interesting to notice that the Boltzmann distribution in the restricted ensemble, calculated for 385, attributes a population of 63% in this lowest energy conformer ($\text{g}^+ \text{g}^- \text{t} \text{g}^+$). This geometry is also in accordance with that observed for 385 in the previously reported crystal structure as well as that elucidated using Murata’s JBCA method. In contrast, the Boltzmann population calculated for the preferred conformer of substance 384 ($\text{g}^+ \text{g}^- \text{t} \text{g}^-$) is 88%. The relatively modest calculated Boltzmann population for 385 would suggest the presence of a significant portion of alternative conformers in the partially aligned sample. This is then expected to lead to deviations between the predicted RDCs for a single conformer and the measured RDCs for the ensemble.

The RDC data was next re-evaluated in the calculation of the probability tensor using the calculated molecular geometries expected for the alternative (wrong) diastereomers. This cross-fitting was performed using PALES as described above and furnished the correlation data between measured and calculated RDC constants. The $\chi^2$ obtained for each cross-fit between measured data for 384 and 385 and all calculated geometries for 384–391 is displayed in Figure 26.

\[ \chi^2 \text{ for cross-fitting of 384} \]

\[
\begin{array}{cccc}
384 & 14.6 & 1.4 & 102 \\
385 & 284 & 180 & 2621 \\
386 & 12.3 & 330 & \\
387 & 388 & 389 & 390 & 391 \\
\end{array}
\]

\[ \chi^2 \text{ for cross-fitting of 385} \]

\[
\begin{array}{cccc}
384 & 82.1 & 40.5 & 274 \\
385 & 390 & 391 & \\
386 & 57.6 & 57.5 & 826 \\
387 & 20.3 & \\
388 & \\
389 & \\
\end{array}
\]

Figure 26: $\chi^2$ for the fit between observed and calculated residual dipolar coupling constants for substances 384 and 385 with each calculated diastereomer structure (y-axis).
The calculation of the probability tensor assuming the incorrect stereoisomers for compounds 384 and 385 show a surprising result. While the fit using the correct stereoisomer had shown good correlation between measured and predicted RDCs, the cross-fit using other structures shows correlations with varying \( \chi^2 \). In most cases, the fit shows poor correlation, represented by a large value of \( \chi^2 \), as is the case for the fit of data for substance 384 with structures of 386, 387, 389, 390, and 391 and the fit of data for substance 385 with structures 390 and 391. This indicates that the solution structure of the measured samples cannot be represented by the calculated conformers indicated. On the other hand, cross-fits with some of the calculated structures show comparable or even better correlation between measured and calculated RDCs. This would, in principle, indicate that the measured samples can be similarly or even better represented by calculated structures for alternative diastereomers. In particular, the fact that the RDC data of 384 and 385 can be significantly better described by computed structures 385 and 386, respectively, is intriguing.

The varying data for \( \chi^2 \) can be explained, in part, by a poor accuracy in representing the solution structures of the measured compounds. In this respect, the rigid, calculated structures represent only a portion, albeit a significant one, of the Boltzmann distribution. The flexible nature of the linear backbone of the chlorosulfolipids therefore seems to preclude the elucidation of its stereochemical and conformational structure by fitting with a rigid model. Given this uncertainty, it is also not possible to exclude any diastereomers based on the \( \chi^2 \) for the fit, since their computed structure might not display any accordance with the equilibrating conformations in solution.

## 5.4 Conclusion

In conclusion, we have studied the NMR properties of trichlorinated hexanediols in a partially aligned medium comprised of a swollen PMMA polymer in CDCl₃. The compounds display the stereochemical array found in the backbone of the chlorosulfolipids and can therefore serve as models for assigning the stereochemical structure of these natural products. Under partial alignment, they display measurable RDC constants which can be used to calculate the corresponding probability tensor for their alignment. This process requires input of an estimated three-dimensional structure for the compound and it was expected that the DFT-minimized structure of the correct diastereomer would yield the best fit of the RDC data. In
the examples studied, while the correct structure yielded good data correlation, we were unable to identify the correct stereoisomer based on this data correlation alone.

We suggest that the problem originates from the assumption that a single, rigid conformer can be used to represent the entire Boltzmann distribution of solution structures, with respect to their RDC constants. It appears that the flexible nature of the chlorosulfolipids precludes estimation of their solution structure using rigid models. This property of such fascinating molecules renders their characterization difficult and hampers the understanding of their mode of action in biological systems. The challenges in their structural elucidation warrant further investigation and it seems only chemical synthesis can provide definitive stereochemical assignment.
6 Experimental Part
6.1 General Methods

All reactions were performed in oven-dried glassware under argon. HPLC grade solvents were dried and degassed by sparging with argon prior to their use. Commercially available chemicals were used as received unless noted otherwise. Triruthenium dodecacarbonyl (Ru₃(CO)₁₂) was recrystallized from hot benzene and dried under vacuum prior to use. ¹H-NMR spectra were recorded on a Bruker 400 MHz spectrometer in the indicated deuterated solvent. ¹³C-NMR spectra were recorded with ¹H-decoupling on a Bruker 101 MHz spectrometer in the indicated deuterated solvent. ¹⁹F-NMR spectra were recorded with ¹H-decoupling on a Bruker Mercury 376 MHz spectrometer in the indicated deuterated solvent. All NMR signals are given in ppm. Infrared spectra were recorded neat on a Varian 800 FT-IR Scimlar Series spectrophotometer. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter in 10 cm, 2 mL cells, the concentration in g/100 mL and the solvent is given in parentheses. High resolution mass spectrometric measurements were performed by the mass spectrometry service of the Laboratorium für Organische Chemie at the ETH Zürich on an Ion Spec Ultima MALDI-FT-ICR MS using the DHB-tl (2,5-Dihydroxybenzoic acid-two layers) method at 4.7 Tesla. EI measurements were performed on a VG Tribrid spectrometer, 70 eV. ESI measurements were performed on a TSQ 7000. Enantiomeric excess was determined by chiral analytical chromatography and was performed on a Jasco2080Plus supercritical fluid chromatography (SFC) apparatus. Columns and conditions are specified, retention times (tᵣ) are given in minutes.
6.2 Experimental Part to Chapter 2

6.2.1 Synthesis of Starting Materials

2-(non-2-yn-4-yl)isoindoline-1,3-dione

To a solution of non-2-yn-4-ol\textsuperscript{148} (13.4 g, 96.0 mmol, 1.00 equiv.), triphenylphosphine (27.3 g, 104 mmol, 1.09 equiv.) and phtalamide (15.5 g, 105 mmol, 1.10 equiv.) in tetrahydrofuran (750 mL) at 0°C was added slowly diisopropyl azodicarboxylate (22.6 mL, 115 mmol, 1.20 equiv.) and the resulting mixture was stirred for 16 h at r.t. The solution was then concentrated and purified by flash chromatography (5\% EtOAc/Hexane) to give the resulting product as a clear oil in 71\% yield (18.3 g, 68.0 mmol).

Rf (hexane:EtOAc = 9:1); 0.36;

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300MHz, 293K): δ 7.86 – 7.82 (m, 2H), 7.73 – 7.69 (m, 2H), 5.01 – 4.93 (m, 1H), 2.15 – 1.93 (m, 2H), 1.82 (dd, $J = 2.1, 0.2$ Hz, 3H), 1.48 – 1.23 (m, 6H), 0.86 (t, $J = 7.0$ Hz, 3H);

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100MHz, 293K): δ 167.3, 133.9, 131.9, 123.3, 79.5, 75.8, 42.0, 33.6, 31.0, 26.1, 22.4, 14.0, 3.6;

IR: ν 2930, 1780, 1710, 1468, 1385, 1355, 1087, 720;

HRMS (EI): calcd for C\textsubscript{17}H\textsubscript{19}NO\textsubscript{2}\textsuperscript{+} (M) 269.1416 Found: 269.1413;

4-aminonon-2-yn
Experimental Part

To a solution of 2-(non-2-yn-4-yl)isoindoline-1,3-dione (18.3 g, 68.0 mmol, 1.00 equiv.) in ethanol (250 mL) was added hydrazine monohydrate (6.00 mL, 136 mmol, 2.00 equiv.) and the resulting mixture was refluxed for 4h. The solution was then cooled to room temperature and the precipitate was removed by filtration. Concentrated hydrochloric acid (75 mL) was then added and the solution was concentrated to solid. The solution was then dissolved in water (300 mL) and extracted with ethyl acetate (3 x 500 mL). The combined extracts were dried (MgSO₄) and concentrated to give the crude product as a pale yellow oil in 91% yield (8.61 g, 61.8 mmol). The product was employed without further purification.

**Rf** (100% EtOAc): 0.23;

**¹H NMR (CDCl₃, 300MHz, 293K):** δ 3.53 – 3.45 (m, 1H), 1.81 (d, J = 2.2 Hz, 3H), 1.61 – 1.25 (m, 10H), 0.89 (t, J = 6.8 Hz, 3H);

**¹³C NMR (CDCl₃, 100MHz, 293K):** δ 82.9, 77.8, 43.7, 38.6, 31.6, 25.8, 22.6, 14.0, 3.5;

**IR:** v 3300, 2929, 1633;

**HRMS (ESI):** calcd for C₉H₁₈N⁺ (M+H) 140.1439 Found: 140.1432;

---

**2,2,2-trifluoro-N-(non-2-yn-4-yl)acetamide**

To a solution of 4-aminonon-2-yn (500 mg, 3.59 mmol, 1.00 equiv.), triethylamine (1.25 mL, 8.98 mmol, 2.50 equiv.), DMAP (8.00 mg, 0.07 mmol, 0.02 equiv.) in dichloromethane (15 mL) at 0°C was added slowly trifluoroacetic anhydride (1.00 mL, 7.18 mmol, 2.00 equiv.) and the resulting mixture was stirred for 16h at r.t. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a white solid in 90% yield (759 mg, 3.23 mmol).

**Rf** (hexane:EtOAc = 9:1): 0.42;

**¹H NMR (CDCl₃, 300MHz, 293K):** δ 6.47 (d, J = 6.7 Hz, 1H), 4.66 (qd, J = 8.3, 2.3 Hz, 1H), 1.82 (d, J = 2.3 Hz, 3H), 1.74 – 1.62 (m, 2H), 1.47 – 1.24 (m, 6H), 0.89 (t, J = 6.9 Hz, 3H);
Experimental Part

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): 156.1 (q, $J = 37.2$ Hz), 115.7 (q, $J = 287.8$ Hz), 80.4, 76.3, 42.7, 35.4, 31.1, 25.1, 22.4, 13.8, 3.2;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -75.8;

IR: $\nu$ 3290, 2931, 1704, 1552, 1366, 1184;

HRMS (ESI): calcd for C$_{11}$H$_{17}$F$_3$NO$^+$ (M+H) 236.1257 Found: 236.1257;

(\textit{Z})-2,2,2-trifluoro-\(\textit{N}\)-(non-2-en-4-yl)acetamide

A suspension of 2,2,2-trifluoro-\(\textit{N}\)-(non-2-yn-4-yl)acetamide (500 mg, 2.13 mmol, 1.00 equiv.) and Lindlar catalyst (225 mg) in absolute methanol (10 mL) was stirred vigorously under 1 atm. of H$_2$ at r.t for 1h. The catalyst was removed by filtration through a Celite pad and the solution was concentrated to give the product as a clear oil in 99% yield (506 mg, 2.12 mmol) as an inseparable mixture of cis/trans isomers in 93:7 ratio.

Rf (hexane:EtOAc = 9:1): 0.42;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) cis: $\delta$ 6.48 (d, $J = 6.0$ Hz, 1H), 5.67 (dqd, $J = 10.7$, 7.0, 1.0 Hz, 1H), 5.27 (ddq, $J = 10.9$, 9.2, 1.8 Hz, 1H), 4.81 – 4.67 (m, 1H), 1.72 (dd, $J = 7.0$, 1.8 Hz, 3H), 1.69 – 1.60 (m, 1H), 1.55 – 1.46 (m, 1H), 1.38 – 1.25 (m, 6H), 0.89 (t, $J = 6.8$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) cis: $\delta$ 156.3 (q, $J = 36.7$ Hz), 128.8, 128.8, 115.9 (q, $J = 288.0$ Hz), 47.4, 35.0, 31.4, 25.1, 22.4, 13.9, 13.3;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -76.0;

IR: $\nu$ 3292, 2933, 1697, 1556, 1184, 724;

HRMS (EI): calcd for C$_{11}$H$_{18}$F$_3$NO$^+$ (M) 237.1340 Found: 237.1340;

\(\textit{N}\)-(non-2-yn-4-yl)acetamide
To a solution of 4-aminonon-2-yn (500 mg, 3.59 mmol, 1.00 equiv.), triethylamine (1.25 mL, 8.98 mmol, 2.50 equiv.), DMAP (8.00 mg, 0.07 mmol, 0.02 equiv.) in dichloromethane (15 mL) at 0°C was added slowly acetyl chloride (0.51 mL, 7.18 mmol, 2.00 equiv.) and the resulting mixture was stirred for 16h at r.t. The solution was then concentrated and purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as a white solid in 96% yield (623 mg, 3.44 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.35;

^1H NMR (CDCl₃, 300MHz, 293K): 5.74 (d, J = 8.2 Hz, 1H), 4.64 (dtd, J = 8.3, 6.1, 2.3 Hz, 1H), 1.96 (s, 3H), 1.79 (d, J = 2.3 Hz, 3H), 1.65 – 1.50 (m, 2H), 1.44 – 1.23 (m, 6H), 0.87 (t, J = 6.9 Hz, 3H);

^13C NMR (CDCl₃, 100MHz, 293K): δ 168.8, 78.7, 78.5, 41.7, 36.1, 31.3, 25.3, 23.2, 22.5, 14.0, 3.4;

**IR**: ν 3292, 2929, 1644, 1548, 1372, 730, 602;

**HRMS (EI)**: calcd for C₁₁H₁₉NO⁺ (M) 181.1467 Found: 181.1461;

(Z)-N-(non-2-en-4-yl)acetamide

A suspension of N-(non-2-yn-4-yl)acetamide (500 mg, 2.76 mmol, 1.00 equiv.) and Lindlar catalyst (292 mg) in absolute methanol (10 mL) was stirred vigorously under 1 atm. of H₂ at r.t. for 1h. The catalyst was removed by filtration through a Celite pad and the solution was concentrated to give the product as a clear oil in 99% yield (509 mg, 2.75 mmol) as an inseparable mixture of cis/trans isomers in 92:8 ratio.

**Rf** (hexane:EtOAc = 1:1): 0.35;
\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K) cis: \(\delta\) 5.63 – 5.52 (m, 2H), 5.20 (ddq, \(J = 10.9, 9.2, 1.8\) Hz, 1H), 4.75 – 4.63 (m, 1H), 1.95 (s, 3H), 1.70 (dd, \(J = 6.9, 1.8\) Hz, 3H), 1.61 – 1.50 (m, 1H), 1.42 – 1.23 (m, 7H), 0.87 (t, \(J = 6.8\) Hz, 3H);

\(^1\)C NMR (CDCl\(_3\), 100MHz, 293K) cis: \(\delta\) 168.9, 131.0, 126.9, 46.5, 35.8, 31.7, 25.3, 23.4, 22.6, 14.0, 13.4;

IR: \(\nu\) 3296, 2930, 1633, 1552, 733, 606;

HRMS (EI): calcd for C\(_{11}\)H\(_{21}\)NO\(^+\) (M) 183.1623 Found: 183.1617;

\(N\)-(non-2-yn-4-yl)benzamide

To a solution of 4-aminonon-2-yn (500 mg, 3.59 mmol, 1.00 equiv.), triethylamine (1.25 mL, 8.98 mmol, 2.50 equiv.), DMAP (8.00 mg, 0.07 mmol, 0.02 equiv.) in dichloromethane (15 mL) at 0°C was added slowly benzoyl chloride (0.83 mL, 7.18 mmol, 2.00 equiv.) and the resulting mixture was stirred for 16h at r.t.. The solution was then concentrated and purified by flash chromatography (10% EtOAc/Hexane) to give the resulting product as a white solid in 98% yield (835 mg, 3.51 mmol).

\(R_f\) (hexane:EtOAc = 9:1): 0.24;

\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K): \(\delta\) 7.81 – 7.74 (m, 2H), 7.53 – 7.37 (m, 3H), 6.34 (d, \(J = 7.9\) Hz, 1H), 4.93 – 4.83 (m, 1H), 1.82 (d, \(J = 2.3\) Hz, 3H), 1.79 – 1.63 (m, 2H), 1.52 – 1.40 (m, 2H), 1.37 – 1.27 (m, 4H), 0.88 (t, \(J = 6.9\) Hz, 3H);

\(^1\)C NMR (CDCl\(_3\), 100MHz, 293K): \(\delta\) 166.2, 134.3, 131.4, 128.5, 126.9, 79.0, 78.5, 42.3, 36.2, 31.3, 25.4, 22.5, 14.0, 3.5;

IR: \(\nu\) 3304, 2929, 1640, 1538, 1490, 694;

HRMS (EI): calcd for C\(_{16}\)H\(_{21}\)NO\(^+\) (M) 243.1623 Found: 243.1618;

\((Z)-N\)-(non-2-en-4-yl)benzamide
A suspension of N-(non-2-yn-4-yl)benzamide (717 mg, 2.95 mmol, 1.00 equiv.) and Lindlar catalyst (115 mg) in absolute methanol (10 mL) was stirred vigorously under 1 atm. of H₂ at rt for 3h. The catalyst was removed by filtration through a Celite pad and the solution was concentrated to give the product as a pale yellow oil in 99% yield (716 mg, 2.92 mmol) as an inseparable mixture of cis/trans isomers in 93:7 ratio.

**Rf** (hexane:EtOAc = 1:1): 0.35;

**¹H NMR (CDCl₃, 300MHz, 293K) cis:** δ 7.79 – 7.76 (m, 1H), 7.52 – 7.40 (m, 2H), 6.03 (d, J = 6.9 Hz, 1H), 5.65 (dqd, J = 10.7, 6.8, 1.0 Hz, 1H), 5.34 (ddq, J = 10.8, 9.1, 1.7 Hz, 1H), 4.99 – 4.87 (m, 1H), 1.78 (dd, J = 6.9, 1.8 Hz, 1H), 1.76 – 1.67 (m, 1H), 1.53 (dt, J = 14.4, 7.5 Hz, 1H), 1.43 – 1.29 (m, 6H), 0.90 (t, J = 7.0 Hz, 3H);

**¹³C NMR (CDCl₃, 100MHz, 293K) cis:** δ 166.4, 134.9, 131.2, 130.8, 128.5, 127.5, 126.8, 47.0, 35.8, 31.7, 25.4, 22.6, 14.0, 13.5;

**IR:** ν 3331, 2930, 1632, 1536, 694;

**HRMS (EI):** calcd for C₁₆H₂₃NO⁺ (M) 245.1780 Found: 245.1775;

**(Z)-2-(non-2-en-4-yl)isoindoline-1,3-dione**

A suspension of 2-(non-2-yn-4-yl)isoindoline-1,3-dione (1.67 g, 6.20 mmol, 1.00 equiv.) and Lindlar catalyst (264 mg) in absolute methanol (20 mL) was stirred vigorously under 1 atm. of H₂ at r.t. for 4h. The catalyst was removed by filtration through a Celite pad and the solution was concentrated to give the product as a clear oil in 99% yield (509 mg, 2.75 mmol).

**Rf** (hexane:EtOAc = 9:1): 0.36;
Experimental Part

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 7.82 (dd, $J = 5.5$, 3.0 Hz, 2H), 7.70 (dd, $J = 5.4$, 3.1 Hz, 2H), 5.94 (ddq, $J = 11.0$, 9.3, 1.8 Hz, 1H), 5.62 (dq, $J = 10.7$, 6.9, 1.1 Hz, 1H), 5.08 (ddd, $J = 16.7$, 8.4, 0.9 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.91 – 1.81 (m, 1H), 1.72 (dd, $J = 6.9$, 1.8 Hz, 3H), 1.37 – 1.21 (m, 6H), 0.87 (t, $J = 7.0$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 168.2, 133.8, 132.0, 128.6, 127.7, 123.1, 47.8, 32.8, 31.4, 26.1, 22.5, 14.0, 13.2;

IR: $\nu$ 2929, 1710, 1387, 719;

HRMS (EI): calcld for C$_{17}$H$_{21}$NO$_2$ $^+$ (M) 271.1572 Found: 271.1570;

$(E)$-2-methyl-N-(pent-3-en-2-yl)propane-2-sulfinamide

To a solution of $(R)$-N-((E)-but-2-en-ylidene)-tert-butanesulfinamide$^2$ (500 mg, 2.89 mmol, 1.00 equiv.) in THF (10 mL) at -78 °C was added slowly a solution of methyllithium (1.60 M in diethyl ether, 3.60 mL, 5.77 mmol, 2.00 equiv.) and the solution was stirred at -78 °C for 2.5h. The solution was then allowed to warm to r.t. and quenched with saturated NH$_4$Cl solution (10 mL). The solution was extracted with Et$_2$O (3 x 20mL), dried over MgSO$_4$ and concentrated. The product was then purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as a pale yellow oil in 86% yield (472 mg, 2.49 mmol) as a 3.6:1 mixture of diastereoisomers.

Rf (hexane:EtOAc = 1:1): 0.34;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) major diastereoisomer: $\delta$ 5.66 – 5.53 (m, 1H), 5.28 (ddq, $J = 15.3$, 7.1, 1.6 Hz, 1H), 3.90 – 3.79 (m, 1H), 3.04 (d, $J = 3.5$ Hz, 1H), 1.68 – 1.59 (m, 3H), 1.23 (d, $J = 6.4$ Hz, 3H), 1.15 (s, 9H);

minor diastereoisomer: $\delta$ 5.66 – 5.53 (m, 1H), 5.42 (ddq, $J = 15.2$, 7.0, 1.5 Hz, 1H), 3.90 – 3.79 (m, 1H), 3.09 (d, $J = 3.7$ Hz, 1H), 1.68 – 1.59 (m, 3H), 1.19 (d, $J = 6.5$ Hz, 3H), 1.15 (s, 9H).
13C NMR (CDCl₃, 100MHz, 293K) major and minor diastereoisomers: δ 133.8, 133.2, 126.8, 126.7, 55.1, 55.1, 52.9, 52.6, 23.0, 22.5, 22.4, 21.3, 17.5;

IR: ν 3436, 3208, 2962, 1455, 1364, 1054, 965;

HRMS (EI): calcd for C₉H₁₉NOS⁺ (M) 189.1187 Found: 189.1182;

(E)-2,2,2-trifluoro-N-(pent-3-en-2-yl)acetamide

To a solution of (E)-2-methyl-N-(pent-3-en-2-yl)propane-2-sulfinamide (365 mg, 1.93 mmol, 1.00 equiv) in methanol (10 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 2.40 mL, 9.64 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (10 mL). Triethylamine (0.59 mL, 4.24 mmol, 2.2 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.35 mL, 2.51 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a pale yellow solid in 88% yield (309 mg, 1.71 mmol).

Rf (hexane:EtOAc = 85:15): 0.42;

1H NMR (CDCl₃, 300MHz, 293K): δ 6.45 (s, 1H), 5.67 (dqdd, J = 15.3, 6.5, 0.6, 0.6 Hz, 1H), 5.42 (ddq, J = 15.3, 6.1, 1.5 Hz, 1H), 4.59 – 4.42 (m, 1H), 1.68 (d, J = 6.4 Hz, 1H), 1.28 (d, J = 6.8 Hz, 1H);

13C NMR (CDCl₃, 100MHz, 293K): δ 156.2 (q, J = 36.8 Hz), 130.3, 127.7, 115.9 (q, J = 288.0 Hz), 47.6, 20.1, 17.6;

19F NMR (CDCl₃, 377MHz, 293K): δ -75.9;

IR: ν 3294, 2981, 1694, 1558, 1158, 966, 727;

HRMS (EI): calcd for C₇H₁₀F₃NO⁺ (M) 181.0714 Found: 181.0709;
Experimental Part

2-methyl-N-(1-phenylhex-4-yn-3-yl)propane-2-sulfinamide

[Image]

To a flask was condensed propyne (approx. 1.3 mL) in THF (25mL) at -78°C. A solution of butyl lithium (1.6 M in hexane, 7.10 mL, 11.29 mmol, 2.00 equiv.) was added slowly and the mixture was stirred for 30 mins at -78°C. A solution of 2-methyl-N-(3-phenylpropylidene)propane-2-sulfinamide (1.34 g, 5.65 mmol, 1.00 equiv.) in THF (3 mL) was added slowly followed by BF$_3$-Et$_2$O (1.39 mL, 11.29 mmol, 2.00 equiv.) and the resulting mixture was stirred for 1h at -78°C then warmed to r.t. for 30min. The reaction was then quenched with NH$_4$Cl and extracted with EtOAc and concentrated. The product was then purified by flash chromatography (30% EtOAc/Hexane) to give the resulting product as a pale yellow oil in 68% yield (1.06g, 3.82 mmol) as a 7.2:1 mixture of diastereoisomers.

$R_f$ (hexane:EtOAc = 1:1): 0.42;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) major diastereoisomer: $\delta$ 7.36 – 7.18 (m, 5H), 4.10 – 4.01 (m, 1H), 3.31 (d, $J = 6.1$ Hz, 1H), 2.87 – 2.72 (m, 2H), 2.10 – 1.92 (m, 2H), 1.89 (d, $J = 2.3$ Hz, 3H), 1.23 (s, 9H);

minor diastereoisomer: $\delta$ 7.36 – 7.18 (m, 5H), 4.10 – 4.01 (m, 1H), 3.25 (d, $J = 5.6$ Hz, 1H), 2.87 – 2.72 (m, 2H), 2.10 – 1.92 (m, 2H), 1.90 (d, $J = 2.2$ Hz, 3H), 1.22 (s, 9H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) major and minor diastereoisomers: $\delta$ 141.3, 141.0, 128.5, 128.5, 128.5, 126.1, 81.5, 78.7, 78.1, 77.2, 56.0, 55.8, 47.9, 47.5, 39.2, 38.8, 32.0, 31.8, 22.6, 22.5, 3.7, 3.6;

IR: $\nu$ 3202, 2954, 1454, 1063, 700;

HRMS (ESI): calcd for C$_{16}$H$_{24}$NOS$^+$ (M+H) 278.1573 Found: 278.1571;

(Z)-2-methyl-N-(1-phenylhex-4-en-3-yl)propane-2-sulfinamide

[Image]
A suspension of 2-methyl-N-(1-phenylhex-4-yn-3-yl)propane-2-sulfinamide (600 mg, 2.16 mmol, 1.00 equiv.) and Lindlar catalyst (229 mg) in absolute methanol (10 mL) was stirred vigorously under 1 atm. of H₂ at r.t. for 90 min. The catalyst was removed by filtration through a Celite pad and the solution was concentrated and purified by flash chromatography (33% EtOAc/Hexane) to give the product as a yellow oil in 95% yield (577 mg, 2.01 mmol) as a mixture of diastereoisomers in 7:1 ratio.

\[ \text{Rf (hexane:EtOAc = 1:1)}: 0.42; \]

\[ ^1\text{H NMR (CDCl₃, 300MHz, 293K)} \]

Major diastereoisomer: \[ \delta 7.34 – 7.12 \text{ (m, 5H)}, 5.67 \text{ (dqd, } J = 10.8, 6.9, 0.7 \text{ Hz, 1H)}, 5.43 \text{ (ddq, } J = 10.8, 9.2, 1.6 \text{ Hz, 1H)}, 4.19 – 4.07 \text{ (m, 1H)}, 3.08 \text{ (d, } J = 5.0 \text{ Hz, 1H)}, 2.73 – 2.55 \text{ (m, 2H)}, 2.11 – 1.96 \text{ (m, 1H)}, 1.81 – 1.70 \text{ (m, 1H)}, 1.68 \text{ (dd, } J = 6.9, 1.8 \text{ Hz, 3H)}, 1.20 \text{ (s, 9H)}; \]

Minor diastereoisomer: \[ \delta 7.34 – 7.12 \text{ (m, 5H)}, 5.79 – 5.59 \text{ (m, 1H)}, 5.27 \text{ (ddq, } J = 11.1, 9.2, 1.6 \text{ Hz, 1H)}, 3.64 \text{ (t, } J = 6.5 \text{ Hz, 1H)}, 3.19 \text{ (d, } J = 2.6 \text{ Hz, 1H)}, 2.76 – 2.54 \text{ (m, 2H)}, 2.12 – 1.65 \text{ (m, 5H)}, 1.17 \text{ (s, 9H)}; \]

\[ ^13\text{C NMR (CDCl₃, 100MHz, 293K)} \]

Major and minor diastereoisomers: \[ \delta 141.7, 141.4, 131.7, 131.0, 128.5, 128.4, 128.4, 128.4, 128.1, 127.5, 125.9, 125.8, 55.6, 55.3, 51.8, 51.2, 38.5, 37.9, 32.0, 31.9, 22.6, 22.6, 13.5, 13.5; \]

\[ \text{IR: } \nu 3209, 1945, 1496, 1454, 1054, 749, 700; \]

\[ \text{HRMS (EI): calcd for C}_{16}\text{H}_{26}\text{NOS}^+ (M+H) 280.1735 \text{ Found: 280.1727}; \]

\[ (Z)-2,2,2\text{-trifluoro-N-(1-phenylhex-4-en-3-yl)acetamide (2f)} \]

To a solution of (Z)-2-methyl-N-(1-phenylhex-4-en-3-yl)propane-2-sulfinamide (398 mg, 1.42 mmol, 1.00 equiv) in methanol (20 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 1.78 mL, 7.12 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (15 mL). Triethylamine (0.44 mL, 3.13 mmol, 2.2 equiv.)
was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.26 mL, 1.85 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a pale yellow solid in 68% yield (263 mg, 0.97 mmol).

**Rf** (hexane:EtOAc = 85:15): 0.42;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 7.35 – 7.15 (m, 5H), 6.24 (s, 1H), 5.74 (dq, $J = 10.7, 7.0$ Hz, 1H), 5.32 (ddq, $J = 10.8, 10.8, 1.6$ Hz, 1H), 4.86 – 4.70 (m, 1H), 2.74 – 2.56 (m, 2H), 2.03 (ddt, $J = 13.5, 9.3, 6.7$ Hz, 1H), 1.91 – 1.77 (m, 1H), 1.70 (dd, $J = 7.0, 1.7$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 156.3 (q, $J = 36.8$ Hz), 140.8, 129.7, 128.6, 128.3, 128.3, 126.2, 115.9 (q, $J = 288.2$ Hz), 47.2, 36.6, 31.9, 13.5;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): δ -75.8;

IR: ν 3298, 2924, 1694, 1558, 1181, 724, 698;

HRMS (EI): calcd for C$_{14}$H$_{16}$F$_3$NO$^+$ (M) 271.1184 Found: 271.1179;

($E$)-N-(2,2-dimethylhex-4-en-3-yl)-2-methylpropane-2-sulfinamide

To a solution of ($R$)-N-((($E$)-but-2-enylidene)-tert-butanesulfinamide$^{149}$ (500 mg, 2.89 mmol, 1.00 equiv.) in THF (10 mL) at -78 °C was added slowly a solution of tert-butyl lithium (1.70 M in pentane, 3.40 mL, 5.77 mmol, 2.00 equiv.) and the solution was stirred at -78 °C for 2.5h. The solution was then allowed to warm to r.t. and quenched with saturated NH$_4$Cl solution (10 mL). The solution was extracted with Et$_2$O (3 x 20mL), dried over MgSO$_4$ and concentrated. The product was then purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as a pale yellow oil in 69% yield (463 mg, 2.00 mmol) as a 4:1 mixture of diastereoisomers.

**Rf** (hexane:EtOAc = 1:1): 0.47;
**1H NMR (CDCl₃, 300MHz, 293K) major diastereoisomer:** δ 5.72 – 5.58 (m, 1H), 5.44 (ddq, J = 15.2, 8.2, 1.5 Hz, 1H), 3.29 (t, J = 8.6 Hz, 1H), 2.99 (d, J = 8.7 Hz, 1H), 1.67 (dd, J = 1.5, 0.4 Hz, 3H), 1.18 (s, 9H), 0.85 (s, 9H);

**minor diastereoisomer:** δ 5.72 – 5.58 (m, 1H), 5.20 (ddq, J = 15.3, 8.9, 1.6 Hz, 1H), 3.39 (dd, J = 9.0, 2.6 Hz, 1H), 2.21 (s, 1H), 1.70 (d, J = 6.5, 1.7 Hz, 3H), 1.17 (s, 9H), 0.86 (s, 9H);

**13C NMR (CDCl₃, 100MHz, 293K) major and minor diastereoisomers:** δ 130.7, 130.0, 128.7, 128.0, 68.6, 65.6, 56.2, 56.2, 35.0, 34.3, 26.4, 26.2, 22.6, 17.8;

**IR:** ν 3448, 3225, 2954, 1476, 1365, 1039;

**HRMS (EI):** calcd for C₁₂H₂₆NOS⁺ (M) 232.1730 Found: 232.1720;

(E)-N-(2,2-dimethylhex-4-en-3-yl)-2,2,2-trifluoroacetamide

To a solution of (E)-N-(2,2-dimethylhex-4-en-3-yl)-2-methylpropane-2-sulfinamide (700 mg, 3.03 mmol, 1.00 equiv) in methanol (40 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 3.80 mL, 15.13 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (15 mL). Triethylamine (0.93 mL, 6.66 mmol, 2.2 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.55 mL, 3.93 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a pale yellow solid in 90% yield (606 mg, 2.71 mmol).

Rf (hexane:EtOAc = 85:15): 0.56;

**1H NMR (CDCl₃, 300MHz, 293K):** δ 6.31 (d, J = 9.2 Hz, 1H), 5.64 (dqd, J = 15.2, 6.4, 0.9 Hz, 1H), 5.39 (ddd, J = 15.2, 7.7, 2.9, 1.3 Hz, 1H), 4.22 (dd, J = 7.8, 8.2 Hz, 1H), 1.68 – 171 (m, 3H), 0.91 (s, 9H);

**13C NMR (CDCl₃, 100MHz, 293K):** 156.5 (q, J = 36.5 Hz), 129.8, 126.2, 116.1 (q, J = 288.2 Hz), 60.4, 34.4, 26.1, 17.8;
Experimental Part

\(^{19}\)F NMR (CDCl\(_3\), 377MHz, 293K): \(\delta -75.7\);

IR: \(\nu\) 3307, 2968, 1704, 1558, 1371, 1181, 970;

HRMS (EI): calcd for C\(_{10}\)H\(_{17}\)F\(_3\)NO\(^+\) (M) 224.1257 Found: 224.1250;

\((E)-N-(1\text{-cyclopropylbut-2-enyl})-2\text{-methylpropane-2-sulfinamide}\)

![Chemical Structure](image)

To a solution of \((R)-N-((E)-but-2-en-ylidene)-tert-butanesulfinamide\)\(^{149}\) (500 mg, 2.89 mmol, 1.00 equiv.) in THF (10 mL) at -78 °C was added slowly a solution of cyclopropyl magnesium bromide (0.50 M in diethyl ether, 8.70 mL, 4.33 mmol, 1.50 equiv.) and the solution was stirred at -78 °C and allowed to warm slowly to r.t. overnight. The solution was then quenched with saturated NH\(_4\)Cl solution (10 mL). The solution was extracted with Et\(_2\)O (3 x 20mL), dried over MgSO\(_4\) and concentrated. The product was then purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as a pale yellow oil in 82% yield (510 mg, 2.37 mmol) as a 7.6:1 mixture of diastereoisomers.

\(\text{Rf (hexane:EtOAc = 1:1): 0.40;}\)

\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K) major diastereoisomer: \(\delta 5.65\) (dqd, \(J = 15.2, 6.5, 0.5\) Hz, 1H), 5.36 (ddq, \(J = 15.2, 7.5, 1.5\) Hz, 1H), 3.28 (s, 1H), 3.01 – 2.93 (m, 1H), 1.70 (dd, \(J = 6.5, 1.6\) Hz, 3H), 1.21 (s, 9H), 1.00 – 0.90 (m, 1H), 0.59 – 0.51 (m, 2H), 0.38 – 0.22 (m, 2H);

minor diastereoisomer: \(\delta 5.72 – 5.59\) (m, 1H), 5.51 (dddd, \(J = 11.5, 6.8, 2.8, 1.4\) Hz, 1H), 3.20 (s, 1H), 3.15 – 3.07 (m, 1H), 1.69 – 1.66 (m, 3H), 1.21 (s, 9H), 1.00 – 0.90 (m, 1H), 0.59 – 0.51 (m, 2H), 0.38 – 0.22 (m, 2H);

\(^{13}\)C NMR (CDCl\(_3\), 100MHz, 293K) major and minor diastereoisomers: \(\delta 131.8, 131.0, 128.1, 127.5, 62.4, 62.0, 55.4, 55.2, 22.6, 22.6, 17.8, 17.5, 16.0, 4.8, 4.2, 3.5, 2.3;\)

IR: \(\nu\) 3446, 3214, 2959, 1456, 1363, 1058, 965, 941, 825;

HRMS (EI): calcd for C\(_{11}\)H\(_{21}\)NOS\(^+\) (M) 215.1344 Found: 215.1339;
(E)-N-(1-cyclopropylbut-2-enyl)-2,2,2-trifluoroacetamide

To a solution of (Z)-N-(1-cyclopropylbut-2-enyl)-2-methylpropane-2-sulfinamide (484 mg, 2.25 mmol, 1.00 equiv) in methanol (25 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 2.8 mL, 15.13 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30 mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (20 mL). Triethylamine (0.69 mL, 4.94 mmol, 2.2 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.41 mL, 2.92 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3 h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a white solid in 82% yield (383 mg, 1.85 mmol).

Rf (hexane:EtOAc = 85:15): 0.40;

^1^H NMR (CDCl₃, 300MHz, 293K): δ 6.44 (s, 1H), 5.73 (dqd, J = 15.3, 6.5, 1.4 Hz, 1H), 5.43 (ddq, J = 15.4, 6.1, 1.6 Hz, 1H), 3.88 (dd, J = 15.0, 7.9 Hz, 1H), 1.73 (ddd, J = 6.5, 1.6, 1.2 Hz, 3H), 1.05 – 0.91 (m, 1H), 0.66 – 0.51 (m, 2H), 0.49 – 0.39 (m, 1H), 0.37 – 0.28 (m, 1H);

^1^3^C NMR (CDCl₃, 100MHz, 293K): δ 156.3 (q, J = 36.7 Hz), 128.3, 128.0, 116.0 (q, J = 288.2 Hz), 56.0, 17.7, 15.3, 3.2, 3.1;

^1^9^F NMR (CDCl₃, 377MHz, 293K): δ -75.9;

IR: ν 3288, 3088, 1698, 1554, 1181, 965;

HRMS (EI): calcd for C₉H₁₃F₃NO⁺ (M+H) 208.0944 Found: 208.0943;

(E)-N-(1-cyanopent-3-en-2-yl)-2-methylpropane-2-sulfinamide

(Continued from next page...)

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to a solution of MeCN at -78°C in THF was added MeLi and the solution was stirred for 1h at -78 then was added to a solution of SM at -78°C. stirred for 2h then quenched with NH4Cl. isolated the product in % yield...flashed 50% EtOAc to 100% EtOAc

To a solution of acetonitrile (0.45 mL, 8.66 mmol, 3.00 equiv.) in THF (10 mL) at-78°C was added a solution of methyl lithium (1.60 M in diethyl ether, 3.61 mL, 5.77 mmol, 2.00 equiv.) and the resulting solution was stirred for 1h at -78°C. This solution was then added slowly to a solution of (R)-N-((E)-but-2-en-ylidene)-tert-butanesulfinamide^2 (500 mg, 2.89 mmol, 1.00 equiv.) in THF (10 mL) at -78 °C and the solution was stirred at -78 °C for 2.5h. The solution was then allowed to warm to r.t. and quenched with saturated NH4Cl solution (10 mL). The solution was extracted with Et2O (3 x 20mL), dried over MgSO4 and concentrated. The product was then purified by flash chromatography (50 to 100% EtOAc/Hexane) to give the resulting product as a pale yellow oil in 95% yield (549 mg, 2.74 mmol) as a 2.2:1 mixture of diastereoisomers.

Rf (hexane:EtOAc = 1:1): 0.14;

^1H NMR (CDCl3, 300MHz, 293K) major diastereoisomer: δ 5.93 – 5.77 (m, 1H), 5.43 (ddq, J = 15.2, 7.1, 1.6 Hz, 1H), 4.15 – 4.02 (m, 1H), 3.56 (d, J = 5.8 Hz, 1H), 2.71 (d, J = 5.7 Hz, 2H), 1.75 (ddd, J = 6.3, 1.9, 0.7 Hz, 3H), 1.22 (s, 9H);

minor diastereoisomer: δ 5.93 – 5.77 (m, 1H), 5.55 (ddq, J = 15.2, 7.2, 1.6 Hz, 1H), 4.14 – 4.03 (m, 1H), 3.38 (d, J = 4.7 Hz, 1H), 2.71 (dd, J = 23.1, 6.3 Hz, 1H), 2.58 (dd, J = 16.7, 5.1 Hz, 1H), 1.74 (ddd, J = 6.5, 1.6, 0.7 Hz, 3H), 1.24 (s, 9H);

^13C NMR (CDCl3, 100MHz, 293K) major and minor diastereoisomers: δ 131.1, 131.1, 128.8, 128.2, 116.9, 116.8, 56.3, 56.1, 54.0, 53.5, 26.1, 25.1, 22.6, 22.5, 17.8;

IR: ν 3443, 3211, 1652, 1046;

HRMS (EI): calcd for C10H18N2OS+ (M) 214.1140 Found: 214.1135;

(E)-N-(1-cyanopent-3-en-2-yl)-2,2,2-trifluoroacetamide
To a solution of (E)-N-(1-cyanopent-3-en-2-yl)-2-methylpropane-2-sulfinamide (430 mg, 2.01 mmol, 1.00 equiv) in methanol (20 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 2.51 mL, 10.0 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (15 mL). Triethylamine (0.62 mL, 4.41 mmol, 2.2 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.36 mL, 2.61 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (25% EtOAc/Hexane) to give the resulting product as a pale yellow solid in 76% yield (313 mg, 1.52 mmol).

**Rf** (hexane:EtOAc = 85:15): 0.11;

**1H NMR (CDCl3, 300MHz, 293K):** δ 7.06 (d, J = 6.2 Hz, 1H), 5.88 (dqdd, J = 15.3, 6.5, 1.3, 0.6 Hz, 1H), 5.53 (ddq, J = 15.2, 7.3, 1.6 Hz, 1H), 4.71 – 4.58 (m, 1H), 2.83 (dd, J = 6.8, 5.9 Hz, 1H), 2.70 (dd, J = 16.9, 5.1 Hz, 1H), 1.76 (ddd, J = 6.5, 1.6, 0.7 Hz, 3H);

**13C NMR (CDCl3, 100MHz, 293K):** δ 156.9 (q, J = 37.9 Hz), 132.4, 125.2, 116.4, 115.5 (q, J = 287.7 Hz), 48.8, 23.3, 17.7;

**19F NMR (CDCl3, 377MHz, 293K):** δ -75.6;

**IR:** ν 3294, 1698, 1559, 1185, 1153;

**HRMS (EI):** calcd for C8H9F3N2O+ (M) 206.0667 Found: 206.0662;

(E)-N-(hexa-1,4-dien-3-yl)-2-methylpropane-2-sulfinamide

To a solution of (R)-N-((E)-but-2-en-ylidene)-tert-butanesulfinamide (600 mg, 3.46 mmol, 1.00 equiv.) in THF (15 mL) at -78 °C was added slowly a solution of vinyl magnesium bromide (1.00 M in THF, 6.90 mL, 6.93 mmol, 2.00 equiv.) and the solution was stirred at -78 °C and allowed to warm slowly to r.t. overnight. The solution was then quenched with saturated NH4Cl solution (10 mL). The solution was extracted with Et2O (3 x 20mL), dried over MgSO4 and concentrated. The product was then purified by flash chromatography (40%
EtOAc/Hexane) to give the resulting product as a pale yellow oil in 81% yield (562 mg, 2.79 mmol) as a 4.1:1 mixture of diastereoisomers.

**RF** (hexane:EtOAc = 1:1): 0.39;

**^1H NMR** (CDCl₃, 300MHz, 293K) major diastereoisomer: \( \delta \) 5.90 – 5.63 (m, 2H), 5.33 (ddddd, \( J = 15.2, 7.3, 3.1, 1.5 \) Hz, 1H), 5.26 – 5.09 (m, 2H), 4.34 – 4.27 (m, 1H), 3.20 (d, \( J = 3.4 \) Hz, 1H), 1.70 (dd, \( J = 6.5, 1.6 \) Hz, 3H), 1.19 (s, 9H);

minor diastereoisomer: \( \delta \) 5.90 – 5.63 (m, 2H), 5.47 (ddddd, \( J = 7.5, 5.2, 3.1, 1.6 \) Hz, 1H), 5.26 – 5.09 (m, 2H), 4.34 – 4.27 (m, 1H), 3.15 (d, \( J = 3.9 \) Hz, 1H), 1.70 – 1.67 (m, 3H), 1.19 (s, 9H);

**^13C NMR** (CDCl₃, 100MHz, 293K) major and minor diastereoisomers: \( \delta \) 138.6, 137.8, 130.9, 129.9, 129.0, 128.3, 116.7, 116.0, 59.7, 55.3, 22.5, 17.7;

**IR**: \( \nu \) 3444, 3210, 2959, 1055, 922;

**HRMS (EI)**: calcd for C₁₀H₁₉NOS⁺ (M) 201.1187 Found: 201.1182;

**\((E)-2,2,2\text{-trifluoro-}\text{-N-(hexa-1,4-dien-3-yl)}\text{-acetamide}\)**

![Chemical Structure](image)

To a solution of (E)-N-(hexa-1,4-dien-3-yl)-2-methylpropane-2-sulfinamide (479 mg, 2.38 mmol, 1.00 equiv) in methanol (20 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 3.00 mL, 11.90 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness. The crude product was then dissolved in DCM (10 mL). Triethylamine (0.73 mL, 5.23 mmol, 2.2 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.43 mL, 3.09 mmol, 1.3 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a pale yellow solid in 97% yield (446 mg, 2.31 mmol).

**RF** (hexane:EtOAc = 85:15): 0.42;
1H NMR (CDCl₃, 300MHz, 293K): δ 6.48 (s, 1H), 5.89 – 5.66 (m, 2H), 5.44 (ddqd, J = 15.3, 6.5, 1.6, 0.7 Hz, 1H), 5.26 – 5.23 (m, 1H), 5.21 – 5.18 (m, 1H), 1.75 – 1.70 (m, 3H);

13C NMR (CDCl₃, 100MHz, 293K): δ 156.2 (q, J = 37.0 Hz), 135.3, 129.8, 127.5, 116.8, 115.8 (q, J = 288.1 Hz), 53.5, 17.7;

19F NMR (CDCl₃, 377MHz, 293K): δ -75.8;

IR: ν 3290, 3089, 2923, 1694, 1552, 1192, 967, 928;

HRMS (EI): calcd for C₈H₉F₃NO⁺ (M-H) 192.0636 Found: 192.0620;

(E)-2-methyl-N-(1-phenylbut-2-enyl)propane-2-sulfinamide

To a solution of (R)–N-((E)-but-2-enylidene)- tert-butanesulfinamide (500 mg, 2.89 mmol, 1.00 equiv.) in THF (10 mL) at -78 °C was added slowly a solution of phenyl lithium (2.00 M in dibutyl ether, 2.20 mL, 4.33 mmol, 1.50 equiv.) and the solution was stirred at -78 °C for 2.5h. The solution was then allowed to warm to r.t. and quenched with saturated NH₄Cl solution (10 mL). The solution was extracted with Et₂O (3 x 20mL), dried over MgSO₄ and concentrated. The product was then purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as a off-white solid in 68% yield (491 mg, 1.95 mmol) as a 2.5:1 mixture of diastereoisomers.

Rf (hexane:EtOAc = 1:1): 0.42;

1H NMR (CDCl₃, 300MHz, 293K) major diastereoisomer: δ 7.36 – 7.23 (m, 5H), 5.79 – 5.60 (m, 2H), 4.95 – 4.89 (m, 1H), 3.42 (d, J = 3.0 Hz, 1H), 1.69 (d, J = 5.4 Hz, 3H), 1.20 (s, 9H);

minor diastereoisomer: δ 7.36 – 7.23 (m, 5H), 5.83 (dq, J = 15.1, 6.6, 0.5 Hz, 1H), 5.52 (ddq, J = 15.2, 8.3, 1.5 Hz, 1H), 4.95 – 4.89 (m, 1H), 3.46 (d, J = 1.4 Hz, 1H), 1.71 (dd, J = 6.5, 1.6 Hz, 3H), 1.24 (s, 9H);
13C NMR (CDCl$_3$, 100MHz, 293K) major and minor diastereoisomers: δ 142.2, 141.1, 132.5, 131.1, 129.3, 128.7, 128.4, 128.3, 127.7, 127.5, 127.5, 126.9, 61.2, 61.0, 55.7, 55.5, 22.8, 22.7, 17.9, 17.9;

IR: ν 3448, 3210, 2960, 1455, 1055, 700;

HRMS (EI): calcd for C$_{14}$H$_{21}$NOS$^+$ (M) 251.1344 Found: 251.1350;

**(E)-2,2,2-trifluoro-N-(1-phenylbut-2-enyl)acetamide**

\[
\begin{align*}
\text{HN} & \quad \text{O} \\
\text{F} & \quad \text{F} \\
\text{F} & \quad \text{F}
\end{align*}
\]

To a solution of (E)-2-methyl-N-(1-phenylbut-2-enyl)propane-2-sulfinamide (800 mg, 3.18 mmol, 1.00 equiv) in methanol (45 mL) at 0°C under argon was added slowly a solution of HCl (4M solution in dioxane, 4.00 mL, 15.91 mmol, 5.00 equiv.). The solution was allowed to warm to r.t. and stirred for 30mins. The reaction was then evaporated to dryness and then quenched with a solution of saturated NaHCO$_3$ (10 mL) and extracted with Et$_2$O (3 x 15 mL). The crude product was then dissolved in DCM (15 mL). Triethylamine (0.67 mL, 4.77 mmol, 1.5 equiv.) was then added at 0°C followed by the slow addition of trifluoroacetic anhydride (0.53 mL, 3.82 mmol, 1.2 equiv.) and the resulting mixture was stirred for 3h. The solution was then concentrated and purified by flash chromatography (5% EtOAc/Hexane) to give the resulting product as a white solid in 57% yield (439 mg, 1.81 mmol).

Rf (hexane:EtOAc = 85:15): 0.42;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 7.45 – 7.27 (m, 2H), 6.54 (s, 1H), 5.82 – 5.50 (m, 1H), 1.78 – 1.75 (m, 1H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 156.1 (q, $J$ = 37.3 Hz), 139.3, 129.6, 129.0, 128.4, 128.2, 126.9, 115.9 (q, $J$ = 288.2 Hz), 55.5, 17.7;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): δ -75.6;

IR: ν 3282, 1698, 1553, 1184, 696;

HRMS (EI): calcd for C$_{12}$H$_{12}$F$_3$NO$^+$ (M) 243.0871 Found: 243.0866;
2,2,2-trifluoro-N-(5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)acetamide

To a solution of (5-amino-2,2-dimethyl-1,3-dioxan-5-yl)methanol (1.00g, 5.29 mmol, 1.00 equiv.) in acetonitrile (10 mL) was treated ethyl trifluoroacetate (1.26 mL, 10.6 mmol, 2.00 equiv.) and the resulting mixture was stirred overnight at r.t. The solution was concentrated and the product was then purified by flash chromatography (hexanes/EtOAc 6:4) to give the product as a white solid in 87% yield (1.19 g, 4.63 mmol).

Rf (hexane:EtOAc = 2:1): 0.19;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 7.06 (s, 1H), 3.99 (dt, $J = 11.3, 0.9$ Hz, 2H), 3.89 (dt, $J = 12.2, 0.9$ Hz, 2H), 3.85 (s, 2H), 3.40 (s, 1H), 1.48 (s, 3H), 1.48 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 157.6 (q, $J = 37.0$ Hz), 115.7 (q, $J = 288.3$ Hz), 99.3, 63.6, 62.5, 56.1, 27.3, 19.5;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -75.7;

IR: $\nu$ 3478, 3282, 1703, 1385, 1226, 1193, 1148, 1046, 824;

HRMS (ESI): calcd for C$_9$H$_{15}$F$_3$NO$_4$ $^+$ (M+H) 258.0948 Found: 258.0947;

2,2,2-trifluoro-N-(5-formyl-2,2-dimethyl-1,3-dioxan-5-yl)acetamide

To a solution of 2,2,2-trifluoro-N-(5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxan-5-yl)acetamide (0.500 g, 1.94 mmol, 1.00 equiv.) in DCM (20 mL) at 0°C was added Dess-Martin periodinane (1.24 g, 2.92 mmol, 1.50 equiv.) portionwise and the resulting cloudy mixture stirred at 0°C for 5 min and then stirred 45 min at r.t. The mixture was diluted with Et$_2$O (20 mL) and quenched with a solution of Sodium thiosulfate (3.38 g, 21.38 mmol, 11.0
equiv.) in 80% saturated aq. NaHCO₃ soln. (20 mL). The resulting slurry was stirred vigorously for 5 min until clear phase separation was observed. The aqueous layer was separated and extracted with DCM (20 mL) and the combined organic layers washed with sat. aq. NaHCO₃ soln. (20 mL), water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 25°C. The product was then obtained in 87% yield (430 mg 1.69 mmol) and was used without further purification.

Rf (hexane:EtOAc = 2:1): 0.32;

¹H NMR (CDCl₃, 300MHz, 293K): δ 9.71 (s, 1H), 7.32 (s, 1H), 4.17 (d, J = 12.0 Hz, 2H), 4.11 (d, J = 12.0 Hz, 2H), 1.51 (s, 2H), 1.50 (s, 2H);

¹³C NMR (CDCl₃, 100MHz, 293K): δ 196.9, 157.6 (q, J = 38.3 Hz), 115.4 (q, J = 287.8 Hz), 99.3, 61.6, 60.9, 26.3, 20.2;

¹⁹F NMR (CDCl₃, 377MHz, 293K): δ -75.6;

IR: ν 3316, 1723, 1185, 1144, 907, 734;

HRMS (ESI): cale for C₉H₁₀F₃NO₄⁺ (M+H) 256.0791 Found: 256.0785;

(Z)-N-(2,2-dimethyl-5-(prop-1-enyl)-1,3-dioxan-5-yl)-2,2,2-trifluoroacetamide

A flame-dried two-necked flask equipped with a reflux condenser under argon was charged with ethyltriphenylphosphonium bromide (1.83 g, 4.94 mmol, 2.5 equiv.) which was then suspended in THF (15 mL) at 0°C. To the mixture was added nBuLi (1.6M in hexane, 2.61 mL, 4.44 mmol, 2.20 equiv.) dropwise and the resulting red-orange solution was stirred for 30 mins at r.t. The solution was then cooled to -78°C and a solution of 2,2,2-trifluoro-N-(5-formyl-2,2-dimethyl-1,3-dioxan-5-yl)acetamide (420 mg, 1.65 mmol, 1.00 equiv.) in THF (10 mL) was added dropwise via canula. The mixture was allowed to warm up to r.t. and stirred for 18h. The solution was then quenched with saturated NH₄Cl solution. (10 mL) and stirred for 10 min. The resulting mixture was then partitioned with saturated NH₄Cl solution (20 mL), water (20 mL) and Et₂O (50 mL). The aqueous washings were then extracted with
additional Et₂O (50 mL) and the combined organic layers dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was then purified by flash chromatography (hexanes/EtOAc 5:1) to give the product as a white solid in 61% yield (267 mg, 1.00 mmol) as a 2:1 mixture of Z/E olefins.

**Rf** (hexane:EtOAc = 1:2): 0.80;

**¹H NMR (CDCl₃, 300MHz, 293K) (Z)-isomer:** δ 6.91 (s, 1H), 5.73 (dq, J = 11.8, 7.4 Hz, 1H), 5.20 (ddd, J = 11.6, 3.3, 1.6 Hz, 1H), 4.09 (dt, J = 12.6, 1.6 Hz, 2H), 3.88 (dt, J = 12.6, 1.6 Hz, 2H), 1.75 (dd, J = 7.4, 1.8 Hz, 3H), 1.50 (s, 3H), 1.44 (s, 3H).

**(E)-isomer:** 6.75 (s, 1H), 5.68 (ddd, J = 16.0, 12.3, 6.1 Hz, 1H), 5.50 (ddd, J = 16.0, 3.2, 1.5 Hz, 1H), 3.99 (dt, J = 12.6, 1.6 Hz, 2H), 3.87 (dt, J = 2.6, 1.5 Hz, 2H), 1.75 (dd, J = 6.1, 1.3 Hz, 3H), 1.49 (s, 3H), 1.44 (s, 3H);

**¹³C NMR (CDCl₃, 100MHz, 293K) mixture of E and Z olefins:** δ 156.5 (q, J = 36.6 Hz), 156.0 (q, J = 36.7 Hz), 130.2, 128.6, 125.9, 123.6, 115.7 (q, J = 289.0 Hz), 115.6 (q, J = 289.2 Hz), 98.6, 65.3, 64.7, 54.2, 53.7, 28.9, 28.9, 18.2, 18.1, 18.0, 14.4;

**¹⁹F NMR (CDCl₃, 377MHz, 293K) mixture of E and Z olefins:** 75.6, -76.0;

**IR:** ν 3385, 1708, 1566, 1192, 1156;

**HRMS (ESI):** calcd for C₁₁H₁₇F₃NO₃⁺ (M+H) 268.1155 Found: 268.1153;

**(S)-2,2,2-trifluoro-N-(1-hydroxy-3-methylbutan-2-yl)acetamide**

L-valinol (1.50 g, 14.54 mmol, 1.00 equiv.) and pyridine (3.53 mL, 43.60 mmol, 3.00 equiv.) were dissolved in DCM (50 mL). Trifluoroacetic anhydride (2.23 mL, 15.99 mmol, 1.10 equiv.) was added slowly at 0 °C and the resulting solution was stirred at r.t. for 2h. The solution was then concentrated and purified by flash chromatography (hexanes/EtOAc 5.1 to 1:1) to give the product as a white solid in 81% yield (2.36 g 11.85 mmol).

**Rf** (hexane:EtOAc = 2:1): 0.24;
**Experimental Part**

**1H NMR (CDCl₃, 300MHz, 293K):** δ 6.68 (s, 1H), 3.84 – 3.72 (m, 3H), 2.19 (s, 1H), 2.05 – 1.92 (m, 1H), 1.02 (d, J = 6.8 Hz, 3H), 0.98 (d, J = 6.8 Hz, 3H);

**13C NMR (CDCl₃, 100MHz, 293K):** δ 157.6 (q, J = 36.8 Hz), 116.0 (q, J = 287.9 Hz), 62.2, 57.2, 28.9, 19.3, 18.8;

**19F NMR (CDCl₃, 377MHz, 293K):** δ -75.8;

**IR:** ν 3288, 2969, 1694, 1558, 1184;

**HRMS (ESI):** calcd for C₇H₁₆F₃N₂O₂⁺ (M+NH₄⁺) 217.1158 Found: 217.1151;

α₀ = -31.32 (c = 1.11)

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**To a solution of (S)-2,2,2-trifluoro-N-(3-methyl-1-oxobutan-2-yl)acetamide (1.335 g, 6.70 mmol, 1.00 equiv.) in DCM (50 mL) at 0°C was added Dess-Martin periodinane (3.70 g, 8.71 mmol, 1.3 equiv.) portionwise and the resulting cloudy mixture stirred at 0°C for 5min and then at r.t. for 45min. The mixture was diluted with Et₂O (20 mL) and quenched with a solution of Sodium thiosulfate (11.66 g, 73.7 mmol, 11.0 equiv.) in 80% saturated aq. NaHCO₃ soln. (20 mL). The resulting slurry was stirred vigorously for 5min until clear phase separation was observed. The aqueous layer was separated and extracted with additional Et₂O (20 mL) and the combined organic layers washed with sat. aq. NaHCO₃ soln. (20 mL), water (20 mL) and brine (20 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 25°C. Upon concentration, the product precipitated as a pale yellow solid in quantitative yield which was used without further purification to prevent epimerization.

**Rf** (hexane:EtOAc = 2:1): 0.43;

**1H NMR (CDCl₃, 300MHz, 293K):** δ 9.72 (s, 1H), 6.98 (s, 1H), 4.69 (dd, J = 7.7, 4.4 Hz, 1H), 2.54 – 2.38 (m, 1H), 1.08 (d, J = 2.6 Hz, 3H), 1.06 (d, J = 2.8 Hz, 3H);
13C NMR (CDCl3, 100MHz, 293K): δ 197.3, 157.34 (q, J = 37.7 Hz), 115.68 (q, J = 287.7 Hz), 63.5, 29.3, 18.7, 17.7;

19F NMR (CDCl3, 377MHz, 293K): δ -75.7;

IR: ν 3317, 2971, 1714, 1551, 1165;

HRMS (ESI): calcd for C7H14F3N2O2+ (M+NH4+) 215.1002 Found: 215.0994;

(S,E)-2,2,2-trifluoro-N-(2-methylhex-4-en-3-yl)acetamide

A flame-dried two-necked flask equipped with a reflux condenser under argon was charged with ethyltriphenylphosphonium bromide (4.66 g, 12.55 mmol, 2.5 equiv.) which was then suspended in THF (30 mL) at 0°C. To the mixture was added nBuLi (1.6M in hexane, 6.90 mL, 11.05 mmol, 2.20 equiv.) dropwise and the resulting red-orange solution was stirred for 30 mins at r.t. The solution was then cooled to -78°C and a solution of (S)-2,2,2-trifluoro-N-(3-methyl-1-oxobutan-2-yl)acetamide (990 mg, 5.02 mmol, 1.00 equiv.) in THF (20 mL) was added dropwise via canula. The mixture was allowed to warm up to r.t. and stirred for 18h. The solution was then quenched with saturated NH4Cl solution (10 mL) and stirred for 10 min. The resulting mixture was then partitioned with saturated NH4Cl solution (20 mL), water (20 mL) and Et2O (50 mL). The aqueous washings were then extracted with additional Et2O (50 mL) and the combined organic layers dried over Na2SO4, filtered and concentrated under reduced pressure. The product was was then purified by flash chromatography (hexanes/EtOAc 15:1) to give the product as a white solid in 71% yield (742 mg, 3.55 mmol) as a 1:3.8 mixture of Z:E olefins.

Rf (hexane:EtOAc = 2:1): 0.60;

1H NMR (CDCl3, 300MHz, 293K) (E)- isomer: δ 6.17 (s, 1H), 5.69 (dq, J = 15.2, 6.3, 1.0 Hz, 1H), 5.37 (ddq, J = 15.3, 7.2, 1.6 Hz, 1H), 4.30 – 4.24 (m, 1H), 1.92 – 1.79 (m, 1H), 1.75 – 1.72 (m, 4H), 0.94 (d, J = 6.8 Hz, 6H);
(Z)-isomer: 6.17 (s, 1H), 5.75 (dqd, J = 10.8, 7.0, 1.0 Hz, 1H), 5.32 (ddq, J = 11.0, 9.4, 1.8 Hz, 1H), 4.65 – 4.55 (m, 1H), 1.93 – 1.79 (m, 1H), 1.75 – 1.72 (m, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.8 Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) mixture of E and Z olefins: δ 156.4 (, J = 36.6 Hz), 129.8, 129.4, 127.4, 126.8, 116.0 (q, J = 288.3 Hz), 57.5, 52.4, 32.5, 32.1, 18.5, 18.3, 18.2, 17.8, 13.5;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K) mixture of E and Z olefins: -75.9;

IR: ν 3291, 2965, 1694, 1558, 1183, 909, 729;

HRMS (ESI): calcd for C$_9$H$_{15}$F$_3$NO$^+$ (M) 210.1100 Found: 210.1095;

$\alpha_D = -45.57 \ (c = 1.05)$

2,2,2-trifluoro-N-(2-methyl-1-oxopropan-2-yl)acetamide

To a solution of 2,2,2-trifluoro-N-(1-hydroxy-2-methylpropan-2-yl)acetamide$^{150}$ (0.700 g, 3.78 mmol, 1.00 equiv.) in DCM (25 mL) at 0ºC was added Dess-Martin periodinane (2.085 g, 4.92 mmol, 1.30 equiv.) portionwise and the resulting cloudy mixture stirred at 0°C for 5 min and then at r.t. After 3h, the solution was cooled to 0ºC and an additional portion of Dess-Martin periodinane (2.085 g, 4.92 mmol) was added portionwise and the solution was allowed to warm to r.t. and stirred for another 3h. The mixture was diluted with Et$_2$O (15 mL) and quenched with a solution of Sodium thiosulfate (6.58 g, 41.6 mmol, 11.0 equiv.) in 80% saturated aq. NaHCO$_3$ soln. (15 mL). The resulting slurry was stirred vigorously for 5min until clear phase separation was observed. The aqueous layer was separated and extracted with additional Et$_2$O (30 mL) and the combined organic layers washed with sat. aq. NaHCO$_3$ soln. (15 mL), water (15 mL) and brine (15 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 25ºC. The product was then purified by flash chromatography (hexanes/EtOAc 5.1 to 2:1) to give the product as a clear oil in 58% yield (401 mg 2.19 mmol).
**Experimental Part**

**Rf** (hexane:EtOAc = 2:1): 0.22;

**$^1$H NMR** (CDCl$_3$, 300MHz, 293K): $\delta$ 9.36 (s, 1H), 7.17 (s, 1H), 1.58 (s, 9H);

**$^{13}$C NMR** (CDCl$_3$, 100MHz, 293K): $\delta$ 197.8, 156.4 (q, $J = 37.2$ Hz), 115.5 (q, $J = 288.6$ Hz), 60.7, 20.5;

**$^{19}$F NMR** (CDCl$_3$, 377MHz, 293K): $\delta$ -76.0;

**IR:** $\nu$ 3346, 2918, 1721, 1712, 1157;

**HRMS (ESI):** calcd for C$_6$H$_9$F$_3$NO$_2$ $^+$ (M+H) 184.0585 Found: 184.0583;

2,2,2-trifluoro-N-(2-methylpent-3-en-2-yl)acetamide

A flame-dried two-necked flask equipped with a reflux condenser under argon was charged with ethyltriphenylphosphonium bromide (1.52 g, 4.10 mmol, 2.5 equiv.) which was then suspended in THF (10 mL) at 0°C. To the mixture was added nBuLi (1.6M in hexane, 2.25 mL, 3.60 mmol, 2.20 equiv.) dropwise and the resulting red-orange solution was stirred for 30 mins at r.t. The solution was then cooled to -78°C and a solution of 2,2,2-trifluoro-N-(2-methyl-1-oxopropan-2-yl)acetamide (300 mg, 1.64 mmol, 1.00 equiv.) in THF (7 mL) was added dropwise via canula. The mixture was allowed to warm up to r.t. and stirred for 18h. The solution was then quenched with saturated NH$_4$Cl solution (10 mL) and stirred for 10 min. The resulting mixture was then partitioned with saturated NH$_4$Cl solution (20 mL), water (20 mL) and Et$_2$O (50 mL). The aqueous washings were then extracted with additional Et$_2$O (50 mL) and the combined organic layers dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The product was then purified by flash chromatography (hexanes/EtOAc 15:1) to give the product as a white solid in 48% yield (152 mg, 0.78 mmol) as a 1:6.3 mixture of olefins.

**Rf** (hexane:EtOAc = 5:1): 0.42;

**$^1$H NMR** (CDCl$_3$, 300MHz, 293K) major product: $\delta$ 6.36 (s, 1H), 5.68 – 5.47 (m, 2H), 1.76 – 1.74 (m, 3H), 1.57 (s, 9H);
Experimental Part

**minor product**: δ 6.17 (s, 1H), 5.68 – 5.47 (m, 2H), 1.77 – 1.71 (m, 3H), 1.50 (s, 6H);

\(^{13}\text{C NMR (CDCl}_3, 100\text{MHz, 293K)}\) mixture of \(E\) and \(Z\) olefins: δ 155.6 (q, \(J = 36.0\) Hz), 134.9, 134.7, 126.2, 124.5, 115.7 (q, \(J = 290.7\) Hz), 55.3, 54.8, 27.7, 26.6, 17.6, 13.9;

\(^{19}\text{F NMR (CDCl}_3, 377\text{MHz, 293K)}\) mixture of \(E\) and \(Z\) olefins: -76.0, -76.2;

**IR**: ν 3306, 2982, 1704, 1558, 1185, 704;

**HRMS (EI)**: calcd for C\(_8\)H\(_{12}\)F\(_3\)N\(_2\)O\(_2\) \((\text{M})\) 195.0871 Found: 195.0867;

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**2,2,2-trifluoro-N-(2-oxopropyl)acetamide**

![Image of 2,2,2-trifluoro-N-(2-oxopropyl)acetamide]

A flame-dried flask was charged with 4A Molecular Sieves (2.5g) and a solution of 2,2,2-trifluoro-N-(2-hydroxypropyl)acetamide (1.00 g, 5.84 mmol, 1.00 equiv.) in DCM (50 mL). The solution was cooled to 0°C and treated portionwise with PCC (Pyridinium chlorochromate) (1.890 g, 8.77 mmol, 1.50 equiv.) which was pre-ground with celite (2.5g) to a light red powder. The resulting brown mixture was allowed to warm to r.t. and stirred for overnight. The crude mixture was then treated with Et\(_2\)O (50mL) and filtered through a short pad of celite which was washed with Et\(_2\)O. The combined filtrates were adsorbed onto silica and subjected to flash chromatography (hexanes/EtOAc 3:2 to 1:1) to give the product as a pale oil in 87% yield (858 mg 5.07 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.39;

\(^{1}\text{H NMR (CDCl}_3, 300\text{MHz, 293K)}\): δ 7.20 (s, 1H), 4.25 (d, \(J = 4.6\) Hz, 2H), 2.28 (s, 3H);

\(^{13}\text{C NMR (CDCl}_3, 100\text{MHz, 293K)}\): δ 200.6, 157.0 (q, \(J = 37.8\) Hz), 115.6 (q, \(J = 287.3\) Hz), 49.4, 27.2;

\(^{19}\text{F NMR (CDCl}_3, 377\text{MHz, 293K)}\): δ -75.9;

**IR**: ν 3306, 1726, 1703, 1568, 1182, 1158;

**HRMS (ESI)**: calcd for C\(_8\)H\(_{10}\)F\(_3\)N\(_2\)O\(_2\) \((\text{M+NH}_4^+)\) 187.0689 Found: 187.0685;
2,2,2-trifluoro-N-(2-methylbut-2-enyl)acetamide

A flame-dried two-necked flask equipped with a reflux condenser under argon was charged with ethyltriphenylphosphonium bromide (1.537 g, 4.14 mmol, 1.4 equiv.) which was then suspended in THF (7 mL) at 0°C. To the mixture was added a solution of KOTBu (0.438 g, 3.90 mmol, 1.30 equiv.) in THF (14 mL) dropwise and the resulting red-orange solution was stirred for 2h at r.t. The solution was then cooled to 0°C and a solution of 2,2,2-trifluoro-N-(2-oxopropyl)acetamide (0.500 g, 2.96 mmol, 1.00 equiv.) in THF (14 mL) was added dropwise via canula. The mixture was allowed to warm up to r.t. and stirred for 30 min and then refluxed for 4h. The mixture was allowed to cool to r.t. and then quenched with saturated NH₄Cl solution. (10 mL) and stirred for 10 min. The resulting mixture was then partitioned with saturated NH₄Cl solution (20 mL), water (20 mL) and Et₂O (50 mL). The aqueous washings were then extracted with additional Et₂O (50 mL) and the combined organic layers dried over Na₂SO₄, filtered and concentrated under reduced pressure. The product was was then purified by flash chromatography (hexanes/EtOAc 5.1 to 1:1) to give the product as a clear oil in 49% yield (76% yield brsm, 262 mg 1.45 mmol) as a 9.4:1 mixture olefins.

Rf (hexane:EtOAc = 2:1): 0.60;

¹H NMR (CDCl₃, 300MHz, 293K) major olefin: δ 6.58 (d, J = 46.3 Hz, 1H), 5.48 (qd, J = 6.9, 1.2 Hz, 1H), 3.98 (d, J = 5.8 Hz, 2H), 1.73 – 1.62 (m, 6H);

minor olefin: δ 6.58 (d, J = 46.3 Hz, 1H), 5.56 – 5.38 (m, 1H), 3.87 (d, J = 6.0 Hz, 2H), 1.73 – 1.60 (m, 6H);

¹³C NMR (CDCl₃, 100MHz, 293K) mixture of E and Z olefins: δ 157.4 (q, J = 36.8 Hz), 130.3, 129.9, 124.9, 123.1, 115.9 (q, J = 287.7 Hz), 47.2, 39.9, 21.4, 13.9, 13.2;

¹⁹F NMR (CDCl₃, 377MHz, 293K) mixture of E and Z olefins: -76.0, -76.0;

IR: ν 3305, 1702, 1556, 1180;

HRMS (ESI): calcd for C₇H₁₁F₃NO⁺ (M+H) 182.0787 Found: 182.0782;
2,2,2-trifluoro-N-(1-hydroxypent-3-en-2-yl)acetamide

To a flask containing tert-butyl 2,2-dimethyl-4-(prop-1-enyl)oxazolidine-3-carboxylate\textsuperscript{91} (1.2 g, 4.97 mmol, 1.00 equiv.) was added a 6M solution of concentrated hydrochloric acid (3.6 mL) and the solution was stirred for 30 mins at rt. The flasked was concentrated to dryness under vacuum until a white waxy solid was formed. Acetonitrile (10 mL) was then added followed by triethylamine (0.76 mL, 5.47 mmol, 1.1 equiv.) and ethyl trifluoroacetate (1.18 mL, 9.94 mmol, 2.00 equiv.). The resulting mixture was stirred for 48h at r.t. The solution was then concentrated and the product was purified by flash chromatography (hexanes/EtOAc 7:3) to give the product as a white solid in 99% yield (979 mg, 4.97 mmol) as a 4.8:1 mixture of Z/E olefins.

Rf (hexane:EtOAc = 7:3): 0.26;

\textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300MHz, 293K) Z-olefins major: δ 6.77 (s, 1H), 5.80 (dqd, J = 10.8, 7.0, 1.2 Hz, 1H), 5.43 (ddq, J = 10.7, 9.0, 1.8 Hz, 1H), 4.91 – 4.83 (m, 1H), 3.81 – 3.68 (m, 2H), 2.27 (s, 1H), 1.77 (dd, J = 7.0, 1.8 Hz, 3H);

E-olefins minor: δ 6.77 (s, 1H), 5.82 – 5.73 (m, 1H), 5.48 (ddq, J = 15.5, 6.4, 1.6 Hz, 1H), 4.57 – 4.51 (m, 1H), 3.81 – 3.68 (m, 2H), 2.27 (s, 1H), 1.77 – 1.74 (m, 2H).

\textsuperscript{13}C NMR (CDCl\textsubscript{3}, 100MHz, 293K) mixture of E and Z olefins: δ 157.0 (q, J = 37.0 Hz), 130.6, 130.2, 125.8, 124.9, 115.8 (q, J = 287.9 Hz), 64.5, 64.2, 53.4, 49.3, 17.8, 13.5;

\textsuperscript{19}F NMR (CDCl\textsubscript{3}, 377MHz, 293K) mixture of E and Z olefins: -75.9, -75.9;

IR: ν 3296, 1699, 1558, 1183, 726;

HRMS (ESI): calcd for C\textsubscript{7}H\textsubscript{14}F\textsubscript{3}NO\textsubscript{2}\textsuperscript{+} (M+H) 198.0736 Found: 198.0727;

\textit{N-(1-(tertbutyldimethylsilyloxy)pent-3-en-2-yl)-2,2,2-trifluoroacetamide}
To a solution of 2,2,2-trifluoro-\(N\)-(1-hydroxypent-3-en-2-yl)acetamide (300 mg, 1.52 mmol, 1.00 equiv.) in DCM (20 mL) was added imidazole (124 mg, 1.83 mmol, 1.20 equiv.) followed by tert-butyldimethylsilane chloride (275 mg, 1.83 mmol, 1.20 equiv.) at r.t. and the resulting mixture was stirred for 24h. The solution was then concentrated and purified by flash chromatography (10% Et\(_2\)O/hexanes) to give the product as a white solid in 99% yield (468 mg, 1.50 mmol) in a ratio of 7.7:1 of \(Z\):\(E\) olefins.

\[ \text{Rf (hexane:Et\(_2\)O = 9:1): 0.35;} \]

\(^1\text{H NMR (CDCl\(_3\), 300MHz, 293K) Z-olefins major:} \delta 6.65 \text{ (s, 1H), } 5.70 \text{ (dqd, } J = 10.6, 6.9, 1.0 \text{ Hz, 1H), } 5.43 \text{ (ddq, } J = 10.8, 9.0, 1.7 \text{ Hz, 1H), } 4.84 \text{ – } 4.74 \text{ (m, 1H), } 3.75 \text{ (dd, } J = 10.1, 3.9 \text{ Hz, 1H), } 3.61 \text{ (dd, } J = 10.1, 4.0 \text{ Hz, 1H), } 1.74 \text{ (dd, } J = 6.9, 1.8 \text{ Hz, 3H), } 0.90 \text{ (s, 9H), 0.07 (s, 6H);} \]

\(^E\)-olefins minor: \( \delta 6.65 \text{ (s, 1H), } 5.79 \text{ – } 5.66 \text{ (m, 1H), } 5.50 \text{ – } 5.39 \text{ (m, 1H), } 4.50 \text{ – } 4.38 \text{ (m, 1H), } 3.74 \text{ (dd, } J = 10.1, 3.6 \text{ Hz, 1H), } 3.64 \text{ (dd, } J = 9.1, 3.9 \text{ Hz, 1H), } 1.71 \text{ (dd, } J = 6.5, 1.0 \text{ Hz, 3H), } 0.91 \text{ – } 0.88 \text{ (m, 9H), 0.10 – 0.02 (m, 6H).} \]

\(^{13}\text{C NMR (CDCl\(_3\), 100MHz, 293K) mixture of } E \text{ and } Z \text{ olefins:} \delta 156.3 \text{ (q, } J = 36.8 \text{ Hz), 129.4, 129.4, 126.7, 125.9, 115.9 \text{ (q, } J = 288.1 \text{ Hz), 64.6, 64.5, 48.5, 25.7, 25.6, 18.2, 17.7, 13.4, -5.6, -5.6, -5.6;} \]

\(^{19}\text{F NMR (CDCl\(_3\), 377MHz, 293K) mixture of } E \text{ and } Z \text{ olefins:} -76.1, -76.1; \]

\( \text{IR: } \nu 3306, 2939, 2860, 1699, 1557, 1259, 1166, 1118, 839, 779, 725; \)

\( \text{HRMS (ESI): caled for } C_{13}H_{25}F_{3}NO_{2}Si^{+} \text{ (M+H) 312.1601 Found: 312.1592;} \)

2-chloro-\(N\)-(1-hydroxypent-3-en-2-yl)acetamide
To a flask containing tert-butyl 2,2-dimethyl-4-(prop-1-enyl)oxazolidine-3-carboxylate (0.96 g, 3.98 mmol, 1.00 equiv.) was added a 6M solution of concentrated hydrochloric acid (2.9 mL) and the solution was stirred for 30 mins at rt. The flasked was concentrated to dryness under vacuum until a white waxy solid was formed. DCM (55 mL) was then added followed by triethylamine (1.11 mL, 7.96 mmol, 2.0 equiv.) and chloroacetyl chloride (0.33 mL, 4.18 mmol, 1.05 equiv.). The resulting mixture was stirred for 18h at r.t. The solution was then concentrated and the product was purified by flash chromatography (hexanes/EtOAc 1:1 to 2:8) to give the product as a white solid in 82% yield (585 mg, 3.28 mmol) as a 5.4:1 mixture of Z/E olefins.

**Rf** (100% EtOAc): 0.53;

**1H NMR (CDCl₃, 300MHz, 293K) Z-olefins major:** δ 6.77 (s, 1H), 5.74 (dqd, J = 10.5, 7.0, 1.0 Hz, 1H), 5.38 (ddq, J = 10.7, 8.9, 1.8 Hz, 1H), 4.87 – 4.77 (m, 1H), 4.06 (d, J = 2.1 Hz, 2H), 3.76 – 3.59 (m, 2H), 2.68 (s, 1H), 1.74 (dd, J = 6.9, 1.8 Hz, 3H);

**E-olefins minor:** δ 6.87 (s, 1H), 5.76 – 5.66 (m, 1H), 5.45 (ddq, J = 15.3, 6.0, 1.6 Hz, 1H), 4.57 – 4.44 (m, 1H), 4.07 (d, J = 3.1 Hz, 2H), 3.76 – 3.59 (m, 2H), 2.48 (s, 1H), 1.73 (dd, J = 6.4, 1.5 Hz, 3H);

**13C NMR (CDCl₃, 100MHz, 293K) mixture of E and Z olefins:** δ 166.3, 129.9, 129.2, 126.8, 125.9, 65.5, 65.1, 53.6, 49.7, 42.7, 42.6, 17.8, 13.6;

**IR:** ν 3289, 1644, 1538, 1263, 1051, 749;

**HRMS (ESI):** caled for C₇H₁₂ClNNaO₂⁺ (M+Na) 200.0449 Found: 200.0450;

5-(prop-1-enyl)morpholin-3-one

To a solution of 2-chloro-N-(1-hydroxypent-3-en-2-yl)acetamide (548 mg, 3.09 mmol, 1.00 equiv.) was added a sodium hydride (74.0 mg, 3.09 mmol) at 0°C under argon and the solution was allowed to warm to r.t then stirred for 2h. The solution was then quenched with saturated NH₄Cl (10 mL) and extracted with EtOAc (2x 10mL) then dried with MgSO₄. The
solution was then concentrated and the product was purified by flash chromatography (hexanes/EtOAc 1:9) to give the product as a white solid in 75% yield (326 mg, 2.31 mmol) as a 9:1 mixture of Z/E olefins.

**Rf** (100% EtOAc): 0.38;

**^1^H NMR (CDCl, 300MHz, 293K) Z-olefins major:** \( \delta \) 6.78 (s, 1H), 5.73 (dq, \( J = 10.8, 6.9, 0.9 \) Hz, 1H), 5.26 (ddq, \( J = 10.8, 9.1, 1.8 \) Hz, 1H), 4.50 (td, \( J = 8.8, 4.3 \) Hz, 1H), 4.20 (d, \( J = 16.7 \) Hz, 1H), 4.08 (d, \( J = 16.7 \) Hz, 1H), 3.85 (dd, \( J = 11.8, 4.2 \) Hz, 1H), 3.37 (dd, \( J = 11.7, 8.7 \) Hz, 1H), 1.70 (dd, \( J = 7.0, 1.8 \) Hz, 3H);

**E-olefins minor:** \( \delta \) 6.78 (s, 1H), 5.83 – 5.71 (m, 1H), 5.35 (ddd, \( J = 7.5, 3.2, 1.6 \) Hz, 1H), 4.17 (d, \( J = 16.4 \) Hz, 1H), 4.26 – 4.01 (m, 1H), 4.10 (dd, \( J = 15.1, 12.4 \) Hz, 1H), 4.07 (d, \( J = 16.5 \) Hz, 1H), 3.90 – 3.80 (m, 1H), 3.41 (dd, \( J = 12.1, 8.4 \) Hz, 1H), 1.71 (d, \( J = 6.3 \) Hz, 3H);

**^1^C NMR (CDCl, 100MHz, 293K) mixture of E and Z olefins:** \( \delta \) 171.4, 168.8, 130.6, 130.2, 126.9, 125.7, 68.1, 67.4, 54.3, 49.1, 17.7, 13.2;

**IR:** \( \nu \) 3206, 2920, 1652, 1419, 1318, 1122, 707;

**HRMS (ESI):** calcd for C\(_7\)H\(_{12}\)NO\(_2\)^+ (M+H) 142.0863 Found: 142.0859;

**4-(prop-1-enyl)oxazolidin-2-one**

![structure](image)

To a flask containing *tert*-butyl 2,2-dimethyl-4-(prop-1-enyl)oxazolidine-3-carboxylate\(^9^1\) (493 mg, 2.04 mmol, 1.00 equiv.) was added a 6M solution of concentrated hydrochloric acid (2.9 mL) and the solution was stirred for 30 mins at rt. The flasked was concentrated to dryness under vacuum until a white waxy solid was formed. DCM (15 mL) was then added followed by triethylamine (0.28 mL, 2.04 mmol, 1.00 equiv.) and the solution was stirred for 15 mins at r.t. The solution was pumped to dryness and the flask was equipped with a distillation condenser and flushed with argon. To the flask was then added potassium carbonate (169 mg, 1.22 mmol, 0.60 equiv.) followed by diethyl carbonate (0.99 mL, 8.16 mmol, 4.00 equiv.). The resulting mixture was dropped in a preheated bath at 120°C and the solution was stirred for 3h during which the ethanol formed was collected in an ice cooled bath. The solution was
then cooled to r.t. and then concentrated. The product was purified by flash chromatography (hexanes/EtOAc 1:1) to give the product as a white solid in 91% yield (236 mg, 1.86 mmol) as a 6.2:1 mixture of Z/E olefins.

Rf (hex:EtOAc = 1:1): 0.19;

\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K) Z-olefins major: \(\delta 6.59\) (s, 1H), 5.64 (dqd, \(J = 10.8, 7.0, 1.1\) Hz, 1H), 5.37 (ddq, \(J = 10.7, 8.9, 1.8\) Hz, 1H), 4.76 – 4.67 (m, 1H), 4.47 (t, \(J = 8.5\) Hz, 1H), 3.92 (dd, \(J = 8.5, 7.3\) Hz, 1H), 1.62 (dd, \(J = 7.0, 1.8\) Hz, 3H);

E-olefins minor: \(\delta 6.59\) (s, 1H), 5.73 – 5.61 (m, 1H), 5.42 – 5.34 (m, 1H), 4.43 (t, \(J = 8.4\) Hz, 1H), 4.29 (dd, \(J = 15.4, 7.7\) Hz, 1H), 3.94 (dd, \(J = 8.2, 6.8\) Hz, 1H), 1.66 – 1.63 (m, 3H);

\(^13\)C NMR (CDCl\(_3\), 100MHz, 293K) mixture of E and Z olefins: \(\delta 160.2, 130.2, 129.4, 128.7, 128.3, 70.2, 54.8, 49.2, 17.5, 13.0\);

IR: \(\nu 3278, 2918, 1748, 1398, 1236, 1022, 923\);

HRMS (ESI): calcd for C\(_6\)H\(_{10}\)NO\(_2\)\(^+\) (M+H) 128.0706 Found: 128.0704;

\(2,2,2\)-trifluoro-N-(2-methylhept-4-en-3-yl)acetamide

A flame-dried two-necked flask equipped with a reflux condenser under argon was charged with \(n\)-propyltriphenylphosphonium bromide (3.84g, 9.96 mmol, 2.2 equiv.) which was then suspended in THF (20 mL) at 0°C. To the mixture was added \(n\)BuLi (1.6M in hexane, 5.60 mL, 9.51 mmol, 2.10 equiv.) dropwise and the resulting red-orange solution was stirred for 30 mins at r.t. The solution was then cooled to -78°C and a solution of \(2,2,2\)-trifluoro-N-(3-methyl-1-oxobutan-2-yl)acetamide (893 mg, 4.53 mmol, 1.00 equiv.) in THF (10 mL) was added dropwise via canula. The mixture was allowed to warm up to r.t. and stirred for 18h. The solution was then quenched with saturated NH\(_4\)Cl solution. (10 mL) and stirred for 10 min. The resulting mixture was then partitioned with saturated NH\(_4\)Cl solution (20 mL), water (20 mL) and Et\(_2\)O (50 mL). The aqueous washings were then extracted with additional Et\(_2\)O (50 mL) and the combined organic layers dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The product was then purified by flash chromatography.
(hexanes/EtOAc 12:1) to give the product as a white solid in 23% yield (234 mg, 1.05 mmol) as a 1:5.7 mixture of Z:E olefins.

Rf (hexane:EtOAc = 2:1): 0.60;

$\text{^1H NMR (CDCl}_3, 300\text{MHz, 293K}}$ (E)-isomer: $\delta$ 6.34 (s, 1H), 5.70 (dtd, $J = 15.4, 6.3, 1.1$ Hz, 1H), 5.34 (ddt, $J = 15.4, 7.3, 1.6$ Hz, 1H), 4.26 (dd, $J = 15.4, 7.3$ Hz, 1H), 2.12 – 2.03 (m, 2H), 1.92 – 1.79 (m, 1H), 1.00 (t, $J = 7.5$ Hz, 3H), 0.94 (s, 3H), 0.92 (s, 3H).

(Z)-isomer: $\delta$ 6.34 (s, 1H), 5.63 (dtd, $J = 10.7, 7.4, 0.9$ Hz, 1H), 5.24 (ddt, $J = 11.0, 9.6, 1.6$ Hz, 1H), 4.55 (dd, $J = 16.7, 8.9$ Hz, 1H), 2.25 – 2.09 (m, 1H), 1.87 – 1.77 (m, 1H), 0.99 (t, $J = 7.5$ Hz, 3H), 0.96 (s, 1H), 0.95 (s, 1H);

$\text{^{13}C NMR (CDCl}_3, 100\text{MHz, 293K}}$: $\delta$ 156.5 (q, $J = 36.5$ Hz), 137.0, 136.1, 125.2, 125.2, 116.0 (q, $J = 288.2$ Hz), 57.6, 52.7, 32.5, 32.3, 25.3, 21.3, 18.5, 18.5, 18.3, 18.3, 13.9, 13.3;

$\text{^{19}F NMR (CDCl}_3, 377\text{MHz, 293K}}$: $\delta$ -75.9;

IR: $\nu$ 3288, 2965, 1693, 1180;

HRMS (ESI): calcd for C$_{10}$H$_{17}$F$_3$NO$^+$ (M) 224.1257 Found: 224.1259;

$\text{(E)-tert-butyldimethyl(oct-2-en-4-yloxy)silane}$

To a solution of trans-2-octen-4-ol$^{151}$ (1.00 g, 7.80 mmol, 1.00 equiv.) in DCM (30 mL) was added imidazole (637 mg, 9.36 mmol, 1.2 0equiv.) followed by tert-butyldimethylsilane chloride (1.41 g, 9.36 mmol, 1.20 equiv.) at r.t. and the resulting mixture was stirred for 24h. The solution was then concentrated and purified by flash chromatography (100% hexanes) to give the product as a white solid in 92% yield (1.74 g, 7.18 mmol).

Rf (100% hexane): 0.36;

$\text{^1H NMR (CDCl}_3, 300\text{MHz, 293K}}$: $\delta$ 5.51 (dq, $J = 15.3, 6.3, 0.7$ Hz, 1H), 5.42 (ddq, $J = 15.3, 6.5, 1.3$ Hz, 1H), 4.01 (q, $J = 6.5$ Hz, 1H), 1.70 – 1.62 (m, 3H), 1.56 – 1.19 (m, 6H), 0.93 – 0.85 (m, 3H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H);
\[ ^{13}C \text{ NMR (CDCl}_3, 100MHz, 293K): \delta 135.0, 124.5, 73.6, 38.1, 27.5, 25.8, 22.6, 18.2, 17.5, 14.0, -4.3, -4.9; \]

**IR:** \(\nu 2930, 2859, 1256, 1083, 1052, 834, 774;\)

**HRMS (EI):** calcd for C\(_{14}\)H\(_{30}\)SiO\(^+\) (M\(^+\)) 242.2066 Found: 242.2061;

\((E)-\text{tert-butylidimethyl(1-phenylbut-2-enyloxy)silane}\)

\[
\begin{align*}
\text{Si} & \quad \text{O} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C} \\
\text{C} & \quad \text{C}
\end{align*}
\]

To a solution of \((E)-1\text{-phenylbut-2-en-1-ol}\)\(^{152}\) (0.5 g, 3.37 mmol, 1.00 equiv.) in DCM (15 mL) was added imidazole (276 mg, 4.05 mmol, 1.2 equiv.) followed by tert-butylidimethylsilane chloride (610 mg, 4.05 mmol, 1.20 equiv.) at r.t. and the resulting mixture was stirred for 24h. The solution was then quenched with H\(_2\)O (10 mL) and extracted with EtOAc (2 x 10 mL), dried over MgSO\(_4\) then concentrated and purified by flash chromatography (100% hexanes) to give the product as a white solid in 74% yield (480 mg, 2.50 mmol). The product exhibited identical spectral as previously reported.\(^{153}\)

\((E)-1\text{-}(benzo}[b]\text{thiophen-2-yl)but-2-en-1-ol}\)

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

To a solution of benzothiophene (1.44 g, 10.7 mmol, 1.50 equiv.) in THF (10 mL) was added slowly \(n\)-BuLi (1.6M in hexane, 5.35 mL, 8.56 mmol, 1.20 equiv.) at -10 °C and the solution was stirred at that temperature for 2h. Trans-crotonaldehyde (0.50 g, 7.13 mmol, 1.00 equiv.) was then added and the solution was allowed to warm to r.t. over 2h. The solution was then quenched with saturated ammonium chloride solution (10 mL), extracted with EtOAc (2 x 10 mL), dried over mixture with MgSO\(_4\), concentrated then purified by flash chromatography (15% Et\(_2\)O/hexanes) to give the product as a clear oil in 94% yield (1.37 g, 6.72 mmol).
Rf (20% EtOAc/hexane): 0.28;

\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K): \(\delta 7.87 - 7.81\) (m, 1H), 7.74 (dd, \(J = 7.1, 1.4\) Hz, 1H), 7.41 – 7.30 (m, 2H), 7.19 (s, 1H), 5.96 – 5.77 (m, 2H), 5.45 (d, \(J = 5.3\) Hz, 1H), 2.61 (s, 1H), 1.81 – 1.78 (m, 3H);

\(^{13}\)C NMR (CDCl\(_3\), 100MHz, 293K): \(\delta 148.3, 139.7, 139.7, 132.3, 128.8, 124.3, 124.1, 123.6, 122.5, 120.3, 71.7, 17.7\);

IR: \(\nu 3344, 1436, 1074, 963, 747\);

HRMS (EI): calcd for C\(_{12}\)H\(_{12}\)OS\(^+\) (M\(^+\)) 204.0609 Found: 204.0604;

\((E)-(1-(benzo[b]thiophen-2-yl)but-2-enyloxy)(tert-butyl)dimethylsilane\)

To a solution of \((E)-1-(benzo[b]thiophen-2-yl)but-2-en-1-ol\) (1.24 g, 6.07 mmol, 1.00 equiv.) in DCM (30 mL) was added imidazole (1.10 g, 7.28 mmol, 1.2 equiv.) followed by tert-butyldimethylsilane chloride (496 mg, 7.28 mmol, 1.20 equiv.) at r.t. and the resulting mixture was stirred for 18h. The solution was then concentrated and purified by flash chromatography in Al\(_2\)O\(_3\) neutral (100% hexanes) to give the product as a clear oil in 94% yield (1.81 g, 5.68 mmol).

Rf (100% hexane): 0.24;

\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K): \(\delta 7.87 - 7.78\) (m, 1H), 7.72 (dd, \(J = 7.2, 1.2\) Hz, 1H), 7.39 – 7.26 (m, 2H), 7.15 – 7.08 (m, 1H), 5.90 – 5.65 (m, 2H), 5.51 – 5.42 (m, 1H), 1.82 – 1.75 (m, 3H), 1.00 (s, 9H), 0.16 (s, 3H), 0.15 (s, 3H);

\(^{13}\)C NMR (CDCl\(_3\), 100MHz, 293K): \(\delta 150.6, 139.9, 139.7, 133.7, 126.6, 124.0, 123.7, 123.3, 122.4, 119.0, 72.6, 25.9, 18.4, 17.6, -4.4, -4.8;\)

IR: \(\nu 2956, 2857, 1459, 1252, 1091, 1034, 837, 777;\)

HRMS (EI): calcd for C\(_{18}\)H\(_{26}\)SSiO\(^+\) (M\(^+\)) 318.1474 Found: 318.1469;
Experimental Part

(S,E)-2,2,3,3,8,8,9,9-octamethyl-5-(prop-1-enyl)-4,7-dioxa-3,8-disiladecane

To a solution of imidazole (420 mg, 6.17 mmol, 3.00 equiv.) in DMF (2.2 mL) was added tert-butyldimethylsilyl chloride (775 mg, 5.14 mmol, 2.5 equiv.) followed by (S,E)-pent-3-ene-1,2-diol\(^{154}\) (210 mg, 2.06 mmol, 1.00 equiv.) at r.t. and the resulting mixture was stirred for 18h. The solution was then quenched with saturated \(\text{NH}_4\text{Cl}\) (15 mL) and extracted with \(\text{Et}_2\text{O}\) (2 x 50mL). The organic layer was then washed with brine (6 x 20mL), dried with \(\text{Na}_2\text{SO}_4\), concentrated and purified by flash chromatography (100% hexanes) to give the product as a clear oil in 85% yield (578 mg, 1.75 mmol).

\(\text{Rf} (90\% \text{ hexane/EtOAc}): 0.80;\)

\(^1\text{H} \text{NMR} (\text{CDCl}_3, 300\text{MHz}, 293\text{K}): \delta 5.54 (\text{dqd}, J = 11.1, 6.9, 1.1 \text{ Hz}, 1\text{H}), 5.32 (\text{ddq}, J = 12.1, 8.6, 1.7 \text{ Hz}, 1\text{H}), 4.51 (\text{ddt}, J = 8.0, 6.7, 1.0 \text{ Hz}, 1\text{H}), 3.58 (\text{dd}, J = 10.1, 6.7 \text{ Hz}, 1\text{H}), 3.43 (\text{dd}, J = 10.1, 5.6 \text{ Hz}, 1\text{H}), 1.68 (\text{dd}, J = 6.9, 1.7 \text{ Hz}, 3\text{H}), 0.91 (\text{s}, 9\text{H}), 0.90 (\text{s}, 9\text{H}), 0.09 (\text{s}, 3\text{H}), 0.07 (\text{s}, 3\text{H}), 0.07 (\text{s}, 6\text{H});\)

\(^{13}\text{C} \text{NMR} (\text{CDCl}_3, 100\text{MHz}, 293\text{K}): \delta 132.1, 125.4, 69.8, 67.8, 26.0, 25.9, 18.5, 18.3, 13.6, -4.6, -4.6, -5.2, -5.3;\)

IR: \(\nu 2930, 1473, 1256, 1122, 1091, 836, 776;\)

HRMS (EI): calcd for C\(_{13}\)H\(_{29}\)Si\(_2\)O\(_2\)\(^+\) (M-C\(_4\)H\(_8\)) 273.1706 Found: 273.1701;

\(\alpha_\theta = 1.824 \text{ (c = 0.99)}\)

(E)-3-(prop-1-enyl)oxetan-3-ol

To a flame-dried flaks was added a suspension of magnesium (304 mg, 12.5 mmol, 3.00 equiv.) in THF (2.5 mL) was added slowly a solution of 1-bromo-1-propene (0.71 mL, 8.33
mmol, 2.0 equiv.) in THF (7.5mL) to maintain a reflux under argon. The solution was then refluxed for 1h and then cooled to rt. This solution was then added slowly to a solution of oxetane-3-one (300 mg, 4.16 mmol, 1.00 equiv.) in THF (10 mL) under argon at -78°C. The solution was then stirred for 30mins at -78°C then allowed to warm to r.t. over 4h. The solution was then quenched with saturated NH₄Cl solution (10 mL). The solution was extracted with Et₂O (3 x 20mL), dried over MgSO₄ and concentrated. The product was then purified by flash chromatography (40% EtOAc/Hexane) to give the resulting product as an oil in 99% yield (470 mg, 4.12 mmol).

Rf (70% hexane/EtOAc): 0.15;

1H NMR (CDCl₃, 300MHz, 293K): δ 5.83 (dq, J = 11.0, 1.5 Hz, 1H), 5.72 (dq, J = 10.9, 6.9 Hz, 1H), 4.76 (s, 2H), 4.75 (s, 2H), 2.59 (s, 1H), 1.69 (dd, J = 6.9, 1.5 Hz, 3H);

13C NMR (CDCl₃, 100MHz, 293K): δ 132.1, 130.3, 85.2, 73.2, 14.2;

IR: ν 3400, 2948, 2874, 1448, 1134, 971, 894, 832, 694;

HRMS (EI): calcd for C₅H₈O⁺ (M-CH₂O) 84.0575 Found: 84.0570;

(E)-tert-butyldimethyl(3-(prop-1-enyl)oxetan-3-yloxy)silane

To a solution of imidazole (416 mg, 6.11 mmol, 1.66 equiv.) in DMF (2.9 mL) was added tert-butyldimethylsilyl chloride (749 mg, 4.97 mmol, 1.35 equiv.) followed by (E)-3-(prop-1-enyl)oxetan-3-ol (420 mg, 3.68 mmol, 1.00 equiv.) at r.t. and the resulting mixture was stirred for 18h. The solution was then quenched with saturated NH₄Cl (15 mL) and extracted with Et₂O (2 x 50mL). The organic layer was then washed with brine (6 x 20mL), dried with Na₂SO₄, concentrated and purified by flash chromatography (92% hexanes/Et₂O) to give the product as a clear oil in 99% yield (834 mg, 3.65 mmol).

Rf (90% hexane/EtOAc): 0.44;
$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 5.85 (ddd, $J = 10.7, 3.2, 1.6$ Hz, 1H), 5.68 (dq, $J = 10.8, 7.1$ Hz, 1H), 4.78 – 4.74 (m, 2H), 4.67 – 4.64 (m, 2H), 1.65 (dd, $J = 7.0, 1.7$ Hz, 3H), 0.89 (s, 9H), 0.01 (s, 6H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 133.7, 130.3, 86.2, 73.5, 25.7, 17.9, 14.6, -3.3;

IR: $\nu$ 2956, 2859, 1473, 1256, 1161, 988, 838, 777;

HRMS (ESI): calcd for C$_{12}$H$_{28}$NSiO$_2$+ (M+NH$_4$)$_7$ 246.1884 Found: 246.1876;

(E)-3-(prop-1-enyl)thietan-3-ol

![Chemical structure](image)

To a flame-dried flaks was added a suspension of magnesium (621 mg, 25.5 mmol, 3.00 equiv.) in THF (5 mL) was added slowly a solution of 1-bromo-1-propene (1.45 mL, 17.0 mmol, 2.0 equiv.) in THF (15 mL) to maintain a reflux under argon. The solution was then refluxed for 1h and then cooled to rt. This solution was then added slowly to a solution of thietane-3-one (750 mg, 8.51 mmol, 1.00 equiv.) in THF (15 mL) under argon at -78°C. The solution was then stirred for 30mins at -78°C then allowed to warm to r.t. over 4h. The solution was then quenched with saturated NH$_4$Cl solution (10 mL). The solution was then extracted with Et$_2$O (3 x 20mL), dried over MgSO$_4$ and concentrated. The solution was then purified by flash chromatography (88% Hexane/ EtOAc) to give the resulting product as an oil in 35% yield (383 mg, 2.94 mmol) as a 1:10 mixture of $Z$:$E$ olefins.

Rf (70% hexane/EtOAc): 0.23;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) ($E$)- isomer: $\delta$ 5.98 (dq, $J = 11.2, 1.7$ Hz, 1H), 5.73 (dq, $J = 11.1, 7.3$ Hz, 1H), 3.55 (dd, $J = 8.3, 1.6$ Hz, 2H), 3.36 (dd, $J = 8.4, 1.6$ Hz, 2H), 2.55 (s, 1H), 1.84 (dd, $J = 7.3, 1.8$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) ($E$)- isomer: $\delta$ 135.7, 130.4, 76.3, 43.6, 14.5;

IR: $\nu$ 3392, 2938, 1443, 1216, 1173, 1059, 987, 699;

HRMS (EI): calcd for C$_6$H$_{10}$SO$^+$ (M+) 130.0452 Found: 130.0447;
**Experimental Part**

**(E)-tert-butyldimethyl(3-(prop-1-enyl)thietan-3-yloxy)silane**

To a solution of imidazole (259 mg, 3.80 mmol, 3.30 equiv.) and (E)-3-(pro-1-enyl)thietan-3-ol (150 mg, 1.15 mmol, 1.00 equiv.) in DMF (0.7 mL) was added tert-butyldimethylsilyl chloride (469 mg, 3.11 mmol, 2.70 equiv.) at r.t. and the resulting mixture was stirred for 48h until completion. The solution was then quenched with saturated NH₄Cl (5 mL) and extracted with Et₂O (2 x 50mL). The organic layer was then washed with brine (6 x 20mL), dried with Na₂SO₂, concentrated and purified by flash chromatography (90% hexanes/DCM) to give the product as a clear oil in 90% yield (195 mg, 0.798 mmol) as a 1:10 mixture of Z:E olefins.

*Rf (90% hexane/EtOAc): 0.54;*

**1H NMR (CDCl₃, 300MHz, 293K) (E)- isomer:** $\delta$ 6.06 (dq, $J = 10.9, 1.7$ Hz, 1H), 5.75 (dq, $J = 10.9, 7.2$ Hz, 1H), 3.66 (d, $J = 1.8$ Hz, 1H), 3.64 (d, $J = 1.9$ Hz, 1H), 3.21 (d, $J = 1.9$ Hz, 1H), 3.19 (d, $J = 1.9$ Hz, 1H), 1.80 (dd, $J = 7.2, 1.8$ Hz, 3H), 0.91 (s, 9H), 0.06 (s, 6H);

**13C NMR (CDCl₃, 100MHz, 293K) (E)- isomer:** $\delta$ 137.0, 131.0, 75.9, 44.8, 25.7, 17.9, 15.0, -3.0;

**IR:** $\nu$ 2936, 1472, 1255, 1214, 1093, 837, 776, 696;

**HRMS (EI):** calcd for C₁₂H₂₄SSiO⁺ (M⁺) 244.1317 Found: 244.1312;

**(E)-tert-butyl 3-hydroxy-3-(prop-1-enyl)azetidine-1-carboxylate**

To a flame-dried flaks was added a suspension of magnesium (298 mg, 12.3 mmol, 3.00 equiv.) in THF (2.5 mL) was added slowly a solution of 1-bromo-1-propene (0.70 mL, 8.18 mmol, 2.0 equiv.) in THF (7.5mL) to maintain a reflux under argon. The solution was then refluxed for 1h and then cooled to rt. This solution was then added slowly to a solution of azetidin-3-one (700 mg, 4.09 mmol, 1.00 equiv.) in THF (10 mL) under argon at -78°C. The
solution was then stirred for 30 mins at -78°C then allowed to warm to r.t. over 4h. The solution was then quenched with saturated NH₄Cl solution (10 mL). The solution was extracted with Et₂O (3 x 20mL), dried over MgSO₄ and concentrated. The product was then purified by flash chromatography (35% EtOAc/Hexane) to give the resulting product as an oil in 97% yield (849 mg, 3.98 mmol).

Rf (70% hexane/EtOAc): 0.30;

¹H NMR (CDCl₃, 300MHz, 293K): δ 5.79 – 5.61 (m, 2H), 4.03 (s, 2H), 4.02 (s, 2H), 2.85 (s, 1H), 1.72 (dd, J = 6.8, 1.3 Hz, 3H), 1.41 (s, 9H);

¹³C NMR (CDCl₃, 100MHz, 293K): δ 156.3, 132.9, 130.2, 79.5, 68.6, 63.9, 28.3, 14.2;

IR: ν 3396, 2977, 2880, 1682, 1428, 1367, 1163, 1076, 934, 772, 697;

HRMS (ESI): calcd for C₁₁H₂₀NO₃⁺ (M+H) 214.1438 Found: 214.1432;

(E)-tert-butyl 3-(tert-butyldimethylsilyloxy)-3-(prop-1-enyl)azetidine-1-carboxylate

To a solution of imidazole (424 mg, 6.23 mmol, 1.66 equiv.) in DMF (2.9 mL) was added tert-butyldimethylsilyl chloride (763 mg, 5.06 mmol, 1.35 equiv.) followed by (E)-tert-butyl 3-hydroxy-3-(prop-1-enyl)azetidine-1-carboxylate (800 mg, 3.75 mmol, 1.00 equiv.) at r.t. and the resulting mixture was stirred for 18h. The solution was then quenched with saturated NH₄Cl (15 mL) and extracted with Et₂O (2 x 50mL). The organic layer was then washed with brine (6 x 20mL), dried with Na₂SO₂, concentrated and purified by flash chromatography (90% hexanes/Et₂O) to give the product as a white solid in 94% yield (1.16 g, 3.53 mmol).

Rf (90% hexane): 0.40;

¹H NMR (CDCl₃, 300MHz, 293K): δ 5.76 (dq, J = 10.8, 1.4 Hz, 1H), 5.64 (dq, J = 10.9, 6.9 Hz, 1H), 3.98 (s, 4H), 1.66 (dd, J = 6.9, 1.5 Hz, 3H), 1.43 (s, 9H), 0.87 (s, 9H), 0.02 (s, 6H);

¹³C NMR (CDCl₃, 100MHz, 293K): δ 156.3, 134.1, 130.5, 79.3, 69.2, 64.6, 28.3, 25.5, 17.7, 14.4, -3.5;
IR: $\nu$ 2957, 2858, 1706, 1473, 1392, 1256, 1170, 1088, 980, 837, 777;

HRMS (ESI): calcd for C$_{17}$H$_{34}$NSiO$_3$ $^+$ (M+H) 328.2302 Found: 328.2302;

6.2.2 Hydroesterification Products

**pyridin-2-ylmethyl 5-(2,2,2-trifluoroacetamido)decanoate**

![Chemical Structure](image)

To a flame dried schlenk tube was added Ru$_3$(CO)$_{12}$ (135 mg, 0.211 mmol, 0.05 equiv.) and tetrabutylammonium iodide (234 mg, 0.632 mmol, 0.15 mmol) and the system was purged with argon. THF (5 mL) was then added and the solution was stirred at r.t. for 5 min. To the schlenk was added a solution of 2-pyridylmethyl formate (1.16 g, 8.43 mmol, 2.00 equiv.), acetic acid (25 mg, 0.422 mmol, 0.10 equiv.) and (Z)-2,2,2-trifluoro-N-(non-2-en-4-yl)acetamide (1.00 g, 4.21 mmol, 1.00 equiv.) in THF (1 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexanes/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 81% yield (1.28 g, 3.42 mmol).

Rf (hexane:EtOAc = 2:1): 0.26;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 8.57 (ddd, $J = 4.9, 1.7, 0.9$ Hz, 1H), 7.71 (td, $J = 7.7, 1.8$ Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.25 (ddd, $J = 7.5, 4.8, 1.0$ Hz, 1H), 6.70 (d, $J = 8.2$ Hz, 1H), 5.28 (d, $J = 13.3$ Hz, 1H), 5.17 (d, $J = 13.3$ Hz, 1H), 4.03 – 3.87 (m, 1H), 2.57 – 2.34 (m, 2H), 1.80 – 1.18 (m, 12H), 0.88 (t, $J = 6.7$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 172.8, 157.2 (q, $J = 36.6$ Hz), 155.6, 149.3, 136.9, 123.0, 122.0, 116.0 (q, $J = 288.2$ Hz), 66.6, 50.4, 34.8, 33.6, 33.5, 31.5, 25.4, 22.4, 21.0, 13.9;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -76.0;

IR: $\nu$ 3307, 2934, 1784, 1574, 1440, 1158, 159;
**Experimental Part**

**HRMS (ESI):** calcd for C\textsubscript{18}H\textsubscript{26}F\textsubscript{3}N\textsubscript{2}O\textsubscript{3}\textsuperscript{+} (M+H) 375.1890 Found: 375.1888;

**pyridin-2-ylmethyl 2-methyl-4-(2,2,2-trifluoroacetamido)nonanoate**

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 15% yield (0.244 g, 0.652 mmol).

**Rf** (hexane:EtOAc = 2:1): 0.31;

\[^1\text{H} NMR (CDCl}_3, 300MHz, 293K\) mixture of diastereoisomers: \(\delta 8.62 – 8.49 (m, 2H), 8.14 (s, 1H), 7.76 – 7.70 (m, 2H), 7.38 – 7.24 (m, 5H), 5.55 (d, \(J = 13.5\) Hz, 1H), 5.34 (d, \(J = 13.2\) Hz, 1H), 5.14 (d, \(J = 13.4\) Hz, 1H), 5.00 (d, \(J = 13.5\) Hz, 1H), 4.14 – 3.88 (m, 2H), 2.77 – 2.53 (m, 2H), 2.11 – 1.87 (m, 3H), 1.73 – 1.46 (m, 5H), 1.37 – 1.23 (m, 18H), 0.90 – 0.85 (m, 6H);

\[^{13}\text{C} NMR (CDCl}_3, 100MHz, 293K\) mixture of diastereoisomers: \(\delta 176.1, 175.8, 157.3 (q, J = 36.9\) Hz), 157.2 (q, \(J = 36.8\) Hz), 155.6, 149.2, 149.0, 137.1, 137.0, 123.1, 122.0, 121.8, 116.0 (q, \(J = 288.3\) Hz), 116.0 (q, \(J = 288.2\) Hz), 66.3, 65.7, 49.5, 48.9, 37.8, 37.4, 37.3, 35.8, 35.6, 34.0, 31.5, 25.6, 25.3, 22.5, 22.4, 17.9, 17.0, 13.9, 13.9;

\[^{19}\text{F} NMR (CDCl}_3, 377MHz, 293K\) mixture of diastereoisomers: -75.5, -75.5;

**IR:** \(\nu 3310, 2934, 1716, 1185;\)

**HRMS (EI):** calcd for C\textsubscript{18}H\textsubscript{26}F\textsubscript{3}N\textsubscript{2}O\textsubscript{3}\textsuperscript{+} (M+) 375.1890 Found: 375.1880;

**pyridin-2-ylmethyl 5-acetamidodecanoate**

To an oven dried screw cap vial was added Ru\textsubscript{3}(CO)\textsubscript{12} (14 mg, 0.022 mmol, 0.05 equiv.) and tetrabutylammonium iodide (24 mg, 0.065 mmol, 0.15 mmol) and the system was purged
with argon. To the vial was added a solution of 2-pyridylmethyl formate (120 mg, 0.873 mmol, 2.00 equiv.), acetic acid (2.6 mg, 0.044 mmol, 0.10 equiv.) and (Z)-N-(non-2-en-4-yl)acetamide (80 mg, 0.436 mmol, 1.00 equiv.) in THF (0.65 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (acetone/DCM 2:8 to 1:1) to give the product as a pale yellow oil in 66% yield (93 mg, 0.290 mmol).

Rf (acetone:DCM = 3:7): 0.32;

^1H NMR (CDCl₃, 300MHz, 293K): δ 8.59 (ddd, J = 4.9, 1.6, 0.9 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.24 (ddd, J = 7.5, 4.9, 0.9 Hz, 1H), 5.48 (d, J = 9.0 Hz, 1H), 5.26 (d, J = 13.4 Hz, 1H), 5.21 (d, J = 13.4 Hz, 1H), 3.98 – 3.86 (m, 1H), 2.54 – 2.36 (m, 2H), 1.97 (s, 3H), 1.79 – 1.18 (m, 12H), 0.88 (t, J = 5.9 Hz, 3H);

^13C NMR (CDCl₃, 100MHz, 293K): δ 173.1, 169.7, 155.8, 149.4, 136.8, 122.9, 121.9, 66.7, 49.0, 35.3, 34.3, 33.8, 31.7, 25.5, 23.5, 22.6, 21.2, 14.0;

IR: ν 3280, 2932, 1740, 1644, 1552, 1438, 1162;

HRMS (ESI): calcd for C₁₈H₂₉N₂O₃⁺ (M+H) 321.2173 Found: 321.2177;

pyridin-2-ylmethyl 4-acetamido-2-methylnonanoate

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 28% yield (39 mg, 0.123 mmol).

Rf (acetone:DCM = 3:7): 0.38;

^1H NMR (CDCl₃, 300MHz, 293K) mixture of diastereoisomers: δ 8.61 – 8.57 (m, 2H), 7.81 – 7.69 (m, 2H), 7.43 – 7.32 (m, 2H), 7.32 – 7.22 (m, 2H), 6.51 (d, J = 8.8 Hz, 1H), 5.86 (d, J = 9.5 Hz, 1H), 5.53 (d, J = 13.4 Hz, 1H), 5.37 (d, J = 13.5 Hz, 1H), 5.14 (d, J = 13.5 Hz, 1H), 5.02 (d, J = 13.4 Hz, 1H), 4.12 – 3.97 (m, 2H), 2.75 – 2.55 (m, 2H), 1.91 (s, 3H), 1.90 (s, 3H),
Experimental Part

2.03 – 1.82 (m, 2H), 1.77 – 1.69 (m, 2H), 1.65 – 1.58 (m, 2H), 1.52 – 1.20 (m, 20H), 0.96 – 0.81 (m, 6H);

\(^{13}\text{C} \text{ NMR} (\text{CDCl}_{3}, 100\text{MHz}, 293\text{K})\) mixture of diastereoisomers: \(\delta\) 176.6, 176.1, 169.9, 169.9, 156.0, 155.8, 149.4, 149.2, 137.0, 136.9, 123.0, 123.0, 122.1, 121.8, 66.3, 65.9, 47.9, 47.1, 38.6, 38.1, 37.4, 36.4, 36.0, 35.0, 31.7, 25.6, 25.5, 23.2, 23.1, 22.6, 17.8, 16.9, 14.0;

\text{IR}: \nu 3278, 2931, 1738, 1644, 1551, 1439, 1169;

\text{HRMS (ESI)}: \text{calcd for } C_{18}H_{29}N_2O_3^+ (M+H) 321.2173 \text{ Found: 321.2167};

\text{pyridin-2-ylmethyl 5-benzamidodecanoate}

To an oven dried screw cap vial was added Ru\(_3\)(CO)\(_{12}\) (10mg, 0.016 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.049 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (89 mg, 0.652 mmol, 2.00 equiv.), acetic acid (1.9 mg, 0.031 mmol, 0.10 equiv.) and \((Z)-N-(\text{non-2-en-4-yl})\text{benzamide (80 mg, 0.326 mmol, 1.00 equiv.})\) in THF (0.5 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 35:65 to 1:1) to give the product as a pale yellow oil in 82% yield (102 mg, 0.267 mmol).

\(\text{Rf (hexane:EtOAc = 1:1): 0.22;}\)

\(^1\text{H} \text{ NMR (CDCl}_{3}, 300\text{MHz}, 293\text{K})\): \(\delta\) 8.57 (dd, \(J = 4.8, 0.6\) Hz, 1H), 7.79 – 7.76 (m, 2H), 7.67 (td, \(J = 7.7, 1.8\) Hz, 1H), 7.47 (ddd, \(J = 6.5, 3.8, 1.3\) Hz, 1H), 7.43 – 7.37 (m, 2H), 7.33 (d, \(J = 7.8\) Hz, 1H), 7.21 (ddd, \(J = 7.5, 4.9, 1.0\) Hz, 1H), 6.17 (d, \(J = 8.5\) Hz, 1H), 5.24 (d, \(J = 13.4\) Hz, 1H), 5.19 (d, \(J = 13.4\) Hz, 1H), 4.20 – 4.09 (m, 1H), 2.59 – 2.38 (m, 2H), 1.89 – 1.19 (m, 12H), 0.87 (t, \(J = 7.0\) Hz, 3H);
13C NMR (CDCl3, 100MHz, 293K): δ 173.1, 167.2, 155.8, 149.4, 136.8, 135.0, 131.2, 128.5, 126.9, 122.9, 121.8, 66.6, 49.5, 35.4, 34.4, 33.8, 31.8, 25.6, 22.6, 21.3, 14.0;

IR: ν 3302, 2931, 1739, 1635, 1538, 1162, 696;

HRMS (ESI): calcd for C23H31N2O3+ (M+H) 383.2329 Found: 383.2332;

pyridin-2-ylmethyl 4-benzamido-2-methylnonanoate

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 11% yield (14 mg, 0.037 mmol).

Rf (hexane:EtOAc = 1:1): 0.30;

1H NMR (CDCl3, 300MHz, 293K) mixture of diastereoisomers: δ 8.55 – 8.53 (m, 2H), 7.77 – 7.73 (m, 4H), 7.71 – 7.62 (dd, J = 17.4, 7.7, 1.8 Hz, 2H), 7.50 – 7.45 (m, 2H), 7.42 – 7.34 (m, 5H), 7.25 – 7.16 (m, 3H), 6.52 (d, J = 8.6 Hz, 1H), 6.12 (d, J = 9.3 Hz, 1H), 5.32 (d, J = 13.5 Hz, 1H), 5.16 (d, J = 13.5 Hz, 1H), 5.10 (d, J = 13.5 Hz, 1H), 5.01 (d, J = 13.5 Hz, 1H), 4.31 (dq, J = 13.1, 11.0 Hz, 1H), 4.22 – 4.09 (m, 1H), 2.84 – 2.64 (m, 2H), 2.09 – 1.99 (m, 2H), 1.85 (ddd, J = 13.9, 9.3, 4.4 Hz, 1H), 1.79 – 1.69 (m, 1H), 1.67 – 1.49 (m, 6H), 1.47 – 1.20 (m, 16H), 0.95 – 0.82 (m, 6H);

13C NMR (CDCl3, 100MHz, 293K) mixture of diastereoisomers: δ 177.0, 176.3, 167.0, 166.9, 155.9, 155.7, 149.3, 149.2, 136.8, 136.7, 134.9, 134.4, 131.4, 131.2, 128.5, 128.4, 126.9, 126.8, 122.8, 121.7, 121.5, 66.6, 66.5, 48.7, 48.3, 38.7, 38.3, 37.3, 36.4, 36.4, 35.1, 31.7, 31.7, 25.7, 25.6, 22.6, 22.6, 18.0, 17.4, 14.0, 14.0;

IR: ν 3301, 2930, 1738, 1636, 1538, 1168, 696;

HRMS (ESI): calcd for C23H31N2O3+ (M+H) 383.2329 Found: 383.2340;

pyridin-2-ylmethyl 5-(1,3-dioxoisooindolin-2-yl)decanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (26 mg, 0.040 mmol, 0.10 equiv.) and tetrabutylammonium iodide (22 mg, 0.060 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (110 mg, 0.800 mmol, 2.00 equiv.), acetic acid (4.9 mg, 0.081 mmol, 0.10 equiv.) and (Z)-2-(non-2-en-4-yl)isoindoline-1,3-dione (109 mg, 0.400 mmol, 1.00 equiv.) in DMF (0.5 mL) and the solution was heated to 135°C for 18h. The solution was cooled to r.t. and concentrated to remove the DMF. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a 4:1 inseperable mixture of regioisomers a pale yellow oil in 82% yield (134 mg, 0.328 mmol).

Rf (hexane:EtOAc = 1:1): 0.40;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) major product only: δ 8.59 – 8.56 (m, 1H), 7.84 – 7.77 (m, 2H), 7.75 – 7.65 (m, 3H), 7.31 (d, $J$ = 7.8 Hz, 1H), 7.24 – 7.19 (m, 1H), 5.20 (s, 2H), 4.22 (tt, $J$ = 10.1, 5.1 Hz, 1H), 2.44 (td, $J$ = 7.4, 4.7 Hz, 2H), 2.21 – 2.08 (m, 2H), 1.85 – 1.58 (m, 4H), 1.30 – 1.19 (m, 6H), 0.83 (t, $J$ = 6.8 Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) major product only: δ 172.9, 168.7, 155.9, 149.5, 136.7, 133.9, 131.8, 123.1, 122.8, 121.7, 66.7, 51.8, 33.7, 32.4, 31.8, 31.4, 26.2, 22.5, 22.0, 14.0;

IR: ν 3460, 2930, 1704, 1372, 1166, 723;

HRMS (ESI): calcd for C$_{24}$H$_{29}$N$_2$O$_4$ + (M+H) 409.2122 Found: 409.2124;

pyridin-2-ylmethyl 5-(2,2,2-trifluoroacetamido)hexanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (14 mg, 0.022 mmol, 0.05 equiv.) and tetrabutylammonium iodide (24 mg, 0.066 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (121 mg, 0.883 mmol, 2.00 equiv.), acetic acid (2.6 mg, 0.044 mmol, 0.10 equiv.) and (E)-2,2,2-trifluoro-N-(pent-3-en-2-yl)acetamide (80 mg, 0.442 mmol, 1.00 equiv.) in THF (0.7 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 35:65 to 1:1) to give the product as a pale yellow oil in 73% yield (103 mg, 0.324 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.26;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 8.59 (ddd, $J = 4.8$, 1.6, 0.9 Hz, 1H), 7.73 (td, $J = 7.7$, 1.8 Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.28 – 7.24 (m, 1H), 6.88 (s, 1H), 5.29 (d, $J = 13.3$ Hz, 1H), 5.20 (d, $J = 13.3$ Hz, 1H), 4.10 – 3.98 (m, 1H), 2.56 – 2.38 (m, 2H), 1.79 – 1.49 (m, 4H), 1.25 (d, $J = 6.6$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 172.8, 156.8 (q, $J = 36.7$ Hz), 155.6, 149.4, 136.9, 123.0, 122.0, 115.9 (q, $J = 288.1$ Hz), 66.6, 46.4, 35.2, 33.5, 21.1, 20.5;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): δ -75.9;

IR: ν 3313, 2946, 1704, 1557, 1440, 1182, 757, 722;

HRMS (ESI): calcd for C$_{14}$H$_{18}$F$_3$N$_2$O$_3$\(^+\) (M+H) 319.1264 Found: 319.1262;

**pyridin-2-ylmethyl 2-methyl-4-(2,2,2-trifluoroacetamido)pentanoate**

![Pyridin-2-ylmethyl 2-methyl-4-(2,2,2-trifluoroacetamido)pentanoate](image)

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 21% yield (30 mg, 0.094 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.32;
Experimental Part

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 8.61 – 8.53 (m, 2H), 7.99 (s, 1H), 7.75 (td, $J = 7.7, 1.8$ Hz, 1H), 7.74 (td, $J = 7.7, 1.8$ Hz, 1H), 7.40 – 7.23 (m, 5H), 5.51 (d, $J = 13.4$ Hz, 1H), 5.33 (d, $J = 13.4$ Hz, 1H), 5.17 (d, $J = 13.4$ Hz, 1H), 5.05 (d, $J = 13.4$ Hz, 1H), 4.24 – 4.03 (m, 2H), 2.77 – 2.53 (m, 2H), 2.09 (ddd, $J = 14.5, 10.4, 8.4$ Hz, 1H), 1.97 – 1.92 (m, 2H), 1.65 (dt, $J = 14.5, 4.8$ Hz, 1H), 1.30 – 1.25 (m, 12H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 176.1, 175.9, 157.0 (q, $J = 36.9$ Hz), 156.9 (q, $J = 36.6$ Hz), 155.5, 155.4, 149.3, 149.1, 137.1, 137.0, 123.1, 123.1, 121.9, 121.8, 115.9 (q, $J = 288.3$ Hz), 115.9 (q, $J = 288.0$ Hz), 66.4, 66.0, 45.7, 44.5, 39.4, 38.7, 37.5, 35.9, 21.3, 19.9, 18.1, 16.8;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -75.6, -75.7;

IR: $\nu$ 3312, 2978, 1716, 1558, 1186, 725;

HRMS (ESI): calcd for C$_{14}$H$_{18}$F$_3$N$_2$O$_3$ $^+$ (M+H) 319.1264 Found: 319.1256;

pyridin-2-ylmethyl 7-phenyl-5-(2,2,2-trifluoroacetamido)heptanoate

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (9.4mg, 0.015 mmol, 0.05 equiv.) and tetrabutylammonium iodide (16 mg, 0.044 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (81 mg, 0.590 mmol, 2.00 equiv.), acetic acid (1.8 mg, 0.029 mmol, 0.10 equiv.) and (Z)-2,2,2-trifluoro-N-(1-phenylhex-4-en-3-yl)acetamide (80 mg, 0.295 mmol, 1.00 equiv.) in THF (0.45 mL) and the solution was heated to 75$^\circ$C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 3:7 to 1:1) to give the product as a pale yellow oil in 76% yield (91 mg, 0.223 mmol).

Rf (hexane:EtOAc = 1:1): 0.37;
**1H NMR (CDCl<sub>3</sub>, 300MHz, 293K):** θ 8.59 – 8.56 (m, 1H), 7.72 (td, J = 7.7, 1.7 Hz, 1H), 7.37 – 7.15 (m, 7H), 6.95 (d, J = 8.8 Hz, 1H), 5.30 (d, J = 13.3 Hz, 1H), 5.19 (d, J = 13.3 Hz, 1H), 4.07 – 3.96 (m, 1H), 2.74 – 2.60 (m, 2H), 2.57 – 2.36 (m, 2H), 1.96 – 1.49 (m, 6H);

**13C NMR (CDCl<sub>3</sub>, 100MHz, 293K):** θ 172.8, 157.23(q, J = 36.7 Hz), 155.6, 149.3, 140.9, 136.9, 128.6, 128.3, 126.2, 123.0, 122.0, 116.0 (q, J = 288.2 Hz), 66.6, 50.3, 36.5, 33.6, 33.5, 32.1, 21.0;

**19F NMR (CDCl<sub>3</sub>, 377MHz, 293K):** θ -75.6;

**IR:** ν 3308, 2944, 1704, 1558, 1455, 1183, 754, 724, 700;

**HRMS (ESI):** calcd for C<sub>21</sub>H<sub>24</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub><sup>+</sup> (M+H) 409.1734  Found: 409.1727;

pyridin-2-ylmethyl 2-methyl-6-phenyl-4-(2,2,2-trifluoroacetamido)hexanoate

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 16% yield (19 mg, 0.047 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.43;

**1H NMR (CDCl<sub>3</sub>, 300MHz, 293K) mixture of diastereoisomers:** θ 8.56 (dd, J = 11.4, 4.4 Hz, 2H), 8.39 (d, J = 8.2 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.48 (d, J = 9.1 Hz, 1H), 7.35 – 7.13 (m, 14H), 5.58 (d, J = 13.6 Hz, 1H), 5.36 (d, J = 13.4 Hz, 1H), 5.15 (d, J = 13.5 Hz, 1H), 4.98 (d, J = 13.6 Hz, 1H), 4.22 – 4.10 (m, 1H), 4.06 – 3.93 (m, 1H), 2.78 – 2.55 (m, 6H), 2.16 – 1.67 (m, 8H), 1.27 (d, J = 7.1 Hz, 3H), 1.25 (d, J = 7.0 Hz, 3H);

**13C NMR (CDCl<sub>3</sub>, 100MHz, 293K) mixture of diastereoisomers:** θ 176.0, 175.8, 157.4 (q, J = 36.9 Hz), 157.3 (q, J = 36.9 Hz), 155.5, 155.4, 149.2, 149.1, 141.0, 140.9, 137.2, 137.0, 128.6, 128.5, 128.3, 126.2, 126.1, 123.1, 123.1, 122.0, 121.9, 116.0 (q, J = 288.0 Hz), 115.9 (q, J = 288.2 Hz), 66.2, 65.6, 49.5, 48.8, 37.7, 37.4, 37.3, 37.3, 35.8, 35.6, 32.5, 32.1, 18.1, 16.8;

**19F NMR (CDCl<sub>3</sub>, 377MHz, 293K) mixture of diastereoisomers:** θ -75.3, -75.5;
Experimental Part

**IR:** ν 3310, 2927, 1716, 1558, 1184, 753, 722, 700;

**HRMS (ESI):** calcd for C_{21}H_{24}F_{3}N_{2}O_{3}^{+} (M+H) 409.1734 Found: 409.1737;

pyridin-2-ylmethyl 6,6-dimethyl-5-(2,2,2-trifluoroacetamido)heptanoate

![Chemical structure](image)

To an oven dried screw cap vial was added Ru_3(CO)_{12} (11mg, 0.018 mmol, 0.05 equiv.) and tetrabutylammonium iodide (20 mg, 0.054 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (98 mg, 0.717 mmol, 2.00 equiv.), acetic acid (2.1 mg, 0.034 mmol, 0.10 equiv.) and (E)-N-(2,2-dimethylhex-4-en-3-yl)-2,2,2-trifluoroacetamide (80 mg, 0.358 mmol, 1.00 equiv.) in THF (0.5 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 75% yield (96 mg, 0.267 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.38;

**^1H NMR (CDCl₃, 300MHz, 293K):** δ 8.58 (ddd, J = 3.4, 1.5, 0.8 Hz, 1H), 7.70 (td, J = 7.7, 1.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.25 – 7.22 (m, 1H), 6.50 (d, J = 9.9 Hz, 1H), 5.27 (dd, J = 13.3 Hz, 1H), 5.17 (d, J = 13.3 Hz, 1H), 3.77 (t, J = 10.2 Hz, 1H), 2.57 – 2.32 (m, 2H), 1.81 – 1.53 (m, 3H), 1.39 – 1.28 (m, 1H), 0.91 (s, 9H);

**^13C NMR (CDCl₃, 100MHz, 293K):** δ 172.7, 157.6 (q, J = 36.5 Hz), 155.7, 149.5, 136.8, 122.9, 121.9, 116.1 (q, J = 288.3 Hz), 66.6, 58.5, 34.7, 33.5, 28.7, 26.2, 21.9;

**^19F NMR (CDCl₃, 377MHz, 293K):** δ –75.5;

**IR:** ν 3320, 2967, 1704, 1558, 1478, 1372, 1154, 758, 723;

**HRMS (ESI):** calcd for C_{17}H_{24}F_{3}N_{2}O_{3}^{+} (M+H) 361.1734 Found: 361.1732;
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (12mg, 0.019 mmol, 0.05 equiv.) and tetrabutylammonium iodide (21 mg, 0.058 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (106 mg, 0.772 mmol, 2.00 equiv.), acetic acid (2.3 mg, 0.038 mmol, 0.10 equiv.) and (E)-N-(1-cyclopropylbut-2-enyl)-2,2,2-trifluoroacetamide (80 mg, 0.386 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 3:2) to give the product as a pale yellow oil in 68% yield (91 mg, 0.264 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.31;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 8.57 – 8.54 (m, 1H), 7.70 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.33 (d, $J$ = 7.8 Hz, 1H), 7.27 – 7.19 (m, 2H), 5.25 (d, $J$ = 13.3 Hz, 1H), 5.17 (d, $J$ = 13.3 Hz, 1H), 3.24 (qd, $J$ = 8.7, 4.3 Hz, 1H), 2.52 – 2.36 (m, 2H), 1.79 – 1.60 (m, 4H), 0.91 – 0.81 (m, 1H), 0.61 – 0.54 (m, 1H), 0.50 – 0.43 (m, 1H), 0.40 – 0.32 (m, 1H), 0.30 – 0.24 (m, 1H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 172.8, 157.0 (q, $J$ = 36.7 Hz), 155.6, 149.3, 136.9, 123.0, 121.9, 116.1 (q, $J$ = 288.2 Hz), 66.6, 55.3, 33.9, 33.7, 21.2, 15.9, 4.2, 2.9;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): δ -75.7;

IR: ν 3321, 2978, 1714, 1266, 1168, 740;

HRMS (ESI): calcd for C$_{16}$H$_{20}$F$_3$N$_2$O$_3$ $^+$ (M+H) 345.1421 Found: 345.1419;
This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 21% yield (28 mg, 0.081 mmol).

Rf (hexane:EtOAc = 1:1): 0.41;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) mixture of diastereoisomers: δ 8.61 – 8.56 (m, 2H), 8.30 (d, $J = 6.6$ Hz, 1H), 7.75 (td, $J = 7.7$, 1.8 Hz, 1H), 7.74 (td, $J = 7.7$, 1.8 Hz, 1H), 7.39 (d, $J = 7.9$ Hz, 1H), 7.34 (dd, $J = 7.8$, 0.5 Hz, 2H), 7.31 – 7.24 (m, 2H), 5.54 (d, $J = 13.4$ Hz, 1H), 5.34 (d, $J = 13.4$ Hz, 1H), 5.17 (d, $J = 13.4$ Hz, 1H), 5.01 (d, $J = 13.4$ Hz, 1H), 3.45 (qd, $J = 9.3$, 4.7 Hz, 1H), 3.24 (qd, $J = 8.7$, 4.6 Hz, 1H), 2.79 (dqd, $J = 9.3$, 7.1, 4.7 Hz, 1H), 2.62 (dqd, $J = 14.1$, 7.1, 5.4 Hz, 1H), 2.25 – 1.99 (m, 3H), 1.84 (dt, $J = 14.4$, 5.0 Hz, 1H), 1.28 (d, $J = 5.5$ Hz, 3H), 1.26 (d, $J = 5.4$ Hz, 3H), 1.15 – 1.04 (m, 1H), 0.98 – 0.87 (m, 1H), 0.63 – 0.22 (m, 8H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) mixture of diastereoisomers: δ 176.0, 175.9, 157.2 (q, $J = 36.8$ Hz), 157.1 (q, $J = 36.9$ Hz), 155.5, 149.3, 149.1, 137.1, 137.0, 123.1, 123.0, 122.0, 121.9, 116.0 (q, $J = 288.3$ Hz), 116.0 (q, $J = 288.2$ Hz), 66.3, 65.8, 54.1, 54.0, 37.9, 37.5, 37.2, 35.9, 18.1, 17.1, 16.6, 14.9, 4.0, 3.9, 3.4, 3.1;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K) mixture of diastereoisomers: δ – 75.4, -75.5;

IR: ν 3316, 2977, 1715, 1555, 1183, 760;

HRMS (ESI): calcd for C$_{16}$H$_{20}$F$_3$N$_2$O$_3$ $^+$ (M+H) 345.1421 Found: 345.1413;

pyridin-2-ylmethyl 6-cyano-5-(2,2,2-trifluoroacetamido)hexanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (12mg, 0.019 mmol, 0.05 equiv.) and tetrabutylammonium iodide (21 mg, 0.058 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (106 mg, 0.776 mmol, 2.00 equiv.), acetic acid (2.3 mg, 0.038 mmol, 0.10 equiv.) and (E)-N-(1-cyanopent-3-en-2-yl)-2,2,2-trifluoroacetamide (80 mg, 0.388 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 1:1 to 1:2) to give the product as a pale yellow oil in 82% yield (109 mg, 0.318 mmol).

\[ \text{Rf (hexane:EtOAc = 1:1): 0.17;} \]

\[ ^1H \text{ NMR (CDCl}_3, 300MHz, 293K): \delta 8.62 (ddd, } J = 4.9, 1.6, 0.9 \text{ Hz, 1H)}, 8.21 (d, } J = 7.3 \text{ Hz, 1H)}, 7.74 (td, } J = 7.7, 1.8 \text{ Hz, 1H)}, 7.35 (d, } J = 7.8 \text{ Hz, 1H)}, 7.28 (ddd, } J = 7.6, 4.9, 1.1 \text{ Hz, 1H)}, 5.32 (d, } J = 13.3 \text{ Hz, 1H)}, 5.17 (d, } J = 13.3 \text{ Hz, 1H)}, 4.15 (dt, } J = 10.7, 5.2 \text{ Hz, 1H)}, 2.79 (dd, } J = 17.0, 5.7 \text{ Hz, 1H)}, 2.69 (dd, } J = 17.0, 5.0 \text{ Hz, 1H)}, 2.60 – 2.41 (m, 2H), 1.88 – 1.74 (m, 4H); \]

\[ ^{13}C \text{ NMR (CDCl}_3, 100MHz, 293K): \delta 172.6, 157.8 (q, } J = 37.9 \text{ Hz), 155.2, 149.4, 137.1, 123.2, 122.1, 116.5, 115.6 (q, } J = 287.8 \text{ Hz), 66.6, 47.2, 33.2, 31.5, 23.1, 21.0;} \]

\[ ^{19}F \text{ NMR (CDCl}_3, 377MHz, 293K): \delta – 75.5; \]

\[ \text{IR: } \nu 3309, 2943, 1716, 1559, 1440, 1158, 761, 726; \]

\[ \text{HRMS (ESI): calcd for C}_{15}H_{17}F_3N_3O_3^+ (M+H) 344.1217 Found: 344.1221;} \]

\[ \text{pyridin-2-ylmethyl 5-cyano-2-methyl-4-(2,2,2-trifluoroacetamido)pentanoate} \]

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 15% yield (20 mg, 0.058 mmol).

\[ \text{Rf (hexane:EtOAc = 1:1): 0.25; } \]
$^1$H NMR (CDCl$_3$, 300MHz, 293K) mixture of diastereoisomers: $\delta$ 9.78 (d, $J = 6.8$ Hz, 1H), 9.31 (d, $J = 7.0$ Hz, 1H), 8.71 – 8.56 (m, 2H), 7.83 – 7.71 (m, 2H), 7.38 – 7.29 (m, 4H), 5.73 (d, $J = 13.8$ Hz, 1H), 5.40 (d, $J = 13.5$ Hz, 1H), 5.19 (d, $J = 13.5$ Hz, 1H), 4.94 (d, $J = 13.8$ Hz, 1H), 4.36 – 4.21 (m, 1H), 4.20 – 4.06 (m, 1H), 3.02 – 2.58 (m, 5H), 2.47 – 2.35 (m, 2H), 2.01 – 1.87 (m, 1H), 1.86 – 1.74 (m, 2H), 1.32 (d, $J = 7.1$ Hz, 3H), 1.28 (d, $J = 7.0$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K) mixture of diastereoisomers: $\delta$ 175.1, 175.1, 158.0 (q, $J = 38.0$ Hz), 157.9 (q, $J = 37.9$ Hz), 155.1, 154.9, 149.4, 149.2, 137.5, 137.3, 123.4, 123.3, 121.9, 121.8, 116.8, 116.4, 115.6 (q, $J = 287.9$ Hz), 115.6 (q, $J = 287.5$ Hz), 65.6, 65.1, 47.0, 45.7, 38.1, 36.2, 35.7, 35.5, 23.6, 22.3, 18.4, 16.1;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K) mixture of diastereoisomers: $\delta$ – 75.2, -75.3;

IR: $\nu$ 3312, 2978, 1722, 1558, 1439, 1183, 761, 726;

HRMS (ESI): calcd for C$_{15}$H$_{17}$F$_3$N$_3$O$_3$$^+$ (M+H) 344.1217 Found: 344.1215;

(E)-pyridin-2-ylmethyl 4-(2,2,2-trifluoroacetamido)hept-5-enoate

![Chemical structure](image)

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (13mg, 0.021 mmol, 0.05 equiv.) and tetrabutylammonium iodide (23 mg, 0.062 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (68 mg, 0.497 mmol, 1.20 equiv.), acetic acid (2.4 mg, 0.041 mmol, 0.10 equiv.) and (E)-2,2,2-trifluoro-N-(hexa-1,4-dien-3-yl)acetamide (80 mg, 0.414 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 3:7 to 1:1) to give the product as a pale yellow oil in 55% yield (75 mg, 0.227 mmol) as a 11:1 mixture of E/Z isomers.

Rf (hexane:EtOAc = 1:1): 0.42;

$^1$H NMR (CDCl$_3$, 300MHz, 293K) E isomer only: $\delta$ 8.63 – 8.56 (m, 1H), 7.73 (td, $J = 7.7$, 1.8 Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.26 (ddd, $J = 7.5$, 4.9, 0.7 Hz, 1H), 7.15 (d, $J = 7.0$ Hz, 1H), ...
Experimental Part

1H NMR (CDCl3, 300MHz, 293K): δ 8.54 (ddd, J = 1.6, 3.3, 0.8 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.41 – 7.29 (m, 7H), 7.27 – 7.22 (m, 1H), 5.30 (d, J = 13.3 Hz, 1H), 5.19 (d, J = 13.3 Hz, 1H), 5.00 (q, J = 7.7 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.08 – 1.89 (m, 2H), 1.87 – 1.62 (m, 2H);

13C NMR (CDCl3, 100MHz, 293K) E isomer only: δ 173.1, 156.6 (q, J = 36.9 Hz), 155.4, 149.5, 136.9, 129.1, 128.4, 123.0, 121.9, 115.9 (q, J = 288.1 Hz), 66.9, 51.9, 30.6, 29.1, 17.7;

19F NMR (CDCl3, 377MHz, 293K) E isomer only: δ – 75.8;

IR: ν 3312, 2943, 1716, 1698, 1596, 1538, 1158, 968, 759, 726;

HRMS (ESI): calcd for C15H18F3N2O3+ (M+H) 331.1264 Found: 331.1271;

pyridin-2-ylmethyl 5-phenyl-5-(2,2,2-trifluoroacetamido)pentanoate

To an oven dried screw cap vial was added Ru3(CO)12 (11mg, 0.016 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.049 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (90 mg, 0.658 mmol, 2.00 equiv.), acetic acid (2.1 mg, 0.034 mmol, 0.10 equiv.) and (E)-2,2,2-trifluoro-N-(1-phenylbut-2-enyl)acetamide (80 mg, 0.329 mmol, 1.00 equiv.) in THF (0.5 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 81% yield (101 mg, 0.266 mmol).

Rf (hexane:EtOAc = 1:1): 0.26;

1H NMR (CDCl3, 300MHz, 293K): δ 8.54 (ddd, J = 1.6, 3.3, 0.8 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.41 – 7.29 (m, 7H), 7.27 – 7.22 (m, 1H), 5.30 (d, J = 13.3 Hz, 1H), 5.19 (d, J = 13.3 Hz, 1H), 5.00 (q, J = 7.7 Hz, 1H), 2.58 – 2.41 (m, 2H), 2.08 – 1.89 (m, 2H), 1.87 – 1.62 (m, 2H);
13C NMR (CDCl₃, 100MHz, 293K): δ 172.8, 156.8 (q, J = 37.1 Hz), 155.6, 149.4, 140.1, 136.9, 129.0, 128.2, 126.5, 123.0, 122.0, 115.9 (q, J = 288.2 Hz), 66.6, 54.2, 34.3, 33.5, 21.4;

19F NMR (CDCl₃, 377MHz, 293K): δ -75.6;

IR: ν 3312, 2947, 1714, 1552, 1184, 1154, 759, 701;

HRMS (ESI): calcd for C₁₉H₂₀F₃N₂O₃⁺ (M+H) 381.1421 Found: 381.1416;

Pyridin-2-ylmethyl 2-methyl-4-phenyl-4-(2,2,2-trifluoroacetamido)butanoate

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 19% yield (25 mg, 0.66 mmol).

Rf (hexane:EtOAc = 1:1): 0.32;

1H NMR (CDCl₃, 300MHz, 293K) mixture of diastereoisomers: δ 8.61 – 8.56 (m, 2H), 8.34 (d, J = 7.8 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 7.79 – 7.72 (m, 2H), 7.42 – 7.24 (m, 14H), 5.50 (d, J = 13.5 Hz, 1H), 5.44 (d, J = 13.5 Hz, 1H), 5.24 – 5.10 (m, 2H), 5.15 (d, J = 13.4 Hz, 1H), 5.06 (d, J = 13.5 Hz, 1H), 2.73 – 2.61 (m, 2H), 2.53 (ddd, J = 14.4, 10.6, 9.1 Hz, 1H), 2.39 (ddd, J = 14.2, 9.6, 4.4 Hz, 1H), 2.24 (ddd, J = 14.4, 7.8, 5.5 Hz, 1H), 1.90 (ddd, J = 14.4, 5.2, 4.0 Hz, 1H), 1.33 (d, J = 3.3 Hz, 3H), 1.31 (d, J = 3.2 Hz, 3H);

13C NMR (CDCl₃, 100MHz, 293K) mixture of diastereoisomers: δ 175.8, 175.6, 157.0 (q, J = 37.3 Hz), 156.8 (q, J = 37.3 Hz), 155.5, 155.4, 149.3, 149.3, 140.7, 140.1, 137.0, 129.0, 128.1, 128.1, 126.5, 126.4, 123.1, 123.1, 121.9, 121.9, 115.9 (q, J = 288.2 Hz), 115.9 (q, J = 288.2 Hz), 66.2, 66.1, 53.6, 51.8, 39.1, 37.9, 37.8, 36.1, 18.4, 16.1;

19F NMR (CDCl₃, 377MHz, 293K) mixture of diastereoisomers: δ -75.4, -75.4;

IR: ν 3312, 2977, 1716, 1553, 1181, 758, 701;

HRMS (ESI): calcd for C₁₉H₂₀F₃N₂O₃⁺ (M+H) 381.1421 Found: 381.1420;
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (9.6 mg, 0.015 mmol, 0.05 equiv.) and tetrabutylammonium iodide (17 mg, 0.045 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (82 mg, 0.599 mmol, 2.00 equiv.), acetic acid (1.8 mg, 0.030 mmol, 0.10 equiv.) and (Z)-N-(2,2-dimethyl-5-(prop-1-enyl)-1,3-dioxan-5-yl)-2,2,2-trifluoroacetamide (80 mg, 0.299 mmol, 1.00 equiv.) in DMF (0.45 mL) and the solution was heated to 135°C for 18h. The solution was cooled to r.t. and concentrated to remove the DMF. The product was then purified by flash chromatography (hexane/EtOAc 1:1 to 1:2) to give the product as a pale yellow oil in 81% yield (99 mg, 0.244 mmol).

R$_f$ (hexane:EtOAc = 1:1): 0.36;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 8.61 (ddd, $J$ = 4.8 1.5, 0.9 Hz, 1H), 7.72 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.35 (d, $J$ = 7.8 Hz, 1H), 7.25 (ddd, $J$ = 7.5, 4.9, 0.7 Hz, 1H), 6.74 (s, 1H), 5.24 (s, 2H), 4.02 (d, $J$ = 12.2 Hz, 2H), 3.73 (d, $J$ = 12.2 Hz, 2H), 2.46 (t, $J$ = 7.1 Hz, 2H), 1.88 – 1.81 (m, 2H), 1.66 – 1.55 (m, 2H), 1.45 (s, 3H), 1.43 (s, 3H);

$^13$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 172.8, 157.0 (q, $J$ = 36.6 Hz), 155.6, 149.516, 136.8, 123.0, 121.9, 115.5 (q, $J$ = 289.1 Hz), 98.8, 66.9, 65.2, 54.1, 33.7, 29.6, 28.1, 18.8, 17.7;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): $\delta$ -75.9;

IR: $\nu$ 3304, 1994, 1724, 1376, 1188, 1154, 1089, 829;

HRMS (ESI): calcd for C$_{18}$H$_{24}$F$_3$N$_2$O$_5^+$ (M+H) 405.1632 Found: 405.1648;

(R)-pyridin-2-ylmethyl 6-methyl-5-(2,2,2-trifluoroacetamido)heptanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (12 mg, 0.019 mmol, 0.05 equiv.) and tetrabutylammonium iodide (21 mg, 0.057 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (105 mg, 0.765 mmol, 2.00 equiv.), acetic acid (2.3 mg, 0.038 mmol, 0.10 equiv.) and (S,E)-2,2,2-trifluoro-N-(2-methylhex-4-en-3-yl)acetamide (80 mg, 0.382 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/ EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 76% yield (100 mg, 0.289 mmol).

Rf (hexane:EtOAc = 1:1): 0.40;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 8.57 (ddd, $J = 4.9$, 1.6, 0.9 Hz, 1H), 7.71 (td, $J = 7.7$, 1.8 Hz, 1H), 7.34 (d, $J = 7.8$ Hz, 1H), 7.27 – 7.22 (m, 1H), 6.77 (d, $J = 9.0$ Hz, 1H), 5.27 (d, $J = 13.3$ Hz, 1H), 5.18 (d, $J = 13.3$ Hz, 1H), 3.86 – 3.77 (m, 1H), 2.56 – 2.36 (m, 2H), 1.88 – 1.58 (m, 4H), 1.51 – 1.38 (m, 1H), 0.93 (d, $J = 4.1$ Hz, 3H), 0.91 (d, $J = 4.1$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 172.8, 157.4 (q, $J = 36.5$ Hz), 155.6, 149.3, 136.9, 123.0, 122.0, 116.1 (q, $J = 288.2$ Hz), 66.6, 55.4, 33.6, 32.0, 30.6, 21.3, 19.0, 17.8;

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): δ – 75.6;

IR: ν 3314, 2665, 1716, 1558, 1162, 759, 723;

HRMS (ESI): calcd for C$_{16}$H$_{22}$F$_3$N$_2$O$_3$ $^+$ (M+H) 347.1577 Found: 347.1566;

SFC: column: IA; eluent: CO$_2$/MeOH 95:5; flow: 3.0 mL/min; T = 25°C; release pressure: 100 bar; $t_R$(major) = 3.78 min, $t_R$(minor) = 4.44 min; >99% ee (minor not detected in enantioenriched sample).

(4R)-pyridin-2-ylmethyl 2,5-dimethyl-4-(2,2,2-trifluoroacetamido)hexanoate
This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 18% yield (24 mg, 0.069 mmol).

\[ \text{Rf (hexane:EtOAc = 1:1): 0.46;} \]

\[ \text{\H{} NMR (CDCl}_3, 300MHz, 293K) \text{ mixture of diastereoisomers: } \delta 8.61 - 8.53 (m, 2H), 7.94 (d, } J = 7.7 \text{ Hz, 2H}), 7.80 - 7.67 (m, 2H), 7.36 - 7.23 (m, 4H), 5.56 (d, } J = 13.6 \text{ Hz, 1H}), 5.38 (d, } J = 13.5 \text{ Hz, 1H}), 5.11 (d, } J = 13.5 \text{ Hz, 1H}), 5.00 (d, } J = 13.6 \text{ Hz, 1H}), 3.98 (tdd, } J = 11.7, 5.5, 3.8 \text{ Hz, 1H}), 3.81 (tdd, } J = 14.2, 8.1, 5.8 \text{ Hz, 1H}), 2.75 - 2.63 (m, 1H), 2.55 (pd, } J = 7.1, 5.5 \text{ Hz, 1H}), 2.09 - 1.79 (m, 5H), 1.66 (ddd, } J = 14.5, 5.4, 3.7 \text{ Hz, 1H}), 1.28 - 1.25 (m, 6H), 0.97 - 0.93 (m, 12H); \]

\[ \text{\H{} NMR (CDCl}_3, 300MHz, 293K) \text{ mixture of diastereoisomers: } \delta 176.1, 175.7, 157.5 (q, } J = 36.8 \text{ Hz}), 157.4 (q, } J = 36.9 \text{ Hz}), 155.6, 155.5, 149.3, 149.1, 137.1, 137.0, 123.0, 121.9, 121.8, 116.1 (q, } J = 288.4 \text{ Hz}), 116.0 (q, } J = 288.3 \text{ Hz}), 66.2, 65.7, 54.5, 53.8, 37.5, 35.9, 34.7, 34.6, 32.7, 31.7, 19.2, 18.8, 18.5, 18.1, 18.0, 16.6; \]

\[ \text{\F{} NMR (CDCl}_3, 377MHz, 293K) \text{ mixture of diastereoisomers: } \delta -75.3, -75.4; \]

\[ \text{IR: } \nu 3316, 2967, 1716, 1558, 1185, 759, 723; \]

\[ \text{HRMS (ESI): } \text{calcd for C}_{16}\text{H}_{22}\text{F}_3\text{N}_2\text{O}_3^+ (M+H) 347.1577 \text{ Found: 347.1568;} \]

\[ \alpha_D = -5.008 (c = 1.16) \]

**pyridin-2-ylmethyl 5-methyl-5-(2,2,2-trifluoroacetamido)hexanoate**

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (13 mg, 0.020 mmol, 0.05 equiv.) and tetrabutylammonium iodide (23 mg, 0.061 mmol, 0.15 mmol) and the system was purged
with argon. To the vial was added a solution of 2-pyridylmethyl formate (112 mg, 0.820 mmol, 2.00 equiv.), acetic acid (2.4 mg, 0.041 mmol, 0.10 equiv.) and 2,2,2-trifluoro-N-(2-methylpent-3-en-2-yl)acetamide (80 mg, 0.410 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48 h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 89% yield (121 mg, 0.364 mmol).

Rf (hexane:EtOAc = 1:1): 0.39;

$^1$H NMR (CDCl$_3$, 300 MHz, 293 K): $\delta$ 8.56 (ddd, $J$ = 4.8, 1.4, 0.8 Hz, 1H), 7.69 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.32 (d, $J$ = 7.8 Hz, 1H), 7.22 (ddd, $J$ = 7.5, 4.9, 0.7 Hz, 1H), 6.57 (s, 1H), 5.22 (s, 2H), 2.44 (t, $J$ = 6.9 Hz, 2H), 1.79 – 1.70 (m, 2H), 1.70 – 1.61 (m, 2H), 1.37 (s, 6H);

$^{13}$C NMR (CDCl$_3$, 100 MHz, 293 K): $\delta$ 173.1, 156.3 (q, $J$ = 36.0 Hz), 155.6, 149.4, 136.8, 122.9, 121.9, 115.6 (q, $J$ = 289.4 Hz), 66.8, 55.1, 39.2, 33.6, 26.0, 19.1;

$^{19}$F NMR (CDCl$_3$, 377 MHz, 293 K): $\delta$ -76.1;

IR: $\nu$ 3332, 2977, 1716, 1555, 1184, 760;

HRMS (ESI): calcd for C$_{15}$H$_{20}$F$_{4}$N$_{2}$O$_{3}$ $^+$ (M+H) 333.1421 Found: 333.1426;

pyridin-2-ylmethyl 4-methyl-5-(2,2,2-trifluoroacetamido)pentanoate

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (12 mg, 0.019 mmol, 0.05 equiv.) and tetrabutylammonium iodide (21 mg, 0.058 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (106 mg, 0.773 mmol, 2.00 equiv.), acetic acid (2.4 mg, 0.041 mmol, 0.10 equiv.) and 2,2,2-trifluoro-N-(2-methylbut-2-enyl)acetamide (70 mg, 0.386 mmol, 1.00 equiv.) in THF (0.6 mL) and the solution was heated to 75°C for 48 h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash
chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 53% yield (65 mg, 0.203 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.29;

**$^1$H NMR (CDCl$_3$, 300MHz, 293K):** $\delta$ 8.59 (ddd, $J = 4.9, 1.6, 0.8$ Hz, 1H), 7.73 (td, $J = 7.7, 1.8$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.28 – 7.24 (m, 1H), 7.18 (s, 1H), 5.28 (d, $J = 13.2$ Hz, 1H), 5.21 (d, $J = 13.2$ Hz, 1H), 3.38 – 3.17 (m, 2H), 2.65 – 2.40 (m, 2H), 1.89 – 1.74 (m, 2H), 1.62 – 1.48 (m, 1H), 0.97 (d, $J = 6.7$ Hz, 3H);

**$^{13}$C NMR (CDCl$_3$, 100MHz, 293K):** $\delta$ 173.4, 157.5 (q, $J = 36.8$ Hz), 155.5, 149.4, 136.9, 123.1, 122.0, 116.0 (q, $J = 287.9$ Hz), 66.8, 45.1, 32.5, 31.3, 28.5, 17.4;

**$^{19}$F NMR (CDCl$_3$, 377MHz, 293K):** $\delta$ – 75.8;

**IR:** $\nu$ 3328, 2936, 1716, 1558, 1210, 1180, 760;

**HRMS (ESI):** calcd for C$_{14}$H$_{18}$F$_3$N$_2$O$_3$ (M+H) 319.1264 Found: 319.1258;

**(R)-tert-butyl 2,2-dimethyl-4-(4-oxo-4-(pyridin-2-ylmethoxy)butyl)oxazolidine-3-carboxylate**

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (11 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.663 mmol, 2.00 equiv.), acetic acid (2.1 mg, 0.034 mmol, 0.10 equiv.) and (R)-tert-butyl 2,2-dimethyl-4-(prop-1-enyl)oxazolidine-3-carboxylate$^9$ (80 mg, 0.382 mmol, 1.00 equiv.) in THF (0.5 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 76% yield (95 mg, 0.251 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.35;
\(^1\)H NMR (CDCl\(_3\), 300MHz, 293K) (1:1 mixture of rotomers): \(\delta\) 8.61 (d, \(J = 4.2\) Hz, 1H), 7.71 (td, \(J = 7.7, 1.8\) Hz, 1H), 7.35 (d, \(J = 7.8\) Hz, 1H), 7.27 – 7.20 (m, 1H), 5.24 (s, 2H), 3.98 – 3.71 (m, 3H), 2.55 – 2.40 (m, 2H), 1.88 – 1.42 (m, 19H);

\(^{13}\)C NMR (CDCl\(_3\), 100MHz, 293K) (1:1 mixture of rotomers): \(\delta\) 173.0, 172.9, 155.9, 155.8, 152.2, 151.8, 149.5, 149.5, 136.7, 122.9, 122.8, 121.8, 121.7, 93.7, 93.2, 80.0, 79.6, 77.2, 67.0, 66.7, 57.3, 57.0, 34.0, 33.3, 32.5, 28.5, 27.6, 26.8, 24.5, 23.2, 21.6;

IR: \(\nu\) 2979, 1740, 1694, 1391, 1173, 1084;

HRMS (ESI): calcd for C\(_{20}\)H\(_{31}\)N\(_2\)O\(_5\)\(^+\) (M+H) 379.2227 Found: 379.2230;

\(\alpha\)\(_D\) = -18.986 (c = 0.424)

SFC: column: IA; eluent: CO\(_2\)/MeOH 98:2; flow: 2.0 mL/min; T = 25°C; release pressure: 100 bar; \(t_R\) (minor) = 16.00 min, \(t_R\) (major) = 17.08 min; >99% ee (minor not detected in enantioenriched sample).

**pyridin-2-ylmethyl 6-(tert-butyldimethylsilyloxy)-5-(2,2,2-trifluoroacetamido)hexanoate**

To an oven dried screw cap vial was added Ru\(_5\)(CO)\(_{12}\) (10 mg, 0.016 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.048 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (88 mg, 0.642 mmol, 2.00 equiv.), acetic acid (1.9 mg, 0.031 mmol, 0.10 equiv.) and \(N\)-(1-(tert-butyldimethylsilyloxy)pent-3-en-2-yl)-2,2,2-trifluoroacetamide (100 mg, 0.321 mmol, 1.00 equiv.) in THF (0.5 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 2:1) to give the product as a pale yellow oil in 78% yield (112 mg, 0.25 mmol).

\(Rf\) (hexane:EtOAc = 1:1): 0.43;
**1H NMR (CDCl₃, 300MHz, 293K):** δ 8.60 – 8.55 (m, 1H), 7.70 (td, J = 7.7, 1.8 Hz, 1H), 7.33 (d, J = 7.8 Hz, 1H), 7.23 (ddd, J = 7.5, 4.9, 0.6 Hz, 1H), 6.88 (d, J = 8.4 Hz, 1H), 5.25 (d, J = 13.3 Hz, 1H), 5.20 (d, J = 13.4 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.66 (d, J = 3.6 Hz, 2H), 2.55 – 2.40 (m, 2H), 1.79 – 1.56 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H);

**13C NMR (CDCl₃, 100MHz, 293K):** δ 172.7, 156.9 (q, J = 36.8 Hz), 155.7, 149.4, 136.8, 122.9, 121.8, 115.9 (q, J = 288.1 Hz), 66.7, 63.7, 51.2, 33.6, 30.3, 25.7, 21.2, 18.2, -5.6, -5.7;

**19F NMR (CDCl₃, 377MHz, 293K):** δ -76.0;

**IR:** ν 3316, 2931, 1714, 1474, 1162, 839;

**HRMS (ESI):** calcd for C₂₀H₃₂F₃N₂O₄Si⁺ (M+H) 449.2078 Found: 449.2079;

**pyridin-2-ylmethyl 5-(tert-butyldimethylsilyloxy)-2-methyl-4-(2,2,2-trifluoroacetamido)pentanoate**

This product was obtained as a minor regioisomer as a 1:1 mixture of diastereoisomers in 11% yield (16 mg, 0.036 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.51;

**1H NMR (CDCl₃, 300MHz, 293K) 1:1 mixture of diastereoisomers:** δ 8.63 – 8.53 (m, 2H), 7.78 – 7.69 (m, 2H), 7.48 (d, J = 8.1 Hz, 1H), 7.39 – 7.32 (m, 2H), 7.28 – 7.23 (m, 2H), 7.08 (d, J = 8.5 Hz, 1H), 5.42 (d, J = 13.5 Hz, 1H), 5.31 (d, J = 13.4 Hz, 1H), 5.20 (d, J = 13.4 Hz, 1H), 5.15 (d, J = 13.5 Hz, 1H), 4.21 – 4.01 (m, 2H), 3.76 – 3.66 (m, 4H), 2.74 – 2.67 (m, 1H), 2.64 – 2.53 (m, 1H), 2.18 (ddd, J = 14.3, 10.2, 7.9 Hz, 1H), 2.02-1.89 (m, 1H), 1.77 – 1.65 (m, 2H), 1.29 (dd, J = 8.7, 7.1 Hz, 6H), 0.95 – 0.85 (m, 18H), 0.10 – 0.04 (m, 12H);

**13C NMR (CDCl₃, 100MHz, 293K) 1:1 mixture of diastereoisomers:** δ 175.9, 175.7, 157.0 (q, J = 36.8 Hz), 157.0 (q, J = 36.9 Hz), 155.7, 155.5, 149.4, 149.3, 136.9, 136.9, 123.0, 122.9, 121.8, 115.9 (q, J = 288.2 Hz), 115.9 (q, J = 288.1 Hz), 66.6, 66.4, 64.3, 64.0, 50.3, 49.7, 37.0, 36.0, 34.5, 34.3, 25.8, 18.2, 18.2, 17.8, 17.2, -5.5, -5.6;
Experimental Part

$^{19}$F NMR (CDCl$_3$, 377MHz, 293K): 1:1 mixture of diastereoisomers: $\delta$ -75.8;

IR: $\nu$ 3320, 2931, 1722, 1163, 838;

HRMS (ESI): calcd for C$_{20}$H$_{32}$F$_3$N$_2$O$_4$Si$^+$ (M+H) 449.2078 Found: 449.2072;

pyridin-2-ylmethyl 4-(5-oxomorpholin-3-yl)butanoate

![structure](image)

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (18mg, 0.028 mmol, 0.05 equiv.) and tetrabutylammonium iodide (31 mg, 0.085 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (155 mg, 1.13 mmol, 2.00 equiv.), acetic acid (3.4 mg, 0.056 mmol, 0.10 equiv.) and 5-(prop-1-enyl)morpholin-3-one (80 mg, 0.567 mmol, 1.00 equiv.) in THF (0.9 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (100% EtOAc then 5% MeOH/DCM) to give the product as a pale yellow oil in 81% yield (127 mg, 0.456 mmol).

Rf (5% MeOH/DCM): 0.26;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 8.63 (ddd, $J$ = 4.8, 1.6, 0.9 Hz, 1H), 7.72 (td, $J$ = 7.7, 1.8 Hz, 1H), 7.35 (d, $J$ = 7.8 Hz, 1H), 7.26 (ddd, $J$ = 7.6, 4.9, 1.0 Hz, 1H), 6.75 (s, 1H), 5.25 (s, 2H), 4.15 (q, $J$ = 16.7 Hz, 2H), 3.95 – 3.85 (m, 1H), 3.59 – 3.48 (m, 2H), 2.49 (td, $J$ = 7.1, 3.3 Hz, 2H), 1.81 – 1.70 (m, 2H), 1.66 – 1.58 (m, 2H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 172.7, 168.9, 155.5, 149.6, 136.8, 123.0, 122.0, 67.8, 67.6, 66.9, 51.3, 33.6, 32.5, 20.4;

IR: $\nu$ 3218, 2917, 1738, 1674, 1162, 1124;

HRMS (ESI): calcd for C$_{14}$H$_{19}$N$_2$O$_4$ (M+H) 279.1339 Found: 279.1334;

pyridin-2-ylmethyl 4-(2-oxooxazolidin-4-yl)butanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (15mg, 0.024 mmol, 0.05 equiv.) and tetrabutylammonium iodide (26 mg, 0.071 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (129 mg, 0.944 mmol, 2.00 equiv.), acetic acid (2.8 mg, 0.047 mmol, 0.10 equiv.) and 4-(prop-1-enyl)oxazolidin-2-one (60 mg, 0.472 mmol, 1.00 equiv.) in THF (0.70 mL) and the solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (DCM/MeOH 20:1 to 15:1) to give the product as a pale yellow oil in 85% yield (106 mg, 0.401 mmol).

**Rf** (5% MeOH/DCM): 0.25;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): δ 8.64 (ddd, $J = 4.8$, 1.6, 0.8 Hz, 1H), 7.73 (td, $J = 7.7$, 1.8 Hz, 1H), 7.35 (d, $J = 7.8$ Hz, 1H), 7.27 (ddd, $J = 7.6$, 4.9, 0.5, 0.5 Hz, 1H), 5.99 (s, 1H), 5.27 (d, $J = 13.2$ Hz, 1H), 5.23 (d, $J = 13.2$ Hz, 1H), 4.50 (t, $J = 8.4$ Hz, 1H), 4.04 (dd, $J = 8.6$, 6.0 Hz, 1H), 3.93 – 3.85 (m, 1H), 2.58 – 2.41 (m, 2H), 1.80 – 1.56 (m, 4H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): δ 172.7, 159.5, 155.4, 149.7, 136.9, 123.1, 122.0, 70.0, 66.9, 52.0, 34.7, 33.5, 20.3;

IR: ν 3268, 2939, 1744, 1239, 1162, 1050;

HRMS (ESI): calcd for C$_{13}$H$_{17}$N$_2$O$_4^+$ (M+H) 265.1183 Found: 265.1193;

**pyridin-2-ylmethyl 7-methyl-6-(2,2,2-trifluoroacetamido)octanoate**

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (14 mg, 0.022 mmol, 0.05 equiv.) and tetrabutylammonium iodide (25 mg, 0.067 mmol, 0.15 mmol) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (123 mg, 0.896
mmol, 2.00 equiv.), acetic acid (2.6 mg, 0.044 mmol, 0.10 equiv.) and 2,2,2-trifluoro-N-(2-
 methylhept-4-en-3-yl)acetamide (100 mg, 0.448 mmol, 1.00 equiv.) in THF (0.7 mL) and the
solution was heated to 75°C for 48h. The solution was cooled to r.t. and concentrated to
remove the excess 2-pyridylmethyl formate. The product was then purified by flash
chromatography (hexane/EtOAc 2:1 to 1:1) to give the product as a pale yellow oil in 61%
yield (98 mg, 0.273 mmol).

**Rf** (hexane:EtOAc = 1:1): 0.39;

**1H NMR (CDCl3, 300MHz, 293K):** δ 8.59 (ddd, J = 4.8, 1.6, 0.8 Hz, 1H), 7.72 (td, J = 7.7,
1.8 Hz, 1H), 7.34 (d, J = 7.8 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.33 (d, J = 9.3 Hz, 1H), 5.22 (s,
2H), 3.87 – 3.77 (m, 1H), 2.43 (t, J = 7.4 Hz, 2H), 1.85 – 1.57 (m, 4H), 1.50 – 1.30 (m, 3H),
0.93 (d, J = 6.9 Hz, 3H), 0.91 (d, J = 6.9 Hz, 3H);

**13C NMR (CDCl3, 100MHz, 293K):** δ 173.1, 157.2 (q, J = 36.4 Hz), 155.7, 149.5, 136.8,
122.9, 121.9, 116.1 (q, J = 288.3 Hz), 66.8, 55.4, 33.8, 31.8, 31.3, 25.4, 24.6, 19.1, 17.7;

**19F NMR (CDCl3, 377MHz, 293K):** δ – 75.6;

**IR:** ν 3316, 2963, 1715, 1558, 1184, 1158;

**HRMS (ESI):** caled for C17H24F3N2O3+ (M+H) 361.1734 Found: 361.1734;

**pyridin-2-ylmethyl 5-(tert-butyldimethylsilyloxy)-5-phenylpentanoate**

![Pyridin-2-ylmethyl 5-(tert-butyldimethylsilyloxy)-5-phenylpentanoate](image)

To a flame dried schlenk tube was added Ru₃(CO)₁₂ (122mg, 0.191 mmol, 0.05 equiv.) and
tetrabutylammonium iodide (211 mg, 0.572 mmol, 0.15 equiv.) and the system was purged
with argon. To the schlenk was added a solution of 2-pyridylmethyl formate (1.05g, 7.62
mmol, 2.00 equiv.) and (E)-tert-butyldimethyl(1-phenylbut-2-enyloxy)silane (1.00g, 3.81
mmol, 1.00 equiv.) in DMF (5 mL) followed by a solution of acetic acid (34 mg, 0.572 mmol,
0.15 equiv.) in DMF (1 mL) and the solution was heated to 120°C. After 10h, an additional
portion of 2-pyridylmethyl formate (523 mg, 3.81 mmol, 1.00 equiv.) was added and the
solution was heated to 120°C for 18h. The solution was cooled to r.t. and concentrated to
remove the DMF. The product was then purified by flash chromatography (20% EtOAc/hexane) to give the product as a pale yellow oil in 64% yield (978 mg, 2.45 mmol).

\[ R_f \text{ (hexane:EtOAc = 2:1): 0.42; } \]

\[ ^1H \text{ NMR (CDCl}_3, 300\text{MHz, 293K): } \delta 8.61 - 8.58 \text{ (m, 1H), 7.69 (td, } J = 7.7, 1.8 \text{ Hz, 1H), } 7.35 - 7.28 \text{ (m, 5H), 7.26 - 7.21 (m, 2H), 5.23 (s, 2H), 4.68 (dd, } J = 6.7, 4.7 \text{ Hz, 1H), 2.43 (t, } J = 7.0 \text{ Hz, 2H), 1.86 - 1.62 \text{ (m, 4H), 0.90 (s, 9H), 0.04 (s, 3H), -0.14 (s, 3H);} \]

\[ ^13C \text{ NMR (CDCl}_3, 100\text{MHz, 293K): } \delta 173.1, 156.0, 149.5, 145.3, 136.7, 128.1, 127.0, 125.8, 122.8, 121.7, 74.7, 66.6, 40.2, 34.1, 25.9, 21.1, 18.2, -4.6, -5.0; \]

\[ \text{IR: } \nu 2929, 1744, 1149, 1096, 837, 776; \]

\[ \text{HRMS (ESI): caled for } C_{23}H_{34}NO_3Si^+ (M+H) 400.2302 \text{ Found: 400.2300; } \]

**pyridin-2-ylmethyl 5-(tert-butyldimethylsilyloxy)nonanoate**

![Chemical structure](image)

To an oven dried screw cap vial was added Ru\(_3\)(CO)\(_{12}\) (10.6 mg, 0.016 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.049 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (90 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and (\(E\))-tert-butyldimethyl(oct-2-en-4-yloxy)silane (80 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.50 mL) and the solution was heated to 120°C for 18h. The solution was cooled to r.t. and concentrated to remove the excess 2-pyridylmethyl formate. The product was then purified by flash chromatography (hexane/EtOAc 7:1 to 5:1) to give the product as a pale yellow oil in 66% yield (83 mg, 0.219 mmol).

\[ R_f \text{ (hexane:EtOAc = 2:1): 0.51;} \]

\[ ^1H \text{ NMR (CDCl}_3, 300\text{MHz, 293K): } \delta 8.59 \text{ (ddd, } J = 4.8, 1.5, 0.9 \text{ Hz, 1H), 7.69 (td, } J = 7.7, 1.8 \text{ Hz, 1H), 7.34 (d, } J = 7.8 \text{ Hz, 1H), 7.22 (dd, } J = 7.5, 4.9, 0.8 \text{ Hz, 1H), 5.24 (s, 2H), 3.65} \]
Experimental Part

1H NMR (CDCl₃, 300MHz, 293K): δ 8.61 (d, J = 4.7 Hz, 2H), 7.76 – 7.66 (m, 2H), 7.37 (d, J = 7.8 Hz, 2H), 7.27 – 7.21 (m, 2H), 5.31 – 5.19 (m, 4H), 3.77 – 3.64 (m, 2H), 2.83 – 2.67 (m, 2H), 2.01 – 1.90 (m, 2H), 1.56 – 1.41 (m, 6H), 1.36 – 1.20 (m, 14H), 1.36 – 1.20 (m, 24H), 0.06 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H), 0.02 (s, 3H);

13C NMR (CDCl₃, 100MHz, 293K): δ 176.6, 176.4, 156.2, 156.2, 149.4, 136.7, 136.7, 122.7, 122.7, 121.7, 121.5, 70.6, 69.8, 66.7, 66.7, 40.9, 40.6, 37.4, 36.9, 36.1, 35.8, 27.2, 27.0, 25.9, 25.9, 22.9, 22.8, 18.6, 18.1, 17.3, 14.1, -4.3, -4.3, -4.6, -4.7;

IR: ν 2931, 1739, 1257, 1166, 1051, 836, 775;

HRMS (ESI): calcd for C₂₁H₃₈NO₃Si⁺ (M+H) 380.2615 Found: 380.2608;

pyridin-2-ylmethyl 5-(benzo[b]thiophen-2-yl)-5-(tert-butyldimethylsilyloxy)pentanoate
To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (10.6 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and (E)-(1-(benzo[b]thiophen-2-yl)but-2-enyloxy)(tert-butyl)dimethylsilane (105 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.50 mL) and the solution was heated to 120$^\circ$C for 18h. The solution was cooled to r.t. and the product was purified by flash chromatography (hexane/EtOAc 85:15) to give the product as a pale yellow oil in 65% yield (98 mg, 0.214 mmol).

$R_f$ (hexane:EtOAc = 85:15): 0.26;

$^1$H NMR (CDCl$_3$, 300MHz, 293K): $\delta$ 8.60 (d, $J = 4.3$ Hz, 1H), 7.83 – 7.80 (m, 1H), 7.70 (dt, $J = 2.2$, 1.4 Hz, 1H), 7.67 (td, $J = 7.7$, 1.8 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.23 (dd, $J = 7.2$, 4.6 Hz, 1H), 7.10 (s, 1H), 5.24 (s, 2H), 5.04 (dd, $J = 5.9$, 5.2 Hz, 1H), 2.47 (t, $J = 7.0$ Hz, 2H), 2.00 – 1.70 (m, 4H), 0.94 (s, 9H), 0.11 (s, 0H), 0.00 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 100MHz, 293K): $\delta$ 173.0, 155.9, 150.6, 149.5, 139.6, 139.3, 136.7, 124.0, 123.8, 123.2, 122.8, 122.4, 121.7, 119.1, 71.3, 66.7, 40.1, 34.0, 25.8, 20.8, 18.2, -4.8, -5.0;

IR: $\nu$ 2954, 1741, 1252, 1157, 1093, 837, 777, 747;

HRMS (ESI): calcd for C$_{25}$H$_{34}$NO$_3$S$i^{-}$ (M+H) 456.2023 Found: 456.2039;

**pyridin-2-ylmethyl 4-(2,2-dimethyl-1,3-dioxolan-4-yl)butanoate**

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (10.6 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and 2,2-dimethyl-4-(prop-1-
enyl)-1,3-dioxolane (47 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.5 mL) and the solution was heated to 120°C for 18 h. The solution was cooled to r.t. and concentrated to remove the DMF. The product was purified by flash chromatography (60% Et₂O/hexane) to give the product as a pale yellow oil in 88% yield (81 mg, 0.290 mmol).

Rf (100% Et₂O): 0.21;

\[ \delta \text{H NMR (CDCl₃, 300MHz, 293K):} \delta 8.61 (\text{ddd, } J = 4.8, 1.6, 0.9 \text{ Hz, 1H}), 7.71 (\text{td, } J = 7.7, 1.8 \text{ Hz, 1H}), 7.36 (\text{d, } J = 7.8 \text{ Hz, 1H}), 7.28 – 7.21 (\text{m, 1H}), 5.25 (\text{s, 2H}), 4.11 (\text{ddd, } J = 12.0, 6.7, 5.5 \text{ Hz, 1H}), 4.05 (\text{dd, } J = 7.7, 6.0 \text{ Hz, 1H}), 3.53 (\text{dd, } J = 7.6, 7.5 \text{ Hz, 1H}), 2.50 (\text{td, } J = 7.3, 1.1 \text{ Hz, 2H}), 1.92 – 1.48 (\text{m, 4H}), 1.41 (\text{s, 3H}), 1.36 (\text{s, 3H}); \]

\[ \delta \text{C NMR (CDCl₃, 100MHz, 293K):} \delta 173.0, 155.8, 149.5, 136.7, 122.9, 121.8, 108.8, 75.6, 69.3, 66.8, 34.0, 32.9, 26.9, 25.7, 21.2; \]

IR: ν 2986, 1738, 2370, 1215, 1163, 1058, 761;

HRMS (ESI): calcd for C₁₅H₂₁O₄Na⁺ (M+Na) 302.1363 Found: 302.1365;

(S)-pyridin-2-ylmethyl 5,6-bis(tert-butyldimethylsilyloxy)hexanoate

To an oven dried screw cap vial was added Ru₃(CO)₁₂ (10.6 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and (S,E)-2,2,3,3,8,8,9,9-octamethyl-5-(prop-1-enyl)-4,7-dioxa-3,8-disiladecane (75 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.50 mL) and the solution was heated to 150°C for 18 h. The solution was cooled to r.t. and the product was purified by flash chromatography (hexane/EtOAc 5:1 to 2:1) to give the product as a pale yellow oil in 73% yield (103 mg, 0.220 mmol).

Rf (100% Et₂O): 0.43;
1H NMR (CDCl₃, 300MHz, 293K): δ 8.61 (d, J = 4.8 Hz, 1H), 7.71 (td, J = 7.7, 1.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.24 (ddd, J = 7.5, 4.9, 0.6 Hz, 1H), 5.25 (s, 2H), 3.74 – 3.64 (m, 1H), 3.54 (dd, J = 10.0, 5.4 Hz, 1H), 3.42 (dd, J = 10.0, 6.5 Hz, 1H), 2.45 (t, J = 7.7 Hz, 2H), 1.91 – 1.38 (m, 4H), 0.93 – 0.85 (m, 18H), 0.11 – 0.02 (m, 12H); 

13C NMR (CDCl₃, 100MHz, 293K): δ 173.2, 156.0, 149.5, 136.7, 122.8, 121.7, 72.7, 67.2, 66.7, 34.5, 33.8, 26.0, 25.9, 20.7, 18.4, 18.1, -4.3, -4.7, -5.3, -5.4; 

IR: ν 2929, 1744, 1473, 1257, 1160, 1123, 1093, 837, 776; 

HRMS (ESI): calcd for C₂₄H₄₅NNaO₄Si₂⁺ (M+Na) 490.2779 Found: 490.2796; 

αD = -12.670 (c = 0.931)

HPLC: column: IC; eluent: Hexanes/iPrOH 99.5:0.5; flow: 1.0 mL/min; T = 25°C; tR(major) = 23.65 min, tR(minor) = 22.48 min; >99% ee (minor not detected in enantioenriched sample).

pyridin-2-ylmethyl 4-(3-(tert-butyldimethylsilyloxy)oxetan-3-yl)butanoate

To an oven dried screw cap vial was added Ru₃(CO)₁₂ (10.6 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and (E)-tert-butyldimethyl(3-(prop-1-enyl)oxetan-3-ylxyloxy)silane (75 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.50 mL) and the solution was heated to 150°C for 18h. The solution was cooled to r.t. and the product was purified by flash chromatography (hexane/EtOAc 2:1) to give the product as a pale yellow oil in 72% yield (81 mg, 0.222 mmol).

Rf (hexane:EtOAc = 1:1): 0.36;

1H NMR (CDCl₃, 300MHz, 293K): δ 8.62 (ddd, J = 4.8, 1.5, 0.8 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.36 (d, J = 7.8 Hz, 1H), 7.27 – 7.23 (m, 1H), 5.26 (s, 2H), 4.64 (d, J = 6.8 Hz,
tert-buty 3-(tert-butyldimethylsilyloxy)-3-(4-oxo-4-(pyridin-2-ylmethoxy)butyl)-azetidine-1-carboxylate

To an oven dried screw cap vial was added Ru$_3$(CO)$_{12}$ (10.6 mg, 0.017 mmol, 0.05 equiv.) and tetrabutylammonium iodide (18 mg, 0.050 mmol, 0.15 equiv.) and the system was purged with argon. To the vial was added a solution of 2-pyridylmethyl formate (91 mg, 0.660 mmol, 2.00 equiv.), acetic acid (3 mg, 0.050 mmol, 0.15 equiv.) and (E)-tert-buty 3-(tert-butyldimethylsilyloxy)-3-(prop-1-enyl)azetidine-1-carboxylate (108 mg, 0.330 mmol, 1.00 equiv.) in DMF (0.5 mL) and the solution was heated to 150°C for 18h. The solution was cooled to r.t. and the product was purified by flash chromatography (65% Et$_2$O/Hexane) to give the product as a pale yellow oil in 85% yield (131 mg, 0.282 mmol).

$\text{Rf (100% Et}_2\text{O): 0.34;}$

$^1\text{H NMR (CDCl}_3, 300MHz, 293K): \delta 8.61 (ddd, J = 4.8, 1.5, 0.8 Hz, 1H), 7.72 (td, J = 7.7, 1.8 Hz, 1H), 7.35 (d, J = 7.8 Hz, 1H), 7.25 (ddd, J = 7.5, 4.9, 1.0 Hz, 1H), 5.26 (s, 2H), 3.85 (d, J = 9.1 Hz, 2H), 3.79 (d, J = 9.1 Hz, 2H), 2.50 – 2.45 (m, 2H), 1.80 – 1.72 (m, 4H), 1.46 (s, 9H), 0.89 (s, 9H), 0.12 (d, J = 2.7 Hz, 6H);

$^{13}\text{C NMR (CDCl}_3, 100MHz, 293K): \delta 172.9, 156.5, 155.8, 149.5, 136.7, 122.9, 121.8, 79.5, 71.7, 66.8, 62.0, 39.8, 34.0, 28.4, 25.7, 19.1, 17.9, -3.0;}$

$\text{IR: } \nu 2955, 1742, 1392, 1255, 1166, 1100, 837, 776;$

$^{13}\text{C NMR (CDCl}_3, 100MHz, 293K): \delta 172.9, 156.5, 155.8, 149.5, 136.7, 122.9, 121.8, 79.5, 71.7, 66.8, 62.0, 39.8, 34.0, 28.4, 25.7, 19.1, 17.9, -3.0;}$

$\text{IR: } \nu 2955, 1742, 1392, 1255, 1166, 1100, 837, 776;$
HRMS (ESI): calcd for C_{24}H_{40}N_{2}O_{5}SiNa^+ (M+Na) 487.2599 Found: 487.2599;

6.2.3 Cyclization Products

6-methylpiperidin-2-one

\[
\begin{align*}
\text{To a solution of pyridin-2-ylmethyl 5-(2,2,2-trifluoroacetamido)hexanoate (50 mg, 0.157 mmol, 1.00 equiv.) in dry MeOH (5.0 mL) was added CaSO}_4 (0.150 g, 1.102 mmol, 7.0 equiv.) and the mixture stirred at r.t. for 10 min. The mixture was then treated with Sodium hydride (60 mg, 1.500 mmol, 9.6 equiv.), stirred at r.t. for 30 min and then heated to reflux for 12 h. The mixture was then cooled to r.t., filtered through a pad of celite, washing with additional methanol (10 ml) and the filtrate treated with dry silica and concentrated under reduced pressure at 40°C. The residue was purified by flash chromatography (3.5% MeOH/DCM) to give the product as a white solid in 86% yield (15.2 mg, 0.134 mmol).}
\end{align*}
\]

\textbf{Rf} (DCM:MeOH = 9:1): 0.46;

\textbf{H NMR (CDCl₃, 400MHz, 293K)}: δ 5.76 (s, 1H), 3.57 – 3.43 (m, 1H), 2.44 – 2.20 (m, 2H), 1.96 – 1.83 (m, 2H), 1.78 – 1.60 (m, 1H), 1.42 – 1.27 (m, 1H), 1.19 (d, J = 6.4 Hz, 3H);

\textbf{C NMR (CDCl₃, 100MHz, 293K)}: δ 172.3, 49.0, 31.1, 30.6, 23.1, 20.0;

\textbf{IR}: ν 3190, 2939, 1683, 1620, 1485, 1447, 1402, 1334, 1181, 796;

\textbf{HRMS (EI)}: calcd for C₆H₁₁NO⁺ (M) 113.0841 Found: 113.0836;

6-phenyltetrahydro-2H-pyran-2-one

\[
\begin{align*}
\end{align*}
\]
To a solution of pyridin-2-ylmethyl 5-(tert-butyldimethylsilyloxy)-5-phenylpentanoate (200 mg, 0.501 mmol, 1.00 equiv.) in DCM (3.5 mL) was added 50% aqueous trifluoroacetic acid (1.00 mL) at 0°C under argon and the solution was allowed to warm to r.t. and stirred for 18h. The reaction was then quenched with saturated aqueous NaHCO₃ solution (5 mL) and extracted with DCM (3 X 10 mL), dried over MgSO₄ and purified by flash chromatography (40% Et₂O/hexane) to give the product as a white solid in 82% yield (72 mg, 0.409 mmol).

\[ \text{Rf} (40\% \text{ Et}_2\text{O/hexane}): 0.26; \]

\[ ^1\text{H NMR (CDCl}_3, 300\text{MHz, 293K)}: \delta 7.44 - 7.28 (m, 5H), 5.35 (dd, J = 10.2, 3.4 Hz, 1H), 2.77 - 2.50 (m, 2H), 2.17 (ddd, J = 12.9, 8.2, 3.7 Hz, 1H), 2.05 - 1.78 (m, 3H); \]

\[ ^{13}\text{C NMR (CDCl}_3, 100\text{MHz, 293K)}: \delta 171.3, 139.7, 128.5, 128.1, 125.6, 81.5, 30.4, 29.4, 18.5; \]

\[ \text{IR: } \nu 2954, 1732, 1240, 1042, 756, 700; \]

\[ \text{HRMS (ESI)}: \text{calcd for C}_{11}\text{H}_{12}\text{NaO}_2^- \text{(M+Na) 199.0730 Found: 199.0723}; \]
6.3 Experimental Part to Chapter 3

6.3.1 General Procedures

General Procedure A:

A flame-dried flask (25 mL) under argon was charged with Chloro(1,5-cyclooctadiene)-iridium(I) dimer (44 mg, 0.066 mmol, 0.025 eq.) and 5-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)-5H-dibenzo[b,f]azepine (54 mg, 0.132 mmol 0.05 eq.), the contents were suspended in THF (8.8 mL), treated with DMF (1.0 mL, 13.1 mmol, 5.0 eq.) and stirred for 15 min at r.t.. The mixture was then treated with sulfamic acid (0.305 g, 3.15 mmol, 1.2 eq.) and the substrate allylic alcohol (2.63 mmol, 1.0 eq.) and stirred at r.t. for 16 h or until TLC-analysis showed complete consumption of the SM. The mixture was then cooled to 0°C (ice bath) and treated with sodium hydrogencarbonate (0.442 g, 5.26 mmol, 2.0 eq.).

In a separate dry flask, formic acid (1.0 mL, 26 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (1.0 mL, 10.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the allylic amine and the resulting mixture stirred at r.t. for 3h.

The mixture was dilluted with EtOAc (100ml), washed with 1N HCl (2x50ml), brine (3x50ml), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 40°C.

The residue was purified by flash column chromatography on silica gel, eluting with 30 – 60% EtOAc in hexanes.
General Procedure B:

Vinylmagnesium bromide (6 mL, 1.0 M solution in THF, 6.00 mmol, 3.0 eq.) was cooled to -78°C (dry-ice/acetone bath) and treated dropwise with a solution of the substrate t-butylsulfinamide (2.0 mmol, 1.0 eq.) in THF (2.0 mL). The resulting mixture was allowed to slowly warm to r.t. over 2h and stirred for 30min. The mixture was then cooled to 0°C and treated with sat. aq. NH₄Cl (5mL). The mixture was extracted with EtOAc (3x 50mL) and the combined organic layers dried over Na₂SO₄, filtered and concentrated under reduced pressure at 40°C. The residue was purified by flash column chromatography on silica gel, eluting with 30 – 50% EtOAc in hexanes.

General Procedure C:

A solution of the substrate allyl-t-butylsulfinamide (1.50 mmol, 1.0 eq.) in MeOH (10 mL) was cooled to 0°C (ice bath) and treated dropwise with a solution of hydrogen chloride in dioxane (1.88 mL, 4M solution, 7.50 mmol, 5 eq.). The resulting solution was allowed to warm to r.t. and stirred for 10min until complete disappearance of the starting material by TLC analysis (silica plate, elution with 100% EtOAc). The solvent was then removed by rotary evaporation at 40°C under reduced pressure and the remaining residue dried at 0.5 mbar for 2h.

The residue was suspended in dry THF (10 mL), cooled to 0°C (ice bath) and treated with sodium hydrogen carbonate (0.151 g, 1.80 mmol, 1.2 eq.).

In a separate dry flask, formic acid (0.58 mL, 15 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.58 mL, 6.0 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was
then added dropwise to the cooled (0°C) mixture containing the allylic amine (prepared above) and the resulting mixture stirred at r.t. for 3h.

The resulting mixture was diluted with EtOAc (50mL) and washed with sat. aq. NaHCO₃ (3x30mL). The aqueous layers were back-extracted with EtOAc (50mL) and the combined organic layers washed with water (20mL) and brine (20mL), dried over Na₂SO₄, filtered and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with 20 – 50% EtOAc in hexanes.

**General Procedure D:**

\[
\begin{align*}
\text{HN} & \quad \text{Ru₃(CO)₁₂ (6\%) } \quad \text{B₄H₄I (15\%)} \\
\text{R₁} & \quad \text{CO (balloon)} \quad \text{DMF, 150°C, 4h} \\
\text{R₂} & \quad \text{HN} \\
\end{align*}
\]

To an oven dried autoclavable septum-sealed screw cap vial (2 mL) was added the substrate allylic formamide (0.350 mmol), triruthenium dodecacarbonyl (Ru₃(CO)₁₂) (11 mg, 0.018 mmol) and tetrabutylammonium iodide (19 mg, 0.053 mmol). The contents were then suspended in DMF (1.1 mL) and the mixture purged with carbon monoxide (balloon) for 15 min. The vial was sealed and the mixture was then heated to 150 °C for 4h. The solution was then cooled to r.t., diluted with EtOAc (30mL) and washed with brine (4x10mL), dried over Na₂SO₄ and concentrated. The residue was then purified by flash column chromatography on silica gel deactivated with 7.5 wt% conc. NH₄OH (elution with 30 – 100 % EtOAc in Hexanes) to give the product pyrrolidone.
6.3.2 Synthesis of Substrates and Products

\( \text{\textit{N-(4-methylpent-1-en-3-yl)formamide}} \)

\[
\begin{array}{c}
\text{HN} \\
\text{N} \\
\text{C} \text{H} \text{O} \\
\text{CH}_2 \text{CH} \\
\end{array}
\]

Prepared following general procedure A, using 4-methylpent-1-en-3-ol (0.263 g, 2.63 mmol) to give the desired product \( \text{\textit{N-(4-methylpent-1-en-3-yl)formamide}} \) (0.217 g, 1.71 mmol, 65%) as a clear oil. The material could be further purified by Kugelrohr distillation (oven at 170°C, 10 mbar).

\( \text{Rf} \) (hexane:EtOAc = 1:1): 0.30;

\( ^1\text{H NMR (CDCl}_3\text{, 400MHz, 293K) (1:0.42 mixture of rotamers):} \) \( \delta \) 8.29 (s, \( 1\text{H}_M \)), 8.05 (d, \( J = 11.7 \text{ Hz, 1H}_M \)), 5.89 – 5.74 (m, \( 1\text{H}_M+\text{m} \)), 5.65 (s br, \( 1\text{H}_M \)), 5.51 (s br, \( 1\text{H}_M \)), 5.27 – 5.16 (m, \( 2\text{H}_M+\text{m} \)), 4.51 – 4.44 (m, \( 1\text{H}_M \)), 3.82 – 3.75 (m, \( 1\text{H}_M \)) 1.93 – 1.79 (m, \( 1\text{H}_M+\text{m} \)) 0.99 – 0.91 (m, \( 6\text{H}_M+\text{m} \));

\( ^{13}\text{C NMR (CDCl}_3\text{, 101MHz, 293K) (1:0.42 mixture of rotamers):} \) \( \delta \) 164.5, 160.5, 137.2, 136.1, 116.4, 116.0, 59.9, 55.3, 32.5, 32.0, 18.9, 18.6, 18.0, 17.5;

\( \text{IR:} \) \( \nu \) 3271, 2963, 2875, 1665, 1535, 1468, 1386, 1235, 921;

\( \text{HRMS (ESI):} \) calcd for \( \text{C}_7\text{H}_{14}\text{NO}^+ \) (M+H)+ 128.1070 Found: 128.1068;

\( \text{5-isopropylpyrrolidin-2-one} \)

\[
\begin{array}{c}
\text{HN} \\
\text{N} \\
\text{C} \text{H} \text{O} \\
\text{CH}_2 \text{CH} \\
\end{array}
\]

Prepared following general procedure D using \( \text{\textit{N-(4-methylpent-1-en-3-yl)formamide}} \) (45 mg, 0.350 mmol) to give the desired product \( \text{\textit{5-isopropylpyrrolidin-2-one}} \) (39 mg, 0.305 mmol, 87%) as an off-white solid.
Rf (100% EtOAc, sat. NH4OH): 0.35;

$^1$H NMR (CDCl$_3$, 400MHz, 293K): $\delta$ 6.96 (s br, 1H), 3.39 (q, $J$ = 7.0 Hz, 1H), 2.38 – 2.12 (m, 3H), 1.83 – 1.70 (m, 1H), 1.73 – 1.54 (m, $J$ = 6.7 Hz, 1H), 0.96 (d, $J$ = 6.7 Hz, 3H), 0.91 (d, $J$ = 6.8 Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): $\delta$ 178.7, 60.6, 33.6, 30.6, 24.7, 18.8, 18.1;

IR: $\nu$ 3181, 3084, 2962, 2873, 1677, 1465, 1420, 1386, 1288, 1267, 1211, 1167, 1080;

HRMS (ESI): calcd for C$_7$H$_{14}$NO$^+$ (M+H)$^+$ 128.1070 Found: 128.1068;

$N$-(5-phenylpent-1-en-3-yl)formamide

Prepared following general procedure A, using 5-phenylpent-1-en-3-ol (0.427 g, 2.63 mmol) to give the desired product $N$-(5-phenylpent-1-en-3-yl)formamide (0.368 g, 1.95 mmol, 74%) as a clear oil.

Rf (hexane:EtOAc = 1:1): 0.32;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.37 mixture of rotamers): $\delta$ 8.25 (s, 1H$_M$), 8.05 (d, $J$ = 11.9 Hz, 1H$_m$), 7.36 – 7.17 (m, 5H$_{M+m}$), 5.92 – 5.78 (m, 1H$_{M+m}$) 5.57 (s br, 1H$_m$), 5.46 (s br, 1H$_M$), 5.28 – 5.17 (m, 2H$_{M+m}$), 4.70 – 4.59 (m, 1H$_M$), 3.99 – 3.88 (m, 1H$_m$), 2.84 – 2.61 (m, 2H$_{M+m}$) 2.05 – 1.78 (m, 2H$_{M+m}$);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.37 mixture of rotamers): $\delta$ 164.3, 160.4, 141.2, 140.4, 138.5, 137.5, 128.7, 128.5, 128.4, 126.3, 126.1, 115.9, 115.7, 53.6, 50.0, 36.8, 36.48, 36.46, 32.1, 31.7;

IR: $\nu$ 3283, 2926, 2860, 1664, 1536, 1384, 922;

HRMS (ESI): calcd for C$_{12}$H$_{16}$NO$^+$ (M+H)$^+$ 190.1226 Found: 190.1227;
**5-phenethylpyrrolidin-2-one**

Prepared following general procedure D using \(N\)-(5-phenylpent-1-en-3-yl)formamide (66 mg, 0.350 mmol) to give the desired product 5-phenethylpyrrolidin-2-one (54 mg, 0.284 mmol, 81%) as a pale-oil.

**Rf (100% EtOAc, sat. NH4OH):** 0.42;

\(^1\text{H NMR (CDCl}_3, 400MHz, 293K): \delta 7.35 – 7.17 (m, 5H), 5.96 (s br, 1H), 3.67 (p, J = 6.7 Hz, 1H), 2.69 (t, J = 7.8 Hz, 2H), 2.44 – 2.24 (m, 3H), 1.95 – 1.72 (m, 3H);**

\(^13\text{C NMR (CDCl}_3, 101MHz, 293K) (1:0.37 mixture of rotamers): \delta 178.0, 140.9, 128.6, 128.3, 126.3, 53.9, 38.4, 32.4, 30.0, 27.4;**

**IR:** \(\nu 3207, 2929, 2060, 1935, 1690, 1455, 1267;**

**HRMS (ESI):** calcd for C\(_{12}\)H\(_{16}\)NO\(^+\) (M+H\(^+\)) 190.1226 Found: 190.1229;

**methyl 4-(3-formamidopent-4-en-1-yl)benzoate**

Prepared following general procedure A, using methyl 4-(3-hydroxypent-4-en-1-yl)benzoate (0.579 g, 2.63 mmol) to give the desired product methyl 4-(3-formamidopent-4-en-1-yl)benzoate (0.397 g, 1.60 mmol, 61%) as a pale yellow oil.

**Rf (hexane:EtOAc = 1:2):** 0.36;

\(^1\text{H NMR (CDCl}_3, 400MHz, 293K) (1:0.37 mixture of rotamers): \delta 8.26 (s, 1H\text{M}), 8.07 – 7.95 (m, 2H\text{M+m} + 1H\text{m}), 7.31 – 7.24 (m, 2H\text{M+m}), 5.91 – 5.78 (m, 1H\text{M+m}), 5.67 (s br, 1H\text{m}), 5.54 (s br, 1H\text{M}), 5.33 – 5.17 (m, 2H\text{M+m}), 4.64 (dt, J = 13.8, 6.6 Hz, 1H\text{M}), 3.96 – 3.90 (m, 3H\text{M+m} + 1H\text{m}), 2.87 – 2.67 (m, 2H\text{M+m}), 2.06 – 1.80 (m, 2H\text{M+m});**
\(^{13}\)C NMR (CDCl\(_3\), 101MHz, 293K) (1:0.37 mixture of rotamers): \(\delta\) 167.0, 166.9, 164.2, 160.4, 146.7, 145.9, 138.3, 137.3, 130.0, 129.9, 128.4, 128.1, 116.2, 116.0, 53.6, 52.1, 52.0, 49.9, 49.8, 36.5, 36.1, 32.2, 31.8;

**IR:** \(\nu\) 3250, 3046, 2953, 2923, 2855, 1720, 1672, 1536, 1436, 1283, 1180, 1112;

**HRMS (ESI):** calcd for C\(_{14}\)H\(_{17}\)NNaO\(_3\)\(^{+}\) (M+Na\(^{+}\)) \(270.1101\) Found: 270.1105;

**methyl 4-(2-(5-oxypyrrolidin-2-yl)ethyl)benzoate**

Prepared following general procedure D using methyl 4-(3-formamidopent-4-en-1-yl)benzoate (87 mg, 0.350 mmol) to give the desired product methyl 4-(2-(5-oxypyrrolidin-2-yl)ethyl)benzoate (64 mg, 0.259 mmol, 74%) as a pale-oil.

**Rf** (100% EtOAc, sat. NH\(_4\)OH): 0.40;

\(^{1}\)H NMR (CDCl\(_3\), 400MHz, 293K): \(\delta\) 8.00 – 7.95 (m, 2H), 7.30 – 7.25 (m, 2H), 7.02 (s br, 1H), 3.92 (s, 3H), 3.67 (p, \(J = 6.6\) Hz, 1H), 2.81 – 2.68 (m, 2H), 2.44 – 2.23 (m, 3H), 1.96 – 1.70 (m, 3H);

\(^{13}\)C NMR (CDCl\(_3\), 101MHz, 293K): \(\delta\) 178.5, 167.0, 146.5, 129.9, 128.4, 128.2, 54.0, 52.0, 38.1, 32.3, 30.2, 27.2;

**IR:** \(\nu\) 3224, 2950, 1720, 1690, 1611, 1436, 1283, 1110;

**HRMS (ESI):** calcd for C\(_{14}\)H\(_{17}\)NNaO\(_3\)\(^{+}\) (M+Na\(^{+}\)) \(270.1101\) Found: 270.1100;
A flame-dried flask (25 mL) under argon was charged with Chloro(1,5-cyclooctadiene)-iridium(I) dimer (71 mg, 0.105 mmol, 0.015 eq.) and 5-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)-5H-dibenzo[b,f]azepine (86 mg, 0.210 mmol 0.03 eq.), the contents were suspended in DMF (14 mL) and stirred for 15 min at r.t.. The mixture was then treated with sulfamic acid (0.680 g, 7.00 mmol, 1.0 eq.) and 1-([1,1'-biphenyl]-4-yl)prop-2-en-1-ol (1.472 g, 7.00 mmol, 1.0 eq.), warmed to 60°C (oil bath) and stirred for 25min.

The mixture was then cooled to 0°C (ice bath) and treated with triethylamine (2.93 mL, 21.0 mmol, 3.0 eq.) and ethyl formate (11.4 mL, 140 mmol, 20.0 eq.). The mixture was warmed to 50°C and stirred for 48h.

The mixture was diluted with EtOAc (200 mL), washed with 1M HCl (2 x 100 mL) and brine (100 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 40°C. The residue was purified by flash column chromatography on silica gel, eluting with 50% – 66% EtOAc in hexanes to give the title compound \(N-1-([1,1'-biphenyl]-4-yl)allyl)formamide\) (0.582 g, 2.45 mmol, 35%) as a white amorphous solid.

**Rf** (hexane:EtOAc = 1:1): 0.24;

\(^1\)H NMR (CDCl₃, 400MHz, 293K) (1:0.24 mixture of rotamers): \(\delta 8.29\) (s, \(1H_M\)), \(8.21\) (d, \(J = 12.0\) Hz, \(1H_m\)), \(7.62 – 7.54\) (m, \(4H_{M+m}\)), \(7.49 – 7.41\) (m, \(2H_{M+m}\)), \(7.41 – 7.33\) (m, \(3H_{M+m}\)), \(6.16 – 5.99\) (m, \(1H_{M+m}\)), \(5.99 – 5.87\) (m, br, \(1H_{M+m}\)), \(5.78\) (dd, \(J = 8.0, 5.6\) Hz, \(1H_M\)), \(5.39 – 5.24\) (m, \(2H_{M+m}\)), \(5.18\) (dd, \(J = 7.9, 5.7\) Hz, \(1H_m\));

\(^1^3\)C NMR (CDCl₃, 101MHz, 293K) (1:0.24 mixture of rotamers): \(\delta 164.1, 160.1, 141.2, 140.9, 140.5, 140.3, 139.0, 138.6, 137.5, 136.6, 128.9, 128.8, 127.8, 127.6, 127.5, 127.3, 127.1, 117.1, 116.4, 58.0, 53.6;

**IR:** \(\nu 3274, 3029, 2862, 1660, 1525, 1487, 1383, 1229, 698\);
**5-((1,1′-biphenyl)-4-yl)pyrrolidin-2-one**

Prepared following general procedure D using \( N \)-(1-((1,1′-biphenyl)-4-yl)allyl)formamide (83 mg, 0.350 mmol) to give the desired product \( 5-((1,1′-biphenyl)-4-yl)pyrrolidin-2-one \) (64 mg, 0.270 mmol, 77%) as an off-white solid.

**\( R_f \) (hexane:EtOAc = 1:2):** 0.15;

\( ^1H \) NMR (CDCl\(_3\), 400MHz, 293K): \( \delta \) 7.65 – 7.52 (m, 4H), 7.51 – 7.29 (m, 5H), 6.00 (s, br, 1H), 4.81 (t, \( J = 7.1 \) Hz, 1H), 2.70 – 2.33 (m, 3H), 2.11 – 1.94 (m, 1H);

\( ^{13}C \) NMR (CDCl\(_3\), 101MHz, 293K): \( \delta \) 178.4, 141.4, 141.0, 140.5, 128.8, 127.7, 127.5, 127.1, 126.1, 57.8, 31.5, 30.3;

**IR:** \( \nu \) 3193, 3080, 2915, 1487, 1454, 1349, 1303, 1263, 768, 730, 697;

**HRMS (EI):** calcd for C\(_{16}\)H\(_{15}\)NO\(^+\) (M\(^+\)) 237.1149 Found: 237.1143;

\[ (S)-N-(1-(4-fluorophenyl)allyl)formamide \]

Prepared following a modified general procedure A, employing a two-fold amount of the chiral ligand derived from (S)-BINOL: \( 5-((11bS)-\text{dinaphtho}[2,1-d:1',2'-f][1,3,2]dioxaphosphepin-4-yl)-5H-dibenzo[b,f]azepine \) as follows:
Experimental Part

A flame-dried flask (25 mL) under argon was charged with Chloro(1,5-cyclooctadiene)-iridium(I) dimer (44 mg, 0.066 mmol, 0.025 eq.) and 5-((11bS)-dinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphospholin-4-yl)-5H-dibenzo[b,f]azepine (133 mg, 0.263 mmol 0.10 eq.), the contents were suspended in THF (8.8 mL), treated with DMF (1.0 mL, 13.1 mmol, 5.0 eq.) and stirred for 15 min at r.t.. The mixture was then treated with sulfamic acid (0.305 g, 3.15 mmol, 1.2 eq.) and the substrate allylic alcohol (2.63 mmol, 1.0 eq.) and stirred at r.t. for 16 h or until TLC-analysis showed complete consumption of the SM. The mixture was then cooled to 0°C (ice bath) and treated with sodium hydrogen carbonate (0.442 g, 5.26 mmol, 2.0 eq.).

In a separate dry flask, formic acid (1.0 mL, 26 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (1.0 mL, 10.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the allylic amine and the resulting mixture stirred at r.t. for 3h.

The mixture was diluted with EtOAc (100ml), washed with 1N HCl (2x50ml), brine (3x50ml), dried over Na2SO4, filtered and concentrated under reduced pressure at 40°C. The residue was purified by flash column chromatography on silica gel, eluting with 30 – 60% EtOAc in hexanes to give the desired product (S)-N-(1-(4-fluorophenyl)allyl)formamide (0.282, 1.57 mmol, 60%) as a pale yellow oil. The level of enantiopurity was determined by chiral analytical SFC chromatography by comparison to a racemic sample. The enantiomeric ratio was found to be 94:6.

Rf (hexane:EtOAc = 1:1): 0.28;

1H NMR (CDCl3, 400MHz, 293K) (1:0.20 mixture of rotamers): δ 8.29 (s, 1Hm), 8.19 (d, J = 11.9 Hz, 1Hm), 7.33 – 7.25 (m, 2Hm+Mm), 7.13 – 7.23 (m, 2Hm+Mm), 6.11 - 5.97 (m, 1Hm+Mm), 5.96 – 5.80 (s br, 1Hm+Mm), 5.77 – 5.69 (m, 1Hm), 5.41 – 5.22 (m, 2Hm+Mm), 5.17 – 5.11 (m, 1Hm);

13C NMR (CDCl3, 101MHz, 293K) (1:0.20 mixture of rotamers, peaks split by C-F coupling): δ 164.0, 163.5, 161.1, 160.0, 137.3, 136.4, 135.8, 135.8, 129.0, 128.9, 128.7, 128.6, 117.3, 116.6, 116.1, 115.9, 115.8, 115.6, 57.5, 53.1;

19F{1H} NMR (CDCl3, 376MHz, 293K) (1:0.20 mixture of rotamers): δ -113.70 (s, 1Fm), -114.34 (s, 1Fm);

IR: ν 3282, 1665, 1510, 1384, 1225, 930, 635;
**HRMS (ESI):** calcd for C_{10}H_{10}FNNaO^+ (M+Na)^+ 202.0639 Found: 202.0643

**SFC:** column: IC; eluent: CO_2/i-PrOH 90:10; flow: 2.5 mL/min; T = 25°C; release pressure: 100 bar; \( \lambda = 200 \) nm; \( t_R(\text{major}) = 8.33 \) min, \( t_R(\text{minor}) = 8.85 \) min; 94:6 er.

(S)-5-(4-fluorophenyl)pyrrolidin-2-one

![Chemical Structure](image)

Prepared following general procedure D using (S)-N-(1-(4-fluorophenyl)allyl)formamide (63 mg, 0.350 mmol) to give the desired product (S)-5-(4-fluorophenyl)pyrrolidin-2-one (48 mg, 0.268 mmol, 77%) as a colorless oil. The level of enantiopurity was determined by chiral analytical SFC chromatography by comparison to a racemic sample. The enantiomeric ratio was found to be 94:6, showing full retention of enantiopurity.

**Rf** (100% EtOAc, sat. NH_{4}OH): 0.62;

**\(^1\)H NMR (CDCl_3, 400MHz, 293K):** \( \delta \) 7.33 – 7.24 (m, 2H), 7.11 – 7.02 (m, 1H), 6.73 (s, 1H), 4.76 (t, \( J = 7.1 \) Hz, 1H), 2.65 – 2.34 (m, 3H), 2.00 – 1.89 (m, 1H);

**\(^13\)C NMR (CDCl_3, 101MHz, 293K):** \( \delta \) 178.6, 162.3 (d, \( J = 246.4 \) Hz), 138.3, 127.3 (d, \( J = 8.2 \) Hz), 115.8 (d, \( J = 21.6 \) Hz), 57.5, 31.4, 30.3;

**\(^{19}\)F{\(^1\)H} NMR (CDCl_3, 376MHz, 293K):** \( \delta \) -114.50 (s, 1F);

**IR:** \( \nu \) 3444, 3174, 3089, 2923, 1662, 1604, 1510, 1459, 1343, 1264, 1219, 1156, 1088, 1014, 832, 787;

**HRMS (ESI):** calcd for C_{10}H_{10}FN^+ (M+H)^+ 180.0819 Found: 180.0819;

**SFC:** column: OB-H; eluent: CO_2/MeOH 90:10; flow: 2.5 mL/min; T = 25°C; release pressure: 100 bar; \( \lambda = 200 \) nm; \( t_R(\text{major}) = 2.77 \) min, \( t_R(\text{minor}) = 3.34 \) min; 94:6 er (full conservation of enantioenrichment).
**N-(1-(4-(tert-butyl)phenyl)allyl)formamide**

Prepared following general procedure A, using 1-(4-(tert-butyl)phenyl)prop-2-en-1-ol (0.500 g, 2.63 mmol) to give the desired product N-(1-(4-(tert-butyl)phenyl)allyl)formamide (0.303 g, 1.39 mmol, 53%) as a pale yellow oil.

Rf (hexane:EtOAc = 1:1): 0.50;

**1H NMR (CDCl₃, 400MHz, 293K) (1:0.25 mixture of rotamers):** δ 8.29 (s, 1H), 8.20 (d, J = 12.0 Hz, 1H), 7.45 – 7.38 (m, 2H), 7.30 – 7.21 (m, 2H), 6.14 – 5.99 (m, 1H), 5.86 – 5.70 (m, 1H), 5.36 – 5.26 (m, 2H), 5.16 – 5.11 (m, 1H), 1.34 (s, 1H);

**13C NMR (CDCl₃, 101MHz, 293K) (1:0.25 mixture of rotamers):** δ 164.1, 160.0, 151.0, 137.7, 136.9, 136.7, 126.9, 126.6, 126.0, 125.8, 116.7, 115.9, 57.9, 53.5, 34.6, 31.3, 31.3;

**IR:** ν 3270, 2964, 2869, 1663, 1527, 1383;

**HRMS (ESI):** calcd for C₁₄H₂₀NO⁺ (M+H)⁺ 218.1539 Found: 218.1544;

**5-(4-(tert-butyl)phenyl)pyrrolidin-2-one**

Prepared following general procedure D using N-(1-(4-(tert-butyl)phenyl)allyl)formamide (76 mg, 0.350 mmol) to give the desired product 5-(4-(tert-butyl)phenyl)pyrrolidin-2-one (56 mg, 0.259 mmol, 74%) as a colorless solid.

Rf (100% EtOAc, sat. NH₄OH): 0.56;

**1H NMR (CDCl₃, 400MHz, 293K):** δ 7.48 – 7.34 (m, 2H), 7.33 – 7.20 (m, 3H), 5.90 (s br, 1H), 4.76 (t, J = 7.1 Hz, 1H), 2.72 – 2.31 (m, 3H), 2.02 (m, 1H), 1.34 (s, 9H);
**13C NMR (CDCl₃, 101MHz, 293K):** δ 178.2, 151.1, 139.3, 125.8, 125.4, 57.8, 34.6, 31.5, 31.3, 30.3;

**IR:** ν 3207, 3091, 2960, 1686, 1281, 1110;

**HRMS (ESI):** calcd for C₁₄H₂₀NO⁺ (M+H)⁺ 218.1539 Found: 218.1537;

\[N-(1-(2-methoxyphenyl)allyl)formamide\]

Prepared following general procedure A, using 1-(2-methoxyphenyl)prop-2-en-1-ol (0.432 g, 2.63 mmol) to give the desired product \(N-(1-(2-methoxyphenyl)allyl)formamide\) (0.246 g, 1.29 mmol, 49%) as a pale yellow oil.

**Rf** (hexane:EtOAc = 1:1): 0.25;

**1H NMR (CDCl₃, 400MHz, 293K) (1:0.33 mixture of rotamers):** δ 8.23 (s, 1Hₘ), 8.18 (d, J = 11.9 Hz, 1Hₘ), 7.35 – 7.16 (m, 2Hₘ+ₘ), 7.00 – 6.89 (m, 2Hₘ+ₘ), 6.68 (s br, 1Hₘ), 6.31 (s br, 1Hₘ), 5.90 – 5.84 (m, 1Hₘ), 5.37 – 5.31 (m, 1Hₘ), 5.29 – 5.26 (m, 1Hₘ), 5.35 – 5.26 (m, 1Hₘ), 5.19 – 5.15 (m, 1Hₘ), 5.15 – 5.12 (m, 1Hₘ) 3.87 (s, 3Hₘ), 3.86 (s, 3Hₘ);

**13C NMR (CDCl₃, 101MHz, 293K) (1:0.33 mixture of rotamers):** δ 164.2, 160.1, 157.1, 156.6, 137.6, 137.1, 129.5, 129.2, 129.1, 128.0, 127.9, 127.8, 121.0, 120.9, 115.7, 115.0, 111.2, 111.0, 55.5, 55.4, 54.4, 51.7;

**IR:** ν 3281, 3032, 2921, 2840, 1668, 1493, 1250, 1028, 755;

**HRMS (ESI):** calcd for C₁₁H₁₃N₃NaO₂⁺ (M+Na)⁺ 214.0838 Found: 214.0839;
**5-(2-methoxyphenyl)pyrrolidin-2-one**

![Structure](image)

Prepared following general procedure D using \(N\)-(1-(2-methoxyphenyl)allyl)formamide (67 mg, 0.350 mmol) to give the desired product 5-(2-methoxyphenyl)pyrrolidin-2-one (50 mg, 0.261 mmol, 75%) as a colorless solid.

**Rf** (100% EtOAc, sat. NH4OH): 0.31;

\(^1\)H NMR (CDCl\(_3\), 400MHz, 293K): \(\delta\) 7.33 – 7.26 (m, 2H), 7.02 – 6.89 (m, 2H), 6.13 (s br, 1H), 5.09 (dd, \(J = 7.8, 5.6\) Hz, 1H), 3.87 (s, 3H), 2.67 – 2.55 (m, 1H), 2.50 – 2.34 (m, 2H), 2.07 – 1.95 (m, 1H);

\(^13\)C NMR (CDCl\(_3\), 101MHz, 293K) (1:0.37 mixture of rotamers): \(\delta\) 178.7, 156.6, 130.3, 128.7, 125.3, 120.7, 110.5, 55.3, 52.5, 29.9, 28.7;

**IR:** \(\nu\) 3217, 3074, 2941, 1690, 1601, 1492, 1463, 1243, 1026, 755;

**HRMS (ESI):** calcd for C\(_{11}\)H\(_{14}\)NO\(_2\)\(^+\) (M+H\(^+\)) 192.1019 Found: 192.1017;

**N-(3-ethylpent-1-en-3-yl)-2-methylpropane-2-sulfinamide**

![Structure](image)

Prepared following general procedure B on larger scale, using 2-methyl-N-(pentan-3-ylidene)propane-2-sulfinamide (0.800 g, 4.23 mmol, 1.0 eq.) to give the desired product \(N\)-(3-ethylpent-1-en-3-yl)-2-methylpropane-2-sulfinamide (0.440 g, 2.02 mmol, 48%) as a pale yellow oil.

**Rf** (hexane:EtOAc = 1:1): 0.41;

\(^1\)H NMR (CDCl\(_3\), 400MHz, 293K): \(\delta\) 5.76 (dd, \(J = 17.5, 10.9\) Hz, 1H), 5.26 – 5.11 (m, 2H), 3.25 (s br, 1H), 1.91 – 1.54 (m, 4H), 1.25 (s, 9H), 0.88 (td, \(J = 7.4, 3.0\) Hz, 6H);
**13C NMR (CDCl₃, 101MHz, 293K):** δ 143.1, 114.6, 62.2, 56.0, 31.6, 30.0, 22.8, 7.7, 7.6;

**IR:** v 3177, 2965, 2939, 1638, 1458, 1166, 1048, 915;

**HRMS (ESI):** calcd for C₁₁H₂₄NOS⁺ (M+H)⁺ 218.1573 Found: 218.1576;

*N-(3-ethylpent-1-en-3-yl)formamide*

![N-(3-ethylpent-1-en-3-yl)formamide](image)

Prepared following general procedure C, using *N-(3-ethylpent-1-en-3-yl)-2-methylpropane-2-sulfinamide* (0.326 g, 1.50 mmol) to give the desired product *N-(3-ethylpent-1-en-3-yl)formamide* (0.210 g, 1.49 mmol, 99%) as a pale yellow oil.

**Rf** (hexane:EtOAc = 2:1): 0.37;

**1H NMR (CDCl₃, 400MHz, 293K) (1:0.6 mixture of rotamers):** δ 8.21 – 8.13 (m, 1H), 5.83 – 5.63 (m, 2H), 5.33 – 5.03 (m, 2H), 2.10 – 1.59 (m, 4H), 0.90 (t, *J* = 7.4 Hz, 3Hm), 0.84 (t, *J* = 7.5 Hz, 3Hm);

**13C NMR (CDCl₃, 101MHz, 293K) (1:0.6 mixture of rotamers):** δ 164.2, 160.2, 141.5, 141.3, 115.3, 113.2, 61.3, 59.6, 31.2, 29.2, 7.7, 7.4;

**IR:** v 3294, 2971, 2938, 2881, 1686, 1525, 1461, 1389, 1308;

**HRMS (ESI):** calcd for C₈H₁₆NO⁺ (M+H)⁺ 142.1226 Found: 142.1223;

**5,5-diethylpyrrolidin-2-one**

![5,5-diethylpyrrolidin-2-one](image)

Prepared following general procedure D using *N-(3-ethylpent-1-en-3-yl)formamide* (49 mg, 0.350 mmol) to give the desired product 5,5-diethylpyrrolidin-2-one (44 mg, 0.315 mmol, 90%) as a colorless oil.
**Experimental Part**

**Rf** (100% EtOAc, sat. NH4OH): 0.40;

**1H NMR** (CDCl$_3$, 400MHz, 293K): $\delta$ 5.88 (s br, 1H), 2.39 (dd, $J$ = 8.8, 7.6 Hz, 2H), 1.91 (dd, $J$ = 8.8, 7.6 Hz, 2H), 1.57 (qd, $J$ = 7.4, 1.3 Hz, 4H), 0.91 (t, $J$ = 7.5 Hz, 6H);

**13C NMR** (CDCl$_3$, 101MHz, 293K): $\delta$ 177.3, 62.2, 32.0, 30.5, 30.3, 8.1;

**IR:** $\nu$ 2968, 2938, 1692, 1463, 1383;

**HRMS (ESI):** calcd for C$_8$H$_{16}$NO$^+$ (M+H)$^+$ 142.1226 Found: 142.1225;

**2-methyl-N-(1-vinylcyclohexyl)propane-2-sulfinamide**

![Chemical Structure](image)

Prepared following general procedure B on larger scale, using N-cyclohexylidene-2-methylpropane-2-sulfinamide (0.850 g, 4.22 mmol, 1.0 eq.) to give the desired product 2-methyl-N-(1-vinylcyclohexyl)propane-2-sulfinamide (0.558 g, 2.43 mmol, 58%) as a pale yellow oil.

**Rf** (hexane:EtOAc = 1:1): 0.35;

**1H NMR** (CDCl$_3$, 400MHz, 293K): $\delta$ 5.92 (dd, $J$ = 17.6, 10.8 Hz, 1H), 5.31 – 5.14 (m, 2H), 3.18 (s br, 1H), 1.91 – 1.34 (m, 10H), 1.22 (s, 9H);

**13C NMR** (CDCl$_3$, 101MHz, 293K): $\delta$ 144.3, 114.2, 58.0, 55.7, 37.4, 36.2, 25.6, 22.7, 22.0, 22.0;

**IR:** $\nu$ 3210, 2932, 2860, 1456, 1052;

**HRMS (ESI):** calcd for C$_{12}$H$_{23}$NNaOS$^+$ (M+Na)$^+$ 252.1393 Found: 252.1392;
**N-(1-vinylcyclohexyl)formamide**

Prepared following general procedure C, using 2-methyl-N-(1-vinylcyclohexyl)propane-2-sulfinamide (0.350 g, 1.53 mmol) to give the desired product N-(1-vinylcyclohexyl)formamide (0.140 g, 0.914 mmol, 60%) as a colorless oil.

**Rf** (hexane:EtOAc = 1:1): 0.40;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.5 mixture of rotamers):  $\delta$ 8.21 – 8.15 (m, 1H), 6.01 (dd, $J = 17.5$, 10.7 Hz, 1H$_m$), 5.91 (dd, $J = 17.4$, 10.7 Hz, 1H$_m$), 5.76 (s, 1H), 5.30 – 5.05 (m, 2H), 2.25 – 1.10 (m, 10H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.5 mixture of rotamers):  $\delta$ 164.4, 160.2, 144.0, 142.6, 114.1, 112.6, 57.1, 55.7, 36.9, 35.1, 25.3, 25.1, 21.7, 21.3;

**IR:** ν 3280, 2932, 2857, 1682, 1536, 1450, 1391;

**HRMS (ESI):** calcd for C$_9$H$_{16}$NO$^+$ (M+H)$^+$ 154.1226 Found: 154.1227;

**1-azaspiro[4.5]decan-2-one**

Prepared following general procedure D using N-(1-vinylcyclohexyl)formamide (54 mg, 0.350 mmol) to give the desired product 5,5-diethylpyrrolidin-2-one (47 mg, 0.303 mmol, 87%) as a colorless oil.

**Rf** (100% EtOAc, sat. NH$_4$OH): 0.45;

$^1$H NMR (CDCl$_3$, 400MHz, 293K):  $\delta$ 6.17 (s, 1H), 2.40 (t, $J = 8.0$ Hz, 2H), 1.93 (t, $J = 8.1$ Hz, 2H), 1.82 – 1.19 (m, 10H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K):  $\delta$ 177.0, 59.1, 38.3, 32.7, 29.8, 25.1, 23.1;
Experimental Part

IR: $\nu$ 3204, 3075, 2928, 2855, 1689, 1453, 1377, 1343;

HRMS (ESI): calcd for $\text{C}_9\text{H}_{16}\text{NO}^+ (M+H)^+$ 154.1226 Found: 154.1225;

2-methyl-N-(1-vinylcycloheptyl)propane-2-sulfinamide

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{t-Bu}
\end{array}
\]

Prepared following general procedure B, using N-cycloheptylidene-2-methylpropane-2-sulfinamide (0.431 g, 2.00 mmol) to give the desired product 2-methyl-N-(1-vinylcycloheptyl)propane-2-sulfinamide (0.097 g, 0.399 mmol, 20%) as a pale yellow oil.

$R_f$ (hexane:EtOAc = 1:1): 0.39;

$^1\text{H} \text{NMR (CDCl}_3, 400\text{MHz, 293K}):$ $\delta$ 5.94 (dd, $J = 17.5$, 10.8 Hz, 1H), 5.26 – 5.08 (m, 2H), 3.13 (s br, 1H), 1.99 – 1.74 (m, 5H), 1.70 – 1.38 (m, 7H), 1.21 (s, 9H);

$^{13}\text{C} \text{NMR (CDCl}_3, 101\text{MHz, 293K}):$ $\delta$ 145.1, 113.0, 62.1, 55.7, 40.1, 39.1, 29.9, 29.8, 22.6, 22.1, 22.0;

IR: $\nu$ 3490, 3168, 2924, 2856, 1638, 1461, 1363, 1185, 1028, 913;

HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{26}\text{NOS}^+ (M+H)^+$ 244.1730 Found: 244.1730;

$N$-(1-vinylcycloheptyl)formamide

\[
\begin{array}{c}
\text{HN} \\
\text{N}
\end{array}
\]

Prepared following general procedure C, on smaller scale, using 2-methyl-$N$-(1-vinylcycloheptyl)propane-2-sulfinamide (0.090 g, 0.370 mmol, 1.0 eq.) to give the desired product $N$-(1-vinylcycloheptyl)formamide (0.052 g, 0.311 mmol, 84%) as a colorless oil.

$R_f$ (hexane:EtOAc = 1:1): 0.30;
$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.5 mixture of rotamers): δ 8.19 – 8.13 (m, 1H), 6.04 (dd, J = 17.4, 10.7 Hz, 1H$_m$), 6.04 (dd, J = 17.4, 10.7 Hz, 1H$_M$), 5.87 (s br, 1H$_M$), 5.35 (s br, 1H$_m$), 2.10 – 1.49 (m, 12H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.5 mixture of rotamers): δ 164.5, 160.2, 144.3, 143.0, 113.1, 111.6, 60.7, 59.5, 40.3, 40.3, 38.6, 29.2, 22.2, 21.9;

IR: ν 3291, 2927, 2860, 1686, 1528, 1461, 1317;

HRMS (ESI): calcd for C$_{10}$H$_{18}$NO$^+$ (M+H)$^+$ 168.1383 Found: 168.1382;

1-azaspiro[4.6]undecan-2-one

Prepared following general procedure D, on smaller scale, using $N$-(1-vinylcycloheptyl)formamide (45 mg, 0.269 mmol, 1.0 eq.) to give the desired product 1-azaspiro[4.6]undecan-2-one (32 mg, 0.191 mmol, 70%) as a colorless oil.

Rf (100% EtOAc, sat. NH$_4$OH): 0.45;

$^1$H NMR (CDCl$_3$, 400MHz, 293K): δ 6.23 (s, 1H), 2.39 (t, J = 7.9 Hz, 2H), 1.94 (t, J = 7.9 Hz, 2H), 1.81 – 1.69 (m, 4H), 1.67 – 1.47 (m, 8H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): δ 176.9, 62.5, 41.3, 34.6, 29.8, 28.9, 22.7;

IR: ν 3171, 3085, 2920, 2855, 1687, 1652, 1459, 1352, 1285, 1217;

HRMS (ESI): calcd for C$_{10}$H$_{18}$NO$^+$ (M+H)$^+$ 168.1383 Found: 168.1385;
**N-(adamantan-2-ylidene)-2-methylpropane-2-sulfinamide**

![Chemical Structure](image)

A dry flask (50mL) equipped with a reflux condenser under argon was charged with 2-methylpropane-2-sulfinamide (0.258 g, 2.130 mmol) and adamantan-2-one (0.320 g, 2.13 mmol). The contents were dissolved in THF (7.10 mL) and finally treated with Titanium(IV)ethoxide (0.892 mL, 4.26 mmol) at r.t. The mixture was then heated to reflux for 48h. The reaction mixture was then poured into rapidly stirring sat. NaHCO₃ (10 mL), rinsing with EtOAc (10 mL), stirred for 10min and filtered through a pad of celite. The mixture was extracted with EtOAc (2 x 20 ml), the combined organic layers were washed with water (10 ml) and brine (10ml), dried over Na₂SO₄ and concentrated at 40°C under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 15 – 25% EtOAc in hexanes to give the desired product N-(adamantan-2-ylidene)-2-methylpropane-2-sulfinamide (0.535 g, 2.11 mmol, 99%) as a pale yellow oil that contained residual starting material but was used without further purification in the next step.

**Rf** (hexane:EtOAc = 3:1): 0.38;

**¹H NMR (CDCl₃, 400MHz, 293K):** δ 3.77 – 3.63 (m, 1H), 2.76 – 2.54 (m, 1H), 2.16 – 1.85 (m, 12H), 1.26 (s, 9H);

**¹³C NMR (CDCl₃, 101MHz, 293K):** δ 195.5, 55.7, 44.5, 39.6, 39.5, 39.2, 38.7, 38.3, 36.3, 27.3, 27.3, 22.1;

**IR:** ν 2909, 2854, 1720, 1612, 1453, 1059;

**HRMS (ESI):** calcd for C₁₄H₂₄NOS⁺ (M+H)⁺ 254.1573 Found: 254.1575;
2-methyl-\(N\)-(2-vinyladamantan-2-yl)propane-2-sulfinamide

Prepared following general procedure B, on smaller scale, using \(N\)-(adamantan-2-ylidene)-2-methylpropane-2-sulfinamide (0.300 g, 1.184 mmol, 1.0 eq.) to give the desired product 2-methyl-\(N\)-(2-vinyladamantan-2-yl)propane-2-sulfinamide (0.275 g, 0.977 mmol, 83%) as a white solid.

\[ \text{Rf (hexane:EtOAc} = 2:1) : 0.20; \]

\( ^1\text{H NMR (CDCl}_3, 400 MHz, 293K) : \delta 5.88 \text{ (dd,} J = 17.9, 11.0 \text{ Hz,} 1\text{H),} 5.40 – 5.22 \text{ (m,} 2\text{H),} 3.45 \text{ (s br,} 1\text{H),} 2.27 \text{ (dd,} J = 13.2, 3.1 \text{ Hz,} 1\text{H),} 2.16 – 1.96 \text{ (m,} 5\text{H),} 1.93 – 1.81 \text{ (m,} 2\text{H),} 1.77 – 1.60 \text{ (m,} 6\text{H),} 1.23 \text{ (s,} 9\text{H);} \]

\( ^13\text{C NMR (CDCl}_3, 101 MHz, 293K) : \delta 143.9, 115.5, 61.8, 56.0, 38.2, 36.3, 35.0, 34.0, 32.2, 32.2, 27.5, 27.4, 27.4, 22.9; \]

\( \text{IR:} \nu 3395, 2911, 1522, 1468, 1201, 1029; \]

\( \text{HRMS (ESI):} \text{ calcd for C}_{16}\text{H}_{28}\text{NOS}^+ (\text{M+H})^+ 282.1886 \text{ Found: 282.1891;} \)

\( N\)-(2-vinyladamantan-2-yl)formamide

Prepared following general procedure C, on smaller scale, using 2-methyl-\(N\)-(2-vinyladamantan-2-yl)propane-2-sulfinamide (0.275 g, 0.977 mmol, 1.0 eq.) to give the desired product \(N\)-(2-vinyladamantan-2-yl)formamide (0.187 g, 0.911 mmol, 91%) as a white solid.

\[ \text{Rf (hexane:EtOAc} = 1:1) : 0.23; \]
Experimental Part

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.71 mixture of rotamers): $\delta$ 8.19 (d, $J = 12.4$ Hz, 1H$_M$), 8.13 (d, $J = 1.9$ Hz, 1H$_m$), 6.28 (dd, $J = 17.6$, 10.8 Hz, 1H$_m$), 6.15 (dd, $J = 17.6$, 10.9 Hz, 1H$_M$), 5.84 (s br, 1H$_M$), 5.39 (s br, 1H$_m$), 5.36 – 5.21 (m, 2H$_{M+m}$) 2.40 – 1.61 (m, 14H$_{M+m}$);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.71 mixture of rotamers): $\delta$ 164.4, 159.7, 143.0, 141.3, 115.7, 114.2, 60.8, 59.3, 38.0, 36.4, 34.5, 33.3, 33.1, 32.8, 32.2, 27.3, 27.1, 26.8, 26.7;

IR: $\nu$ 3280, 2908, 2860, 1683, 1525, 1456, 1389;

HRMS (ESI): calcd for C$_{13}$H$_{20}$NO$^+$ (M+H)$^+$ 206.1539 Found: 206.1537;

**spiro[adamantane-2,2'-pyrrolidin]-5'-one**

Prepared following general procedure D, using N-(2-vinyladamantan-2-yl)formamide (72 mg, 0.350 mmol) to give the desired product spiro[adamantane-2,2'-pyrrolidin]-5'-one (62 mg, 0.304 mmol, 87%) as a white solid.

RF (100% EtOAc, sat. NH$_4$OH): 0.55;

$^1$H NMR (CDCl$_3$, 400MHz, 293K): $\delta$ 6.56 (s br, 1H), 2.40 (t, $J = 8.1$ Hz, 2H), 2.08 (t, $J = 8.0$ Hz, 2H), 1.97 – 1.65 (m, 14H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): $\delta$ 176.9, 63.7, 37.7, 37.6, 34.1, 33.9, 31.7, 30.0, 26.7, 26.5;

IR: $\nu$ 3206, 2905, 1665, 1389;

HRMS (ESI): calcd for C$_{13}$H$_{20}$NO$^+$ (M+H)$^+$ 206.1539 Found: 206.1543;
A dry flask (25 mL) equipped with a reflux condenser under argon was charged with (S)-2-methylpropane-2-sulfinamide (0.492 g, 4.06 mmol) and (2S,5R)-2-isopropyl-5-methylcyclohexanone (0.700 ml, 4.06 mmol). The contents were dissolved in THF (10 mL) and finally treated with Titanium(IV)ethoxide (1.70 mL, 8.12 mmol) at r.t.. The mixture was then heated to reflux for 48h. The reaction mixture was then poured into rapidly stirring sat. NaHCO₃ (10 mL), rinsing with EtOAc (10 mL), stirred for 10min and filtered through a pad of celite. The mixture was extracted with EtOAc (2 x 20 ml), the combined organic layers were washed with water (10 ml) and brine (10ml), dried over Na₂SO₄ and concentrated at 40°C under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with 12 – 17% EtOAc in hexanes to give the desired product (S)-N-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-2-methylpropane-2-sulfinamide (0.616 g, 2.39 mmol, 59%) as a colorless oil.

**Rf** (hexane:EtOAc = 5:1): 0.40;

**¹H NMR (CDCl₃, 400MHz, 293K)**: δ 3.40 (ddd, J = 13.6, 3.9, 1.8 Hz, 1H), 2.34 (pd, J = 7.0, 4.7 Hz, 1H), 2.18 – 1.59 (m, 5H), 1.47 – 1.18 (m, 2H), 1.26 (s, 9H), 1.03 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 6.8 Hz, 3H);

**¹³C NMR (CDCl₃, 101MHz, 293K)**: δ 190.2, 55.8, 54.5, 42.9, 35.1, 33.7, 27.8, 26.3, 22.3, 22.2, 22.0, 21.6, 18.4;

**IR**: ν 2958, 2929, 1707, 1613, 1414, 1163, 1093, 1038, 909;

**HRMS (ESI)**: calcd for C₁₄H₂₉NOS⁺ (M+H)⁺ 258.1886 Found: 258.1885;
(S)-N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)-2-methylpropane-2-sulfinamide

A solution of vinylmagnesium bromide (4.3 mL, 1.0 M solution in THF, 4.30 mmol, 2.0 eq.) was treated dropwise with a solution of dimethylzinc (4.3 mL, 2.0 M solution in Toluene, 4.0 eq.) at room temperature and the resulting solution allowed to stir for 20 min. The mixture was then cooled to -78°C (dry-ice/acetone bath) and treated dropwise with a solution of (S)-N-((2S,5R)-2-isopropyl-5-methylcyclohexylidene)-2-methylpropane-2-sulfinamide (0.554 g, 2.15 mmol, 1.0 eq.) in THF (7.2 mL). The resulting mixture was allowed to slowly warm to room temperature overnight. The mixture was then cooled to 0°C, diluted with Et₂O (20 mL) and treated with sat. aq. NH₄Cl (5 mL). The mixture was extracted with Et₂O (3x 50mL) and the combined organic layers washed with sat. aq. NaHCO₃ (30 mL), water (30 mL) and brine (30 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure at 40°C. The residue was purified by flash column chromatography on silica gel, eluting with 12 – 17% EtOAc in hexanes to give the desired product (S)-N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)-2-methylpropane-2-sulfinamide (0.335 g, 1.17 mmol, 55%) as a pale yellow oil.

Rf (Hexanes/EtOAc 5:1): 0.42;

¹H NMR (CDCl₃, 400MHz, 293K): δ 6.01 (dd, J = 17.4, 11.0 Hz, 1H), 5.47 (dd, J = 17.4, 0.7 Hz, 1H), 5.15 (dd, J = 10.9, 0.7 Hz, 1H), 3.42 (s br, 1H), 2.21 (ddd, J = 14.7, 3.3, 2.3 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.87 – 1.68 (m, 2H), 1.57 – 1.36 (m, 2H), 1.30 (s, 9H), 1.33 – 1.14 (m, 2H), 1.05 – 0.86 (m, 10H);

¹³C NMR (CDCl₃, 101MHz, 293K): δ 146.5, 114.0, 64.6, 56.6, 51.5, 44.0, 35.3, 27.4, 26.0, 24.8, 23.2, 22.2, 21.5, 19.1;

IR: ν 2954, 1457, 1380, 1073;

HRMS (ESI): calcd for C₁₆H₃₂NOS⁺ (M+H)⁺ 286.2199 Found: 286.2200;
**N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)formamide**

![Chemical structure of N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)formamide]

Prepared following general procedure C, on smaller scale, using (S)-N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)-2-methylpropane-2-sulfinamide (0.327 g, 1.15 mmol, 1.0 eq.) to give the desired product N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)formamide (0.186 g, 0.889 mmol, 78%) as a white solid.

**Rf** (Hexanes/EtOAc 3:1): 0.25;

**1H NMR (CDCl₃, 400MHz, 293K) (1:0.37 mixture of rotamers):** δ 8.28 (d, J = 1.9 Hz, 1Hₘ), 8.18 (d, J = 12.3 Hz, 1Hₘ), 5.91 (dd, J = 17.3, 10.9 Hz, 1Hₘ), 5.84 (dd, J = 17.4, 10.8 Hz, 1Hₘ), 5.70 (s br, 1Hₘ), 5.36 (s br, 1Hₘ), 5.26 – 5.06 (m, 2Hₘ+ₙ), 2.77 (dt, J = 13.6, 2.9 Hz, 1Hₘ), 2.16 – 1.92 (m, 1Hₘ+ₙ), 1.90 – 1.49 (m, 3Hₘ+ₙ + 1Hₘ), 1.41 – 1.19 (m, 3H), 1.11 – 0.81 (m, 10H);

**13C NMR (CDCl₃, 101MHz, 293K) (1:0.37 mixture of rotamers):** δ 164.7, 160.3, 144.2, 141.8, 114.2, 112.9, 62.9, 60.9, 50.4, 50.0, 47.2, 42.9, 34.8, 34.7, 27.5, 27.2, 26.1, 26.0, 24.6, 24.5, 22.0, 22.0, 21.5, 21.4, 18.7, 18.5;

**IR:** ν 3342, 2953, 2926, 2873, 1686, 1516, 1458, 1389, 1292;

**HRMS (ESI):** calcd for C₁₃H₂₄NO⁺ (M+H)⁺ 210.1852 Found: 210.1850;


![Chemical structure of (5S,6S,9R)-6-isopropyl-9-methyl-1-azaspiro[4.5]decan-2-one]

Prepared following general procedure D, using N-((1R,2S,5R)-2-isopropyl-5-methyl-1-vinylcyclohexyl)formamide (73 mg, 0.350 mmol) to give the desired product (5S,6S,9R)-6-isopropyl-9-methyl-1-azaspiro[4.5]decan-2-one (58 mg, 0.277 mmol, 79%) as a white solid.

**Rf** (100% EtOAc, sat. NH₄OH): 0.43;
A dry 100 mL flask under argon was charged with 2-methylpropane-2-sulfinamide (3.19 g, 26.3 mmol, 1.1 eq.) which was dissolved in THF (50 ml) and treated dropwise at room temperature with 4-(tert-butyl)benzaldehyde (4.00 mL, 23.9 mmol, 1.0 eq.) and Titanium(IV)ethoxide (10.0 mL, 47.8 mmol, 2.0 eq.). The pale yellow mixture was then stirred at r.t. for 6h. The reaction mixture was quenched with brine (40ml) and stirred for 20min then filtered through a pad of celite, washing with EtOAc (200 mL). The organic layer was washed with brine (20 mL), dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 10 – 20% EtOAc in Hexanes to give the title compound \(\text{N-(4-(tert-butyl)benzylidene)-2-methylpropane-2-sulfinamide}\) (5.81 g, 21.9 mmol, 92%) as a white amorphous solid.

\(\text{Rf (Hexanes/EtOAc 2:1): 0.65;}\)

\(^1\)H NMR (CDCl$_3$, 400MHz, 293K): \(\delta\) 8.59 (s, 1H), 7.82 (d, \(J = 8.4\) Hz, 2H), 7.52 (d, \(J = 8.4\) Hz, 2H), 1.37 (s, 9H), 1.28 (s, 9H);

\(^{13}\)C NMR (CDCl$_3$, 101MHz, 293K): \(\delta\) 162.4, 156.2, 131.6, 129.3, 125.9, 57.7, 35.2, 31.1, 22.6;

IR: \(\nu\) 2956, 1594, 1561, 1362, 1293, 1259, 1073, 833;
**Experimental Part**

**HRMS (ESI):** calcd for C₁₃H₂₄NOS⁺ (M+H)⁺ 266.1573 Found: 266.1576;

**N-(1-(4-(tert-butyl)phenyl)but-3-en-1-yl)formamide**

A solution of N-(4-(tert-butyl)benzylidene)-2-methylpropane-2-sulfinamide (0.500 g, 1.88 mmol, 1.0 eq.) in THF (6.3 mL) was cooled to -78°C (dry ice/acetone bath) and treated dropwise with a solution of allylmagnesium bromide (1.0 M in Et₂O) (3.77 mL, 3.77 mmol, 2.0 eq.). The thick mixture was allowed to warm up to 0°C over 30 min and then quenched by careful addition of sat. aq. NH₄Cl solution (5 mL). The resulting mixture was extracted with EtOAc (80 mL) and the organic layer washed sequentially with sat. aq. NH₄Cl, water and brine (20 mL each), dried over Na₂SO₄ and concentrated to give the addition product as an inconsequential mixture of diastereomers (ratio 2:3 - unassigned).

The crude mixture was taken up in MeOH (12.6 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (2.36 mL, 9.42 mmol, 5.0 eq.). The resulting mixture was stirred for 10 min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (12.6 mL), treated with sodium bicarbonate (0.396 g, 4.71 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.72 mL, 19 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.72 mL, 7.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12 h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 33-50% EtOAc in hexanes to give the title compound N-(1-(4-(tert-butyl)phenyl)but-3-en-1-yl)formamide (0.403 g, 1.74 mmol, 92%) as a clear oil.
Rf (Hexanes/EtOAc 1:1): 0.44;

\(^1\)H NMR (CDCl\(_3\), 400MHz, 293K) (1:0.26 mixture of rotamers): \(\delta\) 8.20 (s, 1H\(_M\)), 8.10 (d, \(J = 12.0\) Hz 1H\(_m\)), 7.42 – 7.32 (m, 2H\(_M+m\)), 7.25 – 7.15 (m, 2H\(_M+m\)), 6.00 – 5.62 (m, 2H\(_M+m\)), 5.25 – 5.04 (m, 3H\(_M + 2H_m\)), 4.57 (td, \(J = 8.2, 5.2\) Hz 1H\(_m\)) 2.68 – 2.46 (m, 2H\(_M+m\)), 1.32 (s, 9H\(_m\)), 1.31 (s, 9H\(_M\));

\(^13\)C NMR (CDCl\(_3\), 101MHz, 293K) (1:0.26 mixture of rotamers): \(\delta\) 164.2, 160.3, 150.9, 150.5, 138.2, 137.9, 133.9, 133.1, 126.1, 125.8, 125.8, 125.6, 119.5, 118.4, 55.2, 50.9, 41.6, 40.3, 34.6, 34.5, 31.3, 31.3;

IR: \(\nu\) 3271, 2963, 2867, 1658, 1532, 1382, 918;

HRMS (ESI): calcd for C\(_{15}\)H\(_{22}\)NO\(^+\) (M+H\(^+\)) 232.1696 Found: 232.1700;

\(N\)-(1-(4-(tert-butyl)phenyl)but-2-y1)formamide

n-Butyllithium (1.6M in hexanes) (4.12 mL, 6.59 mmol, 2.5 eq.) was added dropwise to a cooled (-78°C, dry ice/acetone bath) solution of 1-bromoprop-1-ene (mixture of cis and trans isomers) (0.292 mL, 3.43 mmol, 1.3 eq.) in THF (3.5 mL). The mixture was stirred for 2h at -78°C and then treated with a solution of \(N\)-(1-(4-(tert-butyl)phenyl)but-2-y1)-2-methylpropane-2-sulfinamide in THF (1.8 mL). The resulting mixture was allowed to slowly warm up to room temperature over 2h. The mixture was quenched by the addition of sat. aq. NH\(_4\)Cl (50 mL), extracted with EtOAc (3x 70 mL), the combined organic extracts dried over Na\(_2\)SO\(_4\) and concentrated to give the crude addition product as an inconsequential mixture of diastereomers (ratio 7:1 - unassigned).

The crude mixture was taken up in MeOH (17.6 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (3.30 mL, 13.0 mmol, 5.0 eq.). The resulting mixture was stirred for 10min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (17.6 mL), treated with sodium bicarbonate (0.554 g, 6.60 mmol, 2.5 eq.) and cooled to 0°C.
In a separate flask, formic acid (1.01 mL, 26 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (1.00 mL, 10.6 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5 x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 20-33% EtOAc in hexanes to give the title compound \( N\)-(1-(4-(tert-butyl)phenyl)but-2-yn-1-yl)formamide (0.530 g, 2.31 mmol, 88%) as a clear oil.

\( R_f \) (Hexanes/EtOAc 1:1): 0.56;

\(^1\)H NMR (CDCl₃, 400MHz, 293K) (1:0.15 mixture of rotamers): \( \delta \) 8.31 (d, \( J = 11.9 \) Hz, 1H\(_m\)), 8.18 (s, 1H\( _M\)), 7.46 – 7.35 (m, 4H\(_{M+m}\)), 6.00 (s, br, 1H\( _M\)), 5.89 (s, br, 1H\( _m\)), 5.33 (dq, \( J = 7.7, 2.1 \) Hz, 1H\( _m\)), 5.29 (s, 1H\( _M\)), 1.92 – 1.86 (m, 3H\(_{M+m}\)), 1.32 (s, 9H\( _m\)), 1.31 (s, 9H\( _M\));

\(^{13}\)C NMR (CDCl₃, 101MHz, 293K) (1:0.15 mixture of rotamers): \( \delta \) 163.6, 159.6, 151.6, 151.2, 135.9, 135.6, 126.7, 126.4, 125.8, 125.6, 83.2, 81.0, 77.2, 76.7, 76.2, 53.4, 47.8, 43.2, 34.5, 31.3, 3.6;

\( \text{IR: } \nu \) 3272, 2962, 2867, 1654, 1510, 1380, 1269, 1016;

\( \text{HRMS (ESI): } \text{calcd for C}_{15}\text{H}_{19}\text{NNaO}^+ (M+Na)^+ 252.1359 \text{ Found: 252.1359}; \)

\((Z)-N\)-(1-(4-(tert-butyl)phenyl)but-2-en-1-yl)formamide

\[ \text{A solution of } N\)-(1-(4-(tert-butyl)phenyl)but-2-yn-1-yl)formamide (0.415 g, 1.810 mmol, 1.0eq.) \text{ in Et}_2\text{O (18.1 mL) at 0°C (ice bath) was treated with freshly distilled quinoline (7.7 mg, 0.060 mmol, 0.033 eq.) and Lindlar’s catalyst (Pb poisoned) (0.146 g, 0.069 mmol, 0.038 eq.). The solution was purged with hydrogen (balloon) for 5 min and then stirred under} \]
Experimental Part

hydrogen atmosphere for 30 min at 0°C. The resulting mixture was purged with argon, filtered through a pad of celite under air and concentrated. The residue was purified by flash chromatography on silica gel eluting with 33-50% EtOAc in hexanes to give the title compound \((Z)-N-(1-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{but-2-en-1-yl})\text{formamide}\) (0.419 g, 1.81 mmol, quant.) as a clear oil.

**Rf** (Hexanes/EtOAc 1:1): 0.46;

\( ^1\text{H NMR (CDCl}_3, 400\text{MHz, 293K (1:0.20 mixture of rotamers):} \delta 8.23 \ (s, 1\text{H}_M), 8.20 \ (d, J = 12.2 \text{ Hz, 1H}_m), 7.41 - 7.33 \ (m, 2\text{H}_{M+m}), 7.28 - 7.20 \ (m, 2\text{H}_{M+m}), 5.98 \ (t, \text{br, } J = 8.5 \text{ Hz, 1H}_M), 5.90 - 5.79 \ (s, \text{br, } 1\text{H}_{M+m}), 5.79 - 5.68 \ (m, 1\text{H}_{M+m}), 5.62 - 5.51 \ (m, 1\text{H}_{M+m}), 5.41 \ (dd, J = 8.7, 7.3 \text{ Hz, 1H}_m), 1.78 \ (dd, J = 7.0, 1.7 \text{ Hz, 3H}_M), 1.80 - 1.75 \ (m, 3\text{H}_m), 1.32 \ (s, 9\text{H}_m), 1.31 \ (s, 9\text{H}_m);\)

\( ^{13}\text{C NMR (CDCl}_3, 101\text{MHz, 293K (1:0.20 mixture of rotamers):} \delta 164.1, 160.0, 151.0, 150.4, 138.0, 137.7, 129.9, 129.5, 127.9, 127.3, 126.2, 126.0, 125.9, 125.7, 52.2, 48.3, 34.6, 34.5, 31.3, 31.3, 13.4, 13.3;\)

**IR:** \(\nu 3271, 2962, 2867, 1663, 1521, 1381, 1269, 1019;\)

**HRMS (ESI):** calcd for C\(_{15}\)H\(_{21}\)NNaO\(^+\) (M+Na\(^+\)) 254.1515 Found: 254.1521;

\(5-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{-3-methylpyrrolidin-2-one}\)

**From the homoallylic formamide:** Prepared following general procedure D (on larger scale) from \(N-(1-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{but-3-en-1-yl})\text{formamide}\) (0.110 g, 0.476 mmol, 1.0 eq.). After \(^1\text{H-NMR determination of the diastereomeric ratio from the crude sample (observed ratio: 1:1), the material was purified by flash chromatography on silica gel, eluting with 33-66\% EtOAc in hexanes to give the desired 5-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{-3-methylpyrrolidin-2-one (combined yield of both diastereomers: 89 mg, 0.385 mmol, 81\%) as the two diastereomers (pale yellow oils).}**
From the allylic formamide: Prepared following general procedure D (on larger scale) from (Z)-N-(1-(4-(tert-butyl)phenyl)but-2-en-1-yl)formamide (0.119 g, 0.514 mmol, 1.0 eq.). After $^1$H-NMR determination of the diastereomeric ratio from the crude sample (observed ratio: 1:1), the material was purified by flash chromatography on silica gel, eluting with 33-66% EtOAc in hexanes to give the desired 5-(4-(tert-butyl)phenyl)-3-methylpyrrolidin-2-one (combined yield of both diastereomers: 83 mg, 0.361 mmol, 70%) as the two diastereomers (pale yellow oils).

Diastereomer A:

Rf (Hexanes/EtOAc 1:1): 0.28;

$^1$H NMR (CDCl$_3$, 400MHz, 293K): δ 7.41 – 7.34 (m, 2H), 7.24 – 7.15 (m, 2H), 6.19 (s, br, 1H), 4.71 (t, $J = 6.2$ Hz, 1H), 2.67 – 2.55 (m, 1H), 2.21 (dd, $J = 8.0$, 6.2 Hz, 2H), 1.31 (s, 9H), 1.24 (d, $J = 7.2$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): δ 181.0, 150.8, 139.7, 125.8, 125.2, 55.3, 39.5, 34.9, 34.5, 31.3, 16.0;

IR: ν 3221, 2962, 2869, 1690, 1457, 1266, 1111, 834;

HRMS (ESI): calcd for C$_{15}$H$_{22}$NO$^+$ (M+H)$^+$ 232.1696 Found: 232.1696;

Diastereomer B:

Rf (Hexanes/EtOAc 1:1): 0.21;

$^1$H NMR (CDCl$_3$, 400MHz, 293K): δ 7.42 – 7.36 (m, 2H), 7.27 – 7.18 (m, 2H), 5.81 (s, br, 1H), 4.62 (dd, $J = 9.3$, 6.4 Hz, 1H), 2.74 – 2.51 (m, 2H), 1.61 (ddd, $J = 12.4$, 10.8, 9.3 Hz, 1H), 1.32 (s, 9H), 1.25 (d, $J = 7.0$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): δ 180.2, 151.1, 139.0, 125.8, 125.6, 56.1, 41.0, 37.1, 34.6, 31.3, 15.7;

IR: ν 3238, 2962, 2869, 1647, 1455, 1287, 1113, 833;

HRMS (ESI): calcd for C$_{15}$H$_{22}$NO$^+$ (M+H)$^+$ 232.1696 Found: 232.1696;
**N-(1-(4-(tert-butyl)phenyl)-2-methylallyl)formamide**

A solution of *N*-(4-(tert-butyl)benzylidene)-2-methylpropane-2-sulfinamide (0.500 g, 1.88 mmol, 1.0 eq.) in THF (6.3 mL) was cooled to -78°C (dry ice/acetone bath) and treated dropwise with a solution of isopropanylmagnesium bromide (0.5 M in THF) (6.41 mL, 3.20 mmol, 1.7 eq.). The mixture was allowed to warm up to room temperature over 30 min and stirred for additional 20 min. The mixture was then cooled to 0°C and quenched by careful addition of sat. aq. NH₄Cl solution (5 mL). The resulting mixture was extracted with EtOAc (80 mL) and the organic layer washed sequentially with sat. aq. NH₄Cl, water and brine (20 mL each), dried over Na₂SO₄ and concentrated to give the addition product as an inconsequential mixture of diastereomers (ratio 4:1 - unassigned).

The crude mixture was taken up in MeOH (12.6 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (2.36 mL, 9.42 mmol, 5.0 eq.). The resulting mixture was stirred for 10 min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (12.6 mL), treated with sodium bicarbonate (0.396 g, 4.71 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.72 mL, 19 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.72 mL, 7.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12 h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5 x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 33-50% EtOAc in hexanes to give the title compound *N*-(1-(4-(tert-butyl)phenyl)-2-methylallyl)formamide (0.433 g, 1.87 mmol, 99%) as a clear oil.

**Rf** (Hexanes/EtOAc 1:1): 0.44;
1H NMR (CDCl3, 400MHz, 293K) (1:0.25 mixture of rotamers): δ 8.24 (s, 1H), 8.13 (d, J = 12.0 Hz, 1H), 7.41 – 7.34 (m, 2H), 7.24 – 7.15 (m, 2H), 7.07 – 7.00 (m, 2H), 5.93 – 5.76 (s, br, 1H), 5.93 (d, J = 8.3 Hz, 1H), 5.08 – 5.00 (m, 2H), 4.98 (d, J = 8.2 Hz, 1H), 1.69 (s, 1H), 1.68 (s, 1H), 1.32 (s, 9H), 1.31 (s, 9H);

13C NMR (CDCl3, 101MHz, 293K) (1:0.25 mixture of rotamers): δ 164.2, 159.9, 151.2, 151.0, 144.6, 143.4, 136.3, 135.8, 127.0, 126.7, 125.8, 113.4, 111.6, 61.1, 56.8, 34.6, 34.5, 31.3, 31.3, 20.4, 19.7;

IR: ν 3279, 2963, 2868, 1662, 1510, 1380, 1233, 901, 828;

HRMS (ESI): calcd for C15H22NO+ (M+H)+ 232.1696 Found: 232.1695;

trans-5-(4-(tert-butyl)phenyl)-4-methylpyrrolidin-2-one

Prepared following general procedure D (on larger scale) from N-(1-(4-(tert-butyl)phenyl)-2-methylallyl)formamide (0.145 g, 0.627 mmol, 1.0 eq.). After 1H-NMR determination of the diastereomeric ratio from the crude sample (observed ratio: 20:1), the material was purified by flash chromatography on silica gel deactivated with 7.5 wt% conc. aq. NH4OH, eluting with 33-50% EtOAc in hexanes to give the desired trans-5-(4-(tert-butyl)phenyl)-4-methylpyrrolidin-2-one (119 mg, 0.510 mmol, 82% trans/cis = 20:1) as a white foam.

Rf (Hexanes/EtOAc1:1): 0.13;

1H NMR (CDCl3, 400MHz, 293K) (trans): δ 7.45 – 7.38 (m, 2H), 7.26 (d, J = 8.3 Hz, 2H), 5.96 (s, br, 1H), 4.22 (d, J = 7.3 Hz, 1H), 2.63 (dd, J = 16.5, 8.2 Hz, 1H), 2.31 (m, 1H), 2.14 (dd, J = 16.5, 9.6 Hz, 1H), 1.34 (s, 9H), 1.18 (d, J = 6.6 Hz, 3H);

13C NMR (CDCl3, 101MHz, 293K) (trans): δ 177.4, 151.2, 137.9, 125.9, 125.7, 65.7, 40.5, 38.9, 31.3, 17.7;

IR: ν 3191, 2961, 2870, 1685, 1418, 1338, 913;

HRMS (ESI): calcd for C15H22NO+ (M+H)+ 232.1696 Found: 232.1696;
**N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)formamide**

A solution of 2-bromooct-1-ene (0.600 g, 3.14 mmol, 1.3 eq.) in THF (5.5 mL) was treated dropwise with tert-Butyllithium (1.7 M in pentane) (3.55 mL, 6.04 mmol, 2.5 eq.) at -78°C and the mixture stirred for 1h at this temperature. The mixture was then treated with a solution of N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)-2-methylpropane-2-sulfinamide (0.641 g, 2.42 mmol, 1.0 eq.) in THF (1.8 ml). The resulting mixture was allowed to stir at -78°C for 2h after which complete conversion of the SM was observed by TLC. The mixture was quenched at -78°C by the addition of sat. aq. NH₄Cl (5 mL) and warmed to room temperature. The mixture was then treated with sat. aq. NH₄Cl (40 mL), extracted with EtOAc (3x 70 mL), the combined organic extracts dried over Na₂SO₄ and concentrated to give the crude addition product as an inconsequential mixture of diastereomers (ratio 3.5:1 - unassigned).

The crude mixture was taken up in MeOH (16.1 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (3.0 mL, 12.1 mmol, 5.0 eq.). The resulting mixture was stirred for 10min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (16.1 mL), treated with sodium bicarbonate (0.507 g, 6.04 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.93 mL, 24 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.91 mL, 9.7 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 20% EtOAc in hexanes to give the title compound N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)formamide (0.584 g, 1.94 mmol, 80%) as a clear oil.
Experimental Part

Rf (Hexanes/EtOAc 1:1): 0.68;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.26 mixture of rotamers): $\delta$ 8.21 (s, 1H$_M$), 8.10 (d, $J = 11.9$ Hz, 1H$_m$), 7.39 – 7.33 (m, 2H$_{M+m}$), 7.23 – 7.14 (m, 2H$_{M+m}$), 5.99 – 5.81 (m, br, 1H$_{M+m}$), 5.57 (d, $J = 8.3$ Hz, 1H$_M$), 5.11 – 4.94 (m, 2H$_{M+m}$), 2.02 – 1.84 (m, 2H$_{M+m}$), 1.53 – 1.37 (m, 2H$_{M+m}$), 1.31 (s+s, 9H$_{M+m}$), 1.29 – 1.16 (m, 6H$_{M+m}$), 0.91 – 0.81 (m, 3H$_{M+m}$);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.26 mixture of rotamers): $\delta$ 164.2, 159.8, 151.1, 150.8, 149.2, 148.2, 136.6, 136.1, 127.1, 126.8, 125.8, 125.7, 112.0, 110.0, 60.3, 55.9, 34.5, 34.5, 33.8, 33.1, 31.6, 31.6, 31.3, 31.3, 29.0, 28.9, 27.6, 27.6, 22.5, 22.5, 14.0, 14.0;

IR: $\nu$ 3280, 2958, 2929, 2860, 1662, 1511, 1381, 902;

HRMS (ESI): calcd for C$_{20}$H$_{32}$NO$^+$ (M+H)$^+$ 302.2478 Found: 302.2481;

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trans-5-(4-(tert-butyl)phenyl)-4-hexylpyrrolidin-2-one

Prepared following general procedure D (on larger scale) from N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)formamide (0.145 g, 0.481 mmol, 1.0 eq.). After 1H-NMR determination of the diastereomeric ratio from the crude sample (observed ratio: 8:1), the material was purified by flash chromatography on silica gel deactivated with 7.5 wt% conc. aq. NH$_4$OH, eluting with 25-33% EtOAc in hexanes to give the desired trans-5-(4-(tert-butyl)phenyl)-4-hexylpyrrolidin-2-one (107 mg, 0.355 mmol, 74% trans/cis = 8:1) as a colorless oil.

Rf (Hexanes/EtOAc 1:1): 0.35;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (trans): $\delta$ 7.47 – 7.32 (m, 2H), 7.32 – 7.19 (m, 2H), 5.76 (s, br, 1H), 4.28 (d, $J = 6.9$ Hz, 1H), 2.63 (dd, $J = 16.3$, 8.0 Hz, 1H), 2.31 – 2.05 (m, 2H), 1.70 – 1.55 (m, 1H), 1.47 – 1.12 (m, 18H), 0.94 – 0.77 (m, 3H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (trans): $\delta$ 177.3, 151.2, 138.4, 126.0, 125.7, 64.2, 45.6, 36.9, 34.6, 33.3, 31.7, 31.3, 29.3, 27.6, 22.6, 14.0;

IR (trans/cis 8:1): $\nu$ 3237, 2958, 2925, 2856, 1684, 1645, 1434, 832;
Experimental Part

HRMS (ESI): calcd for C_{20}H_{32}NO^{+} (M+H)^{+} 302.2478 Found: 302.2476;

\[ N-(1-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{pent-4-en-1-yl})\text{formamide} \]

In a 50 mL two-necked flask under argon, equipped with a reflux condenser, a solution of 4-bromobut-1-ene (0.249 mL, 2.45 mmol, 1.3 eq.) in THF (4.3 mL) was added dropwise to Magnesium turnings (60.0 mg, 2.45 mmol, 1.3 eq.) (previously activated with a crystal of iodine) at such a rate that a gentle reflux was observed. The resulting mixture was then stirred at reflux temperature (oil bath, 75°C) for 30 min. The mixture was then cooled to -40°C (dry ice/acetone bath) and treated with a solution of N-(1-(4-(\text{tert}-\text{butyl})\text{phenyl})-2-methyleneoctyl)-2-methylpropane-2-sulfinamide (0.500 g, 1.88 mmol, 1.0 eq.) in THF (1.4 mL). The resulting mixture was allowed to slowly warm up to room temperature and stirred for 20 min, after which complete conversion of the starting material was observed by TLC. The mixture was quenched at 0°C by the addition of sat. aq. NH_{4}Cl (20 mL) and extracted with EtOAc (3x 70 mL), the combined organic extracts dried over Na_{2}SO_{4} and concentrated to give the crude addition product as an inconsequential mixture of diastereomers.

The crude mixture was taken up in MeOH (12.6 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (2.3 mL, 9.4 mmol, 5.0 eq.). The resulting mixture was stirred for 10 min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (12.6 mL), treated with sodium bicarbonate (0.40 g, 4.71 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.72 mL, 19 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.71 mL, 7.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12 h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO_{3} (10 mL) and extracted with EtOAc (50mL). The organic layer was washed sequentially with sat. aq. NaHCO_{3} (5x 10
mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 33 - 50% EtOAc in hexanes to give the title compound \( N-1-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{pent-4-en-1-yl})\text{formamide} \) (0.431 g, 1.46 mmol, 93%) as a clear oil.

\[ R_f \text{ (hexanes/EtOAc 1:1)}: 0.49; \]

\(^1\text{H NMR (CDCl}_3, 400\text{MHz, 293K)} (1:0.29 \text{ mixture of rotamers}): \delta 8.18 \text{ (s, 1H)}_M, 8.10 \text{ (d, } J = 12.0 \text{ Hz, 1H})_m, 7.42 - 7.33 \text{ (m, 2H)}_M + m, 7.25 - 7.14 \text{ (m, 2H)}_M + m, 6.10 - 5.98 \text{ (m, br, 1H)}_m, 5.88 - 5.71 \text{ (m, 2H)}_M + m, 5.13 - 4.94 \text{ (m, 2H)}_M + m, 4.47 \text{ (td, } J = 8.8, 5.8 \text{ Hz, 1H})_m, 2.25 - 1.76 \text{ (m, 4H)}_M + m, 1.31 \text{ (s+s, 9H)}_M + m; \]

\(^{13}\text{C NMR (CDCl}_3, 101\text{MHz, 293K)} (1:0.29 \text{ mixture of rotamers)}: \delta 164.3, 160.3, 150.9, 150.6, 138.7, 138.3, 137.5, 136.9, 126.3, 125.8, 125.7, 116.0, 115.3, 55.3, 51.5, 36.1, 35.1, 34.5, 34.5, 31.3, 31.3, 30.4, 30.1; \]

\[ \text{IR: } \nu 3276, 3055, 2962, 2866, 1657, 1535, 1383, 912; \]

\[ \text{HRMS (ESI): calcd for C}_{16}\text{H}_{24}\text{NO}^+ \text{(M+H)}^+ 246.1852 \text{ Found: 246.1855;} \]

\[ 5-(4-(\text{tert}-\text{butyl})\text{phenyl})-3\text{-ethylpyrrolidin-2-one} \]

Prepared following general procedure D (on larger scale) from \( N-1-(4-(\text{tert}-\text{butyl})\text{phenyl})\text{pent-4-en-1-yl})\text{formamide} \) (0.125 g, 0.509 mmol, 1.0 eq.). After \(^1\text{H-NMR determination of the diastereomeric ratio from the crude sample (observed ratio: 1:1), the material was purified by flash chromatography on silica gel, eluting with 33-66\% EtOAc in hexanes to give the desired 5-(4-(\text{tert}-\text{butyl})\text{phenyl})-3\text{-ethylpyrrolidin-2-one} \) (combined yield of both diastereomers: 82 mg, 0.336 mmol, 66%) as the two diastereomers (colorless oils).

\[ \text{Diastereomer A:} \]

\[ R_f \text{ (Hexanes/EtOAc 1:1): 0.33;} \]
**Experimental Part**

\[ ^{1}H \text{NMR (CDCl}_3, 400\text{MHz, 293K): } \delta 7.44 - 7.33 \text{ (m, 2H), } 7.21 \text{ (d, } J = 8.3 \text{ Hz, 2H), } 5.85 \text{ (s, 1H), } 4.69 \text{ (dd, } J = 8.2, 4.4 \text{ Hz, 1H), } 2.49 \text{ (dd, } J = 8.9, 7.1, 4.6 \text{ Hz, 1H), } 2.29 \text{ (ddd, } J = 12.9, 8.1, 7.1 \text{ Hz, 1H), } 2.16 \text{ (ddd, } J = 13.1, 8.9, 4.5 \text{ Hz, 1H), } 1.89 \text{ (dtd, } J = 13.7, 7.6, 4.6 \text{ Hz, 1H), } 1.50 \text{ (ddq, } J = 14.6, 9.3, 7.3 \text{ Hz, 1H), } 1.32 \text{ (s, 9H), } 0.99 \text{ (t, } J = 7.5 \text{ Hz, 3H);} \]

\[ ^{13}C \text{NMR (CDCl}_3, 101\text{MHz, 293K): } \delta 180.1, 150.9, 139.9, 125.8, 125.2, 55.6, 41.4, 36.8, 34.6, 31.3, 24.0, 11.6; \]

**IR:** \( \nu 3225, 2961, 1691, 1462, 1269, 1111, 835; \)

**HRMS (ESI):** calcd for C\(_{16}\)H\(_{24}\)NO\(^+\) (M+H\(^+\)) \(246.1852\) Found: 246.1850;

**Diastereomer B:**

\[ \text{Rf (Hexanes/EtOAc 1:1): 0.25;} \]

\[ ^{1}H \text{NMR (CDCl}_3, 400\text{MHz, 293K): } \delta 7.45 - 7.30 \text{ (m, 2H), } 7.30 - 7.18 \text{ (m, 2H), } 5.77 \text{ (s, 1H), } 4.62 \text{ (dd, } J = 9.2, 6.6 \text{ Hz, 1H), } 2.65 \text{ (dddd, } J = 12.7, 7.9, 6.8, 0.9 \text{ Hz, 1H), } 2.47 \text{ (dtd, } J = 10.8, 8.8, 4.2 \text{ Hz, 1H), } 2.04 - 1.88 \text{ (m, 1H), } 1.69 - 1.56 \text{ (m, 1H), } 1.54 - 1.39 \text{ (m, 1H), } 1.32 \text{ (s, 9H), } 0.96 \text{ (t, } J = 7.4 \text{ Hz, 3H);} \]

\[ ^{13}C \text{NMR (CDCl}_3, 101\text{MHz, 293K): } \delta 179.5, 151.1, 139.2, 125.8, 125.6, 56.1, 43.6, 38.2, 34.6, 31.3, 23.7, 11.5; \]

**IR:** \( \nu 3217, 2961, 2871, 1694, 1461, 1267, 835; \)

**HRMS (ESI):** calcd for C\(_{16}\)H\(_{24}\)NO\(^+\) (M+H\(^+\)) \(246.1852\) Found: 246.1854;
6.3.3 **Synthesis of Additional Compounds**

*N*-methyl-*N*-(4-methylpent-1-en-3-yl)formamide

![Chemical Structure](image)

A solution of *N*-(4-methylpent-1-en-3-yl)formamide (0.100 g, 0.786 mmol, 1.0 eq.) in DMF (1.5 mL) was treated portionwise with Sodium hydride (60% dispersion in mineral oil) (126 mg, 3.14 mmol, 4.0 eq.). The mixture was stirred for 30 min and then treated dropwise with iodomethane (0.50 mL, 7.9 mmol, 10 eq.) at r.t. and stirred for 1.5h. The mixture was quenched with water (5 mL) and partitioned with EtOAc (50 mL) and brine (20 mL). The organic layer was repeatedly washed with brine (4 x 20 mL), dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 40°C. The crude material was purified by flash column chromatography on silica gel, eluting with 33% – 50% EtOAc in Hexanes to give the product *N*-methyl-*N*-(4-methylpent-1-en-3-yl)formamide (85 mg, 0.602 mmol, 77%) as a clear oil.

**Rf** (hexane:EtOAc = 1:1): 0.49;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (1:0.39 mixture of rotamers): δ 8.14 – 8.07 (m, 1H$_{M+m}$), 5.93 – 5.75 (m, 1H$_{M+m}$), 5.31 – 5.14 (m, 2H$_{M+m}$), 4.45 (dd, $J$ = 10.6, 7.7 Hz, 1H$_{m}$), 3.41 (dd, $J$ = 10.2, 7.1 Hz, 1H$_{M}$), 2.81 (s, 3H$_{m}$), 2.76 (s, 3H$_{M}$), 2.00 – 1.83 (m, 1H$_{M+m}$), 0.98 – 0.86 (m, 6H$_{M+m}$);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K) (1:0.39 mixture of rotamers): δ 162.9, 134.9, 134.3, 119.0, 118.7, 67.8, 60.4, 30.5, 29.0, 28.1, 26.3, 19.9, 19.8, 19.6, 19.3;

**IR**: ν 2963, 1668, 1404, 1054, 763;

**HRMS (ESI)**: calcd for C$_8$H$_{16}$NO$^+$ (M+H)$^+$ 142.1226 Found: 142.1227;
**N-formyl-N-(4-methylpent-1-en-3-yl)acetamide**

\[ \text{H}_2\text{N}-\text{O} \]

A solution of \( N\)-(4-methylpent-1-en-3-yl)formamide (30 mg, 0.236 mmol, 1.0 eq.) in Acetic anhydride (1.0 mL) was treated with DMAP (2.9 mg, 0.024 mmol, 0.10 eq.) and then heated to reflux (oil bath: 140°C) for 4h. The resulting dark solution was cooled to r.t., diluted with EtOAc (20 mL), washed with sat. aq. NaHCO\(_3\) soln. (20 mL) and the aqueous layer extracted with additional EtOAc (20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure at 40°C. The crude material was purified by flash column chromatography on silica gel, eluting with 15% EtOAc in Hexanes to give the product \( N\)-formyl-\( N\)-(4-methylpent-1-en-3-yl)acetamide (33 mg, 0.192 mmol, 81%) as a pale yellow oil.

**Rf** (hexane:EtOAc = 1:1): 0.83;

\[^1\text{H} \text{NMR (CDCl}_3, 400\text{MHz, 293K)}: \delta 9.11 (s, 1\text{H}), 6.19 (ddd, J = 17.1, 10.1, 8.5 \text{Hz}, 1\text{H}), 5.25 - 5.07 (m, 2\text{H}), 4.56 (dd, J = 10.7, 8.5 \text{Hz}, 1\text{H}), 2.51 - 2.28 (m, 4\text{H}), 0.92 (d, J = 6.7 \text{Hz}, 3\text{H}), 0.78 (d, J = 6.6 \text{Hz}, 3\text{H});\]

\[^{13}\text{C} \text{NMR (CDCl}_3, 101\text{MHz, 293K)}: \delta 171.1, 163.1, 135.8, 119.1, 62.6, 28.4, 23.7, 20.5, 19.3;\]

**N-(4-methylpent-1-en-3-yl)-N-tosylformamide**

\[ \text{Ph-N=O} \]

A solution of \( N\)-(4-methylpent-1-en-3-yl)formamide (30 mg, 0.236 mmol, 1.0 eq.) in THF (0.8 mL) was cooled to -40°C and treated dropwise with Lithium hexamethyldisilazide (LHMDS, 1M soln. in THF) (0.47 mL, 0.472 mmol, 2.0 eq.). The mixture was allowed to reach r.t. and then treated in a single portion with p-Toluenesulfonyl chloride (225 mg, 1.179 mmol, 5.0 eq.) and stirred at r.t. overnight. The mixture was then quenched with sat. aq. NH\(_4\)Cl soln. (2 mL), diluted with EtOAc (20 mL), washed with brine (20 mL) and the
aqueous layer extracted with additional EtOAc (10 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure at 40°C. The crude material was purified by flash column chromatography on silica gel, eluting with 6% – 8% EtOAc in Hexanes to give the product N-(4-methylpent-1-en-3-yl)-N-tosylformamide (49 mg, 0.175 mmol, 74%) as a clear oil.

Rf (hexane:EtOAc = 15:1): 0.21;

⁠¹H NMR (CDCl₃, 400MHz, 293K): δ 9.09 (s, 1H), 7.76 – 7.66 (m, 2H), 7.38 – 7.29 (m, 2H), 5.98 (ddd, J = 17.2, 10.2, 9.0 Hz, 1H), 4.91 (dd, J = 10.1, 1.4 Hz, 1H), 4.71 (d, J = 17.2 Hz, 1H), 3.88 (t, J = 9.7 Hz, 1H), 2.55 – 2.41 (m, 4H), 0.89 – 0.79 (m, 6H);

¹³C NMR (CDCl₃, 101MHz, 293K): δ 161.7, 145.2, 135.9, 133.9, 130.0, 127.8, 119.4, 67.8, 28.8, 21.7, 20.5, 19.6;

IR: ν 2970, 1699, 1353, 1208, 1165, 1090, 986, 680;

HRMS (ESI): caled for C₁₄H₂₀NO₃S⁺ (M+H)⁺ 282.1158 Found: 282.1163;

N-((4-(tert-butyl)phenyl)(cyclohex-1-en-1-yl)methyl)formamide

A solution of 1-bromocyclohex-1-ene (0.214 mL, 1.86 mmol, 1.1 eq.) in THF (3.9 mL) was treated dropwise with tert-Butyllithium (1.7 M in pentane) (2.09 mL, 3.56 mmol, 2.1 eq.) at -78°C and the mixture stirred for 1h at this temperature. The mixture was then treated with a solution of N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)-2-methylpropane-2-sulfinamide (0.449 g, 1.69 mmol, 1.0 eq.) in THF (1.3 mL). The resulting mixture was allowed to stir at -78°C for 2h after which complete conversion of the SM was observed by TLC. The mixture was quenched at -78°C by the addition of sat. aq. NH₄Cl (5 mL) and warmed to room temperature. The mixture was then treated with sat. aq. NH₄Cl (40 mL), extracted with Et₂O (3x 70 mL), the combined organic extracts dried over Na₂SO₄ and concentrated to give the crude addition product as an inconsequential mixture of diastereomers.
The crude mixture was taken up in MeOH (11.3 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (2.1 mL, 8.5 mmol, 5.0 eq.). The resulting mixture was stirred for 10 min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (11.3 mL), treated with sodium bicarbonate (0.355 g, 4.23 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.78 mL, 17 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.69 mL, 6.8 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12 h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50 mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 25% - 33% EtOAc in hexanes to give the title compound N-((4-(tert-butyl)phenyl)(cyclohex-1-en-1-yl)methyl)formamide (0.415 g, 1.53 mmol, 90%) as a clear oil.

**Rf (hexane:EtOAc = 3:1):** 0.22;

**1H NMR (CDCl₃, 400MHz, 293K) (1:0.32 mixture of rotamers):** δ 8.24 (s, 1H_M), 8.12 (d, J = 12.0 Hz, 1H_m), 7.39 – 7.31 (m, 2H_M+m), 7.22 – 7.10 (m, 2H_M+m), 5.96 – 5.75 (m, br, 1H_M+m), 5.74 – 5.74 (m, 1H_M+m), 5.50 (d, J = 8.3 Hz, 1H_M), 4.91 (t, J = 9.1 Hz, 1H_m), 2.16 – 2.00 (m, 2H_M+m), 1.97 – 1.66 (m, 2H_M+m), 1.66 – 1.50 (m, 4H_M+m) 1.32 – 1.30 (m, 9H_M+m);

**13C NMR (CDCl₃, 101MHz, 293K) (1:0.32 mixture of rotamers):** δ 164.3, 159.9, 150.8, 150.5, 137.2, 137.0, 136.5, 136.1, 126.9, 126.6, 125.7, 125.6, 125.3, 123.4, 61.4, 56.8, 34.5, 34.5, 31.3, 31.3, 26.3, 25.7, 25.1, 25.1, 22.6, 22.5, 22.3, 22.2;

**IR:** ν 3276, 2929, 2863, 1655, 1523, 1381, 1270, 1230, 837;

**HRMS (ESI):** calcd for C₁₈H₂₆NO⁺ (M+H)⁺ 272.2009 Found: 272.2006;
**N-(1-(4-(tert-butyl)phenyl)-3-methylbut-2-en-1-yl)formamide**

In a dry flask under argon, equipped with a reflux condenser, a suspension of Magnesium (96 mg, 3.96 mmol, 2.1 eq.) in THF (4.3 mL) was activated with a crystal of iodine and then treated with neat 1-bromo-2-methylprop-1-ene (0.386 mL, 3.77 mmol, 2.0 eq.) and the mixture heated to reflux for 4h. The resulting dark mixture was then cooled to -78°C and treated with a solution of N-(1-(4-(tert-butyl)phenyl)-2-methyleneoctyl)-2-methylpropane-2-sulfinamide (0.500 g, 1.88 mmol, 1.0 eq.) in THF (1.4 mL). The resulting mixture was allowed to slowly warm up to r.t. over 1h. The mixture was quenched at r.t. by the addition of sat. aq. NH₄Cl (50 mL), extracted with EtOAc (3x 70 mL), the combined organic extracts dried over Na₂SO₄, filtered and concentrated to give the crude addition product as an inconsequential mixture of diastereomers.

The crude mixture was taken up in MeOH (12.5 mL), cooled to 0°C and treated dropwise with HCl (4M solution in dioxane) (2.4 mL, 9.4 mmol, 5.0 eq.). The resulting mixture was stirred for 10min at room temperature and then evaporated to dryness under reduced pressure.

The crude hydrochloride salt was suspended in dry THF (12.5 mL), treated with sodium bicarbonate (0.396 g, 4.71 mmol, 2.5 eq.) and cooled to 0°C.

In a separate flask, formic acid (0.87 mL, 19 mmol, 10 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.77 mL, 7.5 mmol, 4 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This formic-acetic anhydride (FAA) solution was then added dropwise to the cooled (0°C) mixture containing the amine (prepared above) and the resulting mixture stirred at r.t. for 12h.

The mixture was finally treated with water (5 mL) sat. aq. NaHCO₃ (10 mL) and extracted with EtOAc (50mL). The organic layer was washed sequentially with sat. aq. NaHCO₃ (5x 10 mL), water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash chromatography on silica gel, eluting with 25% - 33% EtOAc in hexanes to give the title compound N-(1-(4-(tert-butyl)phenyl)-3-methylbut-2-en-1-yl)formamide (0.325 g, 1.33 mmol, 70%) as a clear oil.
**Experimental Part**

**Rf** (hexane:EtOAc = 3:1): 0.25;

**$^1$H NMR** (**CDCl$_3$, 400MHz, 293K** (1:0.26 mixture of rotamers): $\delta$ 8.22 (s, 1H$_M$), 8.18 (d, $J = 12.1$ Hz, 1H$_m$), 7.41 – 7.32 (m, 2H$_{M+m}$), 7.26 – 7.19 (m, 2H$_{M+m}$), 5.91 – 5.83 (m, 1H$_{M+m}$), 5.82 – 5.69 (m, br, 1H$_{M+m}$), 5.36 – 5.26 (m, 1H$_{M+m}$), 1.80 – 1.75 (m, 6H$_{M+m}$), 1.31 (s, 9H$_m$), 1.30 (s, 9H$_M$);

**$^{13}$C NMR** (**CDCl$_3$, 101MHz, 293K** (1:0.26 mixture of rotamers): $\delta$ 164.2, 159.9, 150.8, 150.2, 138.6, 138.4, 136.4, 135.9, 126.1, 126.0, 125.8, 125.6, 124.5, 124.1, 53.6, 49.6, 34.5, 34.5, 31.3, 31.3, 25.7, 18.5, 18.3;

**IR:** $\nu$ 3270, 2963, 2868, 1658, 1510, 1380, 1269;

**HRMS (ESI):** calcd for C$_{16}$H$_{24}$NO$^+$ (M+H)$^+$ 246.1852 Found: 246.1847;

$\text{N-(1-(4-(tert-butyl)phenyl)allyl)acetamide}$

A flame-dried flask (25 mL) under argon was charged with Chloro(1,5-cyclooctadiene)-iridium(I) dimer (30 mg, 0.045 mmol, 0.015 eq.) and 5-(dibenzo[d,f][1,3,2]dioxaphosphepin-6-yl)-5H-dibenzo[b,f]azepine (37 mg, 0.090 mmol, 0.03 eq.), the contents were suspended in THF (10 mL), treated with DMF (1.16 mL, 15.0 mmol, 5.0 eq.) and stirred for 15 min at r.t.. The mixture was then treated with sulfamic acid (0.291 g, 3.00 mmol, 1.0 eq.) and 1-(4-(tert-butyl)phenyl)prop-2-en-1-ol (0.571 g, 3.00 mmol, 1.0 eq.) and stirred at r.t. for 12 h.

The mixture was then cooled to 0°C (ice bath) and treated with triethylamine (0.84 mL, 6.0 mmol, 2.0 eq.), acetic anhydride (0.566 mL, 6.00 mmol, 2.0 eq.) and DMAP (37 mg, 0.30 mmol, 0.10 eq.). The mixture was allowed to reach r.t. and stirred for 3h.

The mixture was poured into sat. aq. NaHCO$_3$ (30 mL), extracted with EtOAc (3 x 30 mL), the combined organic extracts dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure at 40°C. The residue was purified by flash column chromatography on silica gel, eluting with 33 – 50% EtOAc in hexanes to give the title compound $\text{N-(1-(4-(tert-butyl)phenyl)allyl)acetamide}$ (0.439 g, 1.90 mmol, 63%) as an off-white amorphous solid.
Experimental Part

Rf (hexane:EtOAc = 1:1): 0.46;

\(^1\)H NMR (CDCl\(_3\), 400MHz, 293K): \(\delta\) 7.39 – 7.34 (m, 2H), 7.25 – 7.20 (m, 2H), 6.01 (ddd, \(J = 17.0, 10.5, 5.2\) Hz, 1H), 5.80 (d, br, \(J = 8.2\) Hz, 1H), 5.62 (ddt, \(J = 8.4, 4.8, 1.8\) Hz, 1H), 5.31 – 5.17 (m, 2H), 2.01 (s, 3H), 1.31 (s, 9H);

\(^{13}\)C NMR (CDCl\(_3\), 101MHz, 293K): \(\delta\) 169.0, 150.7, 137.5, 137.3, 127.0, 125.7, 115.4, 54.8, 34.5, 31.3, 23.4;

IR: \(\nu\) 3273, 3057, 2963, 2868, 1638, 1540, 1371, 1296, 1273, 1110, 922, 836;

HRMS (ESI): calcd for C\(_{15}\)H\(_{22}\)NO\(^+\) (M+H)+ 232.1696 Found: 232.1694;

1-acetyl-5-(4-(tert-butyl)phenyl)pyrrolidin-2-one

Obtained in small amounts by following general procedure D using \(\text{N}-(1-(4-(\text{tert-butyl})\text{phenyl})\text{allyl})\text{acetamide (50 mg, 0.216 mmol) to give the desired product 1-acetyl-5-(4-(tert-butyl)phenyl)pyrrolidin-2-one (11 mg, 0.042 mmol, 19%) as a pale yellow oil.}

Rf (hexane:EtOAc = 1:1): 0.82;

\(^1\)H NMR (CDCl\(_3\), 400MHz, 293K) (1:0.26 mixture of rotamers): \(\delta\) 7.34 (d, \(J = 8.4\) Hz, 2H), 7.08 (d, \(J = 8.3\) Hz, 2H), 5.41 (dd, \(J = 8.6, 1.8\) Hz, 1H), 2.86 – 2.68 (m, 1H), 2.55 (s, 3H), 2.59 – 2.38 (m, 2H), 2.03 – 1.92 (m, 1H), 1.30 (s, 9H);

\(^{13}\)C NMR (CDCl\(_3\), 101MHz, 293K) (1:0.26 mixture of rotamers): \(\delta\) 176.1, 170.6, 150.4, 138.2, 125.7, 124.7, 59.6, 34.5, 31.7, 31.3, 27.1, 25.4;

IR: \(\nu\) 2961, 1740, 1700, 1371, 1326, 1279, 1193;

HRMS (ESI): calcd for C\(_{16}\)H\(_{22}\)NO\(^2+\) (M+H)\(^+\) 260.1645 Found: 260.1651;
**Experimental Part**

(E)-4-(prop-1-en-1-yl)-1,1'-biphenyl

Catalysis byproduct observed when using acetic acid additive and argon atmosphere. Contains small amount of Z-isomer.

Rf (hexane:EtOAc = 1:2): 0.97;

$^1$H NMR (CDCl$_3$, 400MHz, 293K) (major isomer: E): $\delta$ 7.64 – 7.50 (m, 4H), 7.47 – 7.28 (m, 5H), 6.44 (dd, $J = 15.8, 1.7$ Hz, 1H), 6.29 (dq, $J = 15.8, 6.5$ Hz, 1H), 1.91 (dd, $J = 6.6, 1.6$ Hz, 3H);

$^{13}$C NMR (CDCl$_3$, 101MHz, 293K): $\delta$ 140.9, 139.5, 137.0, 130.6, 128.7, 127.2, 127.1, 126.9, 126.2, 125.9, 18.6;

IR: $\nu$ 2927, 1488, 1449, 1408, 1374, 1265, 968, 849, 795, 755;

HRMS (EI): calcd for C$_{15}$H$_{14}$ $^+$ (M)$^+$ 194.1090 Found: 194.1085;

6.3.4 Labeling Experiments:

Preparation of D-Labeled Starting Materials:

N-(4-methylpent-1-en-3-yl)-(1'-$^2$H)formamide

A solution of (E)-2-methyl-N-(2-methylpropylidene)propane-2-sulfinamide (0.351 g, 2.00 mmol, 1.0 eq.) in THF (4.0 mL) was treated dropwise at -78°C (dry ice/acetone bath) with a solution of vinylmagnesium bromide (1M in THF) (2.40 mL, 2.40 mmol, 1.2 eq.) and the
mixture allowed to warm to r.t. for 30 min after which TLC showed complete consumption of the starting material. The mixture was cooled to 0°C and quenched with sat. aq. NH₄Cl (5 mL), extracted with EtOAc (3x 15 mL), the combined extracts dried over Na₂SO₄ and concentrated.

The resulting oil was dissolved in MeOH (13 mL) and cooled to 0°C. The solution was then treated dropwise with HCl solution (4M in dioxane) (2.52 mL, 10.0 mmol, 5 eq.) and allowed to warm to r.t.. After 10 min (TLC showed full consumption of the intermediate), the mixture was evaporated to dryness at 40°C under reduced pressure.

The remaining salt was suspended in THF (13 mL), cooled to 0°C and treated with solid sodium hydrogen carbonate (0.370 g, 4.40 mmol, 2.2 eq.).

In a separate dry flask, formic acid-d₂ (0.303 mL, 8.0 mmol, 4 eq.) was added slowly to cooled (0°C, ice bath) acetic anhydride (0.0.330 mL, 3.50 mmol, 1.75 eq.). This mixture was stirred at 40°C for 15 min and then cooled back to 0°C. This (²H)-formic-acetic anhydride ((²H)-FAA) solution was then added dropwise to the cooled (0°C) mixture containing the allylic amine (prepared above) and the resulting mixture stirred at r.t. for 4h.

The mixture was diluted with EtOAc (20 mL), washed with sat. NaHCO₃ (3x 25 mL) and back extracted with EtOAc (20 mL). The combined organic layers were washed with water (10 mL) and brine (10 mL), dried over Na₂SO₄ and concentrated. The residue was purified by flash column chromatography on silica gel, eluting with 45 - 50% EtOAc in Hexanes to give the desired compound N-(4-methylpent-1-en-3-yl)-(1'-²H)formamide (0.203 g, 1.58 mmol, 79 %) as a clear oil. The product was further dried by evaporation from a Toluene solution (3x 5 mL) under vacuum. Complete incorporation of deuterium was observed by ¹H-NMR (absence of the corresponding signal).

\[ \text{N-(4-methylpent-1-en-3-yl)-(N-²H)formamide} \]

A solution of \( \text{N-(4-methylpent-1-en-3-yl)formamide (1a)} \) (0.150 g, 1.18 mmol, 1.0 eq.) in 1,4-dioxane (4.0 mL) was treated with D₂O (2.0 mL) and stirred for 2h at r.t.. The solution was then evaporated under reduced pressure at 40°C. This process was repeated two more times.
and the resulting residue was dissolved in CDCl$_3$ (5 mL), dried over Na$_2$SO$_4$ and concentrated. The product was further dried by evaporation from a Toluene solution (3x 5 mL) under vacuum. Complete incorporation of deuterium was observed by $^1$H-NMR (absence of the corresponding signal).

**General Procedure for Cyclization of Deuterated Compounds**

In a glovebox, the substrate (150 mg, 1.17 mmol, 1.0 eq.) was charged in a dry 2 mL polypropylene limited volume vial containing a Teflon-coated magnetic stir bar. This was followed by the addition of Ru$_3$(CO)$_{12}$ (37 mg, 0.059 mmol, 0.05 eq.), sodium iodide (26 mg, 0.176 mmol, 0.15 eq.) and finally DMF-$d_7$ (0.75 mL). The vial was sealed with a septum screw-cap and removed from the glovebox. The mixture was then purged for 15 min with carbon monoxide by bubbling it through the septum from a balloon. The vial was finally placed in a pre-heated oil bath at 130°C and stirred for either 3 h (for full conversion) or 0.5 h (for 50 % conversion for re-isolation of starting materials). The vial was then cooled to r.t., opened and the contents diluted with EtOAc (50 mL), washed with brine (5x 10 mL), dried over Na$_2$SO$_4$ and concentrated. The residue was purified by flash chromatography on silica gel eluting with 50 – 60% EtOAc in Hexanes (for re-isolation of the substrate) or 0 – 2% MeOH in EtOAc (for the cyclized product). The incorporation of deuterium was analyzed by $^1$H-NMR spectroscopy by comparison with non-deuterated material. Spectra for the cyclized product were measured in CDCl$_3$ while the recovered substrate was measured in CD$_3$OD to avoid broad rotamer signals and exchangeable protons.
Results

\[
\text{Ru}_2(\text{CO})_6 (5\%) \\
\text{NaI} (15\%) \\
\text{DMF-d}_7, \\
130°C, 3h \\
\text{full conv.}
\]

45% D

\[
\text{Ru}_2(\text{CO})_6 (5\%) \\
\text{NaI} (15\%) \\
\text{DMF-d}_7, \\
130°C, 3h \\
\text{full conv.}
\]

39% D

\[
\text{Ru}_2(\text{CO})_6 (5\%) \\
\text{NaI} (15\%) \\
\text{DMF-d}_7, \\
130°C, 3h \\
\text{full conv.}
\]

97% D

\[
\text{Ru}_2(\text{CO})_6 (5\%) \\
\text{NaI} (15\%) \\
\text{DMF-d}_7, \\
130°C, 3h \\
\text{full conv.}
\]

97% D
6.4 Experimental Part to Chapter 5

6.4.1 General Methods

Trichlorinated hexanediols 6 and 7 were prepared according to previously reported procedure.\textsuperscript{138} Compound 6 was further purified by recrystallization from a hot hexanes/diethylether mixture and compound 7 was further purified by recrystallization from a hot hexanes/benzene mixture. The monomer methyl methacrylate (MMA, 99\% Acros) and cross-linker ethylene glycol dimethylacrylate (EGDMA, 98\%, Acros) were purified by filtration over Alox B to remove polymerization inhibitors. The radical initiator V-70 (2,2’-Azobis(4-methoxy-2,4-dimethyl valeronitrile)) was purchased from IG Instrumenten-Gesellschaft AG and stored at –30\°C. d6-Acetone and CDCl\textsubscript{3} were purchased from Armar. NMR experiments were conducted on a Bruker AVANCE II 600-MHz spectrometer.

6.4.2 Preparation of PMMA

In a 25 ml Schlenk flask, to a cold solution (ca. 5\°C) of MMA (50 ml, 0.467 mol) and d6-Acetone (10 ml) was added V-70 (20 mg, 0.064 mmol). The resulting solution was treated with EGDMA (0.020 ml, 0.136 mol\%) via microsyringe. Three cycles of freeze-pump-thaw were conducted to degass the solution. The solution was filled into several NMR tubes (type 5UP, 178 mm; filling level 10 cm), closed with standard plastic caps and sealed with Parafilm. The tubes were inserted into an oil bath at 60 \°C and the polymerization carried out for 18 h at 60\°C. The NMR tubes were then opened and left in the oil bath for further 3 h. The tubes were then allowed to cool and broken with a glass cutter. By this method, polymer rods of 4 mm diameter were obtained. The polymer rods were dried at 35 \°C for two days before being cut into cylinders of 16 mm length.
6.4.3 NMR Sample Preparation

A rod of the dry PMMA polymer was placed into a standard NMR tube (type 5UP, 178 mm) and treated with a solution of the compound to be analyzed, 384 or 385 (ca. 20 mg, ca. 0.090 mmol) in CDCl₃ (minimal amount required for solubility). To prevent the polymer from floating in the solution, a long Pasteur pipette was used to hold the polymer down during initial swelling (ca. 4 min), after which time the pipette could be removed. The tube was sealed, stored at room temperature and monitored for at least three weeks to allow the polymer to swell. During this time, the tube was regularly refilled with additional CDCl₃ up to just above the level of the swollen polymer, to prevent the gel from drying out. Additionally, for measurements of the coupling constants in unaligned solution phase, samples of 384 and 385 (ca. 20 mg) were prepared in CDCl₃ (0.5 ml). Specific data for the samples is given in the table below.

<table>
<thead>
<tr>
<th></th>
<th>Substance 384</th>
<th>Substance 385</th>
</tr>
</thead>
<tbody>
<tr>
<td>substance amount in solution phase</td>
<td>22 mg</td>
<td>17 mg</td>
</tr>
<tr>
<td>substance amount in gel</td>
<td>21 mg</td>
<td>21 mg</td>
</tr>
<tr>
<td>swelling period length</td>
<td>3 weeks</td>
<td>6 weeks</td>
</tr>
<tr>
<td>length of the gel after swelling</td>
<td>4.0 cm</td>
<td>4.4 cm</td>
</tr>
<tr>
<td>Quadrupolar splitting of CDCl₃ in ²H-NMR</td>
<td>70 Hz</td>
<td>96 Hz</td>
</tr>
</tbody>
</table>

6.4.4 Measurement Procedures

Automated locking on the solvent signal was not successful due to quadrupolar splitting and low signal-to-noise ratio. Manual locking was therefore performed. The sweep rate was reduced by ca. one third of its initial rate to lock the magnetic field on one of the doublet components of the CDCl₃ signal. Shimming was performed directly by line-shape optimization via real-time Fourier transformation. This was done at best using the residual MMA lines in the ¹H-NMR spectrum as reference. ²H-NMR was conducted before and after a set of measurements to monitor any changes in the homogeneity of the magnetic field. The quadrupolar splitting of the CDCl₃ signal was also monitored to estimate the alignment.
induced by the gel. Acquisition of the $^2$H-NMR was performed using a standard Bruker pulse sequence. HSQC was measured without t2 decoupling; INADEQUATE, $^{155}$ HSQC-HECADE$^{156}$ and INEPT measurements were implemented using standard procedures. The acquired data was processed with the program Top Spin 2.1.

6.4.5 **Analysis of RDCs**

The singular-value decomposition fitting of the probability tensor to the measured RDCs using the calculated internuclear unit vectors was performed with the PALES program.$^{145}$ To best fit the measured RDCs (file *RDCtable*) to the input molecular structure (*molecule.pdb*), the following command was used:

```
PALES –bestFit –inD RDCtable.tab –pdb molecule.pdb –outD output.tab
```
7 References


References


the Winstin-Holness equation: new definition and recent extensions to classical concepts. *Journal of Chemical Education* 1986, 63 (1), 42.


68. Cationic rhodium complexes are prominent in hydroacylation and hydroformylation reactions in particular. See reference below.


80. difficulties in the deprotection of a phthalimide group has been previously observed in a molecule bearing an alkene due to diimide formation which can reduce the olefin. See the reference below.


101. See experimental section for additional details.

102. SFC traces of enantioenriched starting materials and products were compared to the respective traces of racemic material for determination of optical enrichment.


118. Lafrance M. personal communication


References


146. All calculations were performed using Spartan 10 and Gaussian 09 softwares.


Appendix
NMR Spectra of All New Compounds
Appendix
1:1 mixture of diastereoisomers
Appendix 341
Appendix