Chiral Brønsted Acid Catalysed Synthesis of Tetrahydropyrans and Tetrahydrofurans.

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1. Abstract

Tetrahydropyrans are important structural motifs, present in various natural products with significant biological and pharmacological properties. During previous efforts into the synthesis of the C20-C32 core of phorboxazoles, a stereodivergent oxa-Michael reaction was encountered and investigated computationally (Scheme 1).

[Diagram showing the stereodivergent oxa-Michael reaction]

TFA and CSA have been shown to act as proton shuttles in the cyclisation. The TFA mediated cyclisation doesn’t depend on inherent structural features and the use of chiral phosphoric acids, with acidities in the range of TFA and CSA, instead of TFA should make the reaction enantiodivergent. This means that with chiral phosphoric acid and it’s (ent) form giving the enantiomers from the same cyclisation precursor. This was shown to be feasible by computational analysis, with the mesityl tetrahydropyran cyclisation precursor more enantioselective than the tolyl precursor. To this end, the chiral brønsted acid catalysed cyclisation of the mesityl and tolyl tetrahydrofuran and tetrahydropyran precursors have been carried out under various solvent, catalyst and temperature conditions. For the tetrahydrofuran precursors, the tolyl substrate shows greater enantioselectivity, with the highest ee being 60% using (R)-TIPSY. For the tetrahydropyran precursors, the mesityl shows greater enantioselectivity, with the highest ee being 69% using (R)-TRIP. Finally, a kinetic resolution of the mesityl tetrahydropyran precursor has been carried out using optimised conditions, resulting in the enantioenrichment of the product at 95%ee and the starting material at 96%ee.
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6. Declaration

I hereby declare that the substance of this thesis has not been submitted, nor is currently being submitted, in candidature for any other degree.

I also declare that the work embodied in this thesis is the result of my own investigations and in the event the work of others has been used this has been fully acknowledged in the text.
7. Introduction

7.1 Tetrahydropyrans in Natural Products

Since ancient times, natural products have been used for medicinal and recreational purposes, and have been a source of fascination and wonder. Over the years, their biological and pharmacological properties have been studied and along with their synthesis, the field of organic chemistry has advanced.

Given that natural products are sources for lead like compounds in drug discovery, consisting of diverse structural motifs that are synthetically challenging to make, methods to construct these motifs in an elegant and efficient manner have been a focus of intense research interest. One such motif occurring regularly in many important natural products is the tetrahydropyran unit. Examples of these include brevetoxin B, [1] phorboxazoles A and B, [2] and leucascandrolide A [3] (Figure 1).

![Brevetoxin B (a potent marine toxin)](image1)

![Phorboxazole A: R$^1$ = H, R$^2$ = OH, Phorboxazole B: R$^1$ = OH, R$^2$ = H](image2)

(a potent antitumor agent)

![Leucascandrolide A (a potent antifungal)](image3)

Figure 1- Natural products containing a tetrahydropyran motif.
The construction of tetrahydropyran rings has been the focus of intense research and various strategies have been adopted, addressing issues of efficiency, stereoselectivity, regioselectivity and yield. Some of these methods include the Prins cyclization, Petasis-Ferrier rearrangement, hetero-Diels Alder reaction (HDA), radical cyclization, transition metal catalyzed cyclization, epoxide mediated cyclization and oxa-Michael reaction, to name a few. The oxa-Michael reaction is of special interest in the Clarke group and hence shall be the sole focus of this review.

7.2 The Oxa-Michael Reaction

The oxa-Michael reaction involves the addition of oxygen nucleophiles (mainly alcohols) to an acceptor conjugated system forming an intermediate enolate, which on protonation gives rise to β-ether compounds. This generates a new stereogenic center in the β-position of the system (Scheme 1.1). [5]

![Scheme 1.1 – The Oxa-Michael reaction](image)

The oxa-Michael reaction can be carried out under basic or acidic conditions. Depending on the conditions, the reaction is under kinetic or thermodynamic control. For example, the intramolecular cyclisation of α,β-unsaturated hydroxyster esters, the 2,6-cis or 2,6-trans disubstituted THP's are generated based on the reaction conditions. In general, under basic conditions, 2,6-trans THPs are kinetically favoured at low temperatures (−78 °C) and short reaction times, whereas 2,6-cis THPs are typically thermodynamically favoured at higher temperatures and longer reaction times. This stereoselectivity observed for base-mediated reactions can be explained by the difference in energy and HOMO/LUMO orbital overlap between the s-cis (TS-A has a lower energy and better orbital overlap) and s-trans (TS-B, has a higher energy and decreased orbital overlap) TS conformations (Scheme 1.2a). However, under acidic conditions, the transition state TS-D leading to the thermodynamic 2,6-cis disubstituted tetrahydropyran is now kinetically favoured based on a frontier molecular orbital (FMO) theory argument (Scheme 1.2b).
Scheme 1.2 – Stereochemical outcome of intramolecular cyclisation based on reaction conditions.

Inspection of the FMO coefficients of the allylic cationic species and the orbital overlap with the oxygen lone pair indicates greater stereoelectronic stabilization in TS-D than TS-C. These arguments validate the observed selectivity for simple 2,6-substituted tetrahydropyrans, but the stereochemical outcome of more complex THPs requires conformational analysis of the resultant heterocycle. [6]
F. Loydl reported the first oxa-Michael reaction, en route his synthesis of malic acid,\(^7\) and there have been many uses since. However, there are some serious drawbacks of this reaction. Some of these include low reactivity of the oxygen nucleophile, reversibility of the intermediate enolate, lack of control in stereoselectivity and instability of the final product, which can prone to the retro-aldol reaction (Scheme 1.3).\(^8\)

**Scheme 1.3 – Challenges of the oxa-Michael reaction**

In spite of these challenges, various protocols have been adopted to address these issues and improve the oxa-Michael reaction to make it more synthetically useful.

### 7.3 Some protocols to overcome the shortcomings of the oxa-Michael Reaction.

The low reactivity of the alcohol moiety can be attributed to the poor nucleophilicity of the oxygen atom. A way to overcome this drawback is to enhance the nucleophilicity of the alcohol by deprotonating it with a strong base. Further, the lack of reactivity can be overcome by tethering the two reactants, resulting in an intramolecular oxa-Michael reaction. An instructive example for such an intramolecular reaction has been developed by Evans and Gauchet-Prunet.\(^9\) In order to construct syn-1,3-diols for the synthesis of polyene macrolide antibiotics in a stereoselective manner, they employed easily accessible homoallylic alcohols 1 as starting materials. Reaction of these alcohols with benzaldehyde in the presence of potassium tert-butoxide (t-BuOK) furnished the corresponding benzylidene acetals 3 in high yield and diastereoselectivity. Addition of the deprotonated alcohol to benzaldehyde yields an acetal alkoxide 2 which served as a tethered oxygen nucleophile in the conjugate addition step. The stereochemical outcome of the reaction relies on thermodynamic control.
and the fact that the syn-diastereomer is energetically favoured due to all substituents on the dioxane ring being equatorial (Scheme 1.4). The substrate scope included unsaturated Weinreb-type amides and, even more interestingly, γ-substituted substrates with equal efficiency.

Scheme 1.4- Stereoselective acetalization of esters

A complementary approach for improving the oxa-Michael reactions involves the activation of the Michael acceptor by acids. An example of this is an interesting reaction developed by Spencer and Wabnitz which employed bis(trifluoromethane)sulfonimide (Tf₂NH)₂ as a strong acid catalyst (Scheme 1.5).¹⁰ The reaction involved various α,β-unsaturated ketones as acceptors and alkyl as well as benzyl alcohols. However, phenols are not suitable substrates due to competing Friedel–Crafts-type reactions triggered by the strong acid.

Scheme 1.5- Acid catalyzed oxa-Michael reaction.

A final way of improving the oxa-Michael reaction is by a bifunctional activation pathway, which involves the simultaneous activation of the alcohol and the Michael acceptor. This could be achieved by the use of bifunctional catalysts such as a chiral phosphoric acid or a tertiary amine thiourea.¹¹,¹² An illustrative example is the chiral phosphoric acid catalyzed asymmetric construction of 1,3-dioxanes by Matsubara et. al.¹³ In this strategy, the homoallyl alcohol 4 reacts with the aldehyde 5, to form
the hemiacetal 6. The dual activation sites of the chiral phosphoric acid CPA activate the Michael acceptor and the alcohol to generate 1,3-dioxanes 7 in excellent yields and selectivities. The utility of this strategy is that the produced 1,3-dioxanes 7 can be further manipulated to generate 1,3-polyols, which are useful building blocks in the de novo synthesis of optically active polyketides (Scheme 1.6).

![Scheme 1.6](image)

Scheme 1.6- 1,3-Dioxane construction via hemiacetalization/intramolecular oxy-Michael addition cascade.

These are just some of the improvements to the oxa-Michael reaction over the years, and as been the subject of intense research interest. This has enabled it to be a useful tool in natural product synthesis.

7.4 Application of the oxa-Michael reaction in the Synthesis of Natural Products.

Nicolaou et al. employed a late stage intramolecular oxa-Michael reaction in the construction of the CDEFG framework en route to the total synthesis of the marine neurotoxin Brevetoxin B. The framework was completed by the deprotection of the C11 alcohol precursor 8, which underwent a base catalyzed ring closure in a stereoselective manner with the desired stereochemistry, giving the C ring moiety of the CDEFG framework 9. The high diastereoselectivity is attributed to the reaction being under thermodynamic control, owing to the reversibility of the cyclisation which results in the more stable thermodynamic product (Scheme 1.7).
The ABC rings of azaspiracid forms a trioxadispiral motif that poses a significant synthetic challenge, and can be constructed by the efficient use of a double oxa-Michael reaction, as reported by the Forsyth group.\(^{[15]}\) The deprotection of the TES-ether molecule 10 gives the free alcohol cyclization precursor 11. The free alcohol on the furan ring initiates the ring closure at C13 to give the hemiketal 12, which is followed by the double oxa-Michael attack of the C13 and C6 alcohol onto the alkynone moiety to generate trioxadispiral ABC ring system in a single step with a decent yield of 55\% (Scheme 1.8). The cyclization is under thermodynamic control and the configuration at the C10 and C13 position is controlled by the configuration of the C6 alcohol.

Patterson completed the synthesis of the C1-C11 subunit (western fragment) of madeirolide A 18\(^{[16]}\) by employing a cis-selective oxa-Michael reaction under ‘Fuwa’ acidic conditions.\(^{[17]}\) The key step involves the condensation of aldehyde 14 with the thioester phosphonate 15 under Masamune-Roush
conditions \[18\] to give the cyclisation precursor 16 in 95% yield. Acetal deprotection by acid treatment facilitated the cis-selective cyclisation of the alcohol, followed by PMB deprotection generated the cis-tetrahydropyran 17, which gave the C1-C11 subunit of madeirolide A 18 in 2 steps (Scheme 1.9).

Reagents and Conditions: a) LiCl, NEt\(_3\), THF, –15 °C, 40 h (95%), b) TsOH, CH\(_2\)Cl\(_2\), 4.5 h, (dr >20:1) c) DDQ, CH\(_2\)Cl\(_2\), pH 7 Buff, 0 °C, 1 h (61%).

Scheme 1.9 – Synthesis of the 2,6-cis tetrahydropyran ring of Madeirolide A

Fuwa et al. employed a stereodivergent strategy to access aspergillide A 22 and aspergillide B 23 by subjecting the cyclisation precursor 19 to different conditions. \[19\] Under basic conditions at a lower temperature, the trans isomer trans 21 was synthesized with excellent yield (96%) and selectivity (dr = 17:1), leading to the synthesis of aspergillide B 23 in 5 steps. However, a switch in selectivity was observed at a higher temperature, generating the cis isomer cis 20 with good yield (81%) and selectivity (dr = 11:1), leading to the synthesis of aspergillide A 2. This change in selectivity can be attributed to the change from kinetic control at lower temperature to the thermodynamic control at a higher temperature (Scheme 1.10)
Reagents and conditions: a) DBU, toluene, 135 °C, 36 h (81%) b) t-BuOK, THF, −78 °C, 30 min (96%)

Scheme 1.10 – Stereodivergent strategy employed in the synthesis of aspergillide A and B

Conversely, Trost employed ruthenium-catalyzed trans-hydrosilylation to synthesise the tetrahydropyran ring of aspergillide B. The key step involves chemoselective reduction of alkyne 24 to an E-alkene via a hydrosilylation/protodesylation, followed by deprotection of the alcohol which facilitates a trans selective cyclization to construct the tetrahydropyran 25 in 38% yield. This completed the synthesis of aspergillide B 26 in 3 steps (Scheme 1.11).

Reagents and conditions: a) Cp*Ru(CH$_3$CN)$_3$PF$_6$, (EtO)$_3$SiH, DCE, 0 °C - rt, 10 h (38%) b) CuI, TBAF, THF, 0 °C - rt, 10 h.

Scheme 1.11 – Synthesis of aspergillide B
Lee et al. constructed the 2,3-trans-2,6-trans-tetrahydropyran ring 30 and 2,6-cis-tetrahydropyran ring 33 of leucascandrolide A macrolactone 34, using a piperidine catalysed oxa-Michael reaction and a tandem allylic oxidation/oxa-Michael reaction respectively to afford the synthesis of the macrolactone in 5 steps. The desired trans product 28 was formed with good selectivity (dr = 10:1) when aldehyde 27 was subjected to piperidine catalysed conditions at −40 °C, but was observed to generate the undesired cis product at 25 °C. This observation can be attributed to the shift in control from kinetic to thermodynamic at higher temperatures. Further, the coupling of 31 with 30 facilitated the tandem allylic oxidation/intramolecular oxa-Michael reaction to construct the 2,6-cis tetrahydropyran ring in 33. The synthesis of the macrolactone 34 was completed in 5 steps with an excellent yield of 96 % (Scheme 1.12). [21] A similar strategy was employed by Evans to construct the tetrahydropyran rings of 34. [22]

Reagents and conditions: a) piperidine, −40 °C, 24 h, CH₂Cl₂ (96%) b) NaH, MeI, DMF, 0-25 °C, 2 h c) t-BuLi, HMPA/THF, −78 °C for 10 min then 25, −78 °C, 1 h, 92%, d) MnO₂, CH₂Cl₂, 25 °C, 12 h (86%).

Scheme 1.12 – Synthesis of the tetrahydropyran rings of Leucascandrolide A
Fuwa undertook pioneering work in the area of tandem metathesis/oxa-Michael cyclization to access substituted tetrahydropyrans in an elegant fashion. A microwave assisted tandem metathesis/oxa-Michael reaction between a $\delta$-hydroxy alkene 35 and a vinyl ketone 36, catalyzed by the second generation Hovyeds-Grubbs catalyst (HG-II), yielded substituted tetrahydropyrans in good to excellent yields (70-94%) and good diastereoselectivities (8:1 to 14:1) (Scheme 1.13, eq (i)). A broader substrate scope involving a variety of coupling partners (38 and 39) under the same conditions gave excellent yields (79-97%) and diastereoselectivities (>20:1) (Scheme 1.13, eq (ii)). Interestingly, this process doesn’t need any additives and is catalyzed solely by the Hovyeda-Grubbs second generation catalyst. This can be explained by the fact that the substrates are ketones and are far easier to cyclise compared to esters. It was observed that no tandem product was formed at lower temperatures (35 °C). Several control experiments carried out in the absence and presence of the catalyst revealed that the active ruthenium species responsible for the cyclisation must have been generated in situ. Further experiments showed that this species was ruthenium hydride that was generated from the decomposition of the thermally unstable ruthenium methylidene complex, and that the presence of 2,6-dichloro-1,4-benzoquinone slowed down the cyclization and resulted in a lower yield of the tandem product 37 (17%). [23, 24]

Reagents and conditions: a) 36 (i) or 39 (ii) (1.5eq), HG-II (10 mol%), CH$_2$Cl$_2$, 100 °C (MW). Yields-i) 70-94% ii) 79-97%

Scheme 1.13- Synthesis of Tetrahydropyrans via Tandem Metathesis/Oxa-Michael reaction

By replacing CH$_2$Cl$_2$ with toluene, the substrate scope was widened to include $\alpha,\beta$-unsaturated carbonyl compounds 42 and was found to improve the yields and diastereoselectivity. However, the
reaction times also increased. To speed up the tandem process, a brønsted acid like CSA was used. Under CSA conditions, the reaction was observed to occur even at room temperature, giving moderate to good yields (48-80%) of the 2,6-cis substituted products with excellent diastereoselectivity (>20:1) (Scheme 1.14). [24]

\[
\begin{align*}
&\text{R}^1 = \text{OTBDPS} \\
&\text{R}^2 = \text{OH, OTIPS} \\
&\text{R}^3 = \text{Me, H} \\
&\text{R}^4 = \text{OMe, H, 2,5-dimethylpyridinyl}
\end{align*}
\]

Reagents and conditions: a) HG-II (10 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 100 °C (MW), 30 min, 19-98% b) HG-II (10 mol%), Toluene, 80-100 °C, 11-14 h, 40-73% c) HG-II (10 mol%), CSA (3-10 mol%), CH\textsubscript{2}Cl\textsubscript{2}, 25-35 °C, (48-80%)

**Scheme 1.14**- Improvements to the Tandem Metathesis/ Oxa-Michael reaction

Mechanistic investigations to confirm the nature of the ruthenium species was undertaken. Under reflux conditions in THF, the cyclisation of ζ-hydroxy α,β-unsaturated ketone 44 using various ruthenium hydride complexes was carried out. Using RuH\textsubscript{2}(PPh\textsubscript{3})\textsubscript{4}, the desired product 45 was obtained with a 78% yield and a diastereoselectivity of 8:1. Also, RuClH(CO)(PPh\textsubscript{3})\textsubscript{3} and RuH\textsubscript{2}(CO)(PPh\textsubscript{3})\textsubscript{3} gave the cyclised product in decent yields (45% and 55%, respectively) with a better diastereoselectivity (13:1 and 15:1 respectively). This confirmed the nature of the active ruthenium species as the ruthenium hydride. (Scheme 1.15) [24]

\[
\begin{align*}
&\text{TIPSO} \\
&\text{44} \\
&\text{OTBDPS} \\
&\text{[RuH]} \\
&\text{45}
\end{align*}
\]

Reagents and conditions: a) THF, Reflux, (45-78%)

**Scheme 1.15**- Ruthenium Hydride catalyzed Oxa-Michael reaction of ζ-hydroxy α,β-unsaturated ketone 44.

Fuwa employed the tandem metathesis/ oxa-Michael reaction methodology in the synthesis of (±)-centrolobine. The cross metathesis between the hydroxyl alkene 46 and an α,β-unsaturated ketone
47, which was synthesised from readily available p-benzyloxybenzaldehyde, afforded a crude mixture containing the desired 2,6-cis disubstituted tetrahydropyran in a ratio of 13:1 with respect to the trans isomer. Upon separation, the desired isomer 48 was isolated with a yield of 74%. Deprotection of the benzyl ether group via hydrogenolysis yielded (±)-centrolobine 49 in a 68% yield. A domino cross metathesis/oxa-Michael addition strategy yielded (±)-centrolobine in just four linear steps, starting from commercially available p-benzyloxybenzaldehyde, illustrated the efficiency and utility of this strategy (Scheme 1.16). \[25\]

![](image)

**Reagents and conditions:** a) HG-II (10 mol%), CH\(_2\)Cl\(_2\), 100 °C (MW), 20 min. b) H\(_2\), Pd/C, THF, rt, (68%).

**Scheme 1.16-** Fuwa’s synthesis of (±)-centrolobine.

Fuwa also employed this strategy in the synthesis of (-)-exiguolide. A microwave assisted cross metathesis was employed between the hydroxyl alkene 50 and an \(\alpha,\beta\)-unsaturated ketone 51, gave the 2,6-cis disubstituted tetrahydropyran intermediate 53, that was then treated without purification with BF\(_3\).OEt\(_2\) and Et\(_3\)SiH to afford the methylene bis(tetrahydropyran) 52 with an 89% yield and 10:1 diastereoselectivity. (-)-Exiguolide 54 was synthesised from this in subsequent steps. This synthesis highlights the utility and efficiency of this strategy in accessing complex structures (Scheme 1.17). \[26\]

![](image)

**Reagents and conditions:** a) HG-II (10 mol%), CH\(_2\)Cl\(_2\), 100 °C (MW), 30 min. b) BF\(_3\).OEt\(_2\), Et\(_3\)SiH, −60 °C to −15 °C, 50 min, (89%)

**Scheme 1.17-** Fuwa’s synthesis of (-)-exiguolide.
In spite of being an attractive strategy to construct substituted tetrahydropyrans, a key challenge to the tandem metathesis/oxa-Michael reaction is lies in controlling the stereoselectivity. The stereoselective synthesis of 2,6-cis disubstituted tetrahydropyrans is of particular interest as it occurs extensively in natural products. Fuwa carried out extensive research in the stereoselective synthesis of 2,6-cis tetrahydropyrans.\textsuperscript{[17,27]} Under basic conditions, $\alpha,\beta$-unsaturated ketones and esters give the kinetic 2,6-trans product, which can be converted to the thermodynamic 2,6-cis product via a base catalyzed ring opening/ring closing sequence. However, under acidic conditions, $\alpha,\beta$-unsaturated ketones give the kinetic 2,6-cis product and $\alpha,\beta$-unsaturated esters generally do not cyclise as they are less reactive (Scheme 1.18)\textsuperscript{[17]}.

\begin{center}
\textbf{Scheme 1.18-} Intramolecular oxa-Michael cyclisation of $\alpha,\beta$-unsaturated ketones/esters.
\end{center}

Several studies into the biosynthesis of polyketide containing tetrahydropyrans\textsuperscript{[28]} suggest that tetrahydropyrans are formed via a pyran synthase catalyzed intramolecular oxa-Michael cyclisation of $\alpha,\beta$-unsaturated thioesters (Scheme 1.19a)\textsuperscript{[27]} Fuwa reasoned that the activation of the carbonyl bond of the $\alpha,\beta$-unsaturated thioesters enhanced the reactivity of the thioester and plays a part in making this reaction feasible. Inspired by this, he proposed a biomimetic synthesis of 2,6-cis tetrahydropyrans via a Brønsted acid catalyzed intramolecular oxa-Michael cyclisation of $\alpha,\beta$-unsaturated ester surrogates (Scheme 1.19b).\textsuperscript{[27]}
Scheme 1.19- a) Proposed biosynthetic pathway of the synthesis of poleketide tetrahydropyrans

b) Biomimetic synthesis of 2,6-cis tetrahydropyrans of ester surrogates.

The thioesters were synthesized via a HG-II catalyzed metathesis between the hydroxyl alkene 55 and various α,β-unsaturated thioesters 56. They were then cyclized by a Brønsted acid catalyzed oxo-Michael reaction using CSA. The most reactive tetrahydropyran 58 was obtained using a tolyl thioester 60, with a yield of 72% and a dr >20:1 (Scheme 1.20a). Using the tolyl thioester 60, a substrate scope was carried out using various hydroxyl alkenes 59 to obtain excellent yields (88-97%) and diastereoselectivities (>20:1) for a variety of tetrahydropyrans 62 (Scheme 1.20b). [27] This methodology is especially attractive due to the versatility of the thioesters.
**Reagents and conditions:** For a) i) HG-II (10 mol%), CH₂Cl₂, 35 °C. ii) CSA (20 mol%), CH₂Cl₂, rt. (82-94%) For b) i) HG-II (10 mol%), CH₂Cl₂, 35 °C. ii) CSA (20 mol%), DCE, 70 °C, (88-97%)

**Scheme 1.20-** a) Preparation and intramolecular oxa-Michael cyclisation of α,β-unsaturated thioesters. b) Substrate scope

Clarke built on this strategy during his study into the occurrence of stereodivergence while synthesizing the C20-C32 fragment of the phorboxazoles. The Clarke group synthesised the C20-C32 core of the phorboxazoles by employing a silyl ether deprotection/oxa-Michael cyclisation as a key step. Interestingly, they observed that both the cis and trans products could be generated from 65, depending on the conditions used. Under acidic conditions, the C20-C32 core 66 was generated while the C22 epimer 67 was generated under buffered fluoride conditions, with an overall yield of 31% over 7 steps (Scheme 1.21).
Reagents and conditions: a) TFA, CH₂Cl₂, H₂O, rt b) TBAF, AcOH, THF (31% over 7 steps)

Scheme 1.21- Synthesis of the C20-C32 core of Phorboxazoles

To understand the occurrence of stereodivergence, substrates containing a 4-hydroxy group were synthesized. The synthesis involved a HG-II catalyzed, CuI mediated metathesis between hydroxyl alkenes 69 and thioacrylate 68 in Et₂O under reflux conditions to yield the cyclisation precursor 70. Unlike Fuwa’s work, a copper iodide additive was used, as optimization studies showed that it enhanced the yield. The 2,6-trans product 71 was observed predominantly under buffered fluoride conditions, with good yields (40-69%) and good diastereoselectivities (8:1 to 20:1). Under TFA or CSA mediated conditions, the 2,6-cis product 72 was observed with better yields (65-74%) and comparable diastereoselectivities (7:1 to 20:1) (Scheme 1.22). When the hydroxyl at the 4 position was removed and the same protocol as above was carried out, the 2,6-cis product 76/77 was observed under both the buffered fluoride and acid conditions. While the yields under buffered fluoride conditions (25-53%) were comparable to that of the acid conditions (36-56%), the diastereoselectivities (>20:1) were much better than the acid conditions (4:1 to 8:1) (Scheme 1.23). [30]
Reagents and conditions: a) HG-II (10 mol%), Cul (15%), Et₂O, reflux. b) TBAF (30 mol%), AcOH (6%), THF, (40-69%) c) TFA, H₂O, CH₂Cl₂, rt or CSA, DCE, 80 °C, (65-74%)

Scheme 1.22 - Stereodivergent synthesis of 4-hydroxy containing substrates.

Reagents and conditions: a) HG-II (10 mol%), Cul (15%), Et₂O, reflux. b) TBAF (30 mol%), AcOH (6%), THF, (25-53%) c) TFA, H₂O, CH₂Cl₂, rt or CSA, DCE, 80 °C, (36-56%)

Scheme 1.23 – Cyclisation of substrates without a 4-hydroxy group.

The general conclusion of the study was that a 4-hydroxy group was crucial for the occurrence of stereodivergence in the thioester oxa-Michael cyclisation (Scheme 1.24). Computational studies were carried out to model the most preferred transition state and understand the underlying mechanism that resulted in the observed stereodivergence. It was found that the flouride mediated
transition state preferred a boat like structure wherein the alkoxide of the cyclizing hydroxyl is involved in hydrogen bonding with the δ hydroxyl. This is not the case with the TFA mediated cyclisation. Here, the molecule adopts a chair-like transition state, with the trifloroacetate acting as a proton shuttle, increasing the nucleophilicity of the alkoxide oxygen and the electrophilicity of the thioester at the same time. The δ-hydroxyl is not involved in the transition state (Figure 2). [30]

Scheme 1.24 General outline of the stereodivergent thioester oxy-michael cyclisation

Figure 2- Transition states adopted in the stereodivergent oxy- Micheal cyclisation

7.5 Aim and Scope of the Project.

Chiral Brønsted acids, such as phosphoric acids and their derivatives in particular, have generated a lot of research interest, [31,32] ever since they were reported separately by Akiyama [33] and Terada [34] in 2004. Chiral Brønsted acids have been shown to catalyze desymmetrisation of cyclohexanediones via an intramolecular oxy-Micheal reaction (Scheme 1.25a) [35] and stereoselective spiroketalisation (Scheme 1.25 b) [36] with excellent enantioselectivities.
As Clarke’s TFA mediated cyclisation doesn’t depend on any structural features, it can be postulated that a chiral acid which acts as a proton shuttle, can replace TFA, resulting in the enantioselective synthesis of tetrahydropyrans. As TFA (pKa = −0.3) and CSA (pKa = 1.2) act as proton shuttles in the thioester oxy-Michael reaction, chiral Brønsted acids with similar pKa values should be able to perform the same function. In simple terms, the acid would form one enantiomer while the ent-acid would form the other enantiomer.

Previous computational work in the group, by Kristaps Ermanis,\[37\] looked into the feasibility of the chiral phosphoric acid catalyzed oxa-Michael cyclisation. Preliminary work modelled the oxa-Michael cyclisation of 81 with the commercially available chiral phosphoric acid (R)-TRIP and the energy barrier of formation between the enantiomers was calculated using a conformational search using molecular mechanics with MacroModel and an MMFF force field (Scheme 1.26a). It was found that the formation of the S-enantiomer was favoured by 8 KJ/mol in case of a tolyl precursor. On changing the tolyl group with a mesityl group, the energy barrier increased to 20 KJ/mol, suggesting that greater enantioselectivities should be observed in cases involving a mesityl precursor (Scheme 1.26b). This computational result shows that the cyclisation is feasible and that increasing the acidity of the acid, which is in the range of TFA (pKa = −0.3) and CSA (pKa = 1.2), could favour better enantioselectivities. The aim of this project is to develop an asymmetric oxa-Michael reaction by replacing TFA with a chiral brønsted acid proton shuttle like chiral phosphoric acids, which would lead to the formation of...
enantioenriched THP products. The enantioselectivities can be switched by using the ent-form of the chiral acid.

Scheme 1.26- Preliminary computational work into the chiral acid catalyzed oxa-Michael cyclisation.
8. Results and Discussions

8.1 Retrosynthetic Analysis of the Tetrahydropyran Precursors

The cyclisation precursors (tolyl 82 and mesityl 89) were accessed via a two-step convergent synthetic route starting from readily available starting materials. Performing retrosynthetic analysis on the cyclisation precursors 82 and 89, they could be simplified to the thioacrylate 83/90 and the alcohol 84 via a cross metathesis reaction. The thioacrylate 83/90 could be prepared via acylation between the thiol 85/91 and acryloyl chloride 86. The alcohol 84, on the other hand, could be synthesized via a simple Grignard reaction between metallated 5-bromopentene 87 and the corresponding aldehyde/ketone 88 (Scheme 2.1).

Scheme 2.1- Retrosynthetic analysis of the cyclisation precursors 82 and 89.

8.2 Synthesis of the Tetrahydropyran Precursors.

For the purpose of this study, the alcohols used included a primary alcohol 84b, a secondary alcohol 84c (with an isopropyl substituent) and a tertiary alcohol 84a (with a dimethyl substituent), of which 84a and 84c were synthesized while 84b was commercially available (Figure 3).

Figure 3- Structures of alcohol 84.
The forward synthetic route to the cyclisation precursors began with the synthesis of the alcohols \( \textbf{84a} \) and \( \textbf{84c} \) based on literature procedures. The synthesis involved the initial generation of the Grignard reagent \( \textbf{92} \), followed by the addition of the corresponding aldehyde \( \textbf{88c}/\textbf{ketone} \textbf{88a} \), to give the necessary alcohol \( \textbf{84} \). Initial attempts at the synthesis of \( \textbf{84a} \) involved the usage of THF as a solvent, which proved difficult in separation upon work-up, resulting in a loss of product. Upon, switching to \( \text{Et}_2\text{O} \), the work-up and separation were much easier, resulting in a disappointing yield of 13%. In the synthesis of \( \textbf{84c} \), there were no issues involving THF and the synthesis was smooth, resulting in a 25% yield (Scheme 2.2)

![Scheme 2.2: Synthesis of alcohols 84.](image)

Reagents and conditions: For \( \textbf{84a} \): a) \( \text{Mg/Et}_2\text{O}, \text{rt}, 2 \text{ h} \) b) \( \textbf{88a} \), rt (13%) and for \( \textbf{84c} \): a) \( \text{Mg/THF}, \text{rt}, 1 \text{ h} \). b) \( \textbf{88c} \), rt, 90 min (25%)

With the synthesis of the alcohols complete, the synthesis of thioacrylate \( \textbf{83} \) was attempted, based on a literature procedure. The synthesis began with the deprotonation of thiol \( \textbf{85} \) by dissolving it in a solution of \( \text{NaOH/NaBH}_4 \), to generate the thiolate anion \( \textbf{93} \). To this, a solution of acryloyl chloride \( \textbf{86} \) in cyclohexane, containing the additive BHT, was added, resulting in the synthesis of thioacrylate \( \textbf{83} \) with a yield of 47% (Scheme 2.3a). The thioacrylate \( \textbf{90} \) was synthesized in an analogous manner with a yield of 50% (Scheme 2.3b).
Reagents and conditions: For 83: a) 15% NaOH, NaBH₄, rt, 1 h b) 86, BHT, cyclohexane, 55 °C, 30 min, (47%) For 90: a) 15% NaOH, NaBH₄, rt, 1 h b) 86, BHT, cyclohexane, 55 °C, 90 min (50%).

Scheme 2.3 - Synthesis of Thioacrylate 83 and 90

The additives play an important role in the efficiency of the synthesis. The addition of NaBH₄ to the thiolate 93 prevents the formation of disulfides, while the addition of BHT to the acryloyl chloride 86 prevents radical polymerization. With the synthesis of the thioacrylate 83/90 and the requisite alcohols 84 complete, the synthesis of the cyclisation precursors 82 and 89 was attempted via a cross metathesis reaction.

The conditions previously employed by Clarke [30] were used to synthesise our cyclisation precursors 82 and 89 from alcohols 84 and thioacrylate 83 and 91 (Scheme 2.4). The metathesis was catalyzed by HG-II and mediated by Cul (1:1 ratio) in Et₂O under reflux conditions, by using the alcohols 84 and the thioacrylate 83/90 in a ratio of 1:3. The synthesis of cyclisation precursor 83 was first attempted. The metathesis occurred smoothly but took longer in the primary and tertiary alcohol cases (entry 1 and 2) (Scheme 2.4a) compared to the secondary alcohol (entry 2). The cyclisation precursors were obtained as brown oils and the yields were excellent. In an analogous manner, the Grubbs metathesis between alcohols 84 and the mesitylthioacrylate 90 was carried out under the same conditions used for the tolyl precursors 82. The synthesis was smooth and the mesityl precursors 89 were made with good to excellent yields (Scheme 2.4b) The yield of the isopropyl precursor 89c (56%) was lower compared to that of 89a (86%) and 89b (91%).
Reagents and conditions: a) HG-II (10 mol%), Cul (10%), Et₂O, reflux.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Alcohol</th>
<th>R</th>
<th>Cyclisation precursor</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>84a</td>
<td>R¹ = R² = Me</td>
<td>82a</td>
<td>24</td>
<td>87</td>
</tr>
<tr>
<td>Entry 2</td>
<td>84b</td>
<td>R¹ = R² = H</td>
<td>82b</td>
<td>24</td>
<td>86</td>
</tr>
<tr>
<td>Entry 3</td>
<td>84c</td>
<td>R¹ = H; R² = i-Pr</td>
<td>82c</td>
<td>2</td>
<td>85</td>
</tr>
</tbody>
</table>

Reagents and conditions: a) HG-II (10 mol%), Cul (10%), Et₂O, reflux.

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Alcohol</th>
<th>R</th>
<th>Cyclisation precursor</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>84a</td>
<td>R¹ = R² = Me</td>
<td>89a</td>
<td>18</td>
<td>86</td>
</tr>
<tr>
<td>Entry 2</td>
<td>84b</td>
<td>R¹ = R² = H</td>
<td>89b</td>
<td>24</td>
<td>91</td>
</tr>
<tr>
<td>Entry 3</td>
<td>84c</td>
<td>R¹ = H; R² = i-Pr</td>
<td>89c</td>
<td>16</td>
<td>56</td>
</tr>
</tbody>
</table>

Scheme 2.4 – Synthesis of cyclisation precursors 82 and 89.

With the synthesis of the cyclisation precursors 82 and 89 complete, the Brønsted acid catalyzed cyclisation was ready to be attempted.
8.3 Brønsted Acid Catalyzed Cyclisation of Tetrahydropyran Precursors.

The general scheme for the Brønsted acid catalyzed cyclisation involves the use of TFA or CSA as acids. The cyclisation of toyl precursors 82 to generate 2,6 disubstituted tetrahydropyrans 95 was first attempted (Scheme 2.5).

![Scheme 2.5 – General scheme for Brønsted Acid Catalyzed Cyclisation](image)

The objectives of carrying out Brønsted acid catalyzed cyclisation of precursors 82 was twofold. Firstly, it was done to observe the reactivity trends of the precursors 82 to acid cyclisation and use that information to carry out the chiral Brønsted acid catalyzed asymmetric cyclisation of the same. Secondly, the generated racemic samples would be used for HPLC analysis and screen conditions for effective resolution, which would be used to determine the %ee of the enantioenriched samples from the asymmetric cyclisation.

We began with the TFA catalyzed cyclisation of 82a, using the conditions employed by Clarke. The initial precursor concentration for all cyclisations was kept at standard of 0.06 M. To this, TFA and H2O were added. The TFA used was also 0.06 M and the ratio of TFA and H2O was maintained at 9:1. The total amount of TFA and H2O were scaled up accordingly [Table1].
<table>
<thead>
<tr>
<th>Reaction</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>(TFA: H₂O) (mL)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>0.9:0.1</td>
<td>nil</td>
</tr>
<tr>
<td>Entry 2</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>0.9:0.1</td>
<td>32</td>
</tr>
<tr>
<td>Entry 3</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>1.8:0.2</td>
<td>32</td>
</tr>
<tr>
<td>Entry 4</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>3.6:0.4</td>
<td>31</td>
</tr>
<tr>
<td>Entry 5&lt;sup&gt;⊥&lt;/sup&gt;</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>0.9:0.1</td>
<td>60</td>
</tr>
<tr>
<td>Entry 6&lt;sup&gt;⊥&lt;/sup&gt;</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>neat</td>
<td>83</td>
</tr>
<tr>
<td>Entry 7*</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>20 mol%</td>
<td>11</td>
</tr>
<tr>
<td>Entry 8*</td>
<td>TFE</td>
<td>rt</td>
<td>24</td>
<td>20 mol%</td>
<td>10</td>
</tr>
<tr>
<td>Entry 9*</td>
<td>HFIP</td>
<td>rt</td>
<td>24</td>
<td>20 mol%</td>
<td>13</td>
</tr>
</tbody>
</table>

<sup>⊥</sup> solvent evaporated before addition. * No water added

**Table 1**: Cyclisation of 82a under TFA conditions.

Similar to previous work in the Clarke group, the cyclisation of 82a was attempted at room temperature, but no cyclisation product was observed even after 24 h (entry 1). As there was no reaction observed at room temperature, it was reasoned that given the low reactivity of the substrate, increasing the temperature might help overcome the lack of reactivity. The solvent was switched to DCE and the reaction was carried out at 50 °C. Maintaining the same amount of TFA and H₂O, some conversion of the substrate to the product was observed (entry 2). The next parameter that could be altered was the amount of TFA and H₂O. The amount was doubled (entry 3) and subsequently quadrupled (entry 4) with respect to entry 1, but the conversion appeared to remain constant. It appears that the cyclisation was unaffected by the amount of acid. The next parameter to change was the amount of solvent. In effect, by removing the solvent, the effective concentration of the precursor increases. To alter this, a 0.06 M solution of the substrate in DCM was prepared and the solvent was evaporated, prior to addition of the acid. To this, TFA and H₂O were added in a ratio of 9:1 (1 mL combined) and reacted. Interestingly, the conversion doubled (entry 5) with respect to entry 2. Encouraged by this result, the reaction was carried out neat in TFA i.e. without the presence of H₂O. This improved the conversion to 83% (entry 6). Seeing that the absence of water gave the best conversion, the effect of catalyst loading and more polar solvents on the reaction was studied. To this end, the reaction was carried out at room temperature without the presence of H₂O, with an initial precursor concentration of 0.06 M, and a TFA loading of 20 mol% (entry 7). Next, DCM was replaced by TFE (entry 8) and HFIP (entry 9). Surprisingly, there was similar conversions, showing that...
decreasing the loading in the absence of H₂O does form some product, unlike entry 1 [Table-1]. The cyclisation of 82a was then attempted using CSA, under the conditions employed by Clarke. [30] In this reaction, CSA was used in 3 eq and the cyclisation was carried out at 80 °C for 24 h. The conversion (75%) was higher than a typical TFA cyclisation.

With the cyclisation of 82a complete, the focus shifted to 82b. The TFA cyclisation was attempted first (Table 2).

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>(TFA: H₂O) (mL)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>0.9:0.1</td>
<td>13</td>
</tr>
<tr>
<td>Entry 2</td>
<td>DCE</td>
<td>60</td>
<td>24</td>
<td>2.7:0.3</td>
<td>41</td>
</tr>
<tr>
<td>Entry 3</td>
<td>DCE</td>
<td>80</td>
<td>24</td>
<td>2.7:0.3</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 2- Cyclisation of 82b under TFA conditions.

Similar to 82a, the cyclisation was first attempted at room temperature, starting with a precursor concentration of 0.06 M. However, the conversion was only 13% (entry 1). Subsequently, the temperature was increased to 60 °C and instead of a 0.06 M solution of substrate, a 0.02 M one was taken and the amount of TFA and H₂O were tripled (entry 2) with respect to entry 1. In essence, two parameters namely temperature and amount of catalyst were varied at the same time. The temperature was further increased to 80 °C, keeping the amount of acid and H₂O the same (entry 3). Interestingly, the conversion tripled compared to the first attempt, and gave a more modest conversion of 41% and 36% at 60 °C and 80 °C respectively [Table-2]. Following this, a CSA catalyzed cyclisation of 82b was attempted analogous to that of 82a. The cyclisation was carried out at 80 °C, using 3eq of CSA, for 24 h. The conversion (94%) was excellent, compared to the TFA cyclisation attempts of 82b.

Finally, the TFA cyclisation of substrate 82c was carried out, based on a literature procedure [31] In the procedure, the precursor concentration was 0.06 M, and the amount of TFA and H₂O used were 0.9 mL and 0.1 mL respectively. The reaction was quenched after 5.5 h. While the conversion was not reported, it was assumed to have undergone complete conversion. However, in our attempt analogous to the procedure, there was still unreacted starting material. Prolonged reaction time of 48 h gave only a 64% conversion.
Reagents and conditions: a) TFA (1.8 mL)/ H₂O (0.2 mL), DCE, 50 °C, 24 h. Yield- 96a (41%) and 96c (52%)

Scheme 2.6- Cyclisation of 89 under TFA conditions.

The cyclisation of mesityl precursors 89 to generate 2,6 disubstituted tetrahydropyran 96 was then attempted (Scheme 2.6). Observing that when H₂O was present, the amount of TFA and H₂O used had no effect on the conversion, it was decided that a screen similar to the toyl precursors 82 would not be undertaken. Instead, it was decided that one set of conditions would be chosen to prepare the racemic samples needed for HPLC analysis. To this effect, the cyclisation of 89a and 89c at 50 °C in DCE, using TFA/ H₂O (1.8 mL : 0.2 mL) and a precursor concentration of 0.06 M was carried out. The conversions for 89a and 89c were 44% and 89% respectively.

With the synthesis of cyclized products 95 and 96 complete, attempts were made to resolve the enantiomers of the racemic mixtures. Since the next part of the study involved the asymmetric oxa-Michael cyclisation using chiral phosphoric acids and determining the enantioselectivities of the cyclized products, conditions to resolve these mixtures in a chiral fashion was of paramount importance. Hence, conditions determined from the successful separation of enantiomers in a racemic mixture could be applied to resolving chiral mixtures.

Chiral HPLC is a very useful technique to resolve complex mixtures and finds wide application in analytical labs and industry. The principle involves the differential retention times of the components in a mixture upon elution on a chiral column, leading to successful chiral resolution. After testing various columns using different eluant concentration (Hexane:IPA) and flow rates, the cyclisation products 95 and 96 were resolved using a CHIRALCEL AD-H column (Figure 4) [Table 3].
<table>
<thead>
<tr>
<th>Cyclisation Product</th>
<th>(Hexane:IPA)</th>
<th>Peak 1 (min)</th>
<th>peak 2 (min)</th>
<th>Flowrate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95a</td>
<td>95/5</td>
<td>3.763</td>
<td>4.484</td>
<td>1.0</td>
</tr>
<tr>
<td>95b</td>
<td>95/5</td>
<td>12.200</td>
<td>13.213</td>
<td>1.0</td>
</tr>
<tr>
<td>95c</td>
<td>95/5</td>
<td>3.314</td>
<td>3.581</td>
<td>1.0</td>
</tr>
<tr>
<td>96a</td>
<td>95/5</td>
<td>4.280</td>
<td>4.891</td>
<td>0.9</td>
</tr>
<tr>
<td>96c</td>
<td>97/3</td>
<td>9.897</td>
<td>12.369</td>
<td>0.9</td>
</tr>
</tbody>
</table>

**Table 3** - HPLC retention times of cyclised products 95 and 96.

**Figure 4** - HPLC traces of cyclised products 95 and 96.
Based on the Brønsted acid catalyzed cyclisations of precursors 82 and 89, it was observed that the amount of acid used had little effect on conversion and that there was no marked improvement in the conversion. This could be attributed to the lower reactivity of thioesters, compared to ketones, to acid cyclisation due to lower activation of the Michael acceptor. Another factor could be the rate of cyclisation itself, which is a 6-exo-trig cyclisation here. It is known that 5-exo-trig cyclisations involving tetrahydrofurans are faster than the 6-exo-trig cyclisations involving tetrahydrofurans. It can thus be reasoned that the conversions of the corresponding tetrahydrofuran precursors under the conditions tested should be better than the tetrahydropyran precursors 82 and 89. To this end, the synthesis of the corresponding tetrahydrofuran precursors was attempted.

8.4 Synthesis of Tetrahydrofuran Precursors.

The synthesis of the tolyl tetrahydrofuran precursors followed the same strategy as the tetrahydropyran precursors. The synthesis began with the preparation of the corresponding alcohols 97. The alcohols 97a and 97c were synthesized while 97b was commercially available (Figure 5).

![Figure 5- Structures of alcohol 97](image)

The forward synthetic route to the tetrahydrofuran precursors began with the synthesis of the alcohols 97a and 97c, analogous to literature procedures (Scheme 2.7).

![Scheme 2.7- Synthesis of alcohols 97](image)

Reagents and conditions: a) MeMgBr/Et₂O, rt, 1 h (39%) b) Mg/THF, rt, 2.5 h c) rt, 2 h (49%)

The synthesis of both 97a and 97c occurred smoothly with a yield of 39% and 49% respectively. The synthesis of the tolyl cyclisation precursor 101 was first attempted. The metathesis between the
alcohols 97 and thioacrylate 85 was carried using similar conditions as the tetrahydropyran precursors (Scheme 2.8). The metathesis occurred smoothly with similar times for all three precursors and were obtained as brown oils with excellent yields (Scheme 2.8a). Similarly, the synthesis of the mesityl precursors 102 was attempted. Using mesitylthioacrylate 91, the Grubbs metathesis between alcohols 97 and the mesitylthioacrylate 91 was carried out under the same conditions. The synthesis was smooth and the mesityl precursors 102 were made with good to excellent yields (Scheme 2.8b). The yields were comparable to the tolyl precursors, with 102a and 102b having a yield of 88% and 82% respectively. The synthesis of the isopropyl precursor 102c was not attempted.

**Reagents and conditions**: a) HG-II (10 mol%), CuI (10%), Et₂O, reflux

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Alcohol</th>
<th>R</th>
<th>Cyclisation precursor</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>97a</td>
<td>R¹ = R² = Me</td>
<td>101a</td>
<td>20</td>
<td>87</td>
</tr>
<tr>
<td>Entry 2</td>
<td>97b</td>
<td>R¹ = R² = H</td>
<td>101b</td>
<td>18</td>
<td>79</td>
</tr>
<tr>
<td>Entry 3</td>
<td>97c</td>
<td>R¹ = H; R² = i-Pr</td>
<td>101c</td>
<td>16</td>
<td>74</td>
</tr>
</tbody>
</table>

**Reagents and conditions**: a) HG-II (10 mol%), CuI (10%), Et₂O, reflux

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Alcohol</th>
<th>R</th>
<th>Cyclisation precursor</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>97a</td>
<td>R¹ = R² = Me</td>
<td>102a</td>
<td>18</td>
<td>88</td>
</tr>
<tr>
<td>Entry 2</td>
<td>97b</td>
<td>R¹ = R² = H</td>
<td>102b</td>
<td>18</td>
<td>82</td>
</tr>
</tbody>
</table>

**Scheme 2.8** – Synthesis of cyclisation precursors 101 and 102.
8.5 Brønsted acid Catalyzed Cyclisation of Tetrahydrofuran Precursors.

The general scheme for the Brønsted acid catalyzed cyclisation involves the use of TFA or CSA as acids. The cyclisation of toyl precursors 101a to generate 2,6 disubstituted tetrahydrofuran 103a was first attempted (Scheme 2.9).

![Scheme 2.9 – Cyclisation of 101a under acid conditions](image)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>(TFA: H₂O) (mL)</th>
<th>Conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>DCM</td>
<td>rt</td>
<td>24</td>
<td>1.8:0.2</td>
<td>6</td>
</tr>
<tr>
<td>Entry 2</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>0.9:0.1</td>
<td>68</td>
</tr>
<tr>
<td>Entry 3</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>1.8:0.2</td>
<td>37</td>
</tr>
<tr>
<td>Entry 4</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>3.6:0.4</td>
<td>38</td>
</tr>
<tr>
<td>Entry 5⊥</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>9:1</td>
<td>46</td>
</tr>
<tr>
<td>Entry 6⊥</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>neat</td>
<td>93</td>
</tr>
<tr>
<td>Entry 7⊥</td>
<td>DCE</td>
<td>50</td>
<td>24</td>
<td>1:1</td>
<td>4</td>
</tr>
</tbody>
</table>

⊥ solvent evaporated before addition

*Table 4 – Cyclisation of 101a under TFA conditions*

The first cyclisation attempted was the TFA catalyzed cyclisation of 101a. The precursor concentration for all cyclisations was kept at standard of 0.06 M. The TFA used was also 0.06 M and the ratio of TFA and H₂O was maintained 9:1. The total amount of TFA and H₂O were scaled up accordingly (Table 4). Unlike the tolyl tetrahydropyran precursor 82a, the cyclisation at room temperature was attempted with 1.8 mL of TFA. This gave very little conversion and the separation was not clean, with a lot of grease accompanying the product (entry 1). Reverting back to using 0.9 mL of TFA, the solvent was switched to DCE and the reaction was carried out at 50 °C. Interestingly, a drastic increase in
conversion (68%) was observed (entry 2). The next parameter that could be altered was the amount of TFA and H₂O. The amount was then doubled (entry 3) and quadrupled (entry 4) with respect to entry 2. However, the conversion (37%) in entry 3 almost halved and remained the same (38%) for entry 4 with respect to entry 2, in spite of increasing the amount of TFA and H₂O. The next parameter to change was the amount of solvent. It appears that the cyclisation was unaffected by the amount of acid. The next parameter to change was the amount of solvent. In effect, by removing the solvent, the effective concentration of the precursor increases. To alter this, a 0.06 M solution of the substrate in DCM was prepared and the solvent was evaporated before addition of the acid. To this, TFA and H₂O were added in a ratio of 9:1 (1 mL combined) and reacted. However, there was only a marginal increase in the conversion (46%) (entry 5). When the reaction was carried out neat i.e. without the presence of H₂O, the conversion (93%) doubled (entry 6) with respect to entry 5. Finally, TFA and H₂O were added in a 1:1 ratio (1 mL combined) after evaporating DCM. Interestingly, a similar result as the room temperature condition of poor conversion and purification was observed (entry 7) [Table-4].

The cyclisation of 101a was then attempted using CSA, under similar conditions as the tolyl precursor 82a. In the reaction, CSA was used in 3 eq and the cyclisation was carried out at 80 °C for 24 h. It was observed that the conversion (97%) was near quantitative.

Reagents and conditions: a) TFA (1.8 mL)/ H₂O (0.2 mL), DCE, 50 °C, 24 h (68%)

Scheme 2.10- Cyclisation of 102a under TFA conditions.

The cyclisation of mesityl precursors 102 to generate 2,6 disubstituted tetrahydropyrans 104 was then attempted (Scheme 2.10). Observing that when H₂O was present, the amount of TFA and H₂O used had no effect on the conversion, it was decided that a screen similar to the tolyl precursors 101 would not be undertaken. Instead, it was decided that one set of conditions would be chosen to prepare the racemic samples needed for HPLC analysis. To this effect, the cyclisation of 102a at 50 °C in DCE, using TFA/ H₂O (1.8 mL : 0.2 mL) and a precursor concentration of 0.06 M was carried out. The conversions for 102a was 77%.
With the synthesis of cyclized products 103a and 104a complete, attempts were made to resolve the enantiomers of the racemic mixtures. Similar HPLC conditions as the tetrahydropyran precursors 95 and 96 were employed, using the CHIRALCEL AD-H column as before. The cyclisation products 103a and 104a were resolved (Figure 6) [Table 5].

Table 5- HPLC retention times of cyclised products 103a and 104a.

<table>
<thead>
<tr>
<th>Cyclisation Product</th>
<th>(Hexane:IPA)</th>
<th>Peak 1 (min)</th>
<th>peak 2 (min)</th>
<th>Flowrate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>103a</td>
<td>97/3</td>
<td>15.319</td>
<td>16.966</td>
<td>0.9</td>
</tr>
<tr>
<td>104a</td>
<td>95/5</td>
<td>4.983</td>
<td>5.866</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Figure 6- HPLC traces of cyclised products 103a and 104a.

Comparing the Brønsted acid mediated cyclisation trends between the tetrahydropyran precursor 82a and 101a, the anticipated improvement in conversion of a tetrahydrofuran precursor 101a with respect to the tetrahydropyran precursor 82a was not found. It was found that the amount of acid had only a marginal effect on conversion. Clarke’s conditions [36] were concluded to be suboptimal for carrying out asymmetric cyclisations and there was a need for different conditions. This was affirmed by the fact that increasing the polarity of the solvent from DCE to the use of TFE and HFIP had no
improvement on conversion [Table1]. The reason we increased polarity was the assumption that a more polar solvent might stabilize the transition state of a chiral Brønsted acid catalyzed cyclisation. This pointed to the possible important role the solvent might play in the asymmetric cyclisation. Given that increase in polarity didn’t improve conversion, we hypothesized that a decrease in polarity might just improve it. Upon a literature search, we came across the enantioselective synthesis of 2,6-cis tetrahydropyrans using a chiral phosphoric acid via an oxa-Michael cyclisation reported by Yoneda (Scheme 2.11). In his study, he carried out novel asymmetric cycloetherification, which was then accompanied by the kinetic resolution of secondary and tertiary alcohols to synthesise tetrahydropyrans bearing two chiral centers with excellent enantioselectivities and high s-factors.

What interested us was the use of toluene to achieve such high enantioselectivities. This indicated that our reasoning was in the right direction and we hypothesized that the use of solvents with similar or lower polarity and dielectric constant to that of toluene would enhance enantioselectivities in an asymmetric cyclisation. The dielectric constant of toluene is 2.38. To this end, solvents with dielectric constants similar to or lower than toluene were chosen-1,4-dioxane (2.21) and cyclohexane (2.02). An important thing to note in the paper was the presence of the $\alpha,\beta$-unsaturated ketone functionality in all the substrates. This has a higher reactivity towards cyclisation compared to thioesters, and hence the reaction occurred at very low temperatures. The substrate scope was limited to only $\alpha,\beta$-unsaturated aryl ketones. We wanted to employ these conditions to the chiral Brønsted acid catalyzed cyclisation of the thioester precursors which are more versatile than $\alpha,\beta$-unsaturated ketones as they can be converted to other functional groups. Reasoning that the cyclisation involving tetrahydrofuran precursors 101 and 102 might be faster than tetrahydropyran precursors 82 and 89, we felt that the chiral Brønsted acid catalyzed cyclisation of the tetrahydrofuran precursors 101 and 102 might be a good place to start.
8.6 Chiral Brønsted Acid Catalyzed Cyclisation of Tetrahydrofuran Precursors.

![Scheme 2.12— Chiral Brønsted Acid Catalyzed Cyclisation of 101a using CPA.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>rt</td>
<td>DCM</td>
<td>(R)-TRIP</td>
<td>11</td>
<td>29</td>
</tr>
<tr>
<td>Entry 2</td>
<td>rt</td>
<td>1,4-Dioxane</td>
<td>(R)-TRIP</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>Entry 3</td>
<td>rt</td>
<td>Toluene</td>
<td>(R)-TRIP</td>
<td>10</td>
<td>26</td>
</tr>
<tr>
<td>Entry 4</td>
<td>rt</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>18</td>
<td>43</td>
</tr>
<tr>
<td>Entry 5</td>
<td>50</td>
<td>Toluene</td>
<td>(R)-TRIP</td>
<td>74</td>
<td>42</td>
</tr>
<tr>
<td>Entry 6</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>99</td>
<td>45</td>
</tr>
<tr>
<td>Entry 7</td>
<td>75</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>99</td>
<td>46</td>
</tr>
<tr>
<td>Entry 8</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TIPSY</td>
<td>89</td>
<td>60</td>
</tr>
<tr>
<td>Entry 9</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-1</td>
<td>99</td>
<td>15</td>
</tr>
<tr>
<td>Entry 10</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-2</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Entry 11</td>
<td>50</td>
<td>Toluene</td>
<td>CPA-2</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Table 6— Chiral Brønsted Acid Catalyzed Cyclisation of 101a using CPA.

We began with the investigation of the chiral Brønsted acid catalyzed cyclisation of 101a. An initial solvent, catalyst and temperature screen was first undertaken using (R)-TRIP, (R)-TIPSY, CPA-1 and CPA-2. The temperature was varied from room temperature to 50 °C and subsequently 75 °C and a catalyst loading of 20 mol% was chosen. The initial precursor concentration was maintained at
The initial solvent screen involving the chosen solvents was attempted at room temperature and was compared to that involving DCM. As expected, the conversion (11%) was low with DCM and the ee was 29% (entry 1). The reaction in dioxane produced multiple products and the conversion could not be ascertained. However, the ee (14%) was observed to decrease by half (entry 2). Interestingly, the conversion (10%) and ee (26%) in toluene (entry 3) was similar to that of entry 1. Finally, in cyclohexane, an improvement in the ee (43%) was observed (entry 4). The cyclisation was then attempted at 50 °C, to increase the conversion. In toluene, there was a significant improvement in the conversion (74%), and no reduction in the ee (42%) (entry 5). Switching to cyclohexane, a quantitative conversion (99%) was observed and the ee (40%) was maintained (entry 6). Increasing the temperature to 75 °C in cyclohexane had no demonstrative effect, with the ee (46%) remaining essentially the same (entry 7). This was a surprising result, as one would expect the %ee to drop with increase in temperature. When (R)-TRIP was replaced with (R)-TIPSY in cyclohexane, there was a slight drop in conversions (99% to 89%). Interestingly, there was an increase in the ee (60%) (entry 8). In the case of CPA-2, the conversion (99%) improved by 10%, but the ee (15%) dropped by 75% compared to (R)-TIPSY (entry 9). Finally, CPA-3 was used and found to have solubility issues in cyclohexane, giving a very poor conversion (12%) and rendering the product essentially racemic (entry 10). On using toluene, conversion (6%) dropped by half with no improvement of the ee (entry 11). The best conditions were determined to be using (R)-TIPSY in cyclohexane at 50 °C which gave a 60% ee [Table 6].

Scheme 2.13—Chiral Brønsted Acid Catalyzed Cyclisation of 101b using CPA.
Next, the cyclisation of 101b was investigated (Scheme 2.13). Seeing that cyclohexane and toluene gave better results than 1,4-dioxane and owing to multiple products generated in it, its use was discontinued. At room temperature, the conversion (10%) in cyclohexane was very low with only a 10% ee (entry 1). Upon increasing the temperature to 50 °C, a marked improvement in the conversion (80%) was observed and the ee was 33% (entry 2). At 75 °C, a near quantitative conversion (97%) was observed (entry 3), but the ee (40%) improved only marginally compared to entry 2. Interestingly, (R)-TIPSY resulted in a decrease in the conversion (60%) (entry 4) and a marked decrease in the ee (14%) compared to entry 2. When, CPA-1 was used, the product was essentially racemic (entry 5), but improvements in the conversion (81%) was observed. Finally, CPA-2 was used and found to have solubility issues in cyclohexane and difficulty in purification, giving a poor conversion (6%). But an improvement in the ee (24%) (entry 6). On using toluene instead of cyclohexane for CPA-2, similar issues as entry 6 were faced and the product was essentially racemic (entry 7) [Table 7].

With the investigation into the chiral acid catalyzed cyclisation of tolyl tetrahydrofuran precursors 101, completed, to focus was shifted to the asymmetric cyclisation of the mesityl tetrahydrofuran precursors 102. The choice of solvent was restricted to cyclohexane, as it gave the highest conversions and ee. The choice of catalyst was restricted to (R)-TRIP.

Table 7 – Chiral Brønsted Acid Catalyzed Cyclisation of 101b using CPA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Catalyst</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>80</td>
<td>33</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>97</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TIPSY</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-1</td>
<td>81</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-2</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Toluene</td>
<td>CPA-2</td>
<td>7</td>
<td>1</td>
</tr>
</tbody>
</table>

Scheme 2.14 – Chiral Brønsted Acid Catalyzed Cyclisation of 102a using (R)-TRIP
Table 8 – Chiral Brønsted Acid Catalyzed Cyclisation of 102a using (R)-TRIP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>rt</td>
<td>Cyclohexane</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Entry 2</td>
<td>50</td>
<td>Cyclohexane</td>
<td>98</td>
<td>31</td>
</tr>
<tr>
<td>Entry 3</td>
<td>75</td>
<td>Cyclohexane</td>
<td>98</td>
<td>21</td>
</tr>
</tbody>
</table>

The chiral Brønsted catalyzed cyclisation of 102a using (R)-TRIP in cyclohexane was investigated (Scheme 2.14). At room temperature, the conversion (23%) was low with only a 14% ee (entry 1). Upon increasing the temperature to 50 °C, a near quantitative conversion (98%) was observed and the ee more than doubled to 31% (entry 2). However, increasing the temperature to 75 °C, decreased the ee (21%), but maintained the conversion (98%) (entry 3) [Table 8].

Scheme 2.15 – Chiral Brønsted Acid Catalyzed Cyclisation of 102b using (R)-TRIP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>rt</td>
<td>Cyclohexane</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Entry 2</td>
<td>50</td>
<td>Cyclohexane</td>
<td>89</td>
<td>10</td>
</tr>
<tr>
<td>Entry 3</td>
<td>75</td>
<td>Cyclohexane</td>
<td>95</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 9 – Chiral Brønsted Acid Catalyzed Cyclisation of 102b using (R)-TRIP.

Finally, the chiral Brønsted catalyzed cyclisation of 102b using (R)-TRIP in cyclohexane was investigated (Scheme 2.15). At room temperature, the conversion (9%) and ee (10%) were low (entry 1). Upon increasing the temperature to 50 °C, a 10-fold increase in the conversion (89%) was observed but it had no effect on the ee (10%) (entry 2). However, increasing the temperature to 75 °C, gave a near quantitative conversion (95%) but the product was essentially racemic (entry 3) [Table 9].

The asymmetric cyclisation of precursors 101 and 102 confirms that the role played by the solvent is crucial to the enantioselectivity. It reinforces our hypothesis that solvents with lower dielectric...
constants improve the conversion and enantioselectivity to a large extent. The best conditions were found to be using (R)-TRIP in cyclohexane at 50 °C. The conversions are now almost quantitative, and the ee doesn’t decrease with increase in temperature. This concludes the asymmetric cyclisation of tetrahydrofuran precursors 101 and 103. The main conclusion that could be drawn from this study is the role of the solvent in asymmetric cyclisation of tetrahydrofuran precursors 101 and 103, and that this hypothesis would be further reinforced if a similar trend (increase in conversion and ee with a decrease in polarity of the solvent) was observed in the asymmetric cyclisation of tetrahydropyran precursors 82 and 89. To this end, the chiral Brønsted acid catalyzed cyclisation of tetrahydropyran precursors 82 and 89 was investigated.

8.7 Chiral Brønsted Acid Catalyzed Cyclisation of the Tetrahydropyran Precursors

The chiral Brønsted acid catalyzed cyclisation of 82a was attempted first. The catalyst of choice was (R)-TRIP, with a catalyst loading of 20 mol%. The concentration of the precursor was maintained at 0.06 M (Scheme 2.16). To test our hypothesis about the effect the polarity of the solvent had on conversion and ee, initial cyclisations focused on more polar solvents. Initial attempts were carried out at room temperature in DCM. As expected, the conversion (9%) was low and the product was essentially racemic (3% ee). Reasoning that H₂O was present in the TFA mediated cyclisation of 82a, it was added at a 5% loading to see if it played any role in the cyclisation. The cyclisation appeared to have shut off, with no observed conversion even after 96 h. The cyclisation was then attempted in less polar solvents like toluene and cyclohexane [Table 10].
Table 10- Chiral Brønsted Acid Catalyzed cyclisation of 82a using (R)-TRIP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry 1</td>
<td>rt</td>
<td>Toluene</td>
<td>6</td>
<td>-</td>
</tr>
<tr>
<td>Entry 2</td>
<td>50</td>
<td>Toluene</td>
<td>30</td>
<td>13</td>
</tr>
<tr>
<td>Entry 3</td>
<td>50</td>
<td>Cyclohexane</td>
<td>77</td>
<td>18</td>
</tr>
</tbody>
</table>

An initial attempt at room temperature in toluene gave a very low conversion (6%) and the product was essentially racemic (entry 1). On raising the temperature to 50 °C, there was a marked improvement in conversion (31%) with the %ee of 13% (entry 2). Finally, toluene was replaced with cyclohexane, and as expected, the conversion improved to 77%. However, there was only a marginal improvement in the ee (18%) (entry 3) [Table 10]. While the conversions improved markedly in less polar solvents, the ee was poor. Due to this, the focus shifted to the chiral Brønsted acid catalyzed cyclisation of mesityl precursors 89a and 89b.

With the choice of cyclohexane and toluene as solvents, a catalyst and temperature screen was decided to be undertaken. The catalysts screened involved (R)-TRIP, (R)-TIPSY, CPA-1 and CPA-2. The temperature at which the reactions were carried out were room temperature, 50 °C and subsequently 75 °C. The initial precursor concentration was maintained at 0.06 M. Initially, cyclisation of 89a was carried out (Scheme 2.17).

![Scheme 2.17– Chiral Brønsted Acid Catalyzed Cyclisation of 89a using CPA](image-url)
Initial attempts at room temperature in toluene gave poor conversion (10%) and ee (10%) (entry 1). The reaction was then carried out at 50 °C. Interestingly, the conversion improved (69%) and there was a marked improvement to the ee (60%) (entry 2). Finally, the cyclisation was done at 75 °C. A near quantitative conversion (97%) was observed with the ee (61%) essentially unchanged (entry 3). This was an interesting result as the enantioselectivity was independent of temperature, contrary to the expectation that it would decrease. It was reasoned that the energetic barrier to induce erosion of enantioselectivity must be higher for the mesityl precursor compared to the tolyl one, and could explain the poor enantioselectivities of the tolyl precursors at higher temperatures. The solvent was changed to cyclohexane and the experiments were repeated at these three temperatures. A marked increase in the %ee (10% to 42%) was observed at room temperature (entry 4) compared to entry 1. At 50 °C, the conversion was near quantitative (96%) (entry 5) and there was a marginal increase in ee (60% to 69 %) compared to entry 2. At 75 °C, the conversion was quantitative (entry 6) but the ee only slightly improved (61% to 66 %) compared to entry 3. As the increase in temperature had no marked effect of the ee, the catalyst screen was carried out at 50 °C using cyclohexane. When (R)-TRIP was replaced with (R)-TIPSY, there was a significant drop in conversion (96% to 23%) (entry 7) and the ee markedly decreased (69% to 40%) in comparison to entry 5. In the case of CPA-1, the conversion (96%) were similar to entry 5, but a drastic fall in ee (69% to 21%) was observed (entry 8). Finally, CPA-2 was used and found to have solubility issues in cyclohexane, giving very poor conversion (3%) and rendering the product essentially racemic (entry 9). On replacing cyclohexane with toluene, there was no change in conversion (4%) (entry 10) and only a marginal improvement in ee (4% to 12 %) with respect to entry 9 was observed. The best conditions were determined to be using (R)-TRIP in

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Solvent</th>
<th>CPA</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>rt</td>
<td>Toluene</td>
<td>(R)-TRIP</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>Toluene</td>
<td>(R)-TRIP</td>
<td>69</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Toluene</td>
<td>(R)-TRIP</td>
<td>97</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>rt</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TRIP</td>
<td>96</td>
<td>69</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
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<td>(R)-TRIP</td>
<td>100</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
<td>Cyclohexane</td>
<td>(R)-TIPSY</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-1</td>
<td>96</td>
<td>21</td>
</tr>
<tr>
<td>9</td>
<td>50</td>
<td>Cyclohexane</td>
<td>CPA-2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>10</td>
<td>50</td>
<td>Toluene</td>
<td>CPA-2</td>
<td>4</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 11—Chiral Brønsted Acid Catalyzed Cyclisation of 89a using CPA.
cyclohexane at 50 °C to give a 69% ee [Table 11]. The fluctuations in the %ee at 50 °C and 75 °C are down to errors in measurement.

\[
\text{\begin{align*}
\text{Table 11} & \quad \begin{array}{|c|c|c|c|}
\hline
\text{Temperature} & \text{CPA} & \text{Solvent} & \text{Conversion} & \text{ee} \\
(\degree{C}) & \text{mol \%} & \text{Conversion} & \text{ee (\%)} \\
\hline
\text{Entry 1} & 50 & (R)-TRIP & Cyclohexane & 98 & 44 \\
\text{Entry 2} & 50 & (R)-TIPSY & Cyclohexane & 56 & 58 \\
\text{Entry 3} & 50 & CPA-1 & Cyclohexane & 83 & 5 \\
\text{Entry 4} & 50 & CPA-2 & Cyclohexane & 11 & 1 \\
\text{Entry 5} & 50 & CPA-3 & Toluene & 7 & 1 \\
\end{array}
\end{align*}}
\]

![Scheme 2.18](image)

**Scheme 2.18**—Chiral Brønsted Acid Catalyzed Cyclisation of 89b using CPA.

Table 12—Chiral Brønsted Acid Catalyzed Cyclisation of 89b using CPA.

Using these conditions, the cyclisation of 89b was investigated (Scheme 2.18). Starting with (R)-TRIP, a near quantitative conversion (98%) was observed and the ee was 44% (entry 1). Interestingly, (R)-TIPSY gave a lower conversion (56%) but showed a marked improvement in the ee (58%) compared to (R)-TRIP (entry 2). However, when CPA-1 was used, there was a sharp dip in ee (44% to 5%) compared to (R)-TRIP, while a marginal dip in the conversion (98% to 83%) was observed (entry 3). Finally, CPA-2 was used and found to have solubility issues in cyclohexane, giving very poor conversion (11%) and the product formed was essentially racemic (entry 4). On replacing cyclohexane with
toluene, only a marginal improvement in ee (5%) was observed (entry 5) [Table 12]. The general trend observed was that the best enantioselectivity was observed while using (R)-TRIP and that it was independent of temperature. Our hypothesis regarding solvent polarity was reinforced, with the cyclisation of the mesityl precursor 89a in cyclohexane at 50 °C giving the best ee of 69%. Further, the trends indicated by the preliminary computation by Kristaps are observed. The ee of 82a under these conditions is 18% while the ee of 89a is 69%, confirming that the mesityl precursor 89a is more enantioselective compared to the tolyl precursor 82a (Scheme 1.27b). With the best sets of conditions identified, we were now in a position to investigate the kinetic resolution of the tetrahydropyran and tetrahydrofuran precursors using (R)-TRIP as the chiral acid.

Among the tetrahydropyran precursors, the mesityl precursors 89 exhibited better enantioselectivities, in contrast to the tolyl precursors 101 among tetrahydrofurans. Hence, it was reasoned that the tolyl isopropyl tetrahydrofuran precursor 101c and mesityl isopropyl tetrahydropyran precursor 89c would be better suited for a kinetic resolution. It is known that under acidic conditions, the tetrahydropyran precursor 82c gave predominantly cis products. A similar behavior can be expected from the mesityl precursor 89c. If that cis-selectivity holds for the tetrahydrofuran precursor 101c as well, the kinetic resolution could be attempted for both 101c and 89c using (R)-TRIP as the catalyst in cyclohexane at 50 °C.

8.8 Kinetic Resolution of the Tetrahydropyran and Tetrahydrofuran Precursors

The synthesis of enantiomerically pure compounds is a major challenge in organic chemistry and various strategies have been devised to address this issue. An important process to address this issue is the kinetic resolution of racemates to generate enantiomerically enriched compounds. Kinetic resolution is a process in which one enantiomer interacts with a chiral catalyst and forms the product, via a diastereomeric transition state, faster than the other enantiomer. As a result, in an ideal reaction, the product and substrate are at 50% conversion. This is a classical kinetic resolution and the main drawback is that the maximum theoretical yield is 50%. (Scheme 2.19). [41]
To the best of our knowledge, the only example of the enantioselective synthesis of 2,6-cis tetrahydropyran using a chiral phosphoric acid via an oxa-Michael cyclisation and kinetic resolution was reported by Yoneda (Scheme 2.11). In his study, he carried out novel asymmetric cycloetherification, which was then accompanied by the kinetic resolution of secondary and tertiary alcohols to synthesise tetrahydropyran bearing two chiral centers with excellent enantioselectivities and high s-factors. As there was α,β-unsaturated aryl ketone functionality in all the substrates, the substrate scope was limited and didn’t include esters. To the best of our knowledge, no study has addressed the kinetic resolution of esters or thioesters. This calls for a much-needed focus into the resolution of esters and we believe that this kinetic resolution of 101c and 89c is a step in that direction. To ascertain if 101c exhibited cis-selectivity under Brønsted acid conditions, the TFA catalyzed cyclisation of 101c at 50 ºC, using a 1.8 : 0.2 mL ratio of TFA and H2O was attempted (Scheme 2.20).

\[
\text{Reagents and conditions: a) TFA (1.8 mL)/ H}_2\text{O (0.2 mL), DCE, 50}^\circ\text{C, 24 h (58%) (dr = 1.41:1)}
\]

\text{Scheme 2.20 – Cyclisation of 101c under TFA conditions}

Unfortunately, an inseparable diastereomeric mixture (dr = 1.41:1) was obtained in 58% yield. It showed that the cis selectivity of tetrahydropyran precursors under these conditions doesn’t hold for tetrahydrofuran precursors. The mixture was resolved by chiral HPLC and as expected, four peaks corresponding to the four stereoisomers were observed (Figure 7). The major and minor peaks were identified. Taking the ratio between the area under the peaks, the dr was determined to be 1.4:1 and was in good agreement with the NMR [Table 13]. However, it was disappointing as the acid may have changed the diastereoselectivity as well. Consequently, attempts to kinetically resolve 101c was abandoned.
The kinetic resolution of 89c was attempted using (R)-TRIP in cyclohexane at 50 °C. In the ideal resolution of the racemic mixture of 89c, under these conditions, one enantiomer would convert completely to the corresponding 2,6-cis product 96c, leaving behind enantioenriched starting material 89c (Scheme 2.21).

Table 13—HPLC data of 101c

<table>
<thead>
<tr>
<th></th>
<th>(Hexane:IPA)</th>
<th>Major isomer</th>
<th>Area (%)</th>
<th>Minor isomer</th>
<th>Area (%)</th>
<th>Flowrate (mL/min)</th>
<th>dr</th>
</tr>
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<tbody>
<tr>
<td>101c</td>
<td>96/4</td>
<td>20.052</td>
<td>59</td>
<td>22.034</td>
<td>41</td>
<td>0.9</td>
<td>1.4:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25.108</td>
<td></td>
<td>29.880</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Reagents and conditions: a) (R)-TRIP (20 mol%), cyclohexane, 50 °C,
To a 0.15 M solution of 89c, (R)-TRIP (20 mol %) was added and heated at 50 °C. At regular intervals, aliquots (0.25 mL) were taken, dissolved in cyclohexane (0.25 mL) and quenched with Et3N (0.2 mL). The aliquots were filtered through a silica pad and analysed by HPLC using an AD-H column (95:5 to 90:10 of Hexane:IPA). Triplicate measurements of each aliquot was undertaken and averaged. The formation of the product (P) and the consumption starting material (SM) was monitored by HPLC (Figure 8a). The reaction was quenched when 52% of the starting material was consumed. The ee was simultaneously monitored and gave interesting observations. Rapid enantioenrichment of the product was observed after 1 h, with a massive jump in ee of the product from 0 to 80%. Simultaneously, the starting material enrichment improved gradually to 85% after 6 h. The apparent increase in conversion of the starting material at t = 4 h (48%) compared to t = 5 h (47%) was a wobble in the
baseline, which enhanced the integration of the starting material. This can be put down to an instrumental error (Figure 8b) [Table 14]. To confirm this observation, the quenched reaction mixture was purified and the product 96c (10.0mg) and starting material 89c (2.9mg) were isolated. The ee of the cyclized product 96c should correspond to 91% and the starting material 89c to 85%. To our delight, the ee of the product (96%) and starting material (95%) were within experimental error [Table 15]. This was compared to the corresponding racemic products (Figure 9). The NMR of enriched 96c matched that of the racemic mixture 82c, indicating that the product 96c is predominantly cis and that no trans product was observed.

Figure 9- a) HPLC trace of 96c b) HPLC trace of 89c
It was observed that the retention times of the racemic and enantioenriched samples of 96c are different. This can be explained by different temperature gradients present during measurement, as the temperature control of the HPLC was not functional. This concludes the studies into the chiral resolution of thioesters using (R)-TRIP in cyclohexane at 50 °C, and an enantioerchment of 95% with respect to the product was achieved. This level of enantioenrichment is better than the one reported by Yoneda [44] (58-90%). This is of importance because it gives us access to a variety of enantioenriched functionalities owing to the versatility of thioesters. This is a very encouraging result and a step in the right direction in making the oxa-Michael cyclisation of thioesters more enantioselective.

8.9 Conclusion and future work.

The synthesis of tetrahydropyran cyclisation precursors 82 and 89 was achieved in excellent yields, via a Hovyeda-Grubbs catalyzed metathesis reaction between readily synthesized alcohols 84 and thioacrylate 83/90 (Scheme 2.4). Their Brønsted acid catalyzed cyclisation using TFA and CSA was studied using the conditions used by Clarke (Scheme 2.45 and 2.6). It was found that the increase in temperature or the amount of catalyst has only a moderate effect on cyclisation, with it often not reaching completion even after 24 hours. It was reasoned that a 5-exo-trig cyclisation involving tetrahydrofuran precursors was faster than the 6-exo-trig cyclisation involving tetrahydropyran precursors and that the conversion should increase. To this end, the corresponding tetrahydrofuran precursors 101 and 103 were synthesized in excellent yields (Scheme 2.8). The Brønsted acid catalyzed cyclisation using TFA and CSA was studied and it was found to display similar reactivity trends as the tetrahydropyran precursors (Scheme 2.9 and 10).

It was reasoned that the nature of the solvent might be a factor and lowering the polarity and dielectric constant of the solvent might improve conversion. This hypothesis was supported by a study by Yoneda [44] wherein he used toluene to achieve excellent enantioselectivities for the chiral Brønsted acid catalyzed synthesis of 2,6-cis tetrahydropyrans. Reasoning that thioesters were more versatile

<table>
<thead>
<tr>
<th></th>
<th>Hexane:IPA</th>
<th>Minor peak (min)</th>
<th>Major Peak (min)</th>
<th>Flowrate (mL/min)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>96c</td>
<td>96/4</td>
<td>7.037</td>
<td>7.806</td>
<td>0.9</td>
<td>95</td>
</tr>
<tr>
<td>89c</td>
<td>90/10</td>
<td>10.953</td>
<td>13.211</td>
<td>0.9</td>
<td>96</td>
</tr>
</tbody>
</table>
than ketones, and the cyclisatisation to form tetrahydrofurans was faster than that of tetrahydropyrans, solvents with dielectric constants similar to or lower than toluene were employed for the asymmetric cyclisation. The asymmetric cyclisation using chiral phosphoric acids like (R)-TRIP, (R)-TIPSY and other commercially available acids under various solvent and temperature conditions were applied to the tolyl precursors 82 and mesityl precursors 89 of tetrahydrofurans. The tolyl substrates showed more promise, exhibiting moderate ee (15-60%), while the mesityl precursors were exhibiting disappointing ee’s (4-30%) (Scheme 2.12 and 2.13). Solvents having a low dielectric constant, like toluene and cyclohexane, were found to favour cyclisation, with 50 °C being the ideal temperature to achieve good conversions and %ee.

The solvent hypothesis was further reinforced when poor conversions and ee were obtained for the asymmetric cyclisation of the tolyl tetrahydropyran precursor 82a (Scheme 2.16). It was concluded that toluene and cyclohexane were the better choices for solvents. Analogous to the tetrahydropyran precursors, the asymmetric cyclisation of the mesityl tetrahydropyran precursor 89 using chiral phosphoric acids like (R)-TRIP, (R)-TIPSY and other commercially available acids under various solvent and temperature conditions were carried out. The best result (69%ee) was obtained for the precursor 89a at 50 °C in cyclohexane using (R)-TRIP (Scheme 2.17 and 2.18).

As the precursors 89 and 101 showed the most promise, it was reasoned that 101c and 89c would be suitable for a kinetic resolution using these conditions. Attempts at kinetically resolving the tolyl tetrahydrofuran precursor 101c were abandoned due to lack of stereoselectivity (dr = 1.41:1) towards the cis isomer under acid conditions. The kinetic resolution of 89c was attempted under the cyclohexane conditions. The conversion was monitored using HPLC, which resulted in a 95% enrichment of the cis product 96c after 6 h with a 52% conversion (Scheme 2.21). To the best of our knowledge, this is the first example of kinetic resolution of thioester substrates using a chiral phosphoric acid.

In conclusion, optimal solvent, temperature and catalyst conditions were identified for the chiral Brønsted acid catalyzed oxa-Michael cyclisation. Future work would involve a broader substrate scope and attempts at kinetic resolution of other tetrahydropyran precursors under the identified conditions. Additionally, attempts at identifying the absolute stereochemistry of all enantioenriched products, including the cis isomer 96c, through a crystal structure would be carried out. This would be supported by computational work into the mechanism of the chiral Brønsted acid cyclisation and the level of agreement between the two would be ascertained.
9. Experimental

9.1 General experimental

Unless otherwise noted all compounds were bought from commercial suppliers and used without further purification. Nuclear magnetic resonance spectra were recorded on a Jeol ECS-400 spectrometer at ambient temperature; chemical shifts are quoted in parts per million (ppm) and were referenced as follows: chloroform-d, 7.26 ppm for $^1$H NMR; chloroform-d, 77.0 ppm for $^{13}$C NMR. Coupling constants ($J$) are quoted in Hertz. Infra-red absorbances were recorded on a PerkinElmer UATR Two FT-IR spectrometer using NaCl plates. Mass spectrometry was performed by the University of York mass spectrometry service using electron spray ionisation (ESI) technique. Optical rotations were carried out using a JASCO-DIP370 polarimeter and $[\alpha]_D$ values are given in 10$^{-1}$ deg.cm$^2$.g$^{-1}$. Thin layer chromatography was performed on aluminium sheets coated with Merck Silica gel 60 F254. The plates were developed using ultraviolet light, basic aqueous potassium permanganate or ethanolic anisaldehyde. Liquid chromatography was performed using forced flow (flash column) with the solvent systems indicated. The stationary phase was silica gel 60 (220–240 mesh) supplied by Sigma-Aldrich. Dry solvents were acquired from a PureSolv PS-MD7 solvent tower. High Performance Liquid Chromatography (HPLC) was performed using an Agilent 1200 series instrument using the chiral columns indicated and a range of wavelengths from 210-280 nm for detection. All other solvents and reagents were used as received from commercial suppliers. All numbering on the structures below is for the benefit of characterisation and does not necessarily conform to IUPAC rules.
9.2 Experimental Procedures

2-Methylhept-6-en-2-ol (84a)

A degassed solution of 5-bromo-1-pentene (5.1 mL, 43 mmol) in Et₂O (20 mL) was added dropwise over an hour, to a mixture of magnesium turnings (1.20 g, 49.4 mmol) in dry Et₂O (40 mL) under a nitrogen atmosphere. The reaction mixture was left to stir at room temperature for two hours. The solution of Grignard reagent was added dropwise, over 5 minutes, to a solution of dry acetone (3.1 mL, 44 mmol) in Et₂O (20 mL). A white precipitate formed immediately. The reaction mixture was then quenched with excess saturated aq NH₄Cl solution and the white precipitate was filtered. The organic layer was separated and washed with H₂O, dried over anhydrous Na₂SO₄ and filtered. It was then concentrated in vacuo to give a colourless oil. The oil was purified by flash column chromatography on silica with ethyl acetate /n-hexane (1:7) to yield 84a as a colourless oil (0.68 g, 13%). Data was consistent with those reported in the literature. [38]

1H NMR (400 MHz, CDCl₃): δ 5.80 (1H, ddt, J = 17.1 Hz, 10.4 Hz, 6.6 Hz, H-6), 4.99 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.4 Hz, H-7 trans), 4.94 (1H, ddt, J = 10.4 Hz, 2.0 Hz, 1.4 Hz, H-7 cis), 2.10-2.00 (2H, m, H-5), 1.50-1.40 (4H, m, H-3 + H-4), 1.27 (1H, s, OH), 1.19 (6H, s, H-1) ppm. 13C NMR (101 MHz, CDCl₃): δ 138.9, 114.7, 71.1, 43.5, 34.3, 29.4, 23.8 ppm. IR (film, NaCl): ν max 3369, 3078, 2971, 1641, 1467, 1377, 1192, 908, 764 cm⁻¹. ESI-MS: m/z calcd for C₇H₁₅O (M⁺-CH₃) 113.0966; found 113.0958

2-Methyloct-7-en-3-ol (84c)

To a suspension of magnesium turnings (296 mg, 12 mmol) in dry THF (20 mL), a solution of 5-bromo-1-pentene (1.79 g, 12 mmol, 1.4 mL) in dry THF (4.0 mL) was added over a period of 5 minutes under a nitrogen atmosphere at 0 °C. After stirring the mixture for 60 minutes at room temperature, the Grignard reagent (11.3 mL, 1.5 eq.) was added over a period of 5 minutes to a solution of isobutyraldehyde (292 mg, 4 mmol, 0.37 mL) in dry THF (2 mL) at 0 °C. The solution was stirred for 90 minutes at room temperature, then quenched with ice water (15 mL) and treated with dilute H₂SO₄ (5 M, 4 mL) until the magnesium salt dissolved. After separating the phases, the aqueous layer was extracted with Et₂O (2 × 10 mL). The combined organic phases were dried over Na₂SO₄, filtered and
concentrated in vacuo to give a yellow oil. This was then purified by column chromatography on silica with 10% ethyl acetate in petroleum ether to yield 84c as a yellow oil (142.8 mg, 25%). Data was consistent with that reported in literature.\[30\]

**3H NMR (400 MHz, CDCl3):** δ 5.80 (1H, ddt, J = 17.1 Hz, 10.2 Hz, 6.8 Hz, H-7), 5.03-4.97 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.8 Hz, H-8), 4.96-4.92 (1H, ddt, J = 10.2 Hz, 2.0 Hz, 1.2 Hz, H-8), 3.35 (1H, ddd, J = 8.5 Hz, 5.1 Hz, 3.5 Hz, H-3), 2.14-1.98 (2H, m, H-6), 1.69 – 1.52 (2H, m, H-4), 1.51-1.43 (1H, m, H-2), 1.40-1.32 (2H, m, H-5), 0.90 (3H, d, J = 4.1 Hz, H-1), 0.89 (3H, d, J = 4.1 Hz, H-1) ppm. 13C-NMR (101 MHz, CDCl3): δ 138.9, 114.7, 76.8, 33.9, 33.7, 25.5, 19.0, 17.2 ppm. IR (film, NaCl): νmax 3370, 3077, 2958, 2934, 2873, 1698, 1641, 1461, 1384, 1367, 1260, 992, 908 cm⁻¹. **ESI-MS:** m/z calcd for C₇H₁₉O⁺ (M+H⁺) 147.1430; found 147.1422

\[S-p-Tolyl prop-2-enethioate (83)\]

NaBH₄ (27.0 mg, 0.70 mmol, 0.03 eq) and 4-methylbenzenethiol (2.74 g, 22 mmol) were added in that order to 15% aqueous NaOH solution (10 mL) and stirred at room temperature for an hour and then cooled to 0°C before use. In a separate flask, butylated hydroxytoluene (72.0 mg, 0.327 mmol, 0.015 eq) and acryloyl chloride (2.7 mL, 33 mmol, 1.5 eq) were dissolved in cyclohexane (15 mL). To this solution under cooling at 0°C, the borohydride solution was added over a period of 10 minutes. The resultant solution was then stirred for 30 minutes. The reaction mixture was then cooled to room temperature and extracted with Et₂O (3 x 10 mL). The organics were washed with saturated NaHCO₃ solution (3x5 mL) and brine solution (3 x 5 mL), dried over anhydrous MgSO₄, and filtered. A portion of butylated hydroxytoluene (36.2 mg) was added prior to evaporation to prevent polymerisation. The reaction mixture was then concentrated in vacuo to give a yellow oil. This was purified by column chromatography on silica using 3% ethyl acetate in hexane to yield 83 as a yellow oil (1.86 g, 47%). Data was consistent with that reported in literature.\[30\]

**3H NMR (400 MHz, CDCl3):** δ 7.32 (2H, d, J = 8.0 Hz, H-2), 7.24 (2H, d, J = 8.0 Hz, H-3), 6.44 (1H, dd, J = 17.2 Hz, 9.6 Hz, H-4), 6.37 (1H, dd, J = 17.2 Hz, 1.6 Hz, H-Strans), 5.75 (1H, dd, J = 9.6 Hz, 1.6 Hz, H-Scis), 2.37 (3H, s, H-1) ppm. 13C NMR (101 MHz, CDCl3): δ 189.2, 139.9, 134.7, 134.5, 130.2, 127.4, 123.7, 21.5 ppm IR (film NaCl): νmax 3027, 2922, 2863, 1683, 1612, 1494, 1394, 1161, 988, 941, 807, 722 cm⁻¹. **ESI-MS:** m/z calcd for C₁₀H₁₉NaOS⁺ (M+Na⁺) 201.0350; found 201.0353
**S-Mesityl prop-2-enethioate (90)**

![Chemical Structure](image)

NaBH₄ (12.8 mg, 0.338 mmol, 0.03 eq) and 2,4,6-trimethylbenzenethiol (1.7 mL, 2.74 g, 11.3 mmol, 1.0 eq) were added in that order to 15% aqueous NaOH solution (5 mL) and stirred at room temperature for an hour and then cooled to 0 °C before use. In a separate flask, butylated hydroxytoluene (25.0 mg, 0.113 mmol, 0.01 eq) and acryloyl chloride (1.4 mL, 17.23 mmol, 1.53 eq) were dissolved in cyclohexane (7 mL). To this solution under cooling at 0 °C, the borohydride solution was added over a period of 10 minutes. The resultant solution was then stirred at 55 °C for an hour. The reaction mixture was then cooled to room temperature and extracted with Et₂O (3 x 15 mL). The organics were washed with saturated NaHCO₃ solution (3 x 5 mL) and brine solution (3 x 5 mL), dried over anhydrous MgSO₄, and filtered. A portion of butylated hydroxytoluene (42.3 mg) was added prior to evaporation to prevent polymerisation. The reaction mixture was then concentrated in vacuo to give a yellow oil. This was purified by column chromatography on silica using 2% ethyl acetate in hexane to yield 90 as a yellow oil (1.17 g, 50%).

**¹H NMR** (400 MHz, CDCl₃): δ 7.00-6.97 (2H, m, H-2), 6.47 (1H, dd, J = 17.2 Hz, 9.6 Hz, H-4), 6.38 (1H, dd, J = 17.2 Hz, 1.6 Hz, H-5trans), 5.73 (1H, dd, J = 9.6 Hz, 1.6 Hz, H-5cis), 2.30 (1H, s, H-1) ppm. **¹³C NMR** (101 MHz, CDCl₃): δ 188.3, 142.8, 140.2, 134.7, 129.4, 127.0, 123.1, 21.7, 21.3 ppm.

**IR** (film NaCl): vmax 3027, 2922, 2863, 1683, 1612, 1494, 1394, 1161, 988, 941, 807, 722 cm⁻¹.

**ESI-MS**: m/z calcd for C₁₂H₁₅OS⁺ (M+H⁺) 207.0838; found 207.0840.

**(E)-S-p-Tolyl 7-hydroxy-7-methyloct-2-enethioate (82a)**

![Chemical Structure](image)

2-Methylhept-6-en-2-ol (102.4 mg, 0.8 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (427.2 mg, 2.4 mmol, 3.0 eq) were dissolved in dry Et₂O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (15.3 mg, 0.08 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (50.2 mg, 0.08 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield 82a as a brown oil (192.7 mg, 87%).
**1H NMR** (400 MHz, CDCl₃): δ7.31 (2H, d, J = 8.0 Hz, H-2), 7.21 (2H, d, J = 8.0 Hz, H-3), 6.96 (1H, dt, J = 15.6 Hz, 7.0 Hz, H-5), 6.18 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 2.36 (3H, s, H-1), 2.24 (2H, qd, J = 7.0 Hz, 1.4 Hz, H-6), 1.62-1.48 (4H, m, H-7 + H-8), 1.22 (6H, s, H-9) ppm. **13C NMR** (101 MHz, CDCl₃): δ188.7, 146.3, 139.8, 134.8, 130.2, 128.2, 124.2, 71.0, 43.4, 32.8, 29.5, 23.0, 21.5 ppm. **IR** (film NaCl): \( \nu_{\text{max}} \) 3383, 2964, 2924, 2853, 1687, 1631, 1494, 1464, 1398, 1376, 1284, 1160, 1017, 972, 807 cm⁻¹. **ESI-MS**: m/z calcd for C₁₈H₂₂NaO₅S⁺ (M+Na⁺) 301.1233; found 301.1230

**S-p-Tolyl-2-(6,6-dimethyltetrahydro-2H-pyran-2-yl)ethanethioate (95a)**

**Acid conditions:**

**TFA**
(\(E\))-S-p-Tolyl 7-hydroxy-7-methyloct-2-enethioate (15.0 mg, 0.054 mmol) was dissolved in DCE (0.9 mL) and H₂O (0.4 mL) was added and cooled in ice. To this, a solution of TFA in DCE (3.6 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO₃ solution (5 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 95a as a yellow oil (4.2 mg, 28%).

**CSA**
To a solution of (\(E\))-S-p-tolyl 7-hydroxy-7-methyloct-2-enethioate (28.9 mg, 0.104 mmol) in DCE (5 mL), a portion of CSA (73.0 mg, 0.314 mmol, 3 eq) was added and heated under reflux at 80 °C for 24 hours. The reaction was quenched with Et₃N (1.0 mL), washed with NaHCO₃ solution (2 x 5 mL) and brine solution (2 x 5 mL), dried over anhydrous Na₂SO₄ and filtered. The filtrate was concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica with dichloromethane to yield 95a as a yellow oil (13.0 mg, 45%).

**1H NMR** (400 MHz, CDCl₃): δ7.27 (d, 2H, J = 8.1 Hz, H-2), 7.19 (2H, d, J = 8.1 Hz, H-3), 4.04 (1H, dtd, J = 11.4 Hz, 6.6 Hz, 2.1 Hz, H-5), 2.82 (1H, dd, J = 14.8 Hz, 6.6 Hz, H-4), 2.64 (1H, dd, J = 14.8 Hz, 6.6 Hz, H-4), 2.36 (3H, s, H-1), 1.68-1.61 (3H, m, 2x H-6 + H-7), 1.48-1.30 (2H, m, H-8), 1.19 (3H, s, H-9), 1.18 (3H, s, H-9), 1.13 (1H, m, H-7) ppm. **13C NMR** (101 MHz, CDCl₃): δ196.1, 139.7, 134.6, 130.1, 124.6, 72.5, 67.7, 50.8, 35.9, 31.9, 31.3, 21.9, 21.5, 19.9 ppm. **IR** (film NaCl): \( \nu_{\text{max}} \) 2973, 2928, 1707, 1494, 1464, 1398, 1376, 1284, 1160, 1017, 972, 807 cm⁻¹.
5-Hexen-1-ol (40.1 mg, 0.4 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (213.6 mg, 1.2 mmol, 3.0 eq) were dissolved in dry Et<sub>2</sub>O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (7.6 mg, 0.04 mmol, 10 mol%) and Hovydta-Grubbs 2<sup>nd</sup> generation catalyst (25.1 mg, 0.04 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield 82b as a brown oil (86.0 mg, 86%).

**1H NMR** (400 MHz, CDCl<sub>3</sub>): δ7.30 (2H, d, J = 8.0 Hz, H-2), 7.20 (2H, d, J = 8.0 Hz, H-3), 6.95 (1H, dt, J = 15.6 Hz, 7.0 Hz, H-5), 6.17 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 3.70-3.60 (2H, m, H-9), 2.36 (3H, s, H-1), 2.25 (2H, qd, J = 7.0 Hz, 1.4 Hz, H-6), 1.64-1.52 (4H, m, H-7 + H-8) ppm. **13C NMR** 101 MHz, CDCl<sub>3</sub>): δ188.7, 146.2, 139.8, 134.7, 130.1, 128.2, 124.1, 62.6, 32.2, 32.1, 24.3, 21.5 ppm. **IR** (film NaCl): ν<sub>max</sub> 3387, 3030, 2928, 2863, 1682, 1631, 1495, 1456, 1384, 1376, 1214, 1184, 1051, 998, 808 cm<sup>-1</sup>. **ESI-MS**: m/z calcd for C<sub>16</sub>H<sub>22</sub>NaO<sub>2</sub>S<sup>+</sup> (M+Na<sup>+</sup>) 301.1233; found 301.1227

**Acid conditions:**

TFA

(Δ)-S-p-Tolyl 7-hydroxyhept-2-enethioate (17.4 mg, 0.070 mmol) was dissolved in DCE (3 mL) and H<sub>2</sub>O (0.3 mL) was added and cooled in ice. To this, a solution of TFA in DCE (2.7 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 60 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO<sub>3</sub> solution (3 mL) and diluted with DCM (2 mL). The phases were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using DCM to yield 95b as a yellow oil (6.1 mg, 35%).
To a solution of (E)-5-p-tolyl 7-hydroxyhept-2-enethioate (14.0 mg, 0.056 mmol) in DCE (5 mL), a portion of CSA (39.0 mg, 0.168 mmol, 3 eq) was added and heated under reflux at 80 °C for 24 hours. The reaction was quenched with Et$_3$N (1.0 mL), washed with NaHCO$_3$ solution (2 x 5 mL) and brine solution (2 x 5 mL), dried over anhydrous Na$_2$SO$_4$ and filtered. The filtrate was concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica with DCM to yield 95b as a yellow oil (5.7 mg, 41%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.28 (d, 2H, J = 8.1 Hz, H-2), 7.20 (2H, d, J = 8.1 Hz, H-3), 3.95 (1H, dt, J = 11.4 Hz, 2.2 Hz, H-9), 3.79 (1H, ddd, J = 10.6 Hz, 7.8 Hz, 5.4 Hz, H-5), 3.43 (1H, td, J = 11.4 Hz, 2.2 Hz, H-9), 2.86 (1H, dd, J = 14.9 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, J = 14.9 Hz, 5.4 Hz, H-4), 2.35 (3H, s, H-1), 1.62-1.44 (6H, m, H-6 + H-7 + H-8) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): 6195.9, 139.8, 134.5, 130.1, 124.4, 74.6, 68.8, 50.3, 31.7, 25.8, 23.4, 21.5 ppm IR (film NaCl): ν$_{max}$ 2926, 2852, 1708, 1494, 1440, 1377, 1360, 1272, 1195, 1180, 1089, 1046, 1005, 965, 807, 742 cm$^{-1}$. ESI-MS: m/z calcd for C$_{14}$H$_{18}$NaO$_5$S$^+$ (M+Na$^+$) 273.0920; found 273.0934.

(5)-5-p-Tolyl 7-hydroxy-8-methylnon-2-enethioate (82c)

2-Methyloct-7-en-2-ol (24.2 mg, 0.170 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (92.0 mg, 0.511 mmol, 3.0 eq) were dissolved in dry Et$_2$O (5 mL) under a nitrogen atmosphere. To this, copper (I) iodide (5.0 mg, 0.026 mmol, 15 mol%) and Hovyeda-Grubbs 2$^{nd}$ generation catalyst (10.7 mg, 0.017 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 2 hours. The mixture was then concentrated and purified by column chromatography on silica using 10-15 % ethyl acetate in petroleum ether to yield 82c as a brown oil (42.2 mg, 85%). Data was consistent with those reported in the literature. [30]

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.30 (2H, d, J = 7.9 Hz, H-2), 7.21 (2H, d, J = 7.9 Hz, H-3), 6.96 (1H, dt, J = 15.6 Hz, 6.9 Hz, H-5), 6.18 (1H, dt, J = 15.6 Hz, 1.4Hz, H-4), 3.35 (2H, ddd, J = 8.6 Hz, 5.2Hz, 3.2 Hz, H-9), 2.36 (3H, s, H-1), 2.29-2.21 (2H, m, H-6), 1.71-1.60 (2H, m, H-8), 1.52-1.38 (3H, m, H-7 + H-10), 0.91 (3H, d, J = 3.7 Hz, H-11), 0.89 (3H, d, J = 3.7 Hz, H-11) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): 6188.7, 146.4, 139.7, 134.7, 130.1, 128.1, 124.2, 76.6, 33.7, 32.4, 24.6, 21.5, 19.0, 17.2 ppm. IR (film NaCl):
\[ v_{\text{max}} 3438, 2959, 2927, 2870, 1678, 1631, 1494, 1384, 1277, 1211, 1140, 1036, 982, 807 \text{ cm}^{-1}. \]

**ESI-MS**: m/z calcd for C_{17}H_{25}NaO_{2}S^{-} (M+Na^{+}) 315.1389; found 315.1380

\[ \text{S-}p\text{-Tolyl-2-(6-isopropyltetrahydro-2H-pyran-2-yl)ethanethioate (95c)} \]

(E)-S-\text{p-Tolyl} 7-hydroxy-8-methylnon-2-enethioate (15.0 mg, 0.051 mmol) was dissolved in DCM (1 mL) and H_{2}O (0.1 mL) was added and cooled in ice. To this, a solution of TFA in DCM (0.9 mL, 0.06 M) was added over three minutes. The reaction mixture stirred at room temperature for 48 hours. The reaction mixture was then quenched with saturated NaHCO_{3} solution (3 mL) and diluted with DCM (2 mL). The phases were separated and the aqueous layer was extracted with DCM (2 x 3 mL). The combined organics were dried over anhydrous Na_{2}SO_{4}, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using DCM to yield 95\text{c} as a yellow oil (6.5 mg, 43%). *Data was consistent with those reported in the literature.*\[^{[30]}\]

\(^{1}\text{H-NMR}\) (400 MHz, CDCl_{3}): \(\delta\) 7.26 (2H, d, \(J = 8.2\) Hz, H-2), 7.19 (2H, \(J = 8.2\) Hz, H-3), 3.78 (1H, dddd, \(J = 11.1\) Hz, 8.2 Hz, 1.8 Hz, H-5), 2.95 (1H, ddd, \(J = 11.1\) Hz, 6.9 Hz, 1.8 Hz, H-9), 2.85 (1H, dd, \(J = 14.4\) Hz, 8.2 Hz, H-4), 2.64 (1H, dd, \(J = 14.4\) Hz, 4.9 Hz, H-4), 2.37 (3H, s, H-1), 1.84-1.74 (1H, m, H-10), 1.65 – 1.43 (6H, m, H-6 + H-7 + H-8), 0.94 (3H, d, \(J = 6.8\) Hz, H-11), 0.86 (3H, d, \(J = 6.8\) Hz, H-11) ppm.

\(^{13}\text{C-NMR}\) (101 MHz, CDCl_{3}): \(\delta\) 196.3, 139.7, 134.6, 130.1, 124.6, 83.4, 75.0, 50.5, 33.6, 31.5, 28.2, 23.7, 21.5, 18.9 ppm. \(\text{IR}\) (film, NaCl): \(v_{\text{max}}\) 2928, 2857, 1706, 1494, 1457, 1339, 1274, 1203, 1071, 1048, 996, 806 cm\(^{-1}\). **ESI-MS**: m/z calcd for C_{17}H_{25}NaO_{2}S^{-} (M+Na^{+}) 315.1389; found 315.1381

\((E)\)-\text{S-Mesityl} 7-hydroxy-7-methyloct-2-enethioate (89\text{a})

2-Methylhept-6-en-2-ol (76.8 mg, 0.6 mmol, 1.0 eq) and \text{S-mesityl prop-2-enethioate} (373 mg, 1.81 mmol, 3.02 eq) were dissolved in dry Et_{2}O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol\%) and Hovyeda-Grubbs 2\text{nd} generation catalyst (37.6mg, 0.06 mmol, 10 mol\%) were added as solids in a single portion and the mixture was stirred at 40 °C for 18
The mixture was then concentrated and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 89a as a brown oil (157.7 mg, 86%).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \): 6.96 (3H, m, H-2 + H-5), 6.22 (1H, dt, \( J = 15.6 \) Hz, 1.6 Hz, H-4), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.24 (2H, dtd, \( J = 7.3 \) Hz, 7.3 Hz, H-6), 1.60-1.55 (4H, m, H-7 + H-8), 1.22 (6H, s, H-9) ppm. \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \): 187.8, 145.9, 142.8, 140.0, 129.3, 128.3, 123.6, 71.0, 43.5, 32.8, 29.5, 23.0, 21.8, 21.5 ppm. IR (film NaCl): \( \nu_{\text{max}} \): 3412, 2969, 2940, 1684, 1631, 1464, 1375, 1284, 1156, 1040, 972, 907, 851, 799, 765, 715 cm\(^{-1}\). ESI-MS: m/z calcd for C\(_{18}\)H\(_{26}\)NaO\(_2\)S\(^+\) (M+Na\(^+\)) 329.1546; found 329.1551.

\( S \)-Mesityl 2-(6,6-dimethyltetrahydro-2H-pyran-2-yl)ethanethioate (96a)

(E)-\( S \)-Mesityl 7-hydroxy-7-methyloct-2-enethioate (18.5 mg, 0.060 mmol) was dissolved in DCE (1.0 mL) and H\(_2\)O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was added over three minutes. The reaction mixture was then heated at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO\(_3\) solution (2 mL) and diluted with DCM (2 mL). The aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield 96a as a yellow oil (7.5 mg, 41%).

\( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \): 6.97 (2H, s, H-2), 4.10-4.00 (1H, m, H-5), 2.82 (1H, dd, \( J = 14.2 \) Hz, 7.8 Hz, H-4), 2.64 (1H, dd, \( J = 14.2 \) Hz, 5.0 Hz, H-4), 2.30 (6H, s, H-3), 2.37 (3H, s, H-1), 1.70-1.60 (3H, m, 2x H-6 + H-7), 1.45-1.35 (3H, m, 2x H-8 + H-7), 1.16 (6H, s, H-9) ppm. \( ^{13}C \) NMR (101 MHz, CDCl\(_3\)) \( \delta \): 195.4, 142.6, 139.9, 129.3, 124.1, 72.3, 68.2, 50.8, 35.9, 31.8, 31.3, 21.9, 21.8, 21.3, 20.0 ppm IR (film NaCl): \( \nu_{\text{max}} \): 2972, 2926, 1702, 1461, 1377, 1364, 1278, 1138, 1063, 1043, 978, 901, 849, 797, 737, 717 cm\(^{-1}\). ESI-MS: m/z calcd for C\(_{18}\)H\(_{26}\)NaO\(_2\)S\(^+\) (M+Na\(^+\)) 329.1546; found 329.1548.
(E)-S-Mesityl 7-hydroxyhept-2-enethioate (89b)

![Chemical Structure](image)

5-Hexen-1-ol (60.1 mg, 0.6 mmol, 1.0 eq) and S-mesityl prop-2-enethioate (378.1 mg, 1.84 mmol, 3.06 eq) were dissolved in dry Et<sub>2</sub>O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.6 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2<sup>nd</sup> generation catalyst (38.1 mg, 0.06 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 24 hours. The mixture was then concentrated and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 89b as a brown oil (151.0 mg, 91%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 7.00-6.90 (3H, m, H-2, H-5), 6.22 (1H, dt, J = 15.3 Hz, 1.7 Hz, H-4), 3.67 (2H, t, J = 5.7 Hz, H-9), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.26-2.23 (2H, m, H-6), 1.65-1.55 (4H, m, H-7 + H-8) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 187.8, 145.8, 142.8, 140.0, 145.7, 142.8, 140.0, 129.3, 128.4, 123.6, 62.7, 32.3, 32.1, 24.3, 21.8, 21.3 ppm. IR (film NaCl): <i>v</i><sub>max</sub> 3357, 2928, 2860, 1683, 1631, 1456, 1376, 1298, 1135, 1049, 996, 850, 803, 745, 715 cm<sup>-1</sup>. ESI-MS: m/z calcd for C<sub>16</sub>H<sub>22</sub>NaO<sub>2</sub>S<sup>+</sup> (M+Na<sup>+</sup>) 301.1233; found 301.1230

S-Mesityl 2-(tetrahydro-2H-pyran-2-yl)ethanethioate (96b)

![Chemical Structure](image)

(E)-S-Mesityl 7-hydroxyhept-2-enethioate (12.0 mg, 0.043 mmol) was dissolved in cyclohexane (2.1 mL). To this, (R)-TRIP (6.5 mg, 0.009 mmol, 20 mol%) was added and stirred at 50 °C under a nitrogen atmosphere for 24 hours. The reaction mixture was then concentrated in vacuo and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield 116b as a yellow oil (10.8 mg, 90%).

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 6.96 (2H, s, H-2), 3.96 (1H, dt, J = 11.4 Hz, 2.2 Hz, H-9), 3.80 (1H, dddd, J = 10.6 Hz, 7.8 Hz, 5.3 Hz, 2.3 Hz, H-5), 3.43 (1H, td, J = 11.4 Hz, 2.2 Hz, H-9), 2.86 (1H, dd, J = 14.7 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, J = 14.7 Hz, 5.3 Hz, H-4), 2.28 (6H, s, H-3), 2.27 (3H, s, H-1), 1.66-1.45 (6H, m, H-6 + H-7 + H-8) ppm. <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>): δ 195.1, 142.6, 140.0, 129.3, 123.9, 75.1, 68.7, 50.3, 31.7, 25.8, 23.4, 21.7, 21.5 ppm IR (film NaCl): <i>v</i><sub>max</sub> 2925, 2852, 1701, 1602, 1571, 1463, 1440,
ESI-MS: m/z calcd for C$_{16}$H$_{22}$NaO$_2$S$^+$ (M+Na$^+$) 301.1233; found 301.1235.

[$\alpha$]$_{D}^{25.0}$ +53.0 (c = 0.51, CHCl$_3$) for the mixture.

HPLC (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, $\lambda = 254$): $t_R$ (minor) = 6.4, $t_R$ (major) = 7.0, ee - 44%

(E)-S-Mesityl 7-hydroxy-8-methylnon-2-enethioate (89c)

2-Methyloct-7-en-2-ol (130.6 mg, 0.92 mmol, 1.0 eq) and S-Mesityl prop-2-enethioate (590.4 mg, 2.87 mmol, 3.12 eq) were dissolved in dry Et$_3$O (30 mL) under a nitrogen atmosphere. To this, copper (I) iodide (17.6 mg, 0.092 mmol, 10 mol%) and Hovyeda-Grubbs 2$^{nd}$ generation catalyst (57.7 mg, 0.092 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 $^\circ$C for 16 hours. The mixture was then concentrated and purified by column chromatography on silica using 20% ethyl acetate in petroleum ether to yield 89c as a brown oil (166.0 mg, 56%).

$^1$H NMR (400 MHz, CDCl$_3$): 7.10-6.93 (3H, m, H-2 + H-5), 6.22 (1H, dt, $J = 15.5$ Hz, 1.4Hz, H-4), 3.37 (1H, m, H-9), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 2.29-2.20 (2H, m, H-6), 1.73-1.60 (2H, m, H-8), 1.53-1.49 (3H, m, H-7 + H-10), 0.92 (3H, d, $J = 3.7$ Hz, H-11), 0.90 (3H, d, $J = 3.7$ Hz, H-11) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): 6188.0, 142.8, 140.0, 129.3, 128.3, 123.6, 76.6, 33.7, 32.4, 24.6, 21.8, 21.3, 19.0, 17.2 ppm. IR (film NaCl): $\nu_{max}$ 3444, 2955, 2929, 2871, 1684, 1630, 1460, 1375, 1298, 1280, 1139, 1033, 982, 850, 801, 715 cm$^{-1}$. ESI-MS: m/z calcd for C$_{19}$H$_{28}$NaO$_2$S$^+$ (M+Na$^+$) 343.1702; found 343.1704

S-Mesityl 2-(6-isopropyltetrahydro-2H-pyran-2-yl)ethanethioate (96c)

(E)-S-mesityl 7-hydroxy-8-methylnon-2-enethioate (19.2 mg, 0.06 mmol) was dissolved in DCE (1 mL) and H$_2$O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was
added over three minutes. The reaction mixture stirred at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO₃ solution (2 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude yellow oil which was purified by column chromatography on silica using 5% ethyl acetate in hexane to yield 96c as a yellow oil (10.0 mg, 52%).

**1H-NMR** (400 MHz, CDCl₃): δ 6.96 (2H, s, H-2), 3.82 (1H, dddd, J = 11.1 Hz, 8.2 Hz, 4.9 Hz, 1.8 Hz, H-5), 2.97 (1H, ddd, J = 11.0 Hz, 6.9 Hz, 1.8 Hz, H-9), 2.88 (1H, dd, J = 14.7 Hz, 7.8 Hz, H-4), 2.65 (1H, dd, J = 14.7 Hz, 4.6 Hz, H-4), 2.28 (6H, s, H-3), 2.27 (3H, s, H-1), 1.89-1.81 (1H, m, H-10), 1.68-1.45 (6H, m, H-6 + H-7 + H-8), 0.91 (3H, d, J = 6.4 Hz, H-11), 0.85 (3H, d, J = 6.4 Hz, H-11) ppm. **13C-NMR** (101 MHz, CDCl₃): δ 195.2, 142.6, 140.0, 129.3, 124.1, 83.3, 75.0, 50.5, 33.4, 31.5, 28.0, 23.7, 21.8, 21.3, 18.9, 18.7 ppm. **IR** (film, NaCl): ν max 2925, 2854, 1703, 1464, 1376, 1274, 1088, 849, 744 cm⁻¹. **ESI-MS**: m/z calcld for C₁₇H₂₈NaO₅S⁺ (M+Na⁺) 343.1702; found 343.1707.

**2-Methylhex-5-en-2-ol (97a)**

A solution of 3M MeMgBr solution in ether (6.3 mL, 19 mmol, 1.1 eq) was charged into a 250 mL round bottom flask and diluted with dry Et₂O (11 mL) under a nitrogen atmosphere. To this, 5-Hexen-2-one (2.0 mL, 17 mmol, 1.0 eq) was added dropwise over 10 minutes and stirred at room temperature for 1h. The reaction mixture was quenched with sat. NH₄Cl solution (5.5 mL), followed by 1M soln of NaHSO₄ solution (4 mL). The layers were separated and the aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (25 mL), dried over anhydrous MgSO₄ and filtered. It was then concentrated in vacuo to give a yellow oil. The oil was purified by flash column chromatography on silica with 1% MeOH in DCM to yield 97a as a colourless oil (0.748 g, 39%).

*Data was consistent with those reported in the literature.*[39]

**1H NMR** (400 MHz, CDCl₃): 6.584 (1H, ddt, J = 17.1 Hz, 10.4 Hz, 6.6 Hz, H-4), 5.03 (1H, ddt, J = 17.1 Hz, 2.0 Hz, 1.4 Hz, H-5,trans), 4.95 (1H, ddt, J = 10.4 Hz, 2.0 Hz, 1.4 Hz, H-5,cis), 2.17-2.10 (2H, m, H-3), 1.60-1.54 (2H, m, H-2), 1.22 (6H, s, H-1) ppm. **13C NMR** (101 MHz, CDCl₃): δ139.1, 114.6, 71.1, 43.0, 34.3, 29.4, 29.0 ppm. **IR** (film, NaCl): ν max 3342, 3045, 2936, 1641, 1453, 1376, 1290, 1221, 1153, 994, 908, 772, 630 cm⁻¹
To a suspension of magnesium turnings (601 mg, 25 mmol) in dry Et₂O (27 mL), a solution of 4-bromo-1-butene (2.54 mL, 25 mmol) in dry Et₂O (4.0 mL) was added over a period of 5 minutes under a nitrogen atmosphere at 0 °C. After stirring the mixture for 2.5 h at room temperature, the Grignard reagent (20.0 mL, 1.5 eq.) was added over a period of 5 minutes to a solution of isobutyraldehyde (0.76 mL, 8.3 mmol) in dry Et₂O (5 mL) at 0 °C. The solution was stirred for 2 hours at room temperature, then quenched with sat. NH₄Cl solution (25 mL) until the magnesium salt dissolved. After separation of the phases, the aqueous layer was extracted with Et₂O (3 × 20 mL). The combined organic phases were dried over Na₂SO₄, filtered and concentrated in vacuo to give a yellow oil. This was then purified by column chromatography on silica with 10 % ethyl acetate in petroleum ether to yield 97c as a yellow oil (519.4 mg, 49 %).

¹H NMR (400 MHz, CDCl₃): δ 5.84 (1H, ddt, J = 17.1 Hz, 10.2 Hz, 6.7 Hz, H-6), 5.04 (1H, ddt, J= 17.1 Hz, 2.0 Hz, 1.8 Hz, H-trans), 4.96 (1H, ddt, J = 10.2 Hz, 2.0 Hz, 1.2 Hz, H-7cis), 3.37 (1H, ddd, J = 8.8 Hz, 5.2 Hz, 3.4 Hz, H-3), 2.30-2.20 (1H, m, H-4), 2.19-2.10 (1H, m, H-4), 1.70-1.55 (3H, m, H-5 + H2), 0.90 (3H, d, J = 3.2 Hz, H-1), 0.89 (3H, d, J = 3.2 Hz, H-1) ppm.¹³C NMR (101 MHz, CDCl₃): δ 138.9, 114.9, 76.4, 33.9, 33.7, 30.1, 18.9, 17.3 ppm. IR (film, NaCl): vₘₐₓ 3354, 3078,2959, 2938, 2875, 1641, 1469, 1450, 1414, 1387, 1368, 1269, 1179, 1095, 1057, 1018, 992, 956, 908, 850, 833, 805, 770, 644 cm⁻¹. ESI-MS: m/z calcd for C₈H₁₇O⁺ (M+H⁺) 129.1274; found 129.1272

(E)-S-p-Tolyl 6-hydroxy-6-methylhept-2-enethioate (101a)

2-Methylhex-5-en-2-ol (68.4 mg, 0.6 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (327.5 mg, 1.84 mmol, 3.1 eq) were dissolved in dry Et₂O (10 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (37.6 mg, 0.06
mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 20 hours. The mixture was then concentrated in vacuo and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 101a as a brown oil (137.5 mg, 87%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.30 (2H, d, J = 8.2 Hz, H-2), 7.21 (2H, d, J = 8.2 Hz, H-3), 7.00 (1H, dt, J = 15.6 Hz, 6.8 Hz, H-5), 6.19 (1H, dt, J = 15.6 Hz, 1.6 Hz, H-4), 2.36 (3H, s, H-1), 2.35-2.30 (2H, m, H-6), 1.66-1.60 (2H, m, H-7), 1.24 (6H, s, H-8) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 188.7, 146.7, 139.8, 134.6, 130.1, 127.9, 124.2, 70.7, 41.7, 29.5, 27.5, 21.5 ppm. IR (film NaCl): $\nu_{\text{max}}$ 3409, 2970, 2925, 1686, 1631, 1494, 1378, 1211, 1140, 1034, 997, 925, 906, 808, 705 cm$^{-1}$. ESI-MS: m/z calcd for C$_{15}$H$_{20}$Na$_2$O$_5$S$^+$ (M+Na$^+$) 287.1076; found 287.1080; C$_{15}$H$_{21}$O$_2$S$^+$ (M+H$^+$) 265.1257; found 265.1258

S-p-Tolyl-2-(5,5-dimethyltetrahydrofuran-2-yl)ethanethioate (103a)

(E)-S-p-Tolyl 6-hydroxy-6-methylhept-2-enethioate (19.2 mg, 0.073 mmol) was dissolved in DCE (1.2 mL) and H$_2$O (0.2 mL) was added and cooled in ice. To this, a solution TFA in DCE (1.8 mL, 0.06 M) was added over three minutes. The reaction mixture was heated at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO$_3$ solution (1 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 103a as a yellow oil (6.9 mg, 36%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.27 (d, 2H, J = 8.1 Hz, H-2), 7.19 (2H, d, J = 8.1 Hz, H-3), 4.40-4.33 (1H, m, H-5), 2.99 (1H, dd, J = 14.8 Hz, 7.3Hz, H-4), 2.64 (1H, dd, J = 14.8 Hz, 5.7Hz, H-4), 2.35 (3H, s, H-1), 2.20-2.10 (m, 1H, H-6) 1.80-1.70 (3H, m, H-6 + 2x H-7), 1.26 (3H, s, H-8), 1.22 (3H, s, H-9) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ 195.8, 139.8, 134.6, 130.1, 124.3, 81.3, 75.0, 50.3, 38.3, 31.8, 29.3, 28.2, 21.5 ppm IR (film NaCl): $\nu_{\text{max}}$ 2960, 2924, 2853, 1705, 1463, 1439, 1365, 1260, 1141, 1055, 1002, 806, 758 cm$^{-1}$. ESI-MS: m/z calcd for C$_{15}$H$_{20}$Na$_2$O$_5$S$^+$ (M+Na$^+$) 287.1076; found 287.1078.
(E)-S-p-Tolyl 6-hydroxyhex-2-enethioate (101b)

Pent-4-en-1-ol (43.1 mg, 0.5 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (274.0 mg, 1.54mmol, 3.08 eq) were dissolved in dry Et₂O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (9.6 mg, 0.05 mmol, 10 mol%) and Hovysda-Grubbs 2nd generation catalyst (31.4 mg, 0.05 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40°C for 18 hours. The mixture was then concentrated in vacuo and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 101b as a brown oil (93.5 mg, 79%).

¹H NMR (400 MHz, CDCl₃): δ 7.70 (2H, d, J = 8.2 Hz, H-2), 7.21 (2H, d, J = 8.2 Hz, H-3), 6.97 (1H, dt, J = 15.5 Hz, 7.0 Hz, H-5), 6.20 (1H, dt, J = 15.5 Hz, 1.6 Hz, H-4), 2.36 (3H, s, H-1), 3.65 (2H, t, J = 6.4 Hz, 6.4 Hz, H-8), 2.36 (3H, s, H-1), 2.32 (2H, dtd, J = 7.0 Hz, 7.0 Hz, 1.6 Hz, H-6), 1.76-1.70 (2H, m, H-7) ppm.

¹³C NMR (101 MHz, CDCl₃): δ 188.7, 145.9, 139.8, 134.7, 130.1, 128.2, 124.1, 62.0, 30.9, 28.7, 21.4 ppm.

IR (film NaCl): v_max 3382, 3024, 2924, 2584, 1705, 1495, 1461, 1378, 1304, 990, 971, 868, 807 cm⁻¹. ESI-MS: m/z calcd for C₁₃H₁₆NaO₂S⁺ (M+Na⁺) 259.0763; found 259.0767

S-p-Tolyl-2-(tetrahydrofuran-2-yl)ethanethioate (103b)

(E)-S-p-Tolyl 6-hydroxyhex-2-enethioate (12.8 mg, 0.054 mmol) was dissolved in cyclohexane (2.6 mL). To this, (R)-TRIP (8.2 mg, 0.011 mmol, 20 mol %) was and stirred at 75 °C under a nitrogen atmosphere for 24 hours. The reaction mixture was then concentrated in vacuo and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield 103b as a yellow oil (10.8 mg, 84%).

¹H NMR (400 MHz, CDCl₃): δ 7.78 (2H, d, J = 8.1 Hz, H-2), 7.20 (2H,d, J = 8.1 Hz, H-3), 4.32-4.24 (1H, m, H-5), 3.98 (1H, dt, J = 8.0 Hz, 6.6 Hz, H-8), 3.75 (1H, td, J = 8.0 Hz, 6.6 Hz, H-8), 2.95 (1H, dd, J = 14.9 Hz, 6.7 Hz H-4), 2.76 (1H, dd, J = 14.9 Hz, 6.2 Hz, H-4), 2.26 (3H, s, H-1), 2.12-2.04 (1H, m, H-6), 1.96-1.84 (2H, m, H-7), 1.64-1.57 (1H, m, H-6) ppm. ¹³C NMR (101 MHz, CDCl₃): δ 195.9, 139.9, 134.6, 130.2, 124.2, 75.6, 68.2, 49.4, 31.4, 25.7, 21.5 ppm IR (film NaCl): v_max 2924, 2584, 1705, 1495, 1461, 1378,
1261, 1181, 1068, 1014, 807, 750 cm$^{-1}$. **ESI-MS**: m/z calcd for C$_{13}$H$_{15}$NaO$_2$S$^+$ (M+Na$^+$) 259.0763; found 259.0765.

$[\alpha]_{D}^{25.0}$ $-14.3$ (c = 0.50, CHCl$_3$) for the mixture.

**HPLC** (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, $\lambda = 254$): $t_R$ (major) = 14.1, $t_R$ (minor) = 17.7, ee - 40%

![Chemical Structure](image)

(\textit{E})-S-p-Toly 6-hydroxy-7-methyloct-2-enethioate (101c)

2-Methylhept-6-en-3-ol (129.0 mg, 1.01 mmol, 1.0 eq) and S-p-tolylprop-2-enethioate (550.1 mg, 3.09 mmol, 3.06 eq) were dissolved in dry Et$_2$O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (19.2 mg, 0.101 mmol, 10 mol%) and Hoyveda-Grubbs 2$^{nd}$ generation catalyst (63.2 mg, 0.101 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 $^\circ$C for 16 hours. The mixture was then concentrated and purified by column chromatography on silica using 15% ethyl acetate in hexane to yield 101c as a brown oil (206.4 mg, 74%).

$^1$H NMR (400 MHz, CDCl$_3$): 6.73 (2H, d, J = 8.0 Hz, H-2), 7.22 (2H, d, J = 8.0 Hz, H-3), 7.00 (1H, dt, J = 15.6 Hz, 6.9 Hz, 6.9 Hz, H-4), 6.21 (1H, dt, J = 15.6 Hz, 1.4 Hz, 1.4 Hz, H-5), 3.37 (1H, br s, OH), 2.50-2.40 (1H, m, H-8), 2.36 (3H, s, H-1), 2.35-2.25 (1H, m, H-9), 1.70-1.50 (4H, m, H-6 + H-7), 0.92 (3H, d, J = 3.7 Hz, H-10), 0.91 (3H, d, J = 3.7 Hz, H-10) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): 6.1867.7, 146.5, 139.8, 134.8, 130.2, 128.1, 124.2, 76.1, 34.0, 32.4, 29.1, 21.5, 18.9, 17.3 ppm. IR (film NaCl): $v_{max}$ 3448, 3025, 2958, 2870, 1677, 1631, 1494, 1461, 1385, 1282, 1210, 1138, 1029, 990, 807 cm$^{-1}$. **ESI-MS**: m/z calcd for C$_{16}$H$_{20}$NaO$_2$S$^+$ (M+Na$^+$) 301.1233; found 301.1234.

$S$-p-Tolyl 2-{5-isopropyltetrahydrofuran-2-yl}ethanethioate (103c)

(\textit{E})-S-p-Toly 6-hydroxy-7-methyloct-2-enethioate (16.5 mg, 0.059 mmol) was dissolved in DCE (1 mL) and H$_2$O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06 M) was
added over three minutes. The reaction mixture was heated at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO₃ solution (2 mL). The aqueous layer was extracted with DCM (3 x 10 mL). The combined organics were dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in hexane to yield 103c as an inseparable diastereomeric mixture (dr = 1.41:1) (9.4 mg, 58%).

**H-NMR** (400 MHz, CDCl₃): δ 7.27 (4H, d, J = 8.2 Hz, H-2), 7.22 (4H, J = 8.2 Hz, H-3), 4.37-4.32 (1H, m, H-5_major), 4.31-4.24 (1H, m, H-5_minor), 3.56-3.50 (1H, m, H-8_major), 3.66-3.44 (1H, m, H-8_minor), 3.00-2.80 (2H, m, H-4_major + H-4_minor), 2.80-2.70 (2H, m, H-4_major + H-4_minor), 2.36 (6H, s, H-1_major + H-1_minor), 2.14-2.02 (2H, m, H-9_major + H-9_minor), 1.98-1.85 (2H, m, H-6_major + H-6_minor), 1.73-1.57 (6H, m, 2x H-7_major + H-6_major + 2x H-7_minor + H-6minor), 0.96-0.94 (6H, m, H-10_major + H-10_minor), 0.86-0.82 (6H, m, H-11_major + H-11_minor) ppm **C-NMR** (101 MHz, CDCl₃): δ 196.9, 139.8, 134.6, 130.1, 124.3, 85.3, 84.7, 75.4, 75.3, 50.0, 49.7, 33.3, 33.2, 32.3, 31.2, 29.3, 28.3, 21.5, 19.5, 18.5, 18.4 ppm. **IR** (film, NaCl): v_max 2958, 2925, 2872, 1705, 1494, 1468, 1380, 1270, 1166, 1070, 987, 806, 753 cm⁻¹. **ESI-MS:** m/z calcd for C₁₂H₂₀NaO₂S⁺ (M+Na⁺) 315.1389; found 315.1381

![Structure of (E)-5-Mesityl-6-hydroxy-6-methylhept-2-ene (102a)](structure.png)

2-Methylhex-5-en-2-ol (68.4 mg, 0.6 mmol, 1.0 eq) and 5-mesityl prop-2-enethioate (372.1 mg, 1.81 mmol, 3.01 eq) were dissolved in dry Et₂O (20 mL) under a nitrogen atmosphere. To this, copper (I) iodide (11.5 mg, 0.06 mmol, 10 mol%) and Hovyeda-Grubbs 2nd generation catalyst (37.6mg, 0.06 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 18 hours. The mixture was then concentrated in vacuo and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 102a as a brown oil (154.0 mg, 88%).

**H NMR** (400 MHz, CDCl₃): 7.03-6.95 (3H, m, H-2 + H-5), 6.23 (1H, dt, J = 15.5 Hz, 1.4 Hz, H-4), 2.36-2.31 (2H, m, H-7), 2.30 (6H, s, H-8), 2.28 (3H, s, H-1), 1.68-1.64 (2H, m, H-6) ppm. **C NMR** (101 MHz, CDCl₃): δ187.8, 146.2, 142.8, 140.0, 129.3, 128.1, 123.6, 70.7, 41.8, 29.5, 27.4, 21.7, 21.3 ppm. **IR** (film NaCl): v_max 3414, 2969, 2924, 1671, 1631, 1465, 1375, 1213, 1157, 1030, 996, 926, 850, 808 cm⁻¹. **ESI-MS:** m/z calcd for C₁₂H₂₁NaO₂S⁺ (M+Na⁺) 315.1389; found 315.1394
(E)-S-Mesityl-6-hydroxy-6-methylhept-2-enethioate (19.0 mg, 0.065 mmol) was dissolved DCE (1.1 mL) and H$_2$O (0.2 mL) was added and cooled in ice. To this, a solution of TFA in DCE (1.8 mL, 0.06M) was added over three minutes. The reaction mixture was then heated at 50 °C for 24 hours. The reaction mixture was then quenched with saturated NaHCO$_3$ solution (2 mL) and diluted with DCM (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo to give a crude yellow oil. The oil was purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield 104a as a yellow oil (13.0 mg, 68%).

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.96 (2H, s, H-2), 4.40-4.33 (1H, m, H-5), 2.99 (1H, dd, J = 14.2 Hz, 6.0 Hz H-4), 2.73 (1H, dd, J = 14.2 Hz, 7.8 Hz H-4), 2.29 (H, s, H-3), 2.27 (3H, s, H-1), 2.20-2.10 (1H, m, H-6) 1.80-1.70 (3H, m, H-6 + 2x H-7), 1.26 (3H, s, H-8), 1.21 (3H, s, H-9) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ192.8, 142.0, 129.3, 123.9, 81.2, 75.3, 50.3, 38.3, 31.8, 29.3, 28.1, 21.7, 21.3 ppm IR (film NaCl): $\nu_{max}$ 2967, 2925, 2855, 1701, 1601, 1460, 1439, 1365, 1249, 1141, 1056, 1000, 980, 909, 849, 806, 737 cm$^{-1}$. ESI-MS: m/z calcd for C$_{13}$H$_{25}$NaO$_2$S$^+$ (M+Na$^+$) 293.1570; found 293.1571.

(E)-S-Mesityl 6-hydroxyhex-2-enethioate (102b)

Pent-4-en-1-ol (34.5 mg, 0.4 mmol, 1.0 eq) and S-mesityl prop-2-enethioate (250.5 mg, 1.22 mmol, 3.04 eq) were dissolved in dry Et$_2$O (20 mL) under nitrogen atmosphere. To this, copper (I) iodide (7.7 mg, 0.04 mmol, 10 mol%) and Hovveda-Grubbs 2nd generation catalyst (25.1 mg, 0.04 mmol, 10 mol%) were added as solids in a single portion and the mixture was stirred at 40 °C for 18 hours. The mixture was then concentrated in vacuo and purified by column chromatography on silica using 10% ethyl acetate in petroleum ether to yield 102b as a brown oil (86.8 mg, 82%).

$^1$H NMR (400 MHz, CDCl$_3$): δ72.02-6.92 (2H, m, H-2 + H-5), 6.24 (1H, dt, J = 15.6 Hz, 1.4 Hz, H-4), 3.69 (2H, t, J = 6.2 Hz, H-8), 2.36-2.32 (2H, m, H-6), 2.30 (6H, s, H-3), 2.28 (3H, s, H-1), 1.80-1.74 (2H, m, H-7) ppm. $^{13}$C NMR (101 MHz, CDCl$_3$): δ198.7, 145.3, 142.8, 129.3, 128.5, 123.5, 62.1, 30.9, 28.7, 21.8, 21.3 ppm. IR (film NaCl): $\nu_{max}$ 3357, 2923, 2855, 1682, 1631, 1437, 1375, 1315, 1280, 1210, 1175,
1136, 1044, 990, 971, 850, 798, 715 cm\(^{-1}\). \textbf{ESI-MS}: m/z calcd for C\(_{15}H_{20}NaO_2S^+\) (M+Na\(^+\)) 287.1076; found 287.1079

\textit{S-Mesityl 2-(tetrahydrofuran-2-yl)ethanethioate (104b)}

(E)-S-Mesityl 6-hydroxyhex-2-enethioate (15.7 mg, 0.0595 mmol) was dissolved in cyclohexane (3 mL). To this, (R)-TRIP (9.0 mg, 0.012 mmol, 20 mol %) was added and stirred at 50 °C under a nitrogen atmosphere for 24 hours. The reaction mixture was diluted with DCM (3 mL) and quenched with saturated NaHCO\(_3\) solution (2 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 5 mL). The combined organics were dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo} and purified by column chromatography on silica using 5% ethyl acetate in petroleum ether to yield 104b as a yellow oil (11.5 mg, 73%).

\textbf{\(^1\)H NMR} (400 MHz, CDCl\(_3\)): \(\delta\) 6.96 (2H, s, H-2), 4.32-4.24 (1H, m, H-5), 3.89 (dt, \(J = 8.1\) Hz, 6.6 Hz, 1H, H-8), 3.74 (td, \(J = 8.1\) Hz, 6.6 Hz, 1H, H-8), 2.97 (1H, dd, \(J = 14.7\) Hz, 6.4 Hz, H-4), 2.75 (1H, dd, \(J = 14.7\) Hz, 6.5 Hz, H-4), 2.30 (6H, s, H-3), 2.27 (3H, s, H-1), 2.14-2.05 (m, 1H, H-6), 2.00-1.85 (2H, m, H-7), 1.66-1.50 (1H, m, H-6) ppm. \textbf{\(^{13}\)C NMR} (101 MHz, CDCl\(_3\)): \(\delta\) 195.0, 142.6, 140, 129.3, 123.8, 75.9, 68.1, 49.4, 31.2, 25.7, 21.7, 21.5 ppm \textbf{IR} (film NaCl): \(\nu_{\text{max}}\) 2953, 2922, 2869, 1700, 1602, 1460, 1376, 1298, 1177, 1068, 850, 751, 715 cm\(^{-1}\). \textbf{ESI-MS}: m/z calcd for C\(_{15}H_{20}NaO_2S^+\) (M+Na\(^+\)) 287.1076; found 287.1073.

\([\alpha]_D^{25.0}\) \(\approx\) 6.1 (c = 0.525, CHCl\(_3\)) for the mixture.

\textbf{HPLC} (Chiralpak AD-H, 5% IPA, 95% hexane, 0.9 mL/min, \(\lambda = 254\)): \(t_R\) (major) = 9.6, \(t_R\) (minor) = 12.5, ee - 10%
## 10. Abbreviations

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<th>Abbreviation</th>
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<td>Å</td>
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<td>Ac</td>
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<td>M</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<td>mg</td>
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<tr>
<td>MMFF</td>
<td>Merck Molecular Force Field</td>
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<tr>
<td>PMB</td>
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<td>TIPS</td>
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<td>3,3′-Bis(triphenylsilyl)-1,1′-binaphthyl-2,2′-diylhydrogenphosphate</td>
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<td>transition state</td>
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11. References

37. Ermanis, K. Unpublished results.