Tertiary thiols via stereospecific α-arylation of lithiated allylic thiocarbamates

A thesis submitted to the University of Manchester for the degree of Doctor of Philosophy in the Faculty of Engineering and Physical Sciences

2014

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School of Chemistry
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Abstract

Tertiary thiols via stereospecific α-arylation of lithiated allylic thiocarbamates

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Gaëlle Mingat
2014

Keywords: thiocarbamate, allylic, organolithium, arylation, vinylation, stereospecific.¹

This thesis describes the work carried out on the lithiation and rearrangement of N-aryl- and N-vinyl allylic thiocarbamates, with the aim of preparing a wide range of versatile tertiary thiols.

The synthesis of the racemic allylic starting materials has been achieved through in situ [3,3]-sigmatropic rearrangement of O-allylthiocarbamates to their S-counterparts (II.A). The enantioselective version relies either on asymmetric metal catalysis (achiral substrates) or stereospecificity (enantiopure substrates) in the [3,3]-sigmatropic rearrangement.

Lithiation followed by N to C aryl migration proceeds in generally good to excellent yields, with both electron-poor and electron-rich rings. The scope and the influence of various substituents at Cα or on the allylic double bond are presented in Section II.B.1.

Section II.B.2 proposes a mechanistic pathway and details NMR studies carried out to get structural data in the α-thioallyllithium intermediates.

Investigations of the stereospecificity of the rearrangement show that most rings migrate without loss of enantioenrichment in substrates bearing an unsubstituted allylic double bond (II.B.3.a). Complete enantiospecificity with all rings has been achieved in thiocarbamates bearing a cyclohexyl-substituted double bond (II.B.3.b).

Section II.C reports the results obtained in the N to C transfer of non-aromatic groups. Excellent enantiospecificities have been achieved in the migration of a vinyl substituent, although yields remain moderate. Higher yields can be obtained but they come along with lower enantiomeric ratios.

Section II.D details the transformations undertaken in the rearranged tertiary allylic thiocarbamates. A wide range of tertiary thiols has been obtained with good to excellent yields. Functionalisation of the allylic double bond in these hindered substrates was not straightforward. Eventually, ring-closing metathesis in S-allyl sulfides allows the preparation of biologically interesting 2,5-dihydrothiophenes bearing a highly enantioenriched quaternary centre.

Finally, evidence for retentive aryl migration in allylic thiocarbamates is outlined in Section II.E. Circular dichroism experiments were carried out in the derivatised 2,5-dihydrothiophenes and compared with predictions obtained via DFT calculations for both enantiomers of a model compound. The absolute configuration of the 2,5-dihydrothiophenes and their tertiary thiocarbamate precursors has been unambiguously established, confirming a retentive pathway in both aryl and vinyl migrations.
DECLARATION

No portion of the work referred to in this thesis has been submitted in support of an application for another degree or qualification of this or any other university or other institute of learning.

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Last but (certainly) not least, a big, a very big, the biggest thank you to you, Nico, who not only came along with me to England, to the North of England... but supported me throughout these three years and a half! You can now say “I have lived with a PhD student and I survive”! More seriously, I am so glad we made the decision to cross the Channel. Our British adventure was amazing, we had such good times (I’ll leave out the 15 °C in “summer” at this point), we have discovered, experienced and learned so much! It was amazing, and I would not have loved it that much had we not shared it together. Let’s hope we’ll manage to enjoy Devon and Germany as much as Manchester!
### Abbreviations

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<td>acetyl</td>
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<td>acetonitrile</td>
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<td>[α]d</td>
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<td>t-butoxycarbonyl</td>
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<td>EPSRC</td>
<td>Engineering and Physical Sciences Research Council</td>
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<td>GC</td>
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Note: for simplicity, we chose not to represent planar chirality in this thesis but \((R,S_p)-(\text{--})\)-COP-Cl exhibiting planar chirality is shown on the right.
$S_{N2}$  second order nucleophilic substitution
$S_N$  nucleophilic substitution
sspec  stereospecificity
t  time, triplet
t  tertiary
T  temperature
TBAI  tetrabutylammonium iodide
TBDMS  $t$-butyldimethylsilyl
TBDPS  $t$-butyldiphenylsilyl
TBHP  $t$-butyl hydroperoxide
TBME  methyl $t$-butyl ether
TCDI  thiocarbonyldiimidazole
Tf  triflate
TFA  trifluoroacetic acid
THF  tetrahydrofuran
TIPS  triisopropylsilyl
TIPT  titanium tetraisopropoxide
TLC  thin layer chromatography
TMCDA  $N,N,N',N'$-tetramethylcyclohexane-1,2-diamine
TMEDA  $N,N,N',N'$-tetramethylethylenediamine
TMS  trimethylsilyl
tol  tolyl
Ts  para-toluenesulfonyl
TS  transition state
TsDPEN  (1S,2S)-$N$-$p$-toluenesulfonyl-1,2-diphenylethylendiamine
UV  ultraviolet
vol%  volume percentage
w  weight
w/w  weight per unit weight
X  halide, heteroatom
xantPhos  4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
$1^\circ$  primary
$2^\circ$  secondary
Preface

The author graduated from ENSCMu (National Graduate School of Chemistry of Mulhouse, France), in 2009. During the course of her studies, she took the opportunity to go on a one-year internship at Scynexis, Inc., a pharmaceutical company, in the Research Triangle Park in North Carolina (USA), developing antiparasitics. Her final year project was undertaken at the Université Joseph Fourié in Grenoble (France) under the supervision of Dr Jean-François Poisson, working on the total synthesis of (+)-lactacystin and (−)-salinosporamide A via [2+2] cycloadditions of enol ethers and ketenes and Beckmann rearrangement.

In 2010, she moved to Manchester to start a PhD in the group of Professor Jonathan Clayden, studying the lithiation and rearrangement of allylic thiocarbamates. This thesis covers the research carried out over the last three years and a half.

In June 2014, she will take up a postdoctoral position in the group of Professor Magnus Rueping, at the RWTH Aachen University, in Germany.
Stench and high reactivity make the thiol the most froward of common functional groups, beloved by misogynists, misanthropes, and masochists alike.

Chapter I: INTRODUCTION

I.A) Asymmetric synthesis of tertiary thiols

I.A.1) Introduction

Thiols are widespread in Nature. Glutathione 1, a key metabolic antioxidant, contains the cysteine residue. Tertiary thiols (R)-thioterpineol 2 and 3 are powerful flavour compounds, 2 possessing the taste of grapefruit, while 3 confers a hint of passion fruit to wines. Less pleasant is chiral, enantiomerically enriched (S)-3-thio-3-methylhexanal-1-ol 4, isolated from sweat (Figure 1).

![Figure 1: Naturally-occurring thiols.](image)

Two of the 21 proteinogenic amino acids contain sulfur (Figure 2).

![Figure 2: Sulfur-containing amino acids.](image)

In addition, the importance of organosulfur compounds in synthetic chemistry and in the biological or pharmaceutical fields has been highlighted in many instances. Sulfur is a constituent of biotin 7 and antibiotics of the penicillin G 8 and thiolactomycin 9 families (Figure 3).
Figure 3: Sulfur-containing biologically-relevant molecules.

Four of the five best-selling drugs in the US in 2012 include a sulfur-based functionality and have been commercialised by some of the largest pharmaceutical companies (Figure 4).⁶

Figure 4: Sulfur-containing best-selling drugs in the US in 2012 (in billions).

Although chiral secondary thiols have received considerable interest from the synthetic chemistry community,⁴,⁷ enantiopure tertiary thiols remain a challenging target as the methods available for their preparation are restricted to compounds bearing specific functionalities, thus narrowing the applications of the process.⁸ For example, inversion at tertiary centres, alkylation of S-substituted enolates and conjugate addition of a sulfur nucleophile require a particular leaving group and/or α- or β-carbonyl substituents.

Two approaches exist for the synthesis of enantiopure tertiary thiols. The asymmetric quaternary centre can be generated by the formation of either the C-S or the C-C bond. The first case relies on stereoselective attack of a sulfur nucleophile on an enantioenriched fully substituted carbon, with removal of a leaving group (Scheme 1, blue route). In the second case, the quaternary centre would be formed via
stereoselective alkylation, arylation or acylation of a secondary sulfur-based carbon pronucleophile (Scheme 1, red route).

\[
\text{Scheme 1: Tertiary thiols via either C-S or C-C bond formation.}
\]

I.A.2) Carbon-sulfur bond formation

I.A.2.a) \(S_N2\) displacement of a leaving group

\(S_N2\) reactions are very sensitive to the steric hindrance of both the nucleophile and the attacked centre. Thus, formation of a quaternary centre via \(S_N2\) is generally not favoured. However, activation of the electrophilic carbon with some very good leaving groups facilitates its substitution by a sulfur nucleophile.

I.A.2.a.i) Sulfonate leaving groups

Displacement of the mesyl group in cyanohydrin (R)-14 was achieved with thioacetic acid, in the presence of collidine and took place with complete stereospecificity to afford the expected thioester (S)-15 in high yield (Scheme 2).\(^9\)

\[
\text{Scheme 2: Displacement of a mesyl group in tertiary cyanohydrin (R)-14.}
\]

Similarly, spirobrassinin 17 was prepared from naturally occurring dioxibrassinin (S)-(−)-16 using methanesulfonyl chloride to activate the hydroxyl group (Scheme 3).\(^10\) The intramolecular \(S_N2\) reaction perfectly maintained the optical activity, which was not the case when thionyl chloride was used (36% e.e. for (R)-(+)17).
Scheme 3: Displacement of a mesyl group in dioxibrassinin (S)-(−)-16.

Tunge and co-workers, needing a general and simple enantioselective synthesis of fully substituted α-aryl-α-sulfonyl allyl esters such as (R)-20, envisaged the stereospecific displacement of a mesylate group in protected α-hydroxy ester (R)-18 by a strong thiolate nucleophile. The enantioenriched tertiary sulfide (R)-19 was then oxidised to the sulfone (Scheme 4).  

Scheme 4: Enantioselective preparation of tertiary α-sulfonyl esters.

The ester group was expected to disfavour the S$_N$1 pathway by destabilising the inherent carbocation intermediate, which would promote racemisation. Moreover, its planar geometry minimises steric hindrance at the electrophilic carbon. However, the erratic enantiomeric excesses determined in the sulfones 20 indicated that partial racemisation occurred despite the ester function.

The methodology was consequently applied to α,α-dialkyl-α-hydroxy carbonyl compounds 21 and 23, where the phenyl group in 18 was replaced by a benzyl/alkoxy one, which was expected to better destabilise any unwanted carbocation. Pleasingly, the α-thioesters were straightforwardly obtained from the corresponding stable mesylates and their direct oxidation provided the highly enantioenriched sulfones 22 and 24 in very good yields (Scheme 5).

Scheme 5: Enantioselective preparation of tertiary α-sulfonyl esters.
Cyclic sulfamidates undergo S
\_\text{N}^2\text{2} ring-opening with complete inversion at the stereogenic centre.\textsuperscript{12} This proved particularly useful in the preparation of \(\alpha\)-thiodisubstituted \(\beta^{2,2}\)-amino acids such as \((S)-27.\textsuperscript{13} Due to their structural and biological properties, \(\beta\)-peptides have attracted much attention.\textsuperscript{14} Moreover, sulfur-containing amino acids have found many applications in the synthesis of biologically relevant molecules.\textsuperscript{14}

Nucleophilic opening of five-membered cyclic \(\text{gem}\)-disubstituted sulfamidate \((R)-25\) using sodium thiolate proceeded with complete stereospecificity to afford tertiary methylsulfide \((S)-26\), subsequently leading to enantiopure \(\beta^{2,2}\)-amino acid \((S)-\alpha\)-dimethylisocysteine \((S)-27\) (Scheme\ 6).

\begin{equation*}
\text{(R)-25} \xrightarrow{\text{NaSMe, DMF, 25 °C}} \text{(S)-26: 93\%} \quad \text{(S)-26} \xrightarrow{\text{MeSMe}} \text{(S)-27: 81\% (2 steps)}
\end{equation*}

Scheme 6: Stereospecific nucleophilic ring-opening of sulfamidate \((R)-25\).

Notably, the scope of the reaction was found to be exceptionally broad as a wide range of sulfur nucleophiles (primary, secondary and tertiary alkyl thiols, that can bear other functional groups such as alcohols, aromatic thiols with either electron-donating or -withdrawing substituents, potassium thioacetate and ammonium thiocyanate) afforded the expected open-chain products in excellent yields (84-99\%). Complete retention of enantiomeric purity was confirmed for one product.\textsuperscript{14}

The synthetic utility of the methodology was demonstrated by the preparation of new sulfur-containing \(\beta^{2,2}\)-amino acids, some of them of interest for the synthesis of novel antibiotics.\textsuperscript{15}

I.A.2.a.ii) Nucleophilic ring opening of epoxides

Under acidic conditions, opening of a tertiary epoxide will take place regioselectively at the more hindered carbon, since the resulting carbocation is more stable.\textsuperscript{16} However, the planarity of this intermediate seems to be a serious drawback in the achievement of high levels of stereoselectivity. Nevertheless, numerous examples of stereospecific reactions of sulfur nucleophiles at the quaternary carbon of an epoxide
have been reported,\textsuperscript{17} the earliest ones occurring in steroids.\textsuperscript{17a-e} They all involved an invertive S\textsubscript{N}2 pathway (Walden inversion) leading to the \textit{trans} product.

The simplest sulfur nucleophile, hydrogen sulfide, was used in conjunction with \textit{para}-toluenesulfonic acid in various 16β,17β-epoxy-pregnenones 28 to afford the corresponding \textit{trans}-16β-hydroxy-17α-mercaptopregnenones. Notably, the transformation produced tertiary thiol 29 in its free form, but displayed low yields (Scheme 7).\textsuperscript{17a}

\begin{center}
\begin{tikzpicture}

\begin{scope}[xshift=-10cm]

\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (a) at (0,0) {\textbf{28-29}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (b) at (-2,0) {\textbf{R}\textsuperscript{1} = OAc, R\textsuperscript{2} = H, R\textsuperscript{3} = O};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (c) at (2,0) {\textbf{R}\textsuperscript{1} = OH, R\textsuperscript{2} = F, R\textsuperscript{3} = O};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (d) at (-2,-2) {\textbf{R}\textsuperscript{1} = H, R\textsuperscript{2} = H, R\textsuperscript{3} = O};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (e) at (2,-2) {\textbf{R}\textsuperscript{1} = H, R\textsuperscript{2} = H, R\textsuperscript{3} = \alpha-H, \beta-OAc};
\end{scope}

\begin{scope}[xshift=0cm]

\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (f) at (0,0) {\textbf{H\textsubscript{2}S, p-TsOH}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (g) at (2,0) {\textbf{AcOH, 0 \textdegree C to rt, 4-8 h}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (h) at (-2,-2) {\textbf{29a: 22\%}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (i) at (2,-2) {\textbf{29b: 22\%}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (j) at (-2,-4) {\textbf{29c: 20\%}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (k) at (2,-4) {\textbf{29d: 41\%}};
\end{scope}

\end{tikzpicture}
\end{center}

\textbf{Scheme 7: Nucleophilic epoxide opening in steroids leading to tertiary thiol.}

Nucleophilic opening of the epoxide in 9β,11β-epoxy-androst-6-en-3,17-dione 30 using thiocyanic acid, in glacial acetic acid, afforded 9α-thiocyanato-androst-6-en-11β-ol-3,17-dione 31 in moderate yields, with full inversion of configuration at C9.\textsuperscript{17b} A few extra steps led to methylthio-steroid 32 (Scheme 8).

\begin{center}
\begin{tikzpicture}

\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (a) at (0,0) {\textbf{30}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (b) at (-2,0) {\textbf{HSCN}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (c) at (2,0) {\textbf{AcOH, rt, 26 h}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (d) at (-2,-2) {\textbf{31: 25-45\%}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] (e) at (2,-2) {\textbf{32}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 8: Stereospecific epoxide opening in steroids leading to tertiary sulfide 32.}

Similar conditions proved more successful in 2-en-5β,6β-epoxide 33, providing 5α-thiocyanato-6β-ol 34 in much better yield.\textsuperscript{17c} Notably, subsequent mesylation and reduction with LiAlH$_4$ afforded tertiary thiol 17β-hydroxy-5α-androst-2-ene-5-thiol 35 in very good yield (Scheme 9). This sequence had previously been used in a similar steroid, bearing the epoxide on carbons C2 and C3, leading to a secondary thiol.\textsuperscript{17d}
Scheme 9: Stereospecific epoxide opening in steroids leading to tertiary thiol 35.

Tertiary thiol 5α-hydroxy-10β-mercapto steroid 37 was obtained in good yield via ring opening of 5α,10α-epoxide 36, carried out with potassium hydrogen sulfide in the presence of the crown ether 18-crown-6 at 140 °C for 2 h (Scheme 10).17e

Scheme 10: Stereospecific epoxide opening in steroids leading to tertiary thiol 37.

Examples of nucleophilic epoxide openings at a quaternary centre, in cyclic but non-steroidal substrates, have been reported by Silverman,17f,g Caine,17h El Sayed,17i and more recently, Tatsuta17j and co-workers.

Silverman investigated both the acid- and the base-catalysed opening of epoxide 38 by ethanethiol.17f,g In the presence of trifluoroacetic acid, quaternary sulfide 39 was obtained in 66% yield after 35 min and 79% yield after 26 h. With triethylamine, 39 was produced in quantitative yield after 4 h (Scheme 11).

Scheme 11: Stereospecific epoxide opening leading to anti-hydroxysulfide 39.

The stereochemistry assigned for 39 was derived from “the known reaction of thiols with epoxides to yield exclusive anti-β-hydroxysulfides”.17f,g It was indeed reported elsewhere18 that “the very large majority of acid-catalysed, as well as basic ionic ring openings proceeds with complete Walden inversion” and that the acid-catalysed
hydrolysis of ditertiary epoxides gives the trans diols exclusively. In addition, in this particular example, the adjacent carbonyl group prevents any stabilisation of a positive charge, favouring the S_N2 mechanism and thus, leading to trans-39.

Similarly, tertiary β-hydroxy-α-phenyl sulfide 41 was obtained in good yield through ring opening of the hindered epoxide in 2,3-dimethylcyclohexanone 40 using thiophenol (Scheme 12).¹⁷h The trans stereochemistry was assigned by analogy with Silverman’s results.¹⁷f,g

![Scheme 12: Stereospecific epoxide opening with thiophenol.](image)

El Sayed et al., aware of the anticancer properties of some sulfur-containing natural and synthetic molecules, were interested in derivatising Sarcophinine 42 with thio-functionalities (Scheme 13).¹⁷i They aimed at opening the C7-C8 epoxide using two different sulfur nucleophiles. Because reaction with ammonium thiocyanate had been reported to form the trans-β-hydroxythiocyanates with high anti-Markovnikov regioselectivity,¹⁷i they were surprised to obtain the Markovnikov adduct cis-β-hydroxythiocyanate 43. They proposed it resulted from an unusual syn-addition on a carbocation intermediate. Lawesson’s reagent, on the contrary, afforded tertiary trans-β-hydroxythiol 45. Isolation of by-product 46 suggested that the epoxide was opened by nucleophilic attack of water to furnish a diol intermediate.

![Scheme 13: Epoxide opening leading to either cis or trans hydroxythio derivatives.](image)
An interesting example of “cascade epoxide openings” was reported in the first total synthesis of (+)-BE-52440A (+)-49 (Scheme 14). Epoxide (-)-47 was treated with sodium sulfide to form the very reactive intermediary t-thiolate 48 which, in turn, attacked another molecule of (-)-47 to provide (+)-49 in almost quantitative yield within 30 min. Its stereochemistry was confirmed by X-ray crystallography. Both nucleophilic attacks took place with complete regioselectivity and inversion at the attacked carbon.

![Scheme 14: An example of “cascade epoxide openings”](image)

The nucleophilic ring opening of epoxides can also be performed in open chains. Syn-epoxyester 50 was treated with sodium benzenethiolate at 0 °C for 4 h (Scheme 15). Simultaneous cyclisation of 51 provided γ-butyrolactone 52 in 60% yield. The stereochemistry was assigned by NOE experiments and confirmed the invertive substitution pathway.

![Scheme 15: Stereospecific epoxide opening in a non-cyclic substrate](image)

Similarly, syn-epoxyesters 53 and 55 provided lactones 54 and 56. NOE experiments again confirmed the S\textsubscript{N}2 mechanism (Scheme 16). As the aim of generating the γ-butyrolactones was only to assign the stereochemistry of the epoxides, no explanation regarding the regioselectivity was sought.
**Scheme 16:** Formation of $\gamma$-butyrolactones from stereospecific epoxide opening.

Since its isolation in 1982,$^5$ antibiotic (+)-thiolactomycin 9, possessing the previously undescribed tertiary thiolactone structure (Figure 3), has generated a constant interest amongst the scientific community due to its activity against numerous bacterial sources, including tuberculosis and malaria.$^{20,21}$ Although various syntheses of thiolactomycin 9 had been reported, analogs were still challenging to synthesise before Brückner and co-workers developed a novel asymmetric method that facilitated their preparation (Scheme 17).$^{21}$

![Scheme 16: Formation of $\gamma$-butyrolactones from stereospecific epoxide opening.](image)

Remarkably, the C-S bond was installed via a diastereoselective $S_N'$ thiolysis of vinyl epoxide 57. Regioselectivity unexpectedly turned out not to be an issue, to the contrary of reactivity and chemoselectivity. Eventually, the combination of thiopropionic acid with AlMe$_3$ furnished the desired syn-$\gamma$-hydroxythioester 58 in 51% yield, as a single diastereomer and with full conservation of enantioenrichment from 57. Subsequent vic-didesoxyxgenation and Dieckmann condensation completed the total synthesis of (+)-thiolactomycin 9 (94% e.e.) in 7 steps and 13% overall yield. Notably, this novel methodology allowed the preparation of three analogous thiotetronic acids in 90-95% e.e., two of them being known antibiotics which for no synthesis had been previously reported.

**Scheme 17:** A novel asymmetric synthesis of thiolactomycin 9 and its derivatives.

![Scheme 17: A novel asymmetric synthesis of thiolactomycin 9 and its derivatives.](image)

a) i. Et(CO)SH (5.0 eq), AlMe$_3$ (5.0 eq), CH$_2$Cl$_2$, -78 °C to rt, 1 h, ii. -78 °C to rt, 2 h, 60%; b) HF/Pyridine, THF, rt, 1.5 h, 85%; c) I$_2$ (4.0 eq), PPh$_3$ (4.0 eq), imidazole (5.0 eq), toluene, 0 °C to rt, 40 min, 69%; d) LiHMDS (2.5 eq), THF, -78 °C, 2.5 h, 65%.
I.A.2.a.iii) Mitsunobu reactions

In the Mitsunobu reaction, a primary or secondary alcohol, activated by a dialkyl azodicarboxylate in the presence of a trialkyl- or triarylphosphine, is displaced by a relatively acidic nucleophile (pKa ≤ 15) to form amines, azides, ethers and thioethers. Complete inversion of configuration is achieved with chiral secondary alcohols and results in the stereospecific generation of optically active products. The usual reagents are diethyl- or diisopropyl azodicarboxylate (DEAD or DIAD) and tributyl- or triphenylphosphine (Scheme 18). Although general with primary and secondary alcohols, the reaction is very sensitive to steric hindrance, and has proven unsuccessful with most tertiary alcohols.22c,23

\[
\text{OH} + H\text{-Nu} + N=\text{N}^{\text{R}^3} \xrightarrow{\text{solvent}} \text{Nu}^{\text{R}^3} + H\text{-N-N-H} + O=\text{PPh}_3 \text{ or PBu}_3
\]

1° or 2° alcohol 
DEAD: R^3 = Et 
DIAD: R^3 = t-Pr

Scheme 18: Principle of the Mitsunobu reaction.

Therefore, generation of chiral tertiary ether (R)-61 via the Mitsunobu reaction was an exciting achievement, despite a moderate yield due to formation of 62 arising from elimination, and harsh conditions (Scheme 19).24

\[
\begin{align*}
\text{MeO} & \quad + \quad \text{HO} - \text{Ph} - \text{OBn} \\
\text{(S)-59} & \quad \text{DIAD, PPh}_3 \\
\text{toluene} & \quad 100 \, ^{\circ}\text{C}, 14 \, \text{h} \\
\text{(R)-61: 54\%} & \quad \text{MeO} \quad \text{Me} \\
\text{60} & \quad + \quad \text{MeO} \quad \text{O} \\
\text{62} & \quad \text{64}
\end{align*}
\]

Scheme 19: Mitsunobu reaction in tertiary alcohol (S)-59.

Milder conditions (50 °C, 16 h) only produced traces of the desired ether, confirming the high sensitivity of the reaction to the steric bulk of the chiral alcohol employed. However, changes in the steric and electronic patterns of phenolic reagent 60 did not affect the yield.

Several examples of the use of sulfur-based nucleophiles in efficient Mitsunobu reactions can be found in the literature.25 The efficiency of Mitsunobu reactions in improving the selectivity in the displacement of a secondary alcohol by a sulfur nucleophile was rapidly demonstrated by Volante in 1981 who obtained the sole inverted 3α-cholesteryl thiol 64 in excellent yield from 3β-cholesterol 63 (Scheme 20).25a
The high stereospecificity of the substitution of steroidal alcohols 65 was further demonstrated by Walker et al. who observed the exclusive formation of the chiral secondary inverted thioethers 67, in excellent yields. Sulfenimides 66 were employed as the sulfur source, in the presence of tributylphosphine (Scheme 21).²⁵ᵇ Notably, no elimination product was detected even in the case of cholesterol, which for other phosphorus-mediated reactions had showed a lack of regio- and stereoselectivity. Nonetheless, the reaction of the most hindered secondary alcohols, like 65, required 18 h to go to completion instead of the usual 1 h.

The mechanism was proposed to start with reaction between sulfenimide 66 and tributylphosphine to give a thiophosphonium intermediate 68 which is displaced by the alcohol to form the reactive thiolate nucleophile 69 and the phosphonium-activated alcohol 70. Substitution of 70 by 69 generated the expected thioether 67 with complete inversion (Scheme 22).²⁵ᵇ
Scheme 22: Mechanism of sulfenimide-mediated Mitsunobu reaction.

Taken aback by the considerable amount of recovered starting material obtained after reaction of a hindered alcohol and 1,2-diphenyldisulfane in the presence of tributylphosphine under harsh Mitsunobu conditions (refluxing THF, 85 h), Kotsuki et al. opted for a high pressure-promoted version.\textsuperscript{25b} Satisfyingly, at 10 kbar, the yield could be improved to 88% (28% at room pressure). Notably, the reaction time was reduced to 40 h and the temperature to 62 °C. The scope was investigated and all reactions were confirmed to be accelerated by the elevated pressure providing the chiral secondary sulfides 72 (R\textsuperscript{3} = H) in good to excellent yields (Scheme 23, Table 2).

The mechanism was also claimed to go via a thiophosphonium intermediate (Scheme 22), which is attacked by the alcohol, resulting in the activation of the latter and release of the thiolate nucleophile.\textsuperscript{25b}

![Scheme 22: Mechanism of sulfenimide-mediated Mitsunobu reaction.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alcohol</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Yield\textsuperscript{a} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71a</td>
<td>3</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>71b</td>
<td>10</td>
<td>64</td>
<td>5</td>
</tr>
<tr>
<td>3</td>
<td>71c</td>
<td>20</td>
<td>No reaction\textsuperscript{b}</td>
<td>No reaction\textsuperscript{b}</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction performed at room pressure (1 atm), for 37-40 h; \textsuperscript{b}1.5 equiv. of PhSSPh and 2 equiv. of PBu\textsubscript{3} used.

Table 2: High pressure Mitsunobu reaction.
Although the last three examples of Mitsunobu reactions exhibit interesting improvement in the preparation of chiral secondary thioethers relatively to both stereospecificity and yield, tertiary alcohols did not react under the reported conditions.

It was therefore not surprising that La Clair’s report\(^{26}\) of the displacement of very hindered tertiary alcohol \((S)-73\) to form thioether \((R)-74\) in an exceptionally high 94\% yield, under mild Mitsunobu conditions, generated much interest from the scientific community (Scheme 24).\(^{27,28}\) Notably, \(73\) was reacted as a mixture of diastereomers and \((R)-73\) (bearing a \((R)-C6\)) did not react at all, in sharp contrast to the almost quantitative substitution reported at \((S)-C6\).

La Clair was aiming to synthesise natural product hexacyclinol, whose structure was originally assumed to be \(75\) (Figure 5).\(^{29}\) Other aspects of his work were rapidly criticised and called into question in particular by Rychnovsky,\(^{27}\) who proposed a revised structure \(76\)\(^{28}\) of hexacyclinol based on NMR predictions which had proven to correlate very well with experimental data for other similar natural products, and Porco, who completed its total synthesis (Figure 5).\(^{30}\)

![Scheme 24](image)

**Scheme 24:** La Clair’s challenging Mitsunobu reaction in tertiary alcohol \((S)-73\).

![Figure 5](image)

**Figure 5:** Assumed and revised structures of hexacyclinol.

Eventually, Mukaiyama and co-workers achieved the synthesis of various chiral tertiary thiols\(^{31}\) based on their variant\(^{32}\) of the Mitsunobu reaction allowing the synthesis of the tertiary esters \(81\) via \(S_N2\) of a carboxylate nucleophile on the activated tertiary diphenylphosphinites \(79\) (Scheme 25). This oxidation-reduction condensation method
took place with complete inversion of configuration with arylcarboxylic acids. In contrast, an aliphatic carboxylic acid always led to incomplete inversion.\textsuperscript{32}

Scheme 25: Mukaiyama’s variant of Mitsunobu reaction in tertiary alcohols.

An early application\textsuperscript{31b} of this method to sulfur nucleophiles made use of rather forcing conditions (A, Scheme 26) to generate alkyldiphenylphosphinites 77 which were displaced by aromatic thiolates to provide the alkyaryl tertiary thioethers 83 in moderate yields (35-64%). Notably, incomplete inversion was observed when starting from chiral tertiary alcohol 71b.

Scheme 26: Mukaiyama’s variant of Mitsunobu reaction with sulfur nucleophiles.

Milder conditions (B, Scheme 27) and a better oxidising agent (DBBQ instead of DMBQ) proved more successful as a variety of chiral tertiary thioethers 83 derived from 2-sulfanyl-1,3-benzothiazole (Btz-SH) were generated with complete stereoinversion and usually good yields.\textsuperscript{31a}

Various oxidants were attempted before DBBQ but a less efficient inversion (66-88%) was usually observed for benzylic phosphinite 77a, due to the stabilisation of the benzylic cation. However, the combination of DBBQ and a lower temperature (-10 °C)
allowed an almost complete stereoinversion (94%, Table 3, entry 1). The low yield obtained for an aliphatic alcohol was attributed to the competitive E2 reaction (entry 5).\textsuperscript{31a}

Scheme 27: Improvement in Mukaiyama’s variant of Mitsunobu reaction with sulfur nucleophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’OH</th>
<th>R’Sbzt</th>
<th>Yield</th>
<th>Inversion (%)\textsuperscript{a}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtOH</td>
<td>83a</td>
<td>75</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>EtOH</td>
<td>83b</td>
<td>73</td>
<td>&gt;99</td>
</tr>
<tr>
<td>3</td>
<td>BnOH</td>
<td>83c</td>
<td>61</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>PhOH</td>
<td>83d</td>
<td>73</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>EtOH</td>
<td>83e</td>
<td>26</td>
<td>97</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Inversion (%) was defined as % e.e. of 83/% e.e. alcohol 71.

Table 3: Mukaiyama’s variant of Mitsunobu reaction with sulfur nucleophiles.

Cleavage of the Btz group using t-BuLi at -78 °C for 1 h followed by addition of a suitable electrophile afforded either a benzyl sulfide or a thiocarbamate. Alternatively, LiAlH\textsubscript{4} in refluxing Et\textsubscript{2}O for 4 h provided tertiary \(\beta\)-hydroxythiol \((-\text{R})\)-84 in excellent yield (Scheme 28). All transformations took place without loss of enantiomeric purity.\textsuperscript{31a}

Scheme 28: An example of highly enantioenriched tertiary thiol by Mukaiyama’s method.
I.A.2.b) Michael reactions

Among the several known methods for the asymmetric construction of C-S bonds,\textsuperscript{7,33} the Michael reaction is particularly attractive as it allows the simultaneous formation of both the new C-S bond and the stereocentre (Scheme 29).

\[
\begin{array}{c}
\text{O} \quad \text{R}^1 \\
\text{X} \quad \text{R}^2 \\
\text{R}^1, \text{R}^2 \neq \text{H}
\end{array}
\xrightarrow{\text{R-S}^{-} \text{Catalyst}^{*}}
\begin{array}{c}
\text{O} \quad \text{SR} \\
\text{X} \quad \text{R}^2 \\
\text{R}^1
\end{array}
\]

**Scheme 29:** Enantioselective formation of a C-S bond via Michael reaction.

The asymmetric construction of the C-S bond relies either on diastereoccontrol (presence of an intramolecular chiral auxiliary) or enantiocontrol (presence of a chiral metal-based catalyst).\textsuperscript{34} However, very few examples generating quaternary centres have been reported.\textsuperscript{34} A tertiary benzyl sulfide was obtained in 53% yield and 85% e.e. from 3-methylcyclohex-2-enone using the lanthanide-based heterobimetallic asymmetric complex LaNa\textsubscript{3}-tris(binaphtoxide) (LSB),\textsuperscript{35} while a chiral N,N'-dioxid-cadmium iodide complex applied to the same starting material gave rise to a poorly enantioenriched tertiary phenyl sulfide, in moderate yield (10% e.e., 43% yield).\textsuperscript{36}

Three reasons can explain the difficulty of this task:\textsuperscript{34} i) the lower reactivity of \(\beta,\beta\)-disubstituted Michael acceptors, ii) the difficulty to control \(\pi\)-facial diastereo- and enantioselectivity in these substrates and iii) the reaction reversibility, especially in the case of heteronucleophiles.\textsuperscript{37}

Palomo and co-workers envisaged that an intramolecular version of the Michael reaction could overcome these difficulties (Scheme 30).\textsuperscript{34} The inherently favourable entropy should enhance the reactivity while a better \(\pi\)-facial discrimination could result from the intramolecular steric constraint. They consequently prepared \(\beta,\beta\)-disubstituted Michael acceptors \textsuperscript{87}, in which the oxazolidine-2-thione part was both the stereocontroller and the sulfur donor.

\[
\begin{array}{c}
\text{Cl} \quad \text{O} \quad \text{R}^1 \\
\text{R}^2 \\
85: \text{R}^1 = \text{Me, Et, n-Bu} \\
\text{R}^2 = \text{aryl}
\end{array}
\xrightarrow{\text{NaH, THF, -78 °C}}
\begin{array}{c}
\text{O} \quad \text{S} \quad \text{NH} \\
\text{R}^1 \\
\text{R}^2
\end{array}
\xrightarrow{\text{Pr}^{*}}
\begin{array}{c}
\text{S} \quad \text{O} \quad \text{R}^1 \\
\text{O} \quad \text{R}^2
\end{array}
\xrightarrow{1.\text{BF}_3\cdot\text{Et}_2\text{O}, \text{-30 °C}, 7-120 \text{ h}}
\begin{array}{c}
\text{O} \quad \text{O} \\
\text{R}^1
\end{array}
\xrightarrow{2. \text{H}_2\text{O}}
\begin{array}{c}
\text{O} \quad \text{O} \quad \text{HS} \quad \text{R}^1
\\
\text{R}^2
\end{array}
\]

**Scheme 30:** Intramolecular Michael reaction forming tertiary thiol 88.
Among various Lewis acids, BF₃·Et₂O was found to give the best results in terms of yield and diastereoselectivity. Yields were generally good (≥65%) and high diastereocotrol (d.r. ≥ 91:9) was achieved when the reaction was carried out at -30 °C.³⁴

Further studies showed that the Brønsted acid TFA also promoted this Michael reaction, in similar yields and equally high diastereoselectivities. Remarkably, the sense of asymmetry was found to be opposite to that observed with the Lewis acid. Thus, either configuration at the quaternary carbon could be obtained in high selectivity by a judicious choice of the acidic reagent without modifying the intrinsic stereocontroller in the substrate.³⁸

Treatment of the thiol adducts 88 with Sm(OTf)₃ provided β-methyl ester tertiary thiol 89b while NaBH₄ led to the corresponding 1,3-hydroxythiols 90a,b with good yields and excellent e.e.’s (Scheme 31).³⁴,³⁸

![Scheme 31: Cleavage of the oxazolidinethione chiral auxiliary.](image)

Xiao and co-workers made use of a Brønsted base catalyst in their organocatalytic asymmetric sulfa-Michael reaction (Scheme 32).³⁷ Addition of sterically and electronically varied thio-nucleophiles 91 to β,β-disubstituted nitroacrylates 92 efficiently generated the tertiary α-ester β-nitrosulfides 94 in high yields (89-100%) and enantioselectivities (87-98% e.e.) under low loading of the bifunctional cinchona thiourea organocatalyst 93 (0.3 mol%). Notably, the chiral tertiary sulfides synthesised are valuable precursors to α-thio-β²²-amino-acids 95. The biological importance of β²²-amino-acids had also been highlighted by other groups.¹³⁻¹⁵
Scheme 32: Organocatalytic asymmetric sulfa-Michael reaction.

As a representative example, $\alpha$-arylothio-$\beta$-amino acid $97$ was prepared from Michael adduct $94a$ through a straightforward three-step sequence (nitro reduction/amine acylation/ester hydrolysis) in 65% overall yield and with retention of optical purity (Scheme 33).$^{37}$

Scheme 33: Preparation of $\alpha$-arylothio-$\beta$-amino acid $97$.

Xiao and co-workers pioneered the field of organocatalytic asymmetric reactions generating chiral tertiary sulfides via C-S bond formation, as numerous studies have since been published.$^{39}$ They feature $\alpha$-sulfonylation of aldehydes,$^{39a}$ lactones, lactams and $\beta$-dicarbonyl compounds,$^{39b}$ $\beta$-keto phosphonates$^{39c}$ and 3-substituted oxindoles$^{39d-g}$ using either a prolinol-derived catalyst,$^{39a,c}$ a quinine-based catalyst$^{39e,f}$ or a squaramide bearing a chiral diamine subunit.$^{39g}$ One example of scandium-catalysed sulfonylation of 3-substituted oxindoles has also been reported.$^{39d}$ A chiral titanium/Taddol complex brought some improvement to the sulfonylation of $\beta$-ketoesters with phenylsulfonyl chloride as it was found to be resistant to acidic conditions, thus allowing a base-free procedure.$^{39h}$

All studies reported excellent yields (up to 99%) and enantioselectivities (up to 99% e.e.),$^{39b-i}$ except for the $\alpha$-sulfonylation of aldehydes method (only one chiral tertiary sulfide obtained with a moderate 61% e.e.).$^{39a}$

Notably, Zhou and co-workers very recently reported the first organocatalytic asymmetric amination of 3-thiooxindoles, leading to 3,3-disubstituted oxindoles bearing two heteroatoms (Scheme 34).$^{39i}$ High yields (up to 98%) and e.e.’s (up to 94%) were also
reported. Thus, in this last case, construction of a C-N bond in a sulfur-containing substrate allowed the generation of a highly enantioenriched tertiary sulfide.

\[
\begin{align*}
R^1 & = \text{H, halogen, alkyl, OMe} \\
R^2 & = \text{2-naphthyl, Ph} \\
R^3 & = \text{H, Me, Bn}
\end{align*}
\]

**Scheme 34:** Organocatalytic asymmetric amination of 3-thiooxindoles 98.

I.A.3) Carbon-carbon bond formation

Amino acids containing enantiopure quaternary centres are key building blocks in natural product synthesis and drug design.\(^4\) The importance of the thio-substituted analogs,\(^4\) and the potential of other tertiary thiols in general,\(^4\) for biological and pharmaceutical applications, was highlighted by the discovery of the antibiotic thiolactomycin 9 in 1982 ([Figure 3]).\(^5\)

The lack of systematic methods to build these valuable motifs prompted Kellogg and co-workers to apply Seebach’s concept of “self-regeneration of chirality” originally explored for the synthesis of tertiary alcohols, to sulfur-substituted substrates ([Scheme 35]).\(^41\)

**Scheme 35:** Seebach’s concept of “self-regeneration of chirality” applied to \(\alpha\)-mercaptocarboxylic acids 102.
Seebach et al. named the method “self-regeneration of chirality” as the highly enantioenriched stereocentre in α-mercapto-carboxylic acid (R)-102, lost in enolate 104, is regenerated in the alkylated product 106 without racemisation and without the use of any chiral auxiliary, relying solely on intramolecular stereocontrol through a second chiral centre generated in 103 prior to the destruction of the initial one (Scheme 35).

Condensation of α-mercapto-carboxylic acids (R)-102 with pivalaldehyde afforded the 2-t-butyl-5-substituted-1,3-oxathiolanones 103 in variable yields (50–92%), generally with a marked preference for the cis-isomer, which could be isolated by crystallisation. Deprotonation at C5 with an alkylithium base (LDA or LiHMDS) led to the corresponding enolates 104. Subsequent alkylation at C5 was efficiently directed by the newly generated acetal-type chiral centre at C2, as revealed by high diastereomeric ratios in compounds 105 (Scheme 36).

X-ray crystal structure analysis confirmed electrophilic attack on the face opposite to the t-butyl group. Thus, the overall substitution of the proton α to the carbonyl took place with retention of configuration from the cis-oxathiolanone or inversion from the trans isomer.

Scheme 36: Highly diastereospecific substitutions of enolates 104 in Kellogg’s method.

Alkylation of enolate (2S)-104 with alkyl and benzyl halides occurred in good to high yields (59–92%) and generally >95% diastereoselectivity. Addition of aldehydes and unsymmetrical ketones to the enolates (2R)- or (2S)-104 provided adducts (2R)-105a and (2S)-105b,c,f with three chiral centres, respectively, in moderate to good yields (40-
85%, Scheme 36). Among the four possible diastereoisomers, only two were formed, thanks to the highly diastereoselective C5-alkylation.\textsuperscript{40,41} However, induction at the newly formed chiral centre (C6) was found to be low (10-33% $d_s$),\textsuperscript{40} except in the example reported by Seebach et al.\textsuperscript{41} ((2R)-105a, 76% $d_s$). In the case of the $\alpha,\beta$-unsaturated ketone, complete selectivity for either 1,2- or 1,4-addition could be obtained using the appropriate temperature.

Eventually, hydrolysis or transesterification of the 2,5-disubstituted oxathiolanones (2S)-105 afforded the highly enantioenriched chiral tertiary $\alpha$-mercaptocarboxylic acids or esters ret-106 ($\geq 78\%$ e.e.).\textsuperscript{40}

This method was notably revived fifteen years later by Townsend et al. who developed an efficient asymmetric synthesis of (R)-thiolactomycin 9.\textsuperscript{42}

Very recently, the group of Palomo reported a catalytic enantioselective method to prepare tertiary $\alpha$-mercapto-carboxylic acids.\textsuperscript{4} In contrast with their previous work on the acid-mediated asymmetric construction of the C-S bond in tertiary thiols using the Michael reaction,\textsuperscript{34,38} the sulfur-substituted quaternary centre would now arise from $\text{C-C}$ bond formation promoted by a ureidopeptide-derived Brønsted base in an organosulfur carbon pronucleophile (Scheme 37).

Thus, they designed a new family of Brønsted base-catalysts inspired from ureidopeptides in which the $\alpha$-amino acid terminus was replaced by an amino cinchona group. Catalyst 109 was found to be the most efficient, leading to up to 95:5 $d.r.$ and 96% $e.e.$ in the reaction with thiozalone 107 and nitroolefin 108a.
Scheme 37: Organocatalytic enantioselective Michael reaction with novel bifunctional Brönsted base catalyst 109.

Varying the aryl substituent on nitroolefin 108 revealed that both electron-rich and electron-deficient rings were well tolerated, giving rise to the desired products in good to excellent yields (68-96%), high diastereoselectivity (>92:8 d.r.) and enantioselectivity (89-99% e.e.). Alkyl substituents, on the contrary, led to moderate yields, and although the diastereoselectivity was equally high in all cases (>95:5 d.r.), the enantioselectivity was found to be lower for a linear alkyl group (76% e.e.) compared to a branched one (91% e.e.).

Modifying the size of the alkyl substituent at the reactive site of the thiazalone 107 did not affect the excellent yields and stereoselectivities. Finally, the reaction was demonstrated to proceed equally well in terms of yield and selectivity when only 10% of catalyst 109 was employed.

As a demonstration of the synthetic utility of the method, several transformations were performed on the Michael adducts 110 and led to the formation of α,α-disubstituted α-mercapto amide 111, oximes 113, γ-lactam 114 and thiopyran-fused isoxazoline 115 (Scheme 38).
Overall, this method allowed the catalytic, enantioselective preparation of tertiary organosulfur compounds, such as 111, remarkable not only for the free thiol group, but also because they bear varied and straightforwardly functionalisable substituents. This constituted a major improvement compared to most existing procedures which furnish only aryl or alkyl thioethers.\(^4\)\(^8\)

Another organocatalysed conjugate addition of a sulfur-containing carbon pronucleophile to an activated alkene, generating an enantioenriched thio-substituted quaternary centre, was developed by Ye and co-workers, who achieved excellent levels of diastereo- and enantioselectivity in the reaction of rhodanines 117 with \(\alpha,\beta\)-unsaturated ketones 116 under iminium activation using a chiral bulky primary amine catalyst 118 (up to 98% yield, 99:1 \(d.r.\), 98% \(e.e.\), Scheme 39).\(^43\)

**Scheme 38**: Derivatisation of Michael adduct 110b obtained by Palomo’s method.

**Scheme 39**: Organocatalysed Michael reaction of rhodanines 117.
They similarly reported the Diels-Alder reaction of rhodanines 121 with dienals 120, catalysed by prolinol-derived compound 122 (Scheme 40).\(^4\) This asymmetric Diels-Alder reaction is promoted by raising the HOMO of the dienal, leading to a trienamine which acts as the diene to attack the rhodanine (the dienophile here). The generality of the reaction was demonstrating using a variety of substituents on both cycloaddition partners which all afforded the spiro-adducts 123 in generally high yields (up to 98%), diastereo- (>19:1 d.r.) and enantioselectivities (up to 99% e.e.).

Scheme 40: Asymmetric Diels-Alder reaction of rhodanines and dienals.

A catalytic enantioselective Diels-Alder reaction was also employed by Ishihara and co-workers who noted that the product 127 of the Diels-Alder reaction between α-(acylthio)acrolein 125 and isoprene 124 would be particularly useful in the synthesis of the bioactive molecule leinamycin 129, bearing a sulfur-substituted quaternary stereogenic centre (Scheme 41).\(^4\)

Scheme 41: Synthesis of leinamycin via asymmetric Diels-Alder of thioacrolein 125.
However, moderate enantioselectivities and low yields were observed: they were attributed to solubility issues and the weak basicity of the acyl group. The carbamoyl group was expected to be a better electron donor (Scheme 42). Indeed, terminal α-(carbamoylthio)acroleins 130 (R₁ = H), reacted with various dienes to give the Diels-Alder adducts 131 in high regioselectivity (>99%) and 67-81% e.e. The enantioselectivity was found to be improved with β-substituted α-(carbamoylthio)acroleins 130 (R₁ ≠ H, 84-91% e.e.).

![Scheme 42: Preliminary results in Diels-Alder reaction of acylthioacroleins 130.](image)

Another example of catalytic enantioselective Diels-Alder reaction for the preparation of sulfur-substituted quaternary centres was reported by Aggarwal et al., who employed a chiral copper-based complex with a bisoxazoline ligand to react cyclopentadiene with α-sulfenyl acrylates. Excellent yields, diastereo- and enantioselectivities were also achieved (up to 92% yield, 88% d.e., >95% e.e.).

Other transformations making use of sulfur-based carbon pronucleophiles for the construction of thio-substituted quaternary centres include the aldol and Mannich reactions (Scheme 43). Kumagai and Shibasaki recently developed a chiral Ag/DBU binary catalyst 134, which allowed chemoselective activation of α-sulfanyl lactones 133 in the presence of aldehydes 132 to furnish the aldol products 135 with high stereoselectivity (up to 20:1 d.r., 99% e.e.). Similarly, the Mannich-type reaction of 133 with imines 136 was found to be syn-selective (>20:1 d.r.) and produced α-thio-β-amino lactones 137 in high enantioselectivity (up to 99% e.e.).
Another interesting type of cycloaddition allowing the generation of hetero-substituted quaternary centres in good stereoselectivity was recently developed. Fu and co-workers reported the first catalytic asymmetric [3+2] cycloaddition of allenes 138 with activated olefins 139 forming a cyclopentene product 141 bearing a N-, P-, O- or S-substituted quaternary carbon. All previous studies reported little or no success in the cycloaddition of allenes and olefins with either partner bearing a heteroatom. This improvement was made possible by the design and synthesis of a new chiral phosphine catalyst, phosphinepine (S)-140 (Scheme 44, a).
Scheme 44: Catalytic asymmetric [3+2] cycloaddition of allenes with activated alkenes.

The catalytic enantioselective [3+2] cycloaddition between racemic γ-substituted allenes 138a and 2-(t-butythio)acrylate 139a employing 10 mol% of catalyst (S)-140 proceeded in high regioselectivity (ratio of regioisomers ≥ 20:1) and diastereoselectivity (d.r. ≥ 8:1), excellent enantioselectivity (97-98% e.e.) and good yields (68-90%), (Scheme 44, b). Notably, tertiary thiol 142a was prepared in good yield from thioether 141a (R = -CH$_2$(C$_5$H$_9$)).$^{48}$

Finally, numerous examples of asymmetric C-alkylation reactions leading to chiral tertiary benzylic and allylic thiols were described by Hoppe et al. in his seminal work on organolithium compounds. These reactions will be discussed in detail further in this thesis (Section I.B.4).
I.B) Configurational stability of \(\alpha\)-heterosubstituted organolithium compounds

I.B.1) Introduction

Organolithiums are nowadays well established as powerful tools in the synthetic chemist’s repertoire.\(^{49}\) It was the first report of an enantiomerically enriched organolithium compound by Letsinger in 1950 which unveiled the potential of such intermediates for application in enantioselective synthesis (Scheme 45).\(^{49}\) Halogen-lithium exchange in alkyl iodide (\(\text{—}\))-143 by s-BuLi at \(-78 \degree\)C, followed by carbonation of the chiral organolithium 144 after 2 min at \(-70 \degree\)C furnished carboxylic acid 145 with 20\% e.e.\(^{49}\)

\[
\begin{align*}
\text{Me} & \quad \text{s-BuLi, -78 \degree\ C} \quad \text{H}_{13}\text{C}_{7} \quad \text{I} \\
\text{H}_{13}\text{C}_{7} \quad \text{Li} & \quad \text{Me} \quad \text{CO}_{2} \quad \text{H} \\
\text{(-)-143} & \quad \text{144} & \quad \text{145; 20\% e.e.}
\end{align*}
\]

Scheme 45: First report of an enantiomerically enriched organolithium compound.

However, chiral carbanions remained marginalised until the 1980’s and the pioneering report by Still and Sreekumar on \(\alpha\)-alkoxyorganolithiums.\(^{50}\) Transmetalation of stannane 146 with \(n\)-BuLi at either \(-78 \degree\)C or \(-30 \degree\)C, followed by trapping with either acetone or trimethylchlorosilane, proceeded with complete stereospecificity, demonstrating the configurational stability of the intermediary \(\alpha\)-alkoxyorganolithium 147 (Scheme 46, a). Similarly, alkylation of \(\alpha\)-alkoxyorganolithium 150 with dimethyl sulfate afforded optically active 2-butanol 152 which was found to be identical to authentic (\(R\))-2-butanol (Scheme 46, b). Thus, the lithiation-alkylation sequence occurred with overall retention of configuration.\(^{50}\)

\[
\begin{align*}
\text{a)} & \quad \text{Bn} \quad \text{OMOM} \quad \text{SnBu}_3 \quad \text{THF, -78 \degree\ C or -30 \degree\ C} \quad \text{15 min} \\
\text{Bn} \quad \text{OMOM} \quad \text{Li} & \quad \text{E} \quad \text{Bn} \quad \text{OMOM} \\
\text{146} & \quad \text{147} & \quad \text{148} \\
\text{E}^+ & = \text{acetone or Me}_3\text{SiCl}
\end{align*}
\]

\[
\begin{align*}
\text{b)} & \quad \text{SnBu}_3 \quad \text{OBOM} \quad \text{THF, -78 \degree\ C} \\
\text{Me}_2\text{SO}_4 & \quad \text{Me} \quad \text{Pd/C (10\%)} \quad \text{EtO}_2 \quad \text{H}_2 \quad \text{Me} \quad \text{OH} \\
\text{149} & \quad \text{150} & \quad \text{151} & \quad \text{(R)-2-butanol 152}
\end{align*}
\]

Scheme 46: Stereospecific alkylation of \(\alpha\)-alkoxyorganolithiums.
Chiral \( \alpha \)-heteroorganolithium compounds are reliable intermediates towards highly enantioenriched products provided that efficient stereocontrol in the lithiation-substitution sequence can be achieved.\(^{51}\) Electrophilic substitution usually takes place stereospecifically,\(^{3}\) hence, an enantioenriched organolithium must prove configurationally stable in order to be of synthetic value in enantioselective synthesis. Alternatively, asymmetry can be achieved in labile organolithiums, via a post-deprotonation resolution. The enantioenrichment of the whole process can therefore result from different mechanistic pathways: an asymmetric deprotonation (enantiotopic differentiation or kinetic resolution) or an asymmetric substitution (dynamic kinetic resolution or dynamic thermodynamic resolution).

I.B.2) Configurational stability of \( \alpha \)-oxy- and \( \alpha \)-aminolithiums

Hoppe’s\(^{52}\) and Beak’s\(^{53}\) extensive work on the lithiation of \( \alpha \)-oxy- and \( \alpha \)-aminolithium compounds, respectively, established their configurational stability. Namely, \( \alpha \)-oxy-alkyl,\(^{52a}\) -allyl,\(^{52b}\) -cinnamyl\(^{52j}\) and -benzyl-lithiums,\(^{52k}\) as well as \( \alpha \)-lithiocyclohexylamine,\(^{53a,b}\) \( \alpha \)-amino-cinnamyl\(^{53a,c-e}\) and other -allyl-lithium\(^{53f}\) compounds were thoroughly investigated.

Notably, Hoppe’s results proved useful in the enantio- and diastereoselective synthesis of homoaldol products.\(^{52c,f}\) The methodology was efficiently applied to the preparation of diverse \( \gamma \)-lactones, such as the natural product (+)-quercus lactone A and the pheromone (+)-eldanolide.\(^{52g}\) The lithiation of allylamines, generating asymmetric homoenolate equivalents,\(^{53g}\) was also found numerous synthetic applications\(^{53d}\) as the highly enantioenriched \( \gamma \)-substituted enecarbamates can be converted to \( \beta \)-substituted carbonyls and \( \gamma \)-substituted amine derivatives.\(^{53f}\) In particular, asymmetric Michael reactions of \( \alpha \)-amino-benzyl- and -cinnamyl-lithiums with \( \alpha,\beta \)-unsaturated compounds proceeded with complete regioselectivity and excellent diastereo- and enantioselectivities.\(^{53h-j}\)

However, in sharp contrast with their \( \alpha \)-oxy- and \( \alpha \)-amino analogues, the configurational lability of \( \alpha \)-thio-alkyl\(^{49e,54,55,56}\) and -benzyl-lithium\(^{49e,56,57,58}\) compounds is well known. On very rare occasions, though, no racemisation was observed, as in \( \alpha \)-lithiosulfides 153\(^{59}\) and 154\(^{60}\) undergoing intramolecular electrophilic substitution ([2,3]-sigmatropic rearrangement, Figure 6).
Figure 6: α-Thioorganolithiums undergoing intramolecular electrophilic substitution.

This was termed a case of “microscopic configurational stability”, wherein extremely rapid trapping occurred faster than epimerisation. Organolithiums are said to be “configurationally stable on a macroscopic scale” when they have been showed to be configurationally stable for about 10 min.

I.B.3) Mechanism of epimerisation of α-thiolithium compounds

I.B.3.a) Preliminary results in α-heterobenzyllithiums

Various factors have been proposed to impact on the barrier to racemisation of α-heterobenzyllithiums:

a) the nature of the heterosubstituent: the oxygen atom in a sulfonyl functionality was thought to coordinate to the lithium atom and bind it to one enantiotopic face, enhancing its configurational stability;

b) intramolecular chelation: chelating groups (such as ether, pyrrolidine) in α-thiolithiums increased the barrier to epimerisation, holding the lithium atom more tightly, preventing inversion of the carbanionic centre;

c) the degree of substitution at the carbanionic centre: some tertiary benzyllithiums showed improved configurational stability compared to their secondary counterparts;

d) the degree of pyramidalisation: a more pyramidal carbanionic centre was suggested to increase configurational stability. However, the opposite conclusion was drawn for α-thioalkyllithiums.

e) the solvent: barriers to epimerisation were showed to be affected by a change in solvent, leading to the assumption that formation of a solvent-separated ion pair could also be the rate-determining step. However, Reich et al. demonstrated that racemisation was 20 times slower in the separated ion pair of an α-thio-α-silylalkyllithium.
Further structural studies by Reich et al. suggested that ion pair separation, pyramidal/planar structure and higher/lower energy barriers in some sulfur- and silicon-
substituted carbanions were not related to each other.\textsuperscript{64} However, other 
stabilising/destabilising interactions in the ion pair, such as maximisation of orbital 
overlap, affected the degree of pyramidalisation upon formation of the separated ion 
pair.

I.B.3.b) Stabilisation \textit{via} negative hyperconjugation

Several groups reported the stabilisation of $\alpha$-heteroalkyllithium compounds by 
negative hyperconjugation.\textsuperscript{49e,55,56,64,65} The carbanion lone pair and the X-R bond are \textit{anti}-periplanar to maximise delocalisation of the carbanion lone pair into the $\sigma^{*}_{X,R}$-orbital 
(Figure 7).

\textbf{Figure 7}: Stabilisation of $\alpha$-heteroalkyllithiums by negative hyperconjugation.

As a consequence of this preferred conformation, the racemisation process had to 
include at least two elementary and successive steps:\textsuperscript{56}

1) inversion of the carbanion centre (\textbf{Scheme 47}, (2)) resulting in the \textit{syn}-
periplanar arrangement of the lone pair orbital and the X-R bond,

2) rotation about the C-X bond (3), to restore negative hyperconjugation.\textsuperscript{55,56,65}

\textbf{Scheme 47}: Proposed mechanism of racemisation of $\alpha$-heteroalkyllithiums.
Therefore, a 3-step mechanism of racemisation was proposed (Scheme 47).\textsuperscript{55,65} The first step may be the decoordination of the lithium from the carbanionic centre of A, allowing motion within the contact ion pair B, followed by either inversion of the pyramidal carbanion to form C (2) or rotation of the X-R bond leading to \textit{ent-C} (3). Finally, recombination of the contact ion pair would provide the enantiomer \textit{ent-A}.

\textbf{I.B.3.c) Insights into the steric effects}

Low inversion barriers in \textgrm{\textalpha}-thiocarbanions MeS-\texttextit{CH}_2^- (0.5 kcal/mol)\textsuperscript{55} and MeS-\texttextit{CH}^-\texttextit{CH}_3 (1.1 kcal/mol)\textsuperscript{56} led to the conclusion that inversion was unlikely to be the rate-determining step in the racemisation of \textgrm{\textalpha}-thioalkyllithiums.\textsuperscript{55,56,58} Rotation, if rate-limiting, would cause increasing bulk in the vicinity of the heteroatom to result in a higher energy barrier to enantiomerisation.\textsuperscript{55,56,65} Modelling the minimum-energy conformation of the phenylthio methyllithium compound 155 revealed a planar geometry in carbanion 155a, deviating from coplanarity by $\theta = 7^\circ$, as well as the parallel orientation of the sulfur-aryl bond and the carbanion lone pair, which lay in the same plane, allowing maximal negative hyperconjugation (Figure 8).\textsuperscript{56} In this conformation, the lone pairs of the sulfur are \textit{gauche} to the lone pair of the carbanion, which should be destabilising. However, this destabilisation can be overcome by delocalisation of the heteroatom lone pairs into the $\pi^*$-orbital of the aryl group. This compels the $C_{\text{ortho}}$, $C_{\text{ipso}}$, S and $C_{\text{\alpha}}$ to lie in the same plane.\textsuperscript{55,56}

\textbf{Figure 8: Conformation of \textalpha-thioalkyl carbanion during rotation of the C-S bond.}

When the rotation around the C-S bond begins (Scheme 48), the aryl group has to move past the hydrogen atom (transition state 155b) or past the methyl group (transition state 155c). While the “coplanar” geometry for $C_{\text{ortho}}$, $C_{\text{ipso}}$, S and $C_{\text{\alpha}}$ can be maintained in 155b, this is not possible in 155c, as the syn-pentane interaction between the phenyl and the methyl substituents forces the aryl group to twist by $\theta = 21^\circ$ (Figure 8). The resulting weaker stabilisation by $n-\pi^*$ delocalisation causes a 3.4 kcal/mol increase in the energy of transition state 155c compared to 155b.\textsuperscript{56}
Therefore, additional steric hindrance on the phenyl ring (Figure 9, b) will further increase the barrier to epimerisation, should rotation be rate-determining. This was confirmed in phenylthiolithium 156 and durylthiolithium 157 (Figure 9).\(^{55}\)

Figure 9: Increased barrier to epimerisation with steric hindrance.

However, similar energy barriers for the enantiomerisation of analogous unsubstituted phenyltelluro, phenylseleno- and phenylthio- 156 lithium compounds (11.8, 12.4 and 11.3 kcal/mol respectively), despite a shorter C-X bond (from Te to S) which was expected to make rotation more difficult in the thiolithium compound, suggested that separation of the ion pair, rather than rotation, was rate-limiting for the less hindered α-heterolithium compounds.\(^{55}\)

Finally, Hoffmann and co-workers slightly altered their initial working hypothesis\(^{55}\) (Scheme 47) based on results by Reich et al.,\(^{63}\) suggesting that rotation around the carbon-sulfur bond should be easier when the lithium was attached to the carbanion. Indeed, when rotation begins, stabilisation by negative hyperconjugation decreases, resulting in a higher charge density on the carbon atom, which is better stabilised by the lithium cation in a contact ion pair D rather than in a solvent-separated ion pair C (Scheme 49).
In summary, Hoffmann, Reich et al. demonstrated that the racemisation of α-heterolithium compounds could occur via different mechanisms depending on inherent properties (nature of the heteroatom and the bulk of its substituent, the degree of substitution at the carbanionic centre) and external factors (solvation and chelation effects).

Notably, ion pair separation, pyramidalisation of the carbanionic centre and inversion barriers were shown to be independent from each other. Nevertheless, recent theoretical calculations have showed that methylolithiums bearing a heteroatom from the third or higher row are less configurationally stable than those bearing one from the second row due to facilitated planarisation at the carbanionic centre.

**I.B.4) Configurational stability of α-thiolithium compounds**

**I.B.4.a) α-Thioalkyllithiums**

Based on Reich’s and Hoffmann’s work, Hoppe et al. admitted that rotation about the C-S bond was the rate-determining step in the enantiomerisation of α-thiolithium compounds. Thus, bulky substituents at the sulfur atom and at the carbanionic centre were expected to enhance the barrier to racemisation. Moreover, N,N-dialkylcarbamoyloxy groups had been shown to lead to improved configurational stability in chiral 1-oxyallyllithium and -benzylithium compounds by chelation.

Following on from their work on lithiation of alkyl carbamates, Hoppe and co-workers synthesised the S-alkylthiocarbamates from 1,3-oxazolidine-3-carbonyl chloride and sodium thiolates and exposed them to s-BuLi/(−)-sparteine (-)-162, followed by various electrophiles E⁺ (Scheme 50).

**Scheme 49: Revised mechanism of racemisation of α-heteroalkyllolithiums.**

![Scheme 49](image-url)
While lithiation-substitution of carbamates proceeded in excellent enantioselectivity (e.e.’s ≥ 95%), enantiomeric excesses in the substituted thiocarbamates 163-165 ranged from 40 to 60% (Table 4).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Compound</th>
<th>R</th>
<th>E</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>163a</td>
<td>C₃H₇</td>
<td>CO₂Me</td>
<td>91</td>
<td>47</td>
</tr>
<tr>
<td>2</td>
<td>163b</td>
<td>C₃H₇</td>
<td>SiMe₃</td>
<td>91</td>
<td>46</td>
</tr>
<tr>
<td>3</td>
<td>164a</td>
<td>Me</td>
<td>CO₂Me</td>
<td>89</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>164b</td>
<td>Me</td>
<td>SiMe₃</td>
<td>95</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>165a</td>
<td>i-Pr</td>
<td>CO₂Me</td>
<td>77</td>
<td>60</td>
</tr>
</tbody>
</table>

Equilibration of the diastereomeric ion pairs 161 and epi-161 at -78°C would explain the low e.e.’s. However, another possibility is that 161 and epi-161 are configurationally stable under the reactions conditions but the enantiotopic differentiation between the pro-R and the pro-S hydrogens by the chiral base complex is not efficient. Deuteration experiments pointed to both configurational lability and insufficient enantiotopic differentiation (Scheme 51).
Scheme 51: (−)-Sparteine-mediated silylation of α-thioalkyllithiums.

Lithiation-substitution of rac-166 led to a slightly enantioenriched product (S)-167 in excellent yield, confirming complete deprotonation of both enantiomers, and consequently, that enantiotopic differentiation was insufficient. Furthermore, a racemic product would have been obtained, had the lithiated ion pairs 161 be configurationally stable.71

Although Reich et al. found evidence for slower racemisation in a separated ion pair, i.e. a less rigid system,49d,63 Hoppe and co-workers proposed that the increased flexibility in lithiated thiocarbamate 161 led to its lower configurational stability, compared to the oxygen analogue. The higher flexibility of the chelate complex 161 was attributed to a better stabilisation of the negative charge by the sulfur atom, driving the lithium cation away from the carbanionic centre, and a longer C-S bond (1.80 Å instead of 1.40 Å for the C-O bond).71

Based on work by Hoffmann et al. suggesting that sterically demanding substituents around the sulfur atom raised the barrier to configurational inversion,55,65 Hoppe and co-workers synthesised thiocarbamate (S)-163b, a α-silylated analog of 160 (Scheme 52).71

Scheme 52: Influence of steric hindrance at the carbanionic centre.
Lithiation under similar conditions and subsequent trapping with deuterated methanol afforded (S)-167 without loss of enantioenrichment. Thus, configurational stability was achieved for the first time in an α-thiolithium compound,\textsuperscript{71} undergoing no racemisation even after several hours at -78 °C in diethyl ether.\textsuperscript{70}

I.B.4.b) (S)-Prolinyl-α-thioalkyllithium

In order to achieve configurational stability in unbranched, non-mesomerically stabilised α-thiocarbanions, Hoppe and co-workers deprotonated (S)-prolinol-derived thiocarbamate 170, bearing a prochiral methylene (Scheme 53).\textsuperscript{72,73}

\[
\text{(S)-prolinol 169} \quad \xrightarrow{\text{1. s-BuLi/TMEDA (1.2 eq) toluene, -78 °C, 3 h}} \quad \text{170} \quad 2. \text{E}^+ (3.0 \text{ eq}) \quad \text{172: 38-98\%, >95:5 d.r.}
\]

Scheme 53: Diastereoselective lithiation-substitution of (S)-prolinyl-α-thioalkyllithiums.

Lithiation with s-BuLi, in the presence of the achiral ligand TMEDA, followed by trapping with silylating, alkylating, allylating and benzylating agents provided the substituted products in excellent diastereoselectivities.\textsuperscript{72,73} NMR studies confirmed abstraction of the pro-\textit{S} proton, leading to lithiated intermediate (S,S)-171, while X-ray crystal structures supported a stereoretentive pathway. Surprisingly, abstraction of the pro-\textit{R} proton was observed in the analogous prolinyl-O-carbamate and led to an overall inverted process.\textsuperscript{72,73}

The excellent level of diastereoselectivity was in accordance with enantiotopic differentiation and configurational stability of (S,S)-171. However, deuteration experiments revealed (S,R)-171 was also formed. Thus, the apparent configurational stability of the lithiated species 171 was actually due to the kinetically favoured formation of (S,S)-171 and rapid isomerisation of (S,R)-171 to the thermodynamically favoured epimer (S,S)-171.\textsuperscript{73}
I.B.4.c) \( \alpha \)-Thiobenzyllithiums

In an effort to enhance configurational stability by increasing the steric hindrance at the carbanionic centre, lithiation of \( \alpha \)-methyl benzylthiocarbamate (S)-175 was investigated (Scheme 54).\(^{68,70}\) Besides, benzylithium (S)-176 was expected to be more prone to form solvent-separated ion pairs due to the additional resonance stabilisation of the carbanion.\(^{70}\)

![Scheme 54: Lithiation-substitution in \( \alpha \)-thiobenzyllithiums.](image)

The configurational stability of (S)-176 was preliminary tested in a reprotooning experiment: no racemisation could be detected when the lithiated intermediate was kept at \(-78\, ^\circ\text{C}\) for 2 h before methanol was added, neither when quenching below \(-70\, ^\circ\text{C}\) after warming the solution to \(1\, ^\circ\text{C}\) for 12 min.\(^{68}\)

Additional warming experiments showed that the enantioenrichment can be maintained if quenching took place after a few minutes at \(0\, ^\circ\text{C}\) (Table 5, entries 1, 4) or even \(17\, ^\circ\text{C}\) (entry 5). A longer exposure at \(0\, ^\circ\text{C}\) led to almost complete racemisation (entry 3).\(^{68}\) From these results, Hoppe and co-workers extrapolated the half-life of racemisation of (S)-176 to be several hours at \(0\, ^\circ\text{C}\).\(^{70}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>( E^+ )</th>
<th>Warming conditions</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{ent-177a} )</td>
<td>Cl(O)OMe</td>
<td>3 min (0 °C)</td>
<td>98</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>( \text{ent-177a} )</td>
<td>Cl(O)OMe</td>
<td>63 min (0 °C)</td>
<td>58</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>( \text{ent-177a} )</td>
<td>Cl(O)OMe</td>
<td>125 min (0 °C)</td>
<td>32</td>
<td>13</td>
</tr>
<tr>
<td>4</td>
<td>( \text{ent-177b} )</td>
<td>AcCl</td>
<td>6 min (0 °C)</td>
<td>89</td>
<td>&gt;99</td>
</tr>
<tr>
<td>5</td>
<td>( \text{ent-177b} )</td>
<td>AcCl</td>
<td>4 min (17 °C)</td>
<td>44</td>
<td>≥96</td>
</tr>
</tbody>
</table>

*Table 5: Lithiation-substitution in \( \alpha \)-thiobenzyllithiums.*
Alkylations, allylation and benzylations with halides, acylations with methyl chloroformate, carbon dioxide, and acid chlorides, and trimethylsilylation all proceeded with complete enantiospecificity and stereoinversion.\textsuperscript{68,70} Additions to an aldehyde also resulted in complete inversion at the carbanionic centre, but without significant diastereoselectivity at the carbonyl group, leading to mixtures of the syn/anti alcohols.\textsuperscript{68}

Thus, steric hindrance caused by the TMEDA/Li chelate on one face of the organolithium was proposed to be the dominant factor for stereocontrol in $\alpha$-thiobenzylolithiums, favouring an antarafacial substitution. However, addition to methanol or acetic acid proceeded with retention: the suprafacial electrophilic attack was preferred in this case due to coordination of the carbonyl oxygen to the lithium cation,\textsuperscript{52k,68,70} and by increased pyramidalisation at the carbanionic centre in benzylolithiums.\textsuperscript{52k,61,68}

The enhanced configurational stability of $\alpha$-thiobenzylithium compound (S)-176 was attributed to the S-carbamoyl group, which was responsible for both increased rate of deprotonation by kinetic acidification and hampered rotation about the C-S bond due to steric hindrance at the carbanionic centre.\textsuperscript{70} This constituted the first example of a highly enantioenriched $\alpha$-thiolithium compound.\textsuperscript{68,70}

Subsequent cleavage of the thiocarbamate group by refluxing in 6 M HCl or using a large excess of DiBAl-H at low temperature led to highly enantioenriched tertiary benzyl thiols, which are not accessible via S\textsubscript{N}2 reactions on chiral tertiary benzyl alcohols. Unlike the conversion of the analogous benzyl carbamates to the tertiary alcohols, no racemisation was observed.\textsuperscript{68}

High enantioenrichment was also achieved in the products of the lithiation-substitution of prochiral primary S-benzyl thiocarbamate 178 in the presence of chiral bisoxazoline (S,S)-179a (Scheme 55).\textsuperscript{51}

\begin{center}
\textbf{Scheme 55: (S,S)-Bisoxazoline-mediated lithiation-substitution of $\alpha$-thiobenzylithiums.}
\end{center}
Deprotonation of 178 at -78 °C followed by trapping with methyl triflate as the electrophile \( E^+ \) proceeded with low enantioselectivity (19% e.e.). However, deprotonation at -30 °C for 4-12 h and subsequent addition to various electrophiles at -78 °C afforded secondary thiocarbamates 181 in excellent enantioenrichment (>94% e.e., Scheme 55). These results showed that the diastereomeric ion pairs equilibrated at -30 °C towards one predominant epimer, which was confirmed to be \( \eta^1-(R)-180 \) by NMR studies. Therefore, the overall enantioenrichment arose from a dynamic thermodynamic resolution. X-ray crystal structures confirmed that all substitutions occurred with inversion of configuration. 51

I.B.4.d) \( \alpha \)-Thiopropargyllithiums

The (‒)-sparteine-mediated lithiation of propargyl thiocarbamate 182 in pentane below -30 °C resulted in the formation of a precipitate 183 162 which was trapped with trimethylsilyl triflate to afford propargylsilane \((S)-184\) in excellent enantioselectivity (≥95% e.e., Scheme 56). 74,75

![Scheme 56: Resolution of \( \alpha \)-thiopropargyllithiums by crystallisation.](image)

X-ray analysis of both the crystalline lithium complex 183 162 and the silylated product \((S)-184\) established a stereoinverted substitution. The stereoselectivity also arose from fast epimerisation at -30 °C with complete crystallisation of one diastereomer of the lithiated complex.
Transmetalation of $^{183}^{162}$ with tri(isopropoxy)titanium chloride also occurred with stereoinversion, to form titanium compound $(R)$-$^{185}$ and the corresponding enantioenriched $S$-allenes $(aS,4R)$-$^{186}$ in excellent enantio- and diastereoselectivity (Scheme 57).$^{74}$

$$\text{(R)}-^{185}: \text{Cb} = \text{CON}(/-\text{Pr})_2$$

$^{186}$: 66-79% yield ≥98:2 d.r., >96% e.e.

Scheme 57: Formation of enantioenriched $S$-allenes.

I.B.4.e) $\alpha$-Thiocinnamyllithiums

Chiral $(R,R)$-bisoxazoline ligands $(R,R)$-$^{179b,c}$ also proved more efficient than $(-)$-sparteine $(-)$-$^{162}$ in resolving $\alpha$-thiocinnamyllithium $^{188}$, achieving high enantioselectivities in silylated $(S)$-$^{189}$ (Scheme 58).$^{75,76}$

An in situ experiment, in which deprotonation was performed in the presence of the electrophile, resulted in a very low enantioenrichment (4% $e.e.$), establishing the absence of enantiotopic differentiation. Extending the deprotonation time and warming the reaction to -25 °C both allowed further improvement of the enantioselectivity, confirming the thermodynamic resolution in the post-deprotonation step.

Under these optimised conditions, silylation, alkylation, allylation and acylation proceeded in good to high yields (53-90%) and excellent enantioselectivities (≥94:6 $e.r.$).
The (S)-configuration of the thermodynamically preferred α-thiocinnamyllithium intermediate **188,179** was established based on X-ray crystal structures of the substituted products and the known stereoinvertive alkylation and silylation in mesomerically stabilised α-thioorganolithiums.\(^{68,69,74,77}\)

### I.B.4.f) α-Thioallyllithiums

I.B.4.f.i) Lithiation of cyclic allylic thiocarbamates

Building upon the excellent level of enantioselectivity achieved in α-branched α-thioalkyl- and α-thiobenzyllithiums bearing a N-carbamoyl moiety,\(^{68,70}\) Hoppe et al. decided to investigate the allylic analogues in which the double bond allows for further transformations.\(^{77}\) A cyclic substrate was chosen in order to avoid any E/Z isomerisation in an allylic anion. Methylation of α-thioallyllithium (R)-**191** took place with low regioselectivity, providing a mixture of the stereoinverted α- and γ-isomers **192** and **193** respectively (Scheme 59).

![Scheme 59: Regio- and enantioselectivity issues in methylation of α-thioallyllithiums.](image)

Both regioselectivity and enantioselectivity were found to be dependent on the solvent.\(^{69,77}\) The γ-products usually dominated but showed a lower enantioenrichment, attributed to the larger distance between the γ-carbon and the carbanion. Tetrahydrofuran, a coordinating solvent, gave the best stereospecificities irrespective of the deprotonation time (up to 4.5 h), confirming the configurational stability of allyllithium (R)-**191** in this solvent. This was consistent with Reich’s et al. observations that enantiomerisation of α-thiolithiums was slower in solvent-separated ion pairs.\(^{63,77}\)

In addition, the branched carbanionic centre was also likely to enhance the configurational stability of α-thioallyllithium (R)-**191**\(^{69,77}\) as this was demonstrated in other
\(\alpha\)-thiolithium compounds by Hoppe\(^{69,71,77}\) and Hoffmann\(^{55,56}\) et al. The cyclohexene substituent, together with the short C-S bond, may prevent the torsion of the C-S bond, thus maintaining stabilisation by negative hyperconjugation between the \(n_c\) orbital and the \(\sigma^*_{S-R}\) orbital (Scheme 60).\(^{69}\)

![Scheme 60: Hampered C-S bond rotation by the cyclohexene substituent.](image)

Inspired by Hoffmann and co-workers’ results,\(^{55,56}\) increase of the configurational stability by a bulkier \(t\)-butyl substituent at the carbamoyl group was investigated.\(^{69}\) Substitution with methyl iodide was unsuccessful but deuteration unexpectedly proceeded with high \(\alpha\)-regioselectivity, which would prove useful in the preparation of enantioenriched tertiary thiols. Given that no general method for their synthesis was available, Hoppe and co-workers took advantage of this observation and investigated the lithiation of allylic thiocarbamate (S)-\(194\), bearing a diisopropyl group at the carbamoyl nitrogen (Scheme 61).\(^{78}\)

![Scheme 61: High \(\alpha\)-regioselectivity in the substitution of \(\alpha\)-thioallyllithiums.](image)

Alkylation, benzylation and allylation proceeded with complete \(\alpha\)-regioselectivity and stereospecificity, regardless of the solvent. X-ray crystal structure analysis gave evidence of stereoinversion. Stirring thiocarbamates \(196\) in THF at 0 °C overnight followed by acidic workup provided the first practical route to allylic tertiary thiols \(197\).
Cycloheptenyl α-thioallyllithium (S)-198 was also studied (Scheme 62).\(^{69}\)

\[
\begin{align*}
\text{(S)-198: 91\% e.e.} \quad & \quad \begin{array}{c}
\text{(S)-199}
\end{array} \\
\Downarrow \quad & \quad \begin{array}{c}
\text{(R)-200: 21\%, 87\% e.e.} \\
\text{(R)-201: 49\%, 88\% e.e.}
\end{array}
\end{align*}
\]

**Scheme 62: Lithiation-substitution of cycloheptenyl α-thioallyllithiums.**

Regarding regioselectivity of the methylation, the same trends as in analogous cyclohexenyl α-thioallyllithium (R)-191 were observed: the γ-isomer was the major one in THF and the minor one in diethyl ether. Both regioisomers were obtained in high stereospecificity and with stereoinversion.\(^{69}\)

I.B.4.f.ii) A deeper insight into the configurational stability of (R)-191

Hoppe and co-workers relied on Reich’s\(^{63,67}\) and Hoffmann’s\(^{55,56}\) conclusions to rationalise the partial configurational stability observed in (R)-191. Later, Haeffner et al., interested in establishing a theoretical model based on DFT calculations to predict the effect of aggregation on the configurational stability of organolithiums, also examined allyllithium (R)-191.\(^{79}\)

Although numerous studies had dealt with configurational stability in α-heterosubstituted organolithiums, very few tackled the relationship between aggregation and racemisation. In coordinating solvents such as THF, the efficient solvation suppressed aggregation. However, in hydrocarbon solvents such as hexane or toluene, the organolithium would aggregate. Therefore, the energy barriers to racemisation in model allyllithium 202 (Figure 10) were calculated for the monomer in THF and the dimer in toluene.

**Figure 10: Allyllithium model for DFT-investigations of configurational stability.**
Since inversion occurs *via* a “charge-separated” transition state (which can be a fully separated ion pair), racemisation is facilitated by efficient solvation of the lithium ion. However, racemisation will easily occur in an aggregated structure if both the lithium cation and the carbanion are well stabilised by the neighbouring lithium atoms and carbanions.

The solvated transition state $E$ of 202 (Figure 11) revealed a strong interaction between the sulfur and the lithium atoms (dihedral angle $\varphi$ far from planarity), preventing efficient solvation of the lithium ion, and thus, decelerating racemisation.

![Solvated transition state $E$ for racemisation of model allyllithium 202.](image)

Figure 11: Solvated transition state $E$ for racemisation of model allyllithium 202.

To conclude, coordination by THF hardly stabilised the transition state towards inversion, due to inefficient solvation of the lithium ion. In non-coordinating toluene, 202 formed aggregates leading to the stabilisation of the ion pair by interactions with the neighbouring carbanions and lithium ions and faster racemisation.

Hence, Haeflner *et al.* proposed that Hoppe’s $\alpha$-thioallyllithium ($R$)-191 owed its configurational stability in coordinating THF to “reduced solvent affinity in the transition state”.79

I.B.4.f.iii) Improved configurational stability in $\alpha$-thioallyllithium sulfides versus benzyl and naphthyl analogs

Thia-[2,3]-Wittig rearrangement in allyl sulfides *anti-* and *syn*-203 afforded the diastereomerically pure homoallylalcohols *syn-* and *anti*-204, demonstrating the stereospecificity of the rearrangement, and thus, the configurational stability of the underlying $\alpha$-lithio allyl sulfides 154 (Scheme 63).60
Scheme 63: Stereospecific thia-[2,3]-Wittig rearrangement in allyl sulfides.

Under the same conditions, the analogous α-lithio benzyl sulfide anti-205 led to a mixture of diastereomers 206 (Scheme 64). The decrease in stereoselectivity was attributed to the longer reaction time needed by the benzyl sulfides to overcome the higher activation barrier caused by dearomatisation.

Scheme 64: Incomplete stereospecificity in thia-[2,3]-Wittig rearrangement of benzyl sulfides.

Allyl α-lithio sulfide (S)-211 also showed enhanced configurational stability compared to its benzyl and naphthyl analogues (Scheme 65). It was found to be configurationally stable on the time scale of its [2,3]-Wittig rearrangement, leading to high e.e.’s in thiol (R)-214 (95% e.e. at -78 °C and 71% e.e. at 0 °C).

Scheme 65: Thia-[2,3]-Wittig rearrangement of allyl, benzyl and naphthyl α-lithio sulfides.

The temperature had to be raised to -50 °C for benzylthiomethylolithium (S)-212 to undergo thia-[2,3]-Wittig rearrangement which furnished racemic 215. Thus, racemisation occurred much faster than intramolecular rearrangement and (S)-212 was
concluded to be “microscopically configurationally unstable” at -50 °C on the time scale of thia-[2,3]-Wittig rearrangement.

Naphthylthiomethyllithium (S)-213 did undergo thia-[2,3]-Wittig rearrangement at -78 °C, providing thiol (R)-217 in 72% e.e. At -50 °C, using MeLi, (R)-217 was still formed in 60% e.e. Due to a lower activation energy, and therefore a higher reaction rate at 50 °C (compared to (S)-212), (S)-213 benefited from a shorter lifetime and thus only a small amount had time to racemise at -50 °C.66

I.C) Determination of the structure of the allyllithium system

Lithiation of a molecule, through replacement of a proton by a lithium atom, results in fundamental changes to its geometry and electronics.49a Numerous studies have been dedicated to the elucidation of the structure of the allyllithium system.80 The nature of the C-Li bond, the position of the lithium atom relative to the carbon skeleton as well as the planarity of the allyl system have been investigated. There are no uniform conclusions80a and many interpretations are in disagreement with one another.80b,c However, a few general trends were established: most results support a delocalised species,80a wherein the lithium atom prefers a bridged position,49a,80b,d,e and the allyl system is not planar.80b,c,f

I.C.1) Covalent C-Li bond or delocalised ionic allyllithium

The importance of solvation, notably in stabilising allyllithiums,80b,81 and aggregation degree, have been underlined in many instances,49a,e,80g as they led to completely different structures than those of the monomers in the gas phase.80b,81

For example, West, Purmort and McKinley found NMR and IR evidence for a delocalised symmetrical structure [AA’BB’C]δ-Liδ+ for allyllithium 217a in THF, indicating two distinct types of terminal hydrogens at low temperature (Figure 12).80h

![217a](image)

Figure 12: Delocalised symmetrical allyllithium.
An AB$_4$ character, with all terminal hydrogens equivalent, had been reported for less ionic allyl compounds (halides, zinc, magnesium). The authors consequently expected allyllithium 217a to be AB$_4$ as well, since lithium is more electropositive than magnesium, zinc or halides. They attributed the prolonged lifetime of the species [AA'BB'C]$_6$Li$_6$ to an increased aggregation degree at lower temperatures.\textsuperscript{80h}

Schleyer and co-workers also reported a symmetrical delocalised structure, but they were in favour of a bridged lithium atom as in 217b rather than an ionic form 217c based on the low rotational barrier observed (10.7 kcal/mol), which indicated the participation of the metal to the transition state (Figure 13).\textsuperscript{80d}

![Figure 13: Bridged delocalised symmetrical allyllithium.](image)

The nature of the solvation proved crucial in the lithiation of buta-1,3-diene as well (Figure 14).\textsuperscript{80g} The NMR spectra were consistent with two non-equilibrating covalent $\sigma$-bonded structures 218a and 218b in hydrocarbon solvents, in agreement with other results for but-2-enyllithium, a non-delocalised species.\textsuperscript{80i} However, the addition of THF revealed that the lithium atom was interacting with the C=C bond, denoting an increased delocalised character, which could develop to a fully delocalised structure 218c.\textsuperscript{80g}

![Figure 14: Non-equilibrating covalent $\sigma$-bonded forms of allyllithium.](image)

Substituted allyllithium 5,5-dimethyl-1-lithio-hex-2-ene 219 was said to exhibit a “chameleon” behavior since it existed as a mixture of covalent 219c and ionic delocalised 219l species in fast equilibrium (Scheme 66).\textsuperscript{80j} In cyclopentane, upon cooling, NMR spectra of 219 revealed two sets of $^{13}$C shifts which were attributed to the covalent isomers cis-219c and trans-219c, equilibrating more slowly at lower temperature.
Scheme 66: Fast equilibrium of covalent and ionic delocalised allyllithiums.

When vicinal trans diamines were added to a solution of 219 in cyclopentane, C1 was shifted downfield while C3 was moved upfield. The C1-C3 shift difference was found to decrease upon cooling. A small C1-C3 shift difference is typical of an ionic delocalised form. Thus, 219 was proposed to exist as a mixture of $219_c$ and $219_i$ in fast equilibrium, being displaced towards the ion pairs $219_i$ in the presence of an amine ligand, particularly at low temperatures.\(^{80j}\)

Schleyer and co-workers similarly showed that in THF, allyllithium formed a rapidly equilibrating dimer $217d$, displaying both $\sigma$- and $\eta^3$-coordination (Figure 15).\(^{80k}\)

**Figure 15: Allyllithium dimer in THF with mixed covalent and ionic characters.**

Strohmann and co-workers also examined the effect of the addition of trans and cis vicinal diamine ligands on the coordination mode of allyllithium.\(^{80l}\) In the presence of TMEDA, each lithium atom was coordinated to the terminal carbons of two allylic skeletons, forming a polymeric chain. However, with cyclic diamine ligand trans-TMCDA, the first monomeric structure $217e$ of allyllithium was observed. The authors also reported the first diamine coordination compound $217f$ containing two different, simple organolithiums, prepared from allyllithium, i-propyllithium and cis-TMCDA (Figure 16).\(^{80l}\) They showed that it was 43 kJ/mol more stable than the corresponding complexes containing only one type of organolithium.
Another uncommon structure was reported by Fraenkel and co-workers who named it a “continuum of intermediate states”. Its covalent character was denoted by different allyl $\pi$-bond orders whilst intermediary ionic behaviour was found for both carbon and lithium atoms.\textsuperscript{80a}

### I.C.2) Symmetrical or unsymmetrical allyllithium structure

Three groups applied Saunders’ isotopic perturbation method to allyllithium \textbf{217} in order to distinguish between the symmetrical monomer \textbf{217}\textsubscript{sym} or a pair of equilibrating unsymmetrical species \textbf{217}\textsubscript{unsym} (Figure 17).\textsuperscript{80k}

**Figure 17:** Symmetrical and pair of equilibrating unsymmetrical allyllithiums.

In unsymmetrical species, deuterium-labelling of either terminal carbon of the allyl group will result in a much larger C1-C3 $^{13}$C shift difference $\Delta\delta^{13}$C[C1-C3] upon lithiation. The small $\Delta\delta^{13}$C[C1-C3] observed (0.3 ppm) was inconsistent with highly unsymmetrical structures.\textsuperscript{80d} Therefore, two groups\textsuperscript{80d,k} concluded that allyllithium \textbf{217} was symmetrical, while Stähle and Schlosser noticed that its behavior was intermediary between rapidly equilibrating allyl magnesium bromide and symmetrical allylpotassium and thus proposed rapidly equilibrating, slightly unsymmetrical structures.\textsuperscript{80m}

Ragué Schleyer and co-workers repeated the $^{13}$C NMR experiments in 1-deuterated allyllithium at various temperatures and observed that $\Delta\delta^{13}$C[C1-C3] was a function of the temperature, as expected for unsymmetrical species which for the
variation of the $^{13}$C shift with the temperature greatly differ between the two terminal carbons. MNDO calculations further evidenced the unsymmetrical character based on the large difference in the C-C bond lengths of the allyl skeleton (Figure 18).\(^{80k}\)

\[ \text{Note: bond lengths are in Å.} \]

**Figure 18:** MNDO-calculated unsymmetrical structure of allyllithium $217_{\text{unsym}}$.

**I.C.3) Planar or non-planar allylic skeleton**

Schlosser and co-workers reported pleated structures for allylpotassium $220$ and pentadienyllithium $221$ based on large $^\text{1}J_{C,H}$ coupling constants suggesting that all C-H bonds tended to deviate from the carbon skeleton plane (Figure 19).\(^{80f}\)

**Figure 19:** Pleated structures for allylpotassium and pentadienyllithium.

They explained that the metal preferably binded to the odd number sites resulting in an increased $\pi$-electron density at these positions on the metal-bearing face, enhancing the interaction. The non-binding sites compensated through an opposite polarisation, leading to an increased $\pi$-electron density on the face opposite to the metal at these positions. Due to electrostatic repulsion, the hydrogen atoms moved towards the electron-deficient face.\(^{80f}\)

Ahlbrecht, Boche and co-workers agreed regarding the non-planar structure of the allyl skeleton: MNDO-calculated heats of formation of planar and non-planar structures demonstrated the enhanced stabilisation of distorted structures compared to their planar counterparts.\(^{80c}\) However, unlike Schlosser,\(^{80f}\) they showed that the inner terminal
hydrogens \( H_i \) were much more bent out of the plane (30°) than the central \( H_m \) (10°), (Figure 20).\textsuperscript{80b,c}

\[ \text{Figure 20: Position of the hydrogens relatively to lithium in allyllithium.} \]

Indeed, Ahlbrecht, Boche and co-workers demonstrated that \( J_{C,H} \) coupling constants, which Schlosser \textit{et al.} based their results on, were not a function of the distortion. If they were, they would undergo large variations between a planar separated ion pair and a more distorted contact ion pair. This was not observed for a large number of allyl-metalated species (Figure 21).\textsuperscript{80c}

\[ \text{Figure 21: MNDO geometry-optimised structures of planar phenylallyl anion } C_6H_5-C_3H_4^+ \text{ and strongly distorted phenylallyllithium } C_6H_5-C_3H_4Li \]

\textbf{I.C.4) Influence of the presence of an \( \alpha \)-sulfur atom}

With regards to their widespread applications in synthetic organic chemistry, understanding the structure of \( \alpha \)-heteroallyllithiums appeared crucial\textsuperscript{81} in order to predict the regioselectivity in their reactions with electrophiles.\textsuperscript{82} Calculating minimum-energy conformations for phenylthioallyllithium 223 revealed an increased stabilisation with a higher number of electrostatic interactions between the metal and the allylic moiety.\textsuperscript{83} Thus, the energy in \( \eta^3 \)-223a-c was lower than in \( \eta^2 \)-bonded 223d, and \textit{endo}-conformers 223a,b were more stable than \textit{exo}-223, due to an additional electrostatic interaction between the lithium and sulfur atoms (Figure 22).
Figure 22: Calculated minimum-energy conformations for phenylthioallyllithium 223.

Including solvation when establishing structural assignments in organolithium compounds again proved indispensable as specific solvation (i.e. coordination of solvent molecules to the lithium atom) enhanced the \( \alpha \)-carbanion character of phenylthioallyllithium 223 - by weakening the C\( \gamma \)-Li contact.\(^8\) This was attributed to the known ability of the sulfur atom to stabilise and localise the negative charge on the \( \alpha \)-carbon via coulomb interactions, hyperconjugation and polarisation effects.\(^8\)

Fast equilibrium between two \( \eta^1 \)-C\( \alpha \)-species was confirmed by NMR studies. Similar structures had been reported for 1-(t-butylthio)allyllithium.\(^8\) This was however in sharp contrast to the \( \eta^1 \)-C\( \gamma \)-Li structures observed in 1-aminoallyllithium compounds.\(^8\)

In sulfoxoallyllithium 224, an additional intramolecular Li-O interaction led to considerable stabilisation in both the \( \eta^3 \)- and the \( \eta^2 \)-bonding patterns (224a-c), suggesting that the two conformers existed in solution (Figure 23). This was in agreement with NMR studies showing two distinct, non-equilibrated lithiated species.\(^8\)

Figure 23: Calculated minimum-energy conformations for sulfoxoallyllithium 224.

Similarly, in sulfonylallyllithium 225, the second oxygen was responsible for the formation of an OLiO scissor contact ion pair 225c. Despite the remarkable absence of any
direct contact between the metal and the allyl skeleton, the conformer was found to be relatively stable (Figure 24).\(^{81}\)

![Image of molecular structures](image)

**Figure 24:** Calculated minimum-energy conformations for sulfonylallyllithium 225.

The “naked” allyl anion structure was also reported in norbornenyl/norbornyl allyl α-lithiosulfones\(^ {84}\) 226/227 and phenylsulfoximine allyllithium 228 (Figure 25),\(^ {85}\) in sharp contrast with previously reported structures for α-heteroallyllithiums, always displaying Li-allyl contact.

![Image of molecular structures](image)

**Figure 25:** Norborn(en)yl allyl α-lithiosulfones and phenylsulfoximine allyllithium.

Several studies reported a shortened S-C\(_\alpha\) bond in the lithiated species, in accordance with the typical S-C\(_\alpha\) conformation in α-thiolithium compounds resulting from negative hyperconjugation (Figure 7).\(^ {84,86}\)

Finally, the influence of solvation and aggregation was also highlighted in investigations of the structure of t-butylthiocrotyllithium 229. The cisoid configuration of 229 was evidenced by its X-ray crystal structure as a complex with TMEDA\(^ {87}\) while NMR studies were consistent with a transoid carbanion (Figure 26, a).\(^ {88}\) The cis-geometry was also established for analogous phenylthiocrotyllithium 230 (Figure 26, b).\(^ {88}\)
I.D) [3,3]-Sigmatropic rearrangement of O-allyl- into S-allylthiocarbamates

S-Allylthiocarbamates are useful precursors to allylic thiols. A straightforward method for their preparation consists in the [3,3]-sigmatropic rearrangement of their O-allyl counterparts.

Aiming at developing a general and high-yielding route for the conversion of phenols 231 to the corresponding thiophenols 234, Newman and Karnes investigated the thermal rearrangement of O-aryl dialkylthiocarbamates 232 to S-aryl dialkylthiocarbamates 233. Heating the starting materials neat between 170 °C and 335 °C, depending on the ring substituents, generally afforded the rearranged products in no less than 90% yield (Scheme 67).

\[
\begin{align*}
\text{R}_1\text{R}_2\text{O} & \quad \xrightarrow{170-335 \degree C} \quad \text{R}_1\text{R}_2\text{S} \\
231 & \quad 232 & \quad 233 & \geq 90\% & \quad 234
\end{align*}
\]

\textbf{Scheme 67: Newman-Karnes rearrangement of O-aryl dialkylthiocarbamates.}

Data showed that electron-withdrawing substituents on the aryl group significantly lowered the required temperature. This suggested a nucleophilic attack of the sulfur on the aromatic carbon bearing the oxygen atom (Scheme 68). The fact that a \(N,N\)-dimethylthiocarbamate rearranged more readily than its \(N,N\)-methyl-\(p\)-
nitrophenylthiocarbamate analog supported this assumption since the dialkylamino group better stabilised the positive charge in intermediate 232a.89

\[
\begin{align*}
\text{232} & \quad \xrightarrow{\Delta} \quad \text{232a} & \quad \xrightarrow{\Delta} \quad \text{233}
\end{align*}
\]

**Scheme 68: Proposed mechanism for Newman-Karnes rearrangement.**

Hackler and Balko deduced from Newman’ and Karnes’ results that “the dialkylthiocarbamate linkage was more stable when joined through the sulfur than when joined through the oxygen” and that “the added stability of the sulfur linkage could provide the driving force for a [3,3]-sigmatropic rearrangement”.90 However, given that both C-S simple and double bonds are weaker than their C-O counterparts,91 it seems more likely than the driving force of a [3,3]-sigmatropic rearrangement stems from the enhanced stability of the newly formed C=O bond92 (127 kcal/mol in CO\textsubscript{2} at 298 K)91 compared to that of the initial C=S bond (95 kcal/mol in CS\textsubscript{2} at 298 K).91

Nevertheless, Hackler and Balko reported the successful [3,3]-sigmatropic rearrangement of a series of O-allyl dialkylthiocarbamates 235 (Scheme 69).90

\[
\begin{align*}
\text{235} & \quad \xrightarrow{\Delta} \quad \text{236}
\end{align*}
\]

**Scheme 69: [3,3]-Sigmatropic rearrangement of O-allyl dialkylthiocarbamates.**

They observed a marked influence of the degree of substitution of the carbon α to oxygen on the rate of the reaction. Rearrangement of primary thiocarbamates (R\textsuperscript{3} = R\textsuperscript{4} = H) required 130-140 °C to reach a 90% conversion after 20 min, that of secondary ones (R\textsuperscript{3} or R\textsuperscript{4} ≠ H) only 100-110 °C while tertiary thiocarbamates (R\textsuperscript{3} and R\textsuperscript{4} ≠ H) rearranged at room temperature or below.90

Basic hydrolysis of thiocarbamates 236 was expected to furnish the free thiols.90 However, the tertiary compounds revealed very unstable: linalylthiol 237a spontaneously rearranged to the less hindered isomer geranylthiol 238 (Scheme 70). Nonetheless, tertiary thiol 237a could be obtained by reduction of the thiocarbamate using LiAlH\textsubscript{4}. This appears as the first synthesis of a tertiary thiol. Compound 237a has notably been used in the synthesis of 9-aryl-2,6-nonadienes, known for their biological activity.93
Scheme 70: Preparation of tertiary allylic thiol 237a.

Kinetic studies of the thermal [3,3]-sigmatropic rearrangement of various thion-esters 239-240 revealed that both the thion-ester structure and the substituents on the allyl group influenced the rate of the rearrangement (Scheme 71).\(^\text{94}\)

Scheme 71: Thermal [3,3]-sigmatropic rearrangement of thion-esters.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Relative rate (k_r)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>239a</td>
<td>241a</td>
<td>1.0(^a)</td>
</tr>
<tr>
<td>2</td>
<td>239b</td>
<td>241b</td>
<td>5.0</td>
</tr>
<tr>
<td>3</td>
<td>239c</td>
<td>241c</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>240a</td>
<td>242a</td>
<td>480</td>
</tr>
</tbody>
</table>

\(^a\) \(k_r \text{(obs)} = 6.7 \times 10^{-5} \text{ min}^{-1}\).

Table 6: Kinetic studies in the thermal [3,3]-sigmatropic rearrangement of thion-esters.

Rearrangement of \(O\)-allylthiocarbamate 239a was the slowest, whereas that of xanthate 240a was the fastest (Table 6). Interestingly, \(k_r\) did not depend on the substrate-product energy difference, but on the strength of the C=S bond and the \(\pi\) electron density on the thion-sulfur group. Indeed, the higher the \(\pi\) bond order of the C=S bond, the faster the rearrangement, suggesting that its rate was controlled by an interaction between the \(\pi\) orbitals of the C=S and the C=C bonds.\(^\text{94}\)
Similarly, the lower the $\pi$ electron density on the thion-sulfur, the faster the rearrangement, indicating that $\pi$ electrons might move favourably from the allyl part to the thion-ester group upon forming the transition state.

Furthermore, a methyl substituent on the allyl moiety in 239b and 239c led to higher rates (Table 6, entries 2-3), compared to unsubstituted 239a (entry 1). This can be explained considering the proposed structure of the transition state F for the [3,3]-sigmatropic rearrangement of thion-esters (Figure 27): although $\pi$ electrons from both the allyl moiety and the C=S bond are delocalised, a positive charge was generated on the allyl part due to the favoured delocalisation of its $\pi$ electrons towards the thio-ester group. Thus, an electron-donating substituent on the allyl moiety, such as methyl, will stabilise this positive charge and lower the energy of the transition state, resulting in an increased rate.  

![Transition state F](image)

**Figure 27**: Transition state F for the [3,3]-sigmatropic rearrangement of thion-esters.

The mechanism of both the thermal and palladium-catalysed [3,3]-sigmatropic rearrangements of O-allylic thiocarbamates was examined by Tamaru and co-workers. Preliminary results in the thermal rearrangement showed that the reactivity of $N$-monosubstituted thiocarbamates was similar to that of $N,N$-disubstituted thiocarbamates: completion was achieved in a few hours at 120-150 °C. However, the regioselectivity was considerably different. While Hackler reported $N,N$-disubstituted thiocarbamates to rearrange with complete allylic transposition, some $N$-monosubstituted thiocarbamates 243 furnished a mixture of the allylic transposition product 244 and the positional retention product 245 (Scheme 72).

![Scheme 72](image)

**Scheme 72**: Thermal and palladium-catalysed [3,3]-sigmatropic rearrangements of O-allylic thiocarbamates.
These contrasting regioselectivities suggested that \(N,N\)-disubstituted thiocarbamates rearranged in a concerted fashion (transition state \(G\)) whereas \(N\)-monosubstituted thiocarbamates could follow either a concerted or a stepwise pathway (transition state \(H\)), which might be generated by either homolytic or heterolytic cleavage of the allylic C-O bond, **Scheme 73**.\(^{95}\)

![Scheme 73](image)

**Scheme 73:** Concerted or stepwise mechanism for thermal [3,3]-sigmatropic rearrangement of O-allylthiocarbamates.

In an effort to improve the selectivity of the rearrangement, palladium(II)-catalysis was attempted, since Pd(II) complexes reportedly led to high regioselectivities via intermediate \(I\) (**Scheme 74**).\(^{95}\)

![Scheme 74](image)

**Scheme 74:** Pd(II)-catalysed [3,3]-sigmatropic rearrangement of O-allylthiocarbamates.

Although the allylic transposition products 244 were obtained exclusively in some cases, the positional retention products 245 were still formed in significant amounts in others. Palladium(0) catalysis also afforded regioisomeric mixtures. However, in each case, the major product was the more thermodynamically stable one (\(i.e.\) bearing the more substituted double bond). This was attributed to a solvent-separated ion pair intermediate \(J\), leading to the preferential attack of the anion on the less substituted carbon of the \(\pi\)-allyl palladium (**Scheme 75**).\(^{95}\)
Scheme 75: Ionic intermediate in Pd(0)-catalysed [3,3]-sigmatropic rearrangement of O-allylthiocarbamates.

Regarding the stereoselectivity, retention was expected to be largely favoured by the palladium(0) catalysis. Indeed, π-allylpalladium intermediate J arose from invertive oxidative addition of Pd followed by substitution by the sulfur anion in an SN2 fashion (i.e. with inversion) and would consequently provide products with overall retention (Scheme 76).

However, the inverted products were still produced in considerable quantities when the rearrangement was carried out in THF. Another intermediate K was proposed, arising from preferential attack of the sulfur anion directly onto the metal instead of SN2 reaction on the π-allyl skeleton of J. Subsequent reductive elimination would lead to the inverted products (Scheme 76). This seemed a reasonable hypothesis given the high affinity of Pd(II) for soft anions.

Eventually, the use of DMF, a very polar solvent favouring ionic intermediate J, allowed the formation of the retention products with excellent stereoselectivity (ratio ret./inv-244 up to 100:0).

Scheme 76: Influence of the solvent on the enantioselectivity of the [3,3]-sigmatropic rearrangement of O-allyl thiocarbamates.

As part of their investigations of the configurational stability of α-thioallyllithiums (Section I.B.4.f), Hoppe and co-workers synthesised enantioenriched S-allyl thiocarbamates (R)-190 and (S)-198 by [3,3]-sigmatropic rearrangement of
enantioenriched O-allyl thiocarbamates (S)-248 and (R)-249, in very good yields and with excellent chirality transfer (Scheme 77).77

\[
\text{(S)-246: } n=1, \text{ 95\% e.e.} \\
\text{(R)-247: } n=2, \text{ >99\% e.e.} \\
\text{(S)-248: } n=1, \text{ 93\%, 95\% e.e.} \\
\text{(R)-249: } n=2, \text{ 87\%, >99\% e.e.} \\
\text{(R)-190: } n=1, \text{ 88\%, 92\% e.e.} \\
\text{(S)-198: } n=2, \text{ 74\%, 91\% e.e.}
\]

Scheme 77: [3,3]-Sigmatropic rearrangement of enantioenriched O-allylthiocarbamates.

The stereochemical course of the rearrangement was elucidated thanks to the X-ray crystal structure of 190.69 It showed the (R)-configuration, demonstrating a suprafacial process (Scheme 78).

\[
\begin{align*}
\text{(S)-248} & \xrightarrow{\Delta, \text{suprafacial}} \text{(R)-190}
\end{align*}
\]

Scheme 78: Demonstration of a suprafacial pathway in the [3,3]-sigmatropic rearrangement of enantioenriched O-allylthiocarbamates.

Gais and Böhme developed the first enantioselective [3,3]-sigmatropic rearrangement of O-allylic thiocarbamates 250-254. Highly enantioenriched S-allylic thiocarbamates 256-260 (85-99% e.e.) were prepared in excellent yields (76-96%, Scheme 79).96a

Following on their successful enantioselective palladium(0)-catalysed synthesis of allylic heteroaryl sulfides from racemic allylic carbonates,96b,c Gais and Böhme employed the same chiral bisphosphane ligand (R,R)-255 in the analogous rearrangement of O-allylic thiocarbamates 250-260.96a Symmetrically 1,3-substituted O-allylic thiocarbamates were chosen in order to avoid issues of regioselectivity.
Influence of various substituents both at the thiocarbamate nitrogen and the carbon skeleton, on enantioselectivity and rate, were investigated (Scheme 79).

In acyclic thiocarbamates 250-252, the best e.e.’s (≥90%) and the shorter reaction times to reach completion (16 h) were obtained for a small alkyl group (R’=Me, Et, n-Pr) at the N atom. The decrease in the enantioselectivity with bigger N-subsitutuents was more pronounced in substrates with a longer linear carbon chain. Those latter thiocarbamates required a 3-fold load of catalyst and longer reaction times to proceed quantitatively. This however, did not allow branched substrate 252b to rearrange at all.

The rearrangement of cyclic thiocarbamates 253-254 proceeded faster (0.5 to 16 h) and with higher enantioselectivities (92-99% e.e.) than that of the acyclic substrates. Likewise, the less hindered the substituent at the N atom, the higher the e.e.’s and yields.

Finally, the absolute configurations of the acyclic thiocarbamates 256-258 was determined to be (R) by chemical correlation with known derivatives, while the (S)-configuration was confirmed for the cyclic products 259-260.96a

Cross-over experiments were consistent with an ionic intermediate: chiral π-allylpalladium(II) complex J (Scheme 80). An equimolar mixture of two O-allylic thiocarbamates, differing in both their carbon skeleton and their substituent at the N atom, furnished four different products in a 30:20:18:30 ratio under the standard rearrangement conditions, demonstrating the formation of four different ionic pairs as intermediates.96a
Scheme 80: Cross-over experiments: evidence for an ionic intermediate.

Overman and co-workers developed the palladium(II)-catalysed rearrangement of unsymmetrical acyclic O-allylic thiocarbamates using the [(R,R)-COP-Cl]₂ complex (S)-(+) -263 and its enantiomer (Scheme 81). Remarkably, high regioselectivity in the nucleophilic substitution of an unsymmetrical η³-allylpalladium intermediate by a sulfur derivative was achieved for the first time.

Like Gais and Böhme, a Overman et al. observed that the highest enantioselectivity was obtained with the smallest substituents at the thiocarbamate nitrogen. They consequently investigated the effect of various substituents on the carbon skeleton in O-allylic 1-azetidinyl- and dimethylthiocarbamates 261 and 262 (Scheme 81, Table 7). 97

Scheme 81: Enantioselective [3,3]-sigmatropic rearrangement of unsymmetrical O-allyl thiocarbamates.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sm</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;a&lt;/sup&gt;</td>
<td>261a</td>
<td>n-Pr</td>
<td>15</td>
<td>(R)-264a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>98</td>
<td>83</td>
</tr>
<tr>
<td>2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>262a</td>
<td>n-Pr</td>
<td>18</td>
<td>(R)-265a&lt;sup&gt;a&lt;/sup&gt;</td>
<td>72</td>
<td>82</td>
</tr>
<tr>
<td>3</td>
<td>261b</td>
<td>i-Bu</td>
<td>42</td>
<td>(S)-264b</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>261c</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OTBDMS</td>
<td>20</td>
<td>(S)-264c</td>
<td>85</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>262c</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OTBDMS</td>
<td>18</td>
<td>(S)-265c</td>
<td>97</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>261d</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OTIPS</td>
<td>42</td>
<td>(S)-264d</td>
<td>99</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>261e</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;OH</td>
<td>13</td>
<td>(S)-264e</td>
<td>55</td>
<td>61</td>
</tr>
<tr>
<td>8</td>
<td>261f</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;NPh(Boc)</td>
<td>44</td>
<td>(S)-264f</td>
<td>68</td>
<td>71</td>
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<tr>
<td>9</td>
<td>262f</td>
<td>CH&lt;sub&gt;2&lt;/sub&gt;NPh(Boc)</td>
<td>43</td>
<td>(S)-265f</td>
<td>77</td>
<td>81</td>
</tr>
<tr>
<td>10</td>
<td>261g</td>
<td>(CH&lt;sub&gt;2&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt;COME</td>
<td>11</td>
<td>(S)-264g</td>
<td>85</td>
<td>76</td>
</tr>
</tbody>
</table>

<sup>a</sup>(R)-(–)-COP-Cl catalyst was used.

**Table 7: Enantioselective [3,3]-sigmatropic rearrangement of unsymmetrical O-allyl thiocarbamates.**

The rearrangement proceeded in high yields in dimethyl- and 1-azetidinyl-thiocarbamates 261 and 262, bearing an alkyl chain (261<sub>a,b</sub> and 262<sub>a</sub>, Table 7, entries 1-3) or containing a protected alcohol function (261<sub>c,d</sub> and 262<sub>c</sub>, entries 4-6). Products 264<sub>e,f</sub> and 265<sub>f</sub> bearing a free hydroxyl group or Boc-protected aniline, were obtained in lower yields and enantioselectivities (entries 7-9), as did 261<sub>g</sub> containing a keto group (entry 10). Otherwise, high enantioselectivities were achieved (80-88% e.e.). The catalyst loading could be reduced to 1.0 mol% but longer reaction times were required to achieve similar yields and enantioselectivities.

Finally, access to enantioenriched secondary allylic thiols was possible via straightforward reduction by LiAlH<sub>4</sub>.<sup>97</sup>

As a comparison, You and co-workers also reported high enantioselectivities (up to 95% e.e.) in their iridium-catalysed enantioselective [3,3]-sigmatropic rearrangement of unsymmetrical O-allyl carbamothioates 262 (R<sup>1</sup>; R<sup>2</sup> = alkyl, aryl; R<sup>3</sup> = H, -(CH<sub>2</sub>)<sub>5</sub>-) but their method suffered from lower regioselectivities than Overman’ and co-workers’: the expected allylic transposition products 265 always came with the achiral positional retention products 245 (see Scheme 72) with 265/245 ratios ranging from 60:40 to 93:7.<sup>98</sup>
I.E) Previous work within the Clayden group

I.E.1) Investigations of the aryl transfer rearrangement in ureas

I.E.1.a) N’-Aryl-N-benzyl ureas

In 2007, while investigating the regioselective lithiation of N-aryl amines, a remarkable aryl transfer rearrangement was uncovered within the group. N-Benzyl urea 266a was treated with s-BuLi followed by methyl iodide to determine the site of deprotonation. Compound 267a, in which the 2,5-dimethylphenyl ring had migrated from N to C, was obtained. Replacing the methylation step by an aqueous quench allowed the formation of 268a in 89% yield (Scheme 82).

![Scheme 82: Lithiation-rearrangement of N’-aryl N-benzyl ureas.]

Ureas 266, bearing electronically and sterically varied rings, all underwent aryl migration. Subsequent cleavage of the urea functionality in products 268 using DiBAI-H, or hydrolysis of the N-nitroso derivatives afforded the corresponding diarylmethylamines 269 in good yields (Scheme 83).

![Scheme 83: Aryl migration in N’-aryl N-benzyl ureas.]

---

85
Tertiary benzyl锂iums derived from ureas 270 were less reactive and required the addition of DMPU to rearrange to 271 in good yields.\(^9\) Remarkably, the \(\text{N}\rightarrow\text{C}\) aryl transfer proceeded with almost complete stereospecificity, regardless the electronic nature of the ring, confirming the configurational stability of the lithiated intermediate. Deprotection of the enantiopure ureas 271 furnished the hindered chiral \(\alpha\)-tertiary amines 272 (Scheme 84).

\[
\begin{align*}
\text{270} & \rightarrow \text{271: } R^1 = \text{EDG, 17 examples} \\
& \hspace{1cm} \text{64-95\%, 90-98\% e.e.} \\
& \hspace{1cm} R^1 = \text{Cl, F, 5 examples} \\
& \hspace{1cm} 34-69\%, 96-98\% e.e.
\end{align*}
\]

**Scheme 84: Aryl migration in \(\alpha\)-methyl \(N'\)-aryl \(N\)-benzyl ureas.**

A mechanism involving dearomatised intermediate 274 was proposed for the rearrangement of 270, based on the isolation of enones 275o and 275p after exposure of the reaction mixtures to dry air (Scheme 85).\(^9\) Overall the rearrangement consists of an intramolecular nucleophilic aromatic substitution, which is particularly unexpected on electron-rich rings.\(^\text{100}\)

\[
\begin{align*}
\text{270} & \rightarrow \text{271} \\
\text{274} & \rightarrow \text{275p: } R^2 = \text{OMe, 45\%} \\
& \hspace{1cm} 275p: R^2 = \text{Cl, 56\%}
\end{align*}
\]

**Scheme 85: Proposed mechanism for the aryl migration in \(\alpha\)-methyl benzylic ureas.**

X-ray crystallography analysis confirmed the absolute stereochemistry of 275p and the retentive pathway. However, further investigations into the mechanism of the aryl transfer using DFT calculations, \textit{in situ} IR and NMR studies showed that the dearomatised
intermediate was only short-lived and detectable under specific conditions (naphthyl migrating ring, presence of DMPU). More importantly, the role of the solvated lithium cation, in moving away from the carbanionic centre to a site close to the migrating ring, thus stabilising its developing negative charge, was emphasised. Its position was found to be critical in determining the retentive character of the rearrangement.

Moreover, DFT calculations revealed that the transition state for 1,4-aryl transfer was lower in energy than that for 1,2-acyl shift, explaining why the unexpected nucleophilic attack on the aromatic ring was observed, rather than the more common attack of a carbonyl group. The loss of aromaticity in the 1,4-aryl migration turned out to be less energetically disfavourable than the strained transition state leading to a 3-membered ring intermediate in the 1,2-acyl shift.

A less nucleophilic base, LDA, was employed in the rearrangement of N-pyridyl ureas 276 to avoid the attack of the pyridyl ring by s-BuLi (Scheme 86). Addition of DMPU allowed a significant improvement of the stereospecificity (from 60:40 to 98:2 e.r. in 276a, R = H). Various substituents on the pyridyl ring similarly led to high enantioselectivities (e.r. > 96:4). Deprotection of rearranged ureas 277 afforded the highly enantioenriched pyridyl-substituted tertiary amines 278.

![Scheme 86: Lithiation-rearrangement of N-pyridyl ureas.](image)

I.E.1.b) N'-Aryl ureas derivatives of amino acids

Amino acid-derived N'-aryl ureas 279 underwent intramolecular C-arylation by attack of the enolate anion 280 onto the aryl ring, followed by cyclisation to hydantoins 282. Hydantoin 282b was deprotected and hydrolysed to the corresponding arylated quaternary amino ester 283b in good yield (Scheme 87).
Sche 87: Lithiation-rearrangement of amino acid-derived N'-aryl ureas.

I.E.1.c) N’-Aryl-N-allyl ureas

Aryl migration in N-allyl ureas 284 furnished Z-vinyl ureas 288 in good to excellent yields, irrespective of the electronic nature of the migrating ring (Scheme 88).\(^{103}\)

\[
\text{284} \xrightarrow{1. \text{LDA (2.0 eq), THF, -78 °C, 10 min}} \text{MeHN} \ \text{PMP} \ \text{288} \\
\text{N-allyl urea} \xrightarrow{2. \text{MeOH}} \text{N-arylated} \ x \text{of} \text{Z-vinyl ureas 288 in good} \ \text{yields.}
\]

Aminoallyllithium 285, of Z-configuration according to structural studies by Beak et al.,\(^{53a,d,e,h,i}\) underwent 1,4-aryl transfer to form Z-allyl urea 286, which was lithiated in turn to give cinnamyllithium 287. Protonation \(\gamma\) to nitrogen furnished Z-vinyl ureas 288 in good yields.

Aiming to prepare hindered allyl amines, Z-vinyl ureas 288 were N-arylated in order to perform a second aryl migration (Scheme 89).\(^{103}\) Rearrangement of Z-vinyl ureas 289 followed by deprotection of Z-allyl ureas 290 provided the tertiary allyl amines 291.
Scheme 89: *Aryl migration in Z-vinyl ureas.*

Following Beak’s work which demonstrated that *N*-acyl allyllithiums may be deprotonated enantioselectively with alkyllithium bases in the presence of (−)-sparteine (−)-162, 53a,c−i (Z)-289i (Ar<sup>1</sup>=Ph, Ar<sup>2</sup>=p-ClC<sub>6</sub>H<sub>4</sub>) was lithiated with s-BuLi, in cumene/(−)-sparteine at −40 °C. The resulting allyl urea (S)-290i was isolated in 45% yield and 80:20 e.r.<sup>103</sup>

Fortunately, chiral lithium amides led to higher e.r.’s, the best results being obtained with (S)-*N*-isopropyl-α-methylbenzylamine (S)-292Li (up to 98% yield, 94:6 e.r., Scheme 90).<sup>103</sup> Notably, replacement of DMPU with LiCl allowed improved yields and e.r.’s.

Scheme 90: *Preparation of highly enantioenriched tertiary allylic ureas.*

Remarkably, using weaker bases such as NaH to convert allylic ureas 290 to the corresponding amines 291 led to C→N aryl migration (Scheme 91).<sup>104</sup> Since electron-deficient rings were found to “retromigrate” preferentially, inversion of configuration of (S)-290h was possible by shunting the cyanophenyl ring onto the nitrogen atom and back to C<sub>a</sub> again using the appropriate chiral amide base to form the chosen enantiomer.

Scheme 91: *Inversion of configuration via “retro-migration”.*
I.E.2) Application to carbamates

I.E.2.a) N’-Aryl-O-benzyl carbamates

Secondary and tertiary benzylic carbamates 295 underwent $N\rightarrow C$ aryl migration on treatment with either LDA in Et$_2$O/DMPU 4:1 or s-BuLi in THF/DMPU 4:1. The rearranged carbamates 296 were obtained in good to excellent yields (Scheme 92). The highest values were obtained for the unsubstituted phenyl ring (75-90%) and the weakly electron-rich para-tolyl ring (62-84%).

![Scheme 92: Aryl migration in racemic benzylic carbamates.](image)

Starting from enantiopure benzylic thiocarbamate (S)-295i, the aryl transfer proved to be enantiospecific, furnishing hindered tertiary alcohol (S)-297i in high e.r. which was used as an intermediate in the first enantioselective synthesis of the antihistamine agent (S,S)-Clemastine 298 (Scheme 93). Surprisingly, the rearrangement was confirmed to be invertive, contrasting with retention observed in ureas.

![Scheme 93: Enantioselective synthesis of (S,S)-clemastine 298 via aryl migration.](image)
I.E.2.b) \( N' \)-Aryl-\( O \)-allyl carbamates

Lithiation of cinnamyl carbamate 299 resulted in the formation of phenyl ketone 301 as the major product. Evidence that this compound arose from \( N\rightarrow C \) migration was supported by the identification of by-product (Z)-300 from which 301 can be derived by hydrolysis (Scheme 94).

![Scheme 94: Lithiation-rearrangement of cinnamyl carbamates.](image)

Employing the same conditions (A, Scheme 95) with \( \alpha \)-methyl cinnamyl carbamate 302 led to aryl migration followed by carbolithiation of the conjugated alkene to give carbamate 303.\(^{107}\) Traces of deprotected tertiary alcohol 304 were isolated. Nevertheless, a one-pot rearrangement-deprotection procedure (conditions B) allowed the sole formation of 304 in good yield.

![Scheme 95: Lithiation-rearrangement of \( \alpha \)-methyl cinnamyl carbamates.](image)

The stereospecificity of the aryl migration in \( O \)-allyl carbamates was investigated in compound (R)-302 (Scheme 96).\(^{107}\)

![Scheme 96: Stereospecificity of the aryl migration in \( O \)-allyl carbamates.](image)
Table 8: Stereospecificity of the aryl migration in O-allyl carbamates.

Although the addition of a chiral ligand allowed partial conservation of the enantoenrichment, probably by preventing the cation from moving from one enantiotopic face to the other, the O-allyllithium derived from carbamate \((R)-302\) was configurationally unstable (Table 8).\textsuperscript{107}

\textit{In situ} IR studies revealed the formation of a pre-lithiated complex in which the LDA dimer is coordinated to the carbonyl oxygen.\textsuperscript{107} Interestingly, the lithiated intermediate exhibited no intramolecular interaction between the lithium and the carbonyl oxygen atoms. This was consistent with DFT calculations showing that the lowest energy charge-separated conformation, leading to inversion, resulted from 1,2-migration of the lithium cation to the adjacent benzylic carbamate oxygen, rather than onto the phenyl ring, as found in ureas.\textsuperscript{100} This major difference was proposed to account for the opposite stereochemical outcome in these two series. Finally, both methods agreed to the absence of any dearomatised intermediate.

I.E.3) Application to thiocarbamates

Standard conditions developed for the rearrangement of carbamates were applied to benzylic thiocarbamates 306 (Scheme 97).\textsuperscript{108} Doubly benzylic thiocarbamates 307a-c were isolated in high yields while 308d was obtained as the deprotected thiol. Straightforward cleavage of the thiocarbamate functionality using sodium ethoxide afforded the free thiols in good to excellent yields.
Optimised conditions allowed high stereospecificities in the rearrangement of enantiopure thiocarbamate (S)-309a (Scheme 98, Table 9). Namely, absence of DMPU proved to be highly beneficial. It had indeed been noted to promote racemisation in benzylic organolithiums. A more hindered base (LiTMP) gave the best e.r. at the expense of the reaction rate though (entry 5). No loss of enantioenrichment was observed when the temperature was raised to -60 °C, provided that the reaction time was shorter (entry 3).

**Scheme 97: Aryl migration in racemic thiocarbamates.**

**Scheme 98: Investigation of the stereospecificity of aryl migration in thiocarbamates.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Temperature T (°C)</th>
<th>Time t (h)</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>-78</td>
<td>1</td>
<td>94</td>
<td>52:48</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>-78</td>
<td>2</td>
<td>86</td>
<td>87:13</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>-60</td>
<td>2 min</td>
<td>87</td>
<td>90:10</td>
</tr>
<tr>
<td>4</td>
<td>s-BuLi</td>
<td>-78</td>
<td>1</td>
<td>77</td>
<td>90:10</td>
</tr>
<tr>
<td>5</td>
<td>LiTMP</td>
<td>-78</td>
<td>15</td>
<td>83</td>
<td>96:4</td>
</tr>
</tbody>
</table>

*aDMPU was added.

**Table 9: Investigation of the stereospecificity of aryl migration in thiocarbamates.**
The absolute stereochemistry of (S)-310a was determined from the X-ray crystal structure of its p-nitrothiobenzoate derivative (S)-312a (Scheme 99). It demonstrated a retentive rearrangement,\textsuperscript{108} similarly as with ureas.\textsuperscript{99}

![Reaction diagram](image)

**Scheme 99: Demonstration of retentive aryl migration in benzylic thiocarbamates.**

Rearrangement of enantioenriched benzylic thiocarbamates was found to tolerate electron-rich (309a-c,g), electron-deficient (309d-f) and moderately hindered (309c,g) rings which generally migrated with complete enantiospecificity, in good to excellent yields (Scheme 100, Table 10).\textsuperscript{108} Cleavage of the thiocarbamates with sodium ethoxide afforded the highly enantioenriched tertiary thiols 311 in generally excellent yields.

![Reaction diagram](image)

**Scheme 100: Preparation of enantioenriched tertiary benzylic thiols.**
Table 10: Preparation of enantioenriched tertiary benzylic thiols.

Notably, the most electron-rich ring (309b) required DMPU to migrate, which resulted in a racemic product 310b (entry 1). Partial loss of enantiomeric purity was also observed in the rearrangement of 309i, bearing an electron-deficient anion-stabilising ring (entry 8). Finally, highly hindered 2,4,6-trimethylphenyl and 3-fluorophenyl rings did not undergo $N\rightarrow C$ transfer at all.

The following mechanism was proposed based on the spirocyclic intermediate observed in ureas (Scheme 101). However, attempts to trap a dearomatised intermediate in the rearrangement of 309g, bearing a naphthyl ring as lithiated ureas only led to isolation of starting material or the rearranged product. This suggested that, should a deoramatised intermediate exist, the rate of its collapse is greater than that of its formation.

Scheme 101: Proposed mechanism for the aryl migration in benzylic thiocarbamates.
Deprotonation at the benzylic site in 309 generated benzyllithium 313, a dipole-stabilised carbanion,\textsuperscript{111} which attacked the distal aryl ring to presumably form dearomatised spirocycle 314. Finally, ring opening gave lithiocarbamate 315 leading to protonated 310.

**I.F) Aims of the project**

The aryl transfer rearrangement has proved to be an efficient methodology for the synthesis of challenging $\alpha$-tertiary amines,\textsuperscript{99} alcohols\textsuperscript{106} and thiols.\textsuperscript{108} However, regarding these last compounds, investigations have so far been limited to benzylic thiocarbamates. Allylic thiocarbamates are interesting targets as the double bond will allow for strategic synthetic transformations, widening further the scope of the organosulfur compounds accessible through this methodology.

Based on previous work on benzylic thiocarbamates,\textsuperscript{108} N-allyl ureas\textsuperscript{103} and O-allyl carbamates\textsuperscript{107} within the group, the aims of the project are to demonstrate the generalisation of the rearrangement to the S-allyl thiocarbamates 316, to investigate its scope and to optimise its stereospecificity. Comparisons between the different series will be interesting and may bring further insight into mechanistical considerations.

A wide range of thiols bearing different substitution patterns both at the allylic double bond and the migrated aryl ring will be prepared, should the straightforward conditions used for the cleavage of the benzylic thiocarbamates be applicable to the allylic analogs.

Eventually, various transformations will be attempted to demonstrate the synthetic utility of these novel organosulfur compounds (Scheme 102).
Scheme 102: Preparation of tertiary allylic thiols and varied derivatives via α-arylation of thiocarbamates.

Another exciting part of the project will be to explore the feasibility of migrating non-aromatic moieties such as vinyl, styrenyl or cyclohexenyl (Scheme 103, a). This indeed constitutes an alternative route to the tertiary thiols 319 which may not be accessible or produced in lower enantiospecificity via aryl migration (Scheme 103, b). Moreover, starting from the same absolute configuration in benzylic and allylic thiocarbamates 326 and 316 and assuming a retentive pathway in both vinyl and aryl migration, as this was shown for aryl migration in benzylic thiocarbamates,108 each route will lead to a different enantiomer of tertiary thiocarbamate 318. Thus, combination of these two methods is expected to broaden the scope of the highly enantioenriched tertiary allylic thiocarbamates 318 and thiols 319 accessible through our N→C transfer methodology.
Scheme 103: Vinyl migration in benzylic thiocarbamates and aryl migration in allylic ones.
II.A) Preparation of the thiocarbamate precursors to the aryl migration

II.A.1) Racemic synthesis

II.A.1.a) Strategy

The first step of the project was to develop an efficient synthesis of the starting materials, as short and high-yielding as possible.

We first envisaged preparing the thiocarbamate precursors 316 via two successive nucleophilic substitutions starting from allylic alcohols 328 and N-methylanilines 329 followed by [3,3]-sigmatropic rearrangement of O-substituted thiocarbamates 332 to furnish the S-substituted thiocarbamates 316 (Scheme 104).\(^{77,90,94,95}\)

\[ \text{R}^2 \text{CH} = \text{CHCH} \text{OH} \rightarrow \text{N} \text{Cl} \rightarrow \text{N} \text{S} \rightarrow \text{R}^3 \text{O} \text{N} \text{S} \rightarrow \text{R}^1 \text{S} \text{N} \text{R}^3 \]

\( \text{R}^2 \text{R}^1 \text{OH} \rightarrow \text{NCl} \rightarrow \text{N} \text{S} \rightarrow \text{R}^3 \text{O} \text{N} \text{S} \rightarrow \text{R}^1 \text{S} \text{N} \text{R}^3 \)

Scheme 104: Envisaged synthesis of allylic S-substituted thiocarbamates (±)-316 via [3,3]-sigmatropic rearrangement of O-allyl thiocarbamates 332.

II.A.1.b) Preparation of racemic allylic alcohols 328d and 328g

All allylic alcohols were commercially available, except 328d and 328g. Reduction of the corresponding methyl ester 333 using DiBAI-H\(^{112}\) afforded 328d in very good yield (Scheme 105).
Scheme 105: Synthesis of 328d via reduction of the corresponding ester.

Phenyl-substituted allylic alcohol 328g was first prepared via stereoselective reduction of its propargylic counterpart 334a,\textsuperscript{113} as this compound was already in our hands.\textsuperscript{114,115} Indeed, Red-Al\textsuperscript{®} had been reported to be the reagent of choice,\textsuperscript{116a,b} preferably to LiAlH\textsubscript{4}\textsuperscript{116c} related to stereoselectivity issues.\textsuperscript{116d-f} The latter reducing agent was also more air- and moisture sensitive and less soluble in organic solvents.\textsuperscript{116g}

We initially aimed for a stereoselective method, anticipating that any E/Z-mixture in enantiopure 328g could be detrimental to the stereospecificity of the following [3,3]-sigmatropic rearrangement, while preparing the enantioenriched thiocarbamates 316.

Thus, reduction of propargylic alcohol 334a\textsuperscript{114} by Red-Al\textsuperscript{®} in diethylether selectively formed (E)-1-phenylbut-2-en-1-ol 328g,\textsuperscript{117} as expected\textsuperscript{113,116} (Scheme 106).

Scheme 106: Preparation of (E)-328g via stereoselective reduction of 334a.

The configuration of the double bond was assigned from the coupling constant between the two olefinic protons\textsuperscript{118} ($J_{\text{max}} = 15.3$ Hz). A very small doublet (integration 0.09) upfield that of the methyl group of (E)-328g led us to infer the complete (E)-stereoselectivity of the reaction ((Z)-328g ≤ 3%).

Unfortunately, (E)-328g was isolated in low yield (27%) after purification by column chromatography, which caused partial rearrangement to 4-phenylbut-3-en-2-ol (11%). The reaction was repeated on a larger scale and stirred for 6 h. The crude $^1$H NMR showed no remaining starting material but traces of the rearranged alcohol (7%). Therefore, we sought another route to 328g and investigated the addition of Grignard reagent 336, derived from 1-bromo-1-propene 335, on benzaldehyde (Scheme 107). Pleasingly, 328g could be isolated in good yield, in a 1:1.3 E/Z ratio.\textsuperscript{119}
II.A.1.c) Improvements in the [3,3]-sigmatropic rearrangement

In order to shorten the reaction time of the [3,3]-sigmatropic rearrangement, a solution of O-substituted thiocarbamate 332a was heated in a microwave for 45 min at 135 °C. We found that the conversion was even higher than for the thermal process, despite a much decreased reaction time (Scheme 108).

However, because thiophosgene rapidly became commercially unavailable, another route had to be sought. Thiocarbonyldiimidazole 337 was considered an interesting replacement for thiophosgene. However, its reaction with various N-methylanilines 329 produced only a complex mixture of unidentified products. Changing the order of the substitutions, with the aim of first converting allylic alcohols 328 to imidazole derivatives 338, revealed that these latter compounds spontaneously rearranged to the S-allyl imidazolthiocarboxylates 339, as previously reported by other groups (Scheme 109).  

Scheme 107: Preparation of 328g via Grignard reaction.

Scheme 108: Improvement in the thermal [3,3]-sigmatropic rearrangement of 332a.

Displacement of the imidazole moiety in 339 is usually achieved by activation via N-methylation. Following up on successful N-methylations of carbonyldiimidazole derivatives within the group, a wide range of conditions were tried, employing methyl iodide in acetonitrile or neat, heating to reflux either thermally or in the microwave, extending the reaction time to up to 48 h, or using a stronger alkylating agent, such as methyl triflate. Unfortunately, they all led to degradation of the starting material.

Inspired by some examples in the literature employing DBU or HOBt to displace acyl imidazole groups, we found that adding either HOBt 340 or ethyl 2-cyano-2-(hydroxyimino)acetate (Oxyma Pure®) 341 to the reaction of 339 with anilines 329 afforded S-substituted thiocarbamates 316 in generally good to excellent yields (Figure 28, Table 11).

Overall, the synthetic route to the starting materials features a one-pot addition of an allylic alcohol onto a thiocarbonyl derivative/[3,3]-sigmatropic rearrangement 直接 displacement of the imidazole moiety by N-methylanilines using a coupling agent (Scheme 109).

A large variety of allylic thiocarbamates 316 bearing different substituents on either the double bond or the carbon α to S were generally obtained in good to excellent yields (Figure 28, Table 11).
**Figure 28:** Cores of allylic thiocarbamates 316.

<table>
<thead>
<tr>
<th>Core</th>
<th>R³: 316, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>316a</strong></td>
<td>H: 316aa 68 4-Me: 316ab 88 4-OMe: 316ac 87 4-Cl: 316ad 65 4-F: 316ae 86 3-OMe: 316af 71 3-Cl: 316ag 45 3-F: 316ah 46 2-OMe: 316ai 87 2,3-benzo: 316aj 51 2,4,6-triMe: 316ak 96 2-pyridyl: 316al 23</td>
</tr>
<tr>
<td><strong>316b</strong></td>
<td>4-Me: 316ba 97 4-OMe: 316bb 89 4-Cl: 316bc 77 4-F: 316bd 93 3-Cl: 316be 46 2-OMe: 316bf 67</td>
</tr>
<tr>
<td><strong>316c</strong></td>
<td>4-Me: 316ca 79 4-OMe: 316cb 59 4-Cl: 316cc 78 4-F: 316cd 78</td>
</tr>
<tr>
<td><strong>316d</strong></td>
<td>4-Me: 316da 84 4-Cl: 316db 81</td>
</tr>
<tr>
<td><strong>316e</strong></td>
<td>4-Me: 316ea 92 4-Cl: 316eb 49 4-F: 316ec 90 2-OMe: 316ed 77 4-Me: 316fa 86 4-OMe: 316fb 96 4-Cl: 316fc 73 4-F: 316fd 79 3-OMe: 316fe 86 3-Cl: 316ff 77 3-Cl: 316fg 60 2-OMe: 316fh 88 2,3-benzo: 316fi 41 2-pyridyl: 316fj 23 6-(NBoc-indole): 316fk 99 6-(NH-indole): 316fl 99</td>
</tr>
<tr>
<td><strong>316g</strong></td>
<td>4-Cl: 316ga 56 4-F: 316gb 73 3-OMe: 316gc 86 3-Cl: 316gd 63 2-OMe: 316ge 76</td>
</tr>
<tr>
<td><strong>316h</strong></td>
<td>4-Cl: 316ha 60</td>
</tr>
</tbody>
</table>

*a-naphthyl.

**Table 11:** Yields of allylic thiocarbamates 316.
II.A.2) Enantioselective synthesis starting from primary allylic alcohols

II.A.2.a) Via dynamic thermodynamic resolution (DTR)

Enantioenriched thiocarbamates 316 could potentially be obtained by resolution of the racemic substrates, via lithiation in the presence of a chiral ligand. Indeed, work by Hoppe and co-workers demonstrated that the diastereomeric ion pairs resulting from lithiation of a prochiral benzylic or cinnamyl thiocarbamate in the presence of a chiral ligand, equilibrated towards one favoured epimer under specific conditions (higher than -78 °C temperature or longer deprotonation time). This was described in Sections I.B.4.c and I.B.4.e.

Thus, we envisaged deprotonating racemic 316aa in the presence of (−)-sparteine 162 at -78 °C, followed by a warming period to allow epimerisation of the diastereomeric ion pairs 317aa 162, hoping that one epimer would be thermodynamically favoured, before reprotonating at -78 °C. However, the temperature must be raised carefully, in order not to trigger the aryl migration (Scheme 110).

Scheme 110: Dynamic thermodynamic resolution of (±)-316aa using (−)-sparteine.

In a preliminary experiment, we opted for warming at -60 °C over 2 h. Disappointingly, only a low enantioenrichment (60:40 e.r.) was reached in (S)-316aa 124 (Scheme 111).
The very low isolated yield resulted from formation of two by-products:
- the major one arising from aryl migration followed by carbolithiation and C-S bond cleavage (see Scheme 135 for the mechanism of formation of this by-product and structure of analogous 361);\textsuperscript{125}
- the minor one containing the characteristic terminal allylic splitting pattern, no proton $\alpha$ to S and no NH broad singlet, presumably the tertiary thiol arising from aryl migration and thiocarbamate deprotection.

As other published methods for the preparation of enantioenriched allylic thiocarbamates seemed more straightforward,\textsuperscript{96,97} this route was not explored further.

II.A.2.b) \textit{Via} a metal-catalysed enantioselective \textit{in situ} [3,3]-sigmatropic rearrangement

Based on work by Gais,\textsuperscript{96a} Overman\textsuperscript{97} and co-workers who achieved high enantioselectivities in the [3,3]-sigmatropic rearrangement of O-allylic thiocarbamates to their S-allylic analogs (see Section I.D), we tested their catalysts on our substrates.

We were very pleased to observe that (R)-316aa was formed in an excellent 91:9 e.r. in the presence of (R)-(−)-COP-Cl$^{97}$ 263 (Scheme 112). The (R)-configuration was initially assumed based on Overman’s assignments, as their published enantioenriched allylic thiocarbamates were compared with known derivatives.\textsuperscript{97}
Gais' conditions, Trost ligand \((R, R)\)-255 in conjunction with \(\text{Pd}_2(\text{dba})_3\cdot\text{CHCl}_3\) gave lower enantioselectivity with 332a (ca. 80:20 e.r.) and were not explored further.

However, as thiophosgene became unavailable, we applied catalyst \((R)\)-(−)-COP-Cl 263 in the \textit{in situ} \([3,3]\)-sigmatropic rearrangement, resulting from the replacement of thiophosgene with thiocarbonyldiimidazole (Scheme 109). This turned out to be problematic as only intermediate 338a and/or degradation was observed in the crude \(^1\)H NMR spectrum (Scheme 113).

We then attempted a two-step process, stirring reagents 328a and 337 at –20 °C for 6 h, aiming at forming intermediate 338a without rearrangement, before adding chiral catalyst (−)-263 and warming the reaction to generate 339a (Scheme 114). In this case, although 338a partially remained, we did observe formation of the desired S-allyl imidazolethiocarboxylate 339a, but in a racemic form.

Thus, we thought that replacing DMAP with HOBt may accelerate the substitution of the imidazole moiety in TCDI 337, so we may be able to isolate 338a in order to submit it pure to the enantioselective \([3,3]\)-sigmatropic rearrangement. Indeed, using HOBt in DCM afforded the imidazole adduct 338a after 1 h without rearrangement, as indicated by \(^1\)H NMR (Scheme 115). However, it could not be isolated as it underwent rapid \([3,3]\)-sigmatropic rearrangement during work-up and purification by filtration through silica. It decomposed over a matter of days in a freezer.
Neither could intermediate $338a$ be used without purification, as it needed to be separated from HOBt. However, we thought it might be possible to isolate it for a very short amount of time and submit it to the next reaction the very same day.

After a careful work-up followed by a quick filtration through silica, unstable intermediate $338a$ could be obtained as a mixture containing only 10% of $339a$, with no other impurity. This mixture was submitted to the conditions we developed to displace the imidazole moiety by $N$-methylanilines $329$ (Scheme 109), in the presence of the chiral catalyst $(R)$-$(−)$-COP-Cl $263$. Unfortunately, the rearranged product was again formed as a racemic mixture (Scheme 116).

II.A.2.c) Via $(R)$-$(−)$-COP-Cl-catalysed enantioselective $[3,3]$-sigmatropic rearrangement of $O$-substituted thiocarbamates $332^{126}$

As thiophosgene $330$ could finally be obtained from another supplier, it became our most reliable tool to develop a fast and efficient enantioselective synthesis of allylic thiocarbamates $316$. Using the route shown earlier (Scheme 104), a series of $O$-allyl thiocarbamates $332$ were prepared in good yields over two steps (Scheme 117).$^{120}$
Scheme 117: Preparation of O-allyl thiocarbamates 332.

Since preliminary results with substrate 332a showed higher enantioselectivity with Overman’s (R)-(-)-COP-Cl 26397 (Scheme 112), this catalyst was applied in the sigmatropic rearrangement of all O-substituted thiocarbamates 332 (Scheme 118).120

Satisfyingly, a series of enantioenriched S-allyl thiocarbamates 316a,b was prepared in generally excellent yields and 80:20 to 95:5 e.r. (Table 12).126,127

Scheme 118: (R)-(-)-COP-Cl-catalysed [3,3]-sigmatropic rearrangement of O-allyl thiocarbamates 332.
<table>
<thead>
<tr>
<th>Entry</th>
<th>332</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>316</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>332aa</td>
<td>Me</td>
<td>H</td>
<td>(R)-316aa</td>
<td>93</td>
<td>91:9</td>
</tr>
<tr>
<td>2</td>
<td>332ab</td>
<td>Me</td>
<td>4-Me</td>
<td>(R)-316ab</td>
<td>99</td>
<td>89:11</td>
</tr>
<tr>
<td>3</td>
<td>332ad</td>
<td>Me</td>
<td>4-Cl</td>
<td>(R)-316ad</td>
<td>95</td>
<td>89:11</td>
</tr>
<tr>
<td>4</td>
<td>332ae</td>
<td>Me</td>
<td>4-F</td>
<td>(R)-316ae</td>
<td>94</td>
<td>89:11</td>
</tr>
<tr>
<td>5</td>
<td>332af</td>
<td>Me</td>
<td>3-OMe</td>
<td>(R)-316af</td>
<td>95</td>
<td>83:17</td>
</tr>
<tr>
<td>6</td>
<td>332ag</td>
<td>Me</td>
<td>3-Cl</td>
<td>(R)-316ag</td>
<td>98</td>
<td>80:20</td>
</tr>
<tr>
<td>7</td>
<td>332ah</td>
<td>Me</td>
<td>3-F</td>
<td>(R)-316ah</td>
<td>97</td>
<td>82:18</td>
</tr>
<tr>
<td>8</td>
<td>332ah</td>
<td>Me</td>
<td>3-F</td>
<td>(R)-316ah</td>
<td>&lt;50\textsuperscript{a}</td>
<td>96:4\textsuperscript{a}</td>
</tr>
<tr>
<td>9</td>
<td>332ai</td>
<td>Me</td>
<td>2-OMe</td>
<td>(R)-316ai</td>
<td>83</td>
<td>86:14</td>
</tr>
<tr>
<td>10</td>
<td>332aj</td>
<td>Me</td>
<td>2,3-benzo\textsuperscript{b}</td>
<td>(R)-316aj</td>
<td>95</td>
<td>84:16</td>
</tr>
<tr>
<td>11</td>
<td>332bc</td>
<td>n-Pr</td>
<td>4-Cl</td>
<td>(R)-316bc</td>
<td>91\textsuperscript{c}</td>
<td>94:6</td>
</tr>
<tr>
<td>12</td>
<td>332bd</td>
<td>n-Pr</td>
<td>4-F</td>
<td>(R)-316bd</td>
<td>92\textsuperscript{d}</td>
<td>91:9</td>
</tr>
<tr>
<td>13</td>
<td>332be</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>(R)-316be</td>
<td>93\textsuperscript{d}</td>
<td>95:5</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction was run at 0 °C for 48 h. 50% conversion was determined by \textsuperscript{1}H NMR spectroscopy. \textsuperscript{b}1-naphthyl. \textsuperscript{c}Rearranged at 21 °C for 4-5 days.

\textsuperscript{d}Rearranged at 14 °C for 48 h.

Table 12: (R)-(−)-COP-Cl-catalysed [3,3]-sigmatropic rearrangement of O-allyl thiocarbamates 332.

Overall, para-substituted N-aryl rings gave the best e.r. values (89:11 to 94:6) while ortho- or meta-substituted rings showed decreased enantioselectivity. Notably, the propyl-bearing allylic thiocarbamates all rearranged with excellent enantioselectivities, whatever the substitution pattern of the aromatic ring.

In order to determine whether the lower enantiomeric ratios were due to racemisation of compounds 316 in the longer (22 h instead of 15 h) larger-scale reactions, rearranged thiocarbamate (R)-316ah was resubjected to the rearrangement conditions for 15 to 40 h. Monitoring the e.r. showed no racemisation, indicating that the rearrangement is irreversible. Reaction at a lower temperature (0 °C) gave a better e.r. (96:4), but the reaction reached only half-completion in 48 h.
II.A.3) Enantioselective synthesis starting from secondary allylic alcohols

Reaction of enantiopure secondary allylic alcohols with thiocarbonyldiimidazole under the conditions we developed for the preparation of racemic thiocarbamates 316 (Scheme 109) was expected to furnish the highly enantioenriched analogs, based on the well-established suprafacial nature of [3,3]-sigmatropic rearrangements of similar substrates.\(^{69,121}\)

We first envisaged resolving racemic allylic alcohols 328f and 328g enzymatically.

II.A.3.a) Enzymatic resolutions

Lipases are the most widely used enzymes for regioselective and enantioselective biotransformations, as they are inexpensive, stable and easy to recycle. They are able to catalyse many reversible reactions in both aqueous and non-aqueous media, such as esterification, transesterification, amidation and hydrolysis.\(^{128}\)

Among them, *Candida antarctica* B lipase (CAL-B, also known as Novozym 435\(^\circledR\)) has been widely used,\(^{128,129}\) and has achieved excellent enantioselectivities in the resolution of secondary alcohols, and in particular allylic ones, usually by their acetylation\(^{129h}\) performed with vinyl acetate\(^{128,129f,g}\) or other vinyl esters\(^{128}\) and acyl donors.\(^{129d,e,i}\) Notably, S-ethyl octanethioate 344 has shown high efficiency in the Novozym 435\(^\circledR\)-mediated enzymatic resolutions of cyclohexyl- and phenyl-substituted alcohols 342 and 343a (Scheme 119),\(^{130}\) similar to 328f and 328g, respectively. A more efficient equilibrium displacement, due to the facile evaporation of ethanethiol 347, and higher enantioselectivities were attributed to octanethioate 344 compared to ethyl octanoate.\(^{130a}\)

\[
\begin{align*}
\text{342: } R &= \text{Cy} \\
\text{343a: } R &= \text{Ph} \\
\text{344: } 3 \text{ eq} \\
\text{345: } R &= \text{Cy} \\
\text{346: } R &= \text{Ph} \\
\text{347: } &
\end{align*}
\]

\(39^\circ C, R = \text{Cy}, 4.4 \text{ h} \) 
\(R = \text{Ph}, 2.5 \text{ h} \)

(S)-342: >98% e.e. 
(S)-343a: >98% e.e.

(R)-345: >95% e.e. 
(R)-346: >97% e.e.

\[
\text{Scheme 119: Novozym 435\(^\circledR\)-mediated enzymatic resolutions of alcohols 342 and 343a.}^{130}\]
We consequently decided to try both the analogous \( S \)-ethyl hexanethioate 349 and the most common acetylating agent, vinyl acetate 348, in the Novozym 435\(^{\circledR} \)-mediated enzymatic resolution of allylic alcohol 328f (Scheme 120).

**Scheme 120: Novozym 435\(^{\circledR} \)-mediated enzymatic resolution of allylic alcohol 328f.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th>( ^1H ) NMR</th>
<th>328f: e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>328f</td>
<td>100 mg</td>
<td>5 days</td>
<td>52:48</td>
</tr>
</tbody>
</table>

**Table 13: Novozym 435\(^{\circledR} \)-mediated enzymatic resolution of allylic alcohol 328f.**

However, similar conditions gave no enantioenrichment in our substrate 328f (Table 13); and more importantly, no ester 350 was formed at all, even after several days. It then seemed that the association of this particular substrate with this enzyme, despite being one of the most widely used for the resolution of allylic and other alcohols,\(^{128-130}\) was so unfavourable that optimisation of the conditions was unlikely to give any satisfying result. Therefore, we attempted the enzymatic resolution of the corresponding acetate (\( \pm \))-350a since enantioselective hydrolysis of esters is known as another straightforward route to enantiopure allylic alcohols (Scheme 121).\(^{129h}\)

**Scheme 121: Novozym 435\(^{\circledR} \)-mediated enzymatic resolution of allylic ester 350a.**

Disappointingly, no enantioenrichment of 350a could be detected while monitoring the resolution over 5 days and no alcohol 328f was observed on the \( ^1H \) NMR spectrum. We consequently decided to turn our efforts towards the enzymatic resolution
of propargylic alcohols (which would then be reduced to their allylic analogs), as a large number of examples could be found in the literature,\textsuperscript{132} several of them employing a very similar substrate \textit{334b} (Scheme 122).\textsuperscript{132b,d,e}

\[ \textbf{Scheme 122: Novozym 435\textsuperscript{\textregistered} -mediated enzymatic resolution of propargylic alcohol 334b.} \textsuperscript{132b,d,e} \]

We therefore attempted the enzymatic resolutions of both propargylic alcohols\textsuperscript{114} (±)-\textit{352} (Scheme 123) and (±)-\textit{334a} (Scheme 124).

\[ \textbf{Scheme 123: Novozym 435\textsuperscript{\textregistered} -mediated enzymatic resolution of propargylic alcohol 352.} \]

Regarding \textit{352}, once more, no acetate \textit{353} was formed at all. We had higher hopes for phenyl-substituted propargylic alcohol \textit{334a} (Scheme 124) because of its high similarity with the literature example \textit{334b} shown in Scheme 122,\textsuperscript{132b,d,e} differing only by a methyl instead of a hydrogen on the terminal carbon of the triple bond.

\[ \textbf{Scheme 124: Novozym 435\textsuperscript{\textregistered} -mediated enzymatic resolution of propargylic alcohol 334a.} \]
Alcohol **334a** was recovered in 65:35 e.r. after a lengthy 9-day reaction, under conditions similar to those found in literature\textsuperscript{132b,d,e} (Table 14, entry 1). Moreover, the amount of recovered alcohol was very low, as shown by \textsuperscript{1}H NMR of the crude mixture (1:4.3 alcohol/acetate ratio).

An increased enzyme loading (100 mg) and higher temperature (60 °C) gave **334a** in 81:19 e.r. within half of the previous reaction time (4.5 days, Table 14, entry 2). However, most of the alcohol had been consumed.

We therefore opted to keep the same reaction temperature (60 °C) and to decrease the amount of vinyl acetate **348** to 1.5 eq with the aim of slowing down the rate of acetylation (Table 14, entry 3). It was expected that a combination of both a “high” temperature and a low amount of vinyl acetate would allow a rapid conversion of only one enantiomer of the alcohol. Indeed, after only 24 h, a 1:0.74 alcohol/acetate ratio was

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Time</th>
<th><strong>334a/351a ratio</strong>&lt;sup&gt;a&lt;/sup&gt;</th>
<th><strong>334a</strong>: e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><strong>334a</strong></td>
<td>50 mg</td>
<td>1 h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Novozym 435°</td>
<td>50 mg</td>
<td>44 h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>348</strong></td>
<td>10 eq</td>
<td>5.5 days</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td>5 mL</td>
<td>9 days</td>
<td>1:4.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>55 °C</strong></td>
</tr>
<tr>
<td>2</td>
<td><strong>334a</strong></td>
<td>50 mg</td>
<td>15 h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Novozym 435°</td>
<td>100 mg</td>
<td>40 h</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td><strong>348</strong></td>
<td>10 eq</td>
<td>4.5 days</td>
<td>&lt;5:95</td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td>7 mL</td>
<td></td>
<td><strong>60 °C</strong></td>
</tr>
<tr>
<td>3</td>
<td><strong>334a</strong></td>
<td>50 mg</td>
<td>24 h</td>
<td>1:0.74</td>
</tr>
<tr>
<td></td>
<td>Novozym 435°</td>
<td>50 mg</td>
<td>43 h</td>
<td>1:2.1</td>
</tr>
<tr>
<td></td>
<td><strong>348</strong></td>
<td>1.5 eq</td>
<td>8 mL</td>
<td><strong>60 °C</strong></td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td><strong>334a</strong></td>
<td>50 mg</td>
<td>21 h</td>
<td>1:0.21</td>
</tr>
<tr>
<td></td>
<td>Novozym 435°</td>
<td>50 mg</td>
<td>45 h</td>
<td>1:0.53</td>
</tr>
<tr>
<td></td>
<td><strong>348</strong></td>
<td>1.0 eq</td>
<td>69 h</td>
<td>1:0.90</td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td>8 mL</td>
<td>77 h</td>
<td>1:0.96</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td><strong>40 °C</strong></td>
</tr>
<tr>
<td>5</td>
<td><strong>334a</strong></td>
<td>50 mg</td>
<td>92 h</td>
<td>1:0.81</td>
</tr>
<tr>
<td></td>
<td>Novozym 435°</td>
<td>50 mg</td>
<td>111 h</td>
<td>1:1.05</td>
</tr>
<tr>
<td></td>
<td><strong>348</strong></td>
<td>0.6 eq</td>
<td>8 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hexane</td>
<td></td>
<td></td>
<td><strong>35 °C</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by \textsuperscript{1}H NMR spectroscopy.

**Table 14**: Novozym 435°-mediated enzymatic resolution of propargylic alcohol **334a**.
reached, along with a promising 70:30 e.r. in the alcohol. After 43 h, the ideal 1:1 alcohol/acetate ratio was largely exceeded and the e.r. only slightly improved (80:20). Nevertheless, we had found that a high enantioenrichment in the alcohol could be achieved using a low concentration of vinyl acetate in a non polar solvent (hexane).

It then seemed sensible to combine a smaller concentration of acetylating agent with a slightly diminished temperature, which would hopefully increase the difference of the acetylation rates for each enantiomer.

Bringing the temperature down to 40 °C and using 1.0 eq of vinyl acetate led to the same e.r. (79:21) after a longer reaction time (77 h instead of 43 h) but a very satisfying 1:0.96 alcohol/acetate ratio had been reached, allowing complete optimisation of the yield of the recovered alcohol (Table 14, entry 4).

Following the same reasoning, both the temperature and the concentration of vinyl acetate were further decreased to 35 °C and 0.6 eq respectively. The higher enantiomeric ratio was then achieved (87:13) in 111 h (4 days and 15 h), with a very satisfying 1:1.05 alcohol/acetate ratio (Table 14, entry 9).

Despite the satisfying optimisation of the conditions of the enzymatic resolution of phenyl-substituted propargylic alcohol 334a, the cyclohexyl-bearing analog 352 could not be resolved using this method.

II.A.3.b) Sharpless catalytic asymmetric epoxidation

Considering all failed attempts to resolve allylic alcohol 328f and its propargylic counterpart 352 enzymatically, we opted for kinetic resolution by the Sharpless asymmetric epoxidation of allylic alcohols. This robust method nevertheless suffers from a poor atom economy, as half of the starting material is “lost”.

Fortunately, Sharpless had already described the kinetic resolution of alcohol 328f using his seminal catalytic asymmetric epoxidation reaction (Scheme 125).

![Scheme 125: Sharpless asymmetric epoxidation of 324f](image-url)
Carefully following the same conditions on a larger scale allowed the preparation of enantioenriched allylic alcohol (R)-328f in 99:1 e.r. and 84% yield (Scheme 126). Yield is based on conversion, i.e. calculated following the formula yield = w[(R)-328f]/[conversion•w[(±)-328f]], as reported by Sharpless and co-workers. A further scale-up of the reaction (2.0 g, 13.0 mmol) improved the yield of the recovered alcohol (R)-328f to 92% (645 mg, 65% conversion) and left the e.r. unchanged (99:1).

II.A.3.c) Noyori catalytic asymmetric hydrogenation

In an attempt to develop a more atom-economic method to prepare enantioenriched allylic alcohol 328f, we then envisaged a synthesis via asymmetric reduction of its corresponding enone 358 based on Noyori’s report of the successful ruthenium-catalysed enantioselective hydrogenation of a similar unsaturated ketone 355 (Scheme 127).

Enone (E)-358 was prepared by oxidation of the corresponding commercially available racemic allylic alcohol (E)-328f using manganese dioxide (Scheme 128).

Scheme 126: Sharpless asymmetric epoxidation of 328f in our hands.

Scheme 127: Asymmetric hydrogenation of enone 355 under Noyori’s conditions.
Aiming both to reduce the reaction time and increase the yield, Swern oxidation of 328f was attempted next (Scheme 129).\textsuperscript{138,140}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {OH} node[below=0.5cm] {328f};
  \node at (2,0) {O};
  \node at (4,0) {358};
  \node at (0,0.5) {(±)-(E)-328f};
  \node at (4,0.5) {(E)-358: 58\%};
  \node at (0,-0.5) {1. (COCl)\textsubscript{2}, DMSO, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 30 min, then 328f};
  \node at (0,-1) {2. -78 °C, 1 h};
  \node at (0,-1.5) {3. Et\textsubscript{3}N, -78 °C to rt, 1 h};
\end{tikzpicture}
\end{center}

\textit{Scheme 129: Preparation of enone 358 via Swern oxidation of 328f.}

Although no significant improvement in the yield was achieved, this method allowed a considerable gain of time. Enone (E)-358\textsuperscript{137} was then submitted to asymmetric hydrogenation under conditions similar as those reported by Noyori and co-workers (Scheme 130, Table 15).\textsuperscript{136b}

\begin{center}
\begin{tikzpicture}
  \node at (0,0) {OH} node[below=0.5cm] {328f};
  \node at (2,0) {O};
  \node at (4,0) {358};
  \node at (0,0.5) {(E)-358};
  \node at (4,0.5) {(E,S)-328f};
  \node at (0,-0.5) {(R,R)-356, K\textsubscript{2}CO\textsubscript{3}, H\textsubscript{2}, i-PrOH};
\end{tikzpicture}
\end{center}

\textit{Scheme 130: Asymmetric hydrogenation of 358 by modified Noyori’s conditions.}
<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>(S)-328f: e.r.</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-356</td>
<td>0.5 mol%</td>
<td>-</td>
<td>358/328f 1:0.07</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>0.04 eq</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pressure</td>
<td>10 bar</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rt, 26 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-356</td>
<td>0.5 mol%</td>
<td>86:14</td>
<td>358/328f 0.9:1</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>0.04 eq</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pressure</td>
<td>60 bar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>rt, 52 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-356</td>
<td>0.5 mol%</td>
<td>88:12</td>
<td>358/328f 0.3:1</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>0.02 eq</td>
<td></td>
<td>500 mg scale</td>
</tr>
<tr>
<td></td>
<td>Pressure</td>
<td>60 bar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 °C, 3.5 days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-356</td>
<td>0.05 mol%</td>
<td>62</td>
<td>No 358 remaining</td>
</tr>
<tr>
<td></td>
<td>K₂CO₃</td>
<td>0.02 eq</td>
<td>88:12</td>
<td>1200 mg scale</td>
</tr>
<tr>
<td></td>
<td>Pressure</td>
<td>40 bar</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 °C, 7 days</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 15: Asymmetric hydrogenation of 358 by modified Noyori’s conditions.

Thus, asymmetric hydrogenation of the corresponding enone (E)-358 furnished enantioenriched cyclohexyl-substituted allylic alchol (S)-328f in a considerably improved yield compared to the Sharpless method, but with lower enantioselectivity. By a careful choice of catalyst configurations, both enantiomers of 328f were in our hands.134

We similarly envisaged the asymmetric hydrogenation of phenyl-substituted enone 359 (Scheme 132), in order to obtain enantiopure allylic alcohol (R)-328g in a single step from the racemic precursor.134 Indeed, enzymatic resolution of its propargylic analog 334a led to a good 87:13 e.r. but an additional step was needed for its reduction to (S)-328g (Scheme 131).

![Scheme 131: Preparation of enantioenriched (S)-328g via enzymatic resolution of 334a.](image-url)
Thus, enone (E)-359 was prepared using the same conditions as (E)-358 (Scheme 128), from racemic allylic alcohol 328g (Scheme 132) which we had previously synthesised (Section II.A.1.b, Scheme 107). We observed the Z/E isomerisation of 328g during its oxidation with MnO₂ which furnished (E)-359 as a single isomer, as this was previously reported by other groups. 137a

![Synthesis and asymmetric hydrogenation of enone 359](image)

**Scheme 132: Synthesis and asymmetric hydrogenation of enone 359.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditions</th>
<th>Yield (%)</th>
<th>(R)-328g: e.r.</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-356 0.5 mol% K₂CO₃ 0.02 eq Pressure 60 bar 30 °C, 3.5 days</td>
<td>62</td>
<td>90:10</td>
<td>No 359 remaining</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-356 0.05 mol% K₂CO₃ 0.02 eq Pressure 40 bar 30 °C, 7 days</td>
<td>63</td>
<td>98:2</td>
<td>359/328g 0.16:1</td>
</tr>
</tbody>
</table>

**Table 16: Asymmetric hydrogenation of enone 359.**

Gratifyingly, highly enantioenriched phenyl-substituted allylic alcohol (R)-328g (98:2 e.r., Table 16, entry 2) could be efficiently prepared by asymmetric reduction of the corresponding enone (E)-359 after modification of the conditions developed by Noyori and co-workers. 136b

II.A.3.d) Synthesis of enantioenriched thiocarbamates derived from secondary allylic alcohols 134

Enantioenriched cyclohexyl-substituted allylic alcohol 328f was treated with thiocarboxydiimidazole following the conditions we developed for the synthesis of the racemic thiocarbamates 316. 120 Pleasingly, the [3,3]-sigmatropic rearrangement was found to be completely stereospecific, as reported for related compounds by other groups. 69,121 Thus, various enantioenriched allylic thiocarbamates 316f could be prepared in generally high yields and enantioselectivity (Scheme 133, Table 17).
Scheme 133: Preparation of enantioenriched allylic thiocarbamates 316f.

<table>
<thead>
<tr>
<th>Entry</th>
<th>339f</th>
<th>R³</th>
<th>316f</th>
<th>Yield (%)</th>
<th>316f: e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)</td>
<td>4-Me</td>
<td>(S)-316fa</td>
<td>83</td>
<td>94:6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>(R)</td>
<td>4-Me</td>
<td>(R)-316fa</td>
<td>87</td>
<td>13:87&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>(S)</td>
<td>4-Cl</td>
<td>(S)-316fc</td>
<td>67</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>(S)</td>
<td>4-F</td>
<td>(S)-316fd</td>
<td>93</td>
<td>94:6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>5</td>
<td>(S)</td>
<td>3-OMe</td>
<td>(S)-316fe</td>
<td>89</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>(S)</td>
<td>2-OMe</td>
<td>(S)-316fh</td>
<td>82</td>
<td>94:6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>(R)</td>
<td>2,3-benzo&lt;sup&gt;c&lt;/sup&gt;</td>
<td>(R)-316fi</td>
<td>62</td>
<td>14:86&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>(S)</td>
<td>2-pyridyl&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(S)-316fj</td>
<td>47</td>
<td>94:6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>(S)</td>
<td>6-(NBoc)indole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(S)-316fk</td>
<td>88&lt;sup&gt;e&lt;/sup&gt;</td>
<td>95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>10</td>
<td>(R)</td>
<td>6-(NBoc)indole&lt;sup&gt;d&lt;/sup&gt;</td>
<td>(R)-316fk</td>
<td>74&lt;sup&gt;e&lt;/sup&gt;</td>
<td>14:86&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>From (R)-328f. <sup>b</sup>From (S)-328f. <sup>c</sup>1-naphthyl. <sup>d</sup>See structure in Table 11. <sup>e</sup>Two steps: imidazole displacement by N-methyl-1H-indol-6-amine 329m and N-Boc protection.

Table 17: Preparation of enantioenriched allylic thiocarbamates 316f.

Following the same route, enantioenriched phenyl-substituted thiocarbamates (R)-316g were prepared from allylic alcohol (E,R)-328g (Scheme 134, Table 18). However, with these substrates, we observed some loss of enantioenrichment, presumably due to formation of a stabilised phenylallyl cation during the in situ “sigmatropic” rearrangement.
Scheme 134: Preparation of enantioenriched allylic thiocarbamates 316g.

<table>
<thead>
<tr>
<th>Entry</th>
<th>339g</th>
<th>R^3</th>
<th>316g</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-339gc</td>
<td>3-OMe</td>
<td>(R)-316gc</td>
<td>61</td>
<td>83:17</td>
</tr>
<tr>
<td>2</td>
<td>(R)-339ge</td>
<td>2-OMe</td>
<td>(R)-316ge</td>
<td>71</td>
<td>83:17</td>
</tr>
</tbody>
</table>

Table 18: Preparation of enantioenriched allylic thiocarbamates 316g.

II.B) N to C aryl migrations in lithiated allylic thiocarbamates\(^{126,134}\)

II.B.1) Racemic substrates

II.B.1.a) Substrates with an unsubstituted allylic double bond\(^{126}\)

II.B.1.a.i) Choice of base

Following standard conditions developed within the group for the lithiation of the related urea series,\(^99\) s-BuLi was first tried in the lithiation of allylic thiocarbamate 316af. However, the desired rearranged product 318af could not be isolated. Instead, compound 361, presumably arising from carbolithiation followed by cleavage of the thiocarbamate moiety in 360, was formed (Scheme 135).
Scheme 135: Carbolithiation and thiocarbamate cleavage when using s-BuLi.

Consequently, the less nucleophilic base LDA, which had proved successful in the rearrangement of lithiated benzylic thiocarbamates, was used instead of s-BuLi (Scheme 136).

II.B.1.a.ii) Influence of the additive

We then investigated the effect of adding DMPU or LiCl as they had allowed improved yields in the rearrangement of benzylic and allylic ureas, respectively.

Scheme 136: Influence of LiCl in the aryl migration of 316a.
<table>
<thead>
<tr>
<th>Entry</th>
<th>316a</th>
<th>R⁴</th>
<th>Conditions</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316af</td>
<td>3-OMe</td>
<td>DMPU (50 vol%) -78 °C, 2 h</td>
<td>318af</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>316af</td>
<td>3-OMe</td>
<td>-60 °C, 2 h</td>
<td>318af</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>316af</td>
<td>3-OMe</td>
<td>LiCl, -60 °C, 2 h</td>
<td>318af</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>316ai</td>
<td>2-OMe</td>
<td>DMPU (50 vol%) -78 °C, 2.5 h</td>
<td>318ai</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>316ai</td>
<td>2-OMe</td>
<td>LiCl, -60 °C, 4 h</td>
<td>318ai</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>316aj</td>
<td>2,3-benzo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>-78 °C, 2 h</td>
<td>318aj</td>
<td>68</td>
</tr>
<tr>
<td>7</td>
<td>316aj</td>
<td>2,3-benzo&lt;sup&gt;a&lt;/sup&gt;</td>
<td>LiCl, -78 °C, 2.5 h</td>
<td>318aj</td>
<td>&gt;99</td>
</tr>
<tr>
<td>8</td>
<td>316ae</td>
<td>4-F</td>
<td>-60 °C, 2.5 h</td>
<td>318ae</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>316ae</td>
<td>4-F</td>
<td>LiCl, -60 °C, 2 h</td>
<td>318ae</td>
<td>36</td>
</tr>
<tr>
<td>10</td>
<td>316ah</td>
<td>3-F</td>
<td>-60 °C, 2.5 h</td>
<td>318ah</td>
<td>66</td>
</tr>
<tr>
<td>11</td>
<td>316ah</td>
<td>3-F</td>
<td>LiCl, -60 °C, 2.5 h</td>
<td>318ah</td>
<td>68</td>
</tr>
</tbody>
</table>

<sup>a</sup>1-naphthyl.

**Table 19: Influence of LiCl in the aryl migration of 316a.**

Although no carbolithiation occurred, yields were poor in the presence of DMPU (Table 19, entries 1, 4). Pleasingly, they were improved considerably by replacing DMPU with LiCl (Table 19, entries 3, 5, 7), which had also been beneficial in the carbamate<sup>106</sup> and the N-allyl urea<sup>103</sup> series. Moreover, DMPU has been known to favour racemisation in the rearrangement of enantioenriched benzylic organolithiums<sup>108</sup> and led to lower e.r.’s in the carbamates<sup>107</sup> and N-allyl ureas.<sup>103</sup> Thus, this exchange of additive should also be an asset in the enantioselective version of the aryl migration.

Surprisingly, the opposite effect was observed in the aryl migration of the para-fluorophenyl ring (Table 19, entries 8-9) while no difference could be detected in the case of the meta-fluorophenyl ring (entries 10-11).

**II.B.1.a.iii) Nature of the migrating ring**

Pleasingly, both electron-deficient and electron-rich rings, including heteroaromatics, substituted in the ortho, meta and para positions migrated successfully (Scheme 137, Table 20). Rearrangement proceeded regiospecifically, as the substitution pattern of the ring was conserved, demonstrating nucleophilic attack at the ipso carbon.<sup>99</sup>
Scheme 137: Influence of the substitution pattern of the migrating aryl ring in 316a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>316a</th>
<th>R^3</th>
<th>Conditions</th>
<th>318a</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316aa</td>
<td>H</td>
<td>-78 °C, 1 h</td>
<td>318aa</td>
<td>68</td>
</tr>
<tr>
<td>2</td>
<td>316ab</td>
<td>4-Me</td>
<td>LiCl, -78 to -60 °C, 2 h</td>
<td>318ab</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>316ad</td>
<td>4-Cl</td>
<td>-78 °C, 3 h</td>
<td>318ad</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>316ag</td>
<td>3-Cl</td>
<td>-78 °C, 2 h</td>
<td>318ag</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>316al</td>
<td>2-pyridyl^b</td>
<td>LiCl, -78 °C, 2 h</td>
<td>318al</td>
<td>54</td>
</tr>
</tbody>
</table>

^aSee Structure in Table 11.

Table 20: Influence of the substitution pattern of the migrating aryl ring in 316a.

Although nucleophilic attack on aromatic rings bearing anion-stabilising groups was not unprecedented,\(^\text{100}\) the migration of electron-rich rings is remarkable. Namely, the tolyl, naphthyl and methoxyphenyl rings all bear substituents that increase their electron density and consequently deactivate them towards nucleophilic attack.\(^\text{16}\) Most deactivated are the para-tolyl (no withdrawing effect by induction) and the para-methoxyphenyl (high electron-density at the attacked ipso carbon, due to delocalisation of the oxygen lone pairs).\(^\text{16}\) Indeed, the migration of these rings displayed the lowest yields: the para-methoxyphenyl ring did not migrate at all, neither did the 2,4,6-trimethylphenyl ring (steric effects must have also played an important role here), and migration of the para-tolyl gave a moderate 56% yield (Table 20, entry 2).

In sharp contrast, rearrangement of 316aj, bearing the 1-naphthyl ring, proceeded in almost quantitative yield (Table 19, entry 7). Despite this ring being electron-rich, the resulting anion is stabilised by delocalisation of the negative charge, leading to a considerable increase in the yield compared to the para-tolyl and para-methoxyphenyl rings.

On the contrary, when the methoxy group sits in meta position, the electron density at the ipso carbon is lower,\(^\text{16}\) which led to a high yield (86%) in the rearrangement of 316af (Table 19, entry 3).
In the case of the ortho-methoxyphenyl ring, although delocalisation of the oxygen lone pairs is expected to increase the electron density at the ipso carbon, this effect is counterbalanced by the proximity of the electronegative oxygen atom, withdrawing electron density by induction. This is clearly shown by the high yield (74%) observed for the rearrangement of 316ai (Table 19, entry 5).

Substrates 316ad,e,g,h, bearing halogen-substituted rings, rearranged in good to excellent yields, as expected from electron-deficient rings. Although chlorine and fluorine are π-donating, like the methoxy group, their increased electronegativity makes them good electron-withdrawing substituents by induction. This effect was clearly highlighted by the almost quantitative yields obtained for the migration of para halogen-substituted rings (Table 19, entry 8; Table 20, entry 3).

However, the lower yields (68-73%) observed for the rearrangement of 316ag,h bearing the halogen atom at the meta position, are surprising, since π-donating groups do not donate in meta (Table 19, entry 11; Table 20, entry 4). Thus, the electron density at the ipso carbon is expected to be lower than in the para-rings, an effect that is reinforced by the halogen atom being closer to the ipso carbon in the meta-rings, which should decrease the electron density further by inductive effect. A possible explanation to these unexpected results lies in the presence of side reactions, such as ortholithiation forming benzyynes. Nevertheless, even if lower than for the para-substituted rings, the yields remained rather good.

Rearrangement of 316aa, bearing an unsubstituted phenyl ring, similarly proceeded in lower yield (68%, Table 20, entry 1), suggesting that the absence of a substituent which may activate the ipso position, such as electron-withdrawing substituents at the para position, was detrimental to the aryl migration.

Finally, migration of the small, electron-deficient 2-pyridyl ring was expected to occur in high yield, but disappointingly resulted in a moderate 54% yield (Table 20, entry 5). We assumed this was due to the different reactivity of the heterocyclic ring, possibly leading to by-products.

II.B.1.a.iv) Influence of the substitution at C_{α}

Bulkier substituents at the carbon α to sulfur unsurprisingly led to slower aryl migrations, requiring the systematic addition of lithium chloride and generally higher
temperatures to improve yields in rearranged 318b,c. Nevertheless, despite lower yields than those obtained in thiocarbamates 318a, migration also took place with electronically and sterically varied aryl rings (Scheme 138, Table 21).

Scheme 138: Influence of the substituent at C\(\alpha\).

<table>
<thead>
<tr>
<th>Entry</th>
<th>316</th>
<th>R(^2)</th>
<th>R(^3)</th>
<th>Conditions</th>
<th>318</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316ba</td>
<td>n-Pr</td>
<td>4-Me</td>
<td>-78 °C, 2 h</td>
<td>318ba</td>
<td>0(^a)</td>
</tr>
<tr>
<td>2</td>
<td>316ba</td>
<td>n-Pr</td>
<td>4-Me</td>
<td>-78 °C, 2.5 h</td>
<td>318ba</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>316ba</td>
<td>n-Pr</td>
<td>4-Me</td>
<td>-78 to -60 °C, 1 h</td>
<td>318ba</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>316bc</td>
<td>n-Pr</td>
<td>4-Cl</td>
<td>-78 to -60 °C, 1 h</td>
<td>318bc</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>316bd</td>
<td>n-Pr</td>
<td>4-F</td>
<td>-78 °C, 3 h</td>
<td>318bd</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>316be</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>-78 to -45 °C, 4 h</td>
<td>318be</td>
<td>33</td>
</tr>
<tr>
<td>7</td>
<td>316be</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>-78 to -45 °C, 4 h</td>
<td>319be</td>
<td>56(^b)</td>
</tr>
<tr>
<td>8</td>
<td>316bf</td>
<td>n-Pr</td>
<td>2-OMe</td>
<td>-78 to -45 °C, 2 h</td>
<td>318bf</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>316bf</td>
<td>n-Pr</td>
<td>2-OMe</td>
<td>-78 to -40 °C, 5 h</td>
<td>319bf</td>
<td>32(^b)</td>
</tr>
<tr>
<td>10</td>
<td>316cb</td>
<td>i-Pr</td>
<td>4-Cl</td>
<td>-78 °C, 3 h</td>
<td>318cb</td>
<td>27</td>
</tr>
</tbody>
</table>

\(^a\)No LiCl was used. \(^b\)The isolated product is the free thiol.

Table 21: Influence of the substituent at C\(\alpha\).

The necessity of both the addition of LiCl and warming the reaction mixture is obvious in the example of the migration of the para-tolyl ring, which occurred at -78 °C only if LiCl was used (Table 21, entries 2-3), but displayed a better yield when the temperature was raised to -60 °C (entry 3). The migration of the more hindered ortho-methoxyphenyl ring required the reaction to be carried out at -40 °C in order to get an acceptable yield (Table 21, entries 8-9). Surprisingly, this triggered the partial in situ cleavage of the thiocarbamate function in the rearranged product 318bf (entry 9). The same phenomenon was observed with the meta-chlorophenyl ring, for which complete deprotection was observed (Table 21, entry 7). The corresponding tertiary thiols 319be and 319bf were generated in 32% and 56% yields, respectively, and were the first tertiary allylic thiols synthesised via our aryl transfer methodology, in an interesting unprecedented one-pot procedure.
The iso-propyl group at the α position turned out to be too bulky to allow the rearrangement to occur in satisfying yields. The para-chlorophenyl ring, a ring which migrates easily in other substrates, led to only poor yields although many different conditions were tested (maximum 27% yield, Table 21, entry 10).

Finally, attempts to migrate a para-tolyl or para-chlorophenyl ring in propenyl-substituted thiocarbamates 316ca,c turned out to be unsuccessful: only starting material was recovered using LDA at -78 °C, while some decomposition occurred at -60 °C with LiCl. This was presumably due to delocalisation of the negative charge resulting in a very unreactive carbanion, prone to side reactions.

II.B.1.b) Effect of substitution of the allylic moiety

II.B.1.b.i) Double substitution

We initially found that when both olefinic carbons bore a methyl substituent, the rearrangement did not proceed as smoothly as in unsubstituted substrates 316a. Standard conditions applied to substrate 316ha produced the rearranged thiocarbamate 318ha in a low 11% conversion (product/sm ratio determined by 1H NMR, Scheme 139).

![Scheme 139: Aryl migration in 316ha bearing a doubly-substituted allylic double bond.](image)

II.B.1.b.ii) Single substitution

Gratifyingly, a single methyl group on the terminal carbon of the allylic moiety allowed interesting improvement in the rearrangement of some lithiated allylic thiocarbamates (Scheme 140, Table 22).
<table>
<thead>
<tr>
<th>Entry</th>
<th>316e</th>
<th>$R^3$</th>
<th>Conditions</th>
<th>318e</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316ea</td>
<td>4-Me</td>
<td>-78 to -60 °C, 2 h</td>
<td>318ea</td>
<td>78</td>
</tr>
<tr>
<td>2</td>
<td>316eb</td>
<td>4-Cl</td>
<td>-78 to -60 °C, 2 h</td>
<td>318eb</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>316ed</td>
<td>2-OMe</td>
<td>-78 to -70 °C, 2 h</td>
<td>318ed</td>
<td>74</td>
</tr>
</tbody>
</table>

Table 22: Influence of a methyl group on the terminal carbon of the double bond.

The yield of the migration of the electron-rich para-tolyl ring was considerably increased compared to the unsubstituted substrate 316aa (from 56% to 78%, Table 22, entry 1) while the ortho-methoxyphenyl ring migrated at a lower temperature and within a shorter time (-70 °C, 2 h instead of -60 °C, 4 h, entry 3). No difference was noted in the $N$ to $C$ transfer of an easily-migrating ring, such as the para-chlorophenyl ring (Table 22, entry 2).

A bulkier alkyl group, such as cyclohexyl, was found to have a similar effect on the yields (Scheme 141). Namely, migration of the para-fluorophenyl ring proceeded in much improved yields in methyl- and cyclohexyl-substituted substrates 316ec and 316fd (Table 23, entries 1-3). The yield for the rearrangement of cyclohexyl-substituted 316fh was also far superior to that of unsubstituted 316ai (Table 23, entries 4, 6).

Scheme 141: Influence of a substituent on the terminal carbon of the double bond.

<table>
<thead>
<tr>
<th>Entry</th>
<th>316</th>
<th>$R^1$</th>
<th>$R^3$</th>
<th>Conditions</th>
<th>318</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316ae</td>
<td>H</td>
<td>4-F</td>
<td>-78 to -60 °C, 2 h</td>
<td>318ae</td>
<td>36</td>
</tr>
<tr>
<td>2</td>
<td>316ec</td>
<td>Me</td>
<td>4-F</td>
<td>-78 to -70 °C, 2 h</td>
<td>318ec</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>316fd</td>
<td>Cy</td>
<td>4-F</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318fd</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>316ai</td>
<td>H</td>
<td>2-OMe</td>
<td>-78 to -60 °C, 4 h</td>
<td>318ai</td>
<td>74</td>
</tr>
<tr>
<td>5</td>
<td>316ed</td>
<td>Me</td>
<td>2-OMe</td>
<td>-78 to -70 °C, 2 h</td>
<td>318ed</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>316fh</td>
<td>Cy</td>
<td>2-OMe</td>
<td>-78 to -60 °C, 3.5 h</td>
<td>318fh</td>
<td>&gt;99</td>
</tr>
</tbody>
</table>

Table 23: Influence of a substituent on the terminal carbon of the double bond.

A detailed investigation of the aryl migration in cyclohexyl-substituted thiocarbamates 316f (Scheme 142) revealed that the reaction proceeded with a wide
variety of aryl rings, including heteroaryls, in good to excellent yields (56 to >99% yield, Table 24).  

![Chemical structure](image)

Scheme 142: Influence of a cyclohexyl group on the terminal carbon of the double bond.

<table>
<thead>
<tr>
<th>Entry</th>
<th>316f</th>
<th>R³</th>
<th>Conditions</th>
<th>318f</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316fa</td>
<td>4-Me</td>
<td>-78 to -60 °C, 3 h</td>
<td>318fa</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>316fb</td>
<td>4-OMe</td>
<td>-78 to -40 °C, 1 h</td>
<td>318fb</td>
<td>24</td>
</tr>
<tr>
<td>3</td>
<td>316fc</td>
<td>4-Cl</td>
<td>-78 to -60 °C, 1.5 h</td>
<td>318fc</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>316fc</td>
<td>4-Cl</td>
<td>-78 to -50 °C, 1.5 h</td>
<td>318fc</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>316fe</td>
<td>3-OMe</td>
<td>-78 to -60 °C, 3 h</td>
<td>318fe</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>316ff</td>
<td>3-Cl</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318ff</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>316ff</td>
<td>3-Cl</td>
<td>-78 to -50 °C, 1.5 h</td>
<td>318ff</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>316ff</td>
<td>3-Cl</td>
<td>-78 to -60 °C, 4 h</td>
<td>318ff</td>
<td>56</td>
</tr>
<tr>
<td>9</td>
<td>316fg</td>
<td>3-F</td>
<td>-78 to -60 °C, 4 h</td>
<td>318fg</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>316fg</td>
<td>3-F</td>
<td>-78 to -40 °C, 1.5 h</td>
<td>318fg</td>
<td>69</td>
</tr>
<tr>
<td>11</td>
<td>316fi</td>
<td>2,3-benzo</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318fi</td>
<td>90</td>
</tr>
<tr>
<td>12</td>
<td>316fj</td>
<td>2-pyridyl</td>
<td>-78°C, 2 h</td>
<td>318fj</td>
<td>42</td>
</tr>
<tr>
<td>13</td>
<td>316fk</td>
<td>6-(NBoc)indole</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318fk</td>
<td>43</td>
</tr>
</tbody>
</table>

*aReaction quenched with MeOH followed by saturated aqueous NH₄Cl. **318f/316f 1:2.5, determined by ¹H NMR. ***318f/316f 1:4.5, determined by ¹H NMR. ^Starting material 316fg recovered. "1-naphthyl." See structure in Table 11 and Figure 35.

Table 24: Influence of a cyclohexyl group on the terminal carbon of the double bond.

However, the rearrangement of lithiated cyclohexyl-substituted allylic thiocarbamates generally required more forcing conditions than that of unsubstituted substrates 316a (Table 19, Table 20). In addition to the systematic use of LiCl, higher temperatures (-50 °C instead of -78 °C, for the para-chlorophenyl ring, Table 24, entries 3-4; -40 °C instead of -60 °C, for the meta-fluorophenyl ring, entries 9-10) and/or longer reaction times (4 h instead of 2 h, for the meta-chlorophenyl ring, entries 6-8) were needed to achieve satisfying yields.
Notably, the substrate bearing a para-tolyl ring, which only migrated in moderate yields in the other series, rearranged in excellent yield, using the same temperature and only a slightly longer time (3 h instead of 2 h, Table 24, entry 1).

The migration of the para-methoxyphenyl ring, although low-yielding due to partial decomposition caused by the higher required temperature (24%, -40 °C, entry 2), constitutes a remarkable achievement since this group never migrated in the unsubstituted substrates 316a, whatever the base, the temperature, and the additive. The quenching solvent was changed to a less acidic one (MeOH) and a basic work up was used in an attempt to trigger *in situ* cleavage of the thiocarbamate function since we had previously observed decomposition of the rearranged product during purification by column chromatography. We hoped that the free thiol would be more stable. However, *in situ* deprotection was unsuccessful in this case, leading to isolation of the rearranged thiocarbamate 318fb.

Another surprising, and remarkable result, was the successful migration of the Boc-indolyl ring (43%, Table 24, entry 13). In comparison, migration of the 2-pyridyl ring, a heteroaryl ring as well, but much smaller and electron-deficient, gave a similar yield (42%, Table 24, entry 12). The Boc-indolyl ring is much more electron-rich than pyridyl due to the contribution of the nitrogen lone pair to the sextet, and in contrast with the naphthyl ring (90%, Table 24, entry 11), the anion resulting from nucleophilic attack of the ring is not very stabilised.

Thus, it seemed that the cyclohexyl group may render the intermediate organolithium more reactive via an electron-donating effect, allowing the migration of some electron-rich and/or hindered rings (Table 24, entries 2, 13), in excellent yields for some of them (Table 23, entry 6; Table 24, entries 1, 11) while its bulkiness may be responsible for slower rates, as showed by the need for higher temperatures and/or longer reaction times.

The cyclohexyl substituent was then replaced by a phenyl ring in order to get a deeper insight into the effect of both the electronics and the sterics of the allylic substitution pattern (*Scheme 143*).

![Scheme 143: Influence of a phenyl group on the terminal carbon of the double bond.](image-url)
### Table 25: Influence of a phenyl group on the terminal carbon of the double bond.

<table>
<thead>
<tr>
<th>Entry</th>
<th>316g</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Conditions</th>
<th>318g</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>316ga</td>
<td>4-Cl</td>
<td>-78 to -60 °C, 2 h</td>
<td>318ga</td>
<td>40&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>316ga</td>
<td>4-Cl</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318ga</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>316gb</td>
<td>4-F</td>
<td>-78 to -60 °C, 2.5 h</td>
<td>318gb</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>316gb</td>
<td>4-F</td>
<td>-78 to -40 °C, 1 h</td>
<td>318gb</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>316gc</td>
<td>3-OMe</td>
<td>-78 to -60 °C, 2 h</td>
<td>318gc</td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td>316gc</td>
<td>3-OMe</td>
<td>-78 to -60 °C, 2 h</td>
<td>318gc</td>
<td>55&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>316gd</td>
<td>3-Cl</td>
<td>-78 to -60 °C, 2 h</td>
<td>318gd</td>
<td>54&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>8</td>
<td>316ge</td>
<td>2-OMe</td>
<td>-78 to -60 °C, 3 h</td>
<td>318ge</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>316ge</td>
<td>2-OMe</td>
<td>-78 to -40 °C, 1 h</td>
<td>318ge</td>
<td>0&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>No LiCl added.

The rearrangement of cinnamyl thiocarbamates 316g was undoubtedly the most difficult of the whole series for several rings could not be migrated at all (Table 25, entries 3-4, 8-9). This confirmed that the electronics, rather than the sterics, around the double bond, play a crucial role in the reactivity of the lithiated allylic thiocarbamates 317.

Indeed, the flat phenyl ring causes less steric hindrance than a cyclohexyl substituent, which may facilitate migration of a substituent at the carbanionic position, but considering the failed or disappointing attempts of aryl migration in cinammyl thiocarbamates, it is obvious that the electronics must play a predominant role. Namely, conjugation of the phenyl substituent and the allylic double bond may deactivate the intermediate organolithium via delocalisation of the negative charge, rendering the nucleophilic attack of the aromatic distal ring more difficult.

We also observed the same trend with regard to the ease of migration, that is, the para-chloro-, meta-chloro- and meta-methoxyphenyl rings are more easily transferred than the para-tolyl or the ortho-methoxyphenyl rings.

The addition of lithium chloride was again found to have opposite effects depending on the substrate: while it increased the yield in the migration of the para-chlorophenyl ring (Table 25, entries 1-2), it diminished the yield in the case of the meta-methoxyphenyl ring (entries 5-6). Unfortunately, no logical reason for the addition of LiCl emerged.
Overall, the methodology allowed the preparation of tertiary allylic thiocarbamates bearing various substituents \( \alpha \) to sulfur and at the terminal carbon of the double bond. A wide range of aryl rings – electron-rich or electron-deficient, hindered and heteroaryl – usually migrated in good to excellent yields (Figure 29, Table 26).

![Figure 29: Cores of the racemic tertiary allylic thiocarbamates 318.](image)

<table>
<thead>
<tr>
<th>Core</th>
<th>( R^3 ): 318/319, yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>318a</td>
<td>H: 318aa 68</td>
</tr>
<tr>
<td></td>
<td>3-OME: 318af 86</td>
</tr>
<tr>
<td></td>
<td>2,3-benzo: (^a) 318aj 99</td>
</tr>
<tr>
<td>318b</td>
<td>4-Me: 318ba 44</td>
</tr>
<tr>
<td></td>
<td>2-OME: 318bf 20</td>
</tr>
<tr>
<td>319b</td>
<td>3-Cl: 319be 56</td>
</tr>
<tr>
<td>318d</td>
<td>4-Cl: 318db 27</td>
</tr>
<tr>
<td>318e</td>
<td>4-Me: 318ea 78</td>
</tr>
<tr>
<td></td>
<td>2,3-benzo: (^a) 318fi 98</td>
</tr>
<tr>
<td>318f</td>
<td>4-Cl: 318ga 67</td>
</tr>
</tbody>
</table>

\(^a\)1-naphthyl. \(^b\)See structure in Table 11 and in Figure 35.

**Table 26: Yields of tertiary allylic thiocarbamates 318 and thiols 319.**
II.B.2) Proposed mechanism and structure of the intermediate organolithium

II.B.2.a) Proposed mechanism

Although each system requires its own detailed investigation,\textsuperscript{100} aryl migration in benzylic\textsuperscript{108} and allylic\textsuperscript{144} thiocarbamates being retentive, its mechanistic pathway is likely to be similar to that determined in ureas, in contrast with that of carbamates which rearrange with inversion.\textsuperscript{106,107}

Thus, the mechanism we propose for the aryl transfer rearrangement in lithiated allylic thiocarbamates involves direct lithiation of the allylic moiety in substrates 316 to form α-thioallyllithiums 317. A “pre-lithiation complex” L arising from initial coordination of the LDA lithium to the carbonyl oxygen as shown in carbamates,\textsuperscript{107,145} may also form (Scheme 144).

![Scheme 144: Proposed mechanism for the rearrangement of allylic thiocarbamates 316.](attachment:image.png)

The allyllithium system in intermediates 317 and M was represented as a delocalised one based on computational calculations showing that the $\eta^3$-bridged structure was more stabilising.\textsuperscript{80,81} However, two $\eta^1$-species could also be in fast equilibrium, with the lithium cation being closer to C\textsubscript{α} on average,\textsuperscript{81} in agreement with the known ability of sulfur to stabilise and localise the negative charge on the α-carbon.\textsuperscript{146}

As typically reported for similar systems, Li-O coordination is likely to be present in lithiated intermediate 317.\textsuperscript{69,77,78,81}

Subsequent C-S rotation leads to the reactive conformation M, bringing the anionic centre closer to the migrating ring. Movement of the solvated cation Li\textsuperscript{+} away...
from the carbanionic centre initiates the rearrangement. In benzylic ureas, Li$^+$ was determined to sit between the two aromatic rings in the transition state leading to retention. It does not seem unreasonable to envisage a similar allyl/phenyl stacked structure in intermediate M.

The fact that our lithiated substrates 317 only underwent $\alpha$-aryl migration ($\gamma$-arylation has never been observed) supports the assumption of a strongly $\alpha$-localised carbanion. Thus, we think it very probable that the nucleophilic attack at the ipso carbon of the aromatic ring is initiated by an organolithium resembling N.

Then, the N to C aryl transfer could go via a transient spirocyclic intermediate O, which may not be observed depending on the conditions, as found in ureas. Ring opening, requiring coordination of lithium to the carbonyl oxygen, completes the 1,4-aryl migration process to form compound P.

II.B.2.b) NMR investigation on $\alpha$-thioallyllithium 317ac

II.B.2.b.i) NMR data for the non-lithiated substrate 316ac

![NMR spectrum of allylic thiocarbamate 316ac at -68 °C.](image)

Figure 30: $^1$H NMR spectrum of allylic thiocarbamate 316ac at -68 °C.
Table 27: Data for $^1$H NMR spectrum of allylic thiocarbamate 316ac at -68 °C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>$^1$H shift (ppm)</th>
<th>Multiplicity (integration)</th>
<th>$J$ (Hz)</th>
<th>$H$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.25</td>
<td>d (2)</td>
<td>8.8</td>
<td>8, 12</td>
</tr>
<tr>
<td>2</td>
<td>6.98</td>
<td>d (2)</td>
<td>8.8</td>
<td>9, 11</td>
</tr>
<tr>
<td>3</td>
<td>5.84</td>
<td>ddd (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.12</td>
<td>dd (1)</td>
<td>17.0, 10.3, 6.7</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>4.97</td>
<td>dd (1)</td>
<td>10.3, 1.0</td>
<td>4</td>
</tr>
<tr>
<td>6</td>
<td>3.98</td>
<td>qn (1)</td>
<td>6.7</td>
<td>2</td>
</tr>
<tr>
<td>7</td>
<td>3.80</td>
<td>s (3)</td>
<td></td>
<td>13</td>
</tr>
<tr>
<td>8</td>
<td>3.22</td>
<td>s (3)</td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>1.29</td>
<td>d (3)</td>
<td>6.7</td>
<td>1</td>
</tr>
<tr>
<td>Entry</td>
<td>$^{13}$C shift (ppm)</td>
<td>C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------</td>
<td>----------------------</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>167.9</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>160.8</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>140.6</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>135.2</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>131.3</td>
<td>8, 12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>115.4</td>
<td>9, 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>114.8</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>55.9</td>
<td>13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>43.2</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>38.4</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>20.0</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 28: Data for $^{13}$C NMR spectrum of allylic thiocarbamate 316ac at -68 °C.

II.B.2.b.ii) NMR data for lithiated 317ac

Figure 32: $^1$H NMR spectrum of lithiated allylic thiocarbamate 317ac at -60 °C.
The main evidence for formation of the allylithium 317ac was disappearance of the quartet at 3.98 ppm in 317ac, confirming deprotonation of H-2 (Figure 32).

Secondly, the signal for H-3 turned from a ddd in 316ac to a dd in 317ac, indicating it was then coupling with only two protons, rather than three, protons (Figure 30, Figure 32). Moreover, its chemical shift had not changed significantly (from 5.84 ppm to 6.09 ppm), in agreement with the literature,\textsuperscript{147} which reports $^1$H chemical shifts around 6 ppm for the middle hydrogen of alkylallyl carbanions.

Finally, signals for both terminal allylic hydrogens had considerably shifted upfield, from 5.12 and 4.97 ppm in 316ac to 2.75 and 2.59 ppm in 317ac. This was consistent with the formation of a delocalised anion resulting in a considerably increased negative charge on the terminal allylic carbon.

The coupling constants measured for these three signals in 317ac are consistent with them coupling together (Table 29). Similar values have been reported for alkylallyl carbanions.\textsuperscript{147}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Shift (ppm)</th>
<th>Multiplicity</th>
<th>Integration</th>
<th>Coupling constant (Hz)</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.09</td>
<td>dd</td>
<td>1</td>
<td>16.0, 9.5</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>2.75</td>
<td>bd</td>
<td>0.65</td>
<td>10.0</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2.59</td>
<td>bd</td>
<td>0.81</td>
<td>15.5</td>
<td>4'</td>
</tr>
</tbody>
</table>

Table 29: $^1$H NMR data for lithiated allylic thiocarbamate 317ac at -60 °C.

The signals for the allylic system in 317ac were accompanied by two sharp doublets in the aromatic region, with similar chemical shifts (7.20/6.90 ppm, Figure 32) compared with 316ac (7.25/6.98 ppm, Figure 30).

In the $^1$H NMR spectrum for 317ac, we also observed another set of broader signals (Table 30), in a 1:1 ratio (Figure 32).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Shift (ppm)</th>
<th>Multiplicity</th>
<th>Integration</th>
<th>Coupling constant (Hz)</th>
<th>H</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.06-6.79</td>
<td>m</td>
<td>-</td>
<td>-</td>
<td>H_{Ar}</td>
</tr>
<tr>
<td>2</td>
<td>5.71</td>
<td>dd</td>
<td>1</td>
<td>17.0, 10.5</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3.94</td>
<td>bd</td>
<td>1.3</td>
<td>17.4</td>
<td></td>
</tr>
</tbody>
</table>

Table 30: $^1$H NMR data for lithiated allylic thiocarbamate 317ac at -60 °C.
We initially thought that this resulted from formation of allyllithium 317ac as an E/Z mixture (Figure 33), but this was not in accordance with the $^{13}$C NMR spectrum, showing no similar double set of peaks (Figure 34).

**Figure 33**: E- and Z-isomers of allyllithium 317ac.

Furthermore, it seems more likely that the allyllithium possesses the Z geometry, as revealed by (carbo)lithiation/reprotonation experiments in allylic thiocarbamates$^{8b}$ and N-allyl-$N'$-ureas$^{103}$ previously reported within the group. Moreover, the broader aspect of this set of peaks, in particular in the aromatic region, suggests a rather different – and more complicated – structure, possibly including metalation of the phenyl ring. Due to large solvent and base peaks, we were unable to identify further this second compound.

Comparison of the $^{13}$C NMR spectra for non-lithiated 316ac and lithiated 317ac brought additional information (Figure 31, Figure 34, Table 31).

**Figure 34**: $^{13}$C NMR spectrum for lithiated allylic thiocarbamate 317ac at -60 °C.


<table>
<thead>
<tr>
<th>Entry</th>
<th>316ac: $^{13}$C shift (ppm)</th>
<th>313ac: $^{13}$C shift (ppm)</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>167.9</td>
<td>186.1</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>160.8</td>
<td>159.9</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>140.6</td>
<td>147.8</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>135.2</td>
<td>136.4</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>131.3</td>
<td>130.2</td>
<td>8, 12</td>
</tr>
<tr>
<td>6</td>
<td>115.4</td>
<td>114.9</td>
<td>9, 11</td>
</tr>
<tr>
<td>7</td>
<td>114.8</td>
<td>55.8</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 31: Comparison of $^{13}$C NMR data in allylic thiocarbamate 316ac and lithiated allylic thiocarbamate 317ac.

The carbonyl peak had significantly shifted from 167.9 ppm in 316ac to 186.1 ppm in 317ac (Table 31), confirming coordination of the carbonyl oxygen with the lithium atom, which rendered the carbon more deshielded.

The chemical shift of C-3 did not vary significantly, slightly increasing to 147.8 ppm in 317ac (Table 31), a similar value to those reported in the literature for the middle carbon of the allyllithium system.\[80d,f,j,k,81,147\]

Moreover, comparing the spectra before and after lithiation clearly showed that one carbon had considerably shifted upfield from the 110-160 ppm region (Table 31). We assumed the “missing carbon” was C-4, due to the disappearance of the localised double bond between C-3 and C-4. Based on literature precedent,\[80d,e,f,k,81\] this carbon was then expected to give a peak around 50-65 ppm, which is very likely to be that observed at 55.8 ppm, given its similar height as those in the 110-190 ppm region.

**II.B.3) Stereospecificity of the aryl migration in lithiated allylic thiocarbamates**

II.B.3.a) Substrates with an unsubstituted double bond\[126\]

II.B.3.a.i) Substrates with a methyl group at C\(_\alpha\)

Enantioenriched thiocarbamates (\(R\)-316a) were lithiated according to the optimised conditions (Scheme 145).
A promising first result was obtained when migrating an unsubstituted phenyl ring in allylic thiocarbamate (R)-316aa, as an almost completely enantiospecific reaction was observed (Table 32, entry 1). This established that rearrangement of the intermediate organolithium occurred faster than racemisation. In other words, allyllithium 317aa was configurationally stable on the time scale of the rearrangement.

When investigating the para-substituted phenyl rings, we found that a methyl group, although a weak electron-donor, led to a racemic product (Table 32, entry 2). We did acknowledge a moderate yield in the rearrangement of the corresponding racemic 316ab, which we attributed to deactivation of the ipso position due to increased electron density (see Section II.B.1.a). Thus, in this case, racemisation was faster than rearrangement.

On the other hand, (R)-316ad, bearing a para-chlorophenyl ring, rearranged with complete enantiospecificity while (R)-316ae (Table 32, entry 3), bearing a para-
fluorophenyl ring, suffered from partial loss of enantioenrichment (67:33 e.r., entry 4). This revealed that both halogens, being electronnegative, activated the ring towards nucleophilic attack enough for rearrangement and racemisation to occur at competing rates. In the case of the chlorine, rearrangement was even faster: no racemisation was observed. The better electron-donating ability of fluorine (orbital overlap being better between C and F than C and Cl)\textsuperscript{16} was most probably deactivating the ipso position and decelerating the rearrangement of (R)-316ae enough to allow partial racemisation to occur on the timescale of the reaction.

In sharp contrast, complete enantiospecificity was observed for both meta-chlorophenyl- and meta-fluorophenyl rings (Table 32, entries 7-8). This again is in agreement with rearrangement being faster than racemisation in substrates bearing aryl rings which ipso position is not deactivated. Indeed, halogens are π-donating substituents, thus they increase the electron density by delocalisation at the ortho and para positions only.

Similar results were observed with the methoxy-substituted rings: rearrangement of (R)-316af, bearing a meta-methoxyphenyl ring, was found to be completely enantiospecific (Table 32, entry 5), while rearrangement of (R)-316ai, bearing an ortho-methoxyphenyl ring, showed some loss of enantioenrichment (63:37 e.r., entry 8).

Overall, we were very pleased to observe complete, or nearly complete conservation of enantioenrichment in the migration of most rings (Table 32, entries 1, 3, 6-9).

Modification of the reaction parameters was explored in order to improve the lower enantiospecificities (Table 33).


<table>
<thead>
<tr>
<th>Entry</th>
<th>(R)-316a</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Conditions</th>
<th>(R)-318a</th>
<th>Yield (%)</th>
<th>318: e.r.</th>
<th>316a: e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-316ab</td>
<td>4-Me</td>
<td>LiCl</td>
<td>(R)-318ab</td>
<td>-&lt;sup&gt;a&lt;/sup&gt;</td>
<td>69:31&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89:11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-78 °C, 1 h</td>
<td></td>
<td>78</td>
<td>50:50</td>
<td>89:11</td>
</tr>
<tr>
<td>2</td>
<td>(R)-316ab</td>
<td>4-Me</td>
<td>LiCl</td>
<td>(R)-318ab</td>
<td>40</td>
<td>70:30</td>
<td>89:11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-78 to -70 °C, 3.5 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(R)-316ae</td>
<td>4-F</td>
<td>LiCl</td>
<td>(R)-318ae</td>
<td>34</td>
<td>69:31</td>
<td>89:11</td>
</tr>
<tr>
<td>4</td>
<td>(R)-316ae</td>
<td>4-F</td>
<td>Et&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>(R)-318ae</td>
<td>0&lt;sup&gt;d&lt;/sup&gt;</td>
<td>-</td>
<td>89:11</td>
</tr>
<tr>
<td>5</td>
<td>(R)-316ae</td>
<td>4-F</td>
<td>LiCl</td>
<td>(R)-318ae</td>
<td>34</td>
<td>69:31</td>
<td>89:11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>-78 to -70 °C, 3 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(R)-316ai</td>
<td>2-OMe</td>
<td>LiCl</td>
<td>(R)-318ai</td>
<td>50</td>
<td>61:39</td>
<td>86:14</td>
</tr>
<tr>
<td>7</td>
<td>(R)-316ai</td>
<td>2-OMe</td>
<td>LiCl</td>
<td>(R)-318ai</td>
<td>38</td>
<td>64:36</td>
<td>86:14</td>
</tr>
</tbody>
</table>

<sup>a</sup>Product/sm ratio 1:3.6.  
<sup>b</sup>e.r. of the recovered sm was 52:48.  
<sup>c</sup>This base was used instead of LDA.  
<sup>d</sup>Decomposition.

**Table 33: Modification of the conditions to improve the enantiospecificity in the aryl migration of some substrates 316a.**

Using a lower temperature for the same reaction time did limit the loss of enantiospecificity in the migration of the para-tolyl ring (Table 33, entry 1). However, the e.r. had still dropped to 70:30 and the conversion was very low. The recovered starting material was found to have already completely racemised, suggesting that epimerisation took place at a much higher rate than rearrangement.

Employing the bulkier base 292 to rearrange (R)-316ab, with the aim of forming a tighter chiral complex to hold the lithium atom on one enantiotopic face, also gave a racemic product (Table 33, entry 2).

Addition of LiCl, changing the solvent or the base allowed no increase in the enantioenrichment of the rearranged thiocarbamate (R)-318ae bearing a para-fluorophenyl ring (Table 33, entries 3-5). Similarly, no improvement could be achieved in the migration of the ortho-methoxyphenyl ring by reducing the reaction time and the temperature (Table 33, entries 6-7).

Thus, strong π-donating substituents at the ortho- and para-positions, by deactivating the ipso-carbon of the migrating aryl ring, may slow the rearrangement down enough for racemisation to occur at the same or higher rate. Less π-donating
groups, such as \textit{para}-chloro, or \textit{\pi}-donating substituents in \textit{meta}-position did allow complete enantiospecificity in the migration of the aryl ring.

II.B.3.a.ii) Influence of the substitution at \textit{C}\textsubscript{\alpha}

Similar results were observed in substrates bearing a propyl chain instead of the methyl group at \textit{C}\textsubscript{\alpha} (\textbf{Scheme 146}).

\begin{center}
\begin{tabular}{cccccccc}
Entry & (\textit{R})-316\textit{b} & \textit{R}\textsuperscript{3} & Conditions & (\textit{R})-318\textit{b} & \textbf{Yield (\%)} & 318\textit{b}: e.r. & 316\textit{b}: e.r. \\
\hline
1 & (\textit{R})-316\textit{bc} & 4-Cl & -78 \degree C, 2.5 h & (\textit{R})-318\textit{bc} & 81 & 94:6 & 94:6 \\
2 & (\textit{R})-316\textit{bd} & 4-F & -78 \degree C, 3 h & (\textit{R})-318\textit{bd} & 52 & 72:28 & 91:9 \\
3 & (\textit{R})-316\textit{be} & 3-Cl & -78 to -50 \degree C, 2 h & (\textit{R})-318\textit{be} & 48 & 94:6 & 95:5 \\
\end{tabular}
\end{center}

\textbf{Table 34: Stereospecificity in the aryl migration of 316\textit{b}.}

Indeed, rearrangement of (\textit{R})-316\textit{bc}, bearing a \textit{para}-chlorophenyl ring occurred without loss of enantioenrichment (\textbf{Table 34}, entry 1), while migration of the \textit{meta}-chlorophenyl ring gave (\textit{R})-318\textit{be} with decreased enantioselectivity (\textbf{Table 34}, 72:28 e.r., entry 2), as in (\textit{R})-318\textit{ae} (\textbf{Table 32}, 67:33 e.r., entry 4).

Similarly, a ring substituted with a \textit{meta}-halogen did migrate with complete enantiospecificity (\textbf{Table 34}, entry 3), as in the previous 316\textit{a} series (\textbf{Table 32}).

Thus, although a larger substituent at \textit{C}\textsubscript{\alpha} increased the rates and reduced the yields of the aryl migration (see Section II.B.1.a), it did not have any effect on its enantioselectivity, neither detrimental (\textbf{Table 34}, entries 1, 3) or beneficial (entry 2).

We then decided to investigate the effect of substitution of the allylic double bond, as a cyclohexyl group at the terminal carbon led to improved yields in the rearrangement of some racemic substrates (see Section II.B.1.b).
II.B.3.b) Effect of substitution of the allylic moiety

A cyclohexyl group at the terminal carbon of the allylic moiety gratifyingly allowed considerable improvements in the enantiospecificity of the aryl migration (Scheme 147).

![Scheme 147: Stereospecificity in the aryl migration of 316f.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>316f</th>
<th>R³</th>
<th>Time (h)</th>
<th>318f</th>
<th>Yield (%)</th>
<th>318f: e.r.</th>
<th>316f: e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-316fa</td>
<td>4-Me</td>
<td>1</td>
<td>(S)-318fa</td>
<td>76</td>
<td>91:9</td>
<td>94:6</td>
</tr>
<tr>
<td>2</td>
<td>(R)-316fa</td>
<td>4-Me</td>
<td>3</td>
<td>(R)-318fa</td>
<td>100</td>
<td>13:87</td>
<td>13:87</td>
</tr>
<tr>
<td>3</td>
<td>(S)-316fc</td>
<td>4-Cl</td>
<td>2</td>
<td>(S)-318fc</td>
<td>63</td>
<td>94:6</td>
<td>95:5</td>
</tr>
<tr>
<td>4</td>
<td>(S)-316fd</td>
<td>4-F</td>
<td>3</td>
<td>(S)-318fd</td>
<td>82</td>
<td>94:6</td>
<td>94:6</td>
</tr>
<tr>
<td>5</td>
<td>(S)-316fe</td>
<td>3-OMe</td>
<td>3</td>
<td>(S)-318fe</td>
<td>100</td>
<td>95:5</td>
<td>95:5</td>
</tr>
<tr>
<td>6</td>
<td>(S)-316fh</td>
<td>2-OMe</td>
<td>3</td>
<td>(S)-318fh</td>
<td>100</td>
<td>94:6</td>
<td>94:6</td>
</tr>
<tr>
<td>7</td>
<td>(R)-316fi</td>
<td>2,3-benzo b</td>
<td>3</td>
<td>(R)-318fi</td>
<td>71</td>
<td>15:85</td>
<td>14:86</td>
</tr>
<tr>
<td>8</td>
<td>(S)-316fj</td>
<td>2-pyridyl c</td>
<td>2 d</td>
<td>(S)-318fj</td>
<td>30</td>
<td>93:7</td>
<td>94:6</td>
</tr>
<tr>
<td>9</td>
<td>(S)-316fk</td>
<td>6-(NBOc)indole c</td>
<td>2.5</td>
<td>(S)-318fk</td>
<td>41</td>
<td>90:10</td>
<td>96:4</td>
</tr>
<tr>
<td>10</td>
<td>(R)-316fk</td>
<td>6-(NBOc)indole c</td>
<td>4</td>
<td>(R)-318fk</td>
<td>30</td>
<td>27:73</td>
<td>14:86</td>
</tr>
<tr>
<td>11</td>
<td>(R)-316fk</td>
<td>6-(NBOc)indole c</td>
<td>3.5 e</td>
<td>(R)-318fk</td>
<td>42</td>
<td>23:77</td>
<td>14:86</td>
</tr>
<tr>
<td>12</td>
<td>(R)-316fk</td>
<td>6-(NBOc)indole c</td>
<td>0.75 f</td>
<td>(R)-319fk</td>
<td>39 f</td>
<td>14:86</td>
<td></td>
</tr>
</tbody>
</table>

a The temperature was -50 °C. b 1-naphthyl. c See structure in Table 11 and Figure 35. d The temperature was -78 °C. e The temperature was 0 °C. f The isolated product is the free thiol, Et₂O left. g No conditions could be found to separate the enantiomers of thiols.

Table 35: Stereospecificity in the aryl migration of 316f.

Aryl migration in enantioenriched cyclohexyl-substituted allylic thiocarbamates 316f was found to be enantiospecific with all kinds of rings, electron-rich and electron-deficient, substituted at the ortho-, meta- and para-positions, including heteroaryls (Table 35).

As observed in unsubstituted allylic thiocarbamates (R)-316a,b, migration of the para-chlorophenyl, meta-methoxyphenyl and 1-naphthyl rings was completely stereospecific (Table 35, entries 3, 5, 7).
Most pleasingly, the para-tolyl ring, which led to a racemic rearranged product (R)-318ab (Table 32, entry 2), the para-fluorophenyl and ortho-methoxyphenyl rings, which both gave products (R)-318ae, (R)-318ai and (R)-318bd in decreased enantioenrichment (about 70:30 e.r., Table 32, entries 4, 8; Table 34, entry 2) all migrated with no loss of enantioselectivity (Table 35, entries 1-2, 4, 6).

This is even more remarkable considering that the reaction time was generally longer (from 1 to 3 h at -60 °C for the para-tolyl ring, Table 35, entry 2; from 2 to 3 h for the para-fluorophenyl ring, Table 35, entry 4) than that used in the unsubstituted substrates (R)-316a,b (Table 32, Table 34). Thus, despite a longer reaction time and/or a higher temperature (Table 35, entry 3), no racemisation occurred on the timescale of the rearrangement.

However, rearrangement of 316fk, bearing the indolyl ring, seemed to lack reproducibility as further attempts gave tertiary thiocarbamates with lower enantiospecificities (Table 35, entries 9-11). Notably, by warming the reaction to 0 °C for 45 min, the free thiol (R)-319fk could be isolated in good yield for this two-step process (Table 35, entry 12).

To conclude, we showed that substitution of the terminal allylic carbon by a cyclohexyl group led to markedly enhanced enantioselectivities in the aryl migration, leading to highly enantioenriched tertiary allylic thiocarbamates 318f. To get a better understanding of this fact, we were interested in comparing the effect of a flatter, but electronically different, phenyl ring at the same position. Rearrangement of enantioenriched thiocarbamate (R)-316gc was investigated (Scheme 148), using the optimised conditions of the racemic fashion (Scheme 143).

Scheme 148: Stereospecificity in the aryl migration of (R)-316gc.

Unfortunately, rearranged 318gc was found to be racemic. This indicated that the nature of the substituent at the terminal carbon of the allylic moiety, both electronic and steric, was crucial regarding the conservation of enantioenrichment.
Conjugation in phenyl-substituted substrate \((R)-316gc\) may render the intermediate organolithium less reactive and/or more prone to racemise, causing rearrangement and epimerisation to occur at competing rates. This is consistent with the lower yields observed in the racemic series, suggesting that aryl migration is slower in these substrates (Table 25).

On the contrary, the electron-donating effect of the cyclohexyl group, with no conjugation possible, may activate carbanions \(317f\) towards nucleophilic attack at the aromatic ring, resulting in racemisation being much slower than rearrangement.

Sterics around the double bond could also play an important part in decelerating epimerisation in the cyclohexyl-substituted organolithiums.

Based on the observation by Beak and co-workers that a cyclohexyl-substituted \(\alpha\)-aminoallyllithium presented a \(\eta^1\)-bonding structure with the lithium atom localised \(\alpha\) to nitrogen,\(^53b\) we hypothesised that \(\alpha\)-thioallyllithiums \(317f\) derived from the cyclohexyl-substituted thiocarbamates \(316f\) may exhibit a similar structure. The cyclohexyl group would then prevent localisation of the lithium atom at the \(\gamma\)-position which may favour isomerisation of the \(\alpha\)-centre (Scheme 149).

\[
\begin{align*}
317a & \equiv \left\{ \begin{array}{c}
\alpha-\eta^1-317a \\
\gamma-\eta^1-317a
\end{array} \right. \\
317f & \equiv \left\{ \begin{array}{c}
\alpha-\eta^1-317f \\
\gamma-\eta^1-317f
\end{array} \right. \\
317g & \equiv \eta^3-317g
\end{align*}
\]

Scheme 149: Proposed structures of allyllithiums \(317a\), \(317f\) and \(317g\).

In unsubstituted \(\alpha\)-thioallyllithiums \(317a\), equilibration between the \(\alpha\)- and \(\gamma-\eta^1\) structures may occur more readily, and depending on the substitution pattern of the migrating ring, rearrangement may or may not be faster than racemisation.

Also, the assumption that our cinnamyl \(\alpha\)-thiolithiums \(317g\) are \(\eta^3\)-bonded like Beak’s cinnamyl \(\alpha\)-aminolithium\(^{53b,d}\) would explain the more difficult aryl migration
observed in these substrates. Indeed, the torsion required to achieve the conformation necessary for the aryl migration to occur, may be less feasible (Scheme 144).

The enantioenriched tertiary allylic thiocarbamates now accessible through stereospecific aryl migration are shown in Figure 35.\textsuperscript{126,134}

![Chemical structures of enantioenriched tertiary allylic thiocarbamates](image)

**Figure 35:** Enantioenriched allylic thiocarbamates 318 synthesised via aryl migration.
II.C) Migration of vinyl- and other non-aromatic groups

Given the successful migration of electron-rich aryl rings via intramolecular nucleophilic aromatic substitution in lithiated \(N\)-aryl ureas, carbamates and \(N\)-aryl thiocarbamates, a similar rearrangement was envisaged in substrates bearing both electron-rich and unactivated alkenyl groups. \(^{148}\) Since organolithiums do not usually undergo direct reaction with vinylic electrophiles (formation of vinylic C-C bonds is generally achieved through transmetallation), such a rearrangement would constitute a useful expansion of the methods available to generate vinylic C-C bonds. \(^{148}\)

II.C.1) Preliminary results in \(N\)’-vinyl ureas and carbamates \(^{148}\)

The migration of several unsaturated non-aromatic groups had initially been achieved in primary benzylic ureas \(^{362}\), leading to their vinylic counterparts \(^{363}\) (Scheme 150).

![Scheme 150: Migration of non-aromatic substituents in benzylic ureas.](image)

The reaction presumably proceeded via an initial deprotonation forming benzyl lithium \(^{364}\) followed by migration of the alkenyl group to give \(Z\)-cinnamyllithium \(^{365}\), and a second deprotonation at the \(\gamma\)-position affording product \(^{363}\) (Scheme 151).

![Scheme 151: Proposed intermediates in the migration of non-aromatic groups.](image)
In α-methylbenzylic ureas 366, vinyl, propenyl and cyclohexenyl migration required the addition of DMPU to proceed. Pleasingly, all products retained their enantioenrichment starting from enantiomerically pure substrates (Scheme 152, Table 36).

This novel N→C transfer reaction considerably enlarged the scope of the existing methodology by allowing the construction of quaternary centres bearing four substituents of different nature, namely a heteroatom, an alkyl, aryl and an alkenyl group.

**Scheme 152: Migration of non-aromatic groups in α-methylbenzylic ureas.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>366</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>367</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-366a</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>(R)-367a</td>
<td>50</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>2</td>
<td>(R)-366b</td>
<td>4-Cl</td>
<td>Me</td>
<td>H</td>
<td>(S)-367b</td>
<td>90</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>3</td>
<td>(S)-366c</td>
<td>3-Cl</td>
<td>Me</td>
<td>H</td>
<td>(R)-367c</td>
<td>73</td>
<td>&gt;99:1</td>
</tr>
<tr>
<td>4</td>
<td>(R)-366d</td>
<td>H</td>
<td>Et</td>
<td>H</td>
<td>(S)-367d</td>
<td>54</td>
<td>99:1</td>
</tr>
<tr>
<td>5</td>
<td>(S)-366e</td>
<td>H</td>
<td>Me</td>
<td>Me</td>
<td>(R)-367e</td>
<td>-ᵃ</td>
<td>99:1</td>
</tr>
<tr>
<td>6</td>
<td>(S)-366f</td>
<td>H</td>
<td>Me</td>
<td>(CH₂)₄</td>
<td>(R)-367f</td>
<td>64</td>
<td>95:5</td>
</tr>
</tbody>
</table>

ᵃToo unstable to purify.

**Table 36: Migration of non-aromatic groups in α-methylbenzylic ureas.**

A remarkable one-pot procedure allowed the direct stereospecific vinylation of benzylic amine (R)-368b to generate tertiary amine (S)-370b in 50% yield over four steps. X-ray crystal analysis of the hydrochloride salt of (S)-370b confirmed the vinyl migration to be a retentive process (Scheme 153).

**Scheme 153: One-pot procedure for the stereospecific vinylation of (R)-368b.**
Styrenyl and vinyl migrations were subsequently attempted in carbamates (Scheme 154, Table 37).

Scheme 154: Migration of non-aromatic groups in α-methylbenzylic carbamates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>(±)−371</th>
<th>R¹</th>
<th>R²</th>
<th>(±)−372</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>371a</td>
<td>H</td>
<td>Ph</td>
<td>372a</td>
<td>nd</td>
</tr>
<tr>
<td>2</td>
<td>371b</td>
<td>H</td>
<td>H</td>
<td>372b</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>371c</td>
<td>4-Cl</td>
<td>H</td>
<td>372c</td>
<td>54</td>
</tr>
<tr>
<td>4</td>
<td>371d</td>
<td>3-CF₃</td>
<td>H</td>
<td>372d</td>
<td>32</td>
</tr>
<tr>
<td>5</td>
<td>371e</td>
<td>3-Me</td>
<td>H</td>
<td>372e</td>
<td>48ᵃ</td>
</tr>
<tr>
<td>6</td>
<td>371f</td>
<td>4-OMe</td>
<td>H</td>
<td>372f</td>
<td>22ᵃᵇ</td>
</tr>
</tbody>
</table>

ᵃReaction time was 4 h.ᵇFree alcohol recovered and starting material remaining.

Table 37: Migration of non-aromatic groups in α-methylbenzylic carbamates.

Vinyl migration was found to be slower than aryl migration, requiring a higher temperature (-45 °C instead of -78 °C) to reach completion. Moreover, an essentially racemic product 372b was recovered from vinylation of enantiopure 371b. This was unfortunately expected based on the previously observed low configurational stability of α-oxybenzyl lithiums under the conditions required to promote rearrangement.¹⁴⁹

Regarding the mechanism of the vinylation, a cyclic intermediate R/R' (Scheme 155) was proposed based on the formation of a cyclised imidazolidinone product from styrenyl migration in urea 366g (R¹ = H, R² = Me, R³ = Ph, Scheme 152). In addition, in situ IR studies revealed a transient absorption at 1646 cm⁻¹ which was attributed to a prelithiated complex 366a's-BuLi. Interestingly, DFT calculations showed that the lowest energy pathway involved coordination of the lithium cation to the aryl ring, rather than to the carbanionic centre (structure Q'). The lithium atom then migrated to the terminal carbon of the vinyl moiety to stabilise the developing negative charge, presumably leading to cyclic intermediate R' having a syn relationship between the lithiomethyl group and the phenyl ring. Subsequent C-N bond cleavage formed the retention urea product
$S/S'$, associated with the absorption at 1575 cm\(^{-1}\) observed after warming at -15 °C for 5 min.\(^{148}\)

Scheme 155: Proposed mechanism for the vinylation of $\alpha$-methylbenzylic ureas.

II.C.2) Application to benzylic thiocarbamates

II.C.2.a) Aim and interest of the methodology

In $N$-vinyl $\alpha$-methylbenzyl thiocarbamates 326, migration of the vinyl moiety will form the same compounds 318a as the aryl transfer in allylic thiocarbamates 316a\(^{126}\) (Scheme 156).

Scheme 156: Aim and interest of the vinylation of $\alpha$-methylbenzylic thiocarbamates.

This could be particularly interesting to access allylic tertiary thiocarbamates 318ac,k bearing aryl rings which could not be migrated ($para$-methoxy- and 2,4,6-trimethylphenyl rings) or to improve the enantioselectivity of unsubstituted 318ab,e,i
containing the para-tolyl, para-fluoro- and ortho-methoxyphenyl rings, should the vinyl migration prove enantiospecific in thiocarbamates.

On the other hand, migration of other non-aromatic groups will diversify further the range of the tertiary thiocarbamates accessible through the lithiation-rearrangement methodology.

II.C.2.b) Vinyl migration in N-vinyl benzylic thiocarbamates

II.C.2.b.i) Preparation of the starting materials

N-Vinyl thiocarbamates 326 were synthesised according to the route used within the group to prepare benzylic thiocarbamates,108,110 following first Mukaiyama’s150 then Hoppe’s68 methods. Mukaiyama’s synthesis150 consists of activating benzylic alcohols 343 towards their S_N2 displacement by sulfur nucleophiles via intermediate 374 formed from Vilsmeier reagent 373. Subsequent displacement of the activated alcohol 374 by thioacetic acid 375 resulted in thioacetate 376 (Scheme 157).

\[
\text{(R)}-343a: \text{R} = \text{H} \\
\text{(t)-343b: R = 4-Cl}
\]

Scheme 157: Preparation of thioacetates 376.

Vilsmeier reagent 373 ((chloromethylene)dimethylammonium chloride) was generated from dimethylformamide and oxalyl chloride, via intermediate 377 (Scheme 158).

\[
\text{N} = \text{O} + \text{Cl} = \text{O} \rightarrow \text{Cl} = \text{O} \rightarrow \text{Cl} = \text{O} \rightarrow \text{Cl} = \text{O} \\
\text{N} = \text{O} \quad \text{N} = \text{O} \quad \text{N} = \text{O}
\]

Scheme 158: Generation of Vilsmeier reagent 373.

Reduction of thioester 376 to free benzylic thiol 378 was achieved using lithium aluminium hydride in refluxing diethylether, according to Hoppe’s conditions.68 It was
followed by addition to vinyl isocyanate 369 to produce vinyl thiocarbamate 379 which was then methylated to obtain the final product 326 (Scheme 159).

Scheme 159: Synthesis of α-methylbenzylic thiocarbamates 326.

Excellent yields could be achieved for each reaction of the sequence, apart from the methylation of 379b. However, all reactions suffered from a lack of reproducibility, showing significant differences in terms of reaction times and yields from one experiment to another. For example, complete consumption of benzylic thiol 378 required from 3 h to 30 h (378a) and 5.5 h to 4 days (378b), despite the subsequent addition of 0.5 to 2 equivalents of vinyl isocyanate. Similarly, superstoichiometric amounts of methyl iodide were added to overcome the slowest methylations.

II.C.2.b.ii) Preparation of enantioenriched phenyl-substituted starting materials

Asymmetric reduction of benzylic ketones

Noyori’s well-known asymmetric hydrogenation of benzylic ketones was seen as an efficient way of preparing various phenyl-substituted enantioenriched benzylic alcohols. Catalyst 383 was easily synthesised from [RuCl₂(η⁶-mesitylene)]₂, 380 and (1S,2S)-N-p-toluenesulfonfyl-1,2-diphenylethlenediamine (TsDPEN) 381 and successfully applied to the reduction of ketones 382 (Scheme 160).
Unfortunately, no thioacetate could be produced from (R)-343b under the conditions used in the racemic fashion (Scheme 157). Instead, the clean $^1$H NMR of the crude reaction is consistent with intermediate 374b although it seems surprising that it is isolable. Running the reaction for a longer time, adding more thioacetic acid in the course of the reaction and heating the reaction generated none of the desired product 376b. Repeating the reaction from (±)-343b was problematic, leading to a product/intermediate 376b/374b ratio of 1:1.2. Similarly, no thioacetate 376c could be generated from (R)-343c. Thus, the lack of reproducibility of this reaction prompted us to turn our attention to Hoppe’s method$^{68}$ to prepare the enantiopure phenyl-substituted benzylic thiocarbamates 326 (Scheme 161). Starting from 4-chloro-phenylethanol 343b, unfortunately, only the starting material, DIAD and an unidentified compound, but no thioacetate 376b, could be recovered.

**Scheme 161: Attempt to prepare thioacetate 370b under Hoppe’s conditions.$^{68}$**

Similarly, all attempts to produce a thioacetate from (±)-4-methoxy-phenylethanol 343d, using either Mukaiyama’s$^{150}$ or Hoppe’s$^{68}$ methods, failed.
Asymmetric α-methylation

Following results by Hoppe showing that high enantioenrichment could be achieved through lithiation-substitution of prochiral benzylic thiocarbamate \(178\) in the presence of chiral (bis)oxazoline \((S,S)-179a\) (see Section I.B.4.c, Scheme 55),\(^{51}\) lithiation of thiocarbamate \(306\) in the presence of the same chiral bisoxazoline ligand was attempted within the group a few years ago.\(^{110}\) Warming to \(-30\) °C allowed equilibration of the diastereomeric complexes towards the favoured \(\alpha\)-thiobenzyl lithium \(313\), as shown by the formation of tertiary benzylic thiocarbamate \((S)-309a\) in 92:8 e.r. after quenching at -78 °C with methyl triflate. Thus, as lithiated intermediate \(313\) did not undergo aryl migration, these conditions allowed the enantioselective α-methylation of \(306\) (Scheme 162).\(^{110}\)

![Scheme 162](image)

**Scheme 162: Asymmetric methylation of benzylic thiocarbamate 306\(^{110}\) by Hoppe’s method.\(^{51}\)**

Thus, we considered synthesising N-vinyl benzylic thiocarbamates \(326\) via asymmetric α-methylation of primary thiocarbamates \(385\), arising from the reaction of inexpensive benzyl mercaptan \(384\) and vinyl isocyanate \(369\) (Scheme 163).

![Scheme 163](image)

**Scheme 163: Envisaged asymmetric α-methylation of N-vinylbenzyl thiocarbamate 385 by Hoppe’s method.\(^{51}\)**
Addition of 4-methoxybenzylthiol 384d to vinyl isocyanate 369 was again problematic, as the resulting product could not be purified (Scheme 164). It was consequently submitted to the N-methylation conditions and primary vinyl thiocarbamate 385d was obtained in 77% over 4 steps (Scheme 164). However, as previously found in secondary vinyl thiocarbamates 379, N-methylation was not reproducible.

Scheme 164: Preparation of N-vinylbenzylic thiocarbamate 385d.

Nevertheless, asymmetric α-methylation of 385d (Scheme 165) was attempted under conditions similar to those reported by Hoppe (Scheme 55). Unfortunately, only starting material was recovered. No methylation occurred, neither did vinyl migration.

Scheme 165: Failed attempt of α-methylation of N-vinylbenzylic thiocarbamate 385d by Hoppe’s method.

The same reaction was attempted again, under more straightforward conditions also used by Hoppe and co-workers, with the aim of assessing the feasibility of α-methylation in this substrate (Scheme 166). The crude 1H NMR showed only starting material.

Scheme 166: Failed attempt of methylation of N-vinylbenzylic thiocarbamate 385d using other conditions reported by Hoppe.

With regard to all the aforementioned difficulties and failures, it was decided to focus on non-substituted benzylic thiocarbamate 326a.
II.C.2.c) Migration of a vinyl group in benzylic thiocarbamate 326a

The first attempt of migrating the vinyl moiety in thiocarbamate 326a was successful, although low-yielding and affording almost racemic product (Scheme 167).

![Scheme 167: Migration of a vinyl group in benzylic thiocarbamate 326a.](image)

Gratifyingly, optimisation of the conditions allowed considerable improvements in both yield and enantioselectivity (Scheme 168). We first investigated the effect of an additive in the LDA-mediated rearrangement of (S)-326a.

As previously found in the aryl migration, absence of DMPU proved beneficial to the stereospecificity of the reaction (Table 38, entry 1). Addition of LiCl further increased the enantioenrichment of the product when used at -78 °C (Table 38, entry 2), but had no effect at -60 °C on a short reaction time (entries 3, 4). However, these latter conditions did lead to high yields.

![Scheme 168: Stereospecificity of the vinylation of 326a.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-78</td>
<td>60</td>
<td>46</td>
<td>80:20</td>
</tr>
<tr>
<td>2</td>
<td>LiCl</td>
<td>-78</td>
<td>60</td>
<td>46</td>
<td>92:8</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-60</td>
<td>2</td>
<td>92(^a)</td>
<td>79:21</td>
</tr>
<tr>
<td>4</td>
<td>LiCl</td>
<td>-60</td>
<td>2</td>
<td>82(^a)</td>
<td>80:20</td>
</tr>
</tbody>
</table>

\(^a\)Clean crude product by \(^1\)H NMR spectroscopy, no purification needed.

Table 38: Stereospecificity of the vinylation of 326a.

Changing the base to LiTMP gave an excellent 96:4 e.r., in absence of LiCl, although the yield remained moderate (Scheme 169, Table 39, entry 3).
Scheme 169: Influence of the base in the vinylation of 326a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>LiCl</td>
<td>1</td>
<td>46</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>LiTMP</td>
<td>LiCl</td>
<td>15</td>
<td>40</td>
<td>84:16</td>
</tr>
<tr>
<td>3</td>
<td>LiTMP</td>
<td>-</td>
<td>15</td>
<td>32</td>
<td>96:4</td>
</tr>
</tbody>
</table>

Table 39: Influence of the base in the vinylation of 326a.

A lower temperature only slightly improved the enantiospecificity of the reaction, but at large expense to the yield (Scheme 170, Table 40, entry 2). Raising the temperature, even when limiting the reaction time to 2 min, led to a significant diminution of the enantioenrichment, but the rearrangement proceeded very cleanly and the crude product could be isolated pure in high yield (Table 40, entry 3).

Scheme 170: Influence of the temperature in the vinylation of 326a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature (°C)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-78</td>
<td>60</td>
<td>46</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>-100</td>
<td>60</td>
<td>14</td>
<td>95:5</td>
</tr>
<tr>
<td>3</td>
<td>-60</td>
<td>2</td>
<td>82</td>
<td>80:20</td>
</tr>
</tbody>
</table>

\(^a\)P/sm 1:0.75. \(^b\)Clean crude product by \(^1\)H NMR spectroscopy, no purification needed.

Table 40: Influence of the temperature in the vinylation of 326a.

Finally, similar e.r.’s were obtained when carrying out the rearrangement at -78 °C over 5 to 60 min (Scheme 171, Table 41, entries 1-4). Unsurprisingly, the rearrangement was not complete, hence the lower yields. The same reaction with LiTMP required a much longer time to reach a similar conversion (Table 41, entries 5, 6).
Scheme 171: Influence of the reaction time in the vinylation of 326a.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Time (min)</th>
<th>Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>60</td>
<td>46</td>
<td>92:8</td>
</tr>
<tr>
<td>2</td>
<td>LDA</td>
<td>5</td>
<td>-</td>
<td>93:7</td>
</tr>
<tr>
<td>3</td>
<td>LDA</td>
<td>10</td>
<td>38(^b)</td>
<td>88:12</td>
</tr>
<tr>
<td>4</td>
<td>LDA</td>
<td>30</td>
<td>-</td>
<td>91:9</td>
</tr>
<tr>
<td>5</td>
<td>LiTMP</td>
<td>15 h</td>
<td>40</td>
<td>84:16</td>
</tr>
<tr>
<td>6</td>
<td>LiTMP</td>
<td>5.5 h</td>
<td>0(^d)</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)P/sm 1:0.9. \(^b\)P/sm 2:1. \(^c\)P/sm 1:0.8. \(^d\)Sm recovered.

Table 41: Influence of the reaction time in the vinylation of 326a.

To conclude, migration of the vinyl moiety in enantiopure (S)-326a led to mixed results: almost complete enantiospecificity was achieved in several instances, but it was always associated to low to moderate yields. On another hand, excellent yields could be obtained under different conditions which, unfortunately, caused a decrease of the enantioenrichment.

With the aim of improving the lowest yields, the reactions were scaled up from 50 mg to 250 mg. Unfortunately, no change was obtained, although we monitored the internal temperature to maintain it below -70 °C, as considerable variations can occur in bigger-scale reactions. We also tried to modify the concentrations of both solutions of starting material and LDA, adding a very dilute LDA solution to a concentrated solution of starting material, and reversely. Disappointingly, the yield remained identical. Thus, it appeared unlikely to achieve both high yield and complete enantiospecificity in this reaction.

We then turned our efforts towards the investigation of the vinyl migration in phenyl-substituted benzylic N-vinyl thiocarbamate 326b, although we could prepare only this single starting material. The first attempt of the vinyl migration was promising, the reaction proceeding neatly to afford a clean crude product in 84% yield (Scheme 172).
**II.C.2.d) Cyclohexene migration**

Following on the encouraging results with the vinyl moiety, we attempted the migration of the more challenging cyclohexenyl group.

**II.C.2.d.i) Preparation of the starting material**

*N-Cyclohexene benzylic thiocarbamate* \(389\) was prepared from cyclohexanone \(386\) (Scheme 173).

![Scheme 173: Preparation of *N*-cyclohexenyl benzylic thiocarbamate 389.](image)

Imine \(387\) was straightforwardly obtained from cyclohexanone \(386\) and methylamine in 1 h in the microwave. After filtration through celite, the clean product was reacted with triphosgene to generate carbamoyl chloride \(388\), which was displaced by 1-phenylethyl mercaptan \(378a\) to furnish *N*-cyclohexene benzylic thiocarbamate \(389\) in 62% overall yield (3 steps).
II.C.2.d.ii) Attempted cyclohexene migration in benzylic thiocarbamate 389

Although many different sets of conditions were tested, migration of the cyclohexenyl group in benzylic thiocarbamate 389 remained unsuccessful, $^1$H NMR spectra only showing starting material and/or decomposition (Scheme 174, Table 42).

![Scheme 174: Attempts of migration of a cyclohexenyl substituent in benzylic thiocarbamate 389.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>RLi</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA</td>
<td>THF</td>
<td>-78</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>LDA·LiCl</td>
<td>THF</td>
<td>-60</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>s-BuLi</td>
<td>THF</td>
<td>-60</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>LiTMP</td>
<td>THF</td>
<td>-78</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>LDA</td>
<td>THF/DMPU 2:1</td>
<td>-60</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>s-BuLi</td>
<td>THF/DMPU 2:1</td>
<td>-60</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>LDA</td>
<td>THF/DMPU 4:1</td>
<td>-45</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>LDA</td>
<td>Et$_2$O/DMPU 4:1</td>
<td>-45</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 42: Failed attempts of migration of a cyclohexenyl substituent in benzylic thiocarbamate 389.
II.D) Functionalisation of the tertiary thiocarbamates: from thiols to biologically-interesting dihydrothiophenes

Derivatisation of the tertiary allylic thiocarbamates produced by our N to C rearrangement method was a key step to achieve in order to demonstrate their synthetic utility, namely towards biological and pharmaceutical applications, since the importance of organosulfur compounds in these fields have been reported in many instances.\(^2,4\-6,14,15,20,21,40\)

II.D.1) Cleavage of the thiocarbamate function

Tertiary allylic thiols \textbf{319} were generated by hydrolysis of the rearranged thiocarbamates \textbf{318}, under the usual mild basic conditions employed within the group for the deprotection of similar compounds (\textbf{Scheme 175}).\(^{8b,105,108}\)

\begin{center}
\textbf{Scheme 175: Synthesis of tertiary allylic thiols via deprotection of thiocarbamates.}
\end{center}
<table>
<thead>
<tr>
<th>Entry</th>
<th>318</th>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>319</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-318ad</td>
<td>H</td>
<td>Me</td>
<td>4-Cl</td>
<td>(R)-319ad</td>
<td>26&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>318ae</td>
<td>H</td>
<td>Me</td>
<td>4-F</td>
<td>319ae</td>
<td>20&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>318af</td>
<td>H</td>
<td>Me</td>
<td>3-OMe</td>
<td>319af</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>(R)-318ag</td>
<td>H</td>
<td>Me</td>
<td>3-Cl</td>
<td>(R)-319ag</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>(R)-318ah</td>
<td>H</td>
<td>Me</td>
<td>3-F</td>
<td>(R)-319ah</td>
<td>59</td>
</tr>
<tr>
<td>6</td>
<td>(R)-318aj</td>
<td>H</td>
<td>Me</td>
<td>1-naphthyl</td>
<td>(R)-319aj</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>318bc</td>
<td>H</td>
<td>n-Pr</td>
<td>4-Cl</td>
<td>319bc</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>(R)-318be</td>
<td>H</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>(R)-319be</td>
<td>80</td>
</tr>
<tr>
<td>9</td>
<td>(R)-318fa</td>
<td>Cy</td>
<td>Me</td>
<td>4-Me</td>
<td>(R)-319fa</td>
<td>100</td>
</tr>
<tr>
<td>10</td>
<td>318fc</td>
<td>Cy</td>
<td>Me</td>
<td>4-Cl</td>
<td>319fc</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>(S)-318fd</td>
<td>Cy</td>
<td>Me</td>
<td>4-F</td>
<td>(S)-319fd</td>
<td>56&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>12</td>
<td>(S)-318fe</td>
<td>Cy</td>
<td>Me</td>
<td>3-OMe</td>
<td>(S)-319fe</td>
<td>81</td>
</tr>
<tr>
<td>13</td>
<td>318fg</td>
<td>Cy</td>
<td>Me</td>
<td>3-F</td>
<td>319fg</td>
<td>42</td>
</tr>
<tr>
<td>14</td>
<td>(S)-318fh</td>
<td>Cy</td>
<td>Me</td>
<td>2-OMe</td>
<td>(S)-319fh</td>
<td>84</td>
</tr>
<tr>
<td>15</td>
<td>(R)-318fi</td>
<td>Cy</td>
<td>Me</td>
<td>1-naphthyl</td>
<td>(R)-319fi</td>
<td>94</td>
</tr>
<tr>
<td>16</td>
<td>318fk</td>
<td>Cy</td>
<td>Me</td>
<td>6-(Boc)indole&lt;sup&gt;c&lt;/sup&gt;</td>
<td>319fk</td>
<td>58</td>
</tr>
</tbody>
</table>

<sup>a</sup>Volatile. <sup>b</sup>Et<sub>2</sub>O left. <sup>c</sup>See structure in Figure 35.

**Table 43: Synthesis of tertiary allylic thiols via deprotection of thiocarbamates.**

The tertiary thiols 319 were obtained in good to high yields, with the exception of a few moderate results (Table 43, entries 1-2, 12). This was due to the extremely low polarity of the compounds, which rendered them particularly difficult to purify by column chromatography. Because they all appeared as oils, they could not be recrystallised and distillation would have resulted in a far larger decrease in yields on small-scale reactions. Increasing the scale of the reaction led to higher yields after column.

Moreover, the thiols turned out to be highly volatile, in particular the low molecular weight compounds 319a (Table 43, entries 1-2), which would have complicated further any purification by distillation. Special care had to be taken when concentrating them on the rotary evaporator: no vacuum was applied and the temperature of the bath did not exceed 40-50 °C.
II.D.2) Alkylation/allylation of the allylic thiols

Because allylic thiols 319, in particular the unsubstituted 319a,b, were difficult to handle due to their volatility, we thought the derived methyl- or benzyl sulfides would be more easily isolated.

Methylation was attempted first following straightforward conditions reported in the literature (Scheme 176).^152

Scheme 176: Alkylation of thiol 319ah to form methyl sulfide 320ah.

Unfortunately, a by-product containing the aryl ring was formed along with the expected methyl sulfide 320ah. The latter was found to be so non polar it could not be separated from the reaction impurities by column chromatography.

Sodium hydride, previously employed within the group to deprotonate a benzylic thiol,^108,110 was subsequently attempted (Scheme 177). Although the crude product was slightly cleaner, removal of a similar by-product bearing the aryl ring required two successive purifications to isolate methyl sulfide 320af in low yield. Moreover, repetition of the reaction on an analogous substrate or using allyl bromide instead of methyl iodide did not produce the sulfides in satisfying purity.

Scheme 177: Attempt to synthesise methyl sulfide 320af using different conditions.

Mild conditions employing cesium carbonate and tetrabutylammonium iodide in DMF seemed more promising as they reportedly furnished a large variety of sulfides in high yield from alkyl, benzyl and aryl thiols. Disappointingly, they failed to alkylate tertiary thiols 319aj and 319fe, only leading to decomposition of the starting materials (Scheme 178).
Failed attempts of alkylation of thiols 319 using mild conditions.

Benzylation of the allylic thiols was also investigated, as a mean of making higher molecular weight sulfides, which were expected to be less volatile. Potassium carbonate in MeCN/CH₂Cl₂ 2:1 did afford the benzylated compound, but again, it came with unseparable impurities. Changing the base to triethylamine pleasingly permitted the isolation of benzyl sulfide 321fc in good yield (Scheme 179). However, the conditions proved unsuccessful on a similar substrate or with allyl bromide as the electrophile.

Scheme 179: Benzylation of thiol 319fc using triethylamine.

Therefore, a general and straightforward method to furnish the alkylated thiols in satisfying purity and yield had to be developed. We thought that n-BuLi, although a far stronger base than needed, would allow a rapid and clean deprotonation (Scheme 180). Thus, the electrophile was added only a few minutes after the base. A very low temperature (-78 °C) was also expected to favour a cleaner process. In addition, side reactions should be avoided by using a stoichiometric quantity (or slight excess) of base: the exact amount of n-BuLi added would be easier to measure than NaH.

Scheme 180: General and efficient alkylation of thiols 319.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfide</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>319af</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>319fa</td>
<td>100</td>
</tr>
<tr>
<td>3</td>
<td>319fe</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>319fg</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>319fh</td>
<td>100</td>
</tr>
<tr>
<td>6</td>
<td>319af</td>
<td>69&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>7</td>
<td>(R)-319ah</td>
<td>95</td>
</tr>
<tr>
<td>8</td>
<td>(R)-319be</td>
<td>30&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>9</td>
<td>(R)-319fa</td>
<td>76</td>
</tr>
<tr>
<td>10</td>
<td>(S)-319fe</td>
<td>100</td>
</tr>
<tr>
<td>11</td>
<td>(S)-319fh</td>
<td>98</td>
</tr>
<tr>
<td>12</td>
<td>(R)-319fi</td>
<td>-c</td>
</tr>
<tr>
<td>13</td>
<td>319fk</td>
<td>53</td>
</tr>
</tbody>
</table>

<sup>a</sup>Contains inseparable impurities. <sup>b</sup>P/sm 1:1. <sup>c</sup>Mixture product/rearranged isomer 1:0.5, see Scheme 181.<sup>d</sup>The equivalent enantioenriched (R)-322fk was prepared on a small scale and could not be purified satisfyingly.

Table 44: Generalisable and efficient alkylation of thiols 319.

Satisfyingly, these conditions proved successful and allowed the preparation of a range of methyl and allyl sulfides 320 and 322 respectively, in good to excellent yields (Table 44). One obvious exception was noted for the n-propyl-substituted compound (R)-322be (Table 44, entry 8): a 1:1 product/starting material ratio was obtained. The crude mixture was resubmitted to the same conditions (Scheme 180), which led to partial decomposition, hence the much lower yield after purification.

On the contrary, the reaction of 1-naphthyl-substituted thiol (R)-319fi proceeded cleanly but we observed the formation of by-product (E)-391, arising from cleavage of the S-allyl group and rearrangement (Scheme 181).

Scheme 181: Formation of by-product 391 arising from rearrangement of allyl sulfide 322fi.
Overall, yields could be significantly improved after we observed that a longer reaction time at -78 °C (from 15 min to 4 h) followed by a very slow warming to room temperature (over a few hours) produced fewer impurities. In some cases, the crude product did not require any further purification (Table 44, entries 2, 5, 10-11).

II.D.3) Reduction of the allylic double bond

Aiming to perform a wide range of transformations of the allylic double bond (for example metathesis, dihydroxylation and oxidative cleavage), we started our investigations with the most obvious one: reduction.

Given the low stability and repulsive odor of the thiols themselves, we chose to use the thiocarbamates or sulfides as starting materials. However, these compounds contain sensitive chemical functions, hence the necessity for a mild procedure. We also dismissed any metal-based hydrogenation, reputed to be incompatible with sulfur-based functions.\textsuperscript{154a,b,155a}

II.D.3.a) Diimide reduction\textsuperscript{154}

Diimide reduction seemed perfectly suited to our substrates. It has been reported to be highly chemo-, stereo- and regioselective,\textsuperscript{154a-d} compatible with sensitive functionality\textsuperscript{154b} and potentially ineffective on polarised multiple double bonds.\textsuperscript{154b,c} Moreover, several examples of efficient reduction of sulfur-substituted allylic double bonds by diimide have been described,\textsuperscript{154a-c} notably one in a tertiary allylic tolylsulfide (Scheme 182).\textsuperscript{154e}

\begin{tikzpicture}
  \node at (0,0) {\( (\text{S})\text{392} \)};
  \node at (1.5,0) {\( (\text{R})\text{393} \)};
  \draw [->] (0.75,0) -- (0.75,0.25);
  \draw [->] (0.75,0) -- (0.75,-0.25);
  \draw (0.75,0) -- (0.75,0.25) -- (0.75,-0.25);\end{tikzpicture}

\textbf{Scheme 182: Diimide reduction of tertiary allylic tolylsulfide (S)-392.\textsuperscript{154e}}

Due to its unstability, diimide must be prepared \textit{in situ}.\textsuperscript{154a,c} Common methods include the oxidation of hydrazine, decarboxylation of azodicarboxylic acid and thermal decomposition of \( p \)-toluenesulfonylhydrazine.\textsuperscript{154a,c} However, numerous studies now rely on arylsulfonyl hydrazides, with 2-nitrobenzenesulfonylhydrazide (NBSH) often selected for its mildness.\textsuperscript{154b,f} It notably allowed Carbery and co-workers to reduce allyl phenyl
sulfide 394 in 97% yield using 2-nitrobenzene-1-sulfonyl chloride 395 and hydrazine hydrate 396 as its precursors (Scheme 183).\textsuperscript{154b}

\[
\begin{align*}
\text{MeCN (0.2 M), 0 °C} & \quad \text{SPh} \\
1. & \quad \text{NO}_2
\end{align*}
\]

\[
\begin{align*}
\text{SO}_2\text{Cl} & \quad 395 (2.0 \text{ eq}) \\
2. & \quad \text{N}_2\text{H}_4\cdot\text{H}_2\text{O} 396 (4.0 \text{ eq}), \text{rt}, 18 \text{ h} \\
\text{SPh} & \quad 397: 97\%
\end{align*}
\]

**Scheme 183:** Diimide reduction of allyl phenyl sulfide 394 by Carbery.\textsuperscript{154b}

We therefore opted for NBSH as our diimide precursor and enthusiastically followed Carbery's conditions (Scheme 183). Disappointingly, none of thiocarbamates 318, thiol 319 or methyl sulfide 320 could be reduced (Scheme 184).

\[
\begin{align*}
\text{MeCN, 0 °C} & \quad \text{SPh} \\
1. & \quad \text{NO}_2
\end{align*}
\]

\[
\begin{align*}
\text{SO}_2\text{Cl} & \quad 395 (2.0 \text{ eq}) \\
2. & \quad \text{N}_2\text{H}_4\cdot\text{H}_2\text{O} 396 (4.0 \text{ eq}), \text{rt}, 20 \text{ h} \\
\text{SPh} & \quad 323
\end{align*}
\]

**Scheme 184:** Attempts of diimide reduction of allylic thiocarbamates, thiol and sulfide.

Methyl sulfide 320fe was cleanly recovered, while thiol 319fe suffered partial decomposition. Thiocarbamates 318ec and 318ed underwent C-S bond cleavage and rearrangement to compounds 398 and 399, as confirmed by NOESY experiments (long-distance correlations observed between red protons, Figure 36).
Figure 36: NMR evidence for by-products 398 and 399 arising from C-S bond cleavage and rearrangement.

Therefore, methyl sulfide 320fa was submitted to stronger conditions (Scheme 185). Unfortunately, we observed the sole formation of a similar rearranged by-product 400 as with thiocarbamates 318ec,d.

Scheme 185: Failed attempt of diimide reduction of cyclohexyl-substituted sulfide 320fa.

Furthermore, we repeated the reduction of allyl phenyl sulfide 394 under Carbery’s conditions and also obtained n-propyl phenyl sulfide 397 in 97% conversion. We then concluded diimide was not the appropriate reducing agent for our substrates and turned our attention to hydroboration.
II.D.3.b) Hydroboration

Sulfur-containing alkenes are known to readily undergo hydroboration, as shown by the reduction of allyl methyl sulfide by NaBH₄/BF₃·OEt₂ in triglyme in 72% yield. In a preliminary experiment, allylic thiol 319fe was submitted to these conditions, but they unsurprisingly turned out to be too harsh as only decomposition occurred (Scheme 186).

![Scheme 186: Failed attempt of NaBH₄-mediated hydroboration in thiol 319fe.](image)

Milder conditions employing bis(3-methyl-2-butyl)borane followed by protonolysis at 100 °C reportedly achieved the reduction of allyl methyl sulfide in 92% yield. Hydroboration of alkenes by catecholborane followed by the radical-mediated reduction of the resulting B-alkylcatecholboranes in the presence of dioxygen or peroxide has also been shown to be a mild alternative for the reduction of double bonds. However, these procedures were not tested as more promising results in the metathesis of our allylic substrates led us to focus on this transformation.

II.D.3.c) Hydrogenation with Pd/C

Facing only failures with mild conditions, and although sulfur-based functions are reputed to be incompatible with metal-catalysed hydrogenations, we decided to try our luck and attempt the palladium-mediated reduction of phenyl allyl sulfide 394. Surprisingly, we did obtain propyl phenylsulfide 397 under straightforward conditions (Scheme 187).

![Scheme 187: Successful Pd-catalysed hydrogenation of allyl phenyl sulfide.](image)
Encouraged by this unexpected result, we investigated the palladium-catalysed hydrogenation of methyl sulfide 320fi (Scheme 188).

Scheme 188: First attempt of Pd-catalysed hydrogenation of tertiary allylic sulfide 320fi.

Unfortunately, only starting material was recovered. More forcing conditions seemed to lead to C-S bond cleavage and rearrangement of unsubstituted allylic methyl sulfide 320af (Scheme 189), as suggested by a triplet in the olefinic region of the crude $^1$H NMR spectrum, and as observed for diimide reduction (Scheme 185).

Scheme 189: More forcing conditions in the Pd-catalysed hydrogenation of tertiary allylic sulfide 320af.

Cleavage of the C-S bond and rearrangement also occurred in cyclohexyl-substituted methyl sulfide 320fa (Scheme 190).

Scheme 190: More forcing conditions in the Pd-catalysed hydrogenation of cyclohexyl-substituted tertiary allylic sulfide 320af.

In conclusion, the quaternary centre in our tertiary allylic organosulfur compounds definitely appeared as the main factor preventing the reduction of the double bond since this transformation was successful in similar primary substrates.
II.D.4) Metathesis in tertiary S,S-diallylsulfides

Although metathesis of sulfur-containing olefins was considered difficult for a long time, the development of second-generation ruthenium catalysts has for example allowed the ring-closing metathesis of allyl sulfides and disulfides, self-cross metathesis of allyl sulfides and thiols and cross-metathesis of various allyl sulfides with prop-2-en-1-ol. We consequently envisaged the cross-metathesis of benzyl sulfide 321fc with TBDPS-protected hex-5-en-1-ol 403b in the presence of Hoveyda-Grubbs second generation catalyst 404, using mild conditions reported by Davis and co-workers (Scheme 191).

![Scheme 191](image_url)

Scheme 191: First attempt of cross-metathesis of tertiary allylic benzylsulfide 321fc.

Unfortunately, both starting materials 321fc and 403b were cleanly recovered, along with traces of the alcohol self-metathesis product.

Since more forcing conditions are usually required for the metathesis of hindered olefins, we attempted the cross metathesis of thiocarbamates 318ab and 318ae at higher temperatures (Scheme 192). We also changed the solvent to dichloromethane or toluene, more commonly used in metathesis reactions. After 1 h stirring at room temperature, a second portion of catalyst was added and the solution was heated to reflux for another hour. The effect of the protecting group of hex-5-en-1-ol 403 was also studied.
Refluxing at a moderate temperature did not allow formation of 325ab (Scheme 192, a), while when refluxing in toluene with free alcohol 403a, we observed the decomposition of 318ae (Scheme 192, b).

As with the failed attempts of reduction of the allylic double bond, we thought that the quaternary centre may be the main issue in the metathesis reaction as well. Grubbs and co-workers have reported the efficiency of catalyst 407 for the cross-metathesis of hindered olefins\textsuperscript{157b} and in the preparation of tetrasubstituted olefins via ring-closing metathesis.\textsuperscript{157a} Moreover, when applied to tertiary allylic alcohol 405, which has a quaternary carbon bearing a heteroatom, an alkyl and an aryl group as in tertiary α-thioallylic thiols 319 and sulfides 320-322, catalyst 407 led to an excellent yield of 89\% (Scheme 193).\textsuperscript{157b}
We therefore submitted methyl sulfide 320af to almost identical conditions (Scheme 194). Disappointingly, only the starting materials 320af and 403c were recovered.

Scheme 194: Attempt of cross-metathesis of tertiary sulfide 320af with catalyst 407.

Inspired by Mioskowski and co-workers’ successful ring-closing metathesis of diene sulfides 409 using the second generation Grubbs catalyst 410 (Scheme 195, a),\textsuperscript{156b} we were keen to try this transformation in our substrates, which would generate dihydrothiophenes 324 (Scheme 195, b).

Scheme 195: Mioskowski’s ring-closing metathesis of diene sulfides 409 and formation of 2,5-dihydrothiophenes 324 from tertiary allylsulfides 322.

Dihydrothiophenes are valuable synthetic targets, as precursors to thiophenes or tetrahydrothiophenes which are important motifs in natural products, biologically active compounds and materials.\textsuperscript{158a-d} Nevertheless, their stereoselective synthesis has received little attention,\textsuperscript{158a,f} with initial examples relying on diastereoselectivity solely,\textsuperscript{158b-d} until the very recent report of organocatalysed asymmetric domino thia-Michael/aldol condensation reactions leading to enantioenriched dihydrothiophenes.\textsuperscript{158e,g} Notably, Xu
and co-workers achieved excellent enantioselectivities in 2,5-dihydrothiophene-3-carbaldehydes 416 generated from 1,4-dithiane-2,5-diols 414 (Scheme 196).^158e

![Chemical Reaction](image)

**Scheme 196: Synthesis of 2,5-dihydrothiophenes 414 bearing an enantioenriched centre.^158e**

Ring-closing metathesis in tertiary S,S-diallylsulfides 322 would furnish enantioenriched dihydrothiophenes 324 bearing a chiral quaternary centre (Scheme 195, eq 2), a motif of particular interest for pharmaceutical applications.\(^{20,158f,159}\) Indeed, it can be found in thiotetronic acids, an important family of antibiotics,\(^{20,159a,b}\) whose first constituent thiolactomycin (R)-9 was isolated in 1982,\(^{5,20}\) and in dideoxyspirothio-nucleosides 417 and 418, interesting analogs of nucleosides with a sulfur-substituted furanose ring, recognised for their antiviral and anticancer properties\(^{159c}\) (Figure 37).

![Chemical Structures](image)

**Figure 37: 2,5-Dihydrothiophenes bearing an enantioenriched quaternary centre highlighted for their medicinal properties.**

Thus, dihydrothiophenes 324 would significantly enlarge the scope of the dihydrothiophenes bearing a synthetically accessible enantiopure quaternary centre. Moreover, although the synthesis of heterocycles by ring-closing metathesis is well established,\(^{160}\) very few examples involve sulfur atoms.\(^{156b,161}\) Should ring-closing metathesis of diallylsulfides 322 be successful, it would push back the current limitations of the reaction, not only regarding the nature of the heteroatom itself, but also in terms
of steric hindrance, as metathesis reactions of hindered alkenes are reputed to be challenging.\textsuperscript{157}

We initially attempted ring-closing metathesis of diallyl sulfide 322ah (Scheme 197), using catalyst 407 specifically designed for hindered olefins\textsuperscript{157b} and the associated conditions for the ring-closing metathesis\textsuperscript{157a} reported by Grubbs and co-workers.

\[
\text{CH}_2\text{Cl}_2, \text{reflux, 24 h} \quad \rightarrow \quad \begin{aligned}
\text{(+)}-322ah & \quad \text{407 (5 mol\%)} \\
\text{(−)}-322ah & \quad \text{(+)}-324d \\
\text{F} & \quad \text{2:1} \\
\text{S} & \quad \text{F}
\end{aligned}
\]

**Scheme 197:** First attempt of ring-closing metathesis in tertiary allylsulfide 322ah.

To our delight, 2,5-dihydrothiophene 324d was obtained as the major product along with remaining starting material in a very clean reaction: no by-product was detectable in the crude $^1$H NMR spectrum (Scheme 197). Because a low-boiling point solvent was used, we were confident that the reaction could be driven to completion by refluxing at a higher temperature.

Therefore, the crude mixture was diluted in DCE, another 5 mol\% of catalyst 407 was added and the reaction was heated to 80 °C for 42 h, after which no starting material remained (Scheme 198). Rapid purification by flash column chromatography to eliminate any metal traces and catalyst degradation-derived impurities allowed the isolation of 2,5-dihydrothiophene 324d in a very satisfying 70\% yield.

\[
\begin{aligned}
\text{CH}_2\text{Cl}_2, \text{reflux, 24 h} & \quad \rightarrow \quad \begin{aligned}
\text{(+)}-322ah & \quad \text{1. 407 (5 mol\%)} \\
\text{(−)}-322ah & \quad \text{2. 407 (5 mol\%)} \\
\text{F} & \quad \text{DCE, 80 °C, 42 h} \\
\text{S} & \quad \text{2:1} \\
\end{aligned}
\end{aligned}
\]

**Scheme 198:** Successful ring-closing metathesis of tertiary allylsulfide 322ah.

We then investigated the scope of the reaction (Scheme 199, Table 45), keeping DCE as the solvent in order to optimise both conversion and reaction time, since a higher temperature did not lead to decomposition in the case of 324d.
Scheme 199: Synthesis of 2,5-dihydrothiophenes 324 via ring-closing metathesis.

<table>
<thead>
<tr>
<th>Entry</th>
<th>322</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>324 Yield (%)</th>
<th>e.r.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>322af</td>
<td>H</td>
<td>Me</td>
<td>3-OMe</td>
<td>324b 45ab</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(R)-322ah</td>
<td>H</td>
<td>Me</td>
<td>3-F</td>
<td>(R)-324d 57c</td>
<td>14:86</td>
</tr>
<tr>
<td>3</td>
<td>322be</td>
<td>H</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>324c 77a</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(R)-322be</td>
<td>H</td>
<td>n-Pr</td>
<td>3-Cl</td>
<td>(R)-324c 31ad</td>
<td>8:92</td>
</tr>
<tr>
<td>5</td>
<td>322fa</td>
<td>Cy</td>
<td>Me</td>
<td>4-Me</td>
<td>324a 87a</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(R)-322fa</td>
<td>Cy</td>
<td>Me</td>
<td>4-Me</td>
<td>(R)-324a 91c</td>
<td>14:86</td>
</tr>
<tr>
<td>7</td>
<td>322fe</td>
<td>Cy</td>
<td>Me</td>
<td>3-OMe</td>
<td>324b 82a</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(S)-322fe</td>
<td>Cy</td>
<td>Me</td>
<td>3-OMe</td>
<td>(S)-324b 94c</td>
<td>94:6</td>
</tr>
<tr>
<td>9</td>
<td>322fh</td>
<td>Cy</td>
<td>Me</td>
<td>2-OMe</td>
<td>324e 91a</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(S)-322fh</td>
<td>Cy</td>
<td>Me</td>
<td>2-OMe</td>
<td>(S)-324e 90a</td>
<td>92:8</td>
</tr>
<tr>
<td>11</td>
<td>322fi</td>
<td>Cy</td>
<td>Me</td>
<td>1-naphthyl</td>
<td>324f -c,e</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(R)-322fi</td>
<td>Cy</td>
<td>Me</td>
<td>1-naphthyl</td>
<td>(R)-324f -c,e</td>
<td>22:78</td>
</tr>
<tr>
<td>13</td>
<td>322fk</td>
<td>Cy</td>
<td>Me</td>
<td>6-(NBoc)indole</td>
<td>324g 63a</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>(R)-322fk</td>
<td>Cy</td>
<td>Me</td>
<td>6-(NBoc)indole</td>
<td>(R)-324g -a,g</td>
<td>23:77</td>
</tr>
</tbody>
</table>

aCatalyst 407 was used. bContains inseparable impurities. cCatalyst 404 was used. dReaction was carried out on a 18 mg scale. eMixture with a rearranged by-product contained in the sm, see Scheme 181, Table 44. fSee structure in Figure 35. gThe exact amount of sm actually used is unknown because it contained inseparable impurities.

Table 45: Synthesis of 2,5-dihydrothiophenes 324 via ring-closing metathesis.

Pleasingly, ring-closing metathesis proceeded in good to high yields (63-94%, Table 45) in structurally varied tertiary allyl sulfides 322.

Substitution by a cyclohexyl group appeared to lead to higher yields (Table 45, entries 5-14 compared to entries 1-4), which is surprising since it confers additional steric hindrance to the substrate. However, the electron-donating effect of this large alkyl group may be beneficial to the ring-closing metathesis reaction, as methyl- andphenyl-substituted olefins have been reported to cyclise in higher yields than their non-substituted counterparts.162
Notably, yield above 90% were obtained for substrates \textbf{322fa,e} bearing electron-rich rings, that is, a \textit{para}-tolyl or \textit{meta}-methoxyphenyl ring, and more surprisingly, \textbf{322fh}, bearing a hindered \textit{ortho}-methoxyphenyl ring.

Thus, electron-rich allylic sulfides seemed to be more suited to the cyclisation process (Table 45, entries 5-10 compared to 1-4). However, yields were lower for \textbf{322f} and \textbf{322g} bearing the naphthyl and indolyl rings: the increased steric hindrance around the quaternary centre generated by these rings may prevail over their electron-richness and be unfavourable to the ring-closing reaction. Nevertheless, moderate to good yields were obtained for both aryl migration and ring-closing metathesis, an altogether significant achievement, given their electron-richness and steric hindrance which render the aryl migration and metathesis reactions, respectively, more difficult.

We also studied the potency of the Hoveyda-Grubbs second generation catalyst \textbf{404} and discovered that it generally led to similar or even higher yields than \textbf{407}, specifically designed for hindered olefins (Table 45, entries 1-2, 5-10).\textsuperscript{157a,b} Thus, the steric bulk on the \textit{N}-heterocyclic carbene part of the catalyst did not seem to impact on the cyclisation of tertiary \textit{S,S}-diallyl sulfides \textbf{322}.

In summary, hindered 2,5-dihydrothiophenes \textbf{324}, bearing an enantoienriched quaternary centre, were obtained via stereospecific \textit{\alpha}-arylation of \textit{S}-allyl thiocarbamates \textbf{316} in four steps (8-76\% overall yield).

**II.E) Evidence for retention in the aryl migration**

**II.E.1) Preliminary information**

Given that no product of the aryl and vinyl migrations, nor any of their derivatives (thiols, sulfides, thioesters, dihydrothiophenes) could be crystallised, we had to turn our attention to another way of getting information on the stereochemical course of the \textit{N} to \textit{C} rearrangements in thiocarbamates.

Circular dichroism (CD) is the differential absorption between the right-hand (R-CPL) and the left-hand circularly polarised light (L-CPL).\textsuperscript{163} Chiral molecules exhibit CD, that is, a solution of a chiral chromophore will absorb different proportions of the R-CPL and the L-CPL (for example 90\% and 92\% respectively), and this ratio will vary from one wavelength to another. Indeed, circular dichroism is measured over a wavelength range.
If R-CPL is absorbed in a larger extent that L-CPL, the signal will be negative, and if in a smaller extent, it will be positive. The resulting CD spectrum is a curve presenting maxima and minima over the appropriately chosen wavelength range. Measurement of CD as a function of wavelength is named circular dichroism spectroscopy.

The CD spectra of two paired enantiomers are mirror images to one another relatively to the horizontal axis. Thus, the absolute configuration of an enantiopure compound can be deduced from the comparison of its CD spectrum with that of a known sample.

Since our tertiary allylic thiocarbamates were made for the first time, comparison of their physical properties with previously reported ones was not possible. We thus envisaged using DFT calculations to predict the CD spectrum of one of our enantioenriched dihydrothiophene and compare it with the experimental one.

Dihydrothiophenes were thought to be well suited to computational modelling as the five-membered ring should limit rotational freedom, compared to our other tertiary products, and thus, give a clearer prediction. Moreover, we chose a substrate containing a simple and symmetrical phenyl ring, dihydrothiophene 324a. Finally, this hydrophobic compound would present the advantage of not having a very solvent dependent CD spectrum, which would facilitate further the modelling.

II.E.2) CD measurement and prediction using DFT calculations

II.E.2.1) CD measurement

Assuming a retentive aryl migration (step c) in the reaction sequence leading to dihydrothiophene 324a from (S)-328f\textsuperscript{133}, the absolute configuration of the latter will be (R) (Scheme 200).
Scheme 200: Expected (R)-configuration in 324a assuming a retentive aryl migration (c).

A 0.1 mg/mL (0.525 mmol/L) solution of 324a in methanol was prepared and CD was measured between 190 and 300 nm, according to the molecule absorption range revealed by its UV spectrum (Figure 38, A). The CD spectrum displays a maximum at 202 nm and a minimum at 235 nm, with a further positive shoulder at 218 nm (Figure 38, B).
II. E. 2. b) CD prediction using DFT calculations

In collaboration with Dr J. McDouall at the University of Manchester, density functional calculations were carried out using the Gaussian suite of programs. The geometry of \( 324a \) was fully optimised at the B3LYP/6-311G(d,p) level (Figure 39).
A potential energy scan revealed that the phenyl ring was able to rotate with a low potential energy barrier of 6.1 kJ/mol (Figure 40). The equilibrium geometry has one ortho proton pointing at the double bond of the thiophene. Rotation of the phenyl ring raises the energy to a maximum in which two hydrogen point at each other. This descends to a very shallow minimum in which the hydrogen opposite on the phenyl ring now points at the sulfur atom. The second maximum comes from this passing by the methyl group.

Figure 40: Potential energy scan for (R)-324a.

Accordingly, the ECD spectra were generated, within the time-dependent density functional formalism, for 10° rotations of the phenyl ring (all other coordinates being optimised) and Boltzmann weighted (298 K) to produce the resultant spectrum (Figure 41).

Figure 41: Electronic CD spectrum for (R)-324a, Boltzmann-weighed for every 10° rotations of the aryl ring.
Pleasingly, the predicted and the experimental CD spectra turned out to be very similar, both showing a maximum around 200-215 nm (Figure 42).

**Figure 42:** Comparison of the experimental and electronic CD spectra.

The shoulder observed at 218 nm in the experimental CD (Figure 42A) can be detected when looking at the individual calculated intensity values but its low intensity only broadens the peak on the electronic CD (Figure 42B).

Despite the slight discrepancy observed for the minimum (235 nm in the experimental spectrum, Figure 42A, and 270 nm in the predicted one, Figure 42B) DFT calculations are clearly in agreement with dihydrothiophene 324a being of (R)-absolute configuration, confirming our working hypothesis that aryl migration in allylic thiocarbamates is retentive, as it is in benzylic thiocarbamates\textsuperscript{108} and ureas,\textsuperscript{99,103} but contrasting with inversion observed in carbamates.\textsuperscript{106,107}
II.E.2.c) Confirmation of the stereochemical course in other allylic thiocarbamates

Assuming a uniformly retentive aryl migration in all thiocarbamates 316, the expected absolute configurations of the other 2,5-dihydrothiophenes 324b-e are shown in Scheme 201.

**Scheme 201: Expected configurations in 2,5-dihydrothiophenes 324 assuming a retentive aryl migration.**

Their CD spectra were also taken and compared with that of 324a (Figure 43, Figure 44).

**Figure 43: Overlayed CD spectra of (R)-2,5-dihydrothiophenes 324.**
Thus, the absolute configurations of 2,5-dihydrothiophenes 324b-e, as well as retentive aryl migration in all allylic thiocarbamates 316 could be unambiguously confirmed.

II.F) Conclusion

We have developed a straightforward and efficient synthesis to prepare allylic thiocarbamates 316, bearing a wide variety of substituents on the phenyl ring, at the position $\alpha$ to sulfur and on the allylic double bond.$^{120}$ The method relies on in situ [3,3]-sigmatropic rearrangement of $O$-substituted thiocarbamates 338, obtained from addition of allylic alcohols 324 to thiocarbonyldimidazole 337, to their $S$-allyl counterparts 339. Subsequent displacement of the imidazole group in 339 by $N$-methylanilines 329, using a coupling agent 340 or 341, led to the desired thiocarbamates 316 in generally good to excellent yields (Scheme 109).

Enantioenriched allylic thiocarbamates 316 were prepared via two different methods, depending on the starting allylic alcohol.

Primary allylic alcohols 328a,b were reacted with thiocarbamoyl chlorides 331 to generate the stable O-substituted thiocarbamates 332 (Scheme 104), which were submitted to enantioselective [3,3]-sigmatropic rearrangement in the presence of the chiral cobalt-based metal catalyst (R)-(−)-COP-Cl 263,97 leading to (R)-316a,b in good to excellent e.r.’s (Scheme 202).


Enantioenriched secondary allylic alcohols 328f,g, bearing either a cyclohexyl or phenyl substituent at the carbon α to oxygen, could be obtained either via the Sharpless asymmetric epoxidation (SAE)133 or Noyori’s asymmetric reduction of enones.136b By a careful choice of the chiral ligand/catalyst, we were able to prepare both enantiomers of cyclohexyl-substituted 328f: (R)-328f (99:1 e.r.) from SAE and (S)-328f (88:12 e.r.) from
Noyori’s enantioselective hydrogenation. Phenyl-substituted \((R)\)-328g (98:2 e.r.) was also obtained via asymmetric reduction of the corresponding enone \((E)\)-359. Reaction of enantioenriched 328f,g with thiocarbonyldiimidazole 337 under the conditions developed for the racemic version formed the highly enantioenriched thiocarbamates 316f,g (Scheme 203).

Scheme 203: Preparation of enantioenriched cyclohexyl- and phenyl-substituted allylic thiocarbamates 316f and 316g.

We have shown that aryl migration in allylic thiocarbamates 316 tolerated both electron-deficient and electron-rich rings, which is remarkable given the nucleophilic aromatic substitution pathway. Regiospecific attack at the ipso carbon of the migrating ring conserved its substitution pattern in tertiary thiocarbamates 318 (Scheme 204). Yields were generally good to excellent (56-99%), although somehow lower in 318b,d (bearing a n-propyl or i-propyl group at \(C_\alpha\)), in 318g (bearing a phenyl group on the terminal carbon of the allylic bond) or with heteroaryl rings (42-54%).

We generally found that substituents which deactivate the ipso position by increasing its electron density led to lower yields.

NMR studies in \(\alpha\)-thioorganolithium 317ac gave information on the \(^1\)H and \(^{13}\)C NMR shifts and coupling constants, which were in close agreement to those reported in the literature.
Regarding the stereospecificity of the rearrangement, we initially found that most rings migrated without loss of enantioenrichment in thiocarbamates 316a, with the unsubstituted allylic double bond. However, decreased e.r.’s (ca. 70:30) were observed when migrating a para-fluorophenyl or ortho-methoxyphenyl ring, and a racemic product 318ab was obtained with the para-tolyl ring. These substituents all share the ability of deactivating the ipso carbon by electron-donating effect, which may result in racemisation becoming faster than rearrangement in these substrates. On the contrary, a para-chloro or meta-methoxy substituent both led to full conservation of enantioenrichment.

We subsequently achieved complete enantiospecificity in the aryl migration of all kinds of rings, including heteroaryl ones, in allylic thiocarbamates 316f, bearing a cyclohexyl group at the terminal carbon of the double bond (Scheme 205).\(^{134}\)

Based on Beak’s studies in cyclohexyl- and cinnamyl α-aminolithiums\(^{53b}\), we assumed lithiated cyclohexyl-substituted thiocarbamates 317f possess a \(\eta^1\)-structure,
preventing epimerisation and potentially increasing reactivity towards nucleophilic attack of the aryl ring (Scheme 149). On the contrary, lithiated cinnamyl thiocarbamates 317g were more likely to be $\eta^3$-bonded, decreasing their reactivity, probably by making their torsion towards the reactive conformation more difficult, thus leading to lower yields. Delocalisation of the negative charge must also flatten the organolithium, favouring racemisation on the timescale of the rearrangement (Scheme 149).

Scheme 149: Proposed structures for allyllithiums 317a, 317f and 317g.

Migration of a non-aromatic group was another significant achievement of this thesis.\textsuperscript{148} Aryl rings had so far been the sole substituents to be migrated in ureas,\textsuperscript{99,102-104} carbamates\textsuperscript{106,107} and benzylic thiocarbamates.\textsuperscript{108} Migration of the vinyl group in N-vinyl benzylic thiocarbamates 326 was similarly found to be highly enantiospecific, leading to tertiary allylic thiocarbamate (R)-318aa in up to 96:4 e.r. (from 99:1 e.r.), in moderate yield. Improvement of the latter could be achieved by warming the reaction, albeit at the expense of the yield (Scheme 206).

Scheme 206: Migration of the vinyl group in N-vinylbenzylic thiocarbamate (S)-326a.
We have shown that the synthesis of challenging enantiomerically enriched tertiary thiols may be overcome via α-arylation in allylic thiocarbamates 316 or α-vinylation in benzylic thiocarbamates 326. The N to C transfer methodology notably expands the scope of C-C bond formation by electrophilic substitution of organolithiums, so far limited to alkylating agents or carbonyl compounds, or in the case of substitution at an sp² carbon, to conjugate additions and aromatic rings bearing anion-stabilising groups.⁴⁹,⁶⁹,¹⁰⁰

The resulting tertiary allylic thiocarbamates 318, via deprotection to thiols 319 and ring-closing metathesis¹⁵⁷,¹⁶⁰ of diallylsulfides 322,¹⁵⁶b are valuable precursors to biologically-interesting 2,5-dihydrothiophenes 324 (Scheme 207).¹⁵⁸ These latter compounds bear an uncommon enantioenriched quaternary centre, making them particularly interesting for pharmaceutical applications.²⁰,¹⁵⁹

Scheme 207: Synthesis of highly enantioenriched tertiary allylic thiols 319 and 2,5-dihydrothiophenes 324.

Finally, the retentive pathway for the aryl migration in lithiated allylic thiocarbamates 317 was unambiguously confirmed by comparison of experimental circular dichroism spectra of 2,5-dihydrothiophenes 324 to the electronic CD spectra generated for model compound 419 (in association with Dr. J. McDouall).¹³⁴
II.G) Future work

The scope of the $\alpha$-alkenylation of benzylic thiocarbamates 326 would be interesting to investigate further. Indeed, despite the failed attempts to migrate a cyclohexenyl group in thiocarbamate 389, this rearrangement was successful in $N$-vinyl ureas 366 (Scheme 152), as was the migration of other non-aromatic substituents in this series, such as propenyl or styrenyl. It would also be interesting to assess the possibility of migrating a $sp$ hybridised group in $N$-alkynylated thiocarbamates 419 (Scheme 208).

Scheme 208: Envisaged migration of an alkynyl substituent in benzylic thiocarbamates.

This leads us to envisage $\alpha$-arylation in propargylic thiocarbamates 421 (Scheme 209). This seems feasible at first glance, based on the successful rearrangement of the similar allylic thiocarbamates 316.

Scheme 209: Envisaged aryl migration in propargylic thiocarbamates.

From there, the logical consequence would be to follow-up on recent work within the group, showing that amino acid-derived $N'$-aryl ureas 279 may undergo C-arylation via attack of an enolate anion intermediate on the aryl ring, resulting in cyclisation to hydantoins 282. Subsequent deprotection and hydrolysis of hydantoins 282 led to quaternary arylated amino acids 283 (Scheme 210, a).
Scheme 210: Envisaged aryl migration in α-carboxyl thiocarbamates 423 and cyclisation to thiazolidines 424.

Should cyclisation to thiazolidines 424 be successful, aryl migration in thiocarbamates 423 would lead to tertiary α-mercaptoacids 425, which have been highlighted for their biological and pharmaceutical properties for many years (Scheme 210, b). 4,40,41

Finally, the stabilisation of the lithiated intermediate may also be achieved by a cyano group instead of the carbonyl function. Differences in organolithium reactivities, formation of thiazolidines 424 and deprotection/hydrolysis to tertiary thiols 425 would be interesting to investigate.
Chapter III: Experimental section

III.A) General information

NMR spectra were recorded on a Bruker Ultrashield 300 MHz, 400 MHz or 500 MHz spectrometer. The chemical shifts (δ) are reported in ppm downfield of trimethylsilane and coupling constants (J) reported in hertz and rounded to 0.1 Hz. Splitting patterns are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), quintet (qn), sextet (sext), octet (oct), multiplet (m), broad (b) or a combination of these. Where this combination involves a splitting pattern the abbreviation of which contains more than one letter, the abbreviations are separated by spaces and x for clarity purposes (for example: quintet of triplet reads qn x t). Other abbreviations include Cq (quaternary carbon), HAr, CHAr and CqAr (aromatic protons and carbons). Two geminal protons with different shifts are assigned the same number XX but noted H-XX and H-XX’. Solvents were used as internal standards when assigning NMR spectra (δH: CDCl3 7.26 ppm; δC: CDCl3 77.0 ppm). Coupling constants were calculated automatically by ChemDraw Ultra 11.0 software.

Low and high resolution mass spectra were recorded by staff at the University of Manchester. Electrospray spectra were recorded on a Micromass Platform II, and high resolution mass spectra were recorded either on a Waters QTOF or a Thermo Finnigan MAT95XP mass spectrometer, and are accurate to ±0.001 Da. For compounds containing chlorine or bromine, only 35Cl and 80Br isotopes are reported. GC-MS was performed on a Agilent 7890 (GC)/5975C (MS) spectrometer using the following parameters, unless otherwise stated:

Oven temperature: 50 °C (3min hold) then 25 °C/min to 300 °C (5min hold), total 18 min
Injector temperature : 300 °C (back injector)
Split injection : split ratio 20:1
Aux Heater: 300 °C
MS source: 230 °C
MS quad: 150 °C
Ionisation mode: EI
Column: Agilent H5-5ms, 30 m x 0.25 mm x 0.25 µm (film thickness)
Carrier gas: helium, column flow 1 mL/min.
Infrared spectra were recorded on a PerkinElmer FT-IR Spectrum BX spectrometer. Absorptions reported are the most intense, and quoted as wavenumbers in cm\(^{-1}\).

Melting points (mp) were determined on a Bibby Stuart Scientific Melting Point SMP10 apparatus and are uncorrected.

Optical rotation measurements \([\alpha]_D\) were taken on a AA-100 polarimeter in a cell with a 0.25 dm pathlength. The temperature \(T\), solvent \(S\) and concentration \(c\) (in grams per 100 mL) are as stated: \([\alpha]_D: x (c, S)\).

Thin layer chromatography (TLC) was performed using commercially available pre-coated plates (Macherey-Nagel Polygram\textsuperscript{\textregistered} Sil G/UV\(_{254}\) for TLC, 0.20 mm) and visualised with UV light at 254 nm, phosphomolybdic acid dip or Seebach’s dip (2.5 g of phosphomolybdic acid hydrate, 1.0 g of cerium(IV) sulfate tetrahydrate, 3.2 mL of conc. sulfuric acid and 90.5 mL of water).

Flash chromatography was carried out using Fluorochem Davisil 40-63 µÅ silica gel by means of compressed air.

Chiral HPLC measurements were carried out using a Hewlett Packard instrument fitted with a Daicel Chiralcel OD-H, a Daicel Chiralcel AD-H, or a \((R,R)\)-Whelk-01 stationary phase with a mixture of hexane and isopropyl alcohol as eluent, at. Absorptions were measured both at 214 and 254 nm. When the internal temperature of the apparatus could be set, it has been specified in the individual experimental procedure. Otherwise, the measurement was carried out at room temperature.

All reactions were conducted under a nitrogen atmosphere unless otherwise stated. Glassware was oven or flame dried. The temperatures stated are those for an external bath. An acetone/dry ice bath was used for -78°C. For all other temperatures, a cryo-cooler apparatus Haake EK 90 was used.

All solvents and reagents requiring purification were done so following standard laboratory techniques.\textsuperscript{165} Tetrahydrofuran was distilled under nitrogen from sodium using benzophenone indicator. Dichloromethane and diisopropylamine were obtained by distillation from calcium hydride under nitrogen. DMPU was distilled under reduced pressure from calcium hydride and stored over molecular sieves. TMEDA was distilled over KOH. \((\sim)\)-Sparteine was purified by Kugelrohr distillation. Triethylamine and pyridine were stored over KOH. Dry diethyl ether and toluene were provided by the SPS (Solvent Purification System) Pure Solv model PS-MD-5, serial PS-08-150 apparatus from Innovative Technology Inc. Petrol refers to the fraction of light petroleum ether boiling between 40 and 65 °C. \(n\)-Butyllithium was generally purchased from Sigma-Aldrich as a
1.6 M solution in hexanes, or occasionally from Acros as a 2.5 M solution in hexanes. s-Butyllithium was obtained from Acros as a 1.3 M solution in cyclohexane/hexane (92/8). All organolithium solutions were titrated prior to use against a solution of N-benzylbenzamide. All other solvents and commercially available reagents were used as received.

III.B) General procedures

General procedure A – Preparation of 1H-imidazole-1-carbothioates 339.

\[
\begin{align*}
\text{R}^1 \text{R}^2 \text{OH} & \quad \text{N} \quad \text{N} \\
328 & \quad \text{S} \\
& \quad \text{N} \quad \text{N} \\
337 & \quad \text{S} \\
& \quad \text{N} \quad \text{N} \\
339 & \quad \text{R}^1 \text{R}^2 \text{N} \\
\end{align*}
\]

By the method developed within the Clayden group. To a stirred solution of alcohol (1.0 eq) in CH₂Cl₂ or DCE at room temperature were added thiocarbonyldiimidazole (2.0 eq) and DMAP (0.1 eq). The reaction was stirred at room temperature or heated to 40 °C until completion. Once at room temperature, EtOAc was added and the crude mixture was washed with brine (x2). The organic layer was separated, dried over MgSO₄, filtered and concentrated. Further purification by column chromatography afforded the pure 1H-imidazole-1-carbothioates 339.

General procedure B – Preparation of phenyl(methyl)carbamothioates 316.

\[
\begin{align*}
\text{R}^1 \text{R}^2 \text{N} \quad \text{S} \quad \text{O} \\
339 & \quad \text{N} \\
& \quad \text{N} \\
329 & \quad \text{S} \\
& \quad \text{N} \quad \text{N} \\
316 & \quad \text{N} \quad \text{R}^3 \\
\end{align*}
\]

By the method developed within the Clayden group, based on a modification of the method reported by Vaidyanathan and co-workers.
To a solution of 1H-imidazole-1-carbamathioate 339 (1.0 eq) in THF (1.0 mL/50 mg of 339) at room temperature were added either HOBT 340 or Oxyma Pure® 341 (0.5 to 1.5 eq) and N-methylaniline 329 (1.2 eq). The reaction was heated to reflux for 24 h. Once cooled to room temperature, EtOAc was added and the organic mixture was washed with aqueous HCl (1.0 mL/50 mg of 339) for 20 min. The organic layer was separated, dried over MgSO₄, filtered and concentrated. Further purification by column chromatography afforded the pure phenyl(methyl)carbamothioates 316.

**General procedure C – Preparation of O-but-2-enyl methyl(phenyl)carbamothioates 332.**

![Chemical structure](image)

**C1 – Preparation of methyl(phenyl)carbamothioic chlorides 331:**

By a modification of the methods reported by Chen,¹⁶⁷ Vidaluc¹⁶⁸ and co-workers.

To a solution of thiophosgene 330 (1.5 eq) in THF (10.0 mL/200 mg of 329) at 0 °C was added a solution of N-methyl aniline 329 (1.0 eq) and triethylamine (1.5 eq) in THF (10.0 mL/200 mg of 329). The reaction was stirred at 0 °C for 5 min, warmed to room temperature and stirred for 20 h. Water was added and the layers were separated. The aqueous layer was extracted with Et₂O (x3). The combined organic fractions were dried over MgSO₄, filtered and concentrated to afford the methyl(phenyl)carbamothioic chlorides 331, used as crudes.
C2 – Preparation of O-but-2-enyl methyl(phenyl)carbamothioates 332:

By the method developed within the Clayden group.\textsuperscript{120}

To a solution of allylic alcohol 328a,b (1.0 eq) in THF (2.0 mL/100mg of 328) at 0 °C, was added sodium hydride (3.0 eq) portionwise. The reaction was stirred at 0 °C for 30 min. Sodium iodide (0.1 eq) followed by a solution of methyl(phenyl)carbamothioic chloride 331 (1.2 eq) in THF (1.0 mL/mmol of 331) were added. The reaction was warmed to room temperature and stirred for 1 h. Saturated aqueous NH\textsubscript{4}Cl was added and the layers were separated. The aqueous layer was extracted with Et\textsubscript{2}O (x3). The combined organic fractions were washed with water and brine, then dried over MgSO\textsubscript{4}, filtered and concentrated. Further purification by column chromatography (Pet 100%, Pet/EtOAc 99:1 to 95:5) afforded the pure O-but-2-enyl methyl(phenyl)carbamothioates 332.

General procedure D – Preparation of enantioenriched phenyl(methyl)carbamothioates (R)-316a,b.

By the method reported by Overman and co-workers.\textsuperscript{97}

To a solution of O-but-2-enyl methyl(phenyl)carbamothioate 332 (1.0 eq) in THF (8.0 mL/200 mg of 332) at room temperature was added (R)(−)-COP Cl 263 (5 mol%). The reaction was stirred at room temperature for 15 h to 4.5 days. The solvent was evaporated. Further purification by column chromatography afforded the pure enantioenriched phenyl(methyl)carbamothioates (R)-316a,b.
**General procedure E** – *Preparation of 1-substituted-but-2-yn-1-ols 334a, 352.*

By the method of Suffert and co workers.\(^{114}\)

To a solution of freshly distilled 1-bromopropene 335 (1.0 eq) in THF (1.0 mL/mmol of 335) cooled to -78 °C was added dropwise n-BuLi (1.5 eq). The reaction was stirred at -78 °C for 2 h and a solution of aldehyde (0.7 eq) in THF (0.5 mL/mmol of aldehyde) was added. The reaction was stirred at -78 °C for 1 h and warmed to room temperature. Saturated aqueous NH\(_4\)Cl was added and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (x3). The combined organic fractions were washed with brine (x2), then dried over MgSO\(_4\), filtered and concentrated to afford the pure 1-phenylbut-2-yn-1-ol 334a and 1-cyclohexylbut-2-yn-1-ol 352.

**General procedure F** – *Preparation of (E)-1-substituted-but-2-en-1-ones (E)-358, (E)-359.*

By a modification of the methods reported by Kobayashi,\(^{139a}\) Nau\(^{139b}\) and co-workers.

To a solution of allylic alcohol 328 (1.0 eq) in CHCl\(_3\) (10.0 mL/mmol of 328) was added oven-dried manganese dioxide (20 eq). The reaction was heated to 40 °C for 5.5 days. The crude mixture was filtered through celite and washed with warm CHCl\(_3\) (55 °C). The filtrate was concentrated under low vaccum, on the rotary evaporator. Further purification by column chromatography afforded the pure (E)-1-substituted-but-2-en-1-ones (E)-358, (E)-359.
General procedure G – Preparation of enantioenriched secondary allylic alcohols \((E)\)-328f,g.

\[
\begin{align*}
\text{O} & \quad \text{OH} \\
\text{R}^1 = \text{Cy}, (E)-358 & \quad \text{R}^1 = \text{Cy}, (E)-328f \\
\text{R}^1 = \text{Ph}, (E)-359 & \quad \text{R}^1 = \text{Ph}, (E)-328g \\
\end{align*}
\]

\[
\begin{align*}
(R,R)-356 & \text{ (0.05 mol\%)} \\
\text{H}_2 & \text{ (40 bar)} \\
\text{K}_2\text{CO}_3 & \text{ (0.02 eq)} \\
\text{i-PrOH} & \text{ (30 °C, 7 days)} \\
\end{align*}
\]

By the method reported by Noyori and co-workers.\textsuperscript{136b}

\(\text{i-PrOH}\) was degassed by bubbling nitrogen through it for 30 min and kept under argon. A test tube was carefully flame-dried and cooled to room temperature in a dessicator under vacuum, then under argon and kept under an argon atmosphere. A solution of 358 or 359 (1.0 eq) in degassed \(\text{i-PrOH}\) (2.0 mL/mmol of 358/359), followed by \((R,R)-356\) (0.05 mol\%) and \(\text{K}_2\text{CO}_3\) (0.02 eq) were added to the testing tube, which was purged with argon before it was put in the autoclave. The reaction was stirred under 40 bar of hydrogen at 30 °C (the autoclave was placed in a sand bath) for 7 days. The crude mixture was concentrated under vacuum. Further purification by column chromatography afforded the pure \((E)\)-1-substituted-but-2-en-1-ols \((E)\)-328f, \((E)\)-328g.

General procedure H – Preparation of \(S\)-1-phenylethyl ethanethioates 376.

\[
\begin{align*}
\text{R}^1 & \quad \text{OH} \\
343 & \quad 376 \\
\end{align*}
\]

\[
\begin{align*}
1. (\text{COCl})_2, \text{DMF} & \quad \text{CH}_2\text{Cl}_2, 0 \degree \text{C, 5 min} \\
2. \text{CH}_3(\text{CO})\text{SH} 375, \text{Et}_3\text{N} & \quad \text{DCM, 18 h} \\
\end{align*}
\]

By the method reported by Mukaiyama and co-workers.\textsuperscript{150}

Oxalyl chloride (1.0 eq) was added dropwise to a stirred solution of DMF (1.1 eq) in \(\text{CH}_2\text{Cl}_2\) (3.0 mL/mmol of oxalyl chloride) at 0 °C. The reaction was stirred at 0 °C for 5 min. 1-Phenylethanol 343 (1.0 eq), triethylamine (2.0 eq) and thioacetic acid 375 (0.7 eq) were...
added sequentially. The reaction was warmed to room temperature and stirred for 18 h. Water was added and the layers were separated. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were dried over MgSO₄, filtered and concentrated. Further purification by column chromatography afforded the pure S-1-phenylethyl ethanethioates 376.

**General procedure I – Preparation of 1-phenylethanethiols 378.**

![Chemical structure](image)

By the method reported by Hoppe and co-workers.⁶⁸

Lithium aluminium hydride (1.0 M in Et₂O, 1.0 eq.) was added dropwise to a solution of S-1-phenylethyl ethanethioate 376 (1.0 eq) in Et₂O (4 mL/mmol of 376). The reaction was heated to reflux for 2 h and cooled to room temperature. Aqueous HCl (1.0 M, 5.0 mL/mmol of 376) was added dropwise, followed by water. The layers were separated and the aqueous layer was extracted with Et₂O (x3). The combined organic layers were washed with water (x2), dried over MgSO₄, filtered and concentrated to afford the pure 1-phenylethanethiols 378 without further purification.

**General procedure J – Preparation of S-1-phenylethyl vinylcarbamothioates 379.**

![Chemical structure](image)

By the method developed within the Clayden group.¹⁴⁸

To a solution of S-1-phenylethanethiol 378 (1.0 eq) in CH₂Cl₂ (5 mL/mmol of 378) at room temperature was added vinyl isocyanate 369 (1.0-3.0 eq). The reaction was stirred at room temperature until completion was confirmed by TLC (Pet/EtOAc 8:2). Volatiles were evaporated under reduced pressure to afford the pure S-1-phenylethyl vinylcarbamothioates 379 without further purification.
General procedure **K** – Preparation of S-1-phenylethyl methyl(vinyl)carbamothioates 326.

![Chemical structure](image)

By the method developed within the Clayden group.\(^{148}\)

To a solution of S-1-phenylethyl vinylcarbamothioate 379 (1.0 eq) in anhydrous DMF (10.0 mL/mmol of 379) was added iodomethane (2.5 eq). The reaction mixture was cooled to 0 °C and NaH (60% in mineral oil, 2.0 eq) was carefully added, portionwise. The reaction was stirred at 0 °C for 20 min, warmed to room temperature and stirred for 18 h. Then water was added, slowly at first and the layers were separated. The aqueous layer was extracted with Et₂O (x3) and the combined organic layers were washed with plenty of water (x3) to afford the pure S-1-phenylethyl methyl(vinyl)carbamothioates 326 without further purification.

General procedure **L** – Preparation of enantioenriched benzylic alcohols (R)-343.

![Chemical structures](image)

By the method reported by Noyori and co-workers.\(^{151}\)

**Preparation of catalyst (S,S)-383:**

A solution of \([RuCl₂(η⁶-mesitylene)]₂\) \(380\) (80 mg, 0.13 mmol, 1.0 eq), \((15,2S)-N-p\)-toluenesulfonyl-1,2-diphenylethylenediamine (S,S)-381 (TsDPEN) (100 mg, 0.27 mmol, 2.0 eq) and triethylamine (0.08 mL, 0.52 mmol, 4.0 eq), (Ru:TsDPEN:Et₃N molar ratio = 200...
1.1:1.2) in i-propanol (2.0 mL) was heated at 80 °C for 1 h. The orange solution was concentrated and the solid ruthenium complex was collected by filtration. The crude material was washed with a small amount of water and dried under reduced pressure for 10 h to afford \((R)-\text{RuCl}[(1S,2S)-p-\text{TsNCH}_2\text{C}_6\text{H}_5\text{CH}_2\text{NH}_2][\eta^6-\text{p-cymene}]\) \((S,S)-383\) as an orange solid.

**Reaction:**

To triethylamine (2.4 eq) stirred at 0 °C was added dropwise formic acid (6.0 eq, 5:2 formic acid/Et\(_3\)N azeotropic mixture). Upon warming to room temperature, ketone \(382\) (1.0 eq) and \((S,S)-383\) (0.5 mol%) were successively added and the reaction was stirred at room temperature for 3-7 days. Water was added and the layers were separated. The aqueous layer was extracted with EtOAc (x3). The combined organic fractions were washed with saturated aqueous NaHCO\(_3\) and brine, then dried over MgSO\(_4\), filtered and concentrated. Further purification by column chromatography afforded the pure chiral \((R)-1\)-phenylethanols \((R)-339\).

**General procedure M – Lithiation of phenyl(methyl)carbamothioates 316 with LDA.**

![Diagram of reaction](image)

By the method developed within the Clayden group.\(^{99,106,108}\)

To a solution of DIPA (3.0 eq) in THF (1.0 mL) at -78 °C \(n\)-BuLi (2.5 eq) was added dropwise. The mixture was stirred at -78 °C for 5 min then warmed to approximately -40 °C by allowing only the bottom of the flask to be in contact with the cooling bath and stirred at this temperature for 15 min, then cooled down to -78 °C for 5-10 min. A solution of phenyl(methyl)carbamothioate \(316\) (50 mg, 1.0 eq) in THF (1.5 mL) was cooled down to -78 °C. LDA was added to the starting material solution at -78 °C and the reaction was either allowed to stir at -78 °C for the stated time or warmed slowly to the desired temperature by addition of room temperature acetone in the cooling bath and stirred at this temperature for the stated time. In this last case, the reaction was cooled back to -78 °C before being quenched. Propionic acid (3.0 eq) was added dropwise, the reaction was allowed to stir at -78 °C for 10 min and warmed to room temperature. Water and Et\(_2\)O
were added and the layers were separated. The aqueous layer was extracted with Et₂O (x3). The combined organic layers were washed with plenty of water and brine, dried over MgSO₄, filtered and concentrated. Further purification by column chromatography afforded the pure rearranged methylcarbamothioates 318.

**General procedure N – Lithiation of phenyl(methyl)carbamothioates 316 with LDA·LiCl.**

By the method developed within the Clayden group. ⁹⁹,¹⁰⁶,¹⁰⁸

To a solution of DIPA (3.0 eq) in THF (1.0 mL) at -78 °C n-BuLi (2.5 eq) was added dropwise. The mixture was stirred at -78 °C for 5 min then warmed to approximately -40 °C by allowing only the bottom of the flask to be in contact with the cooling bath and stirred at this temperature for 15 min, then cooled down to -78 °C for 5-10 min. Oven-dried LiCl (5.0 eq) was added to a solution of phenyl(methyl)carbamothioate 316 (50 mg, 1.0 eq) in THF (1.5 mL) which was cooled to -78 °C before the dropwise addition of LDA. The reaction was either allowed to stir at -78 °C for the stated time or warmed slowly to the desired temperature by addition of room temperature acetone in the cool bath and stirred at this temperature for the stated time. In this last case, the reaction was cooled back to -78 °C before being quenched. Propionic acid (3.0 eq) was added dropwise, the reaction was allowed to stir at -78 °C for 10 min and warmed to room temperature. Water and Et₂O were added and the layers were separated. The aqueous layer was extracted with Et₂O (x3). The combined organic layers were washed with plenty of water and brine, dried over MgSO₄, filtered and concentrated. Further purification by column chromatography afforded the pure rearranged methylcarbamothioates 318.
**General procedure O** – *Lithiation of phenyl(methyl)carbamothioates 316 with LiTMP.*

![Chemical structure](image)

By the method developed within the Clayden group.\(^{99,106,108}\)

To a solution of 2,2,6,6-tetramethylpiperidine (3.0 eq) in THF (1.0 mL) at \(-78 ^\circ C\) \(n\-\text{BuLi} (2.5\) eq) was added dropwise. The mixture was stirred at \(-78 ^\circ C\) for 5 min then warmed to approximately \(-40 ^\circ C\) by allowing only the bottom of the flask to be in contact with the cooling bath and stirred at this temperature for 15 min, then cooled down to \(-78 ^\circ C\) for 5-10 min. A solution of phenyl(methyl)carbamothioate 316 (50 mg, 1.0 eq) in THF (1.5 mL) was cooled down to \(-78 ^\circ C\). LiTMP was added to the starting material solution at \(-78 ^\circ C\) and the reaction was allowed to stir at \(-78 ^\circ C\) for 15 h. Propionic acid (3.0 eq) was added dropwise, the reaction was allowed to stir at \(-78 ^\circ C\) for 10 min and warmed to room temperature. Water and Et\(_2\)O were added and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (x3). The combined organic layers were washed with plenty of water and brine, dried over MgSO\(_4\), filtered and concentrated. Further purification by column chromatography afforded the pure rearranged methylcarbamothioates 318.

**General procedure P** – *Deprotection of methylcarbamothioates 318 to tertiary thiols 319.*

![Chemical structure](image)

By the method developed within the Clayden group.\(^{99,108}\)

To a solution of methylcarbamothioate 318 (1.0 eq) in EtOH/Et\(_2\)O 2:1 (10 mL/mmol of 318) at 0 °C was added NaOEt (21% w/w in EtOH, 2.0 eq) dropwise. The reaction was stirred at 0 °C for 45 min before saturated aqueous NH\(_4\)Cl (2 mL/mmol of 318) was added. The reaction was warmed to room temperature, water and Et\(_2\)O were added and the layers were separated. The aqueous layer was extracted with pentane/Et\(_2\)O 1:1 (x3). The
combined organic layers were washed with plenty of water, dried over MgSO$_4$, filtered and concentrated. Further purification by column chromatography (Pentane 100%, Pentane/Et$_2$O 99:1 to 97:3) and careful evaporation of the solvents on the rotary evaporator without vacuum afforded the pure tertiary thiol 319.

**General procedure Q – Alkylation of tertiary thiols 319 to sulfides 320, 322.**

![Reaction Scheme]

By the method developed within the Clayden group.$^{126,134}$

To a solution of thiol 319 (1.0 eq) in Et$_2$O (10 mL/mmol of 319) at -78 °C $n$-BuLi (1.1 eq) was added dropwise. The reaction was stirred at -78 °C for 2 min before either methyl iodide or allyl bromide (1.2 eq) was added. The reaction was stirred at -78 °C for 15 min to 4 h (generally 2 to 4 h) before it was slowly warmed to room temperature and allowed to stir for 20 h. A few drops of water were carefully added, the reaction was stirred at for 1 min before more water and Et$_2$O were added. The layers were separated and the aqueous layer was extracted with Et$_2$O (x3). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated. Further purification by column chromatography (Pentane 100%, Pentane/Et$_2$O 100:1 to 98:2) and careful evaporation of the solvents on the rotary evaporator without vacuum afforded the pure tertiary sulfides 320 and 322.
General procedure R – Ring-closing metathesis of S-allyl sulfides 322 to 2,5-dihydrothiophenes 324.

By the method developed within the Clayden group, based on a modification of the method reported by Grubbs and co-workers.

Dichloroethane was degassed by bubbling nitrogen through it for 30 min and kept under argon. In a flame-dried flask, cooled in a dessicator under vacuum and purged with argon, was added a solution of 322 (1.0 eq) in degassed DCE (10 mL/mmol of 322), followed by either catalyst 404 or 407. The flask was purged with argon after each addition. The reaction was heated to 80 °C for 24 h and cooled to room temperature. Ethyl vinyl ether (10 mL/mmol of 322) was added, the reaction was stirred for 10 min and concentrated under reduced pressure. Further purification by column chromatography (Pentane 100%, Pentane/Et₂O 100:1 to 98:2) afforded the pure 2,5-dihydrothiophenes 324.

III.C) Experimental procedures and data

316aa: S-But-3-en-2-yl phenyl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (300 mg, 1.65 mmol), HOBT (0.5 eq) and N-methylaniline. Purification by filtration over silica (Pet/Et₂O 9:1) afforded the title compound as a yellow oil (250 mg, 68%).
Rf: 0.32 (Pet/Et₂O 9:1); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.39 (m, 3H, H-9, H-10, H-11), 7.27 (m, 2H, H-8, H-12), 5.87 (ddd, J = 17.0, 10.0, 7.0 Hz, 1H, H-3), 5.18 (dt, J = 17.0, 1.2 Hz, 1H, H-4'), 5.02 (dt, J = 10.0, 1.2 Hz, 1H, H-4), 4.12 (qn x t, J = 7.0, 1.2 Hz, 1H, H-2), 3.32 (s, 3H, H-6), 1.37 (d, J = 7.0 Hz, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 168.3 (C-5), 142.2 (C-7), 139.7 (C-3), 129.6 (C-9, C-11), 128.5 (C-8, C-10, C-12), 114.7 (C-4), 42.9 (C-2), 38.3 (C-6), 20.1 (C-1); IR: ν max(film)/cm⁻¹ 1651 (C=O), 1594 (C=C), 1494 (C=C Ar), 1341, 1268; MS: m/z (ES⁺) 222 [M+H]⁺ (50%), 244 [M+Na]⁺ (100%), 276 [M+Na+MeOH]⁺ (40%); HRMS: found 222.0945, [M+H]⁺ requires 222.0948.

The equivalent enantioenriched thiocarbamate (R)-S-but-3-en-2-yl phenyl(methyl)carbamothioate (R)-316aa (91:9 e.r., 140 mg, 93%) was prepared from O-but-2-enyl phenyl(methyl)carbamothioate 332a (150 mg, 0.68 mmol) following general procedure D.

[α]ᵣ²⁰: +16.1 (c 2.00, CHCl₃); HPLC: (R,R)-Whelk-O1, Hexane/i-PrOH 98:2, 1.0 mL/min, minor 11.5 min, major 13.2 min.

316ab: S-But-3-en-2-yl methyl(p-tolyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (250 mg, 1.37 mmol), HOBt (0.5 eq) and 4-methyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (280 mg, 88%).

Rf: 0.71 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.21 (d, J = 8.4 Hz, 2H, H-8, H-12), 7.14 (d, J = 8.4 Hz, 2H, H-9, H-11), 5.87 (ddd, J = 17.2, 10.2, 7.0 Hz, 1H, H-3), 5.17 (dt, J = 17.2, 1.0 Hz, 1H, H-4'), 5.01 (dt, J = 10.2, 1.0 Hz, 1H, H-4), 4.10 (qn x t, J = 7.0, 1.0 Hz, 1H, H-2), 3.29 (s, 3H, H-6), 2.24 (s, 3H, H-13), 1.36 (d, J = 7.0 Hz, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 168.2 (C-5), 139.6 (C-3), 139.3 (C-10), 138.5 (C-7), 130.1 (C-8, C-12), 128.1 (C-9, C-11), 114.5 (C-4), 42.7 (C-2), 38.2 (C-6), 21.2 (C-13), 19.9 (C-1); IR: ν max(film)/cm⁻¹ 1652 (C=O), 1513 (C=CN), 1342, 1258; MS: m/z (ES⁺) 258 [M+Na]⁺ (100%), 290 [M+Na+MeOH]⁺ (50%); HRMS: found 258.0918, [M+Na]⁺ requires 258.0924.
The equivalent enantioenriched thiocarbamate \((R)-5\text{-but}-3\text{-en}-2\text{-yl}
\text{methyl}(p\text{-tolyl})\text{carbamothioate} \(\text{(R)}-\text{316ab}\) (89:11 e.r., 218 mg, 99\%) was prepared from \(O\text{-but}-2\text{-enyl methyl}(p\text{-tolyl})\text{carbamothioate} \text{332b}\) (220 mg, 0.93 mmol) following general procedure D.

\(\text{[a]}_b^{22}\): \(-6.3 \ (c 0.87, \text{CHCl}_3); \ \text{HPLC:} \ (R,R)-\text{Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, minor 7.6 min, major 8.5 min (254.4 nm).}

\text{316ac: S-But-3-en-2-yl 4-methoxyphenyl(methyl)carbamothioate.}

![Diagram](image)

General procedure B was followed using \(S\text{-but}-3\text{-en}-2\text{-yl 1H-imidazole-1-carbothioate} \text{339a}\) (50 mg, 0.27 mmol), HOBt (0.5 eq) and 4-methoxy-\(N\)-methylaniline. Purification by column chromatography (Pet/EtOAc 95:5) afforded the title compound as a yellow oil (59 mg, 87\%).

\(R_f\): 0.41 (Pet/EtOAc 8:2); \(^{1}H\ \text{NMR:} \ (400 MHz; \text{CDCl}_3) \ \delta\ (ppm) 7.17 (d, \(J = 9.0\) Hz, 2H, H-8, H-12), 6.91 (d, \(J = 9.0\) Hz, 2H, H-9, H-11), 5.87 (ddd, \(J = 17.0, 10.2, 6.8\) Hz, 1H, H-3), 5.17 (dt, \(J = 17.0, 1.2\) Hz, 1H, H-4'), 5.01 (dt, \(J = 10.2, 1.2\) Hz, 1H, H-4), 4.09 (qn, \(J = 6.8\) Hz, 1H, H-2), 3.82 (s, 3H, H-13), 3.28 (s, 3H, H-6), 1.36 (d, \(J = 6.8\) Hz, 3H, H-1); \(^{13}C\ \text{NMR:} \ (100 MHz, \text{CDCl}_3) \ \delta\ (ppm) 168.5 (C-5), 159.4 (C-10), 139.6 (C-3), 134.5 (C-7), 129.7 (C-8, C-12), 114.6 (C-9, C-11), 114.5 (C-4), 55.4 (C-13), 42.7 (C-2), 38.3 (C-6), 19.9 (C-1); \text{IR:} \ \nu_{\text{max}}\text{(film)/cm}^{-1} 1652 \ (C=O), 1511 \ (C=C_Ar), 1246 \ (C_Ar-N); \text{ MS:} \ m/z \ (ES^+) 274 [M+Na]^+ \ (100\%), 306 [M+Na+MeOH]^+ \ (50\%); \text{HRMS:} \ \text{found} 274.0876, [M+Na]^+ \text{ requires} 274.0873.

\text{316ad: S-But-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate.}

![Diagram](image)

General procedure B was followed using \(S\text{-but}-3\text{-en}-2\text{-yl 1H-imidazole-1-carbothioate} \text{339a}\) (50 mg, 0.27 mmol), HOBt (0.5 eq) and 4-chloro-\(N\)-methylaniline. Purification by
column chromatography (Pet/EtOAc 98:2 to 85:15) afforded the title compound as a yellow oil (45 mg, 65%).

\[ R_f: 0.48 \text{ (Pet/EtOAc 8:2)}; ^1H \text{ NMR: (400 MHz; CDCl}_3\text{)} \delta (ppm) 7.37 (d, J = 8.8 Hz, 2H, H-8, H-12), 7.21 (d, J = 8.8 Hz, 2H, H-9, H-11), 5.86 (ddd, J = 17.2, 10.4, 7.2 Hz, 1H, H-3), 5.18 (dt, J = 17.2, 1.2 Hz, 1H, H-4'), 5.03 (dt, J = 10.4, 1.2 Hz, 1H, H-4), 4.11 (qn, J = 7.2 Hz, 1H, H-2), 3.29 (s, 3H, H-6), 1.37 (d, J = 7.2 Hz, 3H, H-1); ^13C \text{ NMR: (100 MHz, CDCl}_3\text{)} \delta (ppm) 168.0 (C-5), 140.5 (C-7), 139.3 (C-3), 134.1 (C-10), 129.7 (C-9, C-11), 129.6 (C-8, C-12), 114.7 (C-4), 42.8 (C-2), 38.1 (C-6), 19.9 (C-1); IR: \nu_{max}(film)/cm^{-1} 1653 (C=O), 1488 (C=C Ar), 1277 (C Ar-N); MS: m/z (ES\text{+}) 278 [M+Na]^{+} (100%), 310 [M+Na+MeOH]^{+} (80%); HRMS: found 256.0561, [M+H]\text{+} requires 274.0558.

The equivalent enantioenriched thiocarbamate \((R)-S\text{-but}-3\text{-en}-2\text{-yl 4-chlorophenyl}(methyl)carbamothioate (R)-316ad\text{ (89:11 e.r., 210 mg, 95%)} was prepared from \text{O-but}-2\text{-enyl 4-chlorophenyl(methyl)carbamothioate 332d\text{ (220 mg, 0.86 mmol)}} following general procedure D.

\([\alpha]_D^{22}: -9.0 \text{ (c 1.16, CHC}_3\text{)}; \text{HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 \degree \text{C, minor 12.4 min, major 14.4 min (254.4 nm)}}.

316ae: S-But-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a\text{ (250 mg, 1.37 mmol)}, HOBt (0.5 eq) and 4-fluoro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (281 mg, 86%).

\[ R_f: 0.73 \text{ (Pet/EtOAc 8:2)}; ^1H \text{ NMR: (400 MHz; CDCl}_3\text{)} \delta (ppm) 7.28 (dd, J = 9.4, 5.6 Hz, 2H, H-8, H-12), 7.12 (t, J = 9.4 Hz, 2H, H-9, H-11), 5.90 (ddd, J = 17.2, 10.0, 7.0 Hz, 1H, H-3), 5.22 (dt, J = 17.2, 1.2 Hz, 1H, H-4'), 5.06 (dt, J = 10.0, 1.2 Hz, 1H, H-4), 4.14 (qn x t, J = 7.0, 1.2 Hz, 1H, H-2), 3.33 (s, 3H, H-6), 1.40 (d, J = 7.0 Hz, 3H, H-1); ^13C \text{ NMR: (100 MHz, CDCl}_3\text{)} \delta (ppm) 168.3 (C-5), 162.2 (d, \text{J}_{CF} = 248.0 \text{ Hz, C-10}), 139.4 (C-3), 138.0 (C-7), 130.3 (bd,
\^3J_{CF} = 8.4 \text{ Hz, C-8, C-12}, 116.5 (d, \^2J_{CF} = 22.9 \text{ Hz, C-9, C-11}), 114.7 (C-4), 42.9 (C-2), 38.2 (C-6), 20.0 (C-1); \textbf{IR:} \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 1652 (C=O), 1508 (C=C_{Ar}), 1220 (C-F); \textbf{MS:} \text{m/z } (\text{ES}^+) 262 [M+Na]^+ (100\%), 294 [M+Na+MeOH]^+ (40\%); \textbf{HRMS:} \text{found } 262.0668, [M+Na]^+ \text{ requires } 262.0673.

The equivalent enantioenriched thiocarbamate \((R)-S\text{-but-3-en-2-yl } 4\text{-fluorophenyl}(methyl)\text{carbamothioate } (R)-\textbf{316ae} \text{ (89:11 } e.r., 164 \text{ mg, 94\%)} \text{ was prepared from } O\text{-but-2-enyl } 4\text{-fluorophenyl}(methyl)\text{carbamothioate } \textbf{332e} \text{ (106 mg, 0.44 mmol) following general procedure D.} \\
[\alpha]_b^{22}: +12.1 \text{ (c 1.10, CHCl}_3); \textbf{HPLC:} \text{(R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, minor 7.3 min, major 8.0 min (214.4 nm, 254.4 nm).}

\textbf{316af:} S-But-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using \textbf{S-but-3-en-2-yl } 1H-imidazole-1-carbothioate \textbf{339a} (50 mg, 0.27 mmol), HOBt (1.0 eq) and 3-methoxy-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 7:3) afforded the title compound as a yellow oil (48 mg, 71\%).

\textbf{Rf:} 0.42 (Pet/EtO 8:2); \textbf{\textsuperscript{1}H NMR:} (400 MHz; CDCl}_3 \delta (ppm) 7.31 (t, J = 8.0 \text{ Hz, } 1H, H-11), 6.90 (ddd, J = 8.0, 2.4, 1.6 \text{ Hz, } 1H, H-12), 6.86 (ddd, J = 8.0, 2.4, 1.6 \text{ Hz, } 1H, H-10), 6.80 (t, J = 1.6 \text{ Hz, } 1H, H-8), 5.88 (ddd, J = 17.2, 10.0, 6.8 \text{ Hz, } 1H, H-3), 5.18 (dt, J = 17.2, 1.2 \text{ Hz, } 1H, H-4'), 5.02 (dt, J = 10.0, 1.2 \text{ Hz, } 1H, H-4), 4.11 (qn x t, J = 6.8, 1.2 \text{ Hz, } 1H, H-2), 3.82 (s, 3H, H-13), 3.31 (s, 3H, H-6), 1.37 (d, J = 6.8 \text{ Hz, } 3H, H-1); \textbf{\textsuperscript{13}C NMR:} (100 MHz, CDCl}_3 \delta (ppm) 168.1 (C-5), 160.2 (C-9), 143.1 (C-7), 139.6 (C-3), 130.1 (C-11), 120.4 (C-10), 114.5 (C-4), 114.0 (C-8), 113.9 (C-12), 55.4 (C-13), 42.7 (C-6), 38.1 (C-2), 19.9 (C-1); \textbf{IR:} \nu_{\text{max}}(\text{film})/\text{cm}^{-1} 1651 (C=O), 1599 (C=C), 1587, 1486 (C=C_{Ar}), 1282 (C_{Ar}-N), 1216 (C-O); \textbf{MS:} \text{m/z } (\text{ES}^+) 274 [M+Na]^+ (100\%), 306 [M+Na+MeOH]^+ (15\%); \textbf{HRMS:} \text{found } 274.0869, [M+Na]^+ \text{ requires } 274.0873.
The equivalent enantioenriched thiocarbamate (R)-S-but-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate (R)-316af (83:17 e.r., 148 mg, 95%) was prepared from O-but-2-eny1 3-methoxyphenyl(methyl)carbamothioate 332f (120 mg, 0.48 mmol) following general procedure D.

$\left[\alpha\right]_D^{22} + 4.9$ (c 1.06, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, minor 10.0 min, major 11.2 min (214.4 nm).

316ag: S-But-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (50 mg, 0.27 mmol), HOBt (1.0 eq) and 3-chloro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (31 mg, 45%).

$R_f$: 0.41 (Pet/Et$_2$O 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.33 (m, 2H, H-10, H-12), 7.28 (m, 1H, H-8), 7.18 (m, 1H, H-11), 5.88 (ddd, $J = 17.2, 10.0, 7.0$ Hz, 1H, H-3), 5.19 (dt, $J = 17.2, 1.4$ Hz, 1H, H-4'), 5.04 (dt, $J = 10.0, 1.4$ Hz, 1H, H-4), 4.12 (qn x t, $J = 7.0, 1.4$ Hz, 1H, H-2), 3.30 (s, 3H, H-6), 1.38 (d, $J = 7.0$ Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.0 (C-5), 143.2 (C-7), 139.3 (C-3), 134.7 (C-9), 130.3 (C-10 or C-12), 128.4 (C-12 or C-10), 126.4 (C-11), 114.8 (C-4), 42.9 (C-2), 38.0 (C-6), 19.9 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1656 (C=O), 1589 (C=CN$_1$), 1337, 1278 (C$_{Ar}$-N); MS: m/z (ES$^+$) 256 [M+H$^+$] (50%), 278 [M+Na$^+$] (100%), 310 [M+Na+MeOH$^+$] (50%); HRMS: found 256.0561, [M+H$^+$] requires 256.0557.

The equivalent enantioenriched thiocarbamate (R)-S-but-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate (R)-316ag (80:20 e.r., 196 mg, 98%) was prepared from O-but-2-eny1 3-chlorophenyl(methyl)carbamothioate 332g (200 mg, 0.78 mmol) following general procedure D.

$\left[\alpha\right]_D^{22} + 4.5$ (c 1.10, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, minor 9.5 min, major 10.9 min (254.4 nm).
316ah: S-But-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (200 mg, 1.10 mmol), HOBt (1.0 eq) and 3-fluoro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 96:4) afforded the title compound as a yellow oil (122 mg, 46%).

$R_f$: 0.53 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.36 (td, J = 8.4, 6.4 Hz, 1H, H-11), 7.09-7.04 (m, 2H, H-10, H-12), 7.01 (dt, J = 9.2, 2.2 Hz, 1H, H-8), 5.88 (ddd, J = 17.0, 10.2, 7.2 Hz, 1H, H-3), 5.20 (dt, J = 17.0, 1.2 Hz, 1H, H-4'), 5.04 (dt, J = 10.2, 1.2 Hz, 1H, H-4), 4.12 (qn x t, J = 7.2, 1.2 Hz, 1H, H-2), 3.31 (s, 3H, H-6), 1.38 (d, J = 7.2 Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.0 (C-5), 162.8 (d, $^3$J$_{CF}$ = 250.0 Hz, C-9), 143.5 (d, $^3$J$_{CF}$ = 9.6 Hz, C-7), 139.3 (C-3), 130.4 (d, $^3$J$_{CF}$ = 9.0 Hz, C-11), 123.8 (C-12), 115.5 (d, $^2$J$_{CF}$ = 20.9 Hz, C-8), 115.3 (d, $^2$J$_{CF}$ = 20.0 Hz, C-10), 114.8 (C-4), 42.8 (C-2), 38.0 (C-6), 19.9 (C-1); IR: $\nu_{max}$(film)/cm$^{-1}$ 1656 (C=O), 1605 (C=C), 1589 (C=C$_N$), 1282 (C-F or C$_N$-N), 921; MS: m/z (ES$^+$) 240 [M+H]$^+$ (100%), 262 [M+Na]$^+$ (40%); HRMS: found 240.0853, [M+H]$^+$ requires 240.0853.

The equivalent enantioenriched thiocarbamate (R)-S-but-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate (R)-316ah (82:18 e.r., 194 mg, 97%) was prepared from O-but-2-enyl 3-fluorophenyl(methyl)carbamothioate 332h (200 mg, 0.84 mmol) following general procedure D.

$[\alpha]_D^{22}$: +1.0 (c 1.50, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, minor 7.3 min, major 7.9 min (254.4 nm).
**316ai**: S-But-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate **339a** (280 mg, 1.54 mmol), HOBt (1.0 eq) and 2-methoxy-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 95:5) afforded the title compound as a yellow oil (336 mg, 87%).

**Rf**: 0.38 (Pet/Et2O 8:2); **1H NMR**: (400 MHz; CDCl3) δ (ppm) 7.36 (td, J = 7.8, 1.6 Hz, 1H, H-11), 7.21 (dd, J = 7.8, 1.6 Hz, 1H, H-12), 6.96 (d, J = 7.8 Hz, 2H, H-9, H-10), 5.87 (ddd, J = 17.0, 10.2, 7.0 Hz, 1H, H-3) -rotamers-, 5.17 (bd, J = 17.0 Hz, 1H, H-4')/5.15 (bd, J = 17.0 Hz, 1H, H-4') -rotamers-, 4.10 (bqn, J = 7.0 Hz, 1H, H-2), 3.86 (s, 3H, H-13) + 3.84 (s, 3H, H-13) -rotamers-, 3.22 (s, 3H, H-6), 1.36 (d, J = 7.0 Hz, 3H, H-1)/1.33 (d, J = 7.0 Hz, 3H, H-1) -rotamers-; **13C NMR**: (100 MHz, CDCl3) δ (ppm) 168.8 (C-5), 156.1 (C-7), 139.8/139.7 -rotamers- (C-3), 130.8/130.7 (C-12) -rotamers-, 130.3 (C-11), 129.9 (C-8), 120.8/120.7 (C-10) -rotamers-, 114.3/114.2 (C-4) -rotamers-, 112.2 (C-9), 55.6 (C-13), 42.5/42.4 (C-2) -rotamers-, 36.7 (C-6), 20.0/19.9 (C-1) -rotamers-; **IR**: νmax(film)/cm⁻¹ 1652 (C=O), 1499 (C=C=N), 1271 (C_N-N); **MS**: m/z (ES⁺) 274 [M+Na]⁺ (100%); **HRMS**: found 274.0875, [M+Na]⁺ requires 274.0873.

The equivalent enantioenriched thiocarbamate (R)-S-but-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate (R)-316ai (86:14 e.r., 166 mg, 83%) was prepared from O-but-2-enyl 2-methoxyphenyl(methyl)carbamothioate **332i** (200 mg, 0.80 mmol) following general procedure D.

[α]D²²: +0.7 (c 1.50, CHCl₃); **HPLC**: (R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, minor 10.6 min, major 11.9 min (254.4 nm).
316aj: S-But-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (50 mg, 0.27 mmol), HOBT (1.2 eq) and N-methyl-naphthalen-1-amine 329j. Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 9:1) afforded the title compound as a yellow oil (37 mg, 51%).

Rf: 0.61 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.91 (dd, $J = 7.0, 2.4$ Hz, 2H, H-10, H-11), 7.81 (d, $J = 8.0$ Hz, 1H, H-14 or H-16), 7.56 (m, 2H, H-12 or H-9 and H-16 or H-14), 7.50 (td, $J = 8.4, 1.2$ Hz, 1H, H-15), 7.45 (d, $J = 7.0$ Hz, 1H, H-9 or H-12), 5.87 (ddd, $J = 17.2, 10.4, 7.2$ Hz, 1H, H-3) -rotamers-, 5.16 (bd, $J = 17.2$ Hz, 1H, H-4) -rotamers-, 4.96 (bd, $J = 10.4$ Hz, 1H, H-4') -rotamers-, 4.12 (m, 1H, H-2), 3.43 (s, 3H, H-6) -rotamers-; $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 169.1/169.0 (C-5) -rotamers-, 139.5 (C-3), 137.9 (C-7 or C-8 or C-13), 134.6 (C-7 or C-8 or C-13), 130.5 (C-7 or C-8 or C-13), 129.4 (C-10 or C-11), 128.6 (C-11 or C-10), 127.6/127.5 (C-9 or C-12) -rotamers-, 127.3 (C-12 or C-9 or C-16 or C-14), 126.7 (C-16 or C-14 or C-12 or C-9), 125.7/125.6 (C-15) -rotamers-, 122.5/122.4 (C-14 or C-16) -rotamers-, 114.5/114.3 (C-4) -rotamers-, 42.6 (C-2), 38.0 (C-6), 19.8 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1651 (C=O), 1276 (C$_{\text{Ar}}$-N), 774; MS: m/z (ES$^+$) 272 [M+H]$^+$ (100%), 294 [M+Na]$^+$ (100%); HRMS: found 272.1109, [M+H]$^+$ requires 272.1104.

The equivalent enantioenriched thiocarbamate ($R$)-S-but-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate ($R$)-316aj (84:16 e.r., 190 mg, 95%) was prepared from O-but-2-enyl methyl(naphthalen-1-yl)carbamothioate 332j (200 mg, 0.74 mmol) following general procedure D.

[$\alpha$]$_D^{22}$: -1.5 (c 1.04, CHCl$_3$); HPLC: ($R$,$R$)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, minor 10.1 min, major 11.6 min (254.4 nm).
316ak: S-But-3-en-2-yl mesityl(methyl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (51 mg, 0.28 mmol), HOBt (0.5 eq) and 2,4,6-trimethyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 8:2) afforded the title compound as a yellow oil (71 mg, 96%).

Rf: 0.80 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 6.92 (bs, 2H, H-9, H-11), 5.85 (ddd, $J = 17.0, 10.0, 7.0$ Hz, 1H, H-3), 5.17 (dt, $J = 17.0, 1.2$ Hz, 1H, H-4'), 4.99 (dt, $J = 10.0, 1.2$ Hz, 1H, H-4), 4.08 (qtn x t, $J = 7.0, 1.2$ Hz, 1H, H-2), 3.16 (s, 3H, H-6), 2.30 (s, 3H, H-14), 2.17 (s, 3H, H-15), 1.34 (d, $J = 7.0$ Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.3 (C-5), 139.7 (C-3), 138.8 (C-10), 136.9 (C-8, C-12), 136.2 (C-7), 129.5 (C-9, C-11), 114.3 (C-4), 42.1 (C-2), 35.2 (C-6), 21.1 (C-14), 19.9 (C-1), 17.6 (C-13, C-15); IR: $\nu_{max}$(film)/cm$^{-1}$ 1655 (C=O), 1300, 1270; MS: $m/z$ (ES$^+$) 286 [M+Na]$^+$ (100%), 318 [M+Na+MeOH]$^+$ (40%); HRMS: found 286.1228, [M+Na]$^+$ requires 286.1237.

316al: S-But-3-en-2-yl methyl(pyridin-2-yl)carbamothioate.

General procedure B was followed using S-but-3-en-2-yl 1H-imidazole-1-carbothioate 339a (300 mg, 1.65 mmol), HOBt (1.0 eq) and 2-(methylamino)pyridine. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 9:1) afforded the title compound as a colourless oil (84 mg, 23%).

Rf: 0.54 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 8.46 (ddd, $J = 4.8, 1.8, 0.8$ Hz, 1H, H-8), 7.70 (ddd, $J = 8.7, 7.4, 1.8$ Hz, 1H, H-10), 7.60 (d, $J = 8.7$ Hz, 1H, H-11), 7.14 (ddd, $J = 7.4, 4.8, 0.8$ Hz, 1H, H-9), 5.94 (ddd, $J = 17.1, 10.3, 6.9$ Hz, 1H, H-3), 5.24 (d, $J = 17.1$ Hz, 1H, H-4'), 5.08 (d, $J = 10.3$ Hz, 1H, H-4), 4.19 (bqn, $J = 6.9$ Hz, 1H, H-2), 3.46 (s, 3H, H-6), 1.45 (d, $J = 6.9$ Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.5 (C-5), 154.2 (C-7),
148.4 (C-8), 139.1 (C-3), 137.6 (C-10), 121.3 (C-9), 120.5 (C-11), 115.0 (C-4), 42.6 (C-2), 35.0 (C-6), 19.8 (C-1); IR: \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1660 (C=O), 1467 (C=Ar), 1337 (C=Ar=N), 1295 (C=Ar-N), 1055; \textbf{MS:} \( m/z \) (ES\(^+\)) 223 [M+H]\(^+\) (100%), 245 [M+Na]\(^+\) (50%); \textbf{HRMS:} found 245.0715, [M+Na]\(^+\) requires 245.0719.

**316ba:** S-Hex-1-en-3-yl methyl(p-tolyl)carbamothioate.

![Chemical Structure](image)

General procedure B was followed using S-hex-1-en-3-yl 1H-imidazole-1-carbothioate \textbf{339b} (50 mg, 0.24 mmol), Oxyma Pure\textsuperscript{®} (0.5 eq) and 4-methyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (61 mg, 97%).

R\(_f\): 0.48 (Pet/EtOAc 9:1); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \( \delta \) (ppm) 7.21 (d, \( J = 8.2 \) Hz, 2H, H-10, H-14), 7.14 (d, \( J = 8.2 \) Hz, 2H, H-11, H-13), 5.73 (ddd, \( J = 17.0, 10.2, 7.4 \) Hz, 1H, H-2), 5.20 (dt, \( J = 17.0, 1.2 \) Hz, 1H, H-1'), 5.03 (dd, \( J = 10.2, 0.8 \) Hz, 1H, H-1), 3.98 (q, \( J = 7.4 \) Hz, 1H, H-3), 3.28 (s, 3H, H-8), 2.38 (s, 3H, H-15), 1.62-1.54 (m, 2H, H-4), 1.39 (sext, \( J = 7.4 \) Hz, 2H, H-5), 0.88 (t, \( J = 7.4 \) Hz, 3H, H-6); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 168.2 (C-7), 139.4 (C-9), 138.8 (C-2), 138.4 (C-12), 130.1 (C-10, C-14), 128.1 (C-11, C-13), 115.4 (C-1), 48.2 (C-3), 38.3 (C-8), 36.4 (C-4), 21.2 (C-15), 20.3 (C-5), 13.7 (C-6); IR: \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1654 (C-O), 1513 (C=Ar), 1270 (C=Ar-N); \textbf{MS:} \( m/z \) (ES\(^+\)) 286 [M+Na]\(^+\) (60%); \textbf{HRMS:} found 286.1237, [M+Na]\(^+\) requires 286.1237.

**316bb:** S-hex-1-en-3-yl 4-methoxyphenyl(methyl)carbamothioate.

![Chemical Structure](image)

General procedure B was followed using S-hex-1-en-3-yl 1H-imidazole-1-carbothioate \textbf{339b} (50 mg, 0.24 mmol), Oxyma Pure\textsuperscript{®} (0.5 eq) and 4-methoxy-N-methylaniline.
Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (60 mg, 89%).

R<sub>f</sub>: 0.53 (Pet/EtOAc 8:2); <sup>1</sup>H NMR: (400 MHz; CDCl<sub>3</sub>) δ (ppm) 7.17 (d, <i>J</i> = 9.4 Hz, 2H, H-10, H-14), 6.90 (d, <i>J</i> = 9.4 Hz, 2H, H-11, H-13), 5.72 (ddd, <i>J</i> = 17.2, 10.0, 7.8 Hz, 1H, H-2), 5.20 (dt, <i>J</i> = 17.2, 1.2 Hz, 1H, H-1'), 5.03 (d, <i>J</i> = 10.0 Hz, 1H, H-1), 3.97 (q, <i>J</i> = 7.8 Hz, 1H, H-3), 3.82 (s, 3H, H-15), 3.27 (s, 3H, H-8), 1.62-1.53 (m, 2H, H-4), 1.37 (sext, <i>J</i> = 7.8 Hz, 2H, H-5), 0.88 (t, <i>J</i> = 7.8 Hz, 3H, H-6); <sup>13</sup>C NMR: (100 MHz, CDCl<sub>3</sub>) δ (ppm) 168.5 (C-7), 159.4 (C-9), 138.8 (C-2), 134.6 (C-12), 129.7 (C-10, C-14), 115.3 (C-1), 114.6 (C-11, C-13), 55.4 (C-15), 48.2 (C-3), 38.4 (C-4), 20.3 (C-5), 13.7 (C-6); IR: <i>ν</i><sub>max</sub>(film)/cm<sup>-1</sup> 1652 (C=O), 1510 (C=C<sub>Ar</sub>), 1244 (C<sub>Ar</sub>-O); MS: m/z (ES<sup>+</sup>) 302 [M+Na]<sup>+</sup> (100%), 334 [M+Na+MeOH]<sup>+</sup> (60%); HRMS: found 302.1190, [M+Na]<sup>+</sup> requires 302.1186.

316bc: S-Hex-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using 5-hex-1-en-3-yl 1H-imidazole-1-carbothioate 339b (50 mg, 0.24 mmol), Oxyma Pure<sup>®</sup> (1.0 eq) and 4-chloro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (52 mg, 77%).

R<sub>f</sub>: 0.70 (Pet/EtOAc 8:2); <sup>1</sup>H NMR: (400 MHz; CDCl<sub>3</sub>) δ (ppm) 7.37 (d, <i>J</i> = 8.6 Hz, 2H, H-10, H-14), 7.21 (d, <i>J</i> = 8.6 Hz, 2H, H-11, H-13), 5.73 (ddd, <i>J</i> = 17.0, 10.0, 7.4 Hz, 1H, H-2), 5.21 (dt, <i>J</i> = 17.0, 1.2 Hz, 1H, H-1'), 5.05 (dt, <i>J</i> = 10.0, 1.0 Hz, 1H, H-1), 3.99 (q, <i>J</i> = 7.4 Hz, 1H, H-3), 3.29 (s, 3H, H-8), 1.64-1.53 (m, 2H, H-4), 1.36 (sext, <i>J</i> = 7.4 Hz, 2H, H-5), 0.89 (t, <i>J</i> = 7.4 Hz, 3H, H-6); <sup>13</sup>C NMR: (100 MHz, CDCl<sub>3</sub>) δ (ppm) 168.1 (C-7), 140.6 (C-9), 138.6 (C-2), 134.1 (C-12), 129.7 (C-11, C-13), 129.6 (C-10, C-14), 115.6 (C-1), 48.3 (C-3), 38.1 (C-8), 36.4 (C-4), 20.3 (C-5), 13.7 (C-6); IR: <i>ν</i><sub>max</sub>(film)/cm<sup>-1</sup> 1648 (C=O), 1485 (C=C<sub>Ar</sub>), 1261 (C<sub>Ar</sub>-N); MS: m/z (ES<sup>+</sup>) 284 [M+H]<sup>+</sup> (100%), 306 [M+Na]<sup>+</sup> (55%); HRMS: found 284.0872, [M+H]<sup>+</sup> requires 284.0871.
The equivalent enantioenriched thiocarbamate \((R)-\text{S-hex-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate (R)-316bc}\) (94:6 e.r., 185 mg, 91%) was prepared from \(O\)-hex-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate \(332j\) (200 mg, 0.70 mmol) following general procedure D.

\([\alpha]_D^{23} -37.2 (c 1.00, \text{CHCl}_3); \text{HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, minor 11.7 min, major 12.7 min (214.4 nm, 254.4 nm)}.

\(316bd\): S-Hex-1-en-3-yl 4-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using \(S\)-hex-1-en-3-yl \(1H\)-imidazole-1-carbothioate \(339b\) (50 mg, 0.24 mmol), Oxyma Pure\textsuperscript{®} (0.5 eq) and 4-fluoro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a yellow oil (60 mg, 93%).

\(R_f\): 0.71 (Pet/EtOAc 8:2); \(^1\text{H NMR:} (400 MHz; \text{CDCl}_3) \delta (ppm) 7.26 (dd, \(J = 9.2, 4.8\) Hz, 2H, H-10, H-14), 7.10 (dd, \(J = 8.8\) Hz, 2H, H-11, H-13), 5.74 (ddd, \(J = 17.0, 10.0, 7.4\) Hz, 1H, H-2), 5.22 (dt, \(J = 17.0, 1.2\) Hz, 1H, H-1’), 5.05 (dd, \(J = 10.0, 0.8\) Hz, 1H, H-1), 3.99 (q, \(J = 7.4\) Hz, 3H, H-8), 3.30 (s, 3H, H-8), 1.65-1.57 (m, 2H, H-4), 1.38 (sext, \(J = 7.4\) Hz, 2H, H-5), 0.90 (t, \(J = 7.4\) Hz, 3H, H-6); \(^{13}\text{C NMR:} (100 MHz, \text{CDCl}_3) \delta (ppm) 168.3 (C=7), 161.8 (d, \(^1JC\text{F} = 247.7\) Hz, C-12), 138.7 (C-2), 138.1 (C-9), 130.2 (m, C-10, C-14), 116.4 (d, \(^2JC\text{F} = 22.7\) Hz, C-11, C-13), 115.6 (C-1), 48.3 (C-2), 38.3 (C-8), 36.4 (C-4), 20.3 (C-5), 13.7 (C-6); \(\text{IR: } \nu_{\max}(\text{film})/\text{cm}^{-1} 1655 (\text{C}=\text{O}), 1508 (\text{C}=\text{C}_{\text{Ar}}), 1220 (\text{C}-\text{F}); \text{MS: } m/z (\text{ES}^+) 268 [\text{M+H}]^+ (70\%), 290 [\text{M+Na}]^+ (100\%), 322 [\text{M+Na+MeOH}]^+ (25\%); \text{HRMS: found 268.1164, [M+H]^+ requires 268.1166.}

The equivalent enantioenriched thiocarbamate \((R)-\text{S-hex-1-en-3-yl 4-fluorophenyl(methyl)carbamothioate (R)-316bd}\) (91:9 e.r., 110 mg, 92%) was prepared from \(O\)-hex-1-en-3-yl 4-fluorophenyl(methyl)carbamothioate \(332k\) (200 mg, 0.75 mmol) following general procedure D.
[α]_D^{22} -27.2 (c 1.00, CHCl₃); **HPLC**: (R,R)-Whelk-01, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, minor 9.4 min, major 10.1 min (214.4 nm, 254.4 nm).

**316be**: S-Hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate

![Chemical Structure](image)

General procedure B was followed using S-hex-1-en-3-yl 1H-imidazole-1-carbothioate **339b** (250 mg, 1.19 mmol) in THF, HOBt (1.0 eq) and 3-chloro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 95:5) afforded the title compound as a yellow oil (157 mg, 46%).

Rᵣ: 0.67 (Pet/EtOAc 8:2); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.34-7.32 (m, 2H, H-12, H-14), 7.28 (m, 1H, H-10), 7.18, (ddd, J = 5.6, 3.6, 2.0 Hz, 1H, H-13), 5.74 (ddd, J = 16.8, 10.0, 8.0 Hz, 1H, H-2), 5.22 (dt, J = 16.8, 1.2 Hz, 1H, H-1‘), 5.05 (ddd, J = 10.0, 1.6, 0.8 Hz, 1H, H-1), 4.00 (q, J = 8.0 Hz, 1H, H-3), 3.30 (s, 3H, H-8), 1.64-1.56 (m, 2H, H-4), 1.38 (sext, J = 7.4 Hz, 2H, H-5), 0.90 (t, J = 7.4 Hz, 3H, H-6); **¹³C NMR**: (100 MHz, CDCl₃) δ (ppm) 168.1 (C-7), 143.3 (C-9), 138.5 (C-2), 134.7 (C-11), 130.3 (C-12 or C-14), 128.4 (C-14 or C-12, C-10), 126.4 (C-13), 115.6 (C-1), 48.3 (C-2), 38.1 (C-8), 36.4 (C-4), 20.3 (C-5), 13.7 (C-6); **IR**: ν_max(film)/cm⁻¹ 1656 (C=O), 1589 (C=C₆), 1336, 1277 (C₆=N); **MS**: m/z (ES⁺) 306 [M+Na]⁺ (100%); **HRMS**: found 284.0868, [M+H]⁺ requires 284.0871.

The equivalent enantioenriched thiocarbamate (R)-S-hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate (R)-**316be** (95:5 e.r., 187 mg, 93%) was prepared from O-hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate **332l** (200 mg, 0.70 mmol) following general procedure D.

[α]_D^{22} -23.2 (c 1.00, CHCl₃); **HPLC**: (R,R)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, minor 10.4 min, major 11.3 min (214.4 nm, 254.4 nm).
316bf: S-Hexa-1,4-dien-3-yl 2-methoxyphenyl(methyl)carbamothioate.  

General procedure B was followed using S-hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate 339b (250 mg, 1.19 mmol), HOBt (1.0 eq) and 2-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 95:5) afforded the title compound as a yellow oil (223 mg, 67%).

\[ \text{Rf: 0.57 (Pet/EtOAc 8:2); }^{1} \text{H NMR: (400 MHz; CDCl}_3\text{)} \delta (\text{ppm}) 7.37 (t, J = 7.6 \text{ Hz, 1H, H-13}), 7.21 (d, J = 7.6 \text{ Hz, 1H, H-14}), 6.97 (d, J = 7.6 \text{ Hz, 2H, H-11, H-12}), 5.73 (ddd, J = 17.0, 10.0, 7.6 \text{ Hz, 1H, H-3})/5.71 (ddd, J = 17.0, 10.0, 7.6 \text{ Hz, 1H, H-3}) \text{-rotamers}, 5.21 (bd, J = 17.0 \text{ Hz, 1H, H-1'})/5.18 (d, J = 17.0 \text{ Hz, 1H, H-1'}) \text{-rotamers}, 5.03 (bd, J = 10.0 \text{ Hz, 1H, H-1})/5.00 (d, J = 10.0 \text{ Hz, 1H, H-1}) \text{-rotamers}, 3.97 (bq, J = 7.6 \text{ Hz, 1H, H-3}), 3.85 (s, 3H, H-15)/3.84 (s, 3H, H-15) \text{-rotamers}.

13C NMR: (100 MHz, CDCl\text{$_3$}) \delta (ppm) 168.9 (C-7), 156.2 (C-10), 139.0/138.9 (C-2) \text{-rotamers}, 130.9/130.7 (C-14) \text{-rotamers}, 130.2 (C-13), 130.2/130.1 (C-9) \text{-rotamers}, 120.8/120.7 (C-12) \text{-rotamers}, 115.2/115.1 (C-1) \text{-rotamers}, 112.2/112.1 (C-11) \text{-rotamers}, 55.6 (C-15), 47.9/47.8 (C-3) \text{-rotamers}, 36.8 (C-8), 36.4 (C-4), 20.4/20.2 (C-5) \text{-rotamers}, 13.7 (C-6); IR: ν\text{max(film)/cm}^{-1} 1655 (C=O), 1499 (C=C_N), 1271 (C=O-N), 747; MS: m/z (ES\text{$^+$}) 302 [M+Na]\text{$^+$} (100%); HRMS: found 280.1353, [M+H]\text{$^+$} requires 280.1366.

316ca: (E)-S-Hexa-1,4-dien-3-yl methyl(\text{p-tolyl})carbamothioate.

General procedure B was followed using (E)-S-hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate 339c (50 mg, 0.24 mmol), HOBt (0.5 eq) and 4-methyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (50 mg, 79%).
Rf: 0.37 (Pet/EtOAc 9:1); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.20 (d, $J = 8.4$ Hz, 2H, H-10, H-14), 7.15 (d, $J = 9.0$ Hz, 2H, H-11, H-13), 5.87 (ddd, $J = 17.0$, 10.0, 7.4 Hz, 1H, H-2), 5.65 (dqd, $J = 15.4$, 6.6, 1.2 Hz, 1H, H-5), 5.48 (dd, $J = 15.4$, 7.4, 1.6 Hz, 1H, H-4), 5.20 (ddd, $J = 17.0$, 1.0, 1.0 Hz, 1H, H-1'), 5.06 (dt, $J = 10.0$, 1.0 Hz, 1H, H-1), 4.62 (bt, $J = 7.4$ Hz, 1H, H-3), 3.29 (s, 3H, H-8), 2.37 (s, 3H, H-15), 1.66 (d, $J = 6.6$ Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 167.8 (C-7), 139.2 (C-9), 138.5 (C-12), 137.4 (C-2), 130.1 (C-10, C-14), 129.0 (C-5), 128.2 (C-11, C-13), 127.9 (C-4), 115.7 (C-1), 49.9 (C-3), 38.3 (C-8), 21.2 (C-15), 17.9 (C-6); IR: ν$_{max}$(film)/cm$^{-1}$ 1653 (C=O), 1513 (C=C Ar), 1268 (C$_{Ar}$-N); MS: m/z (ES$^+$) 262 [M+H]$^+$ (100%), 284 [M+Na]$^+$ (60%); HRMS: found 284.1071, [M+Na]$^+$ requires 284.1080.

$^{316}$cb: (E)-S-Hexa-1,4-dien-3-yl 4-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate 339c (50 mg, 0.24 mmol), Oxyma Pure® (0.5 eq) and 4-methoxy-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (40 mg, 59%).

Rf: 0.65 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.17 (d, $J = 9.0$ Hz, 2H, H-10, H-14), 6.90 (d, $J = 9.0$ Hz, 2H, H-11, H-13), 5.87 (ddd, $J = 17.2$, 10.2, 7.2 Hz, 1H, H-2), 5.65 (m, 1H, H-4), 5.47 (dqd, $J = 15.2$, 7.2, 1.2 Hz, 1H, H-5), 5.20 (dt, $J = 17.2$, 1.2 Hz, 1H, H-1'), 5.06 (d, $J = 10.2$ Hz, 1H, H-1), 4.60 (t, $J = 7.2$ Hz, 1H, H-3), 3.82 (s, 3H, H-15), 3.27 (s, 3H, H-8), 1.67 (d, $J = 7.2$ Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.1 (C-7), 159.5 (C-9), 137.4 (C-2), 134.4 (C-12), 129.7 (C-10, C-14), 129.0 (C-5), 127.8 (C-4), 115.7 (C-1), 114.6 (C-11, C-13), 55.4 (C-15), 49.9 (C-3), 38.4 (C-8), 17.9 (C-6); IR: ν$_{max}$(film)/cm$^{-1}$ 1652 (C=O), 1510 (C$_{Ar}$), 1245 (C$_{Ar}$-O); MS: m/z (ES$^+$) 300 [M+Na]$^+$ (100%), 332 [M+Na+MeOH]$^+$ (55%); HRMS: found 300.1023, [M+Na]$^+$ requires 300.1029.
316cc: (E)-S-hexa-1,4-dien-3-yl 4-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate 339c (50 mg, 0.24 mmol), HOBt (1.0 eq) and 4-chloro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a pale orange oil (53 mg, 78%).

Rf: 0.70 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.37 (d, J = 8.2 Hz, 2H, H-10, H-14), 7.21 (d, J = 8.2 Hz, 2H, H-11, H-13), 5.87 (ddd, J = 17.0, 10.2, 7.4 Hz, 1H, H-2), 5.66 (dqd, J = 15.2, 6.4, 0.8 Hz, 1H, H-5), 5.48 (ddq, J = 15.2, 7.4, 1.6 Hz, 1H, H-4), 5.21 (dt, J = 17.0, 1.2 Hz, 1H, H-1’), 5.08 (dt, J = 10.2, 1.2 Hz, 1H, H-1), 4.62 (bt, J = 7.4 Hz, 1H, H-3), 3.29 (s, 3H, H-8), 1.67 (d, J = 6.4 Hz, 3H, H-6); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 167.6 (C-7), 137.1 (C-2), 129.7 (C-11, C-13), 129.6 (C-10, C-14), 128.7 (C-4), 128.2 (C-5), 116.0 (C-1), 50.0 (C-3), 38.1 (C-8), 17.9 (C-6); IR: ν max (film)/cm⁻¹ 1654 (C=O), 1488 (C=C Ar), 1277 (C₈-N); MS: m/z (ES⁺) 282 [M+H]+ (100%), 304 [M+Na]+ (60%), 336 [M+Na+MeOH]+ (30%); HRMS: found 304.0528, [M+Na]+ requires 304.0533.

316cd: (E)-S-Hexa-1,4-dien-3-yl 4-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate 339c (50 mg, 0.24 mmol), HOBt (1.0 eq) and 4-fluoro-N-methylaniline to afford the title compound as a yellow oil without purification (50 mg, 78%).

Rf: 0.63 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.25 (dd, J = 8.8, 4.8 Hz, 2H, H-10, H-14), 7.08 (t, J = 8.8 Hz, 2H, H-11, H-13), 5.87 (ddd, J = 17.2, 10.0, 7.4 Hz, 1H, H-2), 5.67 (dqd, J = 15.2, 6.4, 1.2 Hz, 1H, H-5), 5.48 (ddq, J = 15.2, 7.4, 1.6 Hz, 1H, H-4), 5.22 (dt, J = 17.2, 1.4 Hz, 1H, H-1’), 5.08 (dt, J = 10.0, 1.4 Hz, 1H, H-1), 4.62 (bt, J = 7.4 Hz, 1H, H-3),
3.29 (s, 3H, H-8), 1.67 (d, J = 6.4 Hz, 3H, H-6); 13C NMR: (100 MHz, CDCl3) δ (ppm) 167.8 (C-7), 161.5 (C-12) -1JCsF not visible-, 137.9 (m, C-9), 137.2 (C-2), 130.3 (m, C-10, C-14), 128.8 (C-4), 128.1 (C-5), 116.4 (d, J = 22.6 Hz, C-11, C-13), 115.9 (C-1), 50.0 (C-2), 38.3 (C-8), 17.9 (C-6); IR: νmax(film)/cm⁻¹ 1650 (C=O), 1503 (C=CAr), 1219 (C-F); MS: m/z (ES⁺) 266 [M+H]+ (30%), 388 [M+Na]+ (70%); HRMS: found 288.0835, [M+Na]+ requires 288.0829.

316da: S-4-Methylpent-1-en-3-yl methyl(p-tolyl)carbamothioate.

General procedure B was followed using S-4-methylpent-1-en-3-yl 1H-imidazole-1-carbothioate 339d (50 mg, 0.24 mmol), HOBt (0.5 eq) and 4-methyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (353 mg, 84%).

Rf: 0.75 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.21 (d, J = 8.2 Hz, 2H, H-10, H-14), 7.15 (d, J = 8.2 Hz, 2H, H-11, H-13), 5.73 (ddd, J = 17.4, 10.6, 9.0 Hz, 1H, H-2), 5.22 (dd, J = 17.4, 1.6 Hz, 1H, H-1’), 5.06 (dd, J = 10.6, 1.6 Hz, 1H, H-1), 3.93 (dd, J = 9.0, 6.2 Hz, 1H, H-3), 3.28 (s, 3H, H-8), 2.38 (s, 3H, H-15), 1.89 (oct, J = 6.2 Hz, 1H, H-4), 0.92 (d, J = 6.2 Hz, 3H, H-5 or H-6), 0.91 (d, J = 6.2 Hz, 3H, H-6 or H-5); 13C NMR: (100 MHz, CDCl3) δ (ppm) 168.2 (C-7), 139.6 (C-9), 138.3 (C-12), 137.0 (C-2), 130.1 (C-10, C-14), 128.1 (C-11, C-13), 116.2 (C-1), 55.6 (C-2), 38.4 (C-8), 32.2 (C-15), 21.2 (C-4), 20.3 (C-5 or C-6), 19.6 (C-6 or C-5); IR: νmax(film)/cm⁻¹ 1654 (C=O), 1513 (C=CAr), 1266 (CAr=N); MS: m/z (ES⁺) 264 [M+H]+ (30%), 286 [M+Na]+ (50%); HRMS: found 264.1413, [M+H]+ requires 264.1417.

316db: S-4-Methylpent-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using S-4-methylpent-1-en-3-yl 1H-imidazole-1-carbothioate 339d (200 mg, 0.95 mmol), HOBt (1.0 eq) and 4-chloro-N-methylaniline.
Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5) afforded the title compound as a pale yellow oil (219 mg, 81%).

Rf: 0.53 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.37 (d, \(J = 8.8\) Hz, 2H, H-10, H-14), 7.21 (d, \(J = 8.8\) Hz, 2H, H-11, H-13), 5.73 (ddd, \(J = 16.8, 10.2, 9.0\) Hz, 1H, H-2), 5.22 (dt, \(J = 16.8, 1.4\) Hz, 1H, H-1’), 5.07 (dd, \(J = 10.2, 1.2\) Hz, 1H, H-1), 3.93 (dd, \(J = 9.0, 6.0\) Hz, 1H, H-3), 3.28 (s, 3H, H-8), 1.91 (oct, \(J = 6.0\) Hz, 1H, H-4), 0.93 (d, \(J = 6.0\) Hz, 3H, H-5 or H-6), 0.91 (d, \(J = 6.0\) Hz, 3H, H-6 or H-5); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.1 (C-7), 140.7 (C-9), 136.7 (C-2), 136.3 (C-12), 129.6 (C-10, C-14), 129.5 (C-11, C-13), 116.4 (C-1), 55.8 (C-3), 38.2 (C-8), 32.2 (C-4), 20.2 (C-5 or C-6), 19.6 (C-6 or C-5); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1657 (C=O), 1488 (C=C\(_{Ar}\)), 1277 (C\(_{Ar}\)-N), 1107; MS: \(m/z\) (ES\(^{+}\)) 284 [M+H]\(^{+}\) (70%), 306 [M+Na]\(^{+}\) (100%), 338 [M+Na+MeOH]\(^{+}\) (540%); HRMS: found 284.0871, [M+H]\(^{+}\) requires 284.0871.

316ea: (E)-S-Pent-3-en-2-yl methyl(p-tolyl)carbamothioate.

General procedure B was followed using (E)-S-pent-3-en-2-yl 1H-imidazole-1-carbothioate 339e (200 mg, 1.02 mmol), HOBt (1.0 eq) and N-methyl-p-toluidine. Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1, 98:2) afforded the title compound as a yellow oil (234 mg, 92%).

Rf: 0.71 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.20 (d, \(J = 8.2\) Hz, 2H, H-9, H-13), 7.14 (d, \(J = 8.2\) Hz, 2H, H-10, H-12), 6.61 (dq, \(J = 15.2, 6.4, 1.0\) Hz, 1H, H-4), 6.47 (ddq, \(J = 15.2, 7.1, 1.3\) Hz, 1H, H-3), 4.07 (qn, \(J = 7.1\) Hz, 1H, H-2), 3.29 (s, 3H, H-7), 2.37 (s, 3H, H-14), 1.63 (dt, \(J = 6.4, 1.3\) Hz, 3H, H-5), 1.35 (d, \(J = 7.1\) Hz, 3H, H-1); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.5 (C-6), 132.3 (C-3), 130.1 (C-9, C-13), 128.1 (C-10, C-12), 125.7 (C-4), 42.5 (C-2), 38.2 (C-7), 21.2 (C-14), 21.0 (C-1), 17.8 (C-5). \(\cdot\)2 \(C_{qAr}\) not visible; IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1651 (C=O), 1513 (C=C\(_{Ar}\)), 1271 (C\(_{Ar}\)-N), 1107; MS: \(m/z\) (ES\(^{+}\)) 250 [M+H]\(^{+}\) (100%), 272 [M+Na]\(^{+}\) (20%); HRMS: found 250.1263, [M+H]\(^{+}\) requires 250.1260.
General procedure B was followed using (E)-S-pent-3-en-2-yl 1H-imidazole-1-carbothioate 339e (50 mg, 0.25 mmol), HOBt (0.5 eq) and 4-chloro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5, 9:1) afforded the title compound as a colourless oil (33 mg, 49%).

Rf: 0.36 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.36 (d, J = 8.8 Hz, 2H, H-9, H-13), 7.20 (d, J = 8.8 Hz, 2H, H-10, H-12), 5.62 (ddq, J = 15.2, 6.6, 1.2 Hz, 1H, H-4), 5.47 (ddq, J = 15.2, 7.0, 1.6 Hz, 1H, H-3), 4.07 (qn, J = 7.0 Hz, 1H, H-2), 3.29 (s, 3H, H-7), 1.64 (d, J = 6.6 Hz, 3H, H-5), 1.36 (d, J = 7.0 Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.4 (C-6), 140.7 (C-8), 134.0 (C-11), 132.1 (C-3), 129.6 (C-9, C-13), 129.5 (C-10, C-12), 126.1 (C-4), 42.7 (C-2), 38.0 (C-7), 21.0 (C-1), 17.8 (C-5); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1651 (C=O), 1487 (C=C Ar); MS: m/z (ES$^+$) 270 [M+H]$^+$ (40%), 292 [M+Na]$^+$ (100%); HRMS: found 292.0525, [M+Na]$^+$ requires 292.0534.

General procedure B was followed using (E)-S-pent-3-en-2-yl 1H-imidazole-1-carbothioate 339e (150 mg, 0.76 mmol), HOBt (1.0 eq) and 4-fluoro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1 to 97:3) afforded the title compound as a yellow oil (174 mg, 90%).

Rf: 0.66 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.24 (dd, J = 8.8, 5.0 Hz, 2H, H-9, H-13), 7.08 (t, J = 8.8 Hz, 2H, H-10, H-12), 5.63 (ddq, J = 15.2, 6.4, 1.0 Hz, 1H, H-4), 5.47 (ddq, J = 15.2, 7.1, 1.5 Hz, 1H, H-3), 4.07 (qn, J = 7.1 Hz, 1H, H-2), 3.29 (s, 3H, H-7), 1.64 (d, J = 6.4 Hz, 3H, H-5), 1.36 (d, J = 7.1 Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 168.6 (C-6), 159.7 (d, $^1$J$_{C,F}$ = 232.2 Hz, C-11), 138.1 (C-8), 132.1 (C-3), 130.2 (bd, $^3$J$_{C,F}$ = 8.8 Hz, C-9, C-13), 126.0 (C-4), 116.4 (d, $^2$J$_{C,F}$ = 22.8 Hz, C-10, C-12), 42.6 (C-2), 38.2 224
(C-7), 21.0 (C-1), 17.8 (C-5); \textbf{IR:} \nu_{\max} \text{(film)/cm}^{-1} 1652 (C=O), 1508 (C=C\text{Ar}), 1220 (C-F), 841; \textbf{MS:} m/z (ES\textsuperscript{+}) 254 [M+H]\textsuperscript{+} (100%), 276 [M+Na]\textsuperscript{+} (100%); \textbf{HRMS:} found 254.1003, [M+Na]\textsuperscript{+} requires 254.1009.

\textbf{316ed:} (E)-S-Pent-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate.

\begin{center}
\includegraphics[width=0.5\textwidth]{chemical STRUCTURE}
\end{center}

General procedure B was followed using (E)-S-pent-3-en-2-yl 1H-imidazole-1-carbothioate \textbf{339e} (200 mg, 1.02 mmol), HOBt (1.0 eq) and 2-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1 to 96:4) afforded the title compound as a yellow oil (208 mg, 77%).

R\textsubscript{f}: 0.63 (Pet/EtOAc 8:2); \textbf{\textsuperscript{1}H NMR:} (400 MHz; CDCl\textsubscript{3}) \delta (ppm) 7.36 (bt, J = 7.9 Hz, 1H, H-12), 7.21 (d, J = 7.9 Hz, 1H, H-13), 6.97-6.94 (m, 2H, H-10, H-11), 5.65-5.54 (m, 1H, H-4) \textsuperscript{\textit{rotamers}}, 5.50-5.43 (m, 1H, H-3) \textsuperscript{\textit{rotamers}}, 4.09-4.04 (m, 1H, H-2) \textsuperscript{\textit{rotamers}}, 3.85 (s, 3H, H-14)/3.84 (s, 3H, H-14) \textsuperscript{\textit{rotamers}}, 3.21 (s, 3H, H-7), 1.63 (bddd, J = 5.6, 5.0 Hz, 3H, H-5), 1.36 (d, J = 7.0 Hz, 3H, H-1)/1.32 (d, J = 7.0 Hz, 3H, H-1) \textsuperscript{\textit{rotamers}}; \textbf{\textsuperscript{13}C NMR:} (100 MHz, CDCl\textsubscript{3}) \delta (ppm) 169.1 (C-6), 156.1 (C-9), 132.5/132.4 (C-3), 130.8 (C-11), 130.2 (C-12), 130.1 (C-8), 125.6/125.5 (C-4), 120.8/120.7 (C-13), 112.2 (C-10), 55.6 (C-14), 42.2/42.1 (C-2), 36.7 (C-7), 21.0/20.9 (C-1), 17.8 (C-5); \textbf{IR:} \nu_{\max} \text{(film)/cm}^{-1} 1651 (C=O), 1596 (C=C), 1500 (C=C\text{Ar}), 1271 (C\text{Ar}-O), 747; \textbf{MS:} m/z (ES\textsuperscript{+}) 266 [M+H]\textsuperscript{+} (100%), 288 [M+Na]\textsuperscript{+} (95%); \textbf{HRMS:} found 266.1213, [M+H]\textsuperscript{+} requires 266.1209.

\textbf{316fa:} (E)-S-4-Cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate.

\begin{center}
\includegraphics[width=0.5\textwidth]{chemical STRUCTURE}
\end{center}

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate \textbf{339f} (180 mg, 0.68 mmol), HOBt (0.5 eq) and 4-methyl-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (185 mg, 86%).
Rf: 0.76 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.20 (d, $J = 8.2$ Hz, 2H, H-14, H-18), 7.14 (d, $J = 8.2$ Hz, 2H, H-15, H-17), 5.52 (dd, $J = 15.6$, 6.2 Hz, 1H, H-4), 5.40 (ddd, $J = 15.6$, 6.8, 1.0 Hz, 1H, H-3), 4.07 (qn, $J = 6.8$ Hz, 1H, H-2), 3.28 (s, 3H, H-12), 2.37 (s, 3H, H-19), 1.91-1.83 (m, 1H, H-5), 1.69-1.60 (m, 4H, H-6, H-7, H-9, H-10), 1.36 (d, $J = 6.8$ Hz, 3H, H-1), 1.27-0.95 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); 13C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 168.6 (C-11), 139.5 (C-16), 138.3 (C-13), 136.9 (C-4), 130.1 (C-14, C-18), 128.3 (C-3), 128.0 (C-15, C-17), 42.6 (C-2), 40.3 (C-5), 38.2 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.2 (C-19), 21.1 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1651 (C=O), 1513 (C=C Ar), 1268 (C=Ar-N), 1107; MS: m/z (ES$^+$) 318 [M+H]$^+$ (100%), 340 [M+Na]$^+$ (60%); HRMS: found 318.1892, [M+H]$^+$ requires 318.1887.

The equivalent enantioenriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate (S)-316fa (94:6 e.r., 101 mg, 83%) was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 100 mg, 0.38 mmol) following the same procedure. [α]$_D^{22}$: -5.3 (c 1.10, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, major 5.8 min, minor 6.7 min (214.4 nm, 254.4 nm).

The other enantiomter (R)-S-4-cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate (R)-316fa (13:87 e.r., 210 mg, 87%) was prepared from (R)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (R)-339f (88:12 e.r., 200 mg, 0.76 mmol) following the same procedure. HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, minor 8.9 min, major 11.0 min (214.4 nm).

316fb: (E)-S-4-Cyclohexylbut-3-en-2-yl 4-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (150 mg, 0.57 mmol), HO8t (1.0 eq), and 4-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5, 9:1) afforded the title compound as a yellow oil (181 mg, 96%).
**Rf:** 0.60 (Pet/EtOAc 8:2); **1H NMR:** (400 MHz; CDCl₃) δ (ppm) 7.17 (d, J = 8.9 Hz, 2H, H-14, H-18), 6.90 (d, J = 8.9 Hz, H-15, H-17), 6.52 (dd, J = 15.6, 6.5 Hz, 1H, H-4), 5.40 (dd, J = 15.6, 6.8 Hz, 1H, H-3), 4.06 (qn, J = 6.8 Hz, 1H, H-2), 3.82 (s, 3H, H-19), 3.27 (s, 3H, H-12), 1.92-1.83 (m, 1H, H-5), 1.70-1.59 (m, 4H, H-6, H-7, H-9, H-10), 1.35 (d, J = 6.8 Hz, 3H, H-1), 1.27-0.96 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); **13C NMR:** (100 MHz, CDCl₃) δ (ppm) 168.8 (C-11), 159.3 (C-16), 136.8 (C-4), 134.7 (C-13), 129.6 (C-14, C-18), 128.4 (C-3), 114.6 (C-15, C-17), 55.4 (C-13), 129.5 (C-7, C-9), 21.1 (C-1); **IR:** νmax(film)/cm⁻¹: 1648 (C=O), 1509 (C=C₆), 1244 (C₆-O), 834; **MS:** m/z (ES⁺) 334 [M+H]⁺ (50%), 356 [M+Na]⁺ (100%); **HRMS:** found 334.1838, [M+Na]⁺ requires 334.1836.

**316fc:** (E)-S-4-Cyclohexylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate **339f** (180 mg, 0.68 mmol), HOBr (0.5 eq) and 4-chloro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (169 mg, 73%).

**Rf:** 0.77 (Pet/EtOAc 8:2); **1H NMR:** (400 MHz; CDCl₃) δ (ppm) 7.36 (d, J = 8.8 Hz, 2H, H-14, H-18), 7.20 (d, J = 8.8 Hz, 2H, H-15, H-17), 5.54 (dd, J = 15.4, 6.4 Hz, 1H, H-4), 5.41 (ddd, J = 15.4, 6.8, 1.2 Hz, 1H, H-3), 4.08 (qn, J = 6.8 Hz, 1H, H-2), 3.28 (s, 3H, H-12), 1.93-1.84 (m, 1H, H-5), 1.71-1.58 (m, 4H, H-6, H-7, H-9, H-10), 1.37 (d, J = 6.8 Hz, 3H, H-1), 1.28-0.96 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); **13C NMR:** (100 MHz, CDCl₃) δ (ppm) 168.4 (C-11), 140.7 (C-13), 137.2 (C-4), 133.9 (C-16), 129.6 (C-14, C-18), 129.5 (C-15, C-17), 128.1 (C-3), 42.7 (C-2), 40.3 (C-5), 38.1 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.1 (C-1); **IR:** νmax(film)/cm⁻¹: 1651 (C=O), 1486 (C=C₆), 1280 (C₆-N), 964; **MS:** m/z (ES⁺) 338 [M+H]⁺ (70%), 360 [M+Na]⁺ (100%); **HRMS:** found 338.1346, [M+H]⁺ requires 338.1340.

The equivalent enantoienriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate (S)-**316fc** (95:5 e.r., 86 mg, 67%) was prepared.
from (S)-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 100 mg, 0.38 mmol) following the same procedure.

$\alpha_d^{25}$: -11.6 (c 1.00, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, major 5.7 min, minor 6.5 min (214.4 nm).

**316fd**: (E)-S-4-Cyclohexylbut-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (190 mg, 0.72 mmol), HOBt (0.5 eq) and 4-fluoro-N-methylaniline.

Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 96:4) afforded the title compound as a yellow oil (182 mg, 79%).

$\text{Rf}$: 0.45 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.24 (dd, $J = 9.0$, 4.9 Hz, 2H, H-14, H-18), 7.08 (t, $J = 9.0$ Hz, 2H, H-15, H-17), 5.54 (dd, $J = 15.5$, 6.0 Hz, 1H, H-4), 5.40 (ddd, $J = 15.5$, 6.9, 1.0 Hz, 1H, H-3), 4.07 (qn, $J = 6.9$ Hz, 1H, H-2), 3.28 (s, 3H, H-12), 1.93-1.84 (m, 1H, H-5), 1.71-1.59 (m, 4H, H-6, H-7, H-9, H-10), 1.36 (d, $J = 6.9$ Hz, 3H, H-1), 1.28-0.96 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 175.9 (d, $^1J_{C,F} = 254.5$ Hz, C-16), 168.7 (C-11), 138.1 (C-13), 137.1 (C-4), 130.2 (m, C-14, C-18), 128.2 (C-3), 116.4 ($^2J_{C,F} = 22.4$ Hz, C-15, C-17), 42.7 (C-2), 40.3 (C-5), 38.2 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0/25.9 (C-7, C-8, C-9), 21.1 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1650 (C=O), 1507 (C=C$_{ar}$), 1220 (C-F), 839; MS: $m/z$ (ES$^+$) 322 [M+H]$^+$ (100%); HRMS: found 322.1628, [M+H]$^+$ requires 322.1636.

The equivalent enantioenriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate (S)-316fd (94:6 e.r., 170 mg, 93%) was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 150 mg, 0.57 mmol) following the same procedure.

$\alpha_d^{26}$: -15.4 (c 1.00, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 $^\circ$C, major 8.2 min, minor 10.0 min (214.4 nm, 254.4 nm).
316fe: (E)-S-4-Cyclohexylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (400 mg, 1.51 mmol), HOBt (1.5 eq) and 3-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 97:3 to 92:8) afforded the title compound as a yellow oil (444 mg, 86%).

Rf: 0.48 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.30 (t, J = 8.2 Hz, 1H, H-17), 6.89 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H, H-16 or H-18), 6.86 (ddd, J = 8.2, 2.4, 0.8 Hz, 1H, H-18 or H-16), 6.80 (t, J = 2.4 Hz, 1H, H-14), 5.53 (ddd, J = 15.6, 6.6, 0.8 Hz, 1H, H-4), 5.41 (ddd, J = 15.6, 6.8, 1.0 Hz, 1H, H-3), 4.08 (qn, J = 6.8 Hz, 1H, H-2), 3.82 (s, 3H, H-19), 3.30 (s, 3H, H-12), 1.93-1.84 (m, 1H, H-5), 1.71-1.58 (m, 4H, H-6, H-7, H-9, H-10), 1.37 (d, J = 6.8 Hz, 3H, H-1), 1.28-0.96 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); 13C NMR: (100 MHz, CDCl3) δ (ppm) 168.4 (C-11), 160.2 (C-15), 143.3 (C-13), 137.0 (C-4), 130.0 (C-17), 128.3 (C-3), 120.3 (C-18 or C-16), 113.9 (C-14), 113.7 (C-16 or C-18), 55.4 (C-19), 42.6 (C-2), 40.4 (C-5), 38.1 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.1 (C-1); IR: νmax(film)/cm⁻¹ 1651 (C=O), 1599 (C=CN), 1283 (C=N), 1217 (C-O), 1042; MS: m/z (ES⁺) 334 [M+H]⁺ (100%), 356 [M+Na]⁺ (40%); HRMS: found 356.1649, [M+Na]⁺ requires 356.1655.

The equivalent enantioenriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate (S)-316fe (95:5 e.r., 169 mg, 89%) was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 150 mg, 0.57 mmol) following the same procedure. [α]D²⁰: -10.8 (c 1.60, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, major 8.9 min, minor 11.2 min (254.4 nm).
**316ff**: (E)-S-4-Cyclohexylbut-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate **339f** (180 mg, 0.68 mmol), HOBt (1.0 eq) and 3-chloro-N-methylaniline. Purification by filtration over silica (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (178 mg, 77%).

**Rf**: 0.79 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.33-7.32 (m, 2H, H-16, H-18), 7.18 (ddd, J = 5.6, 3.6, 2.2 Hz, 1H, H-17), 5.55 (ddd, J = 15.6, 6.6, 0.8 Hz, 1H, H-4), 5.41 (ddd, J = 15.6, 7.0, 1.0 Hz, 1H, H-3), 4.09 (qn, J = 6.8 Hz, 1H, H-2), 3.29 (s, 3H, H-12), 1.93-1.85 (m, 1H, H-5), 1.71-1.60 (m, 4H, H-6, H-7, H-9, H-10), 1.38 (d, J = 6.8 Hz, 3H, H-1), 1.27-0.97 (m, 6H, H-6', H-7', H-8', H-9', H-10'); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 168.4 (C-11), 143.4 (C-13), 137.2 (C-4), 134.7 (C-15), 130.3 (C-16 or C-18), 128.3 (C-14), 128.0 (C-18 or C-16, C-3), 126.4 (C-17), 42.7 (C-2), 40.3 (C-5), 38.0 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.1 (C-1); IR: ν<sub>max</sub>(film)/cm⁻¹ 1656 (C=O), 1589 (C=C<sub>Ar</sub>), 1277 (C<sub>Ar</sub>-N), 965, 694; MS: m/z (ES⁺) 338 [M+H]⁺ 50%, 360 [M+Na]⁺ (100%); HRMS: found 338.1349, [M+H]⁺ requires 338.1340.

**316fg**: (E)-S-4-Cyclohexylbut-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate **339f** (200 mg, 0.76 mmol), HOBt (1.5 eq) and 3-fluoro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 96:4) afforded the title compound as a yellow oil (145 mg, 60%).

**Rf**: 0.68 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.36 (td, J = 8.2, 6.4 Hz, 1H, H-17), 7.08-7.05 (m, 2H, H-16, H-18), 7.03-6.99 (m, 1H, H-14), 5.55 (ddd, J = 15.6, 6.4, 0.8 Hz, 1H, H-4), 5.41 (ddd, J = 15.6, 6.8, 1.0 Hz, 1H, H-3), 4.09 (qn, J = 6.8 Hz, 1H, H-2), 3.30 (s, 230
3H, H-12), 1.94-1.85 (m, 1H, H-5), 1.71-1.60 (m, 4H, H-6, H-7, H-9, H-10), 1.37 (d, J = 6.8 Hz, 3H, H-1), 1.28-0.97 (m, 6H, H-6’, 7’, H-8, H-9’, H-10’); 13C NMR: (100 MHz, CDCl3) δ (ppm) 168.4 (C-11), 162.8 (d, 3JC,F = 246.7 Hz, C-15), 143.7 (d, 3JC,F = 9.5 Hz, C-13), 137.2 (C-4), 130.4 (d, 3JC,F = 9.0 Hz, C-17), 128.1 (C-3), 123.8 (d, 3JC,F = 2.3 Hz, C-18), 115.5 (d, 3JC,F = 21.5 Hz, C-14), 115.1 (d, 3JC,F = 20.7 Hz, C-16), 42.7 (C-2), 40.3 (C-5), 38.0 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.0 (C-1); IR: vmax(film)/cm⁻¹ 1656 (C=O), 1485 (C=C), 1282 (Cₐ-N), 1194 (C-F), 966, 696; MS: m/z (ES⁺) 344 [M+Na]+ (100%); HRMS: found 344.1445, [M+Na]+ requires 344.1455.

316fh: (E)-S-4-Cyclohexylbut-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (400 mg, 1.51 mmol), HOBt (1.5 eq) and 2-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 97:3 to 92:8) afforded the title compound as a colourless sticky oil (444 mg, 88%).

Rf: 0.48 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.36 (td, J = 8.0, 1.4 Hz, 1H, H-18), 7.21 (bd, J = 8.0 Hz, 1H, H-15), 6.96, (m, 2H, H-16, H-17), 5.50 (m, 1H, H-4), 5.40 (m, 1H, H-3), 4.07 (m, H-2), 3.85 (s, 3H, H-19), 3.21 (s, 3H, H-12), 1.91-1.84 (m, 1H, H-5), 1.69-1.60 (m, 4H, H-6, H-7, H-9, H-10), 1.35 (d, J = 6.8 Hz, 3H, H-1)/1.32 (d, J = 6.8 Hz, 3H, H-1) -rotamers-, 1.25-0.95 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); 13C NMR: (100 MHz, CDCl3) δ (ppm) 156.2/156.1 (C-11) -rotamers-, 136.7/136.6 (C-4) -rotamers-, 130.8 (C-15), 130.2 (C-18), 128.6/128.5 (C-3), 120.8 (C-16 or C-17), 112.2/112.1 (C-17 or C-16), 55.6 (C-19), 42.3/42.2 (C-2) -rotamers-, 40.4 (C-5), 36.7 (C-12), 32.8/32.7 (C-6, C-10), 26.1/26.0 (C-7, C-8, C-9), 21.1 (C-1); IR: vmax(film)/cm⁻¹ 1651 (C=O), 1499 (C=C), 1271 (Cₐ-N), 747; MS: m/z (ES⁺) 334 [M+H]+ (100%); HRMS: found 356.1659, [M+Na]+ requires 356.1655.

The equivalent enantioenriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate (S)-316fh (94:6 e.r., 208 mg, 82%) was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 200 mg, 0.76 mmol) following the same procedure.
\([\alpha]_D^{24}\): -16.0 (c 1.00, CHCl₃); **HPLC**: \((R,R)\)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, major 10.7 min, minor 13.7 min (214.4 nm, 254.4 nm).

**316fi**: \((E)\)-4-Cyclohexylbut-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate.

General procedure B was followed using \((E)\)-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (200 mg, 0.76 mmol), HOBT (1.5 eq) and N-methylnaphthalen-1-amine 329j. Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a brown solid (110 mg, 41%).

**Rt**: 0.36 (Pet/EtOAc 8:2); **mp**: 83-85 °C; **\(^1\)H NMR**: (400 MHz; CDCl₃) \(\delta\) (ppm) 7.80-7.76 (m, 2H, H₉), 7.70-7.67 (m, 1H, H₆), 7.47-7.31 (m, 4H, H₉₄), 5.40 (bd, \(J = 15.5, 5.6\) Hz, 1H, H-4)/5.36 (bd, \(J = 15.5, 5.6\) Hz, 1H, H-4) \(-\) rotamers, 5.26 (dd, \(J = 15.5, 6.8\) Hz, 1H, H-3)/5.17 (dd, \(J = 15.5, 6.8\) Hz, 1H, H-3) \(-\) rotamers, 4.01-3.96 (bq, \(J = 6.8\) Hz, 1H, H-2), 3.30 (s, 3H, H-12)/3.29 (s, 3H, H-12) \(-\) rotamers, 1.75-1.68 (m, 1H, H-5), 1.57-1.48 (m, 4H, H-6, H-7, H-9, H-10), 1.21 (d, \(J = 6.8\) Hz, 3H, H-1)/1.19 (d, \(J = 6.8\) Hz, 3H, H-1), 1.12-0.81 (m, 6H, H-6', H-7', H-8', H-9', H-10'); **\(^13\)C NMR**: (100 MHz, CDCl₃) \(\delta\) (ppm) 169.4/169.3 (C-11) \(-\) rotamers, 138.1/138.0 (C₉₄), 136.9/136.6 (C-4), 134.6 (C₉₄), 130.5 (C₉₄), 129.3 (CH₉), 128.5 (C-3), 128.4 (CH₉), 128.2 (CH₉), 127.5/127.4 (CH₉) \(-\) rotamers, 127.2/127.2 (CH₉) \(-\) rotamers, 126.5 (CH₉), 125.6/125.6 (CH₉) \(-\) rotamers, 122.6/122.4 (CH₉) \(-\) rotamers, 124.2 (C-2), 40.3/40.2 (C-5) \(-\) rotamers, 40.0 (C-12), 32.8/32.6 (C-6, C-10), 26.0/25.9 (C-7, C-8, C-9), 20.9/20.7 (C-1) \(-\) rotamers; **IR**: \(\nu_{max}(film)/cm^{-1}\) 1643 (C=O), 1338, 1279 (C₉₄-N), 777; **MS**: m/z (ES⁺) 354 [M+H]⁺ (100%), 376 [M+Na]⁺ (80%); **HRMS**: found 354.1889, [M+H]⁺ requires 354.1887.

The equivalent enantioenriched thiocarbamate \((R)\)-4-cyclohexylbut-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate \((R)\)-316fi (14:86 e.r., 645 mg, 62%) was prepared from \((R)\)-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate \((R)\)-339f (88:12 e.r., 780 mg, 2.95 mmol) following the same procedure.

\([\alpha]_D^{22}\): -4.2 (c 1.00, CHCl₃); **HPLC**: \((R,R)\)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, minor 12.2 min, major 15.1 min (214.4 nm, 254.4 nm).
General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (400 mg, 1.51 mmol), HOBt (1.5 eq) and 2-(methylamino)pyridine. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 85:15) afforded the title compound as a colourless oil (108 mg, 23%).

Rf: 0.67 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 8.45 (ddd, J = 4.8, 1.9, 0.8 Hz, 1H, H-14), 7.69 (ddd, J = 8.2, 7.3, 1.9 Hz, 1H, H-16), 7.61 (d, J = 8.2 Hz, 1H, H-17), 7.12 (ddd, J = 7.3, 4.8, 1.0 Hz, 1H, H-15), 5.61 (ddd, J = 15.5, 6.6, 0.9 Hz, 1H, H-4), 5.47 (ddd, J = 15.5, 6.9, 1.1 Hz, 1H, H-3), 4.16 (qn, J = 6.9 Hz, 1H, H-2), 3.46 (s, 3H, H-12), 1.97-1.88 (m, 1H, H-5), 1.72-1.60 (m, 4H, H-6, H-7, H-9, H-10), 1.43 (d, J = 6.9 Hz, 1H, H-1), 1.30-1.00 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); 13C NMR: (100 MHz, CDCl3) δ (ppm) 168.9 (C-11), 154.3 (C-13), 148.2 (C-14), 137.5 (C4, C-16), 127.9 (C-3), 121.0 (C-15), 120.4 (C-17), 42.5 (C-2), 40.3 (C-5), 34.9 (C-12), 32.8/32.7 (C-6, C-10), 26.1/25.9 (C-7, C-8, C-9), 20.9 (C-1); IR: νmax(film)/cm⁻¹ 1663 (C=O), 1467 (C=CN), 1329 (CN=N), 1294 (CN=N), 1040, 964, 778; MS: m/z (ES⁺) 305 [M+H]⁺ (100%), 327 [M+Na]⁺ (30%); HRMS: found 305.1681, [M+H]⁺ requires 305.1683.

The equivalent enantioenriched thiocarbamate (S)-S-4-cyclohexylbut-3-en-2-yl methyl(pyridin-2-yl)carbamothioate (S)-316fj (94:6 e.r., 93 mg, 47%) was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 170 mg, 0.64 mmol) following the same procedure.

[a]D²²: -66.6 (c 1.00, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, major 6.7 min, minor 7.7 min (214.4 nm, 254.4 nm).
**316fk**: (E)-**tert-Butyl** 6-(((4-cyclohexylbut-3-en-2-yl)thio)carbonyl)(methyl)amino)-1H-indole-1-carboxylate.

To a solution of **316fl** (100 mg, 0.29 mmol, 1.0 eq) in CH$_2$Cl$_2$ (1.0 mL) were sequentially added di-**tert-butyl** dicarbonate (1.2 eq), triethylamine (1.0 eq) and DMAP (0.2 eq). The reaction was stirred at room temperature for 20 h. Water was added. The organic layer was extracted with CH$_2$Cl$_2$ (x3). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 95:5) afforded the title compound as a colourless sticky oil (128 mg, 100%).

**Rf**: 0.77 (Pet/EtOAc 8:2); **$^1$H NMR**: (400 MHz; CDCl$_3$) δ (ppm) 8.08 (bs, 1H, H-14), 7.62 (d, $J = 3.6$ Hz, 1H, H-16), 7.56 (d, $J = 8.2$ Hz, 1H, H-19), 7.12 (dd, $J = 8.2$, 1.9 Hz, 1H, H-20), 6.57 (dd, $J = 3.6$, 0.4 Hz, 1H, H-3), 5.52 (dd, $J = 15.9$, 6.8 Hz, 1H, H-4), 5.40 (dd, $J = 15.9$, 6.8 Hz, 1H, H-3), 4.09 (qn, $J = 6.8$ Hz, 1H, H-2), 1.91-1.82 (m, 1H, H-12), 1.67 (s, 9H, H-23, H-24, H-25), 1.67-1.59 (m, 4H, H-6, H-7, H-9, H-10), 1.36 (d, $J = 6.8$ Hz, 3H, H-1), 1.26-0.95 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); **$^{13}$C NMR**: (100 MHz, CDCl$_3$) δ (ppm) 168.8 (C-11), 149.4 (C-13), 138.5 (C-15), 136.8 (C-4), 128.4 (C-3), 127.3 (C-16), 125.6 (C-18), 123.1 (C-20), 121.4 (C-19), 115.5 (C-14), 107.1 (C-17), 84.1 (C-22), 42.6 (C-2), 40.4 (C-5), 38.6 (C-12), 32.8/32.7 (C-6, C-10), 28.2 (C-23, C-24, C-25), 26.1/26.0 (C-7, C-8, C-9), 21.1 (C-1); **IR**: $v_{\text{max}}$(film)/cm$^{-1}$ 1736 (C=O), 1612 (C=O), 1441 (C=C$_{Ar}$), 1333 (C-O$_{ester}$), 1239 (C$_{Ar}$-N), 1154, 1040; **MS**: $m/z$ (ES$^+$) 443 [M+H]$^+$ (100%), 465 [M+Na]$^+$ (80%); **HRMS**: found 465.2192, [M+Na]$^+$ requires 465.2182.

The equivalent enantioenriched thiocarbamate (S)-**tert-butyl** 6-(((4-cyclohexylbut-3-en-2-yl)thio)carbonyl)(methyl)amino)-1H-indole-1-carboxylate (S)-**316fk** (95:5 e.r., 168 mg, 100%, 88% over 2 steps from (S)-**339f** was prepared from (S)-S-4-cyclohexylbut-3-en-2-yl 1H-indol-6-yl(methyl)carbamothioate (S)-**316fl** (95:5 e.r., 130 mg, 0.38 mmol) following the same procedure.
$\alpha_{D}^{23}$: +14.8 (c 1.00, CHCl$_3$); **HPLC:** (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, major 19.0 min, minor 27.2 min (214.4 nm, 254.4 nm).

The other enantiomer (R)-tert-butyl 6-(((4-cyclohexylbut-3-en-2-yl)thiocarbonyl)(methyl)amino)-1H-indole-1-carboxylate (R)-316fk (14:86 e.r., 471 mg, 91%, 74% over 2 steps from (R)-339f) was prepared from (R)-S-4-cyclohexylbut-3-en-2-yl 1H-indol-6-yl(methyl)carbamothioate (R)-316fl (400 mg, 1.17 mmol) following the same procedure. **HPLC:** (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, minor 21.9 min, major 29.9 min (214.4 nm, 254.4 nm).

316fl: (E)-S-4-Cyclohexylbut-3-en-2-yl 1H-indol-6-yl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339f (125 mg, 0.47 mmol), HOBt (1.1 eq) and N-methyl-1H-indole-6-amine 329m. Purification by column chromatography (Pet 100%, Pet/EtOAc 9:1, 85:15) afforded the title compound as a white solid (159 mg, 99%).

$R_f$: 0.48 (Pet/EtOAc 8:2); **mp**: 133-135 °C; $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 8.27 (bs, 1H, H$_{16}$), 7.65 (d, $J = 8.3$ Hz, 1H, H$_{20}$), 7.31 (bt, $J = 1.3$ Hz, 1H, H$_{14}$), 7.28 (dd, $J = 3.0$, 2.7 Hz, 1H, H$_{17}$), 6.99 (dd, $J = 8.3$, 1.3 Hz, 1H, H$_{21}$), 6.58 (ddd, $J = 3.0$, 2.0, 0.8 Hz, 1H, H$_{18}$), 5.51 (dd, $J = 15.8$, 6.5 Hz, 1H, H$_4$), 5.39 (dd, $J = 15.8$, 6.8 Hz, 1H, H$_3$), 4.07 (qn, $J = 6.8$ Hz, 1H, H$_2$), 3.35 (s, 3H, H$_{12}$), 1.90-1.81 (m, 1H, H$_5$), 1.68-1.58 (m, 4H, H$_6$, H$_7$, H$_9$, H$_{10}$), 1.35 (d, $J = 6.8$ Hz, 3H, H$_1$), 1.26-0.93 (m, 6H, H$_{6'}$, H$_{7'}$, H$_8$, H$_{8'}$, H$_{9'}$, H$_{10'}$); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 160.9 (C$_{11}$), 149.8 (C$_{13}$), 136.7 (C$_4$), 135.5 (C$_{15}$), 128.5 (C$_3$), 125.8 (C$_{17}$), 124.6 (C$_{18}$), 121.4 (C$_{20}$), 120.1 (C$_{21}$), 111.6 (C$_{14}$), 102.9 (C$_{18}$), 42.5 (C$_2$), 40.3 (C$_5$), 38.7 (C$_{12}$), 32.8/32.7 (C$_6$, C$_{10}$), 26.1/26.0 (C$_7$, C$_8$, C$_9$), 21.1 (C$_1$); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3317 (NH), 1633 (C=O), 1450 (C=C$_A$), 1347 (C$_{A'}$-N), 1295 (C$_{A''}$-N), 1093, 655; **MS:** $m/z$ (ES$^+$) 343 [M+H]$^+$ (50%), 365 [M+Na]$^+$ (60%); **HRMS:** found 343.1841, [M+H]$^+$ requires 343.1839.
The equivalent enantioenriched thiocarbamate \((S)-S-4\text{-cyclohexylbut-3-en-2-yl methyl(pyridin-2-yl)carbamothioate (S)}\)-316fk \((95:5 \text{ e.r.}, 154 \text{ mg, 88%})\) was prepared from \((S)-S-4\text{-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)}\)-339f \((95:5 \text{ e.r.}, 135 \text{ mg, 0.51 mmol})\) following the same procedure.

\([\alpha]_D^{24}\): -3.2 \(c 1.00, \text{CHCl}_3\); \text{HPLC}: \((R,R)\)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, major 32.5 min, minor 51.1 min (214.4 nm, 254.4 nm).

The other enantiomer \((R)-S-4\text{-cyclohexylbut-3-en-2-yl methyl(pyridin-2-yl)carbamothioate (R)}\)-316fk \((421 \text{ mg, 81%})\) was prepared from \((R)-S-4\text{-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (R)}\)-339f \((88:12 \text{ e.r.}, 400 \text{ mg, 1.51 mmol})\) following the same procedure.

\(316\text{ga}: (E)-S-4\text{-Phenylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate.}

\[\begin{align*}
\text{General procedure B was followed using (E)-S-4-phenylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339g (200 mg, 0.77 mmol), HOBt (1.2 eq) and 4-chloro-N-methylaniline.}
\text{Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1 to 95:5) afforded the title compound as a yellow oil (144 mg, 56%).}
\end{align*}\]

\(R_f\): 0.66 (Pet/EtOAc 8:2); \text{^1H NMR}: (400 MHz; CDCl\textsubscript{3}) \(\delta\) (ppm) 7.39-7.18 \(\text{m, 5H, H-6, H-7, H-8, H-9, H-10}\), 7.38 \(\text{d, J = 8.7 Hz, 2H, H-14, H-18}\), 7.21 \(\text{d, J = 8.7 Hz, H-15, H-17}\), 6.54 \(\text{d, J = 15.8 Hz, 1H, H-4}\), 6.21 \(\text{dd, J = 15.8, 7.2 Hz, 1H, H-3}\), 4.30 \(\text{qn, J = 7.2 Hz, 1H, H-2}\), 3.30 \(\text{s, 3H, H-12}\), 1.48 \(\text{d, J = 7.2 Hz, 3H, H-1}\); \text{^13C NMR}: (100 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 168.0 (C-11), 140.5 (C-13), 136.8 (C-5), 134.1 (C-16), 130.9 (C-3), 129.9 (C-7, C-9), 129.7 (C-4), 128.5 (C-6, C-8, C-10), 127.4 (C-15, C-17), 126.4 (C-14, C-18), 42.9 (C-2), 38.1 (C-12), 20.5 (C-1); \text{IR}: \nu_{\text{max}}^{\text{film}}/\text{cm}^{-1} 1650 \text{ (C=O), 1486 (C=C=Ar), 1013, 693 (C-Cl)}; \text{MS: m/z (ES\textsuperscript{+}) 354} [M+Na\textsuperscript{+}] (100%); \text{HRMS: found 354.0686, [M+Na\textsuperscript{+}] requires 354.0690.}
316gb: (E)-S-4-Phenylbut-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-phenylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339g (200 mg, 0.77 mmol), HOBt (1.1 eq) and 4-fluoro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 95:5) afforded the title compound as a colourless oil (177 mg, 73%).

Rf: 0.64 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.35-7.33 (m, 2H, H-7, H-9), 7.30-7.18 (m, 5H, H-6, H-8, H-10, H-14, H-18), 7.09 (t, J = 8.6 Hz, 2H, H-15, H-17), 6.54 (d, J = 15.8 Hz, 1H, H-4), 6.21 (dd, J = 15.8, 7.0 Hz, 1H, H-3), 4.29 (qn, J = 7.0 Hz, 1H, H-2), 3.30 (s, 3H, H-12), 1.47 (d, J = 7.0 Hz, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 168.2 (C-11, C-16) ¹J_{CF} not visible, 136.8 (C-13), 131.0 (C-3), 130.3 (m, C-14, C-18), 128.5/127.4 (C-6, C-8, C-10), 129.8 (C-4), 128.5 (C-5), 126.4 (C-7, C-9), 116.4 (d, ¹J_{CF} = 22.4 Hz, C-15, C-17), 42.8 (C-2), 38.3 (C-12), 20.5 (C-1); IR: ν_{max}(film)/cm⁻¹ 1656 (C=O), 1509 (C=CAr), 1273 (CAr-N), 1221 (C-F); MS: m/z (ES⁺) 316 [M+H]⁺ (50%), 338 [M+Na]⁺ (100%); HRMS: found 316.1167, [M+H]⁺ requires 316.1166.

316gc: (E)-S-4-Phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using (E)-S-4-phenylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339g (160 mg, 0.62 mmol), HOBt (1.2 eq) and 3-methoxy-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a pale yellow oil (175 mg, 86%).

Rf: 0.57 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.36-7.28 (m, 5H, H-6, H-7, H-8, H-9, H-10), 7.20 (t, J = 7.8 Hz, 1H, H-17), 6.90 (ddd, J = 7.8, 2.2, 0.8 Hz, 1H, H-16 or H-18), 6.87 (ddd, J = 7.8, 2.2, 0.8 Hz, 1H, H-18 or H-16), 6.81 (t, J = 2.2 Hz, 1H, H-14), 6.54 (d, J = 15.8 Hz, 1H, H-4), 6.23 (dd, J = 15.8, 7.3 Hz, 1H, H-3), 4.31 (qn, J = 7.3 Hz, 1H, H-2), 3.82 (s, 3H, H-19), 3.31 (s, 3H, H-12), 1.48 (d, J = 7.3 Hz, 3H, H-1); ¹³C NMR: (100 MHz,
CDCl$_3$ $\delta$ (ppm) 168.0 (C-11), 160.2 (C-15), 143.1 (C-13), 136.9 (C-5), 131.2 (C-3), 130.1 (C-7, C-9), 129.7 (C-4), 128.5 (C-6, C-10), 127.4 (C-14), 126.4 (C-8), 120.4 (C-16 or C-18), 114.0/113.9 (C-14 and C-18 or C-16), 55.4 (C-19), 42.7 (C-2), 38.2 (C-12), 20.6 (C-1); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 1651 (C=O), 1599 (C=C), 1316 (C$_{\text{Ar}}$-N), 1217 (C$_{\text{Ar}}$-O), 750, 695; MS: $m/z$ (ES$^+$) 328 [M+H]$^+$ (100%); HRMS: found 350.1182, [M+Na]$^+$ requires 350.1186.

The equivalent enantioenriched thiocarbamate $(R)$-S-4-phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate $(R)$-316gc (83:17 e.r., 62 mg, 61%) was prepared from $(R)$-S-(4-phenylbut-3-en-2-yl) 1H-imidazole-1-carbothioate $(R)$-339g (83:17 e.r., 81 mg, 0.31 mmol) following the same procedure. 

$[\alpha]_D^{24}$: +1.2 (c 1.00, CHCl$_3$); HPLC: Chiralpak AD, Hexane/i-PrOH 95:5, 1.0 mL/min, minor 9.2 min, major 11.2 min (254.4 nm).

The equivalent enantioenriched thiocarbamate $(R)$-S-4-phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate $(R)$-316gd (83:17 e.r., 62 mg, 61%) was prepared from $(R)$-S-(4-phenylbut-3-en-2-yl) 1H-imidazole-1-carbothioate $(R)$-339g (83:17 e.r., 81 mg, 0.31 mmol) following the same procedure. 

$[\alpha]_D^{24}$: +1.2 (c 1.00, CHCl$_3$); HPLC: Chiralpak AD, Hexane/i-PrOH 95:5, 1.0 mL/min, minor 9.2 min, major 11.2 min (254.4 nm).

316gd: $(E)$-S-4-Phenylbut-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate.

General procedure B was followed using $(E)$-S-4-phenylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339g (200 mg, 0.77 mmol), HOBt (1.1 eq) and 3-chloro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as an orange oil (161 mg, 63%).

$R_f$: 0.34 (Pet/EtOAc 95:5); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.37-7.17 (m, 9H, H$_{\text{Ar}}$), 6.55 (d, $J$ = 15.8 Hz, 1H, H-4), 6.22 (dd, $J$ = 15.8, 7.3 Hz, 1H, H-3), 4.31 (qn, $J$ = 7.3 Hz, 1H, H-2), 3.31 (s, 3H, H-12), 1.48 (d, $J$ = 7.3 Hz, 3H, H-1).

316ge: $(E)$-S-4-Phenylbut-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate.

General procedure B was followed using $(E)$-S-4-phenylbut-3-en-2-yl 1H-imidazole-1-carbothioate 339g (162 mg, 0.62 mmol), HOBt (1.1 eq) and 2-methoxy-N-methylaniline.
Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 9:1) afforded the title compound as colourless oil (155 mg, 76%).

Rf: 0.53 (Pet/EtOAc 8:2); \( ^1 \)H NMR: (400 MHz; CDCl\(_3\)) \( \delta \) (ppm) 7.39-7.17 (m, 7H, H-6, H-7, H-8, H-9, H-10, H-16, H-18), 6.96 (t, \( J = 7.4 \) Hz, 2H, H-15, H-17), 6.53 (d, \( J = 15.8 \) Hz, 1H, H-4)/6.49 (d, \( J = 15.8 \) Hz, 1H, H-4) \(-rotamers-,\) 6.24 (dd, \( J = 15.8, 7.4 \) Hz, 1H, H-3)/6.20 (dd, \( J = 15.8, 7.4 \) Hz, 1H, H-3) \(-rotamers-,\) 4.28 (qn, \( J = 7.4 \) Hz, 1H, H-2), 3.87 (s, 3H, H-19)/3.82 (s, 3H, H-19) \(-rotamers-,\) 3.22 (s, 3H, H-12), 1.47 (d, \( J = 7.4 \) Hz, 3H, H-1)/1.44 (d, \( J = 7.4 \) Hz, 3H, H-1) \(-rotamers-;\) \( ^{13} \)C NMR: (100 MHz, CDCl\(_3\)) \( \delta \) (ppm) 168.7 (C-11), 156.1 (C-14), 137.1/137.0 (C-5), 131.5/131.4 (C-3) \(-rotamers-,\) 130.9/130.8 (CH\(_{Ar}\)) \(-rotamers-,\) 130.3 (CH\(_{Ar}\)), 129.9 (C-13), 129.5/129.4 (C-4) \(-rotamers-,\) 128.4 (CH\(_{Ar}\)), 127.3/127.2 (CH\(_{Ar}\)) \(-rotamers-,\) 126.4/126.3 (CH\(_{Ar}\)) \(-rotamers-,\) 120.8/120.7 (C-17) \(-rotamers-,\) 112.2 (C-15), 55.7/55.6 (C-19) \(-rotamers-,\) 42.5/42.4 (C-2), 36.7 (C-12), 20.6/20.5 (C-1) \(-rotamers-,\) IR: \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1651 (C=O), 1498 (C=C\(_{Ar}\)), 1270 (C\(_{Ar}\)-N), 1045, 747; MS: \( m/z \) (ES\(^+\)) 328 [M+H\(^+\)] (50%), 350 [M+Na\(^+\)] (60%); HRMS: found 350.1188, [M+Na\(^+\)] requires 350.1186.

The equivalent enantioenriched thiocarbamate \((R)-S\)-4-phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate \((R)-316ge\) (83:17 e.r., 72 mg, 71%) was prepared from \((R)-S\)-(4-phenylbut-3-en-2-yl) 1H-imidazole-1-carbothioate \((R)-339g\) (83:17 e.r., 81 mg, 0.31 mmol) following the same procedure. \((R)-316ge\) was obtained as a white solid.

mp: 88-90 °C; \([\alpha]_D^{24}\): -3.0 (c 1.00, CHCl\(_3\)); HPLC: Chiralpak AD-H, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, minor 9.6 min, major 13.1 min (214.4 nm, 254.4 nm).

**316ha:** \((E)-S\)-4-Methylhept-4-en-3-yl 4-chlorophenyl(methyl)carbamothioate.

![Chemical Structure](image)

General procedure B was followed using \((E)-S\)-4-methylhept-4-en-3-yl 1H-imidazole-1-carbothioate \(339h\) (50 mg, 0.21 mmol), HOBt (0.5 eq) and 4-chloro-N-methylaniline. Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 8:2) afforded the title compound as a pale yellow oil (39 mg, 60%).
Rf: 0.78 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.36 (d, $J = 8.8$ Hz, 2H, H-12, H-16), 7.20 (d, $J = 8.8$ Hz, 2H, H-13, H-15), 5.41 (t, $J = 7.2$ Hz, 1H, H-5), 3.89 (t, $J = 7.0$ Hz, 1H, H-3), 3.28 (s, 3H, H-10), 1.99 (qn, $J = 7.2$ Hz, 2H, H-6), 1.65 (qn, $J = 7.0$ Hz, 2H, H-2), 1.60 (s, 3H, H-8), 0.93 (t, $J = 7.2$ Hz, 3H, H-7), 0.87 (t, $J = 7.0$ Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 168.8 (C-9), 140.9 (C-4), 133.8 (C-11), 132.7 (C-14), 129.8 (C-5), 129.6 (C-13, C-15), 129.5 (C-12, C-16), 55.9 (C-3), 38.2 (C-10), 27.2 (C-2), 21.1 (C-6), 14.0 (C-7), 13.5 (C-8), 12.1 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1651 (C=O), 1488 (C=C Ar), 1275 (C Ar-N); MS: m/z (ES$^+$) 312 [M+H]$^+$ (100%), 334 [M+Na]$^+$ (80%); HRMS: found 312.1176, [M+H]$^+$ requires 312.1184.

318aa: S-(2-Phenyl)but-3-en-2-yl methylcarbamothioate.

General procedure M (-78 °C, 1 h) was followed using S-but-3-en-2-yl phenyl(methyl)carbamoiothioate 316aa (50 mg, 0.23 mmol). Purification by column chromatography (Pet/EtOAc 9:1) afforded the title compound as a yellow oil (34 mg, 68%).

Rf: 0.35 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.55 (d, $J = 7.6$ Hz, 2H, H-9, H-13), 7.34 (t, $J = 7.6$ Hz, 2H, H-10, H-12), 7.23 (m, 1H, H-11), 6.49 (dd, $J = 17.4$, 10.8 Hz, 1H, H-3), 5.26 (dd, $J = 10.8$, 0.4 Hz, 1H, H-4), 5.23 (dd, $J = 17.4$, 0.4 Hz, 1H, H-4'), 5.21 (bs, 1H, H-7), 2.75 (d, $J = 4.8$ Hz, 3H, H-6), 1.95 (s, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 166.2 (C-5), 143.9 (C-8), 142.3 (C-3), 128.1 (C-10, C-12), 127.1 (C-11), 126.9 (C-9, C-13), 114.0 (C-4), 56.7 (C-2), 27.4 (C-6), 26.7 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3314 (NH), 1655 (C=O), 1492 (C=C Ar), 1209, 1007, 293; MS: m/z (ES$^+$) 244 [M+Na]$^+$ (100%); HRMS: found 244.0774, [M+Na]$^+$ requires 244.0767.

The title compound (22 mg, 31%) was also obtained from S-1-phenylethyl methyl(vinyl)carbamothioate 326a (70 mg, 0.32 mmol) following general procedure M (THF/DMPU 4:1, -60 °C, 2 h).
The equivalent enantioenriched thiocarbamate \((R)-S\text{-}2\text{-phenylbut}-3\text{-en}-2\text{-yl methylcarbamothioate}\) \((R)-318\text{aa}\) \((85:15\ e.r., 29 mg, 63%)\) was prepared from \((R)-S\text{-but}-3\text{-en}-2\text{-yl methyl(phenyl)carbamothioate}\) \((R)-316\text{aa}\) \((91:9\ e.r., 46 mg, 0.21 mmol\) following general procedure M \((-78\ ^\circ\text{C}, 1.5\ h)\).


\[\alpha\]_D^{16}: +19.6 (c 1.90, CHCl_3); HPLC: Chiralpak AD-H, Hexane/i-PrOH 96:4, 1.0 mL/min, major 31.6 min, minor 35.2 min.

The equivalent enantioenriched thiocarbamate \((R)-S\text{-2-phenylbut}-3\text{-en}-2\text{-yl methylcarbamothioate}\) \((R)-318\text{aa}\) \((96:4\ e.r., 16 mg, 32%)\) was also prepared from \((S)-S\text{-1-phenylethyl methyl(vinyl)carbamothioate}\) \((S)-326\text{aa}\) \((98:2\ e.r., 50 mg, 0.23 mmol\) following general procedure O.

318\text{ab}: S-2-(p-Tolyl)but-3-en-2-yl methylcarbamothioate.

General procedure N \((-60\ ^\circ\text{C}, 2\ h\) was followed using \(S\)-but-3-en-2-yl methyl(p-tolyl)carbamothioate 316\text{ab} (50 mg, 0.21 mmol). Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a pale yellow oil (28 mg, 56%).

\(R_f\): 0.41 (Pet/EtOAc 8:2); \(^1\text{H NMR}: (400 MHz; CDCl_3) \delta (ppm) 7.42 (d, \(J = 8.2\ Hz, 2\text{H, H-10, H-12}\), 7.14 (d, \(J = 8.2\ Hz, 2\text{H, H-9, H-13}\), 6.47 (dd, \(J = 17.4, 10.8\ Hz, 1\text{H, H-3}\), 5.25 (dd, \(J = 10.8, 0.8\ Hz, 1\text{H, H-4}\), 5.22 (dd, \(J = 17.4, 0.8\ Hz, 1\text{H, H-4'}\), 5.20 (bs, 1H, H-7), 2.75 (d, \(J = 4.8\ Hz, 3\text{H, H-6}\), 2.33 (s, 3H, H-14), 1.94 (s, 3H, H-1); \(^{13}\text{C NMR}: (100 MHz, CDCl_3) \delta (ppm) 166.4 (C-5), 142.5 (C-3), 140.9 (C-11), 136.8 (C-8), 129.0 (C-10, C-12), 126.8 (C-9, C-13), 113.9 (C-4), 56.6 (C-2), 27.4 (C-6), 26.7 (C-1), 21.0 (C-14); IR: \(v_{max}(\text{film})/\text{cm}^{-1} \) 3318 (NH), 1651 (C=O), 1608 (C=C), 1322, 1107; MS: \(m/z (ES^+ \) 236 [M+H]^+ (100%), 258 [M+Na]^+ (90%); HRMS: found 258.0923, [M+Na]^+ requires 258.0924.

The same procedure \((-60\ ^\circ\text{C}, 1\ h\) was used to attempt the preparation of the equivalent enantioenriched thiocarbamate \((R)-S\text{-2-(p-tolyl)but}-3\text{-en}-2\text{-yl methylcarbamothioate}\)
(R)-318ab (53:47 e.r., 23 mg, 46%), from (R)-5-but-3-en-2-yl methyl(p-tolyl)carbamothioate (R)-316ab (89:11 e.r., 50 mg, 0.21 mmol).

**HPLC:** (R,R)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, minor 31.1 min, major 33.2 min (214.4 nm, 254.4 nm).

318ad: 5-2-(4-Chlorophenyl)but-3-en-2-yl methylcarbamothioate.

![Structure of 318ad](image)

General procedure M (-78 °C, 2 h) was followed using 5-but-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate 316ad (37 mg, 0.14 mmol). Purification by column chromatography (Pet/EtOAc 9:1) afforded the title compound as a colourless oil (29 mg, 78%).

Rf: 0.34 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.48 (d, J = 8.8 Hz, 2H, H-10, H-12), 7.28 (d, J = 8.8 Hz, 2H, H-9, H-13), 6.46 (dd, J = 17.2, 10.4 Hz, 1H, H-3), 5.25 (d, J = 10.4 Hz, 1H, H-4), 5.22 (bs, 1H, H-7), 5.20 (d, J = 17.2 Hz, 1H, H-4'), 2.75 (d, J = 5.2 Hz, 3H, H-6), 1.90 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 165.8 (C-5), 142.9 (C-8), 141.9 (C-3), 132.7 (C-11), 128.4 (C-9, C-13), 128.2 (C-10, C-12), 114.3 (C-4), 56.1 (C-2), 27.4 (C-6), 26.8 (C-1); IR: νmax(film)/cm⁻¹ 3313 (NH), 1654 (C=O), 1489 (C=C₆H₄), 1209; MS: m/z (ES⁺) 278 [M+Na]⁺ (100%), 310 [M+Na+MeOH]⁺ (30%); HRMS: found 273.0828, [M+NH₄]⁺ requires 273.0823.

The title compound (42 mg, 84%) was also obtained from 5-1-(4-chlorophenyl)ethyl methyl(vinyl)carbamothioate 326b (50 mg, 0.20 mmol) following general procedure M (-78 °C, 1 h).

The equivalent enantioenriched thiocarbamate (R)-S-2-(4-chlorophenyl)but-3-en-2-yl methylcarbamothioate (R)-318ad (91:9 e.r., 49 mg, 98%) was prepared from (R)-5-but-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate (R)-316ad (91:9 e.r., 50 mg, 0.20 mmol) following general procedure M (-78 °C, 3 h).
$\alpha_D^{22} +6.3$ (c $1.13$, CHCl$_3$); HPLC: ($R,R$)-Whelk-01, Hexane/$i$-PrOH 96:4, 1.0 mL/min, 28 °C, minor 22.9 min, major 24.9 min (214.4 nm, 254.4 nm).

**318ae**: S-2-(4-Fluorophenyl)but-3-en-2-yl methylcarbamothioate.

![Structure of 318ae](image)

General procedure M (-60 °C, 2.5 h) was followed using 5-but-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate 316ae (200 mg, 0.84 mmol). The title compound was obtained as a pale yellow oil without purification (194 mg, 97%).

Rf: 0.13 (Pet/EtOAc 9:1); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.51 (dd, $J = 9.2, 5.2$ Hz, 2H, H-10, H-12), 7.00 (dd, $J = 8.4, 8.4$ Hz, 2H, H-9, H-13), 6.47 (dd, $J = 17.4, 10.6$ Hz, 1H, H-3), 5.25 (d, $J = 10.6$ Hz, 1H, H-4), 5.23 (bs, 1H, H-7), 5.20 (d, $J = 17.4$ Hz, 1H, H-4'), 2.75 (d, $J = 4.8$ Hz, 3H, H-6), 1.92 (s, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 165.9 (C-5), 161.6 (d, $^1$J$_{C,F} = 244.8$ Hz, C-11), 142.2 (C-3), 139.9 (d, $^4$J$_{C,F} = 3.1$ Hz, C-8), 128.7 (d, $^3$J$_{C,F} = 8.0$ Hz, C-9, C-13), 115.0 (d, $^2$J$_{C,F} = 21.2$ Hz, C-10, C-12), 114.1 (C-4), 56.1 (C-2), 27.4 (C-6), 26.9 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3314 (NH), 1655 (C=O), 1505 (C=C$_{\text{Ar}}$), 1219 (C-F); MS: m/z (ES$^+$) 262 [M+Na]$^+$ (100%); HRMS: found 262.0666, [M+Na]$^+$ requires 262.0672.

The equivalent enantioenriched thiocarbamate ($R$)-S-2-(4-fluorophenyl)but-3-en-2-yl methylcarbamothioate ($R$)-318ae (67:33 e.r., 27 mg, 54%) was prepared from ($R$)-5-but-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate ($R$)-316ae (89:11 e.r., 50 mg, 0.21 mmol) following general procedure M (-60 °C, 2 h).

$\alpha_D^{22} +12.0$ (c $1.86$, CHCl$_3$); HPLC: ($R,R$)-Whelk-01, Hexane/$i$-PrOH 96:4, 1.0 mL/min, 28 °C, minor 20.3 min, major 22.5 min (214.4 nm, 254.4 nm).
318af: S-2-(3-Methoxyphenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 2 h) was followed using S-but-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate 316af (50 mg, 0.20 mmol). Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a yellow oil (43 mg, 86%).

R_f: 0.32 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.26 (t, J = 8.0 Hz, 1H, H-10), 7.13 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H, H-11), 7.11 (bt, J = 2.0 Hz, 1H, H-13), 6.79 (ddd, J = 8.0, 2.0, 0.8 Hz, 1H, H-9), 6.47 (dd, J = 17.2, 10.2 Hz, 1H, H-3), 5.26 (d, J = 10.2 Hz, 1H, H-4), 5.23 (d, J = 17.2 Hz, 1H, H-4'), 5.23 (bs, 1H, H-7), 3.81 (s, 3H, H-14), 2.76 (d, J = 4.8 Hz, 3H, H-6), 1.94 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 159.4 (C-5), 145.7 (C-12), 142.2 (C-3), 129.2 (C-10), 125.6 (C-8), 119.2 (C-9), 114.1 (C-4), 113.3 (C-13), 112.1 (C-11), 56.7 (C-2), 55.2 (C-14), 27.4 (C-6), 26.7 (C-1); IR: ν_max (film)/cm⁻¹ 3314 (NH), 1654 (C=O), 1485 (C=C_Ar), 1209 (C_Ar-O); MS: m/z (ES⁺) 274 [M+Na]⁺ (100%); HRMS: found 274.0870, [M+Na]⁺ requires 274.0873.

The equivalent enantioenriched thiocarbamate (R)-S-2-(3-methoxyphenyl)but-3-en-2-yl methylcarbamothioate (R)-318af (82:18 e.r., 40 mg, 89%) was prepared from (R)-S-but-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate (R)-316af (83:17 e.r., 45 mg, 0.18 mmol) following the same procedure.

[α]D²²: +3.5 (c 1.02, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, minor 32.5 min, major 34.4 min (214.4 nm, 254.4 nm).
**318ag**: S-2-(3-Chlorophenyl)but-3-en-2-yl methylcarbamothioate.

General procedure M (-78 °C, 2 h) was followed using S-but-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate 316ag (31 mg, 0.12 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5, 9:1) afforded the title compound as a pale pink solid (23 mg, 73%).

Rf: 0.35 (Pet/EtOAc 8:2); mp: 51-53 °C; $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.53 (t, $J$ = 1.6 Hz, 1H, H-13), 7.44 (dt, $J$ = 7.8, 1.6 Hz, 1H, H-11), 7.26 (t, $J$ = 7.8 Hz, 1H, H-10), 7.20 (dt, $J$ = 7.8, 1.6 Hz, 1H, H-9), 6.46 (dd, $J$ = 17.2, 10.4 Hz, 1H, H-3), 5.26 (d, $J$ = 10.4 Hz, 1H, H-4), 5.24 (bs, 1H, H-7), 5.22 (d, $J$ = 17.2 Hz, 1H, H-4'), 2.75 (d, $J$ = 4.8 Hz, 3H, H-6), 1.90 (s, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 165.7 (C-5), 146.5 (C-8), 141.7 (C-3), 134.0 (C-12), 129.3 (C-10), 127.2 (C-13), 127.1 (C-9), 125.1 (C-11), 114.4 (C-4), 56.1 (C-2), 27.5 (C-6), 26.7 (C-1); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 3305 (NH), 1646 (C=O), 1531 (C=C$_{ar}$), 1229; MS: $m/z$ (ES$^+$) 256 [M+H]$^+$ (15%), 278 [M+Na]$^+$ (100%); HRMS: found 256.0554, [M+H]$^+$ requires 256.0557.

The equivalent enantioenriched thiocarbamate ($R$)-S-2-(3-chlorophenyl)but-3-en-2-yl methylcarbamothioate ($R$)-318ag (80:20 e.r., 47 mg, 94%) was prepared from ($R$)-5-but-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate ($R$)-316ag (80:20 e.r., 50 mg, 0.20 mmol) following the same procedure.

$[\alpha]_D^{22}$: +1.1 (c 1.12, CHCl$_3$); HPLC: ($R,R$)-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, minor 31.5 min, major 35.4 min (214.4 nm, 254.4 nm).
318ah: 5-2-(3-Fluorophenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 2.5 h) was followed using S-but-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate 316ah (53 mg, 0.22 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 9:1) afforded the title compound as a pale yellow oil (36 mg, 68%).

$R_f$: 0.33 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.28-7.19 (m, 3H, H-9, H-11, H-13), 6.90-6.85 (m, 1H, H-12), 6.41 (dd, $J = 17.3, 10.6$ Hz, 1H, H-3), 5.22 (bs, 1H, H-7), 5.21 (dd, $J = 10.6, 0.6$ Hz, 1H, H-4), 5.16 (dd, $J = 17.3, 0.4$ Hz, 1H, H-4'), 2.69 (d, $J = 4.8$ Hz, 3H, H-6), 1.85 (s, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 165.7 (C-5), 162.6 (d, $^1J_{CF} = 243.2$ Hz, C-10), 147.1 (d, $^3J_{CF} = 6.9$ Hz, C-8), 141.8 (C-3), 129.6 (d, $^3J_{CF} = 8.1$ Hz, C-12), 122.4 (C-13), 114.3 (C-4), 114.2 (d, $^2J_{CF} = 22.9$ Hz, C-9), 113.8 (d, $^2J_{CF} = 21.0$ Hz, C-11), 56.1 (C-2), 27.4 (C-6), 26.7 (C-1); IR: $\nu_{max}(\text{film})/\text{cm}^{-1}$ 3313 (NH), 1655 (C=O), 1484 (C=C$_{Ar}$), 1213 (C-F), 921, 784, 695; MS: $m/z$ (ES$^+$) 262 [M+Na]$^+$ (100%), 294 [M+Na+MeOH]$^+$ (80%); HRMS: found 240.0846, [M+H]$^+$ requires 240.0853.

The equivalent enantioenriched thiocarbamate ($R$)-5-2-(3-fluorophenyl)but-3-en-2-yl methylcarbamothioate ($R$)-318ah (82:18 e.r., 50 mg, 100%) was prepared from ($R$)-S-but-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate ($R$)-316ah (80:20 e.r., 50 mg, 0.21 mmol) following the same procedure. 

$[\alpha]_D^{24}$: +14.8 (c 1.00, CHCl$_3$); HPLC: ($R,R$)-Whelk-01, Hexane/i-PrOH 95:5, 0.5 mL/min, minor 30.2 min, major 31.5 min (214.4 nm, 254.4 nm).
318ai: S-2-(2-Methoxyphenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 4 h) was followed using 5-but-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate 316ai (200 mg, 0.80 mmol). Purification by filtration over silica (Pet/EtOAc 8:2) afforded the title compound as an orange oil (148 mg, 74%).

R_f: 0.26 (Pet/EtOAc 8:2); ^1H NMR: (400 MHz; CDCl_3) δ (ppm) 7.51 (dd, J = 7.8, 1.6 Hz, 1H, H-13), 7.27 (m, 1H, H-12), 6.96-6.91 (m, 2H, H-10, H-11), 6.55 (dd, J = 17.3, 10.4 Hz, 1H, H-3), 5.27 (bs, 1H, H-7), 5.16 (d, J = 10.4 Hz, 1H, H-4'), 5.14 (d, J = 17.3 Hz, 1H, H-4), 3.83 (s, 3H, H-14), 2.74 (d, J = 4.8 Hz, 3H, H-6), 2.04 (s, 3H, H-1); ^13C NMR: (100 MHz, CDCl_3) δ (ppm) 167.3 (C-5), 157.6 (C-9), 142.7 (C-3), 131.1 (C-8), 128.9 (C-12), 128.8 (C-13), 120.3 (C-10 or C-11), 112.9 (C-4), 112.5 (C-11 or C-10), 55.8 (C-2), 55.5 (C-14), 27.4 (C-6), 25.4 (C-1); IR: ν_max(film)/cm^-1 3317 (NH), 1650 (C=O), 1488 (C=C_Ar), 1243 (C_Ar-O), 1208, 1024, 730; MS: m/z (ES^+) 252 [M+H]^+ (100%), 274 [M+Na]^+ (80%); HRMS: found 274.0875, [M+Na]^+ requires 274.0873.

The equivalent enantioenriched thiocarbamate (R)-S-2-(2-methoxyphenyl)but-3-en-2-yl methylcarbamothioate (R)-318ai (63:37 e.r., 32 mg, 64%) was prepared from (R)-5-but-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate (R)-316ai (86:14 e.r., 50 mg, 0.20 mmol) following general procedure N (-60 °C, 3 h).

HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 95:5, 1.0 mL/min, minor 25.8 min, major 31.4 min (214.4 nm, 254.4 nm).
318aj: S-2-(Naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-78 °C, 2.5 h) was followed using S-but-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate 316aj (128 mg, 0.47 mmol). Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a colourless oil (127 mg, 99%).

Rf: 0.28 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 8.57 (dd, J = 6.4, 3.6 Hz, 1H, H-14 or H-15), 7.85 (dd, J = 6.4, 3.6 Hz, 1H, H-15 or H-14), 7.81 (d, J = 8.0 Hz, 1H, H-9 or H-11), 7.76 (d, J = 7.2 Hz, 1H, H-11 or H-9), 7.45 (m, 3H, H-10, H-13, H-16), 6.67 (dd, J = 17.2, 10.8 Hz, 1H, H-3), 5.22 (d, J = 10.8 Hz, 1H, H-4), 5.16 (bs, 1H, H-7), 5.05 (d, J = 17.2 Hz, 1H, H-4'), 2.68 (d, J = 4.8 Hz, 3H, H-6), 2.28 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 166.3 (C-5), 143.6 (C-3), 137.9 (C-8 or C-12 or C-17), 134.9 (C-8 or C-12 or C-17), 130.6 (C-8 or C-12 or C-17), 129.3 (C-9 or C-11), 129.1 (C-14 or C-15), 128.1 (C-15 or C-14), 126.2 (C-11 or C-9), 125.1 (C-10 or C-13 or C-16), 124.7 (C-10 or C-13 or C-16), 124.4 (C-10 or C-13 or C-16), 114.7 (C-4), 57.2 (C-2), 29.1 (C-1), 27.4 (C-6); IR: v_max(film)/cm⁻¹ 3312 (NH), 1651 (C=O), 1507 (C=C₆₆), 1204, 775; MS: m/z (ES⁺) 272 [M+H]⁺ (100%), 294 [M+Na]⁺ (70%).

The equivalent enantioenriched thiocarbamate (R)-S-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate (R)-318aj (80:20 e.r., 50 mg, 100%) was prepared from (R)-S-but-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate (R)-316aj (84:16 e.r., 50 mg, 0.18 mmol) following general procedure M (-78 °C, 2 h).

[α]D²²: +77.1 (c 1.07, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 90:10, 1.0 mL/min, minor 10.8 min, major 11.5 min (214.4 nm, 254.4 nm).
**318al**: S-2-(Pyridin-2-yl)but-3-en-2-yl methylcarbamothioate.

![Chemical Structure](image)

General procedure N (-78 °C, 2 h) was followed using S-2-(pyridin-2-yl)but-3-en-2-yl carbamothioate **316aj** (48 mg, 0.22 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 85:15) afforded the title compound as a dark green paste (27 mg, 54%).

Rf: 0.25 (Pet/EtOAc 1:1); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 8.57 (ddd, J = 4.8, 1.7, 0.8 Hz, 1H, H-9), 7.67 (td, J = 8.0, 1.7 Hz, 1H, H-11), 7.51 (d, J = 8.0 Hz, 1H, H-12), 7.17 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H, H-10), 6.54 (dd, J = 17.4, 10.6 Hz, 1H, H-3), 6.38 (bs, 1H, H-7), 5.27 (d, J = 10.6 Hz, 1H, H-4), 5.26 (d, J = 17.4 Hz, 1H, H-4′), 2.74 (d, J = 4.8 Hz, 3H, H-6), 1.93 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 162.9 (C-5), 148.4 (C-9), 141.3 (C-3), 137.0 (C-11), 122.1 (C-10), 121.3 (C-12), 114.8 (C-4), 57.5 (C-2), 27.4 (C-6), 25.7 (C-1) -C-8 not visible; IR: ν_max (film)/cm⁻¹ 3173 (NH), 1659 (C=O), 1523 (C=C Ar), 1216, 918, 780, 628; MS: m/z (ES⁺) 223 [M+H]⁺ (100%), 245 [M+Na]⁺ (50%); HRMS: found 245.0719, [M+Na]⁺ requires 245.0720.

**318ba**: S-3-(p-Tolyl)hex-1-en-3-yl methylcarbamothioate.

![Chemical Structure](image)

General procedure N (-60 °C, 1 h) was followed using S-hex-1-en-3-yl 4-methylphenyl(methyl)carbamothioate **316ba** (200 mg, 0.76 mmol). Purification by column chromatography (Pet/EtOAc 9:1) afforded the title compound as a pale yellow oil (88 mg, 44%).

Rf: 0.40 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.38 (d, J = 8.2 Hz, 2H, H-12, H-14), 7.13 (d, J = 8.2 Hz, 2H, H-11, H-15), 6.41 (dd, J = 17.4, 10.8 Hz, 1H, H-2), 5.30 (d, J = 10.6 Hz, 1H, H-1), 5.28 (d, J = 17.4 Hz, 1H, H-1′), 5.24 (bs, 1H, H-9), 2.72 (d, J = 4.7 Hz, 318
3H, H-8), 2.33 (s, 3H H-16), 2.22 (ddd, J = 13.8, 11.1, 5.7 Hz, 1H, H-4), 2.14 (ddd, J = 13.8, 11.1, 5.7 Hz, 1H, H-4'), 1.22 (m, 2H, H-5), 0.86 (t, J = 7.4 Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 166.2 (C-7), 141.2 (C-2), 139.4 (C-13), 136.6 (C-10), 128.8 (C-11, C-15), 127.4 (C-12, C-14), 114.5 (C-1), 60.9 (C-2), 41.5 (C-4), 27.4 (C-8), 21.0 (C-16), 18.2 (C-5), 14.2 (C-6); IR: ν$_{max}$(film)/cm$^{-1}$ 3314 (NH), 1656 (C=O), 1509 (C=C Ar), 1209, 811; MS: m/z (ES$^+$) 286 [M+Na]$^+$ (100%); HRMS: found 286.1225, [M+Na]$^+$ requires 286.1237.

318bc: S-3-(4-Chlorophenyl)hex-1-en-3-yl methylcarbamothioate.

![Chemical structure](image)

General procedure N (-60 °C, 1 h) was followed using S-hex-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate 316bc (200 mg, 0.70 mmol). Purification by column chromatography (Pet/EtOAc 9:1) afforded the title compound as a dark yellow oil (124 mg, 62%).

Rf: 0.43 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.43 (d, J = 8.8 Hz, 2H, H-12, H-14), 7.27 (d, J = 8.8 Hz, 2H, H-11, H-15), 6.40 (dd, J = 17.2, 10.4 Hz, 1H, H-2), 5.30 (d, J = 10.4 Hz, 1H, H-1), 5.25 (d, J = 17.2 Hz, 1H, H-1'), 5.23 (bs, 1H, H-9), 2.73 (d, J = 4.8 Hz, 3H, H-8), 2.20 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, H-4), 2.07 (ddd, J = 14.0, 11.0, 5.6 Hz, 1H, H-4'), 1.26-1.15 (m, 2H, H-5), 0.85 (t, J = 7.6 Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 165.6 (C-7), 141.5 (C-10), 140.8 (C-2), 132.6 (C-13), 129.0 (C-12, C-14), 128.1 (C-11, C-15), 114.8 (C-1), 60.3 (C-3), 41.3 (C-4), 27.4 (C-8), 18.1 (C-5), 14.2 (C-6); IR: ν$_{max}$(film)/cm$^{-1}$ 3313 (NH), 1656 (C=O), 1488 (C=C$_{Ar}$), 1211, 1012, 808 (C-Cl); MS: m/z (ES$^+$) 306 [M+Na]$^+$ (100%).

The equivalent enantioenriched thiocarbamate (R)-S-3-(4-chlorophenyl)hex-1-en-3-yl methylcarbamothioate. (R)-318bc (94:6 e.r., 39 mg, 81%) was prepared from (R)-S-hex-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate (R)-316bc (94:6 e.r., 48 mg, 0.17 mmol) following general procedure N (-78 °C, 2.5 h).

$[\alpha]_D^{23}$: +9.0 (c 1.00, CHCl$_3$); HPLC: Chiralpak AD-H, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, major 21.2 min, minor 25.5 min (214.4 nm, 254.4 nm).
**318bd**: S-3-(4-Fluorophenyl)hex-1-en-3-yl methylcarbamothioate.

General procedure N (-78 °C, 3 h) was followed using S-hex-1-en-3-yl 4-fluorophenyl(methyl)carbamothioate 316bd (50 mg, 0.19 mmol). Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a pale yellow oil (21 mg, 42%).

Rf: 0.36 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.47 (dd, $J = 8.8, 5.3$ Hz, 2H, H-11, H-15), 7.00 (t, $J = 8.8$ Hz, 2H, H-12, H-14), 6.40 (dd, $J = 17.4, 10.8$ Hz, 1H, H-2), 5.31 (dd, $J = 10.8, 0.6$ Hz, 1H, H-1), 5.26 (dd, $J = 17.4, 0.6$ Hz, 1H, H-1’), 5.23 (bs, 1H, H-9), 2.73 (d, $J = 4.8$ Hz, 3H, H-8), 2.23 (ddd, $J = 13.8, 11.4, 5.2$ Hz, 1H, H-4), 2.09 (ddd, $J = 13.8, 11.4, 5.2$ Hz, 1H, H-4’), 1.22 (m, 2H, H-5), 0.86 (t, $J = 7.4$ Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 165.8 (C-7), 161.5 (d, $^1$J$_{CF}$ = 244.8 Hz, C-13), 141.0 (C-2), 138.5 (d, $^4$J$_{CF}$ = 2.7 Hz, C-10), 129.3 (d, $^3$J$_{CF}$ = 7.6 Hz, C-11, C-15), 114.8 (d, $^2$J$_{CF}$ = 21.1 Hz, C-12, C-14), 114.7 (C-1), 60.4 (C-3), 41.4 (C-4), 27.4 (C-8), 18.1 (C-5), 14.2 (C-6); IR: $\nu_{max}$(film)/cm$^{-1}$ 3317 (NH), 1657 (C=O), 1505 (C=C$_{Ar}$), 1219 (C-F), 1160, 814; MS: m/z (ES$^+$) 290 [M+Na]$^+$ (70%); HRMS: found 290.0977, [M+Na]$^+$ requires 290.0986.

The equivalent enantioenriched thio carbamate (R)-S-2-(4-fluorophenyl)hex-1-en-3-yl methylcarbamothioate (R)-318bd (72:28 e.r., 26 mg, 52%) was prepared from (R)-S-hex-1-en-3-yl 4-fluorophenyl(methyl)carbamothioate (R)-316bd (91:9 e.r., 50 mg, 0.19 mmol) following the same procedure.

[a]$_b^{22}$: +8.5 (c 0.68, CHCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 90:10, 1.0 mL/min, 28 °C, major 11.4 min, minor 16.3 min (214.4 nm, 254.4 nm).
**318be:** 5-3-(3-Chlorophenyl)hex-1-en-3-yl methylcarbamothioate.

![Chemical Structure](image)

General procedure N (-45 °C, 4 h) was followed using 3-hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate **316be** (314 mg, 1.11 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 85:15) afforded the title compound as a yellow oil (105 mg, 33%).

**Rf:** 0.47 (Pet/EtOAc 8:2); **1H NMR:** (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.48 (t, $J = 1.6$ Hz, 1H, H-11), 7.41 (d, $J = 7.8$ Hz, 1H, H-13), 7.25 (t, $J = 7.8$ Hz, 1H, H-14), 7.20 (dt, $J = 7.8$, 1.7 Hz, 1H, H-15), 6.41 (dd, $J = 17.4$, 10.8 Hz, 1H, H-2), 5.32 (dd, $J = 10.8$, 0.6 Hz, 1H, H-1), 5.28 (dd, $J = 17.4$, 0.6 Hz, 1H, H-1′), 5.21 (bs, 1H, H-9), 2.74 (d, $J = 4.8$ Hz, 3H, H-8), 2.20 (ddd, $J = 13.8$, 11.1, 5.5 Hz, 1H, H-4), 2.07 (ddd, $J = 13.8$, 11.1, 5.5 Hz, 1H, H-4′), 1.24-1.16 (m, 2H, H-5), 0.87 (t, $J = 7.3$ Hz, 3H, H-6); **13C NMR:** (100 MHz, CDCl$_3$) $\delta$ (ppm) 165.5 (C-7), 145.2 (C-10), 140.6 (C-2), 133.9 (C-12), 129.1 (C-14), 127.8 (C-11), 127.0 (C-15), 125.8 (C-13), 114.9 (C-1), 60.3 (C-3), 41.2 (C-4), 27.5 (C-8), 18.1 (C-5), 14.2 (C-6); **IR:** $\nu_{\text{max}}$(film)/cm$^{-1}$ 3309 (NH), 1655 (C=O), 1499 (C=C$_{Ar}$), 1410, 1213, 914, 754, 695 (C-Cl); **MS:** $m/z$ (ES$^+$) 284 [M+H]$^+$ (20%), 306 [M+Na]$^+$ (80%); **HRMS:** found 306.0682, [M+Na]$^+$ requires 306.0690.

The equivalent enantioenriched thiocarbamate $(R)$-S-2-(3-chlorophenyl)hex-1-en-3-yl methylcarbamothioate $(R)$-**318be** (94:6 e.r., 24 mg, 48%) was prepared from $(R)$-S-hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate $(R)$-**316be** (95:5 e.r., 50 mg, 0.18 mmol) following general procedure N (-50 °C, 2 h).

$[\alpha]_D^{23}$: +15.1 (c 0.65, CHCl$_3$); **HPLC:** $(R,R)$-Whelk-01, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, major 19.4 min, minor 27.7 min (214.4 nm, 254.4 nm).
318bf: S-3-(2-Methoxyphenyl)hex-1-en-3-yl methylcarbamothioate.

General procedure N (−45 °C, 2 h) was followed using S-hex-1-en-3-yl 2-methoxyphenyl(methyl)carbamothioate 316bf (50 mg, 0.18 mmol). Purification by column chromatography (Pet/EtOAc 95:5, 9:1) afforded the title compound as a pale orange oil (10 mg, 20%).

Rf: 0.24 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.51 (dd, J = 7.8, 1.6 Hz, 1H, H-15), 7.27 (ddd, J = 9.1, 7.6, 1.6 Hz, 1H, H-13), 6.97-6.90 (m, 2H, H-12, H-14), 6.44 (dd, J = 17.3, 10.7 Hz, 1H, H-2), 5.29 (bs, 1H, H-9), 5.20 (dd, J = 10.7, 0.8 Hz, 1H, H-1), 5.18 (dd, J = 17.3, 0.8 Hz, 1H, H-1'), 3.81 (s, 3H, H-16), 2.72 (d, J = 4.8 Hz, 3H, H-8), 2.41 (ddd, J = 13.5, 11.6, 5.2 Hz, 1H, H-4'), 1.23-1.04 (m, 2H, H-5), 0.84 (t, J = 7.3 Hz, 3H, H-6); 13C NMR: (100 MHz, CDCl3) δ (ppm) 166.8 (C-7), 157.6 (C-11), 141.7 (C-2), 130.2 (C-15), 128.8 (C-13), 125.5 (C-10), 120.2 (C-12), 112.9 (C-1), 112.4 (C-14), 61.0 (C-3), 55.4 (C-16), 39.5 (C-4), 27.4 (C-8), 18.5 (C-5), 14.3 (C-6); IR: v_max(film)/cm⁻¹ 3319 (NH), 1652 (C=O), 1487, 1462, 1241 (C=O), 1209, 1025, 750; MS: m/z (ES⁺) 302 [M+Na]⁺ (100%); HRMS: found 280.1365, [M+H]⁺ requires 280.1366.

318db: S-3-(4-Chlorophenyl)-4-methylpent-1-en-3-yl methylcarbamothioate.

General procedure N (−78 °C, 3 h) was followed using S-4-methylpent-1-en-3-yl 4-chlorophenyl(methyl)carbamothioate 316db (50 mg). Purification by column chromatography (Pet/EtOAc 98:2, 95:5) afforded the title compound as a yellow oil (13 mg, 27%).

Rf: 0.63 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.48 (d, J = 8.8 Hz, 2H, H-12, H-14), 7.28 (d, J = 8.8 Hz, 2H, H-11, H-15), 6.31 (dd, J = 17.2, 10.8 Hz, 1H, H-2), 5.50 (dd,
$J = 17.2, 0.7 \text{ Hz, } 1H, H-1')$, 5.48 (dd, $J = 10.8, 0.7 \text{ Hz, } 1H, H-1$), 5.13 (bs, $1H, H-9$), 2.66 (d, $J = 4.6 \text{ Hz, } 3H, H-8$), 2.56 (sept, $J = 6.7 \text{ Hz, } 1H, H-4$), 0.89 (d, $J = 6.7 \text{ Hz, } 1H, H-5 \text{ or } H-6$), 0.80 (d, $J = 6.7 \text{ Hz, } 1H, H-6 \text{ or } H-5$); $^{13}C$ NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 164.2 (C-7), 136.9 (C-2), 135.7 (C-10), 132.6 (C-13), 129.8 (C-12, C-14), 127.8 (C-11, C-15), 117.9 (C-1), 65.2 (C-3), 36.6 (C-4), 27.5 (C-8), 18.4/18.1 (C-5, C-6); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3318 (NH), 1660 (C=O), 1489 (C=C$_{\text{Ar}}$), 1211, 1093, 1012, 800 (C-Cl); MS: $m/z$ (ES$^+$) 306 [M+Na]$^+$ (100%); HRMS: found 306.0677, [M+Na]$^+$ requires 306.0690.

318ea: (E)-S-2-(p-Tolyl)pent-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 2 h) was followed using (E)-S-2-(p-tolyl)pent-3-en-2-yl carbamothioate 316ea (50 mg, 0.20 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 85:15) afforded the title compound as a white solid (39 mg, 78%).

R$_f$: 0.42 (Pet/EtOAc 8:2); mp: 61-63 °C; $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.43 (d, $J = 8.2 \text{ Hz, } 2H, H-11, H-13$), 7.13 (d, $J = 8.2 \text{ Hz, } 2H, H-10, H-14$), 6.07 (dq, $J = 15.5, 1.4 \text{ Hz, } 1H, H-3$), 5.60 (dq, $J = 15.5, 6.5 \text{ Hz, } 1H, H-4$), 5.18 (bs, $1H, H-8$), 2.74 (d, $J = 4.8 \text{ Hz, } 3H, H-7$), 2.32 (s, $3H, H-15$), 1.93 (s, $3H, H-1$), 1.77 (dd, $J = 6.5, 1.4 \text{ Hz, } 3H, H-5$); $^{13}C$ NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 166.6 (C-6), 141.7 (C-12), 136.6 (C-9), 135.6 (C-3), 128.9 (C-10, C-14), 126.8 (C-11, C-13), 125.1 (C-4), 56.4 (C-2), 27.4 (C-1, C-7), 21.0 (C-15), 17.9 (C-5); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3287 (NH), 1644 (C=O), 1531 (C=C$_{\text{Ar}}$), 1232, 814; MS: $m/z$ (ES$^+$) 250 [M+H]$^+$ (20%), 272 [M+Na]$^+$ (40%); HRMS: found 272.1082, [M+Na]$^+$ requires 272.1080.
318eb: (E)-S-2-(4-Chlorophenyl)pent-3-en-2-yl methylcarbamothioate.

![Chemical structure of 318eb]

General procedure N (-60 °C, 2 h) was followed using (E)-S-pent-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate 316eb (30 mg, 0.11 mmol). Purification by column chromatography (Pet/EtOAc 95:5 to 9:1) afforded the title compound as a pale yellow oil (24 mg, 80%).

Rf: 0.43 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.46 (d, J = 8.6 Hz, 2H, H-11, H-13), 7.25 (d, J = 8.6 Hz, 2H, H-10, H-14), 6.03 (dd, J = 15.6, 1.4 Hz, 1H, H-3), 5.56 (dq, J = 15.6, 6.4 Hz, 1H, H-4), 5.19 (bs, 1H, H-8), 2.72 (d, J = 4.8 Hz, 3H, H-7), 1.88 (s, 3H, H-1), 1.74 (dd, J = 6.4, 1.4 Hz, 3H, H-5); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 166.1 (C-6), 143.7 (C-9), 135.1 (C-3), 132.5 (C-12), 128.4 (C-11, C-13), 128.1 (C-10, C-14), 125.5 (C-4), 55.9 (C-2), 27.4 (C-1, C-7), 17.9 (C-5); IR: ν_max (film)/cm⁻¹ 3312 (NH), 1651 (C=O), 1489 (C=C Ar), 1210, 1011, 812; MS: m/z (ES⁺) 270 [M+H]⁺ (50%), 292 [M+Na]⁺ (100%); HRMS: found 292.0532, [M+Na]⁺ requires 292.0534.

318ec: (E)-S-2-(4-Fluorophenyl)pent-3-en-2-yl methylcarbamothioate.

![Chemical structure of 318ec]

General procedure N (-70 °C, 2 h) was followed using (E)-S-2-(4-fluorophenyl)pent-3-en-2-yl carbamothioate 316ec (50 mg, 0.20 mmol). Purification by column chromatography (Pet/EtOAc 95:5 to 9:1) afforded the title compound as a colourless oil (39 mg, 78%).

Rf: 0.36 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.51 (dd, J = 8.8, 5.3 Hz, 2H, H-10, H-14), 6.99 (t, J = 8.8 Hz, 2H, H-11, H-13), 6.06 (dq, J = 15.5, 1.5 Hz, 1H, H-3), 5.59 (dq, J = 15.5, 6.5 Hz, 1H, H-4), 5.17 (bs, 1H, H-8), 2.75 (d, J = 4.8 Hz, 3H, H-7), 1.92 (s, 3H, H-1), 1.77 (dd, J = 6.5, 1.5 Hz, 3H, H-5); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 166.2 (C-6), 161.5 (d, J_C,F = 244.2 Hz, C-12), 140.7 (d, J_C,F = 2.8 Hz, C-9), 135.4 (C-3), 128.7/128.6 (d,
$^3J_{CF} = 7.7$ Hz, C-10, C-14), 125.4 (C-4), 114.9/114.7 (d, $^2J_{CF} = 21.3$ Hz, C-11, C-13), 56.0 (C-2), 27.6 (C-1), 27.4 (C-7), 17.9 (C-5); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 3310 (NH), 1650 (C=O), 1503 (C=C$_{Ar}$), 1218 (C-F), 812; MS: $m/z$ (ES$^+$) 254 [M+H]$^+$ (20%), 276 [M+Na]$^+$ (100%); HRMS: found 276.0822, [M+Na]$^+$ requires 276.0829.

318ed: (E)-S-2-(2-Methoxyphenyl)pent-3-en-2-yl methylcarbamothioate.

General procedure N (-70 °C, 2 h) was followed using (E)-S-2-(2-methoxyphenyl)pent-3-en-2-yl carbamothioate 316ed (50 mg, 0.19). Purification by column chromatography (Pet/EtOA 9:1 to 8:2) afforded the title compound as a colourless oil (37 mg, 74%).

R$_f$: 0.24 (Pet/EtOA 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.51 (dd, $J = 7.8,$ 1.6 Hz, 1H, H-14), 7.26 (td, $J = 7.3,$ 1.6 Hz, 1H, H-12), 6.95-6.90 (m, 2H, H-11, H-13), 6.15 (dq, $J = 15.5,$ 1.6 Hz, 1H, H-3), 5.55 (dq, $J = 15.5,$ 6.5 Hz, 1H, H-4), 5.27 (bs, 1H, H-8), 3.83 (s, 3H, H-15), 2.73 (d, $J = 4.8$ Hz, 3H, H-7), 2.03 (s, 3H, H-1), 1.75 (dd, $J = 6.5,$ 1.6 Hz, 3H, H-5); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 167.6 (C-6), 157.6 (C-10), 135.3 (C-3), 131.7 (C-9), 128.8/128.7 (C-12, C-14), 124.2 (C-4), 120.2 (C-13), 112.6 (C-11), 55.6/55.4 (C-2, C-15), 27.3 (C-7), 26.0 (C-1), 17.9 (C-5); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 3313 (NH), 1649 (C=O), 1487 (C=C$_{Ar}$), 1461 (C=C$_{Ar}$), 1210 (C$_{Ar}$-O), 751; MS: $m/z$ (ES$^+$) 288 [M+Na]$^+$ (100%); HRMS: found 266.1211, [M+H]$^+$ requires 266.1209.

318fa: (E)-S-4-Cyclohexyl-2-(p-tolyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C for 3 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate 316fa (666 mg, 2.10 mmol). The title compound was obtained as a pale yellow oil without purification (717 mg, 99%).

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Rf: 0.45 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.42 (d, $J = 8.2$ Hz, 2H, H-15, H-19), 7.13 (d, $J = 8.2$ Hz, 2H, H-16, H-18), 6.02 (d, $J = 15.7$ Hz, 1H, H-3), 5.55 (dd, $J = 15.7$, 7.0 Hz, 1H, H-4), 5.30 (bs, 1H, H-13), 2.74 (d, $J = 4.8$ Hz, 3H, H-12), 2.32 (s, 3H, H-20), 2.09-2.01 (m, 1H, H-5), 1.92 (s, 3H, H-1), 1.75-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.05 (m, 6H, H-6′, H-7′, H-8′, H-9′, H-10′); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 166.7 (C-11), 141.6 (C-17), 136.6 (C-14), 136.3 (C-4), 132.3 (C-3), 128.9 (C-16, C-18), 126.8 (C-15, C-19), 56.3 (C-2), 40.7 (C-5), 33.0/32.9 (C-6, C-10), 27.6 (C-1), 27.3 (C-12), 26.0/25.9 (C-7, C-8, C-9), 21.0 (C-20); IR: $\nu_{\text{max}}$ (film)/cm$^{-1}$ 3316 (NH), 1652 (C=O), 1510 (C=C Ar), 1448, 1210, 814; MS: m/z (ES$^+$) 340 [M+Na]$^+$ (100%); HRMS: found 318.1888, [M+H]$^+$ requires 318.1887.

The equivalent enantioenriched thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl methylcarbamothioate (S)-318fa (91:9 e.r., 38 mg, 76%) was prepared from (S)-(E)-S-4-cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate (S)-316fa (94:6 e.r., 50 mg, 0.16 mmol) following general procedure N (-60 °C, 1 h).

[$\alpha$]$_D^{22}$: -16.9 (c 2.83, CHCl$_3$); HPLC: Chiralpak AD-H, Hexane/i-PrOH 96:4, 1.0 mL/min, major 12.0 min, minor 17.5 min (214.4 nm, 254.4 nm).

The other enantiomer (R)-(E)-S-4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl methylcarbamothioate (R)-318fa (12:88 e.r., 210 mg, 100%) was prepared from (R)-(E)-S-4-cyclohexylbut-3-en-2-yl methyl(p-tolyl)carbamothioate (R)-316fa (13:87 e.r., 50 mg, 0.16 mmol) following general procedure N (-60 °C, 3 h).

HPLC: Chiralpak AD-H, Hexane/i-PrOH 96:4, 1 mL/min, 28 °C, minor 13.1 min, major 16.4 min (214.4 nm).

318fb: (E)-S-4-Cyclohexyl-2-(4-methoxyphenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-40 °C, 1 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 4-methoxyphenyl(methyl)carbamothioate 316fb (50 mg, 0.15 mmol). Purification by column chromatography (Pet+1%Et$_3$N, Pet+1%Et$_3$N/EtOAc 98:2 to 85:15) afforded the title compound as a pale yellow oil (12 mg, 24%).
$R_f$: 0.41 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.45 (d, $J = 8.8$ Hz, 2H, H-15, H-19), 6.85 (d, $J = 8.8$ Hz, 2H, H-16, H-18), 6.00 (d, $J = 15.8$ Hz, 1H, H-3), 5.53 (dd, $J = 15.8$, 7.2 Hz, 1H, H-4), 5.29 (bs, 1H, H-13), 3.80 (s, 3H, H-20), 2.74 (d, $J = 4.8$ Hz, 3H, H-12), 2.10-1.98 (m, 1H, H-5), 1.92 (s, 3H, H-1), 1.74-1.63 (m, 4H H-6, H-7, H-9, H-10), 1.33-1.05 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); $^{13}$C NMR: (100 MHz, CDCl$_3$) compound too unstable, degraded on the NMR timescale.

$^{318}$fc: (E)-S-4-Cyclohexyl-2-(4-chlorophenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-50 °C, 1.5 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate $^{316}$fc (45 mg, 0.13 mmol). Purification by column chromatography (Pet/EtOAc 95:5) afforded the title compound as a pale yellow oil (35 mg, 77%).

$R_f$: 0.45 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.47 (d, $J = 8.7$ Hz, 2H, H-16, H-18), 7.26 (d, $J = 8.7$ Hz, 2H, H-15, H-19), 5.99 (d, $J = 15.7$ Hz, 1H, H-3), 5.51 (dd, $J = 15.7$, 7.0 Hz, 1H, H-4), 5.26 (bs, 1H, H-13), 2.74 (d, $J = 4.8$ Hz, 3H, H-12), 2.09-2.00 (m, 1H, H-5), 1.89 (s, 3H, H-1), 1.74-1.63 (m, 4H H-6, H-7, H-9, H-10), 1.32-1.05 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 166.1 (C-11), 143.7 (C-14), 136.6 (C-4), 132.5 (C-17), 131.8 (C-3), 128.5 (C-16, C-18), 128.1 (C-15, C-19), 55.9 (C-2), 40.6 (C-5), 32.9/32.8 (C-6, C-10), 29.7 (C-8), 27.5 (C-1), 27.4 (C-12), 26.0/25.9 (C-7, C-9); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3313 (NH), 1651 (C=O), 1489 (C=C$_{\text{ar}}$), 1209, 1011, 821 (C-Cl); MS: $m/z$ (ES$^+$) 360 [M+Na]$^+$ (100%); HRMS: found 360.1159, [M+Na]$^+$ requires 360.1160.

The equivalent enantiomerich thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(4-chlorophenyl)but-3-en-2-yl methylcarbamothioate (S)-$^{318}$fc (94:6 e.r., 29 mg, 63%) was prepared from (S)-(E)-S-4-cyclohexylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate (S)-$^{316}$fc (95:5 e.r., 46 mg, 0.14 mmol) following general procedure N (-50 °C, 2 h).

$[\alpha]_D^{22}$: -18.3 (c 2.74, CHCl$_3$); HPLC: Chiralpak AD-H, Hexane/i-PrOH 96:4, 1.0 mL/min, major 22.7 min, minor 28.2 min (214.4 nm, 254.4 nm).
General procedure N (-60 °C, 2.5 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate 316fd (45 mg, 0.14 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a colourless oil (32 mg, 71%).

Rf: 0.48 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.50 (dd, $J = 8.9$, 5.3 Hz, 2H, H-15, H-19), 6.99 (t, $J = 8.9$ Hz, 2H, H-16, H-18), 6.00 (d, $J = 15.8$ Hz, 1H, H-3), 5.52 (dd, $J = 15.8$, 7.0 Hz, 1H, H-4), 5.27 (bs, 1H, H-13), 2.74 (d, $J = 4.9$ Hz, 3H, H-12), 2.09-2.00 (m, 1H, H-5), 1.90 (s, 3H, H-1), 1.74 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.05 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 166.3 (C-11), 161.5 (d, $J_{C,F}$ = 244.2 Hz, C-17), 140.7 (d, $J_{C,F}$ = 2.8 Hz, C-14), 136.5 (C-4), 132.1 (C-3), 128.8 (d, $J_{C,F}$ = 7.7 Hz, C-15, C-19), 114.8 (d, $J_{C,F}$ = 21.3 Hz, C-16, C-18), 55.9 (C-2), 40.6 (C-5), 33.0/32.9 (C-6, C-10), 27.7 (C-1), 26.0/25.9 (C-7, C-8, C-9); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 3310 (NH), 1650 (C=O), 1504 (C=C$\equiv$), 1220 (C-F), 831; MS: $m/z$ (ES$^+$) 322 [M+H]$^+$ (50%); HRMS: found 344.1458, [M+Na]$^+$ requires 344.1455.

The equivalent enantioenriched thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(4-fluorophenyl)but-3-en-2-yl methylcarbamothioate 318fd (94:6 e.r., 41 mg, 82%) was prepared from (S)-(E)-S-4-cyclohexylbut-3-en-2-yl 4-fluorophenyl(methyl)carbamothioate (S)-316fd (94:6 e.r., 50 mg, 0.16 mmol) following general procedure N (-60 °C, 3 h).

[a]$_D^{26}$: -16.0 ($c$ 1.00, CHCl$_3$); HPLC: Chiralpak AD-H, Hexane/i-PrOH 96:4, 1.0 mL/min, 28 °C, major 11.4 min, minor 13.3 min (214.4 nm, 254.4 nm).
**318fe:** (E)-S-4-Cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 3 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate **316fe** (130 mg, 0.39 mmol). The title compound was obtained as a beige solid without purification (128 mg, 98%).

**Rf:** 0.39 (Pet/EtOAc 8:2); **mp:** 73-75 °C; **1H NMR:** (400 MHz; CDCl₃) δ (ppm) 7.24 (t, J = 8.0 Hz, 1H, H-18), 7.13 (ddd, J = 8.0, 0.7 Hz, 1H, H-17), 7.10 (t, J = 2.4 Hz, 1H, H-15), 6.78 (ddd, J = 8.0, 2.4, 0.7 Hz, 1H, H-19), 6.01 (d, J = 15.7 Hz, 1H, H-3), 5.56 (dd, J = 15.7, 7.1 Hz, 1H, H-4), 5.27 (bs, 1H, H-13), 3.80 (s, 3H, H-20), 2.74 (d, J = 4.8 Hz, 3H, H-12), 2.10-2.02 (m, 1H, H-5), 1.91 (s, 3H, H-1), 1.74-1.64 (m, 4H, H-6, H-7, H-8, H-9, H-10), 1.34-1.06 (m, 6H, H-6', H-7', H-8', H-9', H-10'); **13C NMR:** (100 MHz, CDCl₃) δ (ppm) 166.5 (C-11), 159.3 (C-16), 146.5 (C-14), 136.4 (C-4), 132.1 (C-3), 129.1 (C-18), 119.3 (C-17), 113.3 (C-15), 112.0 (C-19), 56.4 (C-2), 55.2 (C-20), 40.7 (C-5), 33.0/32.9 (C-6, C-10), 27.6 (C-1, C-12), 26.1/25.9 (C-7, C-8, C-9); **IR:** ν max (film)/cm⁻¹ 3262 (NH), 1648 (C=O), 1530 (C=C Ar), 1227 (C₆H₄-O), 1043, 975, 704, 627; **MS:** m/z (ES⁺) 334 [M+H⁺]⁺ (50%), 356 [M+Na⁺]⁺ (100%); **HRMS:** found 334.1837, [M+H⁺]⁺ requires 334.1836.

The equivalent enantioenriched thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl methylcarbamothioate (S)-**318fe** (95:5 e.r., 120 mg, 100%) was prepared from (S)-(E)-S-4-cyclohexylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate (S)-**316fe** (95:5 e.r., 120 mg, 0.36 mmol) following the same procedure.  

[α]D²²: -9.8 (c 0.82, CHCl₃); **HPLC:** Chiralpak AD-H, Hexane/i-PrOH 96:4, 1.0 mL/min, major 27.3 min, minor 29.2 min (254.4 nm).
318ff: (E)-S-4-Cyclohexyl-2-(3-chlorophenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 4 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 3-chlorophenyl(methyl)carbamothioate 316ff (50 mg, 0.15 mmol). Purification by column chromatography (Pet 100% Pet/EtOAc 98:2 to 9:1) afforded the title compound as a pale yellow oil (28 mg, 56%).

Rf: 0.44 (Pet/EtOAc 8:2); ^1H NMR: (400 MHz; CDCl₃) δ (ppm) 7.52 (t, J = 1.8 Hz, 1H, H-15), 7.43 (dt, J = 7.8, 1.4 Hz, 1H, H-17), 7.24 (dd, J = 7.8 Hz, 1H, H-18), 7.19 (ddd, J = 7.8, 1.8, 1.4 Hz, 1H, H-19), 5.99 (d, J = 15.7 Hz, 1H, H-3), 5.53 (dd, J = 15.7, 7.0 Hz, 1H, H-4), 5.26 (bs, 1H, H-13), 2.74 (d, J = 4.8 Hz, 3H, H-12), 2.09-2.01 (m, 1H, H-5), 1.89 (s, 3H, H-1), 1.74-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.06 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10');

^13C NMR: (100 MHz, CDCl₃) δ (ppm) 165.9 (C-11), 147.3 (C-14), 136.7 (C-4), 133.9 (C-16), 131.6 (C-3), 129.2 (C-18), 127.3 (C-15), 126.9 (C-19), 125.2 (C-17), 55.8 (C-2), 40.7 (C-5), 32.9/32.8 (C-6, C-10), 27.4 (C-12), 26.0 (C-1), 25.9 (C-7, C-8, C-9); IR: v$_{max}$(film)/cm⁻¹ 3288 (NH), 1615 (C=O), 1518 (C=C$_{Ar}$), 1447, 1204, 967, 783 (C-Cl), 694; MS: m/z (ES⁺) 360 [M+Na]⁺ (100%); HRMS: found 360.1175, [M+Na]⁺ requires 360.1160.

318fg: (E)-S-4-Cyclohexyl-2-(3-fluorophenyl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-40 °C, 1.5 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 3-fluorophenyl(methyl)carbamothioate 316fg (49 mg, 0.15 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a dark yellow oil (34 mg, 69%).
Rf: 0.39 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.33-7.24 (m, 3H, H-15, H-17, H-19), 6.94-6.89 (m, 1H, H-18), 5.99 (d, \(J = 15.7\) Hz, 1H, H-3), 5.53 (dd, \(J = 15.7, 7.0\) Hz, 1H, H-4), 5.24 (bs, 1H, H-13), 2.74 (d, \(J = 4.8\) Hz, 3H, H-12), 2.09-2.00 (m, 1H, H-5), 1.89 (s, 3H, H-1), 1.74-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.02 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 163.8 (C-11), 162.6 (d, \(^1\)J\(\text{C,F}\) = 243.4 Hz, C-16), 136.7 (C-4), 131.7 (C-3), 129.4 (d, \(^3\)J\(\text{C,F}\) = 8.3 Hz, C-14, C-18), 122.6 (d, \(^4\)J\(\text{C,F}\) = 2.8 Hz, C-19), 114.2 (d, \(^2\)J\(\text{C,F}\) = 22.9 Hz, C-15), 113.7 (d, \(^2\)J\(\text{C,F}\) = 20.5 Hz, C-17), 55.9 (C-2), 40.7 (C-5), 32.9 (C-6, C-10), 27.5 (C-1, C-12), 26.1/25.9 (C-7, C-8, C-9); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3313 (NH), 1660 (C=O), 1447, 1212 (C-F), 967, 782, 697; MS: \(m/z\) (ES\(^+\)) 344 [M+Na\(^+\)] (100%); HRMS: found 344.1445, [M+Na\(^+\)] requires 344.1455.

318fh: (E)-S-4-Cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl methylcarbamothioate.

![structure](image)

General procedure N (-60 °C, 3.5 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate 316fh (50 mg, 0.15 mmol). The title compound was obtained as a dark yellow/orange oil without purification (50 mg, 99%).

Rf: 0.38 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.52 (dd, \(J = 8.0, 1.6\) Hz, 1H, H-19), 7.26 (dd, \(J = 8.0, 1.6\) Hz, 1H, H-17), 6.95-6.89 (m, 2H, H-16, H-18), 6.03 (dd, \(J = 15.8, 0.8\) Hz, 1H, H-3), 5.42 (dd, \(J = 15.8, 7.2\) Hz, 1H, H-4), 5.36 (bs, 1H, H-13), 3.81 (s, 3H, H-20), 2.73 (d, \(J = 4.8\) Hz, 3H, H-12), 2.06-2.00 (m, 1H, H-5), 2.00 (s, 3H, H-1), 1.72-1.62 (m, 4H, H-6, H-7, H-9, H-10); 1.31-1.02 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 167.6 (C-11), 157.6 (C-15), 135.4 (C-4), 132.1 (C-3), 131.4 (C-14), 129.0 (C-19), 128.8 (C-17), 120.2 (C-18), 112.3 (C-16), 56.0 (C-2), 55.3 (C-20), 40.7 (C-5), 33.0 (C-6, C-10), 27.2 (C-12), 26.3 (C-1), 26.1/25.9 (C-7, C-8, C-9); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3305 (NH), 1641 (C=O), 1219 (C\(_{\text{Ar}}\)-O), 749; MS: \(m/z\) (ES\(^+\)) 334 [M+H\(^+\)] (50%), 356 [M+Na\(^+\)] (50%); HRMS: found 334.1838, [M+H\(^+\)] requires 334.1835.

The equivalent enantioenriched thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl methylcarbamothioate (S)-318fh (94:6 e.r., 142 mg, 100%)
was prepared from (5)-(E)-S-4-cyclohexylbut-3-en-2-yl 2-methoxyphenyl(methyl)carbamothioate (5)-316fh (94:6 e.r., 142 mg, 0.43 mmol) following general procedure N (-60 °C, 3 h).

\[\alpha\]D: -16.4 (c 1.00, CHCl3); HPLC: Chiralpak AD-H, Hexane/i-PrOH 90:10, 1.0 mL/min, major 7.6 min, minor 10.4 min (214.4 nm, 254.4 nm).

318fi: (E)-S-4-Cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-60 °C, 2.5 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl methyl(naphthalen-1-yl)carbamothioate 316fi (50 mg, 0.14 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5, 9:1) afforded the title compound as a pale yellow oil (45 mg, 90%).

Rf: 0.38 (Pet/EtOAc 8:2); H NMR: (400 MHz; CDCl3) δ (ppm) 8.55 (m, 1H, H-16), 7.84 (m, 1H, H-19), 7.80 (d, J = 8.2 Hz, 1H, H-21), 7.76 (dd, J = 7.4, 0.9 Hz, 1H, HAr), 7.47-7.41 (m, 3H, HAr), 6.17 (d, J = 15.8 Hz, 1H, H-3), 5.32 (dd, J = 15.8, 7.1 Hz, 1H, H-4), 5.15 (bs, 1H, H-13), 2.66 (d, J = 4.8 Hz, 3H, H-12), 2.25 (s, 3H, H-1), 2.02-1.94 (m, 1H, H-5), 1.67-1.59 (m, 4H, H-6, H-7, H-9, H-10), 1.26-0.94 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); C NMR: (100 MHz, CDCl3) δ (ppm) 166.7 (C-11), 138.5 (CqAr), 137.0 (C-4), 134.9 (CqAr), 133.1 (C-3), 130.6 (CqAr), 129.1/129.0 (C19, C-21), 128.6 (C-16), 126.2 (CHAr), 125.0 (CHAr), 124.7 (CHAr), 124.1 (CHAr), 57.2 (C-2), 40.7 (C-5), 32.6 (C-6, C-10), 30.1 (C-1), 27.3 (C-12), 26.0/25.9 (C-7, C-8, C-9); IR: \( \nu_{\text{max}} \) (film)/cm\(^{-1}\) 3268 (NH), 1650 (C=O), 1507 (C=CAr), 1211, 802, 775; MS: m/z (ES\(^{+}\)) 376 [M+Na]\(^{+}\) (95%); HRMS: found 354.1888, [M+Na]\(^{+}\) requires 354.1887.

The equivalent enantioenriched thiocarbamate (R)-(E)-S-4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate (R)-318fi (15:85 e.r., 438 mg, 71%) was prepared from (R)-(E)-S-4-cyclohexylbut-3-en-2-yl 2-(naphthalen-1-yl)(methyl)carbamothioate (R)-316fi (14:86 e.r., 618 mg, 1.75 mmol) following general procedure N (-60 °C, 3 h).
[α]₀^{25}: +72.6 (c 1.00, CHCl₃); HPLC: Chiralcel OD-H, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, minor 64.7 min, major 68.2 min (214.4 nm, 254.4 nm).

318fj: (E)-S-4-Cyclohexyl-2-(pyridin-2-yl)but-3-en-2-yl methylcarbamothioate.

General procedure N (-78 °C, 2 h) was followed using (E)-S-4-cyclohexylbut-3-en-2-yl methyl(pyridin-2-yl)carbamothioate 316fj (50 mg, 0.16 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 9:1 to 6:4) afforded the title compound as a colourless oil (21 mg, 42%).

Rₓ: 0.29 (Pet/EtOAc 1:1); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 8.56 (ddd, J = 4.8, 1.6, 0.8 Hz, 1H, H-15), 7.66 (td, J = 7.7, 1.6 Hz, 1H, H-17), 7.47 (d, J = 7.7 Hz, 1H, H-18), 7.16 (ddd, J = 7.7, 4.8, 0.6 Hz, 1H, H-16), 6.76 (bs, 1H, H-13), 6.04 (d, J = 15.7 Hz, 1H, H-3), 5.57 (dd, J = 15.7, 7.0 Hz, 1H, H-4), 2.76 (d, J = 4.7 Hz, 3H, H-12), 2.08-2.00 (m, 1H, H-5), 1.93 (s, 3H, H-1), 1.73-1.62 (m, 4H, H-6, H-7, H-9, H-10), 1.31-1.04 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 168.7 (C-11), 163.7 (C-14), 148.3 (C-15), 137.2 (C-4), 136.7 (C-17), 131.3 (C-3), 121.9 (C-16), 121.2 (C-18), 57.3 (C-2), 40.7 (C-5), 32.9 (C-6, C-10), 27.3 (C-12), 26.1 (C-1), 25.9 (C-7, C-8, C-9); IR: ν_{max}(film)/cm⁻¹ 3305 (NH), 1655 (C=O), 1466 (C=C_{Ar}), 1429 (C=C_{Ar}), 967, 782, 745; MS: m/z (ES⁺) 305 [M+H]^+ (100%), 327 [M+Na]^+ (20%); HRMS: found 327.1503, [M+Na]^+ requires 327.1502.

The equivalent enantiopure thiocarbamate (S)-(E)-S-4-cyclohexyl-2-(pyridin-2-yl)but-3-en-2-yl methylcarbamothioate (S)-318fj (93:7 e.r., 15 mg, 30%) was prepared from (S)-(E)-S-4-cyclohexylbut-3-en-2-yl methyl(pyridin-2-yl)carbamothioate (S)-316fj (94:6 e.r., 50 mg, 0.16 mmol) following the same procedure.

[α]₀^{22}: -68.0 (c 1.00, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 90:10, 1.0 mL/min, 28 °C, major 15.4 min, minor 19.3 min (214.4 nm).
318fk: \((E)-\text{tert}-\text{Butyl 6-(4-cyclohexyl-2-((methylcarbamoyl)thio)but-3-en-2-yl)-1H-indole-1-carboxylate.}\)

General procedure N: (-60 °C, 2.5 h) was followed using \((E)-\text{tert}-\text{butyl 6-(((4-cyclohexylbut-3-en-2-yl)thio)carbonyl}(\text{methyl})\text{amino})-1H\text{-indole-1-carboxylate 316fk (60 mg, 0.14 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 9:1) afforded the title compound as a pale yellow oil (26 mg, 43%).}

\[ R_f: 0.40 \text{ (Pet/EtOAc 8:2); } ^1H \text{ NMR: (400 MHz; CDCl}_3 \text{) } \delta \text{ (ppm) 8.36 (bs, 1H, H-15), 7.60 (bd, J = 3.6 Hz, 1H, H-17), 7.48 (t, J = 8.2 Hz, 1H, H-20), 7.44 (dd, J = 8.2, 1.7 Hz, 1H, H-21), 6.52 (d, J = 3.6 Hz, 1H, H-18), 6.08 (d, J = 15.8 Hz, 1H, H-3), 5.56 (dd, J = 15.8, 7.1 Hz, 1H, H-4), 5.32 (bs, 1H, H-13), 2.73 (bd, J = 4.8 Hz, 3H, H-12), 2.11-2.01 (m, 1H, H-5), 2.11 (s, 3H, H-1), 1.74-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.68 (s, 6H, H-24, H-25, H-26), 1.32-1.06 (m, 6H, H-6', H-7', H-8', H-9', H-10'); } ^{13}C \text{ NMR: (100 MHz, CDCl}_3 \text{) } \delta \text{ (ppm) 167.8 (C-11), 151.5 (C-22), 136.3 (C-4), 132.6 (C-3), 126.2 (C-17), 122.2 (C-21), 120.4/120.3 (C-20) \text{-rotamers}, 113.8 (C-15), 107.1/106.9 (C-18) \text{-rotamers}, 83.6 (C-23), 57.2 (C-2), 40.8/40.7 (C-5) \text{-rotamers}, 32.9 (C-6, C-10), 28.2 (C-24, C-25, C-26), 27.9 (C-1), 27.3 (C-12), 26.3/25.9 (C-7, C-8, C-9), C-14/C-16/C-19 not visible; } \text{IR: } v_{\text{max}}(\text{film})/\text{cm}^{-1} 3338 (\text{NH}), 1732 (\text{C=O}), 1153 (\text{C-O ester}), 766; \text{ MS: } m/z (E^+) 465 [\text{M+Na}]^+(30\%); } \text{HRMS: found 465.2176, [M+Na]}^+ \text{ requires 465.2182.}

The equivalent enantioenriched thiocarbamate \((S)-(E)-\text{tert}-\text{butyl 6-(4-cyclohexyl-2-((methylcarbamoyl)thio)but-3-en-2-yl)-1H-indole-1-carboxylate (S)-318fk (90:10 e.r., 24 mg, 41%) was prepared from (S)-(E)-\text{tert}-\text{butyl 6-(((4-cyclohexylbut-3-en-2-yl)thio)carbonyl}(\text{methyl})\text{amino})-1H\text{-indole-1-carboxylate (S)-316fk (95:5 e.r., 58 mg, 0.13 mmol) following the same procedure.}

\[[\alpha]_D^{23} : -1.2 \text{ (c 1.00, CHCl}_3 \text{); HPLC: Chiralcel OD-H, Hexane/i-PrOH 90:10, 1.0 mL/min, 28 °C, major 5.1 min, minor 5.8 min (214.4 nm, 254.4 nm).} \]
The other enantiomer (R)-(E)-tert-butyl 6-(4-cyclohexyl-2-((methylcarbamoyl)thio)but-3-en-2-yl)-1H-indole-1-carboxylate (R)-318fk (23:77 e.r., 21 mg, 42%) was prepared from (R)-(E)-tert-butyl 6-(((4-cyclohexylbut-3-en-2-yl)thio)carbonyl)(methyl)amino)-1H-indole-1-carboxylate (R)-316fk (14:86 e.r., 50 mg, 0.11 mmol) following general procedure N (-50 °C, 3.5 h).

**HPLC:** Chiralcel OD-H, Hexane/i-PrOH 90:10, 1.0 mL/min, 28 °C, minor 5.2 min, major 5.9 min (214.4 nm, 254.4 nm).

318ga: (E)-S-2-(4-Chlorophenyl)-4-phenylbut-3-en-2-yl methylcarbamothioate.

![Chemical structure](image)

General procedure N (-60 °C, 2.5 h) was followed using (E)-S-4-phenylbut-3-en-2-yl 4-chlorophenyl(methyl)carbamothioate 316ga (40 mg, 0.12 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 9:1) afforded the title compound as a pale yellow oil (27 mg, 67%).

**Rf:** 0.34 (Pet/EtOAc 8:2); \(^1^H\) NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.51 (d, \(J = 8.7\) Hz, 2H, H-16, H-18), 7.39 (d, \(J = 7.2\) Hz, 2H, H-7, H-9), 7.27 (d, \(J = 8.7\) Hz, 2H, H-15, H-19), 7.31-7.20 (m, 3H, H-6, H-8, H-10), 6.86 (d, \(J = 16.1\) Hz, 1H, H-3), 6.45 (d, \(J = 16.1\) Hz, 1H, H-4), 5.20 (bs, 1H, H-13), 2.73 (d, \(J = 4.8\) Hz, 3H, H-12), 1.98 (s, 3H, H-1); \(^1^3^C\) NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 165.7 (C-11), 143.4 (C-14), 136.6 (C-5), 133.7 (C-3), 132.8 (C-17), 129.2 (C-4), 128.6 (C-15, C-19), 128.4 (C-16, C-18), 128.3/127.8 (C-7, C-8, C-9), 126.6 (C-6, C-10), 56.2 (C-2), 27.5 (C-1, C-12); \(\text{IR}: \nu_{\text{max}}\) (film)/cm\(^{-1}\) 3306 (NH), 1665 (C=O), 1488 (C=C\(_{Ar}\)), 1203, 826 (C-Cl); \(\text{MS}: m/z\) (ES\(^+\)) 354 [M+Na]\(^+\) (100%), [M+Na]\(^+\) (100%); \(\text{HRMS}: \) found 354.0703, [M+Na]\(^+\) requires 354.0695.
318gc: (E)-S-2-(3-Methoxyphenyl)-4-phenylbut-3-en-2-yl methylcarbamothioate.

General procedure M (-60 °C, 2 h) was followed using (E)-S-4-phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate 316gc (72 mg, 0.22 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 9:1 to 8:2) afforded the title compound as a pale yellow oil (40 mg, 55%).

Rf: 0.31 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.37-7.35 (m, 2H, C-7, C-9), 7.26-7.14 (m, 4H, C-6, C-8, C-10, C-18), 7.11 (ddd, \(J = 8.5, 2.2, 0.9\) Hz, 1H, H-17), 7.09 (t, \(J = 2.2\) Hz, 1H, H-15), 6.81 (d, \(J = 16.2\) Hz, 1H, H-3), 6.73 (ddd, \(J = 8.5, 2.2, 0.9\) Hz, 1H, H-19), 6.44 (d, \(J = 16.2\) Hz, 1H, H-4), 5.17 (bs, 1H, H-13), 3.73 (s, 3H, H-20), 2.68 (d, \(J = 4.8\) Hz, 3H, H-12), 1.97 (s, 3H, H-1); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 168.0 (C-11), 159.4 (C-16), 146.2 (C-14), 136.8 (C-5), 134.0 (C-3), 129.2 (C-8), 129.0 (C-4), 128.5 (C-6, C-10), 127.6 (C-18), 126.6 (C-7, C-9), 119.3 (C-17), 113.4 (C-15), 112.0 (C-19), 55.2 (C-20), 41.0 (C-2), 27.5 (C1, C-12); IR: \(v_{\text{max}}\) (film)/\(\text{cm}^{-1}\) 1662 (C=O), 1598 (C=C), 1484 (C=C\(_{\text{Ar}}\)), 1206 (C\(_{\text{Ar}}\)-O), 1041, 694; MS: \(m/z\) (ES\(^+\)) 350 [M+Na\(^+\)] (60%); HRMS: found 350.1186, [M+Na\(^+\)] requires 350.1186.

The same procedure was used to attempt the preparation of the equivalent enantioenriched thiocarbamate (R)-(E)-S-2-(3-methoxyphenyl)-4-phenylbut-3-en-2-yl methylcarbamothioate (R)-318gc (50:50 e.r., 19 mg, 38%) from (R)-(E)-S-4-phenylbut-3-en-2-yl 3-methoxyphenyl(methyl)carbamothioate (R)-316gc (83:17 e.r., 50 mg, 0.15 mmol).

HPLC: Chiralpak AD-H, Hexane/i-PrOH 95:5, 1.0 mL/min, 28 °C, 30.7/39.4 min (214.4 nm, 254.4 nm).
**318gd**: \((E)-S-2-(3\text{-Chlorophenyl})-4\text{-phenylbut}-3\text{-en}-2\text{-yl} \text{methylcarbamothioate.}\)

![Chemical Structure](image)

General procedure M (-60 °C, 2 h) was followed using \((E)-S-4\text{-phenylbut}-3\text{-en}-2\text{-yl} \text{3-chlorophenyl(methyl)carbamothioate 316gd} \text{ (50 mg, 0.15 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 9:1) afforded the title compound as a pale yellow oil (27 mg, 54%).}

**Rf**: 0.53 (Pet/EtOAc 8:2); **\(^1\)H NMR**: (400 MHz; CDCl₃) \(\delta\) (ppm) 7.58 (t, \(J = 1.8\) Hz, 1H, H-15), 7.49 (dt, \(J = 7.7, 1.7\) Hz, 1H, H-17), 7.44 (d, \(J = 7.4\) Hz, 2H, H-6, H-10), 7.33 (t, \(J = 7.4\) Hz, H-7, H-8, H-9), 7.28 (t, \(J = 7.7\) Hz, 1H, H-18), 7.23 (dt, \(J = 7.7, 1.7\) Hz, 1H, H-19), 6.88 (d, \(J = 16.2\) Hz, 1H, H-3), 6.50 (d, \(J = 16.2\) Hz, 1H, H-4), 5.24 (bs, 1H, H-13), 2.76 (d, \(J = 4.8\) Hz, 3H, H-12), 2.00 (s, 3H, H-11); **\(^{13}\)C NMR**: (100 MHz, CDCl₃) \(\delta\) (ppm) 165.0 (C-11), 147.0 (C-14), 136.6 (C-5), 134.1 (C-16), 133.4 (C-3), 129.4 (C-18), 129.3 (C-4), 128.6 (C-7, C-8, C-9), 127.2 (C-19), 127.1 (C-15), 126.7 (C-6, C-10), 125.2 (C-17), 56.2 (C-2), 27.5 (C-12), 27.4 (C-1); **IR**: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 3312 (NH), 1656 (C=O), 1494 (C=C₉), 1199, 749, 691 (C-Cl); **MS**: \(m/z\) (ES\(^+\)) 354 [M+Na]\(^+\) (100%); **HRMS**: found 354.0694, [M+Na]\(^+\) requires 354.0690.

**Note**: no conditions could be found to separate the enantiomers of thiols 319 and sulfides 320-322. Enantiomeric ratios for the derivatised 2,5-dihydrothiophenes 324 are reported.

**319ad**: \((R)-2-(4\text{-Chlorophenyl})\text{but-3-ene-2-thiol.}\)

![Chemical Structure](image)

General procedure P was followed using \((R)-S-2-(4\text{-chlorophenyl})\text{but-3-en-2-yl} \text{methylcarbamothioate (R)-318ad} \text{ (48 mg, 0.19 mmol) to afford the title compound as a colourless oil (10 mg, 26%).}
[α]D 25: -7.9 (c 1.00, CHCl3); Rf: 0.80 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.46 (d, J = 8.8 Hz, 2H, H-8, H-10), 7.28 (d, J = 8.8 Hz, 2H, H-7, H-11), 6.23 (dd, J = 17.1, 10.4 Hz, 1H, H-3), 5.22 (dd, J = 17.1, 0.4 Hz, 1H, H-4'), 5.14 (dd, J = 10.4, 0.4 Hz, 1H, H-4), 2.210 (s, 1H, H-5), 1.85 (s, 3H, H-1).

319ae: 2-(4-Fluorophenyl)but-3-ene-2-thiol.

General procedure P was followed using S-2-(4-fluorophenyl)but-3-en-2-yl methylcarbamothioate 318ae (275 mg, 1.15 mmol) to afford the title compound as a colourless oil (42 mg, 20%).

Rf: 0.88 (Pent/EtO 98:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.49 (dd, J = 8.9, 5.3 Hz, 2H, H-7, H-11), 7.00 (t, J = 8.9 Hz, 2H, H-8, H-10), 6.25 (dd, J = 17.1, 10.4 Hz, 1H, H-3), 5.22 (dd, J = 17.1, 0.6 Hz, 1H, H-4'), 5.13 (dd, J = 10.4, 0.6 Hz, 1H, H-4), 2.21 (s, 1H, H-5), 1.86 (s, 3H, H-1); 13C NMR: (100 MHz, CDCl3) δ (ppm) 161.7 (d, JCF = 244.5 Hz, C-9), 145.7 (C-3), 141.6 (d, JCF = 3.1 Hz, C-6), 128.2 (d, JCF = 7.9 Hz, C-7, C-11), 115.0 (d, JCF = 21.2 Hz, C-8, C-10), 112.0 (C-4), 50.6 (C-2), 31.5 (C-1); IR: νmax(film)/cm⁻¹ 1506 (C=CAr), 1227 (C-F), 1162, 834; GC-MS: 149.1 (M-SH), 9.65 min; HRMS: found 182.0560, [M]+ requires 182.0560.

319af: 2-(3-Methoxyphenyl)but-3-ene-2-thiol.

General procedure P was followed using S-2-(3-methoxyphenyl)but-3-en-2-yl methylcarbamothioate 318af (260 mg, 1.03 mmol) to afford the title compound as a colourless oil (181 mg, 90%).
Rf: 0.51 (Pent/Et₂O 98:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.25 (t, J = 7.9 Hz, 1H, H-10), 7.10 (ddd, J = 7.9, 2.1, 0.8 Hz, 1H, H-11), 7.08 (t, J = 2.1 Hz, 1H, H-7), 6.78 (ddd, J = 7.9, 2.1, 0.8 Hz, 1H, H-9), 6.27 (dd, J = 17.1, 10.4 Hz, 1H, H-3), 5.24 (dd, J = 17.1, 0.6 Hz, 1H, H-4’), 5.12 (dd, J = 10.4, 0.6 Hz, 1H, H-4), 3.81 (s, 3H, H-12), 2.20 (s, 1H, H-5), 1.86 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 159.4 (C-8), 147.5 (C-6), 145.6 (C-3), 129.2 (C-10), 118.7 (C-11), 112.7 (C-7), 111.9 (C-9), 111.8 (C-4), 55.2 (C-12), 51.0 (C-2), 31.1 (C-1); IR: ν_max (film)/cm⁻¹ 1597 (C=C), 1485 (C=C Ar), 1428, 1256 (Ar-O-), 1043, 779, 697; GC-MS: m/z 161.1 [M-SH]⁺, 194.1 [M]⁺, 10.3 min; HRMS: found 194.0758, [M]⁺ requires 194.0760.

319ag: (R)-2-(3-Chlorophenyl)but-3-ene-2-thiol.

General procedure P was followed using (R)-S-2-(3-chlorophenyl)but-3-en-2-yl methylcarbamothioate (R)-318ag (167 mg, 0.65 mmol) to afford the title compound as a colourless oil (114 mg, 87%).

[α]D²⁴: +2.4 (c 1.00, CDCl₃); Rf: 0.73 (Pent/Et₂O 8:2); ¹H NMR: (500 MHz; CDCl₃) δ (ppm) 7.50 (t, J = 1.9 Hz, 1H, H-7), 7.41 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H, H-9), 7.26 (t, J = 7.8 Hz, 1H, H-10), 7.21 (ddd, J = 7.8, 1.9, 1.3 Hz, 1H, H-11), 6.22 (dd, J = 17.1, 10.4 Hz, 1H, H-3), 5.25 (d, J = 17.1 Hz, 1H, H-4’), 5.16 (d, J = 10.4 Hz, 1H, H-4), 2.22 (s, 1H, H-5), 1.85 (s, 3H, H-1); ¹³C NMR: (125 MHz, CDCl₃) δ (ppm) 148.0 (C-6), 145.1 (C-3), 134.1 (C-8), 129.5 (C-10), 127.1 (C-11), 126.8 (C-7), 124.7 (C-9), 122.5 (C-4), 112.5 (C-2), 50.7 (C-2), 31.1 (C-1); IR: ν_max (film)/cm⁻¹ 1593 (C=C), 1570 (C=C₆H₅), 1477 (C=C₆H₅), 1410, 920, 782, 692 (C-Cl); GC-MS: m/z 165.1 [M-SH]⁺, 10.8 min; HRMS: found 165.0464, [M-SH]⁺ requires 165.0466.
**319ah**: 2-(3-Fluorophenyl)but-3-ene-2-thiol.

General procedure P was followed using S-2-(3-fluorophenyl)but-3-en-2-yl methylcarbamothioate **318ah** (121 mg, 0.51 mmol) to afford the title compound as a colourless liquid (54 mg, 59%).

**Rf**: 0.89 (Pent/Et₂O 95:5); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.30-7.28 (m, 2H, H-9, H-11), 7.26-7.22 (m, 1H, H-10), 6.96-6.91 (m, 1H, H-7), 6.24 (dd, J = 17.1, 10.4 Hz, 1H, H-3), 5.24 (dd, J = 17.1, 0.4 Hz, 1H, H-4'), 5.16 (dd, J = 10.4, 0.4 Hz, 1H, H-4), 2.22 (s, 1H, H-5), 1.86 (s, 3H, H-1); **¹³C NMR**: (100 MHz, CDCl₃) δ (ppm) 162.6 (d, ¹J_C,F = 244.0 Hz, C-8), 148.6 (d, ³J_C,F = 6.5 Hz, C-6), 145.1 (C-3), 129.7 (d, ³J_C,F = 8.2 Hz, C-10), 121.0 (d, ⁴J_C,F = 2.8 Hz, C-11), 113.9 (d, ²J_C,F = 21.0 Hz, C-9), 113.7 (d, ²J_C,F = 22.9 Hz, C-7), 112.3 (C-4), 50.7 (C-2), 31.1 (C-1); **IR**: ν_max(film)/cm⁻¹ 1611 (C=C), 1587 (C=C₆H₅), 1485 (C=C₆H₅), 1436, 1251 (C-F), 922, 784, 695; **GC-MS**: 149.1 (M-SH), 9.1 min; **HRMS**: found 149.0754, [M]⁺ requires 149.0761.

The equivalent enantioenriched thiol (R)-2-(3-fluorophenyl)but-3-ene-2-thiol (R)-**319ah** (40 mg, 53%) was prepared from (R)-S-2-(3-fluorophenyl)but-3-en-2-yl methylcarbamothioate (R)-**318ah** (100 mg, 0.42 mmol) following general procedure P. **[α]_D^{25}**: +5.2 (c 1.00, CDCl₃).

**319aj**: 2-(Naphthalen-1-yl)but-3-ene-2-thiol.

General procedure P was followed using S-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate **318aj** (156 mg, 0.57 mmol) to afford the title compound as a colourless oil (113 mg, 92%).
The equivalent enantioenriched thiol (R)-2-(naphthalen-1-yl)but-3-ene-2-thiol (R)-319aj (27 mg, 75%) was prepared from (R)-S-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate (R)-318aj (45 mg, 0.17 mmol) following general procedure P.

$\alpha_D^{26} +98.6$ (c 1.00, CHCl$_3$).

319bc: 3-(4-Chlorophenyl)hex-1-ene-3-thiol.

![Structure of 319bc]

General procedure P was followed using S-3-(4-chlorophenyl)hex-1-en-3-yl methylcarbamothioate 318bc (124 mg, 0.44 mmol) to afford the title compound as a pale yellow liquid (66 mg, 67%).

Rf: 0.83 (Pet/EtOAc 95:5); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.42 (d, $J = 8.8$ Hz, 2H, H-10, H-12), 7.28 (d, $J = 8.8$ Hz, 2H, H-9, H-13), 6.14 (dd, $J = 17.1$, 10.5 Hz, 1H, H-2), 5.24 (dd, $J = 17.1$, 0.7 Hz, 1H, H-1'), 5.20 (dd, $J = 10.5$, 0.7 Hz, 1H, H-1), 2.09 (ddd, $J = 13.8$, 11.6, 5.1 Hz, 1H, H-4), 2.03 (ddd, $J = 13.8$, 11.6, 5.1 Hz, 1H, H-4'), 1.98 (s, 1H, H-7), 1.38-1.17 (m, 2H, H-5), 0.90 (t, $J = 7.4$ Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 144.3 (C-2), 143.3 (C-8), 132.6 (C-11), 128.6 (C-10, C-12), 128.2 (C-9, C-13), 113.5 (C-1), 55.2 (C-3), 45.1 (C-4), 18.5 (C-5), 14.2 (C-6); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1747 (C=C), 1645 (C=CH$_2$), 1091, 1013, 921, 825 (C-Cl); GC-MS: $m/z$ 193.0 [M-SH]$^+$, 226.1 [M]$^+$, 12.0 min; HRMS: found 226.0580, [M]$^+$ requires 226.0578.
319be: 3-(3-Chlorophenyl)hex-1-ene-3-thiol.

General procedure N (-45 °C, 4 h) was followed using S-hex-1-en-3-yl 3-chlorophenyl(methyl)carbamothioate 316be (50 mg, 0.18 mmol). Purification by column chromatography (Pet 100%) afforded the title compound as a pale yellow oil (23 mg, 56%).

Rf: 0.91 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.48 (t, J = 1.9 Hz, 1H, H-9), 7.37 (dt, J = 7.6, 1.6 Hz, 1H, H-12), 7.23-7.20 (m, 2H, H-11, H-13), 6.13 (dd, J = 17.1, 10.5 Hz, 1H, H-2), 5.27 (dd, J = 17.1, 0.7 Hz, 1H, H-1'), 5.22 (dd, J = 10.5, 0.7 Hz, 1H, H-1), 2.06 (2dd, J = 13.7, 11.2, 5.3 Hz, 2H, H-4, H-4'), 1.38-1.18 (m, 2H, H-5), 0.91 (t, J = 7.3 Hz, 3H, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 147.0 (C-8), 144.0 (C-2), 134.0 (C-10), 129.3 (C-11 or C-13), 127.4 (C-9), 127.0 (C-13 or C-11), 125.3 (C-12), 113.7 (C-1), 55.3 (C-3), 45.0 (C-4), 18.5 (C-5), 14.2 (C-6); $\nu$: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1592 (C=C), 1568 (C=C$_{Ar}$), 1466, 1080, 918, 781 (C-Cl), 693; MS: m/z (ES') 225 [M-H]$^-$ (100%); HRMS: found 225.0516, [M-H]$^-$ requires 225.0510.

The equivalent enantioenriched (R)-3-(3-chlorophenyl)hex-1-ene-3-thiol (R)-319be (15 mg, 80%) was prepared from (R)-S-3-(3-chlorophenyl)hex-1-en-3-yl methylcarbamothioate (R)-318be (23 mg, 0.08 mmol) following general procedure P. [$\alpha$]$_D$$_{24}^\circ$: +16.8 (c 1.00, CHCl$_3$).

319bf: 3-(2-Methoxyphenyl)hex-1-ene-3-thiol.

General procedure N (-45 °C, 5 h) was followed using S-hex-1-en-3-yl 2-methoxyphenyl(methyl)carbamothioate 316bf (50 mg, 0.18 mmol). Purification by
column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a pale yellow (13 mg, 32%).

**Rf:** 0.73 (Pet/EtOAc 8:2); **¹H NMR:** (400 MHz; CDCl₃) δ (ppm) 7.44 (dd, J = 7.7, 1.6 Hz, 1H, H-13), 7.25 (ddd, J = 9.2, 7.5, 1.7 Hz, 1H, H-11), 6.94-6.89 (m, 2H, H-12, H-10), 6.26 (dd, J = 17.3, 10.6 Hz, 1H, H-2), 5.10 (dd, J = 10.6, 0.8 Hz, 1H, H-1'), 5.09 (dd, J = 17.3, 0.8 Hz, 1H, H-1), 3.84 (s, 3H, H-14), 2.33 (ddd, J = 13.7, 10.6, 5.8 Hz, 1H, H-4'), 2.18 (ddd, J = 13.7, 10.6, 6.1 Hz, 1H, H-4), 1.22 (m, 2H, H-5), 0.88 (t, J = 7.4 Hz, 3H, H-6); **¹³C NMR:** (100 MHz, CDCl₃) δ (ppm) 157.4 (C-9), 144.6 (C-2), 132.8 (C-8), 128.4 (C-13), 128.3 (C-11), 120.3 (C-12), 112.0 (C-10), 111.8 (C-1), 55.2 (C-14), 54.5 (C-3), 43.2 (C-4), 18.9 (C-5), 14.3 (C-6); **IR:** ν max (film)/cm⁻¹ 1487 (C=C Ar), 1461, 1433, 1239 (C Ar-O), 1026, 749.

**319fa:** (E)-4-Cyclohexyl-2-(p-tolyl)but-3-ene-2-thiol.

![Chemical Structure](image)

General procedure P was followed using (E)-S-4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl methylcarbamothioate **318fa** (666 mg, 2.10 mmol) to afford the title compound as a colourless oil (546 mg, 100%).

**Rf:** 0.68 (Pent/Et₂O 95:5); **¹H NMR:** (400 MHz; CDCl₃) δ (ppm) 7.40 (d, J = 8.2 Hz, 2H, H-13, H-17), 7.11 (d, J = 8.2 Hz, 2H, H-14, H-16), 5.83 (dd, J = 15.5, 1.1 Hz, 1H, H-3), 5.56 (dd, J = 15.5, 6.8 Hz, 1H, H-4), 2.33 (s, 3H, H-18), 2.17 (s, 1H, H-11), 2.06-1.98 (m, 1H, H-5), 1.84 (s, 3H, H-1), 1.77-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.34-1.06 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); **¹³C NMR:** (100 MHz, CDCl₃) δ (ppm) 143.9 (C-15), 136.3 (C-12), 135.8 (C-3), 133.7 (C-4), 128.8 (C-14, C-16), 126.2 (C-13, C-17), 50.4 (C-2), 40.4 (C-5), 33.1/33.0 (C-6, C-10), 32.1 (C-1), 26.1/26.0 (C-7, C-8, C-9), 20.9 (C-18); **IR:** ν max (film)/cm⁻¹ 1510 (C=C Ar), 1447 (C=C Ar), 968, 815, 772; **GC-MS:** 227.2 (M-SH), 12.3 min; **HRMS:** found 260.1583, [M]⁺ requires 260.1593.
The equivalent enantioenriched thiol (R)-(E)-4-cyclohexyl-2-(p-tolyl)but-3-ene-2-thiol (R)-319fa (153 mg, 91%) was prepared from (R)-(E)-S-4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl methylcarbamothioate (R)-318fa (205 mg, 0.65 mmol) following general procedure P. 

$[\alpha]_D^{24} = +21.0$ (c 1.00, CHCl$_3$).

319fc: (E)-2-(4-Chlorophenyl)-4-cyclohexylbut-3-ene-2-thiol.

General procedure P was followed using (E)-S-4-cyclohexyl-2-(4-chlorophenyl)but-3-en-2-yl methylcarbamothioate 318fc (214 mg, 0.63 mmol) to afford the title compound as a colourless oil (99 mg, 56%).

$R_f$: 0.58 (Pent/Et$_2$O 98:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.45 (d, $J = 8.7$ Hz, 2H, H-14, H-16), 7.27 (d, $J = 8.7$ Hz, 2H, H-13, H-17), 5.80 (dd, $J = 15.5$, 1.2 Hz, 1H, H-3), 5.55 (dd, $J = 15.5$, 6.8 Hz, 1H, H-4), 2.19 (s, 1H, H-11), 2.06-1.98 (m, 1H, H-5), 1.83 (s, 3H, H-1), 1.75-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.05 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 145.4 (C-12), 135.2 (C-3), 134.3 (C-4), 132.5 (C-15), 128.2 (C-13, C-17), 127.9 (C-14, C-16), 50.2 (C-2), 40.4 (C-5), 33.0/32.9 (C-6, C-10), 32.1 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1490 (C=C$_{Ar}$), 1448 (C=C$_{Ar}$), 1095, 969, 828 (C-Cl); GC-MS: 246.1 (M-SH$_2$), 13.5 min; HRMS: found 246.1160, [M]$^+$ requires 246.1170.

(S)-319fd: (S,E)-4-Cyclohexyl-2-(4-fluorophenyl)but-3-ene-2-thiol.

General procedure P was followed using (S,E)-S-4-cyclohexyl-2-(4-fluorophenyl)but-3-en-2-yl methylcarbamothioate (S)-318fd (41 mg, 0.13 mmol) to afford the title compound as a colourless oil (19 mg, 56%).
[α]_D^{25}: -4.2 (c 1.00, CDCl₃); R_f: 0.83 (Pent/Et₂O 98:2); ^1H NMR: (500 MHz; CDCl₃) δ (ppm) 7.48 (dd, J = 8.8, 5.3 Hz, 2H, H-11, H-16), 6.98 (t, J = 8.8 Hz, 2H, H-13, H-17), 5.81 (dd, J = 15.5, 1.2 Hz, 1H, H-3), 5.55 (dd, J = 15.5, 6.9 Hz, 1H, H-4), 2.19 (s, 1H, H-11), 2.04-1.99 (m, 1H, H-5), 1.84 (s, 3H, H-1), 1.75-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.32-1.06 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); ^13C NMR: (125 MHz, CDCl₃) δ (ppm) 161.5 (d, 3J_C,F = 244.3 Hz, C-15), 142.6 (d, 4J_C,F = 2.7 Hz, C-12), 135.5 (C-3), 134.1 (C-4), 128.2 (d, 3J_C,F = 7.9 Hz, C-13, C-17), 114.9/114.7 (d, 2J_C,F = 21.2 Hz, C-14, C-16), 50.1 (C-2), 40.3 (C-5), 33.0/32.9 (C-6, C-10), 32.3 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: ν_max(film)/cm⁻¹ 1603 (C=O), 1506 (C=O), 1448 (C=O), 1231 (C-F), 1161, 969, 832; GC-MS: 231.2 (M-SH), 12.9 min; HRMS: found 231.1535, [M]⁺ requires 231.1544.

319fe: (E)-4-Cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol.

General procedure P was followed using (E)-S-4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl methylcarbamothioate 318fe (128 mg, 0.38 mmol) to afford the title compound as a colourless oil (86 mg, 81%).

R_f: 0.43 (Pent/Et₂O 98:2); ^1H NMR: (400 MHz; CDCl₃) δ (ppm) 7.24 (t, J = 8.0 Hz, 1H, H-10), 7.11 (ddd, J = 8.0, 2.1, 0.8 Hz, 1H, H-17), 7.09 (t, J = 2.1 Hz, 1H, H-13), 6.77 (ddd, J = 8.0, 2.1, 0.8 Hz, 1H, H-15), 5.83 (dd, J = 15.5, 1.2 Hz, 1H, H-3), 5.59 (dd, J = 15.5, 6.9 Hz, 1H, H-4), 3.82 (s, 3H, H-11), 2.20 (s, 1H, H-11), 2.08-1.99 (m, 1H, H-5), 1.85 (s, 3H, H-1), 1.77-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.35-1.07 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); ^13C NMR: (100 MHz, CDCl₃) δ (ppm) 159.3 (C-14), 148.6 (C-12), 135.5 (C-3), 133.9 (C-4), 129.1 (C-10), 118.7 (C-17), 112.7 (C-13), 111.6 (C-15), 55.2 (C-18), 50.5 (C-2), 40.4 (C-5), 33.0/32.9 (C-6, C-10), 32.0 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: ν_max(film)/cm⁻¹ 1653 (C=O), 1598 (C=C), 1486 (C=O), 1255 (C=O), 1043, 697; GC-MS: 242.2 (M-SH), 13.60 min; HRMS: found 276.1533, [M]⁺ requires 276.1542.

The equivalent enantioenriched thiol (S)-(E)-4-cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol (S)-319fe (108 mg, 72%) was prepared from (S)-(E)-S-4-cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol (S)-319fe.
methoxyphenyl)but-3-en-2-yl methylcarbamothioate (S)-318fe (180 mg, 0.54 mmol) following general procedure P. 
\[\alpha\]_D^{25} +2.4 (c 1.00, CDCl_3).

319fg: (E)-4-Cyclohexyl-2-(3-fluorophenyl)but-3-ene-2-thiol.

General procedure P was followed using (E)-S-4-cyclohexyl-2-(3-fluorophenyl)but-3-en-2-yl methylcarbamothioate 318fg (73 mg, 0.23 mmol) to afford the title compound as a colourless oil (25 mg, 42%).

R_f: 0.94 (Pent/Et_2O 95:5); \[^1\text{H NMR}\]: (400 MHz; CDCl_3) δ (ppm) 7.31-7.26 (m, 2H, H-16, H-17), 7.22 (m, 1H, H-15), 6.94-6.89 (sym. m, 1H, H-13), 5.80 (dd, J = 15.5, 1.2 Hz, 1H, H-3), 5.58 (dd, J = 15.5, 6.8 Hz, 1H, H-4), 2.21 (s, 1H, H-11), 2.07-2.00 (m, 1H, H-5), 1.83 (s, 3H, H-1), 1.78-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.06 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); \[^1\text{C NMR}\]: (100 MHz, CDCl_3) δ (ppm) 162.5 (d, \(^3J_{CF} = 243.8\) Hz, C-14), 149.7 (d, \(^3J_{CF} = 6.7\) Hz, C-12), 135.0 (C-3), 134.4 (C-4), 129.6 (d, \(^3J_{CF} = 8.1\) Hz, C-16), 122.0 (d, \(^4J_{CF} = 2.9\) Hz, C-17), 113.8 (d, \(^2J_{CF} = 22.8\) Hz, C-13), 113.5 (d, \(^2J_{CF} = 21.1\) Hz, C-15), 50.2 (C-2), 40.4 (C-5), 33.0/32.9 (C-6, C-10), 31.9 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1586 (C=C), 1447 (C=C\_ar), 906, 775, 730; GC-MS: m/z 231.1 [M-SH]^+, 12.2 min; HRMS: found 231.1537, [M-SH]^+ requires 231.1544.

319fh: (E)-4-Cyclohexyl-2-(2-methoxyphenyl)but-3-ene-2-thiol.

General procedure P was followed using (E)-S-4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl methylcarbamothioate 318fh (450 mg, 1.35 mmol) to afford the title compound as a colourless oil (313 mg, 84%).
**Rf**: 0.43 (Pent/Et₂O 98:2); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.36 (dd, J = 8.1, 1.7 Hz, 1H, H-17), 7.24 (ddd, 8.1, 7.3, 1.7, 1H, H-15), 6.91 (dd, J = 8.1, 1.2 Hz, 1H, H-16), 6.89 (dd, J = 8.1, 1.2 Hz, 1H, H-14), 5.90 (dd, J = 15.6, 1.2 Hz, 1H, H-3), 5.40 (dd, J = 15.6, 7.0 Hz, 1H, H-4), 3.86 (s, 3H, H-18), 3.07 (s, 1H, H-11), 2.03-1.95 (m, 1H, H-5), 1.86 (s, 3H, H-1), 1.73-1.62 (m, 4H, H-6, H-7, H-9, H-10), 1.32-1.03 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); **¹³C NMR**: (100 MHz, CDCl₃) δ (ppm) 157.4 (C-13), 135.2 (C-12), 134.9 (C-3), 133.1 (C-4), 128.3 (C-15), 126.5 (C-17), 120.2 (C-16), 111.8 (C-14), 55.1 (C-18), 48.6 (C-2), 40.5 (C-5), 33.1 (C-6, C-10), 29.8 (C-1), 26.2/26.1 (C-7, C-8, C-9); **IR**: v_max(film)/cm⁻¹ 1487 (C=C Ar), 1447 (C=C Ar), 1242 (C=O), 1118, 750, 544; **GC-MS**: m/z 243.1 [M-SH]+, 12.6 min; **HRMS**: found 243.1737, [M-SH]+ requires 243.1743.

The equivalent enantioenriched thiol (S)-(E)-4-cyclohexyl-2-(2-methoxyphenyl)but-3-ene-2-thiol (S)-319fh (93 mg, 61%) was prepared from (S)-(E)-S-4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl methylcarbamothioate (S)-318fh (185 mg, 0.55 mmol) following general procedure P. **[α]₀** ⁰₂₅: -13.2 (c 1.00, CDCl₃).

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**319fi**: (E)-4-Cyclohexyl-2-(1-naphthalen-1-yl)but-3-ene-2-thiol.

![Diagram](image)

General procedure P was followed using (E)-5-(4-cyclohexyl-2-(1-naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate 318fi (540 mg, 1.53 mmol) to afford the title compound as a colourless oil (427 mg, 94%).

**Rf**: 0.57 (Pent/Et₂O 8:2); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 8.50-8.47 (m, 1H, H-14), 7.86-7.84 (m, 1H, H-17), 7.78 (d, J = 8.1 Hz, 1H, H-19), 7.68 (dd, J = 7.4, 1.0 Hz, 1H, H-20), 7.49-7.42 (m, 3H, H-15, H-16, H-21), 5.96 (dd, J = 15.6, 1.2 Hz, 1H, H-3), 5.47 (d, J = 15.6, 7.0 Hz, 1H, H-4), 2.50 (s, 1H, H-11), 2.07 (s, 3H, H-1), 2.02-1.94 (m, 1H, H-5), 1.82-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.29-0.98 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); **¹³C NMR**: (100 MHz, CDCl₃) δ (ppm) 141.6 (C-13), 136.4 (C-3), 135.0 (C-4), 134.9 (C-18), 130.7 (C-12), 128.9 (C-17), 128.7 (C-19), 128.3 (C-14), 125.1/124.8/124.5 (C-15, C-16, C-21), 123.8
The equivalent enantioenriched thiol (R)-(E)-4-cyclohexyl-2-(naphthalen-1-yl)but-3-ene-2-thiol (R)-319fi (302 mg, 90%) was prepared from (R)-(E)-5-4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl methylcarbamothioate (R)-318fi (400 mg, 1.13 mmol) following general procedure P.

$\alpha^\circ_{D25}$: +67.6 (c 1.00, CDCl$_3$).

319fk: (E)-tert-Butyl 6-(4-cyclohexyl-2-mercaptobut-3-en-2-yl)-1H-indole-1-carboxylate.

General procedure P was followed using (E)-tert-butyl 6-(4-cyclohexyl-2-((methylcarbamoyl)thio)but-3-en-2-yl)-1H-indole-1-carboxylate 318fk (290 mg, 0.66 mmol) to afford the title compound as a colourless oil (148 mg, 58%).

R$_f$: 0.68 (Pent/Et$_2$O 95:5); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 8.36 (bs, 1H, H-13), 7.60 (bd, $J = 3.7$ Hz, 1H, H-15), 7.48 (dd, $J = 8.3$, 0.5 Hz, 1H, H-18), 7.39 (dd, $J = 8.3$, 1.8 Hz, 1H, H-19), 6.53 (dd, $J = 3.7$, 0.5 Hz, 1H, H-16), 5.92 (dd, $J = 15.5$, 1.2 Hz, 1H, H-3), 5.59 (dd, $J = 15.5$, 6.9 Hz, 1H, H-4), 2.27 (s, 1H, H-11), 2.07-1.99 (m, 1H, H-5), 1.94 (s, 3H, H-1), 1.77-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.69 (s, 9H, H-22, H-23, H-24), 1.34-1.07 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 149.8 (C-20), 143.2 (C-14), 136.2 (C-3), 134.9 (C-12), 133.6 (C-4), 129.2 (C-17), 126.4 (C-15), 121.8 (C-19), 120.4 (C-18), 113.0 (C-13), 106.9 (C-16), 83.6 (C-21), 51.2 (C-2), 40.4 (C-5), 33.0/32.9 (C-6, C-10), 32.5 (C-1), 28.2 (C-22, C-23, C-24), 26.2/26.0 (C-7, C-8, C-9); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1732 (C=O), 1433 (C=C$_{\text{Ar}}$), 1369 (C$_{\text{Ar}}$=N), 1334, 1251 (C-O$_{\text{ester}}$), 1154, 1129; GC-MS: m/z 251.2 [M-SH-C$_5$H$_9$O$_2$]$^+$, 14.7 min; HRMS: found 352.2258, [M-SH]$^+$ requires 352.2271.
The equivalent enantioenriched thiol (R)-(E)-tert-butyl 6-(4-cyclohexyl-2-mercaptobut-3-en-2-yl)-1H-indole-1-carboxylate (R)-319fk (30 mg, 39%) was prepared from (R)-(E)-tert-butyl 6-(4-cyclohexyl-2-((methylcarbamoyl)thio)but-3-en-2-yl)-1H-indole-1-carboxylate (R)-318fk (88 mg, 0.20 mmol) following general procedure P. 

\[ \alpha \] D 25: +2.0 (c 1.00, CHCl₃).

**320af:** (2-(3-Methoxyphenyl)but-3-en-2-yl)(methyl)sulfane.

General procedure Q was followed using 2-(3-methoxyphenyl)but-3-ene-2-thiol 319af (115 mg, 0.59 mmol) to afford the title compound as a colourless oil (110 mg, 89%).

**Rf:** 0.44 (Pent/Et₂O 8:2); ⁱH NMR: (400 MHz; CDCl₃) δ (ppm) 7.25 (t, J = 7.9 Hz, 1H, H-10), 7.13-7.10 (m, 2H, H-7, H-11), 6.78 (ddd, J = 7.9, 2.5, 0.8 Hz, 1H, H-9), 6.14 (dd, J = 17.3, 10.6 Hz, 1H, H-3), 5.23 (dd, J = 10.6, 0.9 Hz, 1H, H-4), 5.15 (dd, J = 17.3, 0.9 Hz, 1H, H-4'), 3.81 (s, 3H, H-12), 1.91 (s, 3H, H-5), 1.70 (s, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 159.5 (C-8), 146.1 (C-6), 141.9 (C-3), 129.2 (C-10), 119.4 (C-7 or C-11), 113.3 (C-4), 113.2 (C-11 or C-7), 111.9 (C-9), 55.2 (C-12), 52.6 (C-2), 26.1 (C-1), 12.6 (C-5); IR: \( v_{\text{max}} \) (film)/cm⁻¹: 1598 (C=C), 1581 (C=CH₂), 1485 (C=CH), 1430, 1289, 1257 (C₆H₅-O), 1045, 916, 780, 699; GC-MS: m/z 161.1 [M-SCH₃]⁺, 208.1 [M]⁺, 10.7 min; HRMS: found 208.0926, [M]⁺ requires 208.0916.

**320fa:** (E)-(4-Cyclohexyl-2-(p-tolyl)but-3-en-2-yl)(methyl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(p-tolyl)but-3-ene-2-thiol 319fa (198 mg, 0.76 mmol) to afford the title compound as a colourless oil (209 mg, 100%).
Rf: 0.63 (Pent/Et2O 98:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.41 (d, J = 8.1 Hz, 2H, H-13, H-17), 7.12 (d, J = 8.1 Hz, 2H, H-14, H-16), 5.71 (dd, J = 15.7, 1.1 Hz, 1H, H-3), 5.48 (dd, J = 15.7, 6.9 Hz, 1H, H-4), 2.32 (s, 3H, H-18), 2.11-2.05 (m, 1H, H-5), 1.88 (s, 3H, H-11), 1.77-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.67 (s, 3H, H-1), 1.32-1.07 (m, 6H, H-6', H-7', H-9', H-10'); 13C NMR: (100 MHz, CDCl3) δ (ppm) 142.3 (C-15), 136.2 (C-12), 135.6 (C-4), 132.0 (C-3), 128.8 (C-14, C-16), 126.9 (C-13, C-17), 51.9 (C-2), 40.8 (C-5), 33.4/33.3 (C-6, C-10), 26.8 (C-1), 26.1/26.0 (C-7, C-8, C-9), 20.9 (C-18), 12.7 (C-11); IR: νmax(film)/cm⁻¹ 1510 (C=C Ar), 1147 (C=C Ar), 967, 815, 772; GC-MS: m/z 227.2 [M-SCH3]+, 12.9 min; HRMS: found 227.1790, [M-SCH3]+ requires 227.1794.

320fe: (E)-(4-Cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl)(methyl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol 319fe (44 mg, 0.16 mmol) to afford the title compound as a colourless oil (36 mg, 78%).

Rf: 0.46 (Pent/Et2O 98:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.24 (t, J = 7.9 Hz, 1H, H-16), 7.11 (ddd, J = 7.9, 1.7, 1.0 Hz, 1H, H-17), 7.10 (bt, J = 1.7 Hz, 1H, H-13), 6.76 (ddd, J = 7.9, 2.6, 1.0 Hz, 1H, H-15), 5.71 (d, J = 15.7, 1.1 Hz, 1H, H-3), 5.50 (dd, J = 15.7, 6.9 Hz, 1H, H-4), 3.81 (s, 3H, H-18), 2.11-2.05 (m, 1H, H-5), 1.89 (s, 3H, H-11), 1.78-1.63 (m, 4H, H-6, H-7, H-9, H-10), 1.67 (s, 3H, H-1), 1.34-1.04 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); 13C NMR: (100 MHz, CDCl3) δ (ppm) 159.4 (C-14), 147.0 (C-12), 135.8 (C-4), 131.7 (C-3), 129.0 (C-16), 119.5 (C-17), 113.3 (C-13), 111.7 (C-15), 55.2 (C-18), 52.1 (C-2), 40.8 (C-5), 33.4/33.3 (C-6, C-10), 26.8 (C-1), 26.1/26.0 (C-7, C-8, C-9), 12.7 (C-11); IR: νmax(film)/cm⁻¹ 1599 (C=C), 1447 (C=Ar), 1253 (Ar-O), 1045, 968, 777, 700; GC-MS: 243.2 (M-SCH3), 13.3 min; HRMS: found 243.1738, [M-SCH3]+ requires 243.1743.
**320fg**: (E)-(4-Cyclohexyl-2-(3-fluorophenyl)but-3-en-2-yl)(methyl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(3-fluorophenyl)but-3-ene-2-thiol 319fg (19 mg, 0.07 mmol) to afford the title compound as a colourless oil (12 mg, 60%).

**Rf**: 0.59 (Pent/Et₂O 98:2); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.31-7.26 (m, 2H, H-16, H-17), 7.25-7.22 (m, 1H, H-15), 6.94-6.89 (m, 1H, H-13), 5.68 (dd, J = 15.7, 1.1 Hz, 1H, H-3), 5.50 (dd, J = 15.7, 6.9 Hz, 1H, H-4), 2.11-2.03 (m, 1H, H-5), 1.89 (s, 1H, H-11), 1.78-1.65 (m, 4H, H-6, H-7, H-9, H-10), 1.67 (s, 3H, H-1), 1.34-1.07 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); **¹³C NMR**: (100 MHz, CDCl₃) δ (ppm) 162.7 (d, J_C,F = 243.4 Hz, C-14), 148.1 (d, J_C,F = 6.6 Hz, C-12), 136.3 (C-4), 131.3 (C-3), 129.4 (d, J_C,F = 8.2 Hz, C-16), 122.7 (d, J_C,F = 2.7 Hz, C-17), 114.4/114.2 (d, J_C,F = 22.3 Hz, C-13), 113.6/113.4 (d, J_C,F = 21.1 Hz, C-15), 51.8 (C-2), 10.8 (C-5), 33.3/33.2 (C-6, C-10), 26.9 (C-1), 26.1/26.0 (C-7, C-8, C-9), 12.7 (C-11); **IR**: ν_max(film)/cm⁻¹ 1558 (C=C Ar), 1434 (C=C Ar), 1247 (C-F), 967, 783, 698; **GC-MS**: 231.1 (M-SCH₃), 12.5 min; **HRMS**: found 278.1506, [M]+ requires 278.1499.

**320fh**: (E)-(4-Cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl)(methyl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(2-methoxyphenyl)but-3-ene-2-thiol 319fh (228 mg, 0.82 mmol) to afford the title compound as a colourless oil (240 mg, 100%).

**Rf**: 0.46 (Pent/Et₂O 98:2); **¹H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.58 (dd, J = 7.7, 1.7 Hz, 1H, H-17), 7.24 (ddd, J = 8.2, 7.4, 1.7 Hz, 1H, H-15), 6.93 (td, J = 7.7, 1.2 Hz, 1H, H-16), 6.89 (dd, J = 8.2, 1.0 Hz, 1H, H-14), 5.66 (dd, J = 15.7, 1.2 Hz, 1H, H-3), 5.17 (dd, J = 15.7, 7.2 Hz,

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1H, H-4), 3.80 (s, 3H, H-18), 2.05-1.98 (m, 1H, H-5), 1.90 (s, 3H, H-11), 1.74 (s, 3H, H-1), 1.72-1.62 (m, 4H, H-6, H-7, H-9, H-10), 1.33-1.03 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’);

$^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 157.9 (C-13), 134.3 (C-4), 132.2 (C-12), 131.7 (C-3), 129.2 (C-17), 128.5 (C-15), 120.2 (C-16), 112.2 (C-14), 55.1 (C-18), 52.5 (C-2), 40.8 (C-5), 33.6/33.5 (C-6, C-10), 26.2/26.1 (C-7, C-8, C-9), 25.9 (C-1), 13.2 (C-11); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1484 (C=C), 1448 (C=C), 1242 (C=C), 1030, 965, 752; GC-MS: 243.2 (M-SCH$_3$), 13.3 min; HRMS: found 290.1688, [M]$^+$ requires 290.1699.

321fc: (E)-Benzyl(2-(4-chlorophenyl)-4-cyclohexylbut-3-en-2-yl)sulfane.

![Structural diagram of 321fc]

To a solution of (E)-4-cyclohexyl-2-(4-chlorophenyl)but-3-ene-2-thiol 319fc (85 mg, 0.30 mmol) in THF (1.5 mL) were sequentially added triethylamine (2.0 eq) and benzyl bromide (1.2 eq). The reaction was stirred at rt for 3 days until completion was confirmed by TLC (Pet/EtOAc 95:5). Water and brine were added. The aqueous layer was extracted with Et$_2$O (x3). The combined organic layers were washed with H$_2$O, filtered and concentrated. Purification by column chromatography (Pentane 100%, Pentane/Et$_2$O 95:5) afforded the title compound as a colourless oil (74 mg, 66%).

Rf: 0.51 (Pet/EtOAc 95:5); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.48 (d, $J = 8.7$ Hz, 2H, H-20, H-22), 7.31-7.20 (m, 5H, H-13, H-14, H-15, H-16, H-17), 7.28 (d, $J = 8.7$ Hz, 2H, H-19, H-23), 5.76 (dd, $J = 15.7$, 1.1 Hz, 1H, H-3), 5.55 (dd, $J = 15.7$, 6.9 Hz, 1H, H-4), 3.54 (d, $J = 12.4$ Hz, 1H, H-11), 3.51 (d, $J = 12.4$ Hz, 1H, H-11’), 2.11-2.03 (m, 1H, H-5), 1.76-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.71 (s, 3H, H-1), 1.35-1.08 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 143.8 (C-12), 137.8 (C-18), 136.3 (C-4), 132.5 (C-21), 131.9 (C-3), 129.0/128.6 (C-13, C-14, C-16, C-17), 128.4 (C-20, C-22), 128.2 (C-19, C-23), 126.8 (C-15), 53.4 (C-2), 40.7 (C-5), 34.8 (C-11), 33.3/33.2 (C-6, C-10), 27.6 (C-1), 26.1/26.0 (C-8, C-9); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1491 (C=C), 1448 (C=C), 1094, 1012, 967, 824, 695 (C-Cl); GC-MS: $m/z$ 248.1 [M-SCH$_3$]$^+$, 12.4 min; HRMS: found 248.1326, [M-SCH$_3$]$^+$ requires 248.1326.
**322af**: Allyl(2-(3-methoxyphenyl)but-3-en-2-yl)sulfane.

General procedure Q was followed using 2-(3-methoxyphenyl)but-3-ene-2-thiol 319af (68 mg, 0.35 mmol) to afford the title compound as a pale yellow oil (57 mg, 69%).

\[ \text{IR: } \nu_{\text{max}}(\text{film})/\text{cm}^{-1}: 1598 (\text{C}=\text{C}), 1580 (\text{C}=\text{C}_\text{Ar}), 1485 (\text{C} \equiv \text{C}_\text{Ar}), 1429 (\text{C} \equiv \text{C}), 1046, 916, 779; \]
\[ \text{GC-MS: } 161.1 (\text{M}-\text{SC}_3\text{H}_5), 13.0 \text{ min}; \]
\[ \text{HRMS: found 234.1062, } [\text{M}]^+ \text{ requires 234.1073.} \]

**322ah**: Allyl(2-(fluorophenyl)but-3-en-2-yl)sulfane.

General procedure Q was followed using 2-(3-fluorophenyl)but-3-ene-2-thiol 319ah (80 mg, 0.44 mmol) to afford the title compound as a yellow oil (93 mg, 95%).

\[ \text{IR: } \nu_{\text{max}}(\text{film})/\text{cm}^{-1}: 1598 (\text{C}=\text{C}), 1580 (\text{C}=\text{C}_\text{Ar}), 1485 (\text{C} \equiv \text{C}_\text{Ar}), 1429 (\text{C} \equiv \text{C}), 1046, 916, 779; \]
\[ \text{GC-MS: } 161.1 (\text{M}-\text{SC}_3\text{H}_5), 13.0 \text{ min}; \]
\[ \text{HRMS: found 234.1062, } [\text{M}]^+ \text{ requires 234.1073.} \]
$J = 12.8, 7.2, 1.2 \text{ Hz, } 1H, H-5$, 2.98 (ddt, $J = 12.8, 7.2, 1.2 \text{ Hz, } 1H, H-5'$), 1.74 (s, 3H, H-1);

$^{13}$C NMR: (100 MHz, CDCl$3$) $\delta$ (ppm) 160.3 (d, $^{1}J_{C,F} = 240.3$ Hz, C-10), 147.2 (C-8) $^{2}J_{C,F}$ not visible, 142.0 (C-3), 129.7 (d, $^{3}J_{C,F} = 8.3$ Hz, C-12), 122.7 (d, $^{4}J_{C,F} = 2.8$ Hz, C-13), 117.3 (C-7), 114.3 (d, $^{2}J_{C,F} = 22.7$ Hz, C-9), 113.9 (C-4), 113.8 (d, $^{2}J_{C,F} = 20.9$ Hz, C-11), 113.7 (C-9), 53.7 (C-2), 33.3 (C-5), 26.9 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1586 (C=C), 1484 (C=C Ar), 1433 (C=C Ar), 1250 (C-F), 920, 785; GC-MS: 149.0 (M-SC$_3$H$_5$), 11.0 min; HRMS: found 222.0878, [M]$^+$ requires 222.0873.

The equivalent enantioenriched sulfide (R)-allyl(2-(3-fluorophenyl)but-3-en-2-yl)sulfane (R)-322ah (40 mg, 100%) was prepared from (R)-2-(3-fluorophenyl)but-3-ene-2-thiol (R)-319ah (33 mg, 0.18 mmol) following general procedure Q.

$[\alpha]_{D}^{24} = +2.8$ (c 1.00, CHCl$_3$).

322be: (R)-Allyl(3-(3-chlorophenyl)hex-1-en-3-yl)sulfane.

General procedure Q was followed using (R)-3-(3-chlorophenyl)hex-1-ene-3-thiol (R)-319be (50 mg, 0.22 mmol) to afford the title compound as a pale yellow oil (18 mg, 30%).

$R_f$: 0.70 (Pent/Et$_2$O 98:2); $^1$H NMR: (500 MHz; CDCl$3$) $\delta$ (ppm) 7.47 (t, $J = 1.7$ Hz, 1H, H-11), 7.38 (dt, $J = 7.9, 1.7$ Hz, 1H, H-13), 7.26 (t, $J = 7.9$ Hz, 1H, H-14), 7.21 (dt, $J = 7.9, 1.7$ Hz, 1H, H-15), 6.03 (dd, $J = 17.4, 10.8$ Hz, 1H, H-2), 5.75 (ddt, $J = 17.0, 10.0, 7.1$ Hz, 1H, H-8), 5.31 (d, $J = 10.8$ Hz, 1H, H-1), 5.19 (d, $J = 17.4$ Hz, 1H, H-1'), 5.12 (dq, $J = 17.0, 1.4$ Hz, 1H, H-9'), 5.02 (dq, $J = 10.0, 0.9$ Hz, 1H, H-9), 2.97 (dd, $J = 12.7, 7.1$ Hz, 1H, H-7), 2.87 (dd, $J = 12.7, 7.1$ Hz, 1H, H-7'), 1.93 (m, 2H, H-4), 1.40-1.14 (m, 2H, H-5), 0.85 (t, $J = 7.4$ Hz, 3H, H-6).

Note: no additional analysis was carried out in order to save material for the subsequent metathesis reaction.
322fa: (E)-Allyl(4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl)sulfane.

![Chemical structure of 322fa](image)

General procedure Q was followed using (E)-4-cyclohexyl-2-(p-tolyl)but-ene-2-thiol 319fa (546 mg, 2.10 mmol) to afford the title compound as a colourless oil (479 mg, 76%).

Rf: 0.69 (Pent/Et2O 98:2); ^1H NMR: (500 MHz; CDCl_3) δ (ppm) 7.41 (d, J = 8.2 Hz, 2H, H-15, H-19), 7.12 (d, J = 8.2 Hz, 2H, H-16, H-18), 5.79 (ddt, J = 17.0 Hz, 10.0, 7.2 Hz, 1H, H-12), 5.76 (dd, J = 15.7, 1.1, Hz, 1H, H-3), 5.51 (dd, J = 15.7, 6.9 Hz, 1H, H-4), 5.11 (dq, J = 17.0, 1.0 Hz, 1H, H-13'), 5.00 (bd, J = 12.9, 7.2, 1.0 Hz, 1H, H-11), 2.960 (ddt, J = 12.9, 7.2, 1.0 Hz, 1H, H-11'), 2.32 (s, 3H, H-20), 2.10-2.03 (m, 1H, H-5), 1.78-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.71 (s, 3H, H-1), 1.33-1.08 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); ^13C NMR: (125 MHz, CDCl_3) δ (ppm) 142.3 (C-17), 136.3 (C-14), 135.5 (C-4), 134.8 (C-12), 132.6 (C-3), 128.8 (C-16, C-18), 126.9 (C-15, C-19), 116.8 (C-13), 53.3 (C-2), 40.7 (C-5), 33.4 (C-11), 33.3/33.2 (C-6, C-10), 27.7 (C-1), 26.1/26.0 (C-7, C-8, C-9), 20.9 (C-20); IR: v_{max}(film)/cm^{-1} 1510 (C=C_{Ar}), 1447 (C=C_{Ar}), 983, 913, 815; GC-MS: 227.2 (M-SC_{3}H_{5}), 14.7 min; HRMS: found 300.1897, [M]^+ requires 300.1906.

The equivalent enantiopure (R)-(E)-allyl(4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl)sulfane (R)-322fa (137 mg, 98%, 60% over 3 steps from (R)-316fa) was prepared from (R)-(E)-4-cyclohexyl-2-(p-tolyl)but-3-ene-2-thiol (R)-319fa (121 mg, 0.46 mg) following general procedure Q.

[\alpha]_D^{24}: +36.6 (c 1.00, CDCl_3).
322fe: (E)-Allyl(4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol 319fe (228 mg, 0.82 mmol) to afford the title compound as a pale yellow oil (170 mg, 65%).

Rf: 0.62 (Pent/Et2O 96:4); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.23 (t, J = 8.0 Hz, 1H, H-18), 7.12 (ddd, J = 8.0, 2.0, 0.9 Hz, 1H, H-19), 7.10 (t, J = 2.0 Hz, 1H, H-15), 6.76 (ddd, J = 15.7, 1.1 Hz, 1H, H-3), 5.80 (ddt, J = 17.0, 10.0, 7.1 Hz, 1H, H-12), 5.76 (dd, J = 15.7, 1.1 Hz, 1H, H-4), 5.52 (dd, J = 15.7, 6.9 Hz, 1H, H-4'), 5.11 (dq, J = 17.0, 1.5 Hz, 1H, H-13'), 5.01 (dd, J = 10.0, 1.5 Hz, 1H, H-13), 3.81 (s, 3H, H-20), 3.04 (ddt, J = 12.9, 7.1, 1.0 Hz, 1H, H-11), 2.90 (ddt, J = 12.9, 7.1, 1.0 Hz, 1H, H-11'), 2.09-2.02 (m, 1H, H-5), 1.78-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.72 (s, 3H, H-1), 1.35-1.07 (m, 6H, H-6', H-7', H-8, H-8', H-9', H-10'); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 159.4 (C-16), 147.1 (C-14), 135.8 (C-4), 134.6 (C-12), 132.3 (C-3), 129.1 (C-18), 119.5 (C-19), 116.9 (C-13), 113.3 (C-15), 111.8 (C-17), 55.2 (C-20), 53.5 (C-2), 40.8 (C-5), 33.4 (C-11), 33.3/33.2 (C-6, C-10), 27.7 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: v_max(film)/cm⁻¹ 1599 (C=C), 1580 (C=C), 1483 (C=C₆), 1448 (C=C₆), 1289, 1254 (C₆=O), 1046, 915, 776; MS: m/z (ES⁻) 243 [M-SC₃H₅]⁻ (30%); HRMS: found 243.1733, [M-SC₃H₅]⁻ requires 243.1743.

The equivalent enantioenriched sulfide (S)-(E)-allyl(4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl)sulfane (S)-322fe (114 mg, 100%) was prepared from (S)-(E)-4-cyclohexyl-2-(3-methoxyphenyl)but-3-ene-2-thiol (S)-319fe (100 mg, 0.36 mmol) following general procedure Q.

[α]D⁰: -14.8 (c 1.00, CHCl₃).
322fh: (E)-Allyl(4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(2-methoxyphenyl)but-3-ene-2-thiol 319fh (208 mg, 0.75 mmol) to afford the title compound as a pale yellow oil (234 mg, 98%).

Rf: 0.31 (Pent/Et2O 98:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.58 (dd, J = 7.7, 1.7 Hz, 1H, H-19), 7.24 (ddd, J = 8.1, 7.4, 1.7 Hz, 1H, H-17), 6.92 (td, J = 7.7, 1.2 Hz, 1H, H-18), 6.88 (dd, J = 8.1, 1.1 Hz, 1H, H-16), 5.80 (ddt, J = 17.0, 10.0, 7.1 Hz, 1H, H-12), 5.73 (dd, J = 15.7, 1.2 Hz, 1H, H-3), 5.22 (dd, J = 15.7, 7.1 Hz, 1H, H-4), 5.12 (dq, J = 17.0, 1.6 Hz, 1H, H-13′), 5.00 (dd, J = 10.0, 1.6 Hz, 1H, H-13), 3.79 (s, 3H, H-20), 3.01 (bd, J = 7.1 Hz, 2H, H-11), 2.06-1.99 (m, 1H, H-5), 1.77 (s, 3H, H-1), 1.73-1.61 (m, 4H, H-6, H-7, H-9, H-10), 1.32-1.03 (m, 6H, H-6′, H-7′, H-8, H-8′, H-9′, H-10′); 13C NMR: (100 MHz, CDCl3) δ (ppm) 157.9 (C-15), 134.8 (C-12), 134.8 (C-4), 132.4 (C-14), 132.3 (C-3), 129.1 (C-19), 128.3 (C-17), 120.2 (C-18), 116.7 (C-13), 112.3 (C-16), 55.2 (C-20), 54.1 (C-2), 40.8 (C-5), 33.7 (C-11), 33.5/33.4 (C-6, C-10), 26.6 (C-1), 26.2/26.1 (C-7, C-8, C-9); IR: ν_{max}(film)/cm^{-1} 1486 (C=Ar), 1448 (C=Ar′), 1243 (C_Ar-O), 1029, 914, 752; GC-MS: m/z 243.2 [M-SC3H5]^+ 14.3 min; HRMS: found 243.1734, [M-SC3H5]^+ requires 243.1743.

The equivalent enantioenriched sulfide (S)-(E)-allyl(4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-yl)sulfane (S)-322fh (97 mg, 100%) was prepared from (S)-(E)-4-cyclohexyl-2-(2-methoxyphenyl)but-3-ene-2-thiol (S)-319fh (85 mg, 0.31 mmol) following general procedure Q.

[α]D^{24} = -10.0 (c 1.00, CHCl3).
322fi: (E)-Allyl(4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-thiol 319fi (380 mg, 1.28 mmol) to afford the title compound as a mixture with by-product 391 (350 mg, 322fi/391 1:0.7).

Rf: 0.63 (Pent/Et2O 95:5); ¹H NMR: (500 MHz; CDCl₃) δ (ppm) 8.69-8.67 (m, 1H, H-16), 7.87-7.85 (m, 1H, H-19), 7.78-7.73 (m, 2H, HAr), 7.49-7.40 (m, 3 H, HAr), 5.89 (dd, J = 15.9, 1.2 Hz, 1H, H-3), 5.70 (ddt, J = 17.0, 10.0, 7.1 Hz, 1H, H-12), 5.33 (dd, J = 15.9, 7.1 Hz, 1H, H-4), 5.03 (dq, J = 17.0, 1.2 Hz, 1H, H-13'), 4.95 (dq, J = 10.0, 1.2 Hz, 1H, H-13), 2.98 (ddt, J = 12.9, 7.4, 1.2 Hz, 1 H, H-11), 2.84 (ddt, J = 12.9, 7.1, 1.2 Hz, 1H, H-11), 2.06-2.01 (m, 1H, H-5), 1.97 (s, 3H, H-1), 1.83-1.57 (m, 12H, HCy), 1.31-0.87 (m, 16H, HCy, H₂O); ¹³C NMR: (100 MHz, CDCl₃, δ (ppm) 143.5 (C-15), 139.3 (C₆H₄), 136.1 (C-4), 134.4 (C-12), 133.7 (C-3), 133.5 (C₆H₄), 131.4 (C₆H₄), 128.8/128.7 (C-19), 128.5/128.4 (C-16), 127.1 (C₆H₄), 125.7/125.6/125.5/124.1 (C₆H₄), 116.9 (C-13), 54.9 (C-2), 42.6 (Cy), 40.8 (C-5), 33.4 (C-11), 33.0 (Cy), 30.2 (C-1), 26.5/26.4/26.3/26.1/26.0 (Cy).

The equivalent enantioenriched sulfide (R)-(E)-allyl(4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl)sulfane (R)-322fi (322fi/391 1:0.5) was tentatively prepared from (R)-(E)-4-cyclohexyl-2-(naphthalen-1-yl)but-3-ene-2-thiol (R)-319fi (294 mg, 0.99 mmol) following general procedure Q (warming to 0 °C).
322fk: $(E)$-tert-Butyl 6-(2-(allylthio)-4-cyclohexylbut-3-en-2-yl)-1H-indole-1-carboxylate.

General procedure Q was followed using $(E)$-tert-butyl 6-(4-cyclohexyl-2-mercaptobut-3-en-2-yl)-1H-indole-1-carboxylate 319fk (138 mg, 0.36 mmol) to afford the title compound as a colourless oil (81 mg, 53%).

Rf: 0.72 (Pent/Et2O 95:5); $^1$H NMR: (400 MHz; CDCl3) δ (ppm) 8.33 (bs, 1H, H-15), 7.60 (bd, J = 3.6 Hz, 1H, H-17), 7.49 (d, J = 8.3 Hz, 1H, H-20), 7.45 (dd, J = 8.3, 1.6 Hz, 1H, H-21), 6.53 (dd, J = 3.6, 0.6 Hz, 1H, H-18), 5.86 (dd, J = 15.7, 1.1 Hz, 1H, H-3, 5.79 (ddt, J = 17.0, 10.0, 7.1 Hz, 1H, H-12), 5.54 (dd, J = 15.7, 7.0 Hz, 1H, H-4), 5.10 (dq, J = 17.0, 1.5 Hz, 1H, H-13’), 5.00 (bddd, J = 10.0, 1.5 Hz, 1H, H-13), 3.02 (d, J = 7.1 Hz, 2H, H-11), 2.11-2.03 (m, 1H, H-5), 1.82 (s, 3H, H-1), 1.79-1.64 (m, 4H, H-6, H-7, H-9, H-10), 1.69 (s, 9H, H-24, H-25, H-26), 1.35-1.08 (m, 6H, H-6’, H-7’, H-8, H-8’, H-9’, H-10’); $^{13}$C NMR: (100 MHz, CDCl3) δ (ppm) 149.8 (C-22), 141.6 (C-16), 135.5 (C-4), 134.8 (C-12), 132.9 (C-3), 129.2 (C-19), 126.4 (C-17), 122.4 (C-21), 120.4 (C-20), 116.8 (C-13), 113.7 (C-15), 106.9 (C-18), 83.6 (C-23), 54.1 (C-2), 40.8 (C-5), 33.6 (C-11), 33.4/33.2 (C-6, C-10), 28.2 (C-1), 26.1/26.0 (C-7, C-8, C-9); IR: $\nu_{\max}$(film)/cm$^{-1}$ 1734 (C=O), 1369 (C=N-Ar), 1341, 1155 (C-O ester), 1129; GC-MS: 253.2 (M-SC$_3$H$_5$-(CO)OC$_4$H$_9$), 27.1 min; HRMS: found 253.1837, [M]$^+$ requires 253.1825.

324a: 2-Methyl-2-(p-tolyl)-2,5-dihydrothiophene.

General procedure R was followed using $(E)$-allyl(4-cyclohexyl-2-(p-tolyl)but-3-en-2-yl)sulfane 322fa (100 mg, 0.33 mmol) and 407 to afford the title compound as a pale yellow oil (55 mg, 87%).
Rf: 0.57 (Pet/EtOAc 95:5); \textsuperscript{1}H NMR: (400 MHz; CDCl\textsubscript{3}) \(\delta\) (ppm) 7.31 (d, \(J = 8.1\) Hz, 2H, H-9, H-11), 7.12 (d, \(J = 8.1\) Hz, 2H, H-8, H-12), 5.89 (dt, \(J = 6.2\), 2.3 Hz, 1H, H-4), 5.84 (dt, \(J = 6.2\), 2.2 Hz, 1H, H-3), 3.91 (t, \(J = 2.3\) Hz, 2H, H-5), 2.32 (s, 3H, H-13), 1.90 (s, 3H, H-6); \textsuperscript{13}C NMR: (100 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 144.6 (C-10), 138.8 (C-3), 136.2 (C-7), 128.9 (C-8, C-12), 126.2 (C-4), 125.8 (C-9, C-11), 64.8 (C-2), 39.6 (C-5), 31.0 (C-6), 20.9 (C-13); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1510 (C=C), 1449 (C=C Ar), 814, 750, 719; GC-MS: 190.1 (M) 11.3 min; HRMS: found 190.0816, [M\(^+\)] requires 190.0811.

The equivalent enantioenriched 2,5-dihydrothiophene (\(R\))-2-methyl-2-(\(p\)-tolyl)-2,5-dihydrothiophene (\(R\))-\textbf{324a} (14:86 e.r., 54 mg, 91%) was prepared from (\(R\))-allyl(4-cyclohexyl-2-(\(p\)-tolyl)but-3-en-2-yl)sulfane (\(R\))-\textbf{322fa} (93 mg, 0.31 mmol) following general procedure R (404).

\([\alpha]_{D}^{24}\): +9.6 (c 1.00, CHCl\textsubscript{3}); HPLC: (\(R\),\(R\))-Whelk-01, Hexane/i-PrOH 99:1, 0.5 mL/min, 28 °C, minor 9.7 min, major 10.3 min (214.4 nm).

\textbf{324b}: 2-(3-Methoxyphenyl)-2-methyl-2,5-dihydrothiophene.

General procedure R was followed using (\(E\))-allyl(4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl)sulfane \textbf{322fe} (100 mg, 0.32 mmol) and \textbf{407} to afford the title compound as a pale yellow oil (53 mg, 82%).

Rf: 0.72 (Pent/Et\textsubscript{2}O 95:5); \textsuperscript{1}H NMR: (500 MHz; CDCl\textsubscript{3}) \(\delta\) (ppm) 7.24 (t, \(J = 8.0\) Hz, 1H, H-11), 7.01 (ddd, \(J = 8.0\), 1.6, 0.8 Hz, 1H, H-12), 6.98 (t, \(J = 2.2\) Hz, 1H, H-8), 6.75 (ddd, \(J = 8.0\), 2.2, 0.8 Hz, 1H, H-10), 5.90 (dt, \(J = 6.2\), 2.5 Hz, 1H, H-3), 5.86 (dt, \(J = 6.2\), 2.2 Hz, 1H, H-4), 3.91 (t, \(J = 2.2\) Hz, 2H, H-5), 3.81 (s, 3H, H-13), 1.90 (s, 3H, H-6); \textsuperscript{13}C NMR: (125 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 159.5 (C-9), 149.2 (C-7), 138.5 (C-4), 129.3 (C-11), 126.6 (C-3), 118.3 (C-12), 112.3 (C-8), 111.5 (C-10), 64.9 (C-2), 55.2 (C-13), 39.6 (C-5), 31.0 (C-6); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1581 (C=C), 1485 (C=C\textsubscript{Ar}), 1431 (C=C\textsubscript{Ar}), 1256 (C\textsubscript{Ar}-O), 1040, 694; GC-MS: 206.1 (M), 12.0 min; HRMS: found 206.0753, [M\(^+\)] requires 206.0760.

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The equivalent enantioenriched 2,5-dihydrothiophene (S)-2-methyl-2-(3-methoxyphenyl)-2,5-dihydrothiophene (S)-324b (94:6 e.r., 66 mg, 94%) was prepared from (S)-allyl(4-cyclohexyl-2-(3-methoxyphenyl)but-3-en-2-yl)sulfane (S)-322fe (108 mg, 0.34 mmol) following general procedure R (404).

$[\alpha]_D^{24}$: +9.8 (c 1.00, CDCl$_3$); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 99:1, 0.5 mL/min, 28 °C, major 14.8 min, minor 16.1 min (214.4 nm).

324c: 2-(3-Chlorophenyl)-2-propyl-2,5-dihydrothiophene.

General procedure R was followed using allyl(3-(3-chlorophenyl)hex-1-en-3-yl)sulfane 322be (39 mg, 0.15 mmol) and 407 to afford the title compound as a yellow oil (27 mg, 77%).

Rf: 0.81 (Pent/Et$_2$O 95:5); $^1$H NMR: (500 MHz; CDCl$_3$) δ (ppm) 7.38 (t, $J = 1.9$ Hz, 1H, H-10), 7.28 (dt, $J = 7.8$, 1.4 Hz, 1H, H-12), 7.24 (t, $J = 7.8$ Hz, 1H, H-13), 7.17 (ddd, $J = 7.8$, 1.9, 1.4 Hz, 1H, H-14), 5.94 (dt, $J = 6.3$, 2.5 Hz, 1H, H-4), 5.87 (dt, $J = 6.3$, 2.2 Hz, 1H, H-3), 3.82 (q, $J = 2.5$ Hz, 2H, H-5), 2.07 (sym. m, 2H, H-6), 1.28-1.20 (m, 1H, H-7), 0.92 (t, $J = 7.3$ Hz, 3H, H-8), 1.49-1.41 (m, 1H, H-7'); $^{13}$C NMR: (125 MHz, CDCl$_3$) δ (ppm) 149.3 (C-9), 135.7 (C-3), 134.2 (C-11), 129.5 (C-13), 127.9 (C-4), 126.6 (C-14), 126.5 (C-10), 124.3 (C-12), 69.9 (C-2), 45.7 (C-6), 39.3 (C-5), 19.0 (C-7), 14.2 (C-8); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 1592 (C=C), 1568 (C=C$_{Ar}$), 1464 (C=C$_{Ar}$), 1236, 1081, 871, 782, 742, 689 (C-Cl); GC-MS: $m/z$ 238.1 [M]$^+$, 12.6 min; HRMS: found 238.0582, [M]$^+$ requires 238.0578.

The equivalent enantioenriched 2,5-dihydrothiophene (R)-2-(3-chlorophenyl)-2-propyl-2,5-dihydrothiophene (R)-324c (8:92 e.r., 5 mg, 31%) was prepared from (R)-allyl(3-(3-chlorophenyl)hex-1-en-3-yl)sulfane (R)-322be (18 mg, 0.07 mmol) following general procedure R (407).

$[\alpha]_D^{24}$: -43.2 (c 0.50, CDCl$_3$); HPLC: Chiralcel OD-H, Hexane/i-PrOH 99:1, 0.2 mL/min, 28 °C, major 22.3 min, minor 23.7 min (214.4 nm, 254.4 nm).
324d: 2-(3-Fluorophenyl)-2-methyl-2,5-dihydrothiophene.

General procedure R (CH₂Cl₂, reflux, 24 h then DCE, 80 °C, 42 h) was followed using allyl(2-(3-fluorophenyl)but-3-en-2-y1)sulfane 322ah (80 mg, 0.36 mmol) and 407 (2x5 mol%) to afford the title compound as a yellow oil (49 mg, 70%).

Rᶠ: 0.71 (Pent/Et₂O 95:5); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.26 (t, J = 8.1 Hz, 1H, H-11), 7.19 (ddd, J = 8.1, 1.7, 1.1 Hz, 1H, H-12), 7.12 (dt, J = 10.7, 2.1 Hz, 1H, H-10), 6.89 (tdd, J = 8.1, 2.5, 1.0 Hz, 1H, H-8), 5.93 (dt, J = 6.2, 2.5 Hz, 1H, H-3), 5.83 (dt, J = 6.2, 2.3 Hz, 1H, H-4), 3.92 (t, J = 2.3 Hz, 2H, H-5), 1.90 (s, 3H, H-6); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 164.0/161.5 (C-9), 150.3/150.2 (C-7), 138.1 (C-4), 129.7/129.6 (C-11), 127.0 (C-3), 121.5 (C-12), 113.5/113.4 (C-8), 113.3/113.1 (C-10), 64.6/64.5 (C-2), 39.7 (C-5), 30.8 (C-6); IR: νₘₐₓ(film)/cm⁻¹ 1587 (C=C), 1485 (C=C₆Ar), 1436 (C=C₆Ar), 1251 (C-F), 691; GC-MS: m/z 194.1 [M⁺] 10.8 min; HRMS: found 194.0552, [M⁺] requires 194.0560.

The equivalent enantioenriched 2,5-dihydrothiophene (R)-2-methyl-2-(3-fluorophenyl)-2,5-dihydrothiophene (R)-324d (14:86 e.r., 20 mg, 57%) was prepared from (R)-allyl(2-(3-fluorophenyl)but-3-en-2-y1)sulfane (R)-322ah (40 mg, 0.18 mmol) following general procedure R (404).

[α]D²⁴: -13.4 (c 1.00, CDCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 99:1, 0.2 mL/min, 28 °C, minor 23.9 min, major 24.9 min (214.4 nm, 254.4 nm).

324e: 2-(2-Methoxyphenyl)-2-methyl-2,5-dihydrothiophene.

General procedure R was followed using (E)-allyl(4-cyclohexyl-2-(2-methoxyphenyl)but-3-en-2-y1)sulfane 322fa (100 mg, 0.31 mmol) and 407 to afford the title compound as a pale yellow oil (59 mg, 91%).
Rf: 0.51 (Pent/Et<sub>2</sub>O 95:5); <sup>1</sup>H NMR: (400 MHz; CDCl<sub>3</sub>) δ (ppm) 7.25-7.18 (m, 2H, H-9, H-11), 6.91 (dd, J = 8.2, 1.0 Hz, 1H, H-12), 6.87 (td, J = 7.5, 1.2 Hz, 1H, H-10), 6.16 (dt, J = 6.4, 2.3 Hz, 1H, H-3), 5.90 (dt, J = 6.4, 2.6 Hz, 1H, H-4), 3.91 (s, 3H, H-13), 3.81 (ddd, J = 14.8, 2.6, 2.3 Hz, 1H, H-5), 3.73 (dt, J = 14.8, 2.4 Hz, 1H, H-5), 1.88 (s, 3H, H-6); <sup>13</sup>C NMR: (100 MHz, CDCl<sub>3</sub>) δ (ppm) 156.8 (C-8), 137.2 (C-3), 136.4 (C-7), 127.8 (C-9 or C-11), 126.4 (C-4), 125.1 (C-11 or C-9), 120.2 (C-10), 111.8 (C-12), 126.4 (C-2), 55.4 (C-13), 38.7 (C-5), 31.4 (C-6); IR: ν<sub>max</sub>(film)/cm<sup>-1</sup> 1488 (C=C Ar), 1434 (C=C Ar), 1236 (C=Ar-O), 1025, 751; GC-MS: 206.1 (M), 11.8 min; HRMS: found 206.0759, [M]+ requires 206.0760.

The equivalent enantioenriched 2,5-dihydrothiophene (S)-2-methyl-2-(2-methoxyphenyl)-2,5-dihydrothiophene (S)-324e (92:8 e.r., 55 mg, 90%) was prepared from (S)-allyl(4-cyclohexyl-2-(methoxyphenyl)but-3-en-2-yl)sulfane (S)-322fh (93 mg, 0.29 mmol) following general procedure R (407).

[a]<sup>24</sup>: +173.2 (c 1.00, CDCl<sub>3</sub); HPLC: Chiralpak IB, Hexane/i-PrOH 99:1, 0.5 mL/min, 28 °C, minor 9.5 min, major 10.0 min (214.4 nm, 254.4 nm).

324f: 2-Methyl-2-(naphthalen-1-yl)-2,5-dihydrothiophene.

General procedure R was followed using (E)-allyl(4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl)sulfane 322fi (200 mg, 0.59 mmol, as a 1:0.7 mixture with by-product 391) and 404 to afford the title compound as a mixture with 391 (324f/391 1:0.6).

Rf: 0.41/0.62 (Pent/Et<sub>2</sub>O 95:5); <sup>1</sup>H NMR: (500 MHz; CDCl<sub>3</sub>) δ (ppm) 8.36 (d, J = 8.4 Hz, 1H, H-9), 7.87 (bdd, J = 8.1, 1.4 Hz, 1H, H-12), 7.74 (d, J = 8.1 Hz, 1H, H-14), 7.56 (td, J = 7.0, 1.4 Hz, 1H, H<sub>Ar</sub>), 7.51-7.41 (m, 6H, H-10, H-11, H-15, H<sub>Ar-391</sub>), 7.37 (d, J = 7.9 Hz, 1H, H-16), 6.28 (dt, J = 6.4, 2.2 Hz, 1H, H-3), 6.03 (dt, J = 6.4, 2.6 Hz, 1H, H-4), 3.94 (dt, J = 14.9, 2.4 Hz, 1H, H-5), 3.90 (dt, J = 14.9, 2.4 Hz, 1H, H-5), 2.10 (s, 3H, H-6).

The equivalent enantioenriched 2,5-dihydrothiophene (R)-2-Methyl-2-(naphthalen-1-yl)-2,5-dihydrothiophene (R)-324f (78:22 e.r., a mixture with (R)-322fi and 391 294
(324f/322f/391 1:0.6:1) was tentatively prepared from (R)-allyl(4-cyclohexyl-2-(naphthalen-1-yl)but-3-en-2-yl)sulfane (R)-322f (200 mg, 0.59 mmol, as a 1:0.5 mixture with by-product 391) following general procedure R (404).

**HPLC:** (R,R)-Whelk-01, Hexane/i-PrOH 99:1, 0.5 mL/min, 28 °C, minor 18.4 min, major 19.5 min (214 nm).

324g: tert-Butyl 6-(2-methyl-2,5-dihydrothiophen-2-yl)-1H-indole-1-carboxylate.

General procedure R was followed using (E)-tert-butyl 6-(2-(allylthio)-4-cyclohexylbut-3-en-2-yl)-1H-indole-1-carboxylate 322fk (70 mg, 0.16 mmol) and 407 to afford the title compound as a colourless oil (33 mg, 63%).

R: 0.56 (Pent/Et₂O 95:5); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 8.24 (s, 1H, H-11), 7.59 (d, J = 3.5 Hz, 1H, H-8), 7.50 (d, J = 8.3 Hz, 1H, H-14), 7.34 (dd, J = 8.3, 1.7 Hz, 1H, H-13), 6.52 (d, J = 3.5 Hz, 1H, H-12), 5.94 (s, 2H, H-3, H-4), 3.95 (2H, H-5), 2.00 (s, 3H, H-6), 1.69 (s, 9H, H-17, H-18, H-19); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 149.8 (C-15), 143.8 (C-9), 139.0 (C-3 or C-4), 135.0 (C-7), 129.1 (C-10), 126.3 (C-8), 126.2 (C-4 or C-3), 121.5 (C-13), 120.7 (C-14), 112.3 (C-11), 107.2 (C-12), 83.5 (C-16), 65.6 (C-2), 39.6 (C-5), 31.4 (C-6), 28.2 (C-17, C-18, C-19); IR: ν<sub>max</sub>(film)/cm⁻¹ 1729 (C=O), 1333 (C<sub>Ar</sub>=N), 1151 (C-O<sub>ester</sub>), 1129, 721; GC-MS: m/z 215.0 [M-C₅H₉O₂+H]⁺ 13.7 min; HRMS: found 315.1288, [M]+ requires 315.1288.

The equivalent enantioenriched 2,5-dihydrothiophene (R)-tert-Butyl 6-(2-methyl-2,5-dihydrothiophen-2-yl)-1H-indole-1-carboxylate (R)-324g (23:77 e.r.) was prepared from (R)-tert-butyl 6-(2-(allylthio)-4-cyclohexylbut-3-en-2-yl)-1H-indole-1-carboxylate (R)-322fk (33 mg, 0.08 mmol) following general procedure R (407).

[a]<sub>D</sub>⁰: -14.4 (c 0.125, CHCl₃); HPLC: (R,R)-Whelk-01, Hexane/i-PrOH 99:1, 0.5 mL/min, 28 °C, minor 30.9 min, major 39.9 min (214.4 nm, 254.4 nm).
326a: (S)-S-1-Phenylethyl methyl(vinyl)carbamothioate.

General procedure K (20 h) was followed using S-1-phenylethyl ethylcarbamothioate 379a (33 mg, 0.16 mmol) to afford the title compound as a yellow oil (34 mg, 97%).

**Rf**: 0.67 (Pet/EtOAc 8:2); **1H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.40-7.24 (m, 5H, H-8 to H-12), 6.94 (dd, J = 15.4, 8.6 Hz, 1H, H-5), 4.78 (q, J = 7.2 Hz, 1H, H-1), 4.44 (bd, J = 15.4 Hz, 1H, H-6'), 4.37 (d, J = 8.6 Hz, 1H, H-6), 3.09 (s, 3H, H-4), 1.72 (d, J = 7.2 Hz, 3H, H-2); **13C NMR**: (100 MHz, 50 °C, CDCl₃) δ (ppm) 167.4 (C-3), 142.6 (C-7), 133.0 (C-5), 128.6 (C-9, C-11), 127.6 (C-10), 127.3 (C-8, C-12), 93.5 (C-6), 44.6 (C-1), 29.7 (C-4), 22.7 (C-2); **IR**: νmax(film)/cm⁻¹ 1662 (C=O), 1626 (C=C), 1302; **MS**: m/z (ES⁺) 222 [M+H]⁺ (25%), 244 [M+Na]⁺ (100%); **HRMS**: found 222.0944, [M+H]⁺ requires 222.0948.

The equivalent enantiopure (S)-S-1-Phenylethyl methyl(vinyl)carbamothioate (S)-326a (98:2 e.r., 673 mg, 100%) was prepared from (S)-S-1-phenylethyl ethylcarbamothioate (S)-379a (631 mg, 3.04 mmol) following general procedure K (24 h).

[α]D²⁰: -118.4 (c 1.7, CHCl₃); **HPLC**: (R,R)-Whelk-01, Hex/i-PrOH 90:10, 1.0 mL/min, major 4.7 min, minor 5.8 min (214.4nm, 254.4 nm).

326b: S-1-(4-Chlorophenyl)ethyl methyl(vinyl)carbamothioate.

General procedure K (22 h) was followed using S-1-(4-chlorophenyl)ethyl vinylcarbamothioate 379b (847 mg, 3.50 mmol) to afford the title compound as a pale colourless liquid (337 mg, 38%).

**Rf**: 0.74 (Pet/EtOAc 8:2); **1H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.31-7.23 (m, 4H, H-8, H-9, H-11, H-12), 6.88 (bs, 1H, H-5), 4.70 (q, J = 7.2 Hz, 1H, H-1), 4.42 (d, J = 15.0 Hz, 1H, H-6'), 4.35 (d, J = 9.0 Hz, 1H, H-6), 3.05 (bs, 3H, H-4), 1.64 (d, J = 7.2 Hz, 3H, H-2); **13C NMR**: (100
MHz, CDCl₃) δ (ppm) 167.0 (C-3), 141.5 (C-10), 133.0 (C-7), 132.7 (C-5), 128.7/128.6 (C-8, C-9, C-11, C-12), 93.6 (C-6), 43.8 (C-1), 30.9 (C-4), 22.4 (C-2); IR: ν max (film)/cm⁻¹ 1656 (C=O), 1624 (C=C), 1300, 1077, 827 (C-Cl), 678; MS: m/z (ES⁺) 278 [M+Na]⁺ (60%); HRMS: found 278.0378, [M+Na]⁺ requires 278.0377.

328d: (E)-4-methylpent-2-en-1-ol.¹¹²

To a solution of (E)-methyl 4-methylpent-2-enoate (100 mg, 0.78 mmol, 1.0 eq) in Et₂O (4.0 mL) at 0 °C was added DiBAl-H (1.0 M in hexane, 3.0 eq) dropwise. The reaction was stirred at rt for 18 h, then a Rochelle’s salt solution (3.0 mL) was added. The reaction was stirred until clear. Water and Et₂O were added and the layers were separated. The aqueous layer was extracted with Et₂O (x3), and the combined organic fractions were washed with brine (x2), dried over MgSO₄, filtered and concentrated. Purification by column chromatography (Pet/EtOAc 8:2) afforded the title compound as a pale yellow oil (65 mg, 83%).

Rf: 0.27 (Pet/EtOAC 8:2); ¹H NMR: (400 MHz) δ (ppm) 5.66 (dd, J = 15.2, 6.4 Hz, 1H, H-3), 5.57 (dtd, J = 15.2, 5.6, 0.8 Hz, 1H, H-2), 4.08 (d, J = 5.2 Hz, 2H, H-1), 2.30 (oct, J = 6.4 Hz, 1H, H-4), 1.44 (bs, 1H, H-7), 0.99 (d, J = 6.4 Hz, 6H, H-5, H-6).

Matches published data.¹¹²

(R)-328f: (R,E)-1-Cyclohexylbut-2-en-1-ol.¹³³

To a solution of 1-cyclohexyl-2-buten-1-ol (±)-328f (2.0 g, 13.0 mmol, 1.0 eq) in CH₂Cl₂ (50.0 mL) at rt, was added (+)-diisopropyl tartrate ((+-DIPT) (0.15 eq) followed by powdered 4 Å molecular sieves (500 mg, 20-30% w/w based on 328f, previously dried under reduced pressure at 160 °C overnight). The reaction was cooled to -20 °C (internal temperature monitored). Titanium(IV) isopropoxide (Ti(Oi-Pr)₄) (0.10 eq) was added and the reaction was stirred at -20 °C for 20 to 30 min. Anhydrous tert-butyl hydroperoxide
(TBHP) (5.5 M in decane, 0.6 eq) was added dropwise, maintaining the internal temperature between -22 and -20 °C. The reaction was stirred at -20 °C for 15 h before an aliquot (0.1 mL) was removed and quenched with 2.0 mL of an aqueous solution of FeSO$_4$$\cdot$7H$_2$O and citric acid monohydrate (33 g of FeSO$_4$$\cdot$7H$_2$O, 11 g of citric acid monohydrate, 100 mL of distilled water). $^1$H NMR spectrum of the aliquot showed an allylic alcohol/epoxide ratio of 1:1.3. The reaction was quenched at -20 °C by adding the aforementioned ferrous aqueous solution (40 mL), warming the reaction to rt and stirring vigorously until two clear phases appeared (30 min). The reaction mixture was extracted with CH$_2$Cl$_2$ ($\times$2). The combined organic layers were concentrated to the original volume and washed with 30% NaOH in brine (13 mL, 1.0 mL/mmol of substrate). The mixture was extracted with CH$_2$Cl$_2$ ($\times$3), the combined organic layers were washed with brine ($\times$2), dried over anhydrous MgSO$_4$, filtered and concentrated. Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5 to 85:15) afforded the title compound as a colourless oil (99:1 e.r., 645 mg, 65% conversion based on alcohol/epoxide ratio, 92% isolated yield based on conversion).

$^{[\alpha]}$D$^{20}$: -1.0 (c 1.20, CHCl$_3$), lit$^{133}$ $^{[\alpha]}$D$^{25}$: -13.33, (c 2.76, EtOH); GC: Astec Chiraldex$^{\text{TM}}$ G-TA, method: 50-80 °C (5 °C/min), 80-102 °C (1 °C/min), 102 °C (5 min hold), 102-110 °C (1 °C/min), 110-180 °C (5 °C/min), major 43.91 min, minor 44.67 min [(±)$^{328}$f: 43.94/44.56 min].

R$_f$: 0.58 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 5.62 (dq, $J$ = 15.3, 6.4 Hz, 1H, H-3), 5.47 (ddq, $J$ = 15.3, 7.2, 1.4 Hz, 1H, H-2), 3.75 (t, $J$ = 7.2 Hz, 1H, H-1), 1.87-1.83 (m, 1H, H-6), 1.77-1.63 (m, 4H, H-7, H-8, H-10, H-11), 1.70 (dd, $J$ = 6.4, 1.4 Hz, 3H, H-4), 1.43-0.86 (m, 7H, H-7’, H-8’, H-9, H-10’, H-11’, H-5).

Matches published data.$^{133}$

General procedure G was followed using \((E)\)-1-cyclohexylbut-2-en-1-one 358 (1.21 g, 7.97 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 95:5) afforded the title compound as a pale yellow oil (12:88 e.r., 763 mg, 62%).

**GC:** Astec Chiraldex\textsuperscript{TM} G-TA, method: 50-80 °C (5 °C/min), 80-102 °C (1 °C/min), 102 °C (5 min hold), 102-110 °C (1 °C/min), 110-180 °C (5 °C/min), minor 44.03 min, major 44.53 min [(\(\pm\))-328f: 43.94/44.56 min].

*For other data, see (R)-328f.*

\((E)\)-328g: \((E)\)-1-Phenylbut-2-en-1-ol.

By the method reported by Denmark and co-workers.\textsuperscript{116b}

To a solution of Red-Al\textsuperscript{®} (sodium bis(2-methoxyethoxy)aluminum hydride solution ≥65%w/w in toluene, 1.6 eq, 3.2 eq of hydride) in Et\(_2\)O (1.5 mL) at 0 °C, was added a solution of 334a (100 mg, 0.68 mmol, 1.0 eq) in Et\(_2\)O (2.0 mL) dropwise. The reaction was stirred at 0 °C for 10 min, warmed to rt and stirred for 3 h. Aqueous H\(_2\)SO\(_4\) (1.0 M, 2.0 mL) was carefully added, followed by water (10 mL) and the layers were separated. The aqueous layer was extracted with Et\(_2\)O (x3). The combined organic fractions were washed with water and brine, dried over MgSO\(_4\), filtered and concentrated. Purification by column chromatography (Pet 100%, Pet/EtOAc 97:3 to 85:15) afforded the title compound as a pale yellow oil (27 mg, 27%).

*For NMR data, see 328g and references.*\textsuperscript{117,169}
Magnesium turnings (2.2 eq) were covered with THF (5.0 mL) and a few I₂ crystals were added. A solution of freshly distilled 1-bromoprop-1-ene (1.5 eq) in THF (20.0 mL) was added gradually: first one quarter rapidly and the reaction was stirred vigorously until reflux started and the initial brownish colour turned to grey, then the rest dropwise. The reaction was heated to reflux for 30 min and cooled to rt. A solution of benzaldehyde (2.87 mL, 28.27 mmol, 1.0 eq) in THF (15.0 mL) was added dropwise. The reaction was heated to reflux for 3 h and cooled to rt. Saturated aqueous NH₄Cl was added slowly and the layers were separated. The aqueous layer was extracted with EtOAc (x3). The combined organic layers were washed with brine (x2). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2 to 9:1) afforded the title compound as a yellow oil (3.04 g, 72%, E/Z 1:1.3).

Rᵣ: 0.50 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.42-7.33 (m, 4H⁺4H, H-7, H-8, H-10, H-11), 7.30-7.25 (m, 1H⁺1H, H-9), 5.78 (dqd, J = 15.3, 6.1, 0.6 Hz, 1H, H-3), 5.69 (ddq, J = 15.3, 6.4, 1.0 Hz, 1H, H-2), 5.66 (d, J = 6.6 Hz, 1H, H-2), 5.68-5.62 (m, 1H, H-3), 5.59 (bd, J = 6.6 Hz, 1H, H-1) 5.16 (bd, J = 6.4 Hz, 1H, H-1), 1.85 (bs, 1H⁺1H, H-5), 1.80 (d, J = 5.2 Hz, 3H, H-4), 1.73 (d, J = 6.1 Hz, 3H, H-4); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 143.7 (C⁻6), 143.3 (C⁻6), 133.6 (C⁻2), 132.9 (C⁻2), 128.5/128.4 (C⁻8, C⁻8, C⁻10, C⁻10), 127.5 (C⁻9, C⁻9), 127.4 (C⁻3), 126.4 (C⁻3), 126.1/125.9 (C⁻7, C⁻7, C⁻11, C⁻11), 75.2 (C⁻1), 69.4 (C⁻1), 17.7 (C⁻4), 13.3 (C⁻4).

Matches published data: (E)-328g,¹¹⁷ (Z)-328g.¹¹⁹,¹⁶⁹
(R)-328g: (R,E)-1-Phenylbut-2-en-1-ol.

General procedure G was followed using (E)-1-Phenylbut-2-en-1-one 359 (282 mg, 1.93 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 97:3 to 85:15) afforded the title compound as a pale yellow liquid (98:2 e.r., 180 mg, 63%).

\([\alpha]_D^{23}: +14.4 \text{ (c 1.00, CHCl}_3, \text{ determined for 90:10 e.r.); HPLC: Chiralpak IA, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, major 13.2 min, minor 14.0 min (214 nm).}\)

For NMR data, see 328g.

329m: N-Methyl-1H-indol-6-amine.

To a solution of benzyl 1H-indol-6-ylcarbamate 329n (1.19 g, 4.47 mmol, 1.0 eq) in THF (18.0 mL) at 0 °C was added LiAlH₄ (1.0 M in Et₂O, 1.5 eq) dropwise. The reaction was warmed to rt and heated to reflux for 4 h. At rt, water (0.5 mL) was carefully added followed by NaOH 15% (20.0 mL) and a solution of Rochelle’s salt (10.0 mL). The layers were separated and the aqueous layer was extracted with EtOAc (x3). The combined organic fractions were washed with brine, dried over MgSO₄, filtered and concentrated. Purification by column chromatography (Pet/EtOAc 9:1 to 2:8) afforded the title compound as a brown oil (499 mg, 76%).

IR: 0.16 (Pet/EtOAc 1:1); \(^1\)H NMR: (400 MHz; CDCl₃) \(\delta\) (ppm) 7.89 (bs, 1H, H-1), 7.42 (d, \(J = 8.4\) Hz, 1H, H-5), 7.00 (dd, \(J = 3.1, 2.4\) Hz, 1H, H-2), 6.58 (bs, 1H, H-8), 6.54 (dd, \(J = 8.4, 2.1\) Hz, 1H, H-6), 6.43 (ddd, \(J = 3.0, 2.1, 0.8\) Hz, 1H, H-3), 3.67 (bs, 1H, H-10), 2.88 (s, 3H, H-11); \(^13\)C NMR: (100 MHz, CDCl₃) \(\delta\) (ppm) 145.9 (C-7), 137.4 (C-9), 121.5 (C-2), 121.1 (C-5), 120.2 (C-4), 109.9 (C-6), 102.4 (C-3), 92.5 (C-8), 31.5 (C-11); MS: \(m/z\) (ES\(^+\)) 147 [M+H]\(^+\) (90%); HRMS: found 147.0922, [M+H]\(^+\) requires 147.0917.
To a solution of 1H-indol-6-amine (500 mg, 3.78 mmol, 1.0 eq) and pyridine (2.6 eq) in CH2Cl2 (4.0 mL) at 0 °C was added benzyl chloroformate (2.4 eq) dropwise. The reaction was warmed to rt and stirred for 24 h. Saturated aqueous NaHCO3 (10 mL) was added and the layers were separated. The aqueous layer was extracted with CH2Cl2 (x3). The combined organic layers were dried over MgSO4, filtered and concentrated. Purification by column chromatography (Pet/EtOAc 95:5 to 7:3) afforded the title compound as a beige/yellow solid (968 mg, 96%).

Rf: 0.28 (Pet/EtOAc 8:2); mp: 133-135 °C; 1H NMR: (400 MHz; CDCl3) δ (ppm) 8.13 (bs, 1H, H-1), 7.84 (bs, 1H, H-8), 7.52 (d, J = 8.4 Hz, 1H, H-5), 7.44-7.32 (m, 5H, H-14, H-15, H-16, H-17, H-18), 7.16 (dd, J = 3.2, 2.4 Hz, 1H, H-2), 6.81 (dd, J = 8.4, 1.9 Hz, 1H, H-6), 6.72 (bs, 1H, H-10), 6.49 (ddd, J = 3.2, 2.0, 0.9 Hz, 1H, H-3), 5.22 (s, 1H, H-12); 13C NMR: (100 MHz, CDCl3) δ (ppm) 153.6 (C-11), 136.2/136.1 (C-9, C-13), 132.6 (C7), 128.6/128.3 (C-14, C-15, C-16, C-17, C-18), 124.3 (C-4), 124.1 (C-2), 120.8 (C-5), 112.6 (C-6), 102.8 (C-3), 101.5 (C-8), 66.9 (C-12); IR: νmax(film)/cm⁻¹ 3384 (NH), 3331 (NH), 1700 (C=O), 1527 (C=CN), 1235, 1053, 720, 696; MS: m/z (ES⁺) 289 [M+Na]+ (100%); HRMS: found 267.1120, [M+H]+ requires 267.1128.

Note: for the following carbamothioic chlorides 331, some analytical data such as melting points, is available and can be obtained through the references given (CAS numbers). To the best of our knowledge, no spectroscopic data for compounds 331 has been reported so far, except for 331a. Herein this thesis is given only 1H (and 13C NMR) data as these compounds were used as crude.
**331a**: Methyl(phenyl)carbamothioic chloride.\(^{170}\)

![Methyl(phenyl)carbamothioic chloride](image)

General procedure C1 was followed using \(N\)-methylaniline (2.0 g, 18.7 mmol). The title compound was obtained as a brown/orange oil (3.47 g, 100%).

\[ R_f: 0.50 \text{ (Pet/EtOAc 8:2)}; \]

\[^1\H NMR\]: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.48-7.38 (m, 3H, H-5, H-6, H-7), 7.24 (bd, \(J = 7.1\) Hz, 2H, H-4, H-8), 3.75 (s, 3H, H-2).

*Matches published data.*\(^{171}\)

**331b**: Methyl(p-tolyl)carbamothioic chloride.\(^{172}\)

![Methyl(p-tolyl)carbamothioic chloride](image)

General procedure C1 was followed using \(N\)-methyl-\(p\)-toluidine (200 mg, 1.65 mmol). The title compound was obtained as a brown/orange oil (330 mg, 100%).

\[ R_f: 0.76 \text{ (Pet/EtOAc 8:2)}; \]

\[^1\H NMR\]: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.25 (d, \(J = 8.3\) Hz, 2H, H-4, H-8), 7.10 (d, \(J = 8.3\) Hz, 2H, H-5, H-7), 3.73 (s, 3H, H-2), 2.39 (s, 3H, H-9); \[^{13}\C NMR\]: (100 MHz; CDCl\(_3\)) \(\delta\) (ppm) 175.6 (C-1), 143.5 (C-3), 138.9 (C-6), 130.2 (C-4, C-8), 125.2 (C-5, C-7), 47.2 (C-2), 21.2 (C-9).

**331d**: (4-Chlorophenyl)(methyl)carbamothioic chloride.\(^{173}\)

![Methyl(phenyl)carbamothioic chloride](image)

General procedure C1 was followed using 4-chloro-\(N\)-methylaniline (200 mg, 1.41 mmol). The title compound was obtained as an orange oil (310 mg, 100%).
Rf: 0.74 (Pet/EtOAc 8:2); $^1$H NMR: (300 MHz; CDCl$_3$) δ (ppm) 7.43 (d, $J = 8.6$ Hz, 2H, H-4, H-8), 7.18 (d, $J = 8.6$ Hz, 2H, H-5, H-7), 3.72 (s, 3H, H-2); $^{13}$C NMR: (100 MHz; CDCl$_3$) δ (ppm) 167.4 (C-1), 144.3 (C-3), 134.7 (C-6), 129.9 (C-4, C-8), 127.1 (C-5, C-7), 47.1 (C-2).

**331e:** (4-Fluorophenyl)(methyl)carbamothioic chloride.$^{174}$

General procedure C1 was followed using 4-fluoro-N-methylaniline (200 mg, 1.60 mmol). The title compound was obtained as a beige solid (326 mg, 100%).

Rf: 0.69 (Pet/EtOAc 8:2); mp: 93-94 °C; $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.22 (dd, $J = 9.0$, 5.0 Hz, 2H, H-5, H-7), 7.14 (t, $J = 9.0$ Hz, 2H, H-4, H-8), 3.73 (s, 3H, H-2).

**331f:** 3-Methoxyphenyl(methyl)carbamothioic chloride.$^{175}$

General procedure C1 was followed using 3-methoxy-N-methylaniline (200 mg, 1.46 mmol). The title compound was obtained as a brown/orange oil (248 mg, 100%).

Rf: 0.62 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.35 (t, $J = 8.1$ Hz, 1H, H-7), 6.94 (dd, $J = 8.1$, 2.0 Hz, 1H, H-8), 6.81 (bd, $J = 7.1$ Hz, 1H, H-6), 6.75 (bt, $J = 2.0$ Hz, 1H, H-4), 3.83 (s, 3H, H-9), 3.73 (s, 3H, H-2); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 175.4 (C-1), 160.4 (C-5), 146.9 (C-3), 130.4 (C-7), 117.7 (C-6), 114.4 (C-8), 111.4 (C-4), 55.5 (C-9), 47.1 (C-2).
**331g:** 3-Chlorophenyl(methyl)carbamothioic chloride.\(^{176}\)

![Chemical Structure](image)

General procedure C1 was followed using 3-chloro-\(N\)-methylaniline (200 mg, 1.41 mmol). The title compound was obtained as an orange oil (313 mg, 100%).

**R**\(_f\): 0.72 (Pet/EtOAc 8:2); \(^1H\) NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.40 (bd, \(J = 5.0\) Hz, 2H, H-4,H-7), 7.27 (bs, 1H, H-6), 7.15 (bs, 1H, H-8), 3.72 (s, 3H, H-2).

**331h:** 3-Fluorophenyl(methyl)carbamothioic chloride.\(^{177}\)

![Chemical Structure](image)

General procedure C1 was followed using 3-fluoro-\(N\)-methylaniline (200 mg, 1.60 mmol). The title compound was obtained as a black oil (326 mg, 100%).

**R**\(_f\): 0.67 (Pet/EtOAc 8:2); \(^1H\) NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.43 (td, \(J = 8.1, 6.3\) Hz, 1H, H-7), 7.13 (dd, \(J = 8.1, 1.5\) Hz, 1H, H-6), 7.05 (d, \(J = 8.1\) Hz, 1H, H-4), 6.98 (bd, \(J = 8.1\) Hz, 1H, H-8), 3.73 (s, 3H, H-2).

**331i:** 2-Methoxyphenyl(methyl)carbamothioic chloride.

![Chemical Structure](image)

General procedure C1 was followed using 2-methoxy-\(N\)-methylaniline (200 mg, 1.46 mmol). The title compound was obtained as a brown solid (315 mg, 100%).

**R**\(_f\): 0.60 (Pet/EtOAc 8:2); mp: 62-64 °C; \(^1H\) NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 7.37 (ddd, \(J = 9.3, 7.6, 1.7\) Hz, 1H, H-7), 7.17 (dd, \(J = 8.2, 1.7\) Hz, 1H, H-5), 7.02-6.98 (m, 2H, H-6, H-8), 3.88 (s, 3H, H-9), 3.66 (s, 3H, H-2); \(^{13}C\) NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 176.7 (C-1), 153.4
(C-4), 134.5 (C-3), 130.3 (C-7), 127.0 (C-5), 120.8 (C-6), 112.1 (C-8), 55.8 (C-9), 45.8 (C-2);
**IR:** $v_{\text{max}}$(film)/cm$^{-1}$ 1497, 1475, 1378, 1260, 1107, 919, 753.

**331j:** Methyl(naphthalen-1-yl)carbamothioic chloride.$^{178}$

![Chemical structure of 331j]

General procedure C1 was followed using N-methylnaphtalen-1-amine$^{108}$ (212 mg, 1.35 mmol). The title compound was obtained as a brown paste (318 mg, 100%).

**Rf:** 0.67 (Pet/EtOAc 8:2); **$^1$H NMR:** (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.94 (t, $J = 8.6$ Hz, 1H, H$_{A_1}$), 7.71 (d, $J = 8.2$ Hz, 1H, H$_{A_2}$), 7.61 (m, 2H, H$_{Ar}$), 7.53 (m, 1H, H$_{A_1}$), 7.39 (dd, $J = 7.3$, 0.9 Hz, 1H, H$_{A_1}$), 3.85 (s, 3H, H-2).

**332aa:** O-But-2-enyl methyl(phenyl)carbamothioate.

![Chemical structure of 332aa]

General procedure C2 was followed using 331a (3.47 g, 18.7 mmol) and crotyl alcohol 328a. Purification by column chromatography (Pet/Et$_2$O 95:5 to 7:3) afforded the title compound as a pale yellow powder (2.80 g, 81% over 2 steps).

**Rf:** 0.70 (Pet/EtOAC 8:2); **$^1$H NMR:** (400 MHz; DMSO, 90 °C) $\delta$ (ppm) 7.42 (t, $J = 7.4$ Hz, 2H, H-9, H-11), 7.31 (t, $J = 7.4$ Hz, 1H, H-10), 7.24 (d, $J = 7.4$ Hz, 2H, H-8, H-12), 5.67 (m, 1H, H-2), 5.55 (m, 1H, H-3), 4.85 (d, $J = 6.0$ Hz, 2H, H-1), 3.52 (s, 3H, H-6), 1.64 (d, $J = 6.4$ Hz, 3H, H-4); **$^{13}$C NMR:** (100 MHz, DMSO, 90 °C) $\delta$ (ppm) 138.9 (C-5), 129.4 (C-7), 128.6 (C-8, C-12), 128.4 (C-3), 127.3 (C-10), 127.2 (C-9, C-11), 125.4 (C-2), 70.5 (C-1), 37.2 (C-6), 19.3 (C-4); **IR:** $v_{\text{max}}$(film)/cm$^{-1}$ 1490 (C=Ar), 1445, 1382, 1273 (C$_{Ar}$-N), 1199; **MS:** $m/z$ (ES$^+$) 244 [M+Na]$^+$ (100%); **HRMS:** found 244.0765, [M+Na]$^+$ requires 244.0767.
332ab: O-But-2-enyl methyl(p-tolyl)carbamothioate.

General procedure C2 was followed using 331b (406 mg, 2.03 mmol) and 328a to afford the title compound as a yellow solid (301 mg, 78% over 2 steps).

Rf: 0.71 (Pet/EtOAc 8:2); mp: 36-38 °C; 1H NMR: (400 MHz; CDCl3, rotamers) 7.19 (bs, 2H, H-8, H-12), 7.04 (bs, 2H, H-9, H-11), 5.87-5.51 (m, 2H, H-2, H-3), 4.94/4.87 (2 bs, 2H, H-1), 3.62/3.40 (2 bs, 3H, H-6), 2.37 (s, 3H, H-13), 1.76/1.65 (2 bs, 3H, H-4); IR: \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1509 (C=C Ar), 1443, 1379, 1272 (CAr-N), 1205, 1128, 955, 816, 716; MS: \( m/z \) (ES\(^+\)) 258 [M+Na]\(^+\) (100%).

332ad: O-But-2-enyl 4-chlorophenyl(methyl)carbamothioate.

General procedure C2 was followed using 331d (484 mg, 2.20 mmol) and 328a to afford the title compound as a yellow liquid (430 mg, 76% over 2 steps).

Rf: 0.62 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3, -20 °C, rotamers) \( \delta \) (ppm) 7.40/7.35 (d, \( J = 8.4 \) Hz, 2H, H-9, H-11), 7.22/7.09 (d, \( J = 8.4 \) Hz, 2H, H-8, H-12), 5.89/5.64 (dq, \( J = 15.2, 6.2 \) Hz, 1H, H-3), 5.73/5.47 (dt, \( J = 15.2, 6.2 \) Hz, 1H, H-2), 4.92/4.82 (d, \( J = 6.2 \) Hz, 2H, H-1), 3.61/3.40 (s, 3H, H-6), 1.77/1.64 (d, \( J = 6.2 \) Hz, 3H, H-4); 13C NMR: (100 MHz, CDCl3, -20 °C, rotamers) \( \delta \) (ppm) 189.1/188.0 (C-5), 144.3/141.5 (C-7), 133.2/132.6 (C-10), 132.2 /131.1 (C-3), 129.7/129.2 (C-9, C-11), 128.4/127.1 (C-8, C-12), 124.5/124.3 (C-2), 72.8/72.4 (C-1), 44.1/39.9 (C-6), 18.1/18.0 (C-4); IR: \( \nu_{\text{max}}(\text{film})/\text{cm}^{-1} \) 1489 (C=CAr), 1356, 1281 (CAr-N), 1184, 1088, 961, 839 (C-Cl); MS: \( m/z \) (ES\(^+\)) 278 [M+Na]\(^+\) (100%), 310 [M+Na+MeOH]\(^+\) (30%); HRMS: found 256.0553, [M+H]\(^+\) requires 256.0558.
**332ae: O-But-2-enyl 4-fluorophenyl(methyl)carbamothioate.**

![Chemical Structure]

General procedure C2 was followed using 331e (565 mg, 2.77 mmol) and 328a to afford the title compound as a yellow oil (524 mg, 79% over 2 steps).

R_f: 0.76 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃, -20 °C, rotamers) δ (ppm) 7.26-7.23/7.14-7.05 (m, 4H, H-8, H-9, H-11, H-12), 5.89/5.61 (dq, J = 15.2, 6.4 Hz, 1H, H-2), 4.92/4.82 (d, J = 6.5 Hz, 2H, H-1), 3.61/3.40 (s, 3H, H-6), 1.77/1.64 (d, J = 6.4 Hz, 3H, H-4); ¹³C NMR: (100 MHz, CDCl₃, -20 °C, rotamers) δ (ppm) 189.3/188.1 (C-5), 161.3 (d, J_{C,F} = 245.9 Hz, C-10)/161.1 (d, J_{C,F} = 245.1 Hz, C-10), 141.9/139.1 (d, J_{C,F} = 3.1 Hz, C-7), 132.2/130.9 (C-3), 128.8/127.4 (d, J_{C,F} = 8.6 Hz, C-8, C-12), 124.6/124.4 (C-2), 116.6/116.1 (d, J_{C,F} = 19.4 Hz, C-9, C-11), 72.8/72.2 (C-1), 44.3/40.1 (C-6), 18.1/18.0 (C-4); IR: ν_{max}(film)/cm⁻¹ 1506 (C=C Ar), 1445, 1347, 1220 (C-F), 1182, 1128, 962, 838; MS: m/z (ES⁺) 262 [M+Na]⁺ (100%), 294 [M+Na+MeOH]⁺ (50%); HRMS: found 262.0668, [M+Na]⁺ requires 262.0673.

**332af: O-But-2-enyl 3-methoxyphenyl(methyl)carbamothioate.**

![Chemical Structure]

General procedure C2 was followed using 331f (439 mg, 2.04 mmol) and 328a to afford the title compound as a yellow solid (358 mg, 70 % over 2 steps).

R_f: 0.69 (Pet/EtOAc 8:2); mp: 37-39 °C; ¹H NMR: (400 MHz; CDCl₃, -20 °C, rotamers) δ (ppm) 7.36-7.24 (m, 1H, H-11), 6.86-6.67 (m, 3H, H-8, H-10, H-12), 5.90-5.85/5.66-5.59 (m, 1H, H-3), 5.76-5.71/5.50-5.45 (m, 1H, H-2), 4.91/4.84 (bd, J = 4.7 Hz, 2H, H-1), 3.80/3.79 (s, 3H, H-13), 3.62/3.39 (s, 3H, H-6), 1.76/1.62 (d, J = 4.8 Hz, 3H, H-4); ¹³C NMR: (100 MHz, CDCl₃, -20 °C, rotamers) δ (ppm) 188.8/187.9 (C-5), 160.0/159.6 (C-9), 147.0/144.2 (C-7), 132.0/130.8 (C-3), 130.2/129.7 (C-8), 124.7/124.5 (C-2), 119.0/117.9 and 113.2/112.8 and 112.5/111.3 (C-10, C-11, C-12), 72.6/72.1 (C-1), 55.3 (C-13), 44.3/40.1 (C-6), 18.1/18.0 (C-4); IR: ν_{max}(film)/cm⁻¹ 1506 (C=C Ar), 1445, 1347, 1220 (C-F), 1182, 1128, 962, 838; MS: m/z (ES⁺) 262 [M+Na]⁺ (100%), 294 [M+Na+MeOH]⁺ (50%); HRMS: found 262.0668, [M+Na]⁺ requires 262.0673.
44.2/40.0 (C-6), 18.1/18.0 (C-4); **IR:** $\nu_{\text{max}}$(film)/cm$^{-1}$ 1604 (C=C), 1585 (C=Ar), 1485, 1237 (C$_{Ar}$-O), 1045, 968; **MS:** $m/z$ (ES$^+$) 274 [M+Na]$^+$ (100%), 306 [M+Na+MeOH]$^+$ (40%); **HRMS:** found 252.1063, [M+H]$^+$ requires 252.1053.

332ag: O-But-2-enyl 3-chlorophenyl(methyl)carbamothioate.

General procedure C2 was followed using 331g (352 mg, 1.58 mmol) and 328a to afford the title compound as a yellow oil (251 mg, 62% over 2 steps).

**Rf:** 0.74 (Pet/EtOAc 8:2); **$^1$H NMR:** (400 MHz; CDCl$_3$, -20 °C, rotamers) $\delta$ (ppm) 7.40-7.05 (m, 4H, H-8, H-10, H-11, H-12), 5.92-5.86/5.68-5.59 (m, 1H, H-3), 5.78-5.70/5.51-5.44 (m, 1H, H-2), 4.92/4.82 (d, $J$ = 5.7 Hz, 2H, H-1), 3.61/3.40 (s, 3H, H-6), 1.77-1.65 (d, $J$ = 6.3 Hz, 3H, H-4); **$^{13}$C NMR:** (100 MHz, CDCl$_3$, -20 °C, rotamers) $\delta$ (ppm) 189.1/188.0 (C-5), 146.8/144.0 (C-7), 134.6/134.2 (C-9), 132.3/131.2 (C-3), 130.5/130.0 (C-8), 127.9/127.4 and 126.1/125.6 and 124.5/124.3 (C-10, C-11, C-12), 124.2/123.6 (C-2), 72.8/72.4 (C-1), 44.0/39.9 (C-6), 18.1/18.0 (C-4); **IR:** $\nu_{\text{max}}$(film)/cm$^{-1}$ 1590 (C=C), 1471 (C=C$_{Ar}$), 1356, 1292 (C$_{Ar}$-N), 1186, 1130, 962, 691; **MS:** $m/z$ (ES$^+$) 278 [M+Na]$^+$ (100%), 310 [M+Na+MeOH]$^+$ (20%); **HRMS:** found 256.0550, [M+H]$^+$ requires 256.0558.

332ah: O-But-2-enyl 3-fluorophenyl(methyl)carbamothioate.

General procedure C2 was followed using 331h (392 mg, 1.92 mmol) and 328a to afford the title compound as a yellow oil (289 mg, 63% over 2 steps).

**Rf:** 0.70 (Pet/EtOAc 8:2); **$^1$H NMR:** (400 MHz; CDCl$_3$, -20 °C, rotamers) $\delta$ (ppm) 7.42-7.33 (m, 1H, H-11), 7.08-6.88 (m, 3H, H-8, H-10, H-12), 5.92-5.84/5.68-5.60 (m, 1H, H-3), 5.77-5.70/5.52-5.45 (m, 1H, H-2), 4.92/4.83 (d, $J$ = 5.5 Hz, 2H, H-1), 3.62/3.41 (s, 3H, H-6), 1.77/1.64 (d, $J$ = 5.5 Hz, 3H, H-4); **$^{13}$C NMR:** (100 MHz, CDCl$_3$, -20 °C, rotamers)
δ (ppm) 189.1/188.0 (C-5), 162.7 (d, $^1{J}_{CF} = 248.1$ Hz, C-9)/162.3 (d, $^1{J}_{CF} = 245.7$ Hz, C-9), 147.1 (d, $^3{J}_{CF} = 8.6$ Hz, C-7)/144.3 (d, $^3{J}_{CF} = 10.0$ Hz, C-7), 132.3/131.2 (C-3), 130.7 (d, $^3{J}_{CF} = 7.6$ Hz, C-11)/130.2 (d, $^3{J}_{CF} = 9.0$ Hz, C-11), 124.5/124.3 (C-2), 122.9/121.6 (d, $^4{J}_{CF} = 1.8$ Hz, C-12), 114.9/114.3 (d, $^2{J}_{CF} = 10.7$ Hz, C-10), 114.7 (d, $^2{J}_{CF} = 22.9$ Hz, C-8)/113.4 (d, $^2{J}_{CF} = 20.8$ Hz, C-8), 72.7/72.4 (C-1), 44.0/39.9 (C-6), 18.1/18.0 (C-4); IR: ν_{max}(film)/cm^{-1} 1594 (C=C), 1440 (C=C_{Ar}), 1358, 1217 (C-F), 964, 908, 729; MS: m/z (ES') 262 [M+Na]^+ (100%), 294 [M+Na+MeOH]^+ (20%); HRMS: found 262.0673, [M+Na]^+ requires 262.0673.

332ai: O-But-2-eny1 2-methoxyphenyl(methyl)carbamothioate.

General procedure C2 was followed using 331i (397 mg, 1.84 mmol) and 328a to afford the title compound as a yellow oil (244 mg, 53% over 2 steps).

Rf: 0.59 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$, -20 °C, rotamers) 7.35-7.26 (m, 1H, H-11), 7.22/7.08 (dd, J = 8.0, 1.8 Hz, 1H, H-9), 7.01-6.97 (m, 1H, H-10), 6.94 (bd, J = 8.0 Hz, 1H, H-12), 5.89/5.55 (dqt, J = 15.3, 6.3, 1.2 Hz, 1H, H-3), 5.75/5.45 (dtq, J = 15.3, 6.3, 1.4 Hz, 1H), 5.01-4.91/4.89-4.79 (m, 2H, H-1), 3.85/3.80 (s, 3H, H-13), 3.55/3.32 (s, 3H, H-6), 1.77/1.62 (dd, J = 6.3, 1.2 Hz, 3H, H-4); $^{13}$C NMR: (100 MHz, CDCl$_3$, -20 °C, rotamers) δ (ppm) 189.1/188.6 (C-5), 153.9/153.4 (C-8), 133.9/131.7 (C-7), 131.5/129.9 (C-3), 129.3/128.9 (C-10), 128.8/127.3 (C-11 or C-12), 124.8 (C-12 or C-11), 120.8/120.4 (C-2), 112.0/111.4 (C-9), 72.7/71.8 (C-1), 55.6/55.4 (C-13), 43.0/38.7 (C-6), 18.1/18.0 (C-4); IR: ν_{max}(film)/cm^{-1} 1597 (C=C), 1499 (C=C_{Ar}), 1463, 1376, 1274 (C_{Ar}-N), 1243 (C_{Ar}-O), 1188, 1131, 961, 748; MS: m/z (ES') 274 [M+Na]^+ (100%); HRMS: found 252.1056, [M+H]^+ requires 252.1053.
**332aj:** O-But-2-enyl methyl(naphthalen-1-yl)carbamothioate.

General procedure C2 was followed using **331j** (373 mg, 1.58 mmol) and **328a** to afford the title compound as a yellow oil (253 mg, 59% over 2 steps).

**Rf:** 0.69 (Pet/EtOAc 8:2); **$^1$H NMR:** (400 MHz; CDCl$_3$, -20 °C, rotamers) $\delta$ (ppm) 7.93-7.26 (m, 7H, H-9 to H-12, H-14 to H-16), 6.00-5.90/5.45-5.35 (2m, 1H, H-3), 5.86-5.77/5.32-5.24 (2m, 1H, H-2), 5.01-4.98/4.85-4.37 (2m, 2H, H-1), 3.72-3.71/3.53-3.52 (2m, 3H, H-6), 1.83-1.80/1.53-1.50 (2m, 3H, H-4); **$^{13}$C NMR:** (100 MHz, CDCl$_3$, -20 °C, rotamers) $\delta$ (ppm) 189.4/188.8 (C-5), 142.2/140.0 (C-7), 134.4/134.1 (C-13), 132.1/130.4 (C-3), 128.7 (CHAr), 128.6 (C-8), 128.4/128.3/128.2 (CH$_2$Ar), 127.1/126.9 (CH$_2$Ar), 126.4/125.9 (CH$_2$Ar), 125.6/124.9 (CH$_2$Ar), 124.7/124.4 (C-2), 123.4 (CH$_2$Ar), 122.4/122.2 (CH$_2$Ar), 72.8/71.9 (C-1), 44.0/39.8 (C-6), 18.1/17.8 (C-4); **IR:** $\nu_{max}$(film)/cm$^{-1}$ 1594 (C=C), 1450 (C=C$_{Ar}$), 1389, 1357, 1295 (C$_{Ar}$-N), 1203, 1173, 1124, 952, 780; **MS:** m/z (ES$^+$) 294 [M+Na]$^+$ (100%), 326 [M+Na+MeOH]$^+$ (30%); **HRMS:** found 272.1107, [M+H]$^+$ requires 272.1104.

**332bc:** O-Hex-2-en-1-yl (4-chlorophenyl)(methyl)carbamothioate.

General procedure C2 was followed using **331d** (500 mg, 2.27 mmol) and hex-2-en-1-ol **328b** to afford the title compound as a yellow liquid (343 mg, 64% over 2 steps).

**Rf:** 0.91 (Pet/EtOAc 8:2); **$^1$H NMR:** (400 MHz; CDCl$_3$, rotamers) $\delta$ (ppm) 7.35 (bd, $J = 8.5$ Hz, 2H, H-11, H-13), 7.12 (bs, 2H, H-10, H-14), 5.60 (bs, 1H, H-3), 5.51 (bs, 1H, H-2), 4.88 (bs, 2H, H-1), 3.59 (bs, 3H, H-8), 1.99 (bs, 2H, H-4), 1.37 (bs, 2H, H-5), 0.87 (bs, 3H, H-6).
**332bd**: O-Hex-2-en-1-yl (4-fluorophenyl)(methyl)carbamothioate.

![Chemical structure of O-Hex-2-en-1-yl (4-fluorophenyl)(methyl)carbamothioate](image)

General procedure C2 was followed using **331e** (326 mg, 1.60 mmol) and **328b** to afford the title compound as a yellow oil (143 mg, 40% over 2 steps).

**Rf**: 0.86 (Pet/EtOAc 8:2); **H NMR**: (400 MHz; CDCl$_3$, rotamers) $\delta$ (ppm) 7.24-7.07 (bm, 4H, H$_{10}$, H$_{11}$, H$_{13}$, H$_{14}$), 5.90-5.47 (bm, 2H, H$_2$, H$_3$), 4.95-4.86 (2bs, 2H, H$_1$), 3.62-3.41 (2bs, 3H, H$_8$), 1.96 (bs, 2H, H$_4$), 1.33 (bs, 2H, H$_5$), 0.85 (bs, 3H, H$_6$).

**332be**: O-Hex-2-en-1-yl (3-chlorophenyl)(methyl)carbamothioate.

![Chemical structure of O-Hex-2-en-1-yl (3-chlorophenyl)(methyl)carbamothioate](image)

General procedure C2 was followed using **331g** (500 mg, 2.27 mmol) and **328b** to afford the title compound as a yellow liquid (377 mg, 70% over 2 steps).

**Rf**: 0.88 (Pet/EtOAc 8:2); **H NMR**: (400 MHz; CDCl$_3$, rotamers) $\delta$ (ppm) 7.32 (t, $J$ = 7.8 Hz, 1H, H$_{13}$), 7.28 (dt, $J$ = 8.4, 1.5 Hz, 1H, H$_{12}$), 7.21 (bs, 1H, H$_{11}$), 7.09 (bs, 1H, H$_{14}$), 5.65 (bs, 1H, H$_3$), 5.55 (bs, 1H, H$_2$), 4.89 (bd, $J$ = 5.1 Hz, 2H, H$_1$), 3.57 (bs, 3H, H$_8$), 1.99 (m, 2H, H$_4$), 1.37 (bq, $J$ = 7.2 Hz, 2H, H$_5$), 0.87 (bt, $J$ = 7.2 Hz, 3H, H$_6$).

**334a**: 1-Phenylbut-2-yn-1-ol.

![Chemical structure of 1-Phenylbut-2-yn-1-ol](image)

General procedure E was followed using benzaldehyde (1.10 mL, 11.0 mmol, 0.7 eq) to afford the title compound as a colourless oil without purification (1.82 g, 75%).
RF: 0.48 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.55-7.53 (m, 2H, H-7, H-11), 7.41-7.36 (m, 2H, H-8, H-10), 7.34-7.30 (m, 1H, H-9), 5.44 (bs, 1H, H-1), 2.08 (d, $J = 4.3$ Hz, 1H, H-5), 1.91 (d, $J = 2.2$ Hz, 3H, H-4); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 141.2 (C-6), 128.6 (C-8, C-10), 128.3 (C-9), 126.6 (C-7, C-11), 83.2 (C-3), 79.1 (C-2), 64.9 (C-1), 3.8 (C-4). Matches published data.$^{114a}$

**339a:** S-But-3-en-2-yl 1H-imidazole-1-carbothioate.

General procedure A (CH$_2$Cl$_2$ 180.0 mL, rt, 3 days) was followed using crotyl alcohol (1.78 mL, 6.9 mmol). Purification by column chromatography (Pet/EtOAc 8:2) afforded the title compound as a yellow oil (3.55 g, 94%).

RF: 0.44 (Pet/EtOAc 1:1); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 8.17 (bs, 1H, H-6), 7.44 (t, $J = 1.2$ Hz, 1H, H-8), 7.08 (m, 1H, H-7), 5.94 (ddd, $J = 17.0$, 10.4, 7.0 Hz, 1H, H-3), 5.36 (dt, $J = 17.0$, 1.2 Hz, 1H, H-4'), 5.20 (dt, $J = 10.4$, 1.2 Hz, 1H, H-4), 4.38 (qn x t, $J = 7.0$, 1.2 Hz, 1H, H-2), 1.55 (d, $J = 7.0$ Hz, 3H, H-1); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 165.1 (C-5), 136.9 (C-3), 135.2 (C-6), 130.7 (C-7), 116.8 (C-4), 115.6 (C-8), 43.2 (C-2), 19.4 (C-1); IR: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1687 (C=O), 1468 (C$_{\text{Ar}}$=N), 1210; MS: $m/z$ ([ES$^+$]) 183 [M+H]$^+$ (30%), 205 [M+Na]$^+$ (70%), 237 [M+Na+MeOH]$^+$ (100%); HRMS: found 183.0586, [M+H]$^+$ requires 183.0587.

**339b:** S-Hex-1-en-3-yl 1H-imidazole-1-carbothioate.

General procedure A (DCE 100.0 mL, reflux, 24 h) was followed using hex-2-en-1-ol (2.0 g, 20.0 mmol). Purification by filtration over silica (Pet/EtOAc 7:3) afforded the title compound as a yellow liquid (4.02 g, 95%).
Rf: 0.16 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 8.16 (bs, 1H, H-8), 7.43 (bs, 1H, H-10), 7.06 (bs, 1H, H-9), 5.81 (dd, \(J = 17.2, 10.0, 7.4\) Hz, 1H, H-2), 5.34 (d, \(J = 17.2\) Hz, 1H, H-1'), 5.17 (d, \(J = 10.0\) Hz, 1H, H-1), 4.24 (q, \(J = 7.4\) Hz, 1H, H-3), 1.76 (q, \(J = 7.4\) Hz, 2H, H-4), 1.45 (m, 2H, 5), 0.94 (t, \(J = 7.4\) Hz, 3H, H-6);

\(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 165.2 (C-7), 136.4 (C-2), 135.4 (C-8), 130.8 (C-9), 117.6 (C-1), 115.8 (C-10), 48.7 (C-3), 35.8 (C-4), 20.2 (C-5), 13.5 (C-6); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1689 (C=O), 1467 (C\(_{\text{Ar}}\)=N), 1211; MS: m/z (ES\(^+\)) 233 [M+Na]\(^+\) (50%), 265 [M+Na+MeOH]\(^+\) (100%); HRMS: found 233.0722, [M+Na]\(^+\) requires 233.0719.

339c: (E)-Hexa-1,4-dien-3-yl 1H-imidazole-1-carbothioate.

![Chemical Structure](image)

General procedure A (CH\(_2\)Cl\(_2\) 50.0 mL, rt, 2.5 days) was followed using hexa-2,4-dien-1-ol (500 mg, 5.1 mmol). Purification by filtration over silica (Pet/EtOAc 1:1) afforded the title compound as a yellow oil (689 mg, 65%).

Rf: 0.64 (Pet/EtOAc 1:1); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \(\delta\) (ppm) 8.17 (bs, 1H, H-8), 7.43 (t, \(J = 1.6\) Hz, 1H, H-10), 7.08 (m, 1H, H-9), 5.96 (dd, \(J = 17.2, 10.0, 6.8\) Hz, 1H, H-2), 5.84 (dq, \(J = 15.2, 6.6, 1.0\) Hz, 1H, H-5), 5.59 (ddq, \(J = 15.2, 6.8, 1.6\) Hz, 1H, H-4), 5.36 (dt, \(J = 17.2, 1.0\) Hz, 1H, H-1'), 5.24 (dt, \(J = 10.0, 1.0\) Hz, 1H, H-1), 4.87 (bt, \(J = 6.8\) Hz, 1H, H-3), 1.74 (d, \(J = 6.6\) Hz, 3H, H-6); \(^{13}\)C NMR: (100 MHz, CDCl\(_3\)) \(\delta\) (ppm) 164.9 (C-7), 135.4 (C-8), 134.9 (C-2), 130.9 (C-9), 130.5 (C-3), 126.8 (C-4), 118.0 (C-1), 115.8 (C-10), 50.5 (C-3), 17.9 (C-6); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1690 (C=O), 1468 (C\(_{\text{Ar}}\)=N), 1212; MS: m/z (ES\(^+\)) 209 [M+H]\(^+\) (90%), 231 [M+Na]\(^+\) (40%), 263 [M+Na+MeOH]\(^+\) (100%); HRMS: found 209.0726, [M+H]\(^+\) requires 209.0743.
**339d**: S-4-Methylpent-1-en-3-yl 1H-imidazole-1-carbothioate.

![Chemical Structure](image)

General procedure A (DCE 2.5 mL, 40 °C, 24 h) was followed using 4-methylpent-2-en-1-ol (25 mg, 0.25 mmol). Purification by filtration over silica (Pet/EtOAc 8:2) afforded the title compound as a pale yellow oil (47 mg, 88%).

Rf: 0.27 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 8.19 (bs, 1H, H-8), 7.46 (t, J = 1.6 Hz, 1H, H-10), 7.08 (dd, J = 1.6, 0.8 Hz, 1H, H-9), 5.85 (ddd, J = 16.8, 10.0, 9.0 Hz, 1H, H-2), 5.35 (d, J = 16.8 Hz, 1H, H-1’), 5.21 (ddd, J = 10.0, 1.2, 0.8 Hz, 1H, H-1), 4.18 (dd, J = 9.0, 6.4 Hz, 1H, H-3), 2.08 (oct, J = 6.4 Hz, 1H, H-4), 1.04 (2 dd, J = 6.4, 0.8 Hz, 6H, H-5, H-6); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 165.3 (7), 135.5 (C-8), 134.8 (C-2), 130.8 (C-9), 118.4 (C-1), 115.9 (C-10), 56.2 (C-3), 32.0 (C-4), 20.0 (C-5 or C-6), 19.7 (C-6 or C-5); IR: ν$_{\text{max}}$(film)/cm$^{-1}$ 1689 (C=O), 1467 (C$_{\text{Ar}}$=N), 1211; MS: m/z (ES$^+$) 211 [M+H]$^+$ (20%), 233 [M+Na]$^+$ (100%), 265 [M+Na+MeOH]$^+$ (50%); HRMS: found 233.0729, [M+Na]$^+$ requires 233.0719.

**339e**: (E)-S-Pent-3-en-2-yl 1H-imidazole-1-carbothioate.

![Chemical Structure](image)

General procedure A (DCE 6.0 mL, 40 °C, 26 h) was followed using pent-3-en-2-ol (50 mg, 0.58 mmol). Purification by filtration over silica (Pet/EtOAc 8:2) afforded the title compound as a yellow oil (112 mg, 98%).

Rf: 0.30 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 8.15 (s, 1H, H-7), 7.42 (d, J = 1.6 Hz, 1H, H-8), 7.07 (s, 1H, H-9), 5.80 (dq, J = 15.2, 6.4, 1.2 Hz, 1H, H-4), 5.54 (ddq, J = 15.2, 7.4, 1.6 Hz, 1H, H-3), 4.34 (qn, J = 7.4 Hz, 1H, H-2), 1.70 (d, J = 6.4 Hz, 3H, H-5), 1.52 (d, J = 7.4 Hz, 3H, H-1’); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 165.6 (C-6), 135.4 (C-7), 130.8 (C-9), 130.1 (C-3), 128.5 (C-4), 115.8 (C-8), 43.4 (C-2), 20.5 (C-5), 17.7 (C-1); IR: ν$_{\text{max}}$(film)/cm$^{-1}$ 1686 (C=O), 1211, 880; MS: m/z (ES$^+$) 197 [M+H]$^+$ (100%), 219 [M+Na]$^+$ (70%), 251 [M+Na+MeOH]$^+$ (70%); HRMS: found 219.0567, [M+Na]$^+$ requires 219.0563.
339f: S-4-Cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate.

General procedure A (DCE 40.0 mL, 40 °C, 26 h) was followed using 1-cyclohexylbut-2-en-1-ol (1.0 g, 6.48 mmol). Purification by column chromatography (Pet/EtOAc 9:1 to 8:2) afforded the title compound as a yellow oil (1.55 g, 90%).

Rf: 0.51 (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) δ (ppm) 8.16 (s, 1H, H-12), 7.43 (d, J = 1.2 Hz, 1H, H-14), 7.07 (s, 1H, H-13), 5.73 (dd, J = 15.6, 6.8 Hz, 1H, H-4), 5.47 (ddd, J = 15.6, 7.2, 1.2 Hz, 1H, H-3), 4.34 (qn, J = 7.2 Hz, 1H, H-2), 1.99-1.91 (m, 1H, H-5), 1.74-1.62 (m, 4H, H-6, 7, 9, 10), 1.52 (d, J = 7.2 Hz, 3H, H-1), 1.31-1.01 (m, 6H, H-6', 7', 8, 9', 10'); \(^13\)C NMR: (100 MHz, CDCl\(_3\)) δ (ppm) 165.6 (C-11), 139.6 (C-4), 135.4 (C-12), 130.7 (C-13), 126.2 (C-3), 115.8 (C-14), 43.6 (C-2), 40.3 (C-5), 32.6/32.6 (C-6, C-10), 26.0/25.9 (C-7, C-8, C-9), 20.6 (C-1); IR: \(\nu_{\text{max}}\) (film)/cm\(^{-1}\) 1689 (C=O), 1212, 882; MS: m/z (ES+) 265 [M+H]\(^+\) (100%), 287 [M+Na]\(^+\) (55%); HRMS: found 265.1369, [M+H]\(^+\) requires 265.1370.

The equivalent enantioenriched (S)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (S)-339f (95:5 e.r., 318 mg, 89%) was prepared from (R)-1-cyclohexylbut-2-en-1-ol (R)-328f (99:1 e.r., 208 mg, 1.35 mmol).

\([\alpha]_D^{20}\): -48.0 (c 0.70, CHCl\(_3\)); HPLC: Chiralpak AD-H, Hexane/i-PrOH 97:3, 1.0 mL/min, minor 15.3 min, major 20.3 min (214.4 nm, 254.4 nm).

The other enantiomer (R)-S-4-cyclohexylbut-3-en-2-yl 1H-imidazole-1-carbothioate (R)-339f (12:88 e.r., 1.18 g, 90%) was prepared from (S)-1-cyclohexylbut-2-en-1-ol (S)-328f (12:88 e.r., 763 mg, 4.95 mmol).
339g: (E)-S-(4-Phenylbut-3-en-2-yl) 1H-imidazole-1-carbothioate.

![Chemical Structure](image)

General procedure A (DCE 22.0 mL, 40 °C, 20 h) was followed using 1-phenylbut-2-en-1-ol 328g (779 mg, 5.26 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:15 to 8:2) afforded the title compound as a yellow oil (1.10 g, 81%).

Rf: 0.39 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 8.20 (bs, 1H, H-12), 7.44 (t, J = 7.8 Hz, 2H, H6, H-10), 7.32 (t, J = 7.8 Hz, 2H, H7, H-9), 7.26 (tt, J = 7.8, 1.3 Hz, 1H, H-8), 7.08 (dd, J = 1.4, 0.8 Hz, H-13), 6.70 (d, J = 15.8 Hz, 1H, H-4), 6.27 (dd, J = 15.8, 7.0 Hz, 1H, H-3), 4.58 (qt, J = 7.0 Hz, 1H, H-2), 1.66 (d, J = 7.0 Hz, 3H, H-1); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 165.3 (C-11), 136.0 (C-5), 135.4 (C-12), 132.1 (C-4), 130.9 (C-13), 128.7 (C-7, C-9), 128.3 (C-3), 126.5 (C-6, C-10), 115.8 (C-14), 43.7 (C-2), 20.3 (C-1); IR: νmax(film)/cm⁻¹ 1687 (C=O), 1219, 873; MS/GC-MS/HRMS: the correct mass was not observed in any mass spectra.

The equivalent enantioenriched (R)-S-(4-phenylbut-3-en-2-yl) 1H-imidazole-1-carbothioate (R)-339g (83:17 e.r., 163 mg, 52%) was prepared from (R)-1-phenylbut-2-en-1-ol (R)-328g (98:2 e.r., 180 mg, 1.21 mmol) and obtained as a yellow solid.

[α]D⁰: [-121.2 (c 1.00, CHCl₃); HPLC: Chiralpak AD-H, Hexane/i-PrOH 97:3, 1.0 mL/min, minor 18.8 min, major 20.5 min (214.4 nm, 254.4 nm); mp: 41-43 °C.

339h: (E)-S-4-Methylhept-4-en-3-yl 1H-imidazole-1-carbothioate.

![Chemical Structure](image)

General procedure A (DCE 4 mL, 40 °C, 24 h) was followed using 4-methylhept-4-en-3-ol (50 mg, 0.39 mmol). Purification by column chromatography (Pet/EtOAc 95:5) afforded the title compound as a yellow oil (66 mg, 71%).
343b: (R)-1-(4-Chlorophenyl)ethanol.

General procedure L (3 days) was followed using 4-chloroacetophenone (500 mg, 3.23 mmol) and (S,S)-383 (10 mg). Purification by column chromatography (Pet/EtOAc 85:15) afforded the title compound as a colourless liquid (96:4 e.r., 479 mg, 94%).

Rf: 0.32 (Pet/EtOAc 8:2); 1H NMR: (400 MHz; CDCl3) δ (ppm) 7.31 (s, 4H, H-5, H-6, H-8, H-9), 4.88 (qd, J = 6.4, 3.0 Hz, 1H, H-1), 1.87 (bs, 1H, H-3), 1.47 (d, J = 6.4 Hz, 3H, H-2);
HPLC: Chiralcel OD-H, Hexane/i-PrOH 98:2, 1.0 mL/min, 28 °C, major 14.1 min, minor 15.6 min (254.4 nm).

Matches published data.106

343c: (R)-1-(3-Chlorophenyl)ethanol.

General procedure L (7 days) was followed using 3-chloroacetophenone (100 mg, 0.65 mmol) and (S,S)-383 (2 mg). Purification by column chromatography (Pet/EtOAc 90:10, 85:15) afforded the title compound as a colourless liquid (97:3 e.r.).
\( R_f: 0.34 \) (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \( \delta \) (ppm) 7.39 \((t, J = 1.8 \text{ Hz}, 1\text{H}, H-5)\), 7.31-7.24 \((m, 3\text{H}, H-7, H-8, H-9)\), 4.89 \((q, J = 6.4 \text{ Hz}, 1\text{H}, H-1)\), 1.89 \((bs, 1\text{H}, H-3)\), 1.49 \((d, J = 6.4 \text{ Hz}, 3\text{H}, H-2)\); HPLC: Chiralcel OD-H, Hexane/i-PrOH 99:1, 1.0 mL/min, 28 °C, major 22.9 min, minor 24.7 min (254.4 nm).

**350a**: 1-Cyclohexylbut-2-enyl acetate.

![Chemical structure](image)

To a solution of 1-cyclohexylbut-2-en-1-ol 328f (200 mg, 1.30 mmol, 1.0 eq) in CH\(_2\)Cl\(_2\) (15.0 mL) at 0 °C were added DMAP (0.1 eq) and acetic anhydride (1.2 eq). The reaction was warmed to rt and stirred for 24 h. Water (15 mL) was added followed by brine (10 mL). The aqueous layer was extracted with CH\(_2\)Cl\(_2\) (x3). The combined organic layers were washed with brine, dried over MgSO\(_4\), filtered and concentrated to afford the pure title compound as a colourless oil (254 mg, 100%).

\( R_f: 0.82 \) (Pet/EtOAc 8:2); \(^1\)H NMR: (400 MHz; CDCl\(_3\)) \( \delta \) (ppm) 5.68 \((dq, J = 15.3, 6.5 \text{ Hz}, 1\text{H}, H-3)\), 5.37 \((ddq, J = 15.3, 7.7, 1.5 \text{ Hz}, 1\text{H}, H-2)\), 4.98 \((t, J = 7.7 \text{ Hz}, 1\text{H}, H-1)\), 2.04 \((s, 3\text{H}, H-6)\), 1.74-1.62 \((m, 5\text{H}, H-7, H-8, H-9, H-11, H-12)\), 1.69 \((dd, J = 6.5, 1.5 \text{ Hz}, 3\text{H}, H-4)\), 1.52-1.44/1.25-1.07 \((2m, 4\text{H}, H-8', H-9', H-11', H-12')\), 0.99-0.89 \((m, 2\text{H}, H-10)\).

*Matches published data.*\(^{179}\)

**352**: 1-Cyclohexylbut-2-yn-1-ol.

![Chemical structure](image)

General procedure E was followed using cyclohexanecarbaldehyde (0.13 mL, 1.10 mmol, 0.7 eq). Purification by column chromatography (Pet 100%, Pet/EtOAc 95:5, 9:1) afforded the title compound as a white solid.
**358**: (E)-1-Cyclohexylbut-2-en-1-one.

General procedure F was followed using 328f (1.0 g, 6.5 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1, 98:2) afforded the title compound as a colourless liquid (501 mg, 51%).

**Rf**: 0.66 (Pet/EtOAc 8:2); **1H NMR**: (400 MHz; CDCl₃) δ (ppm) 6.94-6.82 (dq, J = 15.6, 6.8 Hz, 1H, H-3), 6.21-6.15 (dd, J = 15.6, 1.6 Hz, 1H, H-2), 2.57-2.49 (m, 1H, H-5), 1.90-1.87 (dd, J = 6.8, 1.6 Hz, 3H, H-4), 1.81-1.66 (m, 6H, H-6, H-7, H-8, H-9, H-10), 1.43-1.14 (m, 4H, H-6', H-7', H-9', H-10'); **13C NMR**: (100 MHz, CDCl₃) δ (ppm) 203.3 (C-1), 142.1 (C-3), 130.2 (C-2), 48.5 (C-5), 28.7/25.9/25.7 (C-6, C-7, C-8, C-9, C-10), 18.2 (C-4); **IR**: νmax(film)/cm⁻¹ 1691 (C=O), 1663 (C=C), 1627 (C=C), 1444, 968, 730; **MS**: m/z (ES⁺) 153 [M+H]⁺ (100%), 175 [M+Na]⁺ (40%); **HRMS**: found 153.1277, [M+H]⁺ requires 153.1274.

*Matches published data.*

**359**: (E)-1-Phenylbut-2-en-1-one.

General procedure F was followed using 328g (200 mg, 1.35 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 99:1 to 97:3) afforded the title compound as a pale yellow liquid (50 mg, 25%).

**Rf**: 0.68 (Pet/EtOAc 8:2); **1H NMR**: (400 MHz; CDCl₃) δ (ppm) 7.93 (dd, J = 8.3, 1.3 Hz, 2H, H-6, H-10), 7.57-7.53 (m, 1H, H-8), 7.48-7.44 (m, 2H, H-7, H-9), 7.08 (dq, J = 15.3, 6.8 Hz,
1H, H-3), 6.91 (dq, J = 15.3, 1.6 Hz, 1H, H-2), 2.00 (d, J = 6.8, 1.6 Hz, 3H, H-4); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 190.8 (C-1), 145.1 (C-3), 137.9 (C-5), 132.6 (C-8), 128.5 (C-6, C-7, C-9, C-10), 127.5 (C-2), 18.6 (C-4).

*Matches published data.*$^{137a,142}$

361: (*E*-1-Methoxy-3-((5-methylhept-2-en-2-yl)benzene.

![Chemical Structure](image)

$^{Rf}$: 0.93 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.23 (t, J = 8.0 Hz, 1H, H-13), 6.99 (ddd, J = 8.0, 1.5, 0.9 Hz, 1H, H-14), 6.93 (dd, J = 2.3, 1.9 Hz, 1H, H-10), 6.78 (ddd, J = 8.0, 2.5, 0.9 Hz, 1H, H-12), 5.82 (tq, J = 7.4, 0.9 Hz, 1H, H-3), 3.83 (s, 3H, H-15), 2.20 (m, 1H, H-4), 2.05 (m, 1H, H-4), 2.02 (d, J = 0.9 Hz, 3H, H-1), 1.51 (oct, J = 6.5 Hz, 1H, H-5), 1.43 (dq, J = 13.2, 7.4 Hz, 1H, H-6), 1.23 (dq, J = 13.2, 7.4 Hz, 1H, H-6), 0.93 (d, J = 6.5 Hz, 3H, H-8), 0.91 (t, J = 7.4 Hz, 3H, H-7); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 159.5 (C-11), 145.8 (C-9), 134.9 (C-2), 129.0 (C-13), 127.8 (C-3), 118.2 (C-14), 111.7 (C-10), 111.5 (C-12), 55.2 (C-15), 35.7 (C-4), 35.4 (C-5), 29.3 (C-6), 19.3 (C-8), 16.0 (C-1), 11.6 (C-7).

376a: (*S*-S-1-Phenylethyl ethanethioate.$^{108,148}$

![Chemical Structure](image)

General procedure H was followed using (R)-1-phenylethanol (1.20 mL, 10.0 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 95:5) afforded the title compound as a bright orange liquid (98:2 e.r., 1.23 g, 98%).

**HPLC:** Chiralcel OD-H, Hex/i-PrOH 97:3, 1.0 mL/min, major 7.1 min, minor 8.2 min (254.4 nm).

$^{Rf}$: 0.75 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.32-7.22 (m, 4H, H-6, H-7, H-9, H-10), 7.19-7.15 (m, 1H, H-8), 4.68 (q, J = 7.2 Hz, 1H, H-1), 2.23 (s, 3H, H-4), 1.59 (d, J = 7.2 Hz, H-2); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 195.0 (C-3), 142.5 (C-5), 128.5 (C-7, C-9), 127.3 (C-8), 127.1 (C-6, C-10), 42.9 (C-1), 30.4 (C-4), 22.1 (C-2); IR: $v_{\text{max}}$(film)/cm$^{-1}$ 1685
(C=O), 1131, 1103, 950, 764, 697, 629; **MS**: $m/z$ (ES$^+$) 181 [M+H]$^+$ (50%), 203 [M+Na]$^+$ (100%); **HRMS**: found 181.0689, [M+Na]$^+$ requires 181.0682.

*Matches published values.*

**376b**: S-1-(4-Chlorophenyl)ethyl ethanethioate.

![](image)

General procedure H was followed using 1-(4-chlorophenyl)ethanol (1.32 mL, 10.0 mmol). Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 95:5) afforded the title compound as a pale yellow liquid (1.45 g, 97%).

$R_f$: 0.89 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.31-7.25 (m, 4H, H-6, H-7, H-9, H-10), 4.69 (q, $J$ = 7.2 Hz, 1H, H-1), 2.28 (s, 3H, H-4), 1.61 (d, $J$ = 7.2 Hz, 3H, H-2); $^{13}$C NMR: (100 MHz, CDCl$_3$) $\delta$ (ppm) 194.7 (C-3), 141.2 (C-5), 132.9 (C-8), 128.6 (C-6, C-10), 128.5 (C-7, C-9), 42.1 (C-1), 30.4 (C-4), 21.9 (C-2); **IR**: $\nu_{\text{max}}$(film)/cm$^{-1}$ 1686 (C=O), 1493 (C=C$_{\text{Ar}}$), 1134, 1091, 1014, 951, 827 (C-Cl), 627; **MS**: $m/z$ (ES$^+$) 237 [M+Na]$^+$ (70%).

**378a**: (S)-1-Phenylethanethiol.

![](image)

General procedure I was followed using (S)-1-Phenylethyl ethanethioate (S)-376a (1.23 g, 6.82 mmol) to afford the title compound as a pale yellow liquid (98:2 e.r., 890 mg, 94%).

**HPLC**: Chiralcel OD-H, Hex/i-PrOH 97:3, 1.0 mL/min, major 6.8 min, minor 8.5 min (254.4 nm); $^1$H NMR: (400 MHz; CDCl$_3$) $\delta$ (ppm) 7.31-7.22 (m, 4H, H-5, H-6, H-8, H-9), 7.18-7.13 (m, 1H, H-7), 4.15 (qd, $J$ = 7.0, 5.2 Hz, 1H, H-1), 1.91 (d, $J$ = 5.2 Hz, 1H, H-3), 1.59 (d, $J$ = 7.0 Hz, 1H, H-2).

*Matches published data.*
378b: 1-(4-Chlorophenyl)ethanethiol.

General procedure I was followed using S-1-(4-chlorophenyl)ethyl ethanethioate 376b (450 mg, 2.10 mmol) to afford the title compound as a colourless liquid (337 mg, 93%).

Rf: 0.83 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.28-7.22 (m, 4H, H-5, H-6, H-8, H-9), 4.16 (m, 1H, H-1), 1.95 (d, J = 5.1 Hz, 1H, H-3), 1.61 (d, J = 7.0 Hz, 3H, H-2);
¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 144.3 (C-4), 132.7 (C-7), 128.7 (C-5, C-9), 127.8 (C-6, C-8), 38.0 (C-1), 26.0 (C-2); IR: νmax(film)/cm⁻¹ 1491 (C=C Ar), 1092, 1013, 825 (C-Cl); MS: m/z (ES⁻) 171 [M-H]⁻ (100%); HRMS: found 171.0037, [M-H]⁻ requires 171.0040.

379a: (S)-1-Phenylethyl vinylcarbamothioate.¹⁴⁸

General procedure J (3 h) was followed using 1-phenylethanethiol (100 mg, 0.72 mmol) and vinyl isocyanate (1.0 eq) to afford the title compound as a white solid (142 mg, 95%).

Rf: 0.59 (Pet/EtOAc 8:2); mp: 64-66 °C; ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.39-7.24 (m, 5H, H-8 to H-12), 6.94 (bs, 2H, H-4, H-5), 4.80 (q, J = 7.2 Hz, 1H, H-1), 4.56 (d, J = 15.6 Hz, 1H, H-6'), 4.37 (d, J = 8.0 Hz, 1H, H-6), 1.72 (d, J = 7.2 Hz, 3H, H-2); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 164.9 (C-3), 142.5 (C-7), 128.6 (C-9, C-11), 128.4 (C-5), 127.4 (C-10), 127.2 (C-8, C-12), 94.8 (C-6), 44.2 (C-1), 22.8 (C-2); IR: νmax(film)/cm⁻¹ 3291 (NH), 1637 (C=O), 1226; MS: m/z (ES⁺) 230 [M+Na]⁺ (100%); HRMS: found 230.0611, [M+Na]⁺ requires 230.0611.

The equivalent enantiopure (S)-1-phenylethyl vinylcarbamothioate (S)-379a (98:2 e.r., 631 mg, 93%) was prepared from (S)-1-phenylethanethiol (S)-378a (453 mg, 3.28 mmol) following general procedure J (30 h, vinyl isocyanate 1.5 eq).
**HPLC:** (R,R)-Whelk-01, Hex/i-PrOH 90:10, 1.0 mL/min, major 7.9 min, minor 11.4 min (214.4 nm, 254.4 nm).

379b: S-1-(4-Chlorophenyl)ethyl vinylcarbamothioate.

General procedure J (4 days) was followed using 1-(4-chlorophenyl)ethanethiol 378b (695 mg, 4.02 mmol) and vinyl isocyanate (2.0 eq) to afford the title compound as a white solid (863 mg, 89%).

R<sub>f</sub>: 0.41 (Pet/EtOAc 8:2); mp: 70-72 °C; <sup>1</sup>H NMR: (400 MHz; CDCl<sub>3</sub>) δ (ppm) 7.29-7.23 (m, 4H, H-8, H-9, H-11, H-12), 6.86 (bs, 2H, H-4, H-5), 4.71 (q, J = 7.2 Hz, 1H, H-1), 4.51 (d, J = 15.6 Hz, 1H, H-6'), 4.35 (d, J = 7.7 Hz, 1H, H-6), 1.62 (d, J = 7.2 Hz, 3H, H-2); <sup>13</sup>C NMR: (100 MHz, CDCl<sub>3</sub>) δ (ppm) 164.5 (C-3), 141.3 (C-7), 133.1 (C-10), 128.7/128.6 (C-8, C-9, C-11, C-12), 128.3 (C-5), 95.0 (C-6), 43.4 (C-1), 22.5 (C-2); IR: v<sub>max</sub>(film)/cm<sup>-1</sup> 3295 (NH), 1635 (C=O), 1490 (C=C<sub>Ar</sub>), 1236, 828 (C-Cl), 620; MS: m/z ([M+Na]<sup>+</sup>) 264 (100%), 296 [M+Na+MeOH]<sup>+</sup> (30%); HRMS: found 264.1210, [M+Na]<sup>+</sup> requires 264.1221.

385d: S-4-Methoxybenzyl methyl(vinyl)carbamothioate.

To a solution of (4-methoxyphenyl)methanethiol (0.23 mL, 1.62 mmol, 1.0 eq) in CH<sub>2</sub>Cl<sub>2</sub> (8.0 mL) at 0 °C was added vinyl isocyanate (1.0 eq). The reaction was warmed to rt and stirred at 30 °C for 4 h. The crude mixture was concentrated to afford a white solid (350 mg). A solution of this product (100 mg) was dissolved in DMF (5.0 mL) and cooled to 0 °C. Iodomethane (1.5 eq) was added and the reaction was stirred at 0 °C for a few minutes before sodium hydride (60% in mineral oil, 1.2 eq) was added portionwise. The reaction was stirred at 0 °C for 20 min, warmed to rt and stirred for 18 h. As TLC (Pet/EtOAc 8:2) showed remaining starting material, the reaction was heated to 30 °C for 4 h. Water was added and the layers were separated. The aqueous layer was extracted...
with Et₂O (x3). The combined organic layers were washed with HCl 0.5 M (x3), dried over MgSO₄, filtered and concentrated to afford the title compound as a colourless oil (85 mg, 77%).

Rf: 0.72 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.27 (d, J = 8.7 Hz, 2H, H-2, H-6), 6.84 (d, J = 8.7 Hz, 2H, H-3, H-5), 6.80 (bs, 1H, H-10), 4.45 (bd, J = 15.5 Hz, 1H, H-10'), 4.38 (d, J = 9.1 Hz, 1H, H-10), 4.16 (s, 2H, H-1), 3.79 (s, 3H, H-12), 3.12 (bs, 3H, H-9).

388: Cyclohexenyl(methyl)carbamic chloride.¹⁴⁸

Cyclohexanone (2.11 mL, 20.4 mmol, 1.0 eq), methylamine (8.3 M in EtOH, 6.0 eq) and 4 Å molecular sieves (activated powder, 2.0 g) were heated in a microwave at 125 °C for 1 h to generate imine 387.¹⁸² The crude mixture was filtered through celite, concentrated and dissolved in CH₂Cl₂ (40.0 mL). A solution of triphosgene (0.5 eq) in CH₂Cl₂ (60.0 mL) was stirred at 0 °C for 20 min before pyridine (1.0 eq) was added dropwise. The reaction was stirred at 0 °C for 5 min. The imine solution was added to the phosgene solution. The reaction was stirred at 0 °C for 2 h. Aqueous HCl (1.0 M, 40 mL) was added slowly and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (x2). The combined organic layers were washed with saturated aqueous NaHCO₃ (x2), dried over MgSO₄, filtered and concentrated to afford the title compound as a brown liquid (2.39 g, 67%).

¹H NMR: (400 MHz; CDCl₃) δ (ppm) 5.74 (bs, 1H, H-3), 3.10 (bs, 3H, H-8), 2.14-2.09 (m, 4H, H-4, H-7), 1.77-1.69 (m, 2H, H-5 or H-6), 1.63-1.55 (m, 2H, H-6 or H-5).

Matches published data.¹⁸³
To a solution of 388 (500 mg, 2.88 mmol, 1.0 eq) in DCE (15.0 mL) were sequentially added triethylamine (1.0 eq), DMAP (0.2 eq) and 1-phenylethyl mercaptan (1.0 eq). The reaction was stirred at 50 °C for 18 h. Water was added and the layers were separated. The aqueous layer was extracted with CH₂Cl₂ (x2). The combined organic layers were washed with water (x2), dried over MgSO₄, filtered and concentrated to afford the title compound as an orange oil (735 mg, 2.67 mmol, 92%).

Rf: 0.58 (Pet/EtOAc 8:2); ¹H NMR: (400 MHz; CDCl₃) δ (ppm) 7.37 (d, J = 7.3 Hz, 2H, H-12, H-16), 7.30 (t, J = 7.3 Hz, 2H, H-13, H-15), 7.22 (t, J = 7.3 Hz, 1H, H-14), 5.75 (bs, 1H, H-6), 4.63 (q, J = 7.1 Hz, 1H, H-1), 3.02 (s, 3H, H-4), 2.08 (bs, 4H, H-8, H-9), 1.74 - 1.68 (m, 2H, H-7 or H-10), 1.65 (d, J = 7.1 Hz, 3H, H-2), 1.60 - 1.56 (m, 2H, H-10 or H-7); ¹³C NMR: (100 MHz, CDCl₃) δ (ppm) 167.4 (C-3), 143.7 (C-11), 138.5 (C-5), 129.8 (C-6), 128.4 (C-13, C-15), 127.4 (C-12, C-16), 126.9 (C-14), 44.2 (C-1), 35.0 (C-4), 26.0/24.8 (C-8, C-9), 23.0 (C-2), 22.7/21.3 (C-7, C-10); IR: ν_max(film)/cm⁻¹ 1644 (C=O), 1334, 1248, 1090, 1044, 697; MS: m/z (ES⁺) 276 [M+H]⁺ (100%), 298 [M+Na]⁺ (70%); HRMS: found 276.1422, [M+H]⁺ requires 276.1417.

391: (E)-Allyl(1-cyclohexyl-3-(naphthalen-1-yl)but-2-en-1-yl)sulfane.

General procedure Q was followed using (E)-4-cyclohexyl-2-(naphthalen-1-yl)but-3-ene-2-thiol 319fi (380 mg, 1.28 mmol) to afford the title compound as a mixture with the expected product 322fi (350 mg, 322fi/391 1:0.7).

Rf: 0.63 (Pent/EtOAc 95:5); ¹H NMR: (500 MHz; CDCl₃) δ (ppm) 7.95-7.93 (m, 1H, H-16), 7.85-7.83 (m, 1H, H-19), 7.78-7.73/7.49-7.40 (m, 4H, H₉), 7.30 (dd, J = 7.0, 1.2 Hz, 1H, H-22), 5.95 (ddt, J = 17.0, 10.0, 7.0 Hz, 1H, H-12), 5.49 (dq, J = 10.8, 1.4 Hz, 1H, H-2), 5.25
(dq, $J = 17.0$, 1.4 Hz, 1H, H-13$'$), 5.14 (dq, $J = 10.0$, 1.4 Hz, 1H, H-13), 3.67 (dd, $J = 10.8$, 6.7 Hz, 1H, H-1), 3.31 (ddt, $J = 13.8$, 7.0, 1.4 Hz, 1H, H-11), 3.23 (ddt, $J = 13.8$, 7.0, 1.4 Hz, 1H, H-11$'$), 2.10 (d, $J = 1.4$ Hz, 3H, H-4), 2.06-2.01 (m, 1H, H-5), 1.83-1.57 (m, 12H, H-Cy), 1.31-0.87 (m, 16H, H-Cy), 1.31 (143.2 (C-15), 139.3 (C-Ar), 135.2/134.9 (C-12), 133.5 (C-Ar), 131.4 (C-Ar), 131.0/130.9 (C-2), 127.1 (C-Ar), 126.0/125.8 (C-16), 125.7/125.6/125.5/125.1/124.6/124.1 (C-Ar), 116.7 (C-13), 48.5 (C-1), 42.6 (C-Cy), 33.6 (C-11), 33.0 (C-Cy), 26.5/26.4/26.3/26.1/26.0 (C-Cy).

$^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 143.2 (C-15), 139.3 (C-Ar), 135.2/134.9 (C-12), 133.5 (C-Ar), 131.4 (C-Ar), 131.0/130.9 (C-2), 127.1 (C-Ar), 126.0/125.8 (C-16), 125.7/125.6/125.5/125.1/124.6/124.1 (C-Ar), 116.7 (C-13), 48.5 (C-1), 42.6 (C-Cy), 33.6 (C-11), 33.0 (C-Cy), 26.5/26.4/26.3/26.1/26.0 (C-Cy).

$^{184}$

403b: t-Butyl(hex-5-en-1-yloxy)diphenylsilane.

By a modification of the method reported by White and co-workers.

To a solution of hex-5-en-1-ol (1.0 g, 10.0 mmol, 1.0 eq) in THF (20.0 mL) at rt was added sodium hydride (60% in mineral oil, 1.5 eq) portionwise. The reaction was stirred at rt for 30 min and t-butyl(chloro)diphenylsilane (1.2 eq) was added. The reaction was stirred at rt for 3 days. Water was carefully added and the layers were separated. The aqueous layer was extracted with Et$_2$O (x3). The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated. Purification by column chromatography (Pet 100%, Pet/EtOAc 98:2, 95:5) afforded the title compound as a colourless oil (1.61 g, 48%).

$^{184}$

Rf: 0.90 (Pet/EtOAc 8:2); $^1$H NMR: (400 MHz; CDCl$_3$) δ (ppm) 7.67 (dd, $J = 8.0$, 1.5 Hz, 4H, H-12, H-16), 7.44-7.35 (m, 6H, H-13, H-14, H-15), 5.79 (dddd, $J = 17.0$, 13.3, 10.2, 6.9 Hz, 1H, H-5), 4.98 (dq, $J = 17.0$, 2.0 Hz, 1H, H-6$'$), 4.94 (ddt, $J = 10.2$, 2.0, 1.2 Hz, 1H, H-6), 3.66 (t, $J = 6.4$ Hz, 2H, H-1), 2.04 (qt, $J = 6.9$, 1.2 Hz, 2H, H-4), 1.62-1.55 (m, 2H, H-2), 1.50-1.43 (m, 2H, H-3), 1.05 (s, 9H, H-8, H-9, H-10); $^{13}$C NMR: (100 MHz, CDCl$_3$) δ (ppm) 139.0 (C-5), 135.6 (C-12, C-16), 134.1 (C-11), 129.5 (C-14), 127.6 (C-13, C-15), 114.3 (C-6), 63.7 (C-1), 33.5 (C-4), 32.0 (C-2), 26.8 (C-8, C-9, C-10), 25.1 (C-3).

$^{184}$

Matches published data.
403c: Hex-5-en-1-yl acetate.\textsuperscript{185}

By the method reported by Déléris and co-workers.\textsuperscript{185}

A solution of hex-5-en-1-ol (1.0 g, 10.0 mmol, 1.0 eq) and pyridine (1.0 eq) in Et\textsubscript{2}O (5.0 mL) was heated to reflux. Acetyl chloride (1.0 eq) was added dropwise. The reaction was refluxed for 2 h and cooled to rt. The resulting white solid was filtered and washed with petrol ether and Et\textsubscript{2}O. The filtrate was carefully concentrated on the rotary evaporator to afford the title compound as a pale yellow oil (1.17 g, 82%).

\textbf{\textsuperscript{1}H NMR:} (300 MHz; CDCl\textsubscript{3}) \(\delta\) (ppm) 5.79 (ddddd, \(J = 17.0, 13.3, 10.2, 7.0\) Hz, 1H, H-5), 5.01 (dq, \(J = 17.0, 2.0\) Hz, 1H, H-6\textsuperscript{`}), 4.97 (dddt, \(J = 10.2, 2.0, 1.2\) Hz, 1H, H-6), 4.06 (t, \(J = 6.7\) Hz, 2H, H-1), 2.08 (qt, \(J = 7.0, 1.2\) Hz, 2H, H-4), 2.05 (s, 3H, H-8), 1.69-1.60 (m, 2H, H-2), 1.50-1.40 (m, 2H, H-3).

*Matches published data.*\textsuperscript{185}
In the whole thesis, stereospecific and stereospecificity are used according to the definition by Zimmerman; see Zimmerman, H. E.; Singer, L.; Thyagarajan, B. S. *J. Am. Chem. Soc.* 1959, 81, 108.


6 Top 100 pharmaceutical drugs by retail sales in the U.S. in 2012: http://www.drugs.com/stats/top100/2012/sales.


McLellan, P. *Thesis*, The University of Manchester, December **2010**, supervisor Prof. J. P. Clayden.


See Experimental section, general procedure E and data for 334a.


See Experimental Section for detailed NMR data of (E)-328g and (Z)-328g.


Mingat, G.; Clayden, J. *Synthesis* 2012, 44, 2723.


The absolute configuration of this product was assigned based on the HPLC chromatogram showing the major enantiomer opposite to that obtained by (R)-COP-Cl-mediated catalysis, see Section II.A.2.b.

See Scheme 135 for structure and mechanism of formation of this by-product and see Experimental section for NMR data of analogous 361.


The (R)-configuration was initially assumed based on Overman’s assignements, as their published enantioenriched allylic thiocarbamates were compared with known derivatives. Evidence for the absolute configurations of thiocarbamates (R)-316a,b and the stereochemical outcome of the aryl migration is given in Section II.E.


134 Mingat G.; McDouall J. J. W.; Clayden J. *accepted*.

135 The absolute configuration of (R)-328f was confirmed by comparison of the specific rotation with that reported by Sharpless and co-workers, see Experimental section.


The absolute configurations of (S)-328g and (R)-328g were assigned by analogy with those reported by Noyori and co-workers in similar substrates, obtained with the same catalyst (R,R)-356.\(^\text{136b}\)


The absolute configurations of thiocarbamates 316f,g were assigned based on the well-established suprafacial nature of [3,3]-sigmatropic rearrangements of similar substrates.\(^\text{69,121}\)

See further in this thesis, Section II.E.


Fournier, A. M. *Thesis*, The University of Manchester, March 2012, supervisor Prof. J. P. Clayden.


CAS: 19009-45-1.


CAS: 55246-78-1.

CAS: 10218-95-8.

CAS: 10254-60-1.


CAS: 83508-61-6.

CAS: 10219-04-2.


CAS: 138943-57-4.


183 CAS: 33542-26-6.


Appendix

Appendix 1 – List of publications.

1. Mingat, G.; MacDouall, J. J. W.; Clayden, J. accepted. *Enantiopure Dihydrothiophenes Containing Quaternary Centres by Sequential Rearrangements and Ring-Closing Metathesis.*


Appendix 2 – General procedure for enzymatic resolutions of secondary alcohols with Novozym 435®.

To a solution of alcohol in the stated solvent at room temperature were added Novozym 435® and the acylating agent. The reaction was gently stirred (a very small stir bar was used at low speed) at the stated temperature. When required, a 0.05 mL aliquot of the crude reaction was removed, concentrated and diluted in CDCl₃ to be analysed by ¹H NMR and GC. At the end of the experiment, the reaction mixture was filtered through cotton (washed with Et₂O). The filtrate was concentrated under reduced pressure and further analysis was carried out when needed.
Appendix 3 – Procedure for NMR studies of lithiated phenyl(methyl)carbamothioate 317ac.

With special thanks to Dr Renzo Luisi (University of Bari “A. Moro”) for his advice regarding the set-up of these experiments.

1) $^1$H and $^{13}$C NMR spectra were taken in THF-d$_8$ for the non-lithiated substrate 316ac at -68 °C, 45 min after lithiation, and for allyllithium 317ac (resulting from lithiation of 316ac with LDA) at -60 °C, 105 min after lithiation.

2) The NMR samples were prepared on a 10-15 mg scale of 316ac and a small excess of LDA (1.5 eq).

3) The substrate solution was added to the LDA solution, which was prepared in the NMR tube to avoid quenching when transferring the base.

4) It is important to adjust the NMR tube in a ceramic spinner and mark the level before starting. Generating the allyllithium needs to be done at -78 °C and inserting the tube in the spinner afterwards could result in moisture condensation and breakage.

5) A N$_2$/Et$_2$O bath must be used to cool the tube before adding the substrate solution as liquid N$_2$ alone would freeze the sample. By using Et$_2$O, there is no need to wipe the tube before putting it in the NMR spectrometer as Et$_2$O will evaporate under the nitrogen stream while the sample goes down.

Preparation of the NMR sample of 317ac:

An NMR tube was carefully flame-dried, sealed with a septum fitted with an Ar balloon, and allowed to cool to rt. Parafilm was added. The NMR tube was purged with Ar by adding an outlet and squeezing the balloon several times, then cooled in an ice bath. DIPA (13 µL, 0.09 mmol, 1.5 eq) was added, followed by s-BuLi (1.5 eq). The Ar balloon was removed, a needle attached to the vacuum line was inserted and the solvent was carefully removed under vacuum. A viscous opaque liquid was observed within a few minutes. The vacuum line was replaced by the Ar balloon. The NMR tube was cooled to -10 °C in a NaCl/ice bath and THF-d$_8$ (250 µL) was added. The tube was inserted in a ceramic spinner and adjusted according to the previously marked level. In a flame-dried vial kept under Ar was prepared a solution of 316ac (15 mg, 0.060 mmol, 1.0 eq) in THF-d$_8$ (250 µL). The NMR tube was cooled to -78 °C as shown in Figure 45. The solution of 316ac
was added after a few minutes. The Ar balloon was removed right before putting the tube in the spectrometer and the septum was sealed with grease.

**Figure 45:** Set-up used to cool the NMR tube containing organolithium 317ac to -78 °C.