Synthesis and Transition Metal-catalysed Reactivity of Enantioenriched Allenes and Enynes

Farzad Zamani
University of Wollongong

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Synthesis and Transition Metal-catalysed Reactivity of Enantioenriched Allenes and Enynes

Farzad Zamani

Supervisors:
Dr. Christopher J. T. Hyland
Prof. Stephen G. Pyne

This thesis is presented as part of the requirement for the conferral of the degree:
Doctor of Philosophy

The University of Wollongong
School of Chemistry and Molecular Bioscience

February 2019
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Abstract

An allenylamino alcohol was synthesised via a known borono-Mannich method in which the amine group was next to the allene bond. A novel 2-allenylaziridine was then successfully obtained from the allenylamino alcohol under mild reaction conditions. The reactivity of the aziridine towards a number of ring-opening reactions was investigated. However, these ring-opening reactions proved to be capricious, and for the majority of these reactions no product could be isolated, along with many side products being formed. Therefore, the investigation was shifted to synthesise 5-allenyloxazolidinones, which could participate in nucleophilic ring-opening reactions as equivalent analogues of 2-allenylaziridines. To obtain these unique allenyl heterocycles, a series of new allenylamino alcohols was required in which the hydroxy group should be adjacent to the allene bond, as the borono-Mannich method provides a nitrogen heteroatom next to the allene bond. The first examples of simultaneous control of diastereoselectivity and regioselectivity in zinc-catalysed allenylation reactions of N-protected α-amino aldehydes of high enantiomeric purity using an allenylboronic acid pinacol ester were developed to obtain a wide range of novel anti and syn allenylamino alcohols. The resulting allenyl products demonstrated high reactivity in NaH-induced and Au-catalysed intramolecular cyclisation reactions to obtain novel 5-allenyloxazolidinones and 2,5-dihydrofurans, respectively, in high yields. It was described that N-Bn allenylloxazolidinones can be selectively transformed into novel chiral 1,3-(E)-enynes upon treatment with an excess amount of NaH through a decarboxylative conjugate elimination process. Addition of an extra triple bond to the enynes by incorporation of either propargyl or propiolic groups provided a series of novel unconjugated (E)-enediynes. We explored the potential of these versatile scaffolds to undergo cascade Au(I)-catalysed cycloaromatisation reactions to offer enantioenriched versions of a wide range of biologically relevant isoindolines and isoindolinones. The cycloisomerisation reaction of the propargylated enediynes likely involved a known single cleavage skeletal rearrangement mechanism and gave the corresponding isoindolines. However, the N-propiolic enediynes
underwent the Au(I)-catalysed cycloaromatisation through a new dual-gold reaction mechanism, which was supported by experimental, D-labeling experiments, and computational studies.
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Certification

I, Farzad Zamani, declare that this thesis submitted in fulfilment of the requirements for
the conferral of the degree Doctor of Philosophy, from the University of Wollongong, is wholly
my own work unless otherwise referenced or acknowledged. This document has not been submitted
for qualifications at any other academic institution.

Farzad Zamani
February 2019
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
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<tbody>
<tr>
<td>[M]^+</td>
<td>molecular ion</td>
</tr>
<tr>
<td>[α]_D</td>
<td>specific rotation</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>amu</td>
<td>atomic mass units</td>
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</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butyloxy carbonyl</td>
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<tr>
<td>br.</td>
<td>broad</td>
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<td>BQ</td>
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<td>Bu</td>
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<td>Bz</td>
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<td>doublet</td>
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<td>DABCO</td>
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<td>dd</td>
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<tr>
<td>DIAD</td>
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<tr>
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<td>chloro[1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene]gold(I)</td>
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<tr>
<td>$J$</td>
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<tr>
<td>LAH</td>
<td>lithium aluminum hydride</td>
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<td>Definition</td>
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<tr>
<td>LDA</td>
<td>lithium diisopropylamide</td>
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<td>retention factor</td>
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<tr>
<td>s</td>
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<td>Abbreviation</td>
<td>Definition</td>
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<tr>
<td><strong>Sn2</strong></td>
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<td>trifluoroacetic acid</td>
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Part 1. Synthesis and Reactivity of Allenylaziridines, Allenyloxazolidinones and Allenes with Pendant Heteroatoms

Chapter 1. Introduction

1.1. Aziridines and Oxazolidinones Bearing an Unsaturated Carbon–Carbon Bond

Heterocyclic compounds form one of the largest and most important family of organic compounds. Within this family, small-ring heterocycles (\(n = 3\) and 4) are a key structural feature in numerous biologically active molecules having synthetic, pharmaceutical and industrial applications. The small heterocyclic ring is also of great importance both as versatile substrates in organic synthesis of more elaborate structures and as desired targets of synthesis.\(^1\)

In particular, aziridines are valuable three-membered ring building blocks in organic synthesis that can be used to synthesise more complex \(N\)-containing heterocyclic molecules.\(^2\) The reactivity of aziridines can be diversified by introducing an unsaturated carbon-carbon bond at C-2 on the ring to create vinylaziridines 1 or ethynylaziridines 2 (Scheme 1.1a). Due to the presence of both a carbon-carbon multiple bond and a three-membered ring in these molecules, interesting reactivity toward a large number of different reagents could be expected. Since these aziridines are usually stable enough to be isolated and stored for a long period of time, they are widely utilized for the synthesis of biologically active compounds and natural products.\(^2\) Vinylaziridines generally participate in two major classes of transformations in the presence of low-valent transition metals, such as palladium(0); (i) 1,3-dipolar cycloadditions; and (ii) nucleophilic addition reactions (Scheme 1.1b).\(^3\) The vinylaziridine is first activated by an addition of a low-valent transition metal to form the zwitterionic 1,3-dipole 3 (Scheme 1.1b). This dipole (3) is then able to undergo nucleophilic addition reactions or 1,3-dipolar cycloadditions with dipolarophiles to give the corresponding products 4a,b and 5, respectively.
In contrast, ethynylaziridines 2 can also participate in ring-opening reactions to afford the allene adduct 6 and the propargyl product 8 (Scheme 1.1c).

The Trost group described palladium-catalysed asymmetric ring-opening transformations of vinylaziridines 9 with substituted 1H-pyrroles 10 and 1H-indoles 12 as nucleophiles to give ring-opened adducts 11 and 13, respectively, in high yields and high regio- and enantioselectivities (Scheme 1.2a). As illustrated in Scheme 1.2, these reactions proceed via nucleophilic attack of the heterocycle onto the Pd-allyl complex 14 (Scheme 1.2a). Furthermore, the synthetic application of this ring-opening protocol in natural products synthesis was developed for the preparation of the two important bromopyrrole alkaloids agesamide A and B (18 and 19, Scheme 1.2b), in which pyrrole 16 with methyl ester substitution at C-2 position was employed. The reaction proceeds via ring-closure of the amide.
anion in the π-allyl Pd intermediate 14 and the ester group of the pyrrole 16 to form cycloadduct 17.

Scheme 1.2. (a) Palladium-catalysed asymmetric transformation of the vinylaziridine 9 with nucleophiles. (b) Total synthesis of bromopyrrole alkaloids.

Organocopper-mediated ring-opening reactions of 3-alkyl-2-ethynylaziridines to synthesise chiral N-protected amino allenes was reported Ohno and co-workers (Scheme 1.3a). In this study, the ring-opening reaction of 2,3-trans-3-alkyl-2-ethynylaziridines 20 exclusively provided the (S,Sd)-amino allenes 21, whereas the reaction of 2,3-cis-3-alkyl-2-ethynylaziridines 22 provided the (S,Rd)-amino allenes 23 in high yields via the general mechanistic rationale shown in Scheme 1.1c. Mechanistically, the aziridines 20 and 22 undergo ring-opening reactions upon the nucleophilic attack of organocopper, providing the corresponding allene products.
In another study, Tanaka et al. described ring-opening reaction of 3-alkyl-2-ethynylaziridines 24 with aldehydes in the presence of InI/Pd(PPh₃)₄ via initial oxidative addition and transmetalation to provide 2-ethynyl-1,3-amino alcohols 26 in good yields (Scheme 1.3b). The allenylindium complex 25 first formed via treatment of 3-alkyl-2-ethynylaziridines with InI in the presence of Pd(PPh₃)₄ and H₂O. Stereoselective addition of the allenylindium to the aldehyde then occurred to give the final product 26.

Scheme 1.3. (a) Organocopper-mediated ring-opening reactions of ethynylaziridines. (b) Pd-catalysed stereoselective ring-opening reactions of ethynylaziridines using InI and aldehydes.

As an example of a [3 + 2] cycloaddition reaction of vinylaziridines, via their corresponding 1,3-zwitterionic dipoles, a diastereoselective synthesis of densely functionalised pyrroloindolines 30 and 31 was disclosed by the Hyland group. This process proceeded via a Pd-catalysed cycloaddition of vinylaziridine 27 with electron-deficient 3-nitroindoles 28 (Scheme 1.4). The vinylaziridine 27 first undergoes a ring-opening process through oxidative addition of the Pd(0) catalyst to form the π-allyl Pd(II) complex 29. The intermediate 29 then attacks to the electron-deficient indole 28 to form the pyrroloindoline. The cis and trans diastereoselectivity of this reaction is dependent on the substitution of the indole ring, but generally favours a trans relationship between the nitro and vinyl groups.
Vinylaziridines and ethynylaziridines can be synthesised by a series of different methods.\textsuperscript{2-3} For example, direct aziridination of a conjugated diene via the 1,2-addition of a nitrene species is a traditional method for the synthesis of vinylaziridines.\textsuperscript{2} the direct aziridination of the 1,3-diene 34 by 1,2-addition of alkoxy carbonylnitrene 33 was described by Hafner and co-workers, generated by photolysis of the methoxycarbonyl azide 32, to the diene (Scheme 1.5a).\textsuperscript{8} This methodology was highly stereospecific as the direct aziridination of 1,3-diene 34 provided the corresponding \textit{trans}-dimethylaziridine 35. Intramolecular cyclisation of 1,2-amino alcohols is another efficient method for the synthesis of aziridines.\textsuperscript{2} Aziridines can be generally formed in two steps by this approach; activation of the OH in order to make it a good leaving group, followed by intramolecular S\textsubscript{N}2 nucleophilic reaction of the NH to form the aziridine ring. Initial investigations of the ring-closure of vinyl- or ethynyl-substituted amino alcohols were based on the Mitsunobu reaction using PPh\textsubscript{3} and DEAD.\textsuperscript{9} However, low to moderate yields were obtained, mainly due to the formation of a carbamate byproduct resulting from the reaction between the amino alcohol and DEAD.\textsuperscript{9} This could be prevented by changing the ethyl group of DEAD to a bulkier isopropyl group as in DIAD.\textsuperscript{10-11} For example, Somfai and co-workers developed the intramolecular cyclisation of the \textit{N}-trityl allyl amino alcohol 36 to give aziridine 37 in excellent yield under Mitsunobu reaction conditions (Scheme 1.5b).\textsuperscript{12} In 1977, Manisse and Chuche reported the preparation of 2-ethynyl-3-vinylaziridine 39 via the intramolecular cyclisation of the amino alcohol 38 under Appel reaction conditions using PPh\textsubscript{3} and CCl\textsubscript{4} (Scheme 1.5c).\textsuperscript{13} It was shown that the reaction was stereospecific, and the \textit{trans}-aziridine 39 was obtained as a single isomer (Scheme 1.5c).
Interestingly, it has been shown that oxazolidinones could undergo ring cleavage pathways in a similar manner as aziridines. In 1992, the utility of 2-oxazolidinone as a latent aziridine equivalent in ring-opening reactions was reported by Poindexter and co-workers.\textsuperscript{14} They demonstrated that oxazolidinones could readily undergo ring-opening reactions without yielding the same undesired polyamino by-products as in the case of aziridines.\textsuperscript{14} For example, when the ring-opening reaction occurs in the presence of HCl, the oxazolidinone 40 can generate the same product 41 as the aziridine 42 by a decarboxylation reaction process (Scheme 1.6a). More recently, Iseki \textit{et al.} explored the nucleophilic ring-opening of oxazolidinone for the synthesis of a PGI\textsubscript{2} receptor agonist.\textsuperscript{15} Decarboxylative ring-opening of oxazolidinone 43 using 4-piperidinol 45 under heating in DMSO provided the diamine 46 without any significant side products (Scheme 1.6b). They also showed that the same diamine 46 could be obtained using the corresponding aziridine analogue 44. However, because of the toxic and carcinogenic properties of the aziridine, they focused their synthesis based on oxazolidinone precursors. It should be mentioned that the diamine 46 was employed as a key substrate to synthesise the corresponding PGI\textsubscript{2} receptor agonist in multiple steps.\textsuperscript{15}
In a similar vein, vinyloxazolidinones are shown to be equivalents of vinylaziridines after decarboxylative oxidative addition through the same zwitterionic dipole intermediate. Ooi and co-workers reported the synthesis and reactivity of 5-vinyloxazolidinone 48 in a cycloaddition reaction with benzylidenemalononitrile 49 in the presence of Pd(II)\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3} catalyst and ligand 51 (Scheme 1.7).\textsuperscript{16} The oxazolidinone 48 was synthesised in four steps from N\textsuperscript{-}Boc-glycine N\textsuperscript{-'}methoxy-N\textsuperscript{-'}methylamide 47. In this study, the chiral ligand 51 showed a remarkable ability to control the stereoselectivity of the cycloaddition reaction allowing the catalytic asymmetric synthesis of densely functionalised piperidines 50 in high to excellent yields.

Scheme 1.7. Synthesis and reactivity of 5-vinyloxazolidinone 48 in cycloaddition reactions with benzylidenemalononitrile 49 in the presence of Pd(II)\textsubscript{2}(dba)\textsubscript{3}·CHCl\textsubscript{3}.
The Jang group described the synthesis of 5-vinyloxazolidinones 54 via platinum-catalysed cyclisation of N-allyl carbamates 53 in good yields (Scheme 1.8). The reaction was initiated by formation of the electrophilic allyl-platinum intermediate 55 followed by nucleophilic attack of the oxygen. The role of SnCl₂ in this reaction mechanism was proposed as a promoter for the C–O bond cleavage in the carbamate, and as a catalyst activator.

Taking all these studies into consideration, a proposal was designed for the synthesis of 2-allenylaziridine 59 from the cyclisation reaction of allenyl amino alcohols 57 (Scheme 1.9) and subsequent investigation of these systems reactivity. Although the synthetic methods and the reactivity of vinylaziridines 1 and ethynylaziridines 2 have been broadly studied, those for the analogous allenylaziridine 59 skeleton is still unexplored. Allenylaziridines provide one extra π-bond compared to a vinylaziridine, potentially leading to a diene product in metal-catalysed ring-opening pathways. The ability to exploit further manipulation of the resulting diene would make these compounds potentially powerful scaffolds in organic synthesis. Furthermore, since oxazolidinones can undergo ring cleavage pathways in a similar manner as aziridines, it was envisioned to synthesise and investigate the reactivity of 5-allenyloxazolidinones 60 as equivalent analogues of the 2-allenylaziridines 59 in ring-opening reactions. These allenylloxazolidinone or allenylaziridines compounds have not been reported.
in the literature; therefore, a synthetic approach was required to be established for the preparation of these unique heterocycles and the subsequent investigation of their reactivity.

Scheme 1.9. Proposed synthesis of the 2-allenylaziridine and allenlyloxazolidinone from allenyl amino alcohols.

The allenyl amino alcohols 57 and 58, which are the proposed precursors to the allenylaziridines and allenlyloxazolidinones, are intriguing motifs given the presence of two heteroatoms. Allenes bearing a single pendant heteroatom have been widely investigated in terms of their synthesis and subsequent cyclisation reactions. However, systems such as 57 and 58 with two pendant heteroatoms are far less investigated, in part due to a lack of methods for their preparation. An overview of the key methods for the synthesis of allenes bearing a single heteroatom are now detailed, followed by an overview of the limited investigations of their two heteroatom counterparts.

1.2. Allenes Bearing a Single Pendant Heteroatom

Many methods for the synthesis of allenes bearing a single pendant heteroatom have been reported in the literature. Allenylation of carbonyl compounds and imines with allenyl or propargyl organometallic reagents are amongst the most commonly employed methods for the synthesis of such allenes. The easy access to starting materials and reagents, as well as mild and efficient reaction conditions make these methodologies particularly attractive for synthesis of heteroatom-functionalised allenes. However, these methods are also quite challenging due to the requirement for control of regioselectivity between propargyl 64 and allenyl 65 isomers (Scheme 1.10), as well as control of enantiomeric purity of the products. Despite these challenges, there have been many significant developments in allenylation reactions of
carbonyl compounds and imines with control of enantio- and regioselectivity.\textsuperscript{19, 22-23} Carbonyl compounds and imines \textit{61} can generally undergo 1,2-addition reactions with organometallic reagents in the presence of transition metal catalysts, Lewis or Brønsted acids, or Lewis bases, providing propargyl and allenyl products \textit{64} and \textit{65} (Scheme 1.10). The regioselectivity of these reactions for allenyl versus propargyl products mainly depends upon the nature of the metal, the substituents on the organometallic reagents, the reaction temperature, and the solvent – as well as the allenylation reagent employed.\textsuperscript{18-19}

There are two different mechanistic pathways for the allenylation and propargylation reactions of carbonyl compounds and imines with organometallic reagents (Scheme 1.10). The allenylation and propargylation reactions involving the direct addition mechanism (Scheme 1.10a) typically proceed via the direct addition of the organometallic reagent to the electrophile by an SE\textsubscript{2}′-type mechanism in the presence of a Lewis acid or Lewis base. Coordination of the Lewis acid to the carbonyl or imine group can render it sufficiently electrophilic to undergo the nucleophilic addition reaction. On the other hand, Lewis bases generally activate the organometallic species by binding to the metal.\textsuperscript{24} Therefore, in the direct addition mechanism with the allenyl reagent \textit{62}, the propargyl product \textit{64} forms preferentially – in contrast, the use of propargyl reagent \textit{63} gives allenyl product \textit{65}. The regiochemical outcome of these reactions can be explained by the coordination between the metal and the carbonyl oxygen (X = O) or the imine nitrogen (X = NR) (Scheme 1.10a).\textsuperscript{25-26} These intermediates can be used to explain the general direct addition pathways in which allenyl organometallic reagents afford homopropargylic alcohol (or amine) products, and propargyl organometallics favour α-allenyl alcohol (or amine) products. These reactions usually proceed with boron, tin, silicon, zinc, or indium organometallic reagents catalysed by Lewis acids or bases (Scheme 1.10a).\textsuperscript{19, 21}
On the other hand, allenylation and propargylation reactions involving the isomerisation mechanism (Scheme 1.10b) typically proceed by an initial transmetalation step, followed by the addition to the electrophile (Scheme 1.10b). The reaction of allenyl reagent 66 or propargyl reagent 67 with the metal catalyst first generates the propargyl 68 and allenyl 69 complexes, respectively, which can slowly equilibrate (Scheme 1.10b), in which the allenyl intermediate 69 is generally more thermodynamically stable. The final product distributions are determined by a balance between rate of the isomerisation and relative stability of the allenyl-69 and propargyl-metal 68 intermediates. These intermediates can react with the electrophilic carbonyl compounds or imines via an SE2′-type process to give the corresponding allenyl 65 or propargyl 64 products, respectively. Tuning the regioselectivity of the reaction has been a critical challenge in organic synthesis, since the metallotropic rearrangement between the intermediates 68 and 69 often results in poor regioselectivity. In this regard, many research
studies have explored methods to fully control the regiochemistry of these organometallic reactions. 18–22

1.2.1. Allenylation and Propargylation Reactions via Direct Addition

In 2013, the Hoveyda group demonstrated the catalytic enantioselective allenylation reactions of N-protected isatins 70 using allenylboronic acid pinacol ester 71 catalysed by the aminophenol catalyst 72, and NaO\textsubscript{t}Bu under mild reaction conditions (Scheme 1.11). 27 These reactions were highly regioselective for the allenyl products 73 (>98%) and proceeded in high yields (90–91%), as well as affording allenyl products in excellent enantiomeric purities (92–96% ee). However, the scope of the process was quite limited since only a few N-protected isatins 70 were accessible.

Hoveyda and co-workers also described the catalytic enantioselective allenylation reactions of fluoro-substituted ketones 74 using allenylboronic acid pinacol ester 71 in the presence of the triphenylsilyl-substituted aminophenol catalyst 75 (Scheme 1.12). 28 The reactions involve the propargylboron intermediate 77 in which the boron is attached to the phenol oxygen and the benzylamino group of the catalyst (Scheme 1.12). The protonated nitrogen increases the Lewis acidity of the boron, facilitating C–C bond formation. Furthermore, high enantioselectivities (83–98% ee) were obtained because of the rigid catalyst–substrate complex caused by the internal H-bonding to the fluoro-substituted ketone.
A chiral Brønsted-acid catalysed asymmetric allenylation of aldehydes 78 using (trimethylsilyl)propargylboronic acid pinacol ester 79 was developed by Reddy (Scheme 1.13). This methodology exhibited high efficiency towards a broad range of aryl, aliphatic, and heteroaryl aldehydes with high yields (89-94%) and excellent enantiomeric excesses (82-99%). The TMS group of the final allene product was readily removed by treatment with tetrabutylammonium fluoride (TBAF). It was proposed that H-bonding between the phosphonic acid and the pseudoaxial oxygen of the propargyl reagent (intermediate 81) led to the final allene products 80 being obtained in high enantiomeric excess (ee).
1.2.2. Allenylation and Propargylation Reactions via the Isomerisation Mechanism

The allenylation reaction of isatins 82 with propargyl bromides 83 in the presence of different metals (indium, tin, zinc) and additives in aqueous media was reported by Alcaide et al. (Scheme 1.14).\textsuperscript{30} They demonstrated that the steric effect of the substituent (R\textsubscript{2} = Me or Ph) on the propargyl bromide was responsible for high regioselectivity of the allenyl products 86 as the allenyl species 85 could be destabilised due to an unfavourable steric strain interaction.

![Scheme 1.14. Regioselective allenylation reaction of isatins in aqueous media.](image)

An interesting approach towards allenic alcohols 90 or homopropargylic alcohols 91 using the indium-catalysed reaction of trialkylsilyl propargyl bromides 89 with various aldehydes 88 was developed by Loh et al. (Scheme 1.15).\textsuperscript{31} They showed that changing the size of the silyl group and the reaction conditions, either the allenic 90 or homopropargylic 91 alcohols could be provided in good to excellent yields and high regioselectivities. The sterically smaller TMS group favoured the propargyl product 91 at higher temperatures while the larger TIPS and TBDPS groups provided the allenyl products 90 at room temperature. It was also hypothesised that the coordination of the silicon with the halogen of the indium salt may play a significant role in the selectivity of the final products (93, Scheme 1.15).
Scheme 1.15. Indium-mediated reactions of aldehydes with trialkylsilyl propargyl bromides.

In another study, it was described that a mixture of a tin(IV) salt and tetrabutylammonium iodide could be used for allenylation of aldehydes 95 with 2-propynyl mesylates 94 in CH2Cl2 at room temperature (Scheme 1.16).32 This technique showed that the regioselectivity towards the allenic product could be controlled by placing a methyl group on the R2 position of the 2-propynyl mesylate 94.

Scheme 1.16. Allenylation of aldehydes using a combination of tin(IV) iodide and tetrabutylammonium iodide.

The silver-catalysed allenylation and propargylation reactions of methyl 2-oxo-2-phenylacetate100 using allenylboronic acid pinacol ester 71 under mild reaction conditions was reported by Jarvo and co-workers (Scheme 1.17).33 Initially, B/Ag exchange results in an equilibrium between propargylsilver 71a and allenylsilver 71b intermediates (Scheme 1.17).
These silver species react with the carbonyl via an $S_{E2}'$ pathway to provide the propargyl and allenyl products $101$ and $102$. They demonstrated that in the absence of an additional additive, the allenyl product $102$ was the major isomer (allene/propargyl = 5.8:1). However, the addition of Bu$_4$NI led to a switch in regioselectivity favouring the propargyl product $101$ (allene/propargyl = 1:14.4). They reported that the cause of the change in the regioselectivity by the addition of the halide additive was not fully understood and was under investigation, however, it is possible that it increases the rate of equilibration between the allenyl- and propargyl-silver intermediates.$^{33}$

![Scheme 1.17. Silver-catalysed allenylation and propargylation reactions of methyl phenylglyoxylate 100 using allenylboronic acid pinacol ester.]

The allenylation reaction of $N,O$-aminals $103$ using allenylboronic acid pinacol ester $71$ catalysed by a combination of indium(I) chloride and the chiral silver BINOL phosphate ligand $106$ under mild conditions was reported by Kobayashi and co-workers (Scheme 1.18).$^{34}$ The reaction proceeded with high asymmetric induction for the allene products, but with only moderate regioselectivity. The regiochemical outcome would suggest that the reaction follows the general isomerisation mechanism pathway (Scheme 1.10b), in which B/In transmetalation initially occurs to form the corresponding allenyl and propargyl indium intermediates. Indium activation of the methoxy leaving group generates a stabilised carbenium ion intermediate that can react with the indium reagent.
In another study, the Fandrick group demonstrated the regioselective allenylation reactions of aldehydes and ketones 107 using (trimethylsilyl)propargylboronic acid pinacol ester 79 in the presence of copper(II) isobutyrate, LiOtBu, and the chiral bidentate diphosphine ligand 109 (Scheme 1.19).35 Although the regioselectivities for the allenes 108 were good to excellent (83-99%), the ees of the allenyl products were poor to moderate (ca. 5–64%). The regioselectivity of this reaction follows the general isomerisation mechanism pathway (Scheme 1.10b), in which the corresponding copper intermediates initially form as a result of B/Cu transmetalation.

The zinc-catalysed regioselective allenylation reaction of aldehydes and ketones was developed by the Fandrick group using allenylboronic acid pinacol ester 71 and a catalytic amount of Et₂Zn in toluene under mild conditions (Scheme 1.20).36 This methodology worked efficiently for a broad range of aromatic and aliphatic aldehydes and ketones 110, and tolerated...
several reactive functional groups including esters, carbamates, and primary bromides and chlorides. Furthermore, in terms of economical point of view, zinc is a non-precious metal catalyst highlighting the importance of this method. The regioselectivity of this reaction was dependent upon the amount (mol%) of Et₂Zn, the reaction temperature, and the solvent. For example, the allenyl/propargyl ratio decreased from 93:7 to 54:46 in favour of the propargyl product 112 with increasing catalyst loading from 2 mol% to 13 mol%. In the polar solvent THF, low catalyst loadings (7 mol %) also favoured formation of the propargyl product 112 (allene/propargyl = 30:70). The temperature was found to have a minimal effect on the regioselectivity since using 7 mol% of Et₂Zn at 0 °C and 20 °C resulted in the regioselectivity for the allene decrease by only 3%.

Based on earlier studies, the zinc-catalysed allenylation reaction was found to proceed via the general isomerisation mechanism pathway (Scheme 1.10b). Initially, B/Zn exchange results in an equilibrium between propargylzinc 113 and allenylzinc 114 intermediates (Scheme 1.21). The propargylzinc species 113 is kinetically favoured as this is initially formed upon boron to zinc transmetalation. This zinc species reacts with the electrophile under kinetic control conditions via an SE2´ pathway to provide the allene product 117. In contrast, the more thermodynamically stable allenylzinc intermediate 114 is formed by isomerisation of the initially formed propargylzinc and then reacts with the electrophile to give the propargyl isomer 118 – again by the SE2´ pathway. As expected for a transmetalation process, the regioselectivity in the Et₂Zn-catalysed reactions mainly depends on the rate of isomerisation in the equilibrium between the organozinc intermediates. Increasing the amount of zinc catalyses the isomerisation, which is second order in [Zn], and as the equilibrium lies
towards the more thermodynamically stable allenylzinc reagent 114, more propargyl product is observed when the concentration of the zinc catalyst is increased.\(^{36}\) Furthermore, more electrophilic aldehydes bearing electron-withdrawing groups next to the carbonyl typically offered higher regioselectivity for the allene product because they underwent faster addition with the propargylzinc reagent 113, before significant isomerization could occur.\(^{36}\) Moreover, the isomerisation also occurs rapidly in the polar solvent THF, favouring the more stable allenylzinc intermediate 114 to favour formation of the corresponding propargyl product 118 (Scheme 1.21).

Kobayashi and co-workers subsequently disclosed a related zinc-catalysed regioselective allenylation reaction of ketones using allenylboronic acid pinacol ester 120 in the presence of a catalytic amount of Zn(HMDS)_2 (Scheme 1.22).\(^{37}\) In this study, the zinc amide catalyst (Zn(HMDS)_2) was found to undergo a faster rate of B/Zn exchange than Et₂Zn, which enables the reaction to be conducted under milder conditions. However, the zinc amide catalyst is not commercially available and should be prepared, handled and stored in a glove box at −30 °C. Allenyl products 121 were obtained using 2 mol% of the zinc amide catalyst at −40 °C in toluene with high to excellent regioselectivity (Scheme 1.22). Performing the reaction in the non-coordinating solvent toluene and at low temperature favoured the allene product via reaction of the propargylzinc intermediate. The mechanistic results are consistent with those of Frandrick\(^{36}\) (Scheme 1.21).
1.3. Metal-catalysed Cyclisation Reactions of Allenes with a Single Pendant Heteroatom

The allenes tethered to a heteroatom prepared via the methods described in Schemes 1.11-1.22 can participate in powerful heterocyclic-ring-forming reactions. The intramolecular additions of heteroatoms to allene systems is a powerful strategy to directly access a wide variety of highly functionalised and complex heterocyclic molecules in an atom-economical manner. Different regiochemical outcomes can simply be achieved in intramolecular reactions by using different reaction conditions or by changing the tether length of substituents between the heteroatom and the allene bond (Scheme 1.23). Importantly, substituted allenes have axial chirality and can often be prepared in high enantiomeric purities leading to enantioriched products upon cyclisation. Therefore, heteroatom-tethered allenes play a particularly significant role in organic synthesis, since they can be converted under mild conditions into biologically active chiral heterocycles via cyclisation reactions.

The general reaction pathways for the cyclisation of allenes bearing a pendant heteroatom 123 in the presence of a transition metal catalyst are illustrated in Scheme 1.23. The metal can coordinate to either of the two π-bonds of the allene via η²-coordination, activating cyclisation via the endo- or exo- attack mode to the internal or terminal carbons by the pendant nucleophile to provide different heterocyclic structures. In such reactions, one of the allene double bonds remains in the final product as an alkene, which can be manipulated further by other chemical transformations.
The cyclisation reaction of allenes has been extensively explored with a wide variety of pendant nitrogen and oxygen nucleophiles. In particular, the cyclisation reactions of allenols and amino allenes provide a large number of O- or N-heterocycles, and have been broadly investigated for the synthesis of natural products. In this section, some representative examples regarding the cyclisation reactions of heteroatom-pendant allenes will be discussed.

In 1979, the cyclisation reactions of α-allenols and β-allenols in the presence of catalytic amounts of a silver salt were first explored by Claesson and Olsoon (Scheme 1.24). α-Allenols provided 2,5-dihydrofurans in the presence of AgBF₄ or AgNO₃ via 5-endo-trig attack of the pendant oxygen nucleophile to the distal double bond, whereas β-allenols gave 5,6-dihydro-2H-pyrans via 6-endo-trig cyclisation. In another study, Ma and Zhao reported the diastereoselective synthesis of optically active trans-2,3-disubstituted vinylc oxiranes via Pd-catalysed insertion-cyclisation reaction of α-allenols with aryl iodides (Scheme 1.25). The π-allyl-Pd complex is formed as the intermediate, which undergoes cyclisation with the pendant heteroatom. The reaction proceeded with excellent regioselectivity for the epoxide ring, with no five-membered ring dihydrofuran observed in this reaction, presumably because a trans π-allyl complex is favoured and this can only cyclise to give the trans epoxide.
Scheme 1.24. First reported silver-catalysed cyclisation reactions of racemic α-allenols and racemic β-allenols.

Scheme 1.25. Palladium-catalysed insertion-cyclisation reaction of α-allenols.

Toste and co-workers developed Au(I)-catalysed enantioselective cyclisation reaction of allenes with a pendant hydroxyamine or hydrazine group 138 (Scheme 1.26). In this methodology, chiral vinyl isoxolidines, oxazines, and pyrazolidines 139 were afforded in the presence of a Au(I)/Ag(I) catalyst system using chiral ligands (L*, 140) and the chiral anion (S)-trip with moderate to excellent yields and high enantiomeric excesses. These heterocycles could serve as potential precursors in natural products synthesis as they appear frequently in biologically important molecules.
Recently, our group reported the synthesis of pyrrolines 143a,143b and tetrahydropyridines 144 from the cyclisation reactions of β-amino allenes 142 using the Au(I) and Ag(I) catalyst combination (Scheme 1.27). It was shown that the (PPh₃)AuCl/AgBF₄ catalyst (10 mol%) in CH₂Cl₂ at room temperature favoured the 5-endo-dig cyclisation reaction pathway, before rapid rearrangement of 143a to the product 143b with an endocyclic alkene (Scheme 1.27a). Conversely, AgBF₄ (10 mol%) favours the 6-endo-trig cyclisation mode in toluene at room temperature to provide the 6-membered ring product 144 (Scheme 1.27b). The reason for the regioselectivity of this reaction is uncertain, but presumably it appears that silver binds preferentially to the distal π-bond of the allene and gold to the proximal.

Scheme 1.27. Au(I) and Ag(I)-catalysed cyclisation of racemic β-amino allenes.
1.4. Allenes Bearing Two Pendant Heteroatoms

In the previous section, the synthesis and selected reactivity of allenes containing a single heteroatom for the synthesis of heterocycles were discussed. The development of efficient reactions that enable the formation of molecules, in particular heterocycles, with multiple heteroatoms in a highly efficient way is of significant interest for synthesis of complex organic targets. In this regard, introducing a second pendant heteroatom element to the allene would be highly desirable. Allenes bearing two pendant heteroatoms not only provide more active sites in a single molecule, but also offer more diversity in further cyclisation pathways. In addition, the ability to exploit further manipulation of the resulting heterocycles – at either the exocyclic free heteroatom or at the remaining double bond – would make these compounds versatile intermediates in natural product synthesis. As proposed in Scheme 1.9, allenes bearing two pendant heteroatoms could also act as potential precursors to synthesise the allenylaziridine 59 and allenyloxazolidinone 60 that are the primary subject of this thesis.

Despite extensive reports of allenes with a single heteroatom in the literature, methods to prepare allenes with multiple pendant heteroatoms are rare, and the reported studies have not been catalytic. Therefore, the synthesis of such powerful scaffolds is a highly desirable goal. Some of the few existing methods for the synthesis of these allenic skeletons is now discussed.

Alcaide and co-workers described metal-mediated allenylation of azetidine-2,3-diones 145 with differently substituted propargyl bromides 146 in the presence of Zn, In, and Sn (Scheme 1.28). A series of allenyl-substituted 3-hydroxy-lactams 147 were obtained in low to high yields with excellent regioselectivity and diastereoselectivity. The stereoselectivity of this reaction could be attributed to the chiral auxiliary at C-4 blocking one face of the ketone, which forces the organometallic reagent to attack from the less hindered side (148, Scheme 1.28).
The Pyne group disclosed the three component, one-pot borono-Mannich reaction of \( \alpha \)-hydroxy aldehydes 150 (as their cyclic acetal dimers 151) with primary or secondary amines 149 in the presence of allenylboronic acid pinacol ester 71 under mild conditions (Scheme 1.29).\(^5^4\) These reactions were highly regioselective (>98%) and provided exclusively the *anti* allenyl \( \alpha \)-hydroxy amines 152 in moderate to high yields (54-92%). Furthermore, enantiomerically enriched \( \alpha \)-hydroxy aldehydes 150 gave the allenyl products with high enantiomeric excess (*ee* > 96%). The stereoselectivity of the reaction was explained based on the intermediate 153 in which A\(_{1,3}\)-strain about the iminium ion intermediate is minimized.\(^5^4\)

Soon after the initial investigation by Pyne, the Petasis group reported similar findings using \( \alpha \)-hydroxy aldehydes 155 and glyoxylic acid (monohydrate) 156 with primary or secondary amines 154 in the presence of allenylboronic acid 157 (Scheme 1.30).\(^5^5\) It was shown
that the nature of the amine substrate determined the regiochemical outcomes of the reaction. Although secondary amines exclusively provided the α-allenyl amino acids (158a,b), most primary amines formed the α-propargyl amino acids (159a,b), with less regioselectivity for bulkier substrates. These general trends could be explained by some mechanistic insights. It was shown that the intermediate 160 formed from the primary amines were electrostatically more favoured to attack from the γ-position of the allene moiety to generate propargyl products 159a,b. In the case of the secondary amines (intermediate 161), however, the α-addition to the iminium species was more favourable providing allenyl products 158a,b exclusively. It was also found that the bulkier the amine components, the lower were the isolated yields.

Scheme 1.30. The borono-Mannich reactions of α-hydroxy aldehydes and glyoxylic acid (monohydrate) with primary or secondary amines in the presence of allenylboronic acid.

Although these reactions can be performed under mild conditions with high yields and selectivities, there are some limitations regarding these techniques. Most of the allenyl products consist of two alkyl groups on the nitrogen, which restricts them from further synthetic manipulation – for example, a cyclisation reaction would require a free N-H moiety. Furthermore, a large range of the chiral α-hydroxy aldehyde precursors are not generally accessible, which restricts the scope of the reaction. Also, these only give products with the
nitrogen next to the allenyl unit – meaning the allenyloxazolidinone (Scheme 1.9) – as an aziridine equivalent – could not be formed by this method.

Inspired by the study carried out by the Fandrick group (Schemes 1.20), it was proposed in this PhD study that enantiomerically enriched α-amino aldehydes could be utilised as the carbonyl precursors using this technique in order to afford chiral α-allenylamino alcohols (Scheme 1.31) to provide a complementary method to the borono-Mannich reaction.

**Scheme 1.31.** Proposed synthetic pathway for the zinc-catalysed allenylation reaction of enantioenriched chiral α-amino aldehydes in the presence of allenylboronic acid pinacol ester.

α-Amino aldehydes are powerful building blocks because of their ready accessibility in both enantiomeric forms for synthesis of enantiomerically enriched compounds in natural products and pharmaceuticals. The presence of a formyl group and an amino functionality in a single molecule enable α-amino aldehydes to be exploited for further manipulation to construct complex chiral structures. In general, the major challenge in the synthesis of α-amino aldehydes is the labile nature of the α-stereogenic centre, which is prone to undergo racemisation in the presence of base or acid, or upon chromatographic purification and storage. The acidic α-hydrogen of the α-amino aldehyde enables the aldehyde to form the enol under acidic and enolate under basic conditions (Scheme 1.32). This phenomenon results in an extensive loss in enantiomeric purity of the α-amino aldehyde due to forming a mixture of (R) and (S) enantiomers. Therefore, maintaining enantiomerically purities of α-amino aldehydes is the main challenge in their use in organic transformations.
Scheme 1.32. Racemisation of N-protected α-amino aldehydes.

Consequently, in the proposed chemistry, several challenges need to be considered to achieve efficient zinc-catalysed allenylation reactions of α-amino aldehydes. Regioselectivity issues can be challenging, as both the allene and the propargyl isomers may be formed via the general isomerisation mechanism process. The ability to control the diastereoselectivity of the reaction would be another potential issue because of the formation of a new stereogenic centre. The enantiomeric purity of the final allene product can also be challenging, as the enantiomerically enriched α-amino aldehydes can potentially undergo racemisation, leading to products of low enantiopurities. However, it was anticipated that under the very mild zinc-catalysed allenylation reaction conditions that the racemisation of the α-amino aldehydes would be unlikely, which is one reason why this particular method was chosen for investigation.

1.5. Aims of the Project (I)

The first aim of this project was the development of an efficient synthetic route to an allenylaziridine. Inspired by previously reported synthesis of allenyl amino alcohols 170 via borono-Mannich reaction of α-hydroxy aldehydes 168, amines 169 and allenylboronic acid pinacol ester 71,54 it was envisioned to utilise these allenyl scaffolds in the synthesis of the 2-allenylaziridines 171 (Scheme 1.33a). Based on the general reactivity of aziridines, it was assumed that these aziridines might participate in metal-catalysed ring-opening reactions through the formation of the vinyl-π-allylpalladium intermediate 172. This intermediate could undergo an allylic nucleophilic substitution reaction to form the chiral diene 174 containing a pendant N-heteroatom (Scheme 1.33a). Therefore, we aimed to examine the reactivity of these
aziridines in different ring-opening reaction conditions. On the other hand, in order to obtain 5-
allyloxazolidinones, having an OH group adjacent to the allene bond was necessary. 
Therefore, it was intended to investigate the possible synthetic routes for the synthesis of these 
allenes bearing two pendant heteroatoms by the zinc-catalysed allenylation of readily accessible 
\(\alpha\)-amino aldehydes 162 (Scheme 1.33b). \(\alpha\)-Amino aldehydes are susceptible to racemisation 
under acidic or basic conditions, or even upon chromatographic purification and storage. It was 
therefore aimed to investigate whether the proposed methodology would show retention of the 
enantiomeric purity of the aldehyde during the reaction steps. Due to the creation of the new 
chiral centre in the zinc-catalysed allenylation reaction of \(\alpha\)-amino aldehyde, the 
diastereoselectivity of the reaction may also need to be investigated. These allenyl amino 
alcohols 163 could be used as powerful chiral building blocks in the synthesis of 5-
allyloxazolidinone 175, as well as cyclisation reactions catalysed by electrophilic transition 
metals, such as Au(I). Furthermore, as the equivalent analogues of the 2-allenylaziridines 171, 
the 5-allyloxazolidinone 175 should also display similar reactivity via a decarboxylative ring 
cleavage pathway to generate the chiral nitrogen-pendant diene 178 (Scheme 1.33b).
Scheme 1.33. (a) Proposed synthetic pathway for preparation and reactivity of 2-allenylaziridine. (b) Proposed synthetic pathway for preparation and reactivity of 5-allenyloxazolidinone.
Chapter 2. Results and Discussion

2.1. Synthesis of 2-Allenyl-N-benzylaziridine

In order to prepare the allenyl amino alcohols, which is required to synthesise the unexplored allenylaziridines (Scheme 1.33), the borono-Mannich reaction was first investigated. At the beginning of the project, the borono-Mannich reaction was performed using glycolaldehyde dimer 179, benzylamine 180, and allenylboronic acid pinacol ester 71 under microwave condition. The allenyl amino alcohol 181 was obtained after purification by column chromatography in moderate yield (54%) and with excellent regioselectivity (Scheme 2.1). Having the model substrate 181 in hand, different methods were examined in order to obtain the desired 2-allenylaziridine by intramolecular ring-closure.

![Scheme 2.1. Synthesis of the allenyl amino alcohol 181.](image)

Initially, the intramolecular S\textsubscript{N}2 cyclisation of the allenyl amino alcohol 181 under Mitsunobu reaction conditions was investigated. The substrate 181 was subjected to reaction conditions similar to those reported in the literature using PPh\textsubscript{3} and DIAD (Scheme 2.2a).\textsuperscript{12} The reaction mixture was stirred at room temperature for 3 h, but no conversion was observed by TLC analysis. The reaction was stirred and heated at reflux for 18 h, with the reaction monitored by TLC analysis. \textsuperscript{1}H NMR analysis of the crude reaction mixture showed 100% conversion of the starting material, and that a complex mixture of products had been formed. No \textsuperscript{1}H NMR resonances for the expected aziridine product 182 were observed. Also, no discrete products could be isolated after purification by column chromatography.

A simple procedure had been developed for the preparation of a wide range of aziridines, particularly \textit{N}-benzyl aziridines, in a single step using TsCl and DMAP/Et\textsubscript{3}N.\textsuperscript{60} The procedure relies on the \textit{O}-tosylation/intramolecular S\textsubscript{N}2 displacement pathway and the
advantage of this procedure compared to the Mitsunobu methodology is that these reactions typically proceed at room temperature. Therefore, the allenyl amino alcohol 181 was treated with TsCl and DMAP/Et3N in CH2Cl2 at room temperature for 24 h (Scheme 2.2b). However, no aziridine product was detected, and a complex mixture of products resulted as evidenced from 1H NMR analysis.

Cyclisation of the allenyl amino alcohol 181 under Appel reaction conditions using PPh3 in combination with CCl4 or CBr4 was next explored.61 The allenyl amino alcohol 181 was treated with PPh3 and CBr4 in the presence of Et3N in CH2Cl2 at room temperature (Scheme 2.3). The reaction was observed to be fast, with complete consumption of the starting material detected after 10 min based on TLC analysis. Although complete conversion of the starting material was obtained in the reaction, the 1H NMR spectrum of the crude reaction product showed resonances for only a small amount of the desired aziridine product, along with resonances for other unidentified products – these products could not be isolated in their pure form by column chromatography due to their instability. Based-washed silica gel was used for column chromatography to avoid potential acid-catalysed decomposition of the allenylaziridine. The formation of the aziridine 182 was evidenced by a multiplet 1H NMR resonance at 2.05-2.08 ppm in the 1H NMR spectrum that corresponds to the CH (H-2) between the allene bond and NBn group of the ring (Figure 2.1). The two multiplet 1H NMR resonances at 4.86-4.89 ppm (2H) and 5.05-5.08 ppm (1H) were assigned to the allene protons, while the
pair of doublet $^1$H NMR resonances at 1.66 ppm and 1.89 ppm were associated with the
diastereotopic methylene protons at C-3 of the three-membered ring (Figure 2.1). The $^{13}$C NMR
spectrum of the purified product also demonstrated the characteristic resonance for the allene
carbon (210.0 ppm). The HRMS (ESI) of the purified product showed an [M + H]$^+$ ion peak at
$m/z$ 172.1132, which also supported the structure of 182.

Scheme 2.3. Cyclisation of allenyl amino alcohol 181 under Appel reaction conditions.

The activation of the primary alcohol of the allenyl amino alcohol 181 occurs via a
known mechanism. The reaction is initiated by the reaction of PPh$_3$ with CBr$_4$ leading to the
formation of the bromotriphenylphosphonium ion 183 and tribromomethanide 184 (Scheme
2.4). The basic anion 184 removes the proton of the amino alcohol forming the alkoxide
intermediate 185, which reacts with bromotriphenylphosphonium 183, resulting in the
oxyphosphonium intermediate 186. Intramolecular nucleophilic substitution to yield the 2-allenylaziridine 182 occurs with loss of triphenylphosphine oxide 188 (Scheme 2.4).

Scheme 2.4. Mechanism for the Appel reaction of allenyl amino alcohol 181.

With this preliminary result in hand, it was envisioned to optimise the reaction conditions. The reaction was performed in the absence of base and no aziridine product 182 was formed, which highlighted the importance of the base in this reaction (Table 2.1, entry 1). When the reaction was performed in anhydrous Et₂O, although complete conversion occurred by TLC analysis; only a low yield of 15% the product 182 was isolated (Table 2.1, entry 3). Instead, formation of several byproducts was observed. Performing the reaction at 0 °C in CH₂Cl₂ resulted in a less complex crude reaction mixture based on ¹H NMR analysis but only a trace of the desired aziridine product was isolated (3%) (Table 2.1, entry 5). When the reaction was then carried out under reflux conditions in CH₂Cl₂, the isolated yield was significantly increased to 45%, along with a trace amount of the previously observed byproducts (Table 2.1, entry 6). Different amounts of reagents were then utilised in order to improve the reaction efficiency (entries 7-9). Using 1.3 equivalents of the reagents with respect to CCl₄ and PPh₃ gave the best result for the desired aziridine (54%), with only trace amounts of a byproduct observed in the ¹H NMR spectrum of the crude reaction product (Table 2.1, entry 7). The cyclisation reaction was subsequently explored by increasing the amount of base from 1.0 equivalent to 2.0 equivalents (Table 2.1, entries 10 and 11), and 1.5 equivalents of Et₃N showed
the best result of a 67% yield of 182 (Table 2.1, entry 10). Therefore, the conditions consisting of PPh₃ (1.3 eq.), CBr₄ (1.3 eq.), and Et₃N (1.5 eq.) in CH₂Cl₂ at reflux were selected as the optimum reaction conditions (Table 2.1, entry 10).

### Table 2.1. Optimisation conditions for the Appel reaction of 181.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>PPh₃ (eq.)</th>
<th>CBr₄ (eq.)</th>
<th>Et₃N (eq.)</th>
<th>Yielda, b (%)</th>
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<td>1</td>
<td>CH₂Cl₂</td>
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<td>1.0</td>
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<tr>
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<td>1.0</td>
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</tr>
<tr>
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<td>1.0</td>
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</tr>
<tr>
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<td>2.0</td>
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</tbody>
</table>

*Isolated yield (Et₃N was used during packing the silica of column chromatography). †100% consumption of the starting material was observed for all entries.

2.2. Reactivity of 2-Allenyl-N-benzylaziridine

With the desired 2-allenylaziridine 182 in hand, the reactivity of this novel aziridine in nucleophilic ring-opening reactions using organotransition-metal catalysts was investigated. Recently, palladium(II)-catalysed addition of arylboronic acids to vinylaziridines 189 has been developed by the Hyland group (Scheme 2.5a).⁶² The cationic palladium complex 190, which resulted from the interaction between 1,10-phenanthroline-ligand, Pd(OAc)₂, AgSbF₆, and the boronic acid, can activate the aziridine ring to ring-opening. A subsequent migratory insertion and β-H-elimination occurred to provide (Z)-allylsulfonamides 191. Inspired by this work, it was intended for the reactivity of the aziridine 182 to be tested in the palladium(II)-catalysed ring-opening pathway (Scheme 2.5b) in order to obtain the desired product 192. Therefore, the reaction of the 2-allenylaziridine 182 was performed using the standard conditions reported by our group. However, the ¹H NMR analysis of the crude reaction mixture indicated decomposition of the starting material had occurred, and no discrete products could be observed.
Palladium-catalysed substitution reactions of allenes bearing an adjacent leaving group have been investigated with a wide range of carbon- and nitrogen-based nucleophiles and with very high levels of asymmetric induction. Allenes bearing leaving groups, e.g. acetate or phosphonate, can generate a vinyl-π-allylpalladium in the presence of palladium(0) leading to products arising from allylic nucleophilic substitution reactions (Scheme 2.6a). Inspired by these reports, it was anticipated that the ring-opening of the aziridine in the presence of a palladium catalyst could provide the related vinyl-π-allylpalladium intermediate, which could then undergo an allylic nucleophilic substitution reaction (Scheme 2.6b). This process would also be atom-efficient as the nitrogen is retained in the product giving access to a highly functionalised N-containing allene. In this regard, the 2-allenylaziridine was treated with pyrrolidine as the nitrogen-based nucleophile in the presence of catalytic Pd(OAc)$_2$·CHCl$_3$, PPh$_3$, and Cs$_2$CO$_3$ (Scheme 2.6b) in anhydrous THF at room temperature for 24 h. However, the $^1$H NMR spectrum of the crude reaction mixture indicated the presence of many products along with the unreacted starting material. No identifiable products could be obtained after purification of the crude reaction mixture by column chromatography.
Scheme 2.6. (a) General pathway for palladium-catalysed allylation of allenes. (b) Our study regarding palladium(0)-catalysed ring-opening of the 2-allenylaziridine 182.

Given the lack of success with palladium-catalysed reactions, it was envisioned for the aziridine 182 to be investigated in ring-opening reactions with organometallic reagents in the presence of a catalytic amount of a Lewis acid. Lewis acids can activate the aziridine ring to nucleophilic attack by an organometallic reagent. For example, aziridinyl enoates 199 undergo Lewis acid-catalysed ring-opening reactions with organocyanocuprates in THF under mild conditions to give amides 200 (Scheme 2.7).64

Scheme 2.7. An example of the Lewis acid-catalysed ring-opening reaction of aziridinyl enoates 199 with organocyanocuprates.

In the light of these results, the 2-allenylaziridine 182 was treated with several organometallic nucleophiles as well as Lewis acids (Table 2.2). BF3·OEt2 was selected as it is commonly used as a Lewis acid for the nucleophilic ring-opening reactions of aziridines (Scheme 2.7).3, 64

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As the first attempt, 2-allenylaziridine 182 was treated with PhMgBr (2.0 equiv.) and CuCN (0.2 equiv.) in THF at room temperature under a N₂ atmosphere for 18 h (Table 2.2, entry 1). The ¹H NMR spectrum of the crude reaction mixture indicated a multitude of products had formed along with the significant amount of unreacted starting material. No desired product was obtained after purification by column chromatography. Subsequently, the same reaction was repeated but with increased amounts of the reagents, as well as adding BF₃·OEt₂ in order to facilitate the aziridine ring-opening (Table 2.2, entry 2). However, a complex crude reaction mixture was again detected with complete consumption of the starting material. Organocyanocuprates (RCu(CN)Li), which are softer carbon-based nucleophiles compared to Grignard reagents, were next investigated. Using 4.0 equivalents of n-BuLi and 4.0 equivalents of CuCN at −78 °C showed significant decomposition of the aziridine; however, a trace amount (6%) of the desired diene product 201 was isolated by column chromatography (Table 2.2, entry 3).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nucleophile (eq.)</th>
<th>CuCN (eq.)</th>
<th>BF₃·OEt₂ (eq.)</th>
<th>Time</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMgBr (2.0)</td>
<td>0.2</td>
<td>-</td>
<td>18 h</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>PhMgBr (4.0)</td>
<td>2.0</td>
<td>1.5</td>
<td>18 h</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>n-BuLi (4.0)</td>
<td>4.0</td>
<td>-</td>
<td>30 min</td>
<td>d</td>
</tr>
<tr>
<td>4</td>
<td>n-BuLi (2.0)</td>
<td>2.0</td>
<td>-</td>
<td>18 h</td>
<td>a</td>
</tr>
<tr>
<td>5</td>
<td>n-BuLi (2.0)</td>
<td>4.0</td>
<td>-</td>
<td>18 h</td>
<td>a</td>
</tr>
<tr>
<td>6</td>
<td>n-BuLi (4.0)</td>
<td>4.0</td>
<td>-</td>
<td>3.5 h</td>
<td>a</td>
</tr>
<tr>
<td>7</td>
<td>n-BuLi (4.0)</td>
<td>2.0</td>
<td>1.0</td>
<td>18 h</td>
<td>6d</td>
</tr>
<tr>
<td>8</td>
<td>n-BuLi (4.0)</td>
<td>2.0</td>
<td>1.5</td>
<td>18 h</td>
<td>40d</td>
</tr>
<tr>
<td>9</td>
<td>n-BuLi (4.0)</td>
<td>2.0</td>
<td>2.0</td>
<td>18 h</td>
<td>38d</td>
</tr>
<tr>
<td>10</td>
<td>MeLi (4.0)</td>
<td>2.0</td>
<td>1.0</td>
<td>18 h</td>
<td>a</td>
</tr>
</tbody>
</table>

*Reaction initiated at −78 °C and then stirred at room temperature. †Isolated yield. ‡Complex ¹H NMR spectrum of the crude reaction mixture along with the unreacted starting material. §Complex ¹H NMR spectrum of the crude reaction mixture with 100% conversion. ¶Reaction carried out at −78 °C. ¶¶Reaction performed at −78 °C for 1.5 h, then 2 h at room temperature.

The product 201 (R = Bu) was verified by the appearance of a doublet ¹H NMR resonance (6.19 ppm, J = 15.0 Hz, 1H) corresponding to the proton H-3 of the internal trans...
double bond (Figure 2.2). In addition, the singlet resonance for the two benzyl group protons (3.79 ppm, s, 2H) suggested the occurrence of ring-opened product as they are no longer diastereotopic (Figure 2.2). The HRMS (ESI) showed an [M + H]+ ion peak at m/z 230.1908, which supported the NMR-determined structure of diene 201 (R = Bu).

Figure 2.2. 1H NMR spectrum (500 MHz, CDCl₃) of the diene 201 (R = Bu).

Changing the equivalents of the reagents did not help to improve the reaction yield, and decomposition of the aziridine occurred (Table 2.2, entries 4-6). The investigation was then shifted to the use of higher-order organo-cyanocuprates (R₂Cu(CN)Li₂), which generally have higher reactivity than the lower order cyanocuprates.³⁶⁵ Performing the reaction in the presence of n-Bu₂Cu(CN)Li₂ and BF₃·OEt₂ was quickly found to be effective in this reaction (Table 2.2, entry 7). Although the 1H NMR spectrum of the crude reaction mixture was relatively complex, the diene 201 (R = Bu) was isolated in good yield (55%). However, by increasing the amount of BF₃·OEt₂ from 1.0 equivalent to 2.0 equivalents, a declining trend in the yield of the product was observed (Table 2.2, entries 8 and 9). Therefore, the conditions consisting of n-BuLi (4.0
eq.), CuCN (2.0 eq.), and BF₃·OEt₂ (1.0 eq.) in THF at room temperature were selected as the optimal conditions.

A second organo-cyanocuprate (Me₂Cu(CN)Li₂) was then applied to the reaction in order to test the possibility of the extension of the reaction scope. However, no product was obtained under the optimum conditions, and a complex ¹H NMR spectrum of the crude reaction mixture resulted, with complete consumption of the starting material (Table 2.2, entry 10). Upon several repetitions, the ring-opening reaction proved to be capricious, and for all the repeated reactions no desired product could be isolated, with 100% consumption of the starting material. At this point, it was concluded that the ring-opening process of the allenylaziridine was not easy to reproduce and no discrete product was obtained from the attempted reactions. Therefore, the project was shifted to investigate the synthesis and reactivity of allenyloxazolidinones as equivalents to allenylaziridines as it was thought that they may be more stable.

2.3. Synthesis of Allenyl 1,2-Amino Alcohols: Direct Access to 5-Allenyloxazolidinones and 2,5-Dihydrofurans

While the synthesis and reactivity of the novel 2-allenylaziridine 182 were investigated in Sections 2.1 and 2.2, unfortunately, the ring-opening reactions proved to be capricious, and for the majority of the reactions no desired product could be isolated, along with many side products being formed. The investigation was then shifted towards the synthesis of 5-allenyloxazolidinones; analogues of 2-allenylaziridines, which should display similar reactivity via decarboxylative ring cleavage pathways. These substrates were anticipated to be more stable as they have less ring-strain than aziridines and should only be activated in the presence of the catalyst to undergo decarboxylation. Towards this goal, this section describes the synthesis of enantiomerically enriched allenyl 1,2-amino alcohols derived from N-protected chiral α-amino aldehydes as the borono-Mannich method provides a nitrogen heteroatom next to the allene bond, but oxygen is needed to synthesise the allenyloxazolidinones (Scheme 2.8).
These allenyl products 163 could effectively undergo cyclisation reactions to provide highly functionalised chiral 5-allenyloxazolidinones 175 and their cyclisation reactions in the presence of cationic transition metals investigated. The allenylloxazolidinones (equivalents of allenylaziridines) could have their own distinctive reactivity but have yet to be investigated.

Scheme 2.8. Overview of the reaction steps to synthesise 5-allenyloxazolidinones and 2,5-dihydrofurans.

Based on the study carried out by the Fandrick group (Schemes 1.20), the aim was to utilise enantiomerically enriched α-amino aldehydes as the carbonyl precursors in this process in order to afford chiral allenyl 1,2-amino alcohols. Therefore, N-Boc α-alaninal 205a was chosen as the model substrate for the optimisation of the allenylation reaction conditions. This aldehyde was easily synthesised in three synthetic steps starting from naturally occurred L-α-alanine (Scheme 2.9). The amino acid was transformed into the corresponding ester 203a via esterification with SOCl2/MeOH. The α-alanine methyl ester 203a was then converted to the N-Boc α-alanine methyl ester 204a through N-protection using di-tert-butyl dicarbonate ((Boc)2O) in the presence of Et3N. The N-Boc α-amino ester 204a was then reduced with DIBAL-H in THF at −78 °C to afford the N-Boc α-alanal 205a in excellent yield (98%). This compound was immediately utilised in the zinc-catalysed allenylation reaction without further purification, since chiral α-amino aldehydes are known to racemise upon chromatographic purification or storage.56

Scheme 2.9. Synthesis of N-Boc α-amino alanal 205a.
In the next step, it was intended to test the reactivity of the α-amino aldehyde 205a in a zinc-catalysed allenylation reaction (Scheme 2.10). Therefore, the allenylation reaction of the aldehyde 205a was performed via the standard conditions reported by the Fandrick group using Et₂Zn (10 mol%) and allenylboronic acid pinacol ester 71 (1.1 equiv.) in toluene at 0 °C. The ¹H NMR spectrum of the resulting crude reaction mixture indicated complete consumption of the α-amino aldehyde 205a and formation of a mixture of allene and propargyl regioisomers (allenyl (206a)/propargyl (207a) = 92:8); almost exclusively in favour of the desired allenyl product. The allenyl product 206a was isolated by column chromatography in high yield (92%) and as a mixture of two diastereoisomers (syn/anti = 2.6:1).

\[
\text{CHO} \quad \text{Et}_2\text{Zn (10 mol%)} \quad \text{toluene, 0 °C, 18 h} \quad \text{1H NMR} \quad \text{dr 2.6:1 syn/anti} \\
\text{NHBOC} \quad \text{Bpin} \quad \text{205a} \quad \text{71} \quad \text{206a} \quad \text{207a} \quad 92 \%
\]

Scheme 2.10. Zinc-catalysed allenylation reaction of N-Boc α-amino alanal 205a.

The allene product 206a was verified by the appearance of two multiplet ¹H NMR resonances at 4.80-4.90 ppm (2H) and 5.17-5.28 ppm (1H) attributed to the protons of the allene bond (Figure 2.3). The ¹³C NMR spectrum of the purified product demonstrated the characteristic resonance for the central allene carbon (major diastereoisomer at 207.4 ppm and minor diastereoisomer at 207.9 ppm). The existence of two diastereoisomers was evidenced by a series of pairs of resonances in both the ¹H NMR and ¹³C NMR spectra. In the ¹H NMR spectrum (Figure 2.3), distinct doublet resonances at 1.12 ppm (CH₃) and 1.20 (CH₃) ppm were observed for the major and minor diastereoisomers, respectively. The propargyl regioisomer 207a was confirmed by the appearance of singlet and multiplet ¹H NMR resonances at 2.00 ppm (1H) and 2.39-2.42 ppm (2H) assigned to the \( sp \) and \( sp^2 \) protons of the propargyl moiety, respectively (Figure 2.3). The HRMS (ESI) of the purified allene product showed an \([M – H]^+\) ion peak at \( m/z \) 212.1289, which supported the structure of 206a. Determination of the syn and anti stereochemistry of these diastereomeric allene products will be discussed later in this Chapter.
Based on these preliminary results, the focus was then directed towards further optimisation of the reaction conditions in order to increase the diastereoselectivity of the allene product and potentially reverse the regiochemistry. A series of experiments were conducted with different reaction parameters, such as catalyst loading, solvent, temperature, and the nature of the N-protecting group (Table 2.3). Initially, the allenylation reaction of N-Boc α-alanal 205a with allenylboronic acid pinacol ester 71 was performed in toluene in the absence of the Et₂Zn (Table 2.3, entry 1), which gave only the propargyl amino alcohol 207a in a low yield (12%) and but with the same moderate diastereoselectivity (dr = 2.6:1). This indicated that Et₂Zn plays a key role in controlling the regioselectivity and the rate of this reaction is consistent with the previously accepted mechanism which shows allenyl reagents lead to propargyl products. In the absence of the zinc catalyst, the reaction mechanism would follow the general direct addition pathway in which the allenylboronic reagent gives the propargyl product upon nucleophilic addition to the carbonyl group. The addition of 5 mol% of the Et₂Zn catalyst provided the allene 206a with excellent control of allenyl to propargyl regioselectivity (allene/propargyl = 97:3), but with modest syn diastereoselectivity (syn/anti 2.6:1) (Table 2.3, entry 2). Interestingly, increasing the polarity of solvent by using THF resulted in the reversal
of regioselectivity to favour the propargyl product \textbf{207a} along with a decrease in diastereoselectivity (Table 2.3, entries 3 and 4). These results were consistent with the previous studies by Fandrick that showed polar solvents increased the rate of equilibration of the allenyl/propargyl intermediates.\textsuperscript{36-37} An increase in the amount of catalyst from 5 to 10 mol % in toluene improved the yield significantly from 77\% (entry 2) to 92\% (entry 5), but still resulted in moderate diastereoselectivity. It was thought that at lower temperatures, this might lead to increased diastereoselectivity. However, no reaction occurred when the reaction was performed at −40 °C (Table 2.3, entry 6).

Due to the reversal of regioselectivity, it was possible to isolate the propargyl product \textbf{207a}, the structure of which was confirmed by the appearance of singlet and multiplet \textsuperscript{1}H NMR resonances at 2.09 ppm (1H) and 2.39-2.44 ppm (2H) assigned to the terminal alkyne proton and propargylic CH\textsubscript{2} of the propargyl group, respectively (Figure 2.4). These resonances also

<table>
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<th>Entry</th>
<th>NR\textsuperscript{1}R\textsuperscript{2}</th>
<th>Solvent</th>
<th>Catalyst (mol %)</th>
<th>Yield\textsuperscript{b} \textsuperscript{c} \textsuperscript{d} (allene:propargyl)\textsuperscript{c}</th>
<th>dr\textsuperscript{e} (syn:anti)</th>
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<td>2.6:1</td>
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<td>77 (97:3)</td>
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</tr>
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<td>60 (5:95)</td>
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</tr>
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<td>38 (71:29)</td>
<td>2.0:1</td>
</tr>
<tr>
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<td>PhMe</td>
<td>10</td>
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<td>2.6:1</td>
</tr>
<tr>
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<td>PhMe</td>
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<td>10</td>
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<td>10</td>
<td>0\textsuperscript{g}</td>
<td>0</td>
</tr>
<tr>
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<tr>
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<td>PhMe</td>
<td>10</td>
<td>54\textsuperscript{h} (94:6)</td>
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<tr>
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<td>PhMe</td>
<td>10</td>
<td>50\textsuperscript{h} (94:6)</td>
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</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: \textbf{71} (1.10 equiv.), Et\textsubscript{2}Zn, solvent, 0 °C, 18 h. \textsuperscript{b}Isolated yield of allene and propargyl products. \textsuperscript{c}Regioselectivity of determined by \textsuperscript{1}H NMR analysis of the crude reaction product – stereochemistry of propargyl products not determined. \textsuperscript{d}The reaction was carried out at −40 °C. \textsuperscript{e}Decomposition of starting material. \textsuperscript{f}Recov ery of SM. \textsuperscript{g}1.3 equiv. of \textbf{71} was used. \textsuperscript{h}Determined by \textsuperscript{1}H NMR analysis of N-Boc deprotected crude reaction mixture. \textsuperscript{i}Isolated yield for the major allene diastereoisomer.

Due to the reversal of regioselectivity, it was possible to isolate the propargyl product \textbf{207a}, the structure of which was confirmed by the appearance of singlet and multiplet \textsuperscript{1}H NMR resonances at 2.09 ppm (1H) and 2.39-2.44 ppm (2H) assigned to the terminal alkyne proton and propargylic CH\textsubscript{2} of the propargyl group, respectively (Figure 2.4). These resonances also
corresponded to those of the minor propargyl regioisomer assigned in Figure 2.3 providing support to our estimation of the regioselectivity. The HRMS (ESI) analysis of the purified propargyl product showed an \([\text{M + H}]^+\) ion peak at \(m/z\) 214.1446, which further supported the structure of 207a.

![Figure 2.4. 1H NMR spectrum (500 MHz, CDCl3) of the N-Boc propargylamino alcohol 207a.](image)

Based on the above results, toluene was taken as the solvent of choice as well as 10 mol\% of Et2Zn (Table 2.3, entry 5), and these conditions were used for further optimisation of the reaction conditions. Accordingly, the effect of alternate protecting groups on the nitrogen in the allenylation reaction was investigated in an attempt to further enhance or switch the reaction diastereoselectivity. A series of common nitrogen protecting groups were screened for compatibility with this methodology (Table 2.3, entries 7-12). The \(N\)-protected amino aldehydes (208, 211, 214) could be easily prepared starting from the \(\alpha\)-alanine methyl ester 203a using the relevant protecting group reagent in the presence of a base (Scheme 2.11).
The N-Ts and N-Fmoc alanals 208 and 211 (Table 2.3, entries 7 and 8) did not undergo the desired allenylation/propargylation reaction, which was possibly due to the more acidic proton on the NHTs and NHFmoc group being deprotonated by Et₂Zn, thereby deactivating the zinc catalyst. When the triphenylmethyl (Tr) group was employed as the protecting group (Table 2.3, entry 8), the corresponding allenyl product 215 was provided in high yield (82%) and high regioselectivity (allene/propargyl = 84:16), but essentially no diastereoselectivity ($dr = 1.3:1$). It was then decided to increase the steric bulk around the nitrogen atom using two protecting groups (Table 2.3, entries 10–12). Interestingly, introducing a second bulky protecting group on nitrogen reversed the diastereochemical outcome in favour of the anti allene product (Table 2.3, entries 10–12). Doubly protecting the nitrogen with $N$-Bn,$N$-Ts or $N$-Bn,$N$-Bn protecting group combinations gave comparable yields of the allene 221 and 224 with high regioselectivities, but with poor diastereoselectivities (Table 2.3, entries 11 and 12). It should be mentioned that in these cases the major diastereoisomers could be isolated in pure form after column chromatography. Employing the $N$-Bn,$N$-Boc protecting group resulted in a dramatic increase in the diastereoselectivity ($syn:anti = 1:19$), along with high yield (96%) and high regioselectivity (allene:propargyl = 89:11) (Table 2.3, entry 10).
To establish the relative configuration of the major isomer of the allene products, the corresponding oxazolidinones 229a and 230a were synthesised via base-catalysed (NaH) cyclisation (Scheme 2.12). Critically, the major diastereoisomer of the oxazolidinones could be separated by column chromatography. The structure of oxazolidinone 229a was verified by the appearance of two multiplet $^1$H NMR resonances at 4.93-5.00 ppm (2H) and 5.30-5.36 ppm (1H) attributed to the protons H-7 and H-9 of the allene bond, respectively (Figure 2.5). The oxazolidinone 230a was confirmed by the existence of two multiplet $^1$H NMR resonances at 4.80-4.98 ppm (2H) and 5.18-5.25 ppm (1H) attributed to the H-7 and H-9 of the allene bond, respectively (Figure 2.6). The $^{13}$C NMR spectra of the purified products also demonstrated the characteristic signals for the allene central carbon (C-8, 209.2 ppm and 209.7 for 229a and 230a, respectively) and the oxazolidinone carbonyl (158.9 ppm and 157.5 for 229a and 230a, respectively). Furthermore, the IR spectra of the purified products 229a and 230a showed C=O stretching bands at 1739 cm$^{-1}$ and 1743 cm$^{-1}$ for the oxazolidinones 229a and 230a, respectively. The HRMS (ESI) analysis of the purified oxazolidinone products showed [M + Na]$^+$ ion peaks at $m/z$ 162.0537 and [M + H]$^+$ at 252.1003, which supported the structures of 229a and 230a, respectively. It should be mentioned that it is advantageous to convert the N-Bn,N-Boc allenyl 1,2-amino alcohol 218a to the corresponding NBn oxazolidinone 230a so as to resolve the issue of the rotamers in the $^1$H NMR spectra.

Scheme 2.12. Determination of relative configuration of the allenyl products.
The trans stereochemistry of 229a was established from its 1D NOESY spectrum, based on a correlation between H-5 and CH₃, and thus implied the syn-configuration of 207a.
(Figure 2.7). In contrast, the *cis* stereochemistry of 230a was indicated from its 1D NOESY spectrum of the oxazolidinone 230a according to a correlation between H-4 and H-5 for the major isomer, which confirmed the *anti*-configuration of 218a (Figure 2.8). The magnitudes of the $J_{4,5}$ coupling constants ($J_{4,5} = 6.0$ Hz for 229a and $J_{4,5} = 7.2$ Hz for 230a) were consistent with these assignments. It should be mentioned that a subsequent PhD student in our group who is working on the reactivity of the oxazolidinones (Ronald Brown, data obtained by A/Professor Michael Gardiner) obtained a crystal structure of the *trans*-oxazolidinone further confirming this stereochemical assigned.

![Figure 2.7. 1D NOE difference spectrum of the NH allenyloxazolidinone 229a after irradiation at H$^4$.](image)
To explain the divergent stereochemical outcomes in the zinc-catalysed allenylation reactions of the α-amino aldehyde, two common stereochemical models regarding asymmetric nucleophilic addition of organometallics to carbonyl compounds, known as the Cram-chelation and the Felkin–Anh models can be invoked.\(^6\) In these models, the facial preference of the nucleophilic reaction to the carbonyl group is controlled by an adjacent stereocentre. In the Cram-chelation model, the chelation between the carbonyl group and one of the substituents of the α-stereocenter, facilitated by a metal cation, can lock the substrate into the conformation \(^2\) (Scheme 2.13a). The nucleophile then preferentially attacks the carbonyl group \textit{anti} to the largest group \(R^1\) or \(R^2\) from the opposite side of the coordinated α-substituent \(L\) leading to the \textit{syn} isomer \(232\) as the major diastereoisomeric product.\(^5\) On the other hand, this chelation cannot happen because of the crucial steric interaction between the large α-substituent \(L\) and the carbonyl group, resulting in the formation of the proposed conformation \(233\) (Scheme 2.13b). Subsequently, \(L\) is oriented \textit{anti} to the carbonyl group, and the nucleophile preferentially attacks from the side of the small substituent \(R^1\) affording the \textit{anti} isomer \(234\) as the major adduct.\(^6\)
On the basis of these models, it can be proposed that the zinc-catalysed allenylation reaction of N-mono protected α-amino aldehydes follows a Cram–chelation–like model, where a H-bonding interaction between the aldehyde and the Boc N–H drives the direction of nucleophilic attack, affording the syn isomer as the major diastereoisomer product (Scheme 2.13a). The dr for the uncatalysed reaction (Table 2.3, entry 1) is identical to the catalysed reaction offering some support for this H-bond model, rather than Zn playing a role in chelation. In contrast, N,N-doubly protected α-amino aldehydes favour Felkin–Anh control as H-bonding is no longer possible and chelation less likely, resulting to the anti diastereoisomer as the major adduct (Scheme 2.13b). In other words, the presence of the bulky electronegative group (N-Bn,N-Boc) on the α-carbon to the aldehyde drives the direction of nucleophilic attack, in which the nucleophile prefers to attack away from the large group forming the anti-diastereomer as the major product.

The proposed mechanism for the zinc-catalysed allenylation reactions is illustrated in Scheme 2.14, which is in agreement with the previously reported studies. The first step is transmetalation of the allenylboronate 71 with Et2Zn to give the propargylzinc intermediate.
235, which reacts in an S_{E2}' fashion with the aldehyde 237 under Cram-chelation-like or Felkin–Ahn control to form the corresponding zinc alkoxide intermediate 238. The reaction is catalytic in zinc since the alkoxide 238 can undergo boronate-to-zinc exchange with the allenylboronate 71 to give the propargylzinc species 235 as well as the boronate complex of allenyl alcohol 239. In contrast, the propargylzinc intermediate 235 isomerises under thermodynamic conditions to form the more stable allenylzinc species 236. This equilibration has been shown to be second order in [Zn], while the competition of the propargyl 235 and allenylzinc 236 intermediates for the addition to the electrophile are first order in these organozinc species.\textsuperscript{36} The allenyl species 236 then reacts with the aldehyde 237 in an S_{E2}' fashion to finally form the corresponding propargyl amino alcohol 241 after aqueous workup. To achieve high regioselectivity for the allenylation reaction after the formation of the propargyl zinc species 235 in the first step, the related addition to the aldehyde 237 has to effectively compete with the propargyl to allenylzinc equilibration. This isomerisation is slow in non-polar solvents, such as toluene, or with low catalyst loadings, allowing the propargyl-zinc addition to compete with this equilibration.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{scheme}
\caption{Proposed mechanism for the zinc-catalysed allenylation reaction of N-protected \(\alpha\)-amino aldehydes.}
\end{figure}
With the optimised reaction conditions in hand, the substrate scope with regard to the protecting group on nitrogen was investigated in order to provide two types of the *anti* and *syn* \( N \)-protected allenylamino alcohols. A range of \( N \)-Boc \( \alpha \)-amino aldehydes 205a-g were prepared from their corresponding L-\( \alpha \)-amino acids (Scheme 2.15), and were subjected in the zinc-catalysed allenylation reaction using 10 mol% \( \text{Et}_2\text{Zn} \) in toluene at 0 °C (Table 2.4). In all cases, the *syn* \( N \)-Boc allenylamino alcohols 206a-g were obtained in high yields (78-92%), high regioselectivities (allene/propargyl = 89:11-95:5) and moderate to good diastereoselectivities (\( \text{syn/anti} = 2.5:1-9:1 \)). It was also observed that the \( dr \) improved as the size of the R side chain group increased from Me (206a, \( dr = 2.6:1 \)) to \( i \)-Pr (206e, \( dr = 9:1 \)) – consistent with the proposed Cram-chelate-like model. Furthermore, the allenyl tryptophan derivative 206g was synthesised in high yield (78%) and excellent regioselectivity (95:5), which is an interesting example of a heterocyclic analogue.

![Scheme 2.15. Synthesis of \( N \)-Boc \( \alpha \)-amino aldehydes 205a-g from L-\( \alpha \)-amino acids.](image)

<table>
<thead>
<tr>
<th>Table 2.4. Reaction scope of <em>syn</em> ( N )-Boc allenylation alcohol.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>R</strong></td>
</tr>
<tr>
<td>205a-g</td>
</tr>
<tr>
<td>L-( \alpha )-amino acid</td>
</tr>
<tr>
<td>203a-g</td>
</tr>
<tr>
<td>204a-g</td>
</tr>
<tr>
<td>205a-g</td>
</tr>
<tr>
<td>206a-g</td>
</tr>
<tr>
<td>206a</td>
</tr>
<tr>
<td>206b</td>
</tr>
<tr>
<td>206c</td>
</tr>
<tr>
<td>206d</td>
</tr>
<tr>
<td>206e</td>
</tr>
<tr>
<td>206f</td>
</tr>
<tr>
<td>206g</td>
</tr>
</tbody>
</table>

*Isolated yield. *Regioselectivity and \( dr \) estimated by \( ^1 \text{H} \) NMR analysis of purified 206.
Having demonstrated the ability to control diastereoselectivity of the zinc-catalysed allenylation reaction by changing the N-protecting group of the α-amino aldehydes, the influence of α-heteroatom of the aldehydes was next investigated. Therefore, O-protected α-hydroxy aldehydes were chosen as analogues of the α-amino aldehydes to undergo the zinc-catalysed allenylation reaction under the optimised reaction conditions. A range of O-protected α-hydroxy aldehydes 242 was prepared from readily available L-lactic acid ethyl ester (Scheme 2.16). Based on the stereochemical outcomes for the α-amino aldehydes, it was hypothesised that the diastereoselectivity would be protecting group dependent. Although high yields and excellent regioselectivities were obtained for the α-hydroxy allene products 243, the reactions showed almost no preferred diastereoselectivity for any of the different O-protected aldehydes (Scheme 2.16). Due to poor diastereoselectivities of the allenylation reaction of O-protected α-hydroxy aldehydes, further investigations were not carried out, and the stereochemistry of the allene products was not determined.

![Scheme 2.16. Zinc-catalysed allenylation reaction of O-protected α-hydroxy aldehydes.](image)

\[\text{CHO} + \text{Bpin} \xrightarrow{\text{Et}_2\text{Zn (10 mol%)}} \text{toluene, 0} \, ^\circ\text{C, 18 h}} \xrightarrow{} \text{OH} \]

<table>
<thead>
<tr>
<th>R</th>
<th>Yield (%)</th>
<th>Allene/Propargyl</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bn</td>
<td>76</td>
<td>97:3</td>
<td>1.4:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>TBS</td>
<td>70</td>
<td>98:2</td>
<td>1.1:1&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Tr</td>
<td>85</td>
<td>98:2</td>
<td>1:1</td>
</tr>
</tbody>
</table>

<sup>a</sup>Diastereoisomers could not be separated.

\[\text{N-Boc allenlamino alcohols 206} \text{ would offer great potential and utility for heterocycle synthesis due to the presence of two pendant heteroatoms and the allene bond in a single molecule. As discussed previously in this Chapter, despite extensive investigations of allenes with a single heteroatom in the literature, methods to prepare allenes with multiple pendant heteroatoms are extremely rare. There were only two major papers reported by Pyne}^{54} \text{ and} \]

54
Petasis\textsuperscript{55} regarding the preparation of allenes with two heteroatoms (Schemes 1.29 and 1.30). Therefore, the synthesis of such powerful scaffolds, such as 206, is significant.

To demonstrate the utility of such allenes, it was found that the $N$-Boc allenylamino alcohols 206 could undergo base-induced cyclisation reactions offering a convenient method to direct access to the chiral 5-allenyloxazolidinones 229 (Table 2.5). A series of the $N$-Boc allenylamino alcohols 206a-g underwent base-induced cyclisations to provide 5-allenyloxazolidinones 229a-g in yields ranging from 50–74\%. For the majority of cases, diastereomerically enriched oxazolidinone products were isolated after chromatographic purification (up to >98\% \textit{dr}).\textsuperscript{66}

<table>
<thead>
<tr>
<th>Table 2.5. Reaction scope of 5-allenyl oxazolidinones.\textsuperscript{a,b}</th>
</tr>
</thead>
</table>

\textsuperscript{a}Isolated yield. \textsuperscript{b}Reaction initiated at 0 °C and then stirred at room temperature for 1.5 h. \textsuperscript{c}A mixture of two diastereomers. \textsuperscript{d}Isolated yield of the single major diastereoisomer.

This is the first example of oxazolidinones bearing a potentially reactive C5 allenyl side chain along with the free NH, which could be powerful synthetic intermediates for the synthesis of biologically active compounds. Furthermore, diastereoselective methods to prepare oxazolidinones with pendant unsaturated moieties are severely limited in the literature.\textsuperscript{69} As discussed earlier, oxazolidinones can also undergo ring cleavage pathways in a similar manner as an aziridine. Therefore, a synthetic method to synthesise the novel chiral 5-allenyl oxazolidinones 229 as equivalent analogues of the 2-allenylaziridine was developed.
Oxazolidinones are a chemical class of synthetic antimicrobial agents exhibiting unique bacteriostatic activity against many human pathogens.\textsuperscript{70-71} For example, eperezolid 245 and linezolid 246 are the most common and effective synthetic antibiotics derived from an oxazolidinone, which are used for the treatment of diseases caused by many Gram-positive pathogens (Scheme 2.17).\textsuperscript{71-73}

![Scheme 2.17. Structures of oxazolidinone-based eperezolid and linezolid.](image)

The substrate scope of the allenylation reaction of the N-Bn,N-Boc α-amino aldehydes 217 was next explored. A range of the aldehydes 217a-h were prepared from their corresponding L-α-amino acids (Scheme 2.18), and were subjected to the zinc-catalysed allenylation reaction using 10 mol\% Et$_2$Zn in toluene at 0 °C (Table 2.6).
Scheme 2.18. Synthesis of N-Bn,N-Boc α-amino aldehydes from L-α-amino acids.

In all cases, the anti N-Bn,N-Boc allenylamino alcohols 218a-h were obtained in high yields (71-96%). However, except for the alanine-derived allene product 218a, investigation of the 1H NMR spectra for both the pure allene products and in the crude reaction mixture was complicated due to the presence of rotamers (caused by restricted carbamate C−N rotation of the Boc), diastereoisomers and regioisomers. Examination of the 1H NMR spectra at elevated temperature (70 °C in DMSO) with the aim to coalesce the rotamer peaks was also unsuccessful. Furthermore, the direct N-Boc deprotection of these allenes was not straightforward as decomposition of the starting material often occurred. Therefore, it was intended to explore the utility of the allenylamino alcohols 218 as building blocks for the synthesis of more intricate systems through direct conversion of the initial product to a system that could be more readily analysed by NMR spectroscopy. Accordingly, an Au(I)-catalysed
cycloisolation reaction was chosen as the desirable reaction for direct conversion of the allenylamino alcohols to 2,5-dihydrofurans.

Table 2.6. Reaction scope of 2,5-dihydrofurans.²⁴

<table>
<thead>
<tr>
<th>R</th>
<th>NBnBoc</th>
<th>OH</th>
<th>NBnBoc</th>
<th>R</th>
<th>NBnBoc</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>NHBn</td>
<td>250a</td>
<td>66% &gt;98% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250b</td>
<td>68% 81% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250c</td>
<td>62% 76% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250d</td>
<td>58% 89% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250e</td>
<td>61% &gt;98% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250f</td>
<td>54% &gt;98% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>NHBn</td>
<td>250g</td>
<td>48% &gt;98% dr</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>250h</td>
<td>59%&lt;sup&gt;c,d&lt;/sup&gt; 61% dr</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

²²Isolated yields over three steps without any intermediate purification. ²³Diastereomeric ratio determined by ¹H NMR analysis of purified 250. ²⁴The N-Boc-deprotected product could not be obtained due to instability. ²⁵Isolated yield after two steps.

After the zinc-catalysed allenylation reaction of the aldehydes 217, the resulting allene crude reaction mixture was subjected to the Au(I)-catalysed cycloisolation reaction in the presence of AuPPh₃NTf₂ (10 mol%, Table 2.6). Subsequently, N-Boc deprotection was carried out on the resulting crude reaction mixture using TMSCl/MeOH to give the 2,5-dihydrofurans 250 in good yields (48-68%) over the three steps. These products could then be easily analysed by ¹H NMR analysis as the rotamer problem was no longer present. Therefore, the ratio of diastereoisomers could be easily determined using ¹H NMR analysis. In four cases, the products (250a, 250e, 250f and 250g) could be obtained as single diastereoisomers after purification by column chromatography. The N-Boc protected proline-derived amino aldehyde 217h showed good reactivity in the allenylation reaction to give 218h, and then the corresponding cyclised product 250h. However, as reported previously the N-Boc deprotected derivative of 250h proved unstable, and could not be isolated.⁶⁶
2,5-Dihydrofurans are one of the key building blocks in natural product synthesis and pharmaceuticals, exhibiting beneficial biological activities as anti-cancer, HIV, and antifungal agents.\textsuperscript{74-75} For example, elvucitabine 251 and 252 (D and L forms) is an antiviral drug based on a 2,5-dihydrofuran derivative and is used in the treatment of HBV and HIV infections (Scheme 2.19).\textsuperscript{76-77} Despite the importance of these structures, there is no general method to prepare 2,5-dihydrofurans with a pendant nitrogen atom in a stereodefined fashion, therefore the method presented here should be a useful addition to the chemical literature.\textsuperscript{40, 47}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structure.png}
\caption{Scheme 2.19. Structures of 2,5-dihydrofuran-based Elvucitabine.}
\end{figure}

Having established mild and effective conditions for the zinc-catalysed allenylation reactions of \textit{N}-protected \textit{\alpha}-amino aldehydes, the study was next focused on the determination of the enantiomeric excess of the final heterocyclic products. As discussed earlier, \textit{\alpha}-amino aldehydes are susceptible to racemisation under acidic or basic conditions, or even upon chromatographic purification and storage. It was therefore aimed to investigate whether the developed methodology would show retention of the enantiomeric purity of the aldehyde during the reaction steps.

One of the most rapid and reliable techniques for the determination of enantiomeric excess (\textit{ee}) values is using a chiral derivatising agent, in which a enantiomerically pure reagent is used to convert a mixture of enantiomers into diastereomers in order to analyse the quantities of each enantiomer present in a sample.\textsuperscript{78-79} This technique enables the accurate determination of the \textit{ee} value by measuring the ratios of the diastereoisomers in the \textsuperscript{1}H NMR spectrum. 10-Camphorsulfonyl chloride is an inexpensive and readily available chiral derivatizing agent widely used for the assay of enantiomeric purity of alcohols and amines\textsuperscript{70-80} and was used successfully here for determination of the enantiomeric excess (\textit{ee}) of each diastereomerically
pure allenyl oxazolidinone (Table 2.7). The ee of the oxazolidinone was determined by integration of clearly resolved resonances arising from the corresponding α-methylene sulfonyl (CH$_2$H$_2$SO$_2$) protons in each diastereomer in the $^1$H NMR spectrum of the crude reaction mixture (Figure 2.9). The $^1$H NMR resonances for the corresponding camphorsulfonyl derivatives of the diastereomERICALLY pure allenyl oxazolidinones are listed in the Experimental section.

**Table 2.7.** Determination of ee values of the oxazolidinones using (S)-10-camphorsulfonyl chloride.

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>(+ ent-229)</td>
<td>(S)-10-camphorsulfonyl chloride</td>
<td>NaH</td>
<td>THF, 0 °C to r.t</td>
</tr>
<tr>
<td></td>
<td></td>
<td>major isomer</td>
<td>minor isomer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>96% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>94% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>86% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>8% ee</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>92% ee</td>
<td></td>
</tr>
</tbody>
</table>

*Enantionic excess was determined by $^1$H NMR analysis of the resulting diastereomERICALLY (S)-camphorsulfonamide derivatives in the crude reaction mixture.

**Figure 2.9.** An example of determining the ee value of the leucine-derived allenyl oxazolidinone 229c by measuring the ratios of the diastereomers by $^1$H NMR spectroscopy on the crude reaction mixture.
In the majority of cases, high enantiomeric excess values were obtained for the diastereomerically pure allenyl oxazolidinones. However, the phenylglycine-derived oxazolidinone 229f showed extensive loss of enantiomeric purity (8% ee), which can be explained as the α-proton in the phenylglycinal is extremely acidic due to the adjacent carbonyl and the phenyl groups, therefore, the aldehyde can easily undergo the α-deprotonation and partial racemisation.

Having determined the enantiomeric excess (ee) for the diastereomerically pure allenyl oxazolidinones (Table 2.7), the α-amino aldehyde 205a was chosen as the model substrate to investigate the possibility of racemisation of the aldehyde during the reaction steps in our methodology. In this case the ee value of the aldehyde was investigated by chiral normal phase HPLC. A comparison between the enantiomeric purity of the final oxazolidinone product 229c (86% ee, determined from its chiral sulfonamide derivative by 1H NMR analysis in Figure 2.9) and the corresponding aldehyde 205c (86% ee, determined by chiral HPLC of the corresponding alcohol obtained by immediate NaBH₄ reduction of the aldehyde and in comparison to a racemic standard) showed no erosion of enantiomeric purity of the aldehyde during the reaction steps, indicating the zinc allenylation was not responsible for the slight loss of ee.

The chiral derivative method was not suitable for the 2,5-dihydrofuran products due to instability of the corresponding sulfonamide derivatives, so chiral HPLC was employed. The diastereomerically pure product 250a was tested as the model compound by comparing the enantiomeric excess of the final product (91% ee, determined by chiral HPLC in comparison to a synthesised racemic standard) and the aldehyde 217a (91% ee, determined by chiral HPLC of the corresponding alcohol), which proved no erosion of the enantiomeric purity of the aldehyde during the reaction steps (Scheme 2.20). It should be mentioned that the α-amino aldehydes were reduced to their corresponding α-amino alcohols (racemic and pure), and then they were analysed by chiral HPLC, because of the tendency of these aldehydes to racemize before and during HPLC analysis (Scheme 2.20).
2.4. Summary

In summary, the synthesis of the novel 2-allenylaziridine 182 from the allenyl amino alcohol 181 has been developed. The aziridine was prepared in good yield under mild reaction conditions and a series of ring-opening reactions of 182 were investigated. Unfortunately, the ring-opening reactions proved to be capricious, and for the majority of these reactions no product could be isolated, along with many side products being formed. According to previous studies (Scheme 1.6 and 1.7), oxazolidinones could undergo ring cleavage pathways in a similar manner as an aziridine, and therefore, it was envisioned to use the previously unknown 5-allenylloxazolidinones (229 and 230) as equivalent analogues of the 2-allenylaziridines 182 in nucleophilic ring-opening reactions (Scheme 1.33). These compounds have not been reported in the literature, therefore, a synthetic approach was required to be established for the preparation of these unique allenyl heterocycles. Herein, we have developed the first example of simultaneous control of diastereoselectivity and regioselectivity in zinc-catalysed allenylation reactions of \( N \)-protected \( \alpha \)-amino aldehydes. These methodologies provided high regiochemical control to favour the allene products. Stereoinduction with the \( N \)-protected \( \alpha \)-amino aldehydes was significantly protecting group dependent. In the presence of two sterically hindered groups on nitrogen, Felkin–Ahn control was observed affording \textit{anti} allenylamino alcohols. However, employing a single protecting group (Boc) overrides the Felkin–Ahn control by forming H-bonding between the NH of the Boc group and the carbonyl group to enable the synthesis of Cram-chelation-controlled \textit{syn} allenylamino alcohols. Furthermore, the
resulting allene products demonstrated high reactivity in NaH-induced and Au-catalysed intramolecular cyclisation reactions to obtain novel 5-allenyl oxazolidinones and 2,5-dihydrofurans. Although diastereoselective methods to prepare oxazolidinones with pendant unsaturated bonds are extremely rare, most of the final heterocyclic products could be obtained as single diastereoisomers in high enantiomeric excess after simple column chromatography. The existence of a reactive allenyl side chain along with the free NH also make these oxazolidinones as potentially powerful synthetic intermediates for the synthesis of biologically active compounds. Au-catalysed cyclisation of allenes to 2,5-dihydrofurans is also known in the literature, however, using this same method to synthesise heterocycles with a pendant nitrogen is unknown.

As discussed in this Chapter, oxazolidinones can potentially participate in organic reactions through the same nucleophilic ring-opening pathways as aziridines. In Chapter 4, the reactivity the novel 5-allenyloxazolidinones will be demonstrated.
Part 2. Synthesis of Unconjugated Chiral \((E)\)-enediynes from 5- Allenyloxazolidinones and Their Application in Au(I)-Cycloaromatisation Reactions

Chapter 3. Introduction

In Part 1 of Chapter 2, novel and enantiomerically enriched 5-allenyloxazolidinones \(229\) were successfully synthesised via base-induced (NaH) cyclisation of allenyl amino alcohols \(206\).\(^{66}\) It was previously discussed that oxazolidinones could undergo ring cleavage pathways considered as equivalent analogues of aziridines. During the synthesis of the 5-allenyloxazolidinone \(230a\) from allenyl amino alcohol \(218a\) in Chapter 2 (Scheme 2.12), decarboxylative ring-opening reaction of the \(N\)-Bn oxazolidinone \(230a\) simultaneously occurred upon a treatment with an excess amount of NaH under mild reaction conditions, resulting in the formation of the novel 1,3-(\(E\))-enyne \(253\) (Scheme 3.1). This unexpected reactivity of the oxazolidinone in the presence of the base shifted the project towards investigation of potential Au(I)-catalysed reactions rather than the initially planned Pd(0)-catalysed chemistry. The free NH moiety in these enynes could be propargylated to form the novel unconjugated enediyne \(254\). These unique compounds could be potentially utilised in Au(I)-catalysed cycloaromatisation reactions to form the chiral isoindoline \(255\). In this Chapter, literature background regarding the synthesis of enynes and enediynes and their reactivity in metal-catalysed cycloaromatisation reactions will be discussed.
Scheme 3.1. Potential approach for the reactivity of the 5-allenyloxazolidinones 230 as a precursor to synthesise chiral 1,3-(E)-enynes, enediyynes and isoindolines.

3.1. 1,3-Enynes

1,3-Enynes are versatile building blocks in organic synthesis, undergoing numerous transformations to generate structurally diverse products.81-86 They can be also found in many biologically active natural products mainly used as antifungal and antitumor agents.87-88 Therefore, extensive protocols have been investigated to develop efficient strategies to synthesise 1,3-enynes – despite this there are relatively few methods for preparing enantiomerically enriched enynes with a pendant heteroatom.89-98 There are four classical methods to prepare the 1,3-enynes 256 including the metal-catalysed cross-coupling reaction between alkynes and alkenes (Scheme 3.2a), cross-dimerisation of alkynes (Scheme 3.2b), Wittig olefination reactions of alkynyl aldehydes and ketones (Scheme 3.2c), and dehydration reactions of propargyl alcohols (Scheme 3.2d). A select number of these methods are now discussed to put the new method uncovered in this thesis in context.

Scheme 3.2. General pathways to synthesise 1,3-enynes.
3.1.1. Synthesis of 1,3-Enynes via Metal-catalysed Cross-coupling

Jiang et al. demonstrated the stereoselective cross-coupling synthesis of a range of 1,3-(E)-enynes 259 catalysed by Pd(OAc)$_2$ using unactivated styrenes 258 and alkynyl bromides 257 (Scheme 3.3). This protocol could tolerate a variety of functional groups on both substrates, with the enynes 259 obtained in good to excellent yields (41-95%) and stereoselectivities ($E/Z = 75:25$ to 100:0). The reaction pathway involves the formation of an alkynylpalladium(II) intermediate 260 through oxidative addition of the alkynyl bromide 257 to Pd(0) followed by a Heck cross-coupling reaction.

Ranu and co-workers reported the Cu-catalysed Suzuki-type cross-coupling reaction of alkynyl bromides 257 and alkenylboronic acids 261 in the presence of CuFe$_2$O$_4$ nanoparticles to provide unsymmetric 1,3-enynes 262 (Scheme 3.4). In this study, aliphatic, aromatic, and heteroaromatic alkynyl bromides were treated with various substituted trans alkenylboronic acids to access a wide range of trans 1,3-enynes 262 in moderate to high yields (54-89%).

Venkataraman and co-workers disclosed a Sonogashira-type copper(I)-catalysed procedure for the synthesis of both cis and trans 1,3-enynes using vinyl iodides 264 and terminal acetylenes 263 (Scheme 3.5). This methodology tolerated a wide range of substrates
and functional groups, providing the 1,3-enynes 265 in moderate to excellent yields with stereochemical retention of the starting vinyl iodides. [Cu(phen)(PPh₃)₂]NO₃ and [Cu(bipy)PPh₃Br] were shown to be effective in these coupling reactions. In the majority of cases, [Cu(phen)(PPh₃)₂]NO₃ (10 mol%) was utilised as the catalyst in the presence of K₂CO₃ (2.0 equiv.). However, in examples where the vinyl iodide was an (E)-alkene, [Cu(bipy)PPh₃Br] (10 mol%) was employed using Cs₂CO₃ (2.0 equiv.) as the base.

3.1.2. Synthesis of 1,3-Enynes via Metal-catalysed Cross-dimerisation

Transition-metal catalysed cross-dimerisation coupling of terminal alkynes to form 1,3-enynes is an attractive strategy due to the ready availability of the alkyne precursors. However, control over the stereo- or regioselectivity of the enyne product could be highly challenging as homo- or cross-coupling of two alkynes can occur. Rhodium and palladium complexes are the two most common catalyst systems employed to promote the cross-dimerisation coupling of alkynes to give enynes with high levels of stereo- or regioselective control.

The Ozerov group described the efficient cross-dimerisation coupling of acetylenes 266 with excellent stereo- or regioselectivities, catalyzed by the dihydrido-Rh pincer complex 267, providing the (E)-1,3-enynes 268 as the major products (Scheme 3.6). It was suggested that the stereochemical outcomes might be due to the steric interactions between the bulky groups of the Rh complex and the other substituents forming the intermediate 269 during the hydrometalation process (Scheme 3.8).
Scheme 3.6. Synthesis of 1,3-(E)-enynes using acetylenes catalyzed by a Rh pincer complex.

Gevorgyan and Rubina disclosed the Pd-catalysed (E)-selective dimerisation reactions of aryl alkynes 270 to give 1,3-(E)-enynes 271 in good yields and excellent regioselectivities under mild conditions (Scheme 3.7).\(^{100}\) The methodology was shown to be effective for aryl acetylenes, but not for alkyl-substituted substrates. It was also proposed that the E-selective stereochemical outcome of the coupling process to be due to possible coordination of the palladium with the triple bond (Scheme 3.7).

Scheme 3.7. Pd-catalysed synthesis of 1,3-(E)-enynes using acetylenes.

The cross-dimerisation reaction can also occur between two different alkynes acting as donor and acceptor species resulting in a hetero-coupled enyne. Miura et al. reported (E)-selective dimerisation reactions between a series of acetylenes 274 as acceptor species and
donor triisopropylsilylacetylene 273 in the presence of [RhI(COD)]$_2$ in good yields and excellent stereoselectivities (Scheme 3.8).\textsuperscript{101} Xanthphos was found to be the best phosphine ligand regarding the selectivity, possibly because of the biggest bite angle related to the catalyst derived from this ligand.\textsuperscript{101}

![Scheme 3.8. Rh-catalysed hetero-dimerisation of acetylenes.](image)

3.1.3. Synthesis of 1,3-Enynes via Wittig Olefination and Dehydration Reactions

The Schlosser group described stereoselective Wittig olefination reactions of propargyl aldehydes 279 employing different phosphorous ylides 278 under mild reaction conditions (Scheme 3.9).\textsuperscript{102} This protocol was highly Z-selective giving the 1,3-(Z)-enynes 280 in high yields and good to excellent stereoselectivities.

![Scheme 3.9. Z-selective Wittig reactions of propargyl aldehydes and phosphorous ylides.](image)

There are several examples of the dehydration pathway, which is most similar to the synthesis developed in this thesis. For example, Shi and co-workers reported a 1,2,3-traizole-promoted Fe(III)-catalysed dehydration reaction of the propargyl alcohol 281 (Scheme 3.10).\textsuperscript{103}
The 1,3-enynes 282 were prepared in good to excellent yields (46-95%) for a wide range of substrates. This protocol also offered excellent stereoselectivity, providing enynes in which only the Z-isomer was formed. It was shown that the combined σ-donor properties of the nitrogen lone-pair electrons and the π-receptor properties of the highly electron-deficient triazole ring enables the 1,2,3-triazole ligand 283 to increase the reactivity of the Lewis acidic Fe(III) catalyst.

![Scheme 3.10. Z-Selective Fe(III)-catalysed dehydration reaction of propargyl alcohols.](image)

Alcaide et al. disclosed a stereoselective synthesis of (E)-2-aryl-but-1-en-3-ynes 285 from aryl-substituted α-allenols 284 by treatment with acetyl chloride in an aqueous NaOH/CH2Cl2 biphasic mixture (Scheme 3.13). The reaction mechanism could be explained based on the elimination of acetic acid via δ-deprotonation and elimination of the acetate group in the α-allenic acetate intermediate 286.

![Scheme 3.11. NaOH-promoted direct synthesis of 1,3-(E)-enynes 285 from allenols 284.](image)

In another similar study, the Sawama group described a phosphate-promoted synthesis of a variety of disubstituted enyne 288 from α-allenols 287 using trimethyl phosphate in the
presence of NaH (Scheme 3.1). The proposed reaction mechanism was similar to that previously reported in the study by Alcaide, through the transformation of the hydroxy group into a good leaving group followed by the conjugate elimination. This concept could also explain the formation of 1,3-(E)-enyne 253 via the decarboxylative conjugate elimination of the N-Bn oxazolidinone 230a upon a treatment with an excess amount of NaH (Scheme 3.1).


3.2. Heteroatom-tethered 1,3-Enynes and 1,4-Enynes

Heteroatom-tethered 1,3-enynes are of great interest as versatile building blocks for the construction of diversity-oriented complex molecules. Classical strategies for synthesis of highly functionalised heterocycles are often limited by poor functional group tolerance, lack of regioselectivity, inadequate substrate scope, and harsh reaction conditions. Therefore, such heteroatom-pendant enyne scaffolds have attracted significant interest regarding atom-economical protocols in organic synthesis due to easily accessible starting materials, low toxicity, high functional group tolerance, and mild reaction conditions.

Zhang and Herndon reported the formation of alkenylpyrroles 293 through the coupling reactions of enyne-imines 291 with Fischer complexes 292 (Scheme 3.13). The (Z)-enyne precursors 291 were synthesised from ketones 290 in three steps with moderate to excellent yields. The majority of the enyne-imines 291 were used in the next cyclisation reaction step without further purification since they were found to be unstable upon silica column chromatography.

Gabriele et al. described the KOtBu-promoted one-pot, three-component coupling reactions of alkynes (294 and 296) and aldehydes (295) to rapidly access (Z)-2-en-4-yn-1-ols 297 and (E)-1-en-4-yn-3-ols 298 under mild reaction conditions (Scheme 3.14).\textsuperscript{110} Interestingly, they demonstrated that when the crude reaction mixture was quenched with 10% H\textsubscript{2}SO\textsubscript{4} aqueous solution, the (Z)-2-en-4-yn-1-ol 297 could be obtained via a rearrangement of the allylic alcohol. However, using only H\textsubscript{2}O in the workup process gave the (E)-1-en-4-yn-3-ol 298 in high yields and excellent stereoselectivities.

Scheme 3.14. KOtBu-promoted three-component coupling reaction of aldehydes and alkynes to synthesise (Z)-2-en-4-yn-1-ols 297 and (E)-1-en-4-yn-3-ols 298.

Although many methods have been investigated for the synthesis of heteroatom-tethered 1,3-enynes and 1,4-enynes, most of the strategies offered racemic 1,3-(Z)-enynes as the major product, which were not stable in most cases due to being prone to undergo
intramolecular cyclisation. Therefore, a method for the synthesis of chiral heteroatom-containing 1,3-(E)-enynes is highly desirable in organic synthesis.

3.3. Carbon- and Heteroatom-tethered 1,6-Enynes

Carbon- and heteroatom-tethered 1,6-enynes are versatile building blocks in organic synthesis due to their unique highly unsaturated bond systems. Compared with 1,3-enynes, these scaffolds have attracted considerable attention owing to their application to the one-step formation of a diverse array of carbon- and heterocyclic products, from these relatively simple starting materials, in an atom-economical fashion. 1,6-Enynes are also widely employed in the synthesis of bioactive molecules for various medicinal purposes. For example, GSK1360707 is a common anti-depressive agent representing a well-balanced activity for depression and anxiety treatment, which can be prepared from the Au-catalysed cyclisation of the 1,6-enyne (Scheme 3.15a).

Synthesis of carbon- and heteroatom-tethered 1,6-enynes will be not discussed in detail in this Chapter as they can be easily prepared via several classical strategies under mild conditions, as shown in Scheme 3.15b.
3.4. Metal-catalysed Cycloisomerisation Reactions of 1,6-Enynes

Carbon- and heteroatom-tethered 1,6-enynes can readily participate in numerous tandem reactions due to the double and triple bond units in these structures, which offer versatile approaches to a variety of products by simple manipulation. Among the astonishing diversity of transformations, metal-catalysed cycloisomerisation reactions of 1,6-enynes are growing in importance as powerful tools for the synthesis of many cyclic compounds in an one-pot process under mild reaction conditions.\textsuperscript{111, 119} As such, these reactions are fundamentally atom-economical with a concomitant increase in molecular complexity.\textsuperscript{111} Thus, cycloisomerisation reactions of 1,6-enynes have significant potential for applications in the synthesis of natural products and pharmaceuticals.\textsuperscript{120-121}

Cycloisomerisation reactions of 1,6-enynes 311 have been extensively investigated with a wide range of metal complexes.\textsuperscript{111, 119-123} Depending on the interaction modes of the
substrate and the metal, there are three general approaches proposed for these
cycloisomerisation reactions (Scheme 3.16). The concurrent complexation of the metal to the
alkene or alkyne leads favourably to the metallacycle 312 via an oxidative coupling pathway
(Scheme 3.16, pathway a). The presence of a functional group in the allylic position enables
the generation of a π-alloyl-metal complex 313 (Scheme 3.16, pathway b), which then further
reacts with the triple bond to form the desired cyclo 1,\(n\)-dienes 315. In the presence of a metal
hydride as the catalyst, the cycloisomerisation reaction proceeds through a hydrometalation of
the alkyne motif generating the corresponding vinylmetal species 314, carbometalation of the
olefin then occurs if an appropriate substitution at the allylic position is present (Scheme 3.16,
pathway c).

Scheme 3.16. Three main mechanisms for the metal-catalysed cycloisomerisation of 1,6-enynes.

The majority of the established transformations of 1,6-enynes require coordination of
both π-bonds to a single metal centre, which restrict diversity of the stereochemical outcomes
of these reactions. Furthermore, it has been generally established that metal catalysts
favouring ligation of a single π-system are more reactive and selective.

Au(I) complexes have proved to be the one of the most efficient catalyst species for the
activation of 1,6-enynes, even in the presence of different functional groups or stereochemical
elements. Mechanistically, Au(I)-cycloisomerisation reactions of 1,6-enynes are
initiated by selective activation of alkynes through coordination of the metal to the alkyne
providing excellent chemoselectivity and high synthetic efficiency.
3.5. Au(I)-Catalysed Cycloisomerisation of 1,6-Enynes

Cationic Au(I) complexes have emerged as versatile carbophilic π-acid catalysts in cycloisomerisation of 1,6-enynes providing various molecular skeletons which are often challenging to achieve via other transition-metal catalysis. The strong Lewis acidity of cationic Au(I), low oxophilicity, as well as its potential to stabilise cationic reaction intermediates offer unique reactivity to such catalysts in synthetic reactions. The existence of contraction of the 6s orbitals and expansion of the 5d orbitals in the cationic gold(I) species enable it to interact with various ligands.

As mentioned earlier, in metal-catalysed cycloisomerisation reactions of 1,6-enynes, most metal complexes require coordination of the metal to both the alkyne and the alkene bonds, resulting in products arising from a non-skeletal rearrangement mechanism (Scheme 3.16 and Scheme 3.17a). This reaction is initiated by coordination of the transition metal to both π-bonds of the enyne to generate species 317 followed by an oxidative cyclometalation to give the metallacycle intermediate 318. β-Hydrogen elimination from one of the alkyl chains then occurs to form species 319, which finally undergoes reductive elimination to provide the observed product 320.

Considering the mechanistic basis of the Au(I)-catalysed cycloisomerisation of 1,6-enynes, there are two main pathways involving skeletal rearrangements generated through either exo or endo addition of the pendant alkene to the gold π-alkyne complex 321 (Scheme 3.17b). According to the skeletal rearrangement mechanism, Au(I) cannot coordinate to the both π-bonds at the same time. The complexation of Au(I) to the triple bond provides a (η²-alkyne)metal complex 321 acting as an electrophile, which then react with the alkene moiety through either 5-exo-dig or 6-endo-dig cyclisation mode to form the corresponding cyclopropyl gold carbenes 322 or 323, respectively (Scheme 3.17b). In the absence of internal and external nucleophiles, the reaction proceeds via different skeletal rearrangements depending on the enyne structure and gold catalyst. In the case of the single cleavage rearrangement, the cyclic intermediate 322 collapses to form either the 5-membered ring
compound 324 or the 6-membered ring compound 325 via carbon-migration (R³ and R⁴ groups). For the double cleavage rearrangement, diene 326 is formed by a formal insertion of the terminal carbon of the alkene into the alkyne carbon followed by α-proton elimination. In contrast, the six-membered ring intermediate 323 from 6-endo-dig cyclisation can proceed to generate a [4.1.0]hept-2-ene structure 327 by protodeauration. Furthermore, the cyclopropane of the Au(I) 323 can also be expanded to afford cyclobutene derivative 328 (Scheme 3.17b).

Scheme 3.17. (a) Cycloisomerisation of 1,6-enynes with non-skeletal rearrangement approach. (b) Cycloisomerisation of 1,6-enynes with skeletal rearrangement approach.
The regioselectivity between the 5-exo-dig and 6-endo-dig addition modes is highly dependent on the enyne substitution pattern. For example, DFT calculations of the cycloisomerisation reaction of heteroatom-tethered 1,6-enynes have indicated that the Au(I) species often dissymmetrically coordinates to the two carbons of the alkyne bond, which indicates that the regioselectivity between the five- and the six-membered ring intermediates is already decided at the ring closing step.\textsuperscript{127} The dissymmetry is dependent upon on the substituents on the triple bond. Therefore, in cycloisomerisation of heteroatom-tethered 1,6-enynes, the generation of five-membered ring intermediates is kinetically favored for terminal alkynes, while the formation of 6-membered cyclic compounds is preferred for internal alkynes.\textsuperscript{127} For example, the Michelet group reported the enantioselective Au(I)-catalysed cycloisomerisation reactions of heteroatom-tethered 1,6-enynes \textsuperscript{329} in the presence of AuCl/AgOTf under mild reaction conditions (Scheme 3.18).\textsuperscript{128} The enynes \textsuperscript{329} with an internal alkyne bond exclusively underwent the 6-endo-dig addition reaction pathway to give derivatives \textsuperscript{330} in high yields and excellent ee.

\[
\begin{align*}
\text{Scheme 3.18. Enantioselective synthesis of derivatives } & \text{330 via Au(I)-catalysed cycloisomerisation reaction of 1,6-enynes.} \\
\end{align*}
\]

The Au(I)-catalysed cycloisomerisation of nitrogen- and oxygen-tethered alkylidene cyclopropanes \textsuperscript{332} to tricyclic compounds \textsuperscript{333} in the presence of [(t-BuXPhos)Au(NCMe)]SbF\textsubscript{6} catalyst \textsuperscript{336} was disclosed by Shi and co-workers (Scheme 3.19).\textsuperscript{129} They demonstrated that when the alkyne moiety has no terminal substitution, the corresponding five-membered ring 1,3-diene \textsuperscript{335} could be obtained in high yield, through the 5-exo-dig addition reaction mechanism, rather than the six-membered tricyclic product.

In contrast, the regioselectivity between single cleavage and double cleavage rearrangements (Scheme 3.17b) can be more challenging. Mechanistic studies reported by the Echavarren group proposed that 1,6-enynes 337 bearing electron-donating substituents on the alkyne moiety underwent Au(I)-catalysed single cleavage skeletal rearrangement, whereas substrates with electron-withdrawing substituents undergo double cleavage rearrangement (Scheme 3.20).130

Scheme 3.20. Au(I)-catalysed cycloisomerisation of 1,6-yn e 337 via single- and double-cleavage rearrangements.

In the majority of 1,6-enynes with disubstituted alkenes, these skeletal rearrangements are stereospecific pathways in which the configuration of the alkene is retained. However, Echavarren et al. showed that the cycloisomerisation reactions of 1,6-enynes with strongly electron-donating substituents at the terminal alkene carbon are non-stereospecific, in which Z-configured 1,3-dienes 342 are selectively generated via single-cleavage rearrangement using
either (E)-341 or (Z)-343 enynes (Scheme 3.21).\textsuperscript{131} They demonstrated that the carbocationic intermediate 345 could be formed from both (E)-341 and (Z)-343 enynes and that bond rotation is faster than the rearrangement because of the electron-donating R group.

Despite considerable investigations and progress in the Au(I)-catalysed cycloisomerisation of 1,6-enynes,\textsuperscript{86, 111, 120, 123-124, 126} these reactions are still demanded in organic synthesis to construct complex molecules from easily accessible 1,6-enynes. Furthermore, it is essential to develop strategic protocols to prepare chiral 1,6-enynes substrates, as synthetic methodologies for these chiral precursors are rare in the literature.\textsuperscript{120, 124} As an extension of this research area, the association of carbon- and heteroatom-tethered 1,6-enyne skeleton with an extra \( \pi \)-bond system could offer useful advances in the skeletal diversity of the heterocyclic products. However, such unique systems are rarely employed in cycloisomerisation reactions similar to those types discussed above. There are a few isolated examples of other conjugated systems, which will be discussed in the following section.

### 3.6. 1,6-Enynes Bearing Extra \( \pi \)-Bond Substitutions

As discussed earlier, carbon- or heteroatom-tethered 1,6-enynes have emerged as versatile building blocks for the synthesis of valuable cyclic skeletons. Due to the demand for atom-
economy in natural product synthesis and pharmaceuticals, introducing an extra pendant π-bond to such 1,6-enynes could offer more molecular complexity in both atom and step economical ways.

In 2007, the Au(I)-catalysed intramolecular Diels–Alder reaction of the 1,6-enyne bearing an extra double bond substitution at the alkene position was reported by Fürstner and Stimson (Scheme 3.22a).132 Dienyne 347 smoothly underwent the cyclisation reaction to generate the corresponding 1,4-cyclohexadienes 348 in moderate to high yields. Mechanistically, the cycloaddition reaction is initiated by Au(I)-activation of the triple bond followed by attack of the internal alkene bond to generate an electrophilic metal carbene 350 (Scheme 3.22b). This intermediate then undergoes cyclisation to form cation species 351, which finally gives the observed product.

The Echavarren group described the Au(I)-catalysed intramolecular formal [4 + 2] cycloisomerisation of alkenyl-substituted 1,6-enynes 352 to afford bicyclic products 353 (Scheme 3.23).133 Initially, the dienyne 352 undergoes a cycloisomerisation reaction via a formal 5-exo-dig pathway to give the cyclopropyl Au(I)-carbene intermediate 354, which undergoes ring expansion to form the allyl cation 355. Subsequent deprotonation and protodeauration steps occur to provide the observed product 353.
Scheme 3.23. Au(I)-catalysed intramolecular formal [4 + 2] cycloisomerisation of 1,6-enynes 352.

The Rh(I)-catalysed intramolecular [4 + 2] cycloaddition of acyloxy-pendant enediyne 357 to give the cyclic ketone 358 was developed (Scheme 3.24).\textsuperscript{134} Mechanistically, they proposed that Rh catalysed the 1,3-acyloxy migration of the propargyl ester to generate the $\eta^4$-vinylallene 359 (Scheme 3.24). An oxidative cyclisation then occurs to provide the alkylidene metallacyclopentene 360. Subsequently, incorporation of the pendent alkyne bond into the metallacycle 360 gave the metallacycloheptatriene intermediate 361 which, upon reductive elimination, generated the bicyclic ketone product 358.


A Rh-catalysed intramolecular Diels–Alder-type reaction of the dienyne 362 for the preparation of indanes 364 was reported (Scheme 3.25).\textsuperscript{135} This protocol was an inverse
electron-demand Diels–Alder reaction in which the electron-deficient dienoate moiety (diene) reacted with the electron-rich alkyne bond (dienophile) in a Diels–Alder-type reaction cycloaddition. In order to produce the indanes 364, a subsequent oxidation step with DDQ was needed to facilitate aromatisation (Scheme 3.25).

Scheme 3.25. Rh-catalysed Diels–Alder-type reaction cycloaddition and oxidation of dienyne 362.

Taking all the above examples into consideration, it should be mentioned that none of these systems are similar to the novel unconjugated enediyne 254 in this project.

3.7. Aims of the Project (II)

As mentioned earlier in this Chapter, during the synthesis of 5-allenyloxazolidinones (229 and 230) from allenyl amino-alcohols (206 and 218), it was noticed that the N-Bn oxazolidinone 230 was transformed into the novel chiral 1,3-(E)-enyne 253 upon treatment with an excess amount of NaH under mild reaction conditions. Having these readily accessible novel chiral enyne precursors in hand, a proposal was designed for the synthesis of enantioenriched unconjugated enediynes 254 through introducing an additional unsaturated triple bond to the 1,3-enyne. The presence of a nitrogen-pendant-containing 1,3-enyne linked to a triple bond offers a unique unconjugated enediyne scaffold, which has not been investigated before in terms of metal cycloisomerisation and direct access to a range of heterocyclic compounds in an atom efficient manner. In light of the known general reaction mechanism pathways reported by Echavarren (Scheme 3.17), it was proposed that enediynes 254 could act as potential substrates to undergo the cycloisomerisation reaction to give the five-membered ring structure 365.
(Scheme 3.26a). This intermediate would provide an extra triple bond compared to those related dienes in the literature offering the possibility of a cycloaromatisation reaction to produce the enantioenriched isoindoline 255 in a single step (Scheme 3.26a). Such a process has not been described before, so would represent a new cascade cycloaromatisation process to important biologically active heterocycles.

Scheme 3.26. (a) Proposed reaction pathways to direct access chiral isoindoline. (b) Two examples of bioactive isoindolines.

Isoindolinones are highly privileged structures due to their presence as a motif in a diverse range of medicinally and biologically active natural products and other synthetic compounds (Scheme 3.26b).136-138 Despite the importance of these compounds, in comparison to other important bioactive heterocyclic skeletons, there are relatively few known methods for the synthesis of isoindolines in either an enantioenriched or racemic form.139-143 Therefore, the synthesis of chiral isoindolines is highly desirable in organic synthesis.
Chapter 4. Results and Discussion

4.1. Synthesis of 1,3-(E)-Enynes Bearing a Pendant Nitrogen

The alanine-derived N-Bn,N-Boc allenyl amino alcohol 218a was chosen as the model substrate to investigate the proposed cycloaromatisation reaction pathway (Scheme 4.1). The allene 218a was efficiently converted to the 1,3-(E)-enyne 253a upon treatment with an excess amount of NaH (2.00 equiv.) under mild reaction conditions with excellent E-selectivity. It was assumed that the reaction likely proceeded via in-situ formation of N-Bn allenyl oxazolidinone 230a, followed by a decarboxylative conjugate elimination to give the enyne 253a. To support this proposed mechanism, the oxazolidinone 230a was isolated from the reaction mixture and treated with NaH under the same reaction conditions, and the desired enyne product 253a was once again obtained. Furthermore, the proposed decarboxylative conjugate elimination mechanism was also supported by that previously reported study by Alcaide et al. in which 1,3-(E)-enynes were synthesised by the elimination of acetic acid via δ-deprotonation and elimination of the acetate group in the O-acetyl protected α-allenols (Chapter 3, Scheme 3.11). Mechanistically, the reaction of allene 218a with NaH generates the corresponding oxazolidinone 230a via deprotonation of the hydroxy group, followed by nucleophilic attack of the resulting alkoxide on the Boc carbonyl group. The excess amount of base then abstracts the distal allenic proton of the allenyl oxazolidinone 230a providing the N-pendant 1,3-(E)-enyne 253a via subsequent triple bond generation with concurrent decarboxylation (Scheme 4.1).

The formation of enyne product 253a was verified by the appearance of a doublet of doublet 1H NMR resonance at 2.85 ppm (dd, J = 2.2, 0.6 Hz, 1H) attributed to the terminal alkyne proton of the enyne (Figure 4.1). The presence of two distinctive ddd 1H resonances at
5.61 ppm (ddd, $J = 16.0, 2.3, 1.1$ Hz, 1H, $E$ isomer) and 6.10-6.16 ppm (ddd, $J = 16.0, 7.7, 0.6$ Hz, 1H, $E$ isomer) were assigned to the protons of the double bond group. The disappearance of the distinctive allene carbon resonance (around 209.0 ppm) in the $^{13}$C NMR spectrum also supported the formation of the enyne. The HRMS (ESI) of the purified enyne product showed an [M + H]$^+$ ion peak at $m/z$ 186.1279, which supported the structure of enyne 253a.

Encouraged by the potential efficiency of this method to prepare 1,3-enyne 253a with excellent $E$ selectivity, the investigation was then aimed to evaluate the substrate scope of this 1,3-($E$)-enyne synthesis using a range of the $N$-Bn,$N$-Boc allenyl amino alcohols 218 – the synthesis of which were reported in Chapter 2. When these allenyl amino alcohols were treated with NaH, their corresponding enyne products 253a-e were successfully obtained in good to high yields and with excellent $E$-selectivity (Table 4.1). In all cases, only the desired enyne was observed in the $^1$H NMR spectrum of the crude reaction mixture, without any intermediate oxazolidinone being observed when an excess amount of NaH was used. As mentioned earlier in Chapter 2, investigation of the NMR spectra for the pure $N$-Bn,$N$-Boc allenyl amino alcohols.
was complicated due to the presence of a mixture of rotamers (caused by carbamate C−N rotation of Boc), diastereoisomers and regioisomers. Therefore, after the Zn-catalysed allenylation reaction of α-amino aldehydes, the crude reaction mixture was subjected to a short silica column in order to remove unreacted reagents and the catalyst. The resulting semi-purified product mixture was then used for the NaH-mediated synthesis of the enynes in order to establish a protocol that gave excellent overall yields for the two steps.

<table>
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<tr>
<th>Table 4.1. Reaction scope for 1,3-(E)-enynes 253a-e.4,6</th>
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*Isolated yield over three steps. \(^b\)Enantiomeric excess (ee) of 253a was determined as >99% using chiral HPLC analysis.

The allenyl products 218 are obtained in enantiomerically-enriched form as they originate from naturally occurring L-α-amino acids and little or no erosion of the enantiomeric purities during the reaction steps is observed \textit{vide supra}.\(^6\) At this point, it was intended to see whether this methodology would also show retention of enantiopurity of the allene products during the formation of the enyne. Therefore, the enantiomeric excess of the chiral enyne 253a was measured as a model compound using chiral HPLC analysis, and was compared with its corresponding racemic enyne prepared from the racemic N-Bn,N-Boc alanal 217a. Gratifyingly, the enantiomeric excess of 253a was observed as >99%, which indicated no erosion of the enantiomeric purity during the enyne formation process (see Experimental section for details).
4.2. Synthesis of Unconjugated Enediyynes and Au(I)-Catalysed Cycloisomerisation

Having the novel enantiomerically-enriched enynes 253a-e in hand, the investigation then focused on introducing an additional unsaturated triple bond to the enyne system; with 253a chosen as the model substrate. N-Propargylation of the enyne 253a with propargyl bromide mediated by K$_2$CO$_3$ in CH$_3$CN provided the corresponding alkenyl-substituted 1,6-enzyme (enediyne) 254a in good yield (Table 4.2). The formation of this desired product was verified by the appearance of a singlet $^1$H NMR resonance at 2.21 ppm (1H) attributed to the new terminal alkyne proton of the enediyne (Figure 4.2). Furthermore, an AB quartet resonance at 3.26 ppm (2H, $J_{AB} = 15.0$ Hz) was assigned to the diastereotopic CH$_2$ protons of the N-propargyl group. The HRMS (ESI) of the purified enediyne product showed a [M + Na]$^+$ ion peak at $m/z$ 246.1267, which supported the structure of 254a.

![Figure 4.2. $^1$H NMR spectrum (500 MHz, CDCl$_3$) of the enediyne 254a.](image)

A reaction optimisation was performed with enediyne (254a) by employing various Au(I) catalysts, along with an Ag(I) salt to generate a more electrophilic Au(I) species *in-situ,*
solvents, reaction temperature, and quantities of catalyst (Table 4.2). Initial optimisation reactions were carried out in DCE, as a polar halogenated solvent, under an inert atmosphere (Table 4.2, entries 1-6). Running the reaction using 5 mol% of AuPPh₃Cl/AgBF₄ at room temperature showed no conversion to product(s) and only unreacted starting material was recovered (Table 4.2, entry 1). The reaction was then conducted using 10 mol% AuPPh₃Cl/AgBF₄ at 50 °C, but no reaction occurred (Table 4.2, entry 2). Employing the N-heterocyclic carbene gold catalyst system IPrAuCl/AgBF₄ also resulted in no reaction being observed (Table 4.2, entry 3) and increasing the catalyst loading to 20 mol% at 50 °C resulted in complete decomposition of the starting material (Table 4.2, entry 4). The reaction was then performed using 10 mol% of IPrAuCl/AgBF₄ under reflux in DCE, and the ¹H NMR analysis of the crude reaction mixture indicated decomposition of the enediyne substrate (Table 4.2, entry 5). However, when the reaction was conducted under reflux conditions in the presence of IPrAuCl but with AgSbF₆ instead of AgBF₄, the isoindoline 255a was obtained as the major product in 25% yield along with a small amount (28%) of the 5-membered ring product dienyne 365 (Table 4.2, entry 6). Although the role of the counteranion in homogeneous gold catalysis remains unclear, it has been shown that the weakly coordinating and more moisture tolerant SbF₆⁻ counteranion is practically more efficient compared to BF₄⁻. With an effective catalyst system identified, the solvent was then varied in an attempt to increase the yield. Switching to toluene as a less polar solvent showed a noticeable increase in the reaction conversion (Table 4.2, entry 7), although ¹H NMR analysis of the crude reaction mixture indicated a trace amount of the 5-membered dienyne 365. Increasing the reaction temperature to reflux pushed the reaction to completion and gratifyingly the isoindoline 255a was isolated in a 70% yield (Table 4.2, entry 8), with no trace of the 5-membered ring dienyne 365. Lowering the catalyst loading from 10 mol% to 5 mol% had a negative impact on the reaction efficiency resulting in a 56% yield of the desired product 255a (Table 4.2, entry 9). In order to compare the effect of Au(I)-phosphine complex with the NHC-stabilised Au(I) complex on this reaction, AuPPh₃Cl/AgSbF₆ (10 mol%) was used as the catalyst at reflux in toluene, but no reaction was
observed (Table 4.2, entry 10). Furthermore, the reaction did not proceed using either IPrAuCl or AgSbF₆ alone at reflux in toluene (Table 4.2, entries 11 and 12).

The formation of the 5-membered intermediate 365 provides some evidence that the reaction proceeds through the known 5-exo-dig cyclisation (single cleavage) mode as shown in Scheme 3.17b. The intermediate 365 was verified by the disappearance of the ¹H NMR resonances of the terminal alkyne protons and the alkene group of the enediyne starting material (Figure 4.3). Furthermore, the appearance of two sets of alkene ¹H NMR resonances clearly indicated the presence of a mixture of E/Z (1.5:1.0 ratio, Jₐₗₗ = 11.0 Hz and Jₕₕ = 16.0 Hz) isomers of the 5-membered ring intermediate 365. Unfortunately, this compound proved unstable towards purification and further characterisation could not be performed. Moreover, many further attempts to isolate the 5-membered ring intermediate were unsuccessful.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Yielda (%)</th>
<th>Products ratiof (%)</th>
<th>365 (%)</th>
<th>255a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuPPh₃Cl/AgBF₄ (5)</td>
<td>r.t</td>
<td>DCE</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>AuPPh₃Cl/AgBF₄ (10)</td>
<td>50 ºC</td>
<td>DCE</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>IPrAuCl/AgBF₄ (10)</td>
<td>50 ºC</td>
<td>DCE</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>IPrAuCl/AgBF₄ (20)</td>
<td>50 ºC</td>
<td>DCE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>IPrAuCl/AgBF₄ (10)</td>
<td>reflux</td>
<td>DCE</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>IPrAuCl/AgSbF₆ (10)</td>
<td>reflux</td>
<td>DCE</td>
<td>25</td>
<td>28e</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>IPrAuCl/AgSbF₆ (10)</td>
<td>reflux</td>
<td>toluene</td>
<td>47</td>
<td>8</td>
<td>92</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>IPrAuCl/AgSbF₆ (10)</td>
<td>reflux</td>
<td>toluene</td>
<td>70</td>
<td>-</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>IPrAuCl/AgSbF₆ (5)</td>
<td>reflux</td>
<td>toluene</td>
<td>56</td>
<td>-</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>AuPPh₃Cl/AgSbF₆ (10)</td>
<td>reflux</td>
<td>toluene</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>IPrAuCl (10)</td>
<td>reflux</td>
<td>toluene</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>12</td>
<td>AgSbF₆ (10)</td>
<td>reflux</td>
<td>toluene</td>
<td>N.R.</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

aReactions performed under nitrogen atmosphere for 24 h. bIsolated yield of isoindoline 255a. cNo reaction occurred. dDecomposition of starting material. eMixture of Z/E (1:1.5) isomers. fProducts ratio based on ¹H NMR analysis of the crude reaction mixture.

The formation of the 5-membered intermediate 365 provides some evidence that the reaction proceeds through the known 5-exo-dig cyclisation (single cleavage) mode as shown in Scheme 3.17b. The intermediate 365 was verified by the disappearance of the ¹H NMR resonances of the terminal alkyne protons and the alkene group of the enediyne starting material (Figure 4.3). Furthermore, the appearance of two sets of alkene ¹H NMR resonances clearly indicated the presence of a mixture of E/Z (1.5:1.0 ratio, Jₐₗₗ = 11.0 Hz and Jₕₕ = 16.0 Hz) isomers of the 5-membered ring intermediate 365. Unfortunately, this compound proved unstable towards purification and further characterisation could not be performed. Moreover, many further attempts to isolate the 5-membered ring intermediate were unsuccessful.
The isoindoline product 255a was confirmed by the disappearance of the $^1$H NMR resonances of the terminal alkyne protons and the alkene group of the enediyne starting material (Figure 4.4). Furthermore, the presence of four new aromatic $^1$H NMR resonances in the 7.12 ppm to 7.42 ppm range provided support for the formation of a new aromatic ring. This was further supported by the total number of 10 C(sp$^2$) resonances in the aromatic region of the $^{13}$C NMR spectrum. The HRMS (ESI) of the purified enediyne product showed an [M + H]$^+$ ion peak at $m/z$ 224.1450, which supported the structure of 255a.
Having the optimised reaction conditions in hand, the substrate scope of the Au(I)-catalysed cycloisomerisation reaction was evaluated using a series of the enediynes 254b-g (Table 4.3). A range of the novel (E)-enediynes 254a-g was prepared in moderate to high yields using propargyl bromide and K₂CO₃ in CH₃CN at reflux. These enediynes were then subjected to the optimised cycloisomerisation reaction conditions – however, it was quickly realised that the isoindoline products 255 are likely highly unstable towards autoxidation and the reactions were therefore capricious. Employing the enediynes (254) in the Au(I)-catalysed cycloisomerisation reaction resulted in no desired product for each case, and the ¹H NMR spectrum of the crude reaction mixture indicated complete decomposition of the enediyne starting material. In an attempt to synthesise a dihydroisoquinoline, the possible gold-catalysed cycloaromatisation reaction of N-butynoic enediyne 254e was also investigated which resulted in no desired product. The phenylalanine-derived isoindoline 255d was obtained in low yield (24%), although the ¹H NMR spectrum of the crude reaction mixture only showed the product. Unfortunately, this compound rapidly decomposed and satisfactory ¹³C NMR and IR spectra could not be obtained. The cycloisomerisation reactions were repeated numerous times for all
the enediynes 254a-g, but no product was isolated and the 1H NMR spectra of the crude reaction mixtures showed no clear resonances for any significant organic product.

Upon further in-depth analysis of the literature, the instability of N-aryl and N-alkyl isoindolines was noted as they have a high tendency to undergo autoxidation in solution to form isoindoles 368.145-148 These isoindoles are highly susceptible to being further oxidised to cyclic endo peroxides 369,148 followed by decomposition of the cyclic compound to unstable

---

**Table 4.3. Reaction scope for the isoindolines 255.**

<table>
<thead>
<tr>
<th>Enediyne 254</th>
<th>Isoindoline 255</th>
</tr>
</thead>
<tbody>
<tr>
<td>253a-e</td>
<td>255a-g</td>
</tr>
<tr>
<td>254a</td>
<td>66%</td>
</tr>
<tr>
<td>254b</td>
<td>77%</td>
</tr>
<tr>
<td>254c</td>
<td>72%</td>
</tr>
<tr>
<td>254d</td>
<td>80%</td>
</tr>
<tr>
<td>254e</td>
<td>54%</td>
</tr>
<tr>
<td>254f</td>
<td>83%</td>
</tr>
<tr>
<td>254g</td>
<td>43%</td>
</tr>
</tbody>
</table>

| 255a         | 70%<sup>a</sup> |
| 255b         | -<sup>b</sup>   |
| 255c         | -<sup>b</sup>   |
| 255d         | 24%<sup>a</sup> |
| 255e         | -<sup>b</sup>   |
| 255f         | -<sup>b</sup>   |
| 255g         | -<sup>b</sup>   |

<sup>a</sup>These isolated yields obtained only once and the repeated reactions showed decomposition of starting material. <sup>b</sup>Complete decomposition of starting material.
fragments. On this basis, it was speculated that the auto-oxidation of the isoindolines 255 leads to unstable volatile fragments as there were no clear signals detected in the $^1$H NMR spectra of the crude reaction mixtures (Scheme 4.2).

![Scheme 4.2. Speculated auto-oxidation reaction pathway of the isoindoline 255.](image)

Having an electron-withdrawing group on or next to the nitrogen could be an effective solution for this problem. For example, Sarpong et al. reported the synthesis of a range of isoindolines and isoindolinones via the direct C–N coupling between benzylic carbon groups and amines (Scheme 4.3). Due to the high instability of the isoindoline products 372, the yields were only determined by $^1$H NMR analysis using hexamethylenetetramine as an internal standard. However, it was shown that by introducing a carbonyl group in the structure of the starting materials, the corresponding isoindolines 375 and isoindolinones 376 could be isolated in good to high yields without decomposition (Scheme 4.3).

![Scheme 4.3. Effect of carbonyl group on the stability of isoindolines reported by Sarpong and co-workers.](image)
At this point, the investigation switched to introducing a propiolamide into the enyne structure, as the presence of a carbonyl group next to the nitrogen would increase stability and avoid autoxidation. Furthermore, the potential isoindolinone final product is highly desirable in organic synthesis as they are found in many pharmaceuticals and natural products that exhibit important biological activities as shown in the examples in Scheme 4.4.\textsuperscript{149,150} The $N$-benzyl substituted isoindolinone scaffold is particular of interest to medicinal chemistry because of its presence in a variety of biologically active compounds and pharmaceutical target molecules.\textsuperscript{151-153} Since enantiomers could interact differently with biological systems, the synthesis of these biologically active isoindolinones in enantiomerically enriched form is highly desired. For example, it has been showed that the stereospecificity of $N$-benzyl isoindolinones plays a significant role in MDM2-p53 PPI inhibitory activity.\textsuperscript{153}

\begin{center}
\textbf{Scheme 4.4.} Examples of bioactive isoindolinones.
\end{center}

1,3-(\textit{E})-Enyne 253d was chosen as the model substrate to investigate the proposed strategy in the Au(I)-catalysed cycloaromatisation reaction (Scheme 4.5). The unconjugated (\textit{E})-enediyne 380d was prepared using a DCC-amide coupling reaction of the enyne 253d and propiolic acid under mild reaction conditions (Scheme 4.5). Although the $^1$H NMR spectrum of the crude reaction mixture showed 100\% conversion of the starting material to the enediyne, only a moderate yield was obtained due to the difficulty in removing the urea byproduct formed in the DCC-amide coupling reaction. After completion of the reaction, the solvent was evaporated, and the mixture was re-dissolved in a minimum amount of CH$_2$Cl$_2$ and then cooled in a freezer for 18 h. The cooled mixture was then filtered to remove the precipitated urea, followed by purification of the product by column chromatography.
Scheme 4.5. Synthesis of enediyne 380d as the model substrate.

The enediyne product 380d was further verified by the appearance of two singlet $^1$H NMR resonances at 3.05 ppm and 3.16 ppm (a 2:1 mixture of two rotamers) attributed to the new terminal alkyne proton of the enediyne (Figure 4.5). Furthermore, two $^{13}$C NMR resonances at 153.6 ppm and 154.0 ppm (two rotamers) were assigned to the carbonyl of the propiolamide group. The HRMS (ESI) of the purified enediyne product showed an [M + Na]$^+$ ion peak at $m/z$ 336.1357, which supported the structure of 380d.

Figure 4.5. $^1$H NMR spectrum (400 MHz, CDCl3) of the enediyne 380d.

The model substrate 380d was subjected to the cycloisomerisation reaction under similar conditions employed for the synthesis of isoindoline 381d (Scheme 4.6). The $^1$H NMR spectrum of the crude reaction mixture showed formation of isoindolinone 381d as a minor
product, along with a large number of unidentified byproducts. Unfortunately, these byproducts could not be isolated and characterised due to their instability. However, analysis of the $^1$H NMR spectrum of the crude reaction mixture clearly showed that no five-membered ring intermediate 382 was formed. The $^1$H NMR spectrum of the enediyne product 380d also showed a mixture of two rotamers (ca. 2:1 ratio) caused by restricted carbamate C–N rotation of the propiolic substituent. Examination of the $^1$H NMR spectrum at elevated temperature (70 °C in DMSO), in an attempt to coalesce rotamer peaks, was also unsuccessful. It was speculated that the presence of the carbonyl group next to the triple bond might result in a potential change in the cycloaromatisation reaction mechanism. Due to the change in the nature of the electronics on the triple bond, the terminal alkyne proton would be more acidic than the triple bond of the enyne. Therefore, deprotonation of the terminal alkyne by the gold catalyst could offer the possible formation of the gold acetylide intermediate 383 (Scheme 4.6). The generation of gold acetylides is a known process in homogeneous gold catalysis where an alkyne acidic proton is replaced by a gold species. Due to the presence of another triple bond in the enediyne structure, the formation of a dual gold intermediate is possible. The triple bond of the acetylide part can then act as a nucleophile to react with the other Au-activated electrophilic triple bond. The proposed reaction mechanism will be discussed in detail later in this Chapter.

Scheme 4.6. Test reaction for the Au(I)-catalysed cycloaromatisation reaction of enediyne 380d.
The isoindolinone product 381d was confirmed by the disappearance of the $^1$H NMR resonances of the terminal alkyne protons and the alkene group of the enediyne starting material (Figure 4.6). Furthermore, the presence of four new aromatic resonances in the 6.87 ppm to 8.00 ppm range provided support for the formation of a new aromatic ring. The chemical shift of H-7 was significantly downfield consistent with its close proximity to an ortho-carbonyl group. This structure was further supported by the total number of 14 C(sp$^2$) resonances in the $^{13}$C NMR spectrum. The lack of rotamers in the $^1$H NMR spectrum also indicated the formation of the isoindolinone product. The HRMS (ESI) of the purified enediyne product showed an [M + H]$^+$ ion peak at $m/z$ 314.1541, which supported the structure of 381d.

![Figure 4.6. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isoindolinone 381d.](image)

In light of this preliminary result, it was intended to optimise the reaction conditions in order to increase the reaction efficiency. The investigation was initiated using two common electron-rich ligand coordinated gold complexes AuPPh$_3$Cl and IPrAuCl. Initial optimisation was performed in CH$_2$Cl$_2$ as a polar solvent under a nitrogen atmosphere (Table 4.4, entries 1-4). Increasing the temperature to reflux using 5 mol% of AuPPh$_3$Cl/AgSbF$_6$ did not improve the reaction efficiency, leading to a significant decrease in the NMR yield (11%), but with a
lower byproduct formation (Table 4.4, entry 2). In order to calculate the NMR yields, a stoichiometric amount of 3,5-difluorobenzaldehyde (1.0 equiv.), as an internal standard, was added to the crude reaction mixture and the ratio between the aldehyde carbonyl resonance (9.95 ppm, s, 1H) and the corresponding product peaks in $^1$H NMR spectrum of the crude reaction mixture gave the NMR yield. When the reaction was conducted with a higher catalyst loading (10 mol%), no improvement was observed for the yield of the desired isoindolinone 381d (Table 4.4, entry 3). Under the same conditions, the NHC ligand containing Au(I)-complex obtained from IPrAuCl/AgSbF$_6$ was completely ineffective, showing no isoindolinone formation (Table 4.4, entry 4). Toluene was then evaluated as a less polar solvent in the cycloisomerisation reaction (Table 4.4, entries 5-9). This reaction modification gave a low NMR yield (4.6%) of 381d along with a high amount of byproduct formation in the presence of AuPPh$_3$Cl/AgSbF$_6$ (10 mol%) at room temperature (Table 4.4, entry 5). Switching to IPrAuCl/AgSbF$_6$ had also a negative effect, leading to no reaction at room temperature (Table 4.4, entry 6). However, when the reaction was performed in toluene under reflux conditions, a noticeable decrease in by-product formation was observed (Table 4.4, entry 7). It is important to note that the mentioned byproduct was a complex mixture of compounds which could not be isolated or readily identified in the $^1$H NMR spectrum of the crude reaction mixture.

![Table 4.4. Optimisation of Au(I)-catalysed cycloisomerisation reaction of enediyne 380d.](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Temperature</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AuPPh$_3$Cl/AgSbF$_6$ (5)</td>
<td>r.t</td>
<td>CH$_2$Cl$_2$</td>
<td>24 h</td>
<td>9%</td>
</tr>
<tr>
<td>2</td>
<td>AuPPh$_3$Cl/AgSbF$_6$ (5)</td>
<td>reflux</td>
<td>CH$_2$Cl$_2$</td>
<td>24 h</td>
<td>11%</td>
</tr>
<tr>
<td>3</td>
<td>AuPPh$_3$Cl/AgSbF$_6$ (10)</td>
<td>reflux</td>
<td>CH$_2$Cl$_2$</td>
<td>24 h</td>
<td>10%</td>
</tr>
<tr>
<td>4</td>
<td>IPrAuCl/AgSbF$_6$ (5)</td>
<td>r.t to reflux</td>
<td>CH$_2$Cl$_2$</td>
<td>24 h</td>
<td>8$^b$</td>
</tr>
<tr>
<td>5</td>
<td>AuPPh$_3$Cl/AgSbF$_6$ (10)</td>
<td>r.t</td>
<td>toluene</td>
<td>24 h</td>
<td>4.6%</td>
</tr>
<tr>
<td>6</td>
<td>IPrAuCl/AgSbF$_6$ (10)</td>
<td>r.t</td>
<td>toluene</td>
<td>24 h</td>
<td>N.R.$^c$</td>
</tr>
<tr>
<td>7</td>
<td>IPrAuCl/AgSbF$_6$ (5)</td>
<td>reflux</td>
<td>toluene</td>
<td>24 h</td>
<td>32%$^d$</td>
</tr>
<tr>
<td>8</td>
<td>[(Ph$_3$PAu)$_3$O]BF$_4$ (5)</td>
<td>r.t to reflux</td>
<td>toluene</td>
<td>4 h</td>
<td>75%$^d$</td>
</tr>
<tr>
<td>9</td>
<td>[(Ph$_3$PAu)$_3$O]BF$_4$ (2.5)</td>
<td>reflux</td>
<td>toluene</td>
<td>6 h</td>
<td>77%$^d$</td>
</tr>
</tbody>
</table>

$^a$NMR yield based on crude reaction using 3,5-difluorobenzaldehyde as internal standard. $^b$No product detected in the $^1$H NMR spectrum of the crude reaction mixture. $^c$No reaction occurred. $^d$Isolated yield.
A cationic gold-oxo trimer, [(Ph3PAu)3O]BF4, was then evaluated in the cycloisomerisation reaction. It was anticipated that this electron-rich gold complex would be sufficiently basic to facilitate the formation of a gold acetylide. Interestingly, the reaction efficiently proceeded with a shorter reaction time and resulted in a significant improvement in the yield (Table 4.4, entry 8). The 1H NMR spectrum of the crude reaction mixture showed the exclusive formation of isoindolinone 381d with no trace of byproducts, suggesting that a more basic Au(I) complex might offer further benefits including formation of a gold acetylide. Reducing the amount of catalyst from 5 mol% to 2.5 mol% also led to a similar yield, but required a longer reaction time – these conditions were therefore selected as optimal (Table 4.4, entry 9).

A range of novel enantiomerically enriched propiolamide enediynes 380a-e were then prepared from the corresponding 1,3-(E)-enynes 253a-e (Table 4.5). Treating the enediynes 380 under the optimised cycloisomerisation reaction conditions efficiently provided the corresponding isoindolinone products 381 in high yields (Table 4.5).
As discussed earlier in Table 4.1, there was no erosion of the enantiomeric purity during the formation of 1,3-(E)-enyne 253a from the corresponding N-Bn,N-Boc allenyl amino alcohol 218a. At this point, it was intended to see whether this cycloisomerisation methodology would also show the retention of enantiomeric purity of the enyne starting materials for the isoindolinone final products. Therefore, the enantiomeric excess (ee) of the isoindolinone 381a was investigated by chiral HPLC analysis as the model compound to compare with that of previously measured for the 1,3-(E)-enyne 253a. The ee of the chiral isoindolinone 381a was observed as >99% by comparing with its corresponding racemic isoindolinone prepared from racemic 1,3-(E)-enyne (Figure 4.7). This result clearly indicated that no erosion of the enantiomeric purity occurred during the Au(I)-catalysed cycloisomerisation reaction.

<table>
<thead>
<tr>
<th>(E)-N-(hex-3-en-5-yn-2-yl)propiolamides</th>
<th>Isoindolinones</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E)-N-(hex-3-en-5-yn-2-yl)propiolamides</td>
<td>Isoindolinones</td>
</tr>
<tr>
<td>380a</td>
<td>381a</td>
</tr>
<tr>
<td>380b</td>
<td>381b</td>
</tr>
<tr>
<td>380c</td>
<td>381c</td>
</tr>
<tr>
<td>380d</td>
<td>381d</td>
</tr>
<tr>
<td>380e</td>
<td>381e</td>
</tr>
</tbody>
</table>

*Isolated yield. †Enantiomeric excess (ee) of 381a was determined as >99% using chiral HPLC analysis.
In order to increase the structural diversity of the substrates for the cycloisomerisation reaction, the Sonogashira cross-coupling reaction was utilised to introduce aromatic substituents on the terminal alkyne of the enyne unit (Table 4.6). A range of 1,3-(E)-enynes 384 bearing different aromatic groups on the terminal alkyne was prepared using standard Sonogashira conditions with catalytic PdCl$_2$(PPh$_3$)$_2$ and CuI. Aryl iodides bearing π-electron withdrawing groups (NO$_2$, F and CHO) gave the best yields (Table 4.6). These substituted enynes were then employed as the starting materials to synthesise the corresponding propiolamide enediynes 385 via DCC-amide coupling reactions (Table 4.6).

As mentioned earlier, although the $^1$H NMR spectrum of the crude reaction mixture showed 100% conversion of the starting material to the enediyne, only a moderate yield was obtained due to the difficulty in removing the urea byproduct formed in the DCC-amide coupling reaction.
To further explore the scope of the protocol, with respect to the aromatic substitution on the enyne motif, the enediynes 385 were subjected to the cycloisomerisation reaction under optimised conditions (Table 4.7). Substrates with a phenyl group, bearing either an electron-donating or electron-withdrawing substituent gave the corresponding isoindolinone products 386 in good to high yields (Table 4.7). The enediynes 385f and 385g having respectively a thiophene and the sterically demanding naphthalene group, were also well tolerated, providing the isoindolinones 386f and 386g in high yield.

**Table 4.6.** Expanding the structural diversity of the unconjugated (E)-enediynes.\(^a^\)

<table>
<thead>
<tr>
<th>R</th>
<th>Ar</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
<td>51%</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
<td>82%</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
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</tr>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
<td>83%</td>
</tr>
<tr>
<td>n-Pr</td>
<td>n-Pr</td>
<td>71%</td>
</tr>
<tr>
<td>i-Bu</td>
<td>i-Bu</td>
<td>50%</td>
</tr>
<tr>
<td>i-Bu</td>
<td>i-Bu</td>
<td>60%</td>
</tr>
</tbody>
</table>

\(^{a}(i)\) Arl (1.20 equiv.), PdCl\(_2\)(PPh\(_3\))\(_2\) (0.02 equiv.), CuI (0.04 equiv.), Et\(_3\)N (2.00 equiv.), THF, r.t, 18 h. (ii) propiolic acid (1.50 equiv.), DCC (1.50 equiv.), DMAP (0.30 equiv.), CH\(_2\)Cl\(_2\), r.t, 48 h. \(^b\)Isolated yields.

To further explore the scope of the protocol, with respect to the aromatic substitution on the enyne motif, the enediynes 385 were subjected to the cycloisomerisation reaction under optimised conditions (Table 4.7). Substrates with a phenyl group, bearing either an electron-donating or electron-withdrawing substituent gave the corresponding isoindolinone products 386 in good to high yields (Table 4.7). The enediynes 385f and 385g having respectively a thiophene and the sterically demanding naphthalene group, were also well tolerated, providing the isoindolinones 386f and 386g in high yield.

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The structure of the isoindolinone product 386c, derived from the aryl-substituted enediyne 385c, was verified by the disappearance of the $^1$H NMR resonances of the terminal alkyne protons and the alkene group of the enediyne starting material (Figure 4.8). The presence of a distinctive singlet $^1$H NMR resonance at 8.07 ppm (1H) clearly indicated the 6-substituted isoindolinone structure 386c. The HRMS (ESI) of the purified enediyne product showed a [M + Na]$^+$ ion peak at $m/z$ 394.1777, which further supported the structure of 386c.
Figure 4.8. $^1$H NMR spectrum (400 MHz, CDCl$_3$) of the isoindolinone 386c.

Figure 4.9. HMBC spectrum (400 MHz, CDCl$_3$) of the isoindolinone 386c.

The 6-substituted isoindolinone structure 386c was confirmed by HMBC analysis, showing a clear correlation between the $^1$H NMR resonance for H-7 and the carbonyl group $^{13}$C.
NMR resonance (Figure 4.9). Single crystal X-ray crystallography was also taken to verify the structure of the isoindolinone 386c (Figure 4.10). The X-ray crystallography was performed by A/Prof Michael Gardiner from the University of Tasmania (now the Australian National University).

Figure 4.10. X-ray crystal structure of isoindolinone 386c (CCDC 1867833, performed by A/Prof Michael Gardiner). Data were collected at 100 K on a crystal mounted on a Hampton Scientific cryoloop at the MX2 beamline, Australian Synchrotron, Victoria. The thermal parameters of all hydrogen atoms were estimated as $U_{eq}(H) = 1.2U_{eq}(C)$ except for CH$_3$ where $U_{eq}(H) = 1.5U_{eq}(C)$. Blue = N, red = O, grey = H, black = C.

4.3. Mechanistic Study of Au(I)-Catalysed Cycloisomerisation Reaction of Unconjugated Enediynes

Based on the general skeletal rearrangement mechanism of the Au(I)-catalysed cycloisomerisation reactions, the formation of lactam intermediate 387 through 5-exo-dig cyclisation mode was initially anticipated. This, in turn, would lead to a $[2\pi + 2\pi + 2\pi]$ cyclisation reaction to give the 4-substituted isoindolinone 388 (Scheme 3.35). However, the reaction interestingly proceeded via an unexpected regiochemical pathway, providing exclusively the 6-substituted isoindolinone 386, which strongly suggested that the cycloisomerisation reaction advances through a new reaction mechanism.
Recently, there have been significant investigations on uncovering and exploiting gold \(\sigma,\pi\)-dual-activation chemistry that come to be known as dual gold catalysis.\textsuperscript{154-155} In this new class of Au(I)-catalysed cyclisation reactions, two gold centres are involved in the reaction mechanism. In most cases, one alkyne group is \(\sigma\)-bonded to one gold species and another alkyne bond is \(\pi\)-coordinated to a second gold centre (390, Scheme 4.8a). The \(\sigma\)-activation of the alkyne bond generates a nucleophilic Au-acetylide, which reacts with the electrophilic \(\pi\)-complex moiety, leading to different gold intermediates (391, 392, or 393). The use of Au-acetylides as nucleophiles in Au-catalysed reactions has emerged as an important activation mode in the field.\textsuperscript{154-155} There are two general types of \(\sigma\)-activation to form the Au-acetylides, including deprotonation with a base additives and ligand exchange (Scheme 4.8b). In both cases, the acidity of the terminal alkyne hydrogen plays a crucial role in the reaction initiation. \(\sigma\)-Activation by ligand exchange results in the well-defined formation of Au-acetylide and \(\pi\)-activated alkyne, leading to high reaction efficiency (Scheme 4.8b).\textsuperscript{155} Furthermore, as a consequence, a fast initiation process, side products are minimised and reaction rates are higher in the ligand exchange pathway.\textsuperscript{155}
The Zhang group reported gold-catalysed cyclisation reactions of conjugated (Z-)enediynes providing highly efficient formation of a range of fused-aromatic structures (Scheme 4.8c). The reaction mechanism was proposed to proceed via gold σ,π-dual-activation where 5-endo-dig or 6-endo-dig cyclisations provided the highly electrophilic intermediates 398 and 399.
Their subsequent C–H insertion reaction was proposed to give fused polycyclic structures 400 and 401, respectively.

Based on these known dual gold activation processes, it was proposed that the mechanism for the formation of the isoindolinones reported in this thesis could follow a novel dual-gold cascade cycloisomerisation via the allenyl Au(I)/vinylidene Au(I) species 403 (Scheme 4.8d). It was also anticipated that highly selective formation of the Au(I)-acetylide occurred on the propiolic position due to the pKₐ differences between the propiolic amide and the alkyne unit in the enediyne substrate in compounds 380a-e.

Preliminary mechanistic studies commenced by evaluation of the proposed selective formation of Au(I)-acetylide in the dual gold activation mechanism. The enediyne 380b-Me bearing a methyl substitution on the terminal alkyne of propiolamide unit was prepared and subjected to the cycloisomerisation reaction under optimised reaction conditions (Scheme 4.9a). The reaction did not proceed to the corresponding isoindolinone and only the unreacted starting material was recovered. This observation strongly suggested that the initial formation of the Au(I)-acetylide could selectively occur on the terminal alkyne of the propiolamide, potentially due to the pKₐ difference between the propiolic amide and the alkyne unit on substrates 380a-e. A comparison between the gold catalysts also showed that the N-heterocyclic carbene based catalyst system IPrAuCl/AgSbF₆ was significantly less effective than the tris(phosphinegold)oxonium complex [(Ph₃PAu)₃O]BF₄ in promoting the reaction (Scheme 4.9b). These results indicated that the intrinsically basic [(Ph₃PAu)₃O]BF₄ was important in facilitating deprotonation of the terminal propiolic amide to form the Au(I)-acetylide species.

Scheme 4.9. Mechanistic experiments towards the proposed dual gold activation mechanism.

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Deuterium labeling studies were next investigated to gain further mechanistic information. The alkyne terminus of enediyne 385c was deuterated using K$_2$CO$_3$ and D$_2$O in CH$_3$CN at room temperature with excellent deuterium incorporation (98%) (385c-d, Scheme 4.10). The cycloaromatisation reaction with the D-labeled 385c-d led to 42% incorporation of the deuterium atom at the C-7 position of the final isoindolinone 386c-d, with only minor incorporation at C-4 and C-5. The observed significant loss of deuterium could be attributed to initiation of the reaction through the Au(I)-acetylide species formation (385c-Au, Scheme 4.10).

Scheme 4.10. Deuterium labeling study using the enediyne 385c.

Deuterated 385c-d’ was next synthesised with 100% deuterium incorporation, and its reactivity under the cycloaromatisation conditions was examined (Scheme 4.11). Surprisingly, the reaction resulted in significant loss of the deuterium in the final isoindolinone 386c-d’, and the deuterium incorporation predominantly occurred at C-4 and C-5, with relatively little at C-7. These results suggested that a 1,2-D/H-shift could be involved in the reaction mechanism.
A simple example of a [4 + 2] cycloaddition reaction of enediynes to form an aryl ring has been reported as a thermal process. In this work, Echavarren and co-workers showed the concerted intramolecular [4 + 2] cycloaddition of enediyne 404 at 150 °C in xylene afforded fluoranthene 405 (Scheme 4.12a).\textsuperscript{157} This thermal reaction could also be promoted by using a Lewis acid catalyst to obtain the desired product at room temperature. In order to clarify the possibility of a thermal process in the current cycloaromatization project, a number of control experiments were conducted. The enediyne 385c was first heated at reflux in toluene for 18 h in the absence of the gold catalyst (Scheme 4.12b). Only trace conversion to the isoindolinone 386c (<2%) could be detected in the \textsuperscript{1}H NMR spectrum of the crude reaction mixture, indicating a thermal Diels–Alder cycloaddition process is not favoured in this case. It is well-known that concerted [4 + 2] cycloaddition reactions are promoted by oxophilic Lewis acids or Brønsted acids.\textsuperscript{158} Therefore, the strong Bronsted acid Tf$_2$NH (pK$_a$ = $-$11.9) was utilised in the control experiment to rule out the possibility that gold catalyst or \textit{in-situ} generated Brønsted acid may be facilitating the reaction by coordination to the C=O bond. Treatment of the enediyne 380a with
a catalytic amount of Tf₂NH (5 mol%) in toluene at room temperature resulted in no conversion of the starting material to the desired isoindolinone 381a (Scheme 4.12c). Subsequently, heating the reaction in the presence of this strong acid at reflux temperature in toluene over 18 h showed only ~6% conversion to the isoindolinone (Scheme 4.12c). This result suggested that a Brønsted acid-catalysed [4 + 2] cycloaddition appears to be unfavourable for the unconjugated enediynes in the current project.

Having excluded the skeletal rearrangement for the current cycloaromatisation reaction, an NMR experiment was conducted under milder conditions to monitor the possibility of formation of known intermediates related to the skeletal rearrangement. The enediyne 385c
was treated with [(PPh₃Au)₃O]BF₄ (5 mol%) in an NMR tube in toluene-d₈ at room temperature. The experiment showed slow conversion to the final isoindolinone product 386c (<2%) after 24 h, and no clear cyclopropyl or olefinic resonances, corresponding to the common intermediates of the skeletal rearrangement (Scheme 3.17, Chapter 3), were observed.

In order to further support the proposed dual-gold mechanism, an attempt to replicate the reaction pathway was examined by synthesising the proposed gold-acetylide intermediate 385e-Au. It has been shown that gold-acetylide intermediates are quite stable and can be isolated. Gratifyingly, treatment of the enediyne 385e with a stoichiometric amount of PPh₃AuCl (0.90 equiv.) in CH₂Cl₂/Et₃N (4:1) at room temperature provided the corresponding gold-acetylide 385e-Au in high yield (89%, Scheme 4.13a). With this acetylide intermediate in hand, it was first aimed to investigate the possibility of the Au-activated alkyne facilitating the thermal [4 + 2] cycloaddition process. Therefore, the acetylide 385e-Au was heated at reflux in toluene for 18 h in the absence of gold catalyst (Scheme 4.13b). No conversion to the isoindolinone 386e could be detected in the ¹H NMR spectrum of the crude reaction mixture, which indicated a thermal Diels-Alder [4 + 2] cycloaddition of the gold-acetylide is not occurring in this reaction. Furthermore, DFT calculations showed that a [4 + 2] cycloaddition of Au-acetylide proceeds via a higher energy transition state than the dual gold pathway (Scheme 4.15). On the other hand, treatment of the acetylide 385e-Au with a catalytic amount of PPh₃AuCl/AgBF₄ (5 mol%) resulted in the formation of gold-aryl complex 386e-Au (27% yield) and the desired isoindolinone 386e (69%) at room temperature in 5 min (Scheme 4.13c). This result provided compelling support for the proposed dual-gold mechanism.
Consideration of all these results led us to tentatively propose the new Au(I)-catalysed cycloaromatisation reaction mechanism presented in Scheme 4.14. The σ,π dual activation cycle is initiated by the catalyst generating the acetylide 407. The subsequent step is nucleophilic attack from the β-position of the gold acetylide to the double bond of the enyne, which forms the 5-membered ring allenyl Au(I)/vinylidene Au(I) intermediate 408. This species (408) would then undergo 5-exo-trig cyclisation to generate intermediate 409. A ring expansion of this adduct via a 1,2-shift of the vinyl C−C bond to the central carbon of the vinylidene Au(I) would form the 6-membered ring intermediate 411,156 which is consistent with a few examples in the literature.154,159 At this stage, a 1,2-H/D shift may occur to form the intermediate 412, followed by deprotonation-aromatisation to deliver the digold isoindolinone species 413. This step is in agreement with the loss of D incorporation in the C-4 position in the deuterium labeling experiments in Scheme 4.11, as either D or H can be lost to generate the benzene ring. This intermediate (413) then undergoes a double protodeauration with the aid of the starting material 415 and the catalyst ((LAu)3O+) to provide the final isoindolinone product 416 as well as the gold acetylide 407. This step is also in agreement with the presence of D in the C-5 and C-7 positions of the isoindolinone 386c-d (Scheme 4.11) as either H or D can do protodeauration process to form 414 and 416.

In order to gain more insight into the proposed reaction mechanism and to support the proposed reaction cycle above, a series of DFT calculations were performed by collaborators Prof. Brian F. Yates, Dr. Alireza Ariafard and Mr. Rasool Babaahmadi (PhD student) from the University of Tasmania in active collaboration with the UOW group. A DFT investigation was conducted through mapping the reaction profile by using a model system based on the experimental catalytic system, which consisted of the \((E)\)-enediyne model 380a in the presence of \([\text{Ph}_3\text{PAu})_3\text{O}]\text{BF}_4\) complex (Scheme 4.15). The computational study confirmed the proposed mechanism by showing the possible intermediates and transition states which could be formed with low energy barriers. According to the DFT calculations, the overall reaction is highly favourable starting from 0.00 kcal/mol to \(-32.2\) kcal/mol (Scheme 4.15a), rendering it exothermic.

These calculations further showed that initially, the trigold oxo complex \([\text{Ph}_3\text{PAu})_3\text{O}]\text{BF}_4\) coordinates to the enediyne in an endergonic process to form 417 (Scheme
Intramolecular deprotonation of this Au-activated species is energetically favoured, resulting in the relatively stable Au-acetylide intermediate 419. An energetically uphill sequence is then necessary – commencing with the digold hydroxide complex dissociating from 419 and forming the Bronsted basic LAu-OH and Lewis-acidic cationic gold LAu⁺ via the gold acetylide 380a-Au. The LAu⁺ activates the triple bond of the enyne moiety of the gold-acetylide by π-coordination to form the highly reactive intermediate 420. This key intermediate can cyclise by a nucleophilic attack of the Au-acetylide onto the activated enyne to afford 423 via the transition state 421, with an energy barrier of 9.5 kcal/mol. This intermediate 423 is particularly reactive as it has a nucleophilic allenyl gold and an electrophilic vinylidene gold moiety held in close proximity. Either a direct pseudo-6π-electrocyclisation-type pathway or a stepwise route involving a three-centre-two-electron transition state 425 were both shown to be possible and are likely competing with each other. The stepwise pathway proceeds via nucleophilic attack of the allenyl gold moiety on the vinylidene gold to give the 5-membered gold-carbenoid 424, which subsequently undergoes ring-expansion via the transition state 425 to give 426 with concomitant shift of the gold. No intermediate(s) for the direct pathway could be located given the highly favourable nature of the process. The 6-membered intermediate 426 can be converted to the isoindolinone product (381-(4)d' and 381-(5)d') via several potential pathways. As indicated above, at least one of these should include a 1,2-hydride/deuterium transfer to account for the presence of deuterium at the C-4 and C-5 positions of the product (381-(4)d' and 381-(5)d'). For example, the deuterated intermediate 426-d' can undergo a 1,2-H/D shift process to give the species 427-d' via a low energy barrier of 4.6 kcal/mol. This moiety can then simultaneously lose H⁺ or D⁺ and undergo the proto/deutero-deauration to yield gem-diaurated intermediates 428-(4)d' or 428-(5)d' with deuterium incorporated at C-4 or C-5, respectively (Scheme 4.15b). This 1,2-H/D shift/loss can also explain the incomplete deuterium retention observed in the D labeling experiment in Scheme 4.11. Further, gem-diaurated moieties with an aurophilic interaction are well-known competent intermediates in gold-catalysed transformations, which can contribute to the overall stability of the gold intermediates.154 These gem-diaurated intermediates proceed towards the final isoindolinone
products (381-(4)d’ and 381-(5)d’) by conversion to the aryl-Au species (429-(4)d’ and 429-(5)d’) by reaction with a new molecule of substrate 380a-d’ that concurrently forms Au-coordinated species 380a-d’(Au). Finally, protodemetallation by the terminal propiolamide sp proton of 380a-d’(Au) generates the final isoindolinone products (381-(4)d’ and 381-(5)d’) as well as 420-d’ to turn-over the catalytic cycle. This last protodemetallation step is also consistent with the observation that the deuterium in 385c-d is predominantly transferred to the C-7 position of isoindolinone product 386c-d (Scheme 4.10). This is likely because 385c-d would transfer its deuterium to this position selectively by deutero-deauration process (Scheme 4.16). This deutro-deauration process can also explain the incomplete deuterium retention observed in the D labeling experiment in Scheme 4.10.

It is also important to mention that an alternative cyclisation of the gold acetylide 380a-Au in the absence of coordination to cationic gold showed a higher energy transition state 422 (Scheme 4.15). This calculation supported that the proposed dual-gold-catalysed reaction mechanism is more favourable than the Diels-Alder pathway – this calculation is also consistent with the mechanistic experiments shown in Schemes 4.12b and 4.13b.
Scheme 4.15. (a) Calculated mechanism for the cascade cycloaromatisation reaction. (b) Selected pathway for aromatisation and protodemetalation pathways from deuterated 380a-\(d'\). The relative Gibbs energies obtained from M06-CPCM/6-31+G(d,p)//B3LYP-CPCM/6-31G(d) calculations are given in kcal/mol. (Performed by Prof. Brian F. Yates, Dr. Alireza Ariafard, and Mr. Rasool Babaahmadi (PhD student) from University of Tasmania) in conjunction with detailed feedback and guidance by the UOW group).

Scheme 4.16. Deutero-deauration process of 386-\(d\)-Au in the C-7 position by 385c-\(d\).
4.4. Conclusion

In this Chapter, it was demonstrated that the $N$-Bn allenyloxazolidinones 230 could be selectively transformed to the novel 1,3-(E)-enynes 253 upon treatment with an excess amount of NaH through a decarboxylative conjugate elimination process. This reaction highlights just one potential reaction pathway of these intriguing synthetic building blocks. The enantioenriched 1,3-(E)-enynes were utilised to synthesise a series of novel unconjugated (E)-enediynes 254 and 380. These versatile scaffolds could undergo a cascade Au(I)-catalysed cycloaromatisation reaction to offer enantioenriched versions of a wide range of biologically relevant isoindolines 255 and isoindolinones (381 and 386). Initially, the cycloisomerisation reaction of the propargylated enediynes 254 was found to be capricious and inconstant low yields were obtained upon repetition due to instability of the isoindoline product. Based on the isolation of the 5-memebred ring intermediate 365, it was proposed that the known single cleavage skeletal rearrangement is involved as one of the possible reaction mechanisms for the gold-catalysed cycloisomerisation of the propargylated enediynes 254.

The instability challenge of the initial isoindoline product 255 in this project was successfully solved through the design and synthesis of the $N$-propiolic enediynes (380 and 385). These novel enediynes offered an efficient direct access to the enantiomERICALLY enriched isoindolinones (381 and 386), which were stable upon column chromatography and storage. As such, this methodology would enable the formation of a carbon-carbon bond along with the creation of a benzene ring in a one pot process. Furthermore, formation of an unexpected isomer of the isoindolinones led us to believe that the reaction proceeded through a more novel dual-gold activation pathway rather than the known skeletal rearrangement pathway. Combined experimental and computational investigations provided evidence for a new dual-gold reaction mechanism pathway based on electronic differentiation of the triple bonds in the substrates to direct gold acetylide formation to the propiolic unit. It has been shown that a rare intermediate complex 423 containing allenyl $\sigma$-gold and vinylidene gold moieties was formed in this reaction – such reactive intermediates were previously not known. This is the first example of using $pK_a$-differentiated alkynes to facilitate a selective gold-catalysed cycloisomerisation.
Furthermore, σ-gold allenylo moieties are almost unknown in gold-catalysed processes, except for two studies where they were isolated in a stoichiometric fashion,\textsuperscript{160-161} highlighting the importance of this finding. The presence of both nucleophilic allenylo σ-gold species and the electrophilic vinylidene gold in a single structure should present potential interesting chemical reactivity for future reaction design that harness dual-gold mechanistic pathways in organic synthesis.

4.5. Future Directions and Summary

Oxazolidinones can potentially undergo decarboxylative ring cleavage pathways as the analogues of aziridines. In this Chapter, the base-promoted decarboxylative ring opening reaction of stereodefined \textit{N}-Bn allenyloxazolidinones to enantiomerically enriched 1,3-(\textit{E})-enynes was developed. These powerful oxazolidinones could have more synthetic versatility when the allene unit is activated by transition metals such as Pd(0). For example, allenyloxazolidinone 175 could be utilised in Pd(0)-catalysed nucleophilic ring-opening reaction in the presence of boronic acids to form 1,3-dienes 430 and 431 (Scheme 4.17a). In the presence of a base, Pd(0) catalyst may undergo a decarboxylative oxidative addition to the allene to give the intermediate 432. Transmetalation and subsequent reductive elimination could then occur to generate the final diene products. It is important to note that this proposed methodology has recently been performed in the Hyland research group by PhD candidate Mr. R. W. Brown. By introducing a new double bond on the nitrogen as a dienophile, these stereodefined dienes 433 are expected to undergo intramolecular Diels–Alder reactions to provide medicinally relevant isoindolinones 434 (Scheme 4.17b). By the possible formation of three chiral centres in the isoindolinone scaffold, controlling diastereoselectivity of this reaction would be an interesting topic of investigation in the future.
The new dual-gold-catalysed cycloaromatisation reaction of \(N\)-propiolic enediynes to give isoindolinones was demonstrated in this Chapter. The novel combination of allenyl gold and vinlylidene gold intermediates should be harnessed to form other ring systems through the variation of the tether between them.

For example, it will be interesting to see how this catalytic system would perform in a gold-catalysed cycloaromatisation reaction of the \(N\)-butynoic enediynes 437 to obtain 3,4-dihydroisoquinolinones 438 (Scheme 4.18). Due to the presence of the acidic alkyne proton similar to \(N\)-propiolic enediynes, the formation of the gold-acetylide 440 would be expected to initiate the dual-gold-catalysed cycloaromatisation reaction (Scheme 4.18). Isoquinolinones are
the core skeleton in many bioactive natural occurring alkaloids.\textsuperscript{162-163} However, synthetic methods to obtain isoquinolinones and dihydroisoquinolinones are not widely reported in the literature.\textsuperscript{162, 164-167} Therefore, the possible gold-catalysed cycloaromatisation reaction of \(N\)-butynoic enediyne \textsuperscript{437} to access stereodefined dihydroisoquinolinone \textsuperscript{438} would be an interesting topic of investigation in the future.

![Proposed mechanistic pathway](image)

**Scheme 4.18.** Proposed synthetic route for 3,4-dihydroisoquinolinone via gold-catalysed cycloisomerisation of \(N\)-butynoic enediyne.

In summary, the initial aims of this PhD project were to synthesise novel allenylamino alcohols containing two nitrogen and oxygen heteroatoms and utilise them in the synthesis of the allenyl-pendent heterocycles (Scheme 4.19). It was further attempted to manipulate these novel heterocycles in the ring-opening reactions in order to obtain enantiomerically enriched bioactive molecules. The syntheses of a series of \textit{cis} \(N\)-Boc allenylamino alcohols \textsuperscript{206} and \textit{trans} \(N\)-Bn,\(N\)-Boc allenylamino alcohols were demonstrated in Chapter 2. These allene products were then utilised to synthesise the corresponding allenylaziridine \textsuperscript{182}, the 5-allenylloxazolidinones \textsuperscript{229}, and the 2,5-dihydrofurans \textsuperscript{250}. Since the \(N\)-protected \(\alpha\)-amino aldehydes \textsuperscript{205} and \textsuperscript{217} were used as the starting materials, the enantiomeric purity of the
oxazolidinones and the 2,5-dihydrofurans were evaluated by two methods such as chiral auxiliary and chiral HPLC analysis. It was also shown that the 5-allenyloxazolidinones 229 can act as equivalents of the 2-allenylaziridine 182 in ring-opening reactions (Scheme 4.19).

The synthesis of a range of novel N-pendant 1,3-(E)-enynes 253 from the 5-allenyloxazolidinones 229 was described in Chapter 4. Introducing of an extra triple bond to the enynes by incorporation of either propargyl and propiolic groups then provided a series of novel unconjugated (E)-enediynes (254, 380 and 385). We explored the potential of these versatile scaffolds to undergo cascade Au(I)-catalysed cycloaromatisation reactions to offer enantioenriched versions of a wide range of biologically relevant isoindolines 255 and isoindolinones 381 (Scheme 4.19). It was demonstrated that the cycloaromatisation of the enediynes 380 and 385 proceeded via a new dual-gold reaction mechanism including a rare intermediate complex 423 containing allenyl σ-gold and vinylidene gold moieties. The proposed mechanism was supported by deuterium experiments and DFT calculations.

Scheme 4.19. Overview of this thesis.
Chapter 5. Experimental

General Information

Commercial reagents were purchased and used as received without any purification. Dry reaction solvents were passed through activated alumina columns to obtain dryness before being stored under nitrogen over 4Å molecular sieves. All reactions using air/moisture sensitive reagents were performed in oven-dried glassware, under an atmosphere of nitrogen equipped with a stir bar. Reactions were monitored by thin-layer chromatography (TLC) on aluminum backed silica gel sheets, visualizing with UV-light (254 nm) fluorescence quenching, followed by staining of the plates with potassium permanganate or p-anisaldehyde stains. Column chromatography used for compound purification was performed using pre-packed flash grade silica gel (40-75 nm) as the stationary phase. $^1$H NMR and $^{13}$C NMR spectra were recorded either at 300, 400 and 500 MHz $^1$H NMR for or at 75, 100 and 125 MHz for $^{13}$C NMR. All $^1$H NMR and $^{13}$C{$^1$H} NMR were recorded in deuterated chloroform (CDCl$_3$) containing 0.1% (v/v) tetramethylsilane (TMS). Abbreviations used in the description of resonances are: singlet (s), doublet (d), triplet (t), quartet (q), doublet of doublets (dd), broad (br) and multiplet (m). All coupling constants (J) were measured in hertz (Hz). NMR chemical shift abbreviations were reported in parts per millions (ppm) from tetramethylsilane (TMS) and were corrected to 0.00 ppm (TMS) for $^1$H NMR and 77.00 ppm (CDCl$_3$ centre line) for $^{13}$C NMR. Optical rotations were measured on a JASCO P-2000 polarimeter, using a 10 mL cell with a 1.0 dm path length. High-performance liquid chromatography (HPLC) was performed with two different devices; including a Waters 1525 with a PDA detector or a Shimadzu Nexera X2 UHPLC with a PDA detector. Phenomenex Lux i-Cellulose-5 (250 x 30 mm) and Phenomenex Lux Cellulose-3 (250 x 30 mm) were used as chiral HPLC columns. The α-amino amino methyl ester hydrochlorides were prepared from commercially available α-amino acids using a previously reported literature procedure (literature citations to these compounds are provided in the experimental section).
X-ray crystal data for 386c. C_{25}H_{25}NO_{2} (M_r = 371.46): recorded at 100 K with synchrotron radiation (0.9537 Å), crystal dimensions 0.05 mm x 0.02 mm x 0.02 mm, μ = 0.170 mm\(^{-1\)}, monoclinic, space group P2\(_{1}\), \(a = 8.828(3)\), \(b = 5.279(3)\), \(c = 20.671(8)\) Å, \(β = 91.0640(19)°\), \(V = 963.2(7)\) Å\(^3\), \(Z = 2\), \(ρ_{calc} = 1.281\), max/min residuals = 0.129 and -0.136 eÅ\(^{-3}\), Flack parameter = -0.1(3), \(R = 0.029\) for 2210 (\(I > 2σ(I)\)) data and \(wR = 0.076\) for 2231 all data (\(2θ_{max} = 64.37°\), \(R_{int} = 0.050\)). Data were collected at 100 K on a crystal mounted on a Hampton Scientific cryoloop at the MX2 beamline, Australian Synchrotron, Victoria. The structure was solved by direct methods with SHELXS-97, refined using full-matrix least-squares routines against \(F^2\) with SHELXL-97, and visualised using OLEX2. All non-hydrogen atoms were anisotropically refined, while, all hydrogen atoms were positioned in calculated locations and refined using a riding model with fixed C–H distances of 0.95 Å (\(sp^2\)CH), 0.99 Å (CH\(_2\)), 0.98 Å (CH\(_3\)). The thermal parameters of all hydrogen atoms were estimated as \(U_{iso}(H) = 1.2U_{eq}(C)\) except for CH\(_3\) where \(U_{iso}(H) = 1.5U_{eq}(C)\). CCDC 1867833 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

2-(Benzylationo)penta-3,4-dien-1-ol (181)

\[
\text{HO} \quad \text{NH} \quad \text{Bn}
\]

In a microwave tube, glycolaldehyde dimer 179 (0.25 mmol, 0.03 g) was dissolved in methanol (0.50 mL) at room temperature. Then, the solution was mixed with the allenylboronic acid pinacol ester 71 (90.0 μL, 0.50 mmol, 2.0 equiv.) and benzylamine 180 (55.0 μL, 0.50 mmol, 2.0 equiv.). The reaction mixture was then heated at 120 °C in a microwave reactor at 300 W for 20 min. The resulting brownish mixture was concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane = 7:3) to obtain the pure allenic amino alcohol 181. White solid (0.051 g, 54%). Mp = 58-60 °C (lit. ref. = 60-61 °C).\(^{54}\) \(R_f\) (EtOAc/hexane = 7:3) = 0.17. \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) δ 3.27-3.30 (m, 1H, CH-N), 3.36
(dd, 1H, J = 8.0, 10.5 Hz, CH-O), 3.64 (dd, 1H, J = 4.5, 10.5 Hz, CH-O), 3.73 (d, 1H, J = 13.0 Hz, CHPh), 3.94 (d, 1H, J = 13.0 Hz, CHPh), 4.84-4.86 (m, 2H, CH₂=C=), 5.12 (q, 1H, J = 6.5 Hz, CH=C=), 7.21-7.48 (m, 5H, CHAr). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 51.1, 57.6, 64.9, 77.0, 90.1, 127.1, 128.2, 128.4, 140.0, 208.1. The NMR data matched with those previously reported.54

1-Benzyl-2-(propa-1,2-dien-1-yl)aziridine (182)

A solution of allene 181 (0.050 g, 0.26 mmol), CBr₄ (0.11 g, 0.33 mmol, 1.30 equiv.) and Et₃N (54.0 μL, 0.39 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL) was cooled to -10 °C. PPh₃ (0.088 g, 0.33 mmol, 1.30 equiv.) was then added slowly over 10 min with vigorous stirring. The reaction mixture was then heated at reflux under a nitrogen atmosphere with reaction monitoring by thin liquid chromatography (TLC). After 5 min, the reaction was quenched by washing with aqueous saturated NaHCO₃ solution (3×5 mL), followed by extraction with CH₂Cl₂ (10 mL). The mixture was then dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash column chromatography (EtOAc/hexane/Et₃N 2:8 with 3% Et₃N for packing the column) to obtain the pure allenylaziridine 182. Light yellow oil (0.030 g, 67%). Rf (EtOAc/hexane = 2:8) = 0.40. ¹H NMR (500 MHz, CDCl₃) δ 1.67 (d, 1H, J = 6.5 Hz, NCH), 1.89 (d, 1H, J = 6.5 Hz, NCH), 2.04-2.08 (m, 1H, NCH), 2.04-2.08 (m, 1H, NCH), 3.51 (d, 1H, J = 15.0 Hz, CHPh), 3.59 (d, 1H, J = 15.0 Hz, CHPh), 4.86-4.89 (m, 2H, CH₂=C), 5.05-5.08 (m, 1H, CH=C), 7.28-7.40 (m, 5H, 5CHAr), 13C{¹H} NMR (125 MHz, CDCl₃) δ 34.5, 37.5, 64.3, 76.9, 91.3, 127.0, 127.8, 128.3, 138.9, 198.7. IR (νmax/cm⁻¹) 2925 (w), 2854 (w), 1953 (m), 1757 (s), 1647 (s), 1495 (m), 1452 (m), 1355 (m), 1074 (s), 848 (s), 731 (m), 695 (s). HRMS (ESI-TOF) m/z calcd for C₁₂H₁₄N [M+H]+ 172.1126, found 172.1132.
(E)-N-Benzyl-4-methyleneoct-2-en-1-amine (201)

\[
\text{BnHN} \quad - \quad - \quad - \quad - \\
\text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H} \quad \text{H}
\]

\(n\)-BuLi in Et₂O (0.44 mL, 1.60 mol/L, 0.70 mmol, 4.00 equiv.) was added to a stirred slurry of CuCN (0.030 g, 0.348 mmol, 4.00 equiv.) in THF (1 mL) at \(-78\) °C under a nitrogen atmosphere. The mixture was then allowed to warm to 0 °C and stirred for 15 min. The mixture was cooled to \(-78\) °C and a solution of allenylaziridine 182 (0.030 g, 0.175 mmol) in dry THF (1 mL) and then BF₃∙Et₂O (33.0 μL, 0.26 mmol, 1.50 equiv.) were added and stirred at \(-78\) °C for 1 h. The mixture was then warmed to room temperature and stirred for 18 h. It was then quenched with aqueous saturated NH₄Cl (5 mL) and NH₄OH (5 mL) solutions and extracted by EtOAc (3×5 mL). The filtrate was dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash column chromatography (EtOAc/hexane = 2:8) to obtain the pure diene 201. Light yellow oil (0.032 g, 81%). \(R_f\) (EtOAc/hexane = 2:8) = 0.78. \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 0.86-0.92 (m, 3H, \(\text{CH}_3\)), 1.25-1.37 (m, 3H, \(\text{CH}_2\) and \(\text{NH}\)), 1.42-1.49 (m, 2H, \(\text{CH}_2\)), 2.19 (t, 2H, \(J = 8.0\) Hz, \(\text{CH}_2\)), 3.33 (d, 2H, \(J = 6.0\) Hz, \(\text{CH}_2-N\)), 3.79 (s, 2H, \(\text{CH}_2\text{Ph}\)), 4.92 (d, 2H, \(J = 11.0\) Hz, \(\text{CH}_2-C\)), 5.78-5.81 (m, 1H, \(\text{CH}=\text{CH}\)), 6.19 (d, 1H, \(J = 15.5\) Hz, \(\text{CH}=\text{CH}\)), 7.24-7.32 (m, 5H, \(5\text{CH}_\text{Ar}\)). \(^{13}\)C\{\(^1\)H\} NMR (125 MHz, CDCl₃) \(\delta\) 14.0, 22.7, 30.5, 31.9, 51.2, 53.4, 114.6, 127.0, 127.4, 128.2, 128.4, 133.9, 140.2, 146.0. HRMS (ESI-TOF) \(m/z\) calcd for C₁₆H₂₄N [M+H]^+ 230.1909, found 230.1908.
Synthesis of N-Boc α-Amino Aldehydes (205a-g)

L-α-Amino acids were first transformed to their α-amino methyl esters by esterification using SOCl₂ (2.00 equiv.) and MeOH (0.50 M) at room temperature for 4 h. The corresponding α-amino methyl ester hydrochlorides 203a-g were obtained after evaporation of the solvent.

To a solution of α-amino methyl ester hydrochlorides 203a-g in CH₂Cl₂ (60 mL) at 0 °C, was added Et₃N (1.10 equiv.), followed by di-tert-butylpyrocarbonate (Boc₂O) (1.20 equiv.). Stirring was continued for 1 h at 0 °C, and then overnight at room temperature. The reaction mixture was then washed with saturated sodium bicarbonate (30 mL) and brine (30 mL) solutions, dried (Na₂SO₄). The solution was filtered and concentrated in vacuum to yield the corresponding N-Boc α-amino esters 204a-g.

To a solution of N-Boc α-amino ester 204 in Et₂O at −78 °C, was added dropwise diisobutylaluminum hydride (DIBAL-H) (1.00 M solution in hexane, 2.00 equiv.) over a period of 45 min. The mixture was stirred at the same temperature for 1.5 h, and then quenched by the addition of precooled MeOH (1 mL). The reaction mixture was allowed to warm to room temperature, ice (5 g) was added with heavy agitation. The mixture was filtered through a sintered funnel and the filtrate was extracted with CH₂Cl₂. The organic layer was washed with brine (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to yield the title aldehyde 205, which was used for the next step without purification.

**tert-Butyl (S)-(1-oxopropan-2-yl)carbamate (205a)**

Methyl 2-aminopropanoate hydrochloride 203a was prepared following the general procedure using L-alanine (3.00 g, 33.7 mmol) and SOCl₂ (4.90 mL, 67.40 mmol, 2.00 equiv.) in MeOH
(55 mL). White solid (4.51 g, 96%). ¹H NMR (500 MHz, CDCl₃) δ 1.72 (d, 3H, J = 5.0 Hz, CH₃), 3.81 (s, 3H, CH₃), 4.30 (br s, 1H, CH), 8.64 (br s, 3H, NH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 16.0, 49.3, 53.3, 170.6. The NMR data matched with those previously reported.¹⁶⁸

Methyl 2-(tert-butoxycarbonylamino) propanoate 204a was obtained following the general procedure using methyl 2-aminopropanoate hydrochloride 203a (4.00 g, 28.65 mmol), Boc₂O (4.50 g, 34.38 mmol, 1.20 equiv.) and Et₃N 4.51 mL, 31.51 mmol, 1.1 equiv.) in CH₂Cl₂ (60 mL). Colorless oil (5.70 g, 98%). ¹H NMR (300 MHz, CDCl₃) δ 1.31 (d, 3H, J = 6.9 Hz, CH₃), 1.46 (s, 9H, C(CH₃)₃), 3.68 (s, 3H, CH₃), 4.21-4.23 (m, 1H, CH), 5.11 (br s, 1H, NH). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 18.5, 27.3, 49.0, 52.2, 79.7, 155.0, 173.8. The NMR data matched with those previously reported.¹⁶⁸

The title aldehyde 205a was obtained following the general procedure using methyl 2-(tert-butoxycarbonylamino) propanoate 204a (0.35 g, 1.71 mmol) and DIBAL-H (1.00 M solution in hexane, 3.42 mL, 3.42 mmol, 2.00 equiv.) in Et₂O (5 mL). White solid (0.26 g, 98%). ¹H NMR (500 MHz, CDCl₃) δ 1.34 (d, 3H, J = 7.5 Hz, CH₃), 1.45 (s, 9H, C(CH₃)₃), 4.22-4.25 (m, 1H, CH), 5.11 (br s, 1H, NH), 9.56 (s, 1H, CHO). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 14.8, 28.3, 55.5, 80.1, 155.3, 199.7. The NMR data matched with those previously reported.¹⁶⁸

**tert-Butyl (S)-(1-oxopentan-2-yl)carbamate (205b)**

\[ \text{CHO} \]
\[
\text{NHBoc}
\]

Methyl 2-aminopentanoate hydrochloride 203b was obtained following the general procedure using L-norvaline (1.00 g, 8.54 mmol) and SOCl₂ (1.24 mL, 17.08 mmol, 2.00 equiv.) in MeOH (15 mL). White solid (1.38 g, 97%). ¹H NMR (500 MHz, CDCl₃) δ 0.97 (t, 3H, J = 7.0 Hz, CH₃), 1.47-1.54 (m, 1H, CH), 1.57-1.65 (m, 1H, CH), 2.03 (m, 2H, CH₂), 3.82 (s, 3H, CH₃), 4.10 (br s, 1H, CH), 8.82 (br s, 3H, NH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 13.5, 18.5, 32.4, 53.12, 53.17, 169.5. The NMR data matched with those previously reported.¹⁶⁹
Methyl 2-((tert-butoxycarbonyl)amino)pentanoate 204b was obtained following the general procedure using methyl 2-aminopentanoate hydrochloride 203b (1.00 g, 5.96 mmol), di-tert-butylpyrocarbonate (1.56 g, 7.16 mmol, 1.20 equiv.) and Et$_3$N (0.94 mL, 6.55 mmol, 1.10 equiv.) in CH$_2$Cl$_2$ (15 mL). Colorless oil (1.29 g, 93%). $R_f$ (Et$_2$O/hexane = 2:8) = 0.42. $[\alpha]_D^{22} = +84.6$ (c 2.0 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.94 (t, 3H, $J$ = 7.0 Hz, CH$_3$), 1.38 (br s, 2H, CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$), 1.58-1.64 (m, 1H, CH), 1.77 (br s, 1H, CH), 3.74 (s, 3H, CH$_3$), 4.30 (br s, 1H, CH), 5.19 (br s, 1H, NH). $^{13}$C$^{1}$H NMR (125 MHz, CDCl$_3$) $\delta$ 13.5, 18.5, 28.1, 34.6, 52.0, 53.1, 79.5, 155.3, 173.4. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3370 (s), 2963 (m), 2934 (m), 1743 (s), 1743 (s), 1507 (s), 1365 (s), 1249 (s), 1159 (s), 1011 (m), 779 (m). HRMS (ESI) $m/z$ calcd for C$_{11}$H$_{21}$NO$_4$Na [M + Na]$^+$ 254.1368, found 254.1361.

The title compound 205b was obtained following the general procedure using methyl 2-((tert-butoxycarbonyl)amino)pentanoate 204b (0.19 g, 0.82 mmol) and DIBAL-H (dissolved in 0.30 mL $n$-hexane, 0.27 mL, 1.64 mmol, 2.00 equiv.) in Et$_2$O (2 mL). Colorless oil (0.149 g, 91%). $[\alpha]_D^{22} = +80.3$ (c 1.0 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.95 (t, 3H, $J$ = 7.0 Hz, CH$_3$), 1.40-1.41 (m, 2H, CH$_2$), 1.45 (s, 9H, C(CH$_3$)$_3$), 1.52-1.58 (m, 1H, CH), 1.83 (br s, 1H, CH), 4.20-4.22 (m, 1H, CHO), 5.30 (br s, 1H, NH), 9.58 (s, 1H, CHO). $^{13}$C$^{1}$H NMR (125 MHz, CDCl$_3$) $\delta$ 13.7, 18.4, 28.21, 31.1, 59.6, 79.8, 155.6, 200.2. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3370 (s), 2963 (m), 2934 (m), 1743 (s), 1713 (s), 1507 (s), 1365 (s), 1249 (s), 1159 (s), 1054 (m), 779 (m). HRMS (ESI) $m/z$ calcd for C$_{10}$H$_{19}$NO$_3$Na [M + Na]$^+$ 224.1263, found 224.1277.

tert-Butyl (S)-(4-methyl-1-oxopentan-2-yl)carbamate (205c)

![Structure](https://example.com/structure.png)

2-Amino-4-methylpentanoate hydrochloride 203c was obtained following the general procedure using L-leucine (1.00 g, 7.62 mmol) and SOCl$_2$ (1.1 mL, 15.25 mmol, 2.00 equiv.) in MeOH (15 mL). White solid (1.30 g, 94%). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ = 0.98 (d, 6H, $J$ = 5.0 Hz, 2CH$_3$), 1.84 (br s, 1H, CH), 1.97 (br s, 2H, CH$_2$), 3.80 (s, 3H, CH$_3$), 4.09 (br s, 1H,
Methyl (tert-butoxycarbonyl) leucinate 204c was obtained following the general procedure using methyl 2-amino-4-methylpentanoate hydrochloride 203c (1.00 g, 5.50 mmol), Boc₂O (1.44 g, 6.60 mmol, 1.20 equiv.) and Et₃N (0.86 mL, 6.05 mmol, 1.10 equiv.) in CH₂Cl₂ (15 mL). Colorless oil (1.28 g, 95%). \(^1\)H NMR (500 MHz, CDCl₃) δ 0.94 (br d, 6H, \(J = 6.0\) Hz, 2CH₃), 1.44 (s, 9H, C(CH₃)₃), 1.47-1.53 (m, 1H, CH), 1.60 (br d, 1H, \(J = 5.5\) Hz, CH), 1.69-1.71 (m, 1H, CH), 3.73 (s, 3H, CH₃), 4.32 (br s, 1H, CH), 5.06 (br s, 1H, NH). \(^{13}\)C\[^{1}\]H NMR (125 MHz, CDCl₃) δ 21.7, 22.7, 24.7, 28.2, 41.6, 51.9, 52.0, 79.6, 155.4, 173.9. The NMR data matched with those previously reported.\(^{171}\)

The title compound 205c was obtained following the general procedure using using methyl (tert-butoxycarbonyl) leucinate 204c (0.30 g, 1.22 mmol) and DIBAL-H (dissolved in 0.40 mL n-hexane, 0.41 mL, 2.44 mmol, 2.00 equiv.) in Et₂O (3 mL). Colorless oil (0.21 g, 95%). \(^1\)H NMR (500 MHz, CDCl₃) δ 0.96 (d, 6H, \(J = 6.5\) Hz, 2CH₃), 1.40 (br s, 1H, CH), 1.45 (s, 9H, C(CH₃)₃), 1.65 (br s, 1H, CH), 1.76-1.79 (m, 1H, CH), 4.23 (br s, 1H, CH), 5.18 (br s, 1H, NH), 9.58 (s, 1H, CHO). \(^{13}\)C\[^{1}\]H NMR (125 MHz, CDCl₃) δ 21.8, 23.0, 24.5, 28.2, 37.9, 58.3, 79.8, 155.6, 200.5. The NMR data matched with those previously reported.\(^{172}\)

tert-Butyl (S)-(1-oxo-3-phenylpropan-2-yl)carbamate (205d)

Methyl 2-amino-3-phenylpropanoate hydrochloride 203d was obtained following the general procedure using L-phenylalanine (1.00 g, 6.05 mmol) and SOCl₂ (0.87 mL, 12.1 mmol, 2.00 equiv.) in MeOH (15 mL). White solid (1.24 g, 95%). \(^1\)H NMR (500 MHz, CDCl₃) δ 3.38-3.47 (m, 2H, CH₂), 3.69 (s, 3H, CH₃), 4.37-4.41 (m, 1H, CH), 7.26-7.30 (m, 5H, 5CH₃), 8.72 (br s, 3H, NH). \(^{13}\)C\[^{1}\]H NMR (125 MHz, CDCl₃) δ 36.5, 53.2, 54.7, 127.9, 129.1, 129.8, 134.1, 169.3. The NMR data matched with those previously reported.\(^{173}\)
Methyl (tert-butoxycarbonyl) phenylalaninate 204d was obtained following the general procedure using methyl 2-amino-3-phenylpropanoate hydrochloride 203d (1.75 g, 8.11 mmol), Boc₂O (2.03 g, 9.32 mmol, 1.20 equiv.) and Et₃N (1.28 mL, 8.92 mmol, 1.10 equiv.) in CH₂Cl₂ (20 mL). Colorless oil (2.15 g, 95%).

**¹H NMR** (500 MHz, CDCl₃) δ 1.39 (s, 9H, C(CH₃)₃), 2.99-3.11 (m, 2H, CH₂Ph), 3.66 (s, 3H, CH₃), 4.56 (br d, 1H, J = 6.5 Hz, CH), 5.08 (br d, 1H, J = 6.5 Hz, NH), 7.10 (d, 2H, J = 6.5 Hz, 2CH₆), 7.18-7.21 (m, 1H, CH₆), 7.24-7.27 (m, 2H, 2CH₆). **¹³C{¹H} NMR** (125 MHz, CDCl₃) δ 28.4, 38.5, 52.2, 54.7, 79.9, 127.1, 128.7, 129.4, 136.3, 155.3, 172.5. The NMR data matched with those previously reported.¹⁷⁴

The title compound 205d was obtained following the general procedure using methyl (tert-butoxycarbonyl) phenylalaninate 204d (0.20 g, 0.716 mmol) and DIBAL-H (dissolved in 0.30 mL n-hexane, 0.26 mL, 1.50 mmol, 2.10 equiv.) in Et₂O (2 mL). White solid (0.174 g, 98%).

**¹H NMR** (500 MHz, CDCl₃) δ 1.42 (s, 9H, C(CH₃)₃), 3.10 (m, 2H, CH₂Ph), 4.40 (br d, 1H, J = 6.0 Hz, CH), 5.12 (br s, 1H, NH), 7.16 (d, 2H, J = 7.5 Hz, 2CH₆), 7.22-7.25 (m, 1H, CH₆), 7.28-7.31 (m, 2H, 2CH₆), 9.61 (s, 1H, CHO). **¹³C{¹H} NMR** (125 MHz, CDCl₃) δ 28.2, 35.4, 60.8, 80.1, 127.0, 128.7, 129.3, 135.8, 155.4, 199.5. The NMR data matched with those previously reported.¹⁷⁵

**tert-Butyl (S)-(3-methyl-1-oxobutan-2-yl)carbamate (205e)**

![tert-Butyl (S)-(3-methyl-1-oxobutan-2-yl)carbamate](image)

2-Amino-3-methylbutanoate hydrochloride 203e was obtained following the general procedure using L-valine (1.00 g, 8.54 mmol) and SOCl₂ (1.24 mL, 17.08 mmol, 2.00 equiv.) in MeOH (15 mL). White solid (1.37 g, 97%).

**¹H NMR** (500 MHz, CDCl₃) δ 1.15 (d, 6H, J = 5.0 Hz, 2CH₃), 2.47 (br s, 1H, CH), 3.84 (s, 3H, CH₃), 3.94 (br s, 1H, CH), 8.83 (br s, 3H, NH₃). **¹³C{¹H} NMR** (125 MHz, CDCl₃) δ 18.3, 18.4, 29.9, 58.2, 58.7, 168.7. The NMR data matched with those previously reported.¹⁷⁶
Methyl \((\text{tert}-\text{butoxycarbonyl})\) valinate \(204\text{e}\) was obtained following the general procedure using methyl 2-amino-3-methylbutanoate hydrochloride \(203\text{e}\) (2.0 g, 11.93 mmol), Boc\(_2\)O (3.08 g, 14.31 mmol, 1.20 equiv.) and Et\(_3\)N (1.88 mL, 13.12 mmol, 1.10 equiv.) in CH\(_2\)Cl\(_2\) (20 mL). Colorless oil (2.62 g, 95%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) δ 0.89 (d, 3H, \(J = 6.5 \text{ Hz}, CH_3\)), 0.95 (d, 3H, \(J = 7.0 \text{ Hz}, CH_3\)), 1.44 (s, 9H, C(CH\(_3\))\(_3\)), 2.11-2.13 (m, 1H, CH), 3.73 (s, 3H, CH\(_3\)), 4.20-4.23 (m, 1H, CH), 5.21 (br d, 1H, \(J = 8.0 \text{ Hz}, NH\)). \(^{13}\)C\(^{1}H\) NMR (125 MHz, CDCl\(_3\)) δ 17.5, 18.8, 28.1, 31.1, 51.7, 58.4, 79.4, 155.5, 172.7. The NMR data matched with those previously reported.\(^{171}\)

The title compound \(205\text{e}\) was obtained following the general procedure using methyl \((\text{tert}-\text{butoxycarbonyl})\) valinate \(204\text{e}\) (0.23 g, 0.994 mmol) and DIBAL-H (dissolved in 0.40 mL \(n\)-hexane, 0.34 mL, 1.99 mmol, 2.00 equiv.) in Et\(_2\)O (2 mL). Colorless oil (0.174 g, 95%). \(^{1}H\) NMR (500 MHz, CDCl\(_3\)) δ 0.94 (d, 3H, \(J = 7.0 \text{ Hz}, CH_3\)), 1.03 (d, 3H, \(J = 7.0 \text{ Hz}, CH_3\)), 1.45 (s, 9H, C(CH\(_3\))\(_3\)), 2.27-2.29 (m, 1H, CH), 4.22-4.25 (m, 1H, CH), 5.21 (br s, 1H, NH), 9.65 (s, 1H, CHO). \(^{13}\)C\(^{1}H\) NMR (125 MHz, CDCl\(_3\)) δ 17.5, 19.0, 28.2, 28.9, 64.1, 79.8, 155.8, 200.4. The NMR data matched with those previously reported.\(^{171}\)

tert-Butyl (S)-(2-oxo-1-phenylethyl)carbamate (205f)

![Structural formula of tert-Butyl (S)-(2-oxo-1-phenylethyl)carbamate (205f)](Ph\_CHO\_NHBoc)

Methyl aminophenylacetate hydrochloride \(203\text{f}\) was obtained following the general procedure using L-phenylglycine (4.00 g, 26.46 mmol) and SOCl\(_2\) (3.84 mL, 52.92 mmol, 2.00 equiv.) in MeOH (60 mL). White solid (4.97 g, 93%). \(^{1}H\) NMR (500 MHz, DMSO-d\(_6\)) δ 3.71 (s, 3H, \(CH_3\)), 5.30 (s, 1H, CH\(_2\)), 7.45-7.48 (m, 5H, 5CH\(_3\)), 8.89 (br s, 3H, NH\(_3\)). \(^{13}\)C\(^{1}H\) NMR (125 MHz, DMSO-d\(_6\)) δ 53.7, 55.7, 128.6, 129.5, 130.0, 133.0, 169.4. The NMR data matched with those previously reported.\(^{177}\)

Methyl 2-((tert-butoxycarbonyl)amino)-2-phenylacetate \(204\text{f}\) was obtained following the general procedure using methyl aminophenylacetate hydrochloride \(203\text{f}\) (1.14 g, 5.65 mmol), Boc\(_2\)O (1.48 g, 6.78 mmol, 1.20 equiv.) and Et\(_3\)N (0.89 mL, 6.21 mmol, 1.10 equiv.) in
CH₂Cl₂ (20 mL). White solid (1.41 g, 94%). ¹H NMR (500 MHz, CDCl₃) δ 1.42 (s, 9H, C(CH₃)₃), 3.69 (s, 3H, CH₃), 5.32 (d, 1H, J = 7.5 Hz, CH), 5.62 (br d, 1H, J = 5.5 Hz, NH), 7.30-7.36 (m, 5H, 5CHₐ). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 28.3, 52.6, 57.6, 80.1, 127.1, 128.4, 128.9, 136.9, 154.8, 171.6. The NMR data matched with those previously reported.¹⁷⁸

The title compound 205f was obtained following the general procedure using methyl 2-((tert-butoxycarbonyl)amino)-2-phenylacetate 204f (0.20 g, 0.75 mmol) and DIBAL-H (dissolved in 0.40 mL n-hexane, 0.27 mL, 1.50 mmol, 2.00 equiv.) in Et₂O (2 mL). Colorless oil (0.174 g, 95%). ¹H NMR (500 MHz, CDCl₃) δ 1.40 (s, 9H, C(CH₃)₃), 5.29 (br s, 1H, CH), 5.83 (br s, 1H, NH), 7.26-7.37 (m, 5H, 5CHₐ), 9.49 (s, 1H, CHO). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 28.4, 64.8, 80.3, 128.7, 128.9, 129.0, 129.3, 129.6, 134.0, 155.2, 195.3. The NMR data matched with those previously reported.¹⁷⁸

**tert-Butyl (S)-3-((tert-butoxycarbonyl)amino)-3-oxopropyl-1H-indole-1-carboxylate (205g)**

![Chemical structure of tert-Butyl (S)-3-((tert-butoxycarbonyl)amino)-3-oxopropyl-1H-indole-1-carboxylate (205g)](image)

Methyl tryptophanate hydrochloride 203g was obtained following the general procedure using L-tryptophan (3.00 g, 14.69 mmol) and SOCl₂ (2.13 mL, 29.38 mmol, 2.00 equiv.) in MeOH (30 mL). Off-white solid (3.71 g, 99%). ¹H NMR (500 MHz, DMSO-d₆) δ 3.30-3.32 (m, 2H, CH₂), 3.71 (s, 3H, CH₃), 4.28-4.30 (m, 1H, CH), 7.05 (t, 1H, J = 7.0 Hz, CHₐ), 7.14 (t, 1H, J = 8.0 Hz, CHₐ), 7.27 (br s, 1H, CHₐ), 7.41 (d, 1H, J = 8.0 Hz, CHₐ), 7.53 (d, 1H, J = 8.0 Hz, CHₐ), 8.42 (br s, 3H, NH₃), 11.10 (s, 1H, NH). ¹³C{¹H} NMR (125 MHz, DMSO-d₆) δ 26.8, 40.8, 53.3, 107.0, 112.2, 118.6, 119.3, 121.8, 125.6, 127.5, 136.9, 170.4. The NMR data matched with those previously reported.¹⁷⁹

Et₃N (0.56 mL, 3.92 mmol, 1.00 equiv.) was added dropwise to a stirred solution of methyl tryptophanate hydrochloride 203g (1.0 g, 3.92 mmol) in THF (15 mL) at 0 °C. Then,
Boc₂O (1.71 g, 7.85 mmol, 2.00 equiv.) and DMAP (0.72 g, 5.88 mmol, 1.50 equiv.) were added and the mixture was stirred overnight at room temperature. The reaction mixture was concentrated under reduced pressure, and the tert-butyl 3-(2-(tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate 204g was obtained after flash column chromatography (EtOAc/hexane = 3:7). Colorless oil (1.59 g, 97%). 

\[^1\text{H}\text{ NMR}\] (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.43 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 1.66 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 3.15-3.28 (m, 2H, CH\textsubscript{2}), 3.68 (s, 3H, CH\textsubscript{3}), 4.64-4.65 (m, 1H, CH), 5.16 (br d, 1H, \(J = 7.0\) Hz, NH), 7.21-7.23 (m, 1H, CH\textsubscript{Ar}), 7.28-7.31 (m, 1H, CH\textsubscript{Ar}), 7.39 (s, 1H, CH\textsubscript{Ar}), 7.49 (d, 1H, \(J = 8.0\) Hz, CH\textsubscript{Ar}), 8.11 (br s, 1H, CH\textsubscript{Ar}).

\[^{13}\text{C}\{^1\text{H}\}\text{ NMR}\] (125 MHz, CDCl\textsubscript{3}) \(\delta\) 27.8, 28.2, 28.3, 52.3, 53.7, 79.9, 83.6, 115.1, 115.2, 118.9, 122.5, 124.0, 124.5, 130.5, 135.3, 149.5, 155.1, 172.3. The NMR data matched with those previously reported.\(^{180}\)

The title compound 205g was obtained following the general procedure using tert-butyl 3-(2-(tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate 204g (0.11 g, 0.26 mmol) and DIBAL-H (dissolved in 0.10 mL \(n\)-hexane, 0.10 mL, 0.59 mmol, 2.20 equiv.) in Et\(_2\)O (1 mL). Colorless gummy oil (0.064 g, 99%). \([\alpha]^{22}_D = +53.5\) (c 3.2 CHCl\(_3\)).

\[^1\text{H}\text{ NMR}\] (500 MHz, CDCl\textsubscript{3}) \(\delta\) 1.44 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 1.66 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 3.22 (br s, 2H, CH\textsubscript{2}Ph), 4.48 (br s, 1H, CH), 5.22 (br s, 1H, NH), 7.25 (br s, 1H, CH\textsubscript{Ar}), 7.32 (br s, 1H, CH\textsubscript{Ar}), 7.43 (br s, 1H, CH\textsubscript{Ar}), 7.54 (br s, 1H, CH\textsubscript{Ar}), 8.13 (br s, 1H, CH\textsubscript{Ar}), 9.65 (s, 1H, CHO).

\[^{13}\text{C}\{^1\text{H}\}\text{ NMR}\] (125 MHz, CDCl\textsubscript{3}) \(\delta\) 25.0, 28.2, 28.3, 59.6, 80.2, 83.8, 114.8, 115.3, 119.0, 122.7, 124.2, 124.7, 130.2, 135.5, 149.5, 155.4, 199.5. \(\text{IR} (\nu_{\text{max}}/\text{cm}^{-1})\) 3371 (w), 2979 (m), 2361 (w), 1730 (s), 1700 (s), 1507 (s), 1452 (s), 1367 (s), 1253 (s), 1154 (s), 1086 (s), 856 (m), 766 (s), 744 (s).

\(\text{HRMS (ESI)} m/z\) calcd for C\(_{21}\)H\(_{28}\)N\(_2\)O\(_5\)Na [M + Na]\(^+\) 411.1896, found 411.1878.
Synthesis of \( N\)-Ts \( \alpha\)-Amino Aldehyde (208)

To an ice-cooled mixture of methyl 2-aminopropanoate hydrochloride 203a (1.00 g, 7.16 mmol) and TsCl (1.36 g, 7.16 mmol, 1.00 equiv.) in \( \text{CH}_2\text{Cl}_2 \) (15 mL), was added dropwise \( \text{Et}_3\text{N} \) (2.00 mL, 14.32 mmol, 2.00 equiv.) and the suspension was stirred for 1 h at 0 °C and 3 h at room temperature. The reaction was filtered, washed with water (30 mL), dried (\( \text{Na}_2\text{SO}_4 \)), and concentrated under reduced pressure to obtain methyl 2-[(4-methylphenyl)sulfonylamino]propanoate 226. Light yellow oil (1.66 g, 90%). \textbf{\(^{1}\text{H} \text{NMR} (300 \text{ MHz, CDCl}_3) \delta 1.36 \text{ (d, 3H, } J = 3.6 \text{ Hz, CH}_3), 2.41 \text{ (s, 3H, CH}_3), 3.51 \text{ (s, 3H, CH}_3), 3.97 \text{ (m, 1H, CH), 5.29 \text{ (br s, 1H, NH), 7.29 \text{ (d, 2H, } J = 8.1 \text{ Hz, 2CH}_n), 7.72 \text{ (d, 2H, } J = 8.1 \text{ Hz, 2CH}_n). \textbf{\(^{13}\text{C} \text{\{\text{H}\} NMR (75 \text{ MHz, CDCl}_3) \delta 19.8, 21.5, 51.4, 52.5, 127.2, 129.6, 136.7, 143.6, 172.6. The NMR data matched with those previously reported.}^{181}}\)

\[ \text{DIBAL-H (1.00 M solution in cyclohexane, 3.1 mL, 3.10 mmol, 2.00 equiv.) was added dropwise to a solution of methyl 2-[(4-methylphenyl)sulfonylamino]propanoate 226 (0.40 g, 1.55 mmol) at } -78 \text{ °C in } \text{Et}_2\text{O (5 mL) over a period of 15 min. The mixture was stirred at the same temperature for 3 h and quenched by MeOH (5 mL). The reaction mixture was then allowed to warm to room temperature and filtered through silica pad. The organic layer was washed with brine (10 mL), dried (\( \text{Na}_2\text{SO}_4 \)), and concentrated under reduced pressure to yield the title aldehyde 208, which was used for the next step without purification. Colourless oil (0.26 g, 98%).}^{181}\textbf{\text{\(^{1}\text{H} \text{NMR (300 MHz, CDCl}_3) \delta 1.07 \text{ (d, 3H, } J = 6.9 \text{ Hz, CH}_3), 2.45 \text{ (s, 3H, CH}_3), 4.28 \text{ (q, 1H, } J = 7.2, 6.9 \text{ Hz, CH)}), 7.32 \text{ (d, 2H, } J = 7.8 \text{ Hz, 2CH}_n), 7.68 \text{ (d, 2H, } J = 8.1 \text{ Hz, 2CH}_n), 9.71 \text{ (s, 1H, CHO). The NMR data matched with those previously reported.}^{181}}\)
Synthesis of N-Fmoc α-Amino Aldehyde (211)

To a mixture of methyl 2-aminopropanoate hydrochloride \textbf{203a} (0.20 g, 1.43 mmol) and Fmoc-Cl (0.40 g, 1.57 mmol, 1.1 equiv.) in CH$_3$CN (5 mL), was added K$_2$CO$_3$ (0.40 g, 2.86 mmol, 2.00 equiv.) and the mixture was stirred at room temperature for 5 h. The reaction mixture was then washed with saturated aqueous NH$_4$Cl solution (10 mL) and water (15 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure. Methyl-\(((9\text{-H-fluoren-9-yl)methoxy})\text{carbonylamino})\text{propanoate} \textbf{227} was obtained by flash column chromatography (EtOAc/hexane = 2:8). White gummy oil (0.25 g, 54%). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) $\delta$ 1.41 (d, 3H, \(J = 7.0\) Hz, CH$_3$), 3.71 (s, 3H, CH$_3$), 4.19 (t, 1H, \(J = 7.0\) Hz, CH), 4.35-4.40 (br m, 3H, CH$_2$ and CH$_2$), 5.50 (d, 1H, \(J = 7.5\) Hz, NH), 7.28 (t, 2H, \(J = 7.0\) Hz, 2CH$_{Ar}$), 7.36 (m, 2H, 2CH$_{Ar}$), 7.58 (t, 2H, \(J = 7.0\) Hz, 2CH$_{Ar}$), 7.72 (d, 2H, \(J = 7.0\) Hz, 2CH$_{Ar}$). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl$_3$) $\delta$ 18.6, 47.1, 49.6, 52.53, 67.0, 120.0, 125.15, 125.18, 127.12, 127.7, 141.3, 143.8, 143.9, 155.7, 173.6. The NMR data matched with those previously reported.\textsuperscript{182}

DIBAL-H (1.00 M solution in cyclohexane, 3.10 mL, 3.10 mmol, 2.00 equiv.) was added dropwise to a solution of methyl-\(((9\text{-H-fluoren-9-yl)methoxy})\text{carbonylamino})\text{propanoate} \textbf{227} (0.23 g, 0.70 mmol) at \(-78\) °C in Et$_2$O (5 mL) over a period of 30 min. The mixture was stirred at the same temperature for 4 h and was quenched by MeOH (5 mL). the reaction mixture was then allowed to warm to room temperature and filtered through silica pad. The organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to yield the title aldehyde \textbf{211}, which was used for the next step without purification. White gummy oil (0.14 g, 68%). \textsuperscript{1}H NMR (500 MHz, CDCl$_3$) $\delta$ 1.41 (d, 3H, \(J = 7.0\) Hz, CH$_3$), 4.27 (m, 1H, CH), 4.34-4.44 (m, 3H, CH$_2$, CH), 7.29 (t, 2H, \(J = 7.5\) Hz, 7.0 Hz, 2CH$_{Ar}$), 7.33 (t, 2H, \(J = 7.5\) Hz, 7.0 Hz, 2CH$_{Ar}$), 7.58 (m, 2H, 2CH$_{Ar}$), 7.74 (d, 2H, \(J = 8.0\) Hz, 2CH$_{Ar}$), 9.52 (s, 1H, CHO). \textsuperscript{13}C\textsuperscript{1}H NMR (125 MHz, CDCl$_3$) $\delta$ 14.8, 52.5,
The NMR data matched with those previously reported.183

Synthesis of N-Tr α-Amino Aldehyde (214)

To a solution of methyl 2-aminopropanoate hydrochloride 203a (4.85 g, 34.74 mmol) in CH₂Cl₂ (60 mL) at 0 °C, was added dropwise Et₃N (20.24 mL, 69.50 mmol, 2.00 equiv.). TrCl (9.68 g, 34.74 mmol, 1.00 equiv.) was then added and the stirring was continued for 1 h at 0 °C, and then at room temperature overnight. The reaction mixture was next washed with saturated aqueous NaHCO₃ (50 mL) solution and brine (50 mL), dried (Na₂SO₄), and purified with flash column chromatography (Et₂O/hexane = 1:9) to yield methyl tritylalaninate 228. Colourless oil (8.59 g, 71%). Rf (Et₂O/hexane = 1:9) = 0.40. [α]D²² = +25.9 (c 2 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 1.33 (d, 3H, J = 7.0 Hz, CH₃), 2.69 (d, 1H, J = 10.5 Hz, NH), 3.12 (s, 3H, OCH₃), 3.35-3.38 (m, 1H, CH), 7.12 (t, 2H, J = 7.5 Hz, 2CH₃), 7.21 (t, 6H, J = 7.5 Hz, 6CH₃), 7.49 (d, 7H, J = 7.0 Hz, 7CH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 21.8, 51.6, 52.1, 71.3, 126.5, 127.9, 128.9, 146.1, 176.4. IR (νmax/cm⁻¹) 3316 (w), 3056 (w), 2977 (w), 1734 (s), 1447 (s), 1205 (s), 1139 (s), 1062 (s), 734 (s), 704 (s). HRMS (ESI) m/z calcd for C₂₃H₂₃NO₂Na [M + Na⁺] 368.1626, found 368.1638.

DIBAL-H (0.32 mL in 0.30 mL hexane, 1.62 mmol, 2.00 equiv.) was added dropwise to a solution of methyl tritylalaninate 228 (0.28 g, 0.81 mmol) at −78 °C in Et₂O (1 mL) over a period of 20 min. The mixture was stirred at the same temperature for 1.5 h, and was quenched by methanol (5 mL). The reaction mixture was then allowed to warm to room temperature and filtered. The organic layer was washed with water (10 mL), dried (Na₂SO₄), and concentrated under reduced pressure to yield the title aldehyde 214, which was used for the next step without purification. Colorless oil (0.24 g, 98%). [α]D²² = +30.3 (c 2.5 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 1.02 (d, 3H, J = 8.5 Hz, CH₃), 2.60 (br s, 1H, NH), 3.32-3.35 (m, 1H, CH), 7.13-7.27
(m, 10H, 10CH₂), 7.49-7.56 (m, 5H, 5CH₂), 8.98 (s, 1H, CHO). \( ^{13}\text{C}\{^1\text{H}\} \text{ NMR} \) (125 MHz, CDCl₃) δ 19.8, 60.2, 73.7, 129.2, 130.5, 131.1, 148.5, 205.4. \( \text{IR} \ (\nu_{\text{max}}/\text{cm}^{-1}) \) 3205 (w), 2976 (w), 1723 (w), 1472 (s), 1372 (s), 1328 (s), 1314 (s), 1144 (s), 850 (m), 745 (m), 705 (s). \( \text{HRMS} \) (ESI) \( m/z \) calcd for C₂₂H₂₁NONa [M + Na]⁺ 338.1521, found 338.1512.

**Synthesis of N-Bn,N-Boc α-Amino Esters (248a-f)**

![Synthesis of N-Bn,N-Boc α-Amino Esters (248a-f)](image)

All the N-diprotected amino esters 248a-f were synthesised via two steps, N-benzylation followed by N-Boc protection.

To a stirred mixture of the α-amino methyl ester hydrochloride 203 and BnBr (1.00 equiv.) in CH₃CN, was added K₂CO₃ (2.00 equiv.) and the mixture was stirred overnight at room temperature. The reaction mixture was washed with aqueous saturated NH₄Cl solution (30 mL) and water (30 mL), dried (Na₂SO₄), concentrated under reduced pressure and purified by flash column chromatography to obtain the N-benzylated products 247.

Et₃N (2.00 equiv.) was added dropwise to a stirred solution of the N-benzylated amino methyl esters 247 and Boc₂O (1.24 equiv.) in CH₂Cl₂, and the reaction mixture was stirred for 24 h at room temperature. The reaction was washed with aqueous solution of HCl (1 M) (15 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Purification was carried out by flash column chromatography to yield the N-Bn,N-Boc α-amino esters 248.

**Methyl N-benzyl-N-(tert-butoxycarbonyl)-L-alaninate (248a)**

![Methyl N-benzyl-N-(tert-butoxycarbonyl)-L-alaninate (248a)](image)

Methyl N-benzyl amino propanoate 247a was obtained following the general procedure using methyl 2-aminopropanoate hydrochloride 203a (2.8 g, 20.06 mmol), BnBr (2.35 mL, 20.06
mmol, 1.00 equiv.) and K₂CO₃ (5.5 g, 40.12 mmol, 2.00 equiv.) in CH₃CN (30 mL). Light yellow oil (2.75 g, 71%).!

**¹H NMR** (500 MHz, CDCl₃) δ 1.24 (d, 3H, J = 7.0 Hz, CH₃), 1.89 (br s, 1H, NH), 3.31 (q, 1H, J = 7.0 Hz, 7.0 Hz, CH₂), 3.59 (d, 1H, J = 13.0 Hz, CH), 3.61 (s, 3H, CH₃), 3.72 (d, 1H, J = 13.0 Hz, CH), 7.16-7.28 (m, 5H, 5CH₃). **¹³C{¹H} NMR** (125 MHz, CDCl₃) δ 19.0, 51.5, 51.8, 55.7, 126.9, 128.1, 128.3, 139.8, 175.9. The NMR data matched with those previously reported.¹⁸⁴

Methyl N-benzyl-N-( tert-butoxycarbonyl)-L-alaninate 248a was obtained following the general procedure using methyl N-benzyl amino propanoate 247a (2.35 g, 12.16 mmol), Boc₂O (3.29 g, 15.07 mmol, 1.24 equiv.) and Et₃N (7.10 mL, 24.32 mmol, 2.00 equiv.) in CH₂Cl₂ (30 mL). Colourless oil (2.51 g, 70%). **¹H NMR** (300 MHz, CDCl₃) (mixture of rotamers) δ 1.33 (s, 3H, CH₃), 1.39 (br s, 4H, C(CH₃)₃), 1.46 (br s, 5H, C(CH₃)₃), 3.64 (s, 3H, CH₃), 3.93 (br s, 0.5H, CHPh), 4.33 (d, 0.5H, J = 15.9 Hz, CHPh), 4.54 (br s, 2H, CHPh, CH), 7.23-7.29 (m, 5H, 5CH₃). **¹³C{¹H} NMR** (75 MHz, CDCl₃) (mixture of rotamers) δ 15.4, 15.8, 27.3, 28.2, 49.5, 50.8, 51.9, 54.5, 55.3, 80.5, 85.0, 126.8, 127.2, 127.9, 128.3, 138.1, 139.1, 146.7, 155.2, 155.5, 172.5, 172.7. The NMR data matched with those previously reported.¹⁸⁵

**Methyl (S)-2-(benzyl( tert-butoxycarbonyl)amino)pentanoate (248b)**

![CO₂Me]

Methyl 2-(benzylamino)pentanoate 247b was obtained following the general procedure using 2-aminopentanoate hydrochloride 203b (1.30 g, 7.75 mmol), BnBr (0.90 mL, 7.75 mmol, 1.00 equiv.), and K₂CO₃ (2.14 g, 15.50 mmol, 2.00 equiv.) in CH₃CN (20 mL). Colourless oil (1.25 g, 73%). **Rₐ** (Et₂O/hexane = 1:9) = 0.16. [α]₂⁰ D = −35.4 (c 5.5 CHCl₃). **¹H NMR** (300 MHz, CDCl₃) δ 0.88 (t, 3H, J = 7.2 Hz, CH₂), 1.33-1.43 (m, 2H, CH₂), 1.57-1.64 (m, 2H, CH₂), 1.79 (s, 1H, NH), 3.26 (t, 1H, J = 6.6 Hz, CH₂), 3.61 (d, 1H, J = 13.2 Hz, CHPh), 3.67 (s, 3H, CH₃), 3.80 (d, 1H, J = 13.2 Hz, CHPh), 7.22-7.31 (m, 5H, 5CH₃). **¹³C{¹H} NMR** (75 MHz, CDCl₃) δ 13.8, 19.0, 35.7, 51.5, 52.1, 60.5, 126.9, 128.2, 128.3, 139.9, 176.0. **IR** (v max/cm⁻¹) 3735 (m),
Methyl (S)-2-(benzyl(tert-butoxycarbonyl)amino)pentanoate 248b was obtained following the general procedure using methyl 2-(benzylamino)pentanoate 247b (1.00 g, 4.51 mmol), Boc₂O (1.47 g, 6.77 mmol, 1.50 equiv.) and Et₃N (2.58 mL, 9.02 mmol, 2.00 equiv.) in CH₂Cl₂ (10 mL). Colourless oil (0.89 g, 62%). Rᵣ (Et₂O/hexane = 1:9) = 0.23. [α]ᵣ²² = −50.4 (c 9.5 CHCl₃). ¹H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 0.79 (br s, 3H, CH₃), 1.24 (br s, 2H, CH₂), 1.40 (br s, 4.2H, C(CH₃)₃), 1.45 (br s, 4.8H, C(CH₂)₃), 1.62-1.75 (m, 1H, CH), 1.84-1.94 (m, 1H, CH), 3.55 (s, 3H, CH₃), 3.90-4.80 (m, 3H, CH₂Ph, CH), 7.19-7.28 (m, 5H, 5CH₃Ar). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of rotamers, minor rotamer indicated by asterisk) δ 13.5, 19.5, 28.1, 31.6, 32.3*, 32.4, 49.4, 50.7*, 51.5, 58.5, 59.1*, 80.2, 126.8, 127.1, 128.0, 128.3, 138.0, 138.9*, 155.6, 172.1. IR (νmax/cm⁻¹) 3031 (w), 2961 (m), 2875 (w), 1739 (s), 1700 (s), 1452 (s), 1319 (m), 1248 (m), 1163 (m), 979 (m), 862 (m), 734 (m), 699 (s). HRMS (ESI-TOF) m/z calcd for C₁₈H₂₇NO₄Na [M + Na]⁺ 344.1838, found 344.1833.

Methyl N-benzyl-N-(tert-butoxycarbonyl)-L-leucinate (248c)

Methyl N-benzyl leucinate 247c was obtained following the general procedure using methyl leucinate hydrochloride 203c (1.00 g, 5.50 mmol), BnBr (0.70 mL, 6.05 mmol, 1.10 equiv.) and K₂CO₃ (1.52 g, 11.00 mmol, 2.00 equiv.) in CH₃CN (20 mL). Light yellow oil (0.996 g, 77%). ¹H NMR (500 MHz, CDCl₃) δ 0.84 (d, 3H, J = 6.5 Hz, CH₃), 0.91 (d, 3H, J = 7.0 Hz, CH₃), 1.45-1.48 (m, 2H, CH₂), 1.74 (s, 1H, NH), 1.75-1.80 (m, 1H, CH), 3.29 (t, 1H, J = 7.5 Hz, CH), 3.60 (d, 1H, J = 13.0 Hz, CH), 3.69 (s, 3H, CH₃), 3.79 (d, 1H, J = 13.0 Hz, CH), 7.29-7.32 (m, 5H, 5CH₃Ar). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 22.1, 22.8, 24.9, 42.8, 51.5, 52.2, 59.2, 127.0, 128.2, 128.3, 139.9, 176.5. The NMR data matched with those previously reported.¹⁸⁶
Methyl N-benzyl-N-(tert-butoxycarbonyl) leucinate 248c was obtained following the general procedure using methyl N-benzyl leucinate 247c (0.59 g, 2.50 mmol), Boc₂O (0.67 g, 3.10 mmol, 1.24 equiv.) and Et₃N (0.81 mL, 2.75 mmol, 1.10 equiv.) in CH₂Cl₂ (5 mL). Colourless oil (0.59 g, 70%). ¹H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 0.72 (br s, 3H, CH₃), 0.83 (br d, 3H, J = 15.3 Hz, CH₃), 1.40 (br s, 4H, C(CH₃)₃), 1.47 (br s, 5H, C(CH₃)₃), 1.56-1.60 (m, 2H, CH₂), 1.75 (m, 1H, CH), 3.56 (s, 3H, CH₃), 4.16 (br s, 0.5H, CHPh), 4.28-4.42 (br m, 1H, CHPh), 4.56 (m, 1H, CH), 4.72 (br s, 0.5H, CHPh), 7.22 (dd, 5H, J = 4.5, 12.6 Hz, 5CH₃). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of rotamers) δ 21.8, 22.6, 24.6, 28.2, 38.4, 39.2, 49.2, 50.2, 51.7, 56.8, 57.5, 80.3, 126.8, 127.1, 128.1, 128.2, 128.5, 129.8, 172.3, 172.5. The NMR data matched with those previously reported.¹⁸⁷

Methyl N-benzyl-N-(tert-butoxycarbonyl)-L-phenylalaninate (248d)

Methyl N-benzyl phenylalaninate 247d was obtained following the general procedure using methyl 2-amino-3-phenylpropanoate hydrochloride 203d (3.00 g, 13.91 mmol), BnBr (1.60 mL, 13.91 mmol, 1.00 equiv.) and K₂CO₃ (3.84 g, 27.80 mmol, 2.00 equiv.) in CH₃CN (40 mL). Colourless oil (2.96 g, 79%). ¹H NMR (300 MHz, CDCl₃) δ 1.85 (s, 1H, NH), 2.93 (d, 2H, J = 6.6 Hz, CH₂Ph), 3.51 (t, 1H, J = 6.3 Hz, CH), 3.57 (s, 3H, CH₃), 3.59 (d, 1H, J = 13.2 Hz, CHPh), 3.77 (d, 1H, J = 13.2 Hz, CHPh), 7.11-7.25 (m, 10H, 10CH₃). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 39.8, 51.6, 52.0, 62.1, 126.7, 127.1, 128.2, 128.4, 128.5, 129.3, 137.4, 139.7, 175.0. The NMR data matched with those previously reported.¹⁸⁸

Methyl N-benzyl-N-(tert-butoxycarbonyl)-L-phenylalaninate 248d was obtained following the general procedure using methyl N-benzyl phenylalaninate 247d (1.66 g, 6.16 mmol), Boc₂O (1.67 g, 7.64 mmol, 1.24 equiv.) and Et₃N (1.98 mL, 6.77 mmol, 1.10 equiv.) in CH₂Cl₂ (10 mL). Colourless oil (1.46 g, 65%). ¹H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 1.38 (br s, 4H, C(CH₃)₃), 1.48 (br s, 5H, C(CH₃)₃), 3.02-3.21 (m, 0.5H, CH), 3.30 (d, 0.5H, J = 5.7 Hz, CH), 3.57 (s, 3H, CH₃), 3.68 (d, 1H, J = 15.6 Hz, CHPh), 3.92 (br d, 1H,
$J = 15.6$ Hz, $CH_{Ph}$), 4.35 (br d, 1H, $J = 15.6$ Hz, $CH_{Ph}$), 4.54 (d, 1H, $J = 15.6$ Hz, $CH_{Ph}$), 7.05-7.26 (m, 10H, $5CH_{Ar}$). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) (mixture of rotamers) $\delta$ 28.3, 35.6, 36.6, 51.3, 51.6, 51.9, 60.8, 61.0, 80.5, 80.8, 126.5, 126.9, 127.2, 127.6, 128.1, 128.5, 128.6, 129.3, 137.2, 138.0, 138.1, 155.1, 171.3. The NMR data matched with those previously reported.$^{189}$

**Methyl $N$-benzyl-$N$-($tert$-butoxycarbonyl)-L-valinate (248e)**

![Chemical Structure](image)

Methyl $N$-benzyl valinate 247e was obtained following the general procedure using methyl 2-amino-3-methylbutanoate hydrochloride 203e (2.00 g, 11.92 mmol), BnBr (1.38 mL, 11.92 mmol, 1.00 equiv.) and K$_2$CO$_3$ (3.28 g, 23.84 mmol, 2.00 equiv.) in CH$_3$CN (30 mL). Colorless oil (1.86 g, 71%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.92 (d, 3H, $J = 6.5$ Hz, $CH$_3), 0.94 (d, 3H, $J = 7.0$ Hz, $CH$_3), 1.78 (br s, 1H, $N$H), 1.91 (q, 1H, $J = 7.0$ Hz, $CH$), 3.01 (d, 1H, $J = 6.0$ Hz, $CH$), 3.57 (d, 1H, $J = 13.5$ Hz, $CH$), 3.68 (s, 3H, OCH$_3$), 3.81 (d, 1H, $J = 13.5$ Hz, $CH$), 7.20-7.33 (m, 5H, $5CH_{Ar}$). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 18.6, 19.3, 31.7, 51.3, 52.5, 66.6, 127.0, 128.2, 128.3, 140.1, 175.7. The NMR data matched with those previously reported.$^{190}$

Methyl $N$-benzyl-$N$-($tert$-butoxycarbonyl) valinate 248e was obtained following the general procedure using methyl $N$-benzyl valinate 247e (1.28 g, 5.78 mmol), Boc$_2$O (2.14 g, 9.82 mmol, 1.70 equiv.) and Et$_3$N (3.32 mL, 11.56 mmol, 2.00 equiv.) in CH$_2$Cl$_2$ (15 mL). Colourless oil (1.18 g, 63%). $\text{Rf}$ (Et$_2$O/hexane = 1:9) = 0.29. $[\alpha]_D^{22} = -74.7$ (c 3.1 CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$) (mixture of rotamers) $\delta$ 0.81-0.96 (m, 6H, 2 $\times$ $CH$_3), 1.35 (br s, 6H, C($CH$_3)$_3$), 1.47 (br s, 3H, C($CH$_3)$_3$), 2.31 (br s, 1H, $CH$), 3.41 (s, 3H, OCH$_3$), 4.34-4.58 (m, 3H, $CH$_2Ph, $CH$), 7.22 (m, 5H, $5CH_{Ar}$). $^{13}$C{$^1$H} NMR (75 MHz, CDCl$_3$) (mixture of rotamers, minor rotamer indicated by asterisk) $\delta$ 18.5, 19.7, 20.7*, 27.2*, 28.1, 47.9, 49.5*, 51.2, 63.4, 64.8*, 80.3, 126.6, 127.9, 137.9*, 138.7, 155.8, 171.2. IR ($\nu_{max}$/cm$^{-1}$) 2968 (m), 1739 (s), 1693
Methyl (S)-2-(benzyl(tert-butoxycarbonyl)amino)-2-phenylacetate (248f)

Methyl 2-(benzylamino)-2-phenylacetate 247f was obtained following the general procedure using methyl aminophenylacetate hydrochloride 203f (2.50 g, 12.39 mmol), BnBr (1.45 mL, 12.39 mmol, 1.00 equiv.) and K₂CO₃ (3.42 g, 24.79 mmol, 2.00 equiv.) in CH₃CN (35 mL). Colourless oil (2.15 g, 68%). Rᵣ (Et₂O/hexane = 6:4) = 0.64. [α]⁺₂⁰ = +84.6 (c 2 CHCl₃).

1H NMR (300 MHz, CDCl₃) δ 2.34 (s, 1H, NH), 3.56 (s, 3H, OCH₃), 3.68 (s, 2H, CH₂Ph), 4.36 (s, 1H, CH), 7.17-7.36 (m, 10H, 10CHAr). 13C{¹H} NMR (75 MHz, CDCl₃) δ 51.4, 52.1, 64.4, 127.2, 127.6, 128.1, 128.3, 128.4, 128.7, 138.2, 139.6, 173.4. IR (νmax/cm⁻¹) 3336 (w), 3026 (w), 2950 (w), 1735 (s), 1600 (m), 1436 (m), 1378 (m), 1266 (m), 1199 (s), 1131 (m), 1009 (m), 908 (m), 801 (m), 728 (s), 695 (s). HRMS (ESI) m/z calcd for C₁₆H₁₇NO₂Na [M + Na]+ 278.1157, found 278.1164.

Methyl (S)-2-(benzyl(tert-butoxycarbonyl)amino)-2-phenylacetate 248f was obtained following the general procedure using methyl 2-(benzylamino)-2-phenylacetate 247f (2.00 g, 7.83 mmol), Boc₂O (2.12 g, 9.71 mmol, 1.24 equiv.) and triethylamine (4.55 mL, 15.66 mmol, 2.00 equiv.) in CH₂Cl₂ (15 mL). Colourless oil (1.61 g, 58%). Rᵣ (EtOAc/hexane = 2:8) = 0.29. [α]⁺₂⁰ = +47.8 (c 1 CHCl₃).

1H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 1.39 (br s, 9H, C(CH₃)₃), 3.69 (s, 3H, CH₃), 4.15 (d, 1H, J = 15.0 Hz, CHPPh), 4.65 (br d, 1H, J = 15.0 Hz, CHPPh), 5.79 (br s, 1H, CH), 6.95 (br s, 2H, 2CHAr), 7.06-7.16 (m, 4H, 4CHAr), 7.22 (br s, 4H, 4CHAr). 13C NMR (75 MHz, CDCl₃) (mixture of rotamers) δ 28.2, 28.5, 49.1, 49.4, 52.1, 52.2, 63.1, 63.3, 80.6, 81.1, 126.5, 126.7, 127.0, 127.3, 127.6, 127.8, 128.1, 128.3, 128.4, 128.6, 128.7, 129.4, 129.6, 134.5, 134.8, 139.0, 156.0, 171.3, 171.6. IR (νmax/cm⁻¹) 2979 (w), 1747 (s), 1691 (s), 1454 (m), 1365 (s), 1253 (m), 1155 (s), 1006 (m), 856 (m), 748 (m), 696 (s). HRMS (ESI) m/z calcd for C₂₁H₂₅NO₄Na [M + Na]+ 378.1681, found 378.1662.
Methyl tryptophanate hydrochloride 203g (3.60 g, 14.13 mmol) was neutralized into the free base by dissolving in Et₂O (20 mL) followed by washing with saturated aqueous K₂CO₃ solution (20 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to obtain a light yellow oil. To a stirred suspension of the neutralised tryptophan methyl ester and MgSO₄ (2.70 g) in CH₂Cl₂ (40 mL), was added benzaldehyde (1.43 mL, 14.13 mmol, 1.00 equiv.) and the mixture was stirred for 5 h at room temperature. The imine product was obtained after filtration and concentration, which was used for the next step without purification. The imine compound was dissolved in dry MeOH (30 mL) and NaBH₄ (0.58 g, 15.54 mmol, 1.10 equiv.) was added slowly at 0 °C. The solvent was evaporated after 1 h at 0 °C. Then the mixture was washed by NH₄OH (5%, 20 mL), extracted with ethyl acetate and dried (Na₂SO₄). The methyl N-Benzyl tryptophanate 247g was obtained after flash column chromatography (EtOAc/hexane = 2:8). Colourless gummy oil (3.12 g, 72%). 

**1H NMR** (300 MHz, CDCl₃) δ 1.74 (br s, 2H, 2NH), 3.14 (dd, 1H, 6.3, 14.4 Hz, CH₁), 3.18 (dd, 1H, 5.4, 14.4 Hz, CH₁), 3.62 (s, 3H, CH₃), 3.67 (d, 2H, 3.9 Hz, CH₂), 3.82 (d, 1H, 13.2 Hz, CH), 7.02 (d, 1H, 2.4 Hz, CH₆), 7.09 (t, 1H, 7.2, 7.5 Hz, CH₆), 7.17 (d, 1H, 8.1 Hz, CH₆), 7.23 (t, 1H, 4.5, 9.6 Hz, CH₆), 7.34 (d, 1H, 7.8 Hz, CH₆), 7.57 (d, 1H, 7.8 Hz, CH₆), 7.75 (s, 1H, CH₃).
7.5 Hz, CH\textsubscript{Ar}), 8.01 (br s, 1H, CH\textsubscript{Ar}).\textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl\textsubscript{3}) \(\delta\) 29.3, 51.6, 52.1, 61.2, 111.0, 111.4, 118.8, 119.4, 122.0, 122.7, 126.9, 127.5, 128.1, 128.3, 136.1, 139.6, 175.3. The NMR data matched with those previously reported.\textsuperscript{179}

Et\textsubscript{3}N (2.85 mL, 9.92 mmol, 2.00 equiv.) was added dropwise to a stirred solution of methyl \(N^0\)-benzyl tryptophanate \textsuperscript{247g} (1.53 g, 4.96 mmol) and Boc\textsubscript{2}O (1.02 g, 4.71 mmol, 0.95 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (20 mL), and was stirred for 24 h at room temperature. The crude reaction mixture was concentrated under reduced pressure. Then title compound \textsuperscript{248g} was obtained after flash column chromatography (EtOAc/hexane = 2:8). Colourless gummy oil (1.37 g, 67%).\textsuperscript{179}

\(\int\) NMR (300 MHz, CDCl\textsubscript{3}) \(\delta\) 1.40 (br s, 3.6H, C(C\textsubscript{3})\textsubscript{3}), 1.44 (br s, 5.4H, C(C\textsubscript{3})\textsubscript{3}), 3.21-3.29 (br m, 1H, CH\textsubscript{2}), 3.45-3.51 (br m, 2H, CH\textsubscript{2}), 3.55 (s, 3H, CH\textsubscript{3}), 3.77 (br d, 0.6H, \(J = 15.3\) Hz, CHPH), 4.00 (br d, 0.4H, \(J = 15.3\) Hz, CPH), 4.17 (br s, 0.6H, NH), 4.34 (br d, 0.4H, \(J = 15.9\) Hz, CPH), 4.50 (br d, 1H, \(J = 15.9\) Hz, CPH), 7.05 (d, 2H, \(J = 5.7\) Hz, 2CH\textsubscript{Ar}), 7.14 (br s, 4H, 4CH\textsubscript{Ar}), 7.27-7.41 (m, 2H, 2CH\textsubscript{Ar}), 8.35 (m, 1H, CH\textsubscript{Ar}).\textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl\textsubscript{3}) (mixture of rotamers, minor rotamer indicated by asterisk) \(\delta\) 25.2, 26.0, 28.2, 51.2, 51.7, 59.6, 59.9*, 80.4*, 80.7, 111.2, 111.4*, 118.2, 119.1, 121.7, 122.9*, 123.2, 126.8*, 127.0, 127.4, 127.9, 128.3, 136.0, 137.2, 138.0, 155.3, 171.6. The NMR data matched with those previously reported.\textsuperscript{179}

To a stirred solution of methyl \(N^0\)-benzyl-\(N^0\)-(tert-butoxycarbonyl) tryptophanate \textsuperscript{248g} (1.07 g, 2.62 mmol) and Boc\textsubscript{2}O (0.85 g, 3.93 mmol, 1.50 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (15 mL), was added DMAP (0.063 g, 0.52 mmol, 0.20 equiv.) and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with EtOAc (10 mL) and washed with water (30 mL) and saturated aqueous NaHCO\textsubscript{3} solution (30 mL) and brine (30 mL). The organic layer was dried (Na\textsubscript{2}SO\textsubscript{4}) and the filtrate was concentrated under reduced pressure. The title compound \textsuperscript{248g'} was obtained after flash column chromatography (EtOAc/hexane = 2:9). Colourless gummy oil (1.15 g, 86%). \(R_f\) (EtOAc/hexane = 2:9) = 0.48. [\(\alpha\)]\textsubscript{D}\textsuperscript{2} = –67.2 (c 1.0 CHCl\textsubscript{3}). \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}) (mixture of rotamers) \(\delta\) 1.48 (s, 9H, 3CH\textsubscript{3}), 1.65 (s, 9H, 3CH\textsubscript{3}), 3.10-3.39 (m, 2H, CH\textsubscript{2}), 3.62 (s, 3H, CH\textsubscript{3}), 4.15-4.39 (m, 3H, CH\textsubscript{2}, CH), 7.01-7.42 (m, 9H, 9CH\textsubscript{Ar}), 8.11 (br d, 1H, \(J = 6.9\) Hz, CH\textsubscript{Ar}). \textsuperscript{13}C\{\textsuperscript{1}H\} NMR (75 MHz, CDCl\textsubscript{3}) (mixture of
rotamers, minor rotamer indicated by asterisk) δ 24.9*, 25.9, 28.2*, 28.3, 51.8*, 52.0, 59.6, 59.8*, 80.5*, 80.8, 83.2*, 83.4, 115.2, 115.3*, 116.5, 116.7*, 118.5, 118.7, 118.9*, 122.4, 124.00*, 124.09, 124.4, 124.3*, 126.9, 127.0, 127.1*, 127.6*, 127.9, 128.1*, 128.3, 128.5, 130.2*, 130.5, 135.4, 137.2, 137.6*, 149.5, 155.2, 171.4, 174.9*. IR (νmax/cm⁻¹) = 2976 (m), 2931 (m), 2357 (w), 2167 (w), 1732 (s), 1695 (s), 1452 (s), 1365 (s), 1253 (s), 1155 (s), 1083 (s), 1016 (m), 858 (m), 742 (s), 698 (s). HRMS (ESI) m/z calcd for C₂₉H₃₆N₂O₆Na [M + Na]⁺ 531.2471, found 531.2492.

1-((tert-Butyl) 2-methyl (S)-pyrrolidine-1,2-dicarboxylate (248h)

Methyl prolinate hydrochloride 203h was obtained following the general procedure using L-pyroline (3.00 g, 26.06 mmol) and thionyl chloride (2.08 mL, 28.67 mmol, 1.10 equiv.) in MeOH (30 mL) after heating at reflux for 1 h. Light yellow oil (4.60 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ 2.06-2.14 (m, 2H, C₆H₅), 2.16-2.23 (m, 1H, C₆H₅), 2.37-2.46 (m, 1H, C₆H₅), 3.52-3.59 (br m, 2H, C₆H₅), 3.83 (s, 3H, C₆H₅), 4.50 (br s, 1H, CH), 9.21 (br s, 1H, NH), 10.52 (br s, 1H, HCl). ¹³C{¹H} NMR (75 MHz, CDCl₃) δ 23.4, 28.5, 45.7, 53.3, 59.0, 169.2. The NMR data matched with those previously reported.¹⁹¹

To a solution of methyl prolinate hydrochloride 203h (4.60 g, 35.61 mmol) in CH₂Cl₂ (50 mL) at 0 °C, was added dropwise Et₃N (18.40 mL, 64.00 mmol, 1.80 equiv.). After 10 min, Boc₂O (5.67 g, 26.00 mmol, 0.73 equiv.) was added over 30 min. The reaction mixture was stirred at room temperature for 24 h. The mixture was filtered, and the filtrate was diluted with Et₂O (50 mL) and washed with aqueous HCl solution (2 M, 10 mL), aqueous saturated NaHCO₃ solution (20 mL) and brine (20 mL), and dried (Na₂SO₄). The 1-((tert-butyl) 2-methyl pyrrolidine-1,2-dicarboxylate 248h was obtained after flash column chromatography (EtOAc/hexane = 2:8). Colourless oil (6.46 g, 79%). ¹H NMR (500 MHz, CDCl₃) (mixture of rotamers) δ 1.41 (s, 5.4H, C(CH₃)₃), 1.46 (s, 3.6H, C(CH₃)₃), 1.83-1.97 (m, 3H, CH₂), 2.17-
2.52 (m, 1H, CH₂), 3.38-3.58 (m, 2H, NCH₂), 3.72 (s, 3H, CH₃), 4.22 (d, 0.6H, J = 6.5 Hz, NCH), 4.32 (d, 0.4H, J = 6.5 Hz, NCH). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture of rotamers) δ 23.8, 24.4, 28.4, 28.5, 30.0, 31.0, 46.4, 46.6, 52.0, 52.1, 58.8, 59.2, 79.8, 79.9, 153.9, 154.5, 173.6, 173.8. The NMR data matched with those previously reported.¹⁹²

**Methyl N-benzyl-N-tosyl-L-alaninate (S220)**

![Chemical Structure]

To an ice-cooled mixture of methyl 2-aminopropanoate hydrochloride **203a** (3.0 g, 21.49 mmol) and TsCl (4.09 g, 21.49 mmol, 1.00 equiv.) in CH₂Cl₂ (45 mL) 0 °C, was added dropwise Et₃N (6.0 mL, 42.98 mmol, 2 equiv.) and the suspension was stirred for 1 h at 0 °C and 3 h at room temperature. The reaction mixture was filtered, washed with water (30 mL), dried (Na₂SO₄), and concentrated under reduced pressure. K₂CO₃ (2.37 g, 17.32 mmol, 2.00 equiv.) and BnBr (1.50 mL, 13.00 mmol, 1.50 equiv.) in CH₃CN (30 mL) were then added to the crude reaction mixture and the mixture was stirred overnight at room temperature. The reaction mixture was then washed with aqueous saturated NH₄Cl solution (50 mL) and water (50 mL), dried (Na₂SO₄), concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane = 3:7) to obtain the methyl N-benzyl-N-tosyl-L-alaninate **S220**. Colourless oil (2.74 g, 88%). **Rf** (EtOAc/hexane = 3:7) = 0.54. [α]D²² = −42.5 (c 2.5 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 1.26-1.28 (m, 3H, CH₃), 2.42 (br s, 3H, CH₃), 3.42 (br s, 3H, CH₃), 4.42 (br d, 1H, J = 16.0 Hz, CHPh), 4.55 (br d, 1H, J = 16.0 Hz, CHPh), 4.61-4.63 (m, 1H, CH), 7.23-7.32 (m, 7H, 7CH₃), 7.71 (br d, 2H, J = 5.5 Hz, 2CH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 16.4, 21.5, 49.1, 52.0, 55.0, 127.4, 127.5, 128.0, 128.3, 129.5, 137.1, 137.3, 143.4, 171.6. IR (νmax/cm⁻¹) 2950 (w), 1742 (s), 1456 (m), 1339 (s), 1152 (m), 845 (m), 725 (s), 655 (s). HRMS (ESI) m/z calced for C₁₈H₂₁NO₄NaS [M + Na]⁺ 370.1089, found 370.1073.
**Methyl dibenzyl-L-alaninate (S223)**

To a mixture of methyl 2-aminopropanoate hydrochloride 203a (1.00 g, 7.16 mmol) and BnBr (1.48 mL, 15.01 mmol, 2.10 equiv.) in CH₃CN (15 mL), was added K₂CO₃ (3.96 g, 28.64 mmol, 4.00 equiv.) and the mixture was stirred for 24 h under reflux conditions. The reaction mixture was filtered, washed with water (30 mL) and brine (30 mL), dried (Na₂SO₄), and purified by flash column chromatography (Et₂O/hexane = 1:9) to obtain methyl dibenzyl alaninate S223. Light yellow oil (1.73 g, 90%).

**1H NMR** (300 MHz, CDCl₃) δ 1.29 (d, 3H, J = 7.2 Hz, CH₃), 3.46-3.53 (m, 1H, CH), 3.26 (d, 2H, J = 14.1 Hz, 2CH₂Ph), 3.60 (s, 3H, OCH₃), 3.81 (d, 2H, J = 14.1 Hz, 2CH₂Ph), 7.15-7.38 (m, 10H, 10CH₃Ar). **13C{1H} NMR** (75 MHz, CDCl₃) δ 151.1, 51.2, 54.6, 56.2, 127.1, 128.3, 128.7, 140.0, 174.1. The NMR data matched with those previously reported.

**Synthesis of N,N-diprotected α-amino aldehydes**

N,N-diprotected α-amino aldehydes were prepared by three different methods including reduction of esters with DIBAL-H method, or reduction of esters followed by oxidation with TEMPO method and Swern method.

**DIBAL-H method.** To a solution of the N,N-diprotected amino ester 248 in Et₂O at −78 °C, was added dropwise neat DIBAL-H (dissolved in n-hexane (ca 0.5 mL), 2.00 equiv.). The
mixture was stirred at the same temperature for 1 h, and was quenched with methanol (1 mL).
The reaction mixture was allowed to warm to room temperature, followed by adding water (2 mL).
The crude mixture was filtered through a sintered glass funnel and the filtrate was washed
with brine (20 mL). The organic layer was dried (Na$_2$SO$_4$) and concentrated under reduced
pressure to yield the desired aldehyde. All the aldehyde products prepared by the DIBAL-H
method were purified by flash column chromatography.

*Reduction by LiAlH$_4$. To a solution of LiAlH$_4$ (1 M solution in THF, 2.00 equiv.) at 0 °C,
was added dropwise the amino ester 248 in THF (0.2 M) and the mixture was stirred at the
same temperature for 30 min. The reaction was then quenched with water (1 mL), filtered, and
concentrated under reduced pressure. The crude reaction mixture was purified by flash column
chromatography and the resulting alcohol 249 was utilised in the next oxidation step.

*TEMPO oxidation*. To a stirred solution of the amino alcohol 249 in CH$_2$Cl$_2$ (0.05M)
at 0 °C, was added saturated aqueous NaHCO$_3$ solution (CH$_2$Cl$_2$/NaHCO$_3$ 2:1), KBr (1.00
equiv.) and TEMPO (0.05 equiv.). NaOCl (1.20 equiv.) was then added with a syringe pump
over 30 min. The reaction was stirred for another 15 min at 0 °C. Then, the reaction mixture
was quenched with saturated aqueous Na$_2$S$_2$O$_3$ solution (15 mL) and extracted into CH$_2$Cl$_2$
(3×10 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated under reduced
pressure to afford the desired aldehyde. All the aldehyde products prepared by TEMPO method
were used for the next step without purification.

*Swern oxidation*. To a solution of oxalyl chloride (2.00 equiv.) in CH$_2$Cl$_2$ (0.8 M) at
−78 °C, was added DMSO (4.00 equiv.) dropwise and stirred for 15 min. A solution of amino
alcohol 249 in CH$_2$Cl$_2$ (0.5 M) was then added and the mixture was stirred at −78 °C for 1 h.
Et$_3$N (16.00 equiv.) was then added dropwise and the reaction mixture was allowed to warm to
room temperature and stirred for 1 h. The reaction mixture was quenched with aqueous
saturated NaHCO$_3$ solution (5 mL) and extracted into CH$_2$Cl$_2$ (3×3 mL). The combined organic
layers were washed with brine (10 mL), dried (Na$_2$SO$_4$) and concentrated under reduced
pressure to yield the desired aldehyde. All the aldehyde products prepared by the Swern method
were used for the next step without purification.
** tert-Butyl (S)-benzyl(1-oxopropan-2-yl)carbamate (217a)**

![Chemical Structure]

The corresponding amino alcohol 249a was obtained following the LiAlH₄ general procedure using N-benzyl-N-(tert-butoxycarbonyl)-amino propanoate 248a (1.5 g, 5.11 mmol) and LiAlH₄ (1 M solution in THF, 10.22 mL, 10.22 mmol, 2 equiv.) in THF (20 mL). Colourless oil (1.10 g, 81%). Rf (EtOAc/hexane = 4:6) = 0.41. ¹H NMR (500 MHz, CDCl₃) δ 1.11 (br s, 3H, CH₃), 1.39 (br s, 9H, C(CH₃)₃), 3.57 (br s, 2H, CH₂O), 4.04 (br s, 1H, CH), 4.38-4.41 (m, 2H, CH₂Ph), 7.20-7.31 (m, 5H, 5CH₃Ar). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 14.4, 28.1, 48.4, 55.0, 65.8, 80.5, 126.6, 128.6, 139.4, 156.7. The NMR data matched with those previously reported.¹⁹⁶

The title aldehyde 217a was obtained following the general TEMPO procedure using tert-butyl benzyl(1-hydroxypropan-2-yl)carbamate 249a (0.42 g, 1.58 mmol), saturated aqueous NaHCO₃ solution (15 mL), KBr (0.18 g, 1.58 mmol, 1.00 equiv.), TEMPO (12.35 mg, 0.079 mmol, 0.05 equiv.), and NaOCl (3.79 mL, 1.89 mmol, 1.20 equiv.) in CH₂Cl₂ (30 mL). Colourless oil (0.38 g, 91%). The ee was determined by chiral HPLC analysis of the corresponding alcohol (obtained by NaBH₄ reduction of a small quantity of the unpurified aldehyde) using a Phenomenex Lux i-Cellulose-5 column; hexane/isopropanol (95:5); flow rate = 0.5 mL/min; 210 nm; t_major = 23.29 min, t_minor = 25.15 min, 91% ee. ¹H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 1.26 (br d, 3H, J = 5.4 Hz, CH₃), 1.44 (s, 9H, C(CH₃)₃), 3.44 (br s, 0.6H, CH), 3.69 (br s, 0.4H, CH), 4.28 (d, 1H, J = 15.3 Hz, CH₃Ph), 4.65 (d, 0.4H, J = 15.3 Hz, CH₃Ph), 4.82 (d, 0.6H, J = 15.3 Hz, CH₃Ph), 7.26-7.35 (m, 5H, 5CH₃Ar), 9.42 (br s, 0.6H, CHO). 9.46 (br s, 0.4H, CHO). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of rotamers, minor rotamer indicated by asterisk) δ 11.8*, 12.6, 28.2, 50.9*, 51.1, 61.4, 81.1*, 81.6, 127.4*, 127.7, 128.1*, 128.7, 137.7, 138.1*, 154.9, 155.3*, 199.3. The NMR data matched with those previously reported.¹⁹⁷
The corresponding amino alcohol 249b was obtained following the LiAlH₄ general procedure using methyl 2-(benzyl(tert-butoxy carbonyl)amino)pentanoate 248b (0.80 g, 2.49 mmol) and LiAlH₄ (1 M solution in THF, 4.98 mL, 4.98 mmol, 2.00 equiv.) in THF (3 mL). Colourless oil (0.60 g, 82%). Rf (EtOAc/hexane = 4:6) = 0.61. [α]²² = +16.3 (c 4.6 CHCl₃). ¹H NMR (500 MHz, CDCl₃) (mixture of rotamers) δ 0.84 (br s, 3H, CH₃), 1.26 (br s, 2H, CH₂), 1.37 (br s, 7H, C(CH₃)₃, CH), 1.49 (br s, 4H, C(CH₃)₃, CH), 3.40-3.60 (m, 3H), 3.84-3.86 (m, 1H), 4.21-4.70 (m, 2H, CH₂Ph), 7.21-7.27 (m, 5H, 5CH₂Ar). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture of rotamers, minor rotamer indicated by asterisk) δ 13.9, 19.7, 28.3, 30.9, 31.7*, 48.2*, 49.3, 59.2, 64.1, 80.1, 126.9, 127.6, 128.3, 139.6, 156.9. IR (νmax/cm⁻¹) 3446 (m), 2959 (m), 2930 (m), 2873 (m), 1665 (m), 1465 (m), 1410 (s), 1341 (m), 1243 (m), 1166 (s), 1053 (w), 701 (s). HRMS (ESI-TOF) m/z calcd for C₁₇H₂₇NO₃Na [M + Na]⁺ 316.1889, found 319.1891.

The title aldehyde 217b was obtained following the general Swern procedure using methyl tert-butyl benzyl(1-hydroxypentan-2-yl)carbamate 249b (0.59 g, 2.01 mmol), oxalyl chloride (0.37 mL, 4.02 mmol, 2.00 equiv.), DMSO (0.61 mL, 8.04 mmol, 4.00 equiv.) and Et₃N 4.56 mL, 32.17 mmol, 16.00 equiv.) in CH₂Cl₂ (15 mL). Colourless oil (0.50 g, 85%). Rf (EtOAc/hexane = 1:9) = 0.43. [α]²² = −92.3 (c 7.0 CHCl₃). ¹H NMR (300 MHz, CDCl₃) (mixture of rotamers) δ 0.89 (t, 3H, J = 7.2 Hz, CH₃), 1.34-1.41 (m, 2H, CH₂), 1.45 (br s, 9H, C(CH₃)₃), 1.49-1.80 (m, 1H, CH), 1.89-1.99 (m, 1H, CH), 3.45 (br s, 0.6H, CH), 3.76 (br s, 0.4H, CH), 4.11-4.22 (m, 1H, CHPh), 4.70 (br d, 0.4H, J = 15.0 Hz, CHPh), 4.98 (br d, 0.6H, J = 15.0 Hz, CHPh), 7.26-7.35 (m, 5H, 5CH₂Ar), 9.35 (br s, 0.6H, CHO), 9.44 (br s, 0.4H, CHO). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of rotamers, minor rotamer indicated by asterisk) δ 13.8, 19.5, 28.1, 29.2*, 30.4, 51.4*, 51.8, 65.5, 80.9*, 81.3, 127.6, 128.3, 128.6, 137.7, 138.1*, 155.1, 199.5. IR (νmax/cm⁻¹) 2965 (m), 2933 (m), 2876 (w), 1739 (s), 1692 (s), 1452 (s), 1405 (s), 1365 (s), 1249 (s), 1180 (s), 1002 (m), 864 (m), 735 (s), 699 (s). HRMS (ESI-TOF) m/z calcd for C₁₇H₂₅NO₃Na [M + Na]⁺ 314.1732, found 314.1741.
(S)-tert-Butyl benzyl(4-methyl-1-oxopentan-2-yl)carbamate (217c)

\[
\text{CHO} \quad \text{NBnBoc}
\]

The title compound 217c was obtained following the general DIBAL-H procedure using methyl N-benzyl-N-(tert-butoxycarbonyl) leucinate 248c (0.58 g, 1.74 mmol) and DIBAL-H (dissolved in 0.70 mL n-hexane, 0.70 mL, 3.49 mmol, 2.00 equiv.) in Et2O (3 mL). Colorless oil (0.35 g, 65%). \text{Rf} (\text{EtOAc/hexane} = 4:6) = 0.52. \([\alpha]_D^{22} = -98.6 (c 6 \text{ CHCl}_3). \) \text{H NMR} (500 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 0.85-0.90 (m, 6H, 2\text{C}_\text{H}_3), 1.46 (s, 9H, C\text{(C}_\text{H}_3)\text{3}), 1.59-1.66 (m, 2H, CH\text{2}), 1.83-1.85 (m, 1H, CH), 3.55 (br s, 0.6H, CH), 3.89 (br s, 0.4H, CH), 4.12 (d, 0.6H, J = 15.5 Hz, CH\text{Ph}), 4.20 (d, 0.4H, J = 15.5 Hz, CH\text{Ph}), 4.70 (d, 0.4H, J = 15.5 Hz, CH\text{Ph}), 4.99 (d, 0.6H, J = 15.5 Hz, CH\text{Ph}), 7.27-7.34 (m, 5H, 5\text{C}_\text{H}_\text{Ar}), 9.34 (br s, 0.6H, CHO), 9.44 (br s, 0.4H, CHO). \text{13C{1H} NMR} (125 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 22.0, 23.0, 24.8, 28.2, 36.1, 37.4, 51.1, 51.4, 63.8, 81.0, 81.5, 127.6, 127.8, 128.3, 128.8, 137.8, 138.2, 155.2, 155.6, 200.1, 200.2. \text{IR} (\nu_{\text{max}}/\text{cm}^{-1}) 2957 (m), 2870 (w), 1735 (s), 1684 (s), 1454 (s), 1366 (s), 1245 (s), 1162 (s), 701 (s). \text{HRMS (ESI)} m/z calcd for C\text{18}H\text{27}N\text{O}_3\text{Na} [M + Na]^+ 328.1889, found 328.1898.

(S)-tert-Butyl benzyl(1-oxo-3-phenylpropan-2-yl)carbamate (217d)

\[
\text{Ph} \quad \text{CHO} \quad \text{NBnBoc}
\]

The title compound 217d was obtained following the general DIBAL-H procedure using methyl N-benzyl-N-(tert-butoxycarbonyl) phenylalaninate 248d (0.54 g, 1.46 mmol) and DIBAL-H (dissolved in 0.6 mL n-hexane, 0.58 mL, 2.92 mmol, 2 equiv.) in Et\textsubscript{2}O (3 mL). Colourless oil (0.31 g, 63%). \text{H NMR} (500 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 1.50 (s, 9H, C\text{(C}_\text{H}_3)\text{3}), 2.94 (m, 0.6H, CH\text{Ph}), 3.12 (d, 1H, J = 14.5 Hz, CH\text{Ph}), 3.24 (d, 0.4H, J = 15.5 Hz, CH\text{Ph}), 3.30 (d, 1H, J = 14.5 Hz, CH\text{Ph}), 3.57 (m, 1H, CH), 4.58 (d, 0.4H, J = 15.5 Hz, CH\text{Ph}), 4.87 (d, 0.6H, J = 15.5 Hz, CH\text{Ph}), 7.08-7.16 (m, 5H, 5\text{C}_\text{H}_\text{Ar}), 7.20-7.32 (m, 5H, 5\text{C}_\text{H}_\text{Ar}), 9.35 (s, 0.6H, CHO), 9.46 (s, 0.4H, CHO). \text{13C{1H} NMR} (125 MHz, CDCl\textsubscript{3}) (mixture of rotamers)
δ 28.3, 33.2, 34.3, 51.9, 52.4, 67.2, 67.6, 81.2, 81.9, 126.6, 126.8, 127.7, 127.8, 128.4, 128.7, 128.8, 129.3, 137.4, 137.7, 138.0, 138.8, 154.8, 155.4, 198.4, 198.6. The NMR data matched with those previously reported.\textsuperscript{189}

\textbf{(S)-\textit{tert}-Butyl benzyl(3-methyl-1-oxobutan-2-yl)carbamate (217e)}

![Chemical Structure](image)

The corresponding amino alcohol \textit{249e} was obtained following the general procedure using methyl \textit{N}-benzyl-N-\textit{(tert}-butoxycarbonyl) valinate \textit{248e} (1.00 g, 3.11 mmol) and LiAlH\textsubscript{4} (1 M solution in THF, 6.22 mL, 6.22 mmol, 2.00 equiv.) in THF (5 mL). Colourless oil (0.73 g, 80%). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 0.87 (br s, 3H, CH\textsubscript{3}), 0.94 (br s, 3H, CH\textsubscript{3}), 1.40 (br s, 5.4H, C(CH\textsubscript{3})\textsubscript{3}), 1.48 (br s, 3.6H, C(CH\textsubscript{3})\textsubscript{3}), 1.90 (br s, 0.4H, CH\textsubscript{2}), 2.27 (br s, 0.6H, CH\textsubscript{2}), 3.2 (br s, 0.6H, CH\textsubscript{2}), 3.70 (br s, 2.4H, CH\textsubscript{2}), 4.20 (br d, 1H, J = 14.5 Hz, CHO\textsubscript{Ph}), 4.53 (br d, 1H, J = 14.5 Hz, CHO\textsubscript{Ph}), 7.22-7.28 (m, 5H, 5CH\textsubscript{Ar}). \textsuperscript{13}C{\textsuperscript{1}H} NMR (125 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 20.1, 26.7, 28.3, 52.0, 62.2, 63.2, 66.1, 67.2, 80.2, 127.1, 127.4, 127.8, 128.4, 139.1, 157.0. The NMR data matched with those previously reported.\textsuperscript{198}

The title aldehyde \textit{217e} was obtained following the general TEMPO procedure using \textit{tert}-butyl benzyl(1-hydroxypropan-2-yl)carbamate \textit{249e} (0.38 g, 1.08 mmol), saturated aqueous NaHCO\textsubscript{3} solution (5 mL), KBr (0.128 g, 1.08 mmol, 1.00 equiv.), TEMPO (8.50 mg, 0.054 mmol, 0.05 equiv.), and NaOCl (2.6 mL, 1.30 mmol, 1.20 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL). Colourless oil (0.26 g, 83%). $[\alpha]_{D}^{26} = -62.8$ (c 1.0 CH\textsubscript{3}Cl). \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 0.89 (d, 3H, J = 6.5 Hz, CH\textsubscript{3}), 1.03 (d, 3H, J = 6.5 Hz, CH\textsubscript{3}), 1.43 (s, 9H, C(CH\textsubscript{3})\textsubscript{3}), 2.41-2.48 (m, 1H, CH\textsubscript{2}), 3.10 (br s, 0.6H, CH\textsubscript{2}), 3.38 (br s, 0.4H, CH\textsubscript{2}), 4.07 (br d, 0.6H, J = 13.0 Hz, CHO\textsubscript{Ph}), 4.18 (br d, 0.4H, J = 13.0 Hz, CHO\textsubscript{Ph}), 4.68 (br d, 0.6H, J = 13.0 Hz, CHO\textsubscript{Ph}), 5.02 (br d, 0.4H, J = 13.0 Hz, CHO\textsubscript{Ph}), 7.23-7.33 (m, 5H, 5CH\textsubscript{Ar}), 9.34 (br s, 0.6H, CHO), 9.50 (br s, 0.4H, CHO). \textsuperscript{13}C{\textsuperscript{1}H} NMR (125 MHz, CDCl\textsubscript{3}) (mixture of rotamers) δ 19.2,
20.7, 21.4, 27.2, 27.8, 28.1, 52.6, 52.9, 71.2, 80.69, 81.1, 127.6, 128.3, 128.4, 128.5, 137.7, 138.1, 155.1, 155.5, 198.2. The NMR data matched with those previously reported.195

**tert-Butyl benzyl(2-oxo-1-phenylethyl)carbamate (217f)**

The title compound 217f was obtained following the general DIBAL-H procedure using methyl 2-(benzyl(tert-butoxycarbonyl)amino)-2-phenylacetate 248f (0.76 g, 2.14 mmol) and DIBAL-H (dissolved in 0.85 mL n-hexane, 0.85 mL, 4.29 mmol, 2.00 equiv.) in Et2O (3 mL). Colourless oil (0.41 g, 59%). \( R_f \) (Et2O/hexane = 3:7) = 0.48. \([\alpha]_D^{22} = -35.1 \) (c 2.0 CHCl3). 1H NMR (300 MHz, CDCl3) δ 1.45 (s, 9H, C(CH3)3), 3.99 (d, 1H, \( J = 15.6 \) Hz, CH2Ph), 4.71-5.09 (m, 2H, CH2Ph and CH), 7.21-7.36 (m, 10H, 10CHAr), 9.61 (br s, 1H, CHO). 13C{1H} NMR (75 MHz, CDCl3) δ 28.2, 50.6, 69.1, 81.7, 127.4, 127.6, 128.00, 128.06, 128.10, 128.18, 128.3, 128.5, 128.7, 129.1, 133.6, 137.6, 156.0, 195.1. IR (\( \nu_{max}/cm^{-1} \)) 2979 (m), 2819 (w), 1738 (s), 1683 (s), 1452 (s), 1417 (s), 1366 (s), 1244 (s), 1155 (s), 1133 (s), 741 (s), 697 (s). HRMS (ESI) \( m/z \) calcd for C20H23NO3Na [M + Na]+ 348.1576, found 348.1567.

**((S)-tert-Butyl 3-(2-(benzyl(tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-indole-1-carboxylate (217g)**

The title aldehyde 217g was obtained following the general DIBAL-H procedure using tert-butyl 3-(2-(benzyl(tert-butoxycarbonyl)amino)-3-methoxy-3-oxopropyl)-1H-indole-1-carboxylate 248g’ (0.55 g, 1.08 mmol) and DIBAL-H (dissolved in 0.40 mL n-hexane, 0.42 mL, 2.16 mmol, 2.00 equiv.) in Et2O (3 mL). Light orange oil (0.398 g, 77%). \( R_f \)
(EtOAc/hexane = 2:8) = 0.63. \([\alpha]^{22}_D = -113.5 \text{ (c 9.8 CHCl}_3\text{).} \)

**1H NMR** (500 MHz, CDCl\textsubscript{3}) (mixture of rotamers) \(\delta 1.49 \text{ (s, 9H, C(CH}_3\textsubscript{3})}, 1.67 \text{ (s, 9H, C(CH}_3\textsubscript{3})}, 3.04-3.09 \text{ (m, 0.5H, CH)}, 3.29-3.31 \text{ (m, 0.5H, CH)}, 3.47-3.42 \text{ (m, 1H, CH)}, 3.52 \text{ (t, 1H, J = 16.0 Hz, CH)}, 3.74-3.77 \text{ (m, 1H, CHPh)}, 4.50 \text{ (d, 0.5H, J = 15.0 Hz, CHPh)}, 4.76 \text{ (d, 0.5H, J = 15.0 Hz, CHPh)}, 7.00 \text{ (br s, 2H, 2CH}_\text{Ar}), 7.19-7.24 \text{ (m, 4H, 4CH}_\text{Ar}), 7.31-7.41 \text{ (m, 3H, 3CH}_\text{Ar}), 8.16 \text{ (br s, 1H, CH}_\text{Ar}), 9.42 \text{ (s, 0.5H, CHO)}, 9.53 \text{ (0.5H, CHO)}. \(^{13}C\{1H\} \text{ NMR} \text{ (125 MHz, CDCl}_3\text{) (mixture of rotamers) \(\delta 22.7, 23.8, 28.2, 28.3, 52.0, 52.7, 65.3, 66.0, 76.9, 77.2, 77.4, 81.2, 81.8, 83.5, 83.6, 115.4, 115.5, 116.4, 116.7, 118.5, 118.7, 122.6, 124.2, 124.3, 124.5, 124.6, 127.6, 127.75, 127.78, 128.4, 128.63, 128.65, 130.1, 130.4, 135.6, 137.3, 137.5, 149.5, 154.8, 155.3, 198.6, 199.0. \text{ IR} \text{ (\(\nu_{max}/\text{cm}^{-1}\)) 2978 (m), 2814 (w), 2364 (w), 2163 (w), 1730 (s), 1733 (s), 1683 (s), 1452 (s), 1365 (s), 1308 (m), 1251 (s), 1154 (s), 1085 (s), 976 (m), 856 (s), 743 (s), 700 (s). \text{ HRMS} \text{ (ESI) m/z calced for C}_{28}H_{33}N_2O_5 [M – H]^+ 477.2389, found 477.2382.}

(S)-**tert-**Butyl 2-formylpyrrolidine-1-carboxylate (217h)

The title aldehyde 217h was obtained following the general DIBAL-H procedure using 1-(**tert**-butyl) 2-methyl pyrrolidine-1,2-dicarboxylate 248h (0.50 g, 2.18 mmol) and diisobutylaluminum hydride (dissolved in 1 mL n-hexane, 0.87 mL, 4.36 mmol, 2 equiv.) in diethyl ether (3 mL). Colorless oil (0.285 g, 65%). \(^1H\) NMR (300 MHz, CDCl\textsubscript{3}) (mixture of rotamers) \(\delta 1.43 \text{ (s, 5.4H, C(CH}_3\textsubscript{3})}, 1.48 \text{ (s, 3.6H, C(CH}_3\textsubscript{3})}, 1.86-2.18 \text{ (m, 4H, 2CH}_2\textsubscript{2}), 3.44-3.57 \text{ (m, 2H, CH}_2\textsubscript{2}), 4.04 \text{ (br m, 0.6H, CH)}, 4.18 \text{ (br m, 0.4H, CH)}, 9.46 \text{ (d, 0.6H, J = 2.7 Hz, CHO)}, 9.53 \text{ (br s, 0.4H, CHO)}. \(^{13}C\{1H\} \text{ NMR} \text{ (75 MHz, CDCl}_3\text{) (mixture of rotamers) 23.7, 24.4, 26.5, 27.7, 28.0, 28.1, 46.5, 46.6, 64.7, 64.8, 79.8, 80.2, 123.7, 154.6, 200.0, 200.3. The NMR data matched with those previously reported.\(^{199}\)
**N-Benzyl-4-methyl-N-(1-oxopropan-2-yl)benzenesulfonamide (220)**

The title compound 220 was obtained following the general DIBAL-H procedure using methyl N-benzyl-N-tosyl-alaninate S220 (0.20 g, 0.57 mmol) and DIBAL-H (dissolved in 0.2 mL n-hexane, 0.22 mL, 1.15 mmol, 2.00 equiv.) in Et₂O (1 mL). Colourless oil (0.127 g, 70%).

$^1$H NMR (500 MHz, CDCl₃) δ 1.13 (d, 3H, $J$ = 7.5 Hz, CH₃), 2.43 (s, 3H, CH₃), 4.12-4.16 (m, 1H, CH), 4.19 (d, 1H, $J$ = 15.0 Hz, CHPh), 4.52 (d, 1H, $J$ = 15.0 Hz, CHPh), 7.26-7.34 (m, 7H, 7CH₂), 7.76 (d, 2H, $J$ = 8.0 Hz, 2CH₂), 9.29 (s, 1H, CHO).

$^{13}$C NMR (125 MHz, CDCl₃) δ 11.2, 21.5, 49.2, 61.4, 127.3, 128.4, 128.85, 128.86, 130.0, 135.6, 137.0, 144.0, 198.9. The NMR data matched with those previously reported.

**2-(Dibenzylamino)propanal (223)**

The title compound 223 was obtained following the general DIBAL-H procedure using methyl dibenzyl alaninate S223 (0.50 g, 1.85 mmol) and DIBAL-H (dissolved in 0.70 mL n-hexane, 0.66 mL, 3.34 mmol, 1.80 equiv.) in diethyl ether (2 mL). Light yellow oil (0.285 g, 54%).

$^1$H NMR (300 MHz, CDCl₃) δ 1.16 (d, 3H, $J$ = 11.5 Hz, CH₃), 3.31 (q, 1H, $J$ = 6.9 Hz, CH), 3.54 (d, 2H, $J$ = 13.8 Hz, 2CHPh), 3.71 (d, 1H, $J$ = 13.8 Hz, 2CHPh), 7.20-7.40 (m, 10H, 10CH₂), 9.70 (s, 1H, CHO).

$^{13}$C NMR (125 MHz, CDCl₃) δ 6.87, 55.0, 62.9, 127.4, 128.4, 128.8, 139.0, 204.4. The NMR data matched with those previously reported.
General Procedure for Allenylation Reaction of Chiral Singly N-Protected α-Amino Aldehydes

To a solution of allenylboronic acid pinacol ester 71 (1.10 equiv.) and the amino aldehydes (205a-g, 208, 2011, 2014) in toluene at 0 °C, was added Et₂Zn (1 M in toluene, 10 mol%) under nitrogen. The mixture was then stirred at 0 °C for 18 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (1 mL), and washed with saturated aqueous NaHCO₃ solution (15 mL) and water (10 mL). The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane) to afford the allenyl amino alcohol products (206, 209, 212, 215). As mentioned in Chapter 2, no desired allene products 209 and 212 were obtained from the allenylation reaction of the aldehydes 208 and 211.

**tert-Butyl ((2S,3S)-3-hydroxyhexa-4,5-dien-2-yl)carbamate (206a)**

The title compound 206a was obtained after flash column chromatography (EtOAc/hexane = 3:7) as a 2.6:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl (1-oxopropan-2-yl)carbamate 205a (0.06 g, 0.34 mmol), allenylboronic acid pinacol ester 71 (69.0 μL, 0.37 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 35.7 μL, 0.034 mmol, 10 mol%) in dry toluene (1 mL). Yellow oil (0.067 g, 92%). Rf (EtOAc/hexane = 3:7) = 0.36.

**1H NMR** (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.12 (d, 3H, J = 6.5 Hz, CH₃, minor isomer), 1.19 (d, 3H, J = 7.0 Hz, CH₃, major isomer), 1.44 (s, 9H, C(CH₃)₃, for each isomer), 2.87 (br s, 1H, OH, major isomer),
3.17 (br s, 1H, OH, minor isomer), 3.71-3.75 (m, 1H, CH, major isomer), 3.75-3.82 (m, 1H, CH, minor isomer), 4.09 (br s, 1H, CH, major isomer), 4.23 (br s, 1H, CH, minor isomer), 4.86-4.90 (m, 2H, CH=CH=, for each isomer), 5.16-5.28 (m, 1H, CH=CH=, for each isomer). $^{13}$C{1H} NMR (125 MHz, CDCl$_3$) (mixture of two allene diastereomers, minor indicated by asterisk) δ 18.8, 19.9, 20.1, 28.3, 29.8, 30.0*, 60.4, 60.8*, 69.3, 69.4*, 76.8, 79.1, 79.2*, 90.7*, 93.0, 156.6, 156.7*, 207.4, 207.9*. IR (v$_{\text{max}}$/cm$^{-1}$) 3378 (w), 2976 (w), 1955 (w), 1506 (s), 1365 (m), 1257 (m), 1162 (s), 1051 (s), 1024 (s). HRMS (ESI-TOF) m/z calcd for C$_{11}$H$_{18}$NO$_3$ [M − H]$^+$ 212.1287, found 212.1289.

tert-Butyl ((2S)-3-hydroxyhex-5-yn-2-yl)carbamate (207a)

The title compound 207a was obtained after flash column chromatography (EtOAc/hexane = 3:7) as a 1:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl (1-oxopropan-2-yl)carbamate 205a (0.06 g, 0.34 mmol), allenylboronic acid pinacol ester 71 (69.0 μL, 0.37 mmol, 1.10 equiv.) and Et$_2$Zn (1 M in toluene, 18.0 μL, 0.017 mmol, 5 mol%) in dry THF (1 mL). Yellow oil (0.044 g, 60%). R$_f$ (EtOAc/hexane = 2:8) = 0.15. $^1$H NMR (500 MHz, CDCl$_3$) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.18 (d, 3H, J = 6.8 Hz, CH$_3$, for minor isomer), 1.24 (d, 3H, J = 6.8 Hz, CH$_3$, for minor isomer), 1.44 (s, 9H, C(CH$_3$)$_3$, for each isomer), 2.08 (t, 1H, J = 2.7 Hz, CH alkyne, for each isomer), 2.39-2.41 (m, 2H, CH$_2$, for minor isomer), 2.42-2.45 (m, 2H, CH$_2$, for major isomer), 3.00 (br s, 1H, OH, for major isomer), 3.13 (br s, 1H, OH, for minor isomer), 3.70-3.85 (m, 2H, 2CH, for each isomer), 4.85-4.91 (m, 1H, NH, for each isomer). $^{13}$C{1H} NMR (125 MHz, CDCl$_3$) (mixture of two allene diastereomers, minor indicated by asterisk) δ 14.8, 18.2, 23.7*, 24.7, 28.3, 38.47*, 38.49, 49.5, 50.1*, 70.7, 72.7*, 72.9, 79.6*, 79.7, 80.7, 155.9*, 156.2. IR (v$_{\text{max}}$/cm$^{-1}$) 3368 (w), 2980 (w), 2955 (w), 1683 (s), 1506 (s), 1365 (s), 1244 (s), 1163 (s), 845 (s). HRMS (ESI-TOF) m/z calcd for C$_{11}$H$_{20}$NO$_3$ [M + H]$^+$ 214.1443, found
The title compound 206b was obtained after flash column chromatography (EtOAc/hexane = 2:8) as a 5.2:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl(1-oxopentan-2-yl)carbamate 205b (0.149 g, 0.74 mmol), allenylboronic acid pinacol ester 71 (155.6 μL, 0.81 mmol, 1.1 equiv.) and Et₂Zn (1 M in toluene, 79.17 μL, 0.074 mmol, 10 mol%) in dry toluene (2 mL). Colorless oil (0.145 g, 81%). Rf (EtOAc/hexane = 2:8) = 0.45. ¹H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 0.92 (t, 3H, J = 7.0 Hz, CH₃, for each isomer), 1.31-1.40 (m, 3H, CH and CH₂, for each isomer), 1.43 (s, 9H, C(CH₃)₃, for each isomer), 1.50-1.56 (m, H, CH, for each isomer), 3.00 (br s, 1H, OH, minor isomer), 3.17 (br s, 1H, OH, major isomer), 3.59 (br s, 1H, CH, major isomer), 3.70-3.73 (m, 1H, CH, minor isomer), 4.16 (br s, 1H, CH, major isomer), 4.23 (br s, 1H, CH, minor isomer), 4.85-4.90 (m, 2H, CH₂=C=, major isomer), 4.94-4.96 (m, 2H, CH₂=C=, minor isomer), 5.18-5.27 (m, 1H, CH=CH=, for each isomer). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 13.9, 19.3, 28.3, 34.0, 34.2*, 54.9, 55.2*, 70.2*, 71.4, 77.3, 79.2, 79.4*, 90.5*, 92.3, 156.4, 156.5*, 207.6. IR (νmax/cm⁻¹) 3380 (m), 2959 (m), 1955 (m), 1683 (s), 1506 (s), 1365 (s), 1248 (s), 1166 (s), 1055 (s), 1018 (s), 843 (s). HRMS (ESI-TOF) m/z calcd for C₁₃H₂₃NO₃Na [M + Na]⁺ 264.1576, found 264.1573.

The title compound 206c was obtained after flash column chromatography (EtOAc/hexane =
2:8) as a 5.7:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl (4-methyl-1-oxopentan-2-yl)carbamate 205c (0.18 g, 0.83 mmol), allenylboronic acid pinacol ester 71 (176.56 μL, 0.92 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 88.80 μL, 0.083 mmol, 10 mol%) in dry toluene (2 mL). White solid (0.172 g, 81%). Mp = 38-40 °C. Rf (EtOAc/hexane = 2:8) = 0.37. ¹H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 0.92 (d, 6H, J = 6.0 Hz, 2CH₃, for each isomer), 1.27-1.39 (m, 1H, CH, for each isomer), 1.43 (s, 9H, C(CH₃)₃, for each isomer), 1.65-1.68 (m, 2H, CH₂, for each isomer), 3.11 (br s, 1H, OH, major isomer), 2.95 (br s, 1H, OH, minor isomer), 3.68 (br s, 1H, CH, major isomer), 3.70-3.80 (br s, 1H, CH, minor isomer), 4.12 (br s, 1H, CH, major isomer), 4.22 (br s, 1H, CH, minor isomer), 4.79-4.90 (m, 2H, CH=CH=, for each isomer), 5.18-5.20 (m, 1H, CH=CH=C=, minor isomer), 5.25-5.27 (m, 1H, CH=CH=C=, major isomer). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 22.0*, 23.2, 24.8, 28.3, 40.8, 41.3*, 53.2, 53.9*, 71.7, 72.5*, 76.8, 79.2, 79.7*, 91.2*, 92.3, 156.3, 156.5*, 207.6. IR (νmax/cm⁻¹) 3361 (m), 2956 (m), 1955 (m), 1504 (s), 1365 (s), 1248 (s), 1166 (s), 1047 (s), 843 (s). HRMS (ESI-TOF) m/z calcd for C₁₄H₂₅NO₃Na [M + Na]⁺ 278.1732, found 278.1720.

tert-Butyl ((2S,3S)-3-hydroxy-1-phenylhexa-4,5-dien-2-yl)carbamate (206d)

The title compound 206d was obtained after flash column chromatography (EtOAc/hexane = 3:7) as a 2.5:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl (1-oxo-3-phenylpropan-2-yl)carbamate 205d (0.093 g, 0.373 mmol), allenylboronic acid pinacol ester 71 (78.78 μL, 0.41 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 40.00 μL, 0.0373 mmol, 10 mol%) in dry toluene (1 mL). White solid (0.087 g, 80%). Mp = 60-62 °C. Rf (EtOAc/hexane = 3:7) = 0.53. ¹H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.36 (s, 9H, C(CH₃)₃, minor
isomer), 1.43 (s, 9H, C(CH₃)₃, major isomer), 2.61 (br s, 1H, OH, major isomer), 2.88-2.96 (m, 2H, CH₂Ph, for each isomer), 3.76 (br s, 1H, CH, minor isomer), 3.82 (br s, 1H, CH, major isomer), 4.15 (br s, 1H, CH, major isomer), 4.27 (br s, 1H, CH, minor isomer), 4.85-4.91 (m, 2H, CH₂=C=, for each isomer), 5.24-5.29 (m, 1H, CH=C=, for each isomer), 7.19-7.29 (m, 5H, 5CHAr, for each isomer). $^{13}$C{¹H} NMR (125 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 28.5, 36.1*, 38.2, 56.1*, 56.4, 69.4, 77.9*, 78.0, 79.4, 79.8*, 91.2*, 92.6, 126.3*, 126.6, 128.4, 129.2*, 129.32*, 129.37, 138.0*, 138.2, 156.0, 207.4*, 207.6. IR ($ν_{max}$/cm⁻¹) 3379 (m), 2981 (w), 2358 (s), 1954 (w), 1675 (s), 1521 (s), 1452 (m), 1248 (s), 1168 (s), 1002 (m), 837 (s), 759 (m), 703 (s). HRMS (ESI-TOF) m/z calcld for C₁₇H₂₄NO₃ [M + H]^+ 290.1756, found 290.1751.

tert-Butyl ((3S,4S)-4-hydroxy-2-methylhepta-5,6-dien-3-yl)carbamate (206e)

The title compound 206e was obtained after flash column chromatography (EtOAc/hexane = 2:8) as a 9:1 mixture of syn and anti diastereomers following the general procedure using tert-butyl (3-methyl-1-oxobutan-2-yl)carbamate 205e (0.10 g, 0.496 mmol), allenylboronic acid pinacol ester 71 (103.75 μL, 0.54 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 37.14 μL, 0.035 mmol, 7 mol%) in dry toluene (1 mL). White solid (0.106 g, 88%). Mp = 39-41 °C. Rf (EtOAc/hexane = 2:8) = 0.35. $^1$H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 0.94 (d, 3H, J = 6.5 Hz, CH₃, for each isomer), 0.99 (d, 3H, J = 6.5 Hz, CH₃, for each isomer), 1.44 (s, 9H, C(CH₃)₃, for each isomer), 1.87-1.93 (m, 1H, CH, for each isomer), 2.68 (br s, 1H, OH, minor isomer), 2.80 (br s, 1H, OH, major isomer), 3.20-3.23 (m, 1H, CH, minor isomer), 3.26-3.29 (m, 1H, CH, major isomer), 4.28 (br s, 1H, CH, minor isomer), 4.33 (br s, 1H, CH, major isomer), 4.85-4.93 (m, 2H, CH₂=C=, for each isomer), 5.19-5.21 (m, 1H, CH=C=, minor isomer), 5.25-5.26 (m, 1H, CH=C=, major isomer). $^{13}$C{¹H} NMR (125 MHz, CDCl₃) (mixture of two allene
diastereomers, minor indicated by asterisk) δ 18.8, 19.9, 20.1, 28.3, 29.8, 30.0*, 60.4, 60.8*, 69.3, 69.4*, 76.8, 79.1, 79.2*, 90.7*, 93.0, 156.6, 156.7*, 207.4, 207.9*. IR (νmax/cm⁻¹) 3373 (m), 2979 (m), 2361 (m), 1955 (w), 1662 (s), 1525 (s), 1367 (s), 1245 (s), 1166 (s), 1018 (m), 869 (m), 684 (m). HRMS (ESI-TOF) m/z calcd for C₁₃H₂₃NO₃Na [M + Na]⁺ 264.1576, found 264.1581.

**tert-Butyl ((1S,2S)-2-hydroxy-1-phenylpenta-3,4-dien-1-yl)carbamate (206f)**

![Chemical Structure](Ph<sub>●</sub>OH<br>\[
\text{NHBoc}
\]

The title compound **206f** was obtained after flash column chromatography as a 5.5:1 mixture of *syn* and *anti* diastereoisomers following the general procedure using *tert*-butyl (2-oxo-1-phenylethyl)carbamate **205f** (0.15 g, 0.637 mmol), allenylboronic acid pinacol ester **71** (133.80 μL, 0.70 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 68.00 μL, 0.0637 mmol, 10 mol%) in dry toluene (2 mL). White solid (0.124 g, 70%). Mp = 96-98 °C. **R<sub>f</sub>** (EtOAc/hexane = 3:7) = 0.51. **¹H NMR** (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.42 (br s, 9H, C(CH₃)₃, for each isomer), 2.71 (br s, 1H, OH, for each isomer), 4.39 (br s, 1H, CH, for each isomer), 4.71-4.87 (m, 3H, CH₂=C= and CH, for each isomer), 5.22 (q, 1H, J = 6.0 Hz, CH=C=, for minor isomer), 5.47-5.52 (m, 2H, CH₂=C=, for major isomer), 7.25-7.32 (m, 5H, 5CH<sub>Ar</sub>, for each isomer). **¹C<sup>1</sup>H NMR** (125 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 28.3, 59.1, 72.3*, 72.7, 77.9, 79.8, 91.0*, 91.9, 126.7*, 127.0, 127.5, 127.6*, 128.3*, 128.5, 140.0, 156.0, 156.1*, 207.6*, 207.7. IR (νmax/cm⁻¹) 3392 (m), 2979 (w), 2358 (s), 1949 (w), 1683 (s), 1507 (s), 1368 (m), 1166 (m), 1019 (m), 838 (m), 699 (s). HRMS (ESI) m/z calcd for C₁₆H₂₁NO₃Na [M + Na]⁺ 298.1419, found 298.1426.
**tert-Butyl** 3-((2S,3S)-2-((tert-butoxycarbonyl)amino)-3-hydroxyhexa-4,5-dien-1-yl)-1H-indole-1-carboxylate (206g)

The title compound 206g was obtained after flash column chromatography (EtOAc/hexane = 2:8) as a 2.5:1 mixture of *syn* and *anti* diastereomers following the general procedure using tert-butyl 3-(2-(tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-indole-1-carboxylate 205g (0.05 g, 0.128 mmol), allenylboronic acid pinacol ester 71 (27.00 μL, 0.14 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 14.00 μL, 0.0128 mmol, 10 mol%) in dry toluene (1 mL). Colourless oil (0.043 g, 78%). \( R_f \) (EtOAc/hexane = 2:8) = 0.33. \(^1\)H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.39 (s, 9H, C(CH₃)₃, minor isomer), 1.42 (s, 9H, C(CH₃)₃, major isomer), 1.65 (s, 9H, C(CH₃)₃, for each isomer), 2.52 (br s, 1H, OH, major isomer), 2.91-3.06 (m, 2H, CH₂, for each isomer), 3.93 (br s, 1H, CH, major isomer), 4.06 (br s, 1H, CH, minor isomer), 4.23 (br s, 1H, CH, major isomer), 4.32 (br s, 1H, CH, minor isomer), 4.87-5.04 (m, 2H, CH₂=C=, for each isomer), 5.26-5.32 (m, 1H, CH=C=, for each isomer), 7.22-7.66 (m, 4H, 4CHAr, for each isomer), 8.13 (br s, 1H, CHAr, for each isomer). \(^{13}\)C\(^{(1}\)H) NMR (125 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 28.2, 28.3*, 54.7, 55.3*, 69.3, 71.7*, 78.1*, 78.3, 79.5, 79.8*, 83.5, 91.3*, 92.6, 115.21, 115.27*, 116.8*, 117.0, 119.0, 119.2*, 122.5, 123.9, 124.41, 124.46*, 130.7, 135.4, 149.7, 156.1, 207.4, 207.5*. IR (νmax/cm\(^{-1}\)) 3385 (w), 2975 (w), 2930 (w), 1955 (w), 1730 (s), 1684 (s), 1507 (m), 1452 (s), 1367 (s), 1252 (s), 1157 (s), 1085 (s), 1015 (m), 852 (m), 744 (s). HRMS (ESI-TOF) m/z calcd for C₂₃H₂₂N₂O₃Na [M + Na]⁺ 451.2209, found 451.2227.
2-(Tritylamino)hexa-4,5-dien-3-ol (215)

The title compound 215 was obtained after flash column chromatography (Et₂O/hexane = 2:8) as a 1.3:1 mixture of syn and anti diastereomers following the general procedure using 2-(tritylamino)propanal 214 (0.10 g, 0.317 mmol), allenylboronic acid pinacol ester 71 (78.00 μL, 0.41 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 34.0 μL, 0.0317 mmol, 10 mol%) in dry toluene (1 mL). Colourless oil (0.093 g, 82%). Rf (Et₂O/hexane = 2:8) = 0.41. ¹H NMR (300 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 0.43 (d, 3H, J = 6.6 Hz, CH₃, minor isomer), 0.75 (d, 3H, J = 6.6 Hz, CH₃, major isomer), 2.23 (br s, 1H, NH, for each isomer), 2.69-2.77 (m, 1H, CH, for each isomer), 3.40-3.43 (m, 1H, CH, for each isomer), 4.74-4.77 (m, 2H, CH₂=C, major isomer), 4.80-4.83 (m, 2H, CH₂=C, minor isomer), 4.98 (q, 1H, J = 6.0, 6.3 Hz, CH=C, major isomer), 5.22 (q, 1H, J = 6.6 Hz, CH=C, minor isomer), 7.15-7.28 (m, 10H, 10CHAr, for each isomer), 7.54 (d, 5H, J = 7.8 Hz, 5CHAr, for each isomer). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of two allene diastereomers, minor indicated by asterisk) δ 15.9, 17.1*, 52.6, 53.0*, 71.2, 71.3*, 73.2*, 76.6, 91.7*, 92.2, 126.4, 127.9, 128.7, 128.8*, 146.73, 146.76*, 207.1, 207.9*. IR (νmax/cm⁻¹) 3385 (w), 3056 (w), 2970 (w), 1952 (m), 1490 (s), 1447 (s), 1031 (s), 845 (s), 744 (s), 705 (s).


**General Procedure for Base-catalyzed Cyclization of N-Boc Allenylamino Alcohols**

To a solution of the allenyl product 206 in dry THF was added NaH (60% in mineral oil, 2.00 equiv.) at 0 °C and the reaction mixture was stirred at room temperature for 90 min. The
reaction mixture was quenched by saturated aqueous NH₄Cl solution, washed with water (10 mL), dried (MgSO₄), and then purified by flash column chromatography (acetone/n-pentane) to afford the corresponding oxazolidinone products 229.

(4S,5S)-4-Methyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (229a)

The title compound 229a was obtained as a single diastereomer following the general procedure using 206a (0.060 g, 0.28 mmol) and NaH (60% in mineral oil, 18.81 mg, 0.56 mmol, 2.00 equiv.) in THF (1.0 mL). Colourless oil (0.024 g, 61%). \( [\alpha]_D^{12} = -30.3 \) (c 1.2 CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 1.28 (d, 3H, \( J = 6.0 \) Hz, \( CH_3 \)), 3.75-3.80 (m, 1H, \( CH \)), 4.55 (t, 1H, \( J = 7.0 \) Hz, \( CH \)), 4.93-5.00 (m, 2H, \( CH_2=CH= \)), 5.32 (q, 1H, \( J = 7.0 \) Hz, \( CH=CH= \)), 6.02 (br s, 1H, NH). \(^1\)C\(^{1}\)H NMR (125 MHz, CDCl₃) \( \delta \) 20.0, 54.0, 78.6, 81.6, 89.0, 158.9, 209.2. IR (\( \nu_{max}/\text{cm}^{-1} \)) 3272 (m), 2926 (w), 1955 (w), 1739 (s), 1378 (m), 1003 (s), 942 (s), 855 (s), 770 (m). HRMS (ESI-TOF) \( m/z \) calcd for C₇H₉NO₂Na [M + Na]^⁺ 162.0531, found 162.0537.

(4S,5S)-5-(Propa-1,2-dien-1-yl)-4-propyloxazolidin-2-one (229b)

The title compound 229b was obtained as a single diastereomer after column chromatography (acetone/n-pentane = 2:8) following the general procedure using 206b (0.067 g, 0.28 mmol) and NaH (60% in mineral oil, 18.81 mg, 0.56 mmol, 2.00 equiv.) in THF (1.0 mL). Colorless oil (0.026 g, 55%). \( [\alpha]_D^{12} = -24.9 \) (c 1.3 CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 0.95 (t, 3H, \( J = 7.0, 7.5 \) Hz, \( CH_3 \)), 1.32-1.43 (m, 2H, \( CH_2 \)), 1.54-1.57 (m, 2H, \( CH_2 \)), 3.67 (q, 1H, \( J = 6.5 \) Hz, \( CH \)), 4.62-4.65 (m, 1H, \( CH \)), 4.96-4.99 (m, 2H, \( CH_2=CH= \)),
5.34 (q, 1H, J = 6.5, 7.0 Hz, CH=C=), 6.51 (br s, 1H, NH). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) δ 73.7, 78.6, 96.7, 117.8, 138.4, 140.0, 149.4, 219.0, 268.8. IR (υ$_{max}$/cm$^{-1}$) 3266 (m), 2959 (m), 2932 (m), 1955 (m), 1742 (s), 1387 (s), 1239 (s), 1239 (s), 978 (s), 852 (s), 767 (s). HRMS (ESI-TOF) m/z calcd for C$_9$H$_{12}$NO$_2$ [M − H]$^+$ 166.0862, found 166.0870.

(4S,5S)-4-Isobutyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (229c)

The title compound 229c was obtained as a single diastereomer after column chromatography (acetone/n-pentane = 2:8) following the general procedure using 206c (0.05 g, 0.195 mmol) and NaH (60% in mineral oil, 18.81 mg, 0.39 mmol, 2.00 equiv.) in THF (1 mL). Colorless oil (0.021 g, 58%). R$_f$ (acetone/n-pentane = 2:8) = 0.30. [α]$_D^{22}$ = −32.6 (c 1 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 0.91-0.93 (m, 6H, 2CH$_3$), 1.38-1.43 (m, 1H, CH), 1.48-1.53 (m, 1H, CH), 1.61-1.68 (m, 1H, CH), 3.70-3.74 (m, 1H, CH), 4.58-4.61 (m, 1H, CH), 4.93-5.00 (m, 2H, CH$_2$=C=), 5.33 (q, 1H, J = 6.5 Hz, CH=C=), 6.28 (br s, 1H, NH). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) δ 22.2, 23.1, 25.2, 44.1, 56.5, 78.6, 80.5, 89.5, 159.1, 209.1. IR (υ$_{max}$/cm$^{-1}$) 3256 (m), 2962 (m), 2932 (m), 1956 (w), 1742 (s), 1387 (m), 1228 (m), 993 (m), 852 (m), 734 (m). HRMS (ESI-TOF) m/z calcd for C$_{10}$H$_{15}$NO$_2$Na [M + Na]$^+$ 204.0995, found 204.0996.

(4S,5S)-4-Isopropyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (229d)

The title compound 229d was obtained as a 4.3:1 mixture of two diastereomers after column chromatography (acetone/n-pentane = 2:8) following the general procedure using 206d (0.10 g, 0.414 mmol) and NaH (60% in mineral oil, 27.88 mg, 0.83 mmol, 2.00 equiv.) in THF (1 mL). Milky oil (0.106 g, 74%). R$_f$ (acetone/n-pentane = 2:8) = 0.44. $^1$H NMR (500 MHz,
CDCl$_3$) (mixture of two diastereomers, relative integrations given for each diastereomer) $\delta$ 0.94 (br d, 3H, $J = 6.5$ Hz, $CH_3$, major isomer), 0.98 (br d, 3H, $J = 6.0$ Hz, $CH_3$, major isomer), 0.99 (br d, 3H, $J = 6.0$ Hz, $CH_3$, minor isomer), 1.77 (br s, 1H, $CH$, major isomer), 1.90 (br s, 1H, $CH$, minor isomer), 3.45 (br s, 1H, $CH$, major isomer), 3.61-3.63 (m, 1H, $CH$, major isomer), 4.74 (br s, 1H, $CH$, major isomer), 4.92-4.97 (m, 2H, $CH_2=C=,$ for each isomer), 5.04-5.06 (m, 1H, $CH$, minor isomer), 5.32-5.37 (m, 1H, $CH=C=,$ for each isomer), 6.58 (br s, 1H, $NH$, minor isomer), 6.66 (br s, 1H, $NH$, major isomer). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) (mixture of two diastereomers, minor indicated by asterisk) $\delta$ 17.93, 17.97, 28.1*, 32.3, 62.3*, 63.5, 75.5*, 78.0, 78.6, 78.7*, 85.9*, 90.4, 159.1, 159.8*, 208.7, 210.0*. $^{-}$IR $\nu$max/cm$^{-1}$ 3260 (m), 2963 (m), 1955 (w), 1743 (s), 1387 (m), 993 (m), 851 (m), 734 (m). $^{-}$HRMS (ESI-TOF) m/z calcd for C$_9$H$_{13}$NO$_2$Na [M + Na]$^+$ 190.0838, found 190.0840.

(4S,5S)-4-Benzyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (229e)

The title compound 229e was obtained as a 3:1 mixture of two diastereomers after column chromatography (acetone/n-pentane = 2:8) following the general procedure using 206e (0.087 g, 0.30 mmol) and NaH (60% in mineral oil, 20.16 mg, 0.60 mmol, 2.00 equiv.) in THF (1.0 mL). Colorless oil (0.041 g, 63%). $R_t$ (acetone/n-pentane = 2:8) = 0.31. $^1$H NMR (500 MHz, CDCl$_3$) (mixture of two diastereomers, relative integrations given for each diastereomer) $\delta$ 2.70-2.75 (m, 2H, $CH_2$Ph, minor isomer), 2.86-2.90 (m, 2H, $CH_2$Ph, major isomer), 3.90 (q, 1H, $J = 6.5$ Hz, $CH$, major isomer), 4.10-4.14 (m, 1H, $CH$, minor isomer), 4.72 (t, 1H, $J = 6.0$ Hz, $CH$, major isomer), 4.84-4.93 (m, 2H, $CH_2=C=,$ major isomer), 4.96-4.98 (m, 2H, $CH_2=C=,$ minor isomer), 5.13 (t, 1H, $J = 8.0$ Hz, $CH$, minor isomer), 5.24 (q, 1H, $J = 6.5$, 7.0 Hz, $CH=C=,$ major isomer), 5.35 (q, 1H, $J = 7.0$ Hz, $CH=C=,$ minor isomer), 5.65 (br s, 1H, $NH$, minor
isomer), 6.19 (br s, 1H, NH, major isomer), 7.16 (d, 2H, J = 7.5 Hz, 2CHAr, for each isomer), 7.22-7.25 (m, 1H, CHAr, for each isomer), 7.29-7.32 (m, 2H, 2CHAr, for each isomer). \(^1\)C\(^{1}\)H NMR (125 MHz, CDCl\(_3\)) (mixture of two diastereomers, minor indicated by asterisk) \(\delta\) 37.5*, 40.9, 57.5*, 59.3, 78.0*, 78.3*, 78.7, 79.3, 86.3*, 89.5, 127.33, 127.39*, 129.10, 129.18*, 129.2*, 129.4, 136.0, 136.9*, 158.7, 209.0, 210.0*. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)) 3267 (w), 2917 (w), 1955 (w), 1743 (s), 1386 (m), 1230 (s), 992 (s), 854 (s), 699 (s). **HRMS** (ESI-TOF) \(m/z\) calcd for C\(_{13}\)H\(_{13}\)NO\(_2\)Na [M + Na]\(^+\) 238.0838, found 238.0840.

\(\textbf{(4S,5S)-4-Phenyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (229f)}\)

The title compound 229f was obtained as a single diastereoisomer after careful column chromatography following the general procedure from 206f (0.094 g, 0.34 mmol) and NaH (60% in mineral oil, 22.88 mg, 0.68 mmol, 2.00 equiv.) in THF (1.0 mL). White solid (0.050 g, 66%). Mp = 68-70 °C. \(R_f\) (2% CH\(_2\)Cl\(_2\)/Et\(_2\)O) = 0.78. \([\alpha]_D^{22} = -38.5 \text{ (c 2.2 CHCl}_3)\). \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 4.78 (s, 2H, 2CH), 4.96-5.04 (m, 2H, CH\(_2\)=C=), 5.43-5.44 (m, 1H, CH=C=), 6.33 (s, 1H, NH), 7.33-7.40 (m, 5H, 5CH\(_{Ar}\)). \(^1\)C\(^{1}\)H NMR (125 MHz, CDCl\(_3\)) \(\delta\) 61.7, 78.9, 82.2, 88.8, 126.2, 128.8, 129.1, 138.6, 158.8, 209.2. IR (\(\nu_{\text{max}}/\text{cm}^{-1}\)) 3266 (m), 3160 (m), 1958 (w), 1717 (s), 1387 (s), 1228 (s), 1012 (m), 857 (m), 736 (m), 700 (s). **HRMS** (ESI) \(m/z\) calcd for C\(_{12}\)H\(_{11}\)NO\(_2\)Na [M + Na]\(^+\) 224.0687, found 224.0692.
**tert-Butyl 3-(((4R,5R)-2-oxo-5-(propa-1,2-dien-1-yl)oxazolidin-4-y1)methyl)-1H-indole-1-carboxylate (229g)**

The title compound 229g was obtained as a single diastereomer after careful column chromatography (acetone/n-pentane = 2:8) following the general procedure using 206g (0.036 g, 0.084 mmol) and NaH (60% in mineral oil, 5.68 mg, 0.168 mmol, 2.00 equiv.) in THF (1.0 mL). Colourless gummy oil (0.015 g, 50%). $R_f$ (acetone/n-pentane = 2:8) = 0.26. $[\alpha]_D^{22} = -35.8$ (c 0.7 CHCl3). $^1$H NMR (500 MHz, CDCl3) $\delta$ 1.68 (s, 9H, C(CH3)3), 2.90-2.94 (m, 1H, CH), 3.00-3.04 (m, 1H, CH), 4.03 (br s, 1H, CH), 4.81 (br s, 1H, CH), 4.96 (br s, 2H, CH2=C=), 5.19 (br s, 1H, NH), 5.37 (br d, 1H, J = 6.5 Hz, CH=C=), 7.26 (br s, 1H, CHAr), 7.34-7.37 (m, 1H, CHAr), 8.15 (br s, 1H, CHAr). $^{13}$C{1H} NMR (125 MHz, CDCl3) $\delta$ 28.2, 30.5, 57.5, 78.8, 79.4, 84.0, 89.2, 114.9, 115.5, 118.5, 122.8, 123.9, 124.9, 129.7, 135.6, 149.4, 157.7, 208.8. IR (bmax/cm$^{-1}$) 3277 (w), 2982 (w), 2357 (w), 1955 (w), 1751 (s), 1730 (s), 1575 (s), 1368 (s), 1255 (s), 1155 (s), 1086 (m), 854 (m). HRMS (ESI-TOF) m/z calcd for C20H23N2O4 [M + H]+ 355.1658, found 355.1664.

**4S,5R)-3-Benzyl-4-methyl-5-(propa-1,2-dien-1-yl)oxazolidin-2-one (230a)**

To a solution of the allenyl product 218a (0.09 g, 0.29 mmol) in dry THF (1 mL) was added NaH (60% in mineral oil, 16.00 mg, 0.59 mmol, 2.00 equiv.) at 0 °C. The reaction was stirred at room temperature for 60 min. Then, the reaction mixture was quenched with saturated aqueous NH4Cl solution (5 mL), washed with water (10 mL) and dried (MgSO4). Purification by flash column chromatography (EtOAc/hexane = 3:7) afforded the corresponding oxazolidinone product 230a. Light yellow oil (0.022 g, 33%). $R_f$ (EtOAc/hexane = 3:7) = 0.40.
$[\alpha]_D^{22} = -56.7$ (c 1.7 CHCl$_3$). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 1.14 (d, 3H, $J = 6.6$ Hz, CH$_3$), 3.69-3.78 (m, 1H, CH), 4.03 (d, 1H, $J = 15.3$ Hz, CHPh), 4.82 (d, 1H, $J = 15.0$ Hz, CHPh), 4.86-4.98 (m, 3H, CH$_2$=C= and CH), 5.17-5.24 (m, 1H, CH=C=), 7.25-7.37 (m, 5H, 5CH$_2$Ar). $^{13}$C($^1$H)NMR (75 MHz, CDCl$_3$) $\delta$ 13.7, 45.7, 53.3, 76.1, 77.6, 86.1, 127.9, 128.0, 128.8, 135.9, 157.5, 209.7. IR ($\nu_{\text{max}}$/cm$^{-1}$) 2924 (w), 2358 (w), 1358 (w), 1743 (s), 1675 (m), 1414 (s), 1243 (m), 1159 (m), 761 (m), 700 (s). HRMS (ESI-TOF) $m/z$ calcd for C$_{14}$H$_{15}$NO$_2$Na $[M + Na]^+$ 252.1000, found 252.1003.

**Synthesis of O-Protected α-Hydroxy Aldehydes (242a-c)**

O-protected α-hydroxy aldehydes 242a-c were prepared from commercially available ethyl (S)-lactate including O-protection reaction followed by reduction with DIBAL-H.

To a solution of O-protected α-hydroxy ester S242 in Et$_2$O at −78 °C, was added dropwise diisobutylaluminum hydride (DIBAL-H) (1 M solution in hexane, 1.05 equiv.) over a period of 45 min. The mixture was stirred at the same temperature for 1.5 h, and then quenched by the addition of precooled MeOH (1 mL). The reaction mixture was allowed to warm to room temperature, ice (5 g) was added with heavy agitation, filtered through a sintered funnel and the filtrate was extracted with CH$_2$Cl$_2$. The organic layer was washed with brine (10 mL), dried (Na$_2$SO$_4$), and concentrated under reduced pressure to yield the title aldehyde 188a-c, which was used for the next step without purification.
**Ethyl (S)-2-(benzyloxy)propanoate (S242a)**

![Chemical Structure](image)

To a solution of ethyl (S)-lactate (2.00 mL, 17.64 mmol) and BnBr (2.22 mL, 19.40 mmol, 1.10 equiv.) in THF (15 mL) at 0 °C, was added NaH (0.83 g, 21.17 mmol, 1.20 equiv.) under nitrogen. The mixture was then stirred at 0 °C for 15 min followed by stirring at room temperature for 18 h. The reaction mixture was quenched with saturated aqueous NaHCO₃ solution (1 mL), and then washed with water (20 mL). The organic layer was dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash column chromatography (Et₂O/hexane = 2:8) to afford the resulting O-Bn α-hydroxy ester S242a. Colourless oil (2.89 g, 79%).

**1H NMR** (500 MHz, CDCl₃) δ 1.26 (t, 3H, J = 7.0 Hz, CH₃), 1.42 (d, 3H, J = 7.0 Hz, CH₃), 4.03 (q, 1H, J = 6.5 Hz, CH), 4.16-4.21 (m, 2H, CH₂), 4.43 (d, 1H, J = 11.5 Hz, CHPh), 4.68 (d, 1H, J = 11.5 Hz, CHPh), 7.24-7.36 (m, 5H, 5CH₃). **13C{1H} NMR** (125 MHz, CDCl₃) δ 14.2, 18.7, 60.8, 71.98, 71.99, 74.0, 127.8, 127.9, 128.4, 137.6, 173.2. The NMR data matched with those previously reported. ²⁰²

**O-BnCHO**

![Chemical Structure](image)

The title aldehyde 242a was obtained following the general DIBAL-H procedure using ethyl (S)-2-(benzyloxy)propanoate S242a (0.287 g, 1.38 mmol) and DIBAL-H (dissolved in 0.30 mL n-hexane, 0.28 mL, 1.45 mmol, 1.05 equiv.) in Et₂O (5 mL). Colourless oil (0.147 g, 65%). **1H NMR** (500 MHz, CDCl₃) δ 1.32 (dd, 3H, J = 6.9, 4.1 Hz, CH₃), 3.86-3.91 (m, 1H, CH), 4.57-4.66 (m, 2H, CH₂Ph), 7.29-7.36 (m, 5H, 5CH₃). **13C{1H} NMR** (125 MHz, CDCl₃) δ 15.3, 72.0, 79.4, 127.9, 128.0, 128.1, 128.6, 137.3, 203.4. The NMR data matched with those previously reported.²⁰²
Ethyl (S)-2-((tert-butyldimethylsilyl)oxy)propanoate (S242b)

\[
\text{CO}_2\text{Et} \\
\text{OTBS}
\]

To a solution of ethyl (S)-lactate (1.00 mL, 8.82 mmol) and TBSCI (2.22 mL, 17.62 mmol, 2.00 equiv.) in DMF (15 mL), was added imidazole (1.50 g, 22.05 mmol, 2.50 equiv.) under nitrogen and stirred at room temperature for 24 h. The reaction mixture was then poured into water (20 mL) and extracted with EtOAc (3×10 mL). The organic layer was washed with water (10 mL), dried (Na₂SO₄), concentrated under reduced pressure, and purified by flash column chromatography (Et₂O/hexane = 2:8) to afford the resulting O-TBS α-hydroxy ester S242b. Colourless oil (1.85 g, 90%).

\(^1\)H-NMR (500 MHz, CDCl₃) δ 0.04 (s, 3H, CH₃ for TBS), 0.07 (s, 3H, CH₃ for TBS), 0.89 (s, 9H, (CH₃)₃ in TBS), 1.25 (t, 3H, J = 7.1 Hz, CH₃), 1.36 (d, 3H, J = 6.7 Hz, CH₃), 4.11-4.19 (m, 2H, CH₂), 4.28 (q, 1H, J = 6.5, 7.0 Hz, CH). \(^13\)C{\(^1\)H} NMR (125 MHz, CDCl₃) δ -5.3, -5.0, 14.1, 18.2, 21.2, 25.65, 25.66, 60.6, 68.3, 173.9. The NMR data matched with those previously reported.²⁰³

(S)-2-((tert-Butyldimethylsilyl)oxy)propanal (242b)

\[
\text{CHO} \\
\text{OTBS}
\]

The title aldehyde 242b was obtained following the general DIBAL-H procedure using ethyl (S)-2-((tert-butyldimethylsilyl)oxy)propanoate S242b (0.95 g, 4.088 mmol) and DIBAL-H (dissolved in 1.0 mL n-hexane, 0.80 mL, 4.29 mmol, 1.05 equiv.) in Et₂O (5 mL). Colourless oil (0.561 g, 73%). \(^1\)H NMR (500 MHz, CDCl₃) δ 0.05 (s, 3H, CH₃ for TBS), 0.06 (s, 3H, CH₃ for TBS), 0.89 (s, 9H, (CH₃)₃ in TBS), 9.56 (s, 1H, CHO). \(^13\)C{\(^1\)H} NMR (125 MHz, CDCl₃) δ -4.67, -4.61, 18.3, 18.6, 25.85, 25.88, 73.9, 204.0. The NMR data matched with those previously reported.²⁰⁴
Ethyl (S)-2-(trityloxy)propanoate (S242c)

\[ \text{CO}_2\text{Et} \]
\[ \text{OTr} \]

To a solution of ethyl (S)-lactate (1.00 mL, 8.82 mmol) and TrCl (2.95 g, 10.58 mmol, 1.20 equiv.) in CH$_2$Cl$_2$ (15 mL), was added DBU (1.84 mL, 12.35 mmol, 1.40 equiv.) under nitrogen and stirred at room temperature for 48 h. The reaction mixture was then quenched with water (5 mL), washed with brine (3×10 mL), and extracted by CH$_2$Cl$_2$ (3×10 mL). The organic layer was then dried (Na$_2$SO$_4$), concentrated under reduced pressure, and purified by flash column chromatography (Et$_2$O/hexane = 2:8) to afford the resulting O-Tr α-hydroxy ester S242c. White solid (1.98 g, 62%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.98 (t, 3H, $J = 7.0$ Hz, CH$_3$), 1.33 (d, 3H, $J = 6.5$ Hz, CH$_3$), 4.18 (q, 1H, $J = 6.5$ Hz, CH), 3.57-3.65 (m, 2H, CH$_2$), 7.07-7.34 (m, 9H, 9CH$_{Ar}$), 7.36-7.62 (m, 6H, 6CH$_{Ar}$). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 14.1, 20.3, 60.4, 69.9, 82.1, 88.2, 127.3, 127.4, 127.9, 127.9, 128.01, 128.02, 128.04, 128.1, 128.20, 129.25, 144.1, 147.2, 173.7. The NMR data matched with those previously reported.\(^{205}\)

(S)-2-(Trityloxy)propanal (242c)

\[ \text{CHO} \]
\[ \text{OTr} \]

The title aldehyde 242c was obtained following the general DIBAL-H procedure using ethyl (S)-2-(trityloxy)propanoate S242c (0.270 g, 0.74 mmol) and DIBAL-H (dissolved in 0.2 mL n-hexane, 0.14 mL, 0.78 mmol, 1.05 equiv.) in Et$_2$O (5 mL). White solid (0.16 g, 68%). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.28 (d, 3H, $J = 7.0$ Hz, CH$_3$), 4.00 (m, 1H, CH), 7.21-7.30 (m, 9H, 9CH$_{Ar}$), 7.46-7.51 (m, 6H, 6CH$_{Ar}$), 8.72 (d, 1H, $J = 3.2$ Hz, CHO). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$) $\delta$ 17.5, 75.5, 88.1, 127.46, 127.49, 127.8, 128.0, 128.1, 128.2, 128.3, 129.0, 129.3, 144.1, 147.2, 202.8. The NMR data matched with those previously reported.\(^{205}\)
General Procedure for Allenylation of O-Protected Hydroxy Aldehydes

To a solution of allenylboronic acid pinacol ester 71 (1.10 equiv.) and the hydroxy aldehydes (242a-c) in toluene at 0 °C, was added Et₂Zn (1 M in toluene, 10 mol%) under nitrogen. The mixture was then stirred at 0 °C for 18 h. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (1 mL), and washed with saturated aqueous NaHCO₃ solution (15 mL) and water (10 mL). The organic layer was dried (Na₂SO₄), concentrated under reduced pressure and purified by flash column chromatography (EtOAc/hexane) to afford the allenyl hydroxy alcohol products (243a-c).

(2S,3S)-2-(Benzyloxy)hexa-4,5-dien-3-ol (243a)

The title compound 243a was obtained after flash column chromatography (EtOAc/hexane = 3:7) as a 1.4:1 mixture of syn and anti diastereomers following the general procedure using (S)-2-(benzyloxy)propanal 242a (0.051 g, 0.32 mmol), allenylboronic acid pinacol ester 71 (65.0 μL, 0.34 mmol, 1.10 equiv.) and Et₂Zn (1 M in toluene, 33.0 μL, 0.032 mmol, 10 mol%) in dry toluene (1 mL). Colourless oil (0.048 g, 76%). Rf (EtOAc/hexane = 2:8) = 0.45. ¹H NMR (500 MHz, CDCl₃) (mixture of two allene diastereomers, relative integrations given for each diastereomer) δ 1.19-1.25 (m, 3H, C₆H₃, for each isomer), 2.33 (br s, 1H, OH, minor isomer), 2.77 (br s, 1H, OH, major isomer), 3.48-3.53 (m, 1H, CH, major isomer), 3.60-3.65 (m, 1H, CH, minor isomer), 4.04 (br s, 1H, CH, major isomer), 4.24 (br s, 1H, CH, minor isomer), 4.47-4.54 (m, 1H, CHPh, for each isomer), 4.63-4.68 (m, 1H, CHPh, for each isomer), 4.82-4.89 (m, 2H, CH₂=C, for each isomer), 5.21 (q, 1H, J = 6.8 Hz, CH=C, major isomer), 5.27 (q, 1H, J =
6.8 Hz, $CH=\text{C}$, minor isomer), 7.25-7.36 (m, 5H, 5CH$_{Ar}$ for each isomer). $^{13}$C{$_1^H$} NMR (125 MHz, CDCl$_3$) (mixture of two allene diastereomers, minor indicated by asterisk) $\delta$ 14.5*, 15.5, 71.0, 71.3*, 72.0*, 72.3, 76.8, 77.8*, 78.3, 90.6*, 91.0, 127.6, 127.7*, 127.82*, 127.84, 128.4*, 128.5, 138.2, 138.4*, 208.0*, 208.5. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3409 (w), 2975 (w), 2874 (w), 1956 (m), 1453 (m), 1374 (m), 1064 (s), 843 (s), 735 (s), 696 (s). HRMS (ESI-TOF) $m/z$ calcd for C$_{13}$H$_{16}$O$_2$Na$^{[\text{M+Na}]}^+$ 227.1048, found 227.1059.

(2S,3S)-2-((tert-Butyldimethylsilyl)oxy)hexa-4,5-dien-3-ol (243b)

The title compound 243b was obtained after flash column chromatography (EtOAc/hexane = 3:7) as a 1.1:1 mixture of syn and anti diastereomers following the general procedure using (S)-2-((tert-butyltrimethylsilyl)oxy)propanal 242b (0.162 g, 0.86 mmol), allenylboronic acid pinacol ester 71 (180.0 $\mu$L, 0.94 mmol, 1.10 equiv.) and Et$_2$Zn (1 M in toluene, 92.0 $\mu$L, 0.086 mmol, 10 mol%) in dry toluene (5 mL). Colourless oil (0.14 g, 70%). $R_f$ (Et$_2$O/hexane = 1:9) = 0.37. $^1$H-NMR (500 MHz, CDCl$_3$) (mixture of two allene diastereomers, relative integrations given for each diastereomer) $\delta$ 0.01 (br s, 6H, 2CH$_3$ in TBS, for each isomer), 0.82 (s, 9H, (CH$_3$)$_3$ in TBS, for each isomer), 1.05 (d, 3H, $J = 7.0$ Hz, CH$_3$, minor isomer), 1.09 (d, 3H, $J = 7.0$ Hz, CH$_3$, major isomer), 2.18 (br s, 1H, OH, major isomer), 2.48 (br s, 1H, OH, major isomer), 3.67 (br s, 1H, CH, minor isomer), 3.78 (br s, 1H, CH, minor isomer), 3.82 (br s, 1H, CH, major isomer), 3.95 (br s, 1H, CH, major isomer), 4.75 (br s, 2H, CH$_2$C, for each isomer), 5.09-5.14 (m, 1H, CH=C, for each isomer). $^{13}$C{$_1^H$} NMR (125 MHz, CDCl$_3$) (mixture of two allene diastereomers, minor indicated by asterisk) $\delta$ -4.8, -4.4, -4.2*, 18.0*, 18.4, 19.8, 25.75, 25.77, 25.8, 25.9, 71.6*, 71.9, 73.8*, 73.9, 76.8*, 77.0, 90.4*, 91.6, 208.2. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3441 (w), 2928 (m), 2859 (m), 1955 (m), 1463 (m), 1373 (m), 1254 (s), 1057 (s), 834 (s), 774 (s), 667 (s). HRMS (ESI-TOF) $m/z$ calcd for C$_{13}$H$_{16}$O$_2$SiNa$^{[\text{M+Na}]}^+$ 251.1443, found 251.1441.
The title compound 243c was obtained after flash column chromatography (Et2O/hexane = 1:9) as a single diastereomer following the general procedure using (S)-2-(trityloxy)propanal 242c (0.10 g, 0.316 mmol), allenylboronic acid pinacol ester 71 (67.0 μL, 0.35 mmol, 1.10 equiv.) and Et2Zn (1 M in toluene, 34.0 μL, 0.0316 mmol, 10 mol%) in dry toluene (5 mL). Colourless oil (0.046 g, 41%). Rf (Et2O/hexane = 3:7) = 0.41. 1H NMR (500 MHz, CDCl3) δ 0.85 (br s, 3H, C6H5), 2.03 (s, 1H, OCH3), 3.51 (br s, 1H, CH2), 3.71 (br s, 1H, CH2), 4.77 (br s, 2H, CH2=C), 5.21 (br s, 1H, CH=C), 7.16-7.23 (m, 9H, 9C6H5), 7.43 (d, J = 7.0 Hz, 6H, 6C6H5). 13C{1H} NMR (125 MHz, CDCl3) δ 16.2, 71.4, 72.6, 77.7, 87.0, 91.3, 127.1, 127.7, 128.8, 144.8, 207.5. IR (νmax/cm^-1) 3441 (w), 3054 (w), 2982 (w), 1953 (m), 1490 (m), 1448 (s), 1374 (s), 1065 (s), 845 (s), 745 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C25H24O2Na [M+Na]^+ 379.1674, found 379.1668.

General Procedure for Allenylation of N-Bn,N-Boc Amino Aldehydes and Subsequent Au(I)-Catalysed Cyclisation

To a solution of allenylboronic acid pinacol ester 71 (1.30 equiv.) and the aldehyde (217a-h) in toluene at 0 °C, was added Et2Zn (1 M in toluene, 10 mol%) under nitrogen. The mixture was then stirred at 0 °C for 18 h. The reaction mixture was quenched with saturated aqueous NH4Cl solution (1 mL), and then washed with saturated aqueous NaHCO3 solution (15 mL) and water (10 mL). The organic layer was dried (Na2SO4), and then concentrated under reduced
pressure to afford the resulting allenyl amino alcohol product. Then, to a solution of this crude product (218a-h) in dry DCE was added AuPPh3NTf2 (10 mol%). The reaction was stirred at 60 °C for 8 h and then filtered through a pad of silica gel and the crude product was used in the next step without purification. Chlorotrimethylsilane (5.00 equiv.) was added to a solution of the crude dihydrofuran in dry MeOH. The reaction mixture was stirred at room temperature overnight, and then was neutralized by the addition of saturated aqueous NaHCO3 solution to about pH = 7, followed by purification via flash column chromatography to afford the corresponding Boc-deprotected dihydrofuran products 250a-h.

The NMR spectra for the direct allenylation products 218a-h were complicated by the presence of a mixture of rotamers, diastereoisomers, and regioisomers. Therefore, dihydrofurans 250a-h were targeted as the final desired products. In the case of the product 218a was purified by column chromatography as part of the optimization study, and characterized to verify formation of the desired allenyl products.

tert-Butyl benzyl((2S,3R)-3-hydroxyhexa-4,5-dien-2-yl)carbamate (218a)

The title compound 218a was prepared following the general procedure using tert-butyl benzyl(1-oxopropan-2-yl)carbamate 217a (0.065 g, 0.24 mmol), allenylboronic acid pinacol ester 71 (61 μL, 0.32 mmol, 1.30 equiv.) and Et2Zn (1 M in toluene, 25 μL, 0.024 mmol, 10 mol%) in dry toluene (2 mL). The crude product was purified by flash column chromatography (EtOAc/hexane = 2:8) as a 19:1 mixture of anti and syn diastereomers. Colorless oil (0.07 g, 96%). \( R_t \) (EtOAc/hexane = 2:8) = 0.31. \([\alpha]_D^{22} = +7.31 \) (c 7.2 CH3Cl). \(^1\)H NMR (500 MHz, CDCl3) (mixture of rotamers) δ 1.17 (d, 0.7H, J = 7.0 Hz), 1.20 (d, 2.3H, J = 7.0 Hz), 1.33-1.45 (br s, 9H, C(CH3)3), 3.70-3.76 (m, 1H, CH), 4.01-4.12 (m, 0.7H), 4.35-4.49 (m, 3.3H), 4.80 (m, 2H, CH=C=), 5.12-5.17 (m, 1H, CH=C=), 7.23-7.33 (m, 5H, 5CHAr). \(^13\)C\(^{1}\)H NMR (125 MHz, CDCl3) (mixture of rotamers, minor rotamer indicated by asterisk) δ 11.9, 28.3, 51.1, 58.5*, 58.7, 72.9, 77.4, 80.6, 80.6*, 92.8, 127.0, 127.1, 127.3*, 128.4, 128.5*, 139.1, 156.7,
207.1. **IR** (νmax/cm⁻¹) 3473 (m), 2976 (m), 1956 (m), 1452 (s), 1365 (s), 1332 (m), 1250 (m), 1164 (s), 1012 (s), 860 (s), 699 (s). **HRMS** (ESI-TOF) m/z calcd for C₁₈H₂₅NO₃Na [M + Na]⁺ 326.1721, found 326.1731.

**(S)-N-benzyl-1-((R)-2,5-dihydrofuran-2-yl)ethan-1-amine (250a)**

Following the general procedure the crude allenyl product **218a** was treated with AuPPh₃NTf₂ (17.50 mg, 0.024 mmol, 10 mol%), followed by Boc-deprotection of the crude product by treatment with TMSCl (0.14 mL, 1.20 mmol, 5.00 equiv.) in MeOH (2 mL). The title compound **250a** was obtained as a single diastereomer after purification by flash column chromatography (Et₂O/hexane = 7:3). The isolated yield was calculated for the three steps starting from the aldehyde **217a**. Colourless oil (0.03 g, 60%). **Rf** (Et₂O/hexane = 7:3) = 0.15. The ee was determined by chiral HPLC of the corresponding alcohol using a Phenomenex Lux Cellulose-3 column; hexane/isopropanol (98:2); flow rate = 0.5 mL/min; 210 nm; t_major = 9.83 min, t_minor = 10.95 min, 91% ee. [α]D² = +104.5 (c 0.9 CHCl₃). **¹H NMR** (500 MHz, CDCl₃) δ 1.06 (d, 3H, J = 6.5 Hz, CH₃), 1.69 (s, 1H, NH), 2.85-2.88 (m, 1H, CH), 3.79 (d, 1H, J = 13.5 Hz, CH₂), 3.90 (d, 1H, J = 13.5 Hz, CH₂), 4.62-4.69 (m, 2H, CH₂), 4.87-4.88 (m, 1H, CH), 5.81-5.82 (m, 1H, CH), 5.95-5.97 (m, 1H, CH), 7.21-7.33 (m, 5H, 5CH₃). **¹³C{¹H} NMR** (125 MHz, CDCl₃) δ 15.6, 51.4, 55.5, 75.7, 89.4, 126.8, 127.0, 127.7, 128.0, 128.3, 140.7. **IR** (νmax/cm⁻¹) 3327 (w), 3026 (w), 2964 (w), 2845 (m), 1683 (m), 1630 (m), 1494 (m), 1452 (m), 1355 (m), 1269 (m), 1068 (s), 1028 (s), 950 (s), 847 (m), 731 (s), 696 (s). **HRMS** (ESI-TOF) m/z calcd for C₁₃H₁₈NO [M + H]⁺ 204.1388, found 204.1393.
The allenyl precursor was prepared following the general procedure using tert-butyl benzyl(1-oxopentan-2-yl)carbamate 217b (0.485 g, 1.66 mmol), allenylboronic acid pinacol ester 71 (0.41 mL, 2.16 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 180 μL, 0.048 mmol, 10 mol%) in dry toluene (5 mL). Following the general procedure, the crude allenyl product 218b was treated with AuPPh₃NTf₂ (0.117 g, 0.16 mmol, 10 mol%) in dry DCE (5 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (0.95 mL, 8.00 mmol, 5.00 equiv.) in MeOH (5 mL) gave the title compound 250b as a 4.3:1 mixture of syn and anti diastereomers after purification by flash column chromatography (Et₂O/hexane = 2:8). The isolated yield was calculated for the three steps starting from the aldehyde 217b. Colourless oil (0.26 g, 68%), Rf (Et₂O/hexane = 2:8) = 0.30. ¹H NMR (300 MHz, CDCl₃) (mixture of two diastereomers, relative integrations given for each diastereomer) δ 0.88 (t, 3H, J = 6.30, 6.9 Hz, CH₃, for each isomer), 1.28-1.49 (br m, 2H, CH₂, for each isomer), 2.50-2.60 (m, 1H, CH, minor isomer), 2.69 (q, 1H, J = 8.5, 10.5 Hz, CH, major isomer), 3.80 (s, 2H, CH₂Ph, minor isomer), 3.83 (s, 2H, CH₂Ph, major isomer), 4.58-4.70 (m, 2H, CH₂, for each isomer), 4.84-4.86 (m, 1H, CH, minor isomer), 4.93-4.94 (m, 1H, CH, major isomer), 5.81-5.83 (m, 1H, CH=, for each isomer), 5.90-5.96 (m, 1H, CH=, for each isomer), 7.18-7.30 (m, 5H, 5CH₂Ar, for each isomer). ¹³C{¹H} NMR (75 MHz, CDCl₃) (mixture of two diastereomers, minor indicated by asterisk) δ 14.3, 14.4*, 19.3*, 19.5, 33.1*, 33.3, 51.8*, 52.3, 60.2, 60.3*, 75.3*, 75.4, 88.3*, 88.6, 126.7, 127.2, 127.4*, 127.7, 127.8, 128.0*, 128.2, 140.9. IR (νmax/cm⁻¹) 3735 (w), 2956 (m), 2871 (m), 2844 (m), 1457 (m), 1354 (w), 1073 (s), 734 (s), 696 (s). HRMS (ESI-TOF) m/z calcd for C₁₅H₂₁NONa [M + Na]⁺ 254.1521, found 254.1531.
(S)-N-benzyl-1-((R)-2,5-dihydrofuran-2-yl)-3-methylbutan-1-amine (250c)

The allenyl precursor was prepared following the general procedure using tert-butyl benzyl(4-methyl-1-oxopentan-2-yl)carbamate 217c (0.198 g, 0.65 mmol), allenylboronic acid pinacol ester 71 (160 µL, 0.84 mmol, 1.3 equiv.) and Et2Zn (1 M in toluene, 70 µL, 0.065 mmol, 10 mol%) in dry toluene (2 mL). Following the general procedure, the crude allenyl product 218c was treated with AuPPh3NTf2 (44.90 mg, 0.06 mmol, 10 mol%) in dry DCE (2 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (0.38 mL, 3.25 mmol, 5.00 equiv.) in MeOH (3 mL) gave the title compound 250c as a 3.2:1 mixture of syn and anti diastereomers after purification by flash column chromatography (Et2O/hexane = 2:8). The isolated yield was calculated for the three steps starting from the aldehyde 217c. Colorless oil (0.097 g, 62%), \( R_f \) (Et2O/hexane = 2:8) = 0.36. ¹H NMR (300 MHz, CDCl3) (mixture of two diastereomers, relative integrations given for each diastereomer) \( \delta \) 0.81-0.92 (m, 6H, 2CH₃, for each isomer), 1.22-1.33 (m, 1H, CH, for each isomer), 1.74-2.00 (m, 1H, CH, for each isomer), 2.77-2.81 (m, 1H, CH, major isomer), 2.85-2.89 (m, 1H, CH, minor isomer), 3.28 (s, 1H, NH, minor isomer), 3.34 (s, 1H, NH, major isomer), 3.82-3.92 (m, 2H, CH₂Ph, for each isomer), 4.65-4.69 (m, 2H, CH₂O, for each isomer), 4.97-5.00 (m, 1H, CH, for each isomer), 5.80-5.82 (m, 1H, CH=, for each isomer), 5.97-6.00 (m, 1H, CH=, for each isomer), 7.23-7.35 (m, 5H, 5CH₃Ar, for each isomer). ¹³C{¹H} NMR (75 MHz, CDCl3) (mixture of two diastereomers, minor indicated by asterisk) \( \delta \) 22.3, 23.5, 24.9, 40.4, 52.3, 54.0*, 58.2, 75.5, 88.8, 127.1, 126.8, 127.9*, 128.2, 128.33*, 128.36, 140.9. IR (\( v_{max}/\text{cm}^{-1} \)) 3735 (w), 2956 (m), 2926 (m), 2868 (m), 1457 (m), 1131 (m), 1074 (m), 740 (m), 697 (m), 619 (m). HRMS (ESI-TOF) m/z calcd for C₁₆H₂₄NO [M + H]⁺ 246.1858, found 246.1854.
(S)-N-benzyl-1-((R)-2,5-dihydrofuran-2-yl)-2-phenylethan-1-amine (250d)

The allenyl precursor was prepared following the general procedure using tert-butyl benzyl(1-oxo-3-phenylpropan-2-yl)carbamate 217d (0.278 g, 0.82 mmol), allenylboronic acid pinacol ester 71 (0.20 mL, 1.06 mmol, 1.30 equiv.) and Et$_2$Zn (1 M in toluene, 85.00 μL, 0.082 mmol, 10 mol%) in dry toluene (2 mL). Following the general procedure, the crude allenyl product 218d was treated with AuPPh$_3$NTf$_2$ (60.00 mg, 0.08 mmol, 10 mol%) in dry DCE (3 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (0.52 mL, 4.10 mmol, 5.00 equiv.) in MeOH (3 mL) gave the title compound 250d as a 8.3:1 mixture of syn and anti diastereomers after purification by flash column chromatography (EtOAc/hexane = 3:7). The isolated yield was calculated for the three steps starting from the aldehyde 217d. Light yellow oil (0.133 g, 58%). R$_f$ (EtOAc/hexane = 3:7) = 0.34. $^1$H NMR (500 MHz, CDCl$_3$) (mixture of two diastereomers, relative integrations given for each diastereomer) δ 2.70-2.74 (m, 1H, CH$_2$Ph, for each isomer), 2.80-2.83 (m, 1H, CH$_2$Ph, for each isomer), 2.90 (s, 1H, CH, minor isomer), 2.98 (br s, 1H, CH, major isomer), 3.77 (q, 2H, J = 13.5 Hz, CH$_3$Ph, for each isomer), 4.63-4.73 (m, 2H, 2CH−O, for each isomer), 4.89 (br s, 1H, CH, for each isomer), 5.78 (br s, 1H, CH=, minor isomer), 5.89 (br s, 1H, CH=, major isomer), 5.98 (br s, 1H, CH=, for each isomer), 7.12-7.27 (m, 10H, 10CH$_2$Ar, for each isomer). $^{13}$C($^1$H) NMR (125 MHz, CDCl$_3$) (mixture of two diastereomers, minor indicated by asterisk) δ 37.1, 37.4*, 52.10, 52.16*, 61.80, 61.85*, 75.5*, 75.6, 87.8*, 88.0, 126.1*, 126.2, 126.7, 127.2, 127.73*, 127.79*, 128.0, 128.3, 128.4, 129.3, 139.2, 139.5*, 140.5. IR (νmax/cm$^{-1}$) 3333 (w), 3026 (w), 2844 (m), 1494 (m), 1452 (m), 1070 (s), 739 (s), 696 (s). HRMS (ESI-TOF) m/z calcd for C$_{19}$H$_{22}$NO [M + H]$^+$ 280.1695, found 280.1697.
(S)-N-benzyl-1-((R)-2,5-dihydrofuran-2-yl)-2-methylpropan-1-amine (250e)

The allenyl precursor was prepared following the general procedure using tert-butyl benzyl(3-methyl-1-oxobutan-2-yl)carbamate 217e (0.53 g, 1.84 mmol), allenylboronic acid pinacol ester 71 (454 μL, 2.40 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 197 μL, 0.184 mmol, 10 mol%) in dry toluene (5 mL). Following the general procedure, the crude allenyl product 218e was treated with AuPPh₃NTf₂ (0.13 g, 0.18 mmol, 10 mol%) in dry DCE (5 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (1.12 mL, 9.20 mmol, 5.00 equiv.) in MeOH (5 mL) gave the title compound 250e as a single diastereomer after purification by flash column chromatography (Et₂O/hexane = 2:8). The isolated yield was calculated for the three steps starting from the aldehyde 217e. Colorless oil (0.263 g, 61%). Rᵣ (Et₂O/hexane = 2:8) = 0.22. [α]D²² = -43.3 (c 0.65 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 0.98 (d, 6H, J = 6.5 Hz, 2CH₃), 1.84-1.87 (br m, 2H, CH₂N), 2.37 (br d, 1H, J = 3.0 Hz, CH), 3.83 (dd, 2H, J = 13.0, 12.5 Hz, CH₂Ph), 4.64 (br d, 2H, J = 13.0 Hz, CH₂), 4.95 (br s, 1H, CH), 5.80 (br s, 1H, CH=), 5.93 (br s, 1H, CH=), 7.22-7.32 (m, 5H, 5CH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 19.28, 20.2, 30.7, 53.9, 65.7, 75.6, 87.9, 126.9, 127.2, 128.4, 129.2, 141.5. IR (νmax/cm⁻¹) 2955 (m), 2872 (m), 2359 (w), 1457 (m), 1070 (s), 1028 (s), 739 (s), 697 (s). HRMS (ESI-TOF) m/z calcld for C₁₅H₂₂NO [M + H]+ 232.1701, found 232.1703.

(S)-N-benzyl-1-((R)-2,5-dihydrofuran-2-yl)-1-phenylmethanamine (250f)

The allenyl precursor was prepared following the general procedure using tert-butyl benzyl(2-oxo-1-phenylethyl)carbamate 217f (0.26 g, 0.82 mmol), allenylboronic acid pinacol ester 71 (202.00 μL, 1.06 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 88.5 μL, 0.082 mmol, 10 mol%) in dry toluene (2 mL). Following the general procedure the crude allenyl product 218f...
was treated with AuPPh₃NTf₂ (60.62 mg, 0.08 mmol, 10 mol%) in dry DCE (3 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (0.52 mL, 4.10 mmol, 5.00 equiv.) in MeOH (3 mL) gave the title compound 250f as a single diastereoisomer after purification by flash column chromatography (Et₂O/hexane = 3:7). The isolated yield was calculated for the three steps starting from the aldehyde 217f. Colourless oil (0.117 g, 54%). \( R_f \) (Et₂O/hexane = 3:7) = 0.27. \( [\alpha]^{22}_D = -12.8 \) (c 1 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 2.10 (br s, 1H, NH), 3.51 (d, 1H, \( J = 13.5 \) Hz, CH), 3.61 (d, 1H, \( J = 8.0 \) Hz, CH), 3.67 (d, 1H, \( J = 13.5 \) Hz, CH), 4.61-4.63 (m, 2H, CH₂Ph), 4.81-4.87 (m, 1H, CH), 5.42-5.44 (m, 1H, CH=), 5.84-5.89 (m, 1H, CH=), 7.20-7.42 (m, 10H, 10CHAr). ¹³C NMR (125 MHz, CDCl₃) δ 51.0, 67.6, 75.4, 90.5, 126.7, 127.4, 127.5, 127.6, 128.1, 128.30, 128.38, 128.4, 140.1, 140.6. IR (νmax/cm⁻¹) 3326 (w), 3060 (w), 3026 (w), 2848 (m), 2364 (w), 1452 (s), 1071 (s), 1028 (m), 748 (s), 693 (s). HRMS (ESI) m/z calcd for C₁₈H₂₀NO \([M + H]^+\) 266.1545, found 266.1541.

**tert-Butyl 3-((S)-2-(benzylamino)-2-((R)-2,5-dihydrofuran-2-yl)ethyl)-1H-indole-1-carboxylate (250g)**

![Chemical Structure](image)

The allenyl precursor was prepared following the general procedure using tert-butyl 3-(2-(benzyl(tert-butoxycarbonyl)amino)-3-oxopropyl)-1H-indole-1-carboxylate 217g (0.389 g, 0.81 mmol), allenylboronic acid pinacol ester 71 (0.20 mL, 1.05 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 87.30 μL, 0.081 mmol, 10 mol%) in dry toluene (3 mL). Following the general procedure, the crude allenyl product 218g was treated with AuPPh₃NTf₂ (59.15 mg, 0.08 mmol, 10 mol%) in dry DCE (4 mL). Boc-deprotection of the resulting dihydrofuran with TMSCl (0.52 mL, 4.05 mmol, 5.00 equiv.) in MeOH (5 mL) gave the title compound 250g as a single diastereomer after purification by flash column chromatography (EtOAc/hexane = 3:7). The isolated yield was calculated for the three steps starting from the aldehyde 217g. Light yellow oil (0.163 g, 48%). \( R_f \) (EtOAc/hexane = 3:7) = 0.33. \( [\alpha]^{22}_D = +39.3 \) (c 1.3 CHCl₃). ¹H NMR
(300 MHz, CDCl₃) δ 1.66 (br s, 9H, C(CH₃)₃), 2.76-2.92 (m, 2H, CH₂), 3.07-3.13 (m, 1H, CH), 3.81 (m, 2H, CH₂Ph), 4.63-4.78 (m, 2H, CH₂), 4.95 (br s, 1H, CH), 5.93 (m, 1H, CH=), 6.01 (d, 1H, J = 6.3 Hz, CH=), 7.16-7.21 (br m, 5H, 5CH₃), 7.25-7.32 (m, 2H, 2CH₃), 7.44 (t, 2H, J = 7.8 Hz, 2CH₃), 8.12 (m, 1H, CH=). 13C{¹H} NMR (75 MHz, CDCl₃) δ 26.3, 28.2, 52.1, 60.0, 75.6, 83.3, 88.1, 115.2, 117.7, 119.1, 122.3, 123.6, 124.3, 126.7, 127.2, 127.9, 128.0, 128.2, 130.7, 135.5, 140.3, 149.6. IR (νmax/cm⁻¹) 3670 (w), 2978 (w), 2842 (w), 1729 (s), 1451 (s), 1367 (s), 1255 (s), 1155 (s), 1072 (s), 1015 (m), 935 (m), 856 (m), 743 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C₂₆H₃₁N₂O₃ [M + H]+ 419.2335, found 419.2346.

tert-Butyl (S)-2-((R)-2,5-dihydrofuran-2-yl)pyrrolidine-1-carboxylate (250h)

The allenyl precursor was prepared following the general procedure using tert-butyl 2-formylpyrrolidine-1-carboxylate 217h (0.29 g, 1.45 mmol), allenylboronic acid pinacol ester 71 (0.36 mL, 1.89 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 156.3 μL, 0.145 mmol, 10 mol%) in dry toluene (3 mL). Following the general procedure, the crude allenyl product 218h was treated with AuPPh₃NTf₂ (107.4 mg, 0.145 mmol, 10 mol%) in dry DCE (3 mL). The title compound 250h was obtained as a 1.6:1 mixture of syn and anti diastereomers after purification by flash column chromatography (Et₂O/hexane = 3:7). The isolated yield was calculated for the two steps starting from the aldehyde 217h. Colorless oil (0.21 g, 59%), Rf (Et₂O/hexane = 3:7) = 0.18. ¹H NMR (500 MHz, DMSO, 80 °C) (mixture of two diastereomers, relative integrations given for each diastereomer) δ 1.41 (s, 9H, C(CH₃)₃, for each isomer), 1.70 (br s, 2H, 2CH₂, major isomer), 1.80-1.85 (m, 4H, 2CH₂, minor isomer) 3.14-3.22 (m, 2H, CH₂, major isomer), 3.31 (br s, 2H, CH₂, minor isomer), 3.75 (s, 1H, CH, major isomer), 3.90 (s, 1H, CH, minor isomer), 4.47-4.54 (m, 2H, CH₂, for each isomer), 4.97 (br s, 1H CH, for each isomer), 5.79-5.81 (m, 1H, CH=, for each isomer), 6.02 (br s, 1H, CH=, for each isomer). ¹³C{¹H} NMR (125 MHz, DMSO, 80 °C) (mixture of two diastereomers, minor indicated by asterisk) δ 23.9, 25.7,
N-Benzyl-N-((2S,3R)-3-hydroxyhexa-4,5-dien-2-yl)-4-methylbenzenesulfonamide (221)

The major diastereomer of the title compound 221 was obtained after purification by flash column chromatography (EtOAc/hexane = 3:7) following the general procedure using N-benzyl-4-methyl-N-(1-oxopropan-2-yl)benzenesulfonamide 220 (0.072 g, 0.226 mmol), allenylboronic acid pinacol ester 71 (56.50 μL, 0.29 mmol, 1.30 equiv.) and Et2Zn (1 M in toluene, 24.00 μL, 0.0226 mmol, 10 mol%) in dry toluene (1 mL). Colourless oil (0.044 g, 54%). Rf (EtOAc/hexane = 3:7) = 0.44. [α]D22 = +35.2 (c 2.5 CHCl3). 1H NMR (500 MHz, CDCl3) δ 1.01 (d, 3H, J = 7.0 Hz, CH3), 1.84 (d, 1H, J = 4.0 Hz, OH), 2.42 (s, 3H, CH3), 3.88-3.91 (m, 1H, CH), 4.03 (br s, 1H, CH), 4.27 (d, 1H, J = 15.5 Hz, CHPh), 4.60 (d, 1H, J = 16.0 Hz, CHPh), 4.78-4.80 (m, 2H, CH2=C=), 5.15 (q, 1H, J = 6.5, 6.5 Hz, CH=C=), 7.23-7.31 (m, 5H, 5CHAr), 7.37 (d, 2H, J = 7.5 Hz, 2CHAr), 7.69 (d, 2H, J = 8.5 Hz, 2CHAr). 13C{1H} NMR (125 MHz, CDCl3) δ 12.4, 21.5, 48.5, 58.6, 71.8, 78.3, 93.0, 127.1, 127.5, 128.2, 128.5, 129.7, 137.7, 137.9, 143.3, 207.0. IR (νmax/cm⁻¹) 3502 (m), 2984 (w), 2922 (w), 1954 (m), 1598 (m), 1333 (s), 1150 (s), 1088 (s), 1002 (s), 863 (s), 732 (s), 657 (s). HRMS (ESI-TOF) m/z calcd for C20H23NO3NaS [M + Na]⁺ 380.1296, found 380.1285.
(2S,3R)-2-(Dibenzylamino)hexa-4,5-dien-3-ol (224)

The major diastereomer of the title compound 224 was obtained after purification by flash column chromatography (Et₂O/hexane = 1:9) following the general procedure using 2-(dibenzylamino)propanal 223 (0.096 g, 0.339 mmol), allenylboronic acid pinacol ester 71 (84.00 μL, 0.44 mmol, 1.30 equiv.) and Et₂Zn (1 M in toluene, 36.00 μL, 0.0339 mmol, 10 mol%) in dry toluene (1 mL). Colourless oil (0.05 g, 50%). R₆ (Et₂O/hexane = 1:9) = 0.25. [α]D²² = −36.2 (c 4.1 CHCl₃).

¹H NMR (500 MHz, CDCl₃) δ 1.12 (d, 3H, J = 11.5 Hz, CH₃), 2.85-2.89 (m, 1H, CH), 3.42 (d, 2H, J = 23.0 Hz, 2CH₂Ph), 3.82 (d, 2H, J = 23.0 Hz, 2CH₂Ph), 4.07-4.12 (m, 1H, CH), 4.77-4.81 (m, 2H, CH₂=C=), 5.30 (q, 1H, J = 10.5, 10.5 Hz, CH=C=), 7.19-7.34 (m, 10H, 10CH₂Ar).

¹³C{¹H} NMR (125 MHz, CDCl₃) δ 9.2, 54.9, 57.7, 71.1, 76.8, 93.6, 127.2, 128.5, 129.0, 139.9, 207.6. IR (νmax/cm⁻¹) 3379 (w), 3027 (w), 2926 (w), 2801 (w), 1952 (m), 1368 (m), 1244 (w), 1027 (s), 845 (s), 744 (s), 696 (s). HRMS (ESI-TOF) m/z calcd for C₂₀H₂₄NO [M + H]⁺ 294.1858, found 294.1852.

**Determination of Enantiomeric Excess (ee) of Oxazolidinones Using (S)-10-Camphorsulfonyl Chloride**

The enantiomeric excess (ee) of each diastereomerically pure allenyl oxazolidinone was determined by derivatizing with enantiomerically pure (S)-10-camphorsulfonyl chloride and ¹H NMR analysis of the crude reaction mixture. The ee of the oxazolidinone was determined by
integration of clearly resolved resonances arising from the corresponding allenyl methane (CH$_2$SO$_2$) protons in each diastereomer. The resonances used are listed at the end of the characterization data for each compound.

To a solution of the oxazolidinone in dry THF (2 mL) was added sodium hydride (60% in mineral oil, 4.00 equiv.) at 0 °C. The reaction mixture was stirred at room temperature for 30 min then (S)-10-camphorsulfonyl chloride (2.00 equiv.) was added and the reaction mixture was stirred for 3 h. The reaction was quenched with NH$_4$Cl (5 mL), washed with water (10 mL) and NaHCO$_3$ (10 mL), dried (Na$_2$SO$_4$) and concentrated under vacuum.

**229a** (96% ee): $^1$H NMR (500 MHz, CDCl$_3$) δ 3.35 (d, 1H, $J = 15.0$ Hz, CHSO$_2$, minor isomer), 3.65 (dd, 2H, $J = 15.0$, 16.0 Hz, CH$_2$SO$_2$, major isomer), 4.13 (d, 1H, $J = 14.5$ Hz, CHSO$_2$, minor isomer), ratio = 98:2.

**229b** (94% ee): $^1$H NMR (500 MHz, CDCl$_3$) δ 3.32 (d, 1H, $J = 15.0$ Hz, CHSO$_2$, minor isomer), 3.66 (br s, 2H, CH$_2$SO$_2$, major isomer), 4.06 (d, 1H, $J = 15.0$ Hz, CHSO$_2$, minor isomer), ratio = 97:3.

**229c** (86% ee): $^1$H NMR (500 MHz, CDCl$_3$) δ 3.32 (d, 1H, $J = 15.0$ Hz, CHSO$_2$, minor isomer), 3.70 (dd, 2H, $J = 16.5$, 14.5 Hz, CH$_2$SO$_2$, major isomer), 4.08 (d, 1H, $J = 15.0$ Hz, CHSO$_2$, minor isomer), ratio = 93:7.

**229f** (8% ee): $^1$H NMR (500 MHz, CDCl$_3$) δ 2.85 (d, 1H, $J = 15.2$ Hz, CHSO$_2$, minor isomer), 3.21 (d, 1H, $J = 14.5$ Hz, CHSO$_2$, major isomer), 3.45 (d, 1H, $J = 15.2$ Hz, CHSO$_2$, minor isomer), 3.63 (d, 1H, $J = 14.5$ Hz, CHSO$_2$, major isomer), ratio = 54:46.

**229g** (92% ee): $^1$H NMR (500 MHz, Methanol-d$_4$) δ 3.60 (dd, 2H, $J = 14.5$, 17.5 Hz, CH$_2$SO$_2$, major isomer), 4.10 (d, $J = 15.0$ Hz, 1H, CHSO$_2$, minor isomer), ratio = 96:4.
Determination of enantiomeric excess (ee) of aldehydes (167a) and (155c) and dihydrofuran (194a) by chiral HPLC analysis

Racemic aldehydes for chiral HPLC were achieved by heating the corresponding aldehyde to reflux in triethylamine for 2 hours. Then, it was dried under vacuum and then reduced with NaBH₄/MeOH to the corresponding alcohol for chiral HPLC analysis using Phenomenex Lux Cellulose-3 or i-Cellulose-5 columns; hexane/isopropanol; flow rate = 0.5 mL/min with detection at 210 nm.

A comparison between the enantiomeric purity of the final product 229c (determined from its chiral sulfonamide derivative by ¹H NMR analysis) and the corresponding aldehyde 205c (determined by chiral HPLC) showed no erosion of enantiomeric purity during the reaction steps.

In the case of 2,5-dihydrofurans, a representative diastereomerically pure product 250a was tested by comparing the enantiomeric purity of the final product and the aldehyde 217a, which proved no erosion of the enantiomeric ratio of the aldehyde.
Column: Phenomenex Lux Cellulose-3; Solvent: hexane/isopropanol (98:2); flow rate = 0.5 mL/min.

\[ \text{NH}_2 \text{CHO} \xrightarrow{\text{NaBH}_4} \text{OH} \]

86% ee

Project Name: Defaults
Reported by User: System
Report Method: Injection Summary Report
Date Printed: 1/23/2017
Report Method ID: 2227
Page: 1 of 1

**Injection Summary Report**

**Project Name:** Defaults
**Reported by User:** System
**Report Method:** Injection Summary Report
**Date Printed:** 1/23/2017
**Report Method ID:** 2227
**Page:** 1 of 1

**Sample Information:**
- **Sample Name:** NBocleucinolrac (Et$_3$N)
- **Sample Set Name:** Unknown
- **Sample Type:** 70
- **Injection Volume:** 5.00 ul
- **Run Time:** 60.0 Minutes
- **Proc. Chnl. Descr.:** PDA 210.0 nm

**Acquisition Details:**
- **Date Acquired:** 1/12/2017
- **Date Processed:** 1/19/2017
- **Acq. Method Set:** 98hex2ipaisocraticDAD

**Processed Channel Descr.:** PDA 210.0 nm

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Processed Channel Descr.: PDA 201.0 nm
Column: Phenomenex Lux Cellulose-5; Solvent: hexane/isopropanol (95:5); flow rate = 0.5 mL/min.

\[
\begin{align*}
&\text{CHO} \quad \text{NaBH}_4 \quad \text{MeOH} \\
&\text{NBnBoc} \quad \text{217a} \quad \text{NBnBoc} \\
&\text{OH} \\
&91\% \text{ ee}
\end{align*}
\]
Column: Phenomenex Lux Cellulose-3; Solvent: hexane/isopropanol (98:2); flow rate = 0.5 mL/min.

$\text{NHBn}$

91% ee

$250a$
Synthesis of 1,3-(E)-Enynes (253)

To a solution of N-Bn,N-Boc allenyl amino alcohols 218a-e in anhydrous THF (0.6 M) at 0 °C, was slowly added NaH (60% in mineral oil, 2.00 equiv.) in four approximately equal portions. The mixture was stirred at the same temperature for 3 h, and then quenched by the addition of saturated aqueous NH₄Cl solution (5 mL). The reaction mixture was allowed to warm to room temperature, diluted with water (10 mL) and extracted with dichloromethane (3×10 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure. The desired enyne product was obtained after flash column chromatography.

Enantiomeric purity of the enyne 253a was tested as a representative enyne product by chiral HPLC analysis using Phenomenex Lux Cellulose-3 column; hexane/isopropanol (99:1); flow rate = 0.2 mL/min with detection at 254 nm. The result was compared with racemic enyne 253a obtained from the corresponding racemic amino aldehyde 218a.
(S,E)-N-Benzylhex-3-en-5-yn-2-amine (253a)

The title compound 253a was obtained after flash column chromatography (Et₂O/hexane = 3:7) following the general procedure using tert-butyl benzyl(3-hydroxyhexa-4,5-dien-2-yl)carbamate 218a (0.32 g, 1.06 mmol) and NaH (60% in mineral oil, 0.085 g, 2.12 mmol, 2.00 equiv.) in THF (1.80 mL). The isolated yield was calculated for the two steps starting from the aldehyde. Yellow oil (0.141 g, 69%). Rf (Et₂O/hexane = 3:7) = 0.32. [α]D²³ = −74.2 (c 0.3 CHCl₃). The enantiopurity was determined by chiral HPLC using a Phenomenex Lux Cellulose-3 column; hexane/isopropyl alcohol (99:1); flow rate = 0.2 mL/min; 254 nm; single peak, t = 47.71 min, >99% ee. Racemic 253a, prepared from racemic N-Bn,N-Boc alanal 218a, showed two peaks at t = 46.99 min and t = 48.65 min (peak area ratios = 1:1) with the same solvent system and flow rate. ¹H NMR (400 MHz, CDCl₃) δ 1.18 (d, 3H, J = 6.5 Hz, CH₃), 1.48 (br s, 1H, NH), 2.85 (dd, 1H, J = 2.2, 0.6 Hz, CH alkyne), 3.25-3.29 (m, 1H, CH), 3.66 (d, 1H, J = 12.5 Hz, CHPh), 5.61 (ddd, 1H, J = 12.5 Hz, CHPh), 6.14 (ddd, 1H, J = 16.0, 7.7, 0.6 Hz, =CH), 7.22-7.33 (m, 5H, 5CH₆). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 21.5, 51.4, 54.9, 77.0, 82.0, 108.8, 127.0, 128.0, 128.4, 140.3, 149.6. IR (νmax/cm⁻¹) 3288 (m), 3027 (w), 2964 (m), 2841 (w), 1452 (s), 1154 (m), 1104 (m), 958 (s), 732 (s), 697 (s), 623 (s). HRMS (ESI-TOF) m/z calcd for C₁₃H₁₆N [M + H]⁺ 186.1283, found 186.1279.

(S,E)-N-BenzylOct-5-en-7-yn-4-amine (253b)

The title compound 253b was obtained after flash column chromatography (Et₂O/hexane = 3:7) following the general procedure using tert-butyl benzyl(5-hydroxyocta-6,7-dien-4-yl)carbamate 218b (0.31 g, 0.93 mmol) and NaH (60% in mineral oil, 0.075 g, 1.86 mmol, 2.00
equiv.) in THF (1.5 mL). The isolated yield was calculated for the two steps starting from the aldehyde. Yellow oil (0.156 g, 75%). $R_f$ (Et$_2$O/hexane = 3:7) = 0.43. $[\alpha]_D^{23}$ = -49.5 (c 0.4 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.86 (t, 3H, $J = 10.0$ Hz, $CH_3$), 1.18 (br s, 1H, $NH$), 1.25-1.31 (m, 2H, $CH_2$), 1.32-1.47 (m, 2H, $CH_2$), 2.85 (d, 1H, $J = 2.2$ Hz, $CH$ alkyne), 3.03 (q, 1H, $J = 7.0$ Hz, $CH$), 3.57 (d, 1H, $J = 13.5$ Hz, $CH$Ph), 3.76 (d, 1H, $J = 13.5$ Hz, $CH$Ph), 5.24 (dd, 1H, 16.0, 2.0 Hz, $=CH$), 6.06 (dd, 1H, $J = 16.0$, 8.2 Hz, $=CH$), 7.18-7.28 (m, 5H, 5$CH_2$). $^{13}$C$^1$H NMR (125 MHz, CDCl$_3$) $\delta$ 14.1, 19.1, 37.8, 51.3, 59.8, 77.1, 82.1, 109.7, 126.9, 128.1, 128.4, 140.5, 148.8. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3287 (m), 2956 (s), 2930 (s), 2872 (m), 2364 (w), 1453 (s), 1102 (m), 958 (s), 731 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C$_{15}$H$_{20}$N [M + H]$^+$ 214.1596, found 214.1595.

$(S,E)$-N-Benzyl-2-methyloct-5-en-7-yn-4-amine (253c)

The title compound 253c was obtained after flash column chromatography (Et$_2$O/hexane = 3:7) following the general procedure using tert-butyl benzyl(5-hydroxy-2-methylocta-6,7-dien-4-yl)carbamate 218c (0.40 g, 1.157 mmol) and NaH (60% in mineral oil, 0.093 g, 2.31 mmol, 2.00 equiv.) in THF (2.0 mL). The isolated yield was calculated for the two steps starting from the aldehyde. Yellow oil (0.198 g, 71%). $R_f$ (Et$_2$O/hexane = 3:7) = 0.47. $[\alpha]_D^{23}$ = -54.0 (c 0.4 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.85 (t, 6H, $J = 6.5$ Hz, 2$CH_3$), 1.27-1.37 (m, 3H, $NH$ and $CH_2$), 1.62-1.67 (m, 1H, $CH$), 2.86 (dd, 1H, $J = 2.3$, 0.6 Hz, $CH$ alkyne), 3.12 (q, 1H, $J = 7.5$ Hz, $CH$), 3.59 (d, 1H, $J = 13.0$ Hz, $CH$Ph), 3.80 (d, 1H, $J = 13.0$ Hz, $CH$Ph), 5.57 (ddd, 1H, $J = 16.0$, 2.2, 0.8 Hz, $=CH$), 6.04 (ddd, 1H, $J = 16.0$, 8.3, 0.6 Hz, $=CH$), 7.22-7.29 (m, 5H, 5$CH_2$). $^{13}$C$^1$H NMR (125 MHz, CDCl$_3$) $\delta$ 14.1, 19.1, 37.8, 51.3, 59.8, 76.9, 82.0, 109.5, 126.9, 128.1, 128.4, 140.4, 148.9. IR ($\nu_{\text{max}}$/cm$^{-1}$) 3297 (m), 2956 (s), 2930 (s), 2872 (m), 2364 (w), 1453 (s), 1102 (m), 958 (s), 731 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C$_{16}$H$_{22}$N [M + H]$^+$ 228.1752, found 228.1745.
(S,E)-N-Benzyl-1-phenylhex-3-en-5-yn-2-amine (253d)

The title compound 253d was obtained after flash column chromatography (Et$_2$O/hexane = 3:7) following the general procedure using tert-butyl benzyl(3-hydroxy-1-phenylhexa-4,5-dien-2-yl)carbamate 218d (0.57 g, 1.52 mmol) and NaH (60% in mineral oil, 0.121 g, 3.04 mmol, 2.00 equiv.) in THF (2.5 mL). The isolated yield was calculated for the two steps starting from the aldehyde. Colorless oil (0.31 g, 81%). $R_f$ (Et$_2$O/hexane = 3:7) = 0.36. $[\alpha]_{D}^{23} = -56.5$ (c 0.4 CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 1.50 (br s, 1H, N$H$), 2.70-2.85 (m, 2H, C$_2$H$_2$Ph), 2.86 (d, 1H, $J$ = 2.3 Hz, CH alkyne), 3.33-3.38 (m, 1H, CH), 3.57 (d, 1H, $J$ = 16.0 Hz, CHPh), 3.79 (d, 1H, $J$ = 16.0 Hz, CHPh), 5.59 (ddd, 1H, $J$ = 15.9, 2.3, 1.0 Hz, =CH), 6.15 (dd, 1H, $J$ = 16.0, 7.8 Hz, =CH), 7.08-7.24 (m, 10H, 10CH$_2$). $^{13}$C{1H} NMR (100 MHz, CDCl$_3$) δ 42.0, 51.2, 60.7, 77.3, 82.0, 110.0, 126.5, 126.9, 127.9, 128.3, 128.5, 129.3, 137.7, 140.0, 147.8. IR (v$_{max}$/cm$^{-1}$) 3283 (m), 3026 (w), 2917 (w), 2101 (w), 1602 (w), 1494 (s), 1453 (s), 958 (s), 732 (s), 696 (s), 645 (s). HRMS (ESI-TOF) m/z calcd for C$_{19}$H$_{20}$N [M + H]$^+$ 262.1596, found 262.1585.

(3S,3E)-N-Benzyl-2-methylhept-4-en-6-yn-3-amine (253e)

The title compound 253e was obtained after flash column chromatography (Et$_2$O/hexane = 3:7) following the general procedure using tert-butyl benzyl((3S)-4-hydroxy-2-methylhepta-5,6-dien-3-yl)carbamate 218e (0.30 g, 0.90 mmol) and NaH (60% in mineral oil, 0.072 g, 1.81 mmol, 2.00 equiv.) in THF (1.5 mL). The isolated yield was calculated for the two steps starting from the aldehyde. Colourless oil (0.115 g, 57%). $R_f$ (Et$_2$O/hexane = 3:7) = 0.48. $[\alpha]_{D}^{23} = -65.5$ (c 0.4 CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) δ 0.87 (d, 3H, $J$ = 6.8 Hz, CH$_3$), 0.92 (d, 3H, $J$ = 6.8 Hz, CH$_3$), 1.27 (bs, 1H, NH), 1.66-1.75 (m, 1H, CH), 2.80-2.83 (m, 1H, CH), 2.85 (dd, 1H,
\( J = 2.3, 0.6 \text{ Hz, } CH \text{ alkyne) }, 3.58 (d, 1 \text{H, } J = 12.0 \text{ Hz, } CHPh), 3.82 (d, 1 \text{H, } J = 12.0 \text{ Hz, } CHPh),\)
\( 5.55 (ddd, 1 \text{H, } J = 16.0, 2.3, 0.9 \text{ Hz, } =CH), 6.07 (ddd, 1 \text{H, } J = 16.0, 8.4, 0.6 \text{ Hz, } =CH), 7.20-7.33 (m, 5 \text{H, } 5CH_Ar). \)
\( ^{13}\text{C}^{'1}\text{H} \text{ NMR (100 MHz, CDCl}_3 \) \( \delta 18.4, 19.3, 32.5, 51.4, 65.6, 76.7, 82.1, 110.4, 126.8, 128.0, 128.3, 140.5, 146.8. \ IR (v_{\text{max/cm}^{-1}}) 3289 (m), 3027 (w), 2958 (m), 2872 (m), 2101 (w), 1453 (s), 1366 (m), 1100 (m), 960 (s), 732 (s), 697 (s), 606 (s). \ HRMS (ESI-TOF) m/z calcd for C\text{\textsubscript{15}}H\text{\textsubscript{20}}N \ [M + H]^+ 214.1596, found 214.1597.

### Synthesis of Unconjugated (E)-Enediynes (254a-g)

The enediynes 254 were prepared following a previously reported procedure. Potassium carbonate (4.00 equiv.) was added to a stirred solution of the enyne 253 in CH\textsubscript{3}CN (0.2 M). Then, propargyl bromide (80% in toluene, 2.00 equiv.) was added dropwise and the mixture was stirred and heated at reflux for 24 h. The reaction mixture was cooled, then washed with saturated aqueous NaHCO\textsubscript{3} solution (5 mL) and water (10 mL), dried (Na\textsubscript{2}SO\textsubscript{4}), concentrated under reduced pressure and purified by flash column chromatography to obtain the title products 254.

\((S,E)-N\text{-Benzyl-}N\text{-}(prop-2-yn-1-yl)\text{hex-3-en-5-yn-2-amine (254a)}\)

The title compound 254a was obtained after flash column chromatography (EtOAc/hexane = 2:8) following the general procedure using \((S,E)-N\text{-benzylhex-3-en-5-yn-2-amine 253a (0.07 g, 0.38 mmol), propargyl bromide (80% in toluene, 0.084 mL, 2.00 equiv.) and Potassium
carbonate (0.21 g, 1.51 mmol, 4.00 equiv.) in CH$_3$CN (2.0 mL). Yellow oil (0.056 g, 66%). R$_f$
(EtOAc/hexane = 2:8) = 0.73. [α]$^2_0^{+} = -32.0$ (c 1.0 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 1.26
(d, 3H, =C$_H$), 2.21 (s, 1H, CH$_2$), 2.86 (d, 1H, J = 2.2 Hz, CH$,J$), 3.29 (AB$_g$, 2H, J =
16.5 Hz, CH$_2$), 3.41-3.44 (m, 1H, CH), 3.61 (d, 1H, J = 13.0 Hz, CHP$_{	ext{H}}$), 3.74 (d, 1H, J = 13.0
Hz, CHP$_{	ext{H}}$), 5.67 (dd, 1H, J = 16.1, 2.3 Hz, =CH$J$), 6.29 (dd, 1H, J = 16.0, 7.7 Hz, =CH$J$), 7.24-
7.34 (m, 5H, 5CH$_{Ar}$). $^{13}$C$^1$H NMR (125 MHz, CDCl$_3$) δ 17.9, 38.5, 54.1, 58.2, 73.0, 77.3,
79.5, 82.0, 109.6, 127.1, 128.3, 128.8, 139.0, 148.5. IR ($\nu$_{max}/cm$^{-1}$) 3291 (m), 2957 (m), 2871
(w), 2103 (w), 1602 (w), 1454 (m), 1362 (m), 1105 (m), 961 (s), 738 (s), 698 (s), 635 (s).
HRMS (ESI-TOF) m/z calcd for C$_{16}$H$_{17}$NNa [M + Na]$^+$ 246.1259, found 246.1267.

(S,E)-N-Benzyl-N-(prop-2-yn-1-yl)oct-5-en-7-yn-4-amine (254b)

The title compound 254b was obtained after flash column chromatography (Et$_2$O/hexane = 2:8)
following the general procedure using (S,E)-N-benzyloct-5-en-7-yn-4-amine 253b (0.10 g, 0.47
mmol), potassium carbonate (0.26 g, 1.88 mmol, 4.0 equiv.) and propargyl bromide (80% in
toluene, 0.10 mL, 2.0 equiv.) in CH$_3$CN (2 mL). Orange oil (0.091 g, 77%). R$_f$(Et$_2$O/hexane =
2:8) = 0.71. [α]$^2_0^{+} = -33.8$ (c 1.0 CHCl$_3$). $^1$H NMR (500 MHz, CDCl$_3$) δ 0.90 (t, 3H, =C$_H$),
1.32-1.40 (m, 2H, C$_H$), 1.42-1.48 (m, 1H, C$_H$), 1.68-1.72 (m, 1H, CH$J$), 2.20 (d, 1H, J =
2.0 Hz, CH$J$), 2.86 (d, 1H, J = 1.5 Hz, CH$J$), 3.21-3.32 (m, 3H, CH and C$_H$), 3.53 (d, 1H, J =
13.5 Hz, CHP$_{	ext{H}}$), 3.82 (d, 1H, J = 13.5 Hz, CHP$_{	ext{H}}$), 3.61 (dd, 1H, J = 16.0, 1.5 Hz, =CH$J$), 6.25
(dd, 1H, J = 16.0, 7.7 Hz, =CH$J$), 7.21-7.33 (m, 5H, 5CH$_{Ar}$). $^{13}$C$^1$H NMR (125 MHz, CDCl$_3$)
δ 14.1, 19.2, 34.3, 38.6, 54.0, 62.9, 72.7, 77.0, 80.1, 82.0, 111.0, 127.0, 128.3, 128.8, 139.1,
146.1. IR ($\nu$_{max}/cm$^{-1}$) 3291 (m), 2957 (m), 2871 (w), 1602 (w), 1454 (m), 1362 (m), 1105 (m),
961 (s), 738 (s), 698 (s), 635 (s). HRMS (ESI-TOF) m/z calcd for C$_{18}$H$_{22}$N [M + H]$^+$ 252.1752,
found 252.1756.
The title compound 254c was obtained after flash column chromatography (Et₂O/hexane = 2:8) following the general procedure using (S,E)-N-benzyl-2-methyloct-5-en-7-yn-4-amine 253c (0.10 g, 0.44 mmol), potassium carbonate (0.24 g, 1.76 mmol, 4.00 equiv.) and propargyl bromide (80% in toluene, 0.10 mL, 0.88 mmol, 2.00 equiv.) in CH₃CN (2.0 mL). Orange oil (0.084 g, 72%). Rf (Et₂O/hexane = 2:8) = 0.66. \[\alpha\]^23_D = –44.4 (c 0.6 CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) δ 0.88 (t, 6H, J = 6.0, 6.5 Hz, 2C₃H₃), 1.29-1.35 (m, 1H, C₅H₁₅), 1.56-1.62 (m, 1H, CH), 1.66-1.70 (m, 1H, CH), 2.20 (s, 1H, CH), 2.86 (d, 1H, J = 1.5 Hz, CH), 3.25 (m, 2H, CH₂), 3.35 (q, 1H, J = 8.5, 6.5 Hz, CH), 3.49 (d, 1H, J = 14.0 Hz, CHPh), 3.84 (d, 1H, J = 14.0 Hz, CHPh), 5.60 (dd, 1H, J = 16.0, 1.5 Hz, =CH), 6.24 (dd, 1H, J = 16.0, 8.0 Hz, =CH), 7.21-7.33 (m, 5H, 5C₆H₅). \(^1\)H{\(^1\)H} NMR (125 MHz, CDCl₃) δ 22.3, 23.0, 24.7, 38.7, 41.4, 53.9, 60.9, 72.6, 77.0, 80.5, 82.0, 111.0, 127.0, 128.3, 128.8, 139.1, 145.7. IR (νmax/cm⁻¹) 3294 (m), 2955 (m), 2923 (m), 1454 (m), 1366 (m), 1109 (m), 962 (s), 736 (s), 697 (s), 630 (s). HRMS (ESI-TOF) m/z calcd for C₁₉H₂₄N [M + H]⁺ 266.1909, found 266.1898.

The title compound 254d was obtained after flash column chromatography (EtOAc/hexane = 2:8) following the general procedure using (S,E)-N-benzyl-1-phenylhex-3-en-5-yn-2-amine 253d (0.33 g, 1.26 mmol), potassium carbonate (0.70 g, 5.04 mmol, 4.00 equiv.) and propargyl bromide (80% in toluene, 0.27 mL, 2.52 mmol, 2.00 equiv.) in CH₃CN (5.0 mL). Colourless oil (0.23 g, 80%). Rf (Et₂O/hexane = 1:9) = 0.48. \[\alpha\]^23_D = –47.2 (c 0.8 CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃) δ 2.22 (t, 1H, J = 2.5 Hz, CH alkyne), 2.68 (m, 1H, CHPh), 2.80 (d, 1H, J = 2.2 Hz, CH alkyne), 3.13 (dd, 1H, J = 13.5, 5.5 Hz, CHPh), 3.34 (dq, 2H, J = 17.5, 2.4 Hz, CH₂),

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3.53-3.57 (m, 1H, CH), 3.63 (d, 1H, J = 14.0 Hz, CHPh), 3.84 (d, 1H, J = 14.0 Hz, CHPh), 5.44 (dd, 1H, J = 16.0, 2.2 Hz, =CH), 6.23 (dd, 1H, J = 16.0, 8.1 Hz, =CH), 7.12-7.28 (m, 10H, 10CHAr). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 38.2, 38.9, 54.2, 64.6, 73.0, 77.3, 80.1, 81.8, 111.4, 126.2, 127.1, 128.2, 128.3, 128.7, 129.4, 138.6, 138.7, 144.7. IR (νmax/cm⁻¹) 3280 (s), 3027 (w), 2814 (w), 1601 (w), 1493 (m), 1453 (m), 1058 (m), 973 (s), 739 (s), 695 (s), 631 (s).

HRMS (ESI-TOF) m/z calcd for C₂₂H₂₂N [M + H]^+ 300.1752, found 300.1746.

(S,E)-N-Benzyl-N-((but-3-yn-1-yl))-2-methyloct-5-en-7-yn-4-amine (254e)

The title compound 254e was obtained after flash column chromatography (Et₂O/hexane = 2:8) following the general procedure using (S,E)-N-benzyl-2-methyloct-5-en-7-yn-4-amine 253e (0.18 g, 0.79 mmol), potassium carbonate (0.43 g, 3.16 mmol, 4.00 equiv.) and 4-bromo-1-butyne (0.22 mL, 2.37 mmol, 3.00 equiv.) in CH₃CN (2 mL) under reflux conditions. Light yellow oil (0.12 g, 54%). Rf (Et₂O/hexane = 2:8) = 0.77. [α]D⁻²³ = -71.1 (c 1.0 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 0.77 (d, 3H, J = 6.5 Hz, CH₃), 0.82 (d, 3H, J = 6.5 Hz, CH₃), 1.21-1.26 (m, 1H, CH), 1.47-1.53 (m, 1H, CH), 1.67-1.71 (m, 1H, CH), 1.93 (t, 1H, J = 2.5 Hz, CH), 2.24-2.28 (m, 2H, CH₂), 2.54-2.59 (m, 1H, CH), 2.74-2.80 (m, 1H, CH), 2.86 (d, 1H, J = 1.5 Hz, CH), 3.10-3.15 (q, 1H, J = 7.5, 8.0 Hz, CH), 3.46 (d, 1H, J = 14.0 Hz, CHPh), 3.78 (d, 1H, J = 14.0 Hz, CHPh), 5.52 (dd, 1H, J = 16.0, 2.3 Hz, =CH), 6.19 (dd, 1H, J = 16.0, 8.5 Hz, =CH), 7.21-7.33 (m, 5H, 5CHAr). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 19.2, 22.6, 22.7, 24.4, 41.1, 48.8, 54.9, 59.5, 69.0, 77.3, 82.0, 83.0, 110.8, 126.9, 128.2, 128.6, 140.0, 145.0. IR (νmax/cm⁻¹) 3294 (m), 2954 (m), 1452 (m), 1365 (m), 1113 (m), 962 (s), 735 (s), 698 (s), 634 (s). HRMS (ESI-TOF) m/z calcd for C₂₀H₂₆N [M + H]^+ 280.2065, found 280.2052.
(S,E)-N-Benzyl-2-methyl-N-(3-phenylprop-2-yn-1-yl)oct-5-en-7-yn-4-amine (254f)

The title compound 254f was obtained after flash column chromatography (Et2O/hexane = 1:9) following the general procedure using (S,E)-N-benzyl-2-methyloct-5-en-7-yn-4-amine 253c (0.16 g, 0.70 mmol), potassium carbonate (0.39 g, 2.81 mmol, 4.00 equiv.) and 3-chloro-1-phenyl-1-propyne (0.19 mL, 1.40 mmol, 2.00 equiv.) in CH3CN (3 mL). Yellow oil (0.20 g, 83%). Rf (Et2O/hexane = 1:9) = 0.23. [α]D25 = –70.4 (c 0.6 CHCl3). 1H NMR (500 MHz, CDCl3) δ 0.9 (t, 6H, J = 7.5, 7.0 Hz, 2CH3), 1.36 (ddd, 1H, J = 13.8, 8.1, 6.1 Hz, CH), 1.56-1.67 (m, 1H, CH), 1.70-1.85 (m, 1H, CH), 2.85 (d, 1H, J = 2.2 Hz, CH alkyne), 3.40-3.57 (m, 5H, CH, CH3Ph and CHPh), 3.90 (d, 1H, J = 13.0 Hz, CHPh), 5.63 (dd, 1H, J = 16.0, 2.3 Hz, =CH), 6.34 (dd, 1H, J = 16.0, 8.9 Hz, =CH), 7.23 (t, 1H, J = 7.2 Hz, CHAr), 7.26-7.32 (m, 5H, 5CHAr), 7.36 (d, 2H, J = 7.0 Hz, 2CHAr), 7.44 (dd, 2H, J = 6.6, 3.0 Hz, 2CHAr). 13C{1H} NMR (125 MHz, CDCl3) δ 22.5, 23.0, 24.7, 39.6, 41.3, 54.2, 61.3, 77.1, 82.2, 85.1, 86.4, 110.9, 123.4, 127.1, 128.0, 128.3, 128.4, 128.9, 131.7, 139.3, 146.0. IR (νmax/cm−1) 3290 (m), 3030 (w), 2953 (m), 1714 (w), 1598 (w), 1490 (s), 1453 (m), 1365 (m), 1104 (m), 961 (s), 755 (s), 736 (s), 690 (s), 638 (s). HRMS (ESI-TOF) m/z calcld for C25H28N [M + H]⁺ 342.2222, found 342.2216.

(S,E)-N-Benzyl-2-methyl-N-(3-(trimethylsilyl)prop-2-yn-1-yl)oct-5-en-7-yn-4-amine (254g)

The title compound 254g was obtained after flash column chromatography (Et2O/hexane = 1:9) following the general procedure using (S,E)-N-benzyl-2-methyloct-5-en-7-yn-4-amine 253c (0.148 g, 0.65 mmol), potassium carbonate (0.36 g, 2.60 mmol, 4.00 equiv.) and 3-bromo-1-(trimethylsilyl)-1-propyne (0.21 mL, 1.30 mmol, 2.00 equiv.) in CH3CN (3 mL). Yellow oil
Au(I)-Catalysed Cycloaromatisation of Enediynes

To a solution of enediyne 254a-g in anhydrous toluene, was added IPrAuCl (10 mol%), AgSbF₆ (10 mol%) under an atmosphere of N₂. The mixture was stirred and heated at reflux for 18 h and then filtered through a pad of silica gel, followed by purification by flash column chromatography to afford the corresponding isoindoline product 255a-g.

Many attempted Au(I)-catalysed cycloaromatisation reactions of the enediynes 254a-g resulted in no desired product, and the ¹H NMR spectrum of the crude reaction mixture indicated complete decomposition of the enediyne starting material. Only the alanine- and phenylalanine-derived isoindolines 255a and 255d were obtained in yields of 70% and 24% respectively.
(S)-2-Benzyl-1-methylisoindoline (255a)

The title compound 255a was obtained after flash column chromatography (Et2O/pentane = 1:9) following the general procedure using (S,E)-N-benzyl-N-(prop-2-yn-1-yl)hex-3-en-5-yn-2-amine 254a (0.034 g, 0.152 mmol) and IPrAuCl (0.0094 g, 0.0152 mmol, 0.10 equiv.), AgSbF6 (0.0052 g, 0.0152 mmol, 0.10 equiv.) in toluene (1.0 mL). Yellow oil (0.024 g, 70%).

Rf (Et2O/pentane = 3:7) = 0.74. [α]252 = −99.2 (c 0.3 CHCl3).

1H NMR (500 MHz, CDCl3) δ 1.47 (d, 3H, J = 6.5 Hz, CH3), 3.57-3.59 (m, 2H, CH2N), 3.93-3.97 (m, 1H, CH), 4.05 (d, 1H, J = 13.0 Hz, CHPh), 4.23 (d, 1H, J = 13.0 Hz, CHPh), 7.12-7.42 (m, 9H, 9CHAr).

13C{1H} NMR (125 MHz, CDCl3) δ 18.8, 57.8, 58.0, 63.7, 121.8, 122.2, 126.7, 126.8, 127.0, 128.3, 128.9, 139.3, 139.4, 144.7. HRMS (ESI-TOF) m/z calcd for C16H18N [M + H]+ 224.1439, found 224.1450. This compound rapidly decomposed and a satisfactory IR spectrum could not be obtained.

(S)-1,2-Dibenzylisoindoline (255d)

The title compound 255d was obtained after flash column chromatography (Et2O/pentane = 1:9) following the general procedure using (S,E)-N-benzyl-1-phenyl-N-(prop-2-yn-1-yl)hex-3-en-5-yn-2-amine 254d (0.030 g, 0.100 mmol) and IPrAuCl (0.0062 g, 0.010 mmol, 0.10 equiv.), AgSbF6 (0.0034 g, 0.010 mmol, 0.10 equiv.) in toluene (1.0 mL). Yellow oil (0.007 g, 24%).

Rf (Et2O/pentane = 1:9) = 0.80. [α]252 = −107.0 (c 0.2 CHCl3).

1H NMR (500 MHz, CDCl3) δ 1.11 (dd, 1H, J = 6.5 Hz, 13.5 Hz, CHPh), 3.20 (dd, 1H, J = 6.5 Hz, 13.5 Hz, CHPh), 3.56 (d, 1H, J = 13.5 Hz, CHPh), 3.63 (d, 1H, J = 13.5 Hz, CHPh), 4.04 (d, 1H, J = 13.0 Hz, C(3)H), 4.09 (d, 1H, J = 13.0 Hz, C(3)H), 4.36-4.39 (m, 1H, CH), 6.92 (d, 1H, J = 7.0 Hz, CHAr), 7.14-7.41 (m, 13H, 13CHAr). HRMS (ESI-TOF) m/z calcd for C22H22N [M + H]+...
300.1752, found 300.1740. This compound rapidly decomposed and satisfactory $^{13}$C NMR and IR spectra could not be obtained.

**(S)-1-Benzyl-4-(but-1-en-3-yn-1-yl)-2-methyl-2,5-dihydro-1H-pyrrole (365)**

The title compound 365 was obtained after flash column chromatography (Et$_2$O/pentane = 1:9) following the general procedure using (S,E)-N-benzyl-N-(prop-2-yn-1-yl)hex-3-en-5-yn-2-amine 254a (0.020 g, 0.090 mmol) and IPrAuCl (0.0056 g, 0.009 mmol, 0.10 equiv.), AgSbF$_6$ (0.0031 g, 0.009 mmol, 0.10 equiv.) in DCE (1.0 mL). Yellow oil (0.002 g, 10%). The corresponding isoindoline 255a was also isolated (25%). 365: R$_f$ (Et$_2$O/pentane = 1:9) = 0.75.

$^1$H NMR (mixture of two isomers (ca. 1.0:1.5 cis/trans)) (500 MHz, CDCl$_3$) $\delta$ 1.21 (d, 3H, $J$ = 6.0 Hz, CH$_3$, trans isomer), 1.24 (d, 3H, $J$ = 6.0 Hz, CH$_3$, cis isomer), 2.99 (d, 1H, $J$ = 2.0 Hz, CH alkyne, trans isomer), 3.05 (d, 1H, $J$ = 14.5 Hz, CH, cis isomer), 3.15 (d, 1H, $J$ = 2.5 Hz, CH alkyne, cis isomer), 3.23-3.30 (m, 3H, CH$_2$ cis isomer, CH cis isomer), 3.47-3.52 (m, 2H, CH$_2$ trans isomer), 3.55 (d, 1H, $J$ = 13.5 Hz, CHPhe, trans isomer), 3.70-3.74 (m, 2H, CHPhe trans isomer, CH cis isomer), 3.80 (d, 1H, $J$ = 13.5 Hz, CHPhe cis isomer), 4.05 (d, 1H, $J$ = 13.5 Hz, CHPhe, trans isomer), 5.12 (s, 1H, =C(4)H, cis isomer), 5.29 (d, 1H, $J$ = 16.0 Hz, =CH, trans isomer), 5.77 (s, 1H, =C(4)H, trans isomer), 5.89-5.92 (m, 1H, =CH, cis isomer), 6.71-6.76 (m, 2H, =CH cis isomer and =CH trans isomer), 7.23-7.36 (m, 10H, 2 × 5CH$_{5c}$ cis and trans isomers). The compound rapidly decomposed and satisfactory $^{13}$C NMR, IR, and HRMS data could not be obtained.
Synthesis of Unconjugated (E)-Enediynes (380 and 385)

**General Sonogashira Coupling Method for the Synthesis of 384**

The enyne 253 was dissolved in anhydrous THF (0.50 M), and the solution was added to a mixture of aryl iodide (1.20 equiv.), CuI (0.04 equiv.) and Pd(PPh₃)₂Cl₂ (0.02 equiv.) in Et₃N (2.00 equiv.). The reaction mixture was stirred at room temperature for 18 h, followed by filtration through a pad of Celite. Purification by column chromatography on silica gel (Et₂O/hexane) provides the desired product 384.

**Synthesis of Enediynes (380 and 385)**

The enediynes 380 were prepared via amide coupling reactions of enynes (253 and 384) with propiolic acid following a procedure reported in the literature. To a solution of propiolic acid (1.50 equiv.) in anhydrous CH₂Cl₂ (0.2 M) was added the enyne and DMAP (0.30 equiv.) at 0 °C. Then, DCC (1.50 equiv.) was added slowly and the mixture was stirred at room temperature for 48 h. The reaction mixture was quenched by adding a few drops of HOAc at 0 °C, and the mixture was filtered off through a pad of Celite. The organic layer was successively washed with 10% HCl solution (5 mL), saturated aqueous NaHCO₃ solution (5 mL) and saturated aqueous NaCl solution (5 mL), dried (Na₂SO₄), and concentrated under reduced pressure. The residue was dissolved in dichloromethane and kept in the freezer for 12 h. The heterogeneous
mixture was then filtered and the filtrate was then purified by column chromatography on silica gel (Et₂O/pentane) to obtain the enediynes 380 and 385.

(S,E)-N-Benzyl-8-phenyloct-5-en-7-yn-4-amine (384a)

![Chemical structure](image)

The title compound 384a was obtained after flash column chromatography (Et₂O/hexane = 3:7) following the general procedure using (S,E)-N-benzylcyclooct-5-yn-4-amine 253b (0.12 g, 0.56 mmol), 4-iodobenzene (0.075 mL, 0.67 mmol, 1.20 equiv.), CuI (0.004 g, 0.022 mmol, 4 mol%) and Pd(PPh₃)₂Cl₂ (0.008 g, 0.011 mmol, 2 mol%), and Et₃N (0.15 mL, 1.12 mmol, 2.00 equiv.) in THF (1.0 mL). Colourless oil (0.083 g, 51%). Rf (Et₂O/hexane = 3:7) = 0.35. [α]D² = −100.6 (c 0.3 CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 0.89 (t, 3H, J = 8.0 Hz, CH₃), 1.32-1.53 (m, 4H, 2CH₂), 3.10-3.16 (m, 1H, CH₃-N), 3.65 (d, 1H, J = 12.0 Hz, CH₃Ph), 3.86 (d, 1H, J = 12.0 Hz, CH₃Ph), 5.81 (dd, 1H, J = 15.9, 0.8 Hz, =CH), 6.05 (dd, 1H, J = 15.9, 8.2 Hz, =CH), 7.22-7.33 (m, 9H, 9CH₃), 7.43-7.45 (m, 1H, CH₃). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 14.0, 19.1, 37.9, 51.3, 60.0, 87.8, 89.0, 110.8, 123.4, 126.9, 128.0, 128.1, 128.2, 128.4, 131.4, 140.5, 146.9. IR (νmax/cm⁻¹) 3329 (w), 3026 (w), 2956 (m), 2928 (m), 2201 (w), 1595 (m), 1489 (s), 1101 (m), 1028 (s), 753 (s), 689 (s). HRMS (ESI-TOF) m/z calcd for C₂₁H₂₄N [M + H]⁺ 290.1909, found 290.1915.

(S,E)-N-Benzyl-8-(4-nitrophenyl)cyclooct-5-yn-4-amine (384b)

![Chemical structure](image)

The title compound 384b was obtained after flash column chromatography (Et₂O/hexane = 3:7) following the general procedure using (S,E)-N-benzylcyclooct-5-yn-4-amine 253b (0.185 g,
0.87 mmol), 1-iodo-4-nitrobenzene (0.26 g, 1.04 mmol, 1.20 equiv.), CuI (0.007 g, 0.035 mmol, 4 mol%) and Pd(PPh3)2Cl2 (0.012 g, 0.017 mmol, 2 mol%), and Et3N (0.23 mL, 1.74 mmol, 2.00 equiv.) in THF (3.0 mL). Orange oil (0.24 g, 82%). \( R_f \) (Et2O/hexane = 4:6) = 0.48. \([\alpha]_{D}^{23} = -130.0\) (c 0.3 CHCl3).

\( ^1H \) NMR (400 MHz, CDCl3) \( \delta \) 0.90 (t, 3H, \( J = 8.0 \) Hz, \( CH_3 \)), 1.32-1.54 (m, 4H, 2\( CH_2 \)), 3.13-3.19 (m, 1H, \( CH \)), 3.65 (d, 1H, \( J = 13.2 \) Hz, \( CHPh \)), 3.84 (d, 1H, \( J = 13.2 \) Hz, \( CHPh \)), 5.85 (dd, 1H, \( J = 15.9, 0.9 \) Hz, =\( CH \)), 6.17 (dd, 1H, \( J = 15.9, 8.1 \) Hz, =\( CH \)), 7.21-7.34 (m, 5H, 5\( CH_2Ar \)), 7.51-7.54 (m, 2H, 2\( CH_2Ar \)), 8.14 (m, 2H, 2\( CH_2Ar \)).

\( ^13C\{^1H\} \) NMR (100 MHz, CDCl3) \( \delta \) 14.1, 19.1, 37.8, 51.4, 60.0, 87.4, 93.4, 109.9, 123.6, 127.0, 128.1, 128.4, 130.4, 132.1, 140.4, 146.8, 149.5. IR (\( \nu_{max}/cm^{-1} \)) 3329 (w), 3026 (w), 2956 (m), 2160 (m), 1589 (s), 1514 (s), 1337 (s), 1106 (s), 957 (s), 852 (s), 697 (s).

HRMS (ESI-TOF) \( m/z \) calcd for \( C_{21}H_{23}N_2O_2 \) [M + H]+ 335.1759, found 335.1753.

\((S,E)-N\)-Benzyl-8-(4-methoxyphenyl)oct-5-en-7-yn-4-amine (384c)

\[ \begin{align*}
\text{NH} & \quad \text{Bn} \\
\equiv & \quad \equiv \\
\text{O} & \quad \text{Me}
\end{align*} \]

The title compound 384c was obtained after flash column chromatography (Et2O/hexane = 3:7) following the general procedure using \((S,E)-N\)-benzyloct-5-en-7-yn-4-amine 253b (0.156 g, 0.73 mmol), 4-iodoanisole (0.20 g, 0.876 mmol, 1.20 equiv.), CuI (0.006 g, 0.03 mmol, 4 mol%) and Pd(PPh3)2Cl2 (0.010 g, 0.014 mmol, 2 mol%), and Et3N (0.19 mL, 1.46 mmol, 2.00 equiv.) in THF (3.0 mL). Orange oil (0.12 g, 50%). \( R_f \) (Et2O/hexane = 4:6) = 0.31. \([\alpha]_{D}^{23} = -110.6\) (c 0.3 CHCl3). \( ^1H \) NMR (400 MHz, CDCl3) \( \delta \) 0.89 (t, 3H, \( J = 8.0 \) Hz, \( CH_3 \)), 1.34-1.53 (m, 4H, \( 2CH_2 \)), 3.09-3.15 (m, 1H, \( CH \)), 3.65 (d, 1H, \( J = 12.0 \) Hz, \( CHPh \)), 3.81 (s, 3H, \( OCH_3 \)), 3.85 (d, 1H, \( J = 12.0 \) Hz, \( CHPh \)), 5.80 (dd, 1H, \( J = 15.9, 0.8 \) Hz, =\( CH \)), 6.01 (dd, 1H, \( J = 15.9, 8.3 \) Hz, =\( CH \)), 6.82-6.86 (m, 2H, \( 2CH_2Ar \)), 7.22-7.40 (m, 7H, \( 7CH_2Ar \)). \( ^13C\{^1H\} \) NMR (100 MHz, CDCl3) \( \delta \) 14.0, 19.1, 38.0, 51.3, 55.2, 60.1, 86.5, 89.0, 111.1, 114.0, 115.5, 126.9, 128.1, 128.4, 132.9, 140.5, 146.0, 159.5. IR (\( \nu_{max}/cm^{-1} \)) 3326 (w), 3026 (w), 2955 (m), 2928 (m), 2199 (w), 207
The title compound 384d was obtained after flash column chromatography (Et₂O/hexane = 3:7) following the general procedure using (S,E)-N-benzyloct-5-en-7-yn-4-amine 253b (0.148 g, 0.69 mmol), 4-fluoroiodobenzene (0.10 ml, 0.83 mmol, 1.20 equiv.), CuI (0.0055 g, 0.0277 mmol, 4 mol%) and Pd(PPh₃)₂Cl₂ (0.010 g, 0.014 mmol, 2 mol%), and Et₃N (0.18 mL, 1.386 mmol, 2.00 equiv.) in THF (3.0 mL). Yellow oil (0.177 g, 83%). \( \alpha \) \( \text{D} \) \( ^{23} \) = −117.0 (c 0.6 CHCl₃). **1H NMR** (400 MHz, CDCl₃) \( \delta \) 0.89 (t, 3H, \( J = 8.0 \) Hz, \( CH₃ \)), 1.33-1.51 (m, 4H, 2\( CH₂ \)), 3.10-3.16 (m, 1H, \( CH \)), 3.65 (d, 1H, \( J = 13.2 \) Hz, \( CHPh \)), 3.85 (d, 1H, \( J = 13.2 \) Hz, \( CHPh \)), 5.79 (dd, 1H, \( J = 15.9, 0.8 \) Hz, =CH), 6.05 (dd, 1H, \( J = 15.9, 8.2 \) Hz, =CH), 6.97-7.03 (m, 2H, 2\( CHₐ₁ \)), 7.22-7.27 (m, 1H, \( CHₐ₂ \)), 7.29-7.35 (m, 4H, 4\( CHₐ₂ \)), 7.39-7.44 (m, 2H, 2\( CHₐ₂ \)). **13C{1H} NMR** (100 MHz, CDCl₃) \( \delta \) 14.0, 19.1, 37.9, 51.3, 60.0, 87.50, 87.52, 88.0, 110.6, 115.6 (d, \( J_{C,F} = 22.0 \) Hz), 119.5 (d, \( J_{C,F} = 3.6 \) Hz), 126.9, 128.15, 128.19, 128.4, 133.3 (d, \( J_{C,F} = 9.0 \) Hz), 140.5, 147.0, 162.4 (d, \( J_{C,F} = 247.0 \) Hz). **IR** (\( \nu_{max}/cm^{-1} \)) 3327 (w), 3026 (w), 2957 (m), 2929 (m), 2190 (w), 1598 (m), 1504 (s), 1454 (s), 1229 (s), 1154 (s), 956 (s), 731 (s), 697 (s). **HRMS** (ESI-TOF) \( m/z \) calcd for C₂₁H₂₃NF [M + H]⁺ 308.1814, found 308.1809.
(S,E)-4-(5-(Benzylamino)oct-3-en-1-yn-1-yl)benzaldehyde (384e)

The title compound 384e was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyloct-5-en-7-yn-4-amine 253b (0.20 g, 0.94 mmol), 4-iodobenzaldehyde (0.27 ml, 1.13 mmol, 1.20 equiv.), CuI (0.0075 g, 0.038 mmol, 4 mol%) and Pd(PPh₃)₂Cl₂ (0.0135 g, 0.019 mmol, 2 mol%), and Et₃N (0.26 mL, 1.88 mmol, 2.00 equiv.) in THF (3.0 mL). Orange oil (0.212 g, 71%). Rᵋ(Et₂O/hexane = 5:5) = 0.40. [α]²³ = –155.5 (c 0.4 CHCl₃).

¹H NMR (400 MHz, CDCl₃) δ 0.89 (t, 3H, J = 8.0 Hz, CH₃), 1.32-1.51 (m, 4H, 2C₆H₄), 3.12-3.17 (m, 1H, CH), 3.65 (d, 1H, J = 12.0 Hz, CHPh), 3.84 (d, 1H, J = 12.0 Hz, CHPh), 5.85 (dd, 1H, J = 15.9, 0.9 Hz, =CH), 6.14 (dd, 1H, J = 15.9, 8.1 Hz, =CH), 7.22-7.34 (m, 5H, 5CH₃), 7.54-7.57 (d, 2H, J = 8.4 Hz, 2CH₃), 7.80 (d, 2H, J = 8.4 Hz, 2CH₃), 9.95 (s, 1H, CHO). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 14.1, 19.1, 37.8, 51.4, 60.0, 88.3, 92.1, 110.2, 127.0, 128.1, 128.4, 129.5, 129.7, 132.0, 135.3, 140.4, 148.8, 191.3. IR (νmax/cm⁻¹) 3324 (w), 3026 (w), 2956 (m), 2928 (m), 2197 (m), 1698 (s), 1597 (s), 1453 (m), 1205 (s), 1164 (m), 956 (s), 827 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C₂₂H₂₄NO [M + H]^+ 318.1858, found 318.1858.

(S,E)-N-Benzyl-2-methyl-8-(thiophen-2-yl)oct-5-en-7-yn-4-amine (384f)

The title compound 384f was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyloct-5-en-7-yn-4-amine 253c (0.17 g, 0.796 mmol), 2-iodothiophene (0.10 ml, 0.955 mmol, 1.20 equiv.), CuI (0.0076 g, 0.032 mmol, 4 mol%) and Pd(PPh₃)₂Cl₂ (0.011 g, 0.016 mmol, 2 mol%), and Et₃N (0.20 mL, 1.59 mmol,
2.00 equiv.) in THF (2.0 mL). Light yellow oil (0.123 g, 50%). Rf (Et2O/hexane = 3:7) = 0.37. \([\alpha]_D^{23} = -144.6 \) (c 0.3 CHCl3). 1H NMR (400 MHz, CDCl3) δ 0.86 (d, 3H, J = 5.6 Hz, CH3), 0.88 (d, 3H, J = 5.6 Hz, CH3), 1.26-1.43 (m, 2H, CH2), 1.64-1.71 (m, 1H, CH), 3.15-3.20 (m, 1H, CH), 3.64 (d, 1H, J = 13.2 Hz, CHPh), 3.84 (d, 1H, J = 13.2 Hz, CHPh), 5.82 (dd, 1H, J = 15.8, 0.7 Hz, =CH), 6.02 (dd, 1H, J = 15.8, 8.3 Hz, =CH), 6.94-6.97 (m, 1H, CHAr), 7.19 (d, 1H, J = 4.8 Hz, CHAr), 7.21-7.27 (m, 2H, 2CHAr), 7.32 (d, 4H, J = 4.4 Hz, 4CHAr). 13C{1H} NMR (100 MHz, CDCl3) δ 22.4, 22.9, 24.6, 45.0, 51.3, 58.3, 82.3, 91.6, 110.3, 123.4, 126.9, 127.0, 128.1, 128.4, 131.6, 140.4, 147.1. IR (νmax/cm^-1) 3318 (w), 3025 (w), 2953 (m), 2912 (m), 2197 (w), 1494 (m), 1453 (s), 1197 (m), 955 (s), 828 (s), 695 (s). HRMS (ESI-TOF) m/z calcd for C20H24NS [M + H]+ 310.1629, found 310.1635.

\((S,E)-N\)-Benzyl-2-methyl-8-(naphthalen-1-yl)oct-5-en-7-yn-4-amine (384g)

The title compound 384g was obtained after flash column chromatography (Et2O/hexane = 4:6) following the general procedure using \((S,E)-N\)-benzyl-oct-5-en-7-yn-4-amine 253c (0.17 g, 0.796 mmol), 1-iodonaphthalene (0.10 ml, 0.955 mmol, 1.20 equiv.), CuI (0.0045 g, 0.0228 mmol, 4 mol%) and Pd(PPh3)2Cl2 (0.0080 g, 0.0114 mmol, 2 mol%), and Et3N (0.16 mL, 1.14 mmol, 2.00 equiv.) in THF (3.0 mL). Light yellow oil (0.121 g, 60%). Rf (Et2O/hexane = 4:6) = 0.36. \([\alpha]_D^{23} = -49.0 \) (c 0.2 CHCl3). 1H NMR (400 MHz, CDCl3) δ 0.89 (d, 3H, J = 8.0 Hz, CH3), 0.91 (d, 3H, J = 8.0 Hz, CH3), 1.37-1.49 (m, 2H, CH2), 1.68-1.78 (m, 1H, CH), 3.22-3.28 (m, 1H, CH), 3.70 (d, 1H, J = 12.0 Hz, CHPh), 3.91 (d, 1H, J = 12.0 Hz, CHPh), 5.97 (dd, 1H, J = 15.9, 0.7 Hz, =CH), 6.15 (dd, J = 15.9, 8.3 Hz, 1H, =CH), 7.23-7.27 (m, 1H, CHAr), 7.30-7.37 (m, 4H, 4CHAr), 7.43 (t, 1H, J = 7.2 Hz, CHAr), 7.50-7.60 (m, 2H, 2CHAr), 7.68 (d, 1H, J = 8.0 Hz, CHAr), 7.80-7.86 (m, 2H, 2CHAr), 7.35 (d, 1H, J = 8.0 Hz, CHAr). 13C{1H} NMR (100 MHz, CDCl3) δ 22.5, 22.9, 24.7, 45.1, 51.4, 58.4, 87.2, 92.7, 110.8, 121.1, 125.2, 126.2, 126.3,
The title compound 380a was obtained after flash column chromatography (Et₂O/pentane = 4:6) following the general procedure using (S,E)-N-benzylhex-3-en-5-yn-2-amine 253a (0.10 g, 0.54 mmol), propiolic acid (0.053 mL, 0.81 mmol, 1.50 equiv.), DMAP (0.02 g, 0.16 mmol, 0.30 equiv.) and DCC (0.17 g, 0.81 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Yellow oil (0.079 g, 56%). Rᵣ (Et₂O/pentane = 4:6) = 0.38. [α]ᵢ²₀ = −74.2 (c 0.3 CHCl₃). ¹H NMR (500 MHz, CDCl₃) (mixture (ca. 45:55) of two rotamers) δ 1.14 (d, 3H major, J = 7.0 Hz, CH₃), 1.24 (d, 3H min, J = 7.0 Hz, CH₃), 2.86 (d, 1H major, J = 2.0 Hz, CH alkyne), 2.93 (d, 1H minor, J = 2.0 Hz, CH alkyne), 3.07 (s, 1H major, CH alkyne), 3.22 (s, 1H minor, CH alkyne), 4.28 (d, 1H minor, J = 15.5 Hz, CHPH), 4.62 (d, 1H major, J = 15.5 Hz, CHPH), 4.75 (d, 1H minor, J = 15.5 Hz, CHPH), 4.86 (d, 1H major, J = 15.5 Hz, CHPH), 4.96-4.99 (m, 1H major, CH), 5.20-5.23 (m, 1H minor, CH), 5.48 (dt, 1H major, J = 16.1, 2.0 Hz, =CH), 5.58 (dt, 1H minor, J = 16.1, 2.1 Hz, =CH), 6.13 (m, 1H major and minor), 7.22-7.36 (m, 10H major and minor, 10CH₃). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture (ca. 45:55) of two rotamers) δ 17.0, 18.1, 45.1, 50.1, 51.8, 55.7, 75.7, 76.2, 78.5, 78.9, 79.1, 80.1, 80.8, 81.2, 110.9, 111.1, 127.1, 127.2, 127.5, 127.7, 128.5, 128.7, 137.3, 137.7, 143.6, 144.0, 153.8. IR (vₙₐₓ/cm⁻¹) 3289 (m), 3082 (w), 2104 (m), 1620 (s), 1411 (s), 1329 (m), 1168 (m), 958 (s), 725 (s), 647 (s). HRMS (ESI) m/z calcd for C₁₆H₁₄NO [M + H]+ 260.1051 found 260.1058.
(S,E)-N-Benzyl-N-(oct-5-en-7-yn-4-yl)propiolamide (380b)

The title compound 380b was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-oct-5-en-7-yn-4-amine 253b (0.14 g, 0.65 mmol), propiolic acid (0.065 mL, 0.98 mmol, 1.50 equiv.), DMAP (0.024 g, 0.195 mmol, 0.30 equiv.) and DCC (0.21 g, 0.98 mmol, 1.50 equiv.) in CH₂Cl₂ (4.0 mL). Yellow oil (0.078 g, 45%). Rₚ (Et₂O/pentane = 3:7) = 0.40. [α]₂²² = –84.4 (c 0.4 CHCl₃). ¹H NMR (500 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 0.77 (t, 6H two rotamers, J = 7.5 Hz, 2CH₃), 1.11-1.27 (m, 4H two rotamers, 2CH₂), 1.51-1.56 (m, 4H two rotamers, 2CH₂), 2.83 (d, 1H one rotamer, J = 2.3 Hz, CH alkyne), 2.90 (d, 1H one rotamer, J = 2.3 Hz, CH alkyne), 3.08 (d, 1H one rotamer, J = 1.7 Hz, CH alkyne), 3.20 (s, 1H one rotamer, CH alkyne), 4.36 (d, 1H one rotamer, J = 16.0 Hz, CHPh), 4.63-4.70 (m, 3H two rotamers, 2CHPh and CH), 4.81 (d, 1H one rotamer, J = 16.0 Hz, CHPh), 5.01 (q, 1H one rotamer, J = 7.5 Hz, CH), 5.36-5.51 (m, 1H one rotamer, =CH), 5.61 (dd, 1H one rotamer, J = 16.0, 2.1 Hz, =CH), 6.09 (dt, 2H, J = 16.0, 7.5 Hz, 2(=CH)), 7.23-7.36 (m, 10H two rotamers, 10CH₂Ar). ¹³C{¹H} NMR (125 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 13.5, 13.6, 19.2, 19.5, 33.4, 34.0, 45.3, 51.0, 57.2, 60.6, 76.9, 76.3, 78.2, 78.8, 80.1, 80.9, 81.2, 111.7, 111.9, 127.3, 127.5, 127.9, 128.0, 128.4, 128.6, 137.0, 137.6, 142.6, 143.1, 153.8, 154.2. IR (νmax/cm⁻¹) 3283 (m), 2958 (m), 2930 (m), 2104 (m), 1623 (s), 1411 (s), 1338 (m), 1228 (m), 1167 (m), 956 (s), 737 (s), 695 (s). HRMS (ESI) m/z calcd for C₁₈H₁₉NONa [M + Na]⁺ 288.1364, found 288.1377.
The title compound 380c was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-2-methyloct-5-en-7-yn-4-amine 253c (0.098 g, 0.43 mmol), propiolic acid (0.041 mL, 0.64 mmol, 1.50 equiv.), DMAP (0.016 g, 0.13 mmol, 0.30 equiv.) and DCC (0.135 g, 0.64 mmol, 1.50 equiv.) in CH₂Cl₂ (1.0 mL).

Yellow oil (0.066 g, 55%). Rf (Et₂O/pentane = 3:7) = 0.50. \([\alpha]_D^{23} = -91.6 (c 0.4 \text{ CHCl}_3)\).

\(^1\text{H} \text{NMR}\) (500 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 0.64 (d, 3H one rotamer, J = 6.0 Hz, CH₃), 0.68 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 0.82 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 0.88 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 1.31-1.53 (m, 6H two rotamers, 2CH and 2CH₂), 2.84 (d, 1H one rotamer, J = 2.3 Hz, CH alkyne), 2.91 (d, 1H one rotamer, J = 2.3 Hz, CH alkyne), 3.08 (s, 1H one rotamer, CH alkyne), 3.22 (s, 1H one rotamer, CH alkyne), 4.29 (d, 1H one rotamer, J = 15.0 Hz, CHPh), 4.66-4.82 (m, 4H two rotamers, 3CHPh and CH), 5.08-5.12 (m, 1H one rotamer, CH), 5.45 (dt, 1H one rotamer, J = 16.0, 1.7 Hz, =CH), 5.61 (dt, 1H, J = 16.0, 2.0 Hz, =CH), 6.06-6.13 (m, 2H two rotamers, 2(=CH)), 7.23-7.36 (m, 10H two rotamers, 10CH₆). \(^{13}\text{C} \{^1\text{H}\} \text{NMR}\) (125 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 22.0, 22.24, 22.28, 22.6, 24.3, 24.7, 40.2, 40.9, 45.3, 50.9, 55.4, 58.9, 75.9, 76.3, 78.2, 78.92, 78.94, 80.0, 80.9, 81.2, 111.73, 111.78, 127.3, 127.5, 127.9, 128.0, 128.4, 128.6, 137.0, 137.7, 142.9, 143.3, 153.3, 153.3. \(\text{IR}\) (νmax/cm⁻¹) 3287 (m), 2931 (m), 2103 (m), 1620 (s), 1412 (s), 1231 (s), 958 (s), 737 (s), 634 (s). \(\text{HRMS}\) (ESI-TOF) m/z calcd for C₁₉H₂₂NO [M + H]⁺ 280.1701, found 280.1694.
(S,E)-N-Benzyl-N-(1-phenylhex-3-en-5-yn-2-yl)propiolamide (380d)

\[
\text{Ph} \quad \text{BnN} \quad \equiv \quad \equiv \quad \text{O}
\]

The title compound 380b was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-1-phenylhex-3-en-5-yn-2-amine 253d (0.25 g, 0.956 mmol), propionic acid (0.091 mL, 1.43 mmol, 1.50 equiv.), DMAP (0.035 g, 0.287 mmol, 0.30 equiv.) and DCC (0.30 g, 1.43 mmol, 1.50 equiv.) in CH₂Cl₂ (5.0 mL). Yellow oil (0.150 g, 50%). \( R_f \) (Et₂O/pentane = 3:7) = 0.26. \( [\alpha]_D^{23} = -95.5 \) (c 0.4 CHCl₃). \(^1\)H NMR (500 MHz, CDCl₃ (mixture (ca. 60:40) of two rotamers) \( \delta 2.81-2.97 \) (m, 4H major and minor, C₂H₉Ph and 2C₂H₉alkyne), 3.05-3.16 (m, 4H major and minor, C₂H₉Ph and C₂H₉), 4.29 (d, 1H major, \( J = 16.0 \) Hz, C₈H₇Ph), 4.40-4.70 (m, 2H major and minor, C₂H₈Ph and C₂H), 4.70 (d, 1H minor, \( J = 16.0 \) Hz, C₂H₉Ph), 4.77 (d, 1H major, \( J = 16.0 \) Hz, C₂H₉Ph), 5.22-5.27 (m, 1H major and minor, CH and =CH), 5.53 (d, 1H minor, \( J = 16.0 \) Hz, =CH), 6.11-6.15 (m, 1H minor, =CH), 6.31 (m, 1H major, =CH), 7.04 (d, 4H major and minor, \( J = 6.5 \) Hz, 4CH₉₆), 7.19-7.32 (m, 16H major and minor, 16CH₉₆). \(^{13}\)C\(^{1}\)H NMR (125 MHz, CDCl₃) (mixture (ca. 60:40) of two rotamers) \( \delta 37.9, 39.2, 46.0, 52.9, 60.6, 61.8, 75.8, 76.3, 78.4, 78.7, 79.2, 80.1, 80.8, 81.2, 111.9, 112.3, 126.7, 127.0, 127.4, 127.7, 128.01, 128.06, 128.6, 128.71, 128.78, 129.1, 136.3, 136.4, 137.3, 137.4, 141.7, 141.9, 153.6, 154.0. IR (\( \nu_{\text{max}}/\text{cm}^{-1} \)) 3288 (m), 2931 (m), 2103 (m), 1623 (s), 1496 (s), 1455 (s), 1351 (s), 1152 (m), 956 (s), 732 (s), 697 (s). HRMS (ESI-TOF) \( m/z \) calcd for C₂₂H₁₉NONa [M + Na]\(^+\) 336.1364, found 336.1357.

(Š,E)-N-Benzyl-N-(2-methylhept-4-en-6-yn-3-yl)propiolamide (380e)

\[
\text{BnN} \quad \equiv \quad \equiv \quad \text{O}
\]

The title compound 380e was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (Š,E)-N-benzyl-2-methylhept-4-en-6-yn-3-amine
253e (0.085 g, 0.40 mmol), propiolic acid (0.04 mL, 0.60 mmol, 1.50 equiv.), DMAP (0.015 g, 0.12 mmol, 0.30 equiv.) and DCC (0.13 g, 0.60 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Colourless oil (0.044 g, 52%). Rf (Et₂O/pentane = 3:7) = 0.58. [α]D²³ = –111.0 (c 0.4 CHCl₃).

¹H NMR (400 MHz, CDCl₃) (mixture of (ca. 55:45) two rotamers) δ 0.80-0.92 (m, 6H major and minor, 2CH₃), 1.94-2.00 (m, 1H minor, CH), 2.15-2.24 (m, 1H major, CH), 2.85 (dd, 1H minor, J = 2.3, 0.7 Hz, CH alkyne), 3.09 (s, 1H major, CH alkyne), 3.23 (s, 1H minor, CH alkyne), 3.94 (t, 1H major, J = 10.0 Hz, CH), 4.41 (d, 1H minor, J = 16.0 Hz, CHPh), 4.49-4.54 (m, 1H minor, CH), 4.69-4.81 (m, 3H major and minor, CH₂Ph and CHPh), 5.31 (ddd, 1H major, J = 16.0, 2.2, 0.8 Hz, =CH), 6.01 (ddd, 1H minor, J = 16.0, 8.7, 0.7 Hz, =CH), 6.12 (ddd, 1H major, J = 16.0, 9.4, 0.6 Hz, =CH), 7.21-7.38 (m, 10H major and minor, 10CH₃).

¹3C{¹H} NMR (100 MHz, CDCl₃) (mixture (ca. 55:45) of two rotamers) δ 19.5, 20.18, 20.19, 28.9, 29.9, 45.7, 52.4, 65.5, 68.1, 76.1, 76.4, 77.8, 78.6, 80.3, 80.0, 81.2, 112.8, 113.1, 127.3, 127.9, 128.01, 128.06, 128.4, 128.6, 136.5, 137.2, 142.02, 142.07, 153.7, 154.1. IR (νmax/cm⁻¹) 3286 (m), 2963 (m), 2103 (m), 1617 (s), 1496 (s), 1387 (s), 1225 (s), 960 (s), 739 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C₁₈H₁₉NONa [M + Na]^+ 288.1364, found 288.1366.

(S,E)-N-Benzyl-N-(8-phenyloct-5-en-7-yn-4-yl)propiolamide (385a)

![Structure of (S,E)-N-Benzyl-N-(8-phenyloct-5-en-7-yn-4-yl)propiolamide (385a)](structure.png)

The title compound 385a was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-8-phenyloct-5-en-7-yn-4-amine 384a (0.043 g, 0.19 mmol), propiolic acid (0.02 mL, 0.285 mmol, 1.50 equiv.), DMAP (0.007 g, 0.057 mmol, 0.30 equiv.) and DCC (0.06 g, 0.285 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Colourless oil (0.026 g, 60%). Rf (Et₂O/pentane = 3:7) = 0.60. [α]D²³ = –122.6 (c 0.3 CHCl₃).
\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \text{ (mixture (ca. 50:50) of two rotamers)} \delta 0.78 \text{ (t, 6H two rotamers, } J = 8.0 \text{ Hz, } 2\text{CH}_3), 1.13-1.31 \text{ (m, 4H two rotamers, } 2\text{CH}_2), 1.54-1.64 \text{ (m, 4H two rotamers, } 2\text{CH}_2), 3.07 \text{ (s, 1H one rotamer, CH alkyne), 3.21 (s, 1H one rotamer, CH alkyne), 4.37 (d, 1H two rotamers, } J = 16.0 \text{ Hz, CPh), 4.80-4.64 (m, 3H two rotamers, CH and 2CPh), 4.85 (d, 1H one rotamer, } J = 16.0 \text{ Hz, CPh), 5.01-5.11 (m, 1H one rotamer, CH), 5.71 (dd, 1H one rotamer, } J = 16.0, 1.2 \text{ Hz, } =\text{CH}, 5.86 \text{ (dd, 1H one rotamer, } J = 16.0, 1.5 \text{ Hz, } =\text{CH}, 6.06-6.14 \text{ (m, 2H two rotamers, 2(=CH), 7.22-7.42 (m, 20H two rotamers, 20C Ar).} \]

\[ ^{13}\text{C} \{^1\text{H} \} \text{ NMR} \ (100 \text{ MHz, CDCl}_3) \text{ (mixture (ca. 50:50) of two rotamers)} \delta 13.5, 13.6, 19.2, 19.5, 33.7, 34.2, 45.3, 51.0, 57.4, 60.8, 76.0, 78.7, 80.0, 112.8, 113.0, 127.3, 127.5, 127.8, 128.0, 128.2, 128.32, 128.37, 128.4, 128.6, 131.52, 131.55, 137.1, 137.7, 140.6, 141.0, 154.2. \]

IR (ν\text{max/cm}^{-1}) 3278 (m), 3062 (m), 2958 (m), 2103 (m), 1620 (s), 1489 (m), 1411 (s), 1229 (s), 953 (s), 755 (s), 690 (s).

HRMS (ESI-TOF) m/z calcd for C_{24}H_{23}NO_{11}Na [M + Na]^+ 364.1677, found 364.1671.

\((S, E)-N\text{-Benzyl-N-(8-(4-nitrophenyl)oct-5-en-7-yn-4-yl)propiolamide (385b)}\)

\[ \text{The title compound 385b was obtained after flash column chromatography (Et}_2\text{O/pentane = 3:7) following the general procedure using (S, E)-N-benzyl-8-(4-nitrophenyl)oct-5-en-7-yn-4-amine 384b (0.20 g, 0.60 mmol), propiolic acid (0.058 mL, 0.9 mmol, 1.50 equiv.), DMAP (0.022 g, 0.18 mmol, 0.30 equiv.) and DCC (0.185 g, 0.90 mmol, 1.50 equiv.) in CH}_2\text{Cl}_2 (5.0 mL). Light yellow oil (0.122 g, 53%). R}_f (\text{Et}_2\text{O/pentane = 3:7) = 0.26. [\alpha]^{23}_D = -175.3 \text{ (c 0.3 CHCl}_3). \]  

\[ ^1\text{H NMR} \ (400 \text{ MHz, CDCl}_3) \text{ (mixture (ca. 45:55) of two rotamers)} \delta 0.80 \text{ (m, 6H major and minor, } 2\text{CH}_3), 1.17-1.29 \text{ (m, 4H major and minor, } 2\text{CH}_2), 1.59-1.65 \text{ (m, 4H major and minor, } 2\text{CH}_2), 3.11 \text{ (s, 1H major, CH alkyne), 3.24 (s, 1H minor, CH alkyne), 4.42 (d, 1H minor, } J = 16.0 \text{ Hz, CPh), 4.61-4.67 (m, 1H major, CH), 4.71-4.75 (m, 2H major and minor, 2CPh), 4.86 (d, 1H major, } J = 16.0 \text{ Hz, CPh), 5.05-5.12 (m, 1H minor, CH), 5.68 (dd, 1H} \]
major, \( J = 16.0, 1.2 \, \text{Hz}, =\text{CH} \), 5.86 (dd, 1H minor, \( J = 16.0, 1.6 \, \text{Hz}, =\text{CH} \)), 6.14-6.24 (m, 2H major and minor, 2(=\text{CH}))#, 7.22-7.40 (m, 10H major and minor, 10\( \text{CH}_2 \)), 7.49-7.55 (m, 4H major and minor, 4\( \text{CH}_2 \)), 8.15-8.20 (m, 4H major and minor, 4\( \text{CH}_2 \)). \(^{13}\text{C}^1\text{H} \) NMR (100 MHz, CDCl\(_3\)) (mixture (ca. 45:55) of two rotamers) \( \delta \) 13.5, 13.6, 19.2, 19.5, 33.4, 34.0, 45.3, 51.3, 57.6, 60.7, 75.9, 76.3, 78.9, 80.2, 88.3, 88.9, 91.8, 92.4, 111.91, 111.99, 123.60, 123.64, 127.3, 127.6, 127.9, 128.0, 128.5, 128.7, 130.10, 132.17, 132.2, 136.9, 137.6, 143.1, 143.5, 146.9, 153.8, 154.2. IR \( (\nu_{\text{max}}/\text{cm}^{-1}) \) 3276 (m), 3031 (m), 2959 (m), 2104 (m), 1621 (s), 1590 (s), 1514 (s), 1338 (s), 1107 (s), 953 (s), 853 (s), 737 (s), 695 (s). HRMS (ESI-TOF) \( m/z \) calcd for \( \text{C}_{24}\text{H}_{22}\text{N}_2\text{O}_3\text{Na} \) [M + Na]\(^+\) 409.1528, found 409.1522.

\((\text{S},\text{E})\)-\( \text{N} \)-\( \text{Benzyl-} \)\( \text{N}-\)\( (8-(4\text{-methoxyphenyl})\text{oct-5-en-7-yn-4-yl})\)\( \text{propiolamide} \) (385c)

The title compound 385c was obtained after flash column chromatography (Et\(_2\)O/pentane = 3:7) following the general procedure using \((\text{S},\text{E})\)-\( \text{N} \)-\( \text{benzyl-} \)8-(4-methoxyphenyl)oct-5-en-7-yn-4-amine 384c (0.072 g, 0.225 mmol), propiolic acid (0.021 mL, 0.338 mmol, 1.50 equiv.), DMAP (0.008 g, 0.067 mmol, 0.30 equiv.) and DCC (0.07 g, 0.338 mmol, 1.50 equiv.) in CH\(_2\)Cl\(_2\) (2.0 mL). Colourless oil (0.042 g, 50%). \( R_f \) (Et\(_2\)O/pentane = 3:7) = 0.31. \([\alpha]_D^{23} = -149.5 \) (c 0.3 CHCl\(_3\)). \(^1\text{H} \) NMR (400 MHz, CDCl\(_3\)) (mixture (ca. 50:50) of two rotamers) \( \delta \) 0.77 (t, 6H two rotamers, \( J = 8.0 \, \text{Hz}, 2\text{CH}_3 \)), 1.14-1.27 (m, 4H two rotamers, 2\( \text{CH}_2 \)), 1.52-1.63 (m, 4H two rotamers, 2\( \text{CH}_2 \)), 3.07 (s, 1H one rotamer, \( \text{CH} \) alkyne), 3.20 (s, 1H one rotamer, \( \text{CH} \) alkyne), 3.80 (s, 6H two rotamers, 2(\( \text{OCH}_3 \))), 4.35 (d, 1H one rotamer, \( J = 16.0 \, \text{Hz}, \text{CHPh} \)), 4.68-4.88 (m, 4H two rotamers, 3\( \text{CHPh} \) and \( \text{CH} \)), 5.02-5.08 (m, 1H one rotamer, \( \text{CH} \)), 5.70 (dd, 1H one rotamer, \( J = 16.0, 1.5 \, \text{Hz}, =\text{CH} \)), 5.85 (dd, 1H one rotamer, \( J = 16.0, 1.5 \, \text{Hz}, =\text{CH} \)), 6.02-6.10 (m, 2H two rotamers, 2(=\( \text{CH} \))), 6.81-6.86 (m, 4H two rotamers, 4\( \text{CH}_2 \)), 7.22-7.38 (m, 14H two rotamers, 14\( \text{CH}_2 \)). \(^{13}\text{C}^1\text{H} \) NMR (100 MHz, CDCl\(_3\)) (mixture (ca. 50:50) of two
(S,E)-N-Benzyl-N-(8-(4-fluorophenyl)oct-5-en-7-yn-4-yl)propiolamide (385d)

The title compound 385d was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-8-(4-fluorophenyl)oct-5-en-7-yn-4-amine 384d (0.075 g, 0.244 mmol), propiolic acid (0.023 mL, 0.366 mmol, 1.50 equiv.), DMAP (0.009 g, 0.073 mmol, 0.30 equiv.) and DCC (0.077 g, 0.366 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Colourless oil (0.043 g, 49%). Rf (Et₂O/pentane = 3:7) = 0.39. [α]D23 = –144.6 (c 0.3 CHCl₃).

1H NMR (400 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 0.78 (t, 6H two rotamers, J = 8.0 Hz, 2CH₃), 1.14-1.26 (m, 4H two rotamers, 2CH₂), 1.54-1.60 (m, 4H two rotamers, 2CH₂), 3.08 (s, 1H one rotamer, CH alkyne), 3.22 (s, 1H one rotamer, CH alkyne), 4.37 (d, 1H one rotamer, J = 16.0 Hz, CHPh), 4.63-4.77 (m, 3H two rotamers, CH and 2CHPh), 4.85 (d, 1H one rotamer, J = 16.0 Hz, CHPh), 5.03-5.09 (m, 1H one rotamer, CH), 5.68 (dd, 1H one rotamer, J = 16.0, 1.2 Hz, =CH), 5.85 (dd, 1H one rotamer, J = 16.0 Hz, 1.6 Hz, =CH), 6.05-6.14 (m, 2H two rotamers, 2(=CH)), 6.97-7.03 (m, 4H two rotamers, 4CH₃), 7.23-7.40 (m, 14H two rotamers, 14CH₃). 13C{1H} NMR (100 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 13.5, 13.6, 19.2, 19.5, 33.6, 34.2, 45.3, 51.1, 57.5, 60.8, 76.0, 76.4, 78.8, 80.0, 86.44, 86.46, 86.81, 86.80, 89.2, 89.9, 112.6, 112.8, 115.6 (d, JCF = 22.0 Hz), 115.8, 119.1 (d, JCF = 3.6 Hz), 127.3, 127.5, 127.8, 128.0, 128.4, 128.6, 133.3 (d, JCF = 9.0 Hz), 137.0, 137.7,
The title compound 385e was obtained after flash column chromatography (Et₂O/pentane = 4:6) following the general procedure using \((S,E)-4-(5-(benzylamino)oct-3-en-1-yn-1-yl)benzaldehyde 384e (0.17 g, 0.55 mmol), propiolic acid (0.05 mL, 0.83 mmol, 1.50 equiv.), DMAP (0.020 g, 0.165 mmol, 0.30 equiv.) and DCC (0.17 g, 0.83 mmol, 1.50 equiv.) in CH₂Cl₂ (3.0 mL). Light yellow oil (0.118 g, 58%). \(R_f\) (Et₂O/pentane = 4:6) = 0.40. \([\alpha]_D^{23} = -190.5 (c 0.4\text{ CHCl}_3)\).

\(^1\text{H NMR}\) (400 MHz, CDCl₃) (mixture (ca. 53:47) of two rotamers) \(\delta\) 0.80 (t, 6H \(\text{major}\) and \(\text{minor}\), \(J = 8.0 \text{ Hz}, 2\text{CH}_3\)), 1.16-1.30 (m, 4H \(\text{major}\) and \(\text{minor}\), 2\text{CH}_2\)), 1.58-1.64 (m, 4H \(\text{major}\) and \(\text{minor}\), 2\text{CH}_2\)), 3.11 (s, 1H \(\text{major}\), CH alkyne), 3.24 (s, 1H \(\text{minor}\), CH alkyn), 4.41 (d, 1H \(\text{minor}\), \(J = 16.0 \text{ Hz}, \text{CHPh}\)), 4.65-4.76 (m, 3H \(\text{major}\) and \(\text{minor}\), CH and 2CHPh), 4.86 (d, 1H \(\text{major}\), \(J = 16.0 \text{ Hz}, \text{CHPh}\)), 5.07-5.09 (m, 1H \(\text{minor}\), CH), 5.70 (dd, 1H \(\text{major}\), \(J = 16.0, 1.7 \text{ Hz}, =\text{CH}\)), 5.87 (dd, 1H \(\text{minor}\), \(J = 16.0, 1.6 \text{ Hz}, =\text{CH}\)), 6.12-6.22 (m, 2H \(\text{major}\) and \(\text{minor}\), 2(=CH)), 7.23-7.39 (m, 10H \(\text{major}\) and \(\text{minor}\), 10\text{CH}_Ar\)), 7.51-7.56 (m, 4H \(\text{major}\) and \(\text{minor}\), 4\text{CH}_Ar\)), 7.81-7.84 (m, 4H \(\text{major}\) and \(\text{minor}\), 4\text{CH}_Ar\)), 8.11-8.14 (m, 4H \(\text{major}\) and \(\text{minor}\), 4\text{CH}_Ar\)), 9.99 (s, 1H \(\text{major}\), CHO), 10.00 (s, 1H \(\text{minor}\), CHO).

\(^{13}\text{C}\{^1\text{H}\} \text{NMR}\) (100 MHz, CDCl₃) (mixture (ca. 53:47) of two rotamers) \(\delta\) 13.5, 13.6, 19.2, 19.5, 33.5, 34.1, 45.3, 51.2, 57.5, 60.7, 75.9, 76.3, 78.9, 80.2, 89.3, 89.9, 90.6, 91.1, 112.2, 112.3, 127.3, 127.5, 127.9, 128.0, 128.4, 128.7, 129.4, 129.53, 129.57, 132.01, 132.04, 135.4, 135.5, 136.9, 137.6, 142.4, 142.7, 153.8, 154.2, 191.33, 191.37. \(\text{IR} (\nu_{\max}/\text{cm}^{-1})\) 3229 (m), 3032 (w), 2959 (m), 2103 (m), 1698 (s), 1621 (s), 1411 (s), 1205 (s), 1164 (s), 1164 (s).
(S,E)-N-Benzyl-N-(2-methyl-8-(thiophen-2-yl)oct-5-en-7-yn-4-yl)propiolamide (385f)

The title compound 385f was obtained after flash column chromatography (Et₂O/pentane = 4:6) following the general procedure using (S,E)-N-benzyl-2-methyl-8-(thiophen-2-yl)oct-5-en-7-yn-4-amine 384f (0.08 g, 0.258 mmol), propiolic acid (0.025 mL, 0.387 mmol, 1.50 equiv.), DMAP (0.0095 g, 0.077 mmol, 0.30 equiv.) and DCC (0.081 g, 0.387 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Colourless oil (0.059 g, 63%). Rf (Et₂O/pentane = 5:5) = 0.60. [α]²³ dichloromethane = −188.0 (c 0.2 CHCl₃).

1H NMR (500 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 0.65 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 0.69 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 0.83 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 0.89 (d, 3H one rotamer, J = 6.5 Hz, CH₃), 1.3–1.5 (m, 6H two rotamers, 2CH₂ and 2CH), 3.10 (s, 1H one rotamer, CH alkyne), 3.20 (s, 1H one rotamer, CH alkyne), 4.30 (d, 1H one rotamer, J = 15.0 Hz, C=Ph), 4.69 (d, 1H one rotamer, J = 15.0 Hz, C=Ph), 4.72–4.86 (m, 3H two rotamers, 2C=Ph and CH), 5.13–5.17 (m, 1H one rotamer, CH), 5.70 (dd, 1H one rotamer, J = 16.0 Hz, 1.2 Hz, =CH), 5.85 (dd, 1H one rotamer, J = 16.0, 1.6 Hz, =CH), 6.03–6.16 (m, 2H two rotamers, 2(=CH)), 6.95–6.99 (m, 2H two rotamers, 2CH₃S), 7.15 (d, 1H one rotamer, J = 2.5 Hz, CH₃S), 7.18 (d, 1H one rotamer, J = 2.5 Hz, CH₃S), 7.21–7.37 (m, 12H two rotamers, 10CHAr and 2CH₃S). 13C{1H} NMR (125 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 22.0, 22.2, 22.3, 22.7, 24.3, 24.7, 40.4, 41.0, 45.4, 51.0, 55.7, 59.1, 76.0, 76.4, 78.8, 80.8, 83.6, 84.3, 90.5, 90.9, 112.5, 112.6, 122.9, 123.1, 127.1, 127.31, 127.34, 127.57, 127.59, 127.6 127.8, 128.0, 128.4, 128.6, 131.8, 132.0, 137.0, 137.7, 140.9, 141.2, 153.8, 154.2. IR (νmax/cm⁻¹) 3281 (w), 2957 (m), 2105 (m), 1632 (s), 1495 (s), 220
1198 (m), 1080 (m), 953 (m), 737 (s), 696 (s). **HRMS** (ESI-TOF) *m/z* calcld for C\textsubscript{23}H\textsubscript{24}NOS [M + H]\textsuperscript{+} 362.1579, found 362.1588.

\textit{(S,E)-N-Benzyl-N-(2-methyl-8-(naphthalen-1-yl)oct-5-en-7-yn-4-yl)propiolamide} (385g)

The title compound 385g was obtained after flash column chromatography (Et\textsubscript{2}O/pentane = 4:6) following the general procedure using \textit{(S,E)-N-benzyl-2-methyl-8-(naphthalen-1-yl)oct-5-en-7-yn-4-amine} 384g (0.054 g, 0.152 mmol), propiolic acid (0.015 mL, 0.228 mmol, 1.50 equiv.), DMAP (0.0056 g, 0.0456 mmol, 0.30 equiv.) and DCC (0.047 g, 0.228 mmol, 1.50 equiv.) in CH\textsubscript{2}Cl\textsubscript{2} (2.0 mL). Colourless oil (0.035 g, 57%). \textbf{R}\textsubscript{f} (Et\textsubscript{2}O/pentane = 2:8) = 0.24. \([\alpha]_D^{23} = -104.0 \ (c \ 0.3 \ CHCl_3)\). **\textsuperscript{1}H NMR** (400 MHz, CDCl\textsubscript{3}) (mixture (ca. 50:50) of two rotamers) \(\delta\) 0.70 (d, 3H \textit{two rotamers}, \(J = 6.4 \text{ Hz}, \text{CH}_3\)), 0.74 (d, 3H \textit{two rotamers}, \(J = 6.4 \text{ Hz}, \text{CH}_3\)), 0.87 (d, 3H \textit{two rotamers}, \(J = 6.4 \text{ Hz}, \text{CH}_3\)), 0.83 (d, 3H \textit{two rotamers}, \(J = 6.4 \text{ Hz}, \text{CH}_3\)), 1.39-1.61 (m, 6H \textit{two rotamers}, 2CH\textsubscript{2} and 2CH), 3.09 (s, 1H \textit{one rotamer}, CH alkyne), 3.25 (s, 1H \textit{one rotamer}, CH alkyne), 4.43 (d, 1H \textit{one rotamer}, \(J = 16.0 \text{ Hz}, \text{CHPh}\)), 4.77-4.90 (m, 4H \textit{two rotamers}, 3CHPh and CH), 5.21-5.24 (m, 1H \textit{one rotamer}, CH), 5.86 (dd, 1H \textit{one rotamer}, \(J = 16.0, 1.2 \text{ Hz}, =\text{CH}\)), 6.00 (dd, 1H \textit{one rotamer}, \(J = 16.0, 1.5 \text{ Hz}, =\text{CH}\)), 6.14-6.23 (m, 2H \textit{two rotamers}, 2(=CH)), 7.23-7.44 (m, 12H \textit{two rotamers}, 12CH\textsubscript{Ar}), 7.50-7.65 (m, 6H \textit{two rotamers}, 6CH\textsubscript{Ar}), 7.79-7.86 (m, 2H \textit{two rotamers}, 4CH\textsubscript{Ar}), 8.21-8.26 (m, 2H \textit{two rotamers}, 2CH\textsubscript{Ar}). **\textsuperscript{13}C\textsuperscript{\textsuperscript{1}H} NMR** (100 MHz, CDCl\textsubscript{3}) (mixture (ca. 50:50) of two rotamers) \(\delta\) 22.0, 22.2, 22.3, 22.7, 24.3, 24.7, 40.4, 41.0, 45.3, 50.9, 55.6, 59.1, 76.0, 76.4, 78.8, 80.0, 88.4, 89.1, 91.5, 92.0, 112.8, 112.9, 120.5, 120.7, 125.23, 125.24, 126.10, 126.19, 126.42, 126.48, 126.72, 126.79, 127.3, 127.6, 127.9, 128.1, 128.2, 128.3, 128.4, 128.70, 128.77, 128.9, 130.3, 130.4, 133.15, 133.17, 137.1, 137.8, 141.0, 141.4, 153.9, 154.3. **\textbf{IR}** (\(\nu_{\text{max}}/\text{cm}^{-1}\)) 3279 (w), 3059 (w),
The title compound 380b-Me was obtained after flash column chromatography (Et₂O/pentane = 3:7) following the general procedure using (S,E)-N-benzyl-5-en-7-yn-4-amine 253b (0.083 g, 0.39 mmol), butyanoic acid (0.052 g, 0.59 mmol, 1.50 equiv.), DMAP (0.014 g, 0.12 mmol, 0.30 equiv.) and DCC (0.124 g, 0.59 mmol, 1.50 equiv.) in CH₂Cl₂ (2.0 mL). Colourless oil (0.046 g, 55%). Rf (Et₂O/pentane = 3:7) = 0.46. [α]D²³ = −95.0 (c 0.4 CHCl₃). ¹H NMR (400 MHz, CDCl₃) (mixture (ca. 50:50) of two rotamers) δ 0.77 (dt, 6H two rotamers, J = 4.0 Hz, CH₃), 1.14-1.18 (m, 4H two rotamers, CH₂), 1.49-1.55 (m, 4H two rotamers, CH₂), 1.94 (s, 3H one rotamer, CH₃), 2.03 (s, 3H one rotamer, CH₃), 2.83 (dd, 1H one rotamer, J = 2.2, 0.6 Hz, CH alkyne), 2.90 (dd, 1H one rotamer, J = 2.2, 0.6 Hz, CH alkyne), 4.33 (d, 1H one rotamer, J = 16.0 Hz, CHPH), 4.63-4.71 (m, 4H two rotamers, 2CHPh and 2CH), 4.79 (d, 1H one rotamer, J = 16.0 Hz, CHPH), 4.98-5.04 (m, 1H one rotamer, CH), 5.45 (ddd, 1H one rotamer, J = 16.0, 2.3, 1.3 Hz, =CH), 5.59 (ddd, 1H one rotamer, J = 16.0, 2.3, 1.7 Hz, =CH), 5.99-6.26 (m, 2H two rotamers, 2=CH), 7.19-7.37 (m, 10H two rotamers, 10CHₐ). IR (νmax/cm⁻¹) 3288 (m), 2959 (m), 2239 (m), 2102 (w), 1616 (s), 1431 (s), 1334 (s), 1202 (s), 955 (s), 735 (s), 697 (s). HRMS (ESI-TOF) m/z calcd for C₁₉H₂₁NONa [M + Na]⁺ 302.1521, found 302.1534.

Au(I)-Catalysed Cycloaromatisation of Enediynes

To a solution of the unconjugated (E)-enediynes (380 and 385) in anhydrous toluene (0.07 M) was added [(PPh₃Au)₃O]BF₄ (2.5 mol%) under an atmosphere of N₂. The mixture was stirred and heated at reflux for 18 h and then filtered through a pad of silica gel, followed by
puriﬁcation by ﬂash column chromatography to afford the corresponding isoindolinone products 381 and 386.

(\textit{S})-2-Benzyl-3-methylisoindolin-1-one (381a)

![Chemical structure of 381a]

The title compound 381a was obtained after ﬂash column chromatography (Et2O/hexane = 5:5) following the general procedure using (\textit{S,E})-\textit{N}-benzyl-\textit{N}-(\textit{hex}-3-en-5-yn-2-yl)propiolamide 380a (0.02 g, 0.075 mmol) and [\((\text{PPh}3\text{Au})3\text{O}\)]BF4 (0.003 g, 0.0019 mmol, 0.025 equiv.) in toluene (1.0 mL). Colourless oil (0.016 g, 80%). Rf (Et2O/hexane = 5:5) = 0.37. [\(\alpha\)]\text{D}^{23} = -90.6 (c 0.3 CHCl3). The enantiopurity was determined by chiral HPLC using a Phenomenex Lux Cellulose-3 column; hexane/isopropyl alcohol (90:10); ﬂow rate = 0.5 mL/min; 254 nm; single peak, t = 16.75 min, >99% ee. Racemic 381a, prepared from racemic the amino alanal 217a showed two peaks at t = 16.11 min and t = 16.84 min (peak area ratios 1:1) with the same solvent system and ﬂow rate. \(\text{\textit{H NMR (400 MHz, CDCl3)}}\) \(\delta\) 1.43 (d, 3H, \(J = 8.0\) Hz, \(\text{CH}_3\)), 4.26 (d, 1H, \(J = 16.0\) Hz, \(\text{CHPh}\)), 4.35-4.40 (m, 1H, \(\text{CH}\)), 5.34 (d, 1H, \(J = 16.0\) Hz, \(\text{CHPh}\)), 7.26-7.53 (m, 8H, 8\(\text{CH}_\text{Ar}\)), 7.89 (d, 1H, \(J = 8.0\) Hz, \(\text{CH}_\text{Ar}\)). \(\text{\textit{13C\{}\text{\textit{H NMR (100 MHz, CDCl3)}}\) \(\delta\) 18.0, 43.7, 54.9, 121.9, 123.8, 127.5, 128.0, 128.1, 128.7, 131.5, 131.7, 137.3, 147.0, 168.0. \(\text{\textit{IR (}\nu_{\text{max}}/\text{cm}^{-1}\text{)}}\) 3027 (w), 2970 (w), 1672 (s), 1406 (s), 1153 (m), 976 (m), 693 (s). \(\text{HRMS (ESI-TOF)}\) \(m/z\) calcd for C\text{16}H\text{15}NONa \([\text{M + Na}]^+\) 260.1051, found 260.1058.

(\textit{S})-2-Benzyl-3-propylisoindolin-1-one (381b)

![Chemical structure of 381b]

The title compound 381b was obtained after flash column chromatography (Et2O/hexane =
4:6) following the general procedure using \((S,E)-N\text{-}benzyl-N\text{-}(oct-5-en-7-yn-4-yl)propiolamide 380b\) (0.020 g, 0.075 mmol) and \([\text{PPh}_3\text{Au}]_3\text{O}\)BF\(_4\) (0.003 g, 0.0019 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.0159 g, 79%). \(R_f\) (Et\(_2\)O/hexane = 4:6) = 0.26. 

\([\alpha]^{23}_D = -93.0\ (c\ 0.2\ \text{CHCl}_3)\). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 0.76-0.87 (m, 4H, \(\text{C}_3\text{H}_3\) and \(\text{C}_3\text{H}_3\)), 1.05-1.12 (m, 1H, \(\text{C}_3\text{H}_3\)), 1.88-1.92 (m, 2H, \(\text{C}_2\text{H}_2\)), 4.15 (d, 1H, \(J = 16.0\ \text{Hz}, \text{C}_\text{Ph}\)), 4.42 (t, 1H, \(J = 4.0\ \text{Hz}, \text{C}_\text{H}\)), 5.38 (d, 1H, \(J = 16.0\ \text{Hz}, \text{C}_\text{Ph}\)), 7.26-7.52 (m, 8H, 8\(\text{C}_\text{H}_\text{Ar}\)), 7.89 (d, 1H, \(J = 8.0\ \text{Hz}, \text{C}_\text{H}_\text{Ar}\)). \(^{13}\text{C\{H\} NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 13.9, 15.7, 32.5, 43.8, 58.6, 122.0, 123.7, 127.5, 128.0, 128.1, 128.7, 131.3, 132.4, 137.2, 145.4, 168.6. \(^{13}\text{C\{H\} IR}\) (\(\nu_{\text{max}}/\text{cm}^{-1}\)) 2952 (m), 2869 (m), 1669 (s), 1412 (s), 1355 (s), 1240 (s), 981 (m), 725 (s), 696 (s). \(^{13}\text{C\{H\} HRMS (ESI-TOF)}\) m/z calced for \(\text{C}_{18}\text{H}_{19}\text{NONa} [\text{M} + \text{Na}]^+\) 288.1364, found 288.1357.

\((S)\)-2-Benzyl-3-isobutylisoindolin-1-one (381c)

The title compound 381c was obtained after flash column chromatography (Et\(_2\)O/hexane = 3:7) following the general procedure using \((S,E)-N\text{-}benzyl-N\text{-}(2-methyloct-5-en-7-yn-4-yl)propiolamide 380c\) (0.020 g, 0.071 mmol) and \([\text{PPh}_3\text{Au}]_3\text{O}\)BF\(_4\) (0.0026 g, 0.0018 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.0165 g, 82%). \(R_f\) (Et\(_2\)O/hexane = 3:7) = 0.22. 

\([\alpha]^{23}_D = -98.6\ (c\ 0.3\ \text{CHCl}_3)\). \(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 0.73 (d, 3H, \(J = 6.5\ \text{Hz}, \text{C}_3\text{H}_3\)), 0.88 (d, 3H, \(J = 6.5\ \text{Hz}, \text{C}_3\text{H}_3\)), 1.65-1.72 (m, 2H, \(\text{C}_2\text{H}_2\) and \(\text{C}_2\text{H}_2\)), 1.81-1.85 (m, 1H, \(\text{C}_3\text{H}_3\)), 1.52 (d, 1H, \(J = 15.2\ \text{Hz}, \text{C}_\text{Ph}\)), 4.37-4.40 (m, 1H, \(\text{C}_\text{H}\)), 5.44 (d, 1H, \(J = 15.2\ \text{Hz}, \text{C}_\text{Ph}\)), 7.23-7.53 (m, 8H, 8\(\text{C}_\text{H}_\text{Ar}\)), 7.90 (d, 1H, \(J = 8.0\ \text{Hz}, \text{C}_\text{H}_\text{Ar}\)). \(^{13}\text{C\{H\} NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 12.8, 23.8, 40.1, 43.9, 57.6, 122.5, 123.9, 127.5, 128.0, 128.1, 128.7, 131.2, 132.1, 137.1, 146.1, 168.4. \(^{13}\text{C\{H\} IR}\) (\(\nu_{\text{max}}/\text{cm}^{-1}\)) 2954 (m), 2918 (m), 2849 (m), 1673 (s), 1454 (m), 1413 (s), 1235 (m), 753 (s), 693 (s). \(^{13}\text{C\{H\} HRMS (ESI-TOF)}\) m/z calced for \(\text{C}_{19}\text{H}_{22}\text{NO} [\text{M} + \text{H}]^+\) 280.1701, found 280.1711.
(S)-2,3-Dibenzylisoindolin-1-one (381d)

The title compound 381d was obtained after flash column chromatography (Et$_2$O/hexane = 4:6) following the general procedure using (S,E)-N-benzyl-N-(1-phenylhex-3-en-5-yn-2-yl)propiolamide 380d (0.022 g, 0.070 mmol) and [(PPh$_3$Au)$_3$O]BF$_4$ (0.0026 g, 0.0018 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.017 g, 77%). $R_f$ (Et$_2$O/hexane = 4:6) = 0.33. $[\alpha]_D^{23} = -86.6$ (c 0.2 CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 2.80-2.85 (m, 1H, C$_H$Ph), 3.35-3.40 (m, 1H, C$_H$Ph), 4.22 (d, $J = 15.1$ Hz, C$_H$Ph), 4.57 (dd, $J = 4.8, 8.0$ Hz, C$_H$), 5.46 (d, $J = 15.1$ Hz, C$_H$Ph), 6.87 (d, $J = 8.0$ Hz, C$_H\alpha$), 6.91-7.04 (m, 2H, 2C$_H\alpha$), 7.11-7.52 (m, 10H, 10C$_H$), 7.71-8.00 (m, 1H, C$_H\alpha$). $^{13}$C{$_1$H} NMR (100 MHz, CDCl$_3$) $\delta$ 38.4, 44.2, 59.5, 122.9, 123.8, 127.0, 127.6, 128.1, 128.1, 128.5, 129.4, 131.0, 132.0, 136.0, 137.1, 145.1, 168.4. IR (v$_{max}$/cm$^{-1}$) 3031 (w), 2926 (m), 1684 (s), 1496 (m), 1408 (s), 1288 (s). HRMS (ESI-TOF) m/z calcd for C$_{22}$H$_{20}$NO [M + H]$^+$ 314.1545, found 314.1541.

(S)-2-Benzyl-3-isopropylisoindolin-1-one (381e)

The title compound 381e was obtained after flash column chromatography (Et$_2$O/hexane = 5:5) following the general procedure using (S,E)-N-benzyl-N-(2-methylhept-4-en-6-yn-3-yl)propiolamide 380e (0.020 g, 0.075 mmol) and [(PPh$_3$Au)$_3$O]BF$_4$ (0.003 g, 0.0019 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.016 g, 80%). $R_f$ (Et$_2$O/hexane = 5:5) = 0.36. $[\alpha]_D^{23} = -90.6$ (c 0.3 CHCl$_3$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.51 (d, $J = 8.0$ Hz, C$_H$), 4.12 (d, $J = 16.0$ Hz, C$_H$Ph), 4.28 (d, 1H,
\( J = 4.0 \text{ Hz, } CH \), 5.46 (d, 1H, \( J = 16.0 \text{ Hz, } CH_{Ph} \)), 7.24-7.34 (m, 5H, 5\( CH_{Ar} \)), 7.40-7.51 (m, 3H, 3\( CH_{Ar} \)), 7.91-7.92 (m, 1H, \( CH_{Ar} \)). \(^{13}C\{^1H\} \text{ NMR (100 MHz, CDCl}_3\) \( \delta \) 14.9, 19.0, 28.6, 43.8, 63.7, 123.2, 123.8, 127.5, 128.0, 128.7, 131.0, 133.1, 137.1, 143.5, 168.7. \( \text{IR (\( \nu_{max}/\text{cm}^{-1} \))} \) 2960 (m), 2874 (m), 1671 (s), 1616 (m), 1420 (s), 1295 (m), 736 (s), 695 (s). \( \text{HRMS (ESI-TOF)} \) m/z calcd for C\(_{18}\)H\(_{19}\)NONa [M + Na]\(^+\) 288.1364, found 288.1373.

(\(S\))-2-Benzyl-6-phenyl-3-propylisoindolin-1-one (386a)

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

The title compound 386a was obtained after flash column chromatography (Et\(_2\)O/hexane = 4:6) following the general procedure using (\(S,E\))-N-benzyl-N-(8-phenyloct-5-en-7-yn-4-yl)propiolamide 385a (0.020 g, 0.058 mmol) and [(PPh\(_3\)Au)_3O]BF\(_4\) (0.002 g, 0.00146 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.017 g, 85%). \( R_f \) (Et\(_2\)O/hexane = 4:6) = 0.33. \([\alpha]_{D}^{23} = -103.3 \) (c 0.3 CHCl\(_3\)). \(^1H\) \text{ NMR (400 MHz, CDCl}_3\) \( \delta \) 0.82 (t, 3H, \( J = 8.0 \text{ Hz, } CH_{3} \)), 0.85-0.97 (m, 1H, \( CH \)), 1.07-1.18 (m, 1H, \( CH \)), 1.91-1.96 (m, 2H, \( CH_{2} \)), 4.18 (d, 1H, \( J = 16.0 \text{ Hz, } CH_{Ph} \)), 4.46 (t, 1H, \( J = 4.4 \text{ Hz, } CH \)), 5.41 (d, 1H, \( J = 16.0 \text{ Hz, } CH_{Ph} \)), 7.26-7.49 (m, 9H, 9\( CH_{Ar} \)), 7.62-7.65 (m, 2H, 2\( CH_{Ar} \)), 7.75 (d, 1H, \( J = 8.0 \text{ Hz, } CH_{Ar} \)), 8.11 (s, 1H, \( CH_{Ar} \)). \(^{13}C\{^1H\} \text{ NMR (100 MHz, CDCl}_3\) \( \delta \) 14.0, 15.8, 32.5, 43.9, 58.5, 122.2, 122.4, 127.2, 127.5, 127.7, 128.1, 128.7, 128.9, 130.4, 133.1, 137.2, 140.2, 141.4, 144.3, 168.5. \( \text{IR (\( \nu_{max}/\text{cm}^{-1} \))} \) 2952 (m), 2870 (m), 1670 (s), 1430 (s), 1405 (s), 905 (m), 757 (s), 737 (s), 692 (s). \( \text{HRMS (ESI-TOF)} \) m/z calcd for C\(_{24}\)H\(_{23}\)NONa [M + Na]\(^+\) 364.1677, found 364.1672.
(S)-2-Benzyl-6-(4-nitrophenyl)-3-propylisoindolin-1-one (386b)

The title compound 386b was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyl-N-(8-(4-nitrophenyl)oct-5-en-7-yn-4-yl)propiolamide 385b (0.020 g, 0.052 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00140 mmol, 0.025 equiv.), in toluene (1.0 mL). Orange oil (0.0146 g, 73%). \( \alpha \) \( D \) = −162.0 (c 0.2 CHCl₃).

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 0.80-0.91 (m, 4H, C₃H and C₃H), 1.10-1.20 (m, 1H, CH), 1.94-1.99 (m, 2H, CH₂), 4.19 (d, 1H, \( J \) = 16.0 Hz, CHPh), 4.50 (t, 1H, \( J \) = 4.0 Hz, CH), 5.41 (d, 1H, \( J \) = 16.0 Hz, CHPh), 7.26-7.36 (m, 5H, 5CH₃), 7.49 (d, 1H, \( J \) = 8.0 Hz, CH₃), 7.77-7.81 (m, 3H, 3CH₃), 8.15 (s, 1H, CH₃), 8.31-8.35 (m, 2H, 2CH₃).

\( ^13C\{^1H\} \) NMR (100 MHz, CDCl₃) \( \delta \) 14.0, 15.8, 32.4, 44.0, 58.6, 122.6, 122.9, 124.3, 127.7, 127.9, 128.1, 128.8, 130.5, 133.6, 137.0, 139.0, 145.9, 146.6, 147.4, 168.0. IR (\( \nu_{max}/\text{cm}^{-1}\)) 2957 (m), 2871 (w), 1682 (s), 1410 (s), 1342 (s), 1258 (s), 829 (s), 745 (s), 699 (s). HRMS (ESI-TOF) m/z calcd for C₂₄H₂₂N₂O₃Na [M + Na]⁺ 409.1528, found 409.1521.

(S)-2-Benzyl-6-(4-methoxyphenyl)-3-propylisoindolin-1-one (386c)

The title compound 386c was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyl-N-(8-(4-methoxyphenyl)oct-5-en-7-yn-4-yl)propiolamide 385c (0.020 g, 0.054 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00140 mmol, 0.025 equiv.), in toluene (1.0 mL). White solid (0.014 g, 70%). Mp = 187-189 °C. \( R_f \) (Et₂O/hexane = 5:5) = 0.32. [\( \alpha \) \( D \)] = −122.0 (c 0.2 CHCl₃).

\( ^1H \) NMR (400 MHz, CDCl₃) \( \delta \) 0.82
(S)-2-Benzyl-6-(4-fluorophenyl)-3-propylisoindolin-1-one (386d)

The title compound 386d was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyl-N-(8-(4-fluorophenyl)oct-5-en-7-yn-4-yl)propiolamide 385d (0.020 g, 0.055 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00140 mmol, 0.025 equiv.), in toluene (1.0 mL). Light yellow oil (0.013 g, 65%). Rf (Et₂O/hexane = 5:5) = 0.38. [α]₂³⁰D = −159.0 (c 0.2 CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 0.80-0.93 (m, 4H, CH₃ and CH), 1.10-1.16 (m, 1H, CH), 1.91-1.96 (m, 2H, CH₂), 4.16 (d, 1H, J = 15.2 Hz, CHPh), 4.46 (t, 1H, J = 4.0 Hz, CH₂), 5.41 (d, 1H, J = 15.2 Hz, CHPh), 7.13-7.17 (m, 2H, 2CH₃), 7.26-7.33 (m, 5H, 5CH₂), 7.40-7.43 (m, 1H, CH₃), 7.57-7.61 (m, 2H, 2CH₃), 7.70 (dd, 1H, J = 4.0 Hz, 6.0 Hz, CH₃), 8.06 (s, 1H, CH₃). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 14.0, 15.8, 32.5, 43.9, 58.5, 115.8 (d, J_C,F = 21.4 Hz), 122.0, 122.5, 127.6, 128.1, 128.7, 128. (d, J_C,F = 8.0 Hz), 130.2, 133.2, 136.4 (d, J_C,F = 3.3 Hz), 137.1, 140.4, 144.3, 162.7 (d, J_C,F = 245.0 Hz), 168.4. IR (νmax/cm⁻¹) 3282 (w), 2959 (m), 2103 (m), 1622 (s), 1505 (s), 1411 (s), 1222 (s), 953 (s), 834 (s), 737 (s), 696 (s). HRMS (ESI-TOF) m/z calcd for C₂₄H₂₂NOF [M + H]⁺ 360.1764, found 360.1781.
(S)-4-(2-Benzyl-3-oxo-1-propylisoindolin-5-yl)benzaldehyde (386e)

The title compound 386e was obtained after flash column chromatography (Et₂O/hexane = 4:6) following the general procedure using (S,E)-N-benzyl-N-(8-(4-formylphenyl)oct-5-en-7-yn-4-yl)propiolamide 385e (0.020 g, 0.054 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00140 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.013 g, 65%). \( R_f \) (Et₂O/hexane = 4:6) = 0.30. \([\alpha]_{D}^{29} = -196.0 \ (c \ 0.2 \ \text{CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl₃) δ 0.80-0.93 (m, 4H, C₃H and C₃H), 1.10-1.16 (m, 1H, CH), 1.93-1.98 (m, 2H, CH₂), 4.18 (d, 1H, \( J = 16.0 \ \text{Hz} \), CHPh), 4.49 (t, 1H, \( J = 4.0 \ \text{Hz} \), CH), 5.41 (d, 1H, \( J = 16.0 \ \text{Hz} \), CHPh), 7.23-7.36 (m, 5H, 5CH₃Ar), 7.46-7.49 (m, 1H, 1CH₃Ar), 7.78-7.82 (m, 3H, 3CH₃Ar), 7.97-8.00 (m, 2H, 2CH₃Ar), 8.16 (s, 1H, CH₃Ar), 10.08 (s, 1H, CHO). \(^{13}\)C\(^{1}\)H NMR (100 MHz, CDCl₃) δ 14.0, 15.8, 32.5, 43.9, 58.6, 122.5, 122.8, 127.6, 127.8, 128.1, 128.7, 130.4, 130.5, 133.4, 135.5, 137.0, 140.0, 145.5, 146.1, 168.1, 191.8. IR (\( \nu_{\max} / \text{cm}^{-1} \)) 2958 (m), 2871 (w), 1702 (s), 1680 (s), 1507 (s), 1400 (s), 1370 (s), 1213 (s), 1214 (s), 817 (s), 733 (s), 698 (s). HRMS (ESI-TOF) \( m/z \) calcd for C₂₅H₂₄NO₂ [M + H]⁺ 370.1807, found 370.1823.

(S)-2-Benzyl-3-isobutyl-6-(thiophen-2-yl)isoindolin-1-one (386f)

The title compound 386f was obtained after flash column chromatography (Et₂O/hexane = 5:5) following the general procedure using (S,E)-N-benzyl-N-(2-methyl-8-(thiophen-2-yl)oct-5-en-7-yn-4-yl)propiolamide 385f (0.020 g, 0.054 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00140 mmol, 0.025 equiv.), in toluene (1.0 mL). Yellow oil (0.016 g, 80%). \( R_f \) (Et₂O/hexane = 5:5) = 0.46. \([\alpha]_{D}^{29} = -205.0 \ (c \ 0.2 \ \text{CHCl}_3)\). \(^1\)H NMR (400 MHz, CDCl₃) δ 0.76 (d, 3H, \( J = 8.0 \ \text{Hz} \),
(S)-2-Benzyl-3-isobutyl-6-(naphthalen-1-yl)isoindolin-1-one (386g)

The title compound 386g was obtained after flash column chromatography (Et₂O/hexane = 4:6) following the general procedure using (S,E)-N-benzyl-N-(2-methyl-8-(naphthalen-1-yl)oct-5-en-7-yn-4-yl)propiolamide 385g (0.020 g, 0.049 mmol) and [(PPh₃Au)₃O]BF₄ (0.0018 g, 0.00123 mmol, 0.025 equiv.), in toluene (1.0 mL). Light yellow oil (0.016 g, 80%). Rf (Et₂O/hexane = 4:6) = 0.36. [α]D²³ = −113.3 (c 0.3 CHCl₃). ¹H NMR (400 MHz, CDCl₃) δ 0.83 (d, 3H, J = 5.2 Hz, CH₃), 0.95 (d, 3H, J = 5.2 Hz, CH₃), 1.71-1.76 (m, 1H, CH), 1.80-1.86 (m, 1H, CH), 1.89-1.94 (m, 1H, CH), 4.22 (d, 1H, J = 12.0 Hz, CHPh), 4.47-4.49 (m, 1H, CH), 5.49 (d, 1H, J = 12.0 Hz, CHPh), 7.25-7.45 (m, 5H, 5CH₃), 7.49-7.55 (m, 5H, 5CH₃), 7.64 (dd, 1H, J = 2.0 Hz, 4.8 Hz, CH₃), 7.85-7.93 (m, 3H, 3CH₃). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 22.7, 23.9, 24.4, 40.3, 44.0, 57.6, 122.5, 125.3, 125.4, 125.7, 125.9, 126.3, 127.2, 127.6, 128.1, 128.2, 128.3, 128.7, 131.4, 132.4, 133.2, 133.8, 137.1, 139.1, 140.9, 145.1, 168.3. IR (vmax/cm⁻¹) 3043 (w), 2954 (m), 2867 (w), 1682 (s), 1430 (s), 1397 (s), 1199 (m), 777 (s), 700 (s), 632 (m). HRMS (ESI-TOF) m/z calcd for C₂₉H₂₇NONa [M + Na]⁺ 428.1990, found 428.1982.
The deuterated propiolamide \(385c-d\) was prepared from the enediyne \(385c\) following a procedure reported in the literature as described below.\(^{209}\)

\((S,E)-N\text{-Benzyl-}N\text{-}(8-(4\text{-methoxyphenyl})\text{oct-5-en-7-yn-4-yl})\text{propiolamide-d (385c-d)}\)

To a solution of propiolamide \(385c\) (0.02 g, 0.054 mmol) in CH\(_3\)CN (1.00 mL) was added K\(_2\)CO\(_3\) (0.011 g, 1.50 equiv.), and the mixture was stirred at room temperature for 1 h. Then, D\(_2\)O (0.050 mL, 50.0 equiv.) was added and the mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted by CH\(_2\)Cl\(_2\) (3.00 mL) and dried (Na\(_2\)SO\(_4\)) to obtain the deuterated propiolamide \(385c-d\) with 98% deuterium purity, determined by \(^1\)H NMR analysis. Colourless oil (0.018 g, 90%). \(R_t\) (Et\(_2\)O/hexane = 4:6) = 0.41. \([\alpha]_D^{22} = -139.8\) (c 0.5 CHCl\(_3\)). \(^1\)H NMR (400 MHz, CDCl\(_3\)) (mixture (ca. 1:1) of two rotamers) \(\delta\) 0.77 (t, 3H, \(J = 8.0\) Hz, \(CH_3\)), 1.14-1.28 (m, 2H, \(CH_2\)), 1.52-1.60 (m, 2H, \(CH_2\)), 3.81 (s, 3H, \(OCH_3\)), 4.35 (d, 0.5H, \(J = 16.0\) Hz, \(CH\Phi\)), 4.68-4.88 (m, 2H, \(CH\Phi\) and \(CH\)), 5.01-5.18 (m, 0.5H, \(CH\)), 5.70 (dd, 0.5H, \(J = 1.5, 16.0\) Hz, \(=CH\)), 5.85 (dd, 0.5H, \(J = 1.5, 16.0\) Hz, \(=CH\)), 6.02-6.10 (m, 1H, \(=CH\)), 6.81-6.86 (m, 2H, \(2CH_\alpha\)), 7.22-7.38 (m, 7H, \(7CH_\alpha\)). \(^{13}\)C\({}^1\)H NMR (mixture (ca. 1:1) of two rotamers) (100 MHz, CDCl\(_3\)) \(\delta\) 13.5, 13.6, 19.3, 19.5, 33.7, 34.3, 45.3, 51.0, 55.2, 55.3, 57.5, 60.8, 85.5, 85.8, 90.4, 91.1, 113.1, 113.3, 113.9, 114.0, 115.0, 115.2, 127.2, 127.5, 127.8, 128.0, 128.4,
The title compound \textit{386c-d} was obtained after flash column chromatography (Et\textsubscript{2}O/hexane = 4:6) following the general gold-catalysed reaction procedure using (\textit{S,E})-N-benzyl-N-(8-(4-methoxyphenyl)oct-5-en-7-yn-4-yl)propiolamide-\textit{d} \textit{385c-d} (0.017 g, 0.0456 mmol) and [(PPh\textsubscript{3}Au)\textsubscript{3}O]BF\textsubscript{4} (0.0017 g, 0.00114 mmol, 0.025 equiv.), in toluene (1.0 mL). Light yellow oil (0.011 g, 65\%). \textit{R}\textsubscript{f} (Et\textsubscript{2}O/hexane = 5:5) = 0.42. \([\alpha]^{22}_D = -128.1 (c 0.3 \text{ CHCl}_3)\). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) (mixture of \textit{d}-product and \textit{H}-product) \[\delta = 0.82 \text{ (t, } 3\text{H, } J = 5.6 \text{ Hz, CH}_3), 0.86-0.93 \text{ (m, } 1\text{H, CH}), 1.09-1.15 \text{ (m, } 1\text{H, CH}), 1.90-1.95 \text{ (m, } 2\text{H, CH}_2), 3.86 \text{ (s, } 3\text{H, OCH}_3), 4.16 \text{ (d, } 1\text{H, } J = 12.0 \text{ Hz, CHPh}), 4.45 \text{ (t, } 1\text{H, } J = 4.0 \text{ Hz, CH}_2), 5.41 \text{ (d, } 1\text{H, } J = 12.0 \text{ Hz, CHPh}), 7.00 \text{ (d, } 2\text{H, } J = 8.0 \text{ Hz, 2CH}_\alpha), 7.26-7.34 \text{ (m, } 5\text{H, 5CH}_\alpha), 7.39 \text{ (d, } 1\text{H, } J = 8.0 \text{ Hz, CH}_\alpha), 7.58 \text{ (d, } 2\text{H, 2CH}_\alpha), 7.71 \text{ (d, } 0.93\text{H, } J = 6.4 \text{ Hz, CH}_\alpha), 8.07 \text{ (d, } 0.60\text{H, } J = 4.0 \text{ Hz, CH}_\alpha).\] \textsuperscript{13}C\textsuperscript{1}H NMR (100 MHz, CDCl\textsubscript{3}) (mixture of \textit{d}-product and \textit{H}-product) \[\delta = 14.0, 15.8, 32.5, 43.8, 55.3, 58.5, 114.3, 121.6, 122.4, 127.5, 128.1, 128.2, 128.7, 129.96, 129.98, 132.7, 133.1, 137.2, 141.0, 143.6, 159.4, 168.6.\] \textbf{HRMS} (ESI-TOF) \textit{m/z} calcd for C\textsubscript{25}H\textsubscript{25}DNO\textsubscript{2}Na [M + Na]+ 395.1846, found 395.1847. The percentage of mono-deuteration determined by MS analysis was 41\%, and the percentage of di-deuteration was 12\% (LRMS \textit{m/z} 372 C\textsubscript{23}H\textsubscript{26}NO\textsubscript{2} [M + H] 47\%, \textit{m/z} 373 C\textsubscript{23}H\textsubscript{25}DNO\textsubscript{2} [M + H] 41\%, \textit{m/z} 374 C\textsubscript{23}H\textsubscript{25}D\textsubscript{2}NO\textsubscript{2} [M + H] 12\%).
Deuterium labeling study (b)

The amino aldehyde 217b-d' was obtained using lithium aluminum deuteride (LiAlD₄) reduction of the corresponding ester 248b, followed by TEMPO oxidation.

*tert*-Butyl (S)-benzyl(1-hydroxypentan-2-yl-1,1-d₂)carbamate (249b-d')

To a solution of lithium aluminum deuteride (0.11 g in 5 mL THF, 2.50 mmol, 2.00 equiv.) at 0 °C, was added dropwise a solution of the amino ester 248b (0.40 g, 1.25 mmol) in THF (5 mL) and the mixture was stirred at the same temperature for 30 min. The reaction was quenched by the dropwise addition of acetone (5 mL), filtered, and concentrated under reduced pressure. The crude was purified by flash column chromatography (ethanol/n-hexane = 3:7) to obtain the amino alcohol product 249b-d'. Colourless oil (0.26 g, 70%). *R*<sub>r</sub> (Et<sub>2</sub>O/n-hexane = 3:7) = 0.46. <sup>1</sup>H NMR (400 MHz, CDCl₃) (mixture (ca. 3:2) of rotamers) δ 0.87 (t, 3H, *J* = 8.0 Hz, 3H).
 tert-Butyl (S)-benzyl(1-oxopentan-2-yl-1-d)carbamate (217b-d')

To a stirred solution of tert-butyl (S)-benzyl(1-hydroxypentan-2-yl-1,1-d)carbamate (0.26 g, 0.88 mmol) in CH₂Cl₂ (10 mL) at 0 °C were added saturated aqueous NaHCO₃ solution (5 mL), KBr (0.100 g, 0.88 mmol, 1.00 equiv.), and TEMPO (0.0070 g, 0.044 mmol, 0.05 equiv). NaOCl (2.15 mL, 0.49 M, 1.053 mmol, 1.20 equiv.) was then added with a syringe pump over 30 min. Then, the reaction mixture was quenched with saturated aqueous Na₂S₂O₃ solution (5 mL) and extracted into CH₂Cl₂ (3 × 5 mL). The combined organic layers were dried (Na₂SO₄) and concentrated under reduced pressure to afford the aldehyde (0.23 g, 70%). ¹H NMR (400 MHz, CDCl₃) (mixture (ca. 3:2) of rotamers) δ 0.90 (t, 3H, J = 8.0 Hz, CH₃), 1.34-1.42 (m, 1H, CH), 1.46 (br s, 9H, C(CH₃)₃), 1.66-1.71 (m, 1H, CH), 1.92-2.00 (m, 1H, CH), 3.44 (t, 0.6H, J = 8.0 Hz, CH), 3.77 (br s, 0.4H, CH), 4.12 (d, 0.6H, J = 12.0 Hz, CH₂Ph), 4.19 (d, 0.4H, J = 12.0 Hz, CH₂Ph), 4.72 (d, 0.4H, J = 12.0 Hz, CH₂Ph), 5.01 (d, 0.6H, J = 12.0 Hz, CH₂Ph), 7.26-7.36 (m, 5H, 5CHAr). ¹³C{¹H} NMR (100 MHz, CDCl₃) (mixture (ca. 3:2) of rotamers, minor rotamer indicated by an asterisk) δ 13.9, 19.6, 28.2, 29.2*, 30.4, 51.4*, 51.9, 65.3, 65.5*, 81.0*, 81.5, 127.6, 127.8*, 128.3*, 128.8, 137.7, 138.2*, 155.2, 155.6*, 199.5 (t, J_C,D = 22.0 Hz). HRMS (ESI-TOF) m/z calcd for C₁⁷H₂₄DNO₃Na [M + Na]⁺ 315.1795, found 315.1800.
**tert-Butyl benzyl((4S)-5-hydroxyocta-6,7-dien-4-yl-5-d)carbamate (218b-d')**

The title compound 218b-d' was obtained after flash column chromatography (Et₂O/hexane = 3:7) following general allenylation reaction using tert-butyl (S)-benzyl(1-oxopentan-2-yl-1-d)carbamate 217b-d' (0.23 g, 0.786 mmol), allenylboronic pinacol ester 71 (0.14 mL, 1.022 mmol, 1.30 equiv.), and diethylzinc (0.05 mL, 0.055 mmol, 0.07 equiv.) in toluene (5.0 mL). Colourless oil (0.23 g, 88%). Rf (Et₂O/hexane = 3:7) = 0.38. ¹H NMR (400 MHz, CDCl₃) (mixture of rotamers) δ 0.76-0.88 (m, 3H, C₃H₃), 1.18-1.61 (m, 12H, C(C₃H₃)₃ and C₃H₂ and C₃H), 1.76-1.96 (m, 1H, CH), 3.42-3.58 (m, 1H, CH), 4.11-4.75 (m, 3H, C₃H₂Ph and CH), 4.78 (d, 2H, J = 8.0 Hz, =CH₂ allene), 5.07-5.13 (m, 1H, =CH allene), 7.22-7.32 (m, 5H, 5CH₃Ar). ¹³C{¹H} NMR (100 MHz, CDCl₃) (mixture of rotamers) δ 13.8, 13.9, 14.0, 14.1, 19.7, 20.0, 24.6, 24.7, 28.3, 28.4, 31.1, 52.1, 63.5, 70.4, 77.3, 80.5, 93.2, 127.10, 127.18, 127.3, 127.5, 127.8, 128.0, 128.1, 128.3, 128.4, 139.9, 156.9, 207.1. HRMS (ESI-TOF) m/z calcd for C₂₀H₂₈DNO₃Na [M + Na]+ 355.2108, found 355.2112.

**(S,E)-N-Benzylct-5-en-7-yn-5-d-4-amine (253b-d')**

The title compound 253b-d' was obtained following the general procedure using tert-butyl benzyl((4S)-5-hydroxyocta-6,7-dien-4-yl-5-d)carbamate 218b-d' (0.23 g, 0.69 mmol) and NaH (60% in mineral oil, 0.055 g, 1.38 mmol, 2.0 equiv.) in THF (1.20 mL). The crude was pure enough to use for the next step. Colourless oil (0.14 g, 95%). Rf (Et₂O/hexane = 3:7) = 0.31. ¹H NMR (400 MHz, CDCl₃) δ 0.88 (t, 3H, J = 8.0 Hz, CH₃), 1.27-1.50 (m, 4H, 2CH₂), 2.86 (d, 1H, J = 2.4 Hz, CH alkyn), 3.08 (t, 1H, J = 6.4 Hz, CH), 3.61 (d, 1H, J = 12.0 Hz, CHPPh), 3.81 (d, 1H, J = 12.0 Hz, CHPPh), 5.57 (d, 1H, J = 1.6 Hz, =CH), 7.21-7.33 (m, 5H, 5CH₃Ar). ¹³C{¹H} NMR (100 MHz, CDCl₃) δ 14.0, 19.0, 37.7, 51.3, 59.7, 77.3, 82.0, 109.5, 126.9, 128.1,
128.4, 140.4, 148.4 (t, $J_{C,D} = 23.0$ Hz). HRMS (ESI-TOF) $m/z$ calcd for C$_{15}$H$_{19}$DN [M + H]$^+$ 215.1659, found 215.1634.

$(S,E)$-N-Benzyl-8-(4-methoxyphenyl)oct-5-en-7-yn-5-d-4-amine (384c-d')

The title compound 384c-d' was obtained after flash column chromatography (Et$_2$O/hexane = 4:6) following the general Sonogashira coupling procedure using $(S,E)$-N-benzyloct-5-en-7-yn-5-d-4-amine 253b-d' (0.14 g, 0.94 mmol), 4-iodoanisole (0.33 g, 1.13 mmol, 1.50 equiv.), CuI (0.0073 g, 0.038 mmol, 0.04 equiv.) and Pd(PPh$_3$)$_2$Cl$_2$ (0.0133 g, 0.019 mmol, 0.02 equiv.), and Et$_3$N (0.27 mL, 1.90 mmol, 2.00 equiv.) in THF (1.5 mL). Yellow oil (0.138 g, 46%). $R_f$ (Et$_2$O/hexane = 3:7) = 0.35. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 0.89 (t, 3H, $J = 8.0$ Hz, $CH_3$), 1.32-1.51 (m, 4H, $2CH_2$), 3.12 (t, 1H, $J = 8.0$ Hz, $CH$), 3.66 (d, 1H, $J = 12.0$ Hz, $CHPh$), 3.81 (s, 3H, OCH$_3$), 3.85 (d, 1H, $J = 12.0$ Hz, $CHPh$), 5.79 (s, 1H, =$CH$), 5.82-5.86 (m, 2H, $2CH_2$), 7.23-7.26 (m, 1H, $CH_M$), 7.32 (d, 4H, $J = 8.0$ Hz, $4CH_M$), 7.36-7.40 (m, 2H, $2CH_2$). $^{13}$C{^1H} NMR (100 MHz, CDCl$_3$) $\delta$ 14.0, 19.1, 38.0, 51.3, 55.2, 60.0, 86.4, 89.0, 111.0, 114.0, 115.5, 127.0, 128.1, 128.4, 132.9, 140.5, 145.6 (t, $J_{C,D} = 23.4$ Hz), 159.0. HRMS (ESI-TOF) $m/z$ calcd for C$_{22}$H$_{24}$DNONa [M + Na]$^+$ 343.1897, found 343.1906.
(S,E)-N-Benzyl-N-(8-(4-methoxyphenyl)oct-5-en-7-yn-4-yl-5-d)propionamide

\[ 385c-d' \]

The title compound \(385c-d'\) was obtained after flash column chromatography (Et\(_2\)O/pentane = 4:6) following the general procedure using (S,E)-N-benzyl-8-(4-methoxyphenyl)oct-5-en-7-yn-5-d-4-amine \(384c-d'\) (0.137 g, 0.43 mmol), propionic acid (0.041 mL, 0.645 mmol, 1.50 equiv.), DMAP (0.016 g, 0.13 mmol, 0.30 equiv.) and DCC (0.136 g, 0.645 mmol, 1.50 equiv.) in CH\(_2\)Cl\(_2\) (2.0 mL). Orange oil (0.075 g, 47%). \(R_f\) (Et\(_2\)O/pentane = 4:6) = 0.48. \(\alpha\) \[\text{Et}_2\text{O}\] = –188.6 (c 1.0 CHCl\(_3\)). \(^1\)H NMR (500 MHz, CDCl\(_3\)) (mixture (ca. 1:1) of rotamers) \(\delta\) 0.76 (t, 3H, \(J = 7.5\) Hz, CH\(_3\)), 1.14-1.30 (m, 3H, CH\(_2\) and CH), 1.50-1.60 (m, 1H, CH\(_{\text{Ph}}\)), 3.10 (s, 0.5H, CH alkyn, 3.22 (s, 0.5H, CH alkyn), 3.81 (s, 3H, OCH\(_3\)), 3.34 (0.5H, d, \(J = 15.0\) Hz, CH\(_{\text{Ph}}\)), 3.67-3.71 (m, 1H, CH\(_{\text{Ph}}\) and CH), 3.79 (0.5H, d, \(J = 15.0\) Hz, CH\(_{\text{Ph}}\)), 3.86 (0.5H, d, \(J = 15.0\) Hz, CH\(_{\text{Ph}}\)), 5.06 (t, 0.5H, \(J = 7.5\) Hz, CH), 5.07 (s, 0.5H, =CH), 5.85 (s, 0.5H, =CH), 6.83-6.90 (m, 2H, =CH), 7.23-7.48 (m, 7H, 7CH\(_{\text{Ar}}\)). \(^{13}\)C\(^1\)H NMR (125 MHz, CDCl\(_3\)) (mixture (ca. 1:1) of rotamers) \(\delta\) 13.5, 13.6, 19.2, 19.5, 33.6, 34.1, 45.2, 51.0, 55.2, 55.3, 57.3, 60.0, 75.9, 76.3, 78.8, 80.1, 85.4, 85.7, 90.4, 91.0, 112.9, 113.2, 113.9, 114.0, 114.8, 115.0, 127.2, 127.4, 127.7, 128.0, 128.4, 128.6, 137.0, 137.7, 139.3 (t, \(J_{C,D} = 24.0\) Hz), 139.7 (t, \(J_{C,D} = 24.0\) Hz), 153.8, 154.2, 159.5, 159.6. HRMS (ESI-TOF) \(m/z\) calcld for C\(_{25}\)H\(_{25}\)DNO\(_2\) [M + H]\(^+\) 373.2026, found 373.2040.
The title compound 386c-d' was obtained after flash column chromatography (Et₂O/hexane = 4:6) following the general procedure using (S,E)-N-benzyl-N-(8-(4-methoxyphenyl)oct-5-en-7-yn-4-yl-5-d)propiolamide 385c-d' (0.020 g, 0.054 mmol) and [(PPh₃Au)₃O]BF₄ (0.002 g, 0.00134 mmol, 0.025 equiv.) in toluene (1.0 mL). Colourless oil (0.014 g, 70%). R₁ (Et₂O/hexane = 4:6) = 0.30. [α]D 24 = −117.5 (c 0.2 CHCl₃). ¹H NMR (500 MHz, CDCl₃) δ 0.80-0.94 (m, 4H, CH₃ and CH), 1.07-1.17 (m, 1H, CH), 1.91-1.95 (m, 2H, CH₂), 3.87 (s, 3H, OCH₃), 4.16 (d, 1H, J = 15.0 Hz, CHPh), 4.45 (t, 1H, J = 4.0 Hz, CH), 5.43 (d, 1H, J = 15.0 Hz, CHPh), 6.99-7.02 (m, 2H, 2CH₃), 7.26-7.35 (m, 5H, 5CH₃), 7.39-7.41 (m, 0.85H, CH₂), 7.57-8.00 (m, 2H, 2CH₃), 7.70-7.72 (m, 0.76H, CH₃), 8.07 (s, 0.93H, CH). ¹³C{¹H} NMR (125 MHz, CDCl₃) δ 14.0, 15.6, 15.7, 32.45, 32.47, 43.8, 55.3, 58.40, 58.41, 114.3, 121.61, 121.63, 122.3, 122.4, 127.5, 128.1, 128.2, 128.7, 129.8, 129.9, 132.6, 133.0, 137.1, 141.0, 143.6, 159.3, 168.6. HRMS (ESI-TOF) m/z calcd for C₂₅H₂₄DNO₂Na [M + Na]⁺ 395.1846, found 395.1860. The percentage of mono-deuteration determined by MS analysis was 46%, and the percentage of di-deuteration was 2% (LRMS m/z 372 C₂₅H₂₆NO₂ [M + H]⁺ 52%, m/z 373 C₂₅H₂₅DNO₂ [M + H]⁺ 46%, m/z 374 C₂₅H₂₅D₂NO₂ [M + H]⁺ 2%).
To a solution of AuPPh3Cl (0.036 g, 0.073 mmol, 0.90 equiv.) in CH2Cl2/Et3N (1 mL/0.25 mL) was added \((E)\)-N-benzyl-N-(8-(4-formylphenyl)oct-5-en-7-yn-4-yl)propiolamide 385e (0.030 g, 0.81 mmol) under nitrogen atmosphere and the solution stirred in the dark at room temperature for 18 h. The reaction mixture was then passed through a pad of alumina to obtain the gold acetylide 385e-Au. White solid (0.050 g, 89%). Rf on silica TLC (EtOAc/hexane = 2:8) = 0.53. Mp = 70-73 °C. \([\alpha]_D^{25} = -198.1 (c 0.6 \text{ CHCl}_3)\). \(^1\text{H NMR} (500 \text{ MHz, } \text{CDCl}_3)\) (mixture (ca. 1:1) of two rotamers) \(\delta 0.74-0.80\) (m, 3H, \(\text{CH}_3\)), 1.13-1.35 (m, 2H, \(\text{CH}_2\)), 1.51-1.63 (m, 2H, \(\text{CH}_2\)), 4.38 (d, 0.5H, \(J = 15.5 \text{ Hz, } \text{CHPh}\)), 4.74-4.78 (m, 1H, \(\text{CHPh and CH}\)), 4.87 (d, 0.5H, \(J = 15.5 \text{ Hz, } \text{CHPh}\)), 5.06 (d, 0.5H, \(J = 15.5 \text{ Hz, } \text{CHPh}\)), 5.51-5.55 (m, 0.5H, \(\text{CH}\)), 5.65 (dd, 0.5H, \(J = 16.5, 1.4 \text{ Hz, } \text{CH}=\)), 5.91 (dd, 0.5H, \(J = 16.5, 1.7 \text{ Hz, } \text{CH}=\)), 6.17-6.22 (m, 1H, \(\text{CH}=\)), 7.19-7.35 (m, 4H, \(\text{CH}_2\)), 7.42-7.55 (m, 18H, \(\text{CH}_2\)), 7.80-7.83 (m, 2H, \(\text{CH}_2\)), 10.00 (2 × s, 1H, \(\text{CHO}\)). \(^{13}\text{C}(\text{\textsuperscript{1}H}) \text{NMR} (125 \text{ MHz, CDCl}_3)\) (mixture (ca. 1:1) of two rotamers which complicates interpretation. This compound is unstable to heating, therefore a high temperature NMR experiment was not possible) \(\delta 13.7, 13.8, 19.4, 19.6, 33.6, 34.0, 44.8, 51.5, 56.6, 60.5, 88.7, 91.6, 91.8, 111.2, 111.3, 126.8, 127.3, 128.0, 128.1, 128.21, 128.28, 129.3, 129.52, 129.55, 129.6, 129.7, 129.8, 131.7, 131.9, 132.0, 134.2, 134.3, 135.2, 135.3, 138.5, 138.9, 144.1, 144.6, 155.5, 191.4, 191.5. \(^{31}\text{P NMR} (202 \text{ MHz, CDCl}_3)\) \(\delta 41.5. \text{ IR} (\nu_{\text{max}}/\text{cm}^{-1}) 2961 (\text{w}), 2112 (\text{m}), 1697 (\text{s}), 1595 (\text{s}), 1434 (\text{s}), 1099 (\text{s}), 827 (\text{s}), 691 (\text{s}), 535 (\text{s}), 499 (\text{s}). \text{HRMS} (ESI-TOF) \text{m/z caled for } \text{C}_{43}\text{H}_{38}\text{NO}_2\text{PAu} [\text{M + H}]^+ 828.2306, \text{found } 828.2308.
(2-Benzyl-5-(4-formylphenyl)-1-oxo-3-propylisooindolin-4-yl)triphenylphosphine
gold (386e-Au)

To a solution of (E)-(3-(benzyl(8-(4-formylphenyl)oct-5-en-7-yn-4-yl)amino)-3-oxoprop-1-
yn-1-yl)triphenylphosphine gold 385e-Au (0.015 g, 0.018 mmol) in toluene (1 mL) was added

AuPPh3Cl (0.005 g, 0.0009 mmol, 0.05 equiv.) and then AgBF₄ (0.002 g, 0.0009 mmol, 0.05
equiv.) under nitrogen atmosphere and the solution stirred at room temperature for 5 min. The
reaction mixture was then passed through a pad of alumina and purified by column
chromatography using alumina (EtOAc/hexane = 3:7) to obtain the monogold complex 386e-
Au. The corresponding isoindolinone 386e was also isolated in 69% yield due to
protodeauration by trace moisture. White solid (0.004 g, 27%). Rf on silica TLC
(EtOAc/hexane = 3:7) = 0.76. Mp = 158-161 °C. ¹H NMR (400 MHz, CD₂Cl₂) δ 0.80-0.91 (m,
4H, CH₃ and CH), 1.10-1.17 (m, 1H, CH), 1.90-1.96 (m, 2H, CH₂), 4.16 (d, J = 15.5 Hz, 1H,
CHHPh), 4.35 (t, J = 4.0 MHz, CH), 5.28 (d, J = 15.5 Hz, 1H, CHHPh), 7.15-7.57 (m, 22H,
22CH₃), 7.66 (d, 2H, J = 8.0 MHz, 2CH₃), 7.94 (d, 2H, J = 8.0 MHz, 2CH₃), 9.89 (s, 1H,
CHO). ¹³C{¹H}-APT NMR (100 MHz, CD₂Cl₂) δ 192.0 (CHO), 171.0 (CO), 170.1 (d, J = 111
Hz), 155.2 (ArC), 150.2 (ArC), 144.1 (ArC), 141.3 (ArC), 138.2 (ArC), 134.5 (d, J = 13.4 Hz),
132.1 (ArC), 131.3 (d, J = 49.8 Hz), 131.1 (d, J = 2.4 Hz), 130.1 (ArCH), 128.2 (ArCH), 129.1
(d, J = 11.0 Hz), 128.7 (ArCH), 128.2 (ArCH), 127.3 (ArCH), 119.4 (ArCH), 58.2 (CH), 43.9
(CH₂), 32.9 (CH₂), 16.0 (CH₂), 13.9 (CH₃). ³¹P NMR (162 MHz, CD₂Cl₂) δ 42.9, 33.1 (minor
impurity due to AuPPh3Cl). IR (νmax/cm⁻¹) 2922 (m), 1670 (s), 1434 (s), 1099 (s), 818 (s), 691
(s), 532 (s), 501 (s). HRMS (ESI-TOF) m/z calcd for C₄₃H₃₈NO₂PAu [M + H]^+ 828.2306, found
828.2300.
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Appendix
$^{1}H$

CDCl$_3$

$500$ MHz

$^{13}C$

CDCl$_3$

$125$ MHz

256
$1H$
C\text{DCI3}
500\text{ MHz}$

$207a$
($\delta = 1.1:1$)
(regioselectivity = 98:2)

$13C$
C\text{DCI3}
125\text{ MHz}$

$207a$
($\delta = 1.1:1$)
(regioselectivity = 98:2)
$^{1}H$

CDCl$_3$

500 MHz

206d

($dr = 2.5:1$)

(regioselectivity = 91:9)

$^{13}C$

CDCl$_3$

125 MHz

206d

($dr = 2.5:1$)

(regioselectivity = 91:9)
1H
CDCl3
500 MHz

206e
(dr = 9:1)
(regioselectivity = 91.9)

13C
CDCl3
125 MHz

206e
(dr = 9:1)
(regioselectivity = 91.9)
1H
CDCl₃
300 MHz

230a
(major isomer)

13C
CDCl₃
75 MHz

230a
(major isomer)
1H
CDC13
400 MHz

13C
CDC13
100 MHz
1H
CDCl3
500 MHz

380b

13C
CDCl3
125 MHz

380b

324
1H
CDCl₃
400 MHz

381b

13C
CDCl₃
100 MHz

337
1H
CDCl3
400 MHz

385c-d
(98% D)

13C
CDCl3
100 MHz

385c-d
(98% D)
Publications arising from this thesis
