Development and Application of Rhodium-Catalysed Ynamide Carbometallation Reactions

Thesis Submitted in Accordance with the Requirements of The University of Edinburgh for the Degree of Doctor of Philosophy

By

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Declaration

I hereby declare that, except where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in September 2007, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

Benoit Gourdet
Abstract

Highly stereo- and regioselective rhodium-catalysed carbometallations of ynamides using organometallic reagents have been disclosed. The scope of the process was explored, and investigations revealed that Rh(cod)(acac) acts as an effective precatalyst for carbometallation of ynamides using a range of organozinc reagents. A plausible mechanism has been suggested where an alkenylzinc intermediate is formed. This species has been exploited in further transformations with electrophiles and in cross-coupling reactions, thus providing access to multisubstituted enamides in a stereo- and regioselective manner.

It was also possible to carry out the carbometallation of ynamides using organoboron reagents by using [Rh(cod)(MeCN)$_2$]BF$_4$ as a precatalyst. This complementary protocol allowed the introduction of a greater diversity of substituents, including those carrying sensitive functional groups.

Mechanistic studies, including deuterium labelling, suggested that an alkenylrhodium intermediate was produced during the course of the reaction. With a set of optimised conditions, this species was successfully used in a tandem carbometallation–conjugate addition (or annulation) reaction with bifunctional arylboron reagents. The 2-amidoindene products were obtained in good yields and high regioselectivities.
Preliminary studies on the development of an asymmetric variant of this transformation have been undertaken and the initial results have been reported.

In addition, highly enantioselective dihydroxylation of the enamide substrates prepared from the developed rhodium-catalysed carbometallations of ynamides was readily accomplished using commercially available AD-mix-β. This novel procedure provides an access to a wide range of chiral products that might be difficult to access using existing methods. Finally, as a further exemplification of asymmetric enamide dihydroxylation, this method was applied to a concise total synthesis of the antifungal natural product (+)-Tanikolide.
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Finally, I want to dedicate this work to my family; To my parents for being the great persons they are and for all the support; To my grand-parents, I thank you for your kindness and the numerous great memories from ‘les Duroux’; To my brother and his wife for giving us two wonderful princesses. I want also to thank the ‘Kangoo’ family and all the rest of my family in the North of France, which unfortunately I visit not as often as I would like to.
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<table>
<thead>
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<th>Definition</th>
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<tr>
<td>Ac</td>
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<tr>
<td>acac</td>
<td>acetylacetionate</td>
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<td>d</td>
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<tr>
<td>DBU</td>
<td>diaza(1,3)bicyclo[5.4.0]undecane</td>
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<tr>
<td>de</td>
<td>diastereomeric excess</td>
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<td>dppf</td>
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<tr>
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<td>trifluoromethanesulfonate</td>
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<td>tosyl</td>
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<tr>
<td>UV</td>
<td>ultraviolet spectroscopy</td>
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1.0 The Chemistry of Enamides

1.1 Introduction

Silyl enol ethers have been used as effective intermediates in a wide range of transformations for many decades. However, they are relatively unstable compounds and need to be directly prepared before use due to their propensity towards protonolysis and hydrolysis. In addition, the stereoselective synthesis of highly substituted silyl enol ethers is often non-trivial. Enamines have been employed originally as N-analogues of silyl enol ethers. However, enamines are more reactive than silicon ethers and as a result, are more subject to protonolysis and hydrolysis. Enamides feature noticeable nucleophilic reactivity by virtue of their enamine nature; however, the electron-withdrawing functionality upon the nitrogen centre tempers this character. Therefore, enamides display a fine balance of stability and reactivity, which is now leading to their increasing use in organic synthesis (Figure 1.1). The chemical stability of enamides allows them to be purified by silica gel column chromatography and kept for a long period of time.

![Figure 1.1](image-url)

Enamides offer multiple opportunities for the inclusion of nitrogen-based functionality into organic systems. Furthermore, the enamide motif can be found in several biologically active natural products, such as lansiumamide A, TMC-95A-D, crocacin, alatamide, and a range of marine metabolites. It is therefore not
1.0 The Chemistry of Enamides

surprising that many groups have become interested in the chemistry of enamides and their synthesis in a stereo- and regio-controlled manner.²

1.2 Enamides: Valuable Organic Substrates

Enamide substrates offer a wide range of chemistry; they can act as both electrophiles and nucleophiles. They can also be found in heterocyclic syntheses, radical, pericyclic, transition metal catalysed reactions and many more other reactions (Figure 1.2).²

![Figure 1.2](image)

Recent reviews by Carbery²ᵃ and Kobayashi²ᵇ have covered most of these topics in some detail. Within the remit of this discussion, the key areas will be examined, highlighting recent examples to appreciate the importance of enamides in organic synthesis.

1.2.1 Asymmetric Hydrogenation of Enamides

One of the most common reactions using enamides is the preparation of chiral amides or amino acids via asymmetric hydrogenation. Over the past decade, there has been a significant increase in publications covering this area.⁸ Recently, Zhang
and co-workers described a Rh-ZhangPhos complex as an effective catalyst for the asymmetric hydrogenation of enamides (Scheme 1.1). A variety of α-aryl enamides were easily hydrogenated with enantiomeric excesses greater than 99% and in quantitative yields, regardless of the aryl substituent. Indeed, electron-withdrawing or donating substituents on the aryl group did not change the outcome of the reaction.

![Scheme 1.1]

In this publication, Zhang and co-workers also described a facile synthesis of the new ligand ZhangPhos, starting from a commercially available chiral source. In contrast to the common ligands for asymmetric hydrogenation, such as TangPhos or DuanPhos (Figure 1.3), both enantiomers of ZhangPhos can be easily prepared. In addition, this latter ligand gave comparable or better results than TangPhos and DuanPhos.

![Figure 1.3]

Although rhodium is typically used for the asymmetric hydrogenation of enamides, it is possible to use other transition metals. To date there are only limited studies on the hydrogenation of simple enamides by iridium catalysts. At best, moderate
Enantioselectivities of up to 60% ee were achieved. However, much improved results have been described by the Beller group in an iridium-catalysed asymmetric hydrogenation of enamides in the presence of a phosphoramidite ligand 8 (Scheme 1.2).\(^\text{11}\)

![Scheme 1.2](image)

The addition of a salt (NaClO₄) induced an improvement of the enantioselectivity and of the catalytic activity. Since it is known that iridium species can form active dimeric complexes, it was suggested that the addition of a non-coordinating anion might stabilise the more selective monomeric form.

Nowadays, research groups tend to find new catalytic systems to replace the extensively used transition metal catalysts. As a new direction in this research field, enantioselective hydrogenation using organocatalysts has emerged as an attractive strategy due to their environmentally benign nature. Antilla and Li studied the scope of the asymmetric hydrogenation of enamides using a chiral phosphoric acid.\(^\text{12}\) The dual-acid catalyst system they developed was efficient for the preparation of a range of chiral amides (Scheme 1.3).\(^\text{12}\)

![Scheme 1.3](image)
In this reaction, Hantzsch ester 10 acts as a source of hydride. The loading of the chiral phosphoric acid can be as low as 1 mol% whilst still providing excellent yield and enantioselectivity of the reduction product. However, in the absence of the co-catalyst (AcOH) the reaction rate was extremely slow and this was attributed to the slow formation of the iminium ion. It is believed that acetic acid is able to facilitate iminium ion formation, while being inactive in the hydrogenation step. It should also be noted that the hydrogenation was ineffective for aliphatic enamides (R = aliphatic).

### 1.2.2 Enamides as Nucleophiles and Electrophiles

Despite the electron-withdrawing group present on the nitrogen atom, enamides can be seen as tuneable enamines. It is therefore not surprising that they can act as good nucleophiles in a number of transformations. In 2004, the Kobayashi laboratory pioneered the use of enamides as nucleophiles in asymmetric catalytic Michael reactions (Scheme 1.4).\(^\text{13}\)

![Scheme 1.4](image)

The reaction proceeded smoothly at 0 °C over 15 minutes, and high yields and high levels of enantioselectivity were attained with a wide range of substrates. A characteristic of addition reactions of enamides to imines is the formation of the β-aminoimine as a possible end product. Thus, these enantioselective reactions provide new routes to optically active 1,3-diamines as well as amino acids. Since then the Kobayashi group has studied in depth the use of \(C_2\) symmetric diamine ligands such
as 17 in copper-catalysed asymmetric conjugate addition of enamides to a range of electrophiles.\(^{14}\)

More recently, Tsogoeva introduced a chiral Brønsted acid catalysed self coupling of enamides (Scheme 1.5).\(^{15}\) In this reaction the enamides readily isomerise to imines under the influence of the bifunctional character (Brønsted acid / Lewis base) of the phosphoric acid. Steric effects due to the bulkiness of the catalyst were critical to the outcome of the reaction. Indeed, either no conversion or only low yield was observed with groups in the ortho- and meta-positions in the aromatic ring.

![Scheme 1.5](image)

Notably, the reports on asymmetric synthesis of β-aminocarbonyl compounds with a quaternary carbon bearing a nitrogen atom are scarce, and in this communication Tsogoeva’s group established a simple approach to preparing these compounds.

One of the latest examples of the utilisation of enamides as nucleophiles has been reported by Feng and co-workers.\(^{16}\) The group developed the use of an efficient chiral N,N’-dioxide-nickel(II) complex catalyst for the enantioselective aza-ene-type reaction of glyoxal derivatives (as well as glyoxyllates) with enamides.\(^{16}\)

![Scheme 1.6](image)
The synthesis of optically active 2-hydroxy-1,4-dicarbonyl compounds 24 was performed with high enantioselectivity under mild conditions. The scope of the reaction was broad, especially for the glyoxal derivatives, which is in contrast with previous results obtained in this area.

While enamides have generally been used as nucleophiles in acid-catalysed reactions, Zhou and co-workers reported that α-aryl enamides have played the role of an electrophile in the reaction with indoles (Scheme 1.7).\textsuperscript{17,18} A chiral binol-based phosphoric acid 28 was once again used to catalyse this reaction.\textsuperscript{17}

![Scheme 1.7](image)

An important feature of this reaction is that the hydrogen atoms on the nitrogens of both the enamide and indole moieties were essential for the activation of the reactants by the phosphoric acid. The authors suggested that activation of the indole and enamide substrates occur through two hydrogen bonds with the chiral phosphoric acid catalyst. The enamide forms an equilibrium with the corresponding imine, which is protonated and activated by the catalyst to accept the nucleophilic attack of the indole. Finally, this reaction allowed the elegant introduction of a quaternary carbon bearing a nitrogen atom.
1.2.3 Chiral Enamides in Asymmetric Synthesis

Chiral enamides have widely been utilised for asymmetric transformations in the past few years. For example, Hsung and co-workers reported highly stereoselective Simmons–Smith cyclopropanations of chiral enamides for the synthesis of chiral aminocyclopropanes (Scheme 1.8).\(^\text{19}\) In this reaction the dihaloalkane ICH\(_2\)I was used as the methyldiene source.

![Scheme 1.8](image)

Reduction of the major isomer of 30 gave the chiral aminocyclopropane 31, which was used in the synthesis of the de novo cyclopropyl nucleoside (Figure 1.4).\(^\text{20}\)

![Figure 1.4](image)

This study not only illustrated the potential of enamides as chiral templates, but also provided a solution to the design of efficient syntheses of chiral aminocyclopropanes. The Hsung group also described an additional stereoselective cyclopropanation of chiral enamides using rhodium(II) tetracetae as a catalyst.\(^\text{21}\)

Further interesting work employing chiral enamides has been published by Davies and co-workers.\(^\text{22}\) In their publication, homochiral \((E)\)- and \((Z)\)-enamides were shown to undergo highly diastereoselective epoxidation upon treatment with dimethylidioxirane (Scheme 1.9).\(^\text{22}\)
Subsequent epoxide opening with meta-chlorobenzoic acid, with retention of configuration, followed by reductive cleavage, generated the homochiral 1,2-diol with excellent enantioselectivity.

Dujardin described an important transformation of chiral enamides in hetero-Diels–Alder (HDA) reactions with diverse heterodienes.\textsuperscript{23} The HDA reaction proceeded in high yield and endo-selectivity under mild conditions using (Eu(fod))\textsubscript{3} as a catalyst (Scheme 1.10).\textsuperscript{23}

The product 37 was isolated in a high yield of 91\%, and its endo-selectivity and absolute configuration was established by X-ray diffraction.

### 1.2.4 Pericyclic Reactions

In recent years there has been an increasing use of enamide substrates in pericyclic reactions. Examples of cycloaddition, sigmatropic and electrocyclic chemistry have all been reported. Rawal published a highly efficient and stereoselective Diels–Alder reaction using the conjugated enamide 38 as the reactive diene (Scheme 1.11).\textsuperscript{24}
The reaction is promoted by Co(III)-salen complex 41 and yields synthetically useful cyclohexenyl carbamates in high enantiomeric excess. More recently, Nicolaou applied this methodology to the preparation of (−)-Platencin, a novel natural product, exhibiting unique and potent antibacterial activity.

In 2007, Cossy and co-workers established the first example of a sigmatropic rearrangement that incorporated an enamide moiety. Following Cossy’s work, Carbery published the first use of enamides as substrates for the Ireland–Claisen [3,3]-rearrangement (Scheme 1.12). In this instance secondary enamido-allylic esters 42 rearrange via the silyl ketene acetal 43 to β-amino acid products 44.

Although the reaction was highly diastereoselective with the phenyl substituent, leading only to the anti-product, it was shown that simple alkyl functionality led to poor diastereoselectivity.

Enamides have also found themselves amenable to electrocyclic transformations. Funk has utilised 2,3-pyrroline 45 in a thermal 6π-electrocyclic ring closure (Scheme 1.13).

1.0 The Chemistry of Enamides
Enamide 45 underwent an electrocyclic closure in refluxing xylenes, and in the same pot aromatisation with concomitant oxidative desilylation took place by simply lowering the temperature to 0 °C and adding DDQ. Finally, further transformations led to the preparation of the cis-trikentrin B (47), which has shown to exhibit antimicrobial activity.

In many instances, the pericyclic reactions allowed the formation of new nitrogen stereocentres and an overall increase in molecular complexity.

### 1.2.5 Other Reactions

There have been a number of reports detailing the utility of enamides in radical-based transformations. The Ishibashi group have demonstrated the value of these compounds by accomplishing syntheses of lennoxamine (eq 1.1),\(^{29}\) (±)-stemonamide and (±)-isostemonamide,\(^{30}\) where the skeleton is formed through a key enamide radical reaction.

Enamide 48 was observed to undergo a regioselective 7-endo cyclisation followed by subsequent homolytic aromatic substitution. This single pot process allows for the isolation of lennoxamine (49) in 41% yield.
Another application of enamides has been demonstrated in heterocycle syntheses. A number of reports have described the use of these compounds for the preparation of pyridines,\textsuperscript{31} oxazoles,\textsuperscript{32} pyrroles,\textsuperscript{33} and indoles.\textsuperscript{34}

Movassaghi has reported a mild, convergent, and single step synthesis of pyridines.\textsuperscript{31} This chemistry is compatible with a wide range of enamides and \(\pi\)-nucleophiles. This methodology was made possible, in part because of the recognition of the unique electrophile activation of enamides with trifluoromethanesulfonic anhydride (Tf\(_2\)O) in the presence of 2-chloropyridine as the base additive (Scheme 1.14).\textsuperscript{31}

![Scheme 1.14](image)

In this reaction enamide 50 is converted to \(N\)-vinyl iminium triflate through the action of triflic anhydride, subsequently reacting with the electron rich ynamide 51 to form the pyridine derivative 52 without loss of optical activity (Scheme 1.15).\textsuperscript{31}

![Scheme 1.15](image)

This methodology provides rapid access to highly substituted pyridines with predictable control of substituent introduction.
1.2.6 Conclusion

Throughout this section, it has been shown that enamides are important synthetic intermediates. The number of publications covering the chemistry of enamides has exploded over the last decade, and many of them have been applied to total synthesis of natural products. One of the possible explanations of such keen interest in enamides is the development of new synthetic methods to access these compounds. The preparation of enamides will be discussed in detail in the next section.

1.3 Preparation of Enamides

Traditional methods of preparing enamides include the Curtius rearrangement of α,β-unsaturated acyl azides followed by reaction with an alcohol,\(^\text{35}\) the acylation of imines,\(^\text{36}\) the olefination of aldehydes\(^\text{37}\) and the direct condensation of carbonyl compounds with amides or carbamates\(^\text{38}\) (Scheme 1.16).

![Scheme 1.16](image-url)
The Curtius reaction, imine acylation and amide olefination reactions entail multiple steps in the preparation of starting materials, and the yields of the desired enamides are often low. Moreover, the condensation method requires high temperatures and harsh conditions, which often results in unwieldy mixtures of regio- and stereoisomers. Additionally, these isomers are in most cases difficult to purify. Finally, the reaction conditions cause low functional group tolerance. For the purposes of the proposed project, the latest advances in the regio- and stereocontrolled preparation of enamides will be examined.

1.3.1 Transition Metal-Catalysed Cross-Coupling

With advances in cross-coupling technology, another attractive method to prepare enamides from their parent N–H compounds is *via* transition metal-catalysed $N$-alkenylation reactions.\(^{39}\) Within the next section, the recently developed alternative enamide syntheses using cross-coupling reactions starting from vinyl halides and sulfonates will be looked at.

*Palladium-Catalysed Cross-Coupling Reactions*

Palladium-catalysed C–N bond-forming intramolecular reactions between aryl halides and amides, carbamates, and sulfonamides have been utilised in many areas of organic synthesis.\(^{40}\) One of the first syntheses of enamides relying upon palladium-catalysis has been introduced by Mori and co-workers.\(^ {41}\) The group described the reaction between a vinyl halide and an amide catalysed by palladium.\(^ {41}\) Although both halides (bromo and iodo) gave the expected coupling products, the iodide proved to be more effective (Scheme 1.17).\(^ {41}\)

![Scheme 1.17](image)
A crucial aspect of this reaction is the *in situ* preparation of the catalyst complex (in the absence of the base) in order to obtain high conversion. Using this methodology, they prepared a carbapenem antibiotic derivative that shows chemical and biological properties for clinical use.

A more general method for the synthesis of enamides was reported from Merck Research Laboratories starting from vinyl triflates. They were able to selectively prepare the enol triflate, thus allowing the regioselective preparation of the corresponding enamides (Scheme 1.18). The selective formation of a single enol triflate from a ketone may rely on simple kinetic vs thermodynamic control.

Coupling of enol triflates with amides, carbamates and sulfonamides took place under mild conditions. Where enamide isomerisation was not possible, reactions were run at 50 °C. However, for other enamides, running the reaction at this temperature led to slow isomerisation, and therefore these examples were carried out at room temperature to obtain products of high stereoisomeric purity (59b, Scheme 1.18). In addition, the presence of a bromide in the coupling partner did not interfere in the process, highlighting the potential of this strategy in a multi-step synthesis.

A few years later, the same group reported the use of enol tosylates to extend this transformation (Scheme 1.19).
This development offers two advantages: first, tosylating agents are generally less expensive and more readily available than N-phenyltriflimide (NPhTf₂); second, from a process development perspective the crystallinity associated with enol tosylates would provide a convenient means for isolation and purification of the product.

Another preparative approach towards enamides and analogous compounds was found by Stahl. Quite surprisingly, when vinyl ethers were used as substrates in a palladium-catalysed reaction under aerobic conditions, a vinyl transfer occurred (Scheme 1.20). This result is notable because many palladium-catalysed processes are incompatible with oxygen atmosphere, and enol ethers are not expected to be efficient coupling partners for oxidative addition to palladium complexes.

(DPP)Pd(OCOCF₃) was identified as the best catalyst (DPP = 4,7-diphenyl-1,10-phenanthroline). The vinyl ether was used in large excess and served also as solvent for the reaction. Another remarkable fact is that the palladium appears to remain in
the +2 oxidation state throughout the entire catalytic cycle. This observation differs from the other cross-coupling reactions, with vinyl halides or triflates.

The previous examples were restricted to the preparation of a certain class of enamides, and in this context the Chang group became interested in making these products in a stereoselective manner. In their article, they reported a straightforward method for producing Z-enamides with high stereoselectivity through a hydrogen-bond-directed approach (eq 1.2).\(^{45}\)

\[
\begin{align*}
\text{R}^1\text{CO}_2\text{H} + \text{NH}_2\text{CO}_2\text{R}^2 & \xrightarrow{\text{CuPd/O}} \text{O} \quad \text{O} \\
\text{O} & \quad \text{R}^1\text{CO}_2\text{H} + \text{NH}_2\text{CO}_2\text{R}^2 \\
& \quad \text{O} \quad \text{R}^1\text{CO}_2\text{H} + \text{NH}_2\text{CO}_2\text{R}^2
\end{align*}
\]

Equation 1.2

Tetraethyl methylenediphosphonate (TEMDP) (Figure 1.5) was found to increase the reaction rates, as it suppressed the formation of palladium black. In the catalytic cycle, Pd(0) was reoxidised by the action of the copper cocatalyst and molecular oxygen.

![Figure 1.5](image)

In this process a wide range of amides were readily reacted with acrylic esters, acrylic amides, alkyl vinyl ketones, and vinyl phosphonates by the action of a Pd/Cu cocatalyst system (Scheme 1.21).\(^{45}\)
The high stereoselectivity observed in this study is mainly attributed to the favourable β-hydride elimination from one plausible σ-alkylamidopalladium intermediate which bears an intramolecular hydrogen bond.

Another class of enamide-like compounds accessible via the palladium-catalysed cross-coupling strategy is the N-Boc-N-alkenylhydrazines 71 (Scheme 1.22). A new and simple methodology has been reported by the Barluenga group for the synthesis of N-alkenylhydrazines from readily available substrates (alkenyl bromides and chlorides). Moreover, this is the first general route for the preparation of this particular class of hydrazines, which are useful for heterocyclic synthesis.

Palladium-catalysed C–N bond formation has proven to be an attractive method for the preparation of enamides. Nevertheless, this approach represents a small number of protocols, and more general syntheses can be accessed by using another transition metal, copper.
Copper-Catalysed Cross-Coupling Reactions

The pioneering work using copper as the catalyst for the preparation of enamides has been described by the Ogawa group in 1991.\(^{47}\) They reported the copper iodide-promoted substitution of vinyl bromides by potassium amides to afford enamides.\(^{47}\) However, the reaction required harsh conditions and toxic compounds (reaction run in HMPA at 130 °C) and the products were only obtained in low yields. Over the next decade, the synthesis of enamides using copper catalysis remained undeveloped.

It was only in 2000 that Porco reinvestigated this reaction with the goal of preparing enamides. Using a substoichiometric amount of copper(I) thiophene-2-carboxylate (CuTc)\(^{48}\) allowed the formation of various enamides in moderate to good yields (Scheme 1.23).\(^{49}\)

\[
\begin{align*}
\text{(73)} & \quad + \quad \text{(74)} \quad \xrightarrow{\text{CuTc (90 mc.%)}} \quad \text{(75)} \\
\text{Fr} & \quad \text{R}^2 & \quad \text{Fr} & \quad \text{O} & \quad \text{C} & \quad \text{O} & \quad \text{Cu} & \\
77\% & & 77\% & & 77\% & & 77\% & & 77\%
\end{align*}
\]

Scheme 1.23

Preliminary experiments revealed that the reaction had to be performed in polar aprotic solvents (NMP or DMSO), in the presence of Cs\(_2\)CO\(_3\) as a base. It should also be noted that no further ligand had to be added for the successful outcome of the reaction. One major point of his study was the control of \(E/Z\) stereoselectivity of the double bond.

Porco directly applied these catalytic conditions to the synthesis of \(O\)-methylene oxime enamide side chains, moieties present in salicylate antitumor macrolides.\(^{50}\) Extension of this protocol to the coupling of \(\beta\)-iodoacrylates was made possible by the use of rubidium carbonate as base and a modified phenanthroline ligand 80 (Scheme 1.24).\(^{50}\)
The coupling between 76 and 77 proved to be especially robust with the enamide 78 obtained in an excellent yield of 90%. Subsequent deprotections of the acetonide and allyl ester provided CJ-15,801, which was reported as an inhibitor of multiple-drug-resistant *Staphylococcus aureus* strains.\(^{51}\)

Although the previous results proved to be efficient for the synthesis of enamides, there was still a need for a more general process. Partially due to the choice of the appropriate ligand 83, Buchwald’s group have succeeded in this goal and they have introduced a mild and general procedure for the synthesis of enamides in a stereoselective manner (Scheme 1.25).\(^{52}\)

In this process, both cyclic and acyclic amides could be combined with unactivated vinyl halides. Although the reaction time was slightly increased, they were able to prepare the trisubstituted enamde 82a in a good yield of 88%. Vinyl halides
containing a functional group were also effectively coupled under these conditions. Finally, the amidation of vinyl iodides was found to proceed under milder conditions (<70 °C), with one case at room temperature.\textsuperscript{52} At this time his protocol probably remains one of the most efficient for the preparation of enamides.

In Buchwald’s account, \textit{N,N}-dimethylglycine \textbf{84} was reported to be much less active than \textit{N}-\textit{N’}-dimethyl ethylenediamine \textbf{83}.\textsuperscript{52} Ma’s group reasoned that this problem might result from the solvent used, and indeed, switching the solvent to dioxane proved to be effective in this method (Scheme 1.26).\textsuperscript{53}

![Scheme 1.26](image)

As observed in Buchwald’s results (\textit{vide supra}), the use of vinyl bromides required higher temperatures than their iodo-congeners. Another similar observation was when starting with \textit{cis}-starting materials, only the \textit{cis}-products were detected by \textit{1}H NMR analysis. Similarly the \textit{trans}-products result from \textit{trans}-vinyl halides, which demonstrated the retention of the geometry of the double bond throughout the catalytic process. Although the methodology developed by Ma’s group was comparable to the one accomplished previously, it is a good complementary system to prepare the target enamides.

The dedicated work of Porco, Ma and Buchwald led to a number of preparations of natural and biologically active products (Figure 1.6).\textsuperscript{39}
Liu and Coleman developed a unified strategy for the divergent and stereocontrolled introduction of the \((E)\)- and \((Z)\)-enamide side chains (Scheme 1.27).\(^{54}\)

The substrates \(87a\) and \(87b\) can act as universal starting materials to the \((E)\)- and \((Z)\)-enamide side chains of a range of biologically active compounds including oximidines I, II and III, salicylihalamides A and B, lobatamides A and D and CJ-12,950.

So far, the study of intermolecular copper-catalysed reactions between amides and vinyl halides have been focussed on. It was surprising that with the advances
presented earlier, nobody had described this reaction in an intramolecular fashion. The lactam moieties formed are useful compounds, with applications in a number of areas ranging from drug discovery to polymer industry. Li and co-workers introduced the first example in 2005. Once again the use of substoichiometric amounts of CuI and ligand 83 proved to be the system of choice for this reaction (Scheme 1.28).

With terminal (Z)-vinylic iodine substrates, the corresponding six- and seven-membered lactams with an internal double bond could be achieved in high yield (91a). Starting with substrates 90 led to the formation of lactams with an exocyclic double bond. As an extension of the methodology developed they synthesised the bicyclic products (92c and 92d) in high and moderate yield. These last results illustrated the high potentials of this reaction for the preparation of a number of alkaloids containing this benzazepine core.

It has also been possible to prepare optically enriched chiral allenate via the stereospecific amidation of optically enriched allenyl iodides (Scheme 1.29).
Due to the poor thermal stability of allenamides, the reactions needed to be carried out at a maximum of 50 °C. The diastereomeric allenyl iodide 94 was coupled to the oxazolidin-2-one 93 with maintenance of the axial stereochemistry, indicating the stereospecificity of the transformation. At present the synthetic utility of this reaction is limited by the arduous preparation of optically enriched chiral allenyl iodides.

In the process of extending the scope of the amidation reaction, Lam introduced a copper-catalysed C-N and C-O bond cross-coupling with vinyl boronic acids (Scheme 1.30). 57

Unfortunately this method suffers from a lack of generality with only three examples of enamide like products described. Moreover, only one boronic acid 96 was employed in this methodology. However, this work demonstrates the possibility of using an alternative coupling partner in place of alkenyl halides.

A few years later, based on Lam’s results, 57 Batey introduced a more general procedure by using vinyl trifluoroborate derivatives (Scheme 1.31). 58 These
tetracoordinate salts possess increased stability towards air and water. Furthermore, many are now commercially available.

Scheme 1.31

In general good yields were obtained for both cyclic and acyclic amides. This base-free and “ligandless” methodology proved to be efficient for the preparation of a wide range of enamides.

**Conclusions**

Generally, the metal-catalysed cross-coupling approach has proven to be an attractive way of accessing enamides stereoselectively. In particular, advances in cross-coupling technology to prepare enamides from their parent N-H via palladium- or copper-catalysed $\text{N}$-alkenylation reactions prove to be effective. The high stability and low costs of copper catalysts enable these transformations to be a useful complement to the palladium-catalysed processes. Moreover, the robust nature of the copper-catalysed methodology has been demonstrated in its relatively widespread use in natural product syntheses over the last decade. However, the preparation of the requisite vinyl halide coupling partners is often non-trivial and problems of regio- and stereocontrol are now transferred to the synthesis of these coupling partners. These restrictions impose limitations on the synthesis of more diverse enamides.

A further means to access enamides involving C-N bond formation is the catalytic hydroamidation of alkynes.
1.3.2 Hydroamidation of Terminal Alkynes

A catalytic addition of amides to alkynes would be an ideal synthetic entry to enamides, since it would use readily available starting materials and be inherently atom-economic.

The Watanabe group introduced the first synthesis of enamides by direct addition of amides to alkynes in 1995.\textsuperscript{59} They found that the addition of an $N$-aryl substituted amide to non-activated terminal alkynes is efficiently catalysed by a ruthenium complex to afford the $(E)$-enamides selectively (Scheme 1.33).\textsuperscript{59}

\begin{center}
\includegraphics[width=\textwidth]{Scheme_1.32.png}
\end{center}

\textbf{Scheme 1.32}

Watanabe and co-workers established that in the presence of \text{Ru$_3$(CO)$_{12}$/trialkylphosphine} catalysts, a very limited range of formanilides and acetanilides can be added to 1-hexyne, albeit at extremely high temperature (180 °C) and under pressure.\textsuperscript{59} Clearly, much more active catalyst systems are required to allow the general application of this reaction.
A decade after the Watanabe group published their results, Goossen and co-workers introduced a more general methodology. They identified two complementary protocols that provide stereoselective synthetic entries to either the E or Z isomers (Scheme 1.33).  

Scheme 1.33

The choice of ligand was of crucial importance; tri-n-butylphosphine gave the highest E-selectivity, and use of the chelating phosphine, bis(dicyclohexylphosphanyl)methane, led to a reversal of stereoselectivity in favour of the Z-product. However, this latter protocol does not yet reach the level of selectivity of its E-selective counterpart. Moreover, only two examples have been prepared using this latter ligand, and it is therefore difficult to be conclusive. However, the reaction proceeds smoothly and the transformation is tolerant of functional groups such as esters, ethers, ketones, halides, or silanes.

For the primary amide substrates, which should give access to the more valuable secondary enamides, they observed either no conversion at all, or mostly double vinylation products in trace amounts and as a mixture of E/Z isomers and rotamers.

The lower reactivity of primary amides compared to secondary amides is easily explained by their lower nucleophilicity. In this context, they identified a catalytic system that allowed the preparation of secondary Z-enamides, which is
thermodynamically disfavoured, without further conversion of the more nucleophilic products (Scheme 1.34).  

![Chemical reaction diagram](image)

**Scheme 1.34**

The use of the sterically demanding, electron-rich chelating phosphine ligand resulted in a major enhancement of the Z/E ratio. The scope of the reaction was wide with a range of alkynes and primary amide derivatives, sometimes sensitive and highly functionalised, tolerated in this process. Arguably, the unprecedented outcome was the synthesis of enamides 110c and 111c, in which a primary amide functionality was selectively vinylated in the presence of a secondary amide group. The one-pot addition/isomerisation sequence (addition of Et₃N) was successfully applied to the synthesis of a representative selection of E-enamides (111a-111c). The group also addressed the issue of the prohibitive price of the first generation catalyst and soon afterwards reported a new protocol based on RuCl₃•3H₂O as the catalytic precursor.  

Shortly afterwards, the same team reported the preparation of enimides (a near cousin of enamides) using an extension of their methodology (Scheme 1.35).
1.0 The Chemistry of Enamides

With this category of substrates, an additive was necessary to conduct the reaction successfully. They discovered that the use of Lewis acids (scandium or ytterbium triflate), caused a dramatic increase in catalyst productivity.

Previous work by Takai and co-workers shows that rhenium complexes are highly effective for C-C bond-forming reactions. From this perspective, they became interested in expending this process to include C-N bond formation to afford enamides. They found that a commercially available rhenium complex, Re$_2$(CO)$_{10}$, was active for this transformation (Scheme 1.36).$^{64}$

Although the process was limited to the utilisation of cyclic amides, the reaction proceeded highly selectively to give only the $E$-isomer product (except 119d, where the ratio of stereoisomers was poor). They also carried out an interesting experiment showing that when a mixture of isomers ($E:Z = 63:37$) was heated at reflux in
toluene in the presence of the catalyst; the ratio changed to $E:Z = 70:30$ after 12 h, and the ratio changed to $E:Z = 100:0$ after 72 h (eq 1.3).\(^\text{64}\)

This result shows that the rhenium complex also catalysed the isomerisation of the Z-isomer of \textbf{119e} to an $E$-enamide.

The hydroamidation of terminal alkynes is an attractive route to enamides, as the reaction is atom economic and additionally uses readily available starting materials. Unfortunately, although both $E$- and Z-enamides may be prepared selectively, this method is currently limited to the preparation of $\beta$-mono-substituted products.

### 1.3.3 Use of Ynamide Starting Materials

Another major strategy for enamide preparation involves the use of ynamide\(^\text{65}\) starting materials. Over the last decade, ynamides have become an important tool in organic synthesis, as exhibited by the increasing number of reports covering this area. The main reason for this increase is that ynamide synthesis has become more straightforward in light of developments in alkynyliodonium salt chemistry\(^\text{66}\) and copper\(^\text{67}\) and iron-catalysed\(^\text{68}\) alkynylation technologies.

Representative intramolecular examples include domino Heck–Suzuki–Miyaura reactions.\(^\text{69}\) This transformation was effectively used for the preparation of lennoxamine (Scheme 1.37).
In this method, ynamide 120 was a viable substrate for the intramolecular Heck reaction, which was then followed by the Suzuki–Miyaura reaction with the boronic acid 121 to afford the product 123 as a mixture of stereoisomers. The stereochemistry was not an issue as subsequent transformations involved the hydrogenation of the double bond before leading to Lennoxamine (124).

Another example of intramolecular formation of enamides is a keteniminium variant of the Pictet–Spengler cyclisation, leading to synthesis of a nitrogen heterocycle (Scheme 1.38).70

In this reaction, a Brønsted acid proved to be effective in initiating the cyclisation of 125, then further transformations led to 10-desbromoarborescine A (127). For this process, Lewis acids such as Cu(OTf)2 failed to provide the desired cyclised product.
Further exemplifications have been described in the preparation of cyclic dienamides by intramolecular ring-closing enyne metathesis of ene–ynamides (Scheme 1.39) using Grubbs’ second generation ruthenium catalyst. 

The Malacria group also established a platinum-catalysed cycloisomerisation of enetosylynamides (Scheme 1.40). The [2+2] cycloaddition gave the bicyclic intermediate 131, which could be directly transformed into the keto-lactam 132 or cyclobutanone 133 by ozonolysis or hydrolysis respectively.

There are also many relevant intermolecular examples of the preparation of enamides using ynamides as substrates. One of these approaches includes hydroboration of ynamides followed by Suzuki–Miyaura coupling (Scheme 1.41).
Hydroboration of 134 with catecholborane (135) proceeded chemo- and regioselectively to the (E)-vinylborane intermediate 136. Due to its instability, 136 was not isolated and was used in the next step without purification. This two-step one-flask reaction provided the (E)-enamides in moderate yields.

Moreover, the homologation of enamide boronates was possible in the presence of chloromethyl lithium and gave (E)-γ-aminoallylboronates in high yields (Scheme 1.42). The boron moiety was introduced by zirconocene-catalysed hydroboration with pinacolborane (139).

The Cintrat group published a series of papers covering hydro- and silylstannylation of ynamides catalysed by palladium (Scheme 1.43).
In the majority of cases, the reactions proceeded with high levels of regio- and stereoselectivity. The α-substituted stannyl enamides were used in Stille-couplings or lithiation–electrophilic trapping reactions to give more diverse enamides (Scheme 1.44).

The Hsung group has extensively studied the use of ynamides to prepare enamides, and their important contributions in this field resulted in a number of discoveries. For example, they have established a mild, facile, and highly stereoselective preparation of (E)-α-haloenamides. This methodology is applicable to acyclic and cyclic ynamides in high yield and regioselectivity (Scheme 1.45).
Interestingly, the use of ‘wet’ conditions was necessary for the outcome of the process, as an anhydrous environment provided only low conversion. A simple explanation could be that under anhydrous conditions HX is not formed. In addition, α-haloenamides 148 are excellent candidates for use in transition metal mediated reactions such as Sonogashira coupling to give enamide 149a.

One of the most recent examples coming from the Hsung group is the thermal Ficini [2+2] cycloaddition of ynamides (Scheme 1.46). 79

The use of Lewis acid, unsurprisingly, led to the formation of α-haloenamides. In addition, when hydro-halogenation is not competing, hydrolysis of ynamides was observed. Finally, they discovered that cationic Cu(II) was an active system for this reaction. 79 Two possible pathways are suggested for the formation of intermediate 152 (Figure 1.7). 79
A simple and straightforward mechanistic consideration could be that this is a stepwise cycloaddition with a nucleophilic 1,4-addition by the ynamide onto the enone activated via the cationic Cu(II) catalyst (Path A). However, there may be another possibility, which involves activation of the alkyne by the cationic Cu(II) species, leading to an intermediate that could participate in a cuprate-like 1,4-addition.

Another intermolecular approach to prepare enamides is via a reductive coupling reaction employing ynamides as substrates. Sato’s group reported a titanium mediated coupling to prepare different enamides (Scheme 1.47).\(^80\)

It is a powerful method, as the coupling with the carbonyl compound proceeds in a highly regio- and stereoselective manner to give single, stereodefined β,β-disubstituted enamide 160.

Saito and co-workers completed this study in a different publication where they use a catalytic amount of nickel to synthesise functionalised enamides (Scheme 1.48).\(^81\)
The multicomponent coupling of ynamides, aldehydes and silanes allows the formation of functionalised disubstituted enamides in moderate to good yield. The formation of γ-silyloxyenamide derivatives proceeds in a highly regio- and stereoselective fashion.

It is clear from the review that a number of effective methods exist for the synthesis of enamides from ynamide precursors. Nevertheless, they are often restricted to the production of only certain classes of products, or require rather specialised substrates. Another approach, in principle more flexible for enamide synthesis, would be via the carbometallation of ynamides. This alternative route to access enamides will be discussed fully in the next chapter of this review.

### 1.4 Conclusion

Enamides, unlike enamines, had remained relatively obscure in synthesis. The limited use of enamides could be due in part to synthetic inaccessibility. However, recent developments in copper- and palladium-catalyzed N–alkenylation, and hydroamidation have provoked a strong interest in the development of synthesis based on the use of enamides as versatile building blocks. Enamides can now be used as a flexible precursor for the synthesis of natural products and biologically active compounds, as illustrated by the number of publications in the last decade. Moreover, enamides offer long-term stability and a wide range of reactivity.
Nevertheless, these recent strategies to prepare enamides, although in stereoselective fashion, suffer drawbacks. The cross-coupling method requires the often complicated preparation of the vinyl halides especially in highly substituted cases, and the hydroamidation pathway, although both $E$- and $Z$-enamides can be prepared, is restricted to the preparation of $\beta$-monosubstituted enamides.

However, recent developments in enamide synthesis through the utilisation of ynamides as starting materials have been rendered possible thanks to the progress in the preparation of these latter compounds. Despite the recent progress, there are still several issues to be addressed, such as substrate scope, stereoselectivity, and mildness of reaction conditions for the efficient preparation of enamides.
2.0 Rhodium-Catalysed Carbozincation of Ynamides to Access Multisubstituted Enamides

2.1 Background

As discussed previously (see Chapter 1), carbometallation of ynamides could be one of the most flexible approaches to prepare enamides. There are several reasons for this assertion: (1) the majority of carbometallation reactions occur in a syn-fashion,\textsuperscript{82} and therefore issues of selectivity during ynamide carbometallation are reduced to one of regioselectivity, provided E/Z-isomerisation does not take place; (2) in addition, utilisation of the alkenyl metal intermediates, which are presumably generated during ynamide carbometallation, in further functionalisation reactions should allow the preparation of more highly substituted products (Scheme 2.1).

![Scheme 2.1](image)

In a seminal study, Marek and co-workers described the first carbometallation of ynamides.\textsuperscript{83,84} They established an intermolecular carbocupration and copper-catalysed carboalkoxymagnesiolation of ynamides.\textsuperscript{84} As expected, the reaction proceeded in a syn-manner and was highly regioselective (one regioisomer observed by crude NMR analysis). The high regioselectivity was attributed to the coordination of the copper with the oxygen atom present on the ynamide (Scheme 2.2).
Consequently, the Oshima group used this new methodology in the copper-catalysed carbomagnesiation of ynamides, to produce intermediates that undergo aza–Claisen rearrangements to form 4-pentenenitriles 174 (Scheme 2.3). \(^{85}\)

More recently, the Marek group have exploited their carbocupration methodology in a unique approach to access aldol products containing all-carbon quaternary stereocenters (Scheme 2.4). \(^{86}\)
Regio- and stereoselective carbocupration of the ynamides 175 provides the vinyl copper species 176 that is readily homologated using an organozinc reagent. Subsequent nucleophilic allylation of an aldehyde provides the aldol derivatives 177. The presence of TMSCl in the reaction mixture prevents an undesired side reaction and the enamide products are isolated as silyl ethers, which give the alcohol derivatives after acidic hydrolysis. The stereochemistry of the major isomer can be rationalised by the Zimmerman-Traxler transition step (a six-membered ring transition state adopting a chair conformation) (Figure 2.1).86

![Figure 2.1](image)

The benzyl group of the oxazolidin-2-one shields one face in the chelated six-membered ring, and the aldehyde approaches the allyl moiety anti to this group, with its R³ substituent in a pseudo-equatorial position.

Ynamide carbometallation is clearly emerging as an attractive and effective route to the preparation of multisubstituted enamides. However, despite the developments described previously, there remains scope for improvement. Indeed, the reactions rely on the use of Grignard reagents as the organometallic species; this restricts the presence of base- and nucleophile-sensitive functional groups on the ynamide due to the excess Grignard reagents in solution (see Schemes 2.2 and 2.3). Furthermore, the prospects of sensitive functional groups residing on the organometallic reagent itself are somewhat limited with Grignard reagents.87 Therefore, there remains a need for more general ynamide carbometallation procedures to provide a greater diversity of products. This improvement would be possible by using more functional group-tolerant organometallics.
2.2 Results and Discussion\textsuperscript{88}

2.2.1 Preparation of Ynamide Substrates

From a purely historical perspective, the first ynamide derivative was synthesised by Veihe and co-workers in 1972.\textsuperscript{89} Since this date, ynamide syntheses had remained rather obscure with only a few new methods described to prepare these substrates. Although these procedures were efficient, all of them suffered from either low substrate scope, very harsh reaction conditions, or from the requirement for lengthy reaction sequences. However, a major breakthrough in copper-catalysed coupling reactions of amides with bromoalkynes, terminal alkynes or alkynyltrifluoroborates has greatly increased the range of ynamides prepared.\textsuperscript{67} In addition, iron has also proved to be an efficient catalyst to prepare these substrates by a coupling reaction of amides with bromoalkynes.\textsuperscript{68}

The ynamides examined in this current report and the two methods used for their preparation are illustrated in Scheme 2.5.
The majority of ynamides were synthesised using Method A, in which a bromoalkyne is coupled to an amide.\textsuperscript{67c} Even though this procedure is an effective method for the preparation of a wide range of ynamides, a lack of reproducibility in the yields was noticed (for example ynamide 178c was synthesised with yields ranging from 17 to 50%), and this trend had also been observed by other research groups.\textsuperscript{90} A recent study into the reasons of these irregularities has suggested that yield depends highly on the quality of base used.\textsuperscript{91} ‘Wet’ potassium phosphate (i.e. \(\text{K}_3\text{PO}_4\cdot1.5\text{H}_2\text{O}\) and \(\text{K}_3\text{PO}_4\cdot7\text{H}_2\text{O}\)) gave poor yields, and detailed studies revealed that pure and anhydrous \(\text{K}_3\text{PO}_4\) provides higher and reproducible yields of the desired ynamides.

More recently, Stahl proposed an alternative route to ynamides \textit{via} the direct coupling between amides and terminal alkynes, under oxidative conditions (Scheme 2.5, Method B).\textsuperscript{67f} The scope of this method is slightly restricted compared to Hsung’s protocol and requires five equivalents of the amide, which is inefficient, particularly if the amide is not easy to access.
2.2.2 Optimisation of Carbometallation Reaction Conditions

Using ynamide 178a, this study was initiated with evaluation of various combinations of organometallic reagents and metal salts to identify suitable conditions for ynamide carbometallation (Table 2.1).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>precatalyst</th>
<th>Et₃M</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fe(acac)₃</td>
<td>Et₃Al</td>
<td>Complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>Ni(acac)₂</td>
<td>Et₃B</td>
<td>No reaction</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>Et₃Al</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>Et₂Zn</td>
<td>180a:181:182</td>
<td>Formed in 8:1:2 ratio&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>73% Isolated yield of 180a.</td>
</tr>
<tr>
<td>5</td>
<td>Rh(cod)(acac)</td>
<td>Et₃B</td>
<td>No reaction</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>Et₃Al</td>
<td>No reaction</td>
</tr>
<tr>
<td>7</td>
<td>Et₂Zn</td>
<td>180a:181</td>
<td>Formed in 14:1 ratio after 15 min.&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65% Isolated yield of 180a.</td>
</tr>
<tr>
<td>8</td>
<td>CuI</td>
<td>Et₂Zn</td>
<td>180a:181 Formed in &gt;19:1 ratio after 20 h.&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>65% Isolated yield of 180a.</td>
</tr>
<tr>
<td>9</td>
<td>—</td>
<td>Et₂Zn</td>
<td>3–4% of 180a formed after 18 h.</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions proceeded to complete conversion. Ratios determined by <sup>1</sup>H NMR analysis of the unpurified reaction mixtures.

Table 2.1

Conditions that were effective for carbometallation of bis-activated cyclopropenes<sup>92</sup> were unsuccessful with ynamide 178a (entry 1) leading to an unidentified complex mixture. Using Ni(acac)<sub>2</sub> as a precatalyst, no reaction was observed with trialkylborane or trialkylaluminum reagents (entries 2 and 3), but diethylzinc was found to provide a mixture of regioisomeric addition products 180a and 181, along
with the reduction product 182, in high conversion (entry 4). Switching the precatalyst to Rh(cod)(acac), Et₃B and Et₃Al gave no reaction (entries 5 and 6). However, Et₂Zn furnished enamide 180a with high regioselectivity (14:1) in 73% isolated yield in only 15 min (entry 7), with no trace of the reduced product 182. Although CuI was also an effective precatalyst, the reaction time was greatly increased to 20 h and the isolated yield of 180a was only 65% (entry 8). After these promising preliminary results, it was important to perform a control experiment with Et₂Zn in the absence of any precatalyst. This reaction provided 3–4% of 180a after 18 h, demonstrating that a slow uncatalysed background reaction is operative (entry 9).

From the screening of the reaction conditions, it was found that the workable conditions for our study were two equivalents of diethylzinc with Rh(cod)(acac) (5 mol%) as a catalyst (Table 2.1, entry 7).

### 2.2.3 Rhodium-Catalysed Carbozincation using Diorganozinc Reagents

Using the efficient conditions previously identified (Table 2.1, entry 7), the scope and limitation of this process were explored using commercially available dialkylzinc reagents. A variety of ynamides containing oxazolidin-2-one, pyrrolidin-2-one, or imidazolin-2-one functionality smoothly underwent carbometallation with acceptable to excellent regioselectivities and generally good yields (Scheme 2.6).
Alkyl substituents on the ynamide were tolerated with good yields and high regioselectivities using diethylzinc. Similar results were observed when using nBu₂Zn or Me₂Zn, although regioselectivity was slightly diminished with Me₂Zn. Aryl-substituted ynamides proved to be even more competent substrates for the carbozincation reactions using dialkylzinc reagents. Indeed, regioselectivities were close to perfect with only one regioisomer observable by ¹H NMR analysis on the crude reaction mixtures; only one example (180k) with Me₂Zn showed lower regioselectivity. Ynamide 178f containing a chiral oxazolidin-2-one was also a competent substrate, reacting smoothly with Et₂Zn to provide chiral enamide 180j. This example bodes well for the synthesis of chiral enamides that could serve as useful substrates for a range of asymmetric transformations. The possibility of using a cationic rhodium complex ([Rh(cod)(MeCN)₂]BF₄) as an effective precatalyst for the preparation of 180i was also demonstrated. However this result was an isolated case, since with other ynamides this catalyst led to poor stereo- and/or regioselectivity in particular with Me₂Zn, and this trend was predominantly observed with aryl substituted ynamides.

Notably, the reaction is also successful using smaller quantities of the precatalyst and of the dialkylzinc reagent. For example, carbometallation of 178b using 2 mol% of
Rh(cod)(acac) and only 0.55 equivalents of Et₂Zn proceeded smoothly to provide 180l in 69% yield (eq 2.1). This result also shows that transfer of both alkyl groups from zinc is possible during the process.

Since only a limited number of dialkylzinc reagents are commercially available the generality of this methodology would suffer serious restriction. Therefore, studies were undertaken to develop a method employing other readily available organometallic agents. Although this study was motivated by the desire to use organometallics that exhibit broad functional group tolerance, the ready availability of Grignard reagents and their straightforward synthesis prompted us to examine them using Rh(cod)(acac) as the precatalyst. Unfortunately, although the reactions did proceed with disappearance of starting materials as observed by TLC analysis, these reactions were unsuccessful, providing complex mixtures of unidentified products.

Pleasingly, it was discovered that the corresponding diorganozinc reagents generated in situ by transmetallation of the Grignard reagent with ZnCl₂ were much more effective (Scheme 2.7). It was observed that the reaction still proceeded in a syn-fashion with excellent regioselectivities. For example, reaction of ynamide 178c with di-2-thienylzinc (1.0 equiv) generated from 2-thienylmagnesium bromide (2.0 equiv) and ZnCl₂ (1.0 equiv) provided enamide 183a as the only observable regioisomer in good yield of 86%.
Scheme 2.7

Carbometallation with *in situ* generated diarylzinc reagents containing electron-donating or withdrawing substituents at the *para*-position was also possible, and afforded enamides 183b and 183c in an excellent level of regioselectivity and with good yields. Similarly, benzyl groups could be introduced regioselectively with good yield (enamide 183d). Access to the dienamides 183f and 183g was also possible by carbozincation with vinyl and 2-propenyl groups. However, in some cases (183e and 183f) the reactions were carried out at −78 °C to achieve satisfactory regioselectivities.

Reaction of the ynamide 178b with dicyclohexylzinc was found to be problematic under the original conditions, which resulted in a significant amount of the hydrometallation product 184 (Scheme 2.8). It is thought that β-hydride elimination may occur to yield to the formation of a rhodium hydride species, which is then able to hydrometallate ynamide 178b in a *syn*-fashion to give the β-monosubstituted (Z)-enamide 184.
Replacing the rhodium catalyst with Cu(acac)₂, and by using the Grignard reagent itself allowed the clean preparation of the enamide 183h with high regioselectivity, and moreover, no hydrometallation was detected. These reaction conditions are related to those described previously for copper-catalysed carbozincation of ynamides.⁸⁴

The in situ preparation of diorganozinc reagents from Grignard reagents and ZnCl₂ had increased the scope of the preparation of enamides using our methodology. Furthermore, this resolved the issue of the lack of commercially available diorganozinc reagents. Unfortunately, the use of Grignard reagents limits the presence of base- and nucleophile-sensitive groups in the organometallics.⁸⁴

2.2.4 Expansion to Organozinc Halide Reagent

Expansion of the scope of the organometallic reagent to organozinc halides would be highly attractive, since these reagents (including functionalised derivatives) are now

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¹ The work in this section was carried out in collaboration with Mairi E. Radkin. In all cases, the experiments carried out by her have been denoted with an asterix (*). The remainder of the work is my own.
commonly available, and insertion of zinc into polyfunctional iodides may be used to access a wider range of derivatives.\textsuperscript{94}

The reaction conditions described previously were compatible with these reagents. Therefore a study into the scope and limitations of this reaction was undertaken. Arylzinc iodides containing an ester or a chlorine were first applied with a range of ynamide substrates (Scheme 2.9).

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{R'} \\
\hline
\end{array} + \begin{array}{c}
\text{O} \\
\text{N} \\
\text{R'} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{R'} \\
\hline
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{THF 0 °C 1h r.t.}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{THF 0 °C 1h r.t.}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array}
\end{equation}

Scheme 2.9

These reactions resulted in the desired enamides being obtained in good to high yields and with excellent regioselectivities. After these promising results, the study was then directed towards non-aromatic functionalised organozinc halide reagents (Scheme 2.10).

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array} \xrightarrow{\text{THF 0 °C 1h r.t.}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CO}_{2} \text{Et} \\
\hline
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array} \xrightarrow{\text{THF 0 °C 1h r.t.}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array}
\end{equation}

\begin{equation}
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array} \xrightarrow{\text{Rh(cod)}(acac)_{6}mc\%} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array} \xrightarrow{\text{THF 0 °C 1h r.t.}} \begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\hline
\end{array}
\end{equation}

Scheme 2.10
Fortuitously, the reaction conditions were also compatible with the use of aliphatic zinc bromide reagents. However, a relatively low yield of the desired enamide (186b*) was observed when the nitrile-substituted zinc reagent was used. This result was attributed to the low regioselectivity observed during the carbometallation process and the formation of the hydrometallation side-product (12% isolated). The cyanobenzyl zinc bromide reagent displayed sluggish reactivity, and required a slight modification of the reaction conditions (5 mol% [Rh(cod)Cl]$_2$ with 10 mol% rac-BINAP at 60 °C) to deliver the product 186c* in 35% yield along with other unidentified products. The ratio of isomers could not be determined due to the complexity of the unpurified reaction mixture. It has been reported in the literature, that nitrile-containing substrates were found to hinder the rate of transmetallation, presumably by coordination of multiple nitrile groups to the rhodium centre, thus attenuating the metal’s reactivity. This could explain the lower yields and regioselectivities obtained for 186b* and 186c*.

**Regio-/Stereochemical Determinations**

The regioselectivities of the rhodium-catalysed carbozincation reactions of alkyl-substituted ynamides 178a, 178c–178f were obvious from the $^1$H NMR spectra of the corresponding enamide products (by consideration of the signals of the alkene proton, which did not exhibit vicinal proton–proton coupling and was displayed as a singlet).

The stereoselectivities of the rhodium-catalysed carbozincation reactions producing enamides 180h, 183b, and 183f were determined on the basis of NOESY experiments, which displayed the following diagnostic enhancements (Figure 2.2):

![Figure 2.2](image-url)
The regio-/stereoselectivities of the remaining carbozincation reactions were assigned by analogy.

### 2.2.5 Acyclic Ynamides

To further increase the scope and utility of the methodology, it was desirable to investigate the conditions with a more diverse range of ynamides. So far, the rhodium-catalysed carbozincation had proven to be an effective process with ynamides where the carbonyl group is set within a five-membered ring, such as an oxazolidin-2-one, pyrrolidin-2-one, or imidazolin-2-one. Next it was chosen to evaluate a small selection of acyclic ynamides, such as carbamates 179a and 179c, and the yne-sulfonamide 179b (Figure 2.3).

![Figure 2.3](image)

Ynamide substrates containing an aliphatic group at the β-position (such as 179c*) appeared to be largely inert under the standard rhodium-catalysed conditions with Et₂Zn, and only a small amount of decomposed substrate was observed after an extended reaction time.* Phenyl-substituted acyclic ynamides proved to be far more reactive and the carbozincation reactions proceeded extremely rapidly, even at low temperature (–78°C, 179a and 179b). Unfortunately, low selectivity was observed, and the corresponding enamides were isolated as a mixture of isomers, marginally in favour of the unexpected regioisomer 187b (Method A, Scheme 2.11). Similar results were observed with the acyclic yne-sulfonamide (regioselectivity 1:1.4) but these products were not isolated.
Fortunately, a Cu(acac)$_2$ catalyst, which has been advantageously used in partnership with dicyclohexylzinc reagent (see Scheme 2.8) provided the desired enamide 187b with high regioselectivity (Method B, Scheme 2.11)*; although the reaction time was greatly extended. However, these conditions were ineffective with ynamides 179b and 179c, with only starting materials recovered.*

Attempts to broaden the carbozincations of acyclic ynamides with alkylzinc halides using either Rh(cod)(acac) or Cu(acac)$_2$ did not provide satisfactory results, furnishing complex mixtures of products, and in the case of the copper-catalyzed procedure, low conversions were observed. Reactions of acyclic ynamides with arylzinc halides gave no reaction.

After analysis of these results, it is reasonable to assume that the high regioselectivity observed for the cyclic ynamides is due to the directing effect of the carbonyl group with the rhodium and/or zinc in the carbometallation step (vide infra). In the case of acyclic ynamides, the greater degree of rotational freedom diminishes the ability of the carbonyl/sulfonyl groups to direct the metal centre, thus resulting in a poor regioselectivity for these substrates.

### 2.2.6 Mechanistic Discussion

A possible catalytic cycle for our rhodium-catalysed carbozincation of ynamides is presented in Scheme 2.12.
Reaction of Rh(cod)(acac) with the organozinc reagent would generate the organorhodium species 188 which would undergo a syn-carbometallation of the ynamide 178. It is assumed that the regioselectivity of this step is ruled by the prior coordination of 188 with the carbonyl group of the ynamide. It is worth mentioning that the intrinsic polarity of the ynamide is overridden by the directing effect of the carbonyl group. The alkenylrhodium intermediate 189 would then undergo transmetallation with an organozinc species, thus regenerating the organorhodium species 188 and providing the alkenyl zinc intermediate 190, which is protonated upon work-up.

2.2.7 Utilisation of Alkenylzinc Intermediates

In the proposed mechanisms for the rhodium-catalysed carbometallation of ynamides, the catalytic cycle liberates alkenyl zinc intermediate 190. In order to synthesise more highly substituted enamides it was desirable to engage this species in further functionalisation reactions.

Initially, the trapping of the zinc intermediate formed with different electrophiles was investigated. It was found that the carbozincation of the ynamide 178b with 0.55 equivalents of Et₂Zn generated the desired alkenylzinc intermediate 191 which was then acylated with benzoyl chloride in a one-pot procedure, to provide the α,β,β-trisubstituted enamide 192 in 56% overall yield (eq 2.2).
When employing the same approach, it was also possible to trap the alkenylzinc species 193, generated from 178a, with allyl bromide to provide the α,β,β-trisubstituted enamide 194* (eq 2.3).

Additionally, it is well-documented that alkenylzinc intermediates can participate in palladium-catalysed Negishi cross-coupling reactions. This one-pot alternative procedure was possible with aryl, heteroaryl, and alkenyl iodides providing the desired α,β,β-trisubstituted enamides 195a–195c in good overall yields (Scheme 2.13).

This methodology was expended to the preparation of the α,β,β-triarylsubstituted enamides 197 (Scheme 2.14).*
The low yield obtained for this reaction was likely due to the significant steric hindrance that must be overcome during the Negishi coupling.

### 2.2.8 Elaboration of Enamide Products

With the purpose of demonstrating the synthetic utility of the enamides prepared, diverse transformations were investigated. By treating the enamide \(180a\) with TMSOTf, the cyclisation of the enamide substrate to form the tetrahydronaphtalene derivative \(200\) in a high yield of 86% was observed (Scheme 2.15).

It is believed that this reaction proceeds by protonation of the substrate \(180a\) with trace of triflic acid present in TMSOTf. Friedel-Crafts cyclisation onto the iminium
ion 198 formed followed by proton loss gives the product 200. Running the same reaction with 5 mol% of triflic acid gave the product 200 in 88% yield. This experiment confirmed the hypothesis of the protonation of enamide 180a by a trace amount of TfOH present in TMSOTf. In this process, the stereochemical outcome was probably determined during the cyclisation in which a chair-like transition state with substituents in pseudoequatorial positions may be possible. The stereochemistry of tetrahydronaphthalene derivative 200 was assigned on the basis of the indicated proton–proton coupling constant of 10.3 Hz, suggesting a pseudoaxial–pseudoaxial relationship (Figure 2.4), which supports the chair-like transition state proposed.

![Figure 2.4](image)

Diels-Alder reaction of dienamide 183f with N-methylmaleimide (202) proceeded efficiently at room temperature to provide the bicyclic product 201 in 89% yield. The high endo-selectivity (>19:1) of the reaction was confirmed by a crystal structure of 201 (Scheme 2.16).

![Scheme 2.16](image)

In another exemplification of the diene substrate 183f, a reductive coupling that has recently been developed by Tamaru and co-workers was investigated. They described a range of nickel-catalysed reductive coupling reactions of dienes with carbonyl compounds that are mediated by triethylborane or diethylzinc. Based on these results, the use of dienamide 183f in this process was evaluated, since this class of dienes have not been explored previously (eq 2.4).
Dienamide 183f reacted smoothly with p-anisaldehyde in a reductive coupling reaction to give the homoallylic alcohol 203. With more electrophilic substrates, such as benzaldehyde, addition of diethylzinc to the aldehyde was found to be a competitive pathway.

### 2.3 Conclusions

A new rhodium-catalysed carbozincation of ynamides as an efficient method for the preparation of enamides has been developed. This process is highly stereo- and regioselective. The scope of the reaction is broad, with commercially available dialkylzinc reagents, as well as in situ generated diorganozincs from Grignard reagents and organozinc halide reagents tolerated in this methodology. Extension of the procedure to acyclic ynamide substrates has been difficult as poor regioselectivity or reactivity have been observed with our carbometallation procedure. It has also been possible to further react the alkenylzinc intermediates formed during the course of the carbometallation with electrophiles and in palladium-catalysed Negishi couplings. This methodology has allowed the preparation of multisubstituted enamides in a stereo- and regioselective fashion, which would be challenging to access using other methods.
3.0 Rhodium-Catalysed Carbometallation of Ynamides with Organoboron Reagents

3.1 Background

A simple route for the preparation of $\beta,\beta'$-disubstituted and $\alpha,\beta,\beta'$-trisubstituted enamides with high levels of regio- and stereocontrol via a rhodium-catalysed carbozincation of ynamides has been demonstrated (Chapter 2). This reaction also enabled the introduction of moderately base- and nucleophilic-sensitive functional groups. With the prospect of increasing further the range of enamides available through ynamide carbometallation reactions, studies were directed towards organometallics that have an even greater functional group compatibility. Therefore, attention was turned towards organoboron reagents. Boronic acids, boronic esters and boroxines are mostly stable to air and moisture, and are easily available. For those reasons, they are often used as the organometallic compound of choice in transition metal-catalysed carbon–carbon bond forming reactions.

Metal-catalysed additions of arylboron reagents on to alkynes have already been subject to intensive studies. Hydroarylations of alkynes with nickel, rhodium, palladium, copper and cobalt have all been described. For the purpose of this review, only a few examples will be discussed. Hayashi and co-workers pioneered the hydroarylation of alkynes with arylboronic acids. They developed a catalytic rhodium system using a chelating bisphosphine ligand, bis(diphenylphophino)butane (dppb). Representative results are displayed in Scheme 3.1.
Under the optimised conditions, they obtained a range of trisubstituted alkenes in excellent yields regardless of the substituents (electron-donating or withdrawing groups) on the aryl groups. The regioselectivity of the process was not an issue when using symmetrical alkynes, though when using unsymmetrical alkynes the regioselectivity of the reaction was poor (206d). During mechanistic studies, they came across a rather surprising result. In this process the hydrogen on the vinylic carbon is expected to come from water. However, when the reaction was carried out in D$_2$O, they did not observe incorporation of deuterium at the vinylic position but at the ortho-position of the phenyl group instead (Scheme 3.2), suggesting that the reaction proceeds via a 1,4-shift of the rhodium before hydrolysis occurs.$^{100a}$

Although the methodology developed by Hayashi gave high-yielding reactions, it would be more advantageous if the regioselectivity can be controlled. In this regard, Lautens group described a regioselective rhodium-catalysed addition of arylboronic
acids to alkynes. Regioselective addition of the aryl substituent was achieved by the presence of a directing group on the alkyne (Scheme 3.3).\textsuperscript{100b}

\begin{equation}
\text{Scheme 3.3}
\end{equation}

The presence of the pyridine moiety has a dramatic effect on the regiochemistry. Coordination of the nitrogen atom of the substrate to rhodium would give the alkenylrhodium complex 213, and therefore regiocontrolled insertion of aryl groups.

In summary, rhodium-catalysed hydroarylation of alkynes has advantages over other methods due to high syn-selectivity and high efficiency; however, to date this reaction is only applicable to internal alkynes and arylboronic acids.

Another transition metal that has been widely used for this kind of reaction is palladium. A number of reports have been published over the last decade covering this area. Kim and co-workers have established a palladium-catalysed reaction of unsymmetrical alkynes 215 with organoboronic acids to give a mixture of products 216 and 217 (Scheme 3.4).\textsuperscript{101c}
Several features in this process are noteworthy. First, a significant directing effect was observed from the hydroxyl group when it was located in the propargylic position. However, as the alkyl substituent became bulkier, from methyl to finally tert-butyl, the formation of the other regioisomer became predominant. Second, as the distance between the hydroxyl group and the triple bond increases, the regioselectivity diminishes, regardless of the alkyl substituents.

Kim’s group postulated that a certain type of nitrogen group might be a better directing group than oxygen. Under the above conditions, 1-(2-pyridyl)propyne gave exclusively, whereas 1-(4-pyridyl)propyne gave a 1:1 mixture of regioisomers (Scheme 3.5).
Notably, an interesting directing group effect was observed in 2-pyridyl-substituted propargylic alcohol 218b where product 219b was exclusively obtained. In contrast, the 4-pyridyl-substituted propargylic alcohol 220b did not show any selectivity. These results demonstrate that in this case the nitrogen atom provides a better directing group effect than oxygen.

Cobalt has received only scarce attention for the hydroarylation of alkynes. To date, there is only one example described in the literature. Cheng and co-workers introduced an elegant regio- and stereoselective synthesis of trisubstituted olefins (Scheme 3.6)\(^\text{103}\).

![Scheme 3.6](image)

Using alkynes with a carbonyl or a pyridyl group, they could easily prepare a pool of trisubstituted alkenes, usually in a high yield, with only one regioisomer observable. Surprisingly, the hydroarylation of propargylic alcohol and propargylic carbamate provided the other stereoisomer 222 with high regioselectivity. This unusual selectivity may be explained based on the proposed transformation illustrated in Scheme 3.7.

![Scheme 3.7](image)
It is likely that intermediate 223, obtained from carbocobaltation, undergoes facile $E$–$Z$ isomerisation to intermediate 225 via a cobalt carbene species. The presence of the hydroxymethyl group stabilises the cobalt intermediate by forming a five-membered oxametallocycle, which is protonated to give product 222a.

The control of regioselectivity is one of the main challenges for unsymmetrical alkynes. High regioselectivities are usually observed when there are substantial differences in the steric and/or electronic properties between the two substituents attached to the alkyne. Use of a directing group in the substrate is another tactic to control regioselectivity. Our previous results on carbometallation of ynamides (see Chapter 2), made us believe that a similar directing effect could also be observed in carbometallation involving organoboron reagents.

### 3.2 Results and Discussion $^{104,\text{ii}}$

#### 3.2.1 Optimisation of Carbometallation Reaction Conditions

Using ynamide 178a and phenylboronic acid 228, the study was initiated by screening different metal precatalysts. The conditions that were effective for the carbozincation of ynamides (see Chapter 2) were tried first. It was quickly noticed that these conditions (5 mol% of Rh(cod)(acac)) were ineffective, leading to a complex mixture of products when the reaction was carried out at 90 °C under microwave irradiation (Table 3.1, entry 1). No conversion was observed at room temperature. Similar results were obtained when changing the precatalyst to [Rh(cod)Cl]$_2$ (entry 2).

---

$^{\text{ii}}$ The work in this section was carried out in collaboration with Donna L. Smith. In all cases, the experiments carried out by her have been denoted with an asterix (*). The remainder of the work is my own.
Table 3.1

<table>
<thead>
<tr>
<th>entry</th>
<th>precatalyst</th>
<th>temp</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rh(cod)(acac)</td>
<td>90 °C</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>2</td>
<td>[Rh(cod)Cl]₂</td>
<td>90 °C</td>
<td>Complex mixture of products</td>
</tr>
<tr>
<td>3</td>
<td>Rh(acac)(C₂H₄)/dpb</td>
<td>90 °C</td>
<td>No reaction</td>
</tr>
<tr>
<td>4</td>
<td>[Rh(cod)(MeCN)₂]BF₄</td>
<td>90 °C</td>
<td>229a:230 Formed in &gt;19:1 ratio after 10 min.³</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>63% Isolated yield of 2.⁴</td>
</tr>
<tr>
<td>5</td>
<td>Pd(OAc)₂</td>
<td>90 °C</td>
<td>229a:230 Formed in 8:1 ratio (30% conv)⁵</td>
</tr>
<tr>
<td>6</td>
<td>CuOAc</td>
<td>rt</td>
<td>229a:230 Formed in 4:1 ratio after 2 h.⁶</td>
</tr>
</tbody>
</table>

⁴ Reactions proceeded to complete conversion. Ratios determined by ¹H NMR analysis of the unpurified reaction mixtures. ⁵ Isolated as an 8:1 inseparable mixture of 229a and the imide 231 (Figure 3.1). Cited yield of 229a has been adjusted to reflect this impurity. ⁶ Na₂CO₃ (2.0 equiv) was used in this reaction.

Surprisingly, conditions developed previously by Hayashi’s group (entry 3)⁵⁰ were totally ineffective for our methodology. Only starting materials along with some hydrolysis of the ynamide (~10%) were present after an overnight reaction. Cationic rhodium complex, [Rh(cod)(MeCN)₂]BF₄, provided the desired product (in >90% conversion) with high regioselectivity after 3 days of reaction at room temperature. Although the reaction was slow, it was observed that by heating at 90 °C under microwave irradiation for 10 minutes using [Rh(cod)(MeCN)₂]BF₄ (8 mol%), carbometallation was effectively promoted. The desired product 229a was afforded in 63% yield with excellent regioselectivity (entry 4). Under similar conditions, the use of Pd(OAc)₂ along with Na₂CO₃ (2.0 equiv) led only to low conversions into the desired enamides with moderate regioselectivities (entry 5). Although CuOAc proved to be an efficient precatalyst in this process, with complete conversion being obtained at room temperature (entry 6), the regioselectivity was poor (4:1).
3.2.2 Scope and Limitations

With optimised conditions in hand (Table 3.1, entry 4), the scope of the reaction using arylboronic acid reagents with a range of ynamides was explored (Table 3.2).

Phenylboronic acid was a successful reactant in this process for ynamide substrates containing either aliphatic or aromatic substituents at the β-position. These reactions provided the corresponding enamides (229a, 229e and 229h) with generally high...
yields, although the yield was slightly diminished with ynamide 178c due to the formation of the side-product 231 (Figure 3.1) resulting from hydration of the ynamide.

![Figure 3.1](image_url)

Arylboronic acids containing electron-donating substituents at the para-position proved to be of similar reactivity to phenylboronic acid. High yields and regioselectivities were observed, and once again presence of the imide 231 was detected as an inseparable mixture in product 229b. With electron-withdrawing substituents, yields and regioselectivities were somewhat lower (products 229f, 229g, 229i and 229j). These inferior results are probably attributed to the lower nucleophilicity of these reagents. Slightly lower yields were also encountered, although unsurprisingly, with sterically hindering ortho-substitution on the arylboronic acid (products 229d* and 229j).

The regioselectivity observed in these reactions was as expected, with introduction of the aryl group at the β-position of the ynamide (see Mechanistic Studies later in this chapter). The regioisomeric ratios ranged from modest (6:1) to excellent (>19:1). Regarding the scope of the ynamide, oxazolidin-2-one-containing substrates with aliphatic or aromatics substituents all underwent the reaction with comparable efficiency; the variations in yields are likely to be due to the properties (electronic or steric) of the arylboronic acids used.

To our surprise, pyrrolidin-2-one-containing ynamides such as 178h were poorly reactive in this process compared to their closely related substrates, oxazolidin-2-one-containing ynamides (Scheme 3.8).
This poor reactivity was unforeseen since no such results have been observed in the related rhodium-catalysed carbozincation of ynamides (Chapter 2). Carbometallation of 178h with 4-acetylphenylboronic acid (232) produced a complex mixture of products from which 233 was isolated in only 25% yield. With acyclic ynamides such as 179a (Figure 3.2), carbometallation occurred but with negligible regioselectivity (1.7:1 inseparable mixture, regiochemistry not assigned). This was not entirely unexpected as it has been previously documented in the rhodium-catalysed carbozincation of ynamides (Chapter 2/ page 52).

To introduce more diversity to the products, attention was turned to boronic acids containing non-benzene groups. These reagents proved to be viable in the process (eq 3.1 and eq 3.2).
Carbometallation of ynamide 178c with 2-furanboronic acid proceeded smoothly to give enamide 234 as the only observable regioisomer in 66% yield (eq 3.1), while the use of (E)-2-phenylvinylboronic acid gave dienamide 235 in 52% yield, albeit with lower regioselectivity (eq 3.2). Although the reaction with non-benzene boronic acids worked well with an aliphatic substituent on the ynamide, the process proved to be more challenging with aryl substituent on the ynamide (eq 3.3 and eq 3.4). However, comparison of the two present processes is not possible since different boronic acids were used in each reaction.

Carbometallation of ynamide 178b with 2-thiopheneboronic acid provided a complex mixture, and afforded the desired enamide 236 in a moderate yield of 38% (eq 3.3). With trans-3-phenyl-1-propen-1-ylboronic acid, carbometallation proceeded with complete conversion, but in this case the regioselectivity of the reaction was an issue, with a regioisomeric ratio of 2.3:1 in favour of the desired product 237 (eq 3.4). The modest yield for dienamide 237 is accounted for the poor regioselectivity but also by the difficulty in the separation of the isomers.

Interest grew in exploring organoboron reagents other than boronic acids. Pleasingly, under conditions identical to those employed using arylboronic acids, arylboronic esters were found to be competent arylating reagents (Scheme 3.9). Enamide 229g was obtained with a similar yield but with improved regioselectivity (16:1 vs 7:1) when compared to the reaction with the boronic acid (see Table 3.2, 229g).
Triarylboroxines 240 were also found to be efficient arylating reagents (Scheme 3.10), providing product 229a with comparable yield and regioselectivity to the same reaction using phenylboronic acid (see Table 3.2, 229a).

Use of non-arylboroxines was also permitted. For example, 2,4,6-trivinylcyclotriboroxane-pyridine complex (241) was initially successful in the process to give the dienamide 242 in 55% yield as illustrated in Scheme 3.11. However, this reaction was not reproducible, leading to a complex mixture of products.

Finally, attempted carbometallation of ynamide 178a with potassium phenyltrifluoroborate\textsuperscript{105} was unrewarding, providing an unidentified mixture of products.
Regio-/Stereochemical Determinations

The regioselectivities of the rhodium-catalysed carbometallation reactions of alkyl-substituted ynamides 178a and 178c were obvious from the $^1$H NMR spectra of the corresponding enamide products (by consideration of the signals of the alkene proton, which did not exhibit vicinal proton–proton coupling and was displayed as a singlet).

The regiochemical outcome of the rhodium-catalysed carbometallation reaction producing enamide 229h was determined by dihydroxylation of 229h, which provided known $\alpha$-hydroxyaldehyde 243 in low conversion (eq 3.5).

The stereoselectivities of the rhodium-catalysed carbometallation reactions producing enamides 229c, 229g, 233, and 235 were determined on the basis of NOESY experiments, which displayed the following diagnostic enhancements (Figure 3.3):

The regio-/stereoselectivities of the remaining carbometallation reactions were assigned by analogy.
3.2.3 Mechanistic Studies

By analogy with related processes, a possible catalytic cycle for our rhodium-catalysed carbometallation of ynamides is presented in Scheme 3.12.

It is expected that a rhodium(I) species would be generated under the reaction conditions, which would then undergo transmetallation with the organoboron reagent to provide organorhodium intermediate. Subsequently, syn-carborhodation of the ynamide would result in chelated alkenylrhodium species. The regioselectivity of this step is controlled by the prior coordination of the carbonyl group of the ynamide as previously presumed in our rhodium-carbozincation of ynamides (Chapter 2, page 53). Finally, protonation of with water present in the system would release the product and regenerate hydroxyl-rhodium species.

In Hayashi’s work (Chapter 3, paragraph 3.1) describing related alkyne hydroarylations, they established a 1,4-rhodium migration from the alkenyl position to an ortho-position on the phenyl group, as suggested by deuterium labeling studies. In our methodology alkenylrhodium intermediate is presumably involved, and with the aim of understanding the proposed mechanism in more depth, an analogous experiment was carried out (eq 3.6).
Carbometallation of the ynamide 178c was conducted with triphenylboroxine in THF/D₂O. This experiment provided enamide 246 with >97% deuterium incorporation at the alkenyl position along with a small amount of imide 247 as a mixture of isotopologues. It was assumed that the regioselectivity of this reaction was similar to the reaction performed under the original conditions, however, since deuterium is not ‘visible’ by ¹H NMR analysis the regioselectivity could not be established with accuracy. From this study it was clear that 1,4-rhodium migration does not occur in our process. It would be reasonable to assume that the further stability conferred onto alkenylrhodium species 189 through chelation with the carbonyl group present on the ynamide, impedes the catalyst migration.

3.3 Conclusions

Rhodium catalysis enables the carbometallation of ynamides using a range of organoboron reagents, including aryl, heteroaryl, and alkenylboronic acids, arylboronic esters, and trialkylboroxines. This new process is a good complement to our carbozincation of ynamides for the synthesis of multisubstituted enamides in regio- and stereocontrolled fashion. Moreover, this methodology allows even greater functional group compatibility, which broadens the pool of enamides prepared. Additionally, organoboron reagents are readily available, and their stability to air and moisture render them easy to handle. All of these above aspects make this reaction highly attractive for the preparation of multisubstituted enamides.
4.0 Rhodium-Catalysed Annulation of Ynamides with Bifunctional Arylboron Reagents

4.1 Background

The utility of the indene core is widely recognised (Figure 4.1); indenylmetallocene complexes are active catalysts in olefin polymerisation, indene derivatives have been used in materials chemistry (in conducting polymers and discotic liquid crystal) and they are present in many biologically active compounds (Figure 4.1).

![Figure 4.1](image)

Different syntheses are available to prepare such compounds, and probably the most powerful to access structurally complex indene derivatives are transition-metal-catalysed tandem reactions. The advantages of these transformations are the one-pot formation of several bonds using a single catalyst, without isolation of the intermediates, change of reaction conditions, or addition of supplementary reagents. Recently, there has been considerable research interest in palladium- and rhodium-
catalysed tandem transformations with organoboron reagents for the formation of cyclic compounds containing an indene skeleton.\textsuperscript{112,113} One strategy that has been developed is a tandem reaction between alkynes (or strained alkenes) and ambiphilic organoboron compounds that contain an electrophilic functional group (aldehydes, ketones,…), which can eventually accept an organopalladium(II) intermediate or an organorhodium(I) species (\textit{vide infra}) at a later stage (Scheme 4.1).

\begin{equation}
\text{Z} + \text{Fe or Rh} \rightarrow \text{Z1}
\end{equation}

\textbf{Scheme 4.1}

An early example of one such reaction was reported by Yamamoto and co-workers (eq 4.1).\textsuperscript{114}

\begin{equation}
\text{261} + \text{Fe(OCOCF}_2)_2 (20 \text{ mc} \%) \rightarrow \text{262} \text{ (68\%)}
\end{equation}

In the mixed toluene/acetonitrile solvent, the benzynne precursor 251 reacts with two molecules of alkyne to provide the highly substituted indene derivative in a reasonable yield.

More recently, Tsukamoto and Kondo have developed a new preparative method for 2,3-disubstituted indenones through annulation of alkynes with \textit{ortho}-ester-containing phenylboronic acids (Scheme 4.2).\textsuperscript{112j}
Using this methodology, they were able to prepare a variety of symmetrical and unsymmetrical indenones, though regioselectivity was difficult to control in the latter case (indenone 254c).

Shortly afterwards, Lu's group reported the first synthesis of the optically active 1-indenol derivatives catalysed by chiral cationic palladium species. The tandem reaction of ortho-functionalised arylboron reagents and internal alkynes yields optically active indenols (Scheme 4.3). 112h

A range of activated alkynes and bifunctional arylboron reagents provided the desired multisubstituted indenol derivatives in generally high yields and enantioselectivities. A possible mechanism for the asymmetric annulation is shown in Scheme 4.4. 112h
First, reaction between Pd(OTf)$_2$•H$_2$O and the chiral diphosphine ligand generates the active cationic Pd(II) catalyst 259. It is then thought that the annulation reaction would proceed through transmetallation of Pd(II) with the boron reagent to provide the aryl palladium species 261. The σ-coordination of the carbonyl with the palladium centre may stabilise the intermediate and make the transmetallation easier. Insertion of the alkyne would generate vinylpalladium(II) intermediate 264, which undergoes nucleophilic addition to the carbonyl group at the ortho-position resulting in the formation of the alkoxy palladium species 265. Finally, protonolysis occurs to form product 266 and regenerates the cationic palladium species 259. However, in this process, it should be noted that the reaction does not take place with a ketone in place of an aldehyde in reagent 260. In addition, non-activated alkynes, such as terminal alkynes and dialkylsubstituted alkynes failed to give annulation products.

Another metal that has been widely used in this field is rhodium. The Lautens group have pioneered the use of this catalyst, and shortly afterwards the Hayashi and Murakami groups, in independent studies, described the preparation of indene

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skeletons by the rhodium-catalysed annulation of 2-acylphenylboronic acids with alkynes.\textsuperscript{112b,c} The conditions they developed were almost identical to each other and are displayed in Scheme 4.5.

![Scheme 4.5](image)

The mechanism of this reaction is similar to the one proposed by Lu in his palladium-catalysed annulation. This elegant methodology allows the preparation of 1H-inden-1-ols in a simple way and under mild conditions, in uniformly high yield and regioselectivity. Unactivated alkynes, such as dialkylsubstituted alkynes (product 269a) and terminal alkynes were also tolerated in the process, although in the latter case regioselectivity and especially yield were lower (product 269e).

More forcing conditions were required for an analogous reaction of 2-acetylphenylboronic acid (270) (eq 4.2).\textsuperscript{112b,c} Addition of a small amount of water promotes the reaction to give a good yield of 1-methyl-1H-inden-1-ol 271.

![Scheme 4.6](image)

In their work, the Murakami group also described the preparation of indenones where 2-cyanophenylboronic acid 272 acts as an ambiphilic bifunctional reagent, albeit under harsher reaction conditions (Scheme 4.6, path A).\textsuperscript{112d} Interestingly, when ethyl
hex-2-ynoate (274) was employed as the alkyne under similar conditions, seven-membered ring benzotropone 273 was obtained as the major product, instead of the five-membered ring indenone (Scheme 4.6, path B).\textsuperscript{112d}

![Scheme 4.6]

Product 273 results from a second intermolecular carborhodation onto the ethyl hex-2-ynoate (274) followed by ring closure to the cyano group. The steric constraint imposed on the linear cyano-substituent may be responsible for the difference observed in the reactions of acetylenic esters with 260, 270 and 272.

Recently, the rhodium-catalysed annulation reaction using an alkyl chloride group as a second electrophile has been developed for the preparation of substituted indenes (Scheme 4.7).\textsuperscript{112f}

![Scheme 4.7]

Although the reaction afforded the desired indenes in generally good yield and high regioselectivity, terminal alkynes and alkynes having a silyl or ester group were not suitable in this process.

Based on these previous reports and our success in the rhodium-catalysed carbometallation of ynamides with arylboron reagents (see Chapter 3), attention was
turned to the preparation of 2-amidoindenes 279 (or indene–enamide-like products) via annulation of ynamides 178 with bifunctional arylboron reagents 277 (Scheme 4.8).

This methodology offers a one-pot synthesis of relatively complex enamide–indene structures and complements the existing literature in this area. Moreover, the use of chiral catalysts/ligands could potentially generate an enantioselective procedure to allow the synthesis of optically active indene derivatives. The pendant enamide moiety provides an additional functional handle on the indene core that can be used in a wide range of transformations (see Chapter 1 for a full discussion) to gain access to other indene derivatives. For these reasons the scope and limitations of the transformation was studied.

4.2 Results and Discussion

4.2.1 Rhodium-Catalysed Carbometallation–Conjugate Addition Reaction

A small amount of optimisation was needed to find the most favourable conditions for this reaction. Cationic palladium complexes which proved to be efficient with alkynes bearing an ester substituent led to the formation of imide 231 by hydrolysis of the ynamides (see Chapter 3 / Results and Discussion). Therefore, the decision was made to switch to rhodium catalysts that showed larger substrate scope and
above all were effective for our earlier carbometallation reactions (see Chapter 2 and 3).\textsuperscript{88,115} It was found that $[\text{Rh}(\text{cod})\text{Cl}]_2$ (4 mol\%) in the presence of KOH (0.3 equiv) in THF/H\textsubscript{2}O (20:1) was successful to promote the annulation reaction. For this process, the presence of the base was essential, as no reaction or extremely poor conversion were observed without KOH.

With a set of conditions in hand, the reaction was investigated with a series of ynamide substrates and two commercially available bifunctional arylboron reagents, 2-formylphenylboronic acid (\textsuperscript{260}) and 2-acetylphenylboronic acid (\textsuperscript{270}). Due to their efficacy in our previous rhodium-catalysed carbometallation reactions, ynamides \textsuperscript{178a-178c, 178e} and \textsuperscript{178g} were selected for this study (Table 4.1).
The reactions were highly effective for ynamides containing oxazolidinone moieties and an aliphatic group at the R¹ position. The corresponding 2-amidoindenols were obtained with excellent regioselectivities (only one regioisomer detectable by ¹H NMR analysis), and moderate (entry 2, 4 and 6) to good yields (entry 1, 3 and 5). Lower yields were monitored when 2-acetylphenylboronic acid (270) was used instead of 2-formylphenylboronic acid (260). This was not entirely surprising considering the lower electrophilicity of the ketone in 270 compared with the
aldehyde in 260. The inferior reactivity was manifested in the reaction times (overnight for 270, 3 h for 260) and isolated yields due to the formation of unidentified by-products. Ynamides with an aromatic substituent at the R position (entry 7, 8 and 9) also proved to be good coupling partners to provide the desired 2-amidoindenols, although regioselectivity was somewhat lower (9:1) with substrates 178b and 260.

Reaction with an acyclic ynamide 179a proceeded successfully but with low regioselectivity (Scheme 4.9). This was predictable as a similar trend has been previously described in our prior carbometallations of ynamides (see Chapter 2 / page 52).88

![Scheme 4.9](image)

It should be noted that similar conditions furnished the carboannulation product 284 from the ynamide 178c and the aromatic boronate ester bearing an α,β-unsaturated ketone at the ortho-position in high yield and good regioselectivity (eq 4.3).115

![Scheme 4.9](image)

This complementary protocol widely broadens the scope of the methodology as other α,β-unsaturated ketones, esters and aldehydes at the ortho-position can also be used (see examples in Figure 4.2).115
4.2.2 Mechanistic Discussion

Earlier work from Murakami\textsuperscript{112c} and Hayashi\textsuperscript{112b} groups led us to suggest the following mechanism (Scheme 4.10).

The catalytically active L\textsubscript{m}Rh(OH) species 244 would be generated by reaction of the precatalyst with KOH/H\textsubscript{2}O. Then, transmetallation of an arylboronic acid 260 or 270 to the hydrooxorhodium catalyst forms arylrhodium species 285. Carbonyl-directed syn-carbometallation onto ynamide 178 would provide alkenylrhodium intermediate 286. It is assumed that the carbonyl group present in the ynamide moiety directs this step in a regioselective manner. Intramolecular addition to the carbonyl group at the ortho-position results in the formation of an alkoxorhodium species with a five-
membered carbocycle 287. Subsequent protonolysis with water present in the system regenerates the hydroxorhodium catalyst and produces 2-amidoindenols 280. It is thought that the formal oxidation state of the rhodium remains +1 throughout the catalytic cycle.

The regioselectivity of the annulation of ynamide 178c with arylboronic acid 260 was established through X-ray crystallography of a derivative of the resulting indene 280c, which was prepared as shown in Scheme 4.11. The remaining indene products were assigned by analogy.

![Scheme 4.11](image)

### 4.2.3 Enantioselective Variants

Development of an asymmetric version of these reactions would be an attractive way to prepare optically pure indene derivatives. Obviously, to render this process enantioselective, introduction of a chiral ligand is necessary. Hence, using analogous conditions reaction to the one described for the racemic version, the primary focus of our attention was on a range of commercially available ligands. For this survey,
ynamide 178a and 2-formylphenylboronic acid (260) were selected as test substrates (Scheme 4.12).

During initial ligand screening, monodentate and bidentate phosphine based ligands were tested. Although the reactions afforded complete conversion, the level of enantioselectivity was extremely poor; in most of the cases only a racemic mixture of products was observed. The level of regioselectivity was roughly the same as in the reaction without chiral ligands. The highest enantiomeric excess (8%) was obtained with the phosphoramidite ligand (R)-Monophos. It was clear from those results that phosphine based ligand would not be effective in this process. Therefore, a non-phosphine based ligand such as the bis-oxazoline ligand illustrated in Figure 4.3 was investigated. This ligand proved to be even less effective than the previous ligands used, with only 30% conversion and zero enantioselection.

Regarding the poor results attained with the previous ligands used, it was decided to slightly change strategy. After a literature search, it was found that chiral diene ligands are effective in rhodium-catalysed conjugate addition reactions, as
demonstrated by considerable work produced by Hayashi and co-workers.\textsuperscript{112b,116,117} Thus, based on those previous reports, a range of diene ligands derived from (R)-\(\alpha\)-phellandrene was prepared (Scheme 4.13).

![Scheme 4.13](image)

The [4+2] cycloaddition of the inexpensive terpene, (R)-\(\alpha\)-phellandrene (289), was conducted with methyl propiolate (290) in the presence of chlorodimethylaluminium. This reaction results in the formation of enantiomerically enriched bicyclo[2.2.2]octadiene L1, which itself can be transformed into L2 by simple hydrolysis of the ester group. Moreover, further transformations can be applied to L2 (Scheme 4.14).

![Scheme 4.14](image)

The carboxylic acid moiety present in L2 was easily transformed to the corresponding acyl chloride, which then reacted with an amine to provide the amide-
derivatised diene ligands \( \text{L3} \) and \( \text{L4} \). Using an analogous procedure, ligand \( \text{L5} \) was also prepared (Scheme 4.15).

![Scheme 4.15](image)

With those ligands in hand, their reactivity was examined with the same substrates used for the previously studied ligands (Table 4.2).

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>( X )</th>
<th>( \text{rr}^a )</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1(^b)</td>
<td>( \text{L1} )</td>
<td>(-\text{CC}_2\text{Me})</td>
<td>(&gt;19:1)</td>
<td>15</td>
</tr>
<tr>
<td>2(^b)</td>
<td>( \text{L2} )</td>
<td>(-\text{CC}_2\text{H})</td>
<td>(&gt;19:1)</td>
<td>20</td>
</tr>
<tr>
<td>3(^b)</td>
<td>( \text{L3} )</td>
<td>(-\text{NCO})</td>
<td>(&gt;19:1)</td>
<td>26</td>
</tr>
<tr>
<td>4(^c)</td>
<td>( \text{L4} )</td>
<td>(-\text{NMe})</td>
<td>(&gt;19:1)</td>
<td>30</td>
</tr>
<tr>
<td>5(^b)</td>
<td>( \text{L5} )</td>
<td>n.d.</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\(^a\) Regioisomeric ratio as determined by \(^1\)H NMR analysis of the unpurified reaction mixtures. \(^b\) These reactions proceeded to complete conversion. \(^c\) This reaction proceeded to 89% conversion.

Table 4.2

4.0 Rhodium-Catalysed Annulation of Ynamides 88
Although the levels of enantioselectivity were not really high, the utilisation of diene ligands in this process showed promising results. Indeed, with an ester moiety present on the chiral diene ligand (entry 1), the ee remains low but shows a large improvement compared to previously screened phosphine-based ligands. A carboxylic acid function on the diene (entry 2) gave a slightly higher ee. Better progress has been shown by the utilisation of amide-containing diene ligands (entry 3 and 4) with ee’s up to 30%. Another important aspect of this reaction is that the regioselectivity remains high regardless of the diene ligand used. Recently, ligand L5 has proven to be highly effective in an enantioselective rhodium-catalysed addition of arylboronic acids to alkenylheteroarenes,\(^{118}\) however, in our strategy this ligand only led to a complex mixture of products (entry 5). These preliminary results demonstrate the feasibility to prepare 2-amidoindenols enantioselectively, admittedly with modest enantiomeric ratio. Future work will be directed towards the use of this class of diene ligands.

### 4.2.4 Elaboration of Enamide-Indene Products

The methodology developed offers the rapid preparation of relatively complex products, and it was desirable to explore the reactivity of such compounds. When 2-amidoindenol 280g was treated with triethylamine, it underwent a 1,3-hydrogen rearrangement reaction to provide indanone 292 as a 4:1 inseparable mixture of diastereoisomers (eq 4.4).

![Equation 4.4](image)

This reaction most likely proceeds via a series of base-induced [1,5]-hydrogen shift as illustrated in eq 4.5.\(^{119}\)
Another reaction was performed on indene 284, which produced indane 294 by simple hydrogenation of 2-amidoindene 284 (Scheme 4.16). Surprisingly, deprotection of the silyl group was also observed during the process.

**Scheme 4.16**

### 4.3 Conclusions

Reaction of ynamides with bifunctional arylboronic acids proceeded under mild conditions to provide multisubstituted 2-amidoindenes with high levels of regioselectivity. The process was tolerant of ynamide-containing aliphatic or aromatic groups. Furthermore, investigations revealed that aldehydes or ketones were successfully used as a second electrophile present on the arylboronic acid to trap the alkenylrhodium intermediate formed. A mechanism has been suggested for this reaction, involving a carbonyl-directed syn-carbometallation as the key step. In addition, further transformations of the products formed have been carried out. They demonstrated the possible utility of such compounds as a good complement to the previous reactions done with indenes. Finally, early results of an enantioselective variant of this process displayed some promising results, with an enantiomeric excess of up to 30% using chiral diene ligands. Future work will be directed towards further optimisation of this procedure.

4.0 Rhodium-Catalysed Annulation of Ynamides 90
5.0 Catalytic Asymmetric Dihydroxylation of Enamides

5.1 Background

Among the different classes of alkenes available for asymmetric transformations, one, perhaps unsurprisingly, stands out to be particularly challenging: 1,1-disubstituted alkenes. Indeed, it is difficult for a chiral reagent or catalyst to effectively distinguish between the enantiotopic faces of such substrates since they are barely prochiral. However, asymmetric transformations of 1,1-disubstituted alkenes provide important building blocks. Therefore, achieving high levels of enantioselectivity in the transformation of this type of substrate is all the more challenging in asymmetric synthesis. The currently available methods can be subdivided into four main categories: asymmetric hydroboration, epoxidation, hydrogenation and dihydroxylation.

Asymmetric Hydroboration

Hydroboration of alkenes (and alkynes) is among the most valuable synthetic techniques in organic chemistry due to the formation of organoborane intermediates that can be readily converted into various kinds of organic compounds. For example, Hayashi’s group described an asymmetric hydroboration of styrene derivatives with catecholborane (135) catalysed by a rhodium (R)-BINAP complex (Scheme 5.1).

![Scheme 5.1](image-url)
Oxidation of the hydroboration products 295 with hydrogen peroxide provided the desired alcohol derivative compounds. However, this process gave low selectivities with ee of up to 46%, and the yields obtained were also poor. To date, this reaction remains challenging with only few improvements made in this area.\textsuperscript{121} However, alternative methods are available for the preparation of such compounds, like the regio- and stereoselective ring-opening of epoxides. To ensure the success of the entire process, it is preferable to prepare the epoxide derivatives with good optical purities.

\textit{Asymmetric Epoxidation}

Epoxides have fittingly been described as being “one of the main muscles”\textsuperscript{122} of organic synthesis, since a wide range of reactions are available for the conversion of epoxides to useful chiral intermediates.\textsuperscript{123} In addition, the epoxide ring is an important pharmacophore in bioactive natural products. Recently, Norrby and co-workers studied the use of the Jacobsen–Katsuki epoxidation with methyl-substituted styrenes.\textsuperscript{124} Mn(salen)-catalysed epoxidation of \( \text{-methylstyrene} \) \textsuperscript{298} provided the corresponding epoxide \textsuperscript{299} in an enantiomeric excess of 54% (Scheme 5.2).

Another approach for the asymmetric epoxidation of 1,1-disubstituted olefins has been investigated by Shi and co-workers.\textsuperscript{125} In their publication, they described the use of a substoichiometric amount of the chiral ketone catalyst 303 in the presence of an oxidant, oxone, to promote the asymmetric epoxidation of a variety of 1,1-disubstituted alkenes (Scheme 5.3).
This method of epoxidation gave higher enantioselectivities than previously illustrated by Norrby, with the percentages now approaching practical levels for use as part of a larger total synthesis.

**Asymmetric Hydrogenation**

The enantioselective hydrogenation of olefins has a long history and represents one of the most powerful transformations in asymmetric catalysis for preparing optically active compounds.\(^{126}\) Ruthenium, rhodium, and more recently iridium\(^{127}\) have proved to be effective in this process. A recent example has been done by the Andersson group, where they used a new class of ligands to obtain impressive optical purity of the reduced products (Scheme 5.4).\(^{128}\)
asymmetric dihydroxylation for example would provide a higher degree of complexity.

**Asymmetric Dihydroxylation**

Asymmetric dihydroxylation (AD) stands out as one of the most successful methodologies for the asymmetric transformations over a broad range of substrates, which include 1,1-disubstituted alkenes. The osmium catalytic system developed by Sharpless and co-workers remains dominant in this field,\(^{129}\) and this particular process has been constantly developed since its discovery with numerous reviews being published.\(^{130,131}\) The development of cinchona alkaloid ligand derivatives (for some examples see Figure 5.1) was responsible for the boom of the Sharpless AD.

![Figure 5.1](image)

One of the first classes of ligands that has been developed is the PHAL-derived ligand. The use of these ligands has proven to be particularly effective for the substrates illustrated in Scheme 5.5.\(^{130c}\)
Although high levels of enantioselectivity can be obtained for the Sharpless AD of 1,1-disubstituted alkenes, this process only affords low enantioselectivities when the two alkene substituents are of similar steric demand. A possible solution to tackle this drawback is to employ \(\beta,\beta'\)-disubstituted enol derivatives 313 as the substrates, where the discrimination of the enantiotopic faces is expected to be more straightforward (Scheme 5.6).

A potential significant advantage of this approach is the formation of the \(\alpha\)-hydroxyaldehydes 314, which are valuable compounds. They can also be easily reduced to provide the corresponding 1,2-diols. However, to guarantee high levels of enantioselectivity in the dihydroxylation event, it is required to prepare substrates 313 in a highly stereoselective manner. Unfortunately, existing methods\textsuperscript{132,133,134} often give products with poor \(E/Z\) stereoselectivity as can be seen in a representative example illustrated in Scheme 5.7.\textsuperscript{132c}
Although the reaction gave the products in reasonable to good yields, the resulting isomers could not be separated. This trend has also been observed in other methodologies to prepare enol derivatives.\textsuperscript{132,133,134} The difficulties of preparing these compounds stereoselectively, plus the impracticality of separating the resulting stereoisomers, would render such compounds unusable for asymmetric dihydroxylation. Fortunately, Ready and his group have recently found partial solutions to these problems. They have developed stereocontrolled syntheses of $\beta,\beta'$-disubstituted enol esters and enol silanes involving carbocupration of terminal alkynes (Scheme 5.8).\textsuperscript{135}

Addition of $N,N,N',N'$-tetramethylethylenediamine (TMEDA) to the vinyl copper intermediate minimizes the dimerisation during the oxidation of the alkenylmetal species by tert-butylithium peroxide. The oxidation step is likely to generate a metallo-enolate 320, and this intermediate can be trapped with electrophiles such as benzoic anhydride or TMSCl, to give the desired enol derivatives in a stereoselective manner. In a separate study, they also established the carboalumination of terminal alkynes (Scheme 5.9).\textsuperscript{136}
This newer protocol is a good complement to their previously described carbocupration.\textsuperscript{135} The preparation of methyl-substituted products that were not accessible from the previous methodology is now achievable, since methyl-cupration is not efficient. The high levels of stereoselectivity obtained allowed Ready’s group to evaluate the use of the enol benzoate products in catalytic AD reactions (Scheme 5.10).

Treatment of the enol benzoates 325 with AD-mix-\( \beta \), followed by reduction of the \( \alpha \)-hydroxyaldehyde in the same pot by NaBH\(_4\), provided the corresponding 1,2-diols with excellent enantiomeric purity. An example that demonstrates the effectiveness of this methodology is the preparation of the insect pheromone (+)-frontalin (Scheme 5.11).\textsuperscript{136}
Enol benzoate 325e was treated consecutively with AD-mix-β and \([\text{Me}_4\text{N}]\text{BH(OAc)}_3\) to yield (+)-frontalin in 93% ee and in 49% overall yield from the commercially available alkyne. In comparison, the 1,1-disubstituted alkene 328 was dihydroxylated with poor selectivity (32% ee) and in low yield with AD-mix-β.

Although carbocupration\(^{135}\) and carboalumination\(^{136}\) have proven to be effective processes to prepare enol esters stereoselectively, some improvements can be made in particular to increase the diversity of substituents introduced. In the carbocupration procedure,\(^{135,137}\) the organocopper reagents are formed from organolithium or Grignard reagents, which pose restriction on the functional groups that may be present in the organometallic. Although functionalised organocopper reagents may be obtained from the corresponding organozinc halides, these reagents are poorly reactive towards unactivated terminal alkynes.\(^{138}\) Moreover, since only alkylcopper reagents exhibit sufficient reactivity in alkyne carbocupration, the introduction of important groups such as (hetero)aryl substituents is usually not possible. In the carboalumination procedure,\(^{136,139}\) only methyl groups can be transferred. Therefore, the full exploration of asymmetric dihydroxylation of enol derivatives is compromised by these limitations.

These issues can be addressed by the utilisation of β,β′-disubstituted enamides prepared from our rhodium-catalysed carbometallation of ynamides (see Chapters 2 and 3)\(^{88,104}\). This methodology enables the introduction of alkyl, alkenyl, aryl, heteroaryl, and benzyl groups, and the presence of sensitive functional groups such as esters and ketones on the organometallics is permitted (Scheme 5.12).
Consequently, asymmetric dihydroxylation of enamides should provide access to a much wider range of chiral products than is possible using comparable methods described earlier.

### 5.2 Results and Discussion

#### 5.2.1 Scope and Limitations

One of the first concerns was to check if our process would be compatible with simple dihydroxylation conditions (*i.e.* treatment with substoichiometric amount of OsO₄ in the absence of ligand). With only a few optimisations, in particular of the reaction solvent, the methodology allowed the preparation of a range of racemic 1,2-diols from enamides 330 (Scheme 5.13). α-Hydroxyaldehydes 332 were then easily reduced by sodium borohydride to provide the desired tertiary-alcohol-containing terminal 1,2-diols.

![Scheme 5.13](image)

These promising results showed the feasibility of such a reaction. Thus, investigation of the asymmetric dihydroxylation of a series of enamide substrates (Figure 5.2) prepared from our carbometallation of ynamides (see Chapters 2 and 3), employing commercially available AD-mix-β was undertaken. The results of this study are illustrated in Table 5.1.

![Figure 5.2](image)
<table>
<thead>
<tr>
<th>Entry</th>
<th>Enamide</th>
<th>Product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Yield [%]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>ee [%]&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>180k</td>
<td>331a</td>
<td>72</td>
<td>90 (−94)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>2</td>
<td>180l</td>
<td>331b</td>
<td>84</td>
<td>87 (−78)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>236</td>
<td>331c</td>
<td>61</td>
<td>94</td>
</tr>
<tr>
<td>4</td>
<td>229e</td>
<td>331d</td>
<td>68</td>
<td>95</td>
</tr>
<tr>
<td>5</td>
<td>185a</td>
<td>331e</td>
<td>70</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>229a</td>
<td>331f</td>
<td>83</td>
<td>97</td>
</tr>
<tr>
<td>7</td>
<td>229c</td>
<td>331g</td>
<td>82</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>183a</td>
<td>331h</td>
<td>86</td>
<td>94</td>
</tr>
<tr>
<td>9</td>
<td>185b</td>
<td>331i</td>
<td>68</td>
<td>96</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were conducted using 0.20 mmol of 330 and 280 mg of AD-mix-β [0.4 mol% Os and 1 mol% (DHQD)$_2$PHAL (hydroquinidine 1,4-phthalazinediyl diether)] in t-BuOH (2 mL) and H$_2$O (1 mL) for 7–24 h, followed by the addition of NaBH$_4$ (6 equiv) and stirring for a further 1 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] Values in parentheses refer to ee obtained from asymmetric dihydroxylation of the corresponding 1,1-disubstituted alkene using the same chiral ligand (DHQD)$_2$PHAL that is present in AD-mix-β. See ref. 130c.

Table 5.1

5.0 Catalytic Asymmetric Dihydroxylation of Enamides
Interestingly, the asymmetric dihydroxylation of enamide substrates proceeded smoothly without the addition of MeSO₂NH₂, which has been previously reported to increase the rate of the reaction. On the contrary, when MeSO₂NH₂ was utilised, the process did not reach complete conversion even after extended reaction time and lower levels of enantioselectivity were observed.

After dihydroxylation was complete, addition of NaBH₄ to the reaction mixture resulted in the formation of the desired 1,2-diol products with high enantioselectivity. Enamides containing a phenyl substituent at the R¹ position proved to be effective substrates, with a 2-thienyl group at R² (94% ee, entry 3) providing a higher enantioselectivity than a methyl (90% ee, entry 1) or ethyl group (87% ee, entry 2). The formation of diol product 331c in high enantiomeric purity demonstrates the efficiency of our process, since the thiophene and phenyl group can be considered of similar steric demand. Indeed, it was presumed that it would be difficult for the chiral reagent to distinguish the enantiotopic faces in the corresponding 1,1-disubstituted alkene. Enamides containing aliphatic groups (simple alkyl, oxygenated alkyl) at R¹ and (hetero)aryl groups (phenyl, p-tolyl, 3-carboethoxyphenyl, 2-thienyl) at R² showed even higher selectivity, providing products in generally good yields with uniformly high enantioselectivities (94-97% ee, entry 4-9).

To demonstrate that our methodology provides improvements to the asymmetric dihydroxylation of 1,1-disubstituted alkenes, our results were compared with the process employing the same chiral ligand (DHQD)₂PHAL that is present in AD-Mix-β. While diol 331a was obtained from enamide 180k with slightly lower enantioselectivity (90% ee, entry 1) and as the opposite enantiomer compared with asymmetric dihydroxylation of α-methylstyrene (−94% ee), our method gave diol 331b with improved selectivity (87% ee, entry 2) compared with that obtained from the corresponding 1,1-disubstituted alkene (−78% ee). Another example that further illustrated the effectiveness of our process is displayed in eq 5.1.
Interestingly, diol 331d was obtained favouring the (R)-enantiomer from both enamide 229e and alkene 333, but the enantioselectivity was far superior in the case of the enamide (95% ee, entry 4) compared with the alkene (41% ee).

The reaction with β,β’-diarylenamide 229l proved to be more challenging with AD-mix-β. The reaction was sluggish and did not proceed to completion despite an extended reaction time. Fortunately, using increased loadings of K₂OsO₄(OH)₄ and the chiral ligand (DHQD)₂PHAL that is present in AD-mix-β (approximately twice the amount of each) gave improved results, affording diol 331j in 98% ee (eq 5.2).

Although our methodology allows the access of a wide range of 1,2-diol products with high levels of enantioselectivity, the use of β,β’-dialkylenamides has proven to be more difficult (Scheme 5.14).

Enamides 180a and 180i were less competent substrates than the enamides used previously (vide supra) in the asymmetric dihydroxylation with AD-mix-β. The reaction still proceeded smoothly in high yields but diols 331k and 331l were obtained with lower enantioselectivity than observed earlier. However, a simple
change of the ligand may be a solution to improve the enantiomeric excess (see discussion later in this Chapter).

The sense of enantiofacial selectivity by AD-mix-β observed in these reactions is consistent with the Sharpless mnemonic (Figure 5.3).\textsuperscript{131a}

![Figure 5.3](image)

The high enantioselectivities observed with aryl or heteroaryl substituents at the $R^2$ position of the enamide could be explained by invoking attractive phenyl-quinoline interactions leading to the accommodation of the (hetero)aryl substituent in the SW quadrant. Furthermore, it is thought that the oxazolidin-2-one moiety binds well in the NE pocket, thus providing high levels of enantiomeric purity for the asymmetric dihydroxylation of enamides.

### 5.2.2 Utilisation of the $\alpha$-Hydroxyaldehyde Intermediates

The asymmetric dihydroxylation of enamides also provide $\alpha$-hydroxyaldehydes 332, which themselves could be useful compounds. A representative example is the $\alpha$-hydroxyaldehyde 332a, which is used as a key intermediate in the preparation of ($S$)-oxybutynin (Scheme 5.15).
Racemic oxybutynin (Ditropan®) is a widely prescribed drug for the treatment of urinary frequency, urgency and urge incontinence. It has been revealed that it exhibits classical antimuscarinic side effects, such as dry mouth. However, its (S)-enantiomer has been shown to display a better therapeutic profile devoid of antimuscarinic side effects. Kumar and co-workers have described the preparation of the intermediate via Sharpless asymmetric dihydroxylation of the alkene (Scheme 5.16).

Although the enantioselectivity of this reaction was not reported, it was assumed that the dihydroxylation with AD-mix-α did not provide high levels of enantioselectivity due to the necessity of two recrystallisations to obtain the 1,2-diol 328 in 92% ee. Another fact that can confirm this hypothesis is that the dihydroxylation of α-cyclohexylstyrene (337) using (DHQD)2PHAL (ligand present in AD-mix-β that usually shows higher degree of enantioselectivity than (DHQ)2PHAL ligand present in AD-mix-α) provides the corresponding diol as the opposite (R)-enantiomer in only 57% ee.

5.0 Catalytic Asymmetric Dihydroxylation of Enamides
With this in mind, it was decided to apply the methodology developed to the concise preparation of α-hydroxyaldehyde 332a. Unfortunately, reaction of enamide 183h with AD-mix-β was sluggish, but dihydroxylation using increased loadings of K₂OsO₂(OH)₄ and (DHQD)₂PHAL afforded the α-hydroxyaldehyde 332a in 80% yield and 91% ee (eq 5.3).

This excellent result showed the practicality of our process since similar levels of enantiomeric purity compared to Kumar and co-workers¹⁴₂a were attained without the necessity of recrystallisations. This additional result demonstrated that the use of β,β'-disubstituted enamides in place of 1,1-disubstituted alkenes can prove advantageous in asymmetric dihydroxylation.

### 5.2.3 Total Synthesis of (+)-Tanikolide

Tanikolide¹⁴₃ (Figure 5.4) was isolated in 1999 by the Gerwick group from the lipid extract of a collection of the marine cyanobacterium Lyngbya majuscule, collected from Tanikeli Island, Madagascar.

This bioactive natural product shows strong brine shrimp toxicity and antifungal activity. The main organic characteristics of (+)-tanikolide are: (1) a δ-lactone core, (2) a chiral quaternary carbon centre with a hydroxymethyl group at the C-5 position and (3) a saturated alkyl chain of 11 carbons. Since its discovery, tanikolide has been
a particularly attractive target molecule for many research groups. For the purposes of this review, only the most successful syntheses of this natural product will be covered.

Shortly after its discovery, the Ogasawara group reported the first synthesis of (+)-tanikolide. The purpose of this work was probably more focussed on ascertaining the structure proposed by Gerwick and co-workers than providing an efficient route to this compound, since the target molecule was prepared in extremely low yield over 12 steps. Since then, both racemic and asymmetric preparations of this marine natural product have been tackled with efficiency.

For the racemic version, Zhai’s group reported a facile synthesis of (±)-tanikolide starting from the relatively cheap, commercially available ethyl 2-oxocyclopentanecarboxylate (340) (Scheme 5.17).

Substrate 340 was efficiently alkylated with 1-bromoundecane in the presence of \( \text{K}_2\text{CO}_3 \) and KI in refluxing anhydrous acetone to give intermediate 341. Deethoxycarbonylative hydrolysis of 341 in refluxing concentrated HCl–AcOH afforded 2-(n-undecyl)cyclopentanone 342 in 96% yield. Selective hydromethylation at the C-2 position then took place upon treatment of 342 with formaldehyde and KOH to produce aldol 343 with a quaternary carbon centre. Finally, the desired ring expansion was effected under Baeyer-Villiger oxidation conditions to transform 343 to (±)-tanikolide (339). This strategy is advantageous because of its brevity, high overall yield (86%) and suitability for the preparation of the target molecule in
multigram quantities. However, this methodology only allows the preparation of the compound in a racemic manner, which renders this process less attractive than its asymmetric counterparts despite the high yield.

In their study of the synthesis of chiral aldehydes by conjugated addition of carbonyl donors to α,β-unsaturated aldehydes with bifunctional organocatalysts derived from Cinchona alkaloids, the Deng group reported an asymmetric preparation of (+)-tanikolide (339) (Scheme 5.18).\textsuperscript{144q}

![Scheme 5.18](image)

The conjugate addition of β-ketoester 344 to acrolein catalysed by chinchona ligand 346 represents the asymmetric induction step of the synthesis. The reaction occurred smoothly to provide the chiral aldehyde 345 in quantitative yield with virtually perfect enantioselectivity. The aliphatic side chain of (+)-tanikolide was then introduced by the olefination of aldehyde 345 with 1,1-diiodooctane using a modified procedure of the Takai reaction.\textsuperscript{145} Subsequent straightforward functional-group transformations converted ketoester 347 into ketoalcohol 348 by a three-step sequence (Scheme 5.19).\textsuperscript{144d} Under Baeyer-Villiger oxidation conditions, 348 was then transformed into 339 in 87% yield.

![Scheme 5.19](image)
To date, Deng’s concise synthesis of (+)-tanikolide represents one of the most successful routes with a favourable overall yield of 41% and virtually optically pure form of the target compound.

Our total synthesis of (+)-tanikolide started with the preparation of ynamide 351. Bromoalkyne 350 was prepared from commercially available tridecyne 349 using NBS/AgNO₃ (Scheme 5.20). Ynamide 351 was then prepared following the procedure developed by Hsung and co-workers, which consisted of a copper-catalysed coupling of 350 with oxazolidin-2-one.

![Scheme 5.20](image)

Using our previously developed rhodium-catalysed carbozincation of ynamides (see Chapter 2), reaction of commercially available 4-ethoxy-4-oxobutylzinc bromide with ynamide 351 proceeded smoothly to provide enamide 352 in 56% yield. Unfortunately, asymmetric dihydroxylation of enamide 352 using AD-mix-β was poorly selective, and after reduction of the aldehyde intermediate with NaBH₄, diol 353 was produced in only 58% ee (eq 5.4).
However, use of (DHQD)$_2$AQN (hydroquinidine [anthraquinone-1,4-diyl] diether) (see Figure 5.1) as the chiral ligand in place of (DHQD)$_2$PHAL led to 353 being obtained in a much improved 88% ee (eq 5.5). This ligand has been shown to provide superior levels of enantioselection in the dihydroxylation of many alkenes, including those containing only aliphatic substituents. The ee of diol 353 was determined by chiral HPLC analysis of the benzoyl ester of the primary alcohol.

The last steps of the synthesis of the target molecule were straightforward consisting of the basic hydrolysis of the ester group present in 353, followed by heating the resulting acid 354 in CDCl$_3$ at reflux, which led to smooth lactonisation to provide (+)-tanikolide (Scheme 5.21). However, attempts at direct lactonisation, from compound 353 to the target molecule, by heating the solution at reflux in toluene failed, and this has been previously documented.

Although several synthetic studies of (+)-tanikolide have already been reported, our synthesis provides an alternative approach with few steps and high optical purity.

### 5.3 Conclusions

Asymmetric dihydroxylation of β,β'-disubstituted enamides has proven to be an effective process for the preparation of a range of tertiary-alcohol-containing...
terminal 1,2-diols. The diversity of \( \beta,\beta'- \)disubstituted enamides available from our rhodium-catalysed ynamide carbometallation protocols render this method very attractive compared to previously reported work. Indeed, other processes suffer from a lack of variety of substituents that can be introduced. Furthermore, and most importantly, asymmetric dihydroxylation of \( \beta,\beta' \)-disubstituted enamides offers often superior enantioselectivities compared to the utilisation of the corresponding 1,1-disubstituted alkenes. Although the levels of enantioselectivity were lower with enamide-containing two aliphatic substituents, it has been demonstrated that by changing the chiral ligand, high enantiomeric purity can be accessed, as it has been described in the synthesis of \((+)\)-tanikolide.

Using this methodology, a key intermediate for the preparation of \((S)\)-oxybutynin was also prepared with high enantiomeric purity. Finally, application of our rhodium-catalysed stereocontrolled preparation of enamides and asymmetric dihydroxylation of these compounds to the concise synthesis of the antifungal natural product \((+)\)-tanikolide demonstrated the high aptitude of our processes to be employed in further chemistry.
6.0 Experimental

General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Toluene, THF, CH$_2$Cl$_2$, and Et$_2$O were dried and purified by passage through activated alumina columns using a solvent purification system from Glass Contour Solvent Systems. All commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F$_{254}$ 0.2 mm precoated plates. Product spots were visualized by UV light at 254 nm, and subsequently developed using potassium permanganate or ceric ammonium molybdate solution as appropriate. Flash column chromatography was carried out using silica gel (Fisher Scientific 60Å particle size 35-70 micron) employing the method of Still and co-workers.$^{147}$ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded as a thin film on sodium chloride plates or as a dilute solution in CHCl$_3$. $^1$H NMR spectra were recorded on a 500 MHz spectrometer, a 360 MHz spectrometer, or a 250 MHz spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual non-deuterium labelled solvent as internal standard (CDCl$_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (J) are quoted to the nearest 0.1 Hz. Proton-decoupled $^{13}$C NMR spectra were recorded on a Bruker AV500 (125.8 MHz for $^{13}$C) spectrometer or a 360 MHz (90.6 MHz for $^{13}$C) spectrometer or a 250 MHz (62.9 MHz for $^{13}$C) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl$_3$ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer, a Finnigan MAT 95XP spectrometer, or a Thermofisher LTQ Orbitrap XL spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea. Stated calculated mass values refer to that of the ion
(i.e. the actual species being detected), not that of the neutral parent compound. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Chiral HPLC analysis was performed on an Agilent 1100 instrument.
6.1 Rhodium-Catalysed Carbometallation of Ynamides to Access Multisubstituted Enamides

6.1.1 Preparation of Ynamicide Starting Materials

3-(4-Phenylbut-1-ynyl)oxazolidin-2-one (178a)

Following a slight modification of the procedure of Hsung and co-workers,67c a mixture of 1-bromo-4-phenyl-1-butyne (3.00 g, 14.3 mmol), 2-oxazolidinone (1.13 g, 13.0 mmol), K$_3$PO$_4$ (5.50 g, 26.0 mmol), CuSO$_4$-5H$_2$O (325 mg, 1.30 mmol), 1,10-phenanthroline (470 mg, 2.61 mmol) and 18-crown-6 (172 mg, 0.65 mmol) in toluene (30 mL) was heated at 70 °C for 40 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (20 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide 178a (1.70 g, 61%) as a pale yellow solid.

R$_f$ = 0.46 (50% EtOAc/hexane); m.p. 54-56 °C; IR (film) 2956, 2929, 2304 (C=O), 1773 (C=O), 1653, 1481, 1419, 1265, 1115, 1040, 738 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.33-7.29 (2H, m, ArH), 7.24-7.20 (3H, m, ArH), 4.42-4.38 (2H, m, CH$_2$O), 3.85-3.81 (2H, m, CH$_2$N), 2.86 (2H, t, J = 7.6 Hz, =CCH$_2$), 2.61 (2H, t, J = 7.6 Hz, CH$_2$Ph); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 156.5 (C), 140.4 (C), 128.4 (2 × CH), 128.3 (2 × CH), 126.2 (C), 70.7 (C), 70.3 (C), 62.8 (CH$_2$), 46.8 (CH$_2$), 35.1 (CH$_2$), 20.6 (CH$_2$); HRMS (ES) Exact mass calc for C$_{13}$H$_{17}$N$_2$O$_2$ [M+NH$_4$]$^+$: 233.1285, found: 233.1288.
3-Phenylethynyl oxazolidin-2-one (178b)<sup>67f</sup>

Following the procedure of Hsung and co-workers,<sup>67c</sup> a mixture of 1-bromo-2-phenylacetylene (8.69 g, 48.0 mmol), 2-oxazolidinone (3.80 g, 43.6 mmol), K<sub>3</sub>PO<sub>4</sub> (18.5 g, 87.2 mmol), CuSO<sub>4</sub>·5H<sub>2</sub>O (1.09 g, 4.36 mmol), and 1,10-phenanthroline (1.57 g, 8.72 mmol) in toluene (90 mL) was heated at 65 °C for 38 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH₂Cl₂ (50 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide 178b (5.81 g, 71%) as a white solid that displayed identical spectroscopic data to those reported previously.<sup>67f</sup>  

R<sub>f</sub> (25% EtOAc/hexane) = 0.15; mp: 84-86 °C; ¹H NMR (360 MHz, CDCl<sub>3</sub>) δ 7.46-7.44 (2H, m, ArH), 7.32-7.30 (3H, m, ArH), 4.49 (2H, app dd, J = 8.7, 6.8 Hz, CH₂O), 4.01 (2H, app dd, J = 8.7, 6.8 Hz, CH₂N); ¹³C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 155.8 (C), 131.5 (2 × CH), 128.3 (2 × CH), 128.2 (CH), 122.1 (C), 78.9 (C), 76.5 (C), 63.0 (CH₂), 47.0 (CH₂).

3-[4-(tert-Butyldimethylsilyloxy)-1-ynyl] oxazolidin-2-one (178c)

Following the procedure of Hsung and co-workers,<sup>67c</sup> a mixture of 1-bromo-4-tert-butyldimethylsilyloxy-1-butene (14.7 g, 55.8 mmol), 2-oxazolidinone (4.40 g, 50.7 mmol), K<sub>3</sub>PO<sub>4</sub> (21.5 g, 100 mmol), CuSO<sub>4</sub>·5H<sub>2</sub>O (1.27 g, 5.08 mmol), and 1,10-phenanthroline (1.83 g, 10.1 mmol) in toluene (100 mL) was heated at 90 °C for 19 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH₂Cl₂ (15 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide 178c (6.81 g, 50%) as a colourless oil.
3-(4-benzyloxybut-1-ynyl)oxazolidin-2-one (178d)

Following the procedure of Hsung and co-workers,⁶⁷c (4-bromobut-3-ynloxytrimethyl)benzene (2.30 g, 9.61 mmol), 2-oxazolidinone (761 mg, 8.74 mmol), K₃PO₄ (3.71 g, 17.5 mmol), CuSO₄·5H₂O (218 mg, 0.87 mmol), and 1,10-phenanthroline (315 mg, 1.75 mmol) in toluene (18 mL) was heated at 90 °C for 20 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH₂Cl₂ (30 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane → 25% EtOAc/hexane) gave the ynamide 178d (385 mg, 59%) as an orange oil.

R_f = 0.26 (40% EtOAc/hexane); IR (film) 2922, 2856, 1763 (C=O), 1477, 1414, 1302, 1200, 1111, 1030, 736 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.35 (4H, m, ArH), 7.32-7.28 (1H, m, ArH), 4.56 (2H, s, OCH₂Ar), 4.43-4.40 (2H, m, NCH₂CH₂O), 3.89-3.86 (2H, m, CH₂N), 3.61 (2H, t, J = 7.0 Hz, OCH₂), 2.64 (2H, t, J = 7.0 Hz, =CCH₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 156.5 (C), 138.0 (C), 128.4 (2 × CH), 127.7 (3 × CH), 76.7 (CH₂), 70.9 (C), 68.4 (CH₂), 68.0 (C), 62.8 (CH₂), 46.9 (CH₂), 19.8 (CH₂); HRMS (ES) Exact mass calcd for C₁₄H₁₀N₂O₃ [M+NH₄]^+: 263.1390, found: 263.1390.
3-Oct-1-ynyloxazolidin-2-one (178e)\(^{67f}\)

Following the procedure of Hsung and co-workers,\(^{67c}\) a mixture of 1-bromo-1-octyne (4.78 g, 25.3 mmol), 2-oxazolidinone (2.00 g, 23.0 mmol), \(\text{K}_3\text{PO}_4\) (9.75 g, 46.0 mmol), \(\text{CuSO}_4\cdot5\text{H}_2\text{O}\) (573 mg, 2.30 mmol), and 1,10-phenanthroline (828 mg, 4.60 mmol) in toluene (45 mL) was heated at 65 °C for 22 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using \(\text{CH}_2\text{Cl}_2\) (20 mL) as the eluent, and the filtrate was concentrated \textit{in vacuo}. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide \textbf{178e} (1.51 g, 34%) as a pale yellow oil that displayed identical spectroscopic data to those reported previously.\(^{67f}\)

\[\text{Rf (25% EtOAc/hexane) = 0.61; IR (film) 2959, 2926, 2258 (C=C), 1761 (C=O), 1488, 1423, 1256, 1241, 952, 734 \text{ cm}^{-1}; \text{^{1}H NMR (360 MHz, CDCl}_3\text{) }\delta 4.44-4.39 (2\text{H, m, CH}_2\text{O}), 3.90-3.85 (2\text{H, m, CH}_2\text{N}), 2.33 (2\text{H, t, }J= 7.2 \text{ Hz, }\equiv\text{CCH}_2), 1.56-1.50 (2\text{H, m, }\equiv\text{CCH}_2\text{CH}_2), 1.41-1.26 (6\text{H, m, CH}_2\text{CH}_2\text{CH}_2\text{CH}_3), 0.89 (3\text{H, t, }J= 6.9 \text{ Hz, CH}_3\text{CH}_3); \text{^{13}C NMR (62.9 MHz, CDCl}_3\text{) }\delta 156.6 (\text{C}), 71.1 (\text{C}), 70.0 (\text{C}), 62.7 (\text{CH}_2), 47.0 (\text{CH}_2), 31.2 (\text{CH}_2), 28.7 (\text{CH}_2), 28.4 (\text{CH}_2), 22.4 (\text{CH}_2), 18.3 (\text{CH}_2), 13.9 (\text{CH}_3).\]

\textit{(S)-4-Benzyl-3-oct-1-ynyloxazolidin-2-one (178f)}\(^{67f}\)

Following the procedure of Hsung and co-workers,\(^{67c}\) a mixture of 1-bromo-1-octyne (1.28 g, 6.77 mmol), \textit{(S)-4-benzyl-2-oxazolidinone} (1.00 g, 5.64 mmol), \(\text{K}_3\text{PO}_4\) (2.40 g, 11.30 mmol), \(\text{CuSO}_4\cdot5\text{H}_2\text{O}\) (141 mg, 0.56 mmol), and 1,10-phenanthroline (203 mg, 1.13 mmol) in toluene (15 mL) was heated at 65 °C for 22 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using \(\text{CH}_2\text{Cl}_2\) (20 mL) as the eluent, and the filtrate was concentrated \textit{in vacuo}. Purification of the residue by column chromatography (hexane→20% EtOAc/hexane) gave the
ynamide 178f (556 mg, 34%) as a colourless oil that displayed identical spectroscopic data to those reported previously.\textsuperscript{[57f]}

R\textsubscript{f} (25\% EtOAc/hexane) = 0.40; IR (film) 2958, 2925, 2261 (C=\textit{C}), 1759 (C=O), 1477, 1410, 1256, 1239, 1023, 733 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 7.38-7.28 (2H, m, Ar\textit{H}), 7.23-7.19 (2H, m, Ar\textit{H}), 4.30 (1H, dd, J = 8.0, 7.9 Hz, CH\textsubscript{2}O), 4.26-4.16 (1H, m, CH\textsubscript{2}N), 4.09 (1H, dd, J = 7.9, 5.3 Hz, CH\textsubscript{2}O), 3.21 (1H, dd, J = 13.8, 3.6 Hz, CH\textsubscript{2}Ar), 2.92 (1H, dd, J = 13.8, 7.9 Hz, CH\textsubscript{2}Ar), 2.36 (2H, t, J = 7.0 Hz, =CCH\textsubscript{2}CH\textsubscript{2}), 1.62-1.24 (8H, m, CH\textsubscript{2}(CH\textsubscript{2})\textsubscript{3}CH\textsubscript{3}), 0.90 (3H, t, J = 6.8 Hz, CH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 156.1 (C), 134.4 (C), 129.3 (2 × CH), 128.9 (2 × CH), 127.4 (CH), 73.4 (C), 68.9 (C), 67.1 (CH\textsubscript{2}), 58.3 (CH), 37.7 (CH\textsubscript{2}), 31.3 (CH\textsubscript{2}), 28.8 (CH\textsubscript{2}), 28.5 (CH\textsubscript{2}), 22.5 (CH\textsubscript{2}), 18.5 (CH\textsubscript{2}), 14.0 (CH\textsubscript{3}).

\textbf{1-Methylimidazolidin-2-one}\textsuperscript{[148]}

\[
\begin{align*}
\text{HN} & \quad \xrightarrow{\text{1, NaH, 2, Me, \text{dioxane}}} \quad \text{HN'} \\
\text{N} & \quad \text{N'}
\end{align*}
\]

To a solution of 2-imidazolidinone (15.2 g, 177 mmol) in 1,4-dioxane (200 mL) was added NaH (8.33 g, 208 mmol, 60 wt\% in paraffin) under an atmosphere of nitrogen with vigorous stirring. The solution was heated to 65 °C and stirred at this temperature for 2 h and then cooled to 0 °C. CH\textsubscript{3}I was added slowly via syringe pump and the resulting mixture was stirred at rt for 18 h. The mixture was filtered through a celite plug and the filtrate was concentrated \textit{in vacuo}. Purification by silica column chromatography (10\% MeOH/CH\textsubscript{2}Cl\textsubscript{2}) gave the title compound as a white solid (5.61 g, 28\%) which displayed identical spectroscopic data to those described previously.\textsuperscript{[148]}

R\textsubscript{f} = 0.44 (10\% MeOH/CH\textsubscript{2}Cl\textsubscript{2}); mp = 108-110 °C; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 4.73 (1H, br s, NH), 3.41 (4H, s, CH\textsubscript{2}), 2.79 (3H, s, CH\textsubscript{3}N); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \textsuperscript{\delta} 163.3 (C), 47.5 (CH\textsubscript{2}), 38.0 (CH\textsubscript{2}), 30.6 (CH\textsubscript{3}).

\textbf{Method (A): 3-Methyl-1-phenylethynylimidazolidin-2-one (178g)}\textsuperscript{[67f]}

6.0 Experimental

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Following the procedure of Hsung and co-workers,67c a mixture of 1-bromo-2-phenylacetylene (1.60 g, 8.80 mmol), 1-methylimidazolidin-2-one (800 mg, 8.00 mmol), K$_2$PO$_4$ (3.40 g, 16.0 mmol), CuSO$_4$·5H$_2$O (200 mg, 0.80 mmol), and 1,10-phenanthroline (290 mg, 1.60 mmol) in toluene (16 mL) was heated at 65 °C for 42 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (20 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (30% EtOAc/hexane) gave the ynamide 178g (1.37 g, 86%) as a colourless solid that displayed identical spectroscopic data to those reported previously.67f

R$_f$ = 0.25 (50% EtOAc/hexane); mp = 86-88 °C; IR (CHCl$_3$) 2929, 2277 (C≡C), 1765 (C=O), 1481, 1433, 1256, 1202, 1122, 1040, 731 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.45-7.42 (2H, m, ArH), 7.29-7.25 (3H, m, ArH), 3.82-3.78 (2H, m, CH$_2$N), 3.49-3.45 (2H, m, CH$_2$N), 2.88 (3H, s, CH$_3$N); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 157.5 (C), 131.2 (2 × CH), 128.1 (2 × CH), 127.3 (CH), 123.4 (C), 82.2 (C), 70.0 (C), 44.7 (CH$_2$), 44.4 (CH$_2$), 31.3 (CH$_3$).

Method (B): 3-Methyl-1-phenylethynylimidazolidin-2-one (178g)$^{67f}$

Following a slight modification of the procedure of Stahl and co-workers,67f in a three-neck flask, CuCl$_2$·2H$_2$O (68 mg, 0.40 mmol), Na$_2$CO$_3$ (848 mg, 8.00 mmol) and 1-methylimidazolidin-2-one (2.00 g, 20.0 mmol) were combined. The reaction flask was purged with O$_2$ for 15 min. A solution of pyridine (633 mg, 8.00 mmol) in toluene (35 mL) was then added. A balloon filled with O$_2$ was connected to the flask, and the mixture was heated to 70 °C. A solution of phenylacetylene (408 mg, 4.00 mmol) in toluene (5 mL) was added to the mixture over 4 h via syringe pump. The mixture was stirred at 70 °C for 16 h, cooled to room temperature and then filtered through a short pad of silica gel using CH$_2$Cl$_2$ (20 mL) as eluent. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (50% EtOAc/hexane) to give the ynamide 178g (362 mg, 45%) as a colourless solid.
1-Phenylethynylpyrrolidin-2-one (178h)$^{67c}$

Following the procedure of Hsung and co-workers,$^{67c}$ a mixture of 1-bromo-2-phenylacetylene (6.00 g, 33.1 mmol), 2-pyrrolidinone (2.56 g, 30.1 mmol), K$_2$PO$_4$ (12.8 g, 60.3 mmol), CuSO$_4$·5H$_2$O (752 mg, 3.01 mmol), and 1,10-phenanthroline (1.09 g, 6.03 mmol) in toluene (60 mL) was heated at 65 °C for 36 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (20 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide 178h (1.93 g, 35%) as a red oil that displayed identical spectroscopic data to those reported previously.$^{67c}$

R$_f$ (25% EtOAc/hexane) = 0.12; IR (film) 2955, 2924, 2259 (C-H Cl) 175.7 (C), 131.5 (2 × CH), 128.2 (2 × CH), 122.6 (C), 80.4 (C), 72.5 (C), 50.1 (CH$_2$), 29.7 (CH$_2$), 18.8 (CH$_2$).

N-Phenyl-N-phenylethynyl tert-butyl carbonyl ester (179a)$^{149}$

Following the procedure of Tam and co-workers,$^{67d}$ to a solution of N-Boc aniline (1.00 g, 5.18 mmol), 1-bromo-2-phenylacetylene (1.87 g, 10.3 mmol), copper iodide (197 mg, 1.03 mmol), and 1,10-phenanthroline (233 mg, 1.29 mmol) in toluene (9 mL) at 90 °C was added KHMDS (0.5 M in toluene, 12.5 mL, 6.25 mmol) via syringe pump over 4 h. The reaction mixture was stirred at 90 °C for a further 22 h, cooled to room temperature, diluted with Et$_2$O (20 mL) and washed with a 2:1 mixture of saturated aqueous NaCl solution and concentrated NH$_3$OH solution (3 × 10 mL). The combined aqueous washings were extracted with Et$_2$O (3 × 10 mL), and

6.0 Experimental 119
the combined organic layers were then washed with saturated aqueous NaCl solution (50 mL), dried (MgSO₄), and concentrated in vacuo. Purification of the residue by column chromatography (1/50 EtOAc/hexanes) gave the ynamide 179a (766 mg, 50%) as a brown solid that displayed identical spectroscopic data to those reported previously.¹⁴⁹

Rₛ = 0.61 (20% EtOAc/hexane); mp = 62-64 °C; IR (CHCl₃) 2982 (C=O), 1729 (C=O), 1597, 1493, 1369, 1294, 1154, 908, 733, 650 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.61-7.59 (1H, m, ArH), 7.57-7.55 (1H, m, ArH), 7.48-7.41 (5H, m, ArH), 7.38-7.29 (3H, m, ArH), 1.62 (9H, s, O(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 152.9 (C), 139.6 (C), 130.8 (2 × CH), 128.8 (2 × CH), 128.2 (2 × CH), 127.3 (CH), 126.6 (CH), 124.6 (CH), 123.3 (C), 83.6 (C), 83.5 (C), 70.1 (C), 28.0 (3 × CH₃).

N-Benzyl-4-methyl-N-phenylethynylbenzenesulfonamide (179b)⁶⁷b

Following the procedure of Hsing and co-workers,⁶⁷c a mixture of 1-bromo-2-phenylacetylene (3.04 g, 16.8 mmol), N-benzyl-p-toluenesulfonamide (4.00 g, 15.3 mmol), K₂PO₄ (4.23 g, 30.6 mmol), CuSO₄·5H₂O (382 mg, 0.15 mmol), and 1,10-phenanthroline (551 mg, 0.30 mmol) in toluene (16 mL) was heated at 65 °C for 18 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using CH₂Cl₂ (10 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane) gave the ynamide 179b (5.20 g, 94%) as a pale yellow solid that displayed identical spectroscopic data to those reported previously.⁶⁷b

Rₛ (50% EtOAc/hexane) = 0.22; mp: 84-86 °C; ¹H NMR (360 MHz, CDCl₃) δ 7.81 (2H, d, J = 8.2 Hz, ArH), 7.34-7.32 (6H, m, ArH ), 7.27-7.20 (6H, m, ArH), 4.58 (2H, s, CH₂), 2.45 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 144.6 (C), 134.6 (C), 134.4 (C), 131.1 (2 × CH), 129.7 (2 × CH), 128.9 (2 × CH), 128.5 (2 × CH), 128.3 (CH), 128.1 (2 × CH), 127.7 (2 × CH), 127.6 (CH), 122.7 (C), 82.6 (C), 71.3 (C), 55.7 (CH₂), 21.6 (CH₃).
6.1.2 Carbozincation of Cyclic Ynamides Using Commercially Available Dialkylzincs

Using $\text{Me}_2\text{Zn}$: General Procedure A

To a solution of the appropriate ynamide (1.00 mmol) and Rh(cod)(acac) (15.5 mg, 0.05 mmol) in THF (10 mL) at 0 °C was added $\text{Me}_2\text{Zn}$ (1.2 M in toluene, 1.67 mL, 2.00 mmol) over 2 min, and the reaction was then stirred at room temperature for 15 min. The mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (30 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/hexane) afforded the desired enamide.

Using $\text{Et}_2\text{Zn}$: General Procedure B

To a solution of the appropriate ynamide (1.00 mmol) and Rh(cod)(acac) (15.5 mg, 0.05 mmol) in THF (10 mL) at 0 °C was added $\text{Et}_2\text{Zn}$ (1.0 M in hexane, 2.00 mL, 2.00 mmol) over 2 min, and the reaction was then stirred at room temperature for 15 min. The mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (30 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/hexane) afforded the desired enamide.

Using $\text{n-Bu}_2\text{Zn}$: General Procedure C

To a solution of the appropriate ynamide (0.30 mmol) and Rh(cod)(acac) (4.7 mg, 0.015 mmol) in THF (3 mL) at 0 °C was added $\text{n-Bu}_2\text{Zn}$ (1.0 M in heptane, 0.60 mL, 0.60 mmol) over 2 min, and the reaction was then stirred at room temperature for 15 min. The mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (10 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/hexane) afforded the desired enamide.
3-[(Z)-2-Ethyl-4-phenylbut-1-enyl]oxazolidin-2-one (180a).

The title compound was prepared according to General Procedure B from ynamide 178a (215 mg, 1.00 mmol) to give the enamide 180a (180 mg, 73%) as a colourless oil.

$R_f = 0.56$ (50% EtOAc/hexane); IR (film) 3026, 2965, 1754, 1671, 1481, 1407, 1250, 1096, 1040, 733 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.31-7.27 (2H, m, ArH), 7.22-7.18 (3H, m, ArH), 5.86 (1H, s, =CH), 4.28-4.23 (2H, m, CH$_2$O), 3.49-3.44 (2H, m, CH$_2$N), 2.75 (2H, t, $J = 7.9$ Hz, CH$_2$CH$_2$Ph), 2.43 (2H, t, $J = 7.9$ Hz, CH$_2$CH$_2$Ph), 2.16 (2H, d, $J = 7.4$ Hz, CH$_2$CH$_3$), 1.10 (3H, t, $J = 7.4$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 157.1 (C), 141.7 (C), 136.4 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.9 (CH), 118.8 (CH), 62.0 (CH$_2$), 46.4 (CH$_2$), 33.9 (CH$_2$), 31.6 (CH$_2$), 27.3 (CH$_2$), 12.7 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{15}$H$_{19}$NO$_2$ [M$^+$]: 245.1410, found: 245.1403.

3-[(Z)-2-Methyl-4-phenylbut-1-enyl]oxazolidin-2-one (180b).

The title compound was prepared according to General Procedure A from ynamide 178a (215 mg, 1.00 mmol) to give the enamide 180b (141 mg, 61%) as a yellow oil.

$R_f = 0.14$ (25% EtOAc/hexane); IR (film) 2967, 2929, 1754 (C=O), 1676, 1481, 1406, 1256, 1089, 1040, 731 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.32-7.27 (2H, m, ArH), 7.22-7.18 (3H, m, ArH), 5.81 (1H, s, =CH), 4.27-4.22 (2H, m, CH$_2$O), 3.41-3.37 (2H, m, CH$_2$N), 2.77 (2H, t, $J = 7.7$ Hz, CH$_2$CH$_2$Ph), 2.42 (2H, t, $J = 7.7$ Hz, CH$_2$CH$_2$Ph), 1.82 (3H, s, CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 157.1 (C), 141.7 (C), 136.4 (C), 128.4 (2 × CH), 128.3 (2 × CH), 125.9 (CH), 118.8 (CH), 62.0 (CH$_2$), 46.4 (CH$_2$), 33.5 (2 × CH$_2$), 20.4 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{14}$H$_{17}$NO$_2$ [M$^+$]: 231.1254, found: 231.1254.

3-[(Z)-2-Phenethylhex-1-enyl]oxazolidin-2-one (180c).

The title compound was prepared according to General Procedure C from ynamide 178a (65 mg, 0.30 mmol) to give the enamide 180c (70 mg, 85%) as a yellow oil.

6.0 Experimental 122
R$_f$ = 0.61 (50% EtOAc/hexane); IR (film) 3027, 2929, 1749 (C=O), 1672, 1481, 1409, 1252, 1074, 1041, 733 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.33-7.27 (2H, m, ArH), 7.22-7.18 (3H, m, ArH), 5.86 (1H, s, =CH), 4.28-4.24 (2H, m, CH$_2$O), 3.49-3.45 (2H, m, CH$_2$N), 2.74 (2H, app dd, J = 8.9, 6.8 Hz, CH$_2$CH$_2$Ph), 2.42 (2H, app dd, J = 8.9, 6.8 Hz, CH$_2$CH$_2$Ph), 1.51-1.43 (2H, m, CH$_2$CH$_2$CH$_2$CH$_3$), 0.93 (3H, t, J = 7.2 Hz, CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 157.2 (C), 141.7 (C), 135.0 (C), 128.4 (2 × CH), 128.3 (2 × CH), 126.0 (CH), 119.4 (CH), 62.0 (CH$_2$), 46.4 (CH$_2$), 34.0 (CH$_2$), 33.9 (CH$_2$), 31.5 (CH$_2$), 30.2 (CH$_2$), 22.4 (CH$_2$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{17}$H$_{23}$NO$_2$ [M]+: 273.1723, found: 273.1718.


The title compound was prepared according to General Procedure A from ynamide 178e (195 mg, 1.00 mmol) to give the enamide 180d (133 mg, 63%) as a 9:1 mixture of regioisomers as a yellow oil.

R$_f$ = 0.57 (50% EtOAc/hexane); IR (film) 2956, 2927, 1751 (C=O), 1676, 1481, 1466, 1244, 1106, 1041, 732 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 5.85 (1H, br s, =CH), 4.41-4.36 (2H, m, CH$_2$O), 3.78-3.74 (2H, m, CH$_2$N), 2.11-2.08 (2H, m, =CCH$_2$CH$_2$), 1.73 (3H, d, J = 1.4 Hz, =CCMe), 1.47-1.39 (2H, m, =CCH$_2$CH$_2$), 1.32-1.28 (6H, m, CH$_2$CH$_2$CH$_2$CH$_3$), 0.85 (3H, t, J = 6.7 Hz, CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 157.4 (C), 133.1 (C), 118.5 (CH), 62.0 (CH$_2$), 46.7 (CH$_2$), 31.5 (CH$_2$), 31.2 (CH$_2$), 29.2 (CH$_2$), 27.4 (CH$_2$), 22.4 (CH$_2$), 20.3 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{12}$H$_{21}$NO$_2$ [M+H]$^+$: 212.1645, found: 212.1646.

3-[(Z)-2-Ethyloct-1-enyl]oxazolidin-2-one (180e).

The title compound was prepared according to General Procedure B from ynamide 178e (195 mg, 1.00 mmol) to give the enamide 180e (175 mg, 78%) as a yellow oil.

R$_f$ = 0.61 (50% EtOAc/hexane); IR (film) 2960, 2927, 1754 (C=O), 1672, 1483, 1464, 1240, 1112, 1041, 732 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 5.86 (1H, s, =CH), 4.38-4.34 (2H, m, CH$_2$O), 3.77-3.73 (2H, m, CH$_2$N), 2.09-2.02 (4H, m, =CCH$_2$CH$_3$ + =CCH$_2$CH$_3$), 1.40-1.36 (2H, m, =CCH$_2$CH$_2$), 1.29-1.25 (6H, m,
$\text{CH}_3\text{CH}_2\text{CH}_3$, 1.02 (3H, t, $J = 7.5$ Hz, CH$_2$CH$_3$), 0.87 (3H, t, $J = 6.7$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 157.4 (C), 137.5 (C), 118.0 (CH), 62.0 (CH$_2$), 46.6 (CH$_2$), 31.5 (CH$_2$), 29.4 (CH$_2$), 29.3 (CH$_2$), 27.8 (CH$_2$), 27.2 (CH$_2$), 22.4 (CH$_2$), 13.9 (CH$_3$), 12.6 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{13}$H$_{27}$N$_2$O$_2$ [M+NH$_4$]$^+$: 243.2067, found 243.2065.

3-[(Z)-2-Butyloct-1-enyl]oxazolidin-2-one (180f).

The title compound was prepared according to General Procedure C from ynamide 178e (59 mg, 0.30 mmol) to give the enamide 180f (62 mg, 81%) as a yellow oil.

R$_f$ = 0.72 (50% EtOAc/hexane); IR (film) 2958, 2929, 1747 (C=O), 1670, 1481, 1410, 1244, 1043, 733 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 5.87 (1H, s, =CCH$_3$), 4.39-4.34 (2H, m, CH$_2$O), 3.78-3.73 (2H, m, CH$_2$N), 2.09-2.00 (4H, m, 2 × =CCCH$_2$), 1.43-1.35 (4H, m, 2 × =CCH$_2$), 1.33-1.27 (8H, m, CH$_2$CH$_2$CH$_3$ + CH$_2$CH$_3$), 0.89 (3H, t, $J = 6.3$ Hz, CH$_2$CH$_3$), 0.88 (3H, t, $J = 6.9$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 157.4 (C), 136.2 (C), 118.7 (CH), 62.0 (CH$_2$), 46.7 (CH$_2$), 34.0 (CH$_2$), 31.6 (CH$_2$), 30.2 (CH$_2$), 29.4 (2 × CH$_2$), 27.9 (CH$_2$), 22.5 (CH$_2$), 22.3 (CH$_2$), 14.0 (CH$_3$), 13.9 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{15}$H$_{27}$NO$_2$ [M$^+$]: 253.2036, found: 253.2036.

3-[(Z)-4-(tert-Butyldimethylsilyloxy)-2-methylbut-1-enyl]oxazolidin-2-one (180g).

The title compound was prepared according to General Procedure A from ynamide 178c (269 mg, 1.00 mmol) to give the enamide 180g (140 mg, 49%) as a yellow oil.

R$_f$ = 0.52 (50% EtOAc/hexane); IR (film) 2956, 2923, 1753 (C=O), 1673, 1465, 1409, 1247, 1081, 1041, 735 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 6.00 (1H, br s, =CH), 4.38-4.33 (2H, m, NCH$_2$CH$_2$O), 3.87-3.83 (2H, m, CH$_2$N), 3.71 (2H, t, $J = 6.6$ Hz, CH$_2$OSi), 2.36 (2H, dt, $J = 6.6, 0.6$ Hz, =CCH$_2$), 1.75 (3H, d, $J = 1.5$ Hz, =CCH$_3$), 0.88 (9H, s, SiC(CH$_3$)$_3$), 0.04 (6H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 157.4 (C), 127.6 (C), 120.3 (CH), 62.1 (CH$_2$), 60.7 (CH$_2$), 46.7 (CH$_2$), 34.7
(CH₂), 25.8 (3 × CH₃), 20.9 (CH₃), 18.2 (C), –5.5 (2 × CH₃); HRMS (ES) Exact mass calcd for C₁₄H₂₈NO₃Si [M+H]⁺: 286.1833, found: 286.1836.

3-[(Z)-4-(tert-Butyldimethylsilyloxy)-2-ethylbut-1-ynamido]oxazolidin-2-one (180h).

The title compound was prepared according to General Procedure B from ynamide 178c (269 mg, 1.00 mmol) to give the enamide 180h (213 mg, 71%) as a yellow oil.

Rf = 0.66 (50% EtOAc/hexane); IR (film) 2958, 2929, 1759 (C=O), 1676, 1471, 1408, 1220, 1095, 1041, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.04 (1H, s, =CH), 4.38-4.34 (2H, m, NCH₂CH₂O), 3.90-3.85 (2H, m, CH₂N), 3.68 (2H, t, J = 6.8 Hz, CH₂OSi), 2.36 (2H, t, J = 6.8 Hz, CH₂CH₂O), 2.09 (2H, dq, J = 7.4, 1.3 Hz, CH₂CH₃), 1.05 (3H, t, J = 7.4 Hz, CH₂CH₃), 0.88 (9H, s, Si(CH₃)₃), 0.04 (6H, s, Si(CH₃)₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 157.3 (C), 131.7 (C), 119.8 (CH), 62.1 (CH₂), 61.1 (CH₂), 46.5 (CH₂), 32.8 (CH₂), 27.9 (CH₂), 25.8 (3 × CH₃), 18.2 (C), 12.8 (CH₃), –5.5 (2 × CH₃); HRMS (EI) Exact mass calcd for C₁₅H₂₉NO₃Si [M⁺]: 299.1911, found: 299.1909.


To a solution of the ynamide 178d (735 mg, 3.00 mmol) and [Rh(cod)(MeCN)₂]BF₄ (45.6 mg, 0.12 mmol) in THF (30 mL) at 0 °C was added Et₂Zn (1.0 M in hexane, 6.00 mL, 6.00 mmol) over 2 min, and the reaction was then stirred at room temperature for 15 min. The mixture was then filtered through a short pad of silica gel using CH₂Cl₂ (30 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (15% EtOAc/hexane → 40% EtOAc/hexane) gave the enamide 180i (554 mg, 67%) as a colourless oil.

Rf = 0.35 (40% EtOAc/hexane); IR (film) 2964, 2871, 1751 (C=O), 1674, 1481, 1405, 1251, 1098, 1039, 738 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.29 (5H, m, ArH), 6.01 (1H, s, =CH), 4.51 (2H, s, OCH₂Ar), 4.31-4.28 (2H, m, NCH₂CH₂O), 3.79-3.76 (2H, m, CH₂N), 3.55 (2H, t, J = 7.0 Hz, CH₂CH₂O), 2.46 (2H, t, J = 7.0 Hz, CH₂CH₂O), 2.10 (2H, dq, J = 7.4, 1.2 Hz, CH₂CH₃), 1.06 (3H, t, J = 7.4 Hz,
CH$_2$CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 157.4 (C), 138.2 (C), 132.5 (C), 128.4 (2 × CH), 127.6 (3 × CH), 119.9 (CH), 73.0 (CH$_2$), 68.1 (CH$_2$), 62.1 (CH$_2$), 46.5 (CH$_2$), 30.2 (CH$_2$), 27.3 (CH$_2$), 12.8 (CH$_3$); HRMS (EI) Exact mass calcd for C$_{13}$H$_{19}$NO$_2$ [M+H]$^+$: 276.1594, found: 276.1590.

(S)-4-Benzyl-3-(Z)-2-ethyldec-1-enyl]oxazolidin-2-one (180j).

The title compound was prepared according to General Procedure B from ynamide 178f (285 mg, 1.00 mmol) and purified by column chromatography (10% EtOAc/hexane) to give the enamide 180j (222 mg, 70%) as a yellow oil.

$\text{R}_f = 0.47$ (25% EtOAc/hexane); $[\alpha]^{20}_D$ -23.1 (c. 1.00, CHCl$_3$); IR (film) 2962, 2931, 2252, 1749 (C=O), 1664, 1496, 1414, 1236, 1090, 1038, 733 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.36-7.27 (3H, m, ArH), 7.16-7.14 (2H, m, ArH), 5.69 (1H, s, =CH$_2$), 4.27-4.21 (1H, m) and 4.14-4.07 (2H, m, OCH$_2$CH$_2$), 3.11 (1H, dd, $J = 13.5$, 3.6 Hz, CH$_2$Ph), 2.65 (1H, dd, $J = 13.5$, 9.1 Hz, CH$_2$Ph), 2.18-2.12 (4H, m, 2 × =CCCH$_2$), 1.48-1.42 (2H, m, =CCCH$_2$CH$_3$), 1.35-1.31 (6H, m, (CH$_2$)$_3$CH$_3$), 1.07 (3H, t, $J = 7.5$ Hz, =CC(CH$_3$)$_3$), 0.90 (3H, t, $J = 6.8$ Hz, CH$_2$CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 156.7 (C), 143.5 (C), 135.7 (C), 128.0 (2 × CH), 128.1 (2 × CH), 127.1 (CH), 116.1 (CH), 66.6 (CH$_2$), 58.9 (CH), 38.4 (CH$_2$), 31.7 (CH$_2$), 29.9 (CH$_2$), 29.6 (CH$_2$), 27.2 (CH$_2$), 26.9 (CH$_2$), 22.6 (CH$_2$), 14.0 (CH$_3$), 12.6 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{20}$H$_{30}$NO$_2$ [M+H]$^+$: 316.2271, found: 316.2269.

3-[(Z)-2-Phenylpropenyl]oxazolidin-2-one (180k)$^{150}$

The title compound was prepared according to General Procedure A from ynamide 178b (187 mg, 1.00 mmol) to give the enamide 180k (110 mg, 54%) as a yellow oil that displayed spectroscopic data consistent with those reported previously.$^{150}$

$\text{R}_f = 0.58$ (50% EtOAc/hexane); IR (film) 3056, 2968, 1755 (C=O), 1668, 1481, 1405, 1251, 1041, 730 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.36-7.32 (2H, m, ArH), 7.29-7.22 (3H, m, ArH), 6.53 (1H, app d, $J = 1.3$ Hz, =CH$_2$), 4.16-4.12 (2H, m, CH$_2$O), 3.12-3.08 (2H, m, CH$_2$N), 2.05 (3H, d, $J = 1.3$ Hz, CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 157.2 (C), 139.9 (C), 128.3 (2 × CH), 128.1 (2 × CH), 127.3
(CH), 122.8 (C), 120.3 (CH), 62.4 (CH2), 44.9 (CH2), 23.7 (CH3); HRMS (ES) Exact mass calcd for C12H14NO2 [M+H]+: 204.1019, found: 204.1021.

3-[(Z)-2-Phenylbut-1-enyl]oxazolidin-2-one (180l).
The title compound was prepared according to General Procedure B from ynamide 178b (187 mg, 1.00 mmol) to give the enamide 180l (185 mg, 85%) as a white solid. A similar reaction conducted on the same scale but using Rh(cod)(acac) (6.2 mg, 0.02 mmol) and Et2Zn (1.0 M in hexane, 0.55 mL, 0.55 mmol) for a reaction time of 4 h gave enamide 180l (150 mg, 69%). Rf = 0.62 (50% EtOAc/hexane); m.p. 68-70 °C; IR (CHCl3) 2956, 2969, 1757 (C=O), 1668, 1481, 1408, 1251, 1069, 1041, 731 cm⁻¹; 1H NMR (360 MHz, CDCl3) δ 7.36-7.29 (3H, m, ArH), 7.22-7.19 (2H, m, ArH), 6.56 (1H, app t, J = 1.3 Hz, =CH), 4.15-4.10 (2H, m, CH2O), 3.06-3.02 (2H, m, CH2N), 2.38 (2H, dq, J = 7.4, 1.3 Hz, CH2CH3), 1.00 (3H, t, J = 7.4 Hz, CH2CH3), 13C NMR (62.9 MHz, CDCl3) δ 157.2 (C), 138.9 (C), 129.1 (2 × CH), 128.1 (C), 127.9 (2 × CH), 127.2 (CH), 119.7 (CH), 62.4 (CH2), 45.0 (CH2), 30.7 (CH2), 13.1 (CH3); HRMS (EI) Exact mass calcd for C12H14NO2 [M⁺]: 217.1097, found: 217.1094.

3-[(Z)-2-Phenylhex-1-enyl]oxazolidin-2-one (180m).
The title compound was prepared according to General Procedure C from ynamide 178b (56 mg, 0.30 mmol) to give the enamide 180m (68 mg, 91%) as an orange oil. Rf = 0.69 (50% EtOAc/hexane); IR (film) 2956, 2929, 1756 (C=O), 1666, 1481, 1404, 1244, 1106, 1041, 730 cm⁻¹; 1H NMR (360 MHz, CDCl3) δ 7.36-7.25 (3H, m, ArH), 7.21-7.18 (2H, m, ArH), 6.56 (1H, s, =CH), 4.14-4.10 (2H, m, CH2O), 3.06-3.01 (2H, m, CH2N), 2.37-2.32 (2H, m, =CCH2), 1.33-1.28 (4H, m, CH2CH2CH2CH3), 0.86 (3H, t, J = 7.4 Hz, CH2CH3); 13C NMR (62.9 MHz, CDCl3) δ 157.2 (C), 139.0 (C), 129.1 (2 × CH), 128.0 (2 × CH), 127.2 (CH), 126.7 (C), 120.3 (CH), 62.4 (CH2), 45.0 (CH2), 37.4 (CH2), 30.3 (CH2), 22.1 (CH2), 13.8 (CH3); HRMS (EI) Exact mass calcd for C15H19NO2 [M⁺]: 245.1410, found: 245.1411.
3-[(Z)-2-Phenylhex-1-enyl]pyrrolidin-2-one (180n).

The title compound was prepared according to General Procedure C from ynamide 178h (56 mg, 0.30 mmol) to give the enamide 180n (55 mg, 75%) as an orange oil.

R_f = 0.51 (50% EtOAc/hexane); IR (film) 2957, 2931, 1683 (C=O), 1403, 1313, 1298, 1251, 908, 732, 648 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.27 (3H, m, ArH), 7.18-7.15 (2H, m, ArH), 6.72 (1H, s, =CH), 2.89-2.85 (2H, m, CH\(_2\)N), 2.37-2.31 (4H, m, CH\(_2\)C=O and =CC\(_6\)H\(_5\)), 1.83-1.75 (2H, m, CH\(_2\)CH\(_2\)N), 1.32-1.26 (4H, m, CH\(_2\)CH\(_2\)CH\(_3\)), 0.85 (2H, t, J = 7.1 Hz, CH\(_3\)); \(^13\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 174.9 (C), 139.8 (C), 128.9 (2 × CH), 127.8 (2 × CH), 127.6 (C), 127.0 (CH), 120.4 (CH), 48.2 (CH\(_2\)), 37.6 (CH\(_2\)), 30.4 (2 × CH\(_2\)), 22.2 (CH\(_2\)), 18.6 (CH\(_2\)), 13.9 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{16}\)H\(_{21}\)NO \([M+H]^+\): 243.1618, found: 243.1618.

3-Methyl-1-[(Z)-2-phenylpropenyl]-imidazolidin-2-one (180o).

To a solution of ynamide 178g (60 mg, 0.30 mmol) and Rh(cod)(acac) (4.7 mg, 0.015 mmol) in THF (3 mL) at 0 °C was added Me\(_2\)Zn (1.2 M in toluene, 0.50 mL, 0.60 mmol) dropwise over 2 min, and the reaction was then stirred at room temperature for 15 min. The mixture was filtered through a short pad of silica gel using CH\(_2\)Cl\(_2\) (10 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (50% EtOAc/hexane) gave the enamide 180o (44 mg, 61%) as a colourless oil.

R_f = 0.43 (50% EtOAc/hexane); IR (film) 2929, 2882, 1701 (C=O), 1496, 1435, 1405, 1267, 1067, 1026, 731 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.33-7.29 (2H, m, ArH), 7.25-7.20 (3H, m, ArH), 6.67 (1H, q, J = 1.4 Hz, =CH), 3.17-3.12 (2H, m, CH\(_2\)N), 2.95-2.91 (2H, m, CH\(_2\)N), 2.80 (3H, s, NCH\(_3\)), 2.03 (3H, d, J = 1.4 Hz, =CCH\(_3\)); \(^13\)C NMR (90.6 MHz, CDCl\(_3\)) \(\delta\) 159.1 (C), 141.2 (C), 128.7 (2 × CH), 127.8 (2 × CH), 126.6 (CH), 122.1 (CH), 117.2 (C), 145.0 (CH\(_2\)), 42.8 (CH\(_2\)), 31.0 (CH\(_3\)), 23.8 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{13}\)H\(_{17}\)N\(_2\)O \([M+H]^+\): 217.1335, found: 217.1339.
3-Methyl-1-[(Z)-2-phenylbutenyl]-imidazolidin-2-one (180p).

The title compound was prepared according to General Procedure B from ynamide 178g (200 mg, 1.00 mmol) to give the enamide 180p (169 mg, 73%) as a pale yellow oil. 

$R_f = 0.37$ (40% EtOAc/hexane); IR (film) 2954, 2928, 1703 (C=O), 1517, 1414, 1362, 1266, 1057, 1026, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31-7.28 (2H, m, ArH), 7.25-7.22 (1H, m, ArH), 7.21-7.19 (2H, m, ArH), 6.68 (1H, s, $=CH$), 3.13-3.10 (2H, m, CH$_2$N), 2.88-2.85 (2H, m, CH$_2$N), 2.79 (3H, s, NCH$_3$), 2.35 (2H, dq, $J = 7.4, 1.0$ Hz, CH$_2$CH$_3$), 0.96 (3H, d, $J = 7.4$ Hz, CH$_3$CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 159.1 (C), 140.2 (C), 129.4 (2 × CH), 127.7 (2 × CH), 126.6 (CH), 122.8 (C), 121.3 (CH), 117.2 (C), 44.9 (CH$_2$), 42.9 (CH$_2$), 31.0 (CH$_3$), 30.9 (CH$_2$), 23.8 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{14}$H$_{22}$N$_3$O [M+NH$_4$]$^+$: 248.1757, found: 248.1757.

6.1.3 Carbozincation of Ynamides Using In Situ-Generated Diorganozinc Reagents

**General Procedure D**

To a solution of ZnCl$_2$ (0.5 M in THF, 2.00 mL, 1.00 mmol) at 0 °C was added the appropriate Grignard reagent (2.00 mmol) over 1 min. The mixture was then stirred at room temperature for 30 min to give the in situ-generated dioorganozinc reagent. In a separate flask, a solution of the appropriate ynamide (1.00 mmol) and Rh(cod)(acac) (15.5 mg, 0.05 mmol) in THF (10 mL) was cooled to 0 °C, and the solution of the dioorganozinc reagent was then added via cannula over 1 min. The mixture was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as observed by TLC analysis. The mixture was filtered through a short pad of silica gel using CH$_2$Cl$_2$ (30 mL) as eluent, and the filtrate was 6.0 Experimental 129
concentrated in vacuo. Purification of the residue by column chromatography afforded the desired enamide.

**General Procedure E**

This procedure was similar to General Procedure D, except that the reaction was conducted at –78 °C (rather than 0 °C) for 1 h before being allowed to warm slowly to room temperature over 14 h. The reaction was quenched carefully with saturated aqueous NH₄Cl solution (10 mL), and the aqueous layer was separated and extracted with EtOAc (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography afforded the desired enamide.

![3-\{(E)-4-(\text{tert}-\text{Butyldimethylsilyloxy})-2-thiophen-2-ylbut-1-enyl\}oxazolidin-2-one (183a)](image)

To a solution of ZnCl₂ (0.5 M in THF, 4.0 mL, 2.0 mmol) at 0 °C was added 2-thienylmagnesium bromide (1.0 M in THF, 4.0 mL, 4.0 mmol) over 1 min. The mixture was then stirred at room temperature for 30 min to give the in situ generated diorganozinc reagent. In a separate flask, a solution of the ynamide 178c (539 mg, 2.00 mmol) and Rh(cod)(acac) (31 mg, 0.10 mmol) in THF (20 mL) was cooled to –78 °C, and the solution of the diorganozinc reagent was then added via cannula over 2 min. The mixture was stirred at –78 °C for 1 h before being allowed to warm slowly to room temperature over 16 h. The mixture was filtered through a short pad of silica gel using CH₂Cl₂/EtOAc (40 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) afforded the *enamide 183a* (606 mg, 86%) as a dark orange oil (606 mg, 86%).

Rₛ = 0.60 (40% EtOAc/hexane); IR (film) 2956, 2929, 1752 (C=O), 1685, 1559, 1472, 1405, 1258, 907, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.14 (1H, dd, J = 4.9, 1.4 Hz, ArH), 6.99-6.96 (2H, m, ArH), 6.91 (1H, s, =CH), 4.43 (2H, app dd, J = 8.9, 7.0 Hz, OCH₂CH₂N), 4.03 (2H, app dd, J = 8.9, 7.0 Hz, OCH₂CH₂N), 3.76 (2H, t, J = 6.4 Hz, CH₂OSi), 2.80 (2H, t, J = 6.4 Hz, =CCH₂), 0.86 (9H, s, C(CH₃)₃), –0.02 (6H, s, Si(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 157.0 (C), 144.6 (C), 127.3
(CH), 123.5 (CH), 123.0 (CH), 122.7 (CH), 118.7 (C), 62.5 (CH2), 61.4 (CH2), 46.1 (CH2), 33.4 (CH2), 25.8 (3 × CH3), 18.3 (C), −5.5 (2 × CH3); HRMS (ES) Exact mass calcd for \( \text{C}_{17}\text{H}_{28}\text{NO}_3\text{Si}\)[M+H]^+: 354.1554, found: 354.1557.

**3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-(4-fluorophenyl)but-1-enyl]oxazolidin-2-one (183b).**

The title compound was prepared according to General Procedure D using 4-fluorophenylmagnesium bromide (1.0 M in THF, 2.00 mL, 2.00 mmol) and ynamide 178c (269 mg, 1.00 mmol) for a reaction time of 16 h (including the initial 1 h at 0 °C) and purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the enamide 183b (307 mg, 84%) as a pale orange solid. 

\( R_f = 0.67 \) (50% EtOAc/hexane); mp = 69-71 °C; IR (film) 2929, 2856, 1761 (C=O), 1653, 1471, 1404, 1300, 1257, 1041, 777 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.32-7.28 (2H, m, ArH), 7.04-6.99 (2H, m, ArH), 6.54 (1H, s, =CH), 4.46-4.42 (2H, m, CH\(_2\)O), 4.13-4.09 (2H, m, CH\(_2\)N), 3.60 (2H, t, \( J = 6.5 \) Hz, CH\(_2\)OSi), 2.80 (2H, t, \( J = 6.5 \) Hz, =CC\(_2\)), 0.85 (9H, s, SiC(CH\(_3\))\(_3\)), −0.05 (6H, s, Si(CH\(_3\))\(_2\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \( \delta \) 162.1 (C, d, \( J_F = 246.3 \) Hz), 157.3 (C), 136.5 (C, d, \( J_F = 3.3 \) Hz), 128.5 (2 × CH, d, \( J_F = 7.9 \) Hz), 125.6 (C), 123.8 (CH), 115.2 (2 × CH, d, \( J_F = 21.4 \) Hz), 62.4 (CH\(_2\)), 60.9 (CH\(_2\)), 46.3 (CH\(_2\)), 32.9 (CH\(_2\)), 25.8 (3 × CH\(_3\)), 18.2 (C), −5.5 (2 × CH\(_3\)); \(^{19}\)F NMR (235 MHz, CDCl\(_3\)) \( \delta \) −116.7; HRMS (ES) Exact mass calcd for \( \text{C}_{19}\text{H}_{29}\text{FNO}_3\text{Si}\)[M+H]^+: 366.1895, found: 366.1895.

**3-[(E)-2-(4-Methoxyphenyl)-4-phenylbut-1-enyl]oxazolidin-2-one (183c).**

The title compound was prepared according to General Procedure D using 4-methoxyphenylmagnesium bromide (0.5 M in THF, 4.00 mL, 2.00 mmol) and ynamide 178c (215 mg, 1.00 mmol) for a reaction time of 19 h (including the initial 1 h at 0 °C) and purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the enamide 183c (182 mg, 58%) as a colourless oil.

6.0 Experimental
R_f = 0.53 (50% EtOAc/hexane); IR (film) 2929, 2837, 1755 (C=O), 1649, 1479, 1454, 1428, 1029, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.35 (2H, dm, J = 8.9 Hz, ArH), 7.31-7.13 (5H, m, ArH), 6.92 (2H, dm, J = 8.9 Hz, ArH), 6.29 (1H, s, =CH), 4.32-4.27 (2H, m, CH₂O), 3.84 (3H, s, OCH₃), 3.56-3.52 (2H, m, CH₂N), 2.85 (2H, app dd, J = 8.7, 6.5 Hz, CH₂CH₂Ph), 2.69 (2H, dd, J = 8.7, 6.5 Hz, CH₂CH₂Ph); ¹³C NMR (62.9 MHz, CDCl₃) δ 159.1 (C), 157.1 (C), 141.6 (C), 132.2 (C), 132.1 (C), 128.5 (2 × CH), 128.3 (2 × CH), 127.9 (2 × CH), 126.0 (CH), 121.3 (CH), 113.9 (2 × CH), 62.2 (CH₂), 55.2 (CH₃), 46.2 (CH₂), 34.2 (CH₂), 31.6 (CH₂); HRMS (ES) Exact mass calcd for C₂₀H₂₂N₃O⁺: 324.1594, found: 324.1596.

1-[(Z)-2,3-Diphenylpropenyl]-3-methylimidazolidin-2-one (183d).
The title compound was prepared according to General Procedure D using benzylmagnesium chloride (2.0 M in THF, 1.00 mL, 2.00 mmol) and ynamide 178g (200 mg, 1.00 mmol) for a reaction time of 3 h (including the initial 1 h at 0 °C) and purified by column chromatography (50% EtOAc/hexane) to give the enamide 183d (207 mg, 71%) as a white solid.

R_f = 0.35 (50% EtOAc/hexane); m.p. 96-98 °C; IR (CHCl₃) 2930, 2884, 1708 (C=O), 1660, 1650, 1460, 1403, 1265, 754, 701 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.23-7.12 (8H, m, ArH), 7.03-7.02 (2H, m, ArH), 6.86 (1H, s, =CH), 3.63 (2H, s, CH₂Ph), 3.15-3.12 (2H, m, CH₂N), 2.91-2.88 (2H, m, CH₂N), 2.82 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 158.9 (C), 140.0 (C), 139.7 (C), 129.6 (2 × CH), 128.9 (2 × CH), 128.1 (2 × CH), 127.5 (2 × CH), 126.6 (CH), 125.9 (CH), 123.5 (CH), 119.7 (C), 44.8 (CH₂), 44.4 (CH₂), 42.7 (CH₂), 31.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₁N₂O⁺: 293.1648, found: 293.1648.

1-[(E)-2-Phenyl-2-thiophen-2-ylvinyl]pyrrolidin-2-one (183e).
The title compound was prepared according to General Procedure E using 2-thienylmagnesium bromide (1.0 M in THF, 2.00 mL, 2.00 mmol) and ynamide 178h (185 mg, 1.00 mmol) and purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the enamide 183e (177 mg, 66%) as an orange solid.
6.0 Experimental

Rf = 0.45 (50% EtOAc/hexane); mp = 125-127 °C; IR (CHCl3) 2929, 2882, 1703 (C=O), 1634, 1442, 1395, 1270, 1067, 1023, 731 cm⁻¹; ¹H NMR (360 MHz, CDCl3) δ 7.43 (1H, s, =CH), 7.39-7.37 (3H, m, ArH), 7.33-7.31 (2H, m, ArH), 7.13 (1H, dd, J = 5.1, 1.2 Hz, =CH), 6.90 (1H, dd, J = 5.1, 3.6 Hz, =CH), 6.64 (1H, dd, J = 3.6, 1.2 Hz, =CH), 2.97-2.93 (2H, m, CH2N), 2.42-2.38 (2H, m, CH2C=O), 1.90-1.81 (2H, m, CH2CH2N); ¹³C NMR (62.9 MHz, CDCl3) δ 175.2 (C), 146.1 (C), 138.1 (C), 130.5 (2 × CH), 128.0 (2 × CH), 127.2 (CH), 124.6 (CH), 123.7 (CH), 121.2 (CH), 121.0 (C), 48.2 (CH2), 30.3 (CH2), 18.7 (CH2); HRMS (ES) Exact mass calcd for C16H16NOS [M+H]+: 270.0947, found: 270.0945.

3-[(Z)-2-Phenylbuta-1,3-dienyl]oxazolidin-2-one (183f).

The title compound was prepared according to General Procedure E using vinylmagnesium bromide (1.0 M in THF, 2.00 mL, 2.00 mmol) and ynamide 178b (187 mg, 1.00 mmol) and purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the enamide 183f (141 mg, 66%) as an orange solid.

Rf = 0.74 (50% EtOAc/hexane); m.p. 94-96 °C; IR (film) 2987, 2918, 1751 (C=O), 1695, 1479, 1414, 1249, 1123, 1040, 739 cm⁻¹; ¹H NMR (360 MHz, CDCl3) δ 7.39-7.33 (3H, m, ArH), 7.23-7.20 (2H, m, ArH), 6.85 (1H, s, =CH), 6.57 (1H, dd, J = 17.1, 10.7 Hz, CH=CH2), 4.99 (1H, d, J = 10.7 Hz, =CH2), 4.61 (1H, d, J = 17.1 Hz, =CH2), 4.15-4.11 (2H, m, CH2O), 3.07-3.02 (2H, m, CH2N); ¹³C NMR (62.9 MHz, CDCl3) δ 156.6 (C), 138.8 (CH), 135.3 (C), 130.6 (2 × CH), 127.9 (2 × CH), 127.7 (CH), 125.1 (CH), 124.9 (C), 113.8 (CH2), 62.4 (CH2), 44.7 (CH2); HRMS (ES) Exact mass calcd for C13H14NO2 [M+H]+: 216.1019, found: 216.1021.

3-[(E)-3-Methyl-2-phenethylbuta-1,3-dienyl]oxazolidin-2-one (183g).

The title compound was prepared according to General Procedure D using isopropenylmagnesium bromide (0.5 M in THF, 4.00 mL, 2.00 mmol) and ynamide 178a (215 mg, 1.00 mmol) for a reaction time of 15 h (including the initial 1 h at 0 °C) and purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the enamide 183g (121 mg, 47%) as a dark red solid.
R_f = 0.57 (50% EtOAc/hexane); mp = 77-79 °C; IR (film) 2929, 2884, 1735 (C=O), 1699, 1475, 1267, 1224, 1024, 730 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.31-7.28 (2H, m, ArH), 7.22-7.16 (3H, m, ArH), 6.35 (1H, s, NCH=), 5.18 (1H, s, =CH₂), 5.04 (1H, s, =CH₂), 4.29-4.26 (2H, m, CH₂O), 3.57-3.53 (2H, m, CH₂N), 2.77 (2H, app dd, J = 8.9, 6.6 Hz, CH₂CH₂Ph), 2.65 (2H, app dd, J = 8.9, 6.6 Hz, CH₂CH₂Ph), 1.98 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 157.0 (C), 141.7 (C), 141.5 (C), 131.2 (C), 128.4 (2 × CH), 128.3 (2 × CH), 126.0 (CH), 122.2 (CH), 112.8 (CH₂), 62.2 (CH₂), 46.1 (CH₂), 35.0 (CH₂), 29.1 (CH₂), 21.4 (CH₃); HRMS (ES) Exact mass calc'd for C₁₆H₁₉NO₂ [M+H]⁺: 258.1489, found: 258.1493.

3-[(Z)-2-Phenyl-2-cyclohexyl]oxazolidin-2-one (183h) and [(Z)-2-phenyl]oxazolidin-2-one (184)¹⁵¹

To a solution of ZnCl₂ (0.5 m in THF, 4.0 mL, 2.0 mmol) at 0 °C was added a solution of cyclohexylmagnesium chloride (2.0 m in Et₂O, 2.0 mL, 4.0 mmol) over 1 min. The mixture was then stirred at room temperature for 30 min to give the in situ generated diorganozinc reagent. In a separate flask, a solution of the ynamide 178b (374 mg, 2.00 mmol) and Rh(cod)(acac) (31 mg, 0.10 mmol) in THF (20 mL) was cooled to 0 °C, and the solution of the diorganozinc reagent was then added via cannula over 2 min. The mixture was stirred at 0°C for 1 h before being allowed to warm slowly to room temperature over 16 h. The mixture was filtered through a short pad of silica gel using CH₂Cl₂/EtOAc (40 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) afforded the ynamide 183h (86 mg, 23%) as a colourless oil followed by the enamide 184 (120 mg, 22%) as a colourless solid.

Data for 183h: R_f = 0.65 (40% EtOAc/hexane); m.p. 98-100 °C; IR (film) 2929, 2858, 1758 (C=O), 1628, 1516, 1500, 1426, 1282, 915, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.34-7.28 (3H, m, ArH), 7.16-7.13 (2H, m, ArH), 6.54 (1H, s, =CH), 4.10-4.06 (2H, m, CH₂O), 2.95-2.91 (2H, m, CH₂N), 2.21-2.15 (1H, m, CHCH₂),

6.0 Experimental
Using alternative copper-catalysed conditions:

To a solution of ynamide 178b (187 mg, 1.00 mmol) and Cu(acac)₂ (13 mg, 0.05 mmol) in THF (10 mL) at 0 °C was added a solution of cyclohexylmagnesium chloride (2.0 M in Et₂O, 0.60 mL, 1.20 mmol) over 1 min, and the mixture was stirred at room temperature for 30 min. Saturated aqueous NH₄Cl solution (10 mL) was added carefully and the mixture was extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) gave the enamide 183h (201 mg, 74%) as a colourless solid.
6.1.4 Carbozincation of Ynamides Using Organozinc Halide Reagents

General Procedure F
To a solution of the appropriate ynamide (1.0 equiv) and Rh(cod)(acac) (0.05 equiv) in THF (10 mL/mmol of ynamide) at 0 °C was added the appropriate organozinc halide (2 equiv) over 1 min, and the reaction was then stirred at room temperature until complete consumption of starting material was observed by TLC analysis.

Workup A
The reaction mixture was filtered through a short pad of silica gel using CH₂Cl₂ as eluent, and the filtrate was concentrated *in vacuo*.

Workup B
The reaction was quenched with saturated NH₄Cl solution (10 mL) and the mixture was stirred vigorously for 15 min. The aqueous layer was separated and extracted with EtOAc (3 × 10 mL) and the combined organic layers were dried (MgSO₄), and concentrated *in vacuo*.

3-{1-[1-(2-Oxooxazolidin-3-yl)-meth-(E)-ylidene]-3-phenylpropyl}benzoic acid ethyl ester (185a).
The title compound was prepared according to General Procedure F using ynamide 178a (430 mg, 2.00 mmol) and a solution of 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 8.00 mL, 4.00 mmol) for a reaction time of 2 h followed by Workup A and purification by column chromatography (5% EtOAc/hexane→20% EtOAc/hexane) to give the *enamide* 185a (645 mg, 88%) as a yellow oil.
R_f = 0.18 (30% EtOAc/hexane); IR (film) 2985, 1755 (C=O), 1714 (C=O), 1479, 1404, 1265, 1088, 1043, 908, 735 cm^{-1}; ^1H NMR (360 MHz, CDCl_3) δ 8.09 (1H, t, J = 1.6 Hz), 7.99 (1H, dt, J = 7.8, 1.4 Hz), 7.59 (1H, ddd, J = 7.8, 1.8, 1.2 Hz), 7.45 (1H, t, J = 7.8 Hz), 7.30-7.26 (2H, m), 7.22-7.18 (1H, m), 7.15-7.12 (2H, m), 6.44 (1H, s), 4.42 (2H, q, J = 7.1 Hz), 4.33 (2H, app dd, J = 8.7, 7.2 Hz), 3.66-3.58 (2H, m), 2.92 (2H, t, J = 7.6 Hz), 2.68 (2H, t, J = 7.6 Hz), 1.43 (3H, t, J = 7.1 Hz); 13C NMR (62.9 MHz, CDCl_3) δ 166.5 (C), 157.0 (C), 141.2 (C), 140.5 (C), 131.2 (CH), 130.8 (C), 130.0 (C), 128.6 (CH), 128.5 (3 × CH), 128.4 (2 × CH), 127.9 (CH), 126.2 (CH), 123.4 (CH), 62.3 (CH_2), 61.1 (CH_2), 45.9 (CH_2), 34.3 (CH_2), 31.5 (CH_2), 14.3 (CH_3); HRMS (ES) Exact mass calcd for C_{22}H_{27}N_2O_4 [M+NH_4]^+: 383.1965, found: 383.1966.

3-{1-[1-(2-Oxo-oxazolidin-3-yl)meth-(E)-ylidene]heptyl}benzoic acid ethyl ester (185b)

The title compound was prepared according to General Procedure F using ynamide 178e (390 mg, 2.00 mmol) and a solution of 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 8.0 mL, 4.0 mmol) for a reaction time of 45 min followed by Workup A and purification by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) gave the enamide 185b (648 mg, 94%) as a black oil.

R_f = 0.38 (50% EtOAc/hexane); IR (film) 2928, 2858, 1756 (C=O), 1718 (C=O), 1481, 1369, 1256, 1039, 908, 733 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 8.01 (1H, t, J = 1.6 Hz, ArH), 7.95 (1H, dt, J = 7.8, 1.3 Hz, ArH), 7.52 (1H, ddd, J = 7.8, 1.2, 0.5 Hz, ArH), 7.39 (1H, t, J = 7.8 Hz, ArH), 6.40 (1H, s, =CH), 4.54 (2H, app dd, J = 8.9, 7.3 Hz, CH_2O), 4.40 (2H, q, J = 7.1 Hz, OCH_2CH_3), 4.03 (2H, app dd, J = 8.9, 7.3 Hz, CH_2N), 2.58-2.55 (2H, m, =CCH_2), 1.41 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.36-1.20 (8H, m, (CH_2)_3CH_3), 0.84 (3H, t, J = 7.0 Hz, (CH_2)_3CH_3); 13C NMR (125.8 MHz, CDCl_3) δ 166.8 (C), 156.7 (C), 140.6 (C), 133.3 (C), 131.3 (CH), 130.5 (C), 128.5 (2 × CH), 127.9 (CH), 121.8 (CH), 63.2 (CH_2), 61.3 (CH_2), 46.7 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 29.4 (CH_2), 28.5 (CH_2), 22.5 (CH_2), 14.3 (CH_3), 14.0 (CH_3); HRMS (ES) Exact mass calcd for C_{20}H_{31}N_2O_4 [M+NH_4]^+: 363.2278, found: 363.2278.
The enamide 185c was prepared by Mairi E. Rudkin. The title compound was prepared according to General Procedure F using ynamide 178c (54 mg, 0.20 mmol) and 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 2.5 h followed by Workup A and purification by column chromatography (30% EtOAc/hexane) to give the enamide 185c (55 mg, 66%) as a brown oil.

R_f = 0.55 (50% EtOAc/hexane); IR (film) 2956, 1755 (C =O), 1714, 1471, 1254, 1099, 908, 735, 650 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 8.00 (1H, dd, \(J = 2.3, 1.2 \text{ Hz}\)), 7.95 (1H, dt, \(J = 7.8, 1.2 \text{ Hz}\)), 7.53 (1H, ddd, \(J = 7.8, 2.3, 1.2 \text{ Hz}\)), 7.40 (1H, t, \(J = 7.8 \text{ Hz}\)), 6.65 (1H, s), 4.47-4.43 (2H, m), 4.39 (2H, q, \(J = 7.1 \text{ Hz}\)), 4.15 (2H, app dd, \(J = 9.0, 7.0 \text{ Hz}\)), 3.60 (2H, t, \(J = 7.0 \text{ Hz}\)), 2.86 (2H, t, \(J = 6.4 \text{ Hz}\)), 1.41 (3H, t, \(J = 7.1 \text{ Hz}\)), 0.84 (9H, s), –0.05 (6H, s); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 166.5 (C), 157.3 (C), 141.0 (C), 131.4 (CH), 130.6 (C), 128.4 (CH), 128.3 (CH), 127.9 (CH), 125.0 (C), 124.6 (CH), 62.5 (CH\(_2\)), 61.0 (CH\(_2\)), 60.9 (CH\(_2\)), 46.2 (CH\(_2\)), 32.7 (CH\(_2\)), 25.8 (3 × CH\(_3\)), 18.2 (C), 14.3 (CH\(_3\)), –5.5 (2 × CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{22}\)H\(_{37}\)N\(_2\)O\(_5\)Si [M+NH\(_4\)]\(^+\): 437.2466, found: 437.2469.

The enamide 185d was prepared by Mairi E. Rudkin. The title compound was prepared according to General Procedure F from ynamide 178g (40 mg, 0.20 mmol) and 3-chlorophenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 5 h followed by Workup B and purification by column chromatography (40% EtOAc/hexane) to give the enamide 185d (51 mg, 82%) as a yellow oil.

R_f = 0.40 (60% EtOAc/hexane); IR (film) 3054, 1711 (C=O), 1634, 1589, 1483, 1435, 1362, 1265, 896, 737 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.40-7.28 (4H, m), 7.26-7.21 (2H, m), 7.18-7.09 (3H, m), 7.05 (1H, ddd, \(J = 6.7, 2.8, 1.2 \text{ Hz}\)), 3.24-3.17 (2H, m), 3.01-2.93 (2H, m), 2.86 (3H, s); \(^{13}\)C NMR (90.6 MHz, CDCl\(_3\)) \(\delta\) 158.4 (C),
144.1 (C), 138.4 (C), 134.0 (C), 131.2 (2 × CH), 129.2 (CH), 128.1 (2 × CH), 127.4 (CH), 126.7 (CH), 125.9 (CH), 125.1 (CH), 124.8 (CH), 119.4 (C), 44.8 (CH), 42.6 (CH), 31.0 (CH₃); HRMS (ES) Exact mass calcd for C_{18}H_{17}ClN_{2}ONa [M+Na]^+: 335.0922, found: 335.0922.

1-[(E)-2-(3-Chlorophenyl)-4-phenylbut-1-enyl]pyrrolidin-2-one (185e)*

The enamide 185e was prepared by Mairi E. Rudkin. The title compound was prepared according to General Procedure F from ynamide 178h (43 mg, 0.20 mmol) and 3-chlorophenylzinc iodide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 5 h followed by Workup B and purification by column chromatography (40% EtOAc/hexane) to give the enamide 185e (50 mg, 77%) as a brown oil.

R_f = 0.40 (60% EtOAc/hexane); IR (film) 3054, 1699 (C=O), 1641, 1591, 1460, 1415, 1265, 1226, 736, 701 cm⁻¹; ^1H NMR (360 MHz, CDCl₃) δ 7.39 (1H, dt, J = 2.6, 1.2 Hz), 7.32-7.24 (5H, m), 7.23-7.17 (1H, m), 7.15-7.13 (2H, m), 6.55 (1H, s), 3.55-3.50 (2H, m), 2.86 (2H, app dd, J = 9.1, 6.5 Hz), 2.68 (2H, app dd, J = 9.1, 6.5 Hz), 2.43 (2H, t, J = 8.1 Hz), 2.09-2.01 (2H, m); ^13C NMR (90.6 MHz, CDCl₃) δ 174.9 (C), 142.8 (C), 141.3 (C), 134.3 (C), 129.6 (CH), 129.1 (C), 128.4 (4 × CH), 127.2 (CH), 127.0 (CH), 126.1 (CH), 125.0 (CH), 123.8 (CH), 48.9 (CH₂), 34.5 (CH₂), 31.9 (CH₂), 30.4 (CH₂), 18.8 (CH₂); HRMS (ES) Exact mass calcd for C_{20}H_{20}ClNONa [M+Na]^+: 348.1126, found: 348.1125.

5-[1-(2-Oxooxazolidin-3-yl)meth-(Z)-ylidene]-7-phenylheptanoic acid ethyl ester (186a)

The title compound was prepared according to General Procedure F from ynamide 178a (107 mg, 0.50 mmol) and 4-ethoxy-4-oxobutylzinc bromide (Sigma-Aldrich, 0.5 M in THF, 2.00 mL, 1.00 mmol) for a reaction time of 20 min followed by Workup A and purification by column chromatography (2% EtOAc/hexane→5% EtOAc/hexane) to give the enamide 186a (89 mg, 54%) as a pale yellow oil.
Rf = 0.37 (50% EtOAc/hexane); IR (film) 2926, 1750 (C=O), 1732 (C=O), 1670, 1480, 1407, 1245, 1090, 1039, 732 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.27 (2H, m, ArH), 7.21-7.17 (3H, m, ArH), 5.88 (1H, s, =CH), 4.28-4.24 (2H, m, CH₂CH₂O), 4.14 (2H, q, J = 7.1 Hz, CH₃C=O), 3.50-3.45 (2H, m, C₄H₉N), 2.74 (2H, app dd, J = 8.7, 6.9 Hz, CH₂CH₂Ph), 2.41 (2H, app dd, J = 8.7, 6.9 Hz, CH₂CH₂Ph), 2.33 (2H, t, J = 7.4 Hz, CH₂C=O), 2.16 (2H, t, J = 7.4 Hz, CH₂CH₂CH₂C=O), 1.86-1.78 (2H, m, CH₂CH₂C=O), 1.27 (3H, t, J = 7.1 Hz, CH₃CH₂O);

¹³C NMR (62.9 MHz, CDCl₃) δ 173.3 (C), 157.0 (C), 141.4 (C), 133.0 (C), 128.4 (2 × CH), 128.3 (2 × CH), 126.0 (CH), 120.2 (CH), 62.0 (CH₂), 60.3 (CH₂), 46.2 (CH₂), 33.8 (CH₂), 33.6 (CH₂), 31.2 (CH₂), 23.2 (CH₂), 14.2 (CH₃);


2,2-Dimethyl-7-[1-(2-oxooxazolidin-3-yl)meth-(Z)-ylidene]-9-phenylnonanenitrile (186b)*

The *enamide 186b* was prepared by Mairi E. Rudkin. General Procedure F was followed using ynamide 178b (43 mg, 0.20 mmol) and 5-cyano-5-methylhexylzinc bromide (0.5 M in THF, 0.80 mL, 0.40 mmol) for a reaction time of 4 h followed by Workup B and purification by column chromatography (30% EtOAc/hexane→40% EtOAc/hexane) to give the *enamide 355* (5 mg, 12%) as a brown oil followed by the *enamide 186b* (30 mg, 45%) as a yellow oil.

Data for xx: Rf = 0.55 (50% EtOAc/hexane); IR (film) 2930, 1753 (C=O), 1668, 1481, 1419, 1246, 1078, 908, 737, 650 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.28-7.28 (2H, m, ArH), 7.24-7.18 (3H, m, ArH), 6.26 (1H, dt, J = 9.5, 1.6 Hz, CH=CHCH₂), 4.89 (1H, dt, J = 9.5, 7.6 Hz, CH=CHCH₂), 4.34-4.29 (2H, m, CH₂O), 3.78-3.74 (2H, m, CH₂N), 2.73 (2H, t, J = 7.6 Hz, CH₂Ph), 2.50 (2H, app qd, J = 7.4, 1.5 Hz, CH₂CH₂Ph); ¹³C NMR (62.9 MHz, CDCl₃) δ 156.8 (C), 141.2 (C), 128.5 (2 × CH), 128.4 (2 × CH), 126.1 (CH), 122.9 (CH), 114.5 (CH), 62.1 (CH₂), 45.4 (CH₂), 36.2 (CH₂), 28.6 (CH₂); HRMS (ES) Exact mass calculated for C₁₉H₂₆NO₄ [M+H]⁺: 218.1176, found: 218.1179.

6.0 Experimental
Data for **186b**: $R_f = 0.44$ (50% EtOAc/hexane); IR (film) 3055, 2305 (C=O), 1753 (C=N), 7.33-7.25 (2H, m), 7.23-7.16 (3H, m), 5.87 (1H, s), 4.30-4.22 (2H, m), 3.51-3.45 (2H, m), 2.74 (2H, app dd, $J = 8.8, 6.9$ Hz), 2.41 (2H, app dd, $J = 8.8, 6.9$ Hz), 2.15 (2H, t, $J = 6.1$ Hz), 1.67-1.49 (6H, m), 1.35 (6H, s); $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.33-7.25 (2H, m), 7.23-7.16 (3H, m), 5.87 (1H, s), 4.30-4.22 (2H, m), 3.51-3.45 (2H, m), 2.74 (2H, app dd, $J = 8.8, 6.9$ Hz), 2.41 (2H, app dd, $J = 8.8, 6.9$ Hz), 2.15 (2H, t, $J = 6.1$ Hz), 1.67-1.49 (6H, m), 1.35 (6H, s); $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 157.1 (C), 141.5 (C), 134.1 (C), 131.4 (C), 128.4 (2 × CH), 128.4 (2 × CH), 126.1 (CH), 119.8 (CH), 62.1 (CH$_2$), 46.3 (CH$_2$), 40.8 (CH$_2$), 34.0 (CH$_2$), 33.9 (CH$_2$), 32.4 (C), 31.4 (CH$_2$), 27.9 (CH$_2$), 26.6 (2 × CH$_3$), 24.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{21}$H$_{32}$N$_3$O$_2$ [M+NH$_4$]$^+$: 358.2489, found: 358.2486.

![3-[Z)-(2-Oxopyrrolidin-1-yl)-2-phenylallyl]benzonitrile (186c)*](image)

The *enamide* **186c** was prepared by Mairi E. Rudkin. The title compound was prepared according to a slight modification of General Procedure F, in which [Rh(cod)Cl]$_2$ (4.9 mg, 0.01mmol) and rac-BINAP (12.5 mg, 0.02 mmol) were used in place of Rh(cod)(acac), using ynamide **178h** (37 mg, 0.20 mmol) and 3-cyanobenzylzinc bromide (0.5 M in THF, 0.80 mL, 0.40 mmol) at 60 °C for a reaction time of 6 h followed by Workup B and purification by column chromatography (20% EtOAc/hexane—50%EtOAc/hexane) to give the *enamide* **186c** (20 mg, 35%) as a pale orange solid.

$R_f = 0.36$ (60% EtOAc/hexane); m.p. 86-88 °C; IR (CHCl$_3$) 2923, 2228 (C=N), 1695 (C=O), 1483, 1398, 1299, 1266, 789, 727, 704 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.40-7.34 (1H, m), 7.37-7.29 (3H, m), 7.24-7.21 (3H, m), 6.99-6.93 (3H, m), 3.67 (2H, s), 2.93-2.86 (2H, m), 2.37 (2H, t, $J = 8.1$ Hz), 1.87-1.78 (2H, m); $^1$H NMR (90.6 MHz, CDCl$_3$) $\delta$ 175.2 (C), 140.8 (C), 138.3 (C), 133.5 (CH), 132.4 (CH), 130.1 (CH), 129.1 (2 × CH), 129.0 (CH), 127.9 (2 × CH), 127.5 (CH), 123.9 (C), 122.6 (CH), 118.9 (C), 112.1 (C), 48.1 (CH$_2$), 44.1 (CH$_2$), 30.3 (CH$_2$), 18.6 (CH$_2$); HRMS (ES) Exact mass calcd for C$_{20}$H$_{19}$N$_2$O [M+H]$^+$: 303.1492, found: 303.1489.
6.1.5 Carbozincation of Acyclic Ynamides

N-Phenyl-N-[(Z)-2-phenylbut-1-enyl] tert-butyl carbonyl ester (187a) and N-phenyl-N-[1-1-phenylmeth-(Z)-ylidene]propyl] tert-butyl carbonyl ester (187b)

To a solution of ynamide 179a (88 mg, 0.30 mmol) and Rh(cod)(acac) (4.6 mg, 0.015 mmol) in THF (3 mL) at –78 °C was added Et₂Zn (0.5 M in THF, 1.20 mL, 0.60 mmol) dropwise over 2 min, and the reaction was then stirred at –78 °C for 5 min. The mixture was quenched with saturated aqueous NH₄Cl solution (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were combined, dried (MgSO₄), and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexanes) afforded a 1:2.3 inseparable mixture of enamides 187a and 187b (77 mg, 80%) as a pale orange oil.

Rᵣ = 0.60 (20% EtOAc/hexanes); IR (film) 2974, 2934, 2360 (C=C), 1709 (C=O), 1493, 1367, 1302, 1161, 1018, 754 cm⁻¹.

NMR data for minor isomer 187a: ¹H NMR (360 MHz, CDCl₃) δ 7.57-6.98 (10H, m), 6.51 (1H, br s), 2.46 (2H, dq, J = 7.4, 1.3 Hz), 1.42 (9H, s), 1.08 (3H, t, J = 7.4 Hz); ¹³C NMR (62.9 MHz, CDCl₃) δ 153.6 (C), 142.0 (C), 138.9 (C), 127.8 (4 × CH and C), 126.6 (2 × CH), 125.8 (2 × CH), 124.6 (2 × CH), 124.3 (CH), 80.8 (C), 29.3 (CH₂), 28.1 (3 × CH₃), 13.2 (CH₃).

NMR data for major isomer 187b: ¹H NMR (360 MHz, CDCl₃) δ 7.57-6.98 (10H, m), 6.41 (1H, s), 2.26 (2H, q, J = 7.4 Hz), 1.24 (9H, s), 1.15 (3H, t, J = 7.4 Hz); ¹³C NMR (62.9 MHz, CDCl₃) δ 152.7 (C), 140.4 (C), 140.0 (C), 136.0 (C), 128.7 (2 × CH), 128.6 (2 × CH), 127.4 (2 × CH), 127.2 (CH), 125.1 (CH), 124.7 (CH), 124.1 (2 × CH), 80.5 (C), 28.6 (CH₂), 27.7 (3 × CH₃), 11.7 (CH₃).

The regioselectivity of carbometalation of acyclic ynamide 179a was based upon the ROESY spectrum of the resulting mixture of enamides 187a and 187b, which displayed the following diagnostic enhancement for the major isomer 187b:

![Diagram of 187b](image)

**N-Phenyl-N-[(Z)-2-phenylbut-1-enyl]carbamic acid tert-butyl ester (187a)**

The *enamide* 187a was prepared by Mairi E. Rudkin. To a solution of ynamide 179a (147 mg, 0.50 mmol) and Cu(acac)₂ (13.1 mg, 0.05 mmol) in Et₂O (5 mL) at 0 °C was added Et₂Zn (1.0 M in hexane, 1.00 mL, 1.00 mmol) over 1 min and the mixture was then stirred at room temperature for 16 h. The reaction was quenched with saturated aqueous NH₄Cl solution (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄), and concentrated in vacuo. Purification of the residue by column chromatography (1% EtOAc/hexane) gave the *enamide* 187a (106 mg, 66%) as a pale orange oil.

Rₚ = 0.60 (20% EtOAc/hexane); IR (film) 2975, 1700 (C=O), 1597, 1493, 1340, 1266, 1160, 1018, 864, 741 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.16-7.04 (5H, m), 7.03-6.92 (5H, m), 6.46 (1H, br s), 2.41 (2H, dq, J = 7.4, 1.3 Hz), 1.37 (9H, s₃), 1.03 (3H, t, J = 7.4 Hz); ¹³C NMR (62.9 MHz, CDCl₃) δ 153.6 (C), 142.0 (C), 138.9 (C), 127.8 (4 × CH and C), 126.6 (2 × CH), 125.8 (2 × CH), 124.6 (2 × CH), 124.3 (CH), 80.8 (C), 29.3 (CH₂), 28.1 (3 × CH₃), 13.2 (CH₃); HRMS (ES) Exact mass calcd for C₂₃H₂₆NO₂ [M+H]⁺: 324.1958, found: 324.1956.
6.1.6 Synthesis of Trisubstituted Enamides

![Chemical Structure](image)

**General Procedure G**

To a solution of ynamide 178b (94 mg, 0.50 mmol) and Rh(cod)(acac) (7.8 mg, 0.025 mmol) in THF (5 mL) at 0 °C was added Et₂Zn (1.0 M in hexane, 275 µL, 0.275 mmol) dropwise over 0.5 min, and the reaction was then stirred at room temperature for 15 min to produce alkenylzinc species xx. After addition of the appropriate electrophile (0.80 mmol) and other catalysts/reagents and completion of the reaction, the mixture was filtered through a short pad of silica gel using CH₂Cl₂ (20 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the desired enamide.

![Enamide Structure](image)

**3-[(Z)-1-Benzoyl-2-phenylbut-1-enyl]oxazolidin-2-one (192).**

General Procedure G was followed to produce alkenylzinc species 191. Benzoyl chloride (93 µL, 0.80 mmol) was then added to the solution of 191 and the resulting mixture was heated at 65 °C for 36 h. The standard workup and purification of the residue by column chromatography (hexane→25% EtOAc/hexane) gave the **enamide 192** (90 mg, 56%) as a yellow oil.

R₇ = 0.42 (25% EtOAc/hexane); IR (film) 2976, 2929, 1749 (C=O), 1658, 1479, 1446, 1242, 1088, 1038, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.08-8.05 (2H, m, ArH), 7.62-7.57 (1H, m, ArH), 7.53-7.48 (2H, m, ArH), 7.46-7.33 (5H, m, ArH), 4.10-4.06 (2H, m, CH₂O), 3.35-3.31 (2H, m, CH₂N), 2.38 (2H, q, J = 7.4 Hz, CH₃CH₃), 0.79 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 195.1 (C), 156.7 (C), 147.4 (C), 137.9 (C), 133.2 (CH), 129.1 (2 × CH and C), 128.7 (2 × CH), 128.6 (2 × CH), 128.5 (CH), 127.6 (2 × CH and C), 62.8 (CH₂), 46.2 (CH₂), 27.3 (CH₂), 12.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₀H₂₀NO₃ [M+H]^+: 322.1438, found: 322.1435.

6.0 Experimental

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3-[(Z)-1-Allyl-2-ethyl-4-phenylbut-1-enyl]oxazolidin-2-one (194)*.

The enamide 194 was prepared by Mairi E. Rudkin. General Procedure G was followed using ynamide 178a (109 mg, 0.50 mmol) to produce alkenylzinc species 193. To this solution was added a solution of allyl bromide (217 µL, 2.50 mmol) and the resulting mixture was stirred at room temperature for 4.5 h. The standard workup and purification of the residue by column chromatography (25% EtOAc/hexane) gave the enamide 194 (80 mg, 56%) as a pale yellow oil.

R_f = 0.33 (30% EtOAc/hexane); IR (film) 2968, 1750 (C =O), 1637, 1454, 1408, 1227, 1123, 1039, 916, 757 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.32-7.25 (2H, m), 7.22-7.13 (3H, m), 5.79 (1H, ddt, \(J = 16.8, 10.1, 6.5\) Hz), 5.12 (1H, ddt, \(J = 16.8, 3.3, 1.7\) Hz), 5.06 (1H, ddt, 10.1, 3.3, 1.4 Hz), 4.23 (2H, app t, \(J = 8.0\) Hz), 3.38-3.18 (2H, m), 3.03 (2H, d, \(J = 6.5\) Hz), 2.78-2.71 (2H, m), 2.42-2.34 (2H, m), 2.23 (2H, q, \(J = 7.6\) Hz), 1.11 (3H, t, \(J = 7.6\) Hz); \(^{13}\)C NMR (90.6 MHz, CDCl\(_3\)) \(\delta\) 156.8 (C), 142.1 (C), 141.3 (C), 134.9 (CH), 128.4 (2 × CH), 128.3 (2 × CH), 126.9 (C), 125.9 (CH), 116.8 (CH\(_2\)), 62.0 (CH\(_2\)), 46.1 (CH\(_2\)), 34.0 (CH\(_2\)), 33.9 (CH\(_2\)), 33.2 (CH\(_2\)), 23.9 (CH\(_2\)), 13.1 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{18}\)H\(_{24}\)NO\(_2\) [M+H]\(^+\): 286.1802, found: 286.1798.

3-[(Z)-1-(4-Nitrophenyl)-2-phenylbut-1-enyl]oxazolidin-2-one (195a).

General Procedure G was followed to produce alkenylzinc species 191. To this solution was added a solution of Pd\(_2\)(dba)\(_3\) (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol) and 1-iodo-4-nitrobenzene (199 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) via cannula and the resulting mixture was heated at 65 °C for 22 h. The standard workup and purification of the residue by column chromatography (5% EtOAc/hexane→25% EtOAc/hexane) gave the enamide 195a (91 mg, 54%) as a dark red oil.

R_f = 0.11 (25% EtOAc/hexane); IR (film) 2974, 1749 (C=O), 1518, 1408, 1344, 1227, 1109, 1038, 864, 729 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 8.28 (2H, dm, \(J = 8.9\) Hz, Ar\(_{\text{H}}\)), 7.60 (2H, dm, \(J = 8.9\) Hz, Ar\(_{\text{H}}\)), 7.45-7.41 (2H, m, Ar\(_{\text{H}}\)), 7.38-7.32 (3H,
m, ArH), 4.11-4.07 (2H, m, CH₂O), 3.36-3.31 (2H, m, CH₂N), 2.45 (2H, q, J = 7.5 Hz, CH₂CH₃), 0.98 (3H, t, J = 7.5 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 156.5 (C), 147.4 (C), 146.2 (C), 143.7 (C), 138.8 (C), 129.6 (2 × CH), 128.8 (C), 128.7 (2 × CH), 128.1 (CH), 127.4 (2 × CH), 123.8 (2 × CH), 62.2 (CH₂), 45.9 (CH₂), 27.5 (CH₂), 13.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₂N₃O₄ [M+NH₄]⁺: 356.1605, found: 356.1606.

3-[(Z)-4-(tert-Butyldimethylsilyloxy)-2-ethyl-1-thiophen-2-ylbut-1-enyl]oxazolidin-2-one (195b)*

The enamide 195b was prepared by Mairi E. Rudkin. General Procedure G was followed using ynamide 178c (135 mg, 0.50 mmol) to produce alkenylzinc species. To this solution was added a solution of Pd₂dba₃ (11 mg, 0.0125 mmol), tri(2-furyl)phospine (11.0 mg, 0.05 mmol) and 2-iodothiophene (168 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) via cannula and the resulting mixture was heated at 65 °C for 40 h. The standard workup and purification of the residue by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) gave the enamide xx (85 mg, 45%) as a yellow-brown oil.

Rₐ = 0.47 (30% EtOAc/hexane); IR (CHCl₃) 2929, 2360, 1751 (C=O), 1469, 1410, 1415, 1410, 1263, 1092, 908, 835, 735 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.30 (1H, dd, J = 4.9, 1.5 Hz), 7.02-6.98 (2H, m), 4.39-4.31 (2H, m), 3.80 (2H, t, J = 7.0 Hz), 3.60 (2H, app dd, J = 8.7, 7.3 Hz), 2.52 (1H, t, J = 7.0 Hz), 2.29 (2H, q, J = 7.5 Hz), 1.07 (3H, t, J = 7.5 Hz), 0.91 (9H, s), 0.08 (6H, s); ¹³C NMR (62.9 MHz, CDCl₃) δ 156.7 (C), 144.8 (C), 137.7 (C), 127.5 (CH), 126.8 (CH), 125.8 (CH), 123.7 (C), 62.0 (CH₂), 61.2 (CH₂), 45.7 (CH₂), 34.4 (CH₂), 25.9 (3 × CH₃), 25.3 (CH₂), 18.3 (C), 13.1 (CH₃), −5.3 (2 × CH₃); HRMS (ES) Exact mass calcd for C₁₉H₂₂N₃O₄SSi [M+H]⁺: 382.1867, found: 382.1863.

(2E,4Z)-Methyl 4-(2-oxooxazolidin-3-yl)-5-phenylhepta-2,4-dienoate (195c)

General Procedure G was followed to produce alkenylzinc species 191. To this solution was added a solution of Pd₂dba₃ (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol) and methyl (E)-3-iodopropenoate₁⁵² (170 mg,
0.80 mmol) in THF (3 mL + 2 mL rinse) via cannula and the resulting mixture was heated at 65 °C for 22 h. The standard workup and purification of the residue by column chromatography (hexane→30% EtOAc/hexane) gave the enamide 195c (91 mg, 61%) as a grey solid. 

R_f = 0.43 (50% EtOAc/hexane); m.p. 110-112 °C; IR (CHCl_3) 2981, 2254, 1751 (C=O), 1712, 1481, 1417, 1265, 1095, 1041, 733 cm^{-1}; ¹H NMR (360 MHz, CDCl_3) δ 7.73 (1H, d, J = 15.4 Hz, CH=CHCO_2CH_3), 7.42-7.33 (3H, m, ArH), 7.27-7.25 (2H, m, ArH), 5.94 (1H, d, J = 15.4 Hz, =C=CHCO_2CH_3), 4.07 (2H, t, J = 8.1 Hz, CH_2O), 3.79 (3H, s, OCH_3), 3.27 (2H, t, J = 8.1 Hz, CH_2N), 2.72 (2H, q, J = 7.5 Hz, CH_2CH_3), 1.06 (3H, t, J = 7.5 Hz, CH_2CH_3); ¹³C NMR (62.9 MHz, CDCl_3) δ 167.2 (C), 156.9 (C), 154.3 (C), 139.0 (C), 136.5 (CH), 128.5 (2 × CH), 128.3 (CH), 128.0 (C), 127.0 (2 × CH), 118.8 (CH), 62.2 (CH_2), 51.7 (CH_3), 45.4 (CH_2), 27.4 (CH_3), 13.0 (CH_3); HRMS (ES) Exact mass calcd for C_{17}H_{23}N_2O_4 [M+NH_4]^+: 319.1652, found: 319.1650.

3-[(E)-2-(4-Nitrophenyl)-2-(2-oxooxazolidin-3-yl)-1-phenylvinyl]benzoic acid ethyl ester (197) and 3-{(E)-2-(2-oxooxazolidin-3-yl)-1-phenylvinyl}benzoic acid ethyl ester (185f*)

The enamides 197 and 185f were prepared by Mairi E. Rudkin To a solution of ynamide 178b (94 mg, 0.50 mmol) and Rh(cod)(acac) (7.8 mg, 0.025 mmol) in THF (5 mL) at 0 °C was added 3-(ethoxycarbonyl)phenylzinc iodide (0.5 M in THF, 1.10 mL, 0.55 mmol) over 1 min, and the reaction was then stirred at room temperature for 15 min to produce the alkenylzinc species 61. To this solution was added a solution of Pd_2dba_3 (11 mg, 0.0125 mmol), tri(2-furyl)phosphine (11 mg, 0.05 mmol)
and 1-iodo-4-nitrobenzene (199 mg, 0.80 mmol) in THF (3 mL + 2 mL rinse) via cannula and the resulting mixture was heated at 65 °C for 48 h. The standard workup and purification of the residue by column chromatography (40% EtOAc/hexane) gave the enamide 30 (34 mg, 20%) as a brown oil followed by the enamide 62 (42 mg, 18%) as an orange solid.

Data for 62: Rf = 0.28 (40% EtOAc/hexane); m.p. 146-148 °C; IR (CHCl₃) 3055, 2986, 1758 (C=O), 1595, 1520, 1347, 1265, 896, 740 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.04 (2H, d, J = 8.9 Hz), 7.89 (1H, dt, J = 7.5, 1.6 Hz), 7.69 (1H, t, J = 1.6 Hz), 7.42-7.32 (5H, m), 7.30-7.16 (4H, m), 4.33-4.23 (4H, m), 3.52 (2H, app dd, J = 8.6, 7.3 Hz), 1.31 (3H, t, J = 7.1 Hz); ¹³C NMR (90.6 MHz, CDCl₃) δ 165.9 (C), 155.8 (C), 147.0 (C), 143.3 (C), 142.1 (C), 140.1 (C), 140.0 (C), 135.2 (CH), 131.9 (CH), 131.4 (C), 130.7 (C), 130.4 (2 × CH), 129.1 (CH), 129.0 (2 × CH), 128.9 (2 × CH), 128.9 (CH), 128.5 (CH), 123.6 (2 × CH), 62.5 (CH₂), 61.1 (CH₂), 45.8 (CH₂), 14.2 (CH₃); HRMS (ES) Exact mass calcld for C_{26}H_{26}N₃O₆ [M+NH₄]⁺: 476.1816, found: 476.1818.

6.1.7 Elaboration of Enamide Products

**Friedel-Crafts Cyclizations**

Using TMSOTf: To a solution of enamide 180a (49 mg, 0.20 mmol) in CH₂Cl₂ (2 mL) at −78 °C was added TMSOTf (18 µL, 0.10 mmol) and the mixture was allowed to warm slowly to −30 °C over 3 h. The reaction was quenched with saturated aqueous NaHCO₃ solution (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the tetrahydronaphthalene 200 (42 mg, 86%) as a colourless oil.
R_f = 0.58 (50% EtOAc/hexane); IR (film) 2957, 2920, 1747 (C=O), 1485, 1421, 1379, 1254, 1059, 908, 746 cm^{-1}; ^1H NMR (360 MHz, CDCl_3) δ 7.20-7.11 (4H, m, ArH), 4.89 (1H, d, J = 10.3 Hz, ArCHN), 4.42-4.30 (2H, m, CH_2O), 3.36 (1H, ddd, J = 8.9, 8.9, 7.1 Hz, CH_2N), 3.21 (1H, ddd, J = 8.9, 8.9, 7.1 Hz, CH_2N), 2.83-2.80 (2H, m, CH_2Ar), 2.12-2.06 (1H, CHCH_2CH_3), 1.01 (3H, t, J = 7.4 Hz, CH_3); ^13C NMR (62.9 MHz, CDCl_3) δ 159.3 (C), 138.1 (C), 133.9 (C), 129.0 (CH), 127.0 (CH), 126.8 (CH), 126.3 (CH), 62.0 (CH_2), 56.9 (CH), 39.8 (CH_2), 38.7 (CH), 29.1 (CH_2), 26.4 (CH_2), 24.9 (CH_2), 10.6 (CH_3); HRMS (ES) Exact mass calcd for C_{13}H_{20}NO_2 [M+H]^+: 246.1489, found: 246.1487.

Using TfOH: To a solution of enamide 180a (49 mg, 0.20 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added TfOH (1 µL, 0.01 mmol) and the mixture was allowed to warm slowly to −20 °C over 3.5 h. The reaction was quenched with saturated aqueous NaHCO_3 solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (MgSO_4) and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the tetrahydronaphthalene 200 (43 mg, 86%) as a colourless oil that displayed spectroscopic data identical to those observed previously.

(±)-(3aS,4S,7aS)-2-Methyl-4-(2-oxooxazolidin-3-yl)-5-phenyl-3a,4,7,7a-tetrahydro-isoindole-1,3-dione (201)

![Diagram](image.png)

To a solution of dienamide 183f (107 mg, 0.50 mmol) in THF (2.5 mL) was added a solution of N-methylmaleimide 202 (56 mg, 0.50 mmol) in THF (2 mL + 0.5 mL rinse). The mixture was stirred at room temperature for 40 h and the solvent was removed in vacuo. Purification of the residue by column chromatography (25% EtOAc/hexane→75% EtOAc/hexane) gave the Diels-Alder product 201 as a colourless solid (145 mg, 89%). Slow diffusion of hexane into a solution of 201 in EtOAc provided colourless crystals that were suitable for X-ray diffraction.
R_f = 0.11 (25% EtOAc/hexane); m.p. 62-64 °C; IR (CHCl_3) 2974, 1749 (C=O), 1518, 1408, 1344, 1227, 1109, 1038, 864, 729 cm^{-1}; ¹H NMR (360 MHz, CDCl_3) δ 7.36-7.26 (5H, m), 6.44 (1H, dd, J = 5.5, 3.7 Hz), 5.50 (1H, d, J = 7.3 Hz), 4.09-4.04 (2H, m), 3.50 (2H, dd, J = 9.7, 7.3 Hz), 3.29-3.20 (2H, m), 3.09 (1H, ddd, J = 8.2, 8.1, 6.3 Hz), 3.01 (3H, s), 2.87-2.70 (2H, m); ¹³C NMR (62.9 MHz, CDCl_3) δ 179.3 (C), 175.9 (C), 158.0 (C), 138.1 (C), 134.4 (C), 128.9 (2 × CH), 128.1 (CH), 127.5 (CH), 125.5 (2 × CH), 61.9 (CH_2), 48.5 (CH), 43.6 (CH), 37.0 (CH), 24.7 (CH_3), 22.6 (CH_2); HRMS (ES) Exact mass calcd for C_{18}H_{18}N_2O_4Na [M+Na]^+: 349.1159, found: 349.1158.

3-[(Z)-5-Hydroxy-5-(4-methoxyphenyl)-2-phenylpent-1-enyl]oxazolidin-2-one (203)

To a solution of dienamide 183f (107 mg, 0.40 mmol), p-anisaldehyde (49 µL, 0.40 mmol) and Ni(acac)_2 (5.1 mg, 0.02 mmol) in THF (2.0 mL) at 0 °C was added Et_2Zn (1.0 M in hexane, 0.80 mL, 0.80 mmol) over 1 min and the reaction was then stirred at room temperature for 18 h. The reaction was quenched carefully with saturated aqueous NH_4Cl solution (10 ml) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (MgSO_4) and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) gave the homoallylic alcohol 203 (104 mg, 74%) as a colourless oil. R_f = 0.30 (50% EtOAc/hexane); IR (film) 2951, 2252, 1747 (C=O), 1666, 1512, 1481, 1410, 1248, 1036, 910, 739 cm^{-1}; ¹H NMR (360 MHz, CDCl_3) δ 7.36-7.26 (3H, m, ArH), 7.23-7.17 (2H, m, ArH), 6.87 (2H, dm, J = 8.7 Hz, ArH), 6.57 (1H, s, =CH), 4.62 (1H, dd, J = 7.6, 5.8 Hz, CHO), 4.13 (2H, app t, J = 8.1 Hz, CH_2O), 3.81 (3H, s, OCH_3), 3.09-2.99 (2H, m, CH_3N), 2.52-2.43 (1H, m, =CHCH_2), 2.41-2.33 (1H, m, =CHCH_2), 1.88-1.78 (1H, m, CH_2CHOH), 1.74-1.64 (1H, m, CH_2CHOH), 1.61 (1H, br s, OH); ¹³C NMR (62.9 MHz, CDCl_3) δ 159.0 (C), 157.2 (C), 138.6 (C), 136.6 (C), 129.1 (2 × CH), 128.1 (2 × CH), 127.4 (CH), 127.1 (2 × CH), 125.8 (C), 120.8 (CH), 113.8 (2 × CH), 73.3 (CH), 62.4 (CH_2), 55.2 (CH_3), 45.0 (CH_2), 37.3

6.0 Experimental
(CH₂), 33.9 (CH₂); HRMS (ES) Exact mass calcd for C₂₁H₂₃NO₄Na [M+Na]+: 376.1519, found: 376.1517.
6.2 Rhodium-Catalysed Carbometallation of Ynamides with Organoboron Reagents

General Procedure H

$$\text{Ar}^+\text{CH}_2\text{CH}_2\text{Ge}^\circ\text{C}_{6}\text{H}_{12} \quad \text{Ar}^+\text{CH}_2\text{CH}_2\text{Ge}^\circ\text{C}_{6}\text{H}_{12} \quad \text{Ar}^+\text{CH}_2\text{CH}_2\text{Ge}^\circ\text{C}_{6}\text{H}_{12}$$

A solution of the appropriate ynamide (0.40 mmol), the organoboron reagent (1.0–2.0 equiv), and [Rh(cod)(MeCN)\textsubscript{2}]BF\textsubscript{4} (12 mg, 0.032 mmol) in THF (2 mL) and H\textsubscript{2}O (100 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous NaHCO\textsubscript{3} solution (5 mL) was added and the mixture was extracted with CH\textsubscript{2}Cl\textsubscript{2} (3 × 10 mL). The combined organic layers were dried (MgSO\textsubscript{4}), filtered, and concentrated in vacuo. Purification of the residue by column chromatography gave the desired enamide.

3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-phenylbut-1-enyl]oxazolidin-2-one (229a)

The General Procedure H was followed using ynamide 178c (108 mg, 0.40 mmol) and phenylboronic acid (98 mg, 0.80 mmol). Purification by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave an 8:1 inseparable mixture of the enamide 229a and the imide 231 as a pale orange oil (96 mg, 63%, adjusted yield of 229a).

Data for 229a: R\textsubscript{f} = 0.78 (60% EtOAc/hexane); IR (film) 2928, 2857, 1755 (C=O), 1653, 1471, 1297, 1257, 1042, 733 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \delta 7.35-7.25 (5H, m, ArH), 6.61 (1H, s, =CH), 4.43 (2H, app dd, J = 9.0, 6.9 Hz, CH\textsubscript{2}O), 4.13 (2H, app dd, J = 9.0, 6.9 Hz, CH\textsubscript{2}N), 3.61 (2H, t, J = 6.5 Hz, CH\textsubscript{2}OSi), 2.83 (2H, t, J = 6.5 Hz, =CCH\textsubscript{2}), 0.84 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), −0.05 (6H, s, Si(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \delta 157.3 (C), 140.5 (C), 128.3 (2 × CH), 127.2 (CH), 126.8 (2 × CH), 126.3 (C), 123.8 (CH), 62.4 (CH\textsubscript{2}), 61.1 (CH\textsubscript{2}), 46.2 (CH\textsubscript{2}), 32.7 (CH\textsubscript{2}), 25.8 (3 × CH\textsubscript{3}), 18.2 (C), −5.5 (2 × CH\textsubscript{3}); HRMS (ES) Exact mass calcd for C\textsubscript{19}H\textsubscript{30}NO\textsubscript{3}Si [M+H]\textsuperscript{+}: 348.1989, found: 348.1992.

6.0 Experimental

152
3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-(4-
metHoxypHenyl)but-1-enyl]oxazolidin-2-one (229b)

The General Procedure H was followed using ynamide 178c (108 mg, 0.40 mmol) and 4-methoxyphenylboronic acid (122 mg, 0.80 mmol). Purification by column chromatography (15% EtOAc/hexane) gave a 16:1 inseparable mixture of the enamide 229b and the imide 231 as a pale orange oil (119 mg, 75%, adjusted yield of 229b).

Data for 229b: R\textsubscript{f} = 0.72 (60% EtOAc/hexane); IR (film) 2929, 2857, 1747 (C=O), 1654, 1470, 1300, 1248, 1037, 733 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.26 (2H, d, \(J = 8.8\) Hz, ArH), 6.85 (2H, d, \(J = 8.8\) Hz, ArH), 6.50 (1H, s, =CH), 4.42 (2H, app dd, \(J = 8.9, 7.0\) Hz, CH\textsubscript{2}O), 4.08 (2H, app dd, \(J = 8.9, 7.0\) Hz, CH\textsubscript{2}N), 3.81 (3H, s, OCH\textsubscript{3}), 3.60 (2H, t, \(J = 6.5\) Hz, CH\textsubscript{2}OSi), 2.79 (2H, t, \(J = 6.5\) Hz, =CH\textsubscript{2}), 0.84 (9H, s, SiC(C\textsubscript{6}H\textsubscript{3})\textsubscript{3}), –0.05 (6H, s, Si(C\textsubscript{6}H\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \(\delta\) 158.9 (C), 157.4 (C), 132.7 (C), 127.9 (2 \(\times\) CH), 126.9 (C), 113.7 (2 \(\times\) CH), 62.4 (CH\textsubscript{2}), 61.1 (CH\textsubscript{2}), 55.2 (CH\textsubscript{3}), 46.4 (CH\textsubscript{2}), 32.8 (CH\textsubscript{2}), 25.8 (3 \(\times\) CH\textsubscript{2}), 18.2 (C), –5.5 (2 \(\times\) CH\textsubscript{3}); HRMS (ES) Exact mass calcd for C\textsubscript{20}H\textsubscript{32}NO\textsubscript{4}Si [M+H]\textsuperscript{+}: 378.2095, found: 378.2103.

3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-p-tolylbut-1-enyl]oxazolidin-2-one (229c)

The title compound was prepared according to the General Procedure H using ynamide 178c (108 mg, 0.40 mmol) and 4-tolylboronic acid (109 mg, 0.80 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give the enamide 229c (89 mg, 61%) as a pale orange oil.

R\textsubscript{f} = 0.81 (60% EtOAc/hexane); IR (film) 2928, 2857, 1754 (C=O), 1654, 1481, 1297, 1257, 1042, 778 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.23 (2H, d, \(J = 8.1\) Hz, ArH), 7.13 (2H, d, \(J = 8.1\) Hz, ArH), 6.57 (1H, s, =CH), 4.43 (2H, app dd, \(J = 8.9, 7.0\) Hz, CH\textsubscript{2}O), 4.11 (2H, app dd, \(J = 8.9, 7.0\) Hz, CH\textsubscript{2}N), 3.61 (2H, t, \(J = 6.5\) Hz, CH\textsubscript{2}OSi), 2.82 (2H, t, \(J = 6.5\) Hz, =CH\textsubscript{2}), 2.35 (3H, s, ArCH\textsubscript{3}), 0.85 (9H, s, SiC(CH\textsubscript{3})\textsubscript{3}), –0.04 (6H, s, Si(CH\textsubscript{3})\textsubscript{2}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \(\delta\) 157.4 (C), 137.4 (C), 136.9 (C), 129.0 (2 \(\times\) CH), 126.7 (2 \(\times\) CH), 126.5 (C), 123.1 (CH), 62.4 (CH\textsubscript{2}), 61.2 (CH\textsubscript{2}), 46.3 (CH\textsubscript{2}), 32.7 (CH\textsubscript{2}), 25.8 (3 \(\times\) CH\textsubscript{3}), 21.0 (CH\textsubscript{3}), 18.2 (C), –
6.0 Experimental

5.5 (2 × CH₃); HRMS (ES) Exact mass calcd for C₂₀H₃₂NO₃Si [M+H]⁺: 362.2146, found: 362.2143.

3-[E]-4-(tert-Butyldimethylsilyloxy)-2-(4-dibenzofuranyl)but-1-enyl]oxazolidin-2-one (229d)*

The enamide 229d was prepared by Donna L. Smith. The General Procedure H was followed using ynamide 178c (108 mg, 0.40 mmol) and 4-dibenzofuranboronic acid (169 mg, 0.80 mmol). Purification by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave a 13:1 inseparable mixture of the enamide 229d and the imide 231 as a cream solid (84 mg, 46%, adjusted yield of 229d).

Data for 229d: R_f = 0.49 (50% EtOAc/hexane); m.p. 88-91 °C; IR (CHCl₃) 2954, 2857, 1759 (C=O), 1655, 1404, 1226, 1187, 1090, 837 , 750 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.96 (1H, d, J = 7.7, ArH), 7.88 (1H, dd, J = 7.5, 1.4 Hz, ArH), 7.57 (1H, d, J = 8.2 Hz, ArH), 7.48-7.45 (1H, m, ArH), 7.38-7.34 (2H, m, ArH), 7.31 (1H, t, J = 7.6 Hz, ArH), 6.91 (1H, s, =CH), 4.51-4.47 (2H, m, OCH₂CH₂N), 3.62 (2H, t, J = 6.4 Hz, CH₂OSi), 3.11 (2H, t, J = 6.4 Hz, =CC₂H), 0.84 (9H, s, SiC(CH₃)₃), –0.08 (6H, s, Si(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 157.2 (C), 155.8 (C), 153.6 (C), 127.3 (CH), 127.1 (CH), 126.1 (CH), 125.7 (C), 124.4 (C), 124.1 (C), 122.9 (CH), 122.7 (CH), 120.9 (C), 120.6 (CH), 119.5 (CH), 111.7 (CH), 62.5 (CH₂), 61.2 (CH₂), 46.1 (CH₂), 32.6 (CH₂), 25.8 (3 × CH₃), 18.2 (C), –5.6 (2 × CH₃); HRMS (ES) Exact mass calcd for C₂₅H₃₃NO₄Si [M+H]⁺: 438.2095, found: 438.2091.

3-[E]-2,4-Diphenylbut-1-enyl]oxazolidin-2-one (229e)

The title compound was prepared according to the General Procedure H using ynamide 178a (86 mg, 0.40 mmol) and phenylboronic acid (98 mg, 0.80 mmol) and purified by column chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give the enamide 229e (105 mg, 89%) as a pale brown oil.

R_f = 0.71 (60% EtOAc/hexane); IR (film) 2985, 2923, 1751 (C=O), 1480, 1405, 1221, 1087, 908, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.32-7.25 (4H, m, ArH),
7.23-7.15 (3H, m, ArH), 7.11-7.03 (3H, m, ArH), 6.28 (1H, s, =CH), 4.21-4.17 (2H, m, CH₂O), 3.49-3.45 (2H, m, CH₂N), 2.78 (2H, t, J = 7.6 Hz, CH₂CH₂Ph), 2.58 (2H, t, J = 7.6 Hz, CH₂CH₂Ph); ¹³C NMR (62.9 MHz, CDCl₃) δ 157.0 (C), 141.4 (C), 140.0 (C), 131.3 (C), 128.5 (4 × CH), 128.3 (2 × CH), 127.4 (CH), 126.8 (2 × CH), 126.0 (CH), 122.5 (CH), 62.2 (CH₂), 46.9 (CH₂), 34.2 (CH₂), 31.5 (CH₂); HRMS (ES) Exact mass calcd for C₁₉H₂₃N₂O₂ [M+NH₄]⁺: 311.1754, found: 311.1748.

3-[(E)-2-(4-Acetylphenyl)-4-phenylbut-1-enyl]oxazolidin-2-one (229f)
The title compound was prepared according to General Procedure H using ynamide 178a (86 mg, 0.40 mmol) and 4-acetylphenylboronic acid (131 mg, 0.80 mmol) and purified by column chromatography (12% EtOAc/hexane→25% EtOAc/hexane) to give the enamide 229f (81 mg, 60%) as an orange solid.

Rᵣ = 0.47 (60% EtOAc/hexane); m.p. = 116-118 °C; IR (CHCl₃) 2985, 2920, 1759 (C=O), 1679 (C=O), 1479, 1404, 1212, 1087, 910, 731 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.97-7.95 (2H, m, ArH), 7.50-7.48 (2H, m, ArH), 7.30-7.27 (2H, m, ArH), 7.22-7.18 (1H, m, ArH), 7.13-7.11 (2H, m, ArH), 6.56 (1H, s, =CH), 4.34-4.31 (2H, m, CH₂O), 3.66-3.63 (2H, m, CH₂N), 2.91 (2H, t, J = 7.6 Hz, CH₂CH₂Ph), 2.68 (2H, t, J = 7.6 Hz, CH₂CH₂Ph), 2.62 (3H, s, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 197.5 (C), 156.9 (C), 145.2 (C), 141.0 (C), 135.9 (C), 128.7 (2 × CH), 128.4 (4 × CH), 128.3 (C), 126.8 (2 × CH), 126.2 (CH), 124.3 (CH), 62.3 (CH₂), 45.7 (CH₂), 34.4 (CH₂), 31.1 (CH₂), 26.6 (CH₃); HRMS (ES) Exact mass calcd for C₂₁H₂₂N₂O₃ [M+H]⁺: 336.1594, found: 336.1592.

4-{1-[1-(2-Oxooxazolidin-3-yl)meth-(E)-ylidene]-3-phenylpropyl]benzoic acid ethyl ester (229g)
The title compound was prepared according to the General Procedure H using ynamide 178a (86 mg, 0.40 mmol) and 4-ethoxycarbonylphenylboronic acid (155 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the enamide 229g (82 mg, 56%) as a pale yellow oil.
R_{f} = 0.44 \ (50\% \ \text{EtOAc/hexane}); \ \text{IR} \ (\text{film}) \ 2982, \ 2926, \ 1759 \ (\text{C} = \text{O}), \ 1712 \ (\text{C} = \text{O}), \ 1479, \ 1403, \ 1211, \ 1107, \ 910, \ 756 \ \text{cm}^{-1}; \ ^{1}H \ \text{NMR} \ (500 \ \text{MHz}, \ \text{CDCl}_{3}) \ \delta \ 8.05 \ (2H, \ d, \ J = 8.5 \ \text{Hz}, \ \text{Ar}H), \ 7.47 \ (2H, \ d, \ J = 8.5 \ \text{Hz}, \ \text{Ar}H), \ 7.30-7.27 \ (2H, \ m, \ \text{Ar}H), \ 7.22-7.19 \ (1H, \ m, \ \text{Ar}H), \ 7.13-7.11 \ (2H, \ m, \ \text{Ar}H), \ 6.54 \ (1H, \ s, \ =\text{CH}), \ 4.41 \ (2H, \ q, \ J = 7.1 \ \text{Hz}, \ \text{OCH}_{2}\text{CH}_{3}), \ 4.35-4.32 \ (2H, \ m, \ \text{OCH}_{2}\text{CH}_{2}\text{N}), \ 3.66-3.63 \ (2H, \ m, \ \text{CH}_{2}\text{N}), \ 2.92 \ (2H, \ t, \ J = 7.6 \ \text{Hz}, \ \text{CH}_{2}\text{CH}_{2}\text{Ph}), \ 2.69 \ (2H, \ t, \ J = 7.6 \ \text{Hz}, \ \text{CH}_{2}\text{CH}_{2}\text{Ph}), \ 1.43 \ (3H, \ t, \ J = 7.1 \ \text{Hz}, \ \text{OCH}_{2}\text{CH}_{3}); \ ^{13}C \ \text{NMR} \ (125.8 \ \text{MHz}, \ \text{CDCl}_{3}) \ \delta \ 166.3 \ (C), \ 156.9 \ (C), \ 144.9 \ (C), \ 141.1 \ (C), \ 129.8 \ (2 \times \ CH), \ 129.2 \ (C), \ 128.8 \ (C), \ 128.4 \ (4 \times \ CH), \ 126.6 \ (2 \times \ CH), \ 126.2 \ (CH), \ 124.0 \ (CH), \ 62.3 \ (CH_{2}), \ 60.9 \ (CH_{2}), \ 45.7 \ (CH_{2}), \ 34.3 \ (CH_{2}), \ 31.2 \ (CH_{2}), \ 14.3 \ (CH_{3}); \ \text{HRMS} \ (\text{ES}) \ \text{Exact mass calcd for C}_{22}\text{H}_{24}\text{NO}_{4}[\text{M+H}]^{+}: \ 366.1700, \ \text{found:} \ 366.1697.

3-[2,2-Diphenylvinyl]oxazolidin-2-one (229h)

The title compound was prepared according to the General Procedure H using ynamide 178b (75 mg, 0.40 mmol) and phenylboronic acid (98 mg, 0.80 mmol) and purified by column chromatography (15\% EtOAc/hexane→20\% EtOAc/hexane) to give the enamide 229h (71 mg, 67\%) as a white solid.

R_{f} = 0.72 \ (60\% \ \text{EtOAc/hexane}); \ \text{m.p.} \ 90-92 \ ^{\circ}C; \ \text{IR} \ (\text{film}) \ 2925, \ 2855, \ 1755 \ (\text{C} = \text{O}), \ 1685, \ 1444, \ 1265, \ 1213, \ 1042, \ 736 \ \text{cm}^{-1}; \ ^{1}H \ \text{NMR} \ (360 \ \text{MHz}, \ \text{CDCl}_{3}) \ \delta \ 7.39-7.35 \ (3H, \ m, \ \text{Ar}H), \ 7.29-7.22 \ (5H, \ m, \ \text{Ar}H), \ 7.20-7.17 \ (2H, \ m, \ \text{Ar}H), \ 7.15 \ (1H, \ s, \ =\text{CH}), \ 4.22-4.18 \ (2H, \ m, \ \text{CH}_{2}O), \ 3.16-3.12 \ (2H, \ m, \ \text{CH}_{2}\text{N}); \ ^{13}C \ \text{NMR} \ (62.9 \ \text{MHz}, \ \text{CDCl}_{3}) \ \delta \ 157.2 \ (C), \ 140.8 \ (C), \ 138.0 \ (C), \ 130.8 \ (2 \times \ CH), \ 128.2 \ (4 \times \ CH), \ 127.8 \ (CH), \ 127.0 \ (3 \times \ CH), \ 126.1 \ (C), \ 122.4 \ (CH), \ 62.6 \ (CH_{2}), \ 44.9 \ (CH_{2}); \ \text{HRMS} \ (\text{ES}) \ \text{Exact mass calcd for C}_{17}\text{H}_{16}\text{NO}_{2}[\text{M+H}]^{+}: \ 266.1176, \ \text{found:} \ 266.1183.

3-[(E)-2-(4-Chlorophenyl)-2-phenylvinyl]oxazolidin-2-one (229i)

The title compound was prepared according to the General Procedure H using ynamide 178b (75 mg, 0.40 mmol) and 4-chlorophenylboronic acid (125 mg, 0.80 mmol) and purified by column chromatography (15\%
EtOAc/hexane→20% EtOAc/hexane) to give the *enamide* 229i (79 mg, 65%) as a pale yellow solid.

R<sub>f</sub> = 0.57 (50% EtOAc/hexane); m.p. 136-138 °C; IR (film) 2918, 2865, 1759 (C=O), 1637, 1405, 1262, 1211, 1039, 744 cm<sup>-1</sup>; <sup>1</sup>H NMR (360 MHz, CDCl<sub>3</sub>) δ 7.39-7.37 (3H, m, ArH), 7.24-7.22 (4H, m, ArH), 7.14-7.10 (3H, m, ArH and =CH<sub>2</sub>), 4.21 (2H, app t, J = 7.9 Hz, CH<sub>2</sub>O), 3.14 (2H, app t, J = 7.9 Hz, CH<sub>2</sub>N); <sup>13</sup>C NMR (62.9 MHz, CDCl<sub>3</sub>) δ 157.2 (C), 139.4 (C), 137.5 (C), 132.8 (C), 130.8 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 128.0 (CH), 124.8 (C), 122.7 (CH), 62.6 (CH<sub>2</sub>), 44.8 (CH<sub>2</sub>); HRMS (ES) Exact mass calcd for C<sub>17</sub>H<sub>15</sub>ClNO<sub>2</sub> [M+H]<sup>+</sup>: 300.0786, found: 300.0784.

3-[(E)-2-Phenyl-2-o-tolylvinyl]oxazolidin-2-one (229j)

The title compound was prepared according to the General Procedure H using ynamide 178b (75 mg, 0.40 mmol) and o-tolylboronic acid (109 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→12% EtOAc/hexane) to give the *enamide* 229j (59 mg, 53%) as a pale yellow solid.

R<sub>f</sub> = 0.76 (60% EtOAc/hexane); m.p. 99-101 °C; IR (film) 3059, 2983, 2921, 1759 (C=O), 1636, 1443, 1308, 1219, 1038, 732 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.34-7.31 (2H, m, ArH), 7.29-7.13 (7H, m, ArH), 6.74 (1H, s, =CH<sub>2</sub>), 4.30-4.27 (2H, m, CH<sub>2</sub>O), 3.37-3.33 (2H, m, CH<sub>2</sub>N), 2.08 (3H, s, CH<sub>3</sub>); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 157.5 (C), 140.7 (C), 138.4 (C), 136.8 (C), 130.9 (CH), 130.5 (CH), 129.9 (2 × CH), 128.0 (2 × CH), 127.7 (C), 127.6 (CH), 127.4 (CH), 125.5 (CH), 124.1 (CH), 62.7 (CH<sub>2</sub>), 45.1 (CH<sub>2</sub>), 20.6 (CH<sub>3</sub>); HRMS (ES) Exact mass calcd for C<sub>18</sub>H<sub>18</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 280.1332, found: 280.1330.

3-[(E)-2-(3-Chloro-4-isopropoxyphenyl)-2-phenylvinyl]oxazolidin-2-one (229k)

The title compound was prepared according to the General Procedure H using ynamide 178b (75 mg, 0.40 mmol) and 3-chloro-4-isopropoxyphenyl boronic acid (172 mg, 0.80 mmol) and purified by column
chromatography (15% EtOAc/hexane→20% EtOAc/hexane) to give the *enamide* 229k (117 mg, 82%) as a white solid.

\[ R_f = 0.68 \text{ (60\% EtOAc/hexane); m.p. 122-124 °C; IR (film) 2978, 2920, 1761 (C=O), 1639, 1496, 1276, 1214, 1108, 732 cm}^{-1}; ^1H \text{ NMR (360 MHz, CDCl}_3\) δ 7.39-7.37 (3H, m, ArH), 7.24-7.23 (2H, m, ArH), 7.18 (1H, app d, J = 1.4 Hz, ArH), 7.06 (1H, s, =CH), 7.01 (1H, dd, J = 8.5, 1.4 Hz, ArH), 6.84 (1H, d, J = 8.5 Hz, ArH), 4.52 (1H, quint, J = 6.0 Hz, CH(CH}_3)_2), 4.19 (2H, app t, J = 8.0 Hz, CH}_2O), 3.11 (2H, app t, J = 8.0 Hz, CH}_2N); ^13C \text{ NMR (62.9 MHz, CDCl}_3\) δ 157.2 (C), 152.7 (C), 137.5 (C), 134.5 (C), 130.7 (2 × CH), 128.8 (CH), 128.3 (2 × CH), 127.9 (CH), 126.0 (CH), 124.7 (C), 124.0 (C), 121.8 (CH), 115.5 (CH), 72.1 (CH), 62.6 (CH}_2), 44.8 (CH}_2), 22.0 (2 × CH}_3); \text{HRMS (ES) Exact mass calcd for C}_20H}_{21}ClNO}_3 [M+H]^{+}: 358.1203, found: 358.1203.\]

\[ 3-[(E)-2-Naphthalen-2-yl-2-phenylvinyl]oxazolidin-2-one (229l) \]

The title compound was prepared according to General Procedure H using ynamide 178b (187 mg, 1.00 mmol), naphthalene-2-boronic acid (344 mg, 2.00 mmol), and [Rh(cod)(MeCN)_2]BF}_4 (31 mg, 0.08 mmol) in THF (5 mL) and H_2O (250 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous NaHCO}_3 solution (10 mL) was added and the mixture was extracted with CH}_2Cl}_2 (3 × 20 mL). The combined organic layers were dried (MgSO}_4), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane→25% EtOAc/hexane) gave the *enamide* 229l (161 mg, 51%) as a pale yellow solid.

\[ R_f = 0.51 \text{ (40\% EtOAc/hexane); m.p. 110-112 °C; IR (CHCl}_3\) 2921, 2855, 1750 (C=O), 1641, 1596, 1443, 1280, 1210, 1041, 733 cm}^{-1}; ^1H \text{ NMR (500 MHz, CDCl}_3\) δ 7.81-7.79 (1H, m, ArH), 7.75-7.72 (2H, m, ArH), 7.58 (1H, s, =CH), 7.46-7.39 (6H, m, ArH), 7.33-7.31 (3H, m, ArH), 4.24-4.20 (2H, m, CH}_2O), 3.20-3.16 (2H, m, \text{CH}_2N); ^13C \text{ NMR (125.8 MHz, CDCl}_3\) δ 157.2 (C), 138.2 (C), 137.9 (C), 137.5 (C), 133.3 (C), 132.4 (C), 130.9 (2 × CH), 128.3 (2 × CH), 128.0 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 126.2 (CH), 125.9 (CH and C), 125.7 (CH), 125.1 (CH), 122.8 (CH),\]

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6.0 Experimental 158
6.0 Experimental

1-[(E)-2-(4-Acetylphenyl)-2-phenylvinyl]pyrrolidin-2-one (233)

The title compound was prepared according to General Procedure H using ynamide 178h (74 mg, 0.40 mmol) and 4-acetylphenylboronic acid (131 mg, 0.80 mmol) and purified by column chromatography (20% EtOAc/hexane) to give the enamide 233 (31 mg, 25%) as an orange oil.

Rf = 0.38 (60% EtOAc/hexane); IR (film) 2958, 2926, 1681 (C=O), 1460, 1392, 1269, 1222, 907, 733, 650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.86-7.83 (2H, m, ArH), 7.46 (1H, s, =CH), 7.42-7.37 (3H, m, ArH), 7.28-7.26 (2H, m, ArH), 7.23-7.21 (2H, m, ArH), 3.00-2.88 (2H, m, CH₂N), 2.58 (3H, s, CH₃), 2.45-2.42 (2H, t, J = 7.7 Hz, CH₂C=O), 1.89 (2H, quint, J = 7.7 Hz, CH₂CH₂N); ¹³C NMR (125.8 MHz, CDCl₃) δ 197.6 (C), 175.7 (C), 146.3 (C), 138.0 (C), 135.3 (C), 130.9 (2 × CH), 128.3 (2 × CH), 128.2 (2 × CH), 127.9 (CH), 127.1 (2 × CH), 125.1 (C), 124.1 (CH), 48.2 (CH₂), 30.4 (CH₂), 26.6 (CH₃), 18.8 (CH₂); HRMS (ES) Exact mass calcd for C₂₁H₁₈N₂O₂ [M+H]^+: 316.1332, found: 316.1333.

3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-(2-furanyl)but-1-enyl]oxazolidin-2-one (234)*

The enamide 234 was prepared by Donna L. Smith. The title compound was prepared according to the General Procedure H using ynamide 178c (108 mg, 0.40 mmol) and 2-furanboronic acid (90 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the enamide 234 (89 mg, 66%) as a cream solid.

Rf = 0.67 (50% EtOAc/hexane); m.p. 54-56 °C; IR (CHCl₃) 3055, 2986, 1759 (C=O), 1654, 1421, 1403, 1265, 1226, 1082, 739, 705 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33 (1H, d, J = 1.8 Hz, ArH), 7.17 (1H, s, =CH), 6.37 (1H, dd, J = 3.3, 1.8 Hz, ArH), 6.21 (1H, d, J = 3.3 Hz, ArH), 4.44-4.41 (2H, m, OCH₂CH₂N), 4.19-4.17 (2H, m, CH₃N), 3.75 (2H, t, J = 6.5 Hz, CH₂OSi), 2.71 (2H, t, J = 6.5 Hz, =CH₂), 0.86 (9H, s, SiC(CH₃)₃), −0.02 (6H, s, Si(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ
156.9 (C), 154.2 (C), 141.3 (CH), 121.9 (CH), 112.6 (C), 111.1 (CH), 104.7 (CH), 62.4 (CH₂), 61.9 (CH₂), 45.6 (CH₂), 30.5 (CH₂), 25.8 (3 × CH₃), 18.3 (C), −5.5 (2 × CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₈NO₄Si [M+H]+: 338.1782, found: 338.1778.

3-{(1E,3E)-2-[2-(tert-Butyldimethylsilyloxy)ethyl]-4-phenylbuta-1,3-dienyl}-oxazolidin-2-one (235)

The title compound was prepared according to the General Procedure H using ynamide 1a (108 mg, 0.40 mmol) and trans-2-phenylvinylboronic acid (118 mg, 0.8 mmol) and purified by column chromatography (10% EtOAc/hexane) to give the enamide 235 (78 mg, 52%) as a pale brown solid. 

Rᵣ = 0.80 (60% EtOAc/hexane); m.p. = 130-132 °C; IR (film) 2925, 1731 (C=O), 1635, 1461, 1406, 1337, 1250, 1224, 1044, 756 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.39-7.37 (2H, m, ArH), 7.33-7.30 (2H, m, ArH), 7.22-7.19 (1H, m, ArH), 6.77 (1H, s, =CH), 6.75 (1H, d, J = 16.1 Hz, CH=CH), 6.45 (1H, d, J = 16.1 Hz, CH=CH), 4.41 (2H, app dd, J = 9.2, 6.9 Hz, CH₂O), 4.21 (2H, app dd, J = 9.2, 6.9 Hz, CH₂N), 3.77 (2H, t, J = 6.4 Hz, CH₂OSi), 2.70 (2H, t, J = 6.4 Hz, =CCH₂), 0.87 (9H, s, SiC(CH₃)₃), 0.02 (6H, s, Si(CH₃)₂); ¹³C NMR (125.8 MHz, CDCl₃) δ 156.7 (C), 137.6 (C), 130.9 (CH), 128.6 (2 × CH), 127.4 (CH), 127.0 (CH), 126.0 (2 × CH), 125.1 (CH), 120.1 (C), 62.3 (CH₂), 61.6 (CH₂), 45.5 (CH₂), 29.0 (CH₂), 25.8 (3 × CH₃), 18.3 (C), −5.4 (2 × CH₃); HRMS (ES) Exact mass calcd for C₂₁H₃₂NO₅Si [M+H]+: 374.2146, found: 374.2136.

3-[(E)-2-Phenyl-2-thiophen-2-ylvinyl]oxazolidin-2-one (236)

The title compound was prepared according to the General Procedure H using ynamide 178b (374 mg, 2.00 mmol), thiophene-2-boronic acid (511 mg, 4.00 mmol), and [Rh(cod)(MeCN)₂]BF₄ (60 mg, 0.16 mmol) in THF (10 mL) and H₂O (500 µL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous NaHCO₃ solution (20 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 25 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column
chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the enamide 236 (207 mg, 38%) as a pale yellow solid.

$R_f = 0.49$ (40% EtOAc/hexane); m.p. 83-85 °C; IR (film) 2985, 2916, 1757 (C=O), 1638, 1516, 1478, 1400, 1261, 910, 756 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42-7.38 (3H, m, ArH), 7.36-7.34 (2H, m, ArH), 7.25 (1H, s, =CH), 7.13 (1H, dd, $J = 5.1, 1.0$ Hz, ArH), 6.90 (2H, dd, $J = 5.1, 3.6$ Hz, ArH), 6.63 (1H, dd, $J = 3.6, 1.0$ Hz, ArH), 4.20-4.17 (2H, m, CH$_2$O), 3.12-3.09 (2H, m, CH$_2$N); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 156.8 (C), 145.4 (C), 137.3 (C), 130.6 (2 × CH), 128.3 (CH), 128.2 (2 × CH), 127.3 (CH), 124.6 (CH), 123.8 (CH), 121.2 (CH), 120.5 (C), 62.5 (CH$_2$), 44.8 (CH$_2$); HRMS (ES) Exact mass calcd for C$_{15}$H$_{14}$NO$_2$S [M+H]$^+$: 272.0740, found: 272.0733.

3-((1Z,3E)-2,5-diphenylpenta-1,3-dienyl)-oxazolidin-2-one (237) and 3-((E)-4-phenyl-1-[1-phenylmeth-(Z)-ylidene]-but-2-enyl)oxazolidin-2-one (238).

The title compounds were prepared according to General Procedure H using trans-3-Phenyl-1-propenyl-yllboronic acid (130 mg, 0.8 mmol) and ynamide 178b (75 mg, 0.40 mmol) and purified by column chromatography (15% EtOAc/hexane) to give the enamide 237 (45 mg, 37%) as a pale brown followed by the enamide 238 (42 mg, 18%) as an orange solid.

Data for 237: $R_f = 0.79$ (60% EtOAc/hexane); mp = 84-86 °C; IR (film) 3025, 2915, 1758 (C=O), 1641, 1479, 1403, 1329, 1243, 1037, 753 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.37-7.31 (3H, m, ArH), 7.29-7.26 (2H, m, ArH), 7.23-7.17 (3H, m, ArH), 7.13-7.11 (2H, m, ArH), 6.78 (1H, s, =CH), 6.29 (1H, d, $J = 15.3$ Hz, CH=CHCH$_2$), 5.25 (1H, dt, $J = 15.3, 6.8$ Hz, CH=CHCH$_2$), 4.13-4.10 (2H, m, CH$_2$O), 3.39 (2H, d, $J = 6.8$ Hz, CH=CHCH$_2$), 3.03-3.00 (2H, m, CH$_2$N); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 156.6 (C), 140.2 (C), 136.1 (C), 133.5 (CH), 130.5 (2 × CH), 129.5 (CH), 128.5 (2 × CH), 128.3 (2 × CH), 128.0 (2 × CH), 127.6 (CH), 126.0 (CH), 124.8 (C), 123.8

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(CH), 62.4 (CH₂), 44.8 (CH₂), 38.9 (CH₂); HRMS (ES) Exact mass calcd for C₂₀H₂₀NO₂ [M+H]⁺: 306.1494, found: 324.1485.

Data for 238: Rₚ = 0.73 (60% EtOAc/hexane); IR (film) 3028, 2921, 1753 (C=O), 1601, 1495, 1415, 1246, 1077, 1043, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.36-7.21 (10H, m, ArH), 6.53 (1H, s, =CH₂), 6.13 (1H, d, J = 15.4 Hz, CH=CHCH₂), 5.95 (1H, dt, J = 15.4, 6.8 Hz, CH=C₄H₄), 4.41-4.37 (2H, m, CH₂-O), 3.59-3.54 (4H, CH₂), 5.95 (1H, m, CH=CH₂), 5.95 (1H, m, CH₂), 5.95 (1H, m, CH₂), 5.95 (1H, m, CH₂), 5.95 (1H, m, CH₂), 5.95 (1H, m, CH₂); HRMS (ES) Exact mass calcd for C₂₀H₂₀NO₂ [M+H]⁺: 306.1489, found: 306.1486.

**With arylboronic esters**

4-{1-[1-(2-Oxooxazolidin-3-yl)methyl-(E)-ylidene]-3-phenylpropyl}benzoic acid ethyl ester (229g)

The title compound was prepared according to the General Procedure H using ynamide 178c (86 mg, 0.40 mmol) and ethyl-4-(4,4,5,5)-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoate (239) (220 mg, 0.80 mmol) and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the enamide 229g (77 mg, 53%) as a pale yellow oil.

**With boroxine reagents**

3-[(E)-4-(tert-Butyldimethylsilyloxy)-2-phenyl]but-1-enyl]oxazolidin-2-one (229a)

The title compound was prepared according to the General Procedure H using ynamide 178c (108 mg, 0.40 mmol) and triphenylboroxine (240) (124 mg, 0.40
mmol) and purified by column chromatography (10% EtOAc/hexane→15% EtOAc/hexane) to give the enamide 229a (81 mg, 58%) as a pale orange oil.

3-[(E)-2-phenylethylbuta-1,3-dienyl]oxazolidin-2-one (242).

The title compound was prepared according to General Procedure H using 2,4,6-trivinylcyclotriboroxane-pyridine complex (144 mg, 0.6 mmol) and ynamide 178a (86 mg, 0.40 mmol) and purified by column chromatography (15% EtOAc/hexane) to give the enamide 242 (54 mg, 55%) as a pale orange oil.

R<sub>t</sub> = 0.61 (50% EtOAc/hexane); IR (film) 3026, 2924, 1755 (C=O), 1640, 1494, 1419, 1248, 1091, 912, 734 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>) δ 7.31-7.28 (2H, m, ArH), 7.23-7.17 (3H, m, ArH), 6.42 (1H, s, =CH), 6.34 (1H, dd, J = 17.4, 10.9 Hz, CH<sub>2</sub>=CH), 5.29 (1H, d, J = 17.4 Hz, CH<sub>2</sub>=CH), 5.09 (1H, d, J = 10.9 Hz, CH<sub>2</sub>=CH), 4.26-4.23 (2H, m, CH<sub>2</sub>O), 3.61-3.57 (2H, m, CH<sub>2</sub>N), 2.80 (2H, t, J = 7.6 Hz, CH<sub>2</sub>CH<sub>2</sub>Ph), 2.63 (2H, t, J = 7.6 Hz, CH<sub>2</sub>CH<sub>2</sub>Ph); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>) δ 156.5 (C), 141.5 (C), 137.7 (CH), 128.5 (2 × CH), 128.4 (2 × CH), 126.2 (CH), 125.7 (CH), 125.3 (C), 111.4 (CH<sub>2</sub>), 62.2 (CH<sub>2</sub>), 45.2 (CH<sub>2</sub>), 34.8 (CH<sub>2</sub>), 27.5 (CH<sub>2</sub>); HRMS (EI) Exact mass calcd for C<sub>13</sub>H<sub>18</sub>NO<sub>2</sub> [M+H]<sup>+</sup>: 244.1332, found: 244.1336.

**Deuterium incorporation experiment**

3-[(E)-4-(tert-Butyldimethylsilyloxy)-1-deuterio-2-phenyl]but-1-enyl]oxazolidin-2-one (246)
A solution of ynamide 178c (108 mg, 0.40 mmol), triphenylboroxine (124 mg, 0.40 mmol), and [Rh(cod)(MeCN)2]BF4 (12 mg, 0.032 mmol) in THF (2 mL) and D2O (100 μL) was heated at 90 °C for 10 min under microwave irradiation. Saturated aqueous NaHCO3 solution (5 mL) was added and the mixture was extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane→15% EtOAc/hexane) gave a ca. 5:1 inseparable mixture of the enamide 246 and the imide 247 (mixture of isotopologues) as a pale orange oil (96 mg, 59%, adjusted yield of 246).

Data for 246: Rf = 0.80 (60% EtOAc/hexane); IR (film) 2929, 2857, 1753 (C=O), 1639, 1598, 1471, 1297, 1255, 1051, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 7.34-7.30 (4H, m, ArH), 7.27-7.24 (1H, m, ArH), 4.43 (2H, app dd, J = 8.8, 7.1 Hz, CH2O), 4.14 (2H, app dd, J = 9.0, 6.9 Hz, CH2N), 3.60 (2H, t, J = 6.5 Hz, CH2OSi), 2.83 (2H, t, J = 6.5 Hz, =CCH2), 0.84 (9H, s, Si(CH3)3), −0.06 (6H, s, Si(CH3)2); ¹³C NMR (125.8 MHz, CDCl3) δ 157.3 (C), 140.6 (C), 128.3 (2 × CH), 127.1 (CH), 126.8 (2 × CH), 125.6 (C), 123.5 (CD, t, JD = 26 Hz), 62.4 (CH2), 61.1 (CH2), 46.1 (CH2), 32.6 (CH2), 25.8 (3 × CH3), 18.2 (C), −5.5 (2 × CH3); HRMS (ES) Exact mass calcd for C19H26DNO2Si [M+H]+: 349.2052, found: 349.2050.
6.3 Rhodium-Catalysed Annulation of Ynamides with Bifunctional Arylboron Reagents

Reaction with 2-Formylphenylboronic Acid: General Procedure I

To a solution of the appropriate ynamide (0.20 mmol), [Rh(cod)Cl]_2 (3.9 mg, 0.008 mmol), and KOH (3.4 mg, 0.06 mmol) in 20:1 THF/H_2O (2 mL) at 0 °C was added 2-formylphenylboronic acid (260) (36 mg, 0.24 mmol) in one portion. The mixture was stirred at 0 °C for 1 h and then at room temperature until the reaction had stopped progressing as observed by TLC analysis. Saturated aqueous NaHCO_3 solution (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (MgSO_4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography or preparative TLC afforded the indenol.

Reaction with 2-Acetylphenylboronic Acid: General Procedure J

This procedure was identical to General Procedure I, except that 2-acetylphenylboronic acid (270) (39 mg, 0.24 mmol) was used in place of 2-formylphenylboronic acid.
3-(3-Hexyl-1-hydroxy-1H-inden-2-yl)oxazolidin-2-one (280a).

The title compound was prepared according to General Procedure I from ynamide 178e (39 mg, 0.20 mmol) for a total reaction time of 3 h and purified by column chromatography (20% EtOAc/hexane → 30% EtOAc/hexane) to give the indenol 280a (39 mg, 65%) as an orange oil.

Rf = 0.48 (60% EtOAc/hexane); IR (film) 3396 (OH), 2954, 2926, 1735 (C=O), 1642, 1416, 1342, 1114, 983, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.44-7.42 (1H, m, ArH), 7.31-7.26 (1H, m, ArH), 7.22-7.17 (2H, m, ArH), 5.45 (1H, s, CHOH), 4.54-4.49 (2H, m, CH₂O), 4.18-4.11 (1H, m, CH₂N), 3.99 (1H, dt, J = 8.5, 7.0 Hz, CH₂N), 3.22 (1H, br s, OH), 2.51-2.47 (2H, m, =CH₂), 1.61-1.54 (2H, m, =CH₂CH₂), 1.41-1.29 (6H, m, (CH₂)₃CH₃), 0.90 (3H, t, J = 6.8 Hz, CH₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 156.9 (C), 142.0 (C), 141.8 (C), 137.9 (C), 132.7 (C), 128.4 (CH), 126.0 (CH), 123.3 (CH), 119.2 (CH), 74.5 (CH), 62.7 (CH₂), 46.7 (CH₂), 31.6 (CH₂), 29.6 (CH₂), 28.3 (CH₂), 25.4 (CH₂), 22.6 (CH₂), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₄NO₃ [M+H⁺]: 302.1751, found: 302.1749.

3-(3-Hexyl-1-hydroxy-1-methyl-1H-inden-2-yl)oxazolidin-2-one (280b).

The title compound was prepared according to General Procedure J from ynamide 178e (39 mg, 0.20 mmol) for a total reaction time of 19 h and purified by column chromatography (10% EtOAc/hexane → 25% EtOAc/hexane) to give the indenol 280b (30 mg, 48%) as a yellow oil. (Indenol 280b was accompanied by ca. 5-7% of unidentified inseparable impurities.)

Rf = 0.57 (60% EtOAc/hexane); IR (film) 3393 (OH), 2954, 2928, 1742 (C=O), 1416, 1339, 1116, 1043, 908, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.41-7.38 (1H, m, ArH), 7.29-7.22 (3H, m, ArH), 4.53 (2H, t, J = 8.0 Hz, CH₂O), 4.26-4.19 (1H, m, CH₂N), 3.80 (1H, dt, J = 8.8, 7.9 Hz, CH₂N), 3.41 (1H, s, OH), 2.48-2.43 (2H, m, =CH₂), 1.65-1.59 (2H, m, =CH₂CH₂), 1.56 (3H, s, CH₃), 1.41-1.28 (6H, m (CH₂)₃CH₃), 0.90 (3H, t, J = 6.6 Hz, CH₂CH₂CH₃); ¹³C NMR (90.6 MHz, CDCl₃)
δ 157.3 (C), 147.4 (C), 139.9 (C), 139.4 (C), 137.4 (C), 128.4 (CH), 126.9 (CH), 121.4 (CH), 120.0 (CH), 80.4 (C), 63.1 (CH2), 47.1 (CH2), 31.6 (CH2), 29.6 (CH2), 27.7 (CH2), 25.5 (CH2), 23.4 (CH3), 22.6 (CH2), 14.1 (CH3); HRMS (ES) Exact mass calc’d for C19H29N2O3 [M+NH4]+: 333.2173, found: 333.2173.

3-{3-[2-(tert-Butyldimethylsilyloxy)ethyl]-1-hydroxy-1H-inden-1-yl}oxazolidin-2-one (280c).

The title compound was prepared according to General Procedure I from ynamide 178c (54 mg, 0.20 mmol) for a total reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) to give the indenol 280c (62 mg, 82%) as a yellow oil.

Rf = 0.54 (60% EtOAc/hexane); IR (film) 3383 (OH), 2975, 2929, 1740 (C=O), 1471, 1415, 1093, 909, 837, 732 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.46-7.43 (1H, m, ArH), 7.28 (1H, dt, J = 7.4, 1.0 Hz, ArH), 7.20 (1H, dd, J = 7.4, 1.0 Hz, ArH), 7.17-7.14 (1H, m, ArH), 5.58 (1H, s, CHOH), 4.53-4.48 (2H, m, NCH₂CH₂O), 4.37-4.30 (1H, m, CH₂N), 4.14-4.08 (1H, m, CH₂N), 3.88-3.77 (2H, m, CH₂OSi), 2.81-2.76 (2H, m, =CCH₂), 0.85 (9H, s, SiC(CH₃)₃), −0.02 (3H, s, SiCH₃), −0.03 (3H, s, SiCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 156.8 (C), 142.1 (C), 141.1 (C), 140.3 (C), 128.5 (CH), 125.8 (CH), 125.7 (C), 123.4 (CH), 118.7 (CH), 74.6 (CH), 62.8 (CH₂), 61.2 (CH₂), 46.8 (CH₂), 28.8 (CH₂), 25.8 (3 × CH₃), 18.3 (C), −5.5 (2 × CH₃); HRMS (ES) Exact mass calc’d for C₂₀H₃₀NO₄Si [M+H]+: 376.1939, found: 376.1940.

3-{3-[2-(tert-Butyldimethylsilyloxy)ethyl]-1-hydroxy-1H-inden-1-yl}oxazolidin-2-one (280d).

The title compound was prepared according to General Procedure J from ynamide 178c (54 mg, 0.20 mmol) for a total reaction time of 18 h and purified by column chromatography (15% EtOAc/hexane→40% EtOAc/hexane) to give the indenol 280d (62 mg, 48%) as a red oil. (Indenol 280d was accompanied by ca. 5% of unidentified inseparable impurities.)

Rf = 0.50 (60% EtOAc/hexane); IR (film) 3407 (OH), 2954, 2928, 1757 (C=O), 1471, 1413, 1095, 916, 836, 729 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.40-7.38 (1H, m, ArH), 7.28-7.23 (3H, m, ArH), 4.54-4.50 (2H, m, NCH₂CH₂O), 4.32 (1H, dt, J =
9.0, 7.3 Hz, CH$_2$N), 3.94-3.81 (3H, m, CH$_2$N and CH$_2$OSi), 3.64 (1H, s, OH), 2.76-2.71 (2H, m, =CCH$_3$), 0.86 (9H, s, Si(CH$_3$)$_3$), −0.01 (6H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (90.6 MHz, CDCl$_3$) δ 157.4 (C), 147.2 (C), 141.5 (C), 139.8 (C), 133.6 (C), 128.4 (CH), 126.9 (CH), 121.4 (CH), 120.0 (CH), 80.4 (C), 63.2 (CH$_2$), 61.0 (CH$_2$), 47.4 (CH$_2$), 29.2 (CH$_2$), 25.9 (3 × CH$_3$), 23.4 (CH$_3$), 18.3 (C), −5.4 (2 × CH$_3$); HRMS (ES) Exact mass calcd for C$_{21}$H$_{35}$N$_2$O$_4$Si [M+NH$_4$]$^+$: 407.2361, found: 407.2358.

3-(1-Hydroxy-2-phenethyl-3H-inden-1-yl)oxazolidin-2-one (280e). The title compound was prepared according to General Procedure I from ynamide 178a (54 mg, 0.20 mmol) for a total reaction time of 3 h and purified by column chromatography (10% EtOAc/hexane→40% EtOAc/hexane) to give the indenol 280e (43 mg, 67%) as a yellow oil.

R$_f$ = 0.38 (60% EtOAc/hexane); IR (film) 3395 (OH), 2922, 1732 (C=O), 1603, 1478, 1418, 1262, 1088, 912, 733 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.43 (1H, dd, $J$ = 7.2, 0.6 Hz, ArH), 7.34-7.14 (8H, m, ArH), 5.30 (1H, s, CH$_2$OH), 4.33-4.21 (2H, m, CH$_2$O), 3.74-3.07 (1H, m, CH$_2$N), 3.39 (1H, app dt, $J$ = 8.7, 6.2 Hz, CH$_2$N), 2.98-2.84 (3H, m, CH$_2$CH$_2$Ph and OH), 2.82-2.80 (2H, m, CH$_2$CH$_2$Ph); $^{13}$C NMR (90.6 MHz, CDCl$_3$) δ 156.4 (C), 141.8 (C), 141.6 (C), 141.4 (C), 138.7 (C), 131.0 (C), 128.6 (3 × CH), 128.3 (2 × CH), 126.1 (2 × CH), 123.4 (CH), 119.1 (CH), 74.5 (CH), 62.6 (CH$_2$), 46.1 (CH$_2$), 33.9 (CH$_3$), 27.4 (CH$_2$); HRMS (ES) Exact mass calcd for C$_{20}$H$_{23}$N$_2$O$_3$ [M+NH$_4$]$^+$: 339.1703, found: 339.1706.

3-(1-Hydroxy-1-methyl-3-phenethyl-1H-inden-2-yl)oxazolidin-2-one (280f). The title compound was prepared according to General Procedure J from ynamide 178a (43 mg, 0.20 mmol) for a total reaction time of 21 h and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give the indenol 280f (30 mg, 45%) as a yellow oil.

R$_f$ = 0.43 (60% EtOAc/hexane); IR (film) 3434 (OH), 2898, 1747 (C=O), 1602, 1415, 1344, 1217, 1095, 904, 725 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.42-7.40 (1H, m, ArH), 7.34-7.24 (5H, m, ArH), 7.20-7.13 (3H, m, ArH), 4.35-4.23 (2H, m,
3-(1-Hydroxy-3-phenyl-1H-inden-2-yl)oxazolidin-2-one (280g).

The title compound was prepared according to General Procedure I from ynamide 178b (37 mg, 0.20 mmol) for a total reaction time of 3 h. Purification was conducted using preparative TLC (60% EtOAc/hexane) to give a 9:1 mixture of inseparable regioisomers of the indenol 280g (41 mg, 70%) as a yellow oil.

Rf = 0.51 (60% EtOAc/hexane); IR (film) 3384 (OH), 2925, 1752 (C=O), 1411, 1334, 1228, 1111, 1041, 864, 731 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.54-7.51 (1H, m, ArH), 7.46-7.37 (5H, m, ArH), 7.22-7.20 (2H, m, ArH), 6.87-6.85 (1H, m, ArH), 5.92 (1H, d, \(J = 4.6\) Hz, CHOHH), 4.36 (1H, d, \(J = 4.6\) Hz, CHOHH), 4.32 (2H, t, \(J = 8.0\) Hz, CH\(_2\)O), 3.54-3.93 (2H, m, CH\(_2\)N); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 156.9 (C), 143.1 (C), 140.1 (C), 140.0 (C), 133.4 (C), 129.7 (2 \(\times\) CH), 128.9 (C), 128.4 (3 \(\times\) CH), 128.3 (CH), 125.8 (CH), 123.5 (CH), 119.5 (CH), 74.8 (CH), 63.2 (CH\(_2\)), 46.7 (CH\(_2\)); HRMS (ES) Exact mass calcd for C\(_{18}\)H\(_{16}\)NO\(_3\) [M+H]\(^{+}\): 294.1125, found: 294.1125.

3-(1-Hydroxy-1-methyl-3-phenyl-1H-inden-1-yl)oxazolidin-2-one (280h).

The title compound was prepared according to General Procedure J from ynamide 178b (37 mg, 0.20 mmol) for a total reaction time 17 h and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the indenol 280h (37 mg, 60%) as a yellow oil. (Indenol 280h was accompanied by ca. 5-7% of unidentified inseparable impurities.)
R_f = 0.53 (60% EtOAc/hexane); IR (film) 3387 (OH), 2975, 2923, 1730 (C=O), 1413, 1348, 1039, 909, 732 cm^{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \delta 7.51-7.43 (6H, m, ArH), 7.30-7.21 (2H, m, ArH), 7.08-7.06 (1H, m, ArH), 5.83 (1H, s, OH), 4.40 (1H, app td, J = 9.0, 7.3 Hz, \text{CH}_2O), 4.32 (1H, app td, J = 9.0, 6.7 Hz, \text{CH}_2O), 3.58 (1H, app dt, J = 9.3, 7.3 Hz, \text{CH}_2N), 3.29 (1H, app dt, J = 9.2, 6.7 Hz, \text{CH}_2N), 1.69 (3H, s, \text{CH}_3); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \delta 158.3 (C), 146.4 (C), 141.0 (C), 139.9 (C), 133.0 (C), 131.8 (C), 128.9 (2 \times CH), 128.8 (2 \times CH), 128.6 (CH), 128.2 (CH), 127.0 (CH), 121.8 (CH), 120.2 (CH), 80.0 (C), 63.9 (CH\textsubscript{2}), 47.1 (CH\textsubscript{2}), 24.2 (CH\textsubscript{3}); HRMS (ES) Exact mass calcd for C\textsubscript{19}H\textsubscript{21}N\textsubscript{2}O\textsubscript{3} [M+NH\textsubscript{4}]^{+}: 325.1547, found: 325.1547.

1-(1-Hydroxy-3-phenyl-1\textsubscript{H}-inden-2-yl)-3-methylimidazolidin-2-one (280i).

The title compound was prepared according to General Procedure I from ynamide 178g (40 mg, 0.20 mmol) for a total reaction time of 3 h. Purification was conducted using preparative TLC (60% EtOAc/hexane) to give the indenol 280i (49 mg, 80%) as a red oil.

R_f = 0.44 (60% EtOAc/hexane); IR (film) 3360 (OH), 2884, 1690 (C=O), 1594, 1469, 1404, 1280, 1188, 1092, 733 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \delta 7.51 (1H, app d, J = 6.1 Hz, ArH), 7.43-7.36 (5H, m, ArH), 7.18-7.11 (2H, m, ArH), 6.77 (1H, app d, J = 6.1 Hz, ArH), 5.83 (1H, s, \text{CHOH}), 5.51 (1H, br s, \text{CHOH}), 3.34-3.23 (4H, m, N\text{CH}_2\text{CH}_2\text{N}), 2.87 (3H, s, CH\textsubscript{3}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \delta 158.5 (C), 144.3 (C), 142.7 (C), 139.7 (C), 134.7 (C), 130.1 (2 \times CH), 128.2 (CH), 128.1 (2 \times CH), 127.6 (CH), 124.7 (CH), 123.2 (CH), 121.0 (C), 118.6 (CH), 75.1 (CH), 45.1 (CH\textsubscript{2}), 44.2 (CH\textsubscript{2}), 31.1 (CH\textsubscript{3}); HRMS (ES) Exact mass calcd for C\textsubscript{19}H\textsubscript{19}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}: 307.1441, found: 307.1442.

(1-Hydroxy-3-phenyl-1\textsubscript{H}-inden-2-yl)phenylcarbamic acid tert-butyl ester (281) and (3-hydroxy-2-phenyl-3\textsubscript{H}-inden-1-yl)phenylcarbamic acid tert-butyl ester (282)
General Procedure I was followed using ynamide 179a (59 mg, 0.20 mmol) for a total reaction time of 4 h. Purification by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave a 1.7:1 inseparable mixture of indenols 281 and 282 along with small quantities of unidentified inseparable impurities (68 mg, 85%, unadjusted yield) as a yellow foam, R_f = 0.61 (40% EtOAc/hexane); IR (CHCl_3) 3406 (OH), 2981, 2927, 1707 (C=O), 1493, 1367, 1305, 1154, 908, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl_3) (major diastereomer) δ 7.80 (1H, d, J = 7.4 Hz, ArH), 7.69 (1H, d, J = 7.6 Hz, ArH), 7.61 (1H, d, J = 8.1 Hz, ArH), 7.57-7.54 (1H, m, ArH), 7.45-7.05 (10H, m, ArH), 6.81 (1H, d, J = 7.4 Hz, ArH), 5.73 (1H, d, J = 8.6 Hz, CHO), 2.05 (1H, d, J = 8.6 Hz, OH), 1.11 (9H, s, C(CH₃)₃); diagnostic peaks of the minor diastereomer were observed at: δ 5.58 (1H, d, J = 9.9 Hz, CHO), 1.36 (9H, s, C(CH₃)₃); ¹³C NMR (125.8 MHz) Due to the presence of unidentified inseparable impurities, the carbon NMR peaks are not listed here; LRMS (ES) 422 ([M+Na]^+, 100).

Regiochemical Determinations

The regioselectivity of annulation of ynamide 178c with arylboronic acid 260 was established through X-ray crystallography of a derivative 288 of the resulting indene 280c, which was prepared as follows:
To a solution of indenol 280c (60 mg, 0.17 mmol) and TMEDA (15 μL, 0.10 mmol) in CH₂Cl₂ (1.5 mL) at –78 °C was added 4-chlorobenzoyl chloride (23 μL, 0.18 mmol). The mixture was stirred at –78 °C for 30 min and then slowly allowed to warm to room temperature overnight. The reaction was quenched with saturated aqueous NaHCO₃ solution (2 mL), and the mixture was extracted with CH₂Cl₂ (3 × 2 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave the 4-chlorobenzoate ester 288 (78 mg, 89%) as a colourless solid. Recrystallisation of 288 from CH₂Cl₂/heptane gave colourless crystals suitable for X-ray diffraction.

R₁ = 0.72 (40% EtOAc/hexane); IR (CHCl₃) 2954, 2928, 1758 (C=O), 1722 (C=O), 1471, 1462, 1094, 910, 837, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.98 (2H, app d, J = 8.6 Hz, ArH), 7.47 (1H, d, J = 7.3 Hz, ArH), 7.41 (2H, app d, J = 8.6 Hz, ArH), 7.37-7.31 (2H, m, ArH), 7.20 (1H, dt, J = 7.3, 1.9 Hz, ArH), 6.77 (1H, s, CHOCOAr), 4.42 (2H, app t, J = 7.9 Hz, NCH₂CH₂O), 4.15-4.08 (1H, m, NCH₂), 3.97-3.84 (3H, m, CH₂N and CH₂OSi), 2.84 (2H, t, J = 6.7 Hz, =CCH₂), 0.88 (9H, s, SiC(CH₃)₃), 0.03 (3H, s, Si(CH₃)₂), 0.02 (3H, s, Si(CH₃)₂); ¹³C NMR (90.6 MHz, CDCl₃) δ 165.9 (C), 156.0 (C), 142.3 (C), 139.8 (C), 138.9 (C), 136.6 (C), 135.5 (C), 131.2 (2 × CH), 129.2 (CH), 128.8 (2 × CH), 127.9 (C), 126.6 (CH), 124.6 (CH), 120.1 (CH), 74.6 (CH), 62.5 (CH₂), 60.9 (CH₂), 46.9 (CH₂), 29.2 (CH₂), 25.8 (3 ×
CH₃), 18.3 (C), −5.4 (2 × CH₃); HRMS (ES) Mass calcd for C₂₇H₃₃ClNO₅Si [M+H]⁺: 514.1811, found: 514.1799.

**Preparation of Chiral Dienes**

(1R,4R,7R)-Methyl-7-isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylate (L1)¹¹⁶a

To a solution of (R)-α-phellandrene (~70% chemical purity, 2.86 g, 10.5 mmol) and methyl propiolate (840 mg, 10.0 mmol) in CH₂Cl₂ (10 mL) was added Me₂AlCl (1.0 M in hexane, 10 mL, 10.0 mmol) slowly at 0°C. After stirring at 0 °C for 6 h, the mixture was quenched with a saturated aqueous solution of Rochelles’ salt (15 mL) and extracted with Et₂O (3 × 10 mL). The combined organic layer was dried over MgSO₄, filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (1% EtOAc/hexane) gave the *ester L1* (1.54 g, 67%) as a colourless oil.

Rᵣ = 0.42 (20% EtOAc/hexane); [α]₂⁰D −11.4 (c 0.95, CHCl₃); lit [α]₂⁰D −9.0 (c 2.96, CHCl₃); IR (CHCl₃) 2958, 2929, 1732 (C=O), 1604, 1512, 1469, 1228, 981, 861, 733 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.29 (1H, dd, J = 6.3, 1.6 Hz, =C₂H), 5.81 (1H, d, J = 5.9 Hz, =CH), 4.08 (1H, app dt, J = 6.3, 1.6 Hz, =CHCH), 3.73 (3H, s, OC₂H₃), 3.39 (1H, app dd, J = 6.1, 2.1 Hz, =CHCH), 1.83 (3H, d, J = 1.6 Hz, =CH₂H₂), 1.56 (1H, ddd, J = 11.4, 8.5, 2.8 Hz), 1.22-1.06 (2H, m), 0.99 (3H, d, J = 6.1 Hz, CH(CH₃)₂), 0.97-0.96 (1H, m), 0.82 (3H, d, J = 6.1 Hz, CH(CH₃)₂); ¹³C NMR (90.6 MHz, CDCl₃) δ 170.4 (C), 148.9 (CH), 143.1 (C), 140.5 (C), 124.1 (C), 47.7 (CH), 44.2 (CH), 39.3 (CH), 33.7 (CH), 31.4 (CH₂), 21.8 (CH₃), 21.3 (CH₃), 18.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₁₇O₂ [M–H]⁻: 205.1234, found: 205.1232.
(1R,4R,7R)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (L2)

To a solution of L1 (5.00 g, 22.7 mmol) in MeOH (200 mL) at 0 °C was added 1.0 M NaOH solution (100 mL, 100 mmol). The mixture was warmed to room temperature over 15 min and then heated at 50 °C for 9 h. After being cooled to 0 °C, the mixture was acidified to pH 2 with 1.0 M HCl solution, diluted with H2O (100 mL), and extracted with Et2O (3 × 150 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (1% EtOAc/hexane → 20% EtOAc/hexane) gave the carboxylic acid L2 (2.76 g, 59%) as a colourless solid.

Rf = 0.12 (40% EtOAc/hexane); m.p. 62-64 °C; [α]D° –14.2 (c 0.70, CHCl3); IR (CHCl3) 3040 (OH), 2959, 1681 (C=O), 1614, 1421, 1385, 1227, 1025, 861, 741 cm⁻¹; ¹H NMR (360 MHz, CDCl3) δ 7.45 (1H, dd, J = 6.3, 6.3 Hz, =C), 5.82 (1H, d, J = 5.9 Hz, =CH), 4.06 (1H, app dt, J = 6.3, 6.3 Hz, =CHCH), 3.42 (1H, app dd, J = 6.1, 2.1 Hz, =CHCH), 1.83 (3H, d, J = 6.1 Hz, =CHCH3), 1.57 (1H, ddd, J = 11.4, 8.5, 2.8 Hz), 1.22-1.06 (2H, m), 0.99 (3H, d, J = 6.1 Hz, CH(CH3)2), 0.97-0.96 (1H, m), 0.83 (3H, d, J = 6.1 Hz, CH(CH3)2); ¹³C NMR (90.6 MHz, CDCl3) δ 170.4 (C), 148.9 (CH), 143.1 (C), 140.5 (C), 124.1 (C), 47.7 (CH), 44.2 (CH), 39.3 (CH), 33.7 (CH), 31.4 (CH2), 21.8 (CH3), 21.3 (CH3), 18.9 (CH3); HRMS (ES) Exact mass calcd for C13H17O2 [M–H]⁺: 205.1234, found: 205.1232.
(1R,4R,7R)-(7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-dien-2-yl)morpholin-4-ylmethanone (L3)

To a solution of carboxylic acid L2 (500 mg, 2.42 mmol) and DMF (42 µL, 0.55 mmol) in CH₂Cl₂ (4.5 mL) at 0 °C was added oxalyl chloride (230 µL, 2.67 mmol) dropwise over 2 min. The mixture was stirred at 0 °C for 1.5 h (until no more effervescence was observed) to give a solution of the corresponding acid chloride. To a separate mixture of morpholine (190 µL, 2.20 mmol) in CH₂Cl₂ (5 mL) and saturated aqueous Na₂CO₃ solution (5 mL) at 0 °C was added the solution of the acid chloride dropwise via cannula over 2 min. The mixture was then stirred at room temperature for 16 h. The mixture was partitioned between saturated aqueous NaHCO₃ solution (10 mL) and CH₂Cl₂ (10 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with 10% HCl solution (15 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the morpholine amide L3 (605 mg, 99%) as a colourless oil.

Rᵣ = 0.51 (40% EtOAc/hexane); [α]D₂⁰ +36.6 (c 1.20, CHCl₃); IR (film) 3054, 2966, 2869, 1636 (C=O), 1423, 1265, 1115, 1001, 896, 739 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.41 (1H, dd, J = 6.1, 1.7 Hz, =CH), 5.79 (1H, app d, J = 5.9 Hz, =CH), 3.70-3.67 (1H, m, =CHCH), 3.64-3.54 (8H, m, 2 × NCH₂CH₂O), 3.32 (1H, app td, J = 8.2, 2.3 Hz, =CHCH), 1.83 (3H, d, J = 1.5 Hz, =CHCH₃), 1.62 (1H, ddd, J = 11.6, 8.9, 3.0 Hz), 1.41-1.34 (1H, m), 1.27-1.03 (1H, m), 0.96 (3H, d, J = 6.3 Hz, CH(CH₃)₂), 0.96-0.90 (1H, m), 0.81 (3H, d, J = 6.4 Hz, CH(CH₃)₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.4 (C), 144.5 (C), 143.4 (C), 136.1 (CH), 123.4 (CH), 66.9 (2 × CH₂), 48.1 (CH), 43.3 (CH), 42.6 (CH), 33.8 (CH), 32.0 (CH₂), 21.7 (CH₃), 21.3 (CH₃), 19.1 (CH₃) (2 × CH₂ next to nitrogen were not observed); HRMS (ES) Exact mass calcd for C₁₇H₂₆NO₂ [M+H]⁺: 276.1959, found: 276.1958.
(1R,4R,7R)-(7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-dien-2-carboxylic acid diisopropylamide (L4).

To a solution of carboxylic acid L2 (70 mg, 0.34 mmol) and DMF (6 μL, 0.68 mmol) in CH₂Cl₂ (0.6 mL) at 0 °C was added oxalyl chloride (32 μL, 0.37 mmol) dropwise over 2 min. The mixture was stirred at 0 °C for 1.5 h (until no more effervescence was observed) to give a solution of the corresponding acid chloride. To a separate mixture of diisopropylamine (50 μL, 0.35 mmol) in CH₂Cl₂ (1 mL) and saturated aqueous Na₂CO₃ solution (1 mL) at 0 °C was added the solution of the acid chloride dropwise via cannula over 1 min. The mixture was then stirred at room temperature for 20 h. The mixture was partitioned between saturated aqueous NaHCO₃ solution (4 mL) and CH₂Cl₂ (4 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (3 × 4 mL). The combined organic layers were washed with 10% HCl solution (5 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (1% EtOAc/hexane→8% EtOAc/hexane) gave the diisopropyl amide L4 (57 mg, 58%) as a colourless oil.

R_f = 0.47 (20% EtOAc/Hexane); [α]_D²⁰ +28.6 (c. 0.41, CHCl₃); IR (film) 2963, 2870, 1609 (C=O), 1439, 1369, 1213, 1159, 1079, 885, 732 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.20 (1H, dd, J = 6.1, 1.6 Hz, =C[H]), 5.77 (1H, d, J = 5.8 Hz, =C[H]), 3.73 (2H, br s, 2 × NCH) 3.58 (1H, dt, J = 5.7, 1.8 Hz, CH), 3.25 (1H, app dd, J = 5.8, 2.3 Hz, CH), 1.80 (3H, d, J = 1.6 Hz, =CCH₃), 1.62 (1H, ddd, J = 11.6, 8.9, 2.9 Hz, CH), 1.50-1.32 (12H, m, 4 × CH₃), 1.27-1.11 (2H, m, CH₂), 0.94 (3H, d, J = 6.3 Hz, CH₃), 0.89 (1H, ddd, J = 11.6, 8.9, 2.9 Hz, CH), 0.79 (3H, d, J = 6.3 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 170.7 (C), 146.1 (C), 144.3 (C), 131.6 (CH), 123.5 (CH), 48.1 (CH), 43.1 (CH), 42.7 (CH), 33.9 (CH), 32.1 (CH₂), 21.7 (CH₃), 21.3 (CH₃), 20.9 (2 × CH₃), 20.8 (2 × CH₃), 19.1 (CH₃) (2 × CH next to nitrogen were not observed); HRMS (ES) Exact mass calcd for C₁₉H₃₂NO [M+H]+: 290.2478, found: 290.2449.
(1S,2S)-2-(2,5-dimethylpyrrol-1-yl)cyclohexylamine (291) \(^{\text{153}}\)

![Chemical structure of (1S,2S)-2-(2,5-dimethylpyrrol-1-yl)cyclohexylamine (291) with experimental data]

To a solution of (S,S)-diaminocyclohexane (302 mg, 2.64 mmol) in MeOH (13 mL) was added sequentially acetic acid (251 µL, 2.64 mmol) and 2,5-hexanedione (310 µL, 2.64 mmol). The mixture was heated at 50 °C and stirred for 1 h. The solution was partitioned between CH\(_2\)Cl\(_2\) (25 mL) and 1M aqueous NaOH (25 mL). The organic phase was separated, and the aqueous phase extracted three times with CH\(_2\)Cl\(_2\) (20 mL). The combined organic layers were dried over MgSO\(_4\), filtered and concentrated \textit{in vacuo}. The residue was purified by chromatography on silica gel (5% MeOH/CH\(_2\)Cl\(_2\)) to give the desired product (S,S)-291 (418 mg, 82%) as a yellow oil that displayed spectroscopic data consistent with those observed previously.\(^{\text{153}}\)

R\(_f\) = 0.57 (10% MeOH/CH\(_2\)Cl\(_2\)); IR (CHCl\(_3\)) 3224, 2947, 2858, 1717, 1380, 1004 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 5.79 (1H, br s, =CH), 5.76 (1H, br s, =CH), 3.62 (1H, dt, \(J = 6.0, 2.0\) Hz), 3.27 (1H, dt, \(J = 8.7, 2.5\) Hz), 2.44-2.38 (1H, m), 2.37 (3H, br s, ArCH\(_3\)), 2.24 (3H, br s, ArCH\(_3\)), 2.08-2.04 (1H, m), 1.92-1.79 (4H, m), 1.45-1.32 (2H, m), 1.28-1.18 (3H, m); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 129.8 (C), 126.8 (C), 107.8 (CH), 105.2 (CH), 63.9 (CH), 52.9 (CH), 35.4 (CH\(_2\)), 31.3 (CH\(_2\)), 26.2 (CH\(_2\)), 25.0 (CH\(_2\)), 15.2 (CH\(_3\)), 13.7 (CH\(_3\)).

(1R,4R,7R)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid [(1S,2S)-2-(2,5-dimethylpyrrol-1-yl)cyclohexyl]amide (L5)

![Chemical structures of (1R,4R,7R)-7-Isopropyl-5-methylbicyclo[2.2.2]octa-2,5-diene-2-carboxylic acid (L2) and (1S,2S)-2-(2,5-dimethylpyrrol-1-yl)cyclohexyl]amide (L5) with experimental data]

To a solution of carboxylic acid L2 (100 mg, 0.48 mmol) and DMF (9 µL, 0.11 mmol) in CH\(_2\)Cl\(_2\) (1.0 mL) at 0 °C was added oxalyl chloride (46 µL, 0.53 mmol)
dropwise over 2 min. The mixture was stirred at 0 °C for 1 h (until no more effervescence was observed) to give a solution of the corresponding acid chloride. To a separate mixture of amine (S,S)-291 (85 mg, 0.44 mmol) in CH$_2$Cl$_2$ (1 mL) and saturated aqueous Na$_2$CO$_3$ solution (1 mL) at 0 °C was added the solution of the acid chloride dropwise via cannula over 1 min. The mixture was then stirred at room temperature for 19 h. The mixture was partitioned between saturated aqueous NaHCO$_3$ solution (4 mL) and CH$_2$Cl$_2$ (4 mL). The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 × 4 mL). The combined organic layers were washed with 10% HCl solution (5 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the amide L5 (86 mg, 52%) as an orange solid.

$R_f = 0.57$ (40% EtOAc/Hexane); m.p. 128-129 °C; [α]$^D_{24}$ +25.8 (c 0.70, CHCl$_3$); IR (CHCl$_3$) 3322 (NH), 2934, 2866, 1660, 1631 (C=O), 1607 (C=C), 1520, 1397, 1293 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 6.64 (1H, dd, $J = 6.2, 1.9$ Hz, =CH), 5.74-5.69 (3H, m), 5.30 (1H, d, $J = 6.7$ Hz), 4.29 (1H, tdd, $J = 11.0, 6.9, 4.0$ Hz), 3.86 (1H, td, $J = 11.5, 4.5$ Hz), 3.64 (1H, dt, $J = 6.0, 2.0$ Hz), 3.25 (1H, dt, $J = 8.7, 2.5$ Hz), 2.44-2.38 (1H, m), 2.32 (3H, br s, ArCH$_3$), 2.26 (3H, br s, ArCH$_3$), 2.08-1.95 (2H, m), 1.92-1.86 (1H, m), 1.84-1.78 (1H, m), 1.77 (3H, d, $J = 6.2$ Hz, =CCH$_3$), 1.51-1.25 (4H, m), 1.07-0.95 (2H, m), 0.93 (3H, d, $J = 6.2$ Hz, CH(CH$_3$)$_2$), 0.89-0.85 (1H, m), 0.78 (3H, d, $J = 6.2$ Hz, CH(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 165.4 (C), 144.1 (C), 143.7 (C), 139.1 (CH), 127.9 (2 × C), 123.6 (CH), 107.9 (CH), 106.9 (CH), 59.2 (CH), 51.9 (CH), 47.5 (CH), 43.4 (CH), 39.9 (CH), 33.8 (CH$_2$), 33.7 (CH), 32.0 (CH$_2$), 31.6 (CH$_2$), 26.0 (CH$_2$), 24.8 (CH$_2$), 21.7 (CH$_3$), 21.2 (CH$_3$), 18.9 (CH$_3$), 14.9 (CH$_3$), 13.8 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{25}$H$_{37}$N$_2$O [M+H]$^+$: 381.2900, found: 381.2905.
3-(1-Oxo-3-phenylindan-2-yl)oxazolidin-2-one (292)

To a solution of the indenol 280g (9:1 regioisomeric mixture, 29 mg, 0.10 mmol) in CH₂Cl₂ (1 mL) at 0 °C was added Et₃N (21 µL, 0.15 mmol) in one portion, and the mixture was stirred at 0 °C for 2 h. The reaction was concentrated in vacuo and the residue was purified by column chromatography (30% EtOAc/hexane→40% EtOAc/hexane) to give the indanone 292 (23 mg, 77%) as a 4:1 inseparable mixture of diastereomers as a colourless oil.

Rₐ = 0.49 (60% EtOAc/hexane); IR (film) 2921, 1747 (C =O), 1723 (C=O), 1482, 1428, 1255, 1104, 1038, 914, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (major diastereomer) δ 7.86 (1H, d, J = 7.7 Hz, ArH), 7.65 (1H, td, J = 7.7, 1.2 Hz, ArH), 7.49 (1H, app t, J = 7.5 Hz, ArH), 7.42-7.39 (2H, m, ArH), 7.37-7.33 (1H, m, ArH), 7.27-7.23 (3H, m, ArH), 4.60 (1H, d, J = 6.5 Hz, CHCHC=O), 4.56 (1H, d, J = 6.5 Hz, CHCHC=O), 4.46-4.42 (2H, m, CH₂O), 3.74-3.69 (1H, m, CH₂N), 3.62-3.57 (1H, m, CH₂N); diagnostic peaks of the minor diastereomer were observed at: δ 7.92 (1H, d, J = 7.7 Hz, ArH), 7.76 (1H, td, J = 7.6, 1.2 Hz, ArH), 5.20 (1H, d, J = 8.1 Hz, CHCHC=O), 5.10 (1H, d, J = 8.1 Hz, CHCHC=O), 4.14-4.09 (1H, m, CH₂O); ¹³C NMR (125.8 MHz, CDCl₃) (major diastereomer) δ 199.6 (C), 158.2 (C), 153.5 (C), 140.1 (C), 135.9 (CH), 134.4 (C), 129.2 (2 × CH), 128.5 (CH), 128.1 (2 × CH), 127.8 (CH), 126.6 (CH), 123.9 (CH), 68.6 (CH), 62.4 (CH₂), 48.1 (CH), 43.7 (CH₂); HRMS (ES) Exact mass calcd for C₁₈H₁₆NO₃ [M+H]⁺: 294.1125, found: 294.1126.

The relative stereochemistry of the minor diastereomer of 292 was determined on the basis of NOESY spectral data, which displayed the following diagnostic enhancement:

A similar enhancement was absent from the major diastereomer.
3-[1-(2-Hydroxyethyl)-3-(2-oxopropyl)inden-2-yl]oxazolidin-2-one (294)

A suspension of ynamide (41 mg, 0.10 mmol) and Pd/C (10% wt, 10 mg) in EtOH (5 mL) was stirred vigorously under H₂ (1 atm) at room temperature for 4 h. The mixture was filtered through a pad of celite using EtOH as eluent and concentrated in vacuo. The residue was purified by column chromatography (40% EtOAc/hexane→80% EtOAc/hexane) to give a 3:1 inseparable mixture of indanes 294a and 294b as a colourless oil (25 mg, 83%).

Rf = 0.06 (60% EtOAc/hexanes); IR (film) 3430, 2925, 1740 (C=O), 1722 (C=O), 1483, 1423, 1388, 1256, 1037, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) (major diastereomer) δ 7.25-7.19 (3H, m, ArH), 7.02 (1H, app dd, J = 6.9, 1.1 Hz, ArH), 4.83 (1H, t, J = 5.4 Hz, CHCN), 4.11 (2H, t, J = 8.0 Hz, OCH₂CH₂N), 3.91-3.81 (3H, m, CH₂OH and CHCH₂C=O), 3.41 (1H, dt, J = 9.6, 4.7 Hz, CHCH₂CH₂OH), 2.85 (1H, dd, J = 17.8, 7.0 Hz, CH₂C=O), 2.77 (1H, dd, J = 17.8, 6.1 Hz, CH₃C=O), 2.67 (1H, dt, J = 9.6, 7.7 Hz, CH₂N), 2.60-2.55 (1H, m, CH₂N), 2.36-2.31 (1H, m, CH₂CH₂OH), 2.29 (3H, s, CH₃C=O), 1.65-1.58 (1H, m, CH₂CH₂OH); diagnostic peaks of the minor diastereomer were observed at: δ 4.47 (1H, dd, J = 6.3, 2.7 Hz, CHCN), 4.22-4.18 (2H, m, OCH₂CH₂N), 3.75-3.72 (1H, m, CHCH₂C=O), 3.55-3.51 (1H, m, CHCH₂CH₂OH), 3.23 (1H, dt, J = 9.0, 7.5 Hz, CH₂CH₂OH), 2.94-2.89 (1H, m, CH₂C=O), 2.16 (3H, s, CH₂C=O), 1.72-1.66 (1H, m, CH₂CH₂OH); ¹³C NMR (125.8 MHz, CDCl₃) (major diastereomer) δ 206.2 (C), 159.1 (C), 143.9 (C), 143.1 (C), 127.3 (4 × CH), 121.9 (CH), 121.8 (CH), 61.9 (CH and CH₂), 61.2 (CH₂), 44.1 (CH₂), 43.2 (CH), 42.0 (CH₂), 41.5 (CH), 30.2 (CH₃), 30.0 (CH₂); (minor diastereomer) δ 206.6 (C), 158.3 (C), 145.4 (C), 143.3 (C), 127.7 (CH), 127.5 (CH), 124.3 (CH), 123.1 (CH), 62.6 (CH), 62.1 (CH₂), 61.0 (CH₂), 47.2 (CH₂), 43.0 (CH₂), 42.6 (CH), 42.3 (CH), 30.5 (CH₃ and CH₂); HRMS (ES) Mass calcd for C₁₇H₂₂NO₄ [M+H]+: 304.1543, found: 304.1544.
The relative stereochemistry of the major diastereomer 294a was determined on the basis of NOESY spectral data, which displayed the following diagnostic enhancements:
6.4 Catalytic Asymmetric Dihydroxylation of Enamides

Chiral HPLC analysis was performed on an Agilent 1100 instrument. Authentic racemic samples of products for chiral HPLC assay determinations were obtained by dihydroxylation of the enamide substrates using catalytic OsO$_4$ in THF/H$_2$O, followed by reduction of the resulting $\alpha$-hydroxyaldehydes using NaBH$_4$ (except for product 332a, where reduction was not required).

**Preparation of Alkene**

2,4-Diphenyl-1-butene (333)$^{154}$

To a solution of methylphenylphosphonium bromide (2.68 g, 7.50 mmol) in THF (20 mL) at 0 °C was added $n$-BuLi (2.5 M in toluene 3.0 mL, 7.5 mmol) over 1 min, and the solution was stirred at room temperature for 30 min. A solution of 3-phenylpropiophenone (1.05 g, 5.00 mmol) in THF (8 mL + 2 mL rinse) was then added over 2 min and the mixture was heated to 50 °C for 17 h. After cooling to room temperature, the mixture was passed through a filter paper, the filtrate was poured slowly into H$_2$O (20 mL), and the mixture was extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated *in vacuo*. Purification of the residue by column chromatography (1% EtOAc/hexane) gave the alkene 333 as a colourless oil (606 mg, 58%) that displayed spectroscopic data consistent with those observed previously.$^{154}$

R$_f$ = 0.89 (40% EtOAc/hexane); IR (film) 3084, 3062, 2945, 2861, 1601, 1495, 1454, 1300, 908, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.53-7.51 (2H, m, ArH), 7.44-7.41 (2H, m, ArH), 7.37-7.35 (3H, m, ArH), 7.29-7.26 (3H, m, ArH), 5.38 (1H, s, =CH$_2$), 5.15 (1H, s, =CH$_2$), 2.92-2.83 (4H, m, CH$_2$CH$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 147.8 (C), 141.9 (C), 141.0 (C), 128.4 (2 × CH), 128.3 (4 × CH), 127.4 (CH), 126.1 (2 × CH), 125.8 (CH), 112.7 (CH$_2$), 37.2 (CH$_2$), 34.7 (CH$_2$).
General Procedure K

A solution of AD-mix-β (280 mg) in 1:1 t-BuOH/H$_2$O (2 mL) was stirred at room temperature for 10 min and then cooled to 0 °C. The appropriate enamide (0.20 mmol) in t-BuOH (1 mL) was then added and the mixture was stirred vigorously at 0 °C until the reaction had stopped progressing as observed by TLC analysis. NaBH$_4$ (45 mg, 1.20 mmol) was then added in one portion and the reaction was stirred at room temperature for 1 h. The reaction was quenched carefully with saturated aqueous NH$_4$Cl solution (20 mL) and extracted with CH$_2$Cl$_2$ (3 × 15 mL). The combined organic extracts were washed with H$_2$O (20 mL), dried (MgSO$_4$), and concentrated in vacuo. Purification of the residue by column chromatography gave the diol.

(S)-2-Phenylpropane-1,2-diol (331a).

The title compound was prepared according to the General Procedure K from enamide 180k (41 mg, 0.20 mmol) for a dihydroxylation reaction time of 22 h and purified by column chromatography (20% EtOAc/hexane→40% EtOAc/hexane) to give the diol 331a (22 mg, 72%) as a colourless oil that displayed spectroscopic data consistent with those observed previously. R$_f$ = 0.18 (40% EtOAc/hexane); [α]$_D^{20}$ +5.7 (c. 0.70, EtOH), lit.$^{136}$ [α]$_D^{20}$ −5.8 (c. 0.55, EtOH) for (R)-enantiomer of 95% ee; IR (film) 3426 (OH), 3020, 2960, 1608, 1492, 1445, 1139, 1035, 905, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.47-7.45 (2H, m, ArH), 7.40-7.37 (2H, m, ArH), 7.31-7.27 (1H, m, ArH), 3.79 (1H, dd, J = 11.1, 4.1 Hz, CH$_2$OH), 3.63 (1H, dd, J = 11.1, 7.8 Hz, CH$_2$OH), 2.73 (1H, s, OH), 2.05-2.03 (1H, m, OH), 1.54 (1H, s, CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 144.9 (C), 128.4 (2 × CH), 127.2 (CH), 125.0 (2 × CH), 74.8 (C), 71.0 (CH$_2$), 26.0 (CH$_3$). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); tr (major) = 37.1 min; tr (minor) = 46.1 min, 90% ee.
(S)-2-Phenylbutane-1,2-diol (331b). The title compound was prepared according to the General Procedure K from enamide 180l (43 mg, 0.20 mmol) for a dihydroxylation reaction time of 21 h and purified by column chromatography (20% EtOAc/hexane→40% EtOAc/hexane) to give the diol 331b (28 mg, 84%) as a colourless oil that displayed spectroscopic data consistent with those observed previously. Rf = 0.21 (40% EtOAc/hexane); [α]D20 −8.8 (c. 0.70, EtOH), lit. [α]D20 +9.0 (c. 1.20, EtOH) for (R)-enantiomer of 78% ee; IR (film) 3421 (OH), 2931, 2858, 1611, 1526, 1454, 1122, 1055, 911, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.43-7.37 (4H, m, ArH), 7.30-7.27 (1H, m, ArH), 3.85 (1H, d, J = 11.2 Hz, CH₂OH), 3.70 (1H, d, J = 11.2 Hz, CH₂OH), 2.18 (2H, br s, 2 × OH), 1.91-1.79 (2H, m, CH₂CH₃), 0.78 (3H, t, J = 7.5 Hz, CH₂C₃H₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 143.1 (C), 128.4 (2 × CH), 127.0 (CH), 125.6 (2 × CH), 77.5 (C), 70.4 (CH₂), 31.1 (CH₂), 7.4 (CH₃). Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97.5:2.5 hexane:isopropanol, 1.0 mL/min, 254 nm, 25 °C); tr (minor) = 19.3 min; tr (major) = 21.4 min, 87% ee.

(S)-1-Phenyl-1-thiophen-2-ylethane-1,2-diol (331c). The title compound was prepared according to a slight modification of the General Procedure K from enamide 236 (54 mg, 0.20 mmol) in that dihydroxylation was carried out at 0 °C for 2 h and then at room temperature for 15 h, and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the diol 331c (27 mg, 61%) as a pale yellow solid. Rf = 0.40 (40% EtOAc/hexane); m.p. 76-78 °C; [α]D20 −16.0 (c. 1.25, CHCl₃); IR (film) 3507 (OH), 3065, 2959, 1653, 1558, 1448, 1381, 1044, 907, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.53-7.51 (2H, m, ArH), 7.40-7.36 (2H, m, ArH), 7.33-7.30 (1H, m, ArH), 7.29 (1H, dd, J = 5.1, 1.2 Hz, ArH), 6.99 (1H, dd, J = 5.1, 3.6 Hz, ArH), 6.95 (1H, dd, J = 3.6, 1.2 Hz, ArH), 4.16 (1H, d, J = 11.5 Hz, CH₂OH), 4.07 (1H, d, J = 11.5 Hz, CH₂OH), 3.49 (1H, s, OH), 2.07 (1H, br s, OH); ¹³C NMR (125.8 MHz, CDCl₃) δ 148.7 (C), 142.8 (C), 128.4 (2 × CH), 127.8 (CH), 125.9 (2 × CH), 125.6 (CH), 124.8 (CH), 77.5 (C), 70.5 (CH₂); HRMS (ES) Exact mass calcd for C₁₂H₁₆NO₂S [M+NH₄]⁺: 238.0896, found: 238.0896.
Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); tr (major) = 17.4 min; tr (minor) = 18.6 min, 94% ee.

\((R)-2,4\text{-Diphenylbutane-1,2-diol (331d).}\)\(^{155}\)

\textit{From enamide 229e:} The title compound was prepared according to the General Procedure K from enamide 229e (58 mg, 0.20 mmol) for a dihydroxylation time of 19 h and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the \textit{diol 331d} (33 mg, 68%) as a colourless oil that displayed spectroscopic data consistent with those observed previously.\(^{155}\)

\(R_f = 0.48\) (40% EtOAc/hexane); \([\alpha]^{20}_D \text{ = } -37.1\) (c. 0.70, CHCl\(_3\)), lit.\(^{155}\) \([\alpha]^{23}_D \text{ = } +10.6\) (c. 0.15, EtOH) for \((S\)-enantiomer of >98% ee. IR (film) 3399 (OH), 3026, 2932, 1602, 1496, 1447, 1028, 908, 764, 700 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 7.49-7.47\) (2H, m, Ar\(H\)), 7.43-7.40 (2H, m, Ar\(H\)), 7.33-7.30 (1H, m, Ar\(H\)), 7.27-7.24 (2H, m, Ar\(H\)), 7.18-7.15 (1H, m, Ar\(H\)), 7.12-7.11 (2H, m, Ar\(H\)), 3.85 (1H, d, \(J = 11.1\) Hz, CH\(_2\)OH), 3.72 (1H, d, \(J = 11.1\) Hz, CH\(_2\)OH), 2.68 (1H, ddd, \(J = 13.5, 12.2, 5.4\) Hz, CH\(_2\)CH\(_2\)Ar), 2.36 (1H, ddd, \(J = 13.7, 11.8, 4.9\) Hz, CH\(_2\)CH\(_2\)Ar), 2.13 (1H, dddd, \(J = 38.4, 13.8, 11.8, 5.1\) Hz, CH\(_2\)CH\(_2\)Ar); \(^{13}\)C NMR (125.8 MHz, CDCl\(_3\)) \(\delta 143.0\) (C), 142.1 (C), 128.5 (2 × CH), 128.4 (2 × CH), 128.3 (2 × CH), 127.2 (CH), 125.8 (CH), 125.5 (2 × CH), 77.2 (C), 70.6 (CH\(_2\)), 40.3 (CH\(_2\)), 29.4 (CH\(_2\)). HRMS (EI) Exact mass calcd for C\(_{16}\)H\(_{22}\)O\(_2\)N [M+NH\(_4\)]\(^+\): 260.1645, found: 260.1649. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); tr (major) = 14.5 min; tr (minor) = 16.0 min, 95% ee.

\textit{From alkene 333:} The title was prepared according to a modification of the General Procedure K from alkene 333 (41 mg, 0.20 mmol) for a dihydroxylation time of 19 h and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the \textit{diol XX} (42 mg, 82%) as a colourless oil. Enantiomeric excess was determined by HPLC under the same conditions described above, which established that \((R)-331d\) was obtained in 41% ee.
(R)-3-(1-Hydroxy-1-hydroxymethyl-3-phenylpropyl)benzoic acid ethyl ester (331e).

The title compound was prepared according to a slight modification of the General Procedure K from enamide 185a (73 mg, 0.20 mmol) in that dihydroxylation was carried at out 0 °C for 2 h and then at room temperature for 5 h, and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give the *diol* 331e (44 mg, 70%) as a colourless oil.

\[ \text{Rf} = 0.26 \text{ (40\% EtOAc/hexane); [a]_D^{20} = -25.0 (c. 1.20, CHCl}_3; \text{IR (film) 3481 (OH), 3029, 2938, 1712 (C=O), 1604, 1496, 1279, 1024, 908, 733 cm}^{-1}; \text{H NMR (500 MHz, CDCl}_3) \delta 8.14 (1H, t, J = 1.6 Hz, ArH), 7.99 (1H, dt, J = 7.9, 1.6 Hz, ArH), 7.48 (1H, t, J = 7.8 Hz, ArH), 7.26-7.23 (2H, m, ArH), 7.11-7.09 (2H, m, ArH), 4.40 (2H, q, J = 7.1 Hz, OCH}_2CH}_3), 3.88 (1H, dd, J = 11.1, 4.3 Hz, CH}_2OH), 3.77 (1H, d, J = 11.1, 7.1 Hz, CH}_2OH), 2.96 (1H, s, OH), 2.68 (1H, ddd, J = 13.3, 12.3, 5.2 Hz, CH}_2Ph), 2.36 (1H, m, 1H, d, J = 13.3, 11.8, 4.9 Hz, CH}_2Ph), 2.20 (1H, m, d, J = 13.8, 11.7, 5.2 Hz, CH}_2CH}_2Ph), 1.99 (1H, br s, OH), 1.42 (2H, q, J = 7.1 Hz, OCH}_2CH}_3); \text{C NMR (125.8 MHz, CDCl}_3) \delta 166.7 (C), 143.7 (C), 141.9 (C), 130.7 (C), 130.2 (CH), 128.6 (CH), 128.4 (2 × CH), 128.2 (2 × CH), 126.6 (CH), 125.8 (CH), 77.1 (C), 70.5 (CH), 61.1 (CH), 40.3 (CH), 29.4 (CH), 14.3 (CH); \text{HRMS (ES) Exact mass calcd for C}_{19}H_{26}NO_4 [M+NH}_4]^+: 332.1856, found: 332.1853. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (major) = 20.8 min; tr (minor) = 22.3 min, 97% ee.

(R)-4-(tert-Butyldimethylsilyloxy)-2-phenylbutane-1,2-diol (331f).

The title compound was prepared according to a slight modification of the General Procedure K from enamide 229a (70 mg, 0.20 mmol) in that dihydroxylation was carried out at 0 °C for 2 h and then at room temperature for 20 h, and purified by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) to give the *diol* 331f (47 mg, 83%) as a colourless oil.

\[ \text{Rf} = 0.67 \text{ (40\% EtOAc/hexane); [a]_D^{20} = +26.2 (c. 1.60, CHCl}_3; \text{IR (film) 3442 (OH), 2955, 2884, 2858, 1471, 1447, 1101, 1069, 910, 734 cm}^{-1}; \text{H NMR (500 MHz,}} \]
CDCl$_3$ δ 7.45-7.43 (2H, m, ArH), 7.38-7.35 (2H, m, ArH), 7.29-7.26 (1H, m, ArH), 4.88 (1H, br s, OH), 3.78 (1H, app dt, $J = 10.2$, 3.9 Hz, CH$_2$OSi), 3.69-3.66 (1H, m, CH$_2$OH), 3.62-3.56 (2H, m, CH$_2$OSi and CH$_2$OH), 2.58 (1H, br s, OH), 2.41 (1H, ddd, $J = 15.2$, 11.3, 4.2 Hz, CH$_3$CH$_2$O), 1.93-1.89 (1H, m, CH$_2$CH$_2$O), 0.89 (9H, s, C(CH$_3$)$_3$), 0.02 (3H, s, Si(CH$_3$)$_2$), –0.03 (3H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 143.8 (C), 128.2 (2 × CH), 126.9 (CH), 125.4 (2 × CH), 77.9 (C), 70.8 (CH$_2$), 60.5 (CH$_2$), 38.1 (CH$_2$), 25.7 (3 × CH$_3$), 18.0 (C), –5.8 (CH$_3$), –5.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{16}$H$_{32}$NO$_3$Si [M+NH$_4$]$^+$: 314.2146, found: 314.2147. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (minor) = 11.4 min; tr (major) = 12.3 min, 97% ee.

(R)-4-(tert-Butyldimethylsilyloxy)-2-(4-methylphenyl)butane-1,2-diol (331g).

The title compound was prepared according to a slight modification of the General Procedure from enamide 229c (72 mg, 0.20 mmol) in that dihydroxylation was carried out at 0 °C for 2 h and then at room temperature for 22 h, and purified by column chromatography (5% EtOAc/hexane to 15% EtOAc/hexane) to give the diol 331g (51 mg, 82%) as a colourless oil.

R$_f$ = 0.67 (40% EtOAc/hexane); $[a]_D^{20}$ +28.8 (c. 0.90, CHCl$_3$); IR (film) 3451 (OH), 2955, 2883, 2858, 1472, 1388, 1075, 1020, 907, 778 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 7.32 (2H, d, $J = 8.2$ Hz, ArH), 7.17 (2H, d, $J = 8.2$ Hz, ArH), 4.84 (1H, br s, OH), 3.77 (1H, app dt, $J = 10.2$, 3.9 Hz, CH$_2$OSi), 3.65 (1H, d, $J = 11.2$ Hz, CH$_2$OH), 3.59 (1H, td, $J = 10.9$, 2.8 Hz, CH$_2$OSi), 3.56 (1H, d, $J = 11.2$ Hz, CH$_2$OH), 2.55 (1H, br s, OH), 2.42-2.35 (1H, m, CH$_2$CH$_2$O), 2.35 (3H, s, ArCH$_3$), 1.92-1.88 (1H, m, CH$_2$CH$_2$O), 0.89 (9H, s, C(CH$_3$)$_3$), 0.03 (3H, s, Si(CH$_3$)$_2$), –0.02 (3H, s, Si(CH$_3$)$_2$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 140.8 (C), 136.5 (C), 128.9 (2 × CH), 125.3 (2 × CH), 77.8 (C), 70.9 (CH$_2$), 60.5 (CH$_2$), 38.1 (CH$_2$), 25.7 (3 × CH$_3$), 21.0 (CH$_3$), 18.0 (C), –5.77 (CH$_3$), –5.80 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{17}$H$_{31}$O$_3$Si [M+H]$^+$: 311.2037, found: 311.2039. Enantiomeric excess was
determined by HPLC with a Chiralcel OD-H column (97.5:2.5 hexane:isopropanol, 1.0 mL/min, 230 nm, 25 °C); tr (minor) = 8.2 min; tr (major) = 9.3 min, 97% ee.

\((R)-4-(\text{tert-Butyldimethylsilyloxy})-2\text{-thiophen-2-ylbutane-1,2-diol (331h).}\)

The title compound was prepared according to the General Procedure K from enamide 183a (71 mg, 0.20 mmol) for a dihydroxylation time of 18 h and purified by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the diol 331h (52 mg, 86%) as a colourless oil.

R_f = 0.58 (40% EtOAc/hexane); [α]_D^20 +26.2 (c. 2.45, CHCl_3); IR (film) 3426 (OH), 2956, 2884, 2859, 1471, 1389, 1097, 1064, 908, 733 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 7.24 (1H, dd, J = 5.1, 1.1 Hz, ArH), 7.01 (1H, dd, J = 5.1, 3.6 Hz, ArH), 7.01 (1H, dd, J = 3.6, 1.1 Hz, ArH), 5.27 (1H, s, OMe), 3.86-3.78 (2H, m, CH_2OSi), 3.66 (1H, dd, J = 11.3, 5.7 Hz, CH_2OH), 3.62 (1H, dd, J = 11.3, 8.2 Hz, CH_2OH), 2.54 (1H, dd, J = 8.2, 5.7 Hz, CH_2OH), 2.54 (1H, ddd, J = 14.9, 10.5, 4.6 Hz, CH_2CH_2O), 1.94-1.90 (1H, m, CH_2CH_2O), 0.90 (9H, s, C(CH_3)_2), 0.05 (3H, s, Si(CH_3)_2), 0.02 (3H, s, Si(CH_3)_2); ^13C NMR (125.8 MHz, CDCl_3) δ 149.3 (C), 127.1 (CH), 124.2 (CH), 122.7 (CH), 77.5 (C), 71.2 (CH_2), 60.5 (CH_2), 38.8 (CH_2), 25.7 (3 × CH_3), 18.0 (C), –5.76 (CH_3), –5.82 (CH_3); HRMS (ES) Exact mass calcd for C_{14}H_{26}O_3NaSSi [M+Na]^+: 325.1264, found: 325.1262. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); tr (minor) = 15.3 min; tr (major) = 16.8 min, 94% ee.

\[\text{3-}[(R)-1\text{-Hydroxy-1-(hydroxymethyl)heptyl}]\text{benzoic acid ethyl ester (331i).}\]

The title compound was prepared according to a slight modification of the General Procedure K from enamide 185b (73 mg, 0.20 mmol) in that dihydroxylation was carried out a 0 °C for 2 h and then at room temperature for 7 h, and purified by column chromatography (10% EtOAc/hexane→30% EtOAc/hexane) to give the diol 331i (48 mg, 68%) as a colourless oil.

R_f = 0.43 (40% EtOAc/hexane); [α]_D^20 –3.3 (c. 0.60, CHCl_3); IR (film) 3447 (OH), 2931, 2859, 1711 (C=O), 1647, 1458, 1277, 1023, 908, 733 cm^{-1}; ^1H NMR (500 MHz, CDCl_3) δ 8–8.25 (1H, m, ArH), 7.38 (1H, d, J = 8.2 Hz, ArH), 7.25 (1H, d, J = 8.2 Hz, ArH), 4.10-4.02 (2H, m, CH_2OH), 3.86 (3H, s, OMe), 3.65 (1H, dd, J = 11.3, 5.7 Hz, CH_2OH), 3.62 (1H, dd, J = 11.3, 8.2 Hz, CH_2OH), 2.48 (1H, ddd, J = 14.9, 10.5, 4.6 Hz, CH_2CH_2O), 1.94-1.90 (1H, m, CH_2CH_2O), 1.00 (9H, s, C(CH_3)_2), 0.05 (3H, s, Si(CH_3)_2), 0.02 (3H, s, Si(CH_3)_2); ^13C NMR (125.8 MHz, CDCl_3) δ 149.3 (C), 127.1 (CH), 124.2 (CH), 122.7 (CH), 77.5 (C), 71.2 (CH_2), 60.5 (CH_2), 38.8 (CH_2), 25.7 (3 × CH_3), 18.0 (C), –5.76 (CH_3), –5.82 (CH_3); HRMS (ES) Exact mass calcd for C_{14}H_{26}O_3NaSSi [M+Na]^+: 325.1264, found: 325.1262.

6.0 Experimental

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MHz, CDCl$_3$) $\delta$ 8.08 (1H, t, $J = 1.7$ Hz, ArH), 7.96 (1H, dt, $J = 7.8$, 1.3 Hz, ArH), 7.64 (1H, ddd, $J = 7.8$, 1.9, 1.2 Hz, ArH), 7.45 (1H, t, $J = 7.8$ Hz, ArH), 4.39 (2H, q, $J = 7.1$ Hz, OCH$_2$CH$_3$), 3.87 (1H, dd, $J = 11.1$, 4.5 Hz, CH$_2$OH), 3.73 (1H, d, $J = 11.1$, 7.5 Hz, CH$_2$OH), 2.73 (1H, s, OCH$_2$), 1.87-1.77 (3H, m, (CH$_2$)$_5$CH$_3$ and OCH$_2$), 1.41 (3H, t, $J = 7.1$ Hz, OCH$_2$CH$_3$), 1.34-1.15 (7H, m, (CH$_2$)$_5$CH$_3$), 1.04-0.94 (1H, m, (CH$_2$)$_5$CH$_3$), 0.83 (3H, t, $J = 7.0$ Hz, (CH$_2$)$_5$C), 166.7 (C), 144.2 (C), 130.6 (C), 130.2 (CH), 128.4 (CH), 128.2 (CH), 126.5 (CH), 77.2 (C), 70.5 (CH$_2$), 61.1 (CH$_2$), 38.5 (CH$_2$), 31.6 (CH$_2$), 29.6 (CH$_2$), 22.9 (CH$_2$), 22.5 (CH$_2$), 14.3 (CH$_3$), 14.0 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{17}$H$_{30}$NO$_4$ [M+NH$_4$]$^+$: 312.2169, found: 312.2158. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (major) = 14.7 min; tr (minor) = 22.5 min, 96% ee.

(R)-(−)-3-Hydroxymethyl-1-phenylpentane-3-ol (331k). The title compound was prepared according to General Procedure K from enamide 180a (52 mg, 0.20 mmol) for a dihydroxylation reaction time of 7h and purified by column chromatography (20% EtOAc/hexane → 40% EtOAc/hexane) to give the diol 331k (39 mg, 96%) as a colourless oil.

$R_f = 0.18$ (40% EtOAc/hexane); [$\alpha$]$^D_{20} +2.5$ (c. 1.55, CH$_3$Cl); IR (film) 3408 (OH), 2940, 2881, 1603, 1496, 1455, 1132, 1057, 909, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.31-7.28 (2H, m, ArH), 7.22-7.18 (3H, m, ArH), 3.53 (2H, s, CH$_2$OH), 2.71-2.61 (2H, m, CH$_2$Ar), 2.25 (1H, br s, OH), 2.10 (1H, br s, OH), 1.80 (2H, ddd, $J = 6.9$, 4.9, 3.1 Hz, CH$_2$CH$_2$Ar), 1.68-1.57 (2H, m, CH$_2$CH$_3$), 0.95 (3H, t, $J = 7.6$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 144.3 (C), 128.4 (2 × CH), 128.2 (2 × CH), 125.8 (CH), 74.8 (C), 67.5 (CH$_2$), 37.2 (CH$_2$), 29.7 (CH$_2$), 28.3 (CH$_2$), 7.9 (CH$_3$). HRMS (EI) Exact mass calcd for C$_{15}$H$_{19}$NO$_2$ [M+NH$_4$]$^+$: 212.1645, found: 212.1647. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (major) = 36.3 min; tr (minor) = 38.7 min, 64% ee.
**6.0 Experimental**

**The title compound was prepared according to General Procedure K from enamide 180i (55 mg, 0.20 mmol) for a dihydroxylation reaction time of 5 h and purified by column chromatography (20% EtOAc/hexane → 40% EtOAc/hexane) to give the diol 331l (39 mg, 87%) as a colourless oil.**

Rf = 0.14 (40% EtOAc/hexane); [α]D 20 +6.6 (c. 1.50, CHCl3); IR (film) 3447 (OH), 2968, 2872, 1652, 1496, 1455, 1094, 1048, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 7.38-7.35 (2H, m, ArH), 7.33-7.30 (3H, m, ArH), 4.54 (2H, s, OCH2Ar), 3.75 (1H, ddd, J = 9.6, 8.5, 3.4 Hz, CH2OH), 3.66 (1H, ddd, J = 9.6, 8.5, 3.4 Hz, CH2OH), 3.50-3.43 (2H, m, CH2OCH2Ar), 3.24 (1H, s, OH), 2.89 (1H, br s, OH), 1.90 (1H, ddd, J = 15.1, 8.4, 3.4 Hz, CH2CH2O), 1.90 (1H, ddd, J = 15.1, 6.6, 3.4 Hz, CH2CH2O), 1.61-1.49 (2H, m, CH2CH3), 0.89 (3H, t, J = 7.6 Hz, CH3). ¹³C NMR (125.8 MHz, CDCl3) δ 137.3 (C), 128.5 (2 × CH), 127.9 (CH), 127.8 (2 × CH), 74.1 (C), 73.4 (CH2), 67.8 (CH2), 66.7 (CH2), 35.3 (CH2), 30.0 (CH2), 7.8 (CH3). HRMS (EI) Exact mass calcd for C15H19NO2 [M+H]+: 225.1485, found: 225.1486. Enantiomeric excess was determined by HPLC with a Chiralcel OD-H column (97.5:2.5 hexane:isopropanol, 1.0 mL/min, 210 nm, 25 °C); tr (minor) = 25.6 min; tr (major) = 28.2 min, 77% ee.

**Preparation of Modified AD-mix-β with Increased Loadings of K₂OsO₂(OH)₄ and (DHQD)₂PHAL**

A mixture of K₂OsO₂(OH)₄ (7.7 mg, 0.021 mmol), (DHQD)₂PHAL (39 mg, 0.05 mmol), powdered K₃Fe(CN)₆ (2.47 g, 7.50 mmol), and K₂CO₃ (691 mg, 5.00 mmol) was ground to afford modified AD-mix-β.

**The title compound was prepared according to a modification of the General Procedure K from enamide 229l (63 mg, 0.20 mmol) in that modified AD-mix-β (see above) (280 mg) was used, and dihydroxylation was carried out at 0 °C for 2 h and**
then at room temperature for 22 h. Purification was carried out by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) to give the diol 331j (29 mg, 55%) as a colourless solid.

\[ R_f = 0.53 \text{ (40\% EtOAc/hexane); m.p. 68-70 °C; } [\alpha]^{20}_D +2.8 \text{ (c. 0.70, CHCl}_3\text{); IR (CHCl}_3\text{) 3401 (OH), 3060, 2933, 1492, 1447, 1381, 1069, 858, 818 cm}^{-1}; \text{ } ^1H \text{ NMR (500 MHz, CDCl}_3\text{) } \delta 7.98 \text{ (1H, s, ArH), 7.86-7.80 (3H, m, ArH), 7.52-7.47 (5H, m, ArH), 7.37-7.34 (2H, m, ArH), 7.30-7.27 (1H, m, ArH), 4.31 (1H, dd, } J = 11.5, 6.3 \text{ Hz, CH}_2\text{OH), 4.25 (1H, d, } J = 11.5, 6.3 \text{ Hz, CH}_2\text{OH), 3.33 (1H, s, OH), 1.99 (1H, t, } J = 6.5 \text{ Hz, OH); } ^{13}C \text{ NMR (125.8 MHz, CDCl}_3\text{) } \delta 143.6 \text{ (C), 141.1 (C), 133.0 (C), 132.6 (C), 128.5 (2 × CH), 128.3 (CH), 128.2 (CH), 127.55 (CH), 127.52 (CH), 126.5 (2 × CH), 126.3 (CH), 126.2 (CH), 125.0 (CH), 124.8 (CH), 78.7 (C), 69.3 (CH}_2\text{); HRMS (ES) Exact mass calcd for C}_{18}H_{16}O_2Na \text{ [M+Na}^+]: 287.1043, found: 287.1046. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (90:10 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (major) = 22.6 min; tr (minor) = 24.8 min, 98% ee.

\[(S)-\text{Cyclohexylhydroxyphenylacetaldehyde (332a)}\]

\[ \text{A solution of modified AD-mix-β (see above) (280 mg) in 1:1 } t\text{-BuOH/H}_2\text{O (2 mL) was stirred at room temperature for 10 min and then cooled to 0 °C. Enamide 183h (54 mg, 0.20 mmol) in } t\text{-BuOH (1 mL) was then added and the mixture was stirred vigorously at 0 °C for 19 h, before being quenched with saturated aqueous Na}_2\text{S}_2\text{O}_3 \text{solution (20 mL). The mixture was stirred at room temperature for 45 min and then extracted with CH}_2\text{Cl}_2 \text{ (3 × 15 mL). The combined organic extracts were washed with H}_2\text{O (20 mL), dried (MgSO}_4\text{), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the aldehyde 332a (35 mg, 80%) as a colourless solid that displayed spectroscopic data consistent with those observed previously.}\]

6.0 Experimental
Rf = 0.83 (40% EtOAc/hexane); m.p. 83-85 °C, lit.142d m.p. 87-89 °C; [α]D20 +184 (c. 1.25, CH2Cl2), lit.142d [α]D25 +180.3 (c. 0.84, CH2Cl2) for material of 84% ee; IR (CHCl3) 3502 (OH), 3028, 2934, 2856, 1722 (C=O), 1598, 1489, 1383, 1248, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 9.65 (1H, s, C=H), 7.53-7.51 (2H, m, ArH), 7.43-7.40 (2H, m, ArH), 7.33-7.30 (1H, m, ArH), 3.73 (1H, s, OH), 2.25-2.19 (1H, m, CHCH2), 1.82-1.80 (1H, m, (CH2)5), 1.73-1.66 (2H, m, (CH2)5), 1.44-1.27 (5H, m, (CH2)5), 1.23-1.21 (2H, m, (CH2)5); ¹³C NMR (125.8 MHz, CDCl3) δ 201.1 (CH), 138.0 (C), 128.7 (2 × CH), 127.6 (CH), 125.8 (2 × CH), 84.4 (C), 43.5 (CH), 26.8 (CH2), 26.4 (CH2), 26.2 (CH2), 26.1 (CH2), 25.0 (CH2). Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 210 nm, 25 °C); tr (minor) = 10.7 min; tr (major) = 12.9 min, 91% ee.

6.4.1 Total Synthesis of (+)-Tanikolide

1-Bromotridecyne (350)

To a solution of tridecyne (349) (5.00 g, 27.7 mmol) and NBS (5.04 g, 30.5 mmol) in acetone (140 mL) at room temperature was added AgNO3 (470 mg, 2.77 mmol) in one portion, and the mixture was stirred for 6 h. The reaction was diluted with hexane (140 mL), filtered to remove the precipitate, and concentrated in vacuo. The residual oil was redissolved in hexane (20 mL) and the undissolved solid was removed by filtration, using hexane as eluent. The filtrate was collected and concentrated in vacuo to leave the bromoalkyne 350 (6.61 g, 92%) as a colourless oil that required no further purification.

Rf = 0.78 (40% EtOAc/hexane); IR (film) 2927, 2855, 2253 (C=C), 1467, 1379, 908, 735, 651 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 2.20 (2H, t, J = 7.2 Hz, =CH2), 1.55-1.49 (2H, m, =CH2CH2), 1.39-1.35 (2H, m, =CH2CH2CH2), 1.31-1.27 (14H, m, (CH2)5CH3), 0.89 (3H, t, J = 6.9 Hz, CH3); ¹³C NMR (125.8 MHz, CDCl3) δ 80.5 (C), 37.4 (C), 31.9 (CH2), 29.6 (2 × CH2), 29.5 (CH2), 29.3 (CH2), 29.1 (CH2), 28.8 (CH2), 28.3 (CH2), 22.7 (CH2), 19.7 (CH2), 14.1 (CH3).
Following the procedure of Hsung and co-workers, a mixture of 1-bromotridecyne (350) (6.50 g, 25.1 mmol), 2-oxazolidinone (1.98 g, 22.8 mmol), K$_3$PO$_4$ (9.68 g, 45.6 mmol), CuSO$_4$·5H$_2$O (570 mg, 2.28 mmol), and 1,10-phenanthroline (821 mg, 4.56 mmol) in toluene (50 mL) was heated at 95 °C for 24 h. After cooling to room temperature, the mixture was filtered through a short pad of silica gel using 1:1 CH$_2$Cl$_2$/EtOAc (50 mL) as the eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave the ynamide 351 (3.52 g, 58%) as a colourless solid.

$R_f = 0.57$ (40% EtOAc/hexane); m.p. 90-92 °C; IR (film) 2925, 2854, 2270 (C–C), 1771 (C=O), 1480, 1415, 1372, 1206, 1112, 1037, 750 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) δ 4.43-4.40 (2H, m, C$_2$H$_2$O), 3.89-3.86 (2H, m, C$_2$H$_2$N), 2.30 (2H, t, J = 7.2 Hz, C=CH$_2$), 1.56-1.50 (2H, m, =CCH$_2$), 1.39-1.34 (2H, m, =CCH$_2$CH$_2$), 1.32-1.27 (14H, m, (C$_2$H$_2$)$_7$CH$_3$), 0.89 (3H, t, J = 7.0 Hz, CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 156.6 (C), 71.3 (C), 69.9 (C), 62.7 (CH$_2$), 47.0 (CH$_2$), 31.9 (CH$_2$), 29.6 (2 × CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 29.1 (CH$_3$), 28.9 (CH$_2$), 28.8 (CH$_2$), 22.7 (CH$_2$), 18.4 (CH$_2$), 14.1 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{16}$H$_{31}$N$_2$O$_2$ [M+NH$_4]^+$: 283.2380, found: 283.2377.

To a solution of ynamide 351 (2.61 g, 9.83 mmol) and Rh(cod)(acac) (152 mg, 0.49 mmol) in THF (5 mL) at 0 °C was added 4-ethoxy-4-oxobuty zinc bromide (Sigma-Aldrich, 0.5 M in THF, 40.0 mL, 19.7 mmol) over 5 min, and the reaction was then stirred at room temperature for 2.5 h. The mixture was filtered through a pad of silica gel using 1:1 CH$_2$Cl$_2$/EtOAc (100 mL) as eluent, and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography (10%
EtOAc/hexane→20% EtOAc/hexane) gave the enamide 352 (2.12 g, 56%) as a red oil.

R<sub>f</sub> = 0.46 (40% EtOAc/hexane); IR (film) 2926, 2855, 1749 (C=O), 1732 (C=O), 1671, 1481, 1410, 1090, 1042, 733 cm<sup>-1</sup>; H NMR (500 MHz, CDCl<sub>3</sub>) δ 5.91 (1H, s, =CH), 4.40-4.36 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>N), 4.13 (2H, q, J = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.79-3.76 (2H, m, CH<sub>2</sub>N), 2.30 (2H, t, J = 7.5 Hz, CH=CH<sub>2</sub>C=O), 2.09-2.06 (4H, m, =CCH<sub>2</sub>(CH<sub>3</sub>)) and CH<sub>2</sub>CH<sub>2</sub>CH=CH<sub>2</sub>C=O), 1.79-1.73 (2H, m, CH=CH<sub>2</sub>C=O), 1.40-1.37 (2H, m, =CCH<sub>2</sub>(CH<sub>3</sub>)(CH<sub>2</sub>)), 1.32-1.27 (19H, m, (CH<sub>2</sub>)<sub>8</sub>CH<sub>3</sub> and OCH<sub>2</sub>CCH<sub>3</sub>), 0.88 (3H, t, J = 7.0 Hz, (CH<sub>2</sub>)<sub>10</sub>CH<sub>3</sub>); <sup>13</sup>C NMR (125.8 MHz, CDCl<sub>3</sub>) δ 173.4 (C), 157.3 (C), 134.2 (C), 119.5 (CH), 62.1 (CH<sub>2</sub>), 62.3 (CH<sub>2</sub>), 49.6 (CH<sub>2</sub>), 33.75 (CH<sub>2</sub>), 33.67 (CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 29.8 (CH<sub>2</sub>), 29.62 (CH<sub>2</sub>), 29.58 (2 × CH<sub>2</sub>), 29.5 (CH<sub>2</sub>), 29.3 (CH<sub>2</sub>), 29.2 (CH<sub>2</sub>), 28.0 (CH<sub>2</sub>), 23.3 (CH<sub>2</sub>), 22.6 (CH<sub>2</sub>), 14.2 (CH<sub>3</sub>), 14.1 (CH<sub>3</sub>); HRMS (ES) Exact mass calcd for C<sub>22</sub>H<sub>40</sub>NO<sub>4</sub>[M+H]<sup>+</sup>: 382.2952, found: 382.2949.

**Preparation of (DHQD)<sub>2</sub>AQN Dihydroxylation Mixture**

A mixture of K<sub>2</sub>OsO<sub>2</sub>(OH)<sub>4</sub> (11 mg, 0.03 mmol), (DHQD)<sub>2</sub>AQN (64 mg, 0.075 mmol), powdered K<sub>3</sub>Fe(CN)<sub>6</sub> (2.47 g, 7.50 mmol), and K<sub>2</sub>CO<sub>3</sub> (1.04 g, 7.50 mmol) was ground to afford (DHQD)<sub>2</sub>AQN dihydroxylation mixture.

(R)-Ethyl-4-hydroxy-4-hydroxymethylhexadecanoate (353)

A solution of (DHQD)<sub>2</sub>AQN dihydroxylation mixture (see above) (280 mg) in 1:1 <i>t</i>-BuOH/H<sub>2</sub>O (2 mL) was stirred at room temperature for 10 min and then cooled to 0 °C. Enamide 11 (76 mg, 0.20 mmol) in <i>t</i>-BuOH (1 mL) was then added and the mixture was stirred vigorously at 0 °C for 4 h. NaBH<sub>4</sub> (45 mg, 1.20 mmol) was then added in one portion and the reaction was stirred at room temperature for 1 h. The reaction was quenched carefully with saturated aqueous NH<sub>4</sub>Cl solution (20 mL) and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 × 15 mL). The combined organic extracts were washed with H<sub>2</sub>O (20 mL), dried (MgSO<sub>4</sub>), filtered, and concentrated in vacuo. Purification
of the residue by column chromatography (15% EtOAc/hexane→35% EtOAc/hexane) gave the diol 353 (56 mg, 85%) as a colourless oil.

Rf = 0.40 (50% EtOAc/hexane); [α]20D° -1.9 (c. 1.50, CHCl3); IR (film) 3447 (OH), 2927, 2855, 1724 (C=O), 1653, 1558, 1464, 1098, 1038, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl3) δ 4.14 (2H, q, J = 7.1 Hz, OCH₂CH₃), 3.50 (1H, d, J = 11.1 Hz, CH₂OH), 3.46 (1H, d, J = 11.1 Hz, CH₂OH), 2.33 (2H, td, J = 7.1, 1.2 Hz, CH₂C=O), 2.29 (1H, br s, OH), 2.10 (1H, br s, OH), 1.67-1.43 (6H, m, CH₂CH₂CH₂C=O and CH₂(CH₂)₉CH₃), 1.30-1.25 (21H, m, (CH₂)₉CH₃ and OCH₂CH₃), 0.88 (3H, t, J = 7.0 Hz, (CH₂)₁₀CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 173.8 (C), 74.5 (C), 67.9 (CH₂), 60.4 (CH₂), 35.8 (CH₂), 35.0 (CH₂), 34.3 (CH₂), 31.9 (CH₂), 30.2 (CH₂), 29.63 (CH₂), 29.60 (2 × CH₂), 29.58 (CH₂), 29.3 (CH₂), 23.3 (CH₂), 22.7 (CH₂), 18.8 (CH₂), 14.2 (CH₃), 14.1 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₄₂NO₄ [M+NH₄⁺]: 348.3108, found: 348.3113. The enantiomeric excess of diol 12 was determined by chiral HPLC analysis of the monobenzoylester 12Bz, as described below:

(R)-Benzoic acid 2-(3-ethoxycarbonylpropyl)-2-hydroxytridecyl ester (353Bz)

To a solution of the diol 353 (10 mg, 0.03 mmol), Et₃N (7 μL, 0.07 mmol), and DMAP (0.4 mg, 0.003 mmol) in CH₂Cl₂ at 0 °C was added benzoic chloride (5 μL, 0.04 mmol) and the mixture was stirred at 0 °C for 1 h. Saturated aqueous NH₄Cl solution (5 mL) was added and the mixture was extracted with CH₂Cl₂ (3 × 5 mL). The combined organic layers were washed with H₂O (10 mL), dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→15% EtOAc/hexane) gave the benzoate ester 353Bz (12 mg, 92%) as a colourless oil.

Rf = 0.76 (50% EtOAc/hexane); [α]20D° -5.0 (c. 0.40, CHCl₃); IR (film) 2928, 2855, 1719 (C=O), 1653, 1602, 1558, 1465, 1097, 1027, 733 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.06-8.04 (2H, m, ArH), 7.61-7.57 (1H, m, ArH), 7.48-7.45 (2H, m, ArH), 4.27 (1H, d, J = 11.4 Hz, CH₂OBz), 4.25 (1H, d, J = 11.4 Hz, CH₂OBz), 4.13 (2H, q,
$J = 7.1 \text{ Hz, OCH}_2\text{CH}_3$, 2.35 (2H, t, $J = 7.2 \text{ Hz, CH}_2\text{C}=\text{O}$), 2.03 (1H, br s, OH), 1.78-1.72 (2H, m), 1.64-1.58 (4H, m), and 1.38-1.24 (21H, m, CH$_2$CH$_2$CH$_2$C=O, (CH$_2$)$_{10}$CH$_3$, and OCH$_2$CH$_3$), 0.88 (3H, t, $J = 7.0 \text{ Hz, (CH}_2$)$_{10}$CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 173.4 (C), 166.6 (C), 133.2 (CH), 129.9 (C), 129.6 (2 × CH), 128.5 (2 × CH), 73.6 (C), 69.8 (CH$_2$), 60.3 (CH$_2$), 36.8 (CH$_2$), 36.0 (CH$_2$), 34.5 (CH$_2$), 31.9 (CH$_2$), 30.2 (CH$_2$), 29.63 (CH$_2$), 29.60 (CH$_2$), 29.57 (CH$_2$), 29.5 (CH$_2$), 29.3 (CH$_2$), 23.3 (CH$_2$), 22.7 (CH$_2$), 18.8 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{26}$H$_{43}$O$_5$ [M+H]$^+$: 435.3105, found: 435.3109. Enantiomeric excess was determined by HPLC with a Chiralpak AS-H column (98:2 hexane:isopropanol, 0.8 mL/min, 230 nm, 25 °C); tr (major) = 14.5 min; tr (minor) = 17.0 min, 88% ee.

(R)-4-Hydroxy-4-hydroxymethylhexadecanoic acid (354)$^{144s}$

To a solution of the ester 353 (40 mg, 0.12 mmol) in EthOH (1 mL) at 0 °C was added NaOH (4.0 m in H$_2$O, 100 μL, 0.40 mmol). The mixture was stirred at room temperature for 30 min and then HCl (1.0 m in H$_2$O) was added slowly until the solution was pH 2. The mixture was extracted with Et$_2$O (3 × 5 mL) and the combined organic layers washed with H$_2$O (10 mL), dried (MgSO$_4$), filtered, and concentrated in vacuo to leave the carboxylic acid 354 (34 mg, 94%) as a colourless solid which was used in the next step without further purification, and which displayed spectroscopic data consistent with those observed previously.$^{144s}$

R$_f$ = 0.02 (40% EtOAc/hexane); m.p. 72–74 °C, lit.$^{144s}$ m.p. 76.1-76.4 °C; [$\alpha$]$^D_{20}$ –0.7 (c. 0.45, CHCl$_3$), lit.$^{144s}$ [$\alpha$]$^D_{27}$ –0.8 (c. 1.0, CHCl$_3$) for material of >99% ee; IR (CHCl$_3$) 3426 (OH), 2928, 2851, 1732 (C=O), 1642, 1557, 1435, 1221, 1052, 733 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.30 (2H, br s, OH), 3.51-3.47 (2H, m), 2.37 (2H, t, $J = 6.9 \text{ Hz, CH}_2\text{C}=\text{O}$), 1.69-1.57 (2H, m), 1.55-1.41 (4H, m), and 1.32-1.22 (18H, m, CH$_2$CH$_2$CH$_2$C=O and (CH$_2$)$_{10}$CH$_3$), 0.89 (3H, t, $J = 7.0 \text{ Hz, (CH}_2$)$_{10}$CH$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) $\delta$ 178.2 (C), 75.0 (C), 67.7 (CH$_2$), 35.6 (CH$_2$), 34.6 (CH$_2$), 34.0 (CH$_2$), 31.9 (CH$_2$), 30.3 (CH$_2$), 29.67 (CH$_2$), 29.66 (CH$_2$), 23.3 (CH$_2$), 22.7 (CH$_2$), 18.8 (CH$_2$), 14.2 (CH$_3$), 14.1 (CH$_3$);
29.63 (CH₂), 29.61 (CH₂), 29.3 (CH₂), 23.3 (CH₂), 22.7 (CH₂), 18.6 (CH₂), 14.1 (CH₃).

(+)−Tanikolide (339)

A solution of carboxylic acid 354 (34 mg, 0.11 mmol) in CDCl₃ (1.5 mL) was heated at reflux for 50 h. After cooling to room temperature, the solution was filtered through a small plug of silica gel using CDCl₃ as eluent, and the filtrate was concentrated in vacuo to leave (+)-tanikolide (339) (29 mg, 91%) as a pale yellow oil that displayed spectroscopic data consistent with those described previously.¹⁴⁴

Rᵥ = 0.25 (40% EtOAc/hexane); [α]D²⁰ +2.9 (c. 1.35, CHCl₃), lit.¹⁴⁴ [α]D²⁵ +2.3 (c. 0.65, CHCl₃); IR (CHCl₃) 3420 (OH), 2926, 2854, 1717 (C=O), 1653, 1558, 1465, 1251, 1048, 734 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 3.66 (1H, d, J = 11.9 Hz, CH₂OH), 3.56 (1H, d, J = 11.9 Hz, CH₂OH), 2.54-2.43 (2H, m, CH₂C=O), 2.23 (1H, br s, OH), 1.95-1.81 (3H, m, CH₂), 1.77-1.71 (2H, m, CH₂), 1.65-1.59 (1H, m, CH₂), 1.30-1.26 (18H, m, CH₂), 0.88 (3H, t, J = 7.0 Hz, CH₃); ¹³C NMR (125.8 MHz, CDCl₃) δ 171.7 (C), 86.5 (C), 67.5 (CH₂), 36.6 (CH₂), 31.9 (CH₂), 30.0 (CH₂), 29.8 (CH₂), 29.59 (CH₂), 29.57 (CH₂), 29.52 (CH₂), 29.4 (CH₂), 29.3 (CH₂), 26.5 (CH₂), 23.4 (CH₂), 22.7 (CH₂), 16.6 (CH₂), 14.1 (CH₃).
7.0 References


7.0 References


7.0 References


7.0 References


7.0 References


Appendix

List of Publications


