Stereoselective Synthesis of Multisubstituted Alkenes via Ring Opening Reactions of Cyclopropenes

Enantioselective Copper Catalysed Asymmetric Reduction of Alkenylheteroarenes

Thesis Submitted in Accordance with the Requirement 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 in this thesis is the original work of my own research since the registration of the PhD degree in January 2007, and any collaboration has been 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.

Signed

Yi Wang
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At last, I would like to thank my parents for being so supportive over the last few years. I made you proud of me and I love you mum and dad.
Abstract

A catalytic organometallic addition-ring opening sequence of cyclopropenes that enables the efficient and highly stereoselective synthesis of multisubstituted alkenes has been developed. A possible mechanism of organoaluminium reaction is proposed. The metalloenolate resulting from ring opening can be trapped with various electrophiles, enabling a rapid increase in molecular complexity in a one-pot operation.

Also, in the presence of stoichiometric magnesium halides, a range of bis-activated cyclopropenes undergo highly stereoselective ring-opening reactions to produce multisubstituted alkenyl halides. The halogen nucleophile promotes Lewis-acid mediated regioselective S_NV_σ attack at the sp²-carbon of cyclopropene, resulting in the formation of acyclic conjugate enolate, which can be trapped with enones to furnish more highly functionalised products.

At last, copper-catalysed asymmetric conjugate reductions of β,β'-disubstituted 2-alkenylheteroarenes are reported. A range of nitrogen-containing aromatic heterocycles are able to provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate reduction reactions. Extension of the general concept to other classes of heteroarenes has been proven successful. Further manipulation of the condition is required to tolerate more hindered heteroarene substrates.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetonate</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>BINAP</td>
<td>2,2'-bis(diphenylphosphino)-1,1'-binaphthyl</td>
</tr>
<tr>
<td>BIPHEP</td>
<td>(biphenyl-2,2'-diyl)bis(diphenylphosphine)</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Bz</td>
<td>benzoyl</td>
</tr>
<tr>
<td>cat.</td>
<td>catalyst</td>
</tr>
<tr>
<td>calcd</td>
<td>calculated</td>
</tr>
<tr>
<td>conc.</td>
<td>concentrated</td>
</tr>
<tr>
<td>dba</td>
<td>dibenzylideneacetone</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>diisobutylaluminium hydride</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-(dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>(N,N)-dimethylformamide</td>
</tr>
<tr>
<td>DKR</td>
<td>dynamic kinetic resolution</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-(bis)(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>(dr)</td>
<td>diastereomeric ratio</td>
</tr>
<tr>
<td>(ee)</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>EI</td>
<td>electron impact</td>
</tr>
<tr>
<td>equiv.</td>
<td>equivalents</td>
</tr>
<tr>
<td>Acronym</td>
<td>Definition</td>
</tr>
<tr>
<td>---------</td>
<td>------------</td>
</tr>
<tr>
<td>ES</td>
<td>electrospay</td>
</tr>
<tr>
<td>EWG</td>
<td>electron-withdrawing group</td>
</tr>
<tr>
<td>HPLC</td>
<td>high performance liquid chromatography</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
</tr>
<tr>
<td>IR</td>
<td>infrared spectroscopy</td>
</tr>
<tr>
<td>LG</td>
<td>leaving group</td>
</tr>
<tr>
<td>MEM</td>
<td>2-methoxyethoxymethyl</td>
</tr>
<tr>
<td>MOM</td>
<td>methoxymethyl</td>
</tr>
<tr>
<td>m.p.</td>
<td>melting point</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Effect</td>
</tr>
<tr>
<td>PMHS</td>
<td>poly(methylhydrosiloxane)</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>rt</td>
<td>room temperature</td>
</tr>
<tr>
<td>SEGPHOS</td>
<td>5,5’-diylbis(di(3,5-di-t-butyl-4-methoxyphenyl)-phosphine)</td>
</tr>
<tr>
<td>t-AmOH</td>
<td>tert-Amyl alcohol</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBS</td>
<td>t-butyldimethylsilyl</td>
</tr>
<tr>
<td>TES</td>
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</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethlenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
</tbody>
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General Introduction of this work

For the last three years, I have been working on two different kinds of organic synthesis projects involving stereoselective reactions of olefins using transition metal catalyst, one is cyclopropene addition-ring opening reaction, and the other is copper hydride reduction.

Previously in the Lam group, intensive studies on novel cyclopropene chemistry have been carried out. Dr Euan Fordyce developed two new methodologies in silylation and stannylation of cyclopropenes. When he was studying ring-opening reaction of cyclopropenes, I joined in the same project and developed a catalytic organometallic addition-ring opening sequence of cyclopropenes to the highly stereoselective synthesis of multisubstituted alkenes.

![Chemical Structure](image)

During this work, I also found that in the presence of stoichiometric magnesium halides, a range of bis-activated cyclopropenes could undergo highly stereoselective ring-opening reactions to produce multisubstituted alkenyl halides. The enolate intermediate can be trapped with enones to result in more highly functionalised products. However, only a few Michael additions to β-unsubstituted enones using acetonitrile as the solvent were proven successful.

![Chemical Structure](image)

In the meantime, the other part of the group was investigating copper hydride reduction of 2-Alkenylheteroarenes. The asymmetric copper catalysed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks. The aim of the project is to find out whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent
alkene in an analogous reaction, also whether large substituents would be tolerated under our reaction conditions. Dr Leszek Rupnicki and Aakarsh Saxena optimised the reaction conditions and tested a few heteroarenes such as pyridines, benzoazoles, benzothiazole, quinoline and pyrazine. They proved that nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate reduction reactions.

(a) Conventional asymmetric conjugate addition

\[
\begin{align*}
\text{EWG} & \quad \text{Nu} \\
\text{catalyst} & \quad \text{EWG}
\end{align*}
\]

EWG = COR, NO₂, CN, SO₂R, etc.

(b) Aromatic heterocycle induced conjugate addition

\[
\begin{align*}
\text{X} & \quad \text{Nu} \\
\text{catalyst} & \quad \text{X}
\end{align*}
\]

X = C, N, O, S, etc.

After I finished cyclopropene chemistry projects, I joined them and tried to synthesise other substrates bearing heterocycles like imidiazoles, benzimidazoles, caffeines and pyrazoles and applied to the same copper hydride chemistry. However, due to the low reactivity of those moieties, only a few of them were reduced. Further manipulation of the conditions is required to tolerate more challenging heteroarene substrates.
1) Cyclopropene Chemistry: An Overview

Cyclopropenes are the smallest unsaturated cycloalkenes. Due to the high strain of the three-membered ring, these extremely reactive units are endowed with a large spectrum of remarkable reactivities that extend far beyond simple reactions typical for alkenes.

![Scheme 1.1 Cyclopropenes](image)

The strong s-character of the olefinic C-H bond in cyclopropenes is analogous to that in terminal alkynes. Furthermore, significant conformational constraints in cyclopropenes making them ideal models for the design and optimisation of novel diastereo- and enantioselective transformations, which are unknown for normal olefins, allenes, and alkynes.

1.1) Synthesis of Cyclopropenes

Numerous approaches to access cyclopropene and its derivatives have been comprehensively studied by organic chemists over the last century. In Baird’s and Hopf’s reviews, some examples of the key synthetic approaches are summarised (Scheme 1.2): (a) 1,2-elimination from a cyclopropane precursor possessing good leaving groups (Scheme 1.3); (b) cycloisomerisation of vinylcarbenes generated in situ from tosyl hydrazones, diazoalkenes, vinyldiazirines, or allyl halides (Scheme 1.4); (c) [2+1] cycloaddition of carbenoids generated from diazo...
compounds\textsuperscript{9} or iodonium ylides\textsuperscript{10} to alkynes (Scheme 1.5); (d) photochemical or transition-metal-catalysed extrusion of nitrogen from 3\textit{H}-pyrazoles\textsuperscript{11}; (e) cascade 1,3/1,2-elimination from 1,3-dihalopropanes\textsuperscript{12} (Scheme 1.6); and (f) functionalisation of pre-formed cyclopropenes.

Other less common methods involve: (g) ring contraction of cyclobutenes\textsuperscript{13}; (h) addition of nucleophiles to cyclopropyllium species; (i) extrusion of CO\textsubscript{2} from furan-2(5\textit{H})-ones\textsuperscript{14}; (j) 1,3-elimination from 1,3-dihalopropanes\textsuperscript{15}; (k) 1,2-silicon shift in 2-silylcyclopropylidenes\textsuperscript{16}; (l) retro-cycloaddition reactions\textsuperscript{17}; and (m) various rearrangements of allenes\textsuperscript{18}, (n) methylenecyclopropanes\textsuperscript{19}, and (o) alkynes\textsuperscript{20}.

\textbf{Scheme 1.2} Synthetic approaches to cyclopropenes
1.2) Chemistry of Cyclopropenes

Cyclopropenes are powerful and versatile organic synthons. In Scheme 1.7, most of the synthetically useful types of reactions involving cyclopropenes are highlighted. These include: ring-opening metathesis (a); various cycloaddition reactions proceeding with (b) and without (c) ring-opening; ene reactions (d); different types of substitution, cross-coupling, and other functionalisation reactions described here as formal substitution reactions (e); addition reactions with preservation of the ring
(f), and ring-opening (g); various ring-expansion reactions (h); and migrations of the double bond to the side chain (i).

1.3) **Additions across the Double Bond of Cyclopropenes**

Despite the many reactions with cyclopropenes, a significant number involve addition of various entities across the double bond of cyclopropene, in which case the resulting products - cyclopropanes, are very attractive synthetic targets because they are structural components of many natural products, drug candidates and other biologically relevant materials. Some typical examples of addition reactions with cyclopropenes are described below. These include hydrocarbonation, hydrometallation and carbometallation.

---

*Scheme 1.7 Chemistry of cyclopropenes*
1.3.1) Addition of H-C Moieties

In transition-metal-catalysed hydrocarbonation reactions, the H-C unit is added across the double bond of cyclopropene. Similar to reductive cross-coupling with acetylene, cyclopropene (which possesses an ester functionality at C-1) undergoes syn addition of terminal alkynes to access alkynylecyclopropane (Scheme 1.8). 

**Scheme 1.8** Pd-catalysed additions of alkyne and cyclopropene with acetylenes

Another example of formal hydroarylation proceeding via an unusual cyclopropyl cation intermediate, stabilised by a ferrocenyl substituent (Fc), was reported by Klimova. Cyclopropyl cation, obtained upon protonation of 1-ferrocenylycyclopropane, underwent Friedel-Crafts alkylation of dimethylaniline to give in moderate yield (Scheme 1.9).

**Scheme 1.9** Formal hydroarylation of ferrocenyl substituent cyclopropene
1.3.2) Addition of H-M Moieties

Hydrometallation across the double bond of cyclopropanes is described in this section. Although reduction of cyclopropane with LiAlH₄ has been routinely used for the preparation of cyclopropane derivatives since 1972, Negishi was the first to demonstrate that this transformation proceeds via syn-selective hydroalumination of cyclopropanes. He also improved the syn-selectivity of this addition by employing DIBAL-H as a hydrometallating agent (Scheme 1.10).

![Scheme 1.10 syn-Selective hydroalumination of cyclopropanes](image)

The directing effect of the hydroxymethyl group in this reaction was investigated by Marek, who demonstrated the highly diastereoselective reduction of cyclopropenyl carbinol 20 (Scheme 1.11).  

![Scheme 1.11 Diastereoselective reduction of cyclopropenyl carbinol](image)

Gevorgyan reported the palladium-catalysed cis-selective hydrostannation of cyclopropanes which, in contrast to radical hydrostannation, proceeded extremely rapidly and highly stereoselectively, leading to trisubstituted cyclopropylstannane in very good yield (Scheme 1.12). Facial selectivity in this reaction was primarily
controlled by steric factors, affording single diastereomers of cyclopropylstannanes 23.

Scheme 1.12 Palladium-catalysed cis-selective hydrostannation of cyclopropenes

Application of this methodology to enantiomerically enriched cyclopropane 24, as demonstrated by Corey, allowed for the preparation of optically active cyclopropylstannane 25 (Scheme 1.13).

Scheme 1.13 Preparation of optically active cyclopropylstannane

Gevorgyan recently reported that in contrast to non-catalytic hydroboration, catalytic asymmetric hydroboration of 3,3-disubstituted cyclopropenes proceeded highly efficiently to produce cis-cyclopropylboronates with virtually perfect diastereoselectivity and very high enantioselectivity (Scheme 1.14). It was shown that both ester substituents can serve as effective directing groups in the hydroboration reaction. The directing effect was found to be necessary for achieving high degrees of diastereoselectivity. This method allows for easy access to optically active 2,2-disubstituted cyclopropylboronate 27. The synthetic application of the obtained products was demonstrated by the effective synthesis of optically active trisubstituted arylcyclopropane 28 via a Suzuki cross-coupling reaction (Scheme 1.14).
Scheme 1.14 Catalytic asymmetric hydroboration of 3,3-disubstituted cyclopropenes

In similar fashion, hydrophosphorylation of cyclopropenes was achieved by Rubin (Scheme 1.15).  

Scheme 1.15 Hydrophosphorylation of cyclopropenes

The same group also showed the first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes (Scheme 1.16).  

Scheme 1.16 Catalytic diastereo- and enantioselective hydroformylation of cyclopropenes
1.3.3) Addition of C-M Moieties

The carbometallation reaction is one of the most important transformations of cyclopropenes, as it allows for simultaneous installation of two new entities into the three-membered ring in one step.

Carbolithiation

One of the main methods to functionalise cyclopropenes at the sp²-carbons is to generate the cyclopropenylmetal species and then trap with the appropriate electrophile. The first example of a cyclopropene carbometallation reaction was reported in 1967 by Welch and Magid, who showed that sequential treatment of cyclopropene 35 with phenyllithium and CO₂ gives cis-2-phenylcyclopropene carboxylic acid 36 in low yield (Scheme 1.17). Nonetheless, the syn-diastereoselectivity was excellent and subsequent efforts from a number of groups showed that the syn selectivity is a general phenomenon for the addition of organometallic reagents to cyclopropenes. Cyclopropenes undergo carbometallation reactions more easily than ‘normal’ alkenes, and their reactivity more closely parallels the chemistry of alkynes.

Cyclopropene alkene protons have a pKa of ~30, enabling metallation with strong bases in the same fashion as terminal alkynes. Cyclopropenyllithium species can be generated by deprotonation of the corresponding cyclopropene using alkyl lithium bases. Nakamura and co-workers have demonstrated that it is possible to functionalise cyclopropenone ketals using this technique. Deprotonation with n-butyllithium, in the presence of HMPA, and subsequent trapping with alkyl and
metal halides provided a variety of monosubstituted cyclopropenone ketal derivatives 38a-d in good to excellent yields (Scheme 1.18).

Scheme 1.18 Examples of the Reaction of Cyclopropenyllithium Species with Alkyl and Metal Halides

By using carbonyl compounds as electrophiles in these reactions it was possible to synthesise the corresponding cyclopropenone ketal derivatives 39a-d which incorporate allylic alcohol functionality, in good to excellent yields (Scheme 1.19).³⁴

Scheme 1.19 Examples of the Reaction of Cyclopropenyllithium Species with Carbonyl Compounds

Also, an allylic lithium reagent bearing an alkoxy substituent 40 can react with a cyclopropenone acetal to produce an alkoxyallylated cyclopropanone acetal 41 with high stereo- and regioselectivity (Scheme 1.20).³⁶ The regiochemistry of the α- or
γ-addition of the allylic lithium reagent depends strongly on the structure of the lithium reagent. For example, carbon-carbon bond formation takes place at the α-position using a β-,γ- or an α-,γ- disubstituted allylic lithium reagent 40a or 40b, while a monosubstituted alkoxyallylic lithium reagent 40c mainly gives a γ-adduct.

**Scheme 1.20 Allylation of cyclopropenones**

**Carbocupration**

Cyclopropenone acetics can react with organocopper reagents to produce metallated cyclopropanone acetics, which are trapped by electrophiles to afford highly substituted cyclopropanone acetics. Regio- and stereoselective carbocupration of the substituted CPA derived from a chiral 2,4-pentanediol can be used for asymmetric synthesis of a quaternary carbon centre.\(^{37}\) Thus, the addition of dimethyl cuprate to CPA 42 followed by trapping of the resulting cyclopropyl cuprate 43 with benzoyl chloride in the presence of a Pd(0) catalyst produces the cyclopropyl ketone derivative 44 as a single isomer. The ketone can be transformed to the γ-keto acid 45 by sequential treatment of the keto acetal with aqueous HCl, PCC, and K₂CO₃ (Scheme 1.21).
Carbozincation

The first example of carbozincation of cyclopropenes was demonstrated by Negishi and co-workers in 1985. They reported that allylzinc and alkyl copper reagents also gave cis-addition products with cyclopropenes (Scheme 1.22). Of further significance was the observation that a trimethylsilyl group can direct the regioselectivity of carbometallation. Carbozincation of 1-trimethylsilyl-2-alkyl cyclopropene 46 proceeded to form 47 with an all-carboquaternary centre.

In contrast to moderately selective and rather substrate-specific non-catalytic additions of various entities to cyclopropenes, analogous transition metal-catalysed transformations appear to be significantly more general with regard to both cyclopropene substrates and addition reagents. Employment of catalysts also allow for controlling and fine-tuning of the diastereo- and enantioselectivity of the reactions and for significant improvement of the yields.

Nakamura and co-workers developed a number of useful protocols for the catalytic asymmetric carbozincation of cyclopropenone acetal 37 in the presence of an iron catalyst and chiral phosphine ligand (Scheme 1.23). Addition of TMEDA to the
reaction mixture was found to be crucial for achieving high enantioselectivities, as racemic products were obtained in the absence of this additive.

![Scheme 1.23 Catalytic asymmetric carbozincation of cyclopropenone acetals](image)

Another copper catalysed carbozincation reaction of cyclopropenes was reported recently by Fox (Scheme 1.24). It was demonstrated that the diastereoselective addition can be also directed by oxazolidinone chiral auxiliaries (50d-e), and not only ester groups (50a-c). The resulting cyclopropylzinc species can be captured with electrophiles to access highly functionalised cyclopropanes 50b, 50d and 50e.

![Scheme 1.24 Oxazolidinone directed diastereoselective carbozincation of cyclopropenes](image)
Carboindation

Araki and co-workers were the first group to use indium reagents to expand the scope of the allylmetallation of cyclopropenes since 1969, when the carbometallation of cyclopropenes with control of facial diastereoselectivity was first considered. Allylindium reagents were shown to undergo facile addition across the double bond of cyclopropenes. The allyl nucleophile was delivered to 1-alkylcyclopropenes to form an all-carbon quaternary centre. Araki found that the facial selectivity of the carbometallation could be controlled by a directing group at C-3 of the cyclopropene. Hydroxymethyl and carboxylic acid functions directed the addition to the syn-face, whereas analogous addition reactions of their acetates and esters, respectively, occurred on the anti-face (Scheme 1.25). It was demonstrated that the chelation of allylindium species to the hydroxyl moiety in substituent \( Z \) plays a crucial role in controlling the facial selectivity in this carbometallation. Thus, when allylindation of alcohols \( 51a-b \) and carboxylic acid \( 51c \) were carried out in THF, cis-cyclopropanes \( 54a-c \) were obtained as major products.

In aqueous media, where stabilisation of cis-transiton state \( 56 \) by chelation is inefficient, the corresponding trans products \( 57a-b \) were obtained predominantly.

Scheme 1.25 Allylindiation of cyclopropenes in THF
When cyclopropenylmethanol acetate 55b was employed as the substrate, the reaction intermediate 56b often went through a ring-opening sequence, followed by elimination of the acetoxy group to yield the triene product 58 (Scheme 1.27).

**Scheme 1.27** Ring-opening-elimination of cyclopropane intermediate

**Carbomagnesiation**

The work of Araki improved the scope and versatility of reactions that introduce allyl nucleophiles to cyclopropenes. However, the utility of the carbometallation reaction was still greatly diminished by the restriction that simple alkyl, aryl, vinyl or acetylide nucleophiles could not be used.

Nakamura first demonstrated that the use of an iron catalyst facilitated carbomagnesation of cyclopropenone acetals and enabled addition of a wide range of Grignard reagents, including aryl- and alkenylmagnesium halides, which did not
react in the absence of catalyst (Scheme 1.28).\textsuperscript{37}

![Scheme 1.28](image)

**Scheme 1.28** Iron catalysed carbomagnesation of cyclopropenone acetals

Later, Liao and Fox\textsuperscript{43} examined the effect of derivatising a 3-hydroxymethyl cyclopropene 61 with MOM substituent, as it was hoped that this known directing group\textsuperscript{44} could deliver the Grignard reagent to the syn face of the cyclopropene. It was found that with Cu(I) catalyst, the syn-selectivity was highest (97:3) when pentane was used as the solvent. Alkyl and vinyl Grignard reagents generally provided very good syn-selectivity. Aqueous quench or trapping the cyclopropylmagnesium intermediate with different electrophiles allowed for easy installation of various functional groups in the three-membered ring (Scheme 1.29).

![Scheme 1.29](image)

**Scheme 1.29** syn-Selective carbomagnesation of cyclopropenes

Although the regioselectivity for additions of 1-alkyl cyclopropenes is excellent, obtaining high regioselectivity for the addition reactions of 1-aryl substituted cyclopropenes is more challenging. Thus, the Cu-catalysed addition of CH\textsubscript{3}MgBr to 63 proceeds cleanly to give a 2:1 mixture of 64a and b (Scheme 1.30). Improving the diastereoselectivity of such reactions is an outstanding challenge for the field.

![Scheme 1.30](image)

**Scheme 1.30** Carbomagnesation of 1-aryl substituted cyclopropenes

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To summarise, the chemistry of metal catalysed and mediated nucleophilic additions to cyclopropenes has evolved considerably over the past several years, but there are still challenges to be confronted. They include the need to discover new enantioselective carbometallation procedures; to broaden the scope of directed addition reactions to tolerate heteroatom nucleophiles; and to develop complementary schemes for regiocontrol of addition reaction protocols. The field is dynamic and growing, and we look forward to exploring more about cyclopropene reactivity and understanding the ways in which these high energy molecules can be used for the rapid generation of molecular complexity.

1.4) Addition-Ring Opening Reaction of Cyclopropenes

As shown above, cyclopropenes are highly susceptible to a range of useful carbometallation reactions. However, a significant majority of examples result in preservation of the three-membered ring to provide highly functionalised cyclopropanes (Scheme 1.31, left side).

![Scheme 1.31 Addition of organometallic reagents to cyclopropenes](image)

Within the Lam group we are interested in developing new, mild, catalytic methodologies for the ring-opening of cyclopropenes to provide a synthetically useful route to access multisubstituted alkenes. We aim to develop a range of carbometallation reactions that employ cyclopropenes rather than alkynes as substrates which result in cleavage of a C-C σ-bond. This mode of addition is

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expected to be favoured by the presence of anion-stabilising substituents at R² and R³, and selectivity issues that would need to be addressed are: (i) regioselectivity with unsymmetrical cyclopropenes (R¹ ≠ R⁴) and (ii) E/Z stereoselectivity of the alkene in the product (Scheme 1.31, right side).

Despite the potential utility of this transformation, only a limited number of examples have been described in the literature. As mentioned previously in one case, the carboindation of cyclopropenylmethol acetate 55b led to ring-opening triene product in unspecified yield.42

One hydroalumination-ring-opening sequence reported by Marek has achieved excellent yields and good regioselectivities (Scheme 1.32).45 Reduction of cyclopropenylcarbinol 65 using LiAlH₄ generated the cyclopropylaluminium intermediate 66 which underwent an elimination reaction to yield the corresponding diene 67 at 80 °C.

![Scheme 1.32 Hydroalumination-ring-opening of cyclopropenes](image)

The single existing report of catalytic cyclopropene addition-ring-opening reactions using carbon nucleophiles was restricted to 3,3-dihexylcyclopropene 68 as the substrate. In the presence of a palladium catalyst, hydrocarbonation of dihexylcyclopropene 68 with ethyl 2-cyanopropanoate 69 gave the ring-opening product 70 in high yield. Regio- and stereoselectivity issues were not relevant in this case (Scheme 1.33).46
Scheme 1.33 Catalytic addition-ring-opening of 3,3-dihexylcyclopropene

The only examples of cyclopropene addition-ring-opening reactions using hard organometallic reagents as nucleophiles were uncatalysed and displayed low efficiencies and limited scope (Scheme 1.34). Using two equivalents of triisobutylaluminium, trimethylcyclopropene 71 underwent addition-ring-opening sequence to form two isomers in low yields.

Scheme 1.34 Uncatalysed cyclopropene addition-ring-opening using hard organometallic reagents

Therefore, a highly selective catalyst for carbometallation ring-openings reaction is greatly in demand. Meanwhile, the stability and reactivity of cyclopropenes are also essential issues to be concerned with.

To put our work into context, it is worth reviewing the classic schemes for preparing alkenes by carbometallation of alkynes using various organometallic reagents.
1.5) Preparation of Alkenes by Carbometallation of Alkynes

Although numerous methods exist for the preparation of alkenes, the stereoselective synthesis of multisubstituted alkenes can still pose significant challenges. One of the most widely used methods that has enjoyed considerable success in this respect is the carbometallation of alkynes. Depending on the nature of the metal or catalyst used, carbometallation of the alkyne may proceed in a syn or anti fashion (Scheme 1.35).

![Scheme 1.35 Regio- and stereoisomeric possibilities from carbometallation processes](image)

The use of symmetrical alkynes greatly simplifies many of the synthetic issues. However, this results in a decrease in structural flexibility. For example, treating with Schwartz’s reagent, 3-hexyne 76 can form vinylic alane 77 (Scheme 1.36). This intermediate could then be transmetallated to the corresponding copper reagent for subsequent condensation with methyl vinyl ketone (MVK).

![Scheme 1.36 Approach to tetrasubstituted alkenes using symmetric alkynes](image)

Zinc has been used in several instances to prepare tetrasubstituted olefins, primarily through Negishi coupling reactions, but also in other contexts. For example, the
Carbozincation of alkynes was described in which nickel catalysis provided smooth *syn* addition of diethylzinc to diphenylacetylene 79 affording a vinyl zinc intermediate 80. This intermediate could be captured using different electrophiles to give tetrastubstituted products 81a-b (Scheme 1.37). 49

![Scheme 1.37 Carbozincation of alkynes](image)

With unsymmetrical alkyne substrates, the problem of regioselectivity is usually addressed by the use of directing groups. This directing influence may be steric, electronic, or chelating in nature.

For example, the carbomagnesiation of alkyne 82 could be catalysed by a simple chromium salt with high efficiency. 50 The regioselectivity was simply governed by the steric factor of the two substituents of the alkyne (Scheme 1.38).

![Scheme 1.38 Carbomagnesiation of alkynes](image)

Another convenient regio- and stereoselective carbometallation route to tetrastubstituted olefins 51 involves *cis*-addition of Pd to the more electron-deficient...
end of the alkyne 85, and the phenyl group from the aryl iodide 84 to the more electron-rich end. Subsequent Suzuki coupling of the arylboronic acid 86 with vinylic palladium intermediate formed to tetrasubstituted product 87. (Scheme 1.39)

\[
\begin{align*}
\text{Scheme 1.39 Carbopalladation of alkynes}
\end{align*}
\]

The addition of Grignard reagents to alkynes, which often proceeds in an anti fashion, has proven to be highly regioselective by using directing groups. Most of the known methods build on a previously developed carbomagnesiation process, in which the Grignard reagent was added to propargylic alcohol 88 to give the chelated intermediate 89. The magnesium species could then be converted into iodide 90 and cross-coupled using zinc reagents after protecting the hydroxyl group. The anti fashion set the initial stereochemistry is preserved in the subsequent coupling (Scheme 1.40).

\[
\begin{align*}
\text{Scheme 1.40 Directed regioselective carbomagnesiation of alkynes}
\end{align*}
\]

Although the initial addition across the \( \pi \) bond may be stereoselective or stereospecific, in some cases there is configurational erosion or full inversion during the subsequent coupling reaction. Loss of configurational integrity typically occurs
through tautomerisation or elimination processes. This is usually a consequence of the low reactivity of the intermediates and can be suppressed by simply keeping the reaction at low temperatures, by improving substrate design, or by carefully selecting the catalyst.

Some of the earliest attempted carbometallations involved the syn conjugate addition of copper species to α,β-acetylenic ester 92 with excellent regiocontrol (Scheme 1.41). It was noted that isomerisation of the cuprate intermediates occurred at higher temperatures and so quenching the reaction at -78 °C was imperative.

![Scheme 1.41 Carbocupration of alkynes](image)

In order to avoid isomerisation of the copper intermediate, acetals were employed as directing groups (Scheme 1.42). The reaction carried out in THF prevents the competing elimination pathway to form allene 98. The vinyl cuprate intermediate 96 proved to have low reactivity, and tetrasubstituted olefin 97 could only be obtained by using powerful electrophiles such as methyl iodide.
Contrary to propargylic alcohol carboxymagnesiation examples (Scheme 1.40), the opposite regioselectivity was observed with homopropargylic alcohol 99 using an iron salt catalyst (Scheme 1.43).

The proposed mechanism suggested that Fe(III) salt was reduced by the Grignard reagent to yield the Fe(II) complex 101. Alkoxide-directed carbometallation likely to yield a vinyl iron intermediate 102. In principle, direct coordination to the iron centre could occur to give 102a. Alternatively, the interaction could be driven by association of iron with magnesium (102b). The vinyl iron species then undergoes metathesis with the Grignard reagent to provide the carbometallated product 103 and the catalyst is regenerated (Scheme 1.44).
Scheme 1.44 The mechanism for iron catalysed carbomagnesiation of propargylic alcohols

Despite the success of carbometallation of alkynes shown above, the development of new carbometallation procedures that tolerate an increased range of substrates and organometallic reagents to enable access to a correspondingly broader array of alkenes remains an important goal.
1.6) Results and Discussion

In order to attempt our initial idea on cyclopropene carbometallation-ring-opening reaction, a range of trisubstituted cyclopropenes 108a-j were synthesised in our group by rhodium-catalysed cycloaddition of terminal alkynes according to the literature procedures (Scheme 1.46, see details in the Experimental Section). Various electron-withdrawing groups have been equipped at the C-3 of the ring to hopefully promote the desired carbonmetallation reactions. Dialkyl malonates and sulfonyle ylide 104 were firstly treated with tosyl azide 105 to generate diazo compounds 106 (Scheme 1.45). Slow addition of the alkyne substrates 107a-i to the diazo compound solutions significantly suppressed homocoupling of the alkyne and furan formation.

Scheme 1.45 Synthesis of diazo compounds

Scheme 1.46 Synthesis of trisubstituted cyclopropenes

* Result obtained by Euan Fordyce and Jacky Chen
Others obtained by Yi Wang
1.6.1) Synthesis of Trisubstituted Alkenes using Trialkylaluminium

Previous work within the group has concentrated on the use of diethylzinc as a stoichiometric reductant, with various transition metals employed as catalysts. It was found that ring-opening reactions of trisubstituted cyclopropenes did occur in low to moderate yields with or without catalyst (Table 1.1, entry 1-6, results obtained by Dr Euan Fordyce). However, the regioselectivities or the reactions were found to be low, unseparable mixtures of isomers were usually obtained.

**Table 1.1** Catalyst screening for carbometallation-ring-opening reaction of cyclopropenes

<table>
<thead>
<tr>
<th>entry</th>
<th>R-M</th>
<th>catalyst</th>
<th>yield</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂Zn</td>
<td>Blank</td>
<td>33a</td>
<td>mixture of 109a and 109b</td>
</tr>
<tr>
<td>2</td>
<td>Et₂Zn</td>
<td>Zn(OTf)₂</td>
<td>33a</td>
<td>mixture of 109a and 109b</td>
</tr>
<tr>
<td>3</td>
<td>Et₂Zn</td>
<td>Cu(acac)₂</td>
<td>55b</td>
<td>109a</td>
</tr>
<tr>
<td>4</td>
<td>Et₂Zn</td>
<td>Ni(acac)₂</td>
<td>22b</td>
<td>109a</td>
</tr>
<tr>
<td>5</td>
<td>Et₂Zn</td>
<td>Co(acac)₂</td>
<td>55a</td>
<td>mixture of 109a and 109b</td>
</tr>
<tr>
<td>6</td>
<td>Et₂Zn</td>
<td>Fe(acac)₂</td>
<td>47a</td>
<td>mixture of 109a and 109b</td>
</tr>
<tr>
<td>7</td>
<td>Et₃Al</td>
<td>Cu(acac)₂</td>
<td>24b</td>
<td>109a</td>
</tr>
<tr>
<td>8</td>
<td>EtMgBr</td>
<td>Cu(acac)₂</td>
<td>24b</td>
<td>109a</td>
</tr>
<tr>
<td>9</td>
<td>Et₃Al</td>
<td>Fe(acac)₃</td>
<td>30b (82b,c)</td>
<td>109a</td>
</tr>
<tr>
<td>10</td>
<td>Et₃Al</td>
<td>Blank</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

*a* Crude yield, unidentified E/Z isomers  
*b* Isolated yield, only E isomer  
*c* Using Rochelle’s salt solution for aqueous workup
Therefore, our focus switched from zinc to other organometallic reagents, such as Grignard and aluminium reagents. In the presence of Cu(acac)$_2$, Me$_3$Al and the Grignard reagent (entry 7 and 8, results obtained by Dr Euan Fordyce) gave the same low yield.

After a quick survey into other first-row d-block metal salts, I discovered that Fe(acac)$_3$ (5 mol%) is able to promote the desired carbometallation-ring opening sequence using trialkylaluminium reagents. The initial isolated yield was as low as 30%. After introducing Rochelle’s salt solution in the aqueous workup, the alkene product was isolated in 82% (entry 9, results obtained by Yi Wang). Control reaction (entry 10, results obtained by Yi Wang) showed that the same reaction with Et$_3$Al did not proceed in the absence of Fe(acac)$_3$ catalyst. The reaction mixture turned into sticky gels, with no evidence of the desired products.

Under optimised conditions, cyclopropanes 108a-h containing two electron-withdrawing groups at C3 reacted smoothly with trimethylaluminium to provide a variety of trisubstituted alkenes 110a-h in good to excellent yields with uniformly high stereoselectivities (>19:1 by $^1$H NMR analysis of the unpurified reaction mixtures) (Table 1.2).

The sense of regioselection was obvious from their NMR spectra and consistent with the majority of carbometallations of 1-alkylcyclopropanes described previously,$^{1d}$ wherein the alkyl nucleophile is delivered to the more substituted carbon of the alkene.
**Table 1.2** Iron-catalysed carbometallation-ring-opening of cyclopropenes with trimethylaluminium reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108a R = n-Bu</td>
<td>110a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>108b R = CH₂CH₂Ph</td>
<td>110b</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>108c R = CH₂CH₂OBz</td>
<td>110c</td>
<td>78</td>
</tr>
<tr>
<td>4</td>
<td>108d R = Ph</td>
<td>110d</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>108e R = p-Tol</td>
<td>110e</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>108f</td>
<td>110f</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>108g</td>
<td>110g</td>
<td>66</td>
</tr>
<tr>
<td>8</td>
<td>108h</td>
<td>110h</td>
<td>61</td>
</tr>
</tbody>
</table>

The stereochemistries of **110b** and **110d** were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:

**Scheme 1.47** NOESY diagnostic enhancements
Notably, 1-arylcyclopropenes, which have proven to be problematic substrates with respect to regioselectivity using other carbometallation procedures,\textsuperscript{14,40} also undergo highly regioselective reactions under the present conditions. Tolerated functionality at C3 encompassed a range of esters (entry 6 and 7) and a phenylsulfone (entry 8), while both alkyl and aromatic substitution at the cyclopropene alkene was permitted.

Cyclopropenes without two electron-withdrawing groups at C3, such as \textbf{111} and \textbf{112} (Scheme 1.48), were not competent substrates for carbometallation using trialkylaluminium reagents in conjunction with Fe(acac)\textsubscript{3} as the precatalyst, only starting materials were observed in the reaction mixtures.

![Scheme 1.48 Unreacted cyclopropenes](image)

Regarding the organometallic reagent scope, trialkylaluminiums ranging from linear (Me\textsubscript{3}Al, Et\textsubscript{3}Al, \textit{n}-Pr\textsubscript{3}Al, and \textit{n}-Hex\textsubscript{3}Al) to branched (\textit{i}-Bu\textsubscript{3}Al) were effective. Using triethylaluminium (Table 1.3), trisubstituted malonate-derived cyclopropenes also smoothly ring-opened to generate trisubstituted alkenes \textbf{113a-f}. 

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Table 1.3 Iron-catalysed carbometallation-ring-opening of cyclopropenes with triethylaluminium reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108a ( R = n\text{-Bu} )</td>
<td>( \text{EtCO}_2\text{Me} )</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>108b ( R = \text{CH}_2\text{CH}_2\text{Ph} )</td>
<td>( \text{PhCO}_2\text{Me} )</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>108c ( R = \text{CH}_2\text{CH}_2\text{OBz} )</td>
<td>( \text{BzOEtCO}_2\text{Me} )</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>108d ( R = \text{Ph} )</td>
<td>( \text{PhCO}_2\text{Me} )</td>
<td>82(^a)</td>
</tr>
<tr>
<td>5</td>
<td>108e ( R = p\text{-Tol} )</td>
<td>( p\text{-TolCO}_2\text{Me} )</td>
<td>71</td>
</tr>
<tr>
<td>6</td>
<td>108f</td>
<td>( \text{EtCO}_2\text{Et} )</td>
<td>77</td>
</tr>
</tbody>
</table>

Note: The yield is 67% using 0.5 equivalents of \( \text{Et}_3\text{Al} \).

Although two equivalents of the trialkylaluminium reagent were routinely used in all experiments, smaller quantities are tolerated. For example, alkene 113b was isolated in 67% yield using only 0.5 equivalents of \( \text{Et}_3\text{Al} \), demonstrating that transfer of more than one alkyl group from aluminium is possible (entry 4).

The regioselectivities of those reactions using more bulky trialkylaluminium reagents such as \( n\text{-Pr}_3\text{Al} \), \( i\text{-Bu}_3\text{Al} \) and \( n\text{-Hex}_3\text{Al} \) were also uniformly high (>19:1) (Table 1.4). The stereochemistry of 113d was assigned by NOESY experiment, the stereochemistries of the remaining trisubstituted alkenes in Table 1.3 and 1.4 were assigned by analogy.

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However, due to the steric hindrance, butyl and hexyl groups were more difficult to deliver to the cyclopropene ring than methyl and ethyl groups. Some unreacted starting materials were observed and relatively lower yields were obtained.

**Table 1.4** Iron-catalysed carbometallation-ring-opening of cyclopropenes with trialkylaluminium reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>$R^3$Al</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO₂C</td>
<td>(n-Pr)$_3$Al</td>
<td>114a</td>
<td>90</td>
</tr>
<tr>
<td></td>
<td>CO₂Me</td>
<td></td>
<td>CO₂Me</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>P-Tol</td>
<td>(n-Pr)$_3$Al</td>
<td>114b</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>CO₂Me</td>
<td></td>
<td>CO₂Me</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>EnO₂C</td>
<td>(n-Pr)$_3$Al</td>
<td>114c</td>
<td>63</td>
</tr>
<tr>
<td></td>
<td>CO₂Bn</td>
<td></td>
<td>CO₂Bn</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeO₂C</td>
<td>(n-Hex)$_3$Al</td>
<td>114d</td>
<td>66</td>
</tr>
<tr>
<td></td>
<td>CO₂Me</td>
<td></td>
<td>CO₂Me</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>MeO₂C</td>
<td>(n-Hex)$_3$Al</td>
<td>114e</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td>CO₂Me</td>
<td></td>
<td>CO₂Me</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>MeO₂C</td>
<td>(i-Bu)$_3$Al</td>
<td>114f</td>
<td>62</td>
</tr>
<tr>
<td></td>
<td>CO₂Me</td>
<td></td>
<td>CO₂Me</td>
<td></td>
</tr>
</tbody>
</table>
1.6.2) Synthesis of Tetrasubstituted Alkenes using Trialkylaluminium

The more challenging task of tetrasubstituted alkene synthesis was next addressed. According to a previously reported direct silylation procedure developed in the Lam group,\(^{58}\) a few tetrasubstituted cyclopropenes 115a-d have also been prepared conveniently (Table 1.5) using TMSCF\(_3\) as the silylating agent in conjunction with substoichiometric quantities of Cu(acac)$_2$ and dppe.

\[
\begin{align*}
\textbf{Table 1.5} & \quad \text{Direct Silylation of Assorted Cyclopropenes} \\
\text{entry} & \quad \text{substrate} & \quad \text{product} & \quad \text{yield (\%)} \\
1 & \text{MeO}_2\text{C} & \text{CO}_2\text{Me} & 108d & 115a & 88 \\
2 & \text{MeO}_2\text{C} & \text{CO}_2\text{Me} & 108e & 115b & 90 \\
3 & \text{MeO}_2\text{C} & \text{CO}_2\text{Me} & 108a & 115c & 99 \\
4 & \text{MeO}_2\text{C} & \text{CO}_2\text{Me} & 108b & 115d & 75
\end{align*}
\]

Using conditions identical to those employed in Table 1.2-1.4, a range of 1-silylcyclopropenes 115a-d underwent carbometallation-ring-opening to provide $\alpha,\beta,\beta'$-trisubstituted vinylsilanes 116a-d (Table 1.6). Importantly, the sense of regioselectivity obtained in these reactions is opposite to that observed in Table 1.2,
with the alkyl group delivered preferentially to the TMS-bearing carbon. Regioselectivity was highest (>19:1) with aryl-substituted cyclopropenes (entry 1, 2, 4 and 6); with alkyl-substituted cyclopropenes, formation of the regioisomer was observed (entry 3 and 5).

Table 1.6 Iron-catalysed carbometallation-ring-opening of cyclopropenes with trialkylaluminium reagents

<table>
<thead>
<tr>
<th>Entry</th>
<th>substrate</th>
<th>R_2^3Al</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /></td>
<td>Me_3Al</td>
<td><img src="image2.png" alt="Image" /></td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /></td>
<td>Me_3Al</td>
<td><img src="image4.png" alt="Image" /></td>
<td>71</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /></td>
<td>Me_3Al</td>
<td><img src="image6.png" alt="Image" /></td>
<td>68^a</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /></td>
<td>Et_3Al</td>
<td><img src="image8.png" alt="Image" /></td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /></td>
<td>Et_3Al</td>
<td><img src="image10.png" alt="Image" /></td>
<td>72^b</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /></td>
<td>(n-Pr)_3Al</td>
<td><img src="image12.png" alt="Image" /></td>
<td>88</td>
</tr>
</tbody>
</table>

^a 6:1 regioisomeric ratio  ^b 5:1 regioisomeric ratio

By replacing TMSCF_3 with Bu_3SnCF_2CF_3, we were able to access the corresponding stannylated cyclopropenes using stoichiometric KF in DMF at 40 °C. In similar...
fashion, the use of 1-stannylcyclopropenes \textbf{117} enabled the synthesis of \( \alpha,\beta,\beta' \)-trisubstituted vinylstannanes \textbf{118} (Scheme 1.50).

![Scheme 1.50 Ring-opening of stannylated cyclopropenes](image)

\textbf{Scheme 1.50} Ring-opening of stannylated cyclopropenes

Finally, this methodology was applied to preparation of all-carbon tetrasubstituted alkenes (Scheme 1.51). Cyclopropenes \textbf{119a-c} underwent efficient carbometallation-ring-opening to provide tetrasubstituted alkenes \textbf{120a-c}. With unsymmetrical substrate \textbf{119c}, the alkyl group was delivered preferentially to the methyl-substituted carbon of the cyclopropene. This phenomenon could be explained by the steric hindrance when attacking the phenyl substituted carbon of cyclopropene.

![Scheme 1.51 Ring-opening of all-carbon tetrasubstituted cyclopropenes](image)

\textbf{Scheme 1.51} Ring-opening of all-carbon tetrasubstituted cyclopropenes
The regio- and/or stereoselectivities of carbometallation-ring-opening of tetrasubstituted cyclopropenes producing tetrasubstituted alkenes were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:

Scheme 1.52 NOESY diagnostic enhancements

The stereochemistries of the remaining tetrasubstituted alkenes were assigned by analogy.

Scheme 1.53 illustrates a possible catalytic cycle for these reactions. Reaction of Fe(acac)₃ with the trialkylaluminium most likely generates a low-valent iron species 121. Syn-carbometallation of the substrate 122 with 121 would generate cyclopropyl iron species 123. β-Carbon elimination ⁶⁰ of 123 with conservation of the cis-relationship between R₂ and R₃ would then provide iron enolate 124, which can undergo transmetallation with further trialkylaluminium to provide aluminium enolate 125 and regenerate 121. The assistance of β-carbon elimination of 123 by Lewis acid coordination of the trialkylaluminium to the malonate to provide enolate 125 directly is a possibility that should also be considered.
Although *in situ* functionalisation of the aluminium enolate 125 was an attractive possibility for obtaining other compounds of interest, we found these species to be rather unreactive, and attempted trapping with various electrophiles was unsuccessful. Therefore, our attention turned to elaboration of the isolated ring-opened products. A major concern with this approach is the potential sensitivity of these compounds towards isomerisation of the alkene into conjugation with the esters, or scrambling of the $E/Z$ stereochemistry of the alkene. However, we have found these issues not to be problematic. For example, Michael addition or alkylation of the ring-opened products could be accomplished efficiently without compromising the integrity of the alkene (Scheme 1.54).

**Scheme 1.53 Possible catalytic cycle**

**Scheme 1.54 Michael addition or alkylation of the ring-opened products**
Furthermore, Krapcho decarboxylation of both tri- and tetrasubstituted alkenes proceeded smoothly under microwave irradiation to provide $\beta,\gamma$-unsaturated esters 128 and 129 in good yields (Scheme 1.55).

![Scheme 1.55 Krapcho decarboxylation](image)

The stereochemistries of the alkenes in products 126, 128, and 129 were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:

![Scheme 1.56 NOESY diagnostic enhancements](image)

In summary, an iron-catalysed cyclopropene carbometallation-ring-opening sequence that enables the efficient synthesis of tri- and tetrasubstituted alkenes has been developed. The reactions proceed with high levels of regio- and stereocontrol to produce a range of multisubstituted alkenes that may be difficult to access by other means, including $\alpha,\beta,\beta'$-trisubstituted vinylsilanes, $\alpha,\beta,\beta'$-trisubstituted vinylstannanes, and all-carbon tetrasubstituted alkenes. In addition, the ring-opened products may be manipulated without affecting the alkene.
1.6.3) Synthesis of Trisubstituted Alkenes using Grignard Reagents

The ability to prepare trisubstituted alkenes of differing substitution patterns would represent a powerful complement to this methodology. When searching for reaction conditions that would favour the opposite regioselectivity in the initial carbometallation event, various Grignard reagents were employed (Scheme 1.57). Early investigations indicated that methylmagnesium bromide and allylmagnesium bromide actually attacked the diester groups at 0 °C. According to TLC test, no reaction occurred at lower temperature such as -78 °C. Meanwhile, 2-thiophenylmagnesium bromide, (4-fluorophenyl) magnesium bromide and (4-methoxyphenyl)magnesium bromide gave tiny alkene products as mixtures of regioisomers. The presence of iron catalyst made no difference to the yield and regioselectivity in those reactions.

![Scheme 1.57 Attempted Grignard reagents promoted ring-opening reactions](image)

It was discovered that by simply treating malonate-derived cyclopropenes 108a-e with phenylmagnesium bromide and phenethylmagnesium bromide in the absence of catalyst, trisubstituted alkenes 120a-f were obtained efficiently, again with high stereoselectivities (Table 1.7).
It was also found that the aryl group was delivered to the less substituted carbon of the alkene. The yields were relatively high, while slightly lower yield was obtained from propyl benzoate substituted cyclopropene due to decomposition of the starting material. The crude NMR showed the Grignard reagent attacked the phenyl ester.

**Table 1.7** Synthesis of trisubstituted alkenes using Grignard reagents

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>R²MgCl</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO₂C₅CO₂Me</td>
<td>108a</td>
<td>PhCH₂CH₂MgCl</td>
<td>120a</td>
</tr>
<tr>
<td>2</td>
<td>MeO₂C₅CO₂Me</td>
<td>108d</td>
<td>PhCH₂CH₂MgCl</td>
<td>120b</td>
</tr>
<tr>
<td>3</td>
<td>MeO₂C₅CO₂Me</td>
<td>108d</td>
<td>PhMgCl</td>
<td>120c</td>
</tr>
<tr>
<td>4</td>
<td>MeO₂C₅CO₂Me</td>
<td>108b</td>
<td>PhMgCl</td>
<td>120d</td>
</tr>
<tr>
<td>5</td>
<td>MeO₂C₅CO₂Me</td>
<td>108e</td>
<td>PhMgCl</td>
<td>120e</td>
</tr>
<tr>
<td>6</td>
<td>MeO₂C₅CO₂Me</td>
<td>108c</td>
<td>PhMgCl</td>
<td>120f</td>
</tr>
</tbody>
</table>

The regioselectivity of Grignard reagent induced ring-opening of trisubstituted cyclopropenes producing trisubstituted alkenes was obvious from their NMR spectra. The stereochemistries of the alkene products 120b and 120d were assigned on the
basis of NOESY experiments. Due to the similarity of R$^2$ and R$^3$ groups, the remaining trisubstituted alkenes in Table 1.7 were assigned by analogy.

![Diagram](image1)

**Scheme 1.58** NOESY diagnostic enhancements

### 1.6.4) Synthesis of Trisubstituted Alkenes using Magnesium Halide Salts

During previous investigations (Scheme 1.57) into the development of stereoselective carbometallation-ring-opening reactions of bis-activated cyclopropenes and Grignard reagents to produce multisubstituted alkenes, commercially available dioxolane derived Grignard 121 was reacted with cyclopropene 108d (Scheme 1.59).

![Reaction](image2)

**Scheme 1.59** Reaction of dioxolane derived Grignard with cyclopropenes

Surprisingly, instead of furnishing product 122a derived from addition of the nucleophilic dioxolane functionality of 121, the major product isolated in this reaction was the alkenyl bromide 122b. We attributed this initially surprising result to reaction of cyclopropene 108d with magnesium bromide produced from the Schlenk equilibrium of the Grignard reagent. This hypothesis was supported by
reaction of $^{108d}$ with $\text{MgBr}_2$ itself, which also produced $^{122b}$ in 96% yield (Scheme 1.60).

$$\begin{align*}
\text{Scheme 1.60} \quad &\text{MgBr}_2 \text{ promoted ring-opening of cyclopropenes} \\
\text{This process was closely related to the results of Ma and co-workers, who described} \\
a \text{series of alkali metal halide-induced cyclopropene ring-opening-alkylation} \\
\text{reactions.}^{61} \text{ In their work, the majority of examples were conducted using a} \\
\text{bis-activated cyclopropene that was unsubstituted at the alkene, but four results using} \\
\text{trisubstituted cyclopropenes were reported (representative example shown in Scheme} \\
\text{1.61).} \\
\end{align*}$$

To establish whether the serendipitous result (Scheme 1.60) could be translated into a 

general and efficient process, a range of bis-activated cyclopropenes $^{108a-h}$ were 

reacted with stoichiometric quantities of magnesium halides (Table 1.8 and 1.9). 

Using $\text{MgBr}_2$, cyclopropenes $^{108a-e}$ containing alkyl or aryl functionality on the 

alkene efficiently underwent the halide addition-ring-opening reaction to provide 

alkenyl bromides $^{124a-e}$ respectively in good yields and with high stereoselectivities 

(Table 1.8). In all cases, the bromide anion attacked the least substituted carbon of 

the alkene. This regioselectivity is opposite to that seen in the large majority of
cyclopropene carbometallation and hydrometallation reactions described previously, but consistent with the results of Ma and co-workers (Scheme 1.61).

**Table 1.8 MgBr₂ Mediated Ring-Openings of Various Cyclopropenes**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108d</td>
<td>124a</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>108e</td>
<td>124b</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>108a</td>
<td>124c</td>
<td>75</td>
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<tr>
<td>4</td>
<td>108b</td>
<td>124d</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>108c</td>
<td>124e</td>
<td>84</td>
</tr>
</tbody>
</table>

Halide addition-ring-openings with MgI₂ and MgCl₂ also occurred smoothly to furnish alkenyl halides 125a-g (Table 1.9), though a reaction temperature of 40 °C was required in the case of MgCl₂ (entries 5-7). In addition to dimethyl malonate-derived substrates, cyclopropenes containing other activating groups were competent substrates (entries 4 and 7). Unfortunately, an attempt to employ MgF₂ as the fluoride source was unsuccessful, potentially, due to the extremely poor solubility of this salt. Testing more soluble alkali metal fluorides to assess the viability of fluorine atom incorporation was fruitless.
Table 1.9 Magnesium Halides-Mediated Ring-Openings of Various Cyclopropenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>MgX₂</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>108d</td>
<td>MgI₂</td>
<td>125a</td>
<td>97°¹</td>
</tr>
<tr>
<td>2</td>
<td>108e</td>
<td>MgI₂</td>
<td>125b</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>108b</td>
<td>MgI₂</td>
<td>125c</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>108h</td>
<td>MgI₂</td>
<td>125d</td>
<td>77</td>
</tr>
<tr>
<td>5</td>
<td>108e</td>
<td>MgCl₂</td>
<td>125e</td>
<td>83°²</td>
</tr>
<tr>
<td>6</td>
<td>108a</td>
<td>MgCl₂</td>
<td>125f</td>
<td>85°²</td>
</tr>
<tr>
<td>7</td>
<td>108j</td>
<td>MgCl₂</td>
<td>125g</td>
<td>62°²</td>
</tr>
</tbody>
</table>

a Product isolated as an inseparable 9:1 Z:E mixture.
b Reaction conducted at 40 °C

The stereoselectivities of magnesium halide-promoted ring-opening reactions producing alkenyl halides 124a, 124d and 125f were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:

Scheme 1.62 NOESY diagnostic enhancements
The stereochemical outcome of these reactions, where inversion of configuration at the electrophilic vinylic center is observed, suggests that this is not a common addition-elimination process that was proposed in previously described cyclopropene carbometallation-ring-opening reactions.\textsuperscript{1b}

More complicated than classic $S_N2$ reactions on a $sp^3$ carbon (Scheme 1.63a), the nucleophilic substitution on a vinylic $sp^2$ carbon can have many mechanistic possibilities. The most common pathway is an addition-elimination route $S_NV$, in which a nucleophile attacks the $\pi$-bond. If the double bond has an electron-withdrawing group ($R^2$ or $R^3$), the nucleophilic addition gives a stable anion intermediate and the successive elimination of a leaving group completes the reaction to give a mixture of $E/Z$ isomers (Scheme 1.63b). Otherwise, the lifetime of the intermediate becomes short enough and the reaction occurs in one step with retention of configuration of the double bond. It is called as $S_NV\pi$ mechanism because the nucleophile attacks the $\pi^*$ orbital of the vinylic carbons in an out-of-plane fashion (Scheme 1.63c). There is another possibility named $S_NV\sigma$ mechanism where a nucleophile attacks the $\sigma^*$ orbital of C-X bond of a vinylic carbon (Scheme 1.63d).

\begin{align*}
    \text{Scheme 1.63} & \quad \text{Different types of S}_{N2} \text{ reactions}
\end{align*}
This in-plane attack has been considered as an energetically unfavorable process due to steric repulsion, and an early theoretical study also denied the possibility of the $S_N V_\sigma$ pathway.\textsuperscript{62} However, recent theoretical and experimental studies suggest that this process is favourable in certain reactions.\textsuperscript{63, 64} For instance, the $(Z)$-vinyl-$\lambda^3$-iodane 126 undergoes a unusual vinylic $S_N 2$ reaction with $n$-Bu$_4$NBr to give the $(E)$-vinylic halide 128 with exclusive inversion of configuration. The reaction competes with ligand coupling on iodine(III) (Scheme 1.64).\textsuperscript{64c}

![Scheme 1.64](image)

**Scheme 1.64** An example of $S_N V_\sigma$ reaction

Regarding to our magnesium halide-promoted cyclopropene ring-opening reaction, the inversion of configuration at the electrophilic vinylic center suggested that an in-plane $S_N 2$-type mechanism ($S_N V_\sigma$) is operative. A possible mechanism using a dimethyl malonate-derived substrate for illustrative purposes is outlined in Scheme 1.65. It is likely that bidentate coordination of magnesium halide to the cyclopropene (as in 129) promotes nucleophilic attack by the halide ion to provide (via transition state 130) magnesium enolate 131, that is protonated upon workup to furnish the product.

![Scheme 1.65](image)

**Scheme 1.65** Possible mechanism

This mechanistic scenario suggested that trapping of the magnesium enolates to generate more highly functionalised products might be possible, in similar fashion to the results of Ma and co-workers (Scheme 1.61). Accordingly, various one-pot
multicomponent coupling reactions of bis-activated cyclopropenes, magnesium halides, and different electrophiles were investigated. However, we found these enolates to be rather unreactive, though Michael additions to $\beta$-unsubstituted enones using acetonitrile as the solvent were possible (Scheme 1.66).

Comparing with the NaI-catalysed ring-opening reactions previously reported by Ma, there is significant difference between the two works in the fate of the produced enolate intermediate. Thus, Ma demonstrated formation of the C-C bond via trapping of the enolate with allyl iodides and other $S_{N2}$-active alkyl halides. We employed protonolysis or trapping of the enolate via the Michael addition. Furthermore, different halide sources were used to trigger the overall transformation. While Ma employed an organic iodide or bromide in the presence of catalytic amounts of Lewis acid, we used inorganic salts, which also serve as a Lewis acid. Ultimately, this modification allowed for incorporation of iodine, bromine, and chlorine with equally high efficiency.
1.6.5) Conclusions

In summary, we have developed a catalytic, organometallic addition-ring opening sequence of cyclopropenes that enables the efficient and highly stereoselective synthesis of multisubstituted alkenes. A possible mechanism of organoaluminium reaction was proposed. The metalloenolate resulting from ring opening can be trapped with various electrophiles, enabling a rapid increase in molecular complexity in a one-pot operation. However, the Grignard reaction is still not fully investigated. If the diversity of Grignard reagents could be expanded and the enolate be trapped, the mechanism will be better understood.

We also describe a cascade reaction, which begins with Lewis-acid mediated regioselective $S_N\cdot\nu\sigma$ attack by a halogen nucleophile at the $sp^2$-carbon of cyclopropene, resulting in the formation of acyclic conjugate enolate, which can be trapped with enones to result in more highly functionalised products.
1.7) Experimental Section

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<tr>
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General Information

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Microwave reactions were carried out using a Biotage Initiator Eight microwave synthesiser. CH₂Cl₂, THF and MeCN were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystmes.com. ‘Petrol’ refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH₂. Commercially available CoCl₂ was dried by heating under vacuum until it turned from purple to blue. All other commercially available reagents were used as received. Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F₂₅₄ 0.2 mm precoated plates. Product spots were visualised 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. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker DMX500 (500 MHz) spectrometer or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ 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 ¹³C NMR spectra were recorded on a Bruker DPX360 (90.6 MHz) spectrometer or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm). Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. Low-resolution mass spectra were recorded on a Finnigan LCQ spectrometer. High-resolution mass spectra were recorded on a Finnigan MAT 900 XLT spectrometer or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer or a Kratos MS50TC spectrometer at the School of Chemistry, University of Edinburgh. Stated calculated mass values refer to that of the ion (i.e. the actual species being detected), not that of the neutral parent compound.

Preparation of Cyclopropenes

**Dimethyl 2-butylecycloprop-2-ene-1,1-dicarboxylate (108a)**. Prepared according to a previously reported procedure.

**Dimethyl 2-(2-phenylethyl)cycloprop-2-ene-1,1-dicarboxylate (108b)**.

To a stirred solution of Rh₂(OAc)₄ (22 mg, 0.05 mmol) and 4-phenyl-1-butyne (1.30 g, 10.0 mmol) in CH₂Cl₂ (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.09 g, 6.89 mmol) in CH₂Cl₂ (10 mL) via syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 8 h, filtered through a short pad of celite eluting with CH₂Cl₂, and concentrated in vacuo. Purification of the residue by column chromatography (hexane → 10% EtOAc/hexane) gave the cyclopropene **108b** (1.05 g, 59%) as a yellow oil. IR (CHCl₃) 3141, 3029, 2951, 2843, 1731 (C=O), 1603, 1496, 1454, 1435, 1281 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.36-7.34 (2H, m, ArH), 7.32-7.26 (3H, m, ArH), 6.43 (1H, s, =CH), 3.75 (6H, s, 2 x OCH₃), 3.01-2.98 (2H, m, CH₂), 2.95-2.93 (2H, m, CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.7 (2 x C), 140.1 (C), 128.4 (2 x CH), 128.2 (2 x CH), 126.3 (CH), 113.8 (C), 94.3 (CH), 52.2 (2 x CH₃), 32.5 (CH₂), 25.5 (CH₂); HRMS (ES) Exact mass calcd for C₁₅H₁₇O₄ [M+H]+: 261.1121, found: 261.1122.

**Dimethyl 2-(2-benzoyloxyethyl)cycloprop-2-ene-1,1-dicarboxylate (108c)**. Prepared according to a previously reported procedure.

---


Dimethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (108d).
Prepared according to a previously reported procedure.\textsuperscript{e}

Dimethyl 2-(4-methylphenyl)cycloprop-2-ene-1,1-dicarboxylate (108e).
Prepared according to a previously reported procedure.\textsuperscript{f}

Diethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (108f).\textsuperscript{g}
Prepared according to a previously reported procedure.\textsuperscript{g}

Dibenzyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (108g)

To a stirred mixture of Rh\textsubscript{2}(OAc)\textsubscript{4} (22 mg, 0.05 mmol) and phenylacetylene (1.53 g, 15.0 mmol) at room temperature was added a solution of dibenzyl diazomalonate\textsuperscript{h} (1.55 g, 5.00 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (10 mL) via syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite eluting with CH\textsubscript{2}Cl\textsubscript{2}, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) gave the cyclopropene 108g (1.01 g, 53%) as a pale yellow solid. m.p. 46-48 °C; IR (CHCl\textsubscript{3}) 3033, 1735 (C=O), 1497, 1456, 1376, 1271, 1055, 481 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (360 MHz, CDCl\textsubscript{3}) \(\delta\) 7.64-7.61 (2H, m, ArH), 7.44-7.42 (3H, m, ArH), 7.32-7.28 (10H, m, ArH), 6.93 (1H, s, =CH), 5.20 (4H, s, 2 x OCH\textsubscript{2}); \textsuperscript{13}C NMR (62.9 MHz, CDCl\textsubscript{3}) \(\delta\) 170.5 (2 x C), 135.8 (2 x C), 130.6 (CH), 130.4 (2 x CH), 128.8 (2 x CH), 128.4 (4 x

CH), 128.0 (2 x CH), 127.8 (4 x CH), 123.9 (C), 112.4 (C), 95.1 (CH), 66.8 (2 x CH₂), 33.3 (C); HRMS (ES) Exact mass calcd for C₂₅H₂₁O₄ [M+H]⁺: 385.1434, found: 385.1430.

Methyl 2-phenyl-1-(phenylsulfonyl)cycloprop-2-enecarboxylate (108h)

To a stirred mixture of Rh₂(OAc)₄ (22 mg, 0.05 mmol) and phenylacetylene (1.53 g, 15.0 mmol) at room temperature was added a solution of methyl 2-diazo-2-(phenylsulfonyl)acetate (1.20 g, 5.00 mmol) in CH₂Cl₂ (10 mL) via syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite eluting with CH₂Cl₂, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane→20% EtOAc/hexane) gave the cyclopropene 108h (1.39 g, 89%) as a pale yellow solid. m.p. 135-137 °C; IR (CHCl₃) 3137, 1733 (C=O), 1489, 1447, 1305, 1257, 1149, 1087, 1017, 918 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.00-7.98 (2H, m, ArH), 7.64-7.44 (8H, m, ArH), 7.01 (1H, s, =CH), 3.67 (3H, s, OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.9 (C), 140.0 (C), 133.4 (CH), 131.4 (CH), 130.8 (2 x CH), 129.2 (2 x CH), 129.0 (2 x CH), 128.7 (2 x CH), 122.5 (C), 113.1 (C), 95.3 (C), 52.6 (CH₃), 52.2 (C); HRMS (ES) Exact mass calcd for C₁₇H₁₈NO₄S [M+NH₄]^+: 332.0951, found: 332.0951.

Dimethyl 2-hexylcycloprop-2-ene-1,1-dicarboxylate (108i)

To a stirred solution of Rh$_2$(OAc)$_4$ (44 mg, 0.10 mmol) and 1-octyne (2.20 g, 20.0 mmol) in CH$_2$Cl$_2$ (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.58 g, 10.0 mmol) in CH$_2$Cl$_2$ (8 mL) via syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 8 h, filtered through a short pad of celite eluting with CH$_2$Cl$_2$, and concentrated in vacuo. Purification of the residue by column chromatography (5%→10% EtOAc/hexane) gave cyclopropene 108i (1.26 g, 52%) as a yellow oil. IR (CHCl$_3$) 3139, 2955, 2860, 1734 (C=O), 1436, 1279, 1111, 1065, 841 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 6.34 (1H, s, =CH), 3.69 (6H, s, 2 x OCH$_3$), 2.52 (2H, t, $J = 7.1$ Hz, =CCH$_2$), 1.60-1.54 (2H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 1.36-1.24 (6H, m, CH$_2$CH$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 0.86 (3H, t, $J = 6.8$ Hz, CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 171.8 (2 x C), 114.5 (C), 93.4 (CH), 52.1 (2 x CH$_3$), 31.3 (CH$_2$), 28.6 (CH$_2$), 26.3 (CH$_2$), 23.9 (CH$_2$), 22.4 (CH$_2$), 13.9 (CH$_3$); HRMS (ES) Exact mass calc for C$_{13}$H$_{21}$O$_4$ [M+H]$^+$: 241.1434, found: 241.1432.

Diethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (108j). Prepared according to a previously reported procedure.

Dimethyl 2-phenyl-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (115a). Prepared according to a previously reported procedure.

Dimethyl 2-(4-methylphenyl)-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (115b). Prepared according to a previously reported procedure.

---

Dimethyl 2-butyl-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (115c).

Prepared according to a previously reported procedure.\textsuperscript{d}

Dimethyl 2-phenylethyl-3-(trimethylsilyl)cycloprop-2-ene-1,1-dicarboxylate (115d)

\[
\begin{align*}
\text{MeO}_2C & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2C & \quad \text{CO}_2\text{Me}
\end{align*}
\]

A solution of cyclopropene 108b (104 mg, 0.40 mmol), Cu(acac)$_2$ (5.3 mg, 0.02 mmol) and dppe (8.0 mg, 0.02 mmol) in THF (2 mL) was stirred at room temperature for 30 min. TMSCF$_3$ (118 \(\mu\)L, 0.80 mmol) was then added in one portion and the reaction was stirred at room temperature for 48 h. The reaction mixture was filtered through a short plug of SiO$_2$ (ca. 4 cm high x 2 cm diameter) using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated \textit{in vacuo}. Purification of the residue by column chromatography (hexane$\rightarrow$15\% EtOAc/hexane) gave the \textit{silylcyclopropene} 115d (100 mg, 75\%) as a colourless oil. IR (film) 2952, 1836, 1728 (C=O), 1497, 1455, 1435, 1251, 1066, 847, 762 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) \(\delta\) 7.33-7.28 (2H, m, ArH), 7.24-7.20 (3H, m, ArH), 3.68 (6H, s, 2 x OCH$_3$), 2.99-2.94 (2H, m, CH$_2$CH$_2$Ph), 2.92-2.89 (CH$_2$CH$_2$Ph), 0.18 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) \(\delta\) 172.2 (2 x C), 140.2 (C), 128.3 (2 x CH), 128.1 (2 x CH), 126.2 (CH), 122.7 (C), 105.0 (C), 51.8 (2 x CH$_3$), 33.7 (C), 32.7 (CH$_2$), 26.5 (CH$_2$), -1.8 (Si(CH$_3$)$_3$); HRMS (EI) Exact mass calcd for C$_{18}$H$_{24}$O$_4$Si [M]$^+$: 332.1438, found: 332.1438.

Dimethyl 2-phenyl-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (117a)

\[
\begin{align*}
\text{MeO}_2C & \quad \text{CO}_2\text{Me} \\
\text{MeO}_2C & \quad \text{CO}_2\text{Me}
\end{align*}
\]
A solution of cyclopropene 108d (46 mg, 0.20 mmol), KF (11.6 mg, 0.20 mmol), and 
Bu$_3$SnCF$_2$CF$_3$ (164 mg, 0.40 mmol) in DMF (0.8 mL) was stirred at 40 °C for 20 h. 
The reaction mixture was filtered through a short plug of SiO$_2$ (ca. 4 cm high x 2 cm 
diameter) using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. 
Purification of the residue by column chromatography (heptane→7.5% EtOAc/heptane) gave the stannylcyclopropene 117a (85 mg, 82%) as a colourless oil. 
IR (film) 2953, 2922, 1721 (C=O), 1489, 1433, 1278, 1231, 1062, 760, 689 cm$^{-1}$; 
$^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.58-7.54 (2H, m ArH), 7.45-7.34 (3H, m, ArH), 3.69 
(6H, s, 2 x OCH$_3$), 1.70-1.55 (6H, m, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$), 1.43-1.31 (6H, m, 
Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$), 1.24-1.18 (6H, m, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$), 0.93 (9H, t, $J$ = 
7.3 Hz, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 171.3 (2 x C), 129.0 
(CH), 128.8 (2 x CH), 128.1 (2 x CH), 125.7 (C), 123.2(C), 108.5 (C), 52.2 (2 x 
CH$_3$), 34.2 (C), 29.4 ($J_{Sn-C} = 11.1$ Hz, 3 x CH$_2$), 27.7 ($J_{Sn-C} = 30.0$ Hz, 3 x CH$_2$), 14.4 
(3 x CH$_3$), 12.0 ($J_{Sn-C} = 179.6$, 171.6 Hz, 3 x CH$_2$); HRMS (ES) Exact mass calcd for 
C$_{25}$H$_{38}$O$_4^{120}$Sn [M+H]$^+$: 523.1866, found: 523.1864.

**Dimethyl 2-hexyl-3-tributylstannylcycloprop-2-ene-1,1-dicarboxylate (117b)**

A solution of cyclopropene 108i (192 mg, 0.80 mmol), KF (47 mg, 0.80 mmol), and 
Bu$_3$SnCF$_3$ (575 mg, 1.60 mmol) in DMF (3.2 mL) was stirred at 40 °C for 17 h. The 
reaction mixture was filtered through a short plug of SiO$_2$ (ca. 4 cm high x 2 cm 
diameter) using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. 
Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) gave the stannylicyclopropene 117b (222 mg, 52%) as a colourless 
oil. IR (film) 2956, 2930, 2855, 1723 (C=O), 1462, 1434, 1281, 1069, 911, 734 cm$^{-1}$; 
$^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 3.66 (6H, s, 2 x OCH$_3$), 2.54 (2H, t, $J$ = 7.3 Hz, 
=CCH$_2$), 1.60-1.50 (8H, m, Sn(CH$_2$CH$_2$CH$_2$CH$_3$)$_3$ and =CCH$_2$CH$_2$), 1.36-1.26 (12H,
m, Sn(CH₂CH₂CH₃)₃ and CH₂(CH₂)₃CH₃, 1.09-1.05 (6H, m, Sn(CH₂CH₂CH₂CH₃)₃), 0.92 (9H, t, J = 7.3 Hz, Sn(CH₂CH₂CH₂CH₃)₃), 0.89 (3H, t, J = 7.1 Hz, (CH₂)₃CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 173.2 (2 x C), 125.4 (C), 103.4 (C), 51.6 (2 x CH₃), 33.4 (C), 31.5 (CH₂), 28.8 (CH₂), 28.8 (Jₚₙ-C = 11.0 Hz, 3 x CH₂), 27.0 (Jₚₙ-C = 29.4 Hz, 3 x CH₂), 26.6 (CH₂), 25.3 (CH₂), 22.5 (CH₂), 14.0 (CH₃), 13.6 (3 x CH₃), 10.8 (Jₚₙ-C not observable, 3 x CH₂).

**Dimethyl 2,3-diphenylcycloprop-2-ene-1,1-dicarboxylate (119a).** Prepared according to a previously reported procedure.

**Dimethyl 2-methyl-3-phenylcycloprop-2-ene-1,1-dicarboxylate (119b)**

To a stirred mixture of Rh₂(OAc)₄ (11 mg, 0.025 mmol) and 1-phenyl-1-propyne (1.12 g, 10.0 mmol) at room temperature was added a solution of dimethyl diazomalonate (800 mg, 5.00 mmol) in CH₂Cl₂ (8 mL) via syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 10 h, filtered through a short pad of celite eluting with CH₂Cl₂, and concentrated in vacuo. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) gave the cyclopropene 119b (600 mg, 49%) as a white solid. m.p. 89-91 °C; IR (CHCl₃) 2952, 1730 (C=O), 1514, 1492, 1435, 1284, 1243, 1064, 764 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.55-7.51 (2H, m, ArH), 7.44-7.33 (3H, m, ArH), 3.71 (6H, s, 2 x OCH₃), 2.36 (3H, s, =CCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.3 (2 x C), 129.5 (2 x CH), 129.3 (CH), 128.7 (2 x CH), 124.9 (C), 105.1 (C), 104.7 (C), 52.1 (2 x CH₃), 34.9 (C), 9.4 (CH₃); HRMS (EI) Exact mass calcd for C₁₄H₁₄O₄ [M]+: 246.0887, found: 246.0884.
Iron-Catalysed Carbometallation–Ring-Opening Reactions: General Procedure

To a solution of the appropriate cyclopropene (0.20 mmol) and Fe(acac)$_3$ (3.6 mg, 0.01 mmol) in THF (2 mL) at 0 °C was added the appropriate trialkylaluminium reagent (2 equiv, one of Me$_3$Al (2.0 M in hexanes), Et$_3$Al (1.0 M in hexanes), n-Pr$_3$Al (0.7 M in heptane), n-Hex$_3$Al (0.4 M in hexane), or i-Bu$_3$Al (1.0 M in hexanes)) dropwise over 1 min. The reaction was stirred at 0 °C for 1 h and then room temperature for 15 h, diluted with CH$_2$Cl$_2$ (10 mL) and poured into saturated aqueous Rochelle’s salt solution (20 mL). The mixture was stirred vigorously for 30 min and the aqueous layer was then separated and extracted with CH$_2$Cl$_2$ (3 x 15 mL). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. Purification of the residue by column chromatography gave the alkene product.

(1R,1′R)-Dimethyl 2-(2-methylhex-1-enyl)malonate (110a). The title compound was prepared according to the General Procedure from cyclopropene 108a (42 mg, 0.20 mmol) and Me$_3$Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (44 mg, 96%). IR (film) 2955, 2931, 1738 (C=O), 1617, 1435, 1297, 1260, 1214, 1148, 1086 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 5.46 (1H, m, $J = 9.4$ Hz, =CH), 4.28 (1H, d, $J = 9.4$ Hz, =CHCH), 3.74 (6H, s, 2 x OCH$_3$), 2.08-2.04 (2H, m, CH$_2$C=), 1.68 (3H, d, $J = 1.4$ Hz, CH$_3$C=), 1.43-1.37 (2H, m, CH$_3$CH$_2$CH$_2$), 1.32-1.26 (2H, m, CH$_3$CH$_2$CH$_2$), 0.90 (3H, t, $J = 7.2$ Hz, CH$_3$CH$_2$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 169.1 (2 x C), 142.2 (C), 115.5 (CH), 52.6 (2 x CH$_3$), 51.2 (CH), 39.2 (CH$_2$), 29.7 (CH$_2$), 22.2 (CH$_2$), 16.6 (CH$_3$), 13.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{12}$H$_{24}$NO$_4$ [M+NH$_4$]$^+$: 246.1700, found 246.1699.
(E)-Dimethyl 2-(2-methyl-4-phenylbut-1-enyl)malonate (110b). The title compound was prepared according to the General Procedure from cyclopropene 108b (52 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (43 mg, 78%). IR (film) 3027, 2952, 1737 (C=O), 1617 1496, 1454, 1435, 1303, 1213, 1147 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.30-7.26 (2H, m, ArH), 7.20-7.16 (3H, m, ArH), 5.49 (1H, d, J = 9.5 Hz, =CH), 4.29 (1H, d, J = 9.5 Hz, =CH), 3.74 (6H, s, 2 x OC₃H₃), 2.79-2.74 (2H, m, PhCH₂), 2.41-2.36 (2H, m, CH₂C=), 1.75 (3H, d, J = 1.3 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.9 (2 x C), 141.7 (C), 141.2 (C), 128.3 (4 x CH), 125.8 (CH), 116.3 (CH), 52.6 (2 x CH₃), 51.2 (CH), 41.2 (CH₂), 34.1 (CH₂), 16.8 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₄NO₆ [M+NH₄]⁺: 338.1598, found: 338.1599.

(E)-Dimethyl 2-[2-(benzoyloxy)prop-1-enyl]malonate (110c). The title compound was prepared according to General Procedure from cyclopropene 108c (61 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (50 mg, 78%). IR (film) 2954, 1738 (C=O), 1720, 1452, 1435, 1275, 1214, 1150, 1114, 1070 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.04-8.01 (2H, m, ArH), 7.58-7.53 (1H, m, ArH), 7.46-7.42 (2H, m, ArH), 5.64 (1H, d, J = 9.5 Hz, =CH), 4.43 (2H, t, J = 6.5 Hz, OCH₂), 4.31 (2H, d, J = 9.5 Hz, =CHCH), 3.67 (6H, s, 2 x OCH₃), 2.55 (2H, t, J = 6.5 Hz, CH₂C=), 1.80 (3H, d, J = 1.4 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.6 (2 x C), 166.4 (C), 137.7 (C), 132.8 (CH), 130.3 (C), 129.6 (2 x CH), 128.3 (2 x CH), 118.6 (CH), 62.5 (CH₂), 52.5 (2 x CH₃), 51.2 (CH), 38.6 (CH₂), 16.6 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₂₄NO₄ [M+NH₄]⁺: 294.1700, found: 294.1698.
(E)-Dimethyl 2-(2-phenylprop-1-enyl)malonate (110d). The title compound was prepared according to the General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (41 mg, 83%). IR (film) 2953, 1735 (C=O), 1435, 1253, 1196, 1148, 1018, 853, 760, 697 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.49-7.46 (2H, m, ArH), 7.40-7.30 (3H, m, ArH), 6.10 (1H, d, J = 9.5 Hz, =CH), 4.52 (1H, d, J = 9.5 Hz, =CHCH), 3.82 (6H, s, 2 x OCH₃), 2.17 (3H, d, J = 1.1 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.6 (2 x C), 142.3 (C), 140.4 (C), 128.4 (2 x CH), 127.6 (CH), 126.0 (2 x CH), 118.7 (CH), 52.7 (2 x CH₃), 51.8 (CH), 16.5 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₁₉O₄ [M+H]⁺: 249.1121, found: 249.1119.

(E)-Dimethyl 2-[2-(4-methylphenyl)prop-1-enyl]malonate (110e). The title compound was prepared according to General Procedure from cyclopropene 108e (49 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (41 mg, 79%). IR (film) 2952, 2868, 1736 (C=O), 1435, 1196, 1147, 1196, 815, 481, 473 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.33 (2H, d, J = 8.1 Hz, ArH), 7.15 (2H, d, J = 8.1 Hz, ArH), 6.03 (1H, d, J = 9.5 Hz, =CH), 4.47 (1H, d, J = 9.5 Hz, =CHCH), 3.78 (6H, s, 2 x OCH₃), 2.35 (3H, s, ArCH₃), 2.11 (3H, d, J = 1.3 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.7 (2 x C), 140.2 (C), 139.5 (C), 137.4 (C), 128.9 (2 x CH), 125.9 (2 x CH), 117.9 (CH), 52.7 (2 x CH₃), 51.9 (CH), 21.0 (CH₃), 16.4 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₁₉O₄ [M+H]⁺: 263.1278, found: 263.1281.

(E)-Diethyl 2-(2-ethylhex-1-enyl)malonate (110f). The title compound was prepared according to the General Procedure from cyclopropene 108f (48 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (41 mg, 79%).
chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (47 mg, 92%). IR (film) 2933, 2872, 1735 (C=O), 1457, 1367, 1301, 1209, 1147, 1034, 852 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 5.47 (1H, dm, J = 9.4 Hz, =CH), 4.24 (1H, d, J = 9.4 Hz, =CHCH), 4.20 (4H, q, J = 7.1 Hz, 2 x OCH₂), 2.09-2.05 (2H, t, J = 7.1 Hz, CH₂C=), 1.68 (3H, d, J = 1.4 Hz, CH₃C=), 1.45-1.37 (2H, m, CH₂CH₂CH₂), 1.34-1.24 (2H, m, CH₂CH₂CH₂), 1.27 (6H, t, J = 7.1 Hz, 2 x OCH₂CH₃), 0.90 (3H, t, J = 7.1 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.7 (2 x C), 141.9 (C), 115.8 (CH), 61.4 (2 x CH₂), 51.6 (CH), 39.2 (CH₂), 29.7 (CH₂), 22.1 (CH₂), 16.6 (CH₃), 14.0 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₄H₂₅O₄ [M+H]+: 257.1747, found: 257.1750.

(E)-Dibenzy 2-(2-phenylprop-1-enyl)malonate (110g). The title compound was prepared according to the General Procedure from cyclopropene 108g (77 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (53 mg, 66%). IR (film) 3033, 1735 (C=O), 1496, 1456, 1375, 1268, 1146, 1003, 749, 696 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.43-7.40 (2H, m, ArH), 7.37-7.30 (13H, m, ArH), 6.12 (1H, dq, J = 9.4, 1.4 Hz, =CH), 5.21 (4H, s, 2 x OCH₂), 4.57 (1H, d, J = 9.4 Hz, =CHCH), 2.12 (3H, d, J = 1.4 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.8 (2 x C), 142.4 (C), 140.8 (C), 135.3 (2 x C), 128.5 (4 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.0 (4 x CH), 127.6 (CH), 126.0 (2 x CH), 118.6 (CH), 67.3 (2 x CH₂), 52.1 (CH), 16.7 (CH₃); HRMS (EI) Exact mass calcd for C₂₆H₂₄O₄ [M]+: 400.1669, found: 400.1667.

(E)-Benzyl 4-phenyl-2-(phenylsulfonyl)pent-3-enoate (110h). The title compound was prepared according to the General Procedure from cyclopropene 108h (63 mg, 0.20 mmol) and Me₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (40 mg, 61%).

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IR (film) 2953, 2612, 1742 (C=O), 1447, 1324, 1263, 1148, 1082, 999, 914 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.91-7.88 (2H, m, Ar\(H\)), 7.72-7.67 (1H, m, Ar\(H\)), 7.59-7.54 (2H, m, Ar\(H\)), 7.36-7.30 (5H, m, Ar\(H\)), 5.80 (1H, dq, \(J = 10.5, 1.5\) Hz, =CH), 5.01 (1H, d, \(J = 10.5\) Hz, =CHCH), 3.81 (3H, s, OCH\(_3\)), 1.91 (3H, d, \(J = 1.5\) Hz, CH\(_3\)), 1.34 (3CH), 70.8 (CH), 53.3 (CH\(_3\)), 16.6 (CH\(_3\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 165.3 (C), 145.4 (C), 141.6 (C), 137.2 (C), 134.3 (CH), 129.6 (2 x CH), 129.0 (2 x CH), 128.4 (2 x CH), 128.2 (CH), 125.9 (2 x CH), 114.4 (CH), 70.8 (CH), 53.3 (CH\(_3\)), 16.6 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{16}\)H\(_{22}\)NO\(_4\) [M+NH\(_4\)]\(^+\): 348.1264, found: 348.1267.

\((E)\)-Dimethyl 2-(2-ethylhex-1-enyl)malonate (113a). The title compound was prepared according to the General Procedure from cyclopropene 108a (42 mg, 0.20 mmol) and Et\(_3\)Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (44 mg, 91%). IR (film) 2956, 2873, 1739 (C=O), 1435, 1294, 1208, 1147, 1023, 844, 524 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 5.41 (1H, d, \(J = 9.7\) Hz, =CH), 4.31 (1H, d, \(J = 9.7\) Hz, =CHCH), 3.74 (6H, s, 2 x OCH\(_3\)), 2.11-2.05 (4H, m, 2 x CH\(_2\)), 1.45-1.25 (4H, m, CH\(_3\)CH\(_2\)CH\(_2\)), 0.98 (3H, t, \(J = 7.2\) Hz, CH\(_3\)CH\(_2\)), 0.90 (3H, t, \(J = 7.2\) Hz, CH\(_3\)CH\(_2\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 169.1 (2 x C), 147.8 (C), 114.9 (CH), 52.6 (2 x CH\(_3\)), 50.8 (CH), 36.0 (CH\(_2\)), 29.9 (CH\(_2\)), 23.7 (CH\(_2\)), 22.4 (CH\(_2\)), 13.9 (CH\(_3\)), 12.9 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{13}\)H\(_{26}\)NO\(_4\) [M+NH\(_4\)]\(^+\): 260.1856, found: 260.1855.

\((E)\)-Dimethyl 2-(2-ethyl-4-phenylbut-1-enyl)malonate (113b). The title compound was prepared according to the General Procedure from cyclopropene 108b (52 mg, 0.20 mmol) and Et\(_3\)Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (42 mg, 72%). IR (film) 2953, 1738 (C=O), 1617, 1497, 1455, 1435, 1297, 1209, 1146, 1022 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.30-7.26 (2H, m, Ar\(H\)), 7.26 (2H, m, Ar\(H\)), 7.17-6.98 (5H, m, Ar\(H\)), 5.98 (1H, d, \(J = 10.5\) Hz, =CH), 5.01 (1H, d, \(J = 10.5\) Hz, =CHCH), 3.81 (3H, s, OCH\(_3\)), 1.91 (3H, d, \(J = 1.5\) Hz, CH\(_3\)), 1.34 (3CH), 70.8 (CH), 53.3 (CH\(_3\)), 16.6 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{16}\)H\(_{22}\)NO\(_4\) [M+NH\(_4\)]\(^+\): 348.1264, found: 348.1267.
7.21-7.17 (3H, m, ArH), 5.47 (1H, d, J = 9.7 Hz, CH), 4.33 (1H, d, J = 9.7 Hz, CHCH), 3.74 (6H, s, 2 x OCH3), 2.78-2.74 (2H, m, PhCH2), 2.42-2.37 (2H, m, PhCH2CH2), 2.14 (2H, q, J = 7.6 Hz, CH3CH2), 1.02 (3H, t, J = 7.6 Hz, CH3CH2); 13C NMR (62.9 MHz, CDCl3) δ 169.0 (2 x C), 147.9 (C), 141.8 (C), 128.4 (2 x CH), 128.3 (2 x CH), 125.8 (CH), 115.6 (CH), 52.6 (2 x CH3), 50.8 (CH), 38.0 (CH2), 34.3 (CH2), 23.9 (CH2), 12.9 (CH3); HRMS (ES) Exact mass calcd for C17H26NO4 [M+NH4]+: 308.1856, found: 308.1856.

(E)-Dimethyl 2-[4-(benzoyloxy)-2-ethylbut-1-enyl]malonate (113c). The title compound was prepared according to the General Procedure from cyclopropene 108c (61 mg, 0.20 mmol) and Me3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (47 mg, 70%). IR (film) 2954, 1717 (C=O), 1648, 1434, 1275, 1111, 1025, 809, 712, 484 cm⁻¹; 1H NMR (360 MHz, CDCl3) δ 8.05-8.02 (2H, m, ArH), 7.58-7.53 (1H, m, ArH), 7.46-7.42 (2H, m, ArH), 5.60 (1H, d, J = 9.8 Hz, CH), 4.43 (2H, t, J = 6.7 Hz, OCH2), 4.39 (1H, d, J = 9.8 Hz, CHCH), 3.69 (6H, s, 2 x OCH3), 2.56 (2H, dt, J = 6.7, 1.1 Hz, OCH2CH2), 2.18 (2H, q, J = 7.6 Hz, CH3CH2), 1.05 (3H, t, J = 7.6 Hz, CH3CH2); 13C NMR (62.9 MHz, CDCl3) δ 168.7 (2 x C), 166.4 (C), 143.3 (C), 132.9 (CH), 130.3 (C), 129.6 (2 x CH), 128.3 (2 x CH), 118.0 (CH), 62.8 (CH2), 52.6 (2 x CH3), 50.9 (CH), 35.4 (CH2), 23.6 (CH2), 12.8 (CH3); HRMS (ES) Exact mass calcd for C18H26NO6 [M+NH4]+: 352.1755, found: 352.1752.

(E)-Dimethyl 2-(2-phenylbut-1-enyl)malonate (113d). Using 2 equiv of Et3Al: The title compound was prepared according to the General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and Et3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (43 mg, 82%).
Using 0.5 equiv of \( \text{Et}_3\text{Al} \): Following the same procedure as above, but using \( \text{Et}_3\text{Al} \) (1.0 M in hexane, 0.10 mL, 0.10 mmol) instead of the usual 2 equiv provided the title compound (35 mg, 67%) as a colourless oil. IR (film) 2954, 1735 (C=O), 1434, 1253, 1195, 1147, 1020, 856, 767, 698 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.41-7.28 (5H, m, Ar\( H \)), 5.91 (1H, d, \( J = 9.8 \) Hz, =CH), 4.48 (1H, d, \( J = 9.8 \) Hz, =CHCH), 3.78 (6H, s, 2 x OCH\(_3\)), 2.57 (2H, q, \( J = 7.5 \) Hz, CH\(_2\)) 1.00 (3H, t, \( J = 7.5 \) Hz, CH\(_3\)CH\(_2\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \( \delta \) 168.7 (2 x C), 147.1 (C), 141.3 (C), 128.3 (2 x CH), 127.5 (CH), 126.6 (2 x CH), 118.3 (CH), 52.8 (2 x CH\(_3\)), 51.5 (CH), 23.5 (CH\(_2\)), 13.3 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{15}\)H\(_{22}\)NO\(_4\) [M+NH\(_4\)]\(^+\): 280.1543, found: 280.1541.

\( (E)\)-Dimethyl \( 2\)-[2-(4-methylphenyl)but-1-enyl]malonate (113e). The title compound was prepared according to the General Procedure from cyclopropene 108e (49 mg, 0.20 mmol) and \( \text{Et}_3\text{Al} \) and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (39 mg, 71%). IR (film), 1737 (C=O), 1512, 1435, 1267, 1193, 1148, 1022, 818, 512 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \( \delta \) 7.31-7.28 (2H, m, Ar\( H \)), 7.15 (2H, d, \( J = 7.9 \) Hz, Ar\( H \)), 5.89 (1H, d, \( J = 9.8 \) Hz, =CH), 4.48 (1H, d, \( J = 9.8 \) Hz, =CHCH), 3.78 (6H, s, 2 x OCH\(_3\)), 2.56 (2H, q, \( J = 7.5 \) Hz, CH\(_2\)), 2.35 (3H, s, ArCH\(_3\)), 0.99 (3H, t, \( J = 7.5 \) Hz, CH\(_3\)CH\(_2\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \( \delta \) 168.7 (2 x C), 146.9 (C), 138.3 (C), 137.3 (C), 129.0 (2 x CH\(_2\)), 126.5 (2 x CH\(_2\)), 117.5 (CH), 52.7 (2 x CH\(_3\)), 51.5 (CH), 23.4 (CH\(_2\)), 21.0 (CH\(_3\)), 13.3 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{16}\)H\(_{21}\)O\(_4\) [M+H]\(^+\): 277.1434, found: 277.1438.

\( (E)\)-Diethyl \( 2\)-(2-ethylhex-1-enyl)malonate (113f). The title compound was prepared according to the General Procedure from
cyclopropene 108f (48 mg, 0.20 mmol) and Et3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (40 mg, 77%). IR (film) 2962, 1734 (C=O), 1623, 1465, 1297, 1204, 1034, 855, 513, 483 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 5.42 (1H, d, J = 9.7 Hz, =CH), 4.27 (1H, d, J = 9.7 Hz, =CHCH), 4.19 (4H, q, J = 7.1 Hz, 2 x OCH₂), 2.08 (4H, app q, J = 7.6 Hz, 2 x CH₂C=), 1.45-1.27 (4H, m, CH₃CH₂CH₃), 1.27 (6H, t, J = 7.1 Hz, 2 x OCH₂CH₃), 0.99 (3H, t, J = 7.6 Hz, CH₃CH₂C=), 0.90 (3H, t, J = 7.2 Hz, CH₃CH₂CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.8 (2 x C), 147.4 (C), 115.2 (CH), 61.4 (2 x CH₂), 51.2 (CH), 36.0 (CH₂), 29.9 (CH₂), 23.6 (CH₂), 22.3 (CH₂), 14.0 (2 x CH₃), 13.9 (CH₃), 12.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₇O₄ [M+H]⁺: 271.1904, found: 271.1904.

(E)-Dimethyl 2-(2-phenylpent-1-enyl)malonate (114a). The title compound was prepared according to the General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and n-Pr₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (50 mg, 90%). IR (CHCl₃) 2962, 2875, 1738 (C=O), 1593, 1533, 1442, 1265, 1024, 910 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.40-7.38 (2H, m, ArH), 7.35-7.32 (2H, m, ArH), 7.30-7.26 (1H, m, ArH), 5.94 (1H, d, J = 9.9 Hz, =CH), 4.50 (1H, d, J = 9.9 Hz, =CHCH), 3.78 (6H, s, 2 x OCH₃), 2.55-2.52 (2H, m, CH₂CH₂CH₃), 1.41-1.34 (2H, m, CH₂CH₃), 0.88 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.4 (2 x C), 145.6 (C), 141.6 (C), 128.2 (2 x CH), 127.5 (CH), 126.6 (2 x CH), 119.1 (CH), 52.7 (2 x CH₂), 51.6 (CH), 32.1 (CH₂), 21.5 (CH₂), 13.7 (CH₃); HRMS (EI) Exact mass calced for C₁₆H₂₀O₄ [M⁺]: 276.1356, found: 276.1355.

(E)-Dimethyl 2-[2-(4-methylphenyl)pent-1-enyl]malonate (114b). The title compound was prepared according to the General Procedure from cyclopropene 108e (49 mg, 0.20
mmol) and \(n\)-Pr\(_3\)Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (41 mg, 72%). IR (film) 2958, 2873, 1732 (C=O), 1512, 1437, 1261, 1196, 1153, 1022 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.29 (2H, dm, \(J = 8.1\) Hz, ArH), 7.14 (2H, d, \(J = 8.1\) Hz, ArH), 5.92 (1H, d, \(J = 9.9\) Hz, \(=\)CH), 4.48 (1H, d, \(J = 9.9\) Hz, \(=\)CHCH), 3.78 (6H, s, 2 x OCH\(_3\)), 2.51 (2H, t, \(J = 7.5\) Hz, CH\(_2\)CH\(_2\)CH\(_3\)), 2.35 (3H, s, ArCH\(_3\)), 1.37 (2H, app sex, \(J = 7.5\) Hz, CH\(_2\)CH\(_3\)), 0.87 (3H, t, \(J = 7.5\) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 168.7 (2 x C), 145.3 (C), 138.7 (C), 137.3 (C), 128.9 (2 x CH), 126.5 (2 x CH), 118.4 (CH), 52.7 (2 x CH\(_3\)), 51.6 (CH), 32.1 (CH\(_2\)), 21.6 (CH\(_2\)), 21.0 (CH\(_3\)), 13.7 (CH\(_3\)); HRMS (EI) Exact mass calcd for C\(_{17}\)H\(_{22}\)O\(_4\) [M]**: 290.1513, found: 290.1508.

\((E)\)-Dibenzyl 2-(2-phenylpent-1-enyl)malonate (114c). The title compound was prepared according to the General Procedure from cyclopropene 108g (77 mg, 0.20 mmol) and \(n\)-Pr\(_3\)Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (54 mg, 63%). IR (film) 3033, 2960, 2871, 1734 (C=O), 1496, 1456, 1377, 1269, 1215, 1144 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 7.37-7.28 (15H, m, ArH), 5.98 (1H, d, \(J = 9.8\) Hz, \(=\)CH), 5.20 (4H, s, 2 x CH\(_2\)Ph), 4.58 (1H, d, \(J = 9.8\) Hz, \(=\)CHCH), 2.52 (2H, t, \(J = 7.7\) Hz, CH\(_2\)CH\(_2\)CH\(_3\)), 1.37-1.29 (2H, m, CH\(_2\)CH\(_3\)), 0.83 (3H, t, \(J = 7.4\) Hz, CH\(_2\)CH\(_3\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 167.9 (2 x C), 146.0 (C), 141.7 (C), 135.3 (2 x C), 128.5 (4 x CH), 128.3 (2 x CH), 128.2 (2 x CH), 128.1 (4 x CH), 127.5 (CH), 126.7 (2 x CH), 119.0 (CH), 67.3 (2 x CH\(_2\)), 51.9 (CH), 32.3 (CH\(_2\)), 21.5 (CH\(_2\)), 13.8 (CH\(_3\)); HRMS (EI) Exact mass calcd for C\(_{28}\)H\(_{28}\)O\(_4\) [M]**: 428.1982, found: 428.1975.

\((E)\)-Dimethyl 2-(2-phenyloct-1-enyl)malonate (114d). The title compound was prepared according to the General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and \(n\)-Hex\(_3\)Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (42 mg,
66%). IR (film) 2953, 2857, 1737 (C=O), 1437, 1259, 1196, 1148, 1025, 769, 699 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.40-7.28 (5H, m, ArH), 5.92 (1H, d, J = 9.9 Hz, =CH), 4.48 (1H, d, J = 9.9 Hz, =CHCH), 3.78 (6H, s, 2 x OCH₃), 2.53 (2H, t, J = 6.9 Hz, CH₂C=), 1.37-1.18 (8H, m, 4 x CH₂), 0.85 (3H, t, J = 6.9 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.7 (2 x C), 145.8 (C), 141.7 (C), 128.3 (2 x CH), 127.5 (CH), 126.6 (2 x CH), 118.9 (CH), 52.8 (2 x CH₃), 51.6 (CH), 31.6 (CH₂), 30.3 (CH₂), 29.1 (CH₂), 28.4 (CH₂), 22.5 (CH₂), 14.0 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₃₀NO₄ [M+NH₄]^+: 336.2169, found: 336.2173.

(Z)-Dimethyl 2-(2-butyloct-1-enyl)malonate (114e). The title compound was prepared according to the General Procedure from cyclopropene 108a (42 mg, 0.20 mmol) and n-Hex₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 52%). IR (film) 2930, 2858, 1739 (C=O), 1435, 1296, 1147, 1024, 471, 458, 445 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 5.43 (1H, d, J = 9.8 Hz, =CH), 4.31 (1H, d, J = 9.8 Hz, =CHCH), 3.73 (6H, s, 2 x OCH₃), 2.08-2.02 (4H, m, 2 x CH₂C=), 1.45-1.24 (12H, m, CH₃(CH₂)₄ and CH₃(CH₂)₂CH₂C=), 0.90 (3H, t, J = 7.2 Hz, CH₃), 0.87 (3H, t, J = 6.8 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.1 (2 x C), 146.4 (C), 115.4 (CH), 52.5 (2 x CH₃), 50.9 (CH), 36.4 (CH₂), 31.7 (CH₂), 30.6 (CH₂), 30.0 (CH₂), 29.3 (CH₂), 28.2 (CH₂), 22.6 (CH₂), 22.4 (CH₂), 14.0 (CH₃), 13.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₉H₃₁O₄ [M+H]^+: 299.2217, found: 299.2217.

(E)-Dimethyl 2-(4-methyl-2-phenylpent-1-enyl)malonate (114f). The title compound was prepared according to the General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and iBu₃Al (1.1 M in Toluene) and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (36 mg, 62%). IR (film) 2955, 1736 (C=O), 1434, 1308, 1259, 1148, 1026, 857, 769, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.28 (5H, m,
ArH), 5.94 (1H, d, J = 10.0 Hz, =CH), 4.50 (1H, d, J = 10.0 Hz, =CHCH), 3.78 (6H, s, 2 x OCH3), 2.44 (2H, d, J = 6.6 Hz, CH2C=), 1.62-1.53 (1H, m, CH), 0.83 (6H, d, J = 6.6 Hz, (CH3)2CH); 13C NMR (62.9 MHz, CDCl3) δ 168.7 (2 x C), 145.1 (C), 142.0 (C), 128.2 (2 x CH), 127.4 (CH), 126.8 (2 x CH), 120.1 (CH), 52.7 (2 x CH3), 51.7 (CH), 39.0 (CH2), 26.8 (CH), 22.2 (2 x CH3); HRMS (EI) Exact mass calced for C17H22O4 [M]+: 290.1513, found: 290.1511.

(Z)-Dimethyl 2-[1-phenyl-2-(trimethylsilyl)prop-1-enyl]malonate (116a). The title compound was prepared according to the General Procedure from cyclopropene 115a (61 mg, 0.20 mmol) and Me3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (57 mg, 89%). IR (CHCl3) 2953, 1739 (C=O), 1435, 1309, 1248, 1148, 1032, 837, 760, 704 cm⁻¹; 1H NMR (360 MHz, CDCl3) δ 7.23-7.22 (5H, m, ArH), 4.82 (1H, s, =CCH), 3.57 (6H, s, 2 x OCH3), 1.80 (3H, s, CH3C=), -0.24 (9H, s, Si(CH3)3); 13C NMR (360 MHz, CDCl3) δ 168.6 (2 x C), 141.4 (C), 141.2 (C), 140.3 (C), 130.0 (2 x CH), 127.4 (2 x CH), 127.3 (CH), 57.0 (CH), 52.3 (CH3), 18.3 (CH3), -0.5 (3 x CH3); HRMS (ES) Exact mass calced for C18H27O4Si [M+H]+: 335.1673, found: 335.1673.

(Z)-Dimethyl 2-[1-(4-methylphenyl)-2-(trimethylsilyl)prop-1-enyl]malonate (116b). The title compound was prepared according to the General Procedure from cyclopropene 115b (64 mg, 0.20 mmol) and Me3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (48 mg, 71%). IR (CHCl3) 2952, 1741 (C=O), 1596, 1507, 1435, 1310, 1248, 1196, 1148, 1033 cm⁻¹; 1H NMR (360 MHz, CDCl3) δ 7.10-7.03 (4H, m, ArH), 4.81 (1H, s, =CCH), 3.59 (6H, s, 2 x OCH3), 2.71 (3H, s, ArCH3), 1.79 (3H, s,
\( \text{CH}_3\text{C} = \text{CH} \), \(-0.23\) (9H, s, Si(\text{CH}_3)_3); \(^{13}\text{C}\) NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 168.7 (2 x C), 141.3 (C), 140.1 (C), 138.5 (C), 136.8 (C), 129.9 (2 x CH), 128.1 (2 x CH), 57.0 (CH), 52.3 (2 x CH\(_3\)), 21.2 (CH\(_3\)), 18.4 (CH\(_3\)), \(-0.4\) (3 x CH\(_3\)); HRMS (EI) Exact mass calcd for C\(_{18}\)H\(_{26}\)O\(_4\)Si [M\(^{+}\)]: 334.1595, found: 334.1601.

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\text{(E)-Dimethyl 2-[1-(1-trimethylsilyl)ethyldiene]pentyl]malonate (116c).} \text{ The title compound was prepared according to the General Procedure from cyclopropene 115c (57 mg, 0.20 mmol) and Me}_3\text{Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give an inseparable 6:1 mixture of regioisomers as a colourless oil (43 mg, 68\%). 2953, 1738 (C=O), 1597, 1435, 1312, 1249, 1196, 1145, 1032, 837 cm}^{-1}; \text{ }^{1}\text{H NMR (360 MHz, CDCl}_3\text{)} \delta\) 4.48 (1H, s, \(=\text{CCH}\)), 3.74 (6H, s, 2 x OCH\(_3\)), 2.23-2.19 (2H, m, CH\(_2\text{C} = \)), 1.67 (3H, s, CH\(_3\text{C} = \)), 1.37-1.26 (4H, m, CH\(_2\text{CH}_2\text{CH}_3\)), 0.89 (3H, t, \(J = 7.0\) Hz, CH\(_2\text{CH}_3\)), 0.17 (9H, s, Si(\text{CH}_3)_3); \(^{13}\text{C}\) NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 169.1 (2 x C), 140.8 (C), 140.9 (C), 136.2 (C), 55.3 (CH), 52.4 (2 x CH\(_3\)), 36.2 (CH\(_2\)), 32.0 (CH\(_2\)), 23.0 (CH\(_2\)), 18.7 (CH\(_3\)), 13.9 (CH\(_3\)), 0.4 (3 x CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{16}\)H\(_{31}\)O\(_4\)Si [M+H]\(^{+}\): 315.1986, found: 315.1992.

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\text{(Z)-Dimethyl 2-[1-(4-methylphenyl)-2-(trimethylsilyl)but-1-enyl]malonate (116d).} \text{ The title compound was prepared according to the General Procedure from cyclopropene 115a (61 mg, 0.20 mmol) and Et}_3\text{Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (49 mg, 73\%). IR (CHCl}_3\text{) 2952, 2897, 1736 (C=O), 1587, 1490, 1435, 1375, 1308, 1248, 1194 cm}^{-1}; \text{ }^{1}\text{H NMR (360 MHz, CDCl}_3\text{)} \delta\) 7.24 (5H, s, ArH), 4.88 (1H, s, \(=\text{CCH}\)), 3.59 (6H, s, 2 x OCH\(_3\)), 2.25 (2H, q, \(J = 7.6\) Hz, CH\(_2\)), 1.05 (3H, t, \(J = 7.6\) Hz, CH\(_2\text{CH}_3\)), \(-0.21\) (9H, s, Si(\text{CH}_3)_3); \(^{13}\text{C}\) NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 168.8 (2 x C), 146.6 (C), 141.3 (C), 140.9 (C), 130.4 (2 x CH), 127.3 (3 x CH), 56.1 (CH), 52.3 (2 x CH\(_3\)), 25.6
(CH₂), 14.1 (CH₃), 0.3 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁₈H₃₀O₄N [M+NH₄]⁺: 352.1939, found: 352.1939.

(E)-Dimethyl

2-[1-phenyl-4-(trimethylsilyl)hex-3-enyl]malonate (116e). The title compound was prepared according to the General Procedure from cyclopropene 115d (66 mg, 0.20 mmol) and Et₃Al and purified by column chromatography (5%→15% EtOAc/hexane) to give an inseparable 5:1 mixture of regioisomers as a colourless oil (59 mg, 81%). IR (film) 3028, 2954, 2897, 1738 (C=O), 1601, 1496, 1454, 1434, 1311 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.27 (2H, m, ArH), 7.24-7.20 (3H, m, ArH), 4.72 (1H, s, =CHH), 3.79 (6H, s, 2 x OCH₃), 2.70-2.67 (2H, m, CH₂CH₂Ph), 2.58-2.55 (2H, m, CH₂CH₂Ph), 2.16 (2H, q, J = 7.5 Hz, CH₂CH₃), 1.42 (3H, t, J = 7.3 Hz, CH₂CH₃), 0.94 (3H, t, J = 7.5 Hz, CH₃), 0.24 (3H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.3 (2 x C), 144.0 (C), 142.1 (C), 139.6 (C), 128.4 (2 x CH), 128.2 (2 x CH), 125.8 (CH), 54.2 (CH), 52.5 (2 x CH₃), 37.8 (CH₂), 35.8 (CH₂), 25.6 (CH₃), 14.2 (CH₃), 0.96 (3 x CH₃); HRMS (EI) Exact mass calcd for C₂₀H₃₀O₄Si [M⁺]: 362.1908, found: 362.1904.

(Z)-Dimethyl

2-[1-p-tolyl-2-(trimethylsilyl)pent-1-enyl]malonate (116f). The title compound was prepared according to the General Procedure from cyclopropene 115b (64 mg, 0.20 mmol) and n-Pr₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (64 mg, 88%). IR (film) 2954, 2873, 1736 (C=O), 1591, 1508, 1435, 1311, 1248, 1196, 1149 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.11-7.10 (2H, m, ArH), 7.05-7.04 (2H, m, ArH), 4.88 (1H, s, =CHH), 3.60 (6H, s, 2 x OCH₃), 2.31 (3H, s, ArCH₃), 2.18-2.15 (2H, m, CH₂CH₂CH₃), 1.44-1.39 (2H, m, CH₂CH₂), 0.99 (3H, t, J = 7.3 Hz, CH₂CH₃), -0.22 (9H, s, Si(CH₃)₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.8
(2 x C), 145.1 (C), 141.7 (C), 137.9 (C), 136.9 (C), 130.3 (2 x CH), 128.0 (2 x CH), 56.2 (CH), 52.2 (2 x CH₂), 35.0 (CH₂), 23.0 (CH₂), 21.2 (CH₃), 14.4 (CH₃), 0.45 (3 x CH₃); HRMS (EI) Exact mass calcd for C₂₀H₃₀O₄Si [M]+: 362.1908, found: 362.1907.

**Z-Dimethyl**

2-[1-phenyl-2-(tributylstannyl)prop-1-enyl]malonate (118a).

The title compound was prepared according to the General Procedure but using half of all quantities, from cyclopropene 117a (52 mg, 0.10 mmol) and Me₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (44 mg, 82%). IR (film) 2954, 2924, 2853, 1740 (C=O), 1436, 1310, 1147, 1034, 911, 734 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.26-7.21 (5H, m, ArH), 4.88 (1H, s, =CH₂), 3.58 (6H, s, 2 x OCH₃), 1.95 (3H, s, CH₃C=), 1.33-1.26 (6H, m, Sn(CH₂CH₃CH₂CH₃)), 1.24-1.16 (6H, m, Sn(CH₂CH₂CH₂CH₃)), 0.84 (9H, t, J = 7.2 Hz, Sn(CH₂CH₂CH₂CH₃)), 0.53-0.49 (6H, m, Sn(CH₂CH₂CH₂CH₃)); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.8 (2 x C), 145.9 (C), 143.2 (C), 140.9 (C), 129.6 (2 x CH), 127.8 (2 x CH), 127.2 (CH), 55.8 (CH), 52.3 (2 x CH₃), 29.0 (JSn-C = 9.5 Hz, 3 x CH₂), 27.3 (JSn-C = 30.6 Hz, 3 x CH₂), 21.6 (CH₃), 13.6 (3 x CH₃), 10.4 (JSn-C = 167.6, 160.5 Hz, 3 x CH₂); HRMS (FAB) Exact mass calcd for C₂₆H₄₃O₄Sn [M+H]+: 539.2178, found: 539.2186.

**E-Dimethyl**

2-[1-(1-tributylstannylethylidene)heptyl]malonate (118b).

The title compound was prepared according to the General Procedure but using half of all quantities from cyclopropene 117b (53 mg, 0.10 mmol) and Me₃Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a 10:1 inseparable mixture of regioisomers as a colourless oil (38 mg, 70%). IR (film) 2955, 2926, 2854, 1738 (C=O), 1601, 1435, 1146, 1037, 910, 734 cm⁻¹; ¹H NMR (360
MHZ, CDCl 3) δ 4.54 (1H, s, =CCH), 3.73 (6H, s, CO 2CH 3), 2.11-2.08 (2H, m, =CCH 2), 1.83 (3H, s, CH 3=C=), 1.51-1.43 (6H, m, Sn(CH 2CH 2CH 2CH 3) 3), 1.35-1.25 (14H, m, Sn(CH 2CH 2CH 2CH 3) 3 and (CH 2) 4CH 3), 0.95-0.86 (18H, m, Sn(CH 2CH 2CH 2CH 3) 3 and (CH 2) 2CH 3), 13C NMR (62.9 MHZ, CDCl 3) δ 169.2 (2 x C), 141.0 (C), 139.0 (C), 53.8 (CH), 52.3 (2 x CH 3), 40.3 (CH 2), 31.8 (CH 2), 30.1 (CH 2), 29.7 (CH 2), 29.1 (J Sn-C = 9.5 Hz, 3 x CH 2), 27.4 (J Sn-C = 29.0 Hz, 3 x CH 2), 22.6 (CH 2), 21.5 (CH 3), 14.0 (CH 3), 13.7 (3 x CH 3), 10.7 (J Sn-C = 164.6, 157.3 Hz, 3 x CH 2); HRMS (FAB) Exact mass calcd for C 26H 51O 4 120Sn [M+H] +: 547.2804, found: 547.2790.

(Z)-Dimethyl 2-(1,2-diphenylprop-1-enyl)malonate (120a). The title compound was prepared using a slight modification of the quantities described in the General Procedure from cyclopropene 119a (50 mg, 0.16 mmol) and Me 3Al (2.0 M in hexanes, 0.16 mL, 0.32 mmol), and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (34 mg, 66%).
IR (film) 3022, 2951, 1740 (C=O), 1600, 1491, 1435, 1312, 1265, 1195, 1149 cm −1; 
1H NMR (360 MHZ, CDCl 3) δ 7.11-7.00 (10H, m, ArH), 4.89 (1H, s, =CCH), 3.65 (6H, s, 2 x OCH 3), 2.16 (3H, s, CH 3=C=); 13C NMR (62.9 MHZ, CDCl 3) δ 168.8 (2 x C), 143.2 (C), 140.1 (2 x C), 130.1 (2 x CH), 129.9 (C), 128.7 (2 x CH), 127.6 (2 x CH), 127.3 (2 x CH), 126.3 (CH), 126.2 (CH), 56.9 (CH), 52.5 (2 x CH 3), 21.7 (CH 3); HRMS (ES) Exact mass calcd for C 20H 24NO 4 [M+NH 4 ] +: 342.1700, found: 342.1699.

(Z)-Dimethyl 2-(1,2-diphenylbut-1-enyl)malonate (120b). The title compound was prepared using a slight modification of the quantities described in the General Procedure, from cyclopropene 119a (50 mg, 0.16 mmol) and Et 3Al (1.0 M in hexanes, 0.32 mL, 0.32 mmol), and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (48 mg, 87%).
IR (film) 2952, 1750 (C=O), 1600, 1435, 1310, 1269, 1195, 1147, 1029 cm⁻¹; 
¹H NMR (360 MHz, CDCl₃) δ 7.11-6.99 (10H, m, ArH), 4.94 (1H, s, =CH), 3.65 (6H, s, 2 x OCH₃), 2.55 (2H, q, J = 7.5 Hz, CH₂CH₂), 0.93 (3H, t, J = 7.5 Hz, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.0 (2 x C), 146.5 (C), 141.5 (C), 140.0 (C), 130.2 (2 x CH), 129.3 (2 x CH), 129.2 (C), 127.4 (2 x CH), 127.2 (2 x CH), 126.2 (CH), 126.1 (CH), 56.2 (CH), 52.5 (2 x CH₃), 51.7 (CH), 28.1 (CH₂), 12.0 (CH₃); HRMS (ES) Exact mass calcd for C₂₁H₂₂O₄ [M+H]^+: 338.1513, found: 338.1514.

(⁎)-Dimethyl 2-(3-phenylhex-2-enyl)malonate (120c). The title compound was prepared using a slight modification of the quantities described in the General Procedure, from cyclopropene 119b (55 mg, 0.22 mmol) and n-Pr₃Al (0.7 M in heptane, 0.63 mL, 0.44 mmol) and purified by column chromatography (hexane→5% EtOAc/hexane) to give 6:1 inseparable mixture of regioisomers as a colourless oil (59 mg, 92%). IR (film) 2956, 2873, 1734 (C=O), 1437, 1313, 1151, 1030, 908, 732 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.33-7.28 (2H, m, ArH), 7.23-7.20 (3H, m, ArH), 4.78 (1H, s, =CH), 3.60 (6H, s, 2 x OCH₃), 2.15-2.11 (2H, m, CH₂CH₂CH₃), 1.55 (3H, s, =CH₃), 1.54-1.50 (2H, m, CH₂CH₃), 0.98 (3H, t, J = 7.4 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 169.0 (2 x C), 140.3 (C), 139.6 (C), 129.7 (2 x CH), 128.0 (C), 127.8 (2 x CH), 126.7 (CH), 55.6 (CH), 52.2 (2 x CH₃), 36.4 (CH₂), 21.0 (CH₂), 20.2 (CH₃), 14.0 (CH₃); HRMS (EI) Exact mass calcd for C₁₇H₂₂O₄ [M]^+: 290.1513, found: 290.1509.

Chapter 1 Cyclopropene Chemistry: An Overview
Further Manipulation of Ring-Opened Products

(E)-Dimethyl 2-(3-oxobutyl)-2-(2-phenylprop-1-enyl) malonate (16)

[Chemical structure image]

To a solution of alkene 110d (49 mg, 0.20 mmol) in MeOH (2 mL) at room temperature was added NaOMe (5.4 mg, 0.10 mmol) followed by methyl vinyl ketone (32 μL, 0.39 mmol). The reaction was stirred at room temperature for 18 h, filtered through a short plug of SiO₂ using EtOAc as eluent (ca. 20 mL) and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) gave the Michael product 126 (62 mg, 97%) as a colourless oil. IR (film) 2953, 1733 (C=O), 1494, 1439, 1365, 1260, 1214, 1090, 1010, 982 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.35 (2H, m, ArH), 7.32-7.21 (3H, m, ArH), 6.25 (1H, q, J = 1.3 Hz, =CH), 3.74 (6H, s, 2 x OC₃H₃), 2.48-2.39 (4H, m, CH₂CH₂), 2.08 (3H, s, OCH₃), 1.94 (3H, d, J = 1.3 Hz, CH₃C=); ¹³C NMR (62.9 MHz, CDCl₃) δ 207.1 (C), 171.3 (2 x C), 143.4 (C), 139.6 (C), 128.2 (2 x CH), 127.4 (CH), 125.9 (2 x CH), 124.2 (CH), 57.6 (C), 52.9 (2 x CH₃), 38.7 (CH₂), 29.9 (CH₃), 29.5 (CH₂), 16.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₈H₂₃O₅ [M+H]^+: 319.1540, found: 319.1541.

Dimethyl 2-[(E)-2-ethyl-4-phenylbut-1-enyl]-2-[(E)-3-phenylallyl] malonate (127)

[Chemical structure image]

To a solution of alkene 113b (58 mg, 0.20 mmol) in THF (1 mL) at room temperature was added NaH (60% in Vaseline, 80 mg, 2.00 mmol) in one portion, followed by a solution of cinnamyl bromide (41 mg, 0.20 mmol) in THF via cannula. The reaction was stirred at room temperature for 3 h and then filtered through a short
plug of SiO₂ using EtOAc as eluent (ca. 20 mL) and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the allylated product 127 (67 mg, 82%) as a colourless oil. IR (film) 3027, 2951, 1734 (C=O), 1602, 1495, 1435, 1264, 1224, 1048, 968 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.27 (6H, m, ArH), 7.24-7.18 (4H, m, ArH), 6.39 (1H, d, J = 15.7 Hz, =CHPh), 6.03 (1H, dt, J = 15.7, 7.5 Hz, CH₂CH=), 5.82 (1H, s, =CHC(CO₂Me)₂), 3.73 (6H, s, 2 x OCH₃), 2.93 (2H, dd, J = 7.5, 1.2 Hz, CH₂CH=), 2.78-2.75 (2H, m, PhCH₂), 2.44-2.31 (2H, m, PhCH₂CH₂), 2.07 (2H, q, J = 7.5 Hz, CH₃CH₂), 0.98 (3H, t, J = 7.5 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 171.4 (2 x C), 144.9 (C), 141.8 (C), 137.1 (C), 133.5 (CH), 128.4 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 126.2 (2 x CH), 125.8 (CH), 124.5 (CH), 121.3 (CH), 58.5 (C), 52.6 (2 x CH₃), 40.8 (CH₂), 37.9 (CH₂), 34.7 (CH₂), 23.5 (CH₂), 11.7 (CH₃); HRMS (ES) Exact mass calcd for C₂₆H₃₁O₄ [M+H]⁺: 407.2217, found: 407.2215.

(E)-Methyl 4-ethyl-6-phenylhex-3-enoate (18)

A solution of the alkene 113b (87 mg, 0.30 mmol) and NaCl (24 mg, 0.41 mmol) in DMSO (0.5 mL) and H₂O (0.025 mL) was heated at 170 °C for 30 min in the microwave synthesizer. After cooling to room temperature, H₂O (10 mL) was added and the mixture was extracted with Et₂O (3 x 5 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) gave the alkene 128 (59 mg, 85%) as a colourless oil. IR (film) 3027, 2964, 1740 (C=O), 1495, 1454, 1436, 1330, 1257, 1197 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.27 (2H, m, ArH), 7.21-7.17 (3H, m, ArH), 5.35 (1H, t, J = 7.2 Hz, =CH), 3.70 (3H, s, OCH₃), 3.09 (2H, d, J = 7.2 Hz, =CHCH₂), 2.77-2.72 (2H, m, PhCH₂), 2.38-2.32 (2H, m, PhCH₂CH₂), 2.11 (2H, q, J = 7.6 Hz, CH₃CH₂), 1.02 (3H, t, J = 7.6 Hz, CH₃CH₂);
\[^{13}\text{C} \text{NMR}\ (62.9 \ \text{MHz}, \ \text{CDCl}_3) \ \delta \ 172.8 \ (\text{C}), \ 144.3 \ (\text{C}), \ 142.2 \ (\text{C}), \ 128.3 \ (2 \times \text{CH}), \ 128.2 \ (2 \times \text{CH}), \ 125.7 \ (\text{CH}), \ 115.5 \ (\text{CH}), \ 51.7 \ (\text{CH}_3), \ 38.3 \ (\text{CH}_2), \ 34.6 \ (\text{CH}_2), \ 33.2 \ (\text{CH}_2), \ 23.6 \ (\text{CH}_2), \ 12.8 \ (\text{CH}_3); \ \text{HRMS (ES)} \ \text{Exact mass calcd for } C_{15}H_{24}NO_2 [M+\text{NH}_4]^{+}: \ 250.1802, \ \text{found:} \ 250.1803.\]

\((Z)-\text{Methyl 3-}(4\text{-methylphenyl})-4\text{-}(\text{trimethylsilyl})\text{pent-3-enoate (129)}\)

A solution of the alkene 116b (68 mg, 0.20 mmol) and NaCl (24 mg, 0.41 mmol) in DMF (0.5 mL) and H$_2$O (0.025 mL) was heated at 130 °C for 1 h in the microwave synthesizer. After cooling to room temperature, H$_2$O (10 mL) was added and the mixture was extracted with Et$_2$O (3 x 5 mL). The combined organic layers were dried (MgSO$_4$) and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) gave the alkene 129 (40 mg, 72%) as a colourless oil. IR (film) 2952, 1740 (C=O), 1603, 1509, 1434, 1325, 1248, 1158, 1021, 926 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 7.08 (2H, d, $J$ = 7.9 Hz, ArH), 7.02 (2H, d, $J$ = 7.9 Hz, ArH), 3.60 (3H, s, OC$_3$H$_3$), 3.45 (2H, s, CH$_2$), 2.34 (3H, s, ArCH$_3$), 1.85 (3H, s, CH$_3$C=), -0.21 (9H, s, Si(CH$_3$)$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 171.6 (C), 143.1 (C), 142.0 (C), 137.0 (C), 136.4 (C), 128.7 (2 x CH), 128.5 (2 x CH), 51.6 (CH$_3$), 41.1 (CH$_2$), 21.2 (CH$_3$), 18.5 (CH$_3$), -0.3 (3 x CH$_3$); HRMS (ES) Exact mass calcd for C$_{16}$H$_{25}$O$_2$Si [M+H]$^+$: 277.1618, found: 277.1617.
General Procedure for Grignard Reactions

To a solution of the appropriate cyclopropene (0.20 mmol) in THF (2 mL) at 0 °C was added Grignard reagent (0.26 mmol, 1.3 equiv) dropwise over 1 min. The reaction was stirred at 0 °C for 2 hrs and poured into saturated aqueous NH₄Cl solution (20 mL) and the aqueous layer was then separated and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (EtOAc/hexane) gave the alkene product.

(E)-Dimethyl 2-(1,4-diphenylbut-1-en-2-yl)malonate (120a). The title compound was prepared according to General Procedure from cyclopropene 108a (42 mg, 0.20 mmol) and PhCH₂CH₂MgCl and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (40 mg, 63%). IR (CHCl₃) 2954, 2861, 1736(C=O), 1495, 1433, 1313, 1196, 1148, 1028, 747 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.27 (2H, m, ArH), 7.22-7.18 (3H, m, ArH), 5.50 (1H, t, J = 7.2 Hz, =CH), 4.04 (1H, s, C(H(CO₂CH₃))₂), 3.74 (6H, s, 2 x OCH₃), 2.70 (2H, t, J = 7.5 Hz, PhCH₂), 2.40 (2H, app q, J = 7.5 Hz, PhCH₂CH₂), 2.11 (2H, t, J = 7.5 Hz, =CH₂), 1.26-1.22 (4H, m, CH₂CH₂CH₂), 0.88 (3H, t, J = 6.9 Hz, CH₃CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.9 (2 x C), 141.7 (C), 132.5 (C), 130.8 (CH), 128.5 (2 x CH), 128.2 (2 x CH), 125.8 (CH), 58.0 (CH), 52.4 (2 x CH₃), 35.6 (CH₂), 30.4 (CH₂), 30.1 (CH₂), 22.7 (CH₂), 13.9 (CH₃); LRMS (ES) mass calcd for C₁₅H₂₇O₄ [M+H]⁺: 319.18, found: 318.98.

(Z)-Dimethyl 2-(1,4-diphenylbut-1-enyl)malonate (120b).

The title compound was prepared according to General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and PhCH₂CH₂MgCl and purified by column chromatography (hexane→10%
EtOAc/hexane) to give a colourless oil (49 mg, 72%). IR (CHCl₃) 3026, 2952, 1736 (C=O), 1601, 1495, 1434, 1313, 1196, 1149, 1028 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.33-7.15 (6H, m, ArH), 7.11-7.07 (4H, m, ArH), 5.82 (1H, t, J = 7.4 Hz, =CH), 4.37 (1H, s, CH(CO₂CH₃)₂), 3.71 (6H, s, 2 x OCH₃), 2.67 (2H, t, J = 7.6 Hz, PhCH₂), 2.31 (2H, app q, J = 7.6 Hz, PhCH₂CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.5 (2 x C), 141.3 (C), 138.9 (C), 133.3 (C), 132.7 (CH), 128.7 (2 x CH), 128.5 (2 x CH), 128.2 (2 x CH), 128.1 (2 x CH), 127.3 (CH), 125.8 (CH), 59.4 (CH), 52.5 (2 x CH₃), 35.6 (CH₂), 30.9 (CH₂); LRMS (ES) mass calcd for C₂₁H₂₃O₄ [M+H]⁺: 339.15, found: 338.83.

(Z)-Dimethyl 2-(1,2-diphenylvinyl)malonate (120c). The title compound was prepared according to General Procedure from cyclopropene 108d (46 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 51%). IR (CHCl₃) 2953, 1734(C=O), 1492, 1434, 1311, 1150, 1028, 757, 696, 481 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.31-7.24 (5H, m, ArH), 7.11-7.09 (3H, m, ArH), 6.98-6.95 (2H, m, ArH), 6.73 (1H, s, CH), 4.53 (1H, s, CH), 3.76 (6H, s, 2 x OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.3 (2 x C), 139.4 (C), 136.0 (C), 131.5 (C), 129.4 (CH), 129.0 (2 x CH), 128.7 (2 x CH), 127.9 (2 x CH), 127.7 (2 x CH), 127.2 (CH), 60.4 (CH), 52.7 (2 x CH₃); LRMS (ES) mass calcd for C₁₉H₁₉O₄ [M+H]⁺: 311.12, found: 310.89.

(E)-Dimethyl 2-(1,4-diphenylbut-1-en-2-yl)malonate (120d). The title compound was prepared according to General Procedure from cyclopropene 108b (52 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (45 mg, 66%). IR (CHCl₃) 3026, 2952, 1735(C=O), 1495, 1435, 1311, 1150, 1028, 751, 698 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.37-7.12 (10H, m, ArH), 6.64 (1H, s, =CH), 6.04 (1H, d, J = 1.3 Hz), 4.50 (1H, s, CH), 3.77 (6H, s, 2 x OCH₃); LRMS (ES) mass calcd for C₂₁H₂₁O₄ [M+H]⁺: 339.15, found: 338.83.
4.29 (1H, s, CH(CO₂CH₃)₂), 3.81 (6H, s, 2 x OCH₃), 2.78-2.73 (2H, m, CH₂), 2.70-2.64 (2H, m, CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.7 (2 x C), 141.3 (C), 136.8 (C), 133.7 (C), 132.0 (CH), 128.5 (2 x CH), 128.4 (2 x CH), 128.2 (4 x CH), 127.1 (CH), 126.0 (CH), 58.4 (CH), 52.7 (2 x CH₃), 34.2 (CH₂), 33.5 (CH₂); LRMS (ES) mass calcd for C₂₁H₂₃O₄ [M+H]+: 339.15, found: 338.89.

(Z)-Dimethyl 2-(2-phenyl-1-p-tolylvinyl)malonate (120e). The title compound was prepared according to General Procedure from cyclopropene 108e (46 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (34 mg, 52%). IR (CHCl₃) 2952, 1734(C=O), 1510, 1436, 1310, 1149, 1026, 824, 756, 695 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.16-7.10 (7H, m, ArH), 7.01-6.98 (2H, m, ArH), 6.70 (1H, s, CH), 4.53 (1H, s, CH), 3.76 (6H, s, 2 x OCH₃), 2.35 (3H, s, CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 168.4 (2 x C), 137.4 (C), 136.3 (C), 136.1 (C), 131.6 (C), 129.4 (2 x CH), 128.8 (CH), 127.8 (CH), 127.1 (CH), 131.6 (C), 129.3 (2 x CH), 128.3 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 62.8

(Z)-Dimethyl 2-(4-(benzoyloxy)-1-phenylbut-1-en-2-yl) malonate (120f). The title compound was prepared according to General Procedure from cyclopropene 108e (61 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 41%). IR (CHCl₃) 2952, 1715(C=O), 1433, 1268, 1144, 1108, 1023, 752, 709, 481 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.01-7.99 (2H, m, ArH), 7.56-7.34 (8H, m, ArH), 6.78 (1H, s, CH), 4.24 (2H, t, J = 7.0 Hz, CH₂), 4.36 (1H, s, CH), 3.76 (2 x OCH₃), 2.89 (2H, t, J = 7.0 Hz, CH₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.9 (2 x C), 166.4 (C), 136.3 (C), 134.0 (CH), 132.9 (CH), 130.0 (C), 129.9 (C), 129.6 (2 x CH), 128.6 (2 x CH), 128.4 (2 x CH), 128.3 (2 x CH), 127.3 (CH), 62.8
(CH₂), 58.0 (CH), 52.8 (2 x CH₃), 30.6 (CH₂); LRMS (ES) mass calcd for C₂₂H₂₆NO₆ [M+NH₄⁺]: 400.18, found: 399.87.

Magnesium Halide-Promoted−Ring-Opening Reactions: General Procedure A

A solution of the appropriate cyclopropene (0.20 mmol) in THF (1 mL + 1 mL rinse) was added via cannula to a vial containing the appropriate magnesium halide (0.20 mmol) and a stirrer bar. The resulting mixture was stirred at the indicated temperature for the indicated time, and then filtered through a short plug of SiO₂ (ca. 4 cm high x 2 cm diameter) using EtOAc as eluent (ca. 50 mL). After the filtrate was concentrated in vacuo, purification of the residue by column chromatography afforded the alkenyl halide product.

(Z)-Dimethyl 2-(2-bromo-1-phenylvinyl)malonate (124a).

On a 0.20 mmol scale: The title compound was prepared according to General Procedure A from cyclopropene 108d (46 mg, 0.20 mmol) and MgBr₂ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (60 mg, 96%).

On a 2.00 mmol scale: A solution of the cyclopropene 108d (2.00 mmol) in THF (15 mL + 5 mL rinse) was added via cannula over 2 min to a flask containing MgBr₂ (368 mg, 2.00 mmol) and a stirrer bar. The resulting mixture was stirred at room temperature for 30 min, and then filtered through a short plug of SiO₂ (ca. 4 cm high x 2 cm diameter) using EtOAc as eluent (ca. 100 mL). After the filtrate was concentrated in vacuo, purification of the residue by column chromatography
(hexane→5% EtOAc/hexane) afforded the alkenyl bromide 124a (601 mg, 96%) as a colourless oil.

IR (film) 2954, 2846, 1738 (C=O), 1620, 1437, 1265, 1151, 1076 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.41-7.38 (2H, m, ArH), 7.36-7.31 (3H, m, ArH), 6.75 (1H, d, \(J=0.6\) Hz, =CH), 4.50 (1H, d, \(J=0.6\) Hz, CH(CO\(_2\)CH\(_3\))\(_2\)), 3.76 (6H, s, 2 x OCH\(_3\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 167.1 (2 x C), 138.1 (C), 137.2 (C), 128.4 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 110.6 (CH), 58.8 (CH), 52.9 (2 x CH\(_3\)); HRMS (EI) Exact mass calcd for C\(_{13}\)H\(_{13}\)\(^{79}\)BrO\(_4\) [M\(^+\)]: 311.9992, found: 311.9992.

**\((Z)\)-Dimethyl 2-(2-bromo-1-p-tolylinyl)malonate (124b).** The title compound was prepared according to General Procedure A from cyclopropene 108e (49 mg, 0.20 mmol) and MgBr\(_2\) (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (47 mg, 72%). IR (film) 2954, 1739 (C=O), 1616, 1510, 1435, 1308, 1196, 1151, 1022, 976 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\)) \(\delta\) 7.20 (4H, s, ArH), 6.71 (1H, s, =CH), 4.48 (1H, s, CH(CO\(_2\)CH\(_3\))\(_2\)), 3.76 (6H, s, 2 x OCH\(_3\)), 2.37 (3H, s, ArCH\(_3\)); \(^{13}\)C NMR (62.9 MHz, CDCl\(_3\)) \(\delta\) 167.2 (2 x C), 138.1 (C), 137.2 (C), 135.1 (C), 129.0 (2 x CH), 128.2 (2 x CH), 110.2 (CH), 58.9 (CH), 52.9 (2 x CH\(_3\)), 21.2 (CH\(_3\)); HRMS (EI) Exact mass calcd for C\(_{14}\)H\(_{15}\)\(^{79}\)BrO\(_4\) [M\(^+\)]: 326.0148, found: 326.0151.

**\((E)\)-Dimethyl 2-[1-(1-bromomethylidene)pentyl]malonate (124c).** The title compound was prepared according to General Procedure A from cyclopropene 108a (42 mg, 0.20 mmol) and MgBr\(_2\) (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (44 mg, 75%). IR (film) 2956, 2871, 1739 (C=O), 1626, 1456, 1435, 1379, 1308, 1273, 1198 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl\(_3\))
δ 6.36 (1H, d, J = 0.5 Hz, =CH), 4.16 (1H, d, J = 0.5 Hz, CH(CO₂CH₃)₂), 3.75 (6H, s, 2 x OCH₃), 2.36-2.32 (2H, m, =CH₂), 1.44-1.28 (4H, m, CH₂CH₂CH₃), 0.91 (3H, t, J = 7.1 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.4 (2 x C), 137.2 (C), 109.2 (CH), 56.9 (CH), 52.8 (2 x CH₃), 33.1 (CH₂), 28.9 (CH₂), 22.5 (CH₂), 13.8 (CH₃); HRMS (EI) Exact mass calcd for C₁₁H₁₇⁷⁹BrO₄ [M⁺]: 292.0305, found: 292.0304.

(E)-Dimethyl 2-[1-(1-bromomethylene)-3-phenylpropyl]malonate (124d).
The title compound was prepared according to General Procedure A from cyclopropene 108b (52 mg, 0.20 mmol) and MgBr₂ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (59 mg, 87%). IR (film) 3028, 2954, 1738 (C=O), 1624, 1495, 1437, 1269, 1201, 1153, 1026 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.33-7.29 (2H, m, ArH), 7.26-7.20 (3H, m, ArH), 6.46 (1H, br s, =CH), 4.18 (1H, d, J = 0.5 Hz, CH(CO₂CH₃)₂), 3.78 (6H, s, 2 x OCH₃), 2.79-2.73 (2H, m, CH₂Ph), 2.69-2.63 (2H, m, CH₂CH₂Ph); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.3 (2 x C), 141.0 (C), 136.4 (C), 128.4 (2 x CH), 128.3 (2 x CH), 126.1 (CH), 110.3 (CH), 57.4 (CH), 52.9 (2 x CH₃), 35.3 (CH₂), 33.0 (CH₂); HRMS (EI) Exact mass calcd for C₁₅H₁₇⁷⁹BrO₄ [M⁺]: 340.0305, found: 340.0302.

(E)-Dimethyl 2-[3-benzoyloxy-1-(1-bromomethylene)propyl]malonate (124e). The title compound was prepared according to General Procedure A from cyclopropene 108c (61 mg, 0.20 mmol) and MgBr₂ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (64 mg, 84%). IR (film) 2956, 2362, 1720 (C=O), 1602, 1437, 1383, 1273, 1201, 1153, 1113 cm⁻¹; ¹H NMR (360
MHz, CDCl₃) δ 8.06-8.03 (2H, m, ArH), 7.58-7.54 (1H, m, ArH), 7.46-7.42 (2H, m, ArH), 6.58 (1H, s, =CH), 4.45 (2H, t, J = 7.0 Hz, CH₂O), 4.31 (1H, s, CH(CO₂CH₃)₂), 3.73 (6H, s, 2 x OCH₃), 2.88 (2H, t, J = 7.0 Hz, =CC₂H); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.1 (2 x C), 166.3 (C), 133.1 (C), 132.9 (CH), 130.0 (C), 129.6 (2 x CH), 128.3 (2 x CH), 112.2 (CH), 61.7 (CH₂), 57.2 (CH), 53.0 (2 x CH₃), 32.6 (CH₂); HRMS (ES) Exact mass calecd for C₁₆H₁₈⁷⁹BrO₆ [M+H]^+: 385.0281, found: 385.0285.

(Z)-Dimethyl 2-(2-iodo-1-phenylvinyl)malonate (125a). The title compound was prepared according to General Procedure A from cyclopropene 108d (46 mg, 0.20 mmol) and MgI₂ (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a 9:1 mixture of inseparable geometric isomers as a colourless oil (70 mg, 97%). IR (film) 3058, 2952, 2846, 1739 (C=O), 1597, 1491, 1437, 1307, 1265, 1153 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.39-7.32 (3H, m, ArH), 7.25-7.22 (2H, m, ArH), 6.87 (1H, d, J = 0.6 Hz, =CH), 4.51 (1H, d, J = 0.6 Hz, CH(CO₂CH₃)₂), 3.72 (6H, s, 2 x OCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.0 (2 x C), 142.8 (C), 141.0 (C), 128.4 (2 x CH), 128.2 (3 x CH), 84.8 (CH), 59.4 (CH), 52.9 (2 x CH₂); HRMS (EI) Exact mass calecd for C₁₃H₁₃I₉⁷⁹BrO₄ [M⁺]: 359.9853, found: 359.9852.

(Z)-Dimethyl 2-(2-bromo-1-p-tolylvinyl)malonate (125b). The title compound was prepared according to General Procedure A from cyclopropene 108e (49 mg, 0.20 mmol) and MgI₂ (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (70 mg, 94%). IR (film) 2952, 1738 (C=O), 1612, 1508, 1435, 1309, 1198, 1151, 1022, 974 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.20 (2H, d, J = 8.1 Hz, ArH), 7.16 (2H, dm, J = 8.1 Hz, ArH), 6.87
(1H, br s, =CH), 4.53 (1H, s, CH(CO2CH3)2), 3.75 (6H, s, 2 x OCH3), 2.37 (3H, s, ArCH3); 13C NMR (62.9 MHz, CDCl3) δ 167.1 (2 x C), 142.8 (C), 138.1 (C), 138.0 (C), 129.1 (2 x CH), 128.1 (2 x CH), 84.4 (CH), 59.5 (CH), 52.9 (2 x CH3), 21.3 (CH3); HRMS (ES) Exact mass calcd for C14H16IO4 [M+H]+: 375.0088, found: 375.0092.

**CO2Me**

**CO2Me**

**(E)**-Dimethyl 2-[1-(1-iodomethylidene)-3-phenylpropyl]malonate (125c). The title compound was prepared according to General Procedure A from cyclopropene 108b (52 mg, 0.20 mmol) and MgI2 (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (77 mg, 99%). IR (film) 2956, 2254, 1736 (C=O), 1437, 1265, 1153, 1028, 733, 650 cm−1; 1H NMR (500 MHz, CDCl3) δ 7.31-7.19 (5H, m, ArH), 6.57 (1H, s, =CH), 4.26 (1H, s, CH(CO2CH3)2), 3.75 (6H, s, 2 x OCH3), 2.74-2.71 (2H, m, CH2Ph), 2.65-2.62 (2H, CH2CH2Ph); 13C NMR (62.9 MHz, CDCl3) δ 167.2 (2 x C), 141.1 (C), 140.8 (C), 128.4 (2 x CH), 128.3 (2 x CH), 126.2 (CH), 84.2 (CH), 57.8 (CH), 52.9 (2 x CH3), 39.6 (CH2), 33.0 (CH2); HRMS (ES) Exact mass calcd for C14H16IO4 [M+NH4]+: 406.0510, found: 406.0507.

**CO2Me**

**CO2Me**

**SO2Ph**

**SO2Ph**

**(E)**-Methyl 4-ido-3-phenyl-2-(phenylsulfonyl)but-3-enoate (125d). The title compound was prepared according to General Procedure A from cyclopropene 108h (63 mg, 0.20 mmol) and MgI2 (56 mg, 0.20 mmol) at room temperature for 2 h and then at 40 °C for 6 h. Purification of the residue by column chromatography (5%→10% EtOAc/hexane) gave a yellow oil (68 mg, 77%). IR (film) 3062, 2952, 1745 (C=O), 1585, 1491, 1446, 1329, 1147, 1082, 910 cm−1; 1H NMR (360 MHz, CDCl3) δ 7.91-7.88 (2H, m, ArH), 7.72-7.67 (1H, m, ArH), 7.58-7.54 (2H, m, ArH), 7.35 (1H, s, =CH), 7.34-7.32 (3H, m, ArH), 7.13-7.11 (2H, m, ArH), 5.05 (1H, s, CHCO2CH3), 3.73 (3H, s, OCH3); 13C NMR
(62.9 MHz, CDCl₃) δ 164.4 (C), 141.2 (C), 141.5 (C), 137.6 (C), 134.5 (CH), 129.9 (2 x CH), 129.0 (2 x CH), 128.5 (3 x CH), 128.0 (2 x CH), 90.1 (CH), 74.4 (CH), 53.4 (CH₃); HRMS (ES) Exact mass calcd for C₁₇H₁₉INO₄S [M+NH₄]⁺: 460.0074, found: 460.0067.

(Z)-Dimethyl 2-(2-chloro-1-ρ-tolylvinyl)malonate (125e). The title compound was prepared according to General Procedure A from cyclopropene 108e (49 mg, 0.20 mmol) and MgCl₂ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a ~16:1 inseparable mixture of regioisomers as a colourless oil (43 mg, 76%). IR (CHCl₃) 3028, 2954, 1739 (C=O), 1611, 1511, 1435, 1310, 1152, 1024 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.24-7.18 (4H, m, Ar H), 6.53 (1H, s, =C H), 4.46 (1H, s, CH(CO₂CH₃)₂), 3.76 (6H, s, 2 x OCH₃), 2.37 (3H, s, ArCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.4 (2 x C), 138.1 (C), 134.3 (C), 133.6 (C), 129.0 (2 x CH), 128.4 (2 x CH), 120.8 (CH), 58.0 (CH), 52.9 (2 x CH₃), 21.2 (CH₃); HRMS (ES) Exact mass calcd for C₁₄H₁₆₃⁵ClO₄ [M+H]⁺: 283.0732, found: 283.0728.

(E)-Dimethyl 2-[1-(1-chloromethylidene)pentyl]malonate (125f). The title compound was prepared according to General Procedure A from cyclopropene 108a (42 mg, 0.20 mmol) and MgCl₂ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (5% EtOAc/hexane) to give a ~16:1 inseparable mixture of regioisomers as a colourless oil (43 mg, 85%). IR (CHCl₃) 2957, 2873, 1740 (C=O), 1634, 1436, 1308, 1199, 1150, 1027, 948 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.20 (1H, s, =C H), 4.11 (1H, s, CH(CO₂CH₃)₂), 3.75 (6H, s, 2 x OCH₃), 2.35-2.31 (2H, m, =CHCH₃), 1.42-1.32 (4H, m, CH₂CH₂CH₃), 0.91 (3H, t, J = 7.1 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.7 (2 x C), 134.7 (C), 119.8 (CH), 56.1 (CH), 52.8 (2 x CH₃), 30.6 (CH₂), 28.9 (CH₂), 22.5 (CH₂), 13.8
(Z)-Diethyl 2-(2-chloro-1-phenylvinyl)malonate (125g). The title compound was prepared according to General Procedure A from cyclopropene 108j (52 mg, 0.20 mmol) and MgCl₂ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (37 mg, 62%). IR (film) 2983, 1734 (C=O), 1493, 1444, 1367, 1306, 1151, 1095, 1032, 920 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.41-7.31 (5H, m, ArH), 6.56 (1H, d, J = 0.6 Hz, =CH), 4.44 (1H, d, J = 0.6 Hz, CH(CO₂CH₂CH₃)₂), 4.26-4.16 (4H, m, 2 x OCH₂), 1.25 (6H, t, J = 7.2 Hz, 2 x OCH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 167.0 (2 x C), 136.7 (C), 134.7 (C), 128.6 (2 x CH), 128.3 (2 x CH), 128.1 (CH), 120.9 (CH), 62.0 (2 x CH₂), 58.3 (CH), 13.9 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₁H₁₈ClO₄ [M+H]^+: 249.0888, found: 249.0886.

One-Pot Magnesium Halide-Promoted Ring-Opening-Michael Reactions: General Procedure B

A solution of the appropriate cyclopropene (0.20 mmol) in MeCN (1 mL + 1 mL rinse) was added via cannula to a vial containing the appropriate enone (0.40 mmol), MgBr₂ (37 mg, 0.20 mmol), and a stirrer bar. The resulting mixture was stirred at 40 °C for 18 h. After cooling to room temperature, the mixture was filtered through a short plug of SiO₂ (ca. 4 cm high x 2 cm diameter) using EtOAc as eluent (ca. 50 mL) and the filtrate was concentrated in vacuo. Purification of the residue by column chromatography afforded the alkenyl halide product.
**(Z)-Dimethyl 2-(bromo-1-phenylvinyl)-2-(3-oxobutyl)malonate  (132c).**

*On a 0.20 mmol scale:* The title compound was prepared according to General Procedure B from cyclopropene 108d (46 mg, 0.20 mmol) and methyl vinyl ketone (32 μL, 0.40 mmol) and purified by column chromatography (10%→30% EtOAc/hexane) to give a 19:1 inseparable mixture of regioisomers as a colourless oil (60 mg, 78%).

*On an 8.00 mmol scale:* A solution of the cyclopropene 108d (1.86 g, 8.00 mmol) in MeCN (40 mL + 10 mL rinse) was added via cannula over 5 min to a flask containing methyl vinyl ketone (1.22 mL, 15.0 mmol). The resulting mixture was stirred at room temperature for 30 min and then at 40 °C for 17.5 h. After cooling to room temperature, the mixture was filtered through a short pad of SiO₂ (ca. 4 cm high x 6 cm diameter) using EtOAc as eluent (ca. 100 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (10%→30% EtOAc/hexane) gave the *alkenyl bromide 7a* as a 19:1 inseparable mixture of regioisomers (2.34 g, 76%) as a colourless oil. IR (CHCl₃) 2953, 1735 (C=O), 1613, 1491, 1437, 1366, 1254, 1171, 1092, 1030 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.38-7.31 (3H, m, ArH), 7.07-7.05 (2H, m, ArH), 6.92 (1H, s, =CH), 3.71 (6H, s, 2 x OC₃H₃), 2.53-2.50 (2H, m, CH₂CH₂C=O), 2.27-2.24 (2H, m, CH₂CH₂C=O), 2.09 (3H, s, CH₃C=O); ¹³C NMR (62.9 MHz, CDCl₃) δ 206.6 (C), 169.5 (2 x C), 141.4 (C), 137.1 (C), 128.8 (2 x CH), 128.3 (2 x CH), 128.2 (CH), 112.3 (CH), 63.7 (C), 52.8 (2 x CH₃), 39.0 (CH₂), 29.9 (CH₃), 28.2 (CH₂); HRMS (ES) Exact mass calcd for C₁₇H₂₀⁷⁹BrO₅ [M+H]⁺: 383.0489, found: 383.0492.

**(E)-Dimethyl 2-[1-(1-bromomethylidene)pentyl]-2-(3-oxobutyl)malonate  (132b).** The title compound was prepared according to General Procedure B from
cyclopropene 108a (43 mg, 0.20 mmol) and methyl vinyl ketone (32 μL, 0.40 mmol) and purified by column chromatography (5%→10% EtOAc/hexane) to give a colourless oil (56 mg, 78%). IR (CHCl₃) 3105, 2956, 2872, 1734 (C=O), 1610, 1434, 1369, 1255, 1169, 1091 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 6.46 (1H, s, =CH), 3.73 (6H, s, 2 x OCH₃), 2.52-2.49 (2H, m, CH₂C=O), 2.34-2.31 (2H, m, =CCH₂), 2.18-2.14 (2H, m, CH₂CH₂C=O), 2.11 (3H, s, CH₃C=O), 1.44-1.38 (2H, m, CH₂CH₂CH₃), 1.36-1.28 (2H, m, CH₂CH₃), 0.90 (3H, t, J = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 206.8 (C), 169.8 (2 x C), 140.5 (C), 109.5 (CH), 63.6 (C), 52.7 (2 x CH₂), 39.0 (CH₂), 32.5 (CH₂), 30.0 (CH₃), 29.6 (CH₂), 27.3 (CH₂), 23.1 (CH₂), 13.7 (CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₄BrO₅ [M+H]+: 363.0802, found: 363.0799.

(E)-Dimethyl 2-[1-(1-bromomethylidine)-3-phenylpropyl]-2-(3-oxopentyl) malonate (132c). The title compound was prepared according to General Procedure B from cyclopropene 108b (52 mg, 0.20 mmol) and ethyl vinyl ketone (40 μL, 0.40 mmol) and purified by column chromatography (5%→10% EtOAc/hexane) to give a colourless oil (61 mg, 72%). IR (CHCl₃) 2952, 1734 (C=O), 1496, 1455, 1242, 1095, 1031, 753, 700, 557 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.33-7.18 (5H, m, ArH), 6.59 (1H, s, =CH), 3.76 (6H, s, 2 x OCH₃), 2.81-2.76 (2H, m, CH₂), 2.54-2.39 (8H, m, 4 x CH₂), 1.06 (3H, t, J = 7.3 Hz, CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 209.4 (C), 169.6 (2 x C), 141.5 (C), 139.7 (C), 128.4 (2 x CH), 128.1 (2 x CH), 126.1 (CH), 110.4 (CH), 63.7 (C), 52.8 (2 x CH₃), 37.6 (CH₂), 36.0 (CH₂), 35.5 (CH₂), 33.4 (CH₂), 27.4 (CH₂), 7.7 (CH₃); HRMS (EI) Exact mass calcd for C₂₀H₂₆BrO₅ [M+H]+: 425.0958, found: 425.0957.
2) Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes

2.1) Asymmetric 1,4-Conjugate Addition

The asymmetric 1,4-conjugate addition of carbon nucleophiles to acceptor-activated carbon-carbon double bonds is one of the most important methods for the preparation of optically active natural products and pharmaceuticals.

\[
\text{(a) Diastereoselective Conjugate Addition:} \quad X \quad R \quad \overset{\text{Nu}}{\longrightarrow} \quad X \quad R
\]

\[
\text{(b) Enantioselective Conjugate Addition:} \quad X \quad R \quad \overset{\text{Nu+ML*}}{\longrightarrow} \quad X \quad R
\]

\[
\text{(c) Catalytic Enantioselective Conjugate Addition:} \quad X \quad R \quad \overset{\text{Nu+ML* (catalyst)}}{\longrightarrow} \quad X \quad R
\]

*Scheme 2.1 Strategies for stereoselective 1,4-nucleophilic conjugate additions*

There are three strategies to achieve this carbon-carbon bond formation diastereoselectively and enantioselectively (Scheme 2.1):

(a) Diastereoselective addition to Michael acceptor with a covalently-bound chiral auxiliary X*. This strategy is usually employed in target-oriented synthesis, for example, a Michael addition of N-sulfinyl metalloenzyme 134 to the \(\alpha,\beta\)-unsaturated ketone formed N-sulfinylanino ketone with high diastereoselectivity (Scheme 2.2).
Scheme 2.2 Diastereoselective addition of N-sulfinyl metalloenamines to α,β-unsaturated ketones

(b) Enantioselective Michael addition of chirally modified nucleophile Nu-ML* to prochiral substrate, for instance, preformed chiral cuprate species 137 was able to deliver a butyl group to cyclohexenone enantioselectively (Scheme 2.3). Although this strategy has proven to be successful in terms of high enantioselectivities, stoichiometric amounts of the transition metal salt and chiral ligand are required which usually cannot be recovered. Another drawback is high substrate specificity; i.e., a certain chirally-modified reagent often gives high stereoselectivities with one or two specific Michael acceptors.

Scheme 2.3 Enantioselective Michale addition of the chiral amidocuprate

(c) The most atom-economic way is to use only catalytic amounts of the stereo information from chiral metal complexes ML*. Those complexes can be either Lewis acidic catalysts, such as magnesium, zinc, boron, aluminium and lanthanoid, which are di- and trivalent; or transition-metal catalysts, such as ruthenium, iridium, nickel, palladium, rhodium and copper, which might change their oxidation state during the catalytic cycle. Copper catalysts in particular, are still the most noted because of their inexpensiveness and high efficiency towards enantioselective conjugate additions. For example, 1,4-addition of diethylzinc to chalcone 139 could be
catalysed by copper(II) triflate in the presence of the phosphoramidite ligand L1 (Scheme 2.4).  

![Scheme 2.4 Copper-catalysted enantioselective conjugate addition of chalcone](image)

**Scheme 2.4** Copper-catalysted enantioselective conjugate addition of chalcone

### 2.2) Copper Hydride Chemistry

Since the pioneer work by Gilman in 1952, cuprates have become versatile tools in organic synthesis, especially in 1,4-addition reactions to \( \alpha, \beta \)-unsaturated acceptors, which can be performed with stoichiometric or catalytic amounts of copper in a stereo- and enantioselective fashion. However, the corresponding C-H bond formation using copper hydrides, which enjoyed a rich history in the mid 1980’s, stayed highly underdeveloped until late 1990’s.

![Scheme 2.5 The scope of copper hydride chemistry](image)

**Scheme 2.5** The scope of copper hydride chemistry

Chapter 2 Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes
For the last two decades, copper hydride chemistry has been extensively developed and widely used for the synthesis of various chiral building blocks. Some representative types of this chemistry are hydrocupration, S_{N}2’-reduction, 1,2-reduction, and 1,4-reduction (Scheme 2.5).

### 2.2.1) CuH-Catalysed 1,4-Conjugate Reduction

With respect to the generation of copper hydride for 1,4-conjugate reductions, the first remarkable success was recognised as “Stryker’s reagent”. In a series of publications since 1988, Stryker disclosed the synthetic potential of the phosphine-stabilised hexameric copper hydride [(Ph_{3}P)CuH]_{6} in highly regioselective conjugate reduction reactions of carbonyl derivatives (example in Scheme 2.6). This beautiful crystalline red solid has offered an efficient pathway with mild conditions to achieve a broad range of functional group compatibility.

![Scheme 2.6 Conjugate reduction of α,β-unsaturated carbonyl compounds](image)

Since then, modifications on the reaction condition have been made for this transformation (Scheme 2.7). Those include copper source, hydride source, ligand and other additives.

![Scheme 2.7 Preparation of ligated copper hydrides](image)
Not long after his initial report on stoichiometric use of $[(\text{Ph}_3\text{P})\text{CuH}]_6$, Stryker discovered that this reaction could be achieved catalytically. The cycle could be established by using catalytic amount of CuOrt-Bu, PPh$_3$ and molecular hydrogen, which served as hydride source.

These early recipes to generate CuOrt-Bu involved the use of CuCl and one equivalent of NaOrt-Bu. Since copper(I) is susceptible to oxidation, inert conditions were necessary to ensure that the activity of the metal catalyst was maintained. In order to avoid the preparation of extremely air-sensitive CuOrt-Bu in situ, Cu(OAc)$_2$·H$_2$O is found to be an attractive substitute.

Meanwhile, other alternative sources of stoichiometric reducing agents for the generation of copper hydride complexes have been employed to replace hydrogen gas. Silanes, in particular, are the most common source of stoichiometric hydride since they are inexpensive and environmentally friendly. Most popular silanes for copper hydride-catalysed reduction include polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming’s silane (PhMe$_2$SiH), and phenylsilane (PhSiH$_3$) (Scheme 2.8).

![Scheme 2.8 Silanes for CuH reduction](image)

In terms of phosphine ligands, replacing triphenylphosphine with chiral bis-phosphines results in a chiral copper hydride species that performs the reaction in a diastereo- and enantioselective fashion. A majority of success up to date has been focused on biaryl and ferrocenyI bis-phosphines. Selected biaryls from the BIPHEP and SEGPHOS series and certain chelators in the Josiphos series have remarkable discriminatory structural features and also a high turnover number (Scheme 2.9).
A more recently found alternative to phosphine ligands are N-heterocyclic carbenes (NHCs).\textsuperscript{78} Air stability of the corresponding copper-carbene complexes is one of the obvious advantages. As a strong $\sigma$-donor and weak $\pi$-acceptor, NHC effects stronger interaction with the metal comparing with phosphine ligands. Also, a linear arrangement between the carbene carbon, copper, and hydrogen can affect the reactivity and stereoselectivity of CuH complex (Scheme 2.10).

One of the key “tricks” to this chemistry is to take advantage of the tolerance of CuH complexes to alcohols and water. It is noticed that Stryker used water to suppress side reactions for those substrates which were sensitive to base-catalysed aldol condensations. Several subsequent reports rely on the presence of a bulky alcohol (e.g., $t$-BuOH) to enhance reaction rates.

With careful tuning of the conditions as above, CuH chemistry has found to successfully effect, in an asymmetric fashion, the 1,4-conjugate reduction of substrates with various activating functional groups, including carbonyls, nitriles, sulfones, phosphonates and nitro groups. Representative examples of each type will be discussed in the next section.
2.2.2) Reduction of α, β-Unsaturated Carbonyls

Enoates

Inspired by early work, the first copper-catalysed enantioselective conjugate reduction was developed by Buchwald.\textsuperscript{79} A Chiral CuH species was generated in \textit{situ} from CuCl, NaOt-Bu and the chiral ligand (S)-p-tol-BINAP. This combination smoothly promoted 1,4-reduction of α,β-unsaturated esters (enoates) to furnish the corresponding saturated products in very good yields and high ee’s (Scheme 2.11).

![Scheme 2.11 Enantioselective conjugate reduction of enoates](image)

Using both \textit{E}- and \textit{Z}-isomers of the α,β-unsaturated ester 146a and 146b, the asymmetric reductions proceeded equally to give the opposite enantiomers of product 147a and 147b with nearly the same ee.

![Scheme 2.12 The catalytic cycle of enantioselective CuH conjugate reduction](image)
In the catalytic cycle of the reaction (Scheme 2.12), copper hydride 149 is the key intermediate that is responsible for the enantioselectivity. By combining \( p \text{-} \text{tol-BINAP}, \text{CuCl}, \) and \( \text{NaO}t\text{-Bu}, \) copper alkoxide \((p \text{-} \text{tol-BINAP})\text{CuO}t\text{-Bu} 148\) is most likely formed. Addition of PMHS then results in a \( \sigma \)-bond metathesis between copper alkoxide and PMHS, to generate copper hydride 149. Asymmetric conjugate reduction then occurs, resulting in formation of a copper enolate intermediate 150 that subsequently undergoes \( \sigma \)-bond metathesis with PMHS to make a silylketene acetal 151 and regenerate the copper hydride. While there is no clear rationale for the enantioselectivity of the reduction, the catalyst seems to discriminate between enantiotopic faces of the alkene primarily on the basis of the orientation of the ester, since \((E)\)- and \((Z)\)-isomers give the products with opposite chirality.

This method was applied to a tricyclic myrmicarin alkaloid 154 synthesis (Scheme 2.13). To avoid the sensitive CuCl/NaO\(t\)-Bu system, Cu(OAc)\(_2\)H\(_2\)O is found to be an attractive substitute. \( t\)-BuOH was added to enhance the reaction rate. Higher catalyst loading was employed due to high steric hindrance at the \( \beta \)-site of 152. 80

![](image)

**Scheme 2.13** Synthesis tricyclic myrmicarin alkaloid

The absolute stereochemistry of the reduction product could not only be controlled by the configuration of the substrate, but also by the choice of chiral ligands. In 2004, Lipshutz and co-workers reported a CuH mediated reduction of acyclic \( \alpha,\beta \)-unsaturated enoates producing the reduced products in excellent yields and \( ee \)'s (Scheme 2.14). 81 Using different substrates, \( Z\)-155a produced the reduced product \( S\)-156a, whereas \( E\)-155a produced the product with opposite stereochemistry \( R\)-156a.
Alternatively, using (R,S)-Josiphos ligand L3 produced S-156b, whereas using (S,R)-Josiphos ligand ent-L3 furnished the opposite isomer R-156b.

\[
\text{R}^2 \text{Me} \quad \text{Me} \quad \text{Ph} \\
\text{O} \quad \text{O} \\
\text{Me} \quad \text{Me}
\]

\[
\text{OEt} \quad \text{O} \\
\text{Me} \quad \text{Ph} \\
\text{OEt}
\]

\[
\text{L}^* \\
\text{Cu} \quad \text{H} \\
\text{Ph}_3 \text{P} \\
\text{Me} \quad \text{H}
\]

\[
\text{PMHS, t-BuOH, 0 °C} \\
\text{OEt} \quad \text{O} \\
\text{Me} \quad \text{Ph} \\
\text{OEt}
\]

\[
\text{155a-c} \\
\text{156a-c} \\
\text{156b} \\
\text{156c}
\]

\[
\text{92% (S isomer; 99% ee) (Z-155a and L2)} \\
\text{94% (R isomer; 91% ee) (E-155a and L2)} \\
\text{92% (R isomer; 98% ee) (Z-155a and L3)}
\]

\[
\text{Ph} \\
\text{Me} \\
\text{OEt} \\
\text{Me}
\]

\[
\text{98% (S isomer; 99% ee) (E-155b and L3)} \\
\text{96% (R isomer; 98% ee) (E-155b and ent-L3)} \\
\text{91% (98% de) (E-155c and L3)} \\
\text{70% (40% de) (E-155c and ent-L3)}
\]

\[
\text{Scheme 2.14 Cu-catalysed reduction of acyclic enoates}
\]

For the reduction of β-substituted ethyl cinnamate derivative 155a, SEGPHOS L2 gave best results, but it did not give the same level of enantioselectivity with β,β-dialkyl-substituted enoate 155b, suggesting limitations to the substrate-ligand combination. Josiphos ligand L3 was found to be an effective substitute, which displayed outstanding facial discrimination in the dialkyl enoate cases.

The reduction of an optically pure enoate that already incorporated an existing stereocenter at the γ-carbon (155c), using the ligand L3 gave the corresponding reduced product 156c with a 98% de and 91% conversion, suggesting highly favourable si face attack. When the same reduction was tried using ligand ent-L3, the reduced product showed only a 40% de and 70% conversion, showing unfavourable re face attack.
Cyclic enones

Chiral copper hydride can also reduce $\beta$-substituted cyclic enones to afford ketones with high ee’s.

![Scheme 2.15 Conjugate addition of cyclic enones](image)

Although direct asymmetric conjugate addition of nucleophilic alkyl groups to cyclopentenone were well-established procedure to access cyclic ketones (Scheme 2.15a), Buchwald showed that alkylation followed by asymmetric conjugate reduction of $\beta$-substituted enones (Scheme 2.15b) can access the same products with much higher enantioselectivities (Scheme 2.16).

![Scheme 2.16 Copper-catalysed reduction of cyclic enones](image)
Buchwald stressed that the addition of no more than 1.05 equivalents of PMHS was crucial, since excess amount led to overreduction to form the saturated alcohol. Longer reaction time was found necessary for the more sterically hindered substituent on the $\beta$ position of the enone 161c. Larger cyclic substrates 161d and 161e were also tolerated to similar reduction condition. For cyclohexenone 161d, BIPHEMP produced best results. For 3-phenethylcycloheptenone 161e, (S)-BINAP was employed. In this case, a small amount of competing 1,2-reduction was observed.

In the catalytic cycle they proposed (Scheme 2.17), the (bis-phosphine)CuH complex 162 was first generated in situ as the key intermediate. Conjugate reduction of cyclopentenones by such a complex would then result in the formation of the copper enolate 163 that undergoes $\sigma$-bond metathesis with a silane to form silyl enol ether 164.

![Scheme 2.17 Mechanism of asymmetric reduction of $\beta$-alkyl cyclopentenones](image-url)

Chapter 2 Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes
Lactones and lactams

Buchwald next examined the asymmetric conjugate reduction of lactones and lactams. It was found that air-stable CuCl\textsubscript{2}·2H\textsubscript{2}O could replace CuCl as the copper source, allowing the reaction to carry out without the aid of a drybox (Scheme 2.18).

Alcohols of various sizes (EtOH, i-PrOH, 3-pentanol, t-AmOH) were screened as the additive. Lower reaction temperature (-20 °C to -40 °C) and slow addition of the alcohol via syringe pump minimised competitive silylation of the alcohol with concomitant release of H\textsubscript{2}, which allowed for complete consumption of lactones and lactams.

These conditions allowed for the reduction of alkyl substituted butenolides \textbf{165a} and \textbf{165b} to give \textbf{166a} and \textbf{166b} in good yields with excellent enantioselectivities. Initial attempts to reduce pentenolide \textbf{165c} at -20 °C with i-PrOH resulted in a GC yield of only 25% at complete conversion. Switching to a larger alcohol additive tert-amyl alcohol, and lowering the reaction temperature to -40 °C significantly improved the GC yields (80-90%), although the isolated yield is moderate (\textbf{166c}, 71%). BIPHEMP was found to be the best ligand.

\textbf{Scheme 2.18} Cu-catalysed reduction of lactones and lactams
The reaction scope was then expanded to the reduction of lactams. 

*\textit{N*-p-Methoxyphenyl lactam 165d*} was reduced in 94% yield and 94\% ee after 3 h at 0 °C. In contrast to pentenolide 165c, reduction of unsaturated six-membered lactam 165e proceeded with excellent ee using *p*-tol-BINAP as the ligand.

In the previous catalytic cycles of Cu-H reduction, without adding the alcohol, the copper enolate was quenched by the silane, and silyl ketene acetal derivative was initially formed. By adding the alcohol, the reaction could dramatically speed up the reduction. The rate-accelerating effect of alcohols in those lactone reductions was studied by Lipshutz\textsuperscript{81} using deuterated *t*-butanol in benzene-*d*_6 (Scheme 2.19).

![Scheme 2.19 Cu-catalysed reduction of unsaturated lactone using deuterated *t*-BuOD in benzene-*d*_6](image)

Proton NMR spectroscopy showed that 16\% deuterium of *t*-BuOD is incorporated at the \(\beta\)-position, which comes from facile H/D-exchange between CuH and *t*-BuOD. While 61\% deuterium at the \(\alpha\)-position shows that most of the *t*-BuOD is used to quench the copper enolate 170. Since no exchange occurs between PMHS and *t*-BuOD, it is likely that the rate enhancement is due to more rapid quenching of the copper enolate 170 by *t*-BuOD than by PMHS (Scheme 2.20).
Buchwald also reported a total synthesis of Eupomatilone-3 using CuH chemistry to reduce butenolide 172 asymmetrically into cis-4,5-disubstituted lactone 173 (Scheme 2.21). To perform the dynamic kinetic resolution (DKR), addition of excess base NaO\textsubscript{t}-Bu allowed for racemisation of butenolide 172. Complete conversion of the starting material into the desired product was observed. Interestingly, the process was completely diastereoselective, only a single diastereomer was produced with 83% ee, and none of the trans isomer was detected. To improve the enantioselectivity of the reaction, other chiral bisphosphine ligands were used. Replacing $p$-tol-BINAP L\textsubscript{4} with MeO-BIPHEP L\textsubscript{5} provided the desired compound, again as a single diastereomer with 93% ee.
With this promising result, the scope of the reduction was expanded to other \( \gamma \)-aryl-containing unsaturated lactones \( 174a-d \).\(^{84} \) The BIPHEP ligand \( \text{L5} \) used previously did not tolerate the new furanone substrates. Switching to SYNPHOS \( \text{L6} \) allowed the reduction to produce a single diastereomer with high yield and good \( ee \) (Scheme 2.22).
Acyclic enones

Other than enoates, lactones and lactams, acyclic enones have proven to be long-standing challenging substrates in this regard. In 2003, preliminary studies by Lipshutz and Servesko revealed the conjugate reduction of acyclic enones with high yields and enantioselectivities. Extensive ligand screening showed that chiral biaryl ligands such as BIPHEP and SEGPHOS gave low ee’s. Fortunately, Josiphos ligands furnished the reduced product \(177a\) with excellent yields and ee’s (Scheme 2.23).

![Scheme 2.23 Cu-catalysed reduction of acyclic enones](image)

The newly generated stereocentre in the product was controlled by the stereochemistry of the ligand and geometry of the enone double bond in the substrate. In the case of product \(177b\), the \(S\) enantiomer was obtained by using ligand \(L3\), while \(\text{ent-}L3\) resulted in the formation of the \(R\) enantiomer. Interestingly, the reduction to form \(177c\) proceeded in an opposite fashion to other enones. Thus, rather than the \(S\) enantiomer which ligand \(L3\) usually gave, in this case the \(R\) enantiomer was isolated.
2.2.3) Reduction of Other $\alpha,\beta$-Unsaturated Compounds

As well as enones and enoates, other Michael acceptors have also been tested in the enantioselective conjugate reduction.

**Nitroalkenes**

The nitro group is one of the most common functionalities used to activate alkenes toward asymmetric conjugate additions. In 2003, Czekelius and Carreira reported the metal-catalysed enantioselective reduction of $\beta,\beta$-disubstituted nitroalkenes using copper-phosphane complexes to give optically active nitroalkanes in useful yields and selectivities.\(^{87}\)

Inspired by their previously developed catalytic system for the addition of dienolates to aldehydes using CuCl, tol-Binap, and NaOr-Bu,\(^{88}\) Czekelius applied these conditions to nitroalkene reduction which led to a sluggish reaction rate with a moderate yield and ee of the desired product. Later on, they made progress by preparing another catalytic system using tol-Binap and CuOr-Bu, which provided full conversion of nitroalkenes 178 into 179 with much higher ee in a shorter period of time. They concluded that the presence of NaCl inhibited the reactivity of the Cu-phosphine complex and slowed down the reaction. This hypothesis was supported by similar detrimental effects observed using various inorganic salts such as LiCl and KCN (Scheme 2.24).

Further optimisation on the efficiency of the reaction resulted in the use of a combination of PMHS and phenylsilane. Overreduction to oximes could be suppressed by addition of 1.2 equivalents of water.
Scheme 2.24 Cu-catalysed reductions of $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated nitroalkenes

The enantioenriched product could then easily be converted to its corresponding amine, which was otherwise difficult to synthesise (Scheme 2.25).

Scheme 2.25 Reduction of enantioenriched nitro-product to amine

Nitriles

Due to the linearity of the CN group, asymmetric reductions of conjugated nitriles experienced more difficulties. Since the nitrile group prefers end-on coordination to a metal, most asymmetric hydrogenation catalysts are not generally competent. Previous literature has described Rh- and Ru-complexes for these reductions.
However, only substrates with a suitable secondary coordinating atom were reactive under high hydrogen pressure.\textsuperscript{89}

The two recent successful examples of asymmetric reductions of conjugated nitriles were the Co-catalysed conjugate reduction of $\alpha,\beta$-unsaturated nitriles\textsuperscript{90} and the Rh-catalyzed hydrogenation of $\alpha,\beta$-unsaturated nitriles.\textsuperscript{91} However, the enantioselectivities achieved by these catalyst systems were significantly lower than those for analogous esters and amides, presumably because of the steric and coordinating environment exerted by the linear nitrile group (Scheme 2.26).

![Scheme 2.26 Comparison of the coordinating environments of $\alpha,\beta$-unsaturated esters, amides, and nitriles.](image)

These limitations were overcome by the use of a Cu(OAc)$_2$ system complexed effectively with Josiphos-type ligands to induce activity. In 2006, Yun and co-workers reported the Cu-catalysed asymmetric conjugate reduction of $\beta$-aryl-$\beta$-alkyl-disubstituted $\alpha,\beta$-unsaturated nitriles.\textsuperscript{92}

In this report, substrates with no such secondary coordinating functional groups were smoothly reduced using Cu(OAc)$_2$, PMHS, $t$-BuOH and Josiphos ligand L7 (Scheme 2.27). The opposite configurations of the reduced products could be controlled by using (E)- and (Z)-isomers of the alkene or using both enantiomers of the Josiphos ligand.
Scheme 2.27 Cu-catalysed reduction of β-aryl-β-alkyl-disubstituted α,β-unsaturated nitriles

In similar fashion, a range of β,β-diarylacrylonitriles 183a-e were reduced by the same group.93 This process is highly competitive with underperforming Rh- and Ru-based hydrogenation methods.94 Due to end-on coordination to nitriles, those catalysts usually require an additional coordinating centre next to alkene moiety and high pressure of hydrogen gas.

Scheme 2.28 Cu-catalysed reduction of β,β-diaryl-substituted acrylonitriles
The catalytic system developed by Yu showed equal efficiency with acrylonitriles containing 2-, 3-, or 4-pyridyl substitution (183b-d), which indicated that an additional coordination site was not required in this case (Scheme 2.28). Given the similar steric of the phenyl and 3-/4-pyridyl substituent around the C=C bond, this level of enantioselectivity was rather unexpected.

**Sulfones**

Following the significant progress in CuH-catalysed conjugated reductions, in 2007, Carretero and co-workers explored the asymmetric conjugate reduction of β,β-disubstituted α,β-unsaturated sulfones. Initially, reductions on phenyl vinyl sulfones were tested using Cu(OAc)$_2$·H$_2$O, [CuF(PPh$_3$)$_3$]-2MeOH, and CuCl/t-BuONa in corporation with Binap and Josiphos, and phenylsilane as the hydride source. Unfortunately, all variations gave unsatisfied results. Based on prior knowledge of Rh-catalysed conjugate addition of boronic acids to α,β-unsaturated sulfones, they assumed that the use of a 2-pyridylsulfone group would produce a significant increase in reactivity comparing with phenyl vinyl sulfones.

First investigation using 2-pyridylsulfone 185a (Scheme 2.29) produced the desired reduced product in high yield. Ligand screening showed that axial chiral ligands such as BINAP and SEPHOS were more efficient for the reduction than planar chiral ligands such as Josiphos, and Taniaphos. The chiral sulfones 186a-c were afforded with high yields and over 90% ee’s regardless of the substitution at the β-aryl ring. The only exception to this general trend was the bulky naphthyl substrate 185d, which provided 186d with moderate ee.

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To expand the scope of this system, a range of vinylsulfone provided both enantiomers with excellent selectivity (Scheme 2.30).

Scheme 2.29 Cu-catalysed reduction of β-aryl α,β-unsaturated 2-pyridylsulfones

To expand the scope of this system, a range of β,β-dialkyl-substituted and cyclic substrates 187a-e were also submitted to the optimised conditions. The reduced products 188a-e were obtained in high yield and ee. Also, the E and Z isomers of the vinylsulfone provided both enantiomers with excellent selectivity (Scheme 2.30).

Scheme 2.30 Cu-catalysed reduction of β,β-disubstituted α,β-unsaturated 2-pyridylsulfones

Chapter 2 Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes
Another general procedure to reduce $\alpha,\beta$-unsaturated sulfones with no requirement for a 2-pyridyl substituent was described by Charette later that year.$^{97}$ Careful manipulation of the condition resulted in a recipe of CuF$_2$·H$_2$O and the hemilabile bidentate ligand Me-DuPhos monoxide $L_9$ in the presence of NaOH in benzene (Scheme 2.31).

![Scheme 2.31](image)

**Scheme 2.31** Cu-catalysed reduction of $\beta,\beta$-disubstituted $\alpha,\beta$-unsaturated 2-phenylsulfones

The addition of the base was necessary to obtain reproducible conversions. They believed that the presence of NaOH or KOH eliminated the detrimental competitive silylation of water by PhSiH$_3$.

Substrates bearing the $\alpha$-methyl styryl ($189a$) and naphthyl subunit ($189b$) underwent the conjugate reduction with high yield and excellent ee. For the acyclic aliphatic sulfone $189c$, Me-DuPhos(O) $L_9$ gave moderate enantioselectivities (70% ee). However, when the bulkier Et-DuPhos(O) $L_{10}$ was used instead of $L_9$, the reaction afforded $190c$ in 94% yield and 90% ee. Excellent stereocontrol was also observed in the case of cyclic substrates such as the tetrahydronaphthyl derivative ($190d$, 99% ee). When a substrate with a longer lateral $\beta$-propyl chain ($190e$) was
reduced, the yield dropped to 61% but the enantioselectivity remained very high (97% ee).

**Phosphonates**

Very recently, CuH-catalysed asymmetric conjugate reduction of \(\beta\)-substituted \(\alpha,\beta\)-unsaturated phosphonates \textbf{191a-d} was reported by Hu and Zheng (Scheme 2.32). Under optimised condition using Cu(OAc)\(_2\)-H\(_2\)O, (R)-SEGP\(\text{HOS}\), PMHS, and \(t\)-BuOH, chiral \(\beta\)-substituted alkylphosphonates were readily synthesised with high enantioselectivities (up to 95% ee).

![Scheme 2.32 Cu-catalysed reduction of \(\alpha,\beta\)-unsaturated phosphonates](image)

**Conclusions**

The past two decades witnessed significant progress in CuH chemistry. Considered as an integral part of modern organic synthesis, it has become a reliable method for the construction of tertiary stereocentres. However, the selection of reaction condition can be rather fiddly. As seen from literature, using reactive silanes can lead to overreduction and competing 1,2-reductions. Deviance from optimal temperature may cause a drastic drop of yield or ee. Even the addition of water or alcohol would cause either “considerable success or borderline total failure”.

Finally, and the most important, is the choice of ligand, which highly depends on the alkene substrate. BINAP, SEGP\(\text{HOS}\), and JOSIP\(\text{HOS}\) have given the most hits, but fine-tuning all the variables is still necessary for the success of this chemistry.
2.3) Nucleophilic Conjugate Additions to Alkenylheteroarenes

2.3.1) Introduction

Since chemists realised the importance of the conjugate addition reaction of carbon nucleophiles to activated alkenes to form carbon-carbon bond, obvious electron-withdrawing groups mentioned before have been extensively studied. As shown before, carbonyls, nitriles, sulfones, phosphonates and nitro groups can activate alkenes toward asymmetric conjugate reduction using well-established copper hydride chemistry. Recently, our interest turned towards conjugate addition bearing other rarely considered functional groups such as nitrogen-containing aromatic heterocycles. Since oxazoles, thiazoles, pyridines, pyrazines, and other nitrogen-containing heteroarenes are ubiquitous in biologically active natural products and drugs (Scheme 2.33), 100 not only would such a process prove valuable to the pharmaceutical industry, but also for the total synthesis of natural products.

![Scheme 2.33 Aromatic heterocycles in natural products and therapeutic agents](image)

Hypothetically, a C=N moiety within such heterocycles could impart sufficient polarisation to an adjacent alkene to promote reactivity in the metal-catalysed
conjugate addition. In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the catalyst would occur in such a process. However, whether this interaction would be beneficial, trivial, or detrimental was uncertain (Scheme 2.34).

(a) Conventional asymmetric conjugate addition

\[ \text{EWG} \text{C} \overset{\text{Nu}}{\text{\longrightarrow}} \text{EWG} \text{Nu} \]

\( \text{EWG} = \text{COR, NO}_2, \text{CN, SO}_2\text{R, etc.} \)

(b) Aromatic heterocycle induced conjugate addition

\[ \text{X} \overset{\text{Nu}}{\text{C}} \overset{\text{Nu}}{\text{\longrightarrow}} \text{X} \text{Nu} \]

\( \text{X} = \text{C, N, O, S, etc.} \)

*Scheme 2.34* Asymmetric conjugated additions

### 2.3.2) Conjugate Addition to Vinylheteroarenes

Pyridine is a common heteroarene and important precursor to agrochemicals and pharmaceuticals. One of the main methods to functionalise pyridine ring is conjugate addition reaction of vinylpyridine with nucleophiles bearing different electron-withdrawing groups, such as ketone, amine and nitrile.

In the early 1950s, Levine and Wilt reported the conjugate addition of ketone enolates to 2- and 4-vinylpyridine using a small amount of sodium metal (Scheme 2.35).\(^{101}\) Using various aliphatic and aromatic ketones, mono-pyridylethylation products **195a-e** were obtained in modest yields.
Further research showed that di- and tri-pyridylethylation may occur at the α-methylene carbon and α-methyl carbon. The degree of pyridylethylation could be controlled by the molar ratio of the reactants. When the vinylpyridine was the limiting reagent, the major product was mono-pyridylethylated, whereas multi-pyridylethylation was observed when the ketone was the limiting reagent. For an unsymmetrical ketone, such as methyl ethyl ketone, pyridylethylation appeared to occur exclusively at the α-methylene carbon to give 195c, instead of α-methyl carbon.

Following typical procedures for 1,4-conjugate addition reported previously using sodium methoxide, esters and nitriles could be added to 8-vinylquinolinol 196 to extend the side chains in order to improve the stability of the corresponding 8-quinolinol complexes (Scheme 2.36).102
Similar conjugate addition of acetoacetates was reported by Kim more recently for the synthesis of benzothiazolidine derivatives which were known to induce inhibitory effects on gastric $\text{H}^+$/K$^+$-ATPase.$^{103}$ The vinylpyridine substrate tolerating ortho-, meta-, and para-substitution underwent conjugate addition to form the intermediate 200 in moderate yield (Scheme 2.37).

The conjugate addition of amines, amides, and nitriles to vinylpyridines using strong acid or base was reported by Levine in 1956 (Scheme 2.38).$^{104}$
NaOMe was found suitable for amine additions to 2-methyl-5-vinylpyridine (201a-c), while acetic acid gave better results with 4-vinylpyridine (201d-f). They also showed that ammonia could be directly pyridylethylated to form 2-(aminoethyl)pyridine 203. And pyridylethylation of an amide followed by hydrolysis could give the same amine (Scheme 2.39).

Levine also described pyridylethylation of nitriles (Scheme 2.40). Phenylacetonitrile 206a was pyridylethylated in modest yields by both 2- and 4-vinylpyridine; acetonitrile 206b gave low yields; and isobutyronitrile 206c only reacted with
Modified conditions for pyridylethylation of nitriles were applied towards the total synthesis of phenanthroizidine alkaloids by Ciufolini and Roschangar. The intermediates were prepared from hydrocyanation of vinylpyridines 208a and 208b by HCN, which was generated in situ from LiCN and small amount of AcOH (Scheme 2.41a). An alternative addition route could be achieved by employing acetonitrile as the cyanation reagent. This operation was best effected in DMSO at room temperature with excess acetonitrile and t-BuOK as the base, and it furnished compound 209b in high yield (Scheme 2.41b).
Since the 1980s, much attention has been drawn to make this C-C bond formation stereoselective, particularly by the alkylations of lithiocarbanions. Hogen-Esch\textsuperscript{106} reported the addition of lithium anion to 2-vinylpyridine, where intramolecular coordination of the metal ion by a chelating group resulted in a stereodefined asymmetric environment at the reacting carbanion, leading to high enantioselectivities in favourable cases (Scheme 2.42).

Scheme 2.42 Stereoselective alkylation of lithiocarbanion

210c showed lower diastereoselectivity due to the substitution at the 3’ position of the chelating pyridine (R\textsuperscript{1}), which interfered with the methylene group and decreased the stability of the chelated complex. Meanwhile, substitution at the 5’ position (R\textsuperscript{2}) should have no such effect (210a and 210b).

Later reports showed that various nitrogen containing heterocycles, other than pyridine, could also serve as tolerated moiety in conjugate addition reactions. 2-vinylthiazole precursor 213 underwent Michael addition with various secondary amines to furnish 2-aminoethyl-5-carbethoxythiazoles (Scheme 2.43)\textsuperscript{107}.

The reaction efficiency was influenced by steric effect. Acyclic amines and diamines gave best yields, followed by unhindered cyclic amines. N-methyl isopropylamine provided product 214e in only modest yield, whereas diisopropylamine did not react at all (214f).
Scheme 2.43 Syntheses of 2-aminoethyl-5-carbethoxythiazoles

8-Vinylpurine 215, another useful synthetic intermediate, could also react as a Michael acceptor with alcohol, thiol and ester under basic conditions (Scheme 2.44). In the case of diethyl malonate, only half an equivalent of sodium hydride was used to avoid the second addition of 8-vinylpurine to the malonate.

Scheme 2.44 Conjugate addition of 8-vinylpurine
While the products of acid/base-catalysed conjugate additions suffered from undesirable side reactions and poor stereoselectivity, later reports made use of transition metal catalysts to conquer those problems.

Henry and co-workers\textsuperscript{109} published the use of a nickel-catalysed 1,4-conjugate addition of $\beta$-dicarbonyl to 2-vinylpyridine (Scheme 2.45). Besides the good yield of the Michael addition product achieved by employing Ni(acac)$_2$ over its base-catalysed equivalent, such chemistry also minimises several undesirable side reactions typically caused by strongly basic catalysts, including rearrangements, secondary condensations, isomerisations, polymerisations, bis additions, retrogressions, and transesterifications.

\textbf{Scheme 2.45} Pyridylethylation of $\beta$-dicarboxyls using Ni(acac)$_2$

The proposed mechanism (Scheme 2.46) involved the electron-rich methylene carbon of a coordinated $\beta$-dicarbonyl enolate 219, nucleophilically attacking the more positive carbon of the Michael acceptor 193. The resonance stabilised zwitterion 220 thus formed undergoes proton transfer to give coordinated product 221. Ligand exchange of 221 with excess $\beta$-dicarbonyl substrate 217 regenerates the catalyst substrate complex 219 and releases the Michael adduct 218.
Scheme 2.46 Mechanism of Ni(acac)$_2$-catalysed Michael addition

To make this conjugate addition diastereoselective, nucleophiles possessing a chiral auxiliary 222 were employed in the presence of an achiral catalyst (Scheme 2.47).\textsuperscript{110}

Scheme 2.47 Diastereoselective alkylation of active methylene compounds

For the substrate containing chiral auxiliary Xa\textsuperscript{*}, Ni(salicylaldehyde)$_2$·2H$_2$O was used as the achiral catalyst. 2-alkylpyridine 225a was formed in a moderate yield and a poor $dr$. And hydrazine 225b was obtained in quantitative yield and 89:11 $dr$. RuH$_2$($\text{PPh}_3$)$_4$ proved effective for similar conjugate addition (225c) with Xb\textsuperscript{*} as the chiral inductor. However, vinylpyridine gave no desired product 225d using ruthenium catalyst (Scheme 2.48).\textsuperscript{111}
2.3.3) Conjugate Addition to $\beta$-Substituted Alkenylheteroarenes

Compared to vinylheteroarenes, conjugate addition to the corresponding substrate that contains a $\beta$-substituent has experienced severe steric inconvenience.

While base-catalysed conjugate addition of ketone enolates to vinylpyridines had been reported, Skidmore and Tidd addressed the addition of quinaldine 226a and lepidine 226b to 2-styrylquinoline 227 under acidic conditions (Scheme 2.49).\(^{112}\)

Using sulfuric acid or hydrochloric acid as the catalyst, quinaldine and lepidine could add to various $\beta$-substituted 2-styrylquinolines to form saturated diquinolines 228a-c.
Using similar conditions as reported by Magnus and Levine, Cliffe described the high yielding reactions of nitrogen nucleophiles with 5,6-dihydroquinoline 229 for preparation of the primary amino compounds. In refluxing methanol, with catalytic amount of acids, ammonium acetates or chlorides, generated from amines or hydroxylamines, were added to 229 to form 7-amino-5,6,7,8-tetrahydroquinolines 230a-h in moderate yields (Scheme 2.50).

2-styrylbenzoxazoles and thiazoles 231 were applied under similar addition conditions. Dryanska and Ivanov reported the conjugate addition of various
nucleophiles 232 to 2-styrylbenzothiazole and 2-styrylbenzoxazole in the presence of aqueous NaOH and dimethyl sulfoxide. Substitution at the β-position of the electrophile with a bulky phenyl group was tolerated (Scheme 2.51).

**Scheme 2.51** Conjugate addition to 2-styrylbenzoxazoles and thiazoles

Ni-catalysts were found to activate hindered 4-alkenylpyridines for nucleophilic conjugate addition (Scheme 2.52).

**Scheme 2.52** Tri-arylation of 4-alkenylpyridines using nickel and Grignard reagent

By treating substituted 4-alkenylpyridines 234 with Grignard and organozincate reagents, Houpis managed to synthesise triaryl-ethyl derivatives 235 containing one
or more heteroaromatic components. Gently heating the reactions dramatically improved the yields (40% at 25 °C and 93% at 45 °C for 235a) and inhibited biphenyl and other dimer by-products.

Attempts to induce enantioselectivity in this reaction have failed. Chiral ligands such as bisphosphines, diamines, bisulfonamides, aminoalcohols, and diols gave unsatisfactory results with ee’s ranging from 0 to 15%. Phenyl zinicate reagent was found to produce similar results using Ni(acac)$_2$ but with much less by-product (Scheme 2.53).

![Scheme 2.53 Tri-arylation of 4-alkenylpyridine using Organozincate reagents](image)

To conclude, conjugate additions to alkenylheteroarenes have been proven not very successful. Although additions to 2-vinylheteroarenes (R$^2$ = H) are relatively common, the corresponding reactions of substrates containing a β-substituent (R$^2$ ≠ H) are much rarer, presumably for steric reasons (Scheme 2.54a). An alternative way seems to be conjugate reduction of prochiral alkenylheteroarenes, which might provide a high yielding and stereoselective process to afford various heterocycles with chiral functionalities (Scheme 2.54b).

![Scheme 2.54 Strategies for conjugate additions to alkenylheteroarenes](image)
2.4) Aim of the project

Although, as discussed in the introduction, conjugate additions to 2-vinylheteroarenes are relatively common, the corresponding reactions of mono-β-substituted substrates are much rarer. Hypothetically, steric bulk around the β-carbon blocks attack of large nucleophiles, although there are no examples of successful alkylation of β,β-disubstituted alkenes. Therefore, our group initiated a programme targeted at addressing these deficiencies. Several issues have to be addressed to fulfil this goal. The asymmetric copper catalysed conjugate reduction of activated alkenes is a well-established method for the synthesis of various useful chiral building blocks. We will find out whether a nitrogen-containing heteroarene would provide sufficient activation to an adjacent alkene in an analogous reaction. We are going to find out whether large substituents would be tolerated under our reaction conditions.

2.5) Previous Work

Based on the success of copper hydride chemistry and our assumption, extensive investigation towards Cu-catalysed asymmetric conjugate reduction of alkenyl heteroarenes was carried out by Dr Leszek Rupnicki and Aakarsh Saxena in the Lam group. The 2-alkenylbenzoxazole 239a was previously synthesised and used as a test substrate for ligand screening. 10 mol% Cu(OAc)$_2$H$_2$O and 10 mol% of bisphosphine ligand were mixed with substrate in toluene, and 4 equivalents of t-BuOH and PhSiH$_3$ were added at room temperature and stirred for up to 18 h (Scheme 2.55, results obtained by Leszek Rupnicki).
Biaryl-based ligands $L_5$ and $L_{11-13}$ proved competent in promoting conjugate reduction. With (R)-Binap $L_{11}$, both conversion and enantioselectivity were only moderate. Improved results were observed using (R)-MeO-BIPHEP $L_5$ and the SEGPHOS ligands $L_{12}$ and $L_{13}$. The Josiphos ligands $L_3$ and $L_7$ were also effective, providing $240a$ in 89% and 87% ee respectively. Of all the ligands, highest conversion was obtained with $L_{13}$ and $L_7$, where the reaction completed within 2 hours. However, higher enantioselectivity was provided by $L_7$, which convinced us to select this ligand for further optimisation. The effect of temperature was also examined. The reduction was run separately at 0 °C and at room temperature and complete consumption of the starting material within 2 h was recorded in both runs, with no noteworthy difference in ee.

Further optimised conditions for other substrates involved 0.20 mmol of the $\beta,\beta$-disubstituted 2-alkenylheteroarene, 5 mol% of the copper catalyst and ligand $L_7$, Scheme 2.55 Ligand optimisation for CuH reduction
2.0 equivalents of \( t\)-BuOH, and 1.5 equivalents of PhSiH\(_3\) in toluene at 0 °C to room temperature.

\[
\begin{align*}
239 & \xrightarrow{ \text{Cu(OAc)}_2\cdot\text{H}_2\text{O} (5 \text{ mol\%}) \text{, t-BuOH (2.0 equiv) \text{, L7 (5 mol\%) \text{ in toluene, } 0 \degree \text{C to rt, 17 h}}} } 240 \\
\end{align*}
\]

Results obtained by Leszek Rupnicki and Aakarsh Saxena

**Scheme 2.56** CuH reduction of 2-alkenylheteroarene

A broad range of heteroaromatic substrates \(239\text{a-h}\) were prepared and reduced asymmetrically (Scheme 2.56, results obtained by Leszek Rupnicki and Aakarsh Saxena). Benzoxazoles \(240\text{a and b}\), pyridines \(240\text{c and d}\), oxazole \(240\text{e}\), benzothiazole \(240\text{f}\), quinoline \(240\text{g}\) and pyrazine \(240\text{h}\) all underwent asymmetric reduction with high yield and enantioselectivity. Also various functionalities at the \(\beta\)-position of the alkene can be tolerated, including simple aliphatic groups, various oxygenated alkyl groups, and a cyclopropane.

Scaling up the reaction to 1 mmol and lowering the catalyst load to 2 mol% had minimal effect on the yield, but a slight drop in ee was noted (96% against >99%).

One hypothesis to explain the origin of reactivity was that the nitrogen atom at the ortho-position offered a potential coordination site to the CuH complex and provided enantioselectivity. In order to test this hypothesis, reductions of substrate \(239\text{i}\) and
where the nitrogen atom was located at the para- and meta-position were attempted (Scheme 2.57). Surprisingly, the substrate 239i with nitrogen at the para-position reduced asymmetrically in a 60% isolated yield and 94% ee after 4 days (240i, Scheme 2.57b). This experiment proved that the nitrogen atom clearly helped to activate the conjugated alkene bond, in a 1,6-conjugate reduction-like manner, but alkene reduction by copper hydride can occur without the assistance of a directing effect from the nitrogen atom. 239j with the nitrogen at the meta-position was unreactive (Scheme 2.57c), demonstrating the importance of conjugation of the alkene to a C=N moiety for reactivity in this type of reduction (results obtained by Leszek Rupnicki and Aakash Saxena).

Scheme 2.57 CuH reduction of 2-, 3- and 4-alkenylpyridines
2.6) Results and Discussion

Based on the previous success in the group, I tried to expand the scope of this Cu-H asymmetric reduction protocol. My aim is to synthesise other alkene substrates with different heterocycles and test their reactivities towards copper hydride reduction. Bearing in mind the fact that the functionalised heterocycles were rather difficult to obtain, several routes were carried out simultaneously (Scheme 2.58).

![Scheme 2.58 Retrosynthesis of 2-alkenylheteroarenes](image)

2.6.1) $\beta,\beta$-Disubstituted 2-Alkenylheteroarene Synthesis

**Carbometallation**

The initial idea was to synthesise 2-alkenylheteroarenes by carbometallation of corresponding alkynes, which could be obtained by Sonogashira coupling of terminal alkynes with halogenated heteroarenes. Using chloro- and bromo-substituted heteroarenes, various pyridine, quinoline, pyrazine and quinoxaline derivatives were readily obtained by Sonogashira coupling reactions in good to high yields (Scheme 2.59, results obtained by Yi Wang and Gordon Nimmo-Smith). Microwave irradiation greatly shortened the reaction time. Full conversion of the starting materials was observed after 15 minutes. $243a$ was obtained in moderate yield since
the TES group was cleaved at high temperature and decreased the yield. Pyrimidine 243i was obtained in low yield for unclear reasons.

![Scheme 2.59 Synthesis of 2-heteroalkynes by Sonogashira coupling](image)

However, after some quick screening of the carbometallation conditions using alkylating agents (Et₂Zn, EtMgBr, Me₃Al) with various catalyst systems (Rh, Ni, Cu), the carbometallation was found to be not so ideal, suffering from low conversion of the starting materials and/or poor stereoselectivity. Only a few 2-alkenylpyridine substrates were isolated using Cu(acac)₂, (o-tol)₃P and Et₂Zn (Scheme 2.60, results achieved by Yi Wang). The low reliability of this process and limited scope discouraged further investigation.
The low \( E/Z \) selectivity of the carbometallation step can possibly be explained by reversible formation of an allene intermediate 245 which loses \( E/Z \) information and the distribution of \( E/Z \) isomers comes from the relative energy differences of both forms (\( E \) and \( Z-244b \)) and the mechanism of the addition. Presumably this unstable allene can also take part in a series of undesirable reactions, reducing the yield of the final product (Scheme 2.61).

**Scheme 2.61** Allene isomerisation
Negishi coupling

Inspired by a large number of Negishi-type cross-coupling methods in recent literature, I envisioned an efficient set of conditions that allows a direct coupling of vinyl iodides to organozinc heteroarenes (Scheme 2.62).

\[
\begin{align*}
\text{X} & \quad \text{R}^1 \quad \text{R}^2 \quad \equiv \quad \text{I} \\
\text{N} & \quad \text{ZnCl} \\
\text{X} & \quad \text{R}^1 \quad \text{R}^2 \\
\text{N} & \quad \text{ZnCl} \\
\text{X} & \quad \text{Cl} \\
n-\text{BuLi} & \quad \text{ZnCl}_2
\end{align*}
\]

**Scheme 2.62** Retrosynthesis of 2-alkenylheteroarenes from Negishi coupling

Previously in our group, vinyl iodides were obtained through carbo-alumination of substituted acetylenes with \(\text{Cp}_2\text{ZrCl}_2\) and \(\text{Me}_3\text{Al}\) followed by quenching of the aluminium intermediates with iodine. The disadvantage of this transformation is its low reactivity with larger trialkylaluminium reagents. The scope was limited to the possible products containing methyl as one of the substituents of the double bond. As a free hydroxyl group could interfere during coupling to heteroarenes, it was protected with TBS groups using standard procedures (Scheme 2.63, results achieved by Leszek Rupnicki).

\[
\begin{align*}
\text{CH}_2\text{Cl}_2 & \quad \text{Cp}_2\text{ZrCl}_2, \text{Me}_3\text{Al}, \text{Li} \\
\text{CH}_2\text{Cl}_2 & \quad \text{TMSI, Trisacode, DMF, 85%} \\
\text{CH}_2\text{Cl}_2 & \quad \text{TMSI, Trisacode, DMF, 85%}
\end{align*}
\]

**Scheme 2.63** Preparation of vinyl iodides

Following a slightly modified procedure, ethyl substituted vinyl iodides were obtained through carbozincation of terminal alkynes with \(\text{Et}_2\text{Zn}\) and \(\text{Pd}(\text{PPh}_3)_4\), followed by quenching the zinc intermediates with TMS iodide, then iodination with \(N\)-iodosuccinimide (NIS) (Scheme 2.64, results achieved by Yi Wang). Although it requires stoichiometric amounts of TMS iodide reagent and more synthetic steps, this procedure is still preferred due to the excellent selectivity to produce \(E\) isomers with undetectable levels of \(Z\) isomers.
With those vinyl iodide building blocks prepared, the Negishi coupling was tested on various heterocycles. Unfortunately, Negishi’s original conditions using nBuLi/ZnCl\textsubscript{2} and Pd(PPh\textsubscript{3})\textsubscript{4} did not tolerate those heteroaromatic halides. Low reactivity was observed probably because the zinc intermediate \(\text{ZnCl}_2\) was not reactive enough in the transmetallation step of Negishi coupling (Scheme 2.65, results achieved by Yi Wang).

Recently, Knochel\textsuperscript{121} has provided a powerful alternative route to activate those hindered heterocycles using a mild zinc-lithium base \(\text{ZnCl}_2\cdot\text{LiCl}\) generated from 2,2,6,6-tetramethylpiperidine (TMP, 254), nBuLi and ZnCl\textsubscript{2}. For instance, pyrazine 256 was deprotonated by this base and cross-coupled with electrophile 258 to give 259 in good yield (Scheme 2.66).
I employed this chemistry to synthesise new 2-alkenylheteroarenes (Table 2.1). In the first step, metellation of a range of heteroarenes at the most acidic position (normally \( \beta \), except for entry 4 at \( \gamma \) position) by TMP base generated zinc species \textit{in situ}. Then this intermediate was trapped by vinyl iodide in presence of palladium catalyst and ligand at 60 °C in THF to form the desired 2-alkenylheteroarenes with fine preservation of the alkene geometry.

**Table 2.1 Synthesis of trisubstituted alkenes**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>electrophile</th>
<th>product</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>260a</td>
<td>I, Et</td>
<td>261a</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>260a</td>
<td>I, Me</td>
<td>261b</td>
<td>10</td>
</tr>
<tr>
<td>3</td>
<td>260b</td>
<td>I, Me</td>
<td>261c</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>260c</td>
<td>I, Me</td>
<td>261d</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>260d</td>
<td>I, Et</td>
<td>261e</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>260e</td>
<td>I, Et</td>
<td>261f</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>260f</td>
<td>I, Et</td>
<td>261g</td>
<td>0</td>
</tr>
</tbody>
</table>

Chapter 2 Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes
Thiazole 261a and 261b, benzothiazole 261c and pyrimidine 261d substrates were prepared (entry 1-4). Although the yields were low, probably due to the air sensitivity of the TMP base, the coupling reaction proceeded without compromising the integrity of the alkene which allowed us to carry out the following Cu-H asymmetric reduction step.

Other heteroarenes including pyrazole 260d, benzoimidazole 260e and caffeine 260f were also attempted in this process. However, no coupling products were observed in the reaction mixtures (entry 5-7). We assume that zincation with TMP base did proceed, but dialkyl-substituted vinyl iodides showed less reactivity than the aryl iodides that Knochel used. Thus, the cross-coupling did not occur at room temperature. Heating the reaction might destroy the zinc species.

**Cross aldol condensation/Wittig reaction**

A few commercially available aldehydes were employed in cross aldol condensation and Wittig reaction to generate enals bearing a heteroarene at $\gamma$ position. Further manipulation included reduction of the enal to an alcohol and protection with a silyl group to avoid interference with copper hydride in the next step.

The highly efficient solid base-promoted cross-aldol condensation reactions reported by Zlotin\textsuperscript{122} was employed to prepare $\beta,\beta$-disubstituted 2-alkenylheteroarenes (Scheme 2.67, results achieved by Yi Wang).

Although aldehydes conjugated with aromatic rings are stable enough in this system, there is a possibility for aliphatic aldehydes to self-condense and suppress the cross-aldol condensation. To minimise the side-reaction, the aromatic aldehyde 262...
was first added to a vigorously stirred solution of potassium hydroxide and tetrabutylammonium hexafluorophosphate, followed by a slow addition of the aliphatic aldehyde. The obtained \(\alpha,\beta\)-unsaturated aldehyde 263 can be easily reduced with mild reagents such as NaBH\(_4\) in ethanol to give the primary alcohol 264. Protection of the alcohol with PivCl provided the desired 2-alkenyheteroarene 265. Although it requires three steps and the overall yield is moderate, this procedure allows a broad range of substituents on the alkene double bond by varying the aldol condensation partners.

![Scheme 2.67 Cross aldol condensation](image)

Another olefination approach to obtain the \(E\) alkene was treating heteroarene aldehydes with stabilized triphenyl phosphonium ylides. Unsaturated esters 266 and 270 were prepared under Wittig condition and reduced by DIBAL at low temperature to obtain the allylic alcohols, then pivaloated to furnish the desired alkene substrates 268 and 272 (Scheme 2.68, results achieved by Yi Wang). No \(E/Z\) issue is involved as high selectivity is expected in this type of olefination. Low temperatures are required in the DIBAL reduction step in order to avoid the subsequent reduction of the alkene double bond.

![Scheme 2.68 Wittig reactions](image)
2.6.2) CuH-Catalysed Asymmetric Conjugate Reduction

With those new 2-alkenylheteroarenes substrates prepared, I was able to carry out the Cu-H catalysed asymmetric conjugate reduction. Using the optimised conditions that were discovered by Leszek Rupnicki,\textsuperscript{117} I performed a further extension of the copper hydride reduction scope (Table 2.2).

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>244a</td>
<td>273a</td>
<td>66</td>
<td>&gt;99</td>
</tr>
<tr>
<td>2</td>
<td>261b</td>
<td>273b</td>
<td>84</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>261c</td>
<td>273c</td>
<td>82</td>
<td>95</td>
</tr>
<tr>
<td>4</td>
<td>261d</td>
<td>273d</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Reduction of pyridine 244a, thiazole 261b and benzothiazole 261c were found to be successful, the ee of 261b slightly dropped probably due to the similarity of the two \( \beta \)-alkyl substituents. Pyrimidine 261d did not undergo reduction, because the alkene was not conjugated to C=N double bond of pyrimidine. This result was consistent with the previous example of meta-substituted pyridine substrate 239j.
Table 2.3 CuH asymmetric conjugate reduction of 2-alkenylimidazoles

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Substrate Image" /></td>
<td><img src="image2.png" alt="Product Image" /></td>
<td>274a</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Substrate Image" /></td>
<td><img src="image4.png" alt="Product Image" /></td>
<td>274b</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Substrate Image" /></td>
<td><img src="image6.png" alt="Product Image" /></td>
<td>274c</td>
<td>61</td>
</tr>
</tbody>
</table>

Imidazoles 265 and 268 failed to reduce under the standard conditions. Although I initially suspected that the bulky substituent at β position of substrate 265 decreased reactivity, the failure of 268 to reduce suggested that steric hindrance was not a problem. Imidazoles are relatively electron-rich azoles and can be considered to deactivate the adjacent alkene through mesomeric donation of electron density onto the 2-position (Scheme 2.69). Benzimidazole on the other hand, is less electron-rich since the extra benzene ring has the tendency to preserve its aromaticity, and hence this effect reduces the degree of electron donation. Therefore, the activating effect of the electron-withdrawing C=N moiety is greater in the case of benzimidazoles and hence nucleophilic attack of copper hydride is more likely to occur (Scheme 2.69).
To prove the theory, the corresponding benzimidazole substrate 272 was synthesised and subjected to the same conditions, and the reduction product was furnished in 61% yield and excellent ee (Table 2.3, entry 3, 97%).

The stereochemistry of 244a, 261a and 272 were determined using NOE experiments, which displayed the following diagnostic enhancement:

The mechanism for the reactions (Scheme 2.71) are similar to other copper hydride catalysed asymmetric conjugate reductions mentioned before. The (bis-phosphine)CuH complex 275 was first generated *in situ* as the key intermediate. Conjugate reduction of benzoimidazole 272 by copper hydride complex 275 would then result in the formation of the copper species 276. The copper catalyst coordinates to the Lewis basic nitrogen of the heterocycle to form 277. Quenching the copper species 276 with t-BuOH will give the product 274c and generate copper tert-butyl oxide 278 which undergoes σ-bond metathesis with a silane to form silyl enol ether 279 and regenerate copper hydride 275.
In conclusion, nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate reduction reactions. Extension of the general concept to other classes of heteroarenes has been proven successful. Other heterocycles like caffeine and pyrazole were also considered. However, due to the low reactivity of those moieties, we could not prepare the desired substrates from any of those methods mentioned before. Further manipulation of the conditions is required to tolerate more challenging heteroarene substrates.
2.7) Experimental Section

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**General Information**

All non-aqueous reactions were carried out under a nitrogen atmosphere in oven-dried apparatus. Toluene and THF were dried and purified by passage through activated alumina columns using a solvent purification system from http://www.glasscontoursolventsystems.com. 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 visualised 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.$^a$ Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on a Jasco FT/IR-460 Plus instrument as a thin film on sodium chloride.

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plates or as a dilute solution in CHCl₃. ¹H NMR spectra were recorded on a Bruker DMX500 (500 MHz) spectrometer or a Bruker DPX360 (360 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using residual protonated solvent as internal standard (CDCl₃ 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 ¹³C NMR spectra were recorded on a Bruker AVA500 (125.1 MHz) spectrometer, a Bruker DPX360 (90.6 MHz) spectrometer, or a Bruker ARX250 (62.9 MHz) spectrometer. Chemical shifts (δ) are quoted in parts per million (ppm) downfield of tetramethylsilane, using deuterated solvent as internal standard (CDCl₃ at 77.0 ppm, CD₂OD at 49.9 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 or a Finnigan MAT 95XP spectrometer at the EPSRC National Mass Spectrometry Service Centre, University of Wales, Swansea, or on a Finnigan MAT 900 XLT spectrometer at the School of Chemistry, University of Edinburgh. Chiral HPLC analysis was performed on an Agilent 1100 instrument. Optical rotations were performed on an Optical Activity POLAAR 20 polarimeter. Microwave reactions were performed using a Biotage microwave synthesizer. Authentic racemic samples of products for chiral HPLC assay determinations were obtained by hydrogenation of the alkene substrates in EtOH using a Pd/C catalyst.
Preparation of Starting Materials

\((E)\) 1-(t-Butyldimethylsiloxy)-4-iodo-3-methyl-3-butene (248).\(^b\) Prepared according to previously reported procedures.

\((E)\)-3-(Iodomethylene)heptane (250a).\(^c\) Prepared according to previously reported procedures.

\((E)\)-3-(Iodomethylene)pentyl benzoate (250b).\(^c\) Prepared according to previously reported procedures.

\((E)\)-(3-(iodomethylene)pentyl)benzene (250c).\(^c\) Prepared according to previously reported procedures.

3-Triethylsilyloxybut-1-yne (242a). To a solution of 3-butynol (3.50 g, 50.0 mmol), Et\(_3\)N (10.5 mL, 75.0 mmol), and DMAP (300 mg, 2.50 mmol) in CH\(_2\)Cl\(_2\) (200 mL) at room temperature was added chlorotriethylsilane (10.0 mL, 60.0 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NaHCO\(_3\) solution (200 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 100 mL). The combined organic layers were dried (Na\(_2\)SO\(_4\)), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (20% EtOAc/hexane) gave the silyl ether 242a (8.60 g, 93%) as a colourless oil. IR (film) 3314, 2955, 2877, 2120 (C≡C), 1459, 1415, 1239, 1105, 1008, 802, 744 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.73 (2H, t, \(J = 7.2\) Hz, CH\(_2\)O), 2.41 (2H, dt, \(J = 7.2\), 2.7 Hz, CH\(_2\)CH\(_2\)O), 1.96 (1H, t, \(J = 2.7\) Hz, \(\equiv\)CH), 0.96 (9H, t, \(J = 8.0\) Hz, Si(CH\(_2\)CH\(_3\))\(_3\)), 0.61 (6H, q,


\(^{c}\) Normant, J-F.; Cahiez, G.; Chuit, C. J. Organomet. Chem. 1974, 77, 269-279
$J = 8.0$ Hz, Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (125.8 MHz, CDCl$_3$) δ 81.4 (C), 69.3 (CH), 61.4 (CH$_2$), 22.8 (CH$_2$), 6.7 (3 x CH$_3$), 4.3 (3 x CH$_2$).

**Preparation of Alkenyl Pyridine**

2-(4-Triethylsilyloxybut-1-ynyl)pyridine (243a). To a solution of PdCl$_2$(PPh$_3$)$_2$ (701 mg, 1.00 mmol), CuI (96 mg, 0.50 mmol), and 3-triethylsilyloxybut-1-yn-242a (5.10 g, 30.0 mmol) in DMF (30 mL) at room temperature was added 2-bromopyridine (1.90 mL, 20.0 mmol) followed by Et$_3$N (11.2 mL, 80 mmol). The mixture was stirred at room temperature for 72 h, quenched with saturated aqueous NH$_4$Cl solution (100 mL), and extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the alkenylpyridine 243a (2.50 g, 50%) as a brown oil. IR (film) 2954, 2910, 2876, 2228 (C≡C), 1583, 1561, 1464, 1427, 1239, 1104 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 8.52 (1H, ddd, $J = 4.0$, 1.8, 1.0 Hz, ArH), 7.59 (1H, dt, $J = 7.7$, 1.8 Hz, ArH), 7.35 (1H, td, $J = 7.8$, 1.1 Hz, ArH), 7.17 (1H, ddd, $J = 7.6$, 4.9, 1.2 Hz, ArH), 3.84 (2H, t, $J = 7.4$ Hz, CH$_2$O), 2.67 (2H, t, $J = 7.4$ Hz, CH$_2$CH$_2$O), 0.96 (6H, t, $J = 7.9$ Hz, Si(CH$_2$CH$_3$)$_3$), 0.65-0.58 (9H, m, Si(CH$_2$CH$_3$)$_3$); $^{13}$C NMR (90.6 MHz, CDCl$_3$) δ 149.8 (CH), 143.6 (C), 136.0 (CH), 126.7 (CH), 122.4 (CH), 87.5 (C), 81.3 (C), 61.2 (CH$_2$), 23.6 (CH$_2$), 6.6 (3 x CH$_3$), 4.3 (3 x CH$_2$); HRMS (EI) Exact mass calcd for C$_{15}$H$_{23}$NOSi [M$^+$]: 261.1544, found: 261.1545.

2-[(Z)-2-Ethyl-4-triethylsilyloxybut-1-enyl]pyridine (244a). To a stirred solution of Cu(acac)$_2$ (105 mg, 0.40 mmol), (2-Fur)$_3$P (93
mg, 0.40 mmol) and the alkyne **243a** (1.04 g, 4.00 mmol) in THF (40 mL) at 0 °C was added Et₂Zn (1.0 M in hexane, 8.0 mL, 8.0 mmol) over 2 min. The mixture was stirred at room temperature for 18 h, quenched with brine (100 mL), and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (5% EtOAc/hexane) gave the alkene **244a** (620 mg, 50%) as a colourless oil. IR (film) 2957, 2875, 1646, 1586, 1560, 1472, 1428, 1377, 1239, 1093 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.56 (1H, d, J = 4.0 Hz, ArH), 7.59 (1H, app dt, J = 7.7, 1.8 Hz, ArH), 7.27 (1H, d, J = 7.9 Hz, ArH), 7.06 (1H, app dd, J = 6.9, 5.1 Hz, ArH), 6.35 (1H, s, =CH), 3.79 (2H, t, J = 7.4 Hz, CH₂O), 2.81 (2H, t, J = 7.4 Hz, CH₂CH₂O), 2.25 (2H, dq, J = 7.4, 1.4 Hz, =CCH₂CH₃), 1.14 (3H, t, J = 7.4 Hz, CH₂CH₃), 0.95 (6H, t, J = 7.9 Hz, Si(CH₂CH₃)₃), 0.60 (9H, q, J = 7.9 Hz, Si(CH₂CH₃)₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 157.1 (C), 149.1 (CH), 146.3 (C), 135.8 (CH), 124.9 (CH), 123.7 (CH), 120.6 (CH), 61.6 (CH₂), 35.1 (CH₂), 31.5 (CH₂), 12.6 (CH₃), 6.7 (3 x CH₃), 4.3 (3 x CH₂); HRMS (El) Exact mass calcd for C₁₇H₂₉NOSi [M⁺]: 291.2013, found: 291.2013.

**Preparation of the reagent TMPZnCl·LiCl**

A dry and argon-flushed 100 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (3.40 mL, 20.0 mmol) dissolved in THF (20 mL). This solution was cooled to -40 °C and n-BuLi (2.5 M in hexane, 8 mL, 20 mmol) was dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. ZnCl₂ (0.5 M in THF, 44 mL, 22 mmol) was added dropwise and the resulting solution was stirred for 30 min at -10 °C and then for 30 min at 25 °C. The freshly
prepared TMPZnCl·LiCl solution was titrated prior to use at 25 °C with benzoic acid using Methyl Orange as the indicator.

Negishi Coupling Reactions Using TMPZnCl·LiCl

2-[(E)-2-Ethylhex-1-enyl]-4,5-dimethylthiazole (261a).

To a solution of TMPZnCl·LiCl (0.25 M in THF/hexane, 12.0 mL, 3.0 mmol) at room temperature was added a solution of 4,5-dimethylthiazole (350 mg, 3.00 mmol) in THF (2 mL) via cannula over 1 min and the mixture was stirred for 30 min. To this mixture was added a solution of alkenyl iodide 250a (476 mg, 2.00 mmol), Pd(dba)$_2$ (57 mg, 0.10 mmol), and (2-Fur)$_3$P (46 mg, 0.20 mmol) in THF (5 mL) via cannula and the resulting mixture was heated at 60 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH$_4$Cl solution (20 mL) and extracted with Et$_2$O (3 x 50 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (2% EtOAc/hexane) gave the alkene 261a (246 mg, 55%) as a colourless oil. IR (film) 2959, 2929, 2871, 1634, 1548, 1457, 1375, 1132, 448, 435 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) $\delta$ 6.41 (1H, s, $=CH$), 2.51 (2H, q, $J = 7.5$ Hz, $=CH_2CH_3$), 2.35 (3H, s, ArCH$_3$), 2.31 (3H, s, ArCH$_3$), 2.19 (2H, t, $J = 7.5$ Hz, $=CH_2CH_3$), 1.53-1.45 (2H, m, $=CH_2C$H$_2$), 1.40-1.30 (2H, m, CH$_2$CH$_2$CH$_3$), 1.11 (3H, t, $J = 7.5$ Hz, $=CH_2CH_3$), 0.92 (3H, t, $J = 7.3$ Hz, CH$_2$CH$_2$CH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) $\delta$ 160.7 (C), 150.2 (C), 147.4 (C), 125.1 (C), 118.7 (CH), 37.4 (CH$_2$), 30.1 (CH$_2$), 25.3 (CH$_2$), 22.4 (CH$_2$), 14.6 (CH$_3$), 14.0 (CH$_3$), 12.1 (CH$_3$), 11.2 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{13}$H$_{22}$NS [M+H]$^+$: 224.1467, found: 224.1470.
(E)-2-(4-(tert-butyldimethylsilyloxy)-2-methylbut-1-enyl)-4,5-dimethylthiazole (261b). 4,5-Dimethylthiazole (0.23 g, 2.0 mmol) in THF (10 mL) was added to a solution of TMPZnCl·LiCl (0.25 M in THF, 8 mL, 2.0 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min. Pd_{2}(dba)_{3} (46 mg, 2.5 mol%) and P(o-furyl)_{3} (46 mg, 10 mol%) dissolved in THF (5 mL), and mixed with iodo compound 248 (0.49 g, 1.5 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 18 h at 60 °C. The reaction mixture was then quenched with a sat. aq. NH_{4}Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_{2}SO_{4}. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (2% to 5% EtOAc/Hexane) furnished compound 261b (48 mg, 10%) as a colourless oil. IR (film) 2927, 2857, 1641, 1548, 1471, 1378, 1254, 1100, 1006, 835 cm⁻¹; ^{1}H NMR (360 MHz, CDCl₃) δ 6.48 (1H, s, =CH), 3.78 (2H, t, J = 7.0 Hz, CH₂), 2.42 (2H, t, J = 6.9 Hz, CH₂), 2.35 (3H, s, CH₃), 2.32 (3H, s, CH₃), 2.08 (3H, s, CH₃), 0.89 (9H, s, SiC(CH₃)₃), 0.05 (6H, s, Si(CH₃)₂); ^{13}C NMR (62.9 MHz, CDCl₃) δ 160.9 (C), 147.7 (C), 140.8 (C), 125.6 (C), 121.1 (CH), 62.1 (CH₂), 44.3 (CH₂), 25.9 (3 × CH₃), 19.5 (CH₃), 18.3 (C), 14.6 (CH₃), 11.2 (CH₃), -5.3 (2 × CH₃); HRMS (ESI) Exact mass calcd for C₁₆H₃₀ONSSi [M+H]^+: 312.1812, found: 312.1808.

2-[(E)-4-(tert-Butyldimethylsilyloxy)-2-methylbut-1-enyl]benzothiazole (261c).

To a solution of TMPZnCl·LiCl (0.25 M in THF/hexane, 8.0 mL, 2.0 mmol) at room temperature was added a solution of benzothiazole (282 mg, 2.00 mmol) in THF (10 mL) over 2 min and the mixture was stirred at room temperature for 30 min. To this solution was added a solution of alkenyl iodide 248 (490 mg, 1.50 mmol), Pd_{2}(dba)_{3}
(46 mg, 0.05 mmol), and (2-Fur)3P (46 mg, 0.20 mmol) in THF (5 mL) via cannula and the resulting mixture was heated at 60 °C for 18 h. After cooling to room temperature, the reaction was quenched with saturated aqueous NH4Cl solution (20 mL) and extracted with Et2O (3 x 50 mL). The combined organic layers were dried (Na2SO4), filtered, and concentrated in vacuo. Purification of the residue by column chromatography (2% EtOAc/hexane) gave the alkene 261c (120 mg, 24%) as a colourless oil. IR (film) 2953, 2856, 1637, 1500, 1471, 1435, 1312, 1254, 1099, 1007 cm−1; 1H NMR (360 MHz, CDCl3) δ 8.00 (1H, d, J = 8.1 Hz, ArH), 7.87 (1H, d, J = 7.8 Hz, ArH), 7.49-7.44 (1H, m, ArH), 7.37-7.33 (1H, m, ArH), 6.65 (1H, s, =CH), 3.85 (2H, t, J = 6.7 Hz, CH2O), 2.51 (2H, t, J = 6.7 Hz, CH2CH2O), 2.30 (3H, s, CH=CC3), 0.90 (9H, s, SiC(CH3)3), 0.07 (6H, s, Si(CH3)2); 13C NMR (62.9 MHz, CDCl3) δ 165.4 (C), 153.2 (C), 146.7 (C), 134.8 (C), 126.0 (CH), 124.6 (CH), 122.8 (CH), 121.2 (CH), 120.8 (CH), 61.7 (CH2), 44.5 (CH2), 25.9 (3 x CH3), 19.9 (CH3), 18.3 (C), -5.3 (2 x CH3); HRMS (ES) Exact mass calcd for C18H28ONSSi [M+H]+: 334.1655, found: 334.1658.

(E)-5-(4-(tert-butyldimethylsilyloxy)-2-methylbut-1-enyl)-4,6-dichloropyrimidine (261d).

4,6-Dichloropyrimidine (0.29 g, 2.0 mmol) in THF (10 mL) was added to a solution of TMPZnCl-LiCl (0.25 M in THF, 8 mL, 2.0 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min Pd2(dba)3 (46 mg, 2.5 mol%) and P(o-furyl)3 (46 mg, 10 mol%) dissolved in THF (5 mL), and mixed with iodo compound 248 (0.49 g, 1.5 mmol) were then transferred via cannula to the reaction mixture. The resulting mixture was stirred for 18 h at 60 °C. The reaction mixture was then quenched with a sat. aq. NH4Cl solution (20 mL), extracted with diethyl ether...
ether (3 × 50 mL) and dried over anhydrous Na₂SO₄. After filtration, the solvent was evaporated in vacuo. Purification by flash-chromatography (1% EtOAc/Hexane) furnished compound 261d (88 mg, 17%) as a colourless oil. IR (film) 2929, 2857, 1537, 1507, 1471, 1395, 1361, 1254, 1101, 835 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 8.66 (1H, s, ArH), 6.02 (1H, s, =CH), 3.84 (2H, t, J = 6.5 Hz, CH₂), 2.46 (2H, t, J = 6.5 Hz, CH₂), 1.62 (3H, s, CH₃), 0.91 (9H, s, SiC(CH₃)₃), 0.08 (6H, s, Si(CH₃)₂); ¹³C NMR (62.9 MHz, CDCl₃) δ 161.5 (C), 155.9 (CH), 144.1 (2 x C), 130.7 (C), 116.8 (CH), 61.6 (CH₂), 42.3 (CH₂), 25.9 (3 x CH₃), 19.0 (CH₃), 18.2 (C), -5.4 (2 x CH₃); HRMS (ES) Exact mass calcd for C₁₅H₂₄Cl₂N₂O₃Si [M⁺]: 346.1029, found: 346.1021.

Preparation of Alkenyl Imidazoles

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\text{(E)-2-Benzyl-3-(1-methyl-1H-imidazol-2-yl)-propenal (263).}
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Following a slight modification of a literature procedure for a similar compound, to a vigorously stirred suspension of Bu₄NPF₆ (387 mg, 1.00 mmol) and KOH (84 mg, 1.50 mmol) in toluene (35 mL) was added 1-methyl-2-imidazole-carboxaldehyde 262 (1.10 g, 10.0 mmol) dropwise over 1 min, followed by hydrocinnamaldehyde (1.58 mL, 12.0 mmol) dropwise over 2 min. The reaction was stirred vigorously at room temperature for 18 h, and then partitioned between H₂O (50 mL) and CH₂Cl₂ (50 mL). The aqueous layer was separated and extracted with CH₂Cl₂ (2 x 50 mL) and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Purification of the residue by column chromatography (30%-50% EtOAc/hexane) gave the enal 263 (1.99 g, 88%) as a

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yellow solid. m.p. 108-110 °C; IR (CHCl₃) 3029, 2828, 2716, 1673 (C=O), 1625 (C=C), 1476, 1420, 1285, 1240, 1126; ¹H NMR (360 MHz, CDCl₃) δ 9.58 (1H, s, CHO), 7.46-7.44 (2H, m, ArH), 7.33 (1H, s, CH=CCH₂Ph), 7.25-7.14 (3H, m, ArH), 7.06-7.04 (2H, m, ArH), 4.50 (2H, s, CH₂Ph), 3.77 (3H, s, NCH₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 194.2 (CH), 142.7 (C), 142.0 (C), 139.4 (C), 131.1 (CH), 130.8 (CH), 128.9 (2 x CH), 128.0 (2 x CH), 125.8 (CH), 123.6 (CH), 33.0 (CH₃), 29.9 (CH₂); HRMS (ESI) Exact mass calcd for C₁₄H₁₅ON₂ [M+H]⁺: 227.1179, found: 227.1181.

(Ê)-2-Benzyl-3-(1-methyl-1H-imidazol-2-yl)-prop-2-en-1-ol (264). To a solution of aldehyde 263 (452 mg, 2.00 mmol) and CeCl₃·7H₂O (894 mg, 2.40 mmol) in EtOH (20 mL) at room temperature was added NaBH₄ (227 mg, 6.00 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature for 1 h and quenched carefully with saturated aqueous NH₄Cl solution (20 mL). Most of the EtOH was removed in vacuo, and the aqueous residue was extracted with EtOAc (3 x 30 mL). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by column chromatography (80% EtOAc/hexane) gave the alcohol 264 (358 mg, 78%) as a yellow oil. IR (film) 3321 (OH), 3025, 2921, 2358, 1666 (C=C), 1600, 1493, 1452, 1412, 1282 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.25-7.14 (5H, m, ArH), 7.06 (1H, s, ArH), 6.83 (1H, s, ArH), 6.42 (1H, s, CH=CCH₂Ph), 4.11 (2H, d, J = 7.1 Hz, CH₂OH), 4.07 (2H, s, CH₂Ph), 3.58 (3H, s, NCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 147.0 (C), 144.9 (C), 139.4 (C), 128.8 (2 x CH), 128.3 (2 x CH), 127.8 (CH), 126.0 (CH), 120.5 (CH), 110.2 (CH), 65.2 (CH₂), 35.0 (CH₂), 32.9 (CH₃); HRMS (ESI) Exact mass calcd for C₁₄H₁₇N₂O [M+H]⁺: 229.1335, found: 229.1334.
2,2-Dimethyl-propionic acid

\((E)-2\text{-benzyl-3-}(1\text{-methyl-1H-imidazol-2-yl})\text{-allyl ester (265).}\)

To a solution of the alcohol 264 (200 mg, 0.88 mmol), Et₃N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH₂Cl₂ (10 mL) at room temperature was added trimethylacetyl chloride (246 μL, 2.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na₂CO₃ solution (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (Na₂SO₄) and concentrated \textit{in vacuo}. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the \textit{pivaloate ester} 265 (203 mg, 74%) as a yellow oil. IR (film) 2972, 1728 (C=O), 1480, 1452, 1397, 1364, 1150, 1031, 865, 740 cm⁻¹; \(^1\)H NMR (360 MHz, CDCl₃) \(\delta 7.26-7.16 (5H, m, \text{Ar H}), 7.13 (1H, s, \text{Ar H}), 6.88 (1H, s, \text{Ar H}), 6.37 (1H, s, \text{CH=CCH}_2\text{Ph}), 4.56 (2H, d, \text{J} = 0.8 \text{ Hz, CH}_2\text{O}), 4.22 (2H, s, \text{CH}_2\text{Ph}), 3.65 (3H, s, \text{NC}_3\text{H}_3), 1.23 (9H, s, \text{C(CH}_3)_3); \(^{13}\)C NMR (90.6 MHz, CDCl₃) \(\delta 177.9 (\text{C}), 144.1 (\text{C}), 141.0 (\text{C}), 138.9 (\text{C}), 128.9 (2 \times \text{CH}), 128.4 (2 \times \text{CH}), 128.2 (\text{CH}), 126.1 (\text{CH}), 120.7 (\text{CH}), 113.1 (\text{CH}), 66.9 (\text{CH}_2), 38.8 (\text{C}), 35.0 (\text{CH}_2), 32.8 (\text{CH}_3), 27.2 (3 \times \text{CH}_3); \text{HRMS (ES) Exact mass calcld for C}_{19}\text{H}_{25}\text{N}_{2}\text{O}_{2} [\text{M}+\text{H}]^+: 313.1911, \text{found: 313.1909.}

Ethyl \((E)-2\text{-methyl-3-}(1\text{-methyl-1H-imidazol-2-yl})\text{propenoate (266).}\) A solution of 1-methyl-2-imidazole carboxaldehyde 262 (550 mg, 5.00 mmol) and (carbethoxyethylidene)triphenylphosphorane (94%, 2.31 g, 6.00 mmol) in toluene (50 mL) was heated under reflux for 18 h. After cooling to room temperature, the mixture was concentrated \textit{in vacuo} and the residue was purified by column chromatography (50% EtOAc/hexane→80% EtOAc/hexane) to give the \textit{alkene} 266 (760 mg, 78%) as a white solid. m.p. 72-74 °C. IR (CHCl₃) 3127, 2978,
1695 (C=O), 1483, 1424, 1276, 1160, 1107, 1082, 990 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.43 (1H, s, ArH), 7.23 (1H, s, ArH), 6.94 (1H, s, =CH), 4.28 (2H, q, J = 7.2 Hz, OCH₂), 3.74 (3H, s, NCH₃), 2.47 (3H, d, J = 1.3 Hz, =CH₂), 1.35 (3H, t, J = 7.2 Hz, OCH₂CH₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 168.6 (C), 143.8 (C), 131.1 (C), 129.8 (CH), 122.1 (CH), 121.5 (CH), 61.0 (CH₂), 33.1 (CH₃), 14.3 (CH₃), 14.2 (CH₃); HRMS (ES) Exact mass calcd for C₁₀H₁₅N₂O₂ [M+H]⁺: 195.1128, found: 195.1127.

(E)-2-Methyl-3-(1-methyl-1H-imidazol-2-yl)prop-2-en-1-ol (267). To a solution of the ester 266 (585 mg, 3.0 mmol) in CH₂Cl₂ (50 mL) at -78 °C was added DIBAL (1.0 M in hexane, 6.5 mL, 6.5 mmol) over 2 min, and the resulting mixture was stirred at -78 °C for 1.5 h, then at -20 °C for 1 h, and finally at -10 °C for 2 h. The reaction was quenched carefully with saturated aqueous Rochelle’s salt solution (50 mL) and the resulting mixture was stirred vigorously for 1 h. The aqueous layer was separated and extracted with CH₂Cl₂ (3 x 50 mL), and the combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to leave the alcohol 267 (370 mg, 81%) as a yellow oil which was used in the next step without further purification. IR (film) 3326 (OH), 2908, 1724, 1668, 1520, 1486, 1413, 1378, 1282, 1125 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.03 (1H, s, ArH), 6.80 (1H, s, ArH), 6.30 (1H, br s, =CH), 4.15 (2H, s, CH₂O), 3.56 (3H, s, NCH₃), 2.03 (3H, s, =CCH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 145.5 (C), 145.1 (C), 127.6 (CH), 120.1 (CH), 108.8 (CH), 67.0 (CH₂), 32.8 (CH₃), 15.7 (CH₃).

(E)-2-Methyl-3-(1-methyl-1H-imidazol-2-yl)propenyl pivaloate (268). To a solution of the alcohol 267 (210 mg, 1.50 mmol), Et₃N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH₂Cl₂ (10 mL) at room temperature was added trimethylacetyl chloride
(369 μL, 3.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na₂CO₃ solution (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated in vacuo to leave the pivaloate ester 268 (340 mg, 96%) as a yellow oil which required no further purification. IR (film) 2976, 1808, 1737 (C=O), 1480, 1397, 1368, 1280, 1150, 1044, 1006 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.10 (1H, d, J = 0.9 Hz, ArH), 6.14 (1H, d, J = 0.9 Hz, ArH), 6.24 (1H, app d, J = 1.3 Hz, =CH), 4.64 (2H, s, CH₂O), 3.60 (3H, s, NCH₃), 2.18 (3H, s, =CH), 1.24 (9H, s, C(CH₃)₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 178.0 (C), 144.5 (C), 138.7 (C), 128.1 (CH), 120.4 (CH), 111.9 (CH), 68.9 (CH₂), 38.8 (C), 32.8 (CH₃), 27.2 (3 x CH₃), 15.9 (CH₃); HRMS (ES) Exact mass calcd for C₁₃H₂₂N₂O₂ [M+H]⁺: 237.1598, found: 237.1595.

**Ethyl**

(E)-2-methyl-3-(1-methyl-1H-benzoimidazol-2-yl)propenoate (270). A solution of 1-methylbenzimidazole-2-carboxaldehyde 269 (480 mg, 3.00 mmol) and (carbethoxyethylidene)triphenylphosphorane (94%, 1.54 g, 4.00 mmol) in toluene (30 mL) was heated under reflux for 18 h. After cooling to room temperature, the mixture was concentrated in vacuo and the residue was purified by column chromatography (10% EtOAc/hexane→50% EtOAc/hexane) to give the alkene 270 (550 mg, 75%) as a white solid. m.p. 95-96 °C. IR (CHCl₃) 2977, 1698 (C=O), 1641, 1459, 1374, 1324, 1293, 1264, 1243, 1159 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 7.86-7.82 (1H, m, ArH), 7.62 (1H, q, J = 1.5 Hz, =CH), 7.36-7.28 (3H, ArH), 4.34 (2H, q, J = 7.1 Hz, OCH₂), 3.83 (3H, s, NCH₃), 2.60 (3H, d, J = 1.5 Hz, =CH), 1.40 (3H, t, J = 7.1 Hz, OCH₂CH₃); ¹³C NMR (90.6 MHz,
CDCl$_3$ δ 167.9 (C), 148.8 (C), 143.2 (C), 136.5 (C), 135.1 (C), 123.4 (CH), 122.6 (CH), 122.1 (CH), 120.1 (CH), 109.3 (CH), 61.3 (CH$_2$), 29.9 (CH$_3$), 14.9 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{14}$H$_{17}$N$_2$O$_2$ [M+H]$^+$: 245.1285, found: 245.1284.

(E)-2-Methyl-3-(1-methyl-1H-benzoimidazol-2-yl)prop-2-en-1-ol (271). To a solution of the ester 270 (488 mg, 2.00 mmol) in CH$_2$Cl$_2$ (30 mL) at -78 °C was added DIBAL (1.0 M in hexane, 4.5 mL, 4.5 mmol) over 2 min, and the resulting mixture was stirred at -78 °C for 1.5 h, then at 0 °C for 2 h. The reaction was quenched carefully with saturated aqueous Rochelle’s salt solution (50 mL) and the resulting mixture was stirred vigorously for 1 h. The aqueous layer was separated and extracted with CH$_2$Cl$_2$ (3 x 50 mL), and the combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated in vacuo to leave the alcohol 271 (370 mg, 91%) as a yellow oil which was used immediately in the next step without further purification.

(E)-2-Methyl-3-(1-methyl-1H-benzoimidazol-2-yl)propenyl pivaloate (272). To a solution of the alcohol 271 (303 mg, 1.50 mmol), Et$_3$N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH$_2$Cl$_2$ (10 mL) at room temperature was added trimethylacetyl chloride (369 μL, 3.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na$_2$CO$_3$ solution (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$) and concentrated in vacuo and purified by column chromatography (40% EtOAc/hexane) to give the pivaloate ester 272 (273 mg, 64%) as a yellow oil. IR (film) 2970, 2360, 1732 (C=O), 1636, 1457, 1374, 1284, 1154, 862, 740 cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.81-7.78 (1H, m, ArH), 7.34-7.26 (3H, m, ArH), 4.73 (1H, app d, $J = 1.1$ Hz, =CH), 4.73 (2H, s, CH$_2$O), 3.97 (3H, s, OCH$_3$), 2.15 (3H, s, CO$_2$Me).
3.75 (3H, s, NCH$_3$), 2.29 (3H, s, =CCH$_3$), 1.29 (9H, s, C(CH$_3$)$_3$); $^{13}$C NMR (90.6 MHz, CDCl$_3$) δ 177.9 (C), 150.0 (C), 143.8 (C), 142.9 (C), 134.9 (C), 122.6 (CH), 122.2 (CH), 119.5 (CH), 112.0 (CH), 109.0 (CH), 68.4 (CH$_2$), 38.9 (C), 29.9 (CH$_3$), 27.2 (3 x CH$_3$), 16.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{17}$H$_{23}$N$_2$O$_2$ [M+H]$^+$: 287.1754, found: 287.1749.

**General Procedure for Enantioselective Copper-Catalysed Reductions**

A solution of the appropriate alkene (0.20 mmol), Cu(OAc)$_2$·H$_2$O (2.0 mg, 0.01 mmol), Josiphos ligand L5 (6.1 mg, 0.01 mmol), and t-BuOH (38 μL, 0.40 mmol) in toluene (1 mL) was stirred at 0 °C for 15 min. PhSi$_3$(74 μL, 0.60 mmol) was then added dropwise. The mixture was stirred at 0 °C for 2 h, then at room temperature for 15 h. The reaction was quenched carefully with silica gel (ca. 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short pad of silica gel using EtOAc (20 mL) as eluent. The filtrate was concentrated in vacuo and the residue was purified by column chromatography to give the reduced product.

**2-[(S)-2-Ethyl-4-triethoxysiloxybutyl]pyridine (273a).** A solution of alkene 244a (117 mg, 0.40 mmol), Cu(OAc)$_2$·H$_2$O (4.0 mg, 0.02 mmol), Josiphos ligand L5 (12.2 mg, 0.02 mmol), and t-BuOH (76 μL, 0.80 mmol) in toluene (2 mL) was stirred at 0 °C for 15 min. PhSi$_3$(74 μL, 0.60 mmol) was then added dropwise, and the mixture was stirred at 0 °C for 1 h and then at room temperature for 3 d. The reaction was quenched carefully with silica gel (ca. 500 mg), and the resulting suspension was stirred for 15 min before being filtered through a short pad of silica gel using EtOAc (40 mL) as eluent. The filtrate was
concentrated in vacuo and the residue was purified by column chromatography (5% EtOAc/hexane→10% EtOAc/hexane) to give the reduction product 273a (78 mg, 66%) as a colourless oil. [α] D 21 +15.0 (c 0.53, CHCl₃); IR (film) 2952, 2874, 1589, 1568, 1472, 1434, 1238, 1095, 1016, 746 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 8.53-8.52 (1H, m, ArH), 7.58-7.55 (1H, m, ArH), 7.14-7.12 (1H, m, ArH), 7.10-7.07 (1H, m, ArH), 3.65-3.57 (2H, m, CH₂O), 2.77 (1H, dd, J = 13.5, 7.1 Hz, N=CH₂H₂), 2.70 (1H, dd, J = 13.5, 7.5 Hz, N=CH₂H₂), 1.98-1.90 (1H, m, N=CCH₂CH₂), 1.61-1.49 (2H, m, CH₂CH₂O), 1.37-1.31 (2H, m, CH₂CH₃), 0.93 (9H, t, J = 8.0 Hz, Si(CH₂CH₃)₃), 0.86 (3H, t, J = 8.0 Hz, CH₂CH₂CH₃), 0.56 (6H, q, J = 8.0 Hz, Si(CH₂CH₃)₃); ¹³C NMR (90.6 MHz, CDCl₃) δ 161.5 (C), 149.2 (CH), 136.0 (CH), 123.6 (CH), 120.8 (CH), 61.1 (CH₂), 42.8 (CH₂), 36.9 (CH), 36.1 (CH₂), 26.1 (CH₂), 10.7 (CH₃), 6.7 (3 x CH₃), 4.4 (3 x CH₃); HRMS (ES) Exact mass calcd for C₁⁷H₃₂NOSi [M+H]⁺: 294.2248, found: 294.2248. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.5:0.5 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); tᵣ (minor) ca 14 min (not detected); tᵣ (major) = 15.8 min; >99% ee.

2-[(S)-2-Ethylhexyl]-4,5-dimethylthiazole (273b). The title compound was prepared according to General Procedure from alkene 261b (45 mg, 0.20 mmol) for a reaction time of 5 days and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (38 mg, 84%). [α] D 21 +8.0 (c 0.50, CHCl₃); IR (film) 2959, 2925, 2859, 1557, 1460, 1378, 1131, 1064, 700, 488 cm⁻¹; ¹H NMR (360 MHz, CDCl₃) δ 2.79 (2H, app d, J = 7.1 Hz, N=CCH₂H₂), 2.29 (3H, s, ArCH₃), 2.27 (3H, s, ArCH₃), 1.75-1.68 (1H, m, CHCH₂H₂), 1.38-1.24 (8H, m, CHCH₂CH₃ and (CH₂)₃CH₃), 0.87 (6H, t, J = 7.4 Hz, 2 x CH₂CH₃); ¹³C NMR (62.9 MHz, CDCl₃) δ 166.0 (C), 147.1 (C), 124.8 (C), 40.4 (CH), 37.6 (CH₂), 32.4 (CH₂), 28.7 (CH₂), 25.6 (CH₂), 22.9 (CH₂), 14.6 (CH₃), 14.1 (CH₃), 11.2 (CH₃), 10.7 (CH₃); HRMS (EI) Exact mass calcd for C₁₃H₂₃NS [M]⁺:
225.1546, found: 225.1546. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99.5:0.5 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); $t_r$ (major) = 13.5 min; $t_r$ (minor) = 14.3 min; 88% ee.

2-[(S)-4-(tert-Butyldimethylsilyloxy)-2-methylbutyl]benzothiazole (273c). A solution of alkene 261c (41 mg, 0.12 mmol), Cu(OAc)$_2$·H$_2$O (2.0 mg, 0.01 mmol), Josiphos ligand L5 (6.1 mg, 0.01 mmol), and $t$-BuOH (38 μL, 0.40 mmol) in toluene (1 mL) was stirred at room temperature for 15 min. PhSiH$_3$ (37 μL, 0.30 mmol) was then added dropwise, and the mixture was stirred at room temperature for 5 h. The reaction was quenched carefully with silica gel (ca. 250 mg), and the resulting suspension was stirred for 15 min before being filtered through a short pad of silica gel using EtOAc (20 mL) as eluent. The filtrate was concentrated in vacuo and the residue was purified by column chromatography (hexane→2% EtOAc/hexane) to give the reduction product 273c (34 mg, 82%) as a colourless oil. $[\alpha]_D^{21} +12.0$ (c 0.50, CHCl$_3$); IR (film) cm$^{-1}$; $^1$H NMR (360 MHz, CDCl$_3$) δ 7.99-7.97 (1H, m, ArH), 7.86-7.83 (1H, m, ArH), 7.48-7.45 (1H, m, ArH), 7.38-7.33 (1H, m, ArH), 3.77-3.66 (2H, m, C$_3$H$_2$O), 3.16 (1H, dd, $J = 14.4$, 6.2 Hz, N=CCH$_2$), 2.96 (1H, dd, $J = 14.4$, 8.2 Hz, N=CCH$_2$), 2.33-2.19 (1H, m, CHCH$_3$), 1.77-1.68 (1H, m, CH$_2$CH$_2$O), 1.56-1.46 (1H, m, CH$_2$CH$_2$O), 1.03 (3H, d, $J = 6.7$ Hz, CHCH$_3$), 0.90 (9H, s, C(CH$_3$)$_3$), 0.05 (3H, s, SiCH$_3$), 0.04 (3H, s, SiCH$_3$); $^{13}$C NMR (62.9 MHz, CDCl$_3$) δ 171.2 (C), 153.2 (C), 135.3 (C), 125.8 (CH), 124.6 (CH), 122.5 (CH), 121.4 (CH), 61.0 (CH$_2$), 41.7 (CH$_2$), 39.4 (CH$_2$), 31.3 (CH), 25.9 (3 x CH$_3$), 19.6 (CH$_3$), 18.3 (C), -5.3 (CH$_3$), -5.4 (CH$_3$); HRMS (ES) Exact mass calcd for C$_{18}$H$_{30}$NOSSi [M+H]$^+$: 336.1812, found: 336.1813. Enantiomeric excess was determined by HPLC with a Chiralpak OD-H column (99:1 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); $t_r$ (major) = 6.7 min; $t_r$ (minor) = 7.8 min; 95% ee.
(R)-2-Methyl-3-(1-methyl-1H-benzoimidazol-2-yl) pivaloate (274c). The title compound was prepared according to General Procedure from alkene 272 (57 mg, 0.20 mmol) and purified by column chromatography (50% EtOAc/hexane→60% EtOAc/hexane) to give a yellow oil (35 mg, 61%). \([\alpha]^D_{21}\) -8.3 (c 0.96, CHCl3); IR (film) 2971, 2360, 1726 (C=O), 1478, 1396, 1322, 1284, 1160, 1034, 742 cm\(^{-1}\); \(^1\)H NMR (360 MHz, CDCl3) \(\delta\) 7.66-7.63 (1H, m, ArH), 7.24-7.15 (3H, m, ArH), 3.99-3.97 (2H, m, CH\(_2\)O), 3.65 (3H, s, NCH\(_3\)), 2.94 (1H, dd, \(J = 14.8, 5.9\) Hz, N=CCH\(_2\)), 2.67 (1H, dd, \(J = 14.8, 8.6\) Hz, N=CCH\(_2\)), 2.55-2.42 (1H, m, CHCH\(_3\)), 1.13 (9H, s, C(CH\(_3\))\(_3\)), 0.99 (3H, d, \(J = 6.7\) Hz, CHCH\(_3\)); \(^13\)C NMR (125.8 MHz, CDCl3) \(\delta\) 178.4 (C), 153.3 (C), 142.5 (C), 135.6 (C), 122.1 (CH), 121.9, (CH), 119.1 (CH), 109.0 (CH), 68.4 (CH\(_2\)), 38.9 (C), 32.4 (CH\(_3\)), 31.2 (CH\(_2\)), 29.8 (CH), 27.2 (3 x CH\(_3\)), 16.8 (CH\(_3\)); HRMS (ES) Exact mass calcd for C\(_{17}\)H\(_{25}\)N\(_2\)O\(_2\) [M+H]: 289.1911, found: 289.1913. Enantiomeric excess was determined by HPLC with a Chiralpak AD-H column (98:2 hexane:isopropanol, 0.8 mL/min, 254 nm, 25 °C); \(t_r\) (minor) = 35.0 min; \(t_r\) (major) = 44.9 min; 97% ee.
Conclusion and future direction

In summary, I have developed a catalytic, organometallic addition-ring opening sequence of cyclopropenes that enables the efficient and highly stereoselective synthesis of multisubstituted alkenes. A possible mechanism of organoaluminium reaction was proposed. The metalloenolate resulting from ring opening can be trapped with various electrophiles, enabling a rapid increase in molecular complexity in a one-pot operation. However, the Grignard reaction is still not fully investigated. If the diversity of Grignard reagents could be expanded and the enolate be trapped, the mechanism will be better understood.

I also describe a cascade reaction, which begins with Lewis-acid mediated regioselective $S_N V\sigma$ attack by a halogen nucleophile at the sp$^2$-carbon of cyclopropene, resulting in the formation of acyclic conjugate enolate, which can be trapped with enones to result in more highly functionalised products. However, only a few Michael additions to $\beta$-unsubstituted enones using acetonitrile as the solvent were proven successful. The scope of enolate trapping reactions still needs to be investigated.

As shown in the second chapter, nitrogen-containing aromatic heterocycles can provide effective activation of an adjacent alkene for highly enantioselective catalytic conjugate reduction reactions. Extension of the general concept to other classes of heteroarenes has been proven successful. Other heterocycles like caffeine and pyrazole were also considered. However, due to the low reactivity of those moieties, we could not prepare the desired substrates from any of those methods mentioned before. Further manipulation of the conditions is required to tolerate more challenging heteroarene substrates.
References


69. For review, see: Christoffers, J.; Koripelly, G.; Rosiak, A.; Rössle, M.; *Synthesis* 2007, 9, 1899.


