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

Acknowledgements

First of all, I would like to thank Hon for the great opportunity to work in his group. Thanks for always being there when I felt lost. I have to say, yes, you are Chinese.

As for my collagues, I'd like to thank all the people in the Lam group, past and present. I'm so so lucky to have you around. I couldn't go through this without your help. Special thanks to Euan, I started from zero and learned everything from you. Thanks for winnie me up every morning after you heard about bad things happened in China on the news. Also to Ralph, I really enjoyed your English history lectures and Family Guy jokes. To Myriam Angel Scansetti, everytime I'm having Tiramisu, I think about you.To Mairi and Claire, you two brought so much fun to our lab, Claire on the radio, the Halloween costume, Cake Idol, the badminton tournament...the smiles on your faces will always be in my memory. To Leszek, I enjoyed the fancy gadget chat, your weird taste Vodka and jokes about commy. Gordon, thanks for all your help on the project. I loved the Venezuelan dance. Keep up the good work. Benoit, well...what can I say about Ben, you are a great runner, and you are always calm, even when you passed me the timing chip in the Marathon Relay, even when you heard the breaking news about Michael Jackson. To Sam and Charlene, thanks for bearing my whining and always being so supportive. I enjoyed Singstar, ceilidhs and yells on the street at 2am. To Aakarsh, you are my bro. Asians rule the world! Or at least we cram. To Darryl, you have a heart of gold. Keep smiling and singing. To Donna, Graham, Jacky, Iain, Pekka, Isabel, Gordon and Serghei my comrade, you are not only good collagues but also my truely friends.

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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 $S_NV\sigma$ attack at the sp^2-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

Ac	acetyl
acac	acetylacetonate
aq	aqueous
Ar	aryl
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BIPHEP	(biphenyl-2,2'-diyl)bis(diphenylphosphine)
Bn	benzyl
Bz	benzoyl
cat.	catalyst
calcd	calculated
conc.	concentrated
dba	dibenzylideneacetone
DIBAL-H	diisobutylaluminium hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DKR	dynamic kinetic resolution
dppe	1,2-*bis*(diphenylphosphino)ethane
dr	diastereomeric ratio
ee	enantiomeric excess
EI	electron impact
equiv.	equivalents

ES	electrospray
EWG	electron-withdrawing group
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
IR	infrared spectroscopy
LG	leaving group
MEM	2-methoxyethoxymethyl
MOM	methoxymethyl
m.p.	melting point
NMR	nuclear magnetic resonance
NOE	Nuclear Overhauser Effect
PMHS	poly(methylhydrosiloxane)
ppm	parts per million
rt	room temperature
SEGPHOS	5,5'-diylbis(di(3,5-di-*t*-butyl-4-methoxyphenyl)-phosphine)
t-AmOH	*tert*-Amyl alcohol
TBAF	tetrabutylammonium fluoride
TBS	*t*-butyldimethylsilyl
TES	triethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl

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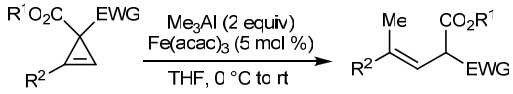
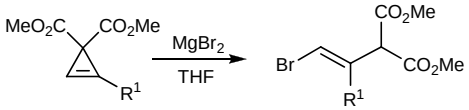
General Introduction of this work

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 studing ring-opening reaciton 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.



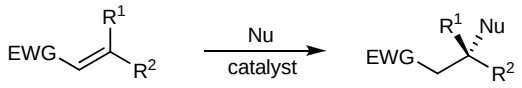
During this work, I also found that in the presence of stoichiometric magnesium halides, a range of bis-activated cyclopropenes could undergo highly stereoselective ring-opening reactions to produce multisubstituted alkenyl halides. The enolate intermediate can be trapped with enones to result in more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



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

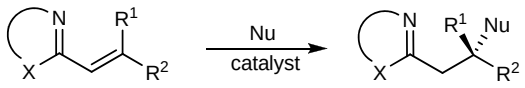
alkene in an analogous reaction, also whether large substituents would be tolerated under our reaction conditions. Dr Leszek Rupnicki and Aakarsh Saxena optimised the reaction conditions and tested a few heteroarenes such as pyridines, benzoxazoles, benzothiazole, quinoline and pyrazine. They proved 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



EWG = COR, NO_2, CN, SO_2R, etc.

(b) Aromatic heterocycle induced conjugate addition

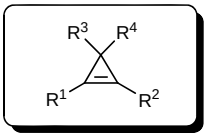


X = C, N, O, S, etc.

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.



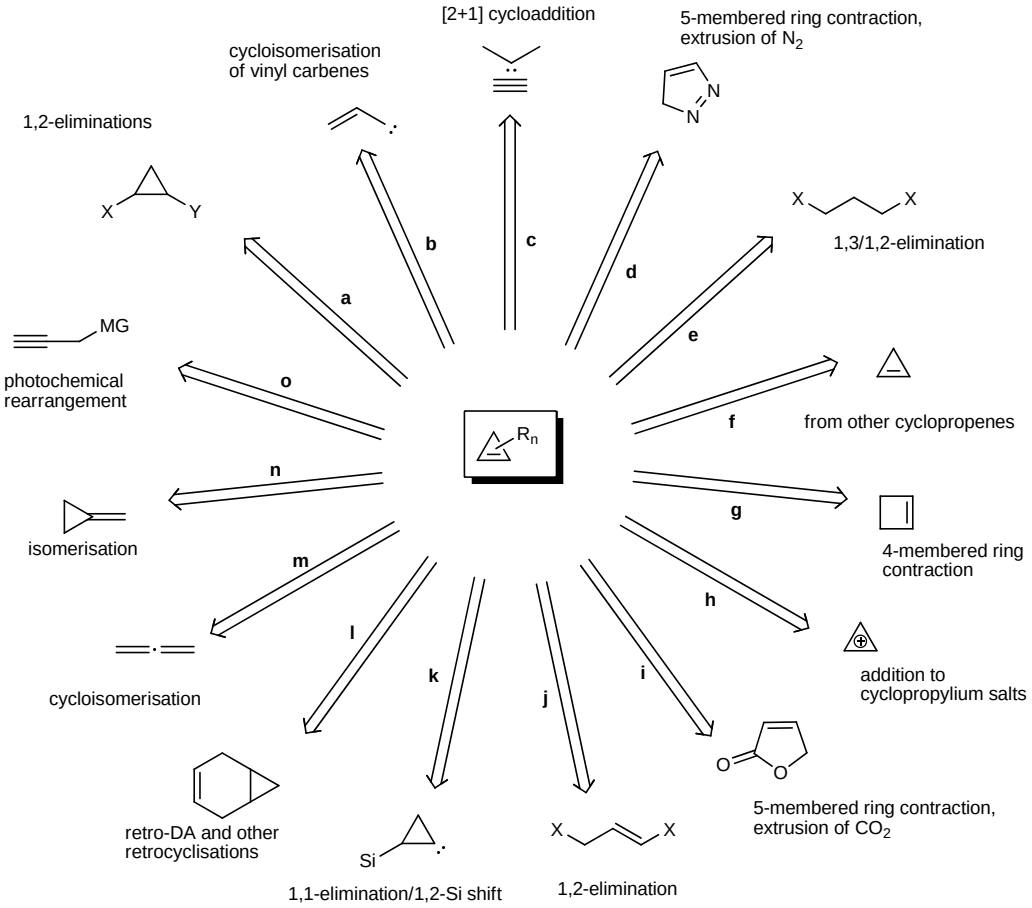
Scheme 1.1 Cyclopropenes

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]

1.1) Synthesis of Cyclopropenes

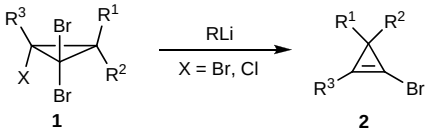
Numerous approaches to access cyclopropene and its derivatives have been comprehensively studied by organic chemists over the last century. In Baird's and Hopf's reviews,[2,3] some examples of the key synthetic approaches are summarised[1e] (Scheme 1.2): (a) 1,2-elimination from a cyclopropane precursor possessing good leaving groups (Scheme 1.3)[4]; (b) cycloisomerisation of vinylcarbenes generated in situ from tosyl hydrazones,[5] diazoalkenes,[6] vinyldiazirines,[7] or allyl halides[8] (Scheme 1.4); (c) [2+1] cycloaddition of carbenoids generated from diazo

compounds[9] or iodonium ylides[10] to alkynes (Scheme 1.5); (d) photochemical or transition-metal-catalysed extrusion of nitrogen from 3*H*-pyrazoles[11]; (e) cascade 1,3/1,2-elimination from 1,3-dihalopropanes [12] (Scheme 1.6); and (f) functionalisation of pre-formed cyclopropenes.



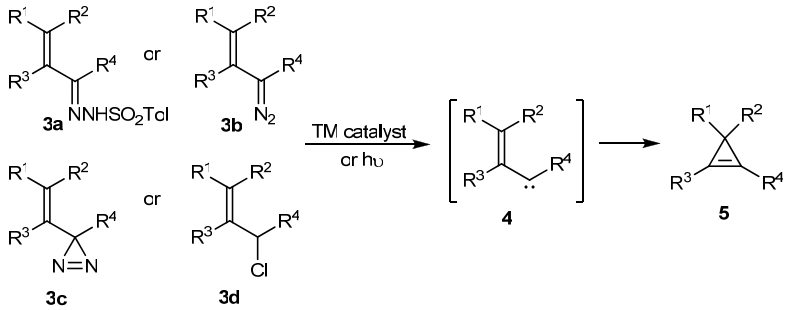
Scheme 1.2 Synthetic approaches to cyclopropenes

Other less common methods involve: (g) ring contraction of cyclobutenes[13]; (h) addition of nucleophiles to cyclopropylium species; (i) extrusion of CO_2 from furan-2(5*H*)-ones[14]; (j) 1,3- elimination from 1,3-dihalopropenes[15]; (k) 1,2-silicon shift in 2-silylcyclopropylidenes[16]; (l) retro-cycloaddition reactions[17]; and (m) various rearrangements of allenes[18], (n) methylenecyclopropanes[19], and (o) alkynes[20].



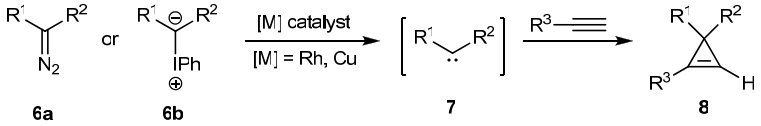
1 2

Scheme 1.3 1,3-Elimination from 1,2,2-trihalocyclopropanes



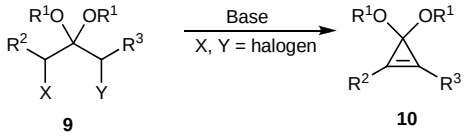
3a 3b 3c 3d 4 5

Scheme 1.4 Cycloisomerisation of vinylcarbenes



6a 6b 7 8

Scheme 1.5 [2 + 1] Cycloaddition of metal carbenoids to alkynes



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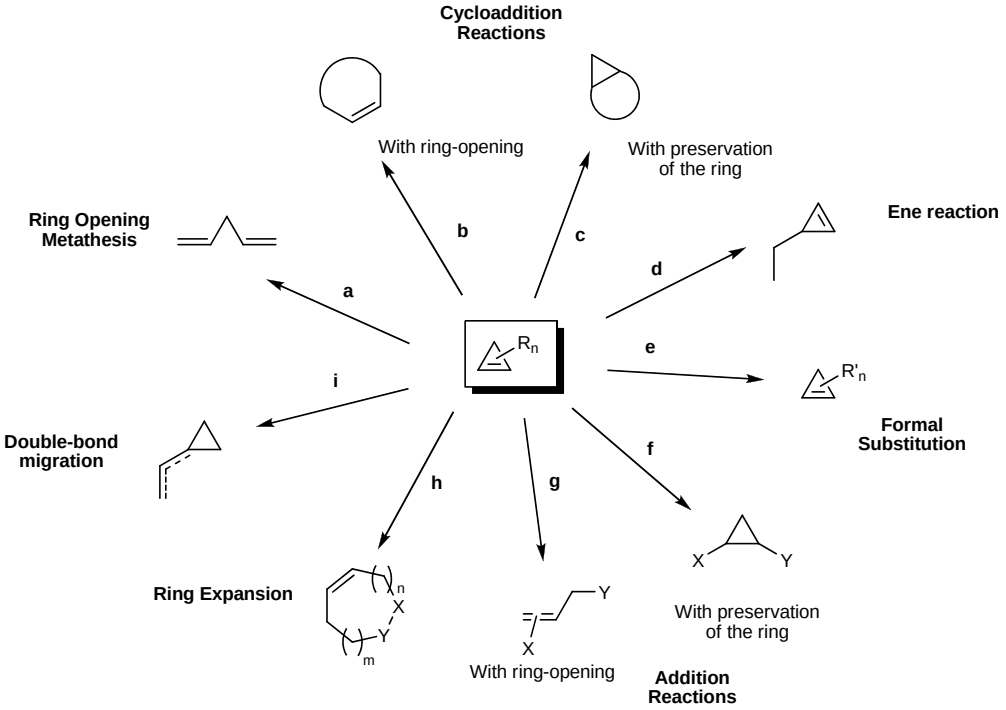
Scheme 1.6 Cascade 1,3/1,2-eliminations

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.[1e] 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).



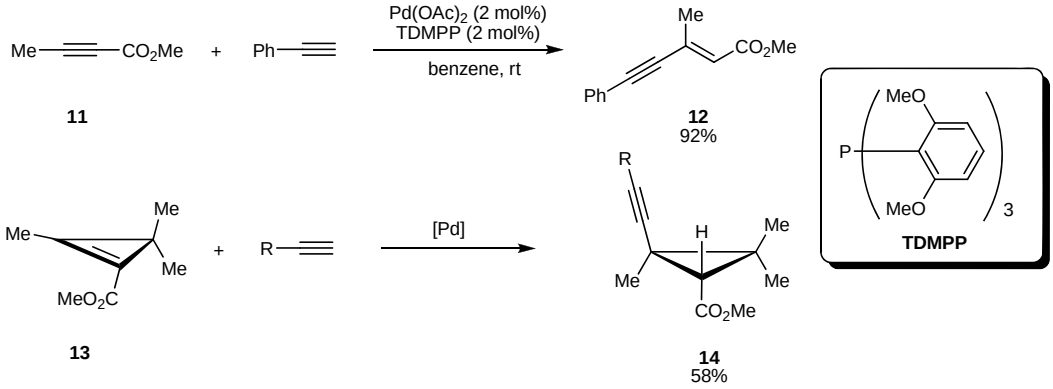
Scheme 1.7 Chemistry of cyclopropenes

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.[21] Some typical examples of addition reactions with cyclopropenes are described below. These include hydrocarbonation, hydrometallation and carbometallation.

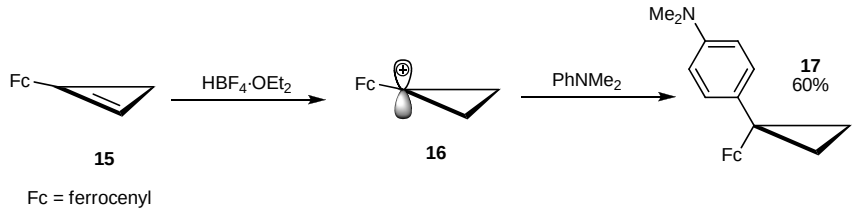
1.3.1) Addition of H-C Moieties

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 **11**,[22] cyclopropene **13** (which possesses an ester functionality at C-1) undergoes *syn* addition of terminal alkynes to access alkynylcyclopropane **14** (Scheme 1.8).[1d]



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

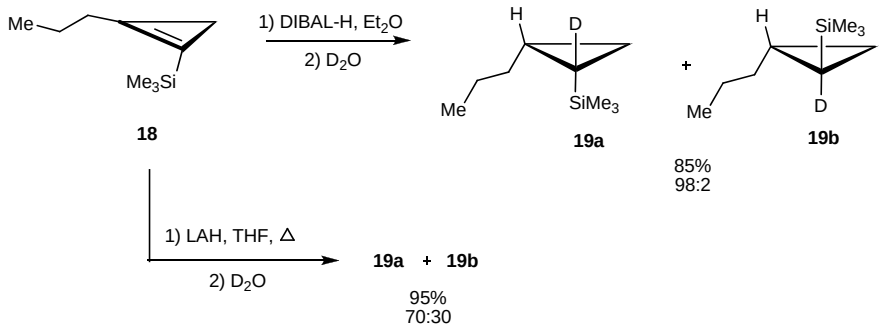
Another example of formal hydroarylation proceeding via an unusual cyclopropyl cation intermediate **16**, stabilised by a ferrocenyl substituent (Fc), was reported by Klimova. [23] Cyclopropyl cation **16**, obtained upon protonation of 1-ferrocenylcyclopropene **15**, underwent Friedel-Crafts alkylation of dimethylaniline to give **17** in moderate yield (Scheme 1.9).



Scheme 1.9 Formal hydroarylation of ferrocenyl substituent cyclopropene

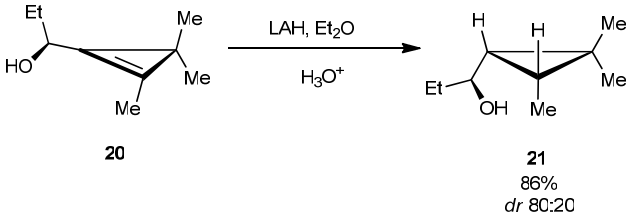
1.3.2) Addition of H-M Moieties

Hydrometallation across the double bond of cyclopropenes is described in this section. Although reduction of cyclopropene with $LiAlH_4$ has been routinely used for the preparation of cyclopropane derivatives since 1972,[24] Negishi was the first to demonstrate that this transformation proceeds via *syn*-selective hydroalumination of cyclopropenes.[25] 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 cyclopropenes

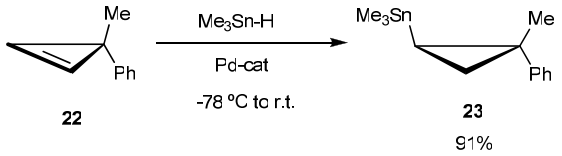
The directing effect of the hydroxymethyl group in this reaction was investigated by Marek, who demonstrated the highly diastereoselective reduction of cyclopropenyl carbinol **20** (Scheme 1.11).[26]



Scheme 1.11 Diastereoselective reduction of cyclopropenyl carbinol

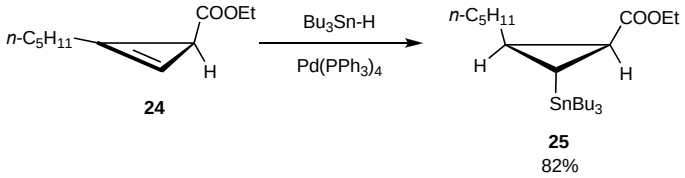
Gevorgyan[27] reported the palladium-catalysed *cis*-selective hydrostannation of cyclopropenes which, in contrast to radical hydrostannation, proceeded extremely rapidly and highly stereoselectively, leading to trisubstituted cyclopropylstannane in very good yield (Scheme 1.12). Facial selectivity in this reaction was primarily

controlled by steric factors, affording single diastereomers of cyclopropylstannanes **23**.



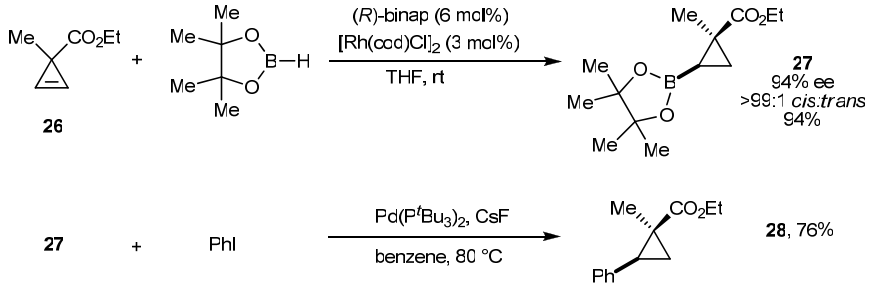
Scheme 1.12 Palladium-catalysed *cis*-selective hydrostannation of cyclopropenes

Application of this methodology to enantiomerically enriched cyclopropene **24**, as demonstrated by Corey, [28] allowed for the preparation of optically active cyclopropylstannane **25** (Scheme 1.13).



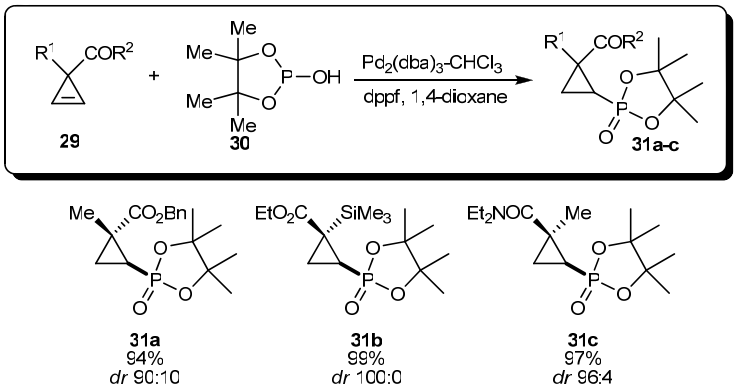
Scheme 1.13 Preparation of optically active cyclopropylstannane

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).[29] 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).



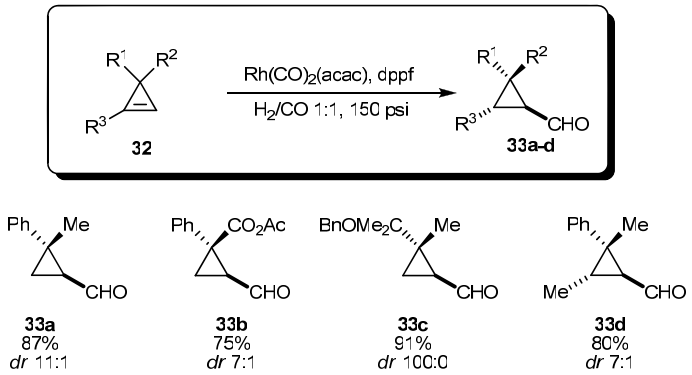
Scheme 1.14 Catalytic asymmetric hydroboration of 3,3-disubstituted cyclopropenes

In similar fashion, hydrophosphorylation of cyclopropenes was achieved by Rubin (Scheme 1.15).[30]



Scheme 1.15 Hydrophosphorylation of cyclopropenes

The same group also showed the first catalytic diastereo- and enantioselective hydroformylation of cyclopropenes (Scheme 1.16).[31]



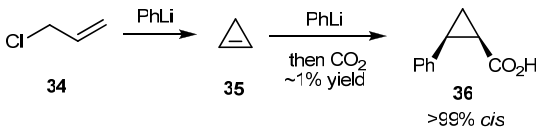
Scheme 1.16 Catalytic diastereo- and enantioselective hydroformylation of cyclopropenes

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

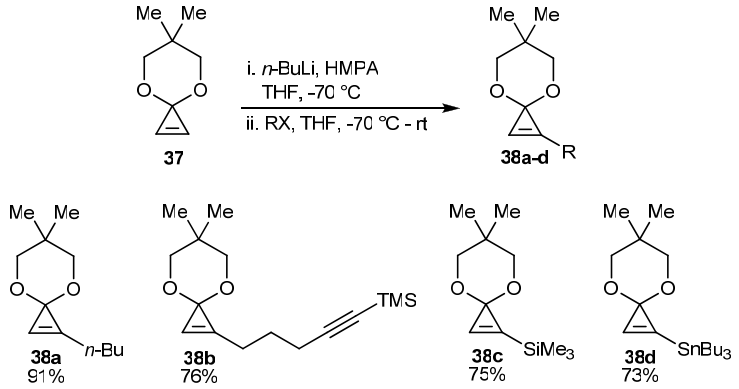
One of the main methods to functionalise cyclopropenes at the sp^2-carbons is to generate the cyclopropenylmetal species and then trap with the appropriate electrophile. The first example of a cyclopropene carbometallation reaction was reported in 1967 by Welch and Magid, who showed that sequential treatment of cyclopropene **35** with phenyllithium and CO_2 gives *cis*-2-phenylcyclopropene carboxylic acid **36** in low yield (Scheme 1.17). [32] 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.[33]



Scheme 1.17 Cyclopropene carbolithiation

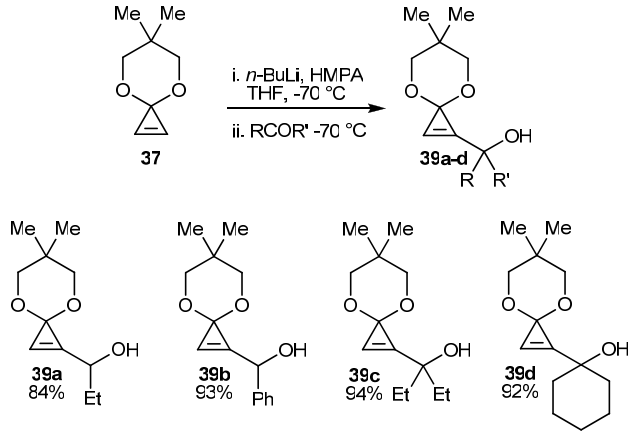
Cyclopropene alkene protons have a pKa of ~30, enabling metallation with strong bases in the same fashion as terminal alkynes.[34] Cyclopropenyllithium species can be generated by deprotonation of the corresponding cyclopropene using alkyl lithium bases. Nakamura and co-workers have demonstrated that it is possible to functionalise cyclopropenone ketals using this technique.[35] 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

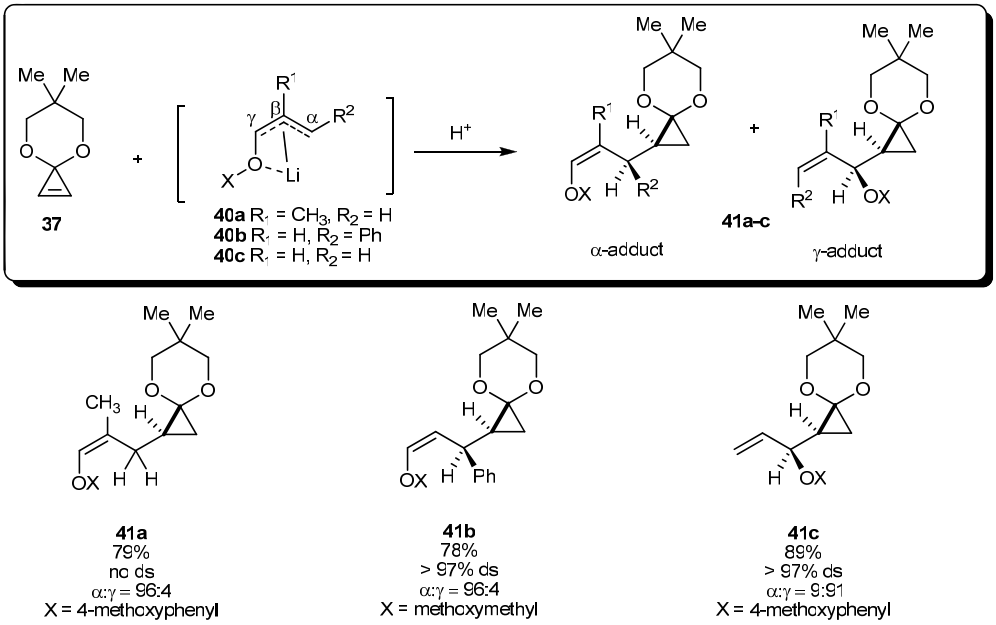
By using carbonyl compounds as electrophiles in these reactions it was possible to synthesise the corresponding cyclopropenone ketal derivatives **39a-d** which incorporate allylic alcohol functionality, in good to excellent yields (Scheme 1.19).[34]



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

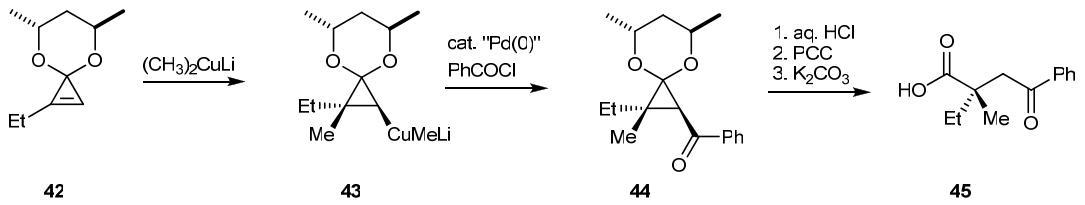
γ-addition of the allylic lithium reagent depends strongly on the structure of the lithium reagent. For example, carbon-carbon bond formation takes place at the α-position using a *β*-,*γ*- or an *α*-,*γ*- disubstituted allylic lithium reagent **40a** or **40b**, while a monosubstituted alkoxyallylic lithium reagent **40c** mainly gives a *γ*-adduct.



Scheme 1.20 Allylation of cyclopropenones

Carbocupration

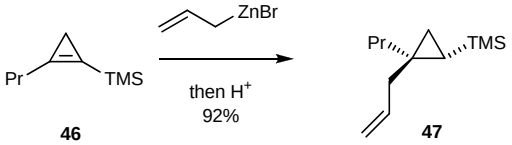
Cyclopropenone acetals can react with organocopper reagents to produce metallated cyclopropanone acetals, which are trapped by electrophiles to afford highly substituted cyclopropanone acetals. Regio- and stereoselective carbocupration of the substituted CPA derived from a chiral 2,4-pentanediol can 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 K_2CO_3 (Scheme 1.21).



Scheme 1.21 Carbocupration of cyclopropenone acetals

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).[38] 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.

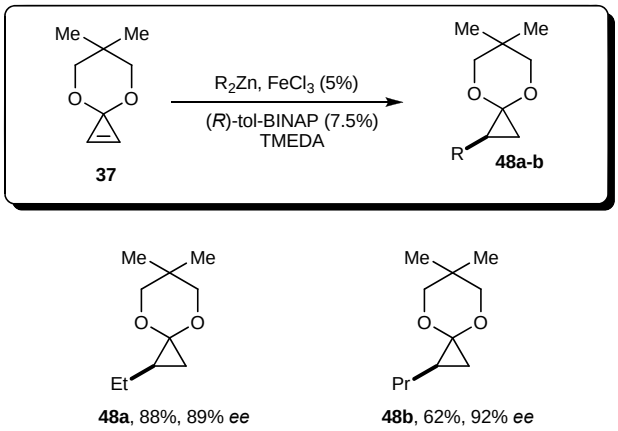


Scheme 1.22 Carbozincation of cyclopropenes

In contrast to moderately selective and rather substrate-specific non-catalytic additions of various entities to cyclopropenes,[1f] 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.[1e]

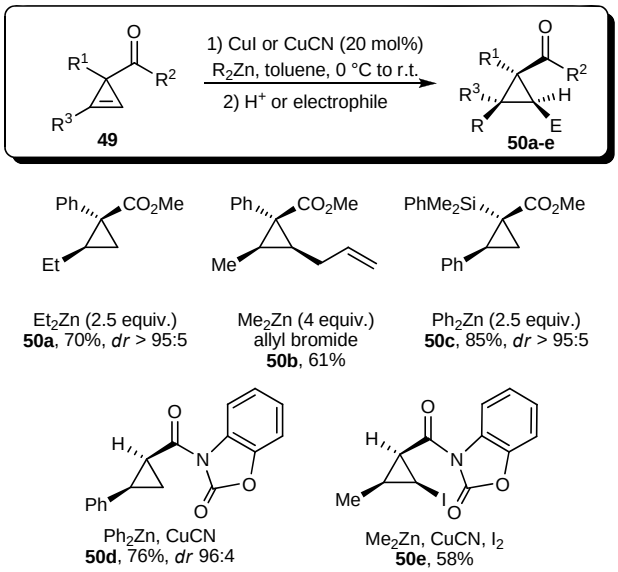
Nakamura and co-workers developed a number of useful protocols for the catalytic asymmetric carbozincation of cyclopropenone acetal **37** in the presence of an iron catalyst and chiral phosphine ligand (Scheme 1.23).[39] Addition of TMEDA to the

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

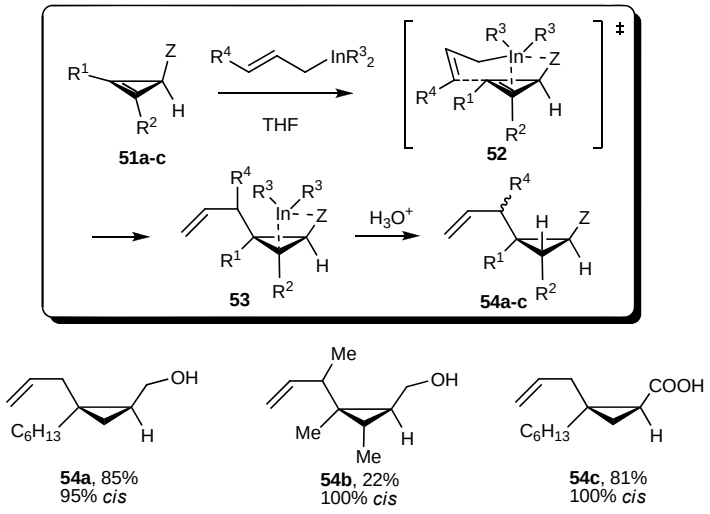
Another copper catalysed carbozincation reaction of cyclopropenes was reported recently by Fox (Scheme 1.24).[40] It was demonstrated that the diastereoselective addition can be also directed by oxazolidinone chiral auxiliaries (**50d-e**), and not only ester groups (**50a-c**). The resulting cyclopropylzinc species can be captured with electrophiles to access highly functionalised cyclopropanes **50b**, **50d** and **50e**.



Scheme 1.24 Oxazolidinone directed diastereoselective carbozincation of cyclopropenes

Carboindation

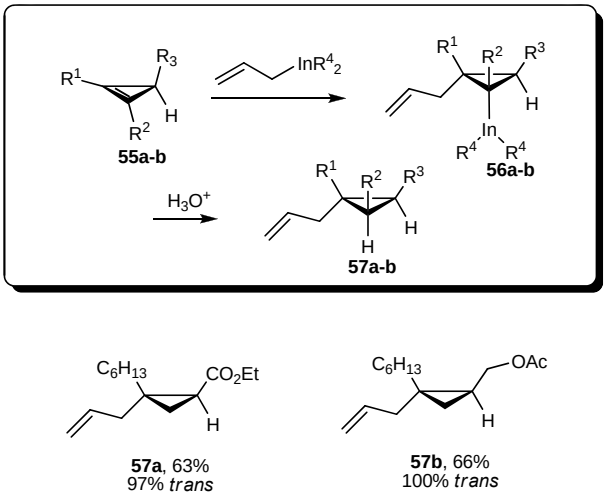
Araki and co-workers were the first group to used indium reagents to expand the scope of the allylmetallation of cyclopropenes since 1969, when the carbometallation of cyclopropenes with control of facial diastereoselectivity was first considered.[41] Allylindium reagents were shown to undergo facile 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.



Scheme 1.25 Allylindiation of cyclopropenes in THF

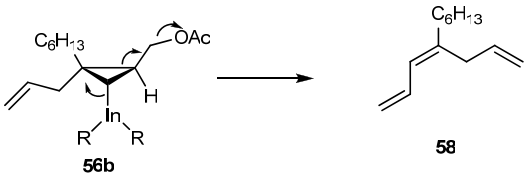
In aqueous media, where stabilisation of *cis*-transiton state **56** by chelation is inefficient, the corresponding *trans* products **57a-b** were obtained predominantly

(Scheme 1.26).[42]



Scheme 1.26 Allylindiation of cyclopropenes in water

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).



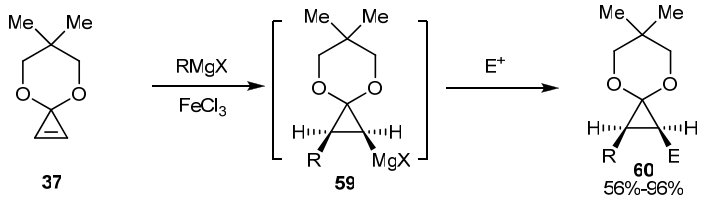
Scheme 1.27 Ring-opening-elimination of cyclopropane intermediate

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.

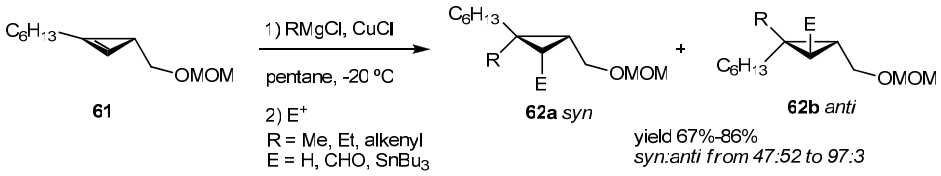
Nakamura first demonstrated that the use of an iron catalyst facilitated carbomagnesation of cyclopropenone acetals and enabled addition of a wide range of Grignard reagents, including aryl- and alkenylmagnesium halides, which did not

react in the absence of catalyst (Scheme 1.28).[37]



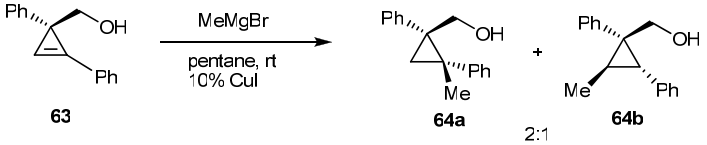
Scheme 1.28 Iron catalysed carbomagnesation of cyclopropenone acetals

Later, Liao and Fox[43] examined the effect of derivatising a 3-hydroxymethyl cyclopropene **61** with MOM substituent, as it was hoped that this known directing group[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 *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_3MgBr 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.

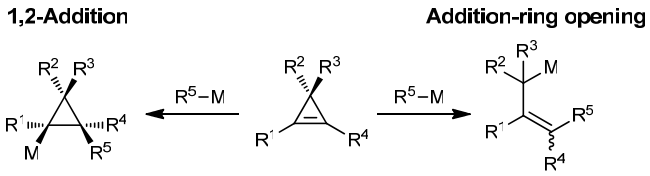


Scheme 1.30 Carbomagnesation of 1-aryl substituted cyclopropenes

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).



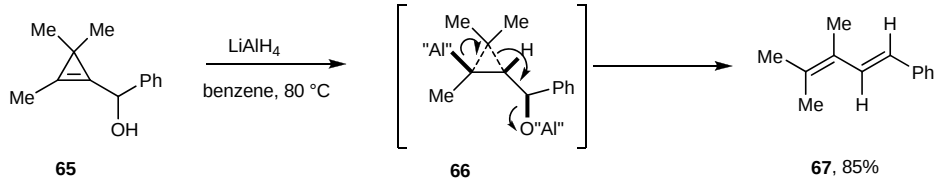
Scheme 1.31 Addition of organometallic reagents to cyclopropenes

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

expected to be favoured by the presence of anion-stabilising substituents at R^2 and R^3, and selectivity issues that would need to be addressed are: (i) regioselectivity with unsymmetrical cyclopropenes ($R^1 \neq R^4$) 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]

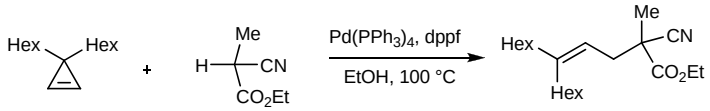
One hydroalumination-ring-opening sequence reported by Marek has achieved excellent yields and good regioselectivities (Scheme 1.32).[45] Reduction of cyclopropenylcarbinol **65** using $LiAlH_4$ generated the cyclopropylaluminium intermediate **66** which underwent an elimination reaction to yield the corresponding diene **67** at 80 °C.



65 **66** **67**, 85%

Scheme 1.32 Hydroalumination-ring-opening of cyclopropenes

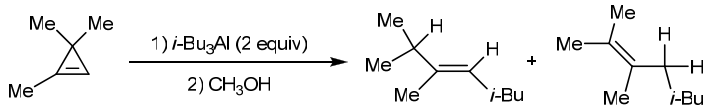
The single existing report of catalytic cyclopropene addition-ring-opening reactions using carbon nucleophiles was restricted to 3,3-dihexylcyclopropene **68** as the substrate. In the presence of a palladium catalyst, hydrocarbonation of dihexylcyclopropene **68** with ethyl 2-cyanopropanoate **69**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



68 **69** **70**, 82%

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).[47] Using two equivalents of triisobutylaluminium, trimethylcyclopropene **71** underwent addition-ring-opening sequence to form two isomers in low yields.



71 **72a**, 17% **72b**, 11%

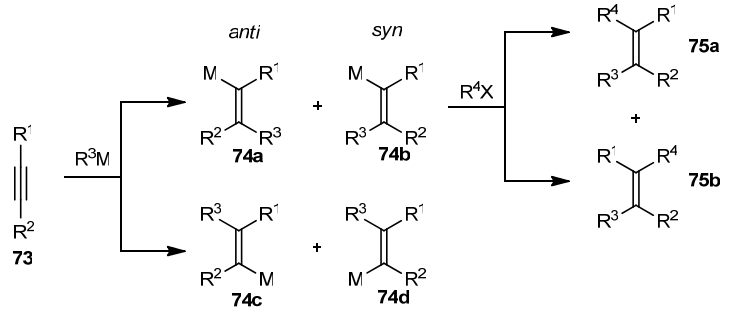
Scheme 1.34 Uncatalysed cyclopropene addition-ring-opening using hard organometallic reagents

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.

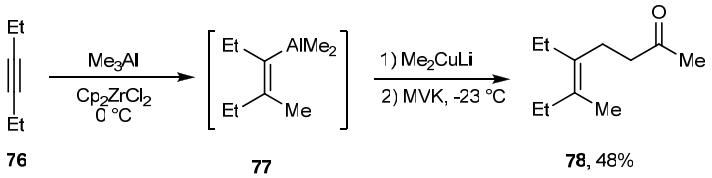
1.5) Preparation of Alkenes by Carbometallation of Alkynes

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

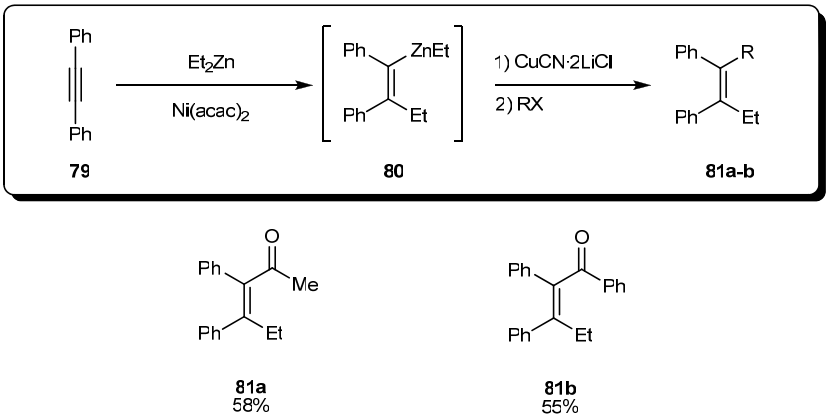
The use of symmetrical alkynes greatly simplifies many of the synthetic issues. However, this results in a decrease in structural flexibility. For example, treating with Schwartz's reagent, 3-hexyne **76** can form vinylic alane **77** (Scheme 1.36).[48] This intermediate could then be transmetallated to the corresponding copper reagent for subsequent condensation with methyl vinyl ketone (MVK).



Scheme 1.36 Approach to tetrasubstituted alkenes using symmetric alkynes

Zinc has been used in several instances to prepare tetrasubstituted olefins, primarily through Negishi coupling reactions, but also in other contexts. For example, the

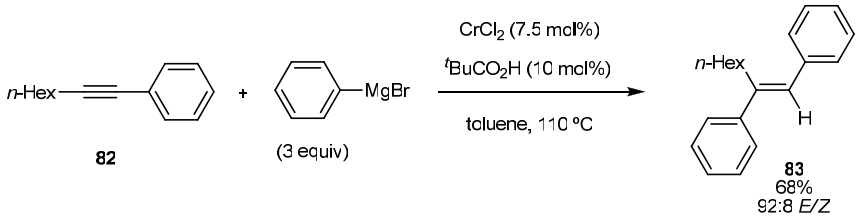
carbozincation of alkynes was described in which nickel catalysis provided smooth *syn* addition of diethylzinc to diphenylacetylene **79** affording a vinyl zinc intermediate **80**. This intermediate could be captured using different electrophiles to give tetrasubstituted products **81a-b** (Scheme 1.37).[49]



Scheme 1.37 Carbozincation of alkynes

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.

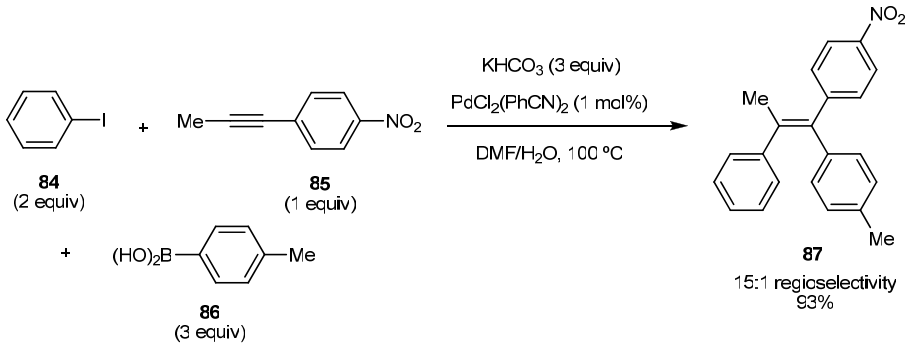
For example, the carbomagnesiation of alkyne **82** could be catalysed by a simple chromium salt with high efficiency.[50] The regioselectivity was simply governed by the steric factor of the two substituents of the alkyne (Scheme 1.38).



Scheme 1.38 Carbomagnesiation of alkynes

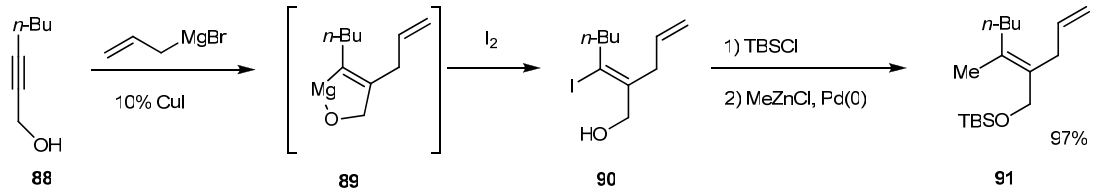
Another convenient regio- and stereoselective carbometallation route to tetrasubstituted olefins[51] involves *cis*-addition of Pd to the more electron-deficient

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)



Scheme 1.39 Carbopalladation of alkynes

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,[52] 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.[53] The *anti* fashion set the initial stereochemistry is preserved in the subsequent coupling (Scheme 1.40).

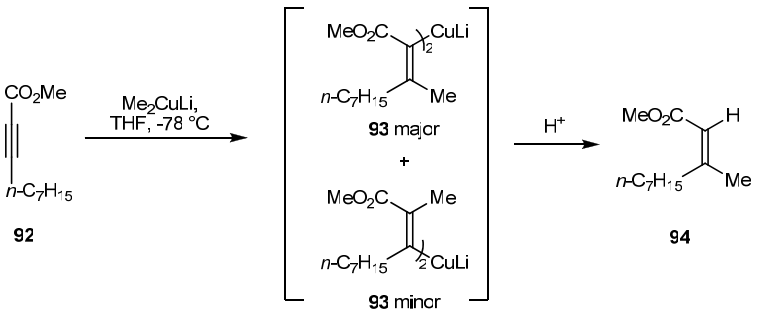


Scheme 1.40 Directed regioselective carbomagnesiation of alkynes

Although the initial addition across the π 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

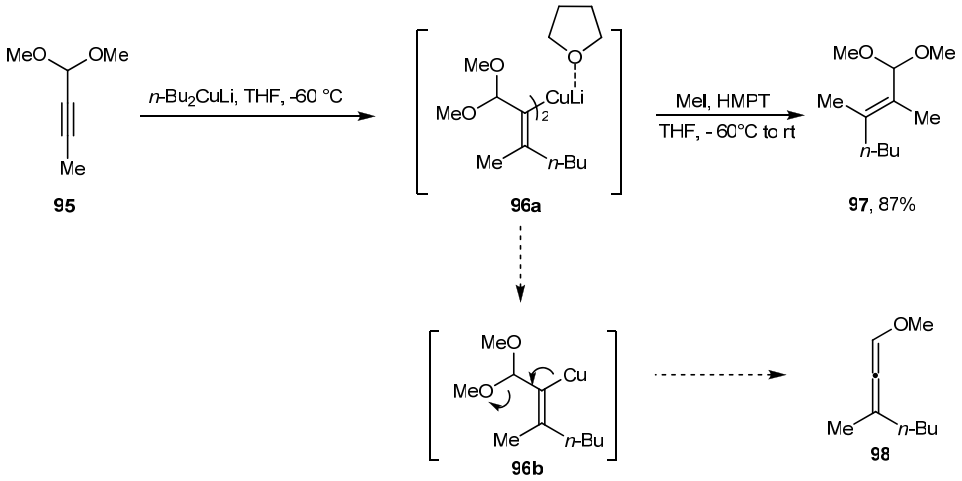
through tautomerisation or elimination processes. This is usually a consequence of the low reactivity of the intermediates and can be suppressed by simply keeping the reaction at low temperatures, by improving substrate design, or by carefully selecting the catalyst.

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).[54] It was noted that isomerisation of the cuprate intermediates occurred at higher temperatures and so quenching the reaction at -78 °C was imperative.



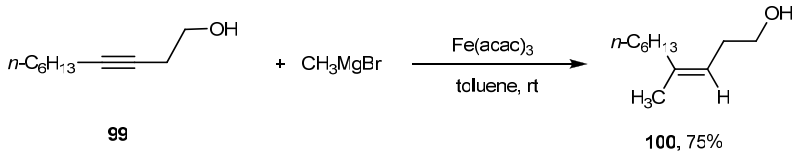
Scheme 1.41 Carbocupration of alkynes

In order to avoid isomerisation of the copper intermediate, acetals were employed as directing groups (Scheme 1.42).[55] 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.



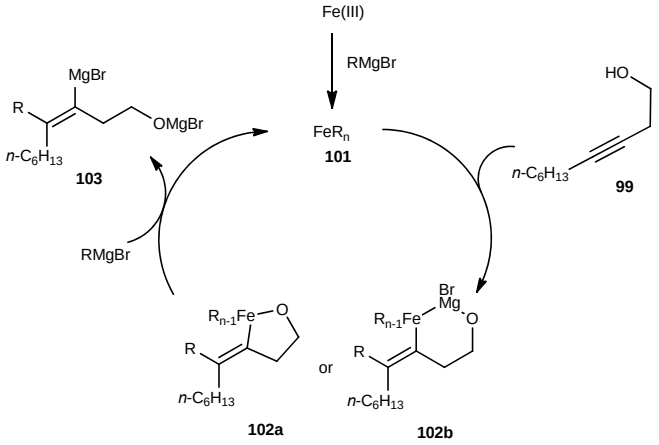
Scheme 1.42 Acetal directed carbocupration of alkynes

Contrary to propargylic alcohol carbomagnesiation examples (Scheme 1.40), the opposite regioselectivity was observed with homopropargylic alcohol **99** using an iron salt catalyst (Scheme 1.43).[56]



Scheme 1.43 Iron catalysed *syn* addition of Grignard reagent to homopropargylic alcohols

The proposed mechanism suggested that Fe(III) salt was reduce 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).

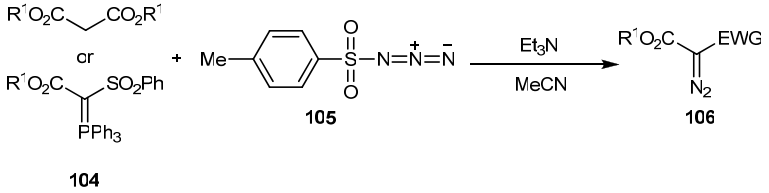


Scheme 1.44 The mechanism for iron catalysed carbomagnesiation of propargylic alcohols

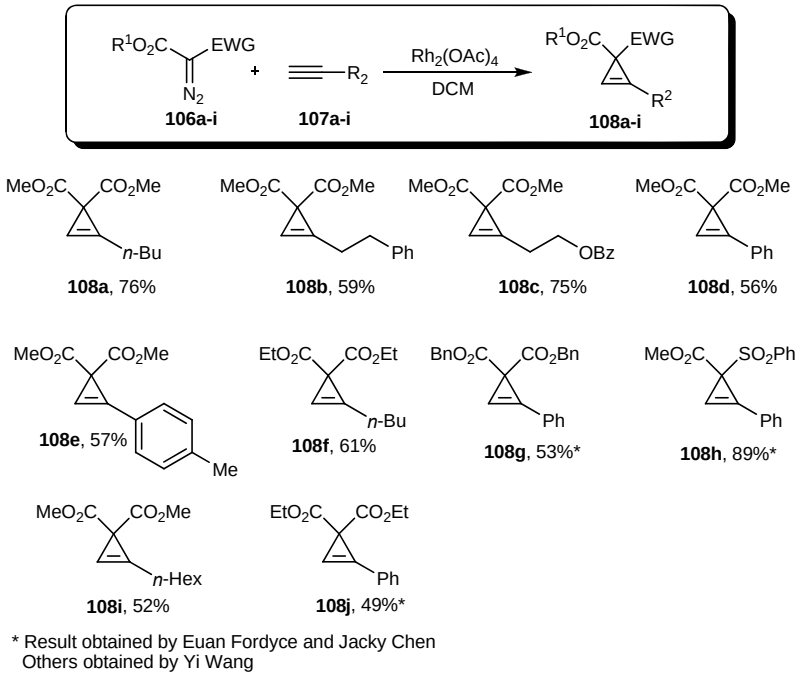
Despite the success of carbometallation of alkynes shown above, the development of new carbometallation procedures that tolerate an increased range of substrates and organometallic reagents to enable access to a correspondingly broader array of alkenes remains an important goal.

1.6) Results and Discussion[57]

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 sulfonyl 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

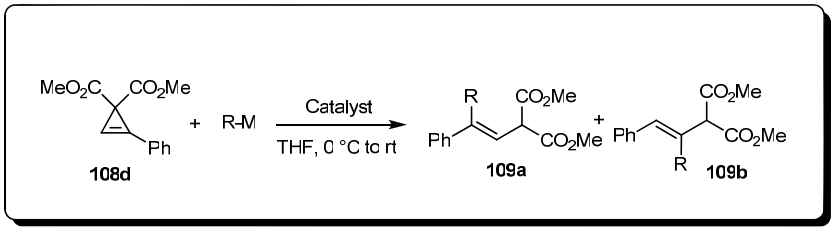


Scheme 1.46 Synthesis of trisubstituted cyclopropenes

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, unseparatable mixtures of isomers were usually obtained.

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



entry	R-M	catalyst	yield	Product
1	Et_2Zn	Blank	33[a]	mixture of **109a** and **109b**
2	Et_2Zn	$Zn(OTf)_2$	33[a]	mixture of **109a** and **109b**
3	Et_2Zn	$Cu(acac)_2$	55[b]	**109a**
4	Et_2Zn	$Ni(acac)_2$	22[b]	**109a**
5	Et_2Zn	$Co(acac)_2$	55[a]	mixture of **109a** and **109b**
6	Et_2Zn	$Fe(acac)_2$	47[a]	mixture of **109a** and **109b**
7	Et_3Al	$Cu(acac)_2$	24[b]	**109a**
8	EtMgBr	$Cu(acac)_2$	24[b]	**109a**
9	Et_3Al	$Fe(acac)_3$	30[b] (82[b,c])	**109a**
10	Et_3Al	Blank	0	-

a Crude yield, unidentified *E/Z* isomers
b Isolated yield, only *E* isomer
c Using Rochelle's salt solution for aqueous workup

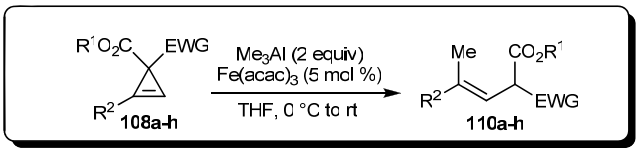
Therefore, our focus switched from zinc to other organometallic reagents, such as Grignard and aluminium reagents. In the presence of $Cu(acac)_2$, Me_3Al and the Grignard reagent (entry 7 and 8, results obtained by Dr Euan Fordyce) gave the same low yield.

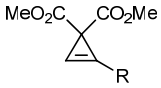
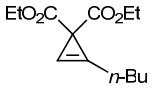
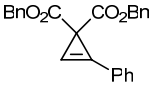
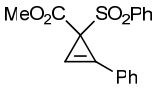
After a quick survey into other first-row d-block metal salts, I discovered that $Fe(acac)_3$ (5 mol%) is able to promote the desired carbometallation-ring opening sequence using trialkylaluminium reagents. The initial isolated yield was as low as 30%. After introducing Rochelle's salt solution in the 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_3Al 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, cyclopropenes **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 ^1H NMR analysis of the unpurified reaction mixtures) (Table 1.2).

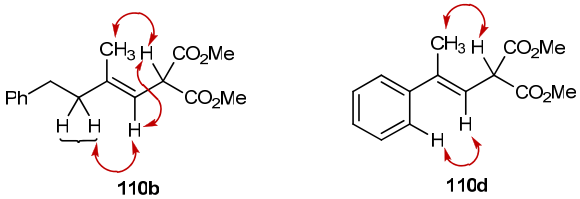
The sense of regioselection was obvious from their NMR spectra and consistent with the majority of carbometallations of 1-alkylcyclopropenes described previously,[1d] wherein the alkyl nucleophile is delivered to the more substituted carbon of the alkene.

Table 1.2 Iron-catalysed carbometallation-ring-opening of cyclopropenes with trimethylaluminium reagents



Entry	substrate		product		yield (%)
1		**108a** R = *n*-Bu		**110a**	96
2		**108b** R = CH_2CH_2Ph		**110b**	78
3		**108c** R = CH_2CH_2OBz		**110c**	78
4		**108d** R = Ph		**110d**	83
5		**108e** R = *p*-Tol		**110e**	79
6		**108f**		**110f**	92
7		**108g**		**110g**	66
8		**108h**		**110h**	61

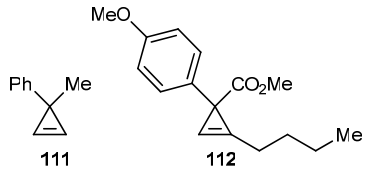
The stereochemistries of **110b** and **110d** were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:



Scheme 1.47 NOESY diagnostic enhancements

Notably, 1-arylcyclopropenes, which have proven to be problematic substrates with respect to regioselectivity using other carbometallation procedures,[1d,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.

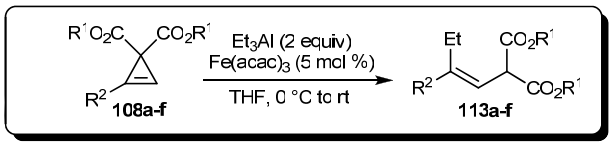
Cyclopropenes without two electron-withdrawing groups at C3, such as **111** and **112** (Scheme 1.48), were not competent substrates for carbometallation using trialkylaluminium reagents in conjunction with $Fe(acac)_3$ as the precatalyst, only starting materials were observed in the reaction mixtures.

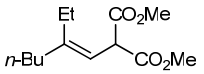
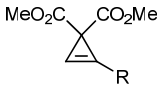
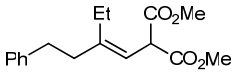
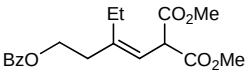
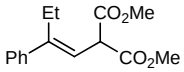
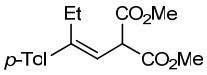
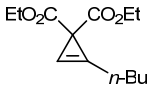
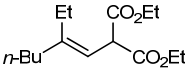


Scheme 1.48 Unreacted cyclopropenes

Regarding the organometallic reagent scope, trialkylaluminiums ranging from linear (Me_3Al, Et_3Al, *n*-Pr_3Al, and *n*-Hex_3Al) to branched (*i*-Bu_3Al) were effective. Using triethylaluminium (Table 1.3), trisubstituted malonate-derived cyclopropenes also smoothly ring-opened to generate trisubstituted alkenes **113a-f**.

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

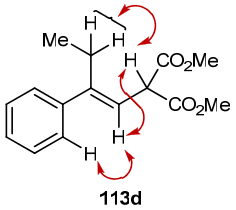


Entry	substrate		product		yield (%)
1		**108a** R = *n*-Bu		**113a**	91
2		**108b** R = CH_2CH_2Ph		**113b**	72
3		**108c** R = CH_2CH_2OBz		**113c**	70
4		**108d** R = Ph		**113d**	82[a]
5		**108e** R = *p*-Tol		**113e**	71
6		**108f**		**113f**	77

a Yield 67% using 0.5 equivalents of Et_3Al.

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 Et_3Al, demonstrating that transfer of more than one alkyl group from aluminium is possible (entry 4).

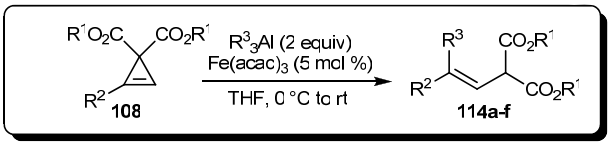
The regioselectivities of those reactions using more bulky trialkylaluminium reagents such as *n*-Pr_3Al, *i*-Bu_3Al and *n*-Hex_3Al were also uniformly high (>19:1) (Table 1.4). The stereochemistry of **113d** was assigned by NOESY experiment, the stereochemistries of the remaining trisubstituted alkenes in Table 1.3 and 1.4 were assigned by analogy.

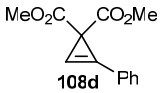
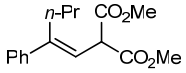
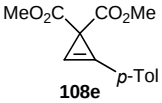
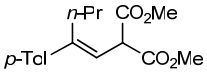
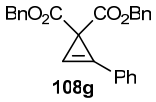
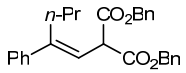
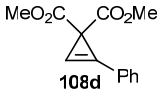
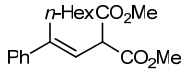
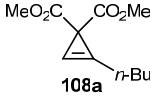
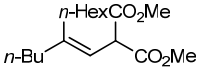
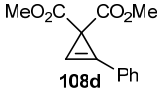
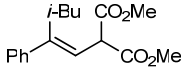


Scheme 1.49 NOESY diagnostic enhancements

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

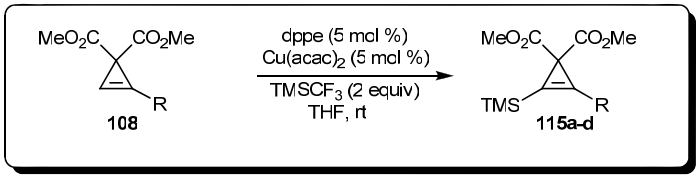


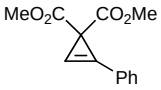
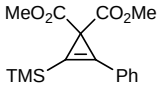
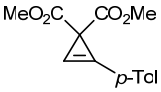
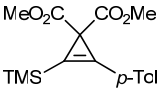
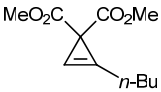
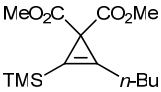
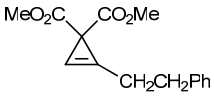
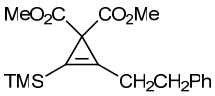
Entry	substrate	R^3_3Al	product		yield (%)
1		$(n\text{-Pr})_3Al$		**114a**	90
2		$(n\text{-Pr})_3Al$		**114b**	72
3		$(n\text{-Pr})_3Al$		**114c**	63
4		$(n\text{-Hex})_3Al$		**114d**	66
5		$(n\text{-Hex})_3Al$		**114e**	55
6		$(i\text{-Bu})_3Al$		**114f**	62

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.

Table 1.5 Direct Silylation of Assorted Cyclopropenes

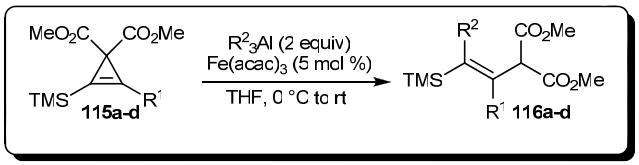


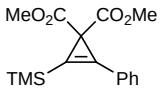
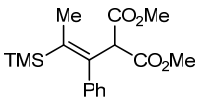
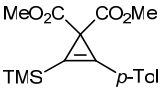
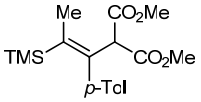
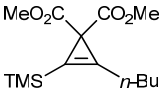
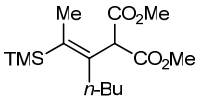
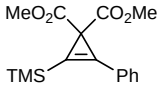
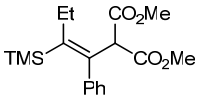
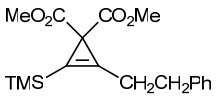
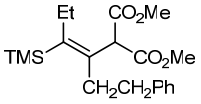
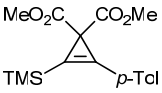
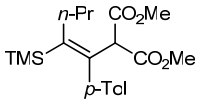
entry	substrate		product		yield (%)
1		**108d**		**115a**	88
2		**108e**		**115b**	90
3		**108a**		**115c**	99
4		**108b**		**115d**	75

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 α,β,β'-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

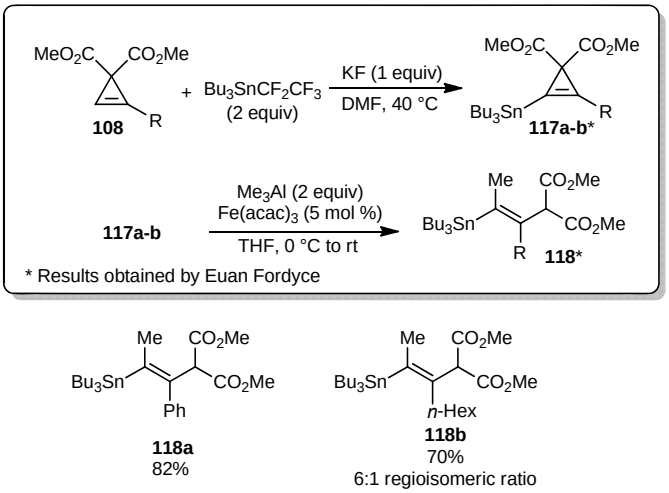


Entry	substrate		$R^2{}_3Al$	product		yield (%)
1		**115a**	Me_3Al		**116a**	89
2		**115b**	Me_3Al		**116b**	71
3		**115c**	Me_3Al		**116c**	68[a]
4		**115a**	Et_3Al		**116d**	73
5		**115d**	Et_3Al		**116e**	72[b]
6		**115b**	$(n\text{-}Pr)_3Al$		**116f**	88

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

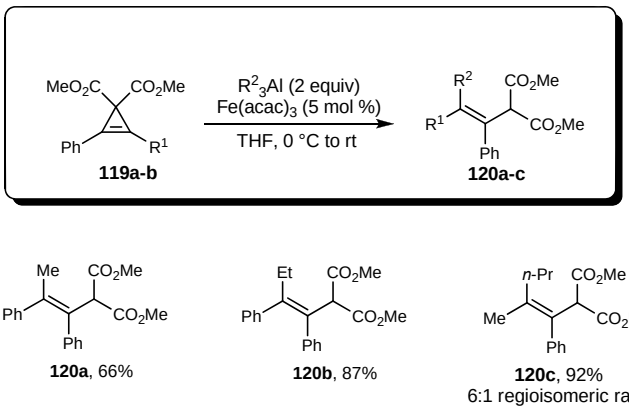
By replacing $TMSCF_3$ with $Bu_3SnCF_2CF_3$, we were able to access the corresponding stannylated cyclopropenes using stoichiometric KF in DMF at 40 °C.[59] In similar

fashion, the use of 1-stannylcyclopropenes **117** enabled the synthesis of α,β,β'-trisubstituted vinylstannanes **118** (Scheme 1.50).



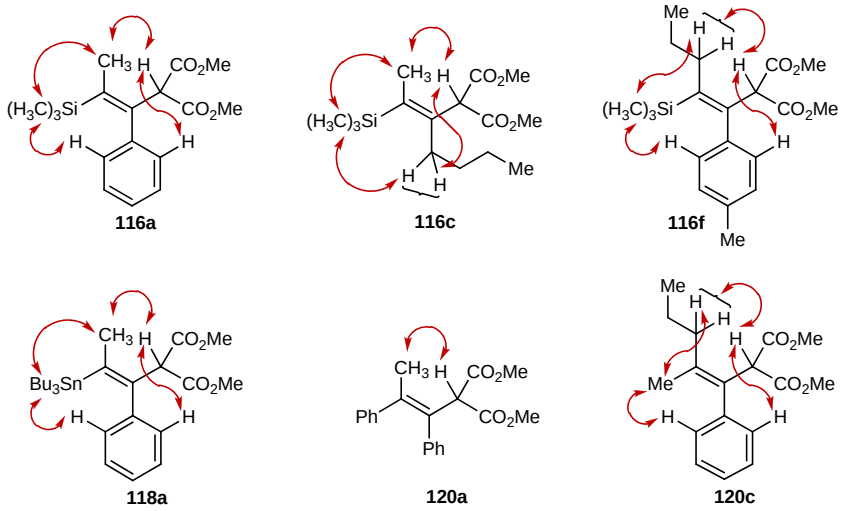
Scheme 1.50 Ring-opening of stannylated cyclopropenes

Finally, this methodology was applied to preparation of all-carbon tetrasubstituted alkenes (Scheme 1.51). Cyclopropenes **119a-c** underwent efficient carbometallation-ring-opening to provide tetrasubstituted alkenes **120a-c**. With unsymmetrical substrate **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

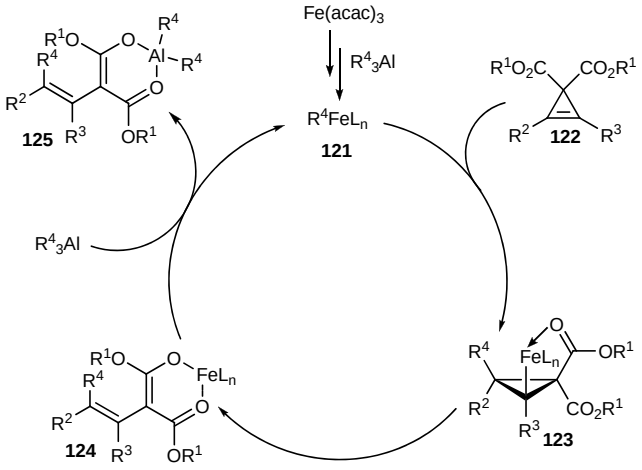
The regio- and/or stereoselectivities of carbometallation-ring-opening of tetrasubstituted cyclopropenes producing tetrasubstituted alkenes were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:



Scheme 1.52 NOESY diagnostic enhancements

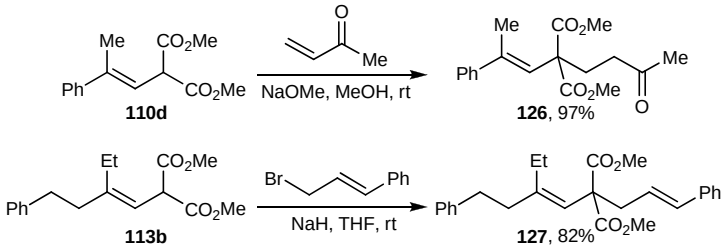
The stereochemistries of the remaining tetrasubstituted alkenes were assigned by analogy.

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 R^2 and R^3 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.



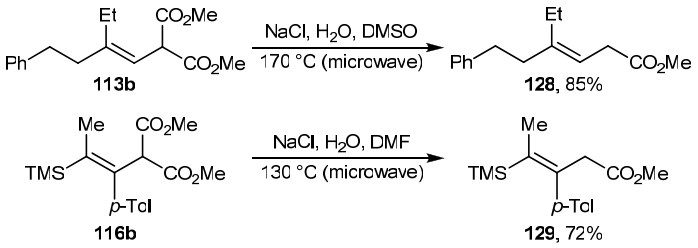
Scheme 1.53 Possible catalytic cycle

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).



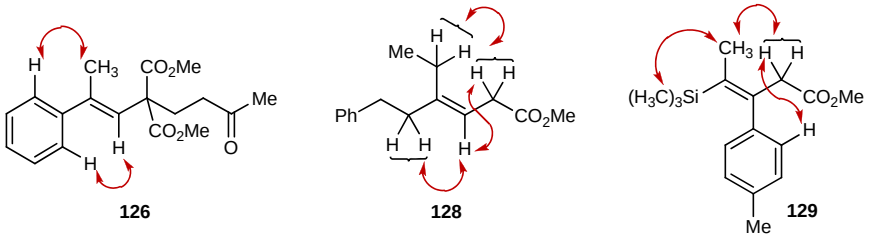
Scheme 1.54 Michael addition or alkylation of the ring-opened products

Furthermore, Krapcho decarboxylation of both tri- and tetrasubstituted alkenes proceeded smoothly under microwave irradiation to provide *β,γ*-unsaturated esters **128** and **129** in good yields (Scheme 1.55).



Scheme 1.55 Krapcho decarboxylation

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:

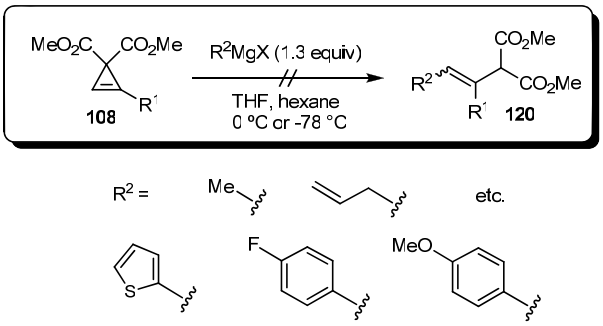


Scheme 1.56 NOESY diagnostic enhancements

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 *α,β,β′*-trisubstituted vinylsilanes, *α,β,β′*-trisubstituted vinyl-stannanes, 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 allymagnesium 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.

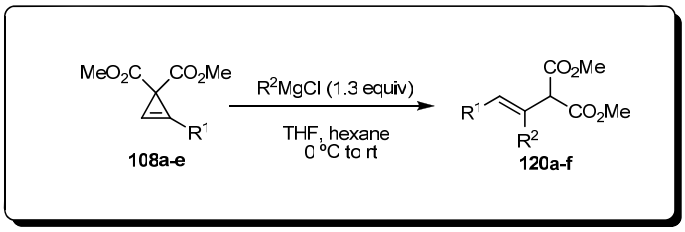


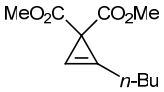
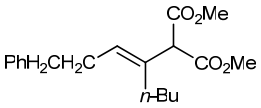
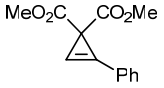
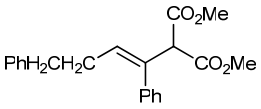
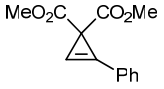
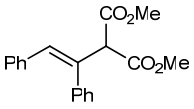
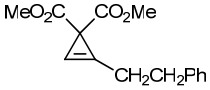
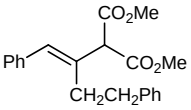
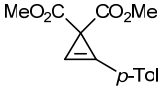
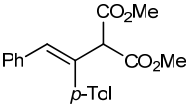
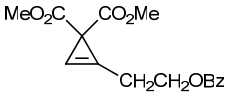
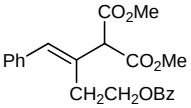
Scheme 1.57 Attempted Grignard reagents promoted ring-opening reactions

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



entry	substrate		R^2MgCl	product		yield (%)
1		**108a**	$PhCH_2CH_2MgCl$		**120a**	63
2		**108d**	$PhCH_2CH_2MgCl$		**120b**	73
3		**108d**	PhMgCl		**120c**	51
4		**108b**	PhMgCl		**120d**	66
5		**108e**	PhMgCl		**120e**	52
6		**108c**	PhMgCl		**120f**	41

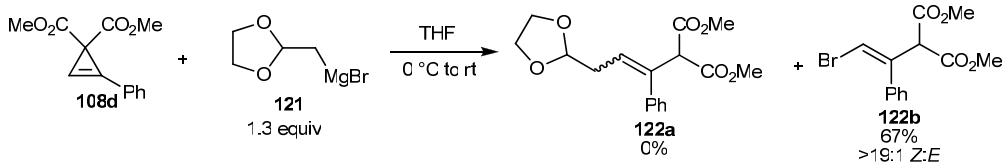
The regioselectivity of Grignard reagent induced ring-opening of trisubstituted cyclopropenes producing trisubstituted alkenes was obvious from their NMR spectra. The stereochemistries of the alkene products **120b** and **120d** were assigned on the

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.

Scheme 1.58 NOESY diagnostic enhancements

1.6.4) Synthesis of Trisubstituted Alkenes using Magnesium Halide Salts

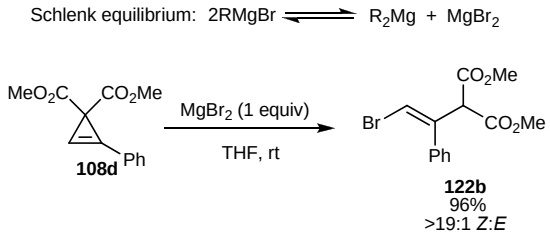
During previous investigations (Scheme 1.57) into the development of stereoselective carbometallation-ring-opening reactions of bis-activated cyclopropenes and Gringard reagents to produce multisubstituted alkenes, commercially available dioxolane derived Grignard **121** was reacted with cyclopropene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



Scheme 1.59 Reaction of dioxolane derived Grignard with cyclopropenes

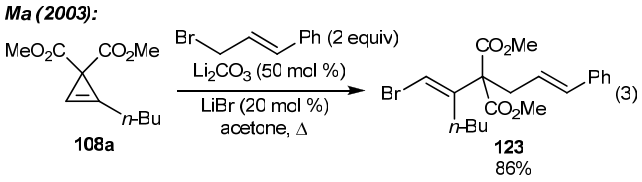
Surprisingly, instead of furnishing product **122a** derived from addition of the nucleophilic dioxolane functionality of **121**, the major product isolated in this reaction was the alkenyl bromide **122b**. We attributed this initially surprising result to reaction of cyclopropene **108d** with magnesium bromide produced from the Schlenk equilibrium of the Grignard reagent. This hypothesis was supported by

reaction of **108d** with $MgBr_2$ itself, which also produced **122b** in 96% yield (Scheme 1.60).



Scheme 1.60 $MgBr_2$ promoted ring-opening of cyclopropenes

This process was closely related to the results of Ma and co-workers, who described a series of alkali metal halide-induced cyclopropene ring-opening-alkylation reactions.[61] In their work, the majority of examples were conducted using a bis-activated cyclopropene that was unsubstituted at the alkene, but four results using trisubstituted cyclopropenes were reported (representative example shown in Scheme 1.61).

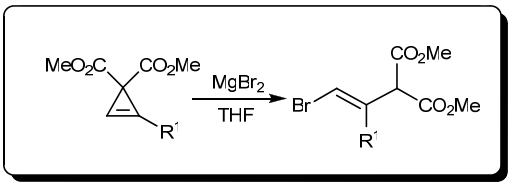


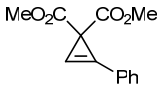
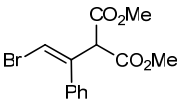
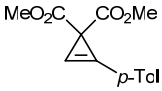
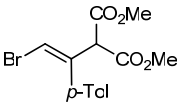
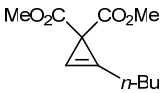
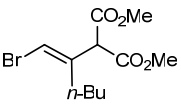
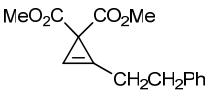
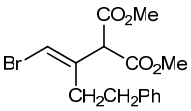
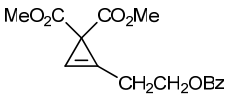
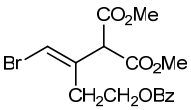
Scheme 1.61 Ring-opening-alkylation reactions

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 $MgBr_2$, 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).

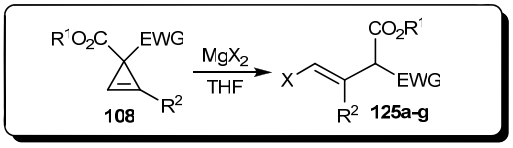
Table 1.8 $MgBr_2$ Mediated Ring-Openings of Various Cyclopropenes

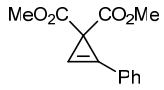
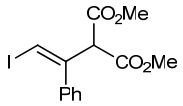
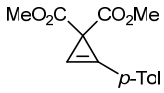
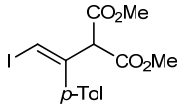
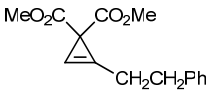
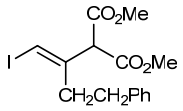
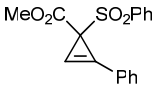
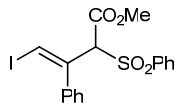
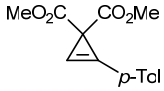
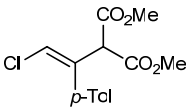
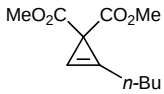
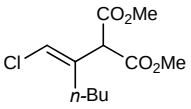
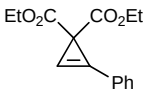
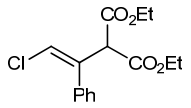


Entry	Substrate		product		yield (%)
1		**108d**		**124a**	96
2		**108e**		**124b**	72
3		**108a**		**124c**	75
4		**108b**		**124d**	87
5		**108c**		**124e**	84

Halide addition-ring-openings with MgI_2 and $MgCl_2$ 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 $MgCl_2$ (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 MgF_2 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

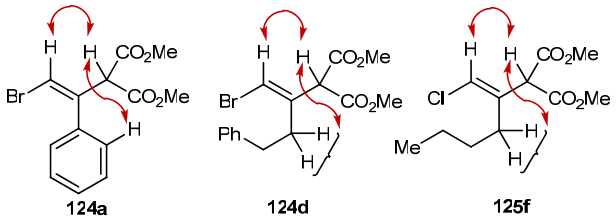


Entry	substrate		MgX_2	product		yield (%)
1		**108d**	MgI_2		**125a**	97[a]
2		**108e**	MgI_2		**125b**	94
3		**108b**	MgI_2		**125c**	99
4		**108h**	MgI_2		**125d**	77
5		**108e**	$MgCl_2$		**125e**	83[b]
6		**108a**	$MgCl_2$		**125f**	85[b]
7		**108j**	$MgCl_2$		**125g**	62[b]

a Product isolated as an inseparable 9:1 *Z*:*E* mixture.

b Reaction conducted at 40 °C

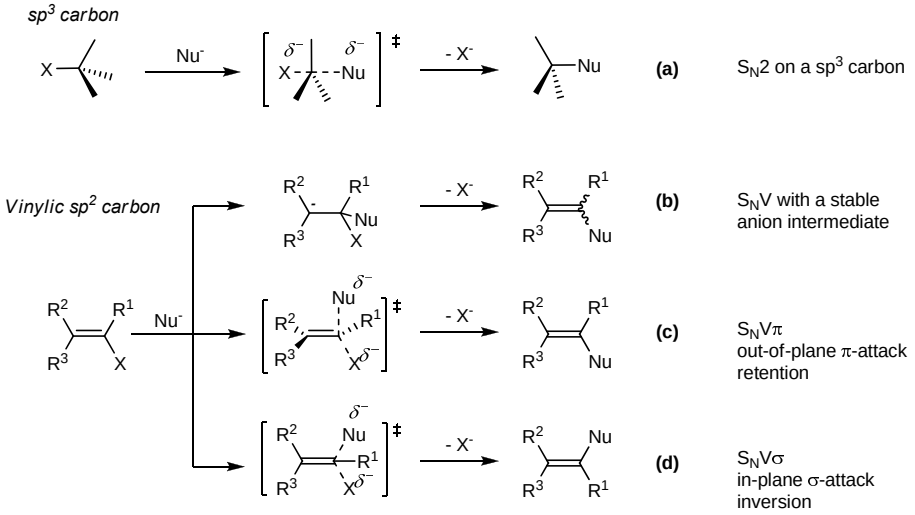
The stereoselectivities of magnesium halide-promoted ring-opening reactions producing alkenyl halides **124a**, **124d** and **125f** were assigned on the basis of NOESY experiments, which displayed the following diagnostic enhancements:



Scheme 1.62 NOESY diagnostic enhancements

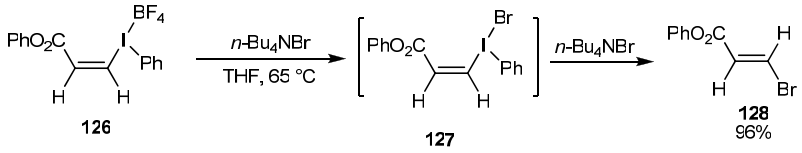
The stereochemical outcome of these reactions, where inversion of configuration at the electrophilic vinylic center is observed, suggests that this is not a common addition-elimination process that was proposed in previously described cyclopropene carbometallation-ring-opening reactions.[1b]

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 π-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 π^* 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 σ^* orbital of C-X bond of a vinylic carbon (Scheme 1.63d).



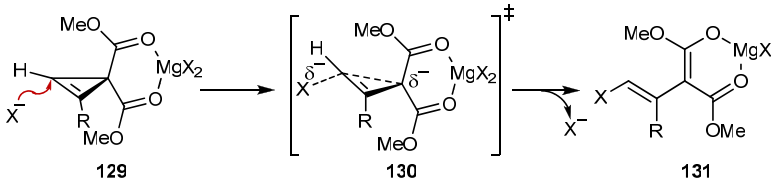
Scheme 1.63 Different types of S_N2 reactions

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 $S_NV\sigma$ pathway.[62] However, recent theoretical and experimental studies suggest that this process is favourable in certain reactions.[63, 64] For instance, the (*Z*)-vinyl-λ^3-iodane **126** undergoes a unusual vinylic S_N2 reaction with *n*-Bu_4NBr to give the (*E*)-vinyl halide **128** with exclusive inversion of configuration. The reaction competes with ligand coupling on iodine(III) (Scheme 1.64).[64c]



Scheme 1.64 An example of $S_NV\sigma$ reaction

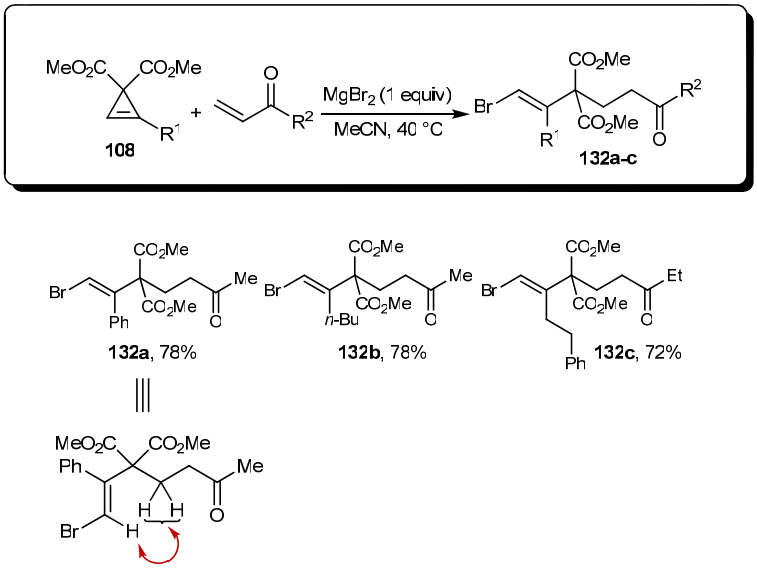
Regarding to our magnesium halide-promoted cyclopropene ring-opening reaction, the inversion of configuration at the electrophilic vinylic center suggested that an in-plane S_N2-type mechanism ($S_NV\sigma$) is operative. A possible mechanism using a dimethyl malonate-derived substrate for illustrative 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 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 β-unsubstituted enones using acetonitrile as the solvent were possible (Scheme 1.66).



Scheme 1.66 One-pot cyclopropene ring-opening-Michael reactions

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 $S_NV\sigma$ 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

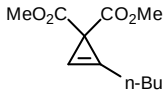
General Information

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. CH_2Cl_2, THF and MeCN were dried and purified by passage through activated alumina columns using a solvent purification system from www.glasscontoursolventsystems.com. 'Petrol' refers to the fraction of light petroleum ether boiling in the range 40-60 °C. Crotonoyl chloride was distilled from CaH_2. Commercially available $CoCl_2$ 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 $60F_{254}$ 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 plates or as a dilute solution in $CHCl_3$. ^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 ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker 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 ($CDCl_3$ 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.

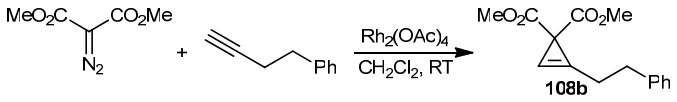
[a] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

Preparation of Cyclopropenes

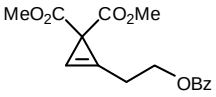


Dimethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (108a).[b] Prepared according to a previously reported procedure.[b]

Dimethyl 2-(2-phenylethyl)cycloprop-2-ene-1,1-dicarboxylate (108b).[c]



To a stirred solution of $Rh_2(OAc)_4$ (22 mg, 0.05 mmol) and 4-phenyl-1-butyne (1.30 g, 10.0 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.09 g, 6.89 mmol) in CH_2Cl_2 (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 CH_2Cl_2, 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 ($CHCl_3$) 3141, 3029, 2951, 2843, 1731(C=O), 1603, 1496, 1454, 1435, 1281 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.36-7.34 (2H, m, Ar**H**), 7.32-7.26 (3H, m, Ar**H**), 6.43 (1H, s, =C**H**), 3.75 (6H, s, 2 x OC**H**$_3$), 3.01-2.98 (2H, m, C**H**$_2$), 2.95-2.93 (2H, m, C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 32.5 (CH_2), 25.5 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{17}O_4$ $[M+H]^+$: 261.1121, found: 261.1122.

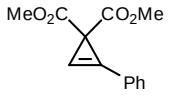


Dimethyl 2-(2-benzoyloxyethyl)cycloprop-2-ene-1,1-dicarboxylate (108c).[d] Prepared according to a previously reported procedure.[d]

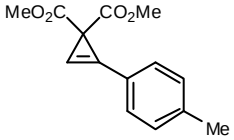
[b] Rubina, M.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2003**, *125*, 7198-7199.

[c] Ma, S.; Zhang, J.; Lu, L.; Jin, X.; Cai, Y.; Hou, H. *Chem. Commun.* **2005**, 909-911.

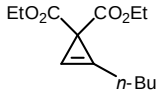
[d] Fordyce, E. A. F.; Wang, Y.; Luebbers, T.; Lam, H. W. *Chem. Commun.* **2008**, 1124−1126.



Dimethyl 2-phenylcycloprop-2-ene-1,1-dicarboxylate (108d).[e] Prepared according to a previously reported procedure.[e]

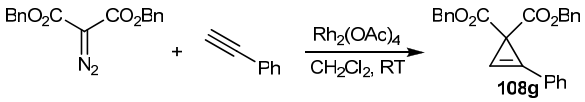


Dimethyl 2-(4-methylphenyl)cycloprop-2-ene-1,1-dicarboxylate (108e).[f] Prepared according to a previously reported procedure.[f]



Diethyl 2-butylcycloprop-2-ene-1,1-dicarboxylate (108f).[g] Prepared according to a previously reported procedure.[g]

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



To a stirred mixture of $Rh_2(OAc)_4$ (22 mg, 0.05 mmol) and phenylacetylene (1.53 g, 15.0 mmol) at room temperature was added a solution of dibenzyl diazomalonate[h] (1.55 g, 5.00 mmol) in CH_2Cl_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_2Cl_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 ($CHCl_3$) 3033, 1735 (C=O), 1497, 1456, 1376, 1271, 1055, 747, 695, 481 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.64-7.61 (2H, m, Ar**H**), 7.44-7.42 (3H, m, Ar**H**), 7.32-7.28 (10H, m, Ar**H**), 6.93 (1H, s, =C**H**), 5.20 (4H, s, 2 x OC**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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

[e] Liao, L.-a.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetrahedron* **2004**, *60*, 1803-1816.

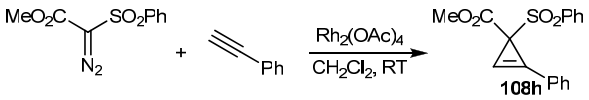
[f] Chuprakov, S.; Rubin, M.; Gevorgyan, V. *J. Am. Chem. Soc.* **2005**, *127*, 3714-3715.

[g] Müller, P.; Gränicher, C. *Helv. Chim. Acta* **1993**, *76*, 521-534.

[h] Wyatt, P.; Hudson, A.; Charmant, J.; Orpen, A. G.; Phetmung, H. *Org. Biomol. Chem.* **2006**, *4*, 2218-2232.

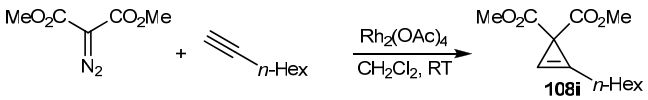
CH), 128.0 (2 x CH), 127.8 (4 x CH), 123.9 (C), 112.4 (C), 95.1 (CH), 66.8 (2 x CH_2), 33.3 (C); HRMS (ES) Exact mass calcd for $C_{25}H_{21}O_4$ $[M+H]^+$: 385.1434, found: 385.1430.

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



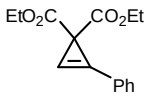
To a stirred mixture of $Rh_2(OAc)_4$ (22 mg, 0.05 mmol) and phenylacetylene (1.53 g, 15.0 mmol) at room temperature was added a solution of methyl 2-diazo-2-(phenylsulfonyl)acetate[i] (1.20 g, 5.00 mmol) in CH_2Cl_2 (10 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 16 h, filtered through a short pad of celite eluting with CH_2Cl_2, 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 ($CHCl_3$) 3137, 1733 (C=O), 1489, 1447, 1305, 1257, 1149, 1087, 1017, 918 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.00-7.98 (2H, m, Ar**H**), 7.64-7.44 (8H, m, Ar**H**), 7.01 (1H, s, =C**H**), 3.67 (3H, s, OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_3), 52.2 (C); HRMS (ES) Exact mass calcd for $C_{17}H_{18}NO_4S$ $[M+NH_4]^+$: 332.0951, found: 332.0951.

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

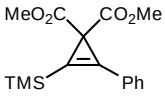


[i] Aitken, R. A.; Armstrong, J. M.; Drysdale, M. J.; Ross, F. C.; Ryan, B. M. *J. Chem. Soc.*, *Perkin Trans 1* **1999**, 593-604.

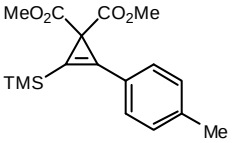
To a stirred solution of $Rh_2(OAc)_4$ (44 mg, 0.10 mmol) and 1-octyne (2.20 g, 20.0 mmol) in CH_2Cl_2 (2 mL) at room temperature was added a solution of dimethyl diazomalonate (1.58 g, 10.0 mmol) in CH_2Cl_2 (8 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 8 h, filtered through a short pad of celite eluting with CH_2Cl_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}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.34 (1H, s, =C**H**), 3.69 (6H, s, 2 x OC**H**$_3$), 2.52 (2H, t, *J* = 7.1 Hz, =CC**H**$_2$), 1.60-1.54 (2H, m, C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$CH$_3$), 1.36-1.24 (6H, m, C**H**$_2$C**H**$_2$C**H**$_2$C**H**$_2$CH$_3$), 0.86 (3H, t, *J* = 6.8 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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 calcd for $C_{13}H_{21}O_4$ $[M+H]^+$: 241.1434, found: 241.1432.



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

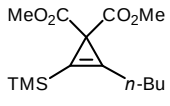


Dimethyl 2-phenyl-3-trimethylsilylcycloprop-2-ene-1,1-dicarboxylate (115a).[d] Prepared according to a previously reported procedure.[d]



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

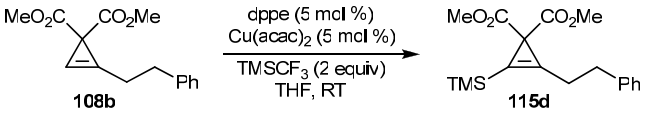
[j] Davies, H. M. L.; Romines, K. R. *Tetrahedron* **1998**, *44*, 3343-3348.



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

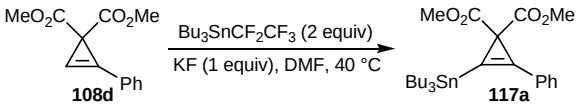
Prepared according to a previously reported procedure.[d]

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



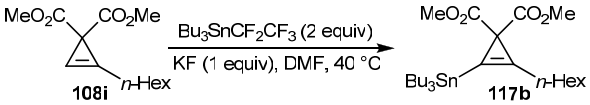
A solution of cyclopropene **108b** (104 mg, 0.40 mmol), $Cu(acac)_2$ (5.3 mg, 0.02 mmol) and dppe (8.0 mg, 0.02 mmol) in THF (2 mL) was stirred at room temperature for 30 min. $TMSCF_3$ (118 μL, 0.80 mmol) was then added in one portion and the reaction was stirred at room temperature for 48 h. The reaction 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 *in vacuo*. Purification of the residue by column chromatography (hexane→15% EtOAc/hexane) gave the *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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.28 (2H, m, Ar**H**), 7.24-7.20 (3H, m, Ar**H**), 3.68 (6H, s, 2 x $OC\mathbf{H}_3$), 2.99-2.94 (2H, m, $C\mathbf{H}_2C\mathbf{H}_2Ph$), 2.92-2.89 ($C\mathbf{H}_2C\mathbf{H}_2Ph$), 0.18 (9H, s, $Si(C\mathbf{H}_3)_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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 $C_{18}H_{24}O_4Si$ $[M]^+$: 332.1438, found: 332.1438.

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



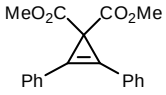
A solution of cyclopropene **108d** (46 mg, 0.20 mmol), KF (11.6 mg, 0.20 mmol), and $Bu_3SnCF_2CF_3$ (164 mg, 0.40 mmol) in DMF (0.8 mL) was stirred at 40 °C for 20 h. The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) 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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.58-7.54 (2H, m Ar**H**), 7.45-7.34 (3H, m, Ar**H**), 3.69 (6H, s, 2 x OC**H**$_3$), 1.70-1.55 (6H, m, Sn($CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3$)$_3$), 1.43-1.31 (6H, m, Sn($CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3$)$_3$), 1.24-1.18 (6H, m, Sn($C\mathbf{H}_2CH_2CH_2CH_3$)$_3$), 0.93 (9H, t, J = 7.3 Hz, Sn($CH_2CH_2CH_2C\mathbf{H}_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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)



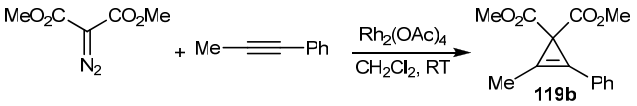
A solution of cyclopropene **108i** (192 mg, 0.80 mmol), KF (47 mg, 0.80 mmol), and Bu_3SnCF_3 (575 mg, 1.60 mmol) in DMF (3.2 mL) was stirred at 40 °C for 17 h. The reaction mixture was filtered through a short plug of SiO_2 (*ca.* 4 cm high x 2 cm diameter) using EtOAc as eluent (*ca.* 50 mL) and the filtrate was concentrated *in vacuo*. Purification of the residue by column chromatography (hexane→10% EtOAc/hexane) gave the *stannylcyclopropene* **117b** (222 mg, 52%) as a colourless oil. IR (film) 2956, 2930, 2855, 1723 (C=O), 1462, 1434, 1281, 1069, 911, 734 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 3.66 (6H, s, 2 x OC**H**$_3$), 2.54 (2H, t, J = 7.3 Hz, =CC**H**$_2$), 1.60-1.50 (8H, m, Sn($CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3$)$_3$ and =$CCH_2C\mathbf{H}_2$), 1.36-1.26 (12H,

m, $Sn(CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3)_3$ and $CH_2(C\mathbf{H}_2)_3CH_3$), 1.09-1.05 (6H, m, $Sn(C\mathbf{H}_2CH_2CH_2CH_3)_3$), 0.92 (9H, t, J = 7.3 Hz, $Sn(CH_2CH_2CH_2C\mathbf{H}_3)_3$), 0.89 (3H, t, J = 7.1 Hz, $(CH_2)_5C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 173.2 (2 x C), 125.4 (C), 103.4 (C), 51.6 (2 x CH_3), 33.4 (C), 31.5 (CH_2), 28.8 (CH_2), 28.8 (J_{Sn-C} = 11.0 Hz, 3 x CH_2), 27.0 (J_{Sn-C} = 29.4 Hz, 3 x CH_2), 26.6 (CH_2), 25.3 (CH_2), 22.5 (CH_2), 14.0 (CH_3), 13.6 (3 x CH_3), 10.8 (J_{Sn-C} not observable, 3 x CH_2).



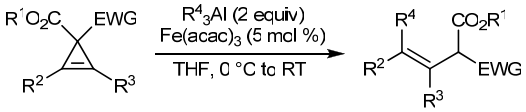
Dimethyl 2,3-diphenylcycloprop-2-ene-1,1-dicarboxylate (119a).[f] Prepared according to a previously reported procedure.[f]

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

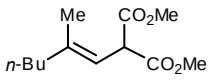


To a stirred mixture of $Rh_2(OAc)_4$ (11 mg, 0.025 mmol) and 1-phenyl-1-propyne (1.12 g, 10.0 mmol) at room temperature was added a solution of dimethyl diazomalonate (800 mg, 5.00 mmol) in CH_2Cl_2 (8 mL) *via* syringe pump (0.793 mL/h). After the addition was complete, the mixture was stirred for 10 h, filtered through a short pad of celite eluting with CH_2Cl_2, 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 ($CHCl_3$) 2952, 1730 (C=O), 1514, 1492, 1435, 1284, 1243, 1064, 840, 764 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.55-7.51 (2H, m, Ar**H**), 7.44-7.33 (3H, m, Ar**H**), 3.71 (6H, s, 2 x $OC\mathbf{H}_3$), 2.36 (3H, s, $=CC\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 34.9 (C), 9.4 (CH_3); HRMS (EI) Exact mass calcd for $C_{14}H_{14}O_4$ $[M]^+$: 246.0887, found: 246.0884.

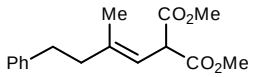
Iron-Catalysed Carbometallation−Ring-Opening Reactions: General Procedure



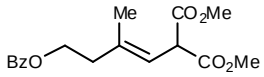
To a solution of the appropriate cyclopropene (0.20 mmol) and $Fe(acac)_3$ (3.6 mg, 0.01 mmol) in THF (2 mL) at 0 °C was added the appropriate trialkylaluminium reagent (2 equiv, one of Me_3Al (2.0 M in hexanes), Et_3Al (1.0 M in hexanes), *n*-Pr_3Al (0.7 M in heptane), *n*-Hex_3Al (0.4 M in hexane), or *i*-Bu_3Al (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_2Cl_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_2Cl_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.



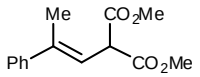
(*E*)-Dimethyl 2-(2-methylhex-1-enyl)malonate (110a). The title compound was prepared according to the General Procedure from cyclopropene **108a** (42 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (44 mg, 96%). IR (film) 2955, 2931, 1738 (C=O), 1617, 1435, 1297, 1260, 1214, 1148, 1086 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.46 (1H, m, *J* = 9.4 Hz, =C**H**), 4.28 (1H, d, *J* = 9.4 Hz, =CHC**H**), 3.74 (6H, s, 2 x OC$\mathbf{H}_3$), 2.08-2.04 (2H, m, C$\mathbf{H}_2$C=), 1.68 (3H, d, *J* = 1.4 Hz, C$\mathbf{H}_3$C=), 1.43-1.37 (2H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.32-1.26 (2H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 0.90 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.



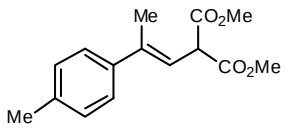
(*E*)-Dimethyl 2-(2-methyl-4-phenylbut-1-enyl)malonate (110b). The title compound was prepared according to the General Procedure from cyclopropene **108b** (52 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (43 mg, 78%). IR (film) 3027, 2952, 1737 (C=O), 1617 1496, 1454, 1435, 1303, 1213, 1147 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.26 (2H, m, Ar**H**), 7.20-7.16 (3H, m, Ar**H**), 5.49 (1H, d, *J* = 9.5 Hz, =C**H**), 4.29 (1H, d, *J* = 9.5 Hz, =CHC**H**), 3.74 (6H, s, 2 x OC**H**$_3$), 2.79-2.74 (2H, m, PhC**H**$_2$), 2.41-2.36 (2H, m, C**H**$_2$C=), 1.75 (3H, d, *J* = 1.3 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.2 (CH), 41.2 (CH_2), 34.1 (CH_2), 16.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{16}H_{24}NO_4$ $[M+NH_4]^+$: 294.1700, found: 294.1698.



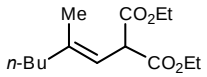
(*E*)-Dimethyl 2-[2-(benzoyloxy)prop-1-enyl]malonate (110c). The title compound was prepared according to General Procedure from cyclopropene **108c** (61 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (50 mg, 78%). IR (film) 2954, 1738 (C=O), 1720, 1452, 1435, 1275, 1214, 1150, 1114, 1070 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 8.04-8.01 (2H, m, Ar**H**), 7.58-7.53 (1H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 5.64 (1H, d, *J* = 9.5 Hz, =C**H**), 4.43 (2H, t, *J* = 6.5 Hz, OC**H**$_2$), 4.31 (2H, d, *J* = 9.5 Hz, =CHC**H**), 3.67 (6H, s, 2 x OC**H**$_3$), 2.55 (2H, t, *J* = 6.5 Hz, C**H**$_2$C=), 1.80 (3H, d, *J* = 1.4 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_2), 52.5 (2 x CH_3), 51.2 (CH), 38.6 (CH_2), 16.6 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{24}NO_6$ $[M+NH_4]^+$: 338.1598, found: 338.1599.



(*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 Me_3Al 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, $CDCl_3$) δ 7.49-7.46 (2H, m, Ar**H**), 7.40-7.30 (3H, m, Ar**H**), 6.10 (1H, d, *J* = 9.5 Hz, =C**H**), 4.52 (1H, d, *J* = 9.5 Hz, =CHC**H**), 3.82 (6H, s, 2 x OC**H**$_3$), 2.17 (3H, d, *J* = 1.1 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.8 (CH), 16.5 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{17}O_4$ $[M+H]^+$: 249.1121, found: 249.1119.

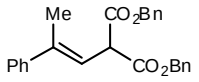


(*E*)-Dimethyl 2-[2-(4-methylphenyl)prop-1-enyl]malonate (110e). The title compound was prepared according to General Procedure from cyclopropene **108e** (49 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (41 mg, 79%). IR (film) 2952, 2868, 1736 (C=O), 1435, 1196, 1147, 1196, 815, 481, 473 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.15 (2H, d, *J* = 8.1 Hz, Ar**H**), 6.03 (1H, d, *J* = 9.5 Hz, =C**H**), 4.47 (1H, d, *J* = 9.5 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC**H**$_3$), 2.35 (3H, s, ArC**H**$_3$), 2.11 (3H, d, *J* = 1.3 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.9 (CH), 21.0 (CH_3), 16.4 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{19}O_4$ $[M+H]^+$: 263.1278, found: 263.1281.

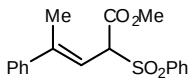


(*E*)-Diethyl 2-(2-ethylhex-1-enyl)malonate (110f). The title compound was prepared according to the General Procedure from cyclopropene **108f** (48 mg, 0.20 mmol) and Me_3Al and purified by column

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, $CDCl_3$) δ 5.47 (1H, dm, *J* = 9.4 Hz, =C**H**), 4.24 (1H, d, *J* = 9.4 Hz, =CHC**H**), 4.20 (4H, q, *J* = 7.1 Hz, 2 x OC**H**$_2$), 2.09-2.05 (2H, t, *J* = 7.1 Hz, C**H**$_2$C=), 1.68 (3H, d, *J* = 1.4 Hz, C**H**$_3$C=), 1.45-1.37 (2H, m, CH_3C**H**$_2$C**H**$_2$), 1.34-1.24 (2H, m, CH_3C**H**$_2$C**H**$_2$), 1.27 (6H, t, *J* = 7.1 Hz, 2 x OCH_2C**H**$_3$), 0.90 (3H, t, *J* = 7.1 Hz, C**H**$_3$$CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.7 (2 x C), 141.9 (C), 115.8 (CH), 61.4 (2 x CH_2), 51.6 (CH), 39.2 (CH_2), 29.7 (CH_2), 22.1 (CH_2), 16.6 (CH_3), 14.0 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{25}O_4$ $[M+H]^+$: 257.1747, found: 257.1750.

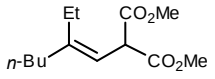


(*E*)-Dibenzyl 2-(2-phenylprop-1-enyl)malonate (110g). The title compound was prepared according to the General Procedure from cyclopropene **108g** (77 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (53 mg, 66%). IR (film) 3033, 1735 (C=O), 1496, 1456, 1375, 1268, 1146, 1003, 749, 696 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43-7.40 (2H, m, Ar**H**), 7.37-7.30 (13H, m, Ar**H**), 6.12 (1H, dq, *J* = 9.4, 1.4 Hz, =C**H**), 5.21 (4H, s, 2 x OC**H**$_2$), 4.57 (1H, d, *J* = 9.4 Hz, =CHC**H**), 2.12 (3H, d, *J* = 1.4 Hz, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_2), 52.1 (CH), 16.7 (CH_3); HRMS (EI) Exact mass calcd for $C_{26}H_{24}O_4$ $[M]^+$: 400.1669, found: 400.1667.

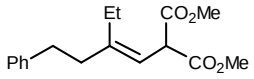


(*E*)-Benzyl 4-phenyl-2-(phenylsulfonyl)pent-3-enoate (110h). The title compound was prepared according to the General Procedure from cyclopropene **108h** (63 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (40 mg, 61%).

IR (film) 2953, 2612, 1742 (C=O), 1447, 1324, 1263, 1148, 1082, 999, 914 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 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, =C**H**), 5.01 (1H, d, *J* = 10.5 Hz, =CHC**H**), 3.81 (3H, s, OC$\mathbf{H}_3$), 1.91 (3H, d, *J* = 1.5 Hz, C$\mathbf{H}_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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 $C_{18}H_{22}NO_4S$ $[M+NH_4]^+$: 348.1264, found: 348.1267.

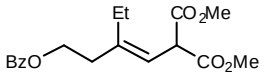


(*E*)-Dimethyl 2-(2-ethylhex-1-enyl)malonate (113a). The title compound was prepared according to the General Procedure from cyclopropene **108a** (42 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (44 mg, 91%). IR (film) 2956, 2873, 1739 (C=O), 1435, 1294, 1208, 1147, 1023, 844, 524 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.41 (1H, d, *J* = 9.7 Hz, =C**H**), 4.31 (1H, d, *J* = 9.7 Hz, =CHC**H**), 3.74 (6H, s, 2 x OC$\mathbf{H}_3$), 2.11-2.05 (4H, m, 2 x C$\mathbf{H}_2$C=), 1.45-1.25 (4H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 0.98 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3CH_2$), 0.90 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

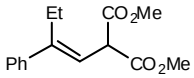


(*E*)-Dimethyl 2-(2-ethyl-4-phenylbut-1-enyl)malonate (113b). The title compound was prepared according to the General Procedure from cyclopropene **108b** (52 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (42 mg, 72%). IR (film) 2953, 1738 (C=O), 1617, 1497, 1455, 1435, 1297, 1209, 1146, 1022 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.30-7.26 (2H, m, Ar**H**),

7.21-7.17 (3H, m, Ar**H**), 5.47 (1H, d, *J* = 9.7 Hz, =C**H**), 4.33 (1H, d, *J* = 9.7 Hz, =CHC**H**), 3.74 (6H, s, 2 x OC**H**$_3$), 2.78-2.74 (2H, m, PhC**H**$_2$), 2.42-2.37 (2H, m, PhCH$_2$C**H**$_2$), 2.14 (2H, q, *J* = 7.6 Hz, CH$_3$C**H**$_2$), 1.02 (3H, t, *J* = 7.6 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 50.8 (CH), 38.0 (CH_2), 34.3 (CH_2), 23.9 (CH_2), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{26}NO_4$ $[M+NH_4]^+$: 308.1856, found: 308.1856.



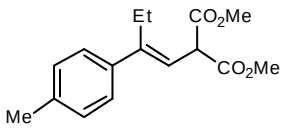
(*E*)-Dimethyl 2-[4-(benzoyloxy)-2-ethylbut-1-enyl]malonate (113c). The title compound was prepared according to the General Procedure from cyclopropene **108c** (61 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (47 mg, 70%). IR (film) 2954, 1717 (C=O), 1648, 1434, 1275, 1111, 1025, 809, 712, 484 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.05-8.02 (2H, m, Ar**H**), 7.58-7.53 (1H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 5.60 (1H, d, *J* = 9.8 Hz, =C**H**), 4.43 (2H, t, *J* = 6.7 Hz, OC**H**$_2$), 4.39 (1H, d, *J* = 9.8 Hz, =CHC**H**), 3.69 (6H, s, 2 x OC**H**$_3$), 2.56 (2H, dt, *J* = 6.7, 1.1 Hz, OCH$_2$C**H**$_2$), 2.18 (2H, q, *J* = 7.6 Hz, CH$_3$C**H**$_2$), 1.05 (3H, t, *J* = 7.6 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_2), 52.6 (2 x CH_3), 50.9 (CH), 35.4 (CH_2), 23.6 (CH_2), 12.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{26}NO_6$ $[M+NH_4]^+$: 352.1755, found: 352.1752.



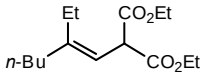
(*E*)-Dimethyl 2-(2-phenylbut-1-enyl)malonate (113d).

Using 2 equiv of Et_3Al: The title compound was prepared according to the General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (43 mg, 82%).

Using 0.5 equiv of Et_3Al: Following the same procedure as above, but using Et_3Al (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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.28 (5H, m, Ar**H**), 5.91 (1H, d, *J* = 9.8 Hz, =C**H**), 4.48 (1H, d, *J* = 9.8 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC**H**$_3$), 2.57 (2H, q, *J* = 7.5 Hz, C**H**$_2$) 1.00 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

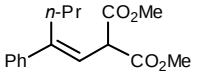


(*E*)-Dimethyl 2-[2-(4-methylphenyl)but-1-enyl]malonate (113e). The title compound was prepared according to the General Procedure from cyclopropene **108e** (49 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (39 mg, 71%). IR (film), 1737 (C=O), 1512, 1435, 1267, 1193, 1148, 1022, 818, 512 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 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, =C**H**), 4.48 (1H, d, *J* = 9.8 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC**H**$_3$), 2.56 (2H, q, *J* = 7.5 Hz, C**H**$_2$), 2.35 (3H, s, ArC**H**$_3$), 0.99 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

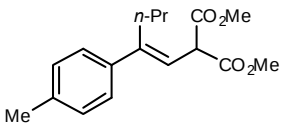


(*E*)-Diethyl 2-(2-ethylhex-1-enyl)malonate (113f). The title compound was prepared according to the General Procedure from

cyclopropene **108f** (48 mg, 0.20 mmol) and Et_3Al 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, $CDCl_3$) δ 5.42 (1H, d, *J* = 9.7 Hz, =C**H**), 4.27 (1H, d, *J* = 9.7 Hz, =CHC**H**), 4.19 (4H, q, *J* = 7.1 Hz, 2 x OC$\mathbf{H}_2$), 2.08 (4H, app q, *J* = 7.6 Hz, 2 x C$\mathbf{H}_2$C=), 1.45-1.27 (4H, m, $CH_3C\mathbf{H}_2C\mathbf{H}_2$), 1.27 (6H, t, *J* = 7.1 Hz, 2 x $OCH_2C\mathbf{H}_3$), 0.99 (3H, t, *J* = 7.6 Hz, C$\mathbf{H}_3CH_2C$=), 0.90 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3CH_2CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.8 (2 x C), 147.4 (C), 115.2 (CH), 61.4 (2 x CH_2), 51.2 (CH), 36.0 (CH_2), 29.9 (CH_2), 23.6 (CH_2), 22.3 (CH_2), 14.0 (2 x CH_3), 13.9 (CH_3), 12.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{27}O_4$ $[M+H]^+$: 271.1904, found: 271.1904.

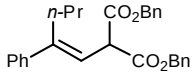


(*E*)-Dimethyl 2-(2-phenylpent-1-enyl)malonate (114a). The title compound was prepared according to the General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and *n*-Pr_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (50 mg, 90%). IR ($CHCl_3$) 2962, 2875, 1738 (C=O), 1593, 1533, 1442, 1265, 1024, 910 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40-7.38 (2H, m, Ar**H**), 7.35-7.32 (2H, m, Ar**H**), 7.30-7.26 (1H, m, Ar**H**), 5.94 (1H, d, *J* = 9.9 Hz, =C**H**), 4.50 (1H, d, *J* = 9.9 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC$\mathbf{H}_3$), 2.55-2.52 (2H, m, C$\mathbf{H}_2CH_2CH_3$), 1.41-1.34 (2H, m, C$\mathbf{H}_2CH_3$), 0.88 (3H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.6 (CH), 32.1 (CH_2), 21.5 (CH_2), 13.7 (CH_3); HRMS (EI) Exact mass calcd for $C_{16}H_{20}O_4$ $[M]^+$: 276.1356, found: 276.1355.

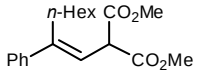


(*E*)-Dimethyl 2-[2-(4-methylphenyl)pent-1-enyl]malonate (114b). The title compound was prepared according to the General Procedure from cyclopropene **108e** (49 mg, 0.20

mmol) and *n*-Pr_3Al 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}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 (2H, dm, *J* = 8.1 Hz, Ar**H**), 7.14 (2H, d, *J* = 8.1 Hz, Ar**H**), 5.92 (1H, d, *J* = 9.9 Hz, =C**H**), 4.48 (1H, d, *J* = 9.9 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC$\mathbf{H}_3$), 2.51 (2H, t, *J* = 7.5 Hz, C$\mathbf{H}_2CH_2CH_3$), 2.35 (3H, s, ArC$\mathbf{H}_3$), 1.37 (2H, app sex, *J* = 7.5 Hz, C$\mathbf{H}_2CH_3$), 0.87 (3H, t, *J* = 7.5 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

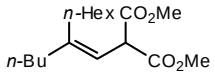


(*E*)-Dibenzyl 2-(2-phenylpent-1-enyl)malonate (114c). The title compound was prepared according to the General Procedure from cyclopropene **108g** (77 mg, 0.20 mmol) and *n*-Pr_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (54 mg, 63%). IR (film) 3033, 2960, 2871, 1734 (C=O), 1496, 1456, 1377, 1269, 1215, 1144 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.37-7.28 (15H, m, Ar**H**), 5.98 (1H, d, *J* = 9.8 Hz, =C**H**), 5.20 (4H, s, 2 x C$\mathbf{H}_2$Ph), 4.58 (1H, d, *J* = 9.8 Hz, =CHC**H**), 2.52 (2H, t, *J* = 7.7 Hz, C$\mathbf{H}_2CH_2CH_3$), 1.37-1.29 (2H, m, C$\mathbf{H}_2CH_3$), 0.83 (3H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

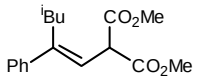


(*E*)-Dimethyl 2-(2-phenyloct-1-enyl)malonate (114d). The title compound was prepared according to the General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and *n*-Hex_3Al and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (42 mg,

66%). IR (film) 2953, 2857, 1737 (C=O), 1437, 1259, 1196, 1148, 1025, 769, 699 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.40-7.28 (5H, m, Ar**H**), 5.92 (1H, d, *J* = 9.9 Hz, =C**H**), 4.48 (1H, d, *J* = 9.9 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC$\mathbf{H}_3$), 2.53 (2H, t, *J* = 6.9 Hz, C$\mathbf{H}_2$C=), 1.37-1.18 (8H, m, 4 x C$\mathbf{H}_2$), 0.85 (3H, t, *J* = 6.9 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.6 (CH), 31.6 (CH_2), 30.3 (CH_2), 29.1 (CH_2), 28.4 (CH_2), 22.5 (CH_2), 14.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{30}NO_4$ $[M+NH_4]^+$: 336.2169, found: 336.2173.

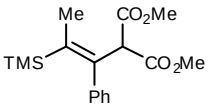


(*Z*)-Dimethyl 2-(2-butyloct-1-enyl)malonate (114e). The title compound was prepared according to the General Procedure from cyclopropene **108a** (42 mg, 0.20 mmol) and *n*-Hex_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 52%). IR (film) 2930, 2858, 1739 (C=O), 1435, 1296, 1147, 1024, 471, 458, 445 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 5.43 (1H, d, *J* = 9.8 Hz, =C**H**), 4.31 (1H, d, *J* = 9.8 Hz, =CHC**H**), 3.73 (6H, s, 2 x OC$\mathbf{H}_3$), 2.08-2.02 (4H, m, 2 x C$\mathbf{H}_2$C=), 1.45-1.24 (12H, m, $CH_3(C\mathbf{H}_2)_4$ and $CH_3(C\mathbf{H}_2)_2CH_2C$=), 0.90 (3H, t, *J* = 7.2 Hz, C$\mathbf{H}_3$), 0.87 (3H, t, *J* = 6.8 Hz, C$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.1 (2 x C), 146.4 (C), 115.4 (CH), 52.5 (2 x CH_3), 50.9 (CH), 36.4 (CH_2), 31.7 (CH_2), 30.6 (CH_2), 30.0 (CH_2), 29.3 (CH_2), 28.2 (CH_2), 22.6 (CH_2), 22.4 (CH_2), 14.0 (CH_3), 13.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{31}O_4$ $[M+H]^+$: 299.2217, found: 299.2217.

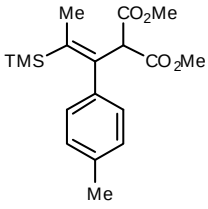


(*E*)-Dimethyl 2-(4-methyl-2-phenylpent-1-enyl)malonate (114f). The title compound was prepared according to the General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and $^iBu_3Al$ (1.1 M in Toluene) and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (36 mg, 62%). IR (film) 2955, 1736 (C=O), 1434, 1308, 1259, 1148, 1026, 857, 769, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.39-7.28 (5H, m,

Ar**H**), 5.94 (1H, d, *J* = 10.0 Hz, =C**H**), 4.50 (1H, d, *J* = 10.0 Hz, =CHC**H**), 3.78 (6H, s, 2 x OC**H**$_3$), 2.44 (2H, d, *J* = 6.6 Hz, C**H**$_2$C=), 1.62-1.53 (1H, m, C**H**), 0.83 (6H, d, *J* = 6.6 Hz, (C**H**$_3$)$_2$CH); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.7 (CH), 39.0 (CH_2), 26.8 (CH), 22.2 (2 x CH_3); HRMS (EI) Exact mass calcd for $C_{17}H_{22}O_4$ $[M]^+$: 290.1513, found: 290.1511.

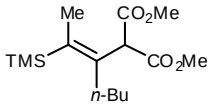


(*Z*)-Dimethyl 2-[1-phenyl-2-(trimethylsilyl)prop-1-enyl]malonate (116a). The title compound was prepared according to the General Procedure from cyclopropene **115a** (61 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (57 mg, 89%). IR ($CHCl_3$) 2953, 1739 (C=O), 1435, 1309, 1248, 1148, 1032, 837, 760, 704 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.23-7.22 (5H, m, Ar**H**), 4.82 (1H, s, =CC**H**), 3.57 (6H, s, 2 x OC**H**$_3$), 1.80 (3H, s, C**H**$_3$C=), -0.24 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_3), 18.3 (CH_3), -0.5 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{27}O_4Si$ $[M+H]^+$: 335.1673, found: 335.1673.

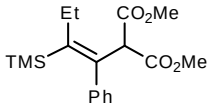


(*Z*)-Dimethyl 2-[1-(4-methylphenyl)-2-(trimethylsilyl)prop-1-enyl]malonate (116b). The title compound was prepared according to the General Procedure from cyclopropene **115b** (64 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (48 mg, 71%). IR ($CHCl_3$) 2952, 1741 (C=O), 1596, 1507, 1435, 1310, 1248, 1196, 1148, 1033 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.10-7.03 (4H, m, Ar**H**), 4.81 (1H, s, =CC**H**), 3.59 (6H, s, 2 x OC**H**$_3$), 2.71 (3H, s, ArC**H**$_3$), 1.79 (3H, s,

C**H**$_3$C=CH), −0.23 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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 $C_{18}H_{26}O_4Si$ $[M]^+$: 334.1595, found: 334.1601.

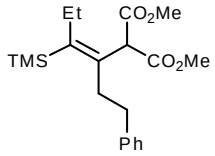


(*E*)-Dimethyl 2-[1-(1-trimethylsilylethylidene)pentyl]malonate (116c). The title compound was prepared according to the General Procedure from cyclopropene **115c** (57 mg, 0.20 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give an inseparable 6:1 mixture of regioisomers as a colourless oil (43 mg, 68%). 2953, 1738 (C=O), 1597, 1435, 1312, 1249, 1196, 1145, 1032, 837 cm^{-1} ^{1}H NMR (360 MHz, $CDCl_3$) δ 4.48 (1H, s, =CC**H**), 3.74 (6H, s, 2 x OC**H**$_3$), 2.23-2.19 (2H, m, C**H**$_2$C=), 1.67 (3H, s, C**H**$_3$C=), 1.37-1.26 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.89 (3H, t, *J* = 7.0 Hz, CH$_2$C**H**$_3$), 0.17 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 169.1 (2 x C), 140.8 (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 $C_{16}H_{31}O_4Si$ $[M+H]^+$: 315.1986, found: 315.1992.

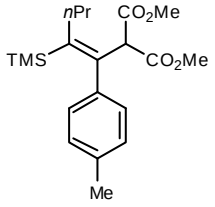


(*Z*)-Dimethyl 2-[1-(4-methylphenyl)-2-(trimethylsilyl)but-1-enyl]malonate (116d). The title compound was prepared according to the General Procedure from cyclopropene **115a** (61 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (49 mg, 73%). IR ($CHCl_3$) 2952, 2897, 1736 (C=O), 1587, 1490, 1435, 1375, 1308, 1248, 1194 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.24 (5H, s, Ar**H**), 4.88 (1H, s, =CC**H**), 3.59 (6H, s, 2 x OC**H**$_3$), 2.25 (2H, q, *J* = 7.6 Hz, C**H**$_2$), 1.05 (3H, t, *J* = 7.6 Hz, CH$_2$C**H**$_3$), −0.21 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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

(CH_2), 14.1 (CH_3), 0.3 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{30}O_4N$ $[M+NH_4]^+$: 352.1939, found: 352.1939.

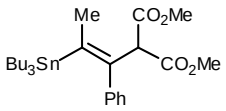


(*E*)-Dimethyl 2-[1-phenyl-4-(trimethylsilyl)hex-3-enyl]malonate (116e). The title compound was prepared according to the General Procedure from cyclopropene **115d** (66 mg, 0.20 mmol) and Et_3Al and purified by column chromatography (5%→15% EtOAc/hexane) to give an inseparable 5:1 mixture of regioisomers 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, $CDCl_3$) δ 7.33-7.27 (2H, m, Ar**H**), 7.24-7.20 (3H, m, Ar**H**), 4.72 (1H, s, =CC**H**), 3.79 (6H, s, 2 x OC$\mathbf{H}_3$), 2.70-2.67 (2H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph), 2.58-2.55 (2H, m, C$\mathbf{H}_2$C$\mathbf{H}_2$Ph), 2.16 (2H, q, *J* = 7.5 Hz, C$\mathbf{H}_2$$CH_3$), 0.94 (3H, t, *J* = 7.5 Hz, CH_2C$\mathbf{H}_3$), 0.24 (3H, s, Si(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 37.8 (CH_2), 35.8 (CH_2), 25.6 (CH_3), 14.2 (CH_3), 0.96 (3 x CH_3); HRMS (EI) Exact mass calcd for $C_{20}H_{30}O_4Si$ $[M]^+$: 362.1908, found: 362.1904.

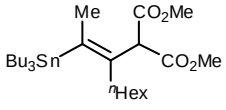


(*Z*)-Dimethyl 2-[1-p-tolyl-2-(trimethylsilyl)pent-1-enyl]malonate (116f). The title compound was prepared according to the General Procedure from cyclopropene **115b** (64 mg, 0.20 mmol) and *n*-Pr_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (64 mg, 88%). IR (film) 2954, 2873, 1736 (C=O), 1591, 1508, 1435, 1311, 1248, 1196, 1149 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.11-7.10 (2H, m, Ar**H**), 7.05-7.04 (2H, m, Ar**H**), 4.88 (1H, s, =CC**H**), 3.60 (6H, s, 2 x OC$\mathbf{H}_3$), 2.31 (3H, s, ArC$\mathbf{H}_3$), 2.18-2.15 (2H, m, C$\mathbf{H}_2$$CH_2CH_3$), 1.44-1.39 (2H, m, C$\mathbf{H}_2$$CH_3$), 0.99 (3H, t, *J* = 7.3 Hz, CH_2C$\mathbf{H}_3$), -0.22 (9H, s, Si(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 35.0 (CH_2), 23.0 (CH_2), 21.2 (CH_3), 14.4 (CH_3), 0.45 (3 x CH_3); HRMS (EI) Exact mass calcd for $C_{20}H_{30}O_4Si$ $[M]^+$: 362.1908, found: 362.1907.

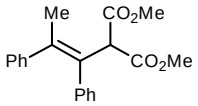


(*Z*)-Dimethyl 2-[1-phenyl-2-(tributylstannyl)prop-1-enyl]malonate (118a). The title compound was prepared according to the General Procedure but using half of all quantities, from cyclopropene **117a** (52 mg, 0.10 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give 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, $CDCl_3$) δ 7.26-7.21 (5H, m, Ar**H**), 4.88 (1H, s, =CC**H**), 3.58 (6H, s, 2 x OC**H**$_3$), 1.95 (3H, s, C**H**$_3$C=), 1.33-1.26 (6H, m, Sn(CH_2C**H**$_2$C**H**$_2$$CH_3$)$_3$), 1.24-1.16 (6H, m, Sn($CH_2$C**H**$_2$C**H**$_2$$CH_3$)$_3$), 0.84 (9H, t, J = 7.2 Hz, Sn($CH_2CH_2CH_2$C**H**$_3$)$_3$), 0.53-0.49 (6H, m, Sn(C**H**$_2$$CH_2CH_2CH_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 29.0 (J_{Sn-C} = 9.5 Hz, 3 x CH_2), 27.3 (J_{Sn-C} = 30.6 Hz, 3 x CH_2), 21.6 (CH_3), 13.6 (3 x CH_3), 10.4 (J_{Sn-C} = 167.6, 160.5 Hz, 3 x CH_2); HRMS (FAB) Exact mass calcd for $C_{26}H_{43}O_4{}^{120}Sn$ $[M+H]^+$: 539.2178, found: 539.2186.

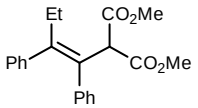


(*E*)-Dimethyl 2-[1-(1-tributylstannylethylidene)heptyl]malonate (118b). The title compound was prepared according to the General Procedure but using half of all quantities from cyclopropene **117b** (53 mg, 0.10 mmol) and Me_3Al and purified by column chromatography (hexane→5% EtOAc/hexane) to give 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, =CC**H**), 3.73 (6H, s, $CO_2C\mathbf{H}_3$), 2.11-2.08 (2H, m, =CC$\mathbf{H}_2$), 1.83 (3H, s, $C\mathbf{H}_3C$=), 1.51-1.43 (6H, m, $Sn(CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3)_3$), 1.35-1.25 (14H, m, $Sn(CH_2C\mathbf{H}_2C\mathbf{H}_2CH_3)_3$ and $(C\mathbf{H}_2)_4CH_3$), 0.95-0.86 (18H, m, $Sn(C\mathbf{H}_2CH_2CH_2C\mathbf{H}_3)_3$ and $(CH_2)_5C\mathbf{H}_3$), ^{13}C 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 $C_{26}H_{51}O_4{}^{120}Sn$ $[M+H]^+$: 547.2804, found: 547.2790.

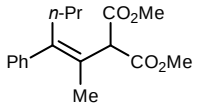


(*Z*)-Dimethyl 2-(1,2-diphenylprop-1-enyl)malonate (120a). The title compound was prepared using a slight modification of the quantities described in the General Procedure from cyclopropene **119a** (50 mg, 0.16 mmol) and Me_3Al (2.0 M in hexanes, 0.16 mL, 0.32 mmol), and purified by column chromatography (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}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.11-7.00 (10H, m, Ar**H**), 4.89 (1H, s, =CC**H**), 3.65 (6H, s, 2 x $OC\mathbf{H}_3$), 2.16 (3H, s, $C\mathbf{H}_3C$=); ^{13}C 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 $C_{20}H_{24}NO_4$ $[M+NH_4]^+$: 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%).

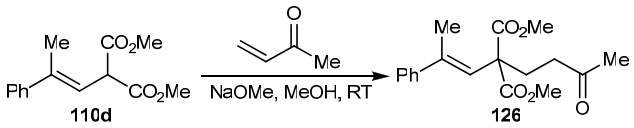
IR (film) 2952, 1750 (C=O), 1600, 1490, 1435, 1310, 1269, 1195, 1147, 1029 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.11-6.99 (10H, m, Ar**H**), 4.94 (1H, s, =CC**H**), 3.65 (6H, s, 2 x OC**H**$_3$), 2.55 (2H, q, *J* = 7.5 Hz, $CH_3C\mathbf{H}_2$), 0.93 (3H, t, *J* = 7.5 Hz, $C\mathbf{H}_3CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 51.7 (CH), 28.1 (CH_2), 12.0 (CH_3); HRMS (ES) Exact mass calcd for $C_{21}H_{23}O_4$ $[M+H]^+$: 338.1513, found: 338.1514.



(*E*)-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*-Pr_3Al (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, $CDCl_3$) δ 7.33-7.28 (2H, m, Ar**H**), 7.23-7.20 (3H, m, Ar**H**), 4.78 (1H, s, =CC**H**), 3.60 (6H, s, 2 x OC**H**$_3$), 2.15-2.11 (2H, m, C**H**$_2CH_2CH_3$), 1.55 (3H, s, =CC**H**$_3$), 1.54-1.50 (2H, m, C**H**$_2CH_3$), 0.98 (3H, t, *J* = 7.4 Hz, $CH_2C\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 36.4 (CH_2), 21.0 (CH_2), 20.2 (CH_3), 14.0 (CH_3); HRMS (EI) Exact mass calcd for $C_{17}H_{22}O_4$ $[M]^+$: 290.1513, found: 290.1509.

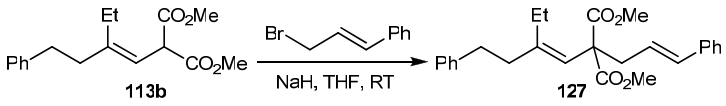
Further Manipulation of Ring-Opened Products

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



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 SiO_2 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, $CDCl_3$) δ 7.39-7.35 (2H, m, Ar**H**), 7.32-7.21 (3H, m, Ar**H**), 6.25 (1H, q, *J* = 1.3 Hz, =C**H**), 3.74 (6H, s, 2 x OC**H**$_3$), 2.48-2.39 (4H, m, C**H**$_2$C**H**$_2$), 2.08 (3H, s, OC**H**$_3$), 1.94 (3H, d, *J* = 1.3 Hz, C**H**$_3$C=); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 38.7 (CH_2), 29.9 (CH_3), 29.5 (CH_2), 16.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{23}O_5$ $[M+H]^+$: 319.1540, found: 319.1541.

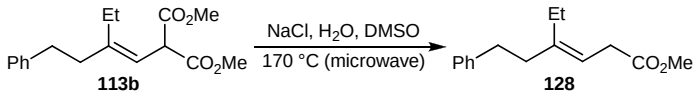
Dimethyl 2-[(*E*)-2-ethyl-4-phenylbut-1-enyl]-2-[(*E*)-3-phenylallyl] malonate (127)



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 SiO_2 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, $CDCl_3$) δ 7.31-7.27 (6H, m, Ar**H**), 7.24-7.18 (4H, m, Ar**H**), 6.39 (1H, d, *J* = 15.7 Hz, =C**H**Ph), 6.03 (1H, dt, *J* = 15.7, 7.5 Hz, CH_2C**H**=), 5.82 (1H, s, =C**H**C($CO_2Me)_2$), 3.73 (6H, s, 2 x OC**H**$_3$), 2.93 (2H, dd, *J* = 7.5, 1.2 Hz, C**H**$_2$CH=), 2.78-2.75 (2H, m, PhC**H**$_2$), 2.44-2.31 (2H, m, PhCH_2C**H**$_2$), 2.07 (2H, q, *J* = 7.5 Hz, CH_3C**H**$_2$), 0.98 (3H, t, *J* = 7.5 Hz, C**H**$_3$CH_2); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 40.8 (CH_2), 37.9 (CH_2), 34.7 (CH_2), 23.5 (CH_2), 11.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{26}H_{31}O_4$ $[M+H]^+$: 407.2217, found: 407.2215.

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

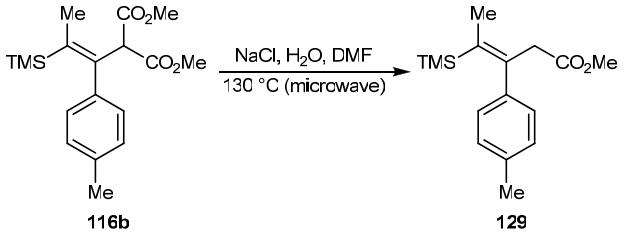


113b **128**

A solution of the alkene **113b** (87 mg, 0.30 mmol) and NaCl (24 mg, 0.41 mmol) in DMSO (0.5 mL) and H_2O (0.025 mL) was heated at 170 °C for 30 min in the microwave synthesizer. After cooling to room temperature, H_2O (10 mL) was added and the mixture was extracted with Et_2O (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* **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, $CDCl_3$) δ 7.31-7.27 (2H, m, Ar**H**), 7.21-7.17 (3H, m, Ar**H**), 5.35 (1H, t, *J* = 7.2 Hz, =C**H**), 3.70 (3H, s, OC**H**$_3$), 3.09 (2H, d, *J* = 7.2 Hz, =CHC**H**$_2$), 2.77-2.72 (2H, m, PhC**H**$_2$), 2.38-2.32 (2H, m, PhCH_2C**H**$_2$), 2.11 (2H, q, *J* = 7.6 Hz, CH_3C**H**$_2$), 1.02 (3H, t, *J* = 7.6 Hz, CH_3C**H**$_2$);

^{13}C NMR (62.9 MHz, $CDCl_3$) δ 172.8 (C), 144.3 (C), 142.2 (C), 128.3 (2 x CH), 128.2 (2 x CH), 125.7 (CH), 115.5 (CH), 51.7 (CH_3), 38.3 (CH_2), 34.6 (CH_2), 33.2 (CH_2), 23.6 (CH_2), 12.8 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}NO_2$ $[M+NH_4]^+$: 250.1802, found: 250.1803.

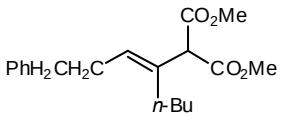
(*Z*)-Methyl 3-(4-methylphenyl)-4-(trimethylsilyl)pent-3-enoate (129)



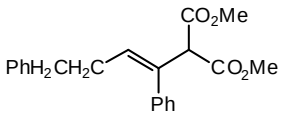
A solution of the alkene **116b** (68 mg, 0.20 mmol) and NaCl (24 mg, 0.41 mmol) in DMF (0.5 mL) and H_2O (0.025 mL) was heated at 130 °C for 1 h in the microwave synthesizer. After cooling to room temperature, H_2O (10 mL) was added and the mixture was extracted with Et_2O (3 x 5 mL). The combined organic 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, $CDCl_3$) δ 7.08 (2H, d, J = 7.9 Hz, Ar**H**), 7.02 (2H, d, J = 7.9 Hz, Ar**H**), 3.60 (3H, s, OC**H**$_3$), 3.45 (2H, s, C**H**$_2$), 2.34 (3H, s, ArC**H**$_3$), 1.85 (3H, s, C**H**$_3$C=), -0.21 (9H, s, Si(C**H**$_3$)$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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 $C_{16}H_{25}O_2Si$ $[M+H]^+$: 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 NH_4Cl solution (20 mL) and the aqueous layer was then separated and extracted with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification of the residue by column chromatography (EtOAc/hexane) gave the alkene product.

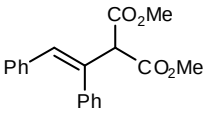


(*E*)-Dimethyl 2-(1,4-diphenylbut-1-en-2-yl)malonate (120a). The title compound was prepared according to General Procedure from cyclopropene **108a** (42 mg, 0.20 mmol) and $PhCH_2CH_2MgCl$ and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (40 mg, 63%). IR ($CHCl_3$) 2954, 2861, 1736(C=O), 1495, 1433, 1313, 1196, 1148, 1028, 747 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31-7.27 (2H, m, Ar**H**), 7.22-7.18 (3H, m, Ar**H**), 5.50 (1H, t, *J* = 7.2 Hz, =C**H**), 4.04 (1H, s, C**H**$(CO_2CH_3)_2$), 3.74 (6H, s, 2 x OC**H**$_3$), 2.70 (2H, t, *J* = 7.5 Hz, PhC**H**$_2$), 2.40 (2H, app q, *J* = 7.5 Hz, $PhCH_2C$**H**$_2$), 2.11 (2H, t, *J* = 7.5 Hz, =CC**H**$_2$), 1.26-1.22 (4H, m, CH_3C**H**$_2C$**H**$_2$), 0.88 (3H, t, *J* = 6.9 Hz, C**H**$_3CH_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 35.6 (CH_2), 30.4 (CH_2), 30.1 (CH_2), 22.7 (CH_2), 13.9 (CH_3); LRMS (ES) mass calcd for $C_{19}H_{27}O_4$ $[M+H]^+$: 319.18, found: 318.98.

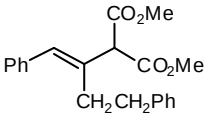


(*Z*)-Dimethyl 2-(1,4-diphenylbut-1-enyl)malonate (120b). The title compound was prepared according to General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and $PhCH_2CH_2MgCl$ and purified by column chromatography (hexane→10%

EtOAc/hexane) to give a colourless oil (49 mg, 72%). IR ($CHCl_3$) 3026, 2952, 1736 (C=O), 1601, 1495, 1434, 1313, 1196, 1149, 1028 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.15 (6H, m, Ar**H**), 7.11-7.07 (4H, m, Ar**H**), 5.82 (1H, t, *J* = 7.4 Hz, =C**H**), 4.37 (1H, s, C**H**(CO_2CH_3)$_2$), 3.71 (6H, s, 2 x OC**H**$_3$), 2.67 (2H, t, *J* = 7.6 Hz, Ph C**H**$_2$), 2.31 (2H, app q, *J* = 7.6 Hz, $PhCH_2C\mathbf{H}_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 35.6 (CH_2), 30.9 (CH_2); LRMS (ES) mass calcd for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.15, found: 338.83.

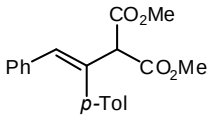


(*Z*)-Dimethyl 2-(1,2-diphenylvinyl)malonate (120c). The title compound was prepared according to General Procedure from cyclopropene **108d** (46 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 51%). IR ($CHCl_3$) 2953, 1734(C=O), 1492, 1434, 1311, 1150, 1028, 757, 696, 481 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.31-7.24 (5H, m, Ar**H**), 7.11-7.09 (3H, m, Ar**H**), 6.98-6.95 (2H, m, Ar**H**), 6.73 (1H, s, C**H**), 4.53 (1H, s, C**H**), 3.76 (6H, s, 2 x OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3); LRMS (ES) mass calcd for $C_{19}H_{19}O_4$ $[M+H]^+$: 311.12, found: 310.89.

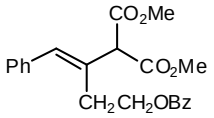


(*E*)-Dimethyl 2-(1,4-diphenylbut-1-en-2-yl)malonate (120d). The title compound was prepared according to General Procedure from cyclopropene **108b** (52 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→10% EtOAc/hexane) to give a colourless oil (45 mg, 66%). IR ($CHCl_3$) 3026, 2952, 1735(C=O), 1495, 1435, 1311, 1150, 1028, 751, 698 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.37-7.12 (10H, m, Ar**H**), 6.64 (1H, s, =C**H**),

4.29 (1H, s, C**H**$(CO_2CH_3)_2$), 3.81 (6H, s, 2 x OC**H**$_3$), 2.78-2.73 (2H, m, C**H**$_2$), 2.70-2.64 (2H, m, C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 34.2 (CH_2), 33.5 (CH_2); LRMS (ES) mass calcd for $C_{21}H_{23}O_4$ $[M+H]^+$: 339.15, found: 338.89.



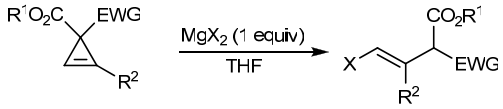
(*Z*)- Dimethyl 2-(2-phenyl-1-p-tolylvinyl)malonate (120e). The title compound was prepared according to General Procedure from cyclopropene **108e** (46 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (34 mg, 52%). IR ($CHCl_3$) 2952, 1734(C=O), 1510, 1436, 1310, 1149, 1026, 824, 756, 695 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.16-7.10 (7H, m, Ar**H**), 7.01-6.98 (2H, m, Ar**H**), 6.70 (1H, s, C**H**), 4.53 (1H, s, C**H**), 3.76 (6H, s, 2 x OC**H**$_3$), 2.35 (3H, s, C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 168.4 (2 x C), 137.4 (C), 136.3 (C), 136.1 (C), 133.6 (CH), 131.6 (C), 129.4 (2 x CH), 128.8 (CH), 127.8 (CH), 127.1 (CH), 60.5 (CH), 52.7 (2 x CH_3), 21.2 (CH_3); LRMS (ES) mass calcd for $C_{20}H_{21}O_4$ $[M+H]^+$: 325.37, found: 324.85.



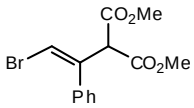
(*Z*)-Dimethyl 2-(4-(benzoyloxy)-1-phenylbut-1-en-2-yl) malonate (120f). The title compound was prepared according to General Procedure from cyclopropene **108c** (61 mg, 0.20 mmol) and PhMgCl and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (31 mg, 41%). IR ($CHCl_3$) 2952, 1715(C=O), 1433, 1268, 1144, 1108, 1023, 752, 709, 481 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.01-7.99 (2H, m, Ar**H**), 7.56-7.34 (8H, m, Ar**H**), 6.78 (1H, s, C**H**), 4.24 (2H, t, J = 7.0 Hz, C**H**$_2$), 4.36 (1H, s, C**H**), 3.76 (s, 2 x OC**H**$_3$), 2.89 (2H, t, J = 7.0 Hz, C**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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

(CH_2), 58.0 (CH), 52.8 (2 x CH_3), 30.6 (CH_2); LRMS (ES) mass calcd for $C_{22}H_{26}NO_6$ [M+NH_4^+]: 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 SiO_2 (*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.



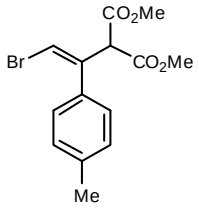
(*Z*)-Dimethyl 2-(2-bromo-1-phenylvinyl)malonate (124a).

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 $MgBr_2$ (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 (60 mg, 96%).

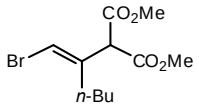
On a 2.00 mmol scale: A solution of the cyclopropene **108d** (2.00 mmol) in THF (15 mL + 5 mL rinse) was added via cannula over 2 min to a flask containing $MgBr_2$ (368 mg, 2.00 mmol) and a stirrer bar. The resulting mixture was stirred at room temperature for 30 min, and then filtered through a short plug of SiO_2 (*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, 1491, 1437, 1265, 1201, 1151, 1076 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.38 (2H, m, Ar**H**), 7.36-7.31 (3H, m, Ar**H**), 6.75 (1H, d, J = 0.6 Hz, =C**H**), 4.50 (1H, d, J =0.6 Hz, C**H**$(CO_2CH_3)_2$), 3.76 (6H, s, 2 x OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

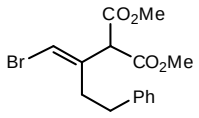


(*Z*)-Dimethyl 2-(2-bromo-1-*p*-tolylvinyl)malonate (124b). The title compound was prepared according to General Procedure A from cyclopropene **108e** (49 mg, 0.20 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (47 mg, 72%). IR (film) 2954, 1739 (C=O), 1616, 1510, 1435, 1308, 1196, 1151, 1022, 976 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.20 (4H, s, Ar**H**), 6.71 (1H, s, =C**H**), 4.48 (1H, s, C**H**$(CO_2CH_3)_2$), 3.76 (6H, s, 2 x OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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.

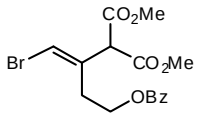


(*E*)-Dimethyl 2-[1-(1-bromomethylidene)pentyl]malonate (124c). The title compound was prepared according to General Procedure A from cyclopropene **108a** (42 mg, 0.20 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (44 mg, 75%). IR (film) 2956, 2871, 1739 (C=O), 1626, 1456, 1435, 1379, 1308, 1273, 1198 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$)

δ 6.36 (1H, d, *J* = 0.5 Hz, =C**H**), 4.16 (1H, d, *J* = 0.5 Hz, C**H**$(CO_2CH_3)_2$), 3.75 (6H, s, 2 x OC**H**$_3$), 2.36-2.32 (2H, m, =CC**H**$_2$), 1.44-1.28 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.91 (3H, t, *J* = 7.1 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.4 (2 x C), 137.2 (C), 109.2 (CH), 56.9 (CH), 52.8 (2 x CH_3), 33.1 (CH_2), 28.9 (CH_2), 22.5 (CH_2), 13.8 (CH_3); HRMS (EI) Exact mass calcd for $C_{11}H_{17}{}^{79}BrO_4$ [M^+]: 292.0305, found: 292.0304.

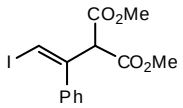


(*E*)-Dimethyl 2-[1-(1-bromomethylidene)-3-phenylpropyl]malonate (124d). The title compound was prepared according to General Procedure A from cyclopropene **108b** (52 mg, 0.20 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (59 mg, 87%). IR (film) 3028, 2954, 1738 (C=O), 1624, 1495, 1437, 1269, 1201, 1153, 1026 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.33-7.29 (2H, m, Ar**H**), 7.26-7.20 (3H, m, Ar**H**), 6.46 (1H, br s, =C**H**), 4.18 (1H, d, *J* = 0.5 Hz, C**H**$(CO_2CH_3)_2$), 3.78 (6H, s, 2 x OC**H**$_3$), 2.79-2.73 (2H, m, C**H**$_2$Ph), 2.69-2.63 (2H, m, C**H**$_2$CH$_2$Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 35.3 (CH_2), 33.0 (CH_2); HRMS (EI) Exact mass calcd for $C_{15}H_{17}{}^{79}BrO_4$ [M^+]: 340.0305, found: 340.0302.

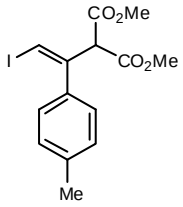


(*E*)-Dimethyl 2-[3-benzoyloxy-1-(1-bromomethylidene)propyl]malonate (124e). The title compound was prepared according to General Procedure A from cyclopropene **108c** (61 mg, 0.20 mmol) and $MgBr_2$ (37 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (64 mg, 84%). IR (film) 2956, 2362, 1720 (C=O), 1602, 1437, 1383, 1273, 1201, 1153, 1113 cm^{-1}; ^{1}H NMR (360

MHz, $CDCl_3$) δ 8.06-8.03 (2H, m, Ar**H**), 7.58-7.54 (1H, m, Ar**H**), 7.46-7.42 (2H, m, Ar**H**), 6.58 (1H, s, =C**H**), 4.45 (2H, t, *J* = 7.0 Hz, C**H**$_2$O), 4.31 (1H, s, C**H**(CO_2CH_3)$_2$), 3.73 (6H, s, 2 x OC**H**$_3$), 2.88 (2H, t, *J* = 7.0 Hz, =CC**H**$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_2), 57.2 (CH), 53.0 (2 x CH_3), 32.6 (CH_2); HRMS (ES) Exact mass calcd for $C_{16}H_{18}{}^{79}BrO_6$ $[M+H]^+$: 385.0281, found: 385.0285.

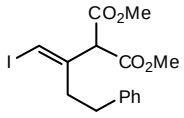


(*Z*)-Dimethyl 2-(2-iodo-1-phenylvinyl)malonate (125a). The title compound was prepared according to General Procedure A from cyclopropene **108d** (46 mg, 0.20 mmol) and MgI_2 (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a 9:1 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}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.39-7.32 (3H, m, Ar**H**), 7.25-7.22 (2H, m, Ar**H**), 6.87 (1H, d, *J* = 0.6 Hz, =C**H**), 4.51 (1H, d, *J* = 0.6 Hz, C**H**(CO_2CH_3)$_2$), 3.72 (6H, s, 2 x OC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3); HRMS (EI) Exact mass calcd for $C_{13}H_{13}IO_4$ $[M^+]$: 359.9853, found: 359.9852.

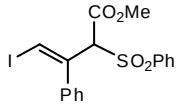


(*Z*)-Dimethyl 2-(2-bromo-1-*p*-tolylvinyl)malonate (125b). The title compound was prepared according to General Procedure A from cyclopropene **108e** (49 mg, 0.20 mmol) and MgI_2 (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (70 mg, 94%). IR (film) 2952, 1738 (C=O), 1612, 1508, 1435, 1309, 1198, 1151, 1022, 974 cm^{-1}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.20 (2H, d, *J* = 8.1 Hz, Ar**H**), 7.16 (2H, dm, *J* = 8.1 Hz, Ar**H**), 6.87

(1H, br s, =C**H**), 4.53 (1H, s, C**H**(CO_2CH_3)$_2$), 3.75 (6H, s, 2 x OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 21.3 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{16}IO_4$ $[M+H]^+$: 375.0088, found: 375.0092.

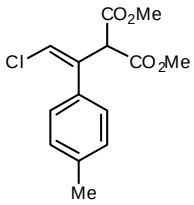


(*E*)-Dimethyl 2-[1-(1-iodomethylidene)-3-phenylpropyl]malonate (125c). The title compound was prepared according to General Procedure A from cyclopropene **108b** (52 mg, 0.20 mmol) and MgI_2 (56 mg, 0.20 mmol) at room temperature for 2 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (77 mg, 99%). IR (film) 2956, 2254, 1736 (C=O), 1437, 1265, 1153, 1028, 908, 733, 650 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31-7.19 (5H, m, Ar**H**), 6.57 (1H, s, =C**H**), 4.26 (1H, s, C**H**(CO_2CH_3)$_2$), 3.75 (6H, s, 2 x OC**H**$_3$), 2.74-2.71 (2H, m, C**H**$_2$Ph), 2.65-2.62 (2H, C**H**$_2$CH$_2$Ph); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 39.6 (CH_2), 33.0 (CH_2); HRMS (ES) Exact mass calcd for $C_{15}H_{21}NIO_4$ $[M+NH_4]^+$: 406.0510, found: 406.0507.

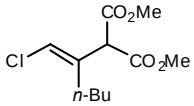


(*E*)-Methyl 4-iodo-3-phenyl-2-(phenylsulfonyl)but-3-enoate (125d). The title compound was prepared according to General Procedure A from cyclopropene **108h** (63 mg, 0.20 mmol) and MgI_2 (56 mg, 0.20 mmol) at room temperature for 2 h and then at 40 °C for 6 h. Purification of the residue by column 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}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.91-7.88 (2H, m, Ar**H**), 7.72-7.67 (1H, m, Ar**H**), 7.58-7.54 (2H, m, Ar**H**), 7.35 (1H, s, =C**H**), 7.34-7.32 (3H, m, Ar**H**), 7.13-7.11 (2H, m, Ar**H**), 5.05 (1H, s, C**H**CO_2CH_3), 3.73 (3H, s, OC**H**$_3$); ^{13}C NMR

(62.9 MHz, $CDCl_3$) 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 (CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{19}INO_4S$ $[M+NH_4]^+$: 460.0074, found: 460.0067.

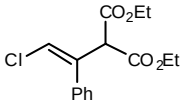


(*Z*)-Dimethyl 2-(2-chloro-1-*p*-tolylvinyl)malonate (125e). The title compound was prepared according to General Procedure A from cyclopropene **108e** (49 mg, 0.20 mmol) and $MgCl_2$ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a ~16:1 inseparable mixture of regioisomers as a colourless oil (43 mg, 76%). IR ($CHCl_3$) 3028, 2954, 1739 (C=O), 1611, 1511, 1435, 1310, 1197, 1152, 1024 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.24-7.18 (4H, m, Ar**H**), 6.53 (1H, s, =C**H**), 4.46 (1H, s, C**H**$(CO_2CH_3)_2$), 3.76 (6H, s, 2 x OC**H**$_3$), 2.37 (3H, s, ArC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 21.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{16}{}^{35}ClO_4$ $[M+H]^+$: 283.0732, found: 283.0728.



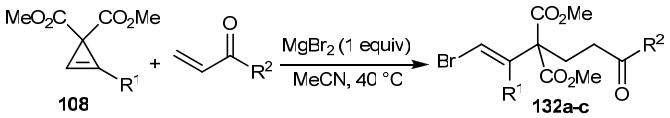
(*E*)-Dimethyl 2-[1-(1-chloromethylidene)pentyl]malonate (125f). The title compound was prepared according to General Procedure A from cyclopropene **108a** (42 mg, 0.20 mmol) and $MgCl_2$ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (5% EtOAc/hexane) to give a ~16:1 inseparable mixture of regioisomers as a colourless oil (43 mg, 85%). IR ($CHCl_3$) 2957, 2873, 1740 (C=O), 1634, 1436, 1308, 1199, 1150, 1027, 948 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.20 (1H, s, =C**H**), 4.11 (1H, s, C**H**$(CO_2CH_3)_2$), 3.75 (6H, s, 2 x OC**H**$_3$), 2.35-2.31 (2H, m, =CC**H**$_2$), 1.42-1.32 (4H, m, C**H**$_2$C**H**$_2$CH$_3$), 0.91 (3H, t, J = 7.1 Hz, CH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 167.7 (2 x C), 134.7 (C), 119.8 (CH), 56.1 (CH), 52.8 (2 x CH_3), 30.6 (CH_2), 28.9 (CH_2), 22.5 (CH_2), 13.8

(CH_3); HRMS (ES) Exact mass calcd for $C_{11}H_{18}{}^{35}ClO_4$ $[M+H]^+$: 249.0888, found: 249.0886.

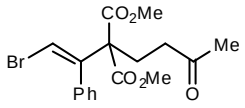


(*Z*)-Diethyl 2-(2-chloro-1-phenylvinyl)malonate (125g). The title compound was prepared according to General Procedure A from cyclopropene **108j** (52 mg, 0.20 mmol) and $MgCl_2$ (19 mg, 0.20 mmol) at 40 °C for 18 h and purified by column chromatography (hexane→5% EtOAc/hexane) to give a colourless oil (37 mg, 62%). IR (film) 2983, 1734 (C=O), 1493, 1444, 1367, 1306, 1151, 1095, 1032, 920 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.41-7.31 (5H, m, Ar**H**), 6.56 (1H, d, J = 0.6 Hz, =C**H**), 4.44 (1H, d, J = 0.6 Hz, C**H**$(CO_2CH_2CH_3)_2$), 4.26-4.16 (4H, m, 2 x OC**H**$_2$), 1.25 (6H, t, J = 7.2 Hz, 2 x OCH_2C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_2), 58.3 (CH), 13.9 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{21}ClO_4N$ $[M+NH_4]^+$: 314.1154, found: 314.1157.

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

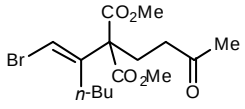


A solution of the appropriate cyclopropene (0.20 mmol) in MeCN (1 mL + 1 mL rinse) was added *via* cannula to a vial containing the appropiate enone (0.40 mmol), $MgBr_2$ (37 mg, 0.20 mmol), and a stirrer bar. The resulting mixture was stirred at 40 °C for 18 h. After cooling to room temperature, the mixture was filtered through a short plug of 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 afforded the alkenyl halide product.



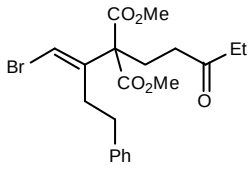
(*Z*)-Dimethyl 2-(2-bromo-1-phenylvinyl)-2-(3-oxobutyl)malonate (132c). *On a 0.20 mmol scale:* The title compound was prepared according to General Procedure B from cyclopropene **108d** (46 mg, 0.20 mmol) and methyl vinyl ketone (32 μL, 0.40 mmol) and purified by column chromatography (10%→30% EtOAc/hexane) 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 SiO_2 (*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 ($CHCl_3$) 2953, 1735 (C=O), 1613, 1491, 1437, 1366, 1254, 1171, 1092, 1030 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.38-7.31 (3H, m, Ar**H**), 7.07-7.05 (2H, m, Ar**H**), 6.92 (1H, s, =C**H**), 3.71 (6H, s, 2 x OC**H**$_3$), 2.53-2.50 (2H, m, C**H**$_2$C**H**$_2$C=O), 2.27-2.24 (2H, m, C**H**$_2$C**H**$_2$C=O), 2.09 (3H, s, C**H**$_3$C=O); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 39.0 (CH_2), 29.9 (CH_3), 28.2 (CH_2); HRMS (ES) Exact mass calcd for $C_{17}H_{20}{}^{79}BrO_5$ $[M+H]^+$: 383.0489, found: 383.0492.



(*E*)-Dimethyl 2-[1-(1-bromomethylidine)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 ($CHCl_3$) 3105, 2956, 2872, 1734 (C=O), 1610, 1434, 1369, 1255, 1169, 1091 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.46 (1H, s, =C**H**), 3.73 (6H, s, 2 x OC**H**$_3$), 2.52-2.49 (2H, m, C**H**$_2$C=O), 2.34-2.31 (2H, m, =CC**H**$_2$), 2.18-2.14 (2H, m, C**H**$_2$CH$_2$C=O), 2.11 (3H, s, C**H**$_3$C=O), 1.44-1.38 (2H, m, C**H**$_2$CH$_2$CH$_3$), 1.36-1.28 (2H, m, C**H**$_2$CH$_3$), 0.90 (3H, t, J = 7.3 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.8 (C), 169.8 (2 x C), 140.5 (C), 109.5 (CH), 63.6 (C), 52.7 (2 x CH_3), 39.0 (CH_2), 32.5 (CH_2), 30.0 (CH_3), 29.6 (CH_2), 27.3 (CH_2), 23.1 (CH_2), 13.7 (CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}{}^{79}BrO_5$ $[M+H]^+$: 363.0802, found: 363.0799.

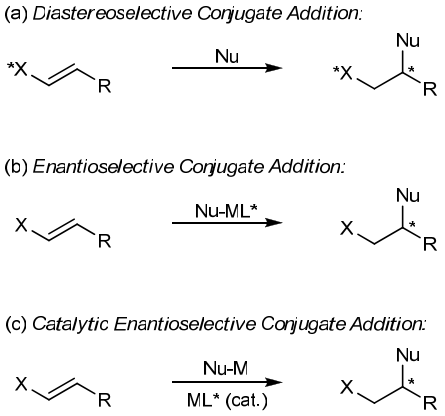


(*E*)-Dimethyl 2-[1-(1-bromomethylidine)-3-phenylpropyl]-2-(3-oxopentyl) malonate (132c). The title compound was prepared according to General Procedure B from cyclopropene **108b** (52 mg, 0.20 mmol) and ethyl vinyl ketone (40 μL, 0.40 mmol) and purified by column chromatography (5%→10% EtOAc/hexane) to give a colourless oil (61 mg, 72%). IR ($CHCl_3$) 2952, 1734 (C=O), 1496, 1455, 1242, 1095, 1031, 753, 700, 557 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.33-7.18 (5H, m, Ar**H**), 6.59 (1H, s, =C**H**), 3.76 (6H, s, 2 x OC**H**$_3$), 2.81-2.76 (2H, m, C**H**$_2$), 2.54-2.39 (8H, m, 4 x C**H**$_2$), 1.06 (3H, t, J = 7.3 Hz, CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 CH_3), 37.6 (CH_2), 36.0 (CH_2), 35.5 (CH_2), 33.4 (CH_2), 27.4 (CH_2), 7.7 (CH_3); HRMS (EI) Exact mass calcd for $C_{20}H_{26}{}^{79}BrO_5$ $[M+H]^+$: 425.0958, found: 425.0957.

2) Enantioselective Copper-Catalysed Reduction of 2-Alkenylheteroarenes

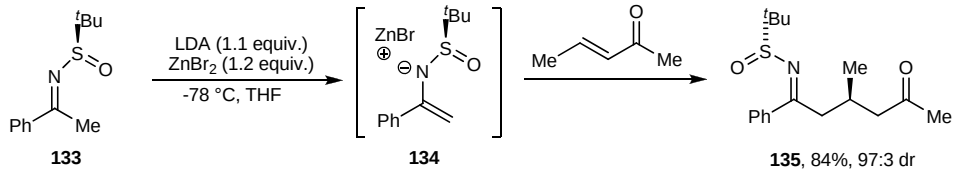
2.1) Asymmetric 1,4-Conjugate Addition

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.



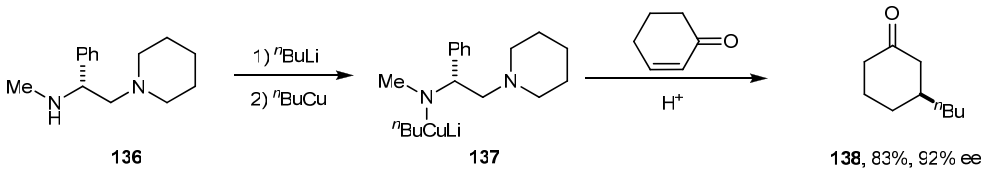
Scheme 2.1 *Strategies for stereoseletive 1,4-nucleophilic conjugate additions*

There are three strategies to achieve this carbon-carbon bond formation diastereoselectively and enantioselectively (Scheme 2.1):[65] (a) Diastereoselective addition to Michael acceptor with a covalently-bound chiral auxiliary X*.[66] This strategy is usually employed in target-oriented synthesis, for example, a Michael addition of *N*-sulfinyl metalloenamine **134** to the *α,β*-unsaturated ketone formed *N*-sulfinylamino ketone with high diastereoselectivity (Scheme 2.2).[67]



Scheme 2.2 *Diastereoselective addition of N-sulfinyl metalloenamines to α,β-unsaturated ketones*

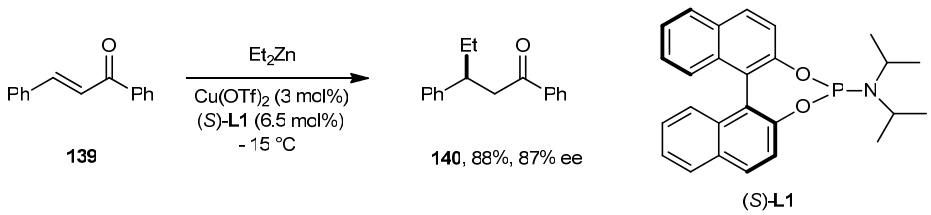
(b) Enantioselective Michael addition of chirally modified nucleophile Nu-ML* to prochiral substrate, for instance, preformed chiral cuprate species **137** was able to deliver a butyl group to cyclohexenone enantioselectively (Scheme 2.3).[68] Although this strategy has proven to be successful in terms 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.[69] 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

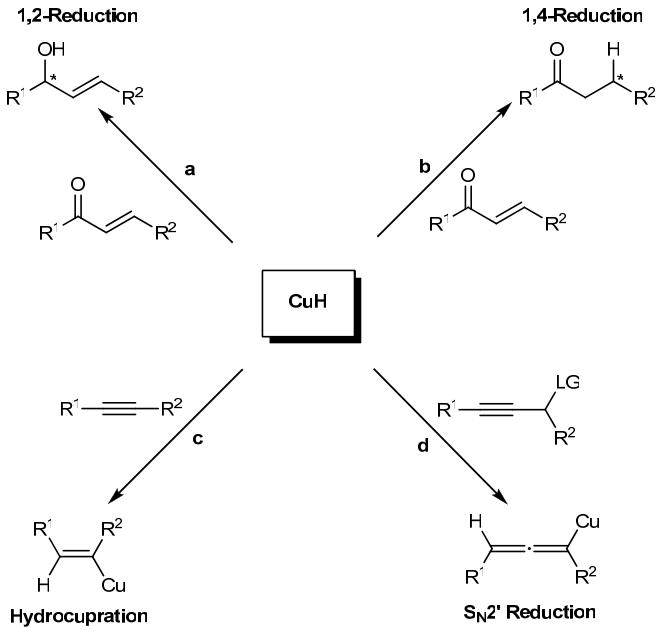
catalysed by copper(II) triflate in the presence of the phosphoramidite ligand **L1** (Scheme 2.4).[70]



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

2.2) Copper Hydride Chemistry

Since the pioneer work by Gilman in 1952,[71] cuprates have become versatile tools in organic synthesis, especially in 1,4-addition reactions to α,β-unsaturated acceptors,[72] 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.

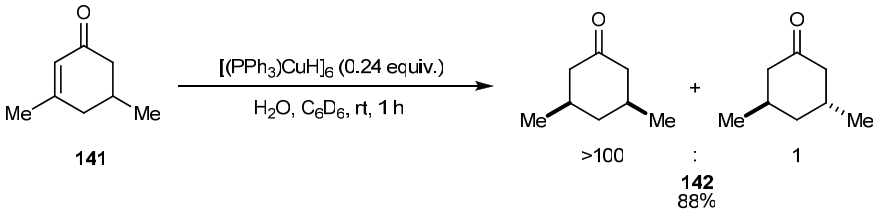


Scheme 2.5 The scope of copper hydride chemistry

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[73], S_N2'-reduction[74], 1,2-reduction[75], and 1,4-reduction (Scheme 2.5).

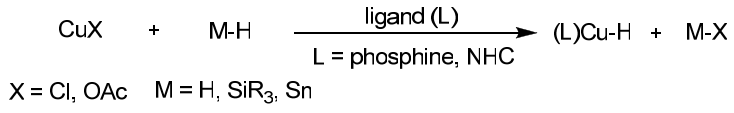
2.2.1) CuH-Catalysed 1,4-Conjugate Reduction

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,[76] Stryker disclosed the synthetic potential of the phosphine-stabilised hexameric copper hydride $[(Ph_3P)CuH]_6$ in highly regioselective conjugate reduction reactions of carbonyl derivatives (example in Scheme 2.6).[76b] 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

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.

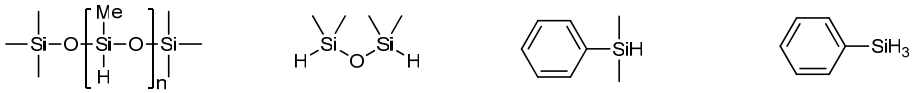


Scheme 2.7 Preparation of ligated copper hydrides

Not long after his initial report on stoichiometric use of $[(Ph_3P)CuH]_6$, Stryker discovered that this reaction could be achieved catalytically.[79d] The cycle could be established by using catalytic amount of CuO*t*-Bu, PPh_3 and molecular hydrogen, which served as hydride source.

These early recipes to generate CuO*t*-Bu involved the use of CuCl and one equivalent of NaO*t*-Bu. Since copper(I) is susceptible to oxidation, inert conditions were necessary to ensure that the activity of the metal catslyst was maintained. In order to avoid the preparation of extremely air-sensitive CuO*t*-Bu *in situ*, $Cu(OAc)_2 \cdot H_2O$ is found to be an attractive substitute.[77]

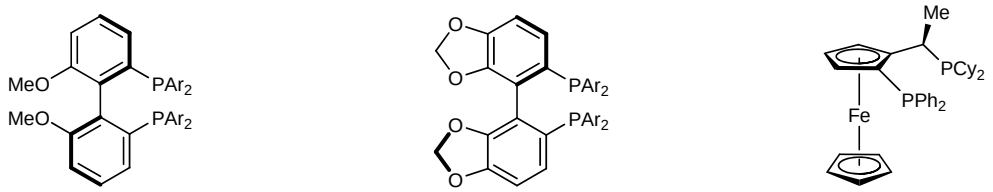
Meanwhile, other alternative sources of stoichiometric reducing agents for the generation of copper hydride complexes have been employed to replace hydrogen gas. Silanes, in particular, are the most common source of stoichiometric hydride since they are inexpensive and environmentally friendly. Most popular silanes for copper hydride-catalysed reduction include polymethylhydrosiloxane (PMHS), tetramethyldisiloxane (TMDS), Fleming's silane ($PhMe_2SiH$), and phenylsilane ($PhSiH_3$) (Scheme 2.8).



PMHS TMDS dimethyl(phenyl)silane (Fleming's silane) phenylsilane

Scheme 2.8 Silanes for CuH reduction

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 ferrocenyl 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).



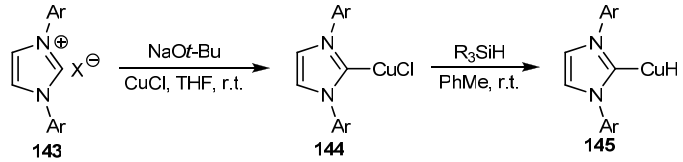
(*R*)-MeO-BIPHEP (Ar = Ph)
(*R*)-Xyl-MeO-BIPHEP (Ar = 3,5-$Me_2C_6H_3$)

(*R*)-SEGPHOS (Ar = Ph)
(*R*)-DTBM-SEGPHOS (Ar = 3,5-*t*-$Bu_{2\text{-}4}$-$MeOC_6H_2$)

(*R,S*)-JOSIPHOS

Scheme 2.9 Typical chiral ligands for CuH reduction

A more recently found alternative to phosphine ligands are N-heterocyclic carbenes (NHCs).[78] Air stability of the corresponding copper-carbene complexes is one of the obvious advantages. As a strong σ-donor and weak π-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).



Scheme 2.10 Preparation of CuH-NHC complex

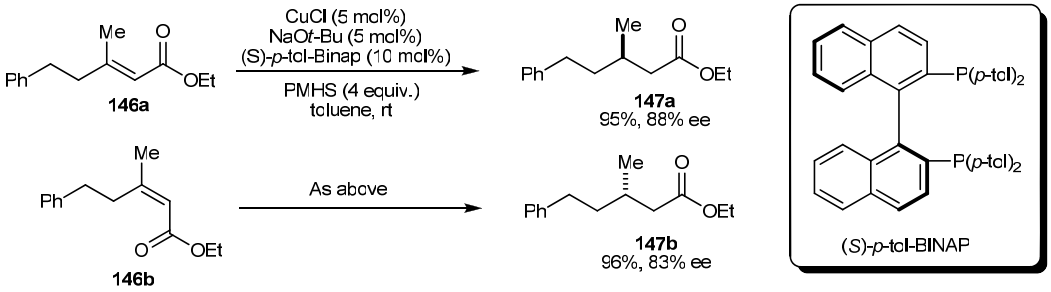
One of the key "tricks" to this chemistry is to take advantage of the tolerance of CuH complexes to alcohols and water. It is noticed that Stryker used water to suppress side reactions for those substrates which were sensitive to base-catalysed aldol condensations. Several subsequent reports rely on 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

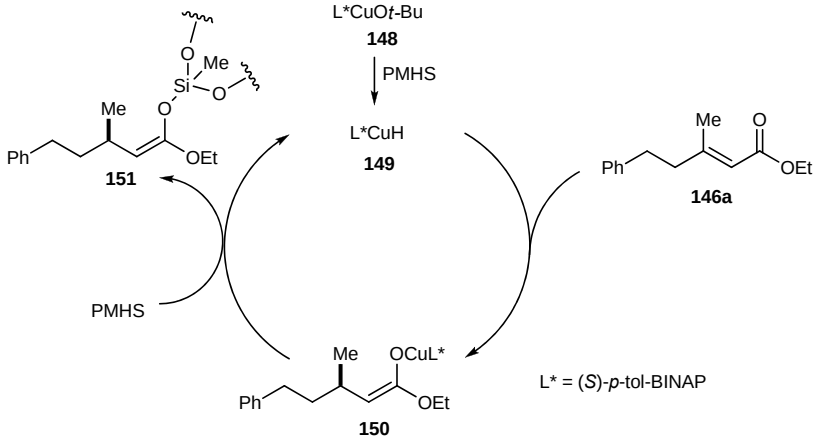
Enoates

Inspired by early work, the first copper-catalysed enantioselective conjugate reduction was developed by Buchwald.[79] A Chiral CuH species was generated in *situ* from CuCl, NaO*t*-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

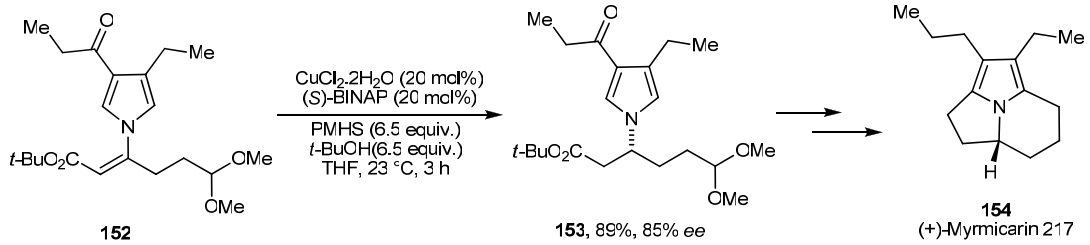
Using both *E*- and *Z*-isomers of the *α,β*-unsaturated ester **146a** and **146b**, the asymmetric reductions proceeded equally to give the opposite enantiomers of product **147a** and **147b** with nearly the same *ee*.



Scheme 2.12 The catalytic cycle of enantioselective CuH conjugate reduction

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*-tol-BINAP, CuCl, and NaO*t*-Bu, copper alkoxide (*p*-tol-BINAP)CuO*t*-Bu **148** is most likely formed. Addition of PMHS then results in a σ-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 σ-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.

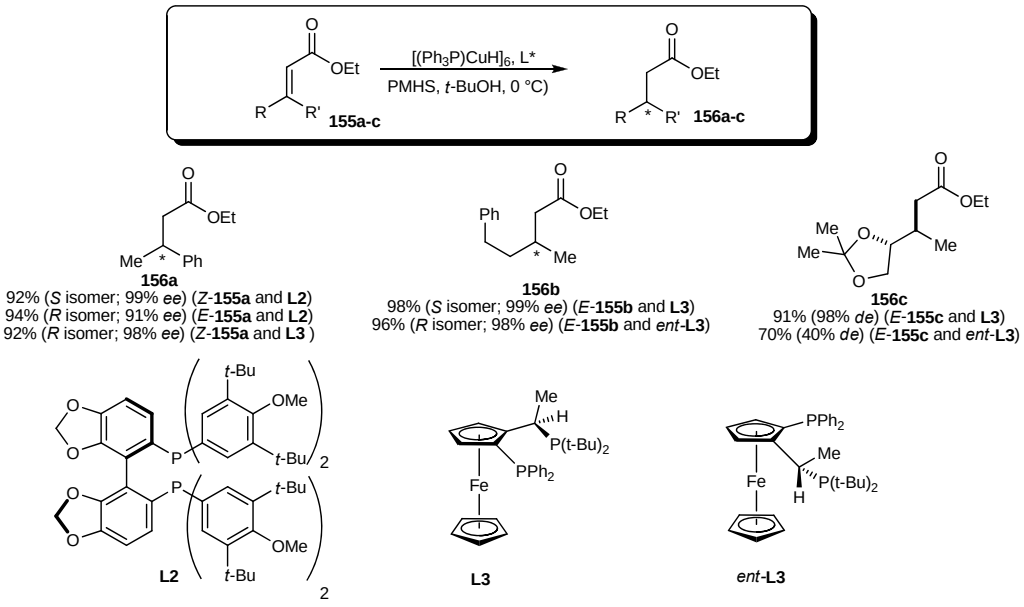
This method was applied to a tricyclic myrmicarin alkaloid **154** synthesis (Scheme 2.13). To avoid the sensitive CuCl/NaOt-Bu system, $Cu(OAc)_2 \cdot H_2O$ is found to be an attractive substitute. *t*-BuOH was added to enhance the reaction rate. Higher catalyst loading was employed due to high steric hindrance at the β-site of **152**.[80]



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 α,β-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**.



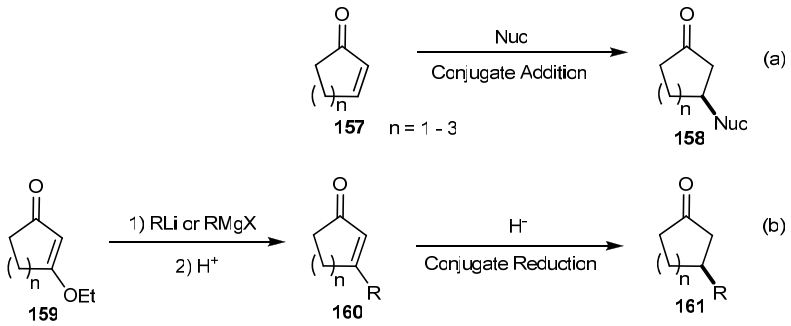
Scheme 2.14 Cu-catalysed reduction of acyclic enoates

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.

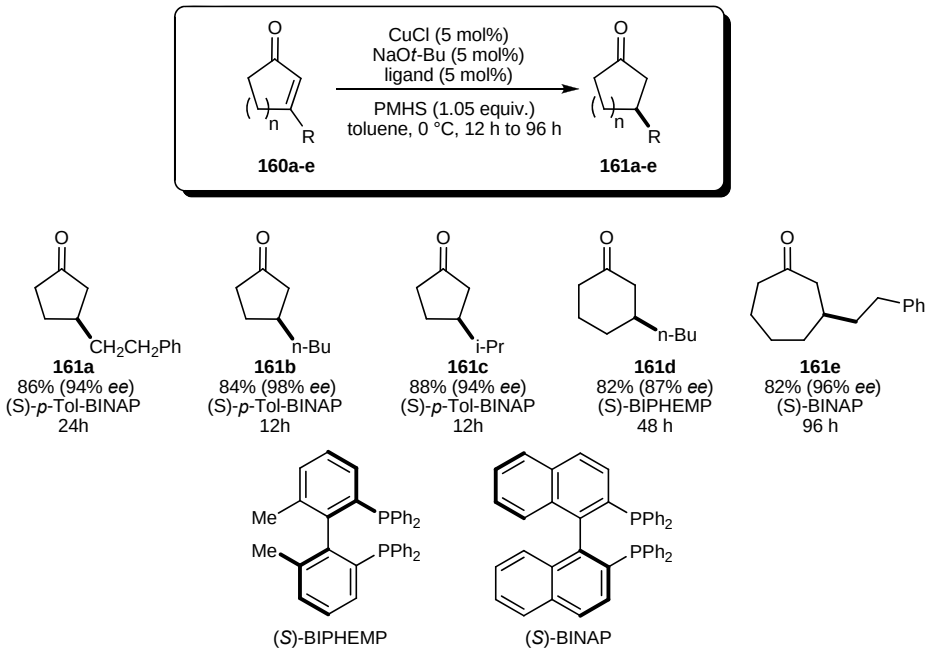
Cyclic enones

Chiral copper hydride can also reduce β-substituted cyclic enones to afford ketones with high *ee*'s.



Scheme 2.15 Conjugate addition of cyclic enones

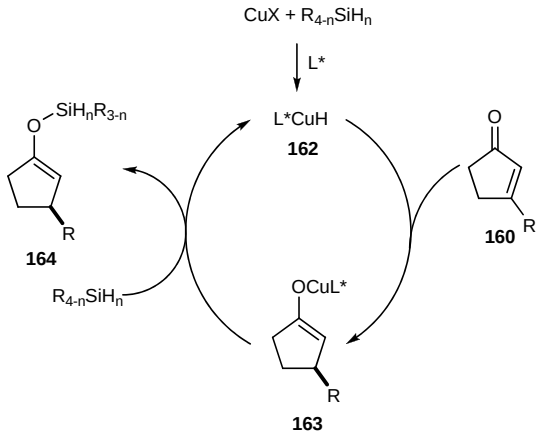
Although direct asymmetric conjugate addition of nucleophilic alkyl groups to cyclopentenone were well-established procedure to access cyclic ketones (Scheme 2.15a),[82] Buchwald showed that alkylation followed by asymmetric conjugate reduction of β-substituted enones (Scheme 2.15b) can access the same products with much higher enantioselectivities (Scheme 2.16).[83]



Scheme 2.16 Copper-catalysed reduction of cyclic enones

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 β 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 σ-bond metathesis with a silane to form silyl enol ether **164**.

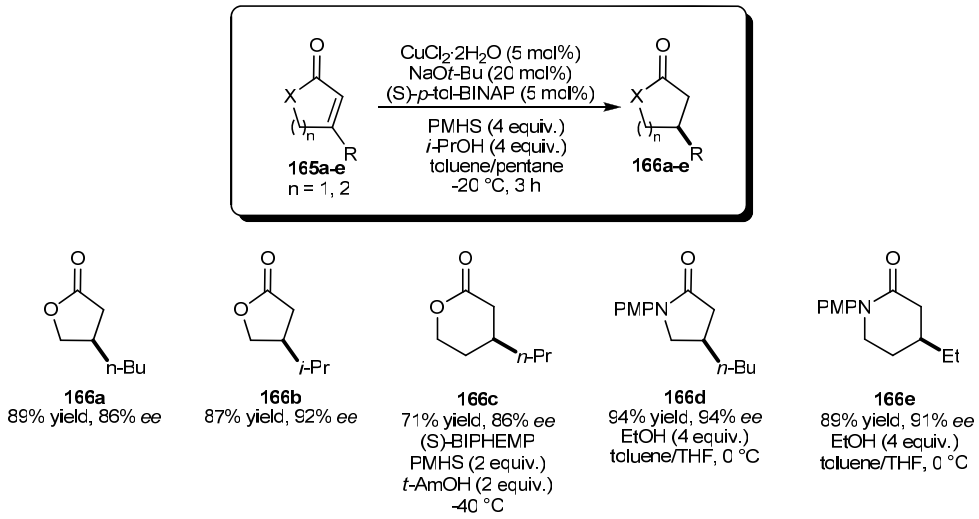


Scheme 2.17 Mechanism of asymmetric reduction of β-alkyl cyclopentenones

Lactones and lactams

Buchwald next examined the asymmetric conjugate reduction of lactones and lactams.[84] It was found that air-stable $CuCl_2 \cdot 2H_2O$ 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_2, which allowed for complete consumption of lactones and lactams.



166a
89% yield, 86% *ee*

166b
87% yield, 92% *ee*

166c
71% yield, 86% *ee*
(S)-BIPHEMP
PMHS (2 equiv.)
t-AmOH (2 equiv.)
-40 °C

166d
94% yield, 94% *ee*
EtOH (4 equiv.)
toluene/THF, 0 °C

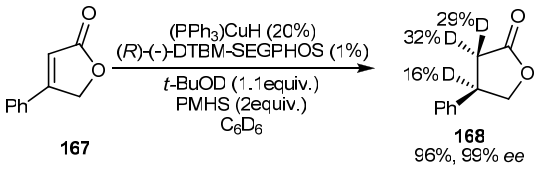
166e
89% yield, 91% *ee*
EtOH (4 equiv.)
toluene/THF, 0 °C

Scheme 2.18 Cu-catalysed reduction of lactones and lactams

These conditions allowed for the reduction of alkyl substituted butenolides **165a** and **165b** to give **166a** and **166b** in good yields with excellent enantioselectivities. Initial attempts to reduce pentenolide **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 (**166c**, 71%). BIPHEMP was found to be the best ligand.

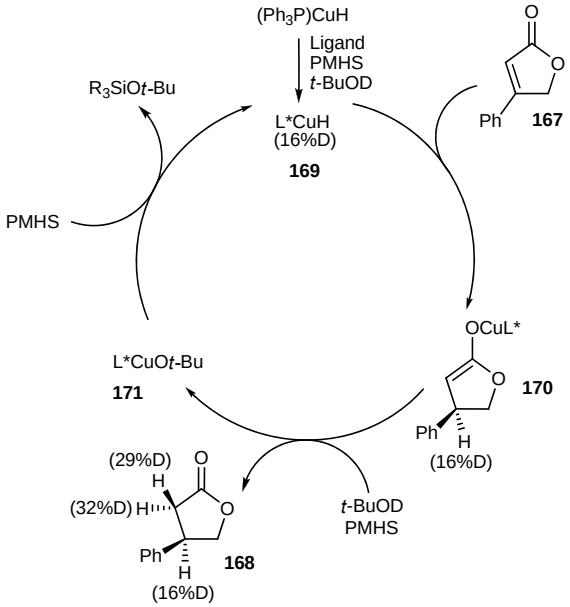
The reaction scope was then expanded to the reduction of lactams. *N*-*p*-Methoxyphenyl lactam **165d** was reduced in 94% yield and 94% *ee* after 3 h at 0 °C. In contrast to pentenolide **165c**, reduction of unsaturated six-membered lactam **165e** proceeded with excellent *ee* using *p*-tol-BINAP 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[81] using deuterated *t*-butanol in benzene-d_6 (Scheme 2.19).



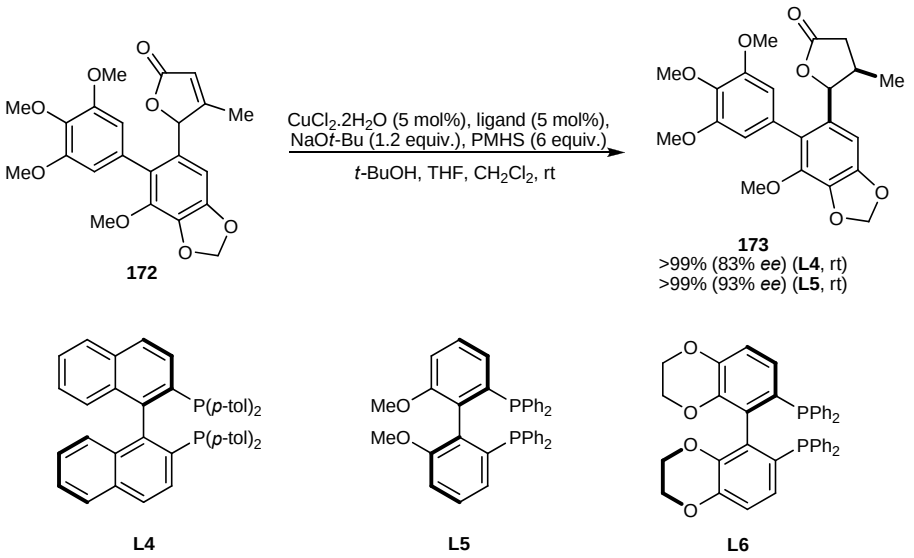
Scheme 2.19 Cu-catalysed reduction of unsaturated lactone using deuterated *t*-BuOD in benzene-d_6

Proton NMR spectroscopy showed that 16% deuterium of *t*-BuOD is incorporated at the *β*-position, which comes from facile H/D-exhange between CuH and *t*-BuOD. While 61% deuterium at the *a*-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).



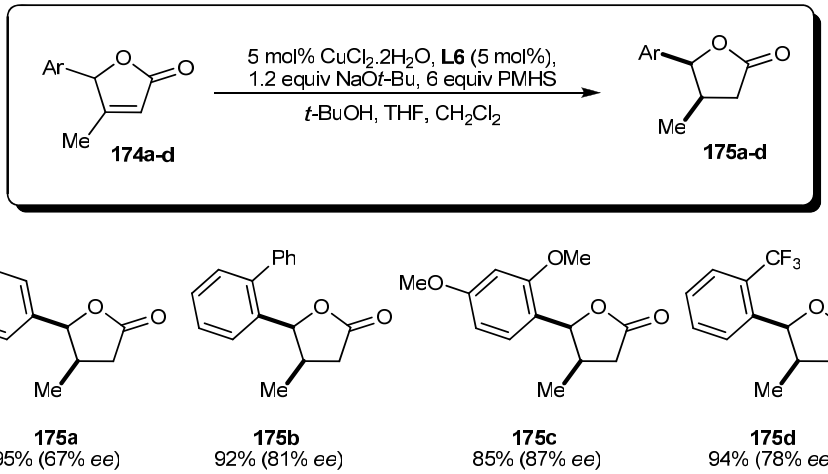
Scheme 2.20 Possible mechanistic cycle

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).[85] To perform the dynamic kinetic resolution (DKR), addition of excess base NaO*t*Bu alloweded 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 **L4** with MeO-BIPHEP **L5** provided the desired compound, again as a single diastereomer with 93% *ee*.



Scheme 2.21 Cu-catalysed synthesis of intermediate for total synthesis of Eupomatilone-3

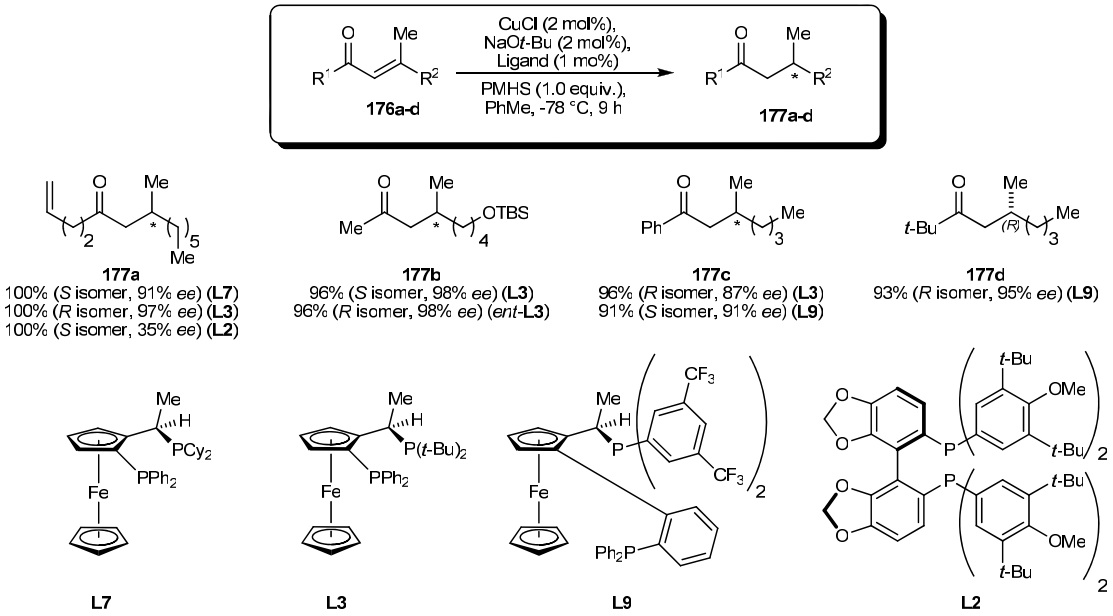
With this promising result, the scope of the reduction was expanded to other γ-aryl-containing unsaturated lactones **174a-d**.[84] The BIPHEP ligand **L5** used previously did not tolerate the new furanone substrates. Switching to SYNPHOS **L6** allowed the reduction to produce a single diastereomer with high yield and good *ee* (Scheme 2.22).



Scheme 2.22 DKR of aryl-substituted furanones

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 enantioselectivites.[86] 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

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 *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 *α,β*-Unsaturated Compounds

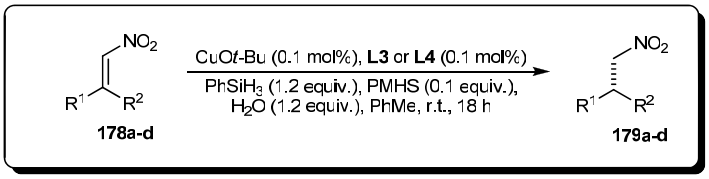
As well as enones and enoates, other Michael acceptors have also been tested in the enantioselective conjugate reduction.

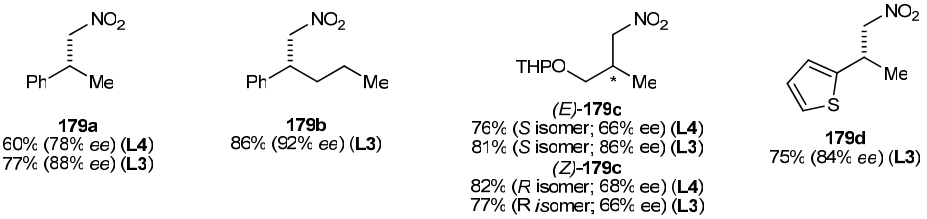
Nitroalkenes

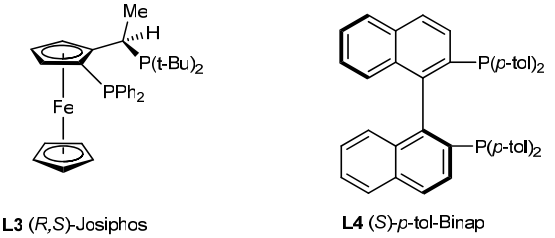
The nitro group is one of the most common functionalities used to activate alkenes toward asymmetric conjugate additions. In 2003, Czekelius and Carreira reported the metal-catalysed enantioselective reduction of *β,β*-disubstituted nitroalkenes using copper-phosphane complexes to give optically active 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 NaO*t*-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 CuO*t*-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.

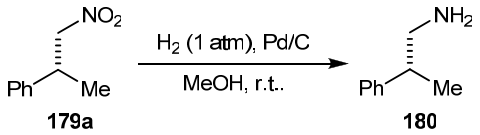






Scheme 2.24 Cu-catalysed reductions of β,β-disubstituted α,β-unsaturated nitroalkenes

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



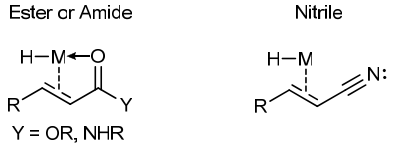
Scheme 2.25 Reduction of enantioenriched nitro-product to amine

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.[89]

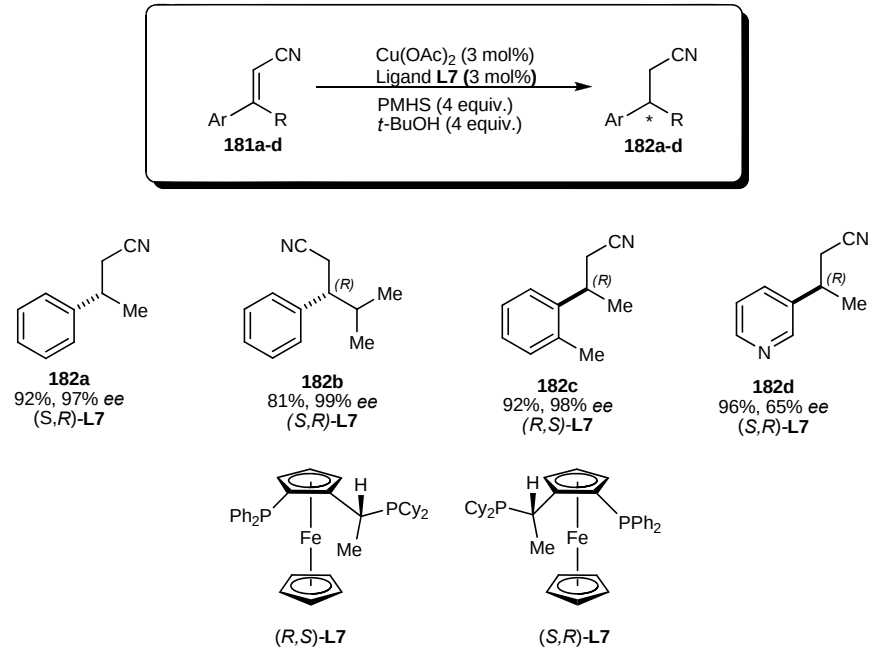
The two recent successful examples of asymmetric reductions of conjugated nitriles were the Co-catalysed conjugate reduction of *α,β*-unsaturated nitriles[90] and the Rh-catalyzed hydrogenation of *α,β*-unsaturated nitriles.[91] However, the enantioselectivities achieved by these catalyst systems were 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 *α,β*-unsaturated esters, amides, and nitriles.

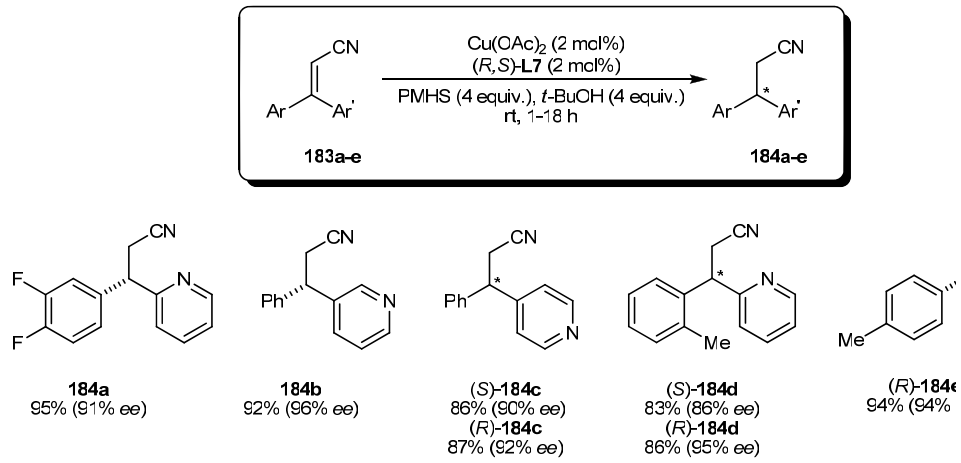
These limitations were overcome by the use of a $Cu(OAc)_2$ system complexed effectively with Josiphos-type ligands to induce activity. In 2006, Yun and co-workers reported the Cu-catalysed asymmetric conjugate reduction of *β*-aryl-*β*-alkyl-disubstituted *α,β*-unsaturated nitriles.[92]

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

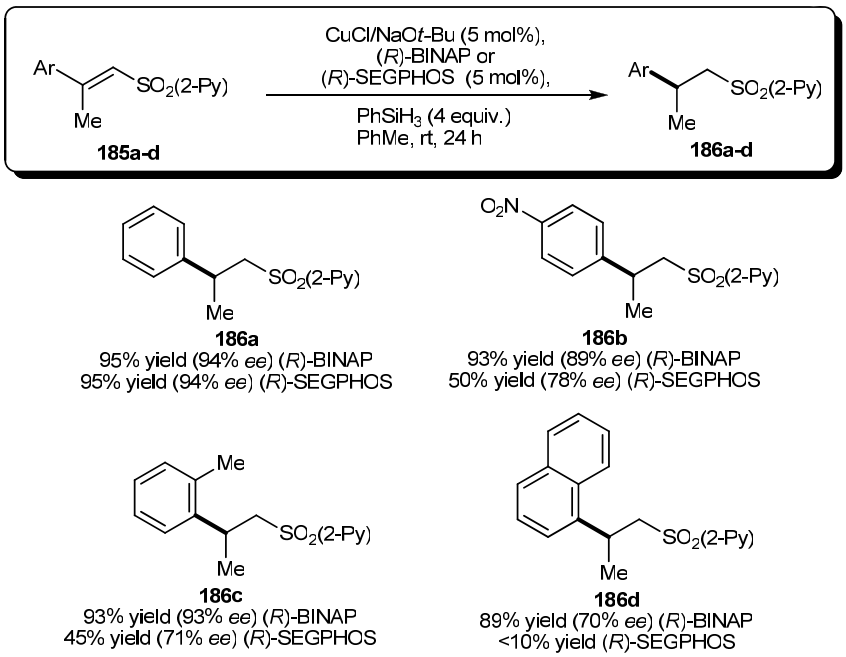
The catalytic system developed by Yu showed equal effiency with acrylonitriles containing 2-, 3-, or 4-pyridyl substitution (**183b-d**), which indicated that an additional coordination site was not required in this case (Scheme 2.28). Given the similar sterics of the phenyl and 3-/4-pyridyl substituent 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.[95]

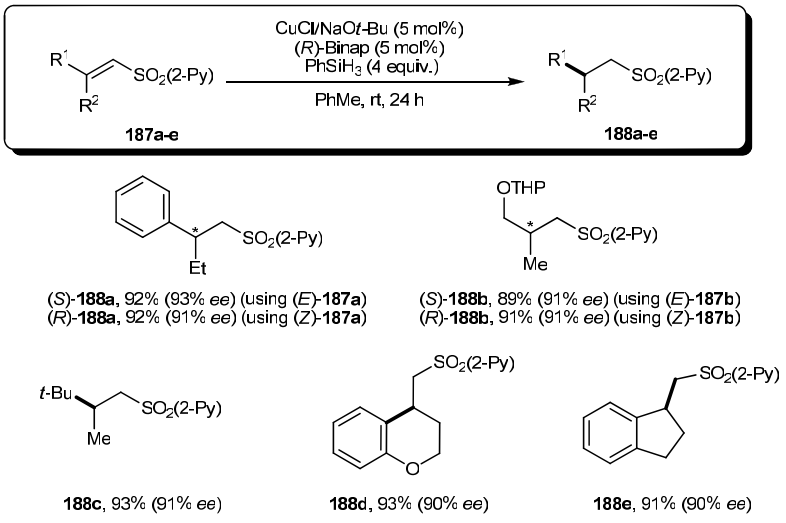
Initially, reductions on phenyl vinyl sulfones were tested using $Cu(OAc)_2 \cdot H_2O$, $[CuF(PPh_3)_3] \cdot 2MeOH$, and CuCl/*t*-BuONa in corporation with Binap and Josiphos, and phenylsilane as the hydride source. Unfortunately, all variations gave unsatisfied results. Based on prior knowledge of 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.[96]

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 SEGPHOS 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*.



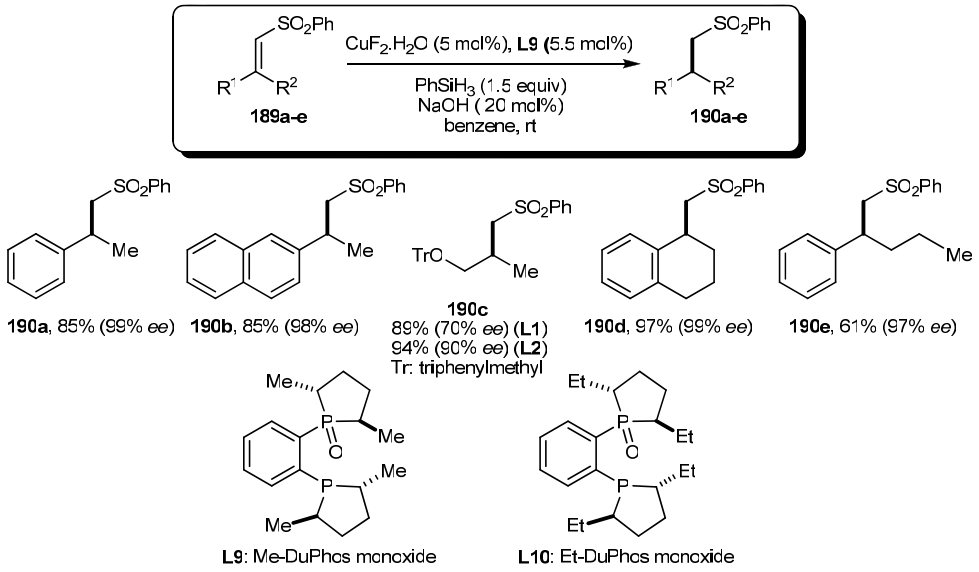
Scheme 2.29 Cu-catalysed reduction of β-aryl α,β-unsaturated 2-pyridylsulfones

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

Another general procedure to reduce α,β-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 $CuF_2{\cdot}H_2O$ and the hemilabile bidentate ligand Me-DuPhos monoxide **L9** in the presence of NaOH in benzene (Scheme 2.31).



Scheme2.31 Cu-catalysed reduction of β,β-disubstituted α,β-unsaturated 2-phenylsulfones

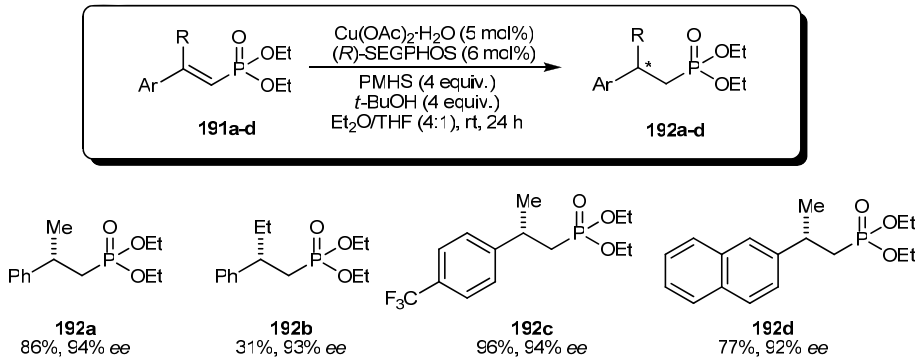
The addition of the base was necessary to obtain reproducible conversions. They believed that the presence of NaOH or KOH eliminated the detrimental competitive silylation of water by $PhSiH_3$.

Substrates bearing the α-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) **L9** gave moderate enantioselectivities (70% *ee*). However, when the bulkier Et-DuPhos(O) **L10** was used instead of **L9**, 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 β-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 *β*-substituted *α,β*-unsaturated phosphonates **191a-d** was reported by Hu and Zheng (Scheme 2.32).[98] Under optimised condition using $Cu(OAc)_2 \cdot H_2O$, (*R*)-SEGPHOS, PMHS, and *t*-BuOH, chiral *β*-substituted alkylphosphonates were readily synthesised with high enantioselectivities (up to 95% ee).



Scheme2.32 Cu-catalysed reduction of *α,β*-unsaturated phosphonates

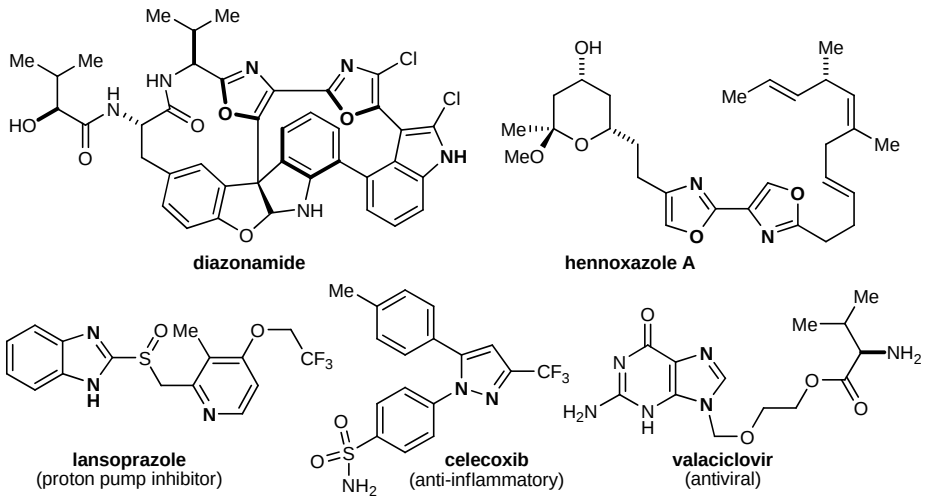
Conclusions

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".[99] Finally, and the most important, is the choice of ligand, which highly depends on the alkene substrate. BINAP, SEGPHOS, and JOSIPHOS 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.

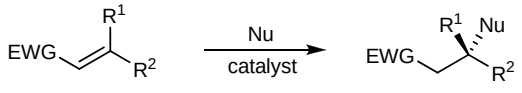


Scheme 2.33 Aromatic heterocycles in natural products and therapeutic agents

Hypothetically, a C=N moiety within such heterocycles could impart sufficient polarisation to an adjacent alkene to promote reactivity in the metal-catalysed

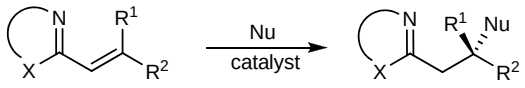
conjugate addition. In addition, it seemed likely that coordination of the Lewis basic nitrogen of the heteroarene to the catalyst would occur in such a process. However, whether this interaction would be beneficial, trivial, or detrimental was uncertain (Scheme 2.34).

(a) Conventional asymmetric conjugate addition



EWG = COR, NO_2, CN, SO_2R, etc.

(b) Aromatic heterocycle induced conjugate addition



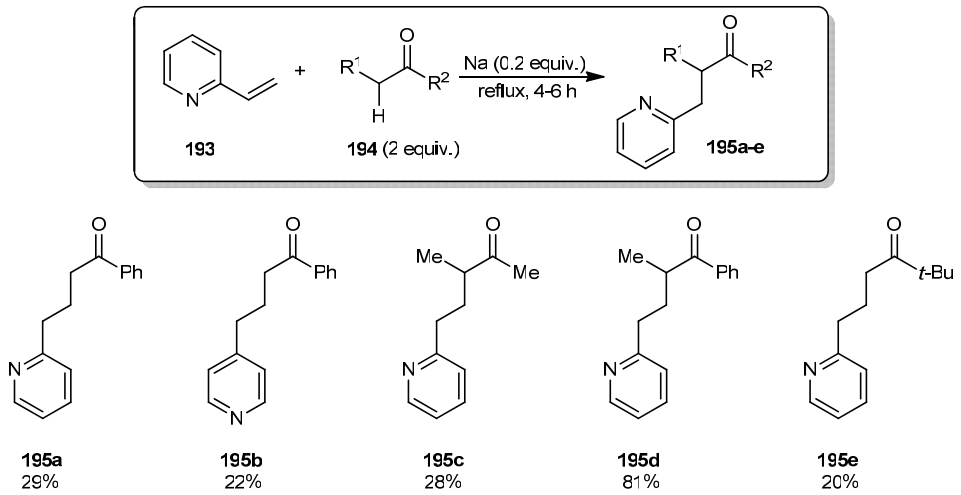
X = C, N, O, S, etc.

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.

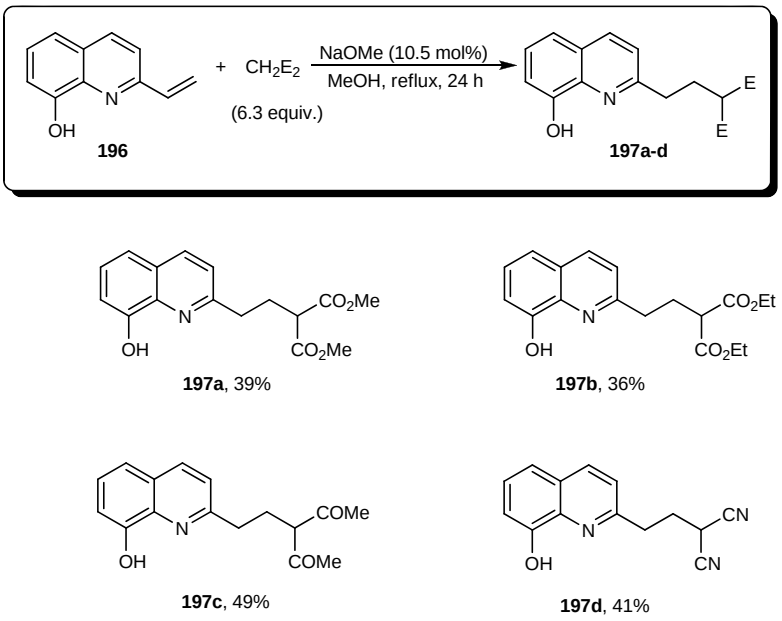
In the early 1950s, Levine and Wilt reported the conjugate addition of ketone enolates to 2- and 4-vinylpyridine using a small amount of sodium metal (Scheme 2.35).[101] Using various aliphatic and aromatic ketones, mono-pyridylethylation products **195a-e** were obtained in modest yields.



Scheme 2.35 Pyridylethylation of ketone enolates

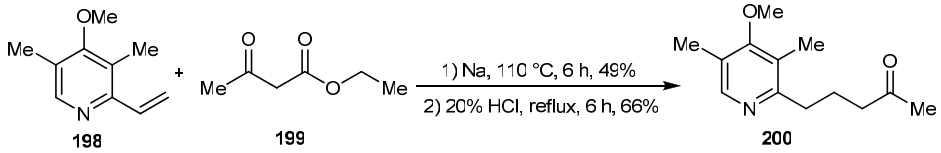
Further research showed that di- and tri-pyridylethylation may occur at the α-methylene carbon and α-methyl carbon. The degree of pyridylethylation could be controlled by the molar ratio of the reactants. When the vinylpyridine was the limiting reagent, the major product was mono-pyridylethylated, whereas 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 enxtend the side chains in order to improve the stability of the corresponding 8-quinolinol complexes (Scheme 2.36).[102]



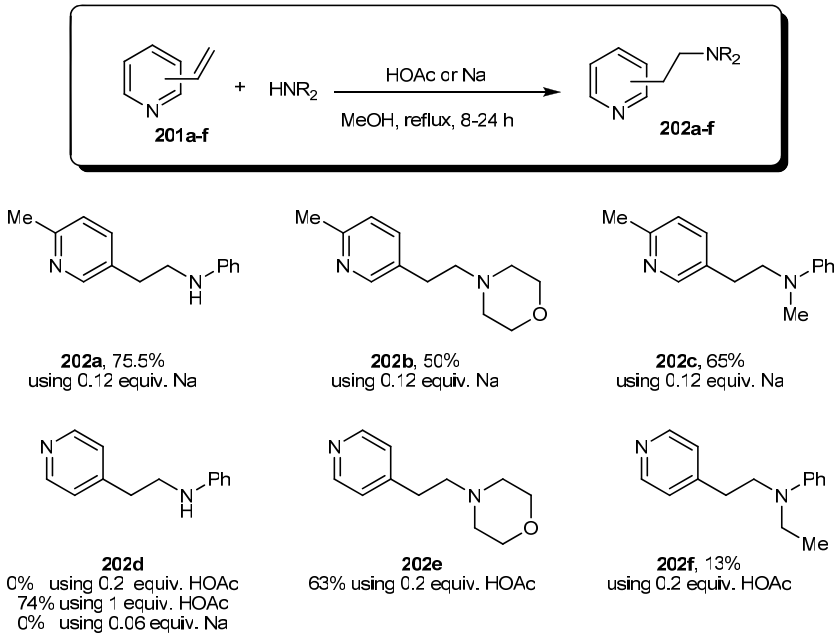
Scheme 2.36 Preparation of 2-substituted 8-quinolinols

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 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).



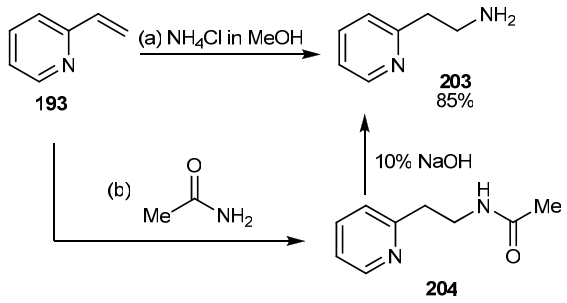
Scheme 2.37 Preparation of intermediate for the synthesis of 2-[(3,5-dimethyl-4-methoxypyridyl)alkyl]-benzothiazolidine derivatives

The conjugate addition of amines, amides, and nitriles to vinylpyridines using strong acid or base was repoted by Levine in 1956 (Scheme 2.38).[104]



Scheme 2.38 Pyridylethylation of amines

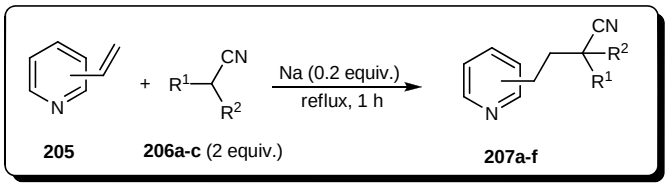
NaOMe was found suitable for amine additions to 2-methyl-5-vinylpyridine (**201a-c**), while acetic acid gave better results with 4-vinylpyridine (**201d-f**). They also showed that ammonia could be directly pyridylethylated to form 2-(aminoethyl)pyridine **203**. And pyridylethylation of an amide followed by hydrolysis could give the same amine (Scheme 2.39).

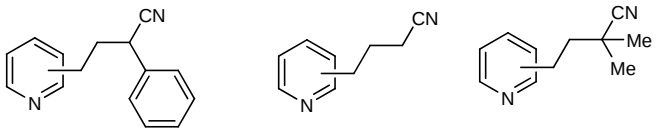


Scheme 2.39 Pyridylethylation of ammonia and amide

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

2-vinylpyridine.





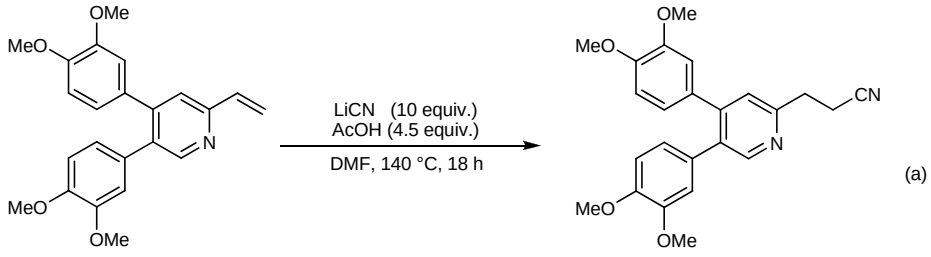
207a 2-Py (40%)
207b 4-Py (59%)

207c 2-Py (8%)
207d 4-Py (8%)

207e 2-Py (27%)
207f 4-Py (0%)

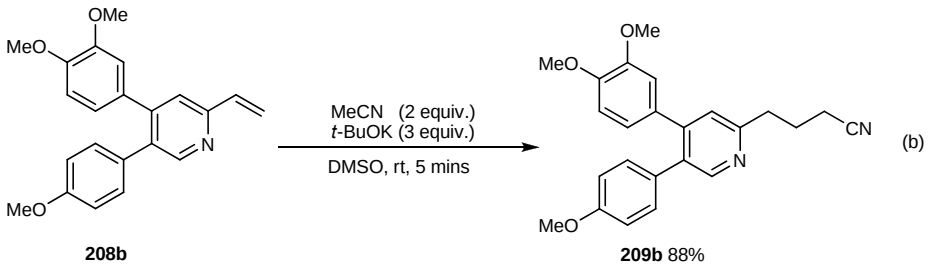
Scheme 2.40 Pyridylethylation of nitriles

Modified conditions for pyridylethylation of nitriles were applied towords the total synthesis of phenanthroizidine alkaloids by Ciufolini and Roschangar.[105] 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).



208a

209a 99%

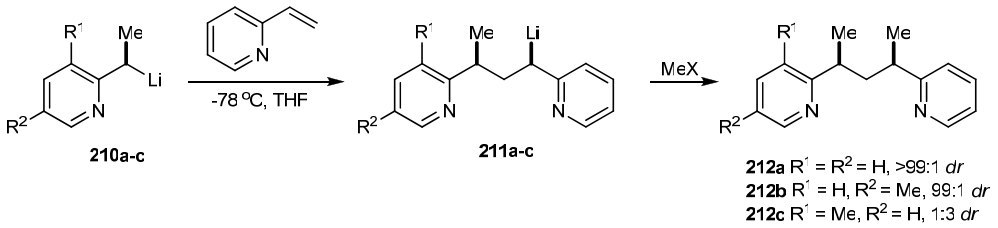


208b

209b 88%

Scheme 2.41 Preparation of intermediates for phenanthroizidine alkoloids

Since the 1980s, much attention has been drawn to make this C-C bond formation stereoselective, particularly by the alkylations of lithiocarbanions. Hogen-Esch[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 enantioselectivites in favourable cases (Scheme 2.42).

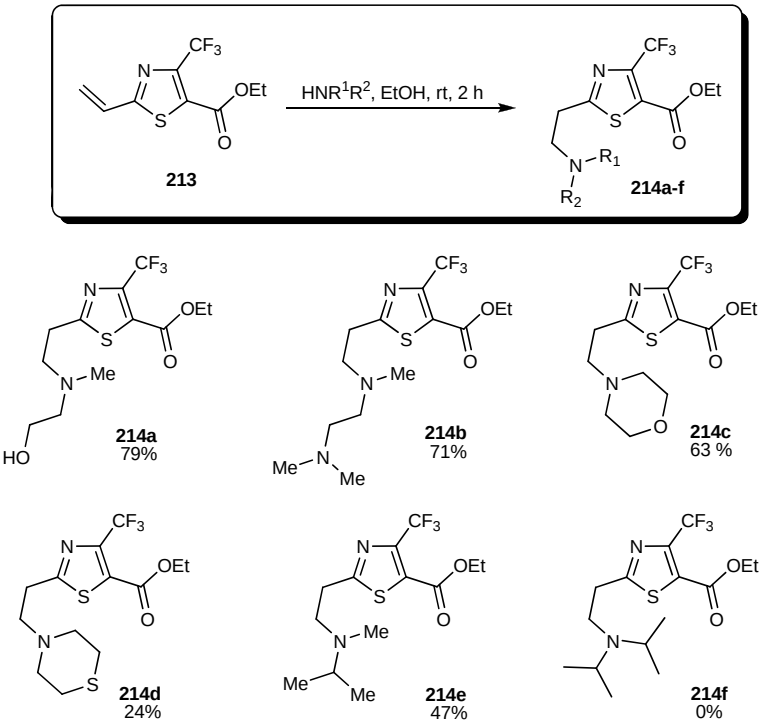


Scheme 2.42 Stereoselective alkylation of lithiocarbanion

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

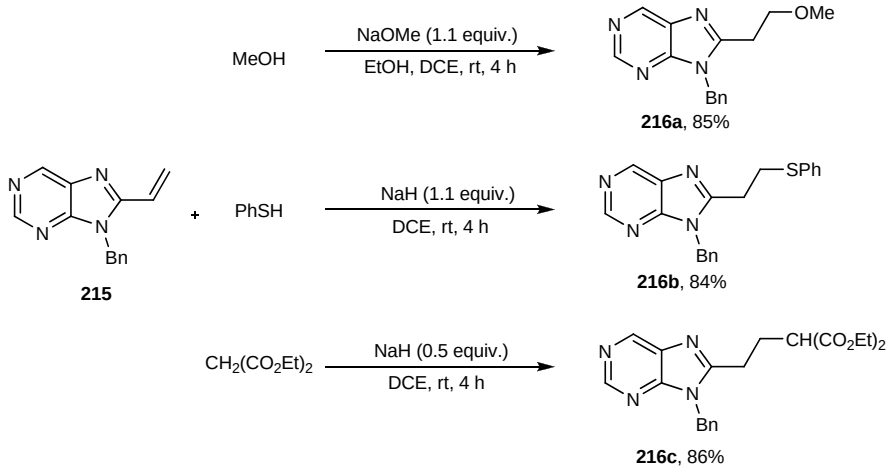
Later reports showed that various nitrogen containing heterocycles, other than pyridine, could also serve as tolerated moiety in conjugate addition reactions. 2-vinylthiazole precursor **213** underwent Michael addition with various secondary amines to furnish 2-aminoethyl-5-carbethoxythiazoles (Scheme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

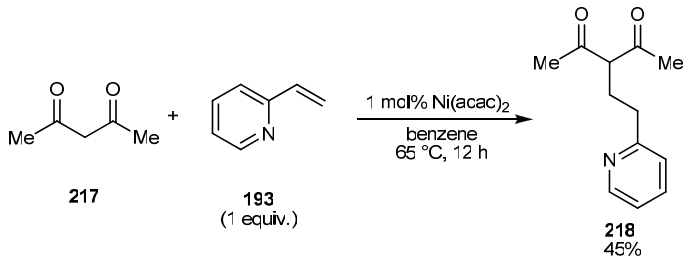
8-Vinylpurine **215**, another useful synthetic intermediate, could also react as a Michael acceptor with alcohol, thiol and ester under basic conditions (Scheme 2.44).[108] In the case of diethyl malonate, only half an equivalent of sodium hydride was used to avoid the second addition of 8-vinylpurine to the malonate.



Scheme 2.44 Conjugate addition of 8-vinylpurine

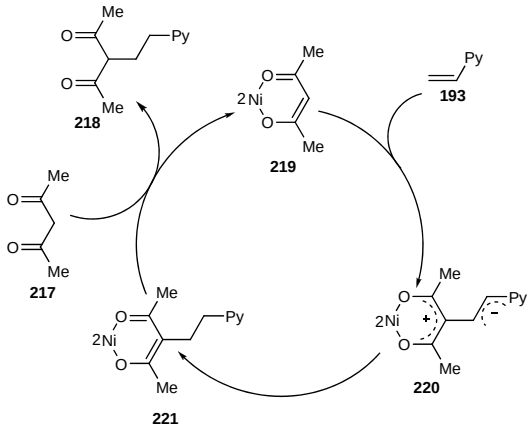
While the products of acid/base-catalysed conjugate additions suffered from undesirable side reactions and poor stereoselectivity, later reports made use of transition metal catalysts to conquer those problems.

Henry and co-workers[109] published the use of a nickel-catalysed 1,4-conjugate addition of β-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.



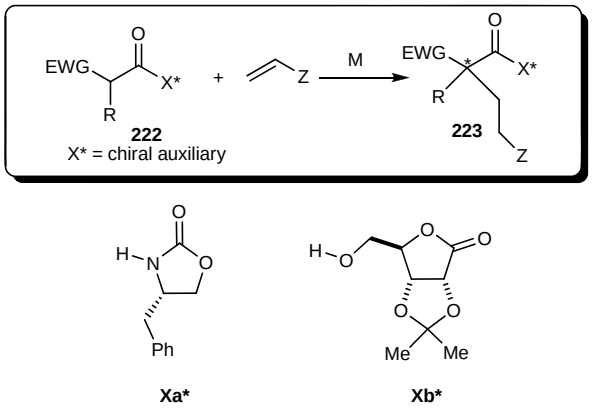
Scheme 2.45 Pyridylethylation of β-dicarbonyls using $Ni(acac)_2$

The proposed mechanism (Scheme 2.46) involved the electron-rich methylene carbon of a coordinated β-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 β-dicarbonyl substrate **217** regenerates the catalyst substrate complex **219** and releases the Michael adduct **218**.



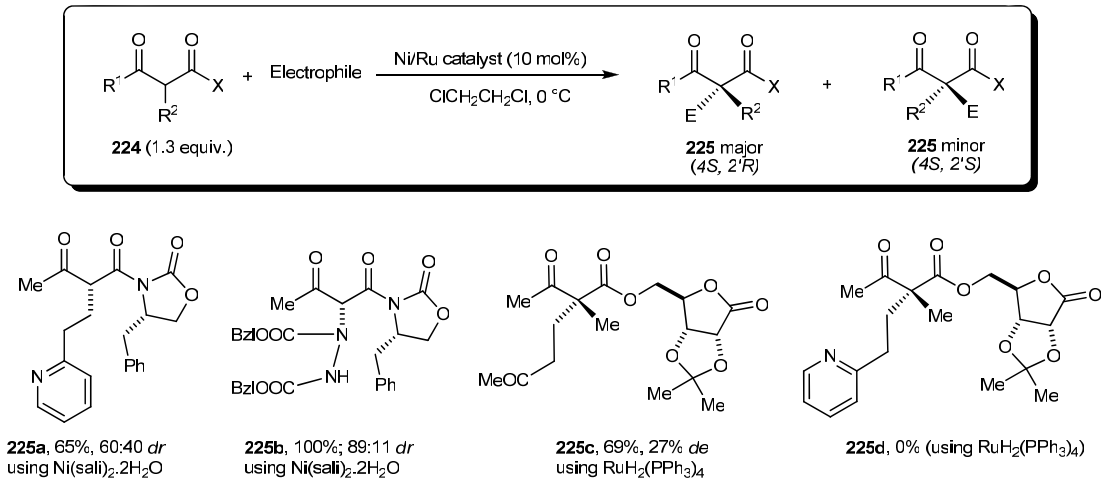
Scheme 2.46 Mechanism of $Ni(acac)_2$-catalysed Michael addition

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



Scheme 2.47 Diastereoselctive alkylation of active methylene compounds

For the substrate containing chiral auxiliary **Xa***, $Ni(salicylaldehydate)_2 \cdot 2H_2O$ 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*. $RuH_2(PPh_3)_4$ proved effective for similar conjugate addition (**225c**) with **Xb*** as the chiral inductor. However, vinylpyridine gave no desired product **225d** using ruthenium catalyst (Scheme 2.48).[111]



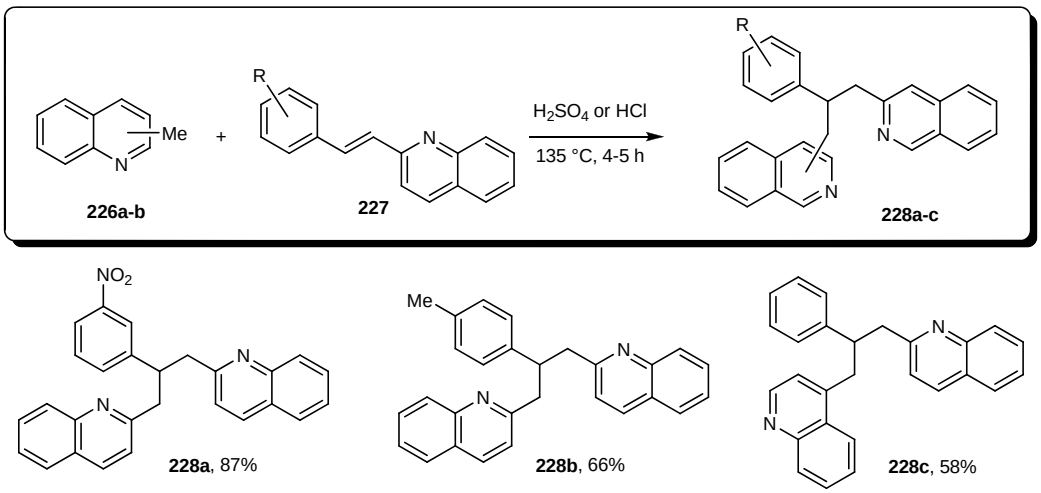
Scheme 2.48 Ni(II)-mediated reactions of (4*S*)-acetoacetyl-4-benzyloxazolidin-2-one with Michael acceptors

2.3.3) Conjugate Addition to *β*-Substituted Alkenylheteroarenes

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

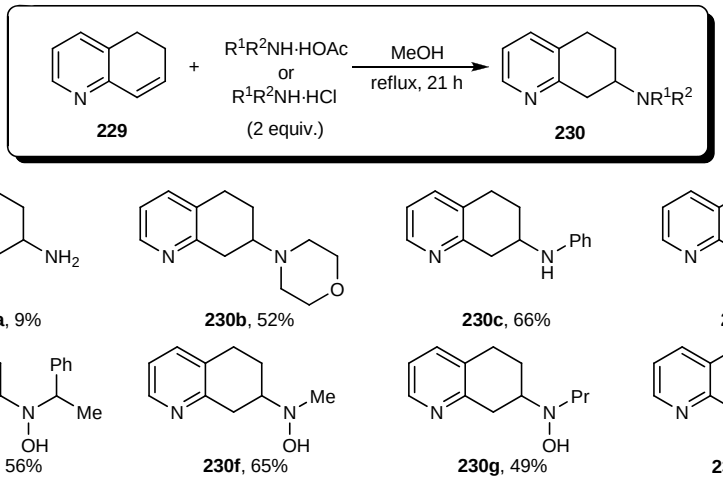
While base-catalysed conjugate addition of ketone enolates to vinylpyridines had been reported, Skidmore and Tidd addressed the addition of quinaldine **226a** and lepidine **226b** to 2-styrylquinoline **227** under acidic conditions (Scheme 2.49).[112]

Using sulfuric acid or hydrochloric acid as the catalyst, quinaldine and lepidine could add to various *β*-substituted 2-styrylquinolines to form saturated diquinolines **228a-c**.



Scheme 2.49 Addition of quinaldine and lepidine to 2-styrylquinolines

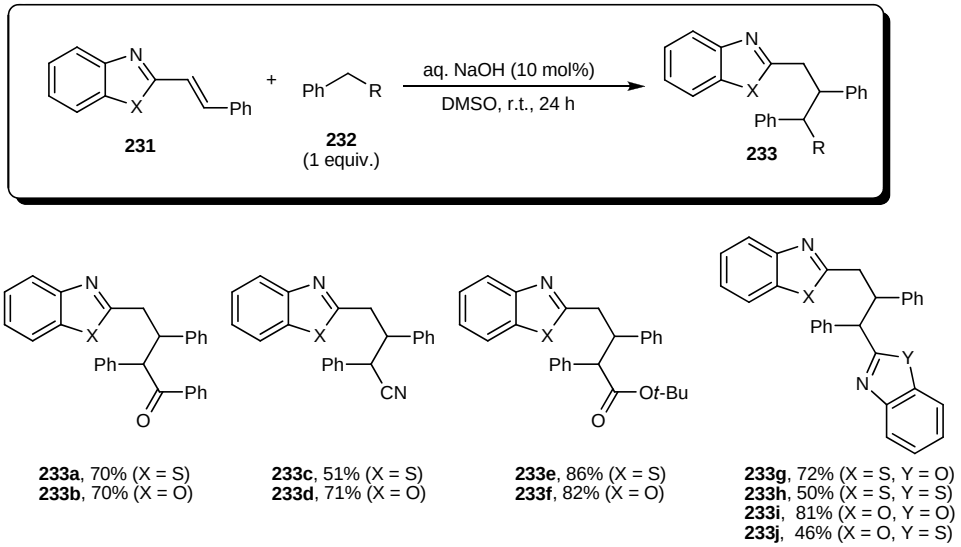
Using similar conditions as reported by Magnus and Levine, Cliffe described the high yielding reactions of nitrogen nucleophiles with 5,6-dihydroquinoline **229** for preparation of the primary amino compounds.[113] In refluxing methanol, with catalytic amount of acids, ammonium acetates or chlorides, 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).



Scheme 2.50 Preparation of 7-amino-5,6,7,8-tetrahydroquinolines

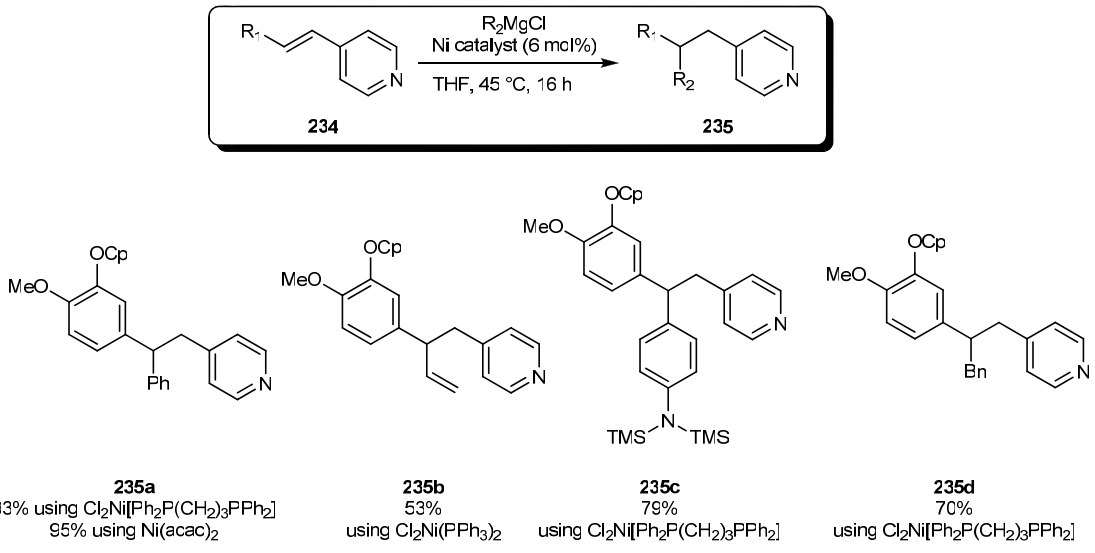
2-styrylbenzoxazoles and thiazoles **231** were applied under similar addition conditions. Dryanska and Ivanov[114] reported the conjugate addition of various

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).

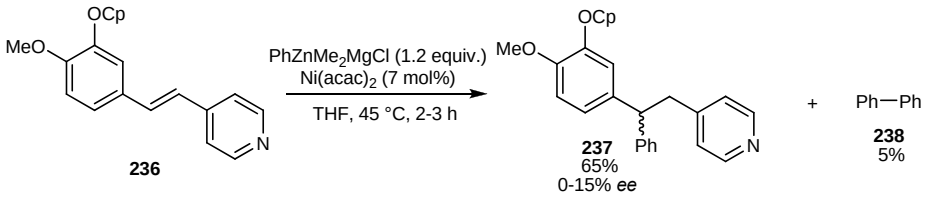


Scheme 2.52 Tri-arylation of 4-alkenylpyridines using nickel and Grignard reagent

By treating substituted 4-alkenylpyridines **234** with Grignard and organozincate reagents, Houpis mananged to synthesise triaryl-ethyl derivatives **235** containing one

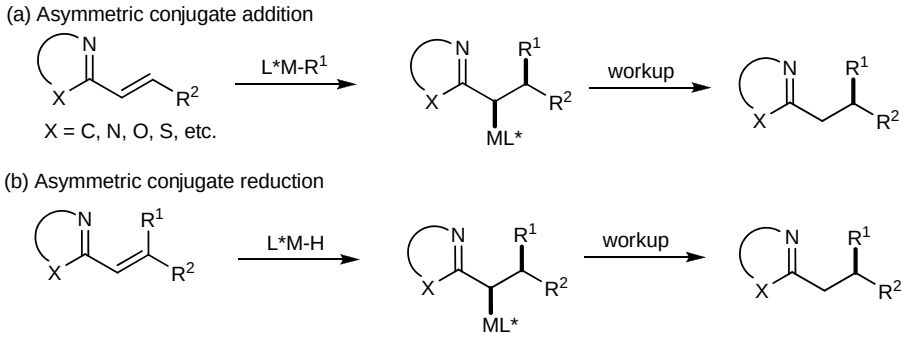
or more heteroaromatic components.[115] Gently heating the reactions dramatically improved the yields (40% at 25 °C and 93% at 45 °C for **235a**) and inhibited biphenyl and other dimer by-products.

Attempts to induce enantioselectivity in this reaction have failed. Chiral ligands such as bisphosphines, diamines, bissulfonamides, aminoalcohols, and diols gave unsatisfactory results with *ee*'s ranging from 0 to 15%. Phenyl zincate reagent[116] 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

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 ($R^2 \neq$ 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).



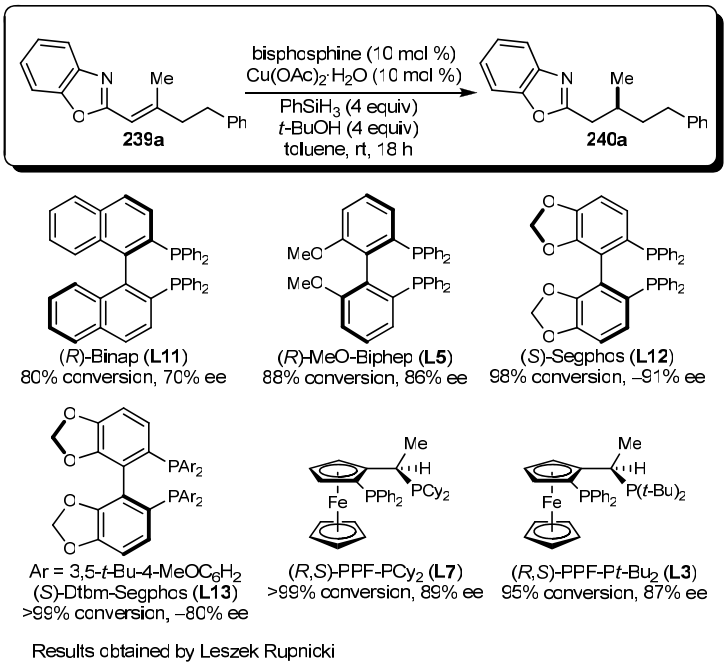
Scheme 2.54 Strategies for conjugate additions to alkenylheteroarenes

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 our 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 Lesezk Rupnicki and Aakarsh Saxena in the Lam group.[117] The 2-alkenylbenzoxazole **239a** was previously synthesised and used as a test substrate for ligand screening. 10 mol% $Cu(OAc)_2 \cdot H_2O$ 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).

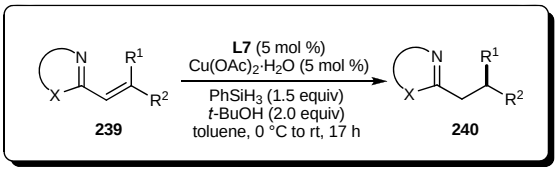


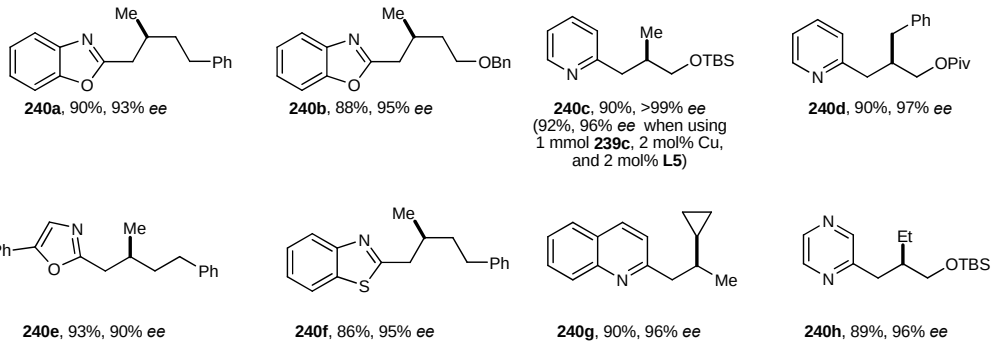
Scheme 2.55 Ligand optimisation for CuH reduction

Biaryl-based ligands **L5** and **L11-13** proved competent in promoting conjugate reduction. With (*R*)-Binap **L11**, both conversion and enantioselectivity were only moderate. Improved results were observed using (*R*)-MeO-BIPHEP **L5** and the SEGPHOS ligands **L12** and **L13**. The Josiphos ligands **L3** and **L7** were also effective, providing **240a** in 89% and 87% *ee* respectively. Of all the ligands, highest conversion was obtained with **L13** and **L7**, where the reaction completed within 2 hours. However, higher enantioselectivity was provided by **L7**, which convinced us to select this ligand for further optimisation. The effect of temperature was also examined. The reduction was run seperately 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 *β,β*-disubstituted 2-alkenylheteroarene, 5 mol% of the copper catalyst and ligand **L7**,

2.0 equivalents of *t*-BuOH, and 1.5 equivalents of $PhSiH_3$ in toluene at 0 °C to room temperature.





Results obtained by Leszek Rupnicki and Aakarsh Saxena

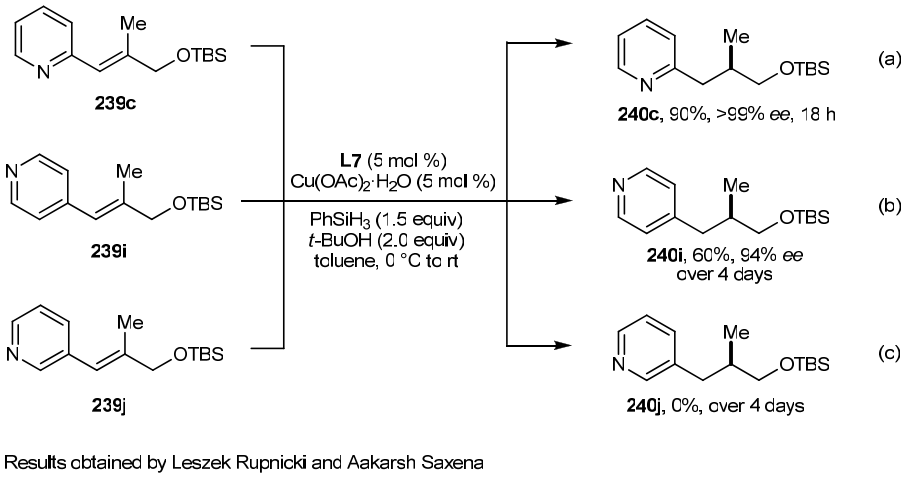
Scheme 2.56 CuH reduction of 2-alkenylheteroarene

A broad range of heteroaromatic substrates **239a-h** were prepared and reduced asymmetrically (Scheme 2.56, results obtained by Leszek Rupnicki and Aakarsh Saxena). Benzoxazoles **240a** and **240b**, pyridines **240c** and **240d**, oxazole **240e**, benzothiazole **240f**, quinoline **240g** and pyrazine **240h** all underwent asymmetric reduction with high yield and enantioselectivity. Also various functionalities at the *β*-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 **239i** and

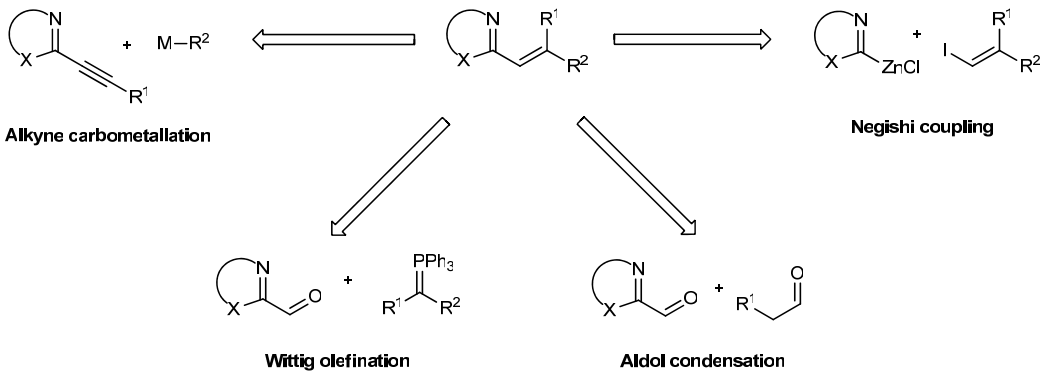
239j where the nitrogen atom was located at the *para*- and *meta*-position were attempted (Scheme 2.57). Surprisingly, the substrate **239i** with nitrogen at the *para*-position reduced asymmetrically in a 60% isolated yield and 94% *ee* after 4 days (**240i**, Scheme 2.57b). This experiment proved 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 Aakarsh 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).



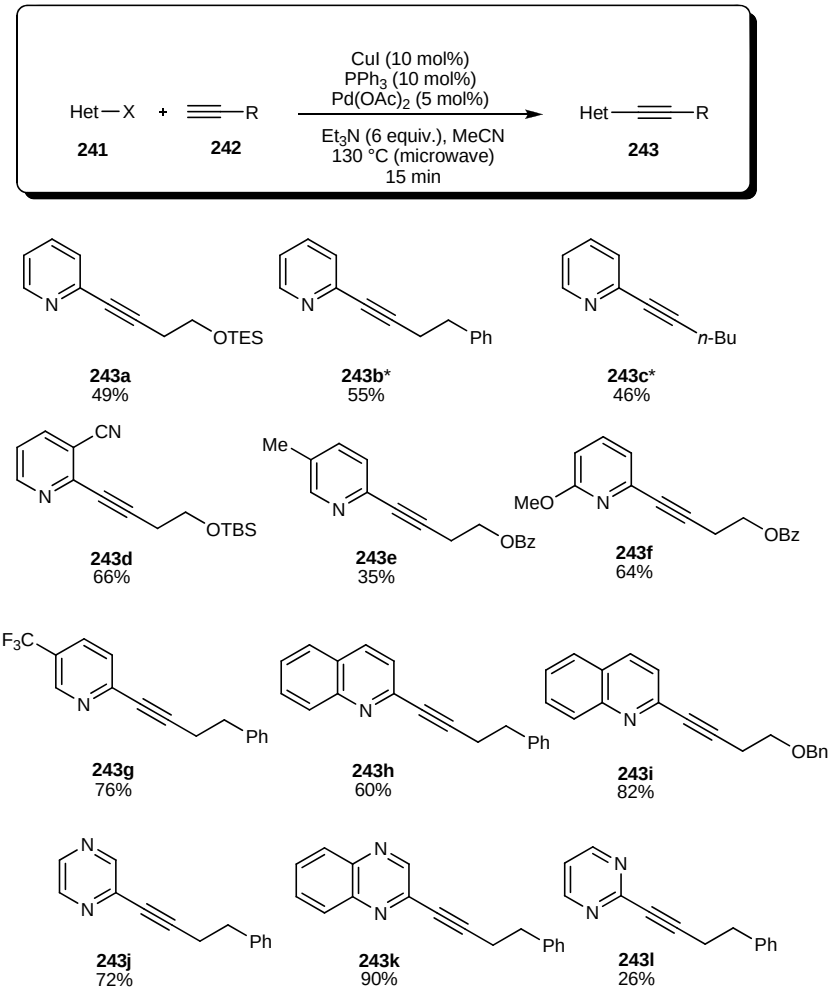
Scheme 2.58 Retrosynthesis of 2-alkenylheteroarenes

2.6.1) β,β-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

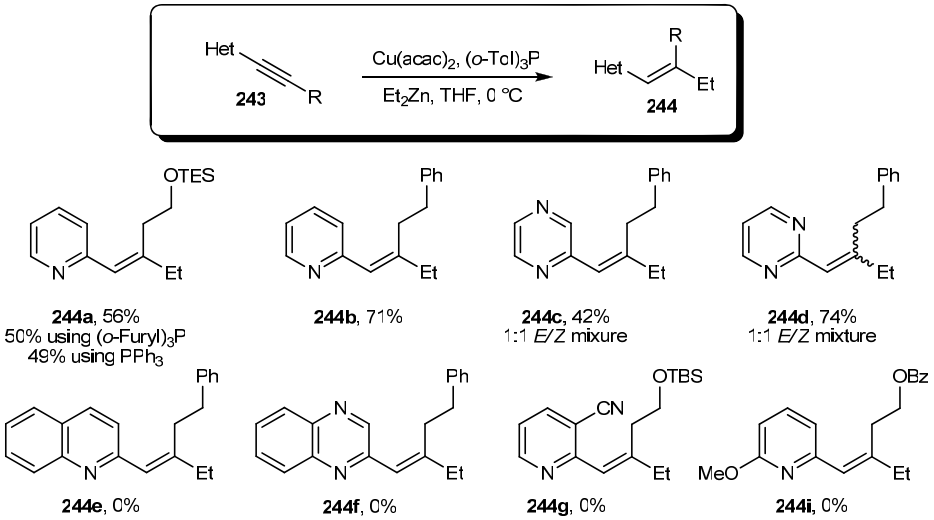
the TES group was cleaved at high temperature and decreased the yield. Pyrimidine **243i** was obtained in low yield for unclear reasons.



* **243b** and **243c** were achieved by Gordon Nimmo-Smith
Others were achieved by Yi Wang

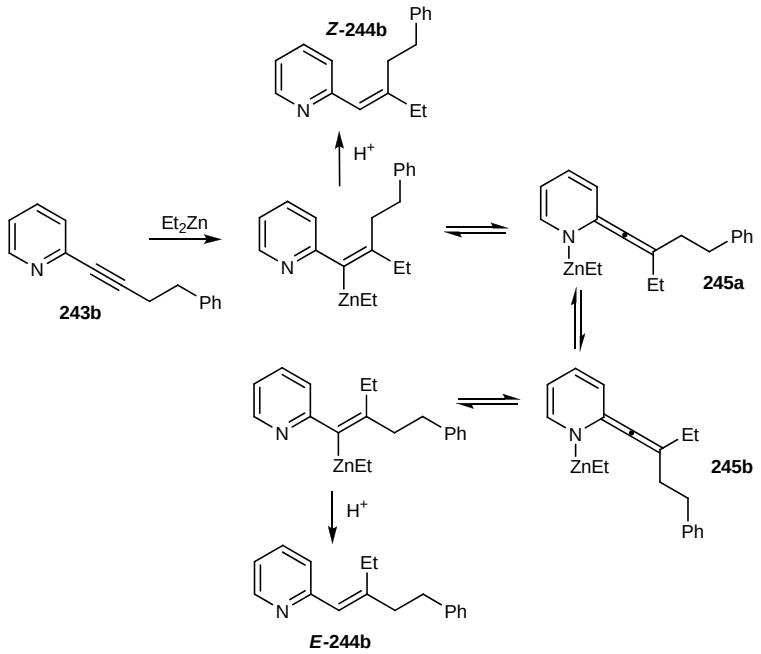
Scheme 2.59 Synthesis of 2-heteroalkynes by Sonogashira coupling

However, after some quick screening of the carbometallation conditions using alkylating agents (Et_2Zn, EtMgBr, Me_3Al) 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)$_3$P and Et_2Zn (Scheme 2.60, results achieved by Yi Wang). The low reliability of this process and limited scope discouraged further investigation.



Scheme 2.60 Carbometallation of 2-heteroalkynes

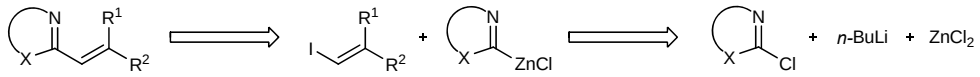
The low *E/Z* selectivity of the carbometallation step can possibly be explained by reversible formation of an allene intermediate **245** which loses *E/Z* information and the distribution of *E/Z* isomers comes from the relative energy differences of both forms (*E* and *Z*-**244b**) and the mechanism 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

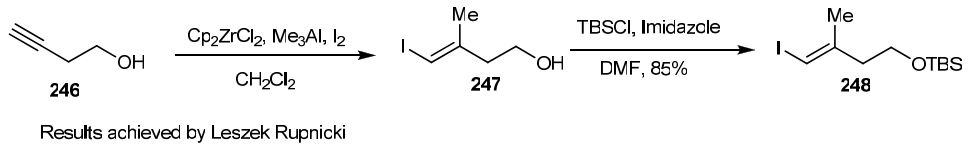
Negishi coupling

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).



Scheme 2.62 Retrosynthesis of 2-alkenylheteroarenes from Negishi coupling

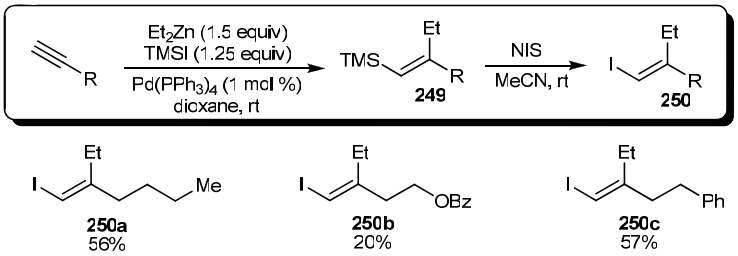
Previously in our group, vinyl iodides were obtained through carbo-alumination of substituted acetylenes with Cp_2ZrCl_2 and Me_3Al followed by quenching of the aluminium intermediates with iodine. The disadvantage of this transformation is its low reactivity with larger trialkylaluminium reagents. The 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).[118]



Results achieved by Leszek Rupnicki

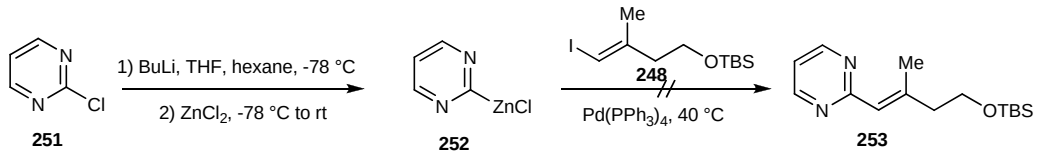
Scheme 2.63 Preparation of vinyl iodides

Following a slightly modified procedure,[119] ethyl substituted vinyl iodides were obtained through carbozincation of terminal alkynes with Et_2Zn and $Pd(PPh_3)_4$, 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.



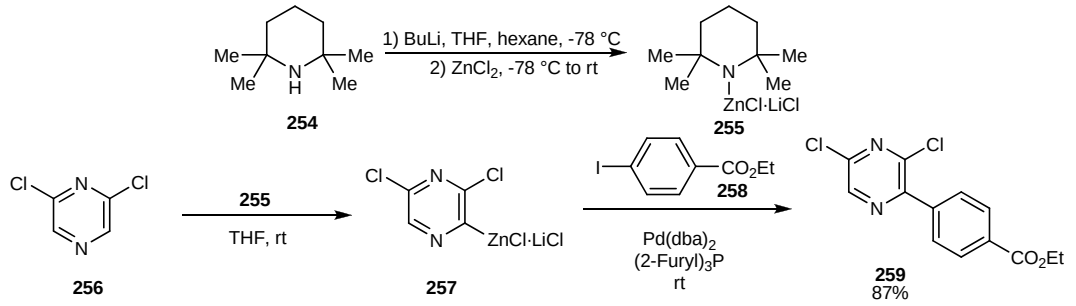
Scheme 2.64 Preparation of vinyl iodides

With those vinyl iodide building blocks prepared, the Negishi coupling was tested on various heterocycles. Unfortunately, Negishi's original conditions [120] using *n*BuLi/$ZnCl_2$ and $Pd(PPh_3)_4$ did not tolerate those heteroaromatic halides. Low reactivity was observed probably because the zinc intermediate **252** was not reactive enough in the transmetallation step of Negishi coupling (Scheme 2.65, results achieved by Yi Wang).



Scheme 2.65 Negishi coupling

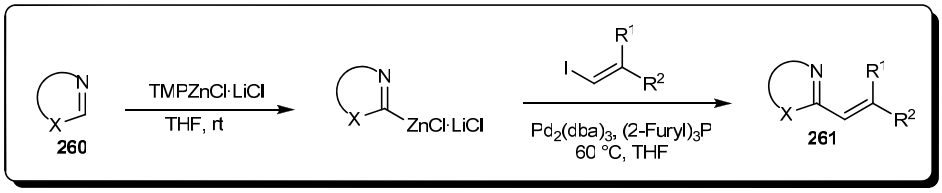
Recently, Knochel[121] has provided a powerful alternative route to activate those hindered heterocycles using a mild zinc-lithium base **255** generated from 2,2,6,6-tetramethylpiperidine (TMP, **254**), *n*BuLi and $ZnCl_2$. For instance, pyrazine **256** was deprotonated by this base and cross-coupled with electrophile **258** to give **259** in good yield (Scheme 2.66).

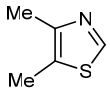
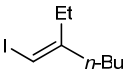
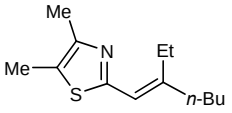
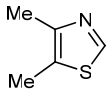
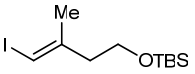
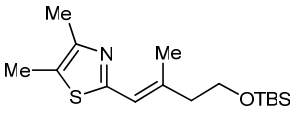
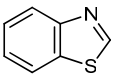
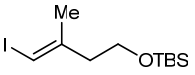
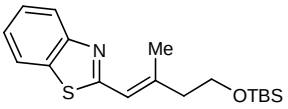
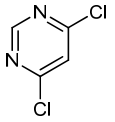
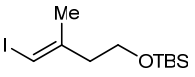
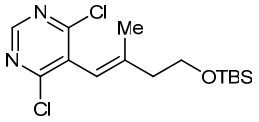
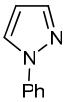
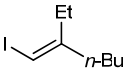
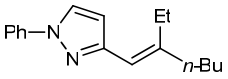
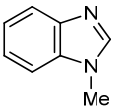
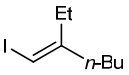
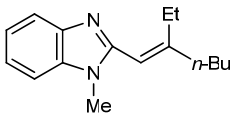
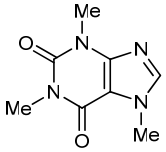
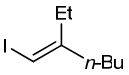
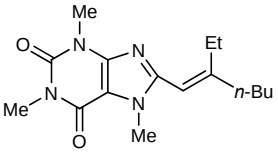


Scheme 2.66 Negishi coupling using TMP base

I employed this chemistry to synthesise new 2-alkenylheteroarenes (Table 2.1). In the first step, metallation of a range of heteroarenes at the most acidic position (normally *β*, except for entry 4 at *γ* position) by TMP base generated zinc species *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



entry	substrate		electrophile	product		yield (%)
1		**260a**			**261a**	41
2		**260a**			**261b**	10
3		**260b**			**261c**	24
4		**260c**			**261d**	17
5		**260d**			**261e**	0
6		**260e**			**261f**	0
7		**260f**			**261g**	0

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.

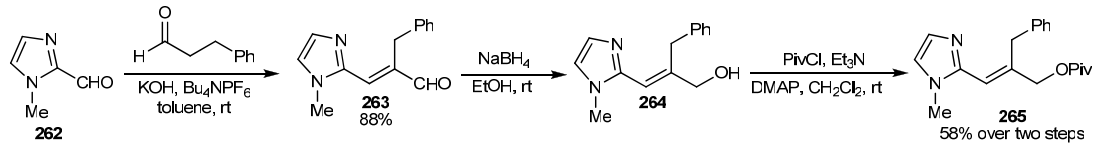
Cross aldol condensation/Wittig reaction

A few commercially available aldehydes were employed in cross aldol condensation and Wittig reaction to generate enals bearing a heteroarene at γ 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 [122] was employed to prepare β,β-disubstituted 2-alkenylheteroarenes (Scheme 2.67, results achieved by Yi Wang).

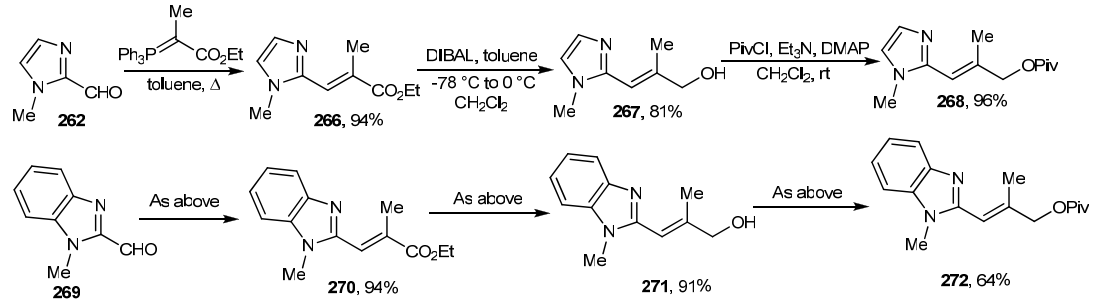
Although aldehydes conjugated with aromatic rings are stable enough in this system, there is a possibility for aliphatic aldehydes to self-condense and suppress the cross-aldol condensation. To minimise the side-reaction, the aromatic aldehyde **262**

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 *α,β*-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-alkenylheteroarene **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

Another olefination approach to obtain the *E* alkene was treating heteroarene aldehydes with stablised 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.

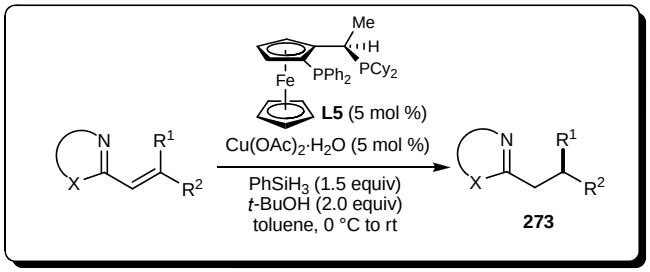


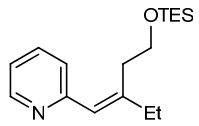
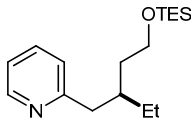
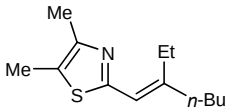
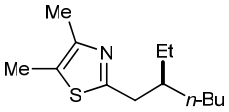
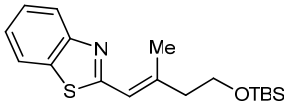
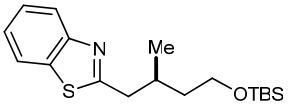
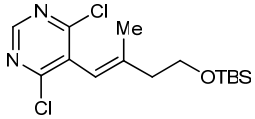
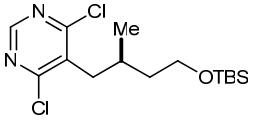
Scheme 2.68 Wittig reactions

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,[117] I performed a further extension of the copper hydride reduction scope (Table 2.2).

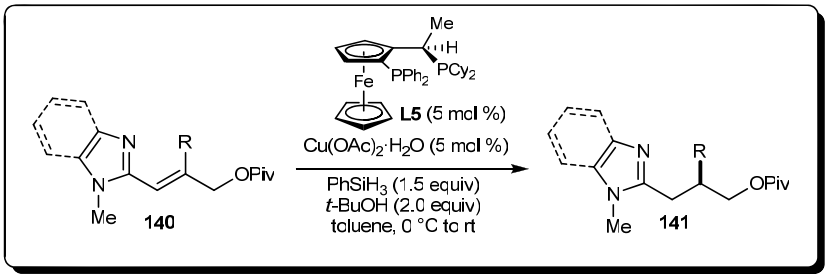
Table 2.2 CuH asymmetric conjugate reduction of 2-alkenylheteroarenes

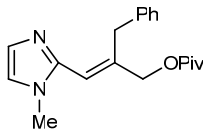
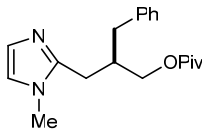
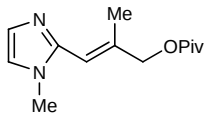
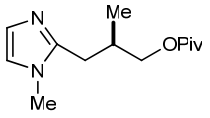
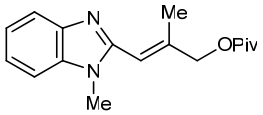
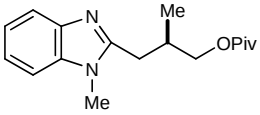


entry	substrate		product		yield (%)	ee (%)
1		**244a**		**273a**	66	>99
2		**261b**		**273b**	84	88
3		**261c**		**273c**	82	95
4		**261d**		**273d**	0	-

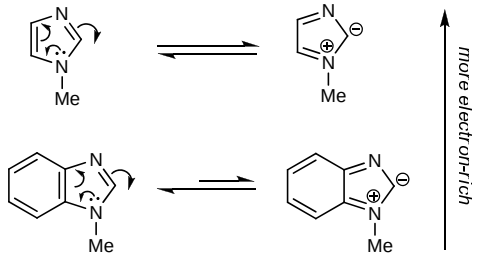
Reduction of pyridine **244a**, thiazole **261b** and benzothiazole **261c** were found to be successful, the *ee* of **261b** slightly dropped probably due to the similarity of the two *β*-alkyl substituents. Pyrimidine **261d** did not undergo reduction, because the alkene was not conjugated to C=N 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-alkenylimidiazoles



entry	substrate		product		yield (%)	ee (%)
1		**265**		**274a**	0	-
2		**268**		**274b**	0	-
3		**272**		**274c**	61	97

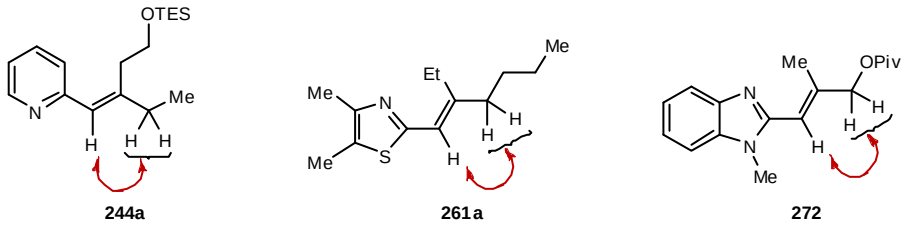
Imidiazoles **265** and **268** failed to reduce under the standard conditions. Although I initially suspected that the bulky substituent at β position of substrate **265** decreased reactivity, the failure of **268** to reduce suggested that steric hindrance was not a problem. Imidazoles are relatively 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).



Scheme 2.69 Electron-rich imidazole systems

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%).

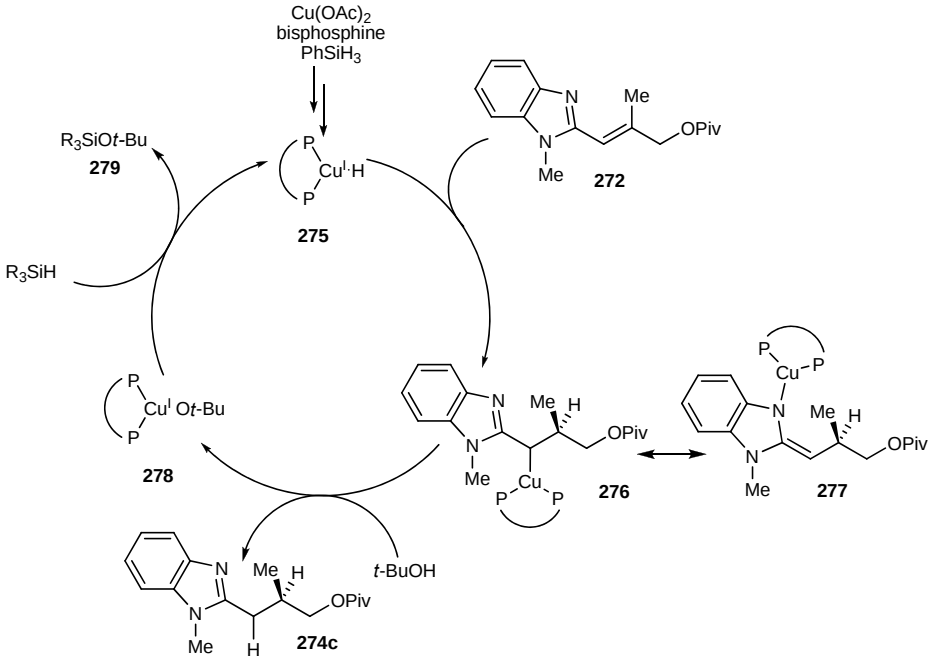
The stereochemistry of **244a**, **261a** and **272** were determined using NOE experiments, which displayed the following diagnostic enhancement:



Scheme 2.70 The mechanism for CuH reduction of 2-alkenylbenzoimidazole

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**.



Scheme 2.71 The mechanism for CuH reduction of 2-alkenylbenzoimidazole

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

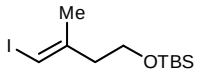
General Information

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

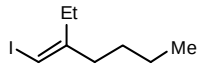
[a] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

plates or as a dilute solution in $CHCl_3$. ^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 ($CDCl_3$ at 7.27 ppm). Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q, (quartet), app (apparent), br (broad). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Proton-decoupled ^{13}C NMR spectra were recorded on a Bruker 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 ($CDCl_3$ at 77.0 ppm, CD_3OD 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.

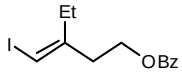
Preparation of Starting Materials



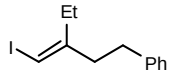
(*E*) 1-(*t*-Butyldimethylsiloxy)-4-iodo-3-methyl-3-butene (248).[b] Prepared according to previously reported procedures.



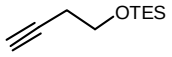
(*E*)-3-(Iodomethylene)heptane (250a).[c] Prepared according to previously reported procedures.



(*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.



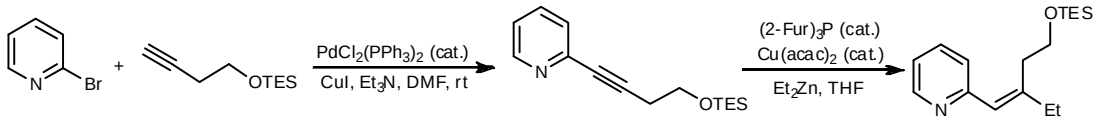
3-Triethylsilyloxybut-1-yne (242a). To a solution of 3-butynol (3.50 g, 50.0 mmol), Et_3N (10.5 mL, 75.0 mmol), and DMAP (300 mg, 2.50 mmol) in CH_2Cl_2 (200 mL) at room temperature was added chlorotriethylsilane (10.0 mL, 60.0 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (200 mL) and extracted with CH_2Cl_2 (3 x 100 mL). The combined organic layers were dried (Na_2SO_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}; ^1H NMR (500 MHz, $CDCl_3$) δ 3.73 (2H, t, *J* = 7.2 Hz, C**H**$_2$O), 2.41 (2H, dt, *J* = 7.2, 2.7 Hz, C**H**$_2$CH$_2$O), 1.96 (1H, t, *J* = 2.7 Hz, ≡C**H**), 0.96 (9H, t, *J* = 8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 0.61 (6H, q,

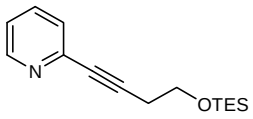
[b] Marshall, J. A.; Eidam, P. *Org. Lett.* **2004**, 6, 445-448.

[c] Normant, J-F.; Cahiez, G.; Chuit, C. *J. Organomet. Chem.* **1974**, 77, 269-279

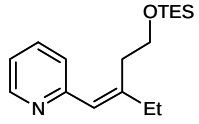
J = 8.0 Hz, Si(C**H**$_2$CH$_3$)$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 81.4 (C), 69.3 (CH), 61.4 (CH_2), 22.8 (CH_2), 6.7 (3 x CH_3), 4.3 (3 x CH_2).

Preparation of Alkenyl Pyridine





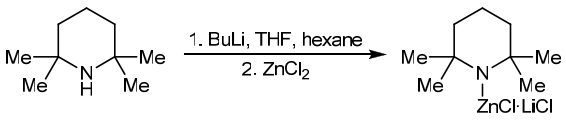
2-(4-Triethylsilyloxybut-1-ynyl)pyridine (243a). To a solution of $PdCl_2(PPh_3)_2$ (701 mg, 1.00 mmol), CuI (96 mg, 0.50 mmol), and 3-triethylsilyloxybut-1-yne **242a** (5.10 g, 30.0 mmol) in DMF (30 mL) at room temperature was added 2-bromopyridine (1.90 mL, 20.0 mmol) followed by Et_3N (11.2 mL, 80 mmol). The mixture was stirred at room temperature for 72 h, quenched with saturated aqueous NH_4Cl solution (100 mL), and extracted with Et_2O (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 *alkynylpyridine* **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, Ar**H**), 7.59 (1H, dt, J = 7.7, 1.8 Hz, Ar**H**), 7.35 (1H, td, J = 7.8, 1.1 Hz, Ar**H**), 7.17 (1H, ddd, J = 7.6. 4.9, 1.2 Hz, Ar**H**), 3.84 (2H, t, J = 7.4 Hz, C**H**$_2$O), 2.67 (2H, t, J = 7.4 Hz, C**H**$_2$CH$_2$O), 0.96 (6H, t, J = 7.9 Hz, Si(CH$_2$C**H**$_3$)$_3$), 0.65-0.58 (9H, m, Si(C**H**$_2$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 Et_2Zn (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 ($MgSO_4$), 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, $CDCl_3$) δ 8.56 (1H, d, *J* = 4.0 Hz, Ar**H**), 7.59 (1H, app dt, *J* = 7.7, 1.8 Hz, Ar**H**), 7.27 (1H, d, *J* = 7.9 Hz, Ar**H**), 7.06 (1H, app dd, *J* = 6.9, 5.1 Hz, Ar**H**), 6.35 (1H, s, =C**H**), 3.79 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$O), 2.81 (2H, t, *J* = 7.4 Hz, C$\mathbf{H}_2$$CH_2$O), 2.25 (2H, dq, *J* = 7.4, 1.4 Hz, =CC$\mathbf{H}_2$$CH_3$), 1.14 (3H, t, *J* = 7.4 Hz, CH_2C$\mathbf{H}_3$), 0.95 (6H, t, *J* = 7.9 Hz, Si(CH_2C$\mathbf{H}_3$)$_3$), 0.60 (9H, q, *J* = 7.9 Hz, Si(C$\mathbf{H}_2$$CH_3$)$_3$; ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 157.1 (C), 149.1 (CH), 146.3 (C), 135.8 (CH), 124.9 (CH), 123.7 (CH), 120.6 (CH), 61.6 (CH_2), 35.1 (CH_2), 31.5 (CH_2), 12.6 (CH_3), 6.7 (3 x CH_3), 4.3 (3 x CH_2); HRMS (EI) Exact mass calcd for $C_{17}H_{29}NOSi$ $[M]^+$: 291.2013, found: 291.2013.

Preparation of the reagent TMPZnCl·LiCl

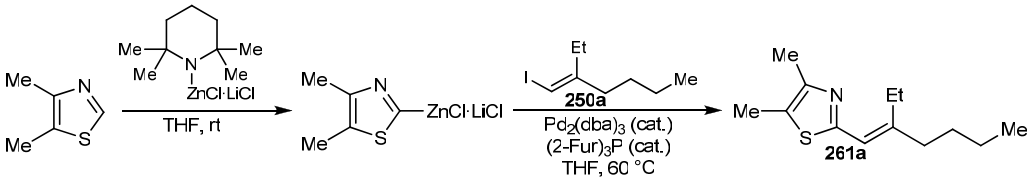


A dry and argon-flushed 100 mL Schlenk flask, equipped with a magnetic stirrer and a septum, was charged with freshly distilled 2,2,6,6-tetramethylpiperidine (3.40 mL, 20.0 mmol) dissolved in THF (20 mL). This solution was cooled to -40 °C and *n*-BuLi (2.5 M in hexane, 8 mL, 20 mmol) was dropwise. After the addition was complete, the reaction mixture was allowed to warm up slowly to -10 °C for 1 h. $ZnCl_2$ (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

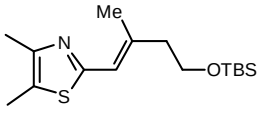
prepared TMPZnCl·LiCl solution was titrated prior to use at 25 °C with benzoic acid using Methyl Orange as the indicator.

Negishi Coupling Reactions Using TMPZnCl·LiCl

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

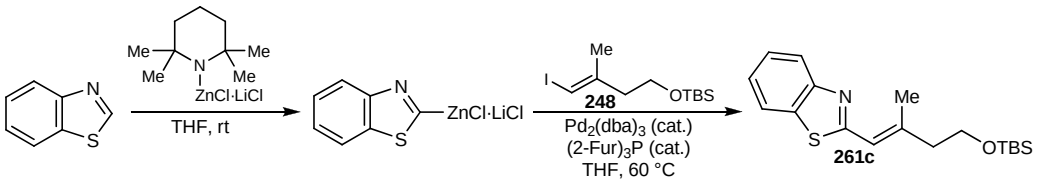


To a solution of TMPZnCl·LiCl (0.25 M in THF/hexane, 12.0 mL, 3.0 mmol) at room temperature was added a solution of 4,5-dimethylthiazole (350 mg, 3.00 mmol) in THF (2 mL) *via* cannula over 1 min and the mixture was stirred for 30 min. To this mixture was added a solution of alkenyl iodide **250a** (476 mg, 2.00 mmol), $Pd(dba)_2$ (57 mg, 0.10 mmol), and $(2\text{-Fur})_3P$ (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 NH_4Cl solution (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried ($NaSO_4$), 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}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.41 (1H, s, =C**H**), 2.51 (2H, q, *J* = 7.5 Hz, =CC**H**$_2$CH$_3$), 2.35 (3H, s, ArC**H**$_3$), 2.31 (3H, s, ArC**H**$_3$), 2.19 (2H, t, *J* = 7.5 Hz, =CC**H**$_2$CH$_2$), 1.53-1.45 (2H, m, =CCH$_2$C**H**$_2$), 1.40-1.30 (2H, m, CH$_2$C**H**$_2$CH$_3$), 1.11 (3H, t, *J* = 7.5 Hz, =CCH$_2$C**H**$_3$), 0.92 (3H, t, *J* = 7.3 Hz, CH$_2$CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 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_4Cl solution (20 mL), extracted with diethyl ether (3 × 50 mL) and dried over anhydrous Na_2SO_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}; ^1H NMR (360 MHz, $CDCl_3$) δ 6.48 (1H, s, =C**H**), 3.78 (2H, t, *J* = 7.0 Hz, C**H**$_2$), 2.42 (2H, t, *J* = 6.9 Hz, C**H**$_2$), 2.35 (3H, s, C**H**$_3$), 2.32 (3H, s, C**H**$_3$), 2.08 (3H, s, C**H**$_3$), 0.89 (9H, s, SiC(C**H**$_3$)$_3$), 0.05 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 160.9 (C), 147.7 (C), 140.8 (C), 125.6 (C), 121.1 (CH), 62.1 (CH_2), 44.3 (CH_2), 25.9 (3 x CH_3), 19.5 (CH_3), 18.3 (C), 14.6 (CH_3), 11.2 (CH_3), -5.3 (2 x CH_3); HRMS (ESI) Exact mass calcd for $C_{16}H_{30}ONSSi$ $[M+H]^+$: 312.1812, found: 312.1808.

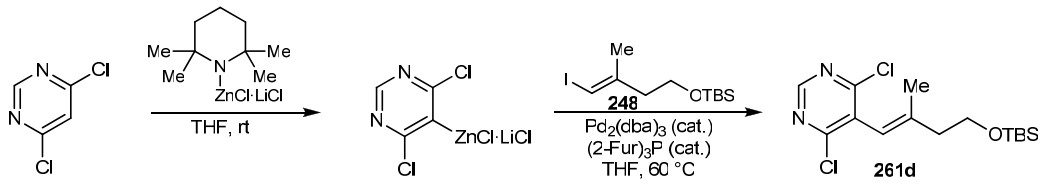
2-[(*E*)-4-(*tert*-Butyldimethylsilyloxy)-2-methylbut-1-enyl]benzothiazole (261c).



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)$_3$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_4Cl solution (20 mL) and extracted with Et_2O (3 x 50 mL). The combined organic layers were dried ($NaSO_4$), 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}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 8.00 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.87 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.49-7.44 (1H, m, Ar**H**), 7.37-7.33 (1H, m, Ar**H**), 6.65 (1H, s, =C**H**), 3.85 (2H, t, *J* = 6.7 Hz, C**H**$_2$O), 2.51 (2H, t, *J* = 6.7 Hz, C**H**$_2$CH$_2$O), 2.30 (3H, s, CH=CC**H**$_3$), 0.90 (9H, s, SiC(C**H**$_3$)$_3$), 0.07 (6H, s, Si(C**H**$_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_2), 44.5 (CH_2), 25.9 (3 x CH_3), 19.9 (CH_3), 18.3 (C), -5.3 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{18}H_{28}ONSSi$ $[M+H]^+$: 334.1655, found: 334.1658.

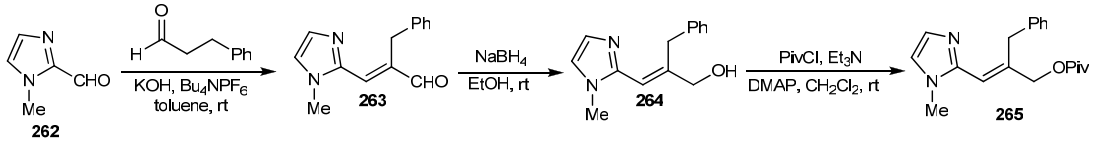
(*E*)-5-(4-(tert-butyldimethylsilyloxy)-2-methylbut-1-enyl)-4,6-dichloropyrimidine (261d).

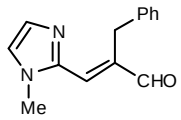


4,6-Dichloropyrimidine (0.29 g, 2.0 mmol) in THF (10 mL) was added to a solution of TMPZnCl·LiCl (0.25 M in THF, 8 mL, 2.0 mmol) at 25 °C and the reaction mixture was then stirred at this temperature for 30 min $Pd_2(dba)_3$ (46 mg, 2.5 mol%) and P(*o*-furyl)$_3$ (46 mg, 10 mol%) dissolved in THF (5 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_4Cl solution (20 mL), extracted with diethyl

ether (3 × 50 mL) and dried over anhydrous Na_2SO_4. 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, $CDCl_3$) δ 8.66 (1H, s, Ar**H**), 6.02 (1H, s, =C**H**), 3.84 (2H, t, *J* = 6.5 Hz, C$\mathbf{H}_2$), 2.46 (2H, t, *J* = 6.5 Hz, C$\mathbf{H}_2$), 1.62 (3H, s, C$\mathbf{H}_3$), 0.91 (9H, s, SiC(C$\mathbf{H}_3$)$_3$), 0.08 (6H, s, Si(C$\mathbf{H}_3$)$_2$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 161.5 (C), 155.9 (CH), 144.1 (2 x C), 130.7 (C), 116.8 (CH), 61.6 (CH_2), 42.3 (CH_2), 25.9 (3 x CH_3), 19.0 (CH_3), 18.2 (C), -5.4 (2 x CH_3); HRMS (ES) Exact mass calcd for $C_{15}H_{24}Cl_2N_2OSi$ $[M]^+$: 346.1029, found: 346.1021.

Preparation of Alkenyl Imidazoles

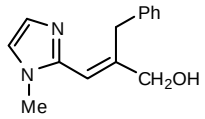




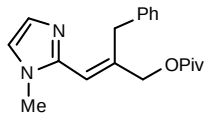
(*E*)-2-Benzyl-3-(1-methyl-1H-imidazol-2-yl)-propenal (263). Following a slight modification of a literature procedure for a similar compound,[d] to a vigorously stirred suspension of Bu_4NPF_6 (387 mg, 1.00 mmol) and KOH (84 mg, 1.50 mmol) in toluene (35 mL) was added 1-methyl-2-imidazole-carboxaldehyde **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 H_2O (50 mL) and CH_2Cl_2 (50 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layers were dried (Na_2SO_4) 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

[d]. Kryshtal, G. V.; Zhdankina, G. M.; Zlotin, S. G. *Eur. J. Org. Chem.* **2005**, 2822-2827.

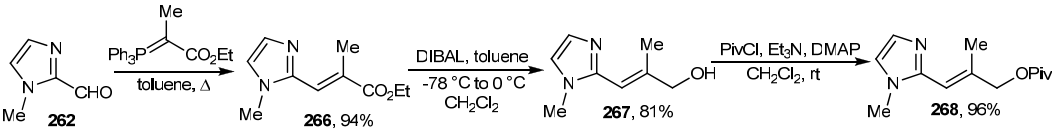
yellow solid. m.p. 108-110 °C; IR ($CHCl_3$) 3029, 2828, 2716, 1673 (C=O), 1625 (C=C), 1476, 1420, 1285, 1240, 1126; ^{1}H NMR (360 MHz, $CDCl_3$) δ 9.58 (1H, s, C**H**O), 7.46-7.44 (2H, m, Ar**H**), 7.33 (1H, s, C**H**=CCH_2Ph), 7.25-7.14 (3H, m, Ar**H**), 7.06-7.04 (2H, m, Ar**H**), 4.50 (2H, s, C$\mathbf{H}_2$Ph), 3.77 (3H, s, NC$\mathbf{H}_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) 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 (CH_3), 29.9 (CH_2); HRMS (ESI) Exact mass calcd for $C_{14}H_{15}ON_2$ $[M+H]^+$: 227.1179, found: 227.1181.

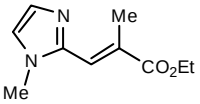


(*E*)-2-Benzyl-3-(1-methyl-1H-imidazol-2-yl)-prop-2-en-1-ol (264). To a solution of aldehyde **263** (452 mg, 2.00 mmol) and $CeCl_3 \cdot 7H_2O$ (894 mg, 2.40 mmol) in EtOH (20 mL) at room temperature was added $NaBH_4$ (227 mg, 6.00 mmol) portionwise over 5 min. The resulting mixture was stirred at room temperature for 1 h and quenched carefully with saturated aqueous NH_4Cl 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 ($MgSO_4$) 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}; ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.25-7.14 (5H, m, Ar**H**), 7.06 (1H, s, Ar**H**), 6.83 (1H, s, Ar**H**), 6.42 (1H, s, C**H**=CCH_2Ph), 4.11 (2H, d, J = 7.1 Hz, C$\mathbf{H}_2$OH), 4.07 (2H, s, C$\mathbf{H}_2$Ph), 3.58 (3H, s, NC$\mathbf{H}_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) 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 (CH_2), 35.0 (CH_2), 32.9 (CH_3); HRMS (ESI) Exact mass calcd for $C_{14}H_{17}N_2O$ $[M+H]^+$: 229.1335, found: 229.1334.



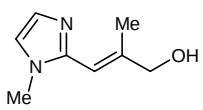
2,2-Dimethyl-propionic acid (*E*)-2-benzyl-3-(1-methyl-1H-imidazol-2-yl)-allyl ester (265). To a solution of the alcohol **264** (200 mg, 0.88 mmol), Et_3N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) at room temperature was added trimethylacetyl chloride (246 μL, 2.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (10% EtOAc/hexane) gave the *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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.26-7.16 (5H, m, Ar**H**), 7.13 (1H, s, Ar**H**), 6.88 (1H, s, Ar**H**), 6.37 (1H, s, C**H**=CCH_2Ph), 4.56 (2H, d, J = 0.8 Hz, C$\mathbf{H}_2$O), 4.22 (2H, s, C$\mathbf{H}_2$Ph), 3.65 (3H, s, NC$\mathbf{H}_3$), 1.23 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 177.9 (C), 144.1 (C), 141.0 (C), 138.9 (C), 128.9 (2 x CH), 128.4 (2 x CH), 128.2 (CH), 126.1 (CH), 120.7 (CH), 113.1 (CH), 66.9 (CH_2), 38.8 (C), 35.0 (CH_2), 32.8 (CH_3), 27.2 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{19}H_{25}N_2O_2$ $[M+H]^+$: 313.1911, found: 313.1909.



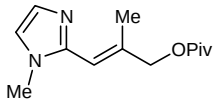


Ethyl (*E*)-2-methyl-3-(1-methyl-1*H*-imidazol-2-yl)propenoate (266). A solution of 1-methyl-2-imidazole carboxaldehyde **262** (550 mg, 5.00 mmol) and (carbethoxyethylidene)triphenylphosphorane (94%, 2.31 g, 6.00 mmol) in toluene (50 mL) was heated under reflux for 18 h. After cooling to room temperature, the mixture was concentrated *in vacuo* and the residue was purified by column chromatography (50% EtOAc/hexane→80% EtOAc/hexane) to give the *alkene* **266** (760 mg, 78%) as a white solid. m.p. 72-74 °C. IR ($CHCl_3$) 3127, 2978,

1695 (C=O), 1483, 1424, 1276, 1160, 1107, 1082, 990 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.43 (1H, s, Ar**H**), 7.23 (1H, s, Ar**H**), 6.94 (1H, s, =C**H**), 4.28 (2H, q, *J* = 7.2 Hz, OC**H**$_2$), 3.74 (3H, s, NC**H**$_3$), 2.47 (3H, d, *J* = 1.3 Hz, =CC**H**$_3$), 1.35 (3H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 168.6 (C), 143.8 (C), 131.1 (C), 129.8 (CH), 122.1 (CH), 121.5 (CH), 61.0 (CH_2), 33.1 (CH_3), 14.3 (CH_3), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{10}H_{15}N_2O_2$ $[M+H]^+$: 195.1128, found: 195.1127.

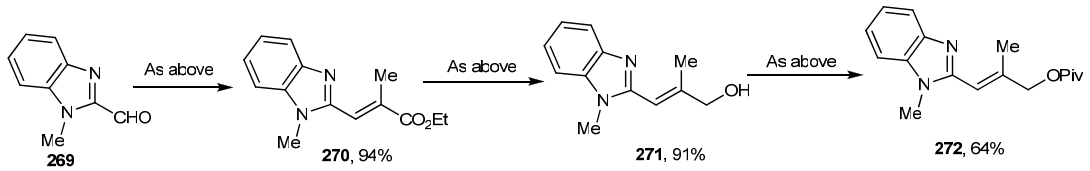


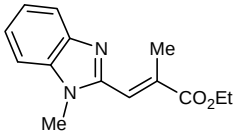
(*E*)-2-Methyl-3-(1-methyl-1*H*-imidazol-2-yl)prop-2-en-1-ol (267). To a solution of the ester **266** (585 mg, 3.0 mmol) in CH_2Cl_2 (50 mL) at -78 °C was added DIBAL (1.0 M in hexane, 6.5 mL, 6.5 mmol) over 2 min, and the resulting mixture was stirred at -78 °C for 1.5 h, then at -20 °C for 1 h, and 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 CH_2Cl_2 (3 x 50 mL), and the combined organic layers were dried (Na_2SO_4), 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, $CDCl_3$) δ 7.03 (1H, s, Ar**H**), 6.80 (1H, s, Ar**H**), 6.30 (1H, br s, =C**H**), 4.15 (2H, s, C**H**$_2$O), 3.56 (3H, s, NC**H**$_3$), 2.03 (3H, s, =CC**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 145.5 (C), 145.1 (C), 127.6 (CH), 120.1 (CH), 108.8 (CH), 67.0 (CH_2), 32.8 (CH_3), 15.7 (CH_3).



(*E*)-2-Methyl-3-(1-methyl-1*H*-imidazol-2-yl)propenyl pivaloate (268). To a solution of the alcohol **267** (210 mg, 1.50 mmol), Et_3N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) at room temperature was added trimethylacetyl chloride

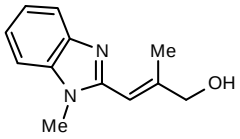
(369 μL, 3.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo* 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, $CDCl_3$) δ 7.10 (1H, d, *J* = 0.9 Hz, Ar**H**), 6.82 (1H, d, *J* = 0.9 Hz, Ar**H**), 6.24 (1H, app d, *J* = 1.3 Hz, =C**H**), 4.64 (2H, s, C**H**$_2$O), 3.60 (3H, s, NC**H**$_3$), 2.18 (3H, s, =CC**H**$_3$), 1.24 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 178.0 (C), 144.5 (C), 138.7 (C), 128.1 (CH), 120.4 (CH), 111.9 (CH), 68.9 (CH_2), 38.8 (C), 32.8 (CH_3), 27.2 (3 x CH_3), 15.9 (CH_3); HRMS (ES) Exact mass calcd for $C_{13}H_{22}N_2O_2$ $[M+H]^+$: 237.1598, found: 237.1595.



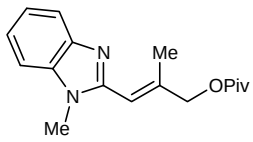


Ethyl (*E*)-2-methyl-3-(1-methyl-1*H*-benzoimidazol-2-yl)propenoate (270). A solution of 1-methylbenzimidazole-2-carboxaldehyde **269** (480 mg, 3.00 mmol) and (carbethoxyethylidene)triphenylphosphorane (94%, 1.54 g, 4.00 mmol) in toluene (30 mL) was heated under reflux for 18 h. After cooling to room 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 ($CHCl_3$) 2977, 1698 (C=O), 1641, 1459, 1374, 1324, 1293, 1264, 1243, 1159 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.86-7.82 (1H, m, Ar**H**), 7.62 (1H, q, *J* = 1.5 Hz, =C**H**), 7.36-7.28 (3H, Ar**H**), 4.34 (2H, q, *J* = 7.1 Hz, OC**H**$_2$), 3.83 (3H, s, NC**H**$_3$), 2.60 (3H, d, *J* = 1.5 Hz, =CC**H**$_3$), 1.40 (3H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$); ^{13}C 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), 14.2 (CH_3); HRMS (ES) Exact mass calcd for $C_{14}H_{17}N_2O_2$ $[M+H]^+$: 245.1285, found: 245.1284.



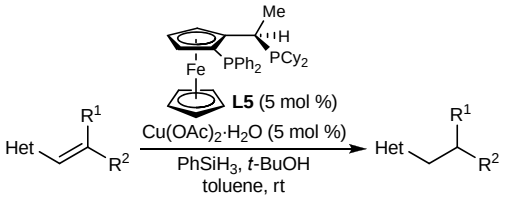
(*E*)-2-Methyl-3-(1-methyl-1*H*-benzoimidazol-2-yl)prop-2-en-1-ol (271). To a solution of the ester **270** (488 mg, 2.00 mmol) in CH_2Cl_2 (30 mL) at -78 °C was added DIBAL (1.0 M in hexane, 4.5 mL, 4.5 mmol) over 2 min, and the resulting mixture was stirred at -78 °C for 1.5 h, then at 0 °C for 2 h. 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_2Cl_2 (3 x 50 mL), and the combined organic layers were dried (Na_2SO_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.



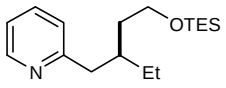
(*E*)-2-Methyl-3-(1-methyl-1*H*-benzoimidazol-2-yl)propenyl pivaloate (272). To a solution of the alcohol **271** (303 mg, 1.50 mmol), Et_3N (425 μL, 3.00 mmol), and DMAP (12 mg, 0.10 mmol) in CH_2Cl_2 (10 mL) at room temperature was added trimethylacetyl chloride (369 μL, 3.00 mmol) over 1 min, and the resulting mixture was stirred at room temperature for 3 h. The reaction was quenched with saturated aqueous Na_2CO_3 solution (20 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The combined organic layers were dried (Na_2SO_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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.81-7.78 (1H, m, Ar**H**), 7.34-7.26 (3H, m, Ar**H**), 6.47 (1H, app d, J = 1.1 Hz, =C**H**), 4.73 (2H, s, C$\mathbf{H}_2$O),

3.75 (3H, s, NC**H**$_3$), 2.29 (3H, s, =CC**H**$_3$), 1.29 (9H, s, C(C**H**$_3$)$_3$); ^{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 $C_{17}H_{23}N_2O_2$ $[M+H]^+$: 287.1754, found: 287.1749.

General Procedure for Enantioselective Copper-Catalysed Reductions

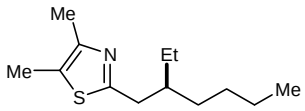


A solution of the appropriate alkene (0.20 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mg, 0.01 mmol), Josiphos ligand **L5** (6.1 mg, 0.01 mmol), and *t*-BuOH (38 μL, 0.40 mmol) in toluene (1 mL) was stirred at 0 °C for 15 min. $PhSiH_3$ (37 μL, 0.30 mmol) was then added dropwise. The mixture was stirred at 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.



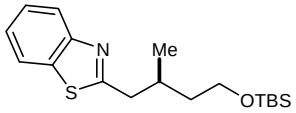
2-[(*S*)-2-Ethyl-4-triethylsilyloxybutyl]pyridine (273a). A solution of alkene **244a** (117 mg, 0.40 mmol), $Cu(OAc)_2{\cdot}H_2O$ (4.0 mg, 0.02 mmol), Josiphos ligand **L5** (12.2 mg, 0.02 mmol), and *t*-BuOH (76 μL, 0.80 mmol) in toluene (2 mL) was stirred at 0 °C for 15 min. $PhSiH_3$ (74 μL, 0.60 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. $[\alpha]_D^{21}$ +15.0 (*c* 0.53, $CHCl_3$); IR (film) 2952, 2874, 1589, 1568, 1472, 1434, 1238, 1095, 1016, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.53-8.52 (1H, m, Ar**H**), 7.58-7.55 (1H, m, Ar**H**), 7.14-7.12 (1H, m, Ar**H**), 7.10-7.07 (1H, m, Ar**H**), 3.65-3.57 (2H, m, C**H**$_2$O), 2.77 (1H, dd, *J* = 13.5, 7.1 Hz, N=CC**H**$_2$), 2.70 (1H, dd, *J* = 13.5, 7.5 Hz, N=CC**H**$_2$), 1.98-1.90 (1H, m, N=CCH$_2$C**H**), 1.61-1.49 (2H, m, C**H**$_2$CH$_2$O), 1.37-1.31 (2H, m, C**H**$_2$CH$_3$), 0.93 (9H, t, *J* = 8.0 Hz, Si(CH$_2$C**H**$_3$)$_3$), 0.86 (3H, t, *J* = 8.0 Hz, CHCH$_2$C**H**$_3$), 0.56 (6H, q, *J* = 8.0 Hz, Si(C**H**$_2$CH$_3$)$_3$); ^{13}C NMR (90.6 MHz, $CDCl_3$) δ 161.5 (C), 149.2 (CH), 136.0 (CH), 123.6 (CH), 120.8 (CH), 61.1 (CH_2), 42.8 (CH_2), 36.9 (CH), 36.1 (CH_2), 26.1 (CH_2), 10.7 (CH_3), 6.7 (3 x CH_2), 4.4 (3 x CH_3); HRMS (ES) Exact mass calcd for $C_{17}H_{32}NOSi$ $[M+H]^+$: 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); t_r (minor) *ca* 14 min (not detected); t_r (major) = 15.8 min; >99% ee.

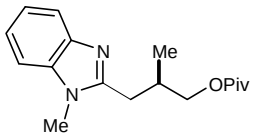


2-[(*S*)-2-Ethylhexyl]-4,5-dimethylthiazole (273b). The title compound was prepared according to General Procedure from alkene **261b** (45 mg, 0.20 mmol) for a reaction time of 5 days and purified by column chromatography (2% EtOAc/hexane) to give a colourless oil (38 mg, 84%). $[\alpha]_D^{21}$ +8.0 (*c* 0.50, $CHCl_3$); IR (film) 2959, 2925, 2859, 1557, 1460, 1378, 1131, 1064, 700, 488 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 2.79 (2H, app d, *J* = 7.1 Hz, N=CC**H**$_2$), 2.29 (3H, s, ArC**H**$_3$), 2.27 (3H, s, ArC**H**$_3$), 1.75-1.68 (1H, m, C**H**CH$_2$), 1.38-1.24 (8H, m, CHC**H**$_2$CH$_3$ and (C**H**$_2$)$_3$CH$_3$), 0.87 (6H, t, *J* = 7.4 Hz, 2 x CH$_2$C**H**$_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 166.0 (C), 147.1 (C), 124.8 (C), 40.4 (CH), 37.6 (CH_2), 32.4 (CH_2), 28.7 (CH_2), 25.6 (CH_2), 22.9 (CH_2), 14.6 (CH_3), 14.1 (CH_3), 11.2 (CH_3), 10.7 (CH_3); HRMS (EI) Exact mass calcd for $C_{13}H_{23}NS$ $[M]^+$:

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), $Cu(OAc)_2 \cdot H_2O$ (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}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.99-7.97 (1H, m, Ar**H**), 7.86-7.83 (1H, m, Ar**H**), 7.48-7.45 (1H, m, Ar**H**), 7.38-7.33 (1H, m, Ar**H**), 3.77-3.66 (2H, m, C**H**$_2$O), 3.16 (1H, dd, *J* = 14.4, 6.2 Hz, N=CC**H**$_2$), 2.96 (1H, dd, *J* = 14.4, 8.2 Hz, N=CC**H**$_2$), 2.33-2.19 (1H, m, C**H**CH_3), 1.77-1.68 (1H, m, C**H**$_2CH_2$O), 1.56-1.46 (1H, m, C**H**$_2CH_2$O), 1.03 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$), 0.90 (9H, s, C(C**H**$_3$)$_3$), 0.05 (3H, s, SiC**H**$_3$), 0.04 (3H, s, SiC**H**$_3$); ^{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-1*H*-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, $CHCl_3$); IR (film) 2971, 2360, 1726 (C=O), 1478, 1396, 1322, 1284, 1160, 1034, 742 cm^{-1}; ^1H NMR (360 MHz, $CDCl_3$) δ 7.66-7.63 (1H, m, Ar**H**), 7.24-7.15 (3H, m, Ar**H**), 3.99-3.97 (2H, m, C**H**$_2$O), 3.65 (3H, s, NC**H**$_3$), 2.94 (1H, dd, *J* = 14.8, 5.9 Hz, N=CC**H**$_2$), 2.67 (1H, dd, *J* = 14.8, 8.6 Hz, N=CC**H**$_2$), 2.55-2.42 (1H, m, CHC**H**$_3$), 1.13 (9H, s, C(C**H**$_3$)$_3$), 0.99 (3H, d, *J* = 6.7 Hz, CHC**H**$_3$); ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 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 $C_{17}H_{25}N_2O_2$ $[M+H]^+$: 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 $S_NV\sigma$ 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 β-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.

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