Towards a Geometry-Selective Alkene Metathesis Method to Form New Trisubstituted Alkenes in Functionalised Terpenoids

A thesis submitted

by

Zhensheng Shi

To Imperial College London in partial fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Declaration

I, Zhensheng Shi, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

The copyright of this thesis rests with the author. Unless otherwise indicated, its contents are licensed under a Creative Commons Attribution-Non Commercial 4.0 International Licence (CC BY-NC). Under this licence, you may copy and redistribute the material in any medium or format. You may also create and distribute modified versions of the work. This is on the condition that: you credit the author and do not use it, or any derivative works, for a commercial purpose. When reusing or sharing this work, ensure you make the licence terms clear to others by naming the licence and linking to the licence text. Where a work has been adapted, you should indicate that the work has been changed and describe those changes. Please seek permission from the copyright holder for uses of this work that are not included in this licence or permitted under UK Copyright Law.

Zhensheng Shi

January 2021

Abstract

This thesis describes synthetic attempts at geometry-selective formation of new terpenoid, trisubstituted olefins *via* olefin metathesis reactions between a terpenoid and a suitable trisubstituted olefin. This thesis was divided into three parts, with experimental procedures and appendices included to cover practical details and spectroscopic data.

The first part of this thesis introduces the theoretical background of terpene synthesis and olefin metathesis, with an emphasis on the recent development of geometry-selective metathesis.

The second part of this thesis describes the relay cross-metathesis approach in the synthesis of terpenoid, trisubstituted olefins and efforts on altering the *E/Z*-selectivity in this process.

The third part of this thesis describes attempts at developing geometry-selective relay ring-closing metathesis methods between terpenoid, trisubstituted olefins.

Contents

Declaration i

Abstract ii

Contents iii

Acknowledgements x

Abbreviations xi

Chapter 1 Introduction to Terpenes and Linear Terpene Synthesis

1.1 Biosynthesis of terpenes 1

1.2 Chemical synthesis of terpenes 7

1.2.1 Olefination approaches 7

1.2.2 Cross-coupling approaches 10

1.2.2.1 Negishi Coupling 10

1.2.2.2 Cu- and Fe-mediated cross-coupling 12

1.2.3. Allyl-allyl coupling approaches 13

1.2.3.1 Biellmann coupling 13

1.2.3.2 Stereodefined allylic metal reagents 16

1.3 Summary and outlook 17

Chapter 2 Cross-metathesis reactions in the synthesis of trisubstituted olefins

2.1 General introduction to olefin metathesis chemistry 19

2.2 Classification and reactivity of olefins in olefin metathesis reactions 20

2.3 Cross-metathesis reactions in the construction of trisubstituted olefins ... 24

2.3.1 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a terminal olefin 26

2.3.2 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a disubstituted olefin 34

2.3.3 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a trisubstituted olefin 37

2.3.4 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and a terminal olefin 40

2.3.5 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and a disubstituted olefin 42

2.3.6 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and an another trisubstituted olefin 43

2.3.7 Formation of trisubstituted olefin from CM reactions involving a tetrasubstituted olefin 44

2.4 Summary and Outlook 45

Chapter 3 Catalyst-Controlled Geometry-Selective Olefin Metathesis

3.1 *Z*-Selective olefin metathesis catalysed by molybdenum and tungsten complexes 47

3.2 *E*-Selective olefin metathesis catalysed by molybdenum and tungsten complexes 58

3.3 *Z*-selective and stereoretentive olefin metathesis catalysed by ruthenium complexes 63

3.4 Summary and outlook 81

Chapter 4 Relay cross-metathesis (ReXM) strategy in the synthesis of terpenoid, trisubstituted olefins

4.1 General introduction to relay strategy in olefin metathesis 82

4.2 Literature precedent for the cyclisation of *Z*-polyenes and proposed ReXM strategy for the synthesis of polyene precursors 85

4.3 Substrate preparation and optimisation of ReXM 89

4.4 Mechanism of ReXM reaction 93

4.5 Scope of ReXM reaction 102

4.6 Attempts at altering the *E/Z*-selectivity in ReXM reactions 104

4.7 Attempts at separating *E*- and *Z*-products of ReXM reactions 111

4.8 Conclusion and future work 118

Chapter 5 Relay ring-closing metathesis (RRCM) strategy in the synthesis of terpenoid, trisubstituted olefins

5.1 Proposed relay ring-closing metathesis for the stereoselective construction of terpenoid, trisubstituted olefins 119

5.2 Literature precedent for stereoselective (relay) ring-closing metathesis 120

5.3 Literature precedent for the formation of cyclic trisubstituted olefin *via* ring-closing metathesis between a 1,1-disubstituted olefin and a trisubstituted olefin 124

5.4 Syntheses of RRCM precursors and attempted RRCM reactions 126

5.4.1 RRCM precursor with an ester linker 126

5.4.2 RRCM precursor with an acetal linker 136

5.4.3 RRCM precursor with an ether linker 143

5.5 Conclusion and future work 153

Chapter 6 Experimental

General Experimental 155

(*E*)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene (4.28) 156

(*E*)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (4.26) 157

1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (4.27) and 1-Methoxy-4-methylbenzene (4.35) 158

General Procedure for ReXM reactions 159

3-(6-(4-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (4.21) 159

((*E*)-6-(((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)oxy)hex-4-en-1-yl)-benzene (4.43) and 2,2-Dimethyl-3-((3*E*)-3-methyl-5-(prop-1-en-1-yloxy)pent-3-en-1-yl)oxirane (4.44) 160

(*E*)-3,7-Dimethylocta-2,6-dien-1-yl acetate (4.48) 161

(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (4.49) 162

(*2E,6E*)-8-(Allyloxy)-3,7-dimethylocta-2,6-dien-1-yl acetate (4.50) and (*2E,6E*)-1,8-bis(allyloxy)-2,6-dimethylocta-2,6-diene (4.50a) 163

(*2E,6E*)-8-(Allyloxy)-3,7-dimethylocta-2,6-dienal (4.47) 164

General procedure for preparation of trisubstituted olefins 4.58 and 4.59 *via* Wittig olefination 165

1-Methoxy-3-(4-methylpent-3-en-1-yl)benzene (4.58) 165

1-Methyl-4-(4-methylpent-3-en-1-yl)benzene (4.59) 166

General procedure for the preparation of aldehyde substrate 4.63 and 4.66 *via* sequential reduction-oxidation reactions of corresponding carboxylic acids 167

3-(3-Methoxyphenyl)propanol (4.62) 168

3-(3-Methoxyphenyl)propanal (4.63) 169

3-(*p*-Tolyl)propan-1-ol (4.65) 170

3-(*p*-Tolyl)propanal (4.66) 171

3-(6-(3-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (4.58a) 172

2,2-Dimethyl-3-(3-methyl-6-(p-tolyl)hex-3-en-1-yl)oxirane (4.59a) 173

(*Z*)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene (4.70)..... 174

(*Z*)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (4.69) 175

(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate (4.73)..... 176

(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-ol (4.75) 177

(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienal (4.71)..... 178

(*S*,*E*)-8-(Allyloxy)-2,6-dimethyloct-6-ene-2,3-diol (4.85)..... 179

(*S*,*E*)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-4,4-dimethyl-2-phenyl-1,3,2-dioxaborolane (4.83)..... 180

(*E*)-3,7-dimethylocta-2,6-dienal (4.86) and (*Z*)-3,7-dimethylocta-2,6-dienal (4.72) 181

(*E*)-3,7-Dimethylocta-2,6-dienoic acid (4.82) 182

(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl acetate (4.88)..... 183

(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl benzoate (4.87)..... 184

(*S*,*E*)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2,4,4-tetramethyl1,3-dioxolane (4.89) 185

(2*E*)-3,7-Dimethyl-9-((*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienal (4.92)..... 186

(2*E*)-3,7-Dimethyl-9-((S)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienoic acid (4.93)..... 187

(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl (*E*)-3,7-dimethylocta-2,6-dienoate (5.18) and (*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl (*Z*)-3,7-dimethylocta-2,6-dienoate (5.21) 188

(5*S*)-5-((*E*)-5-(Allyloxy)-3-methylpent-3-en-1-yl)-2-((*E*)-2,6-dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-1,3-dioxolane (5.30) and (5*S*)-5-((*E*)-5-(Allyloxy)-3-

methylpent-3-en-1-yl)-2-((*Z*)-2,6-dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-1,3-dioxolane (5.31) 189

General procedure for RRCM reactions under diluted conditions..... 190

General procedure for RRCM reactions under neat conditions 190

(5*S*)-2-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-5-(3-methylbut-3-en-1-yl)-1,3-dioxolane (5.32) and (5*S*)-2-(*Z*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-5-(3-methylbut-3-en-1-yl)-1,3-dioxolane (5.33) 191

(*E*)-1-Bromo-3,7-dimethylocta-2,6-diene (5.40) and (*Z*)-1-Bromo-3,7-dimethylocta-2,6-diene (5.41) 192

(*S,E*)-8-(Allyloxy)-3-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-2,6-dimethyloct-6-en-2-ol (5.38) and (*S,E*)-8-(allyloxy)-3-(((*Z*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-2,6-dimethyloct-6-en-2-ol (5.39)..... 193

(*E*)-6-(Allyloxy)-4-methylhex-4-en-1-ol (5.58) 194

(*E*)-1-(((*E*)-6-(Allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.57) and (*Z*)-1-(((*E*)-6-(allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.57) 195

(*E*)-3,7-Dimethyl-1-((4-methylpent-4-en-1-yl)oxy)octa-2,6-diene (5.60) and (*Z*)-1-(((*E*)-6-(allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.61) 196

(*E*)-1,6-Bis(allyloxy)-3-methylhex-2-ene (5.63) and (*E*)-1-(allyloxy)-3-methyl-6-((3-methylbut-2-en-1-yl)oxy)hex-2-ene (5.64) 197

References 198

Appendices

Appendix I – Query used for searching different olefin combinations used in the synthesis of trisubstituted olefin *via* metathesis reactions..... 223

Appendix II – Determination of *E/Z*-ratio of the internal olefin of 4.71 *via* global spectral deconvolution 224

Appendix III – Setup for the gas collection experiments..... 225

Acknowledgements

Firstly, I would like to express my deepest gratitude to Prof. Chris Braddock, who has been constantly guiding me with his patience and wisdom through difficult times, and cheering me up with his encouragements in those serendipitous moments. It has been an honour to work with Chris and the memorable lessons passed to me will be of great value.

I would also to thank all the members of Braddock group, who created a vibrant lab environment throughout my PhD study. In particular, Shijia, Tianyou, Yusrah, Dan, Karim and Gajan. Shijia and Tianyou, who have proved to be worthy friends. Yusrah and Dan generously shared my happiness and sorrow, as well as the knowledge of chemistry. Karim and Gajan were of great help, particularly in my first year.

My thanks also go to the supporting staff and technicians. Pete Haycock has helped me a lot with some delicate NMR experiments and Lisa Haigh have been excellent in acquiring elusive data.

I am enormously grateful to my parents, who were unconditionally supporting me in numerous ways through all the years, as well as being the source of encouragement and love.

Abbreviations

ADMET acyclic diene metathesis

Bn benzyl

Boc *tert*-butyloxycarbonyl

Bz benzoyl

CM cross-metathesis

CSA camphorsulfonic acid

DCC dicyclohexylcarbodiimide

DCE dichloroethane

DCM dichloromethane

DMAP *p*-dimethylaminopyridine

DMC dimethyl carbonate

DMF *N,N*-dimethylformamide

DMP dimethoxypropane

DMPU dimethylpropyleneurea

EDC *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide

GI Grubbs 1st generation catalyst

GII Grubbs 2nd generation catalyst

HGI Hoveyda-Grubbs 1st generation catalyst

HGII Hoveyda-Grubbs 2nd generation catalyst

Mcb metallocyclobutane

MOM methoxymethyl

*m*CPBA *m*-chloroperoxybenzoic acid

NBS *N*-bromosuccinimide

NHC *N*-heterocyclic carbene

Ph phenyl

PMB p-methoxybenzyl

PPTS pyridinium *p*-toluenesulfonate

PTSA *p*-toluenesulfonic acid

RCM ring-closing metathesis

r.t. room temperature

TBAI tetrabutylammonium iodide

TBS *tert*-butyldimethylsilyl

TBHP *tert*-butylhydroperoxide

TfO trifluoromethanesulfonate

THP tetrahydropyran

TON turnover number

TS transition state

acac acetyl acetone

NBS *N*-bromosuccinimide

NMP *N*-methyl-2-pyrrolidone

DME dimethoxyethane

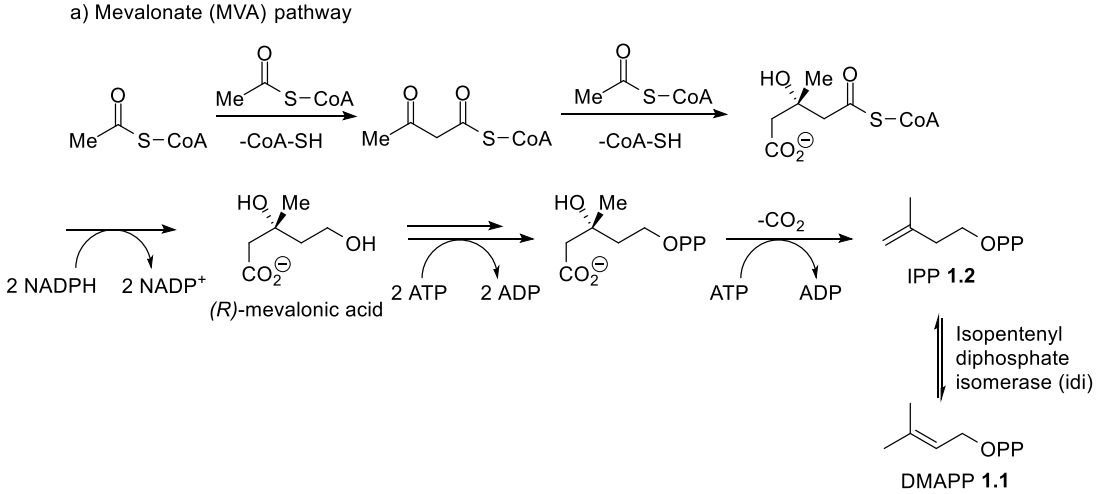
TIPS triisopropylsilyl

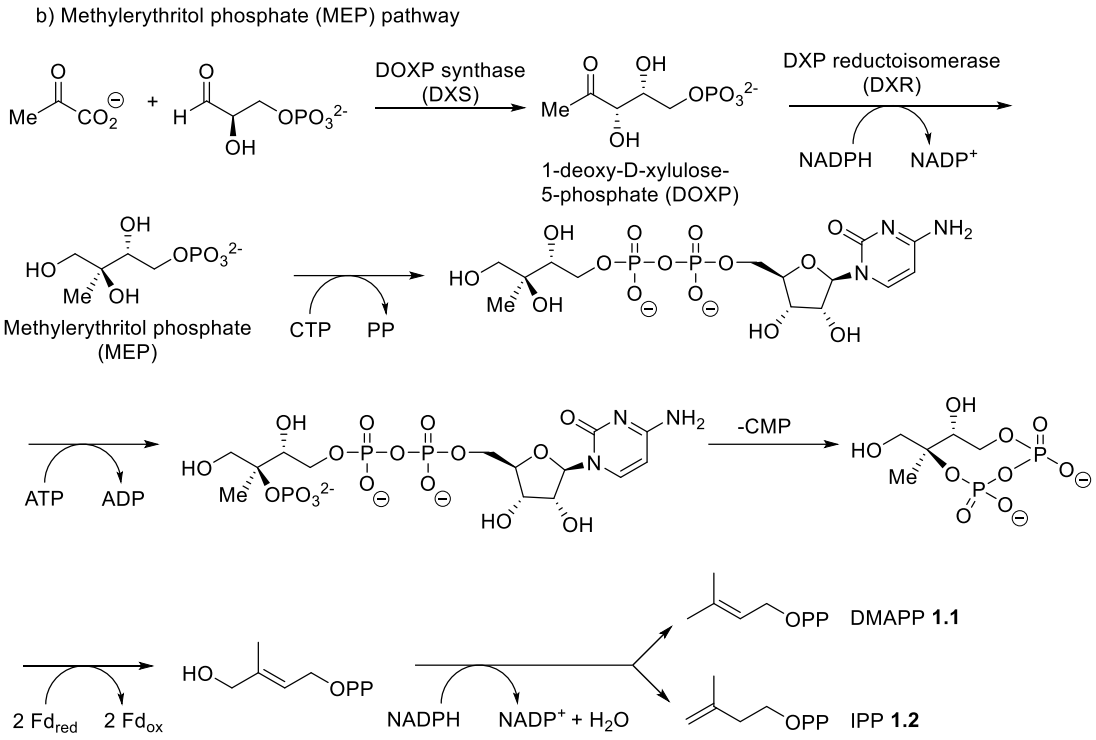
Chapter 1 Introduction to Terpenes and Linear Terpene Synthesis

1.1 Biosynthesis of terpenes

Terpenes are organic compounds composed of 'head-to-tail' and 'head-to-head' arrangements of five-carbon (C_5) isoprene units. They are the most abundant natural product by mass and account for ~60% of known natural products.[1] Many terpenes are also bioactive compounds that have important biological functionalities and participate in various biochemical processes including lipid membrane modulation, light harvesting, photooxidative protection, electron transport, intercellular signalling as hormones, and interspecies defence amongst others.[2]

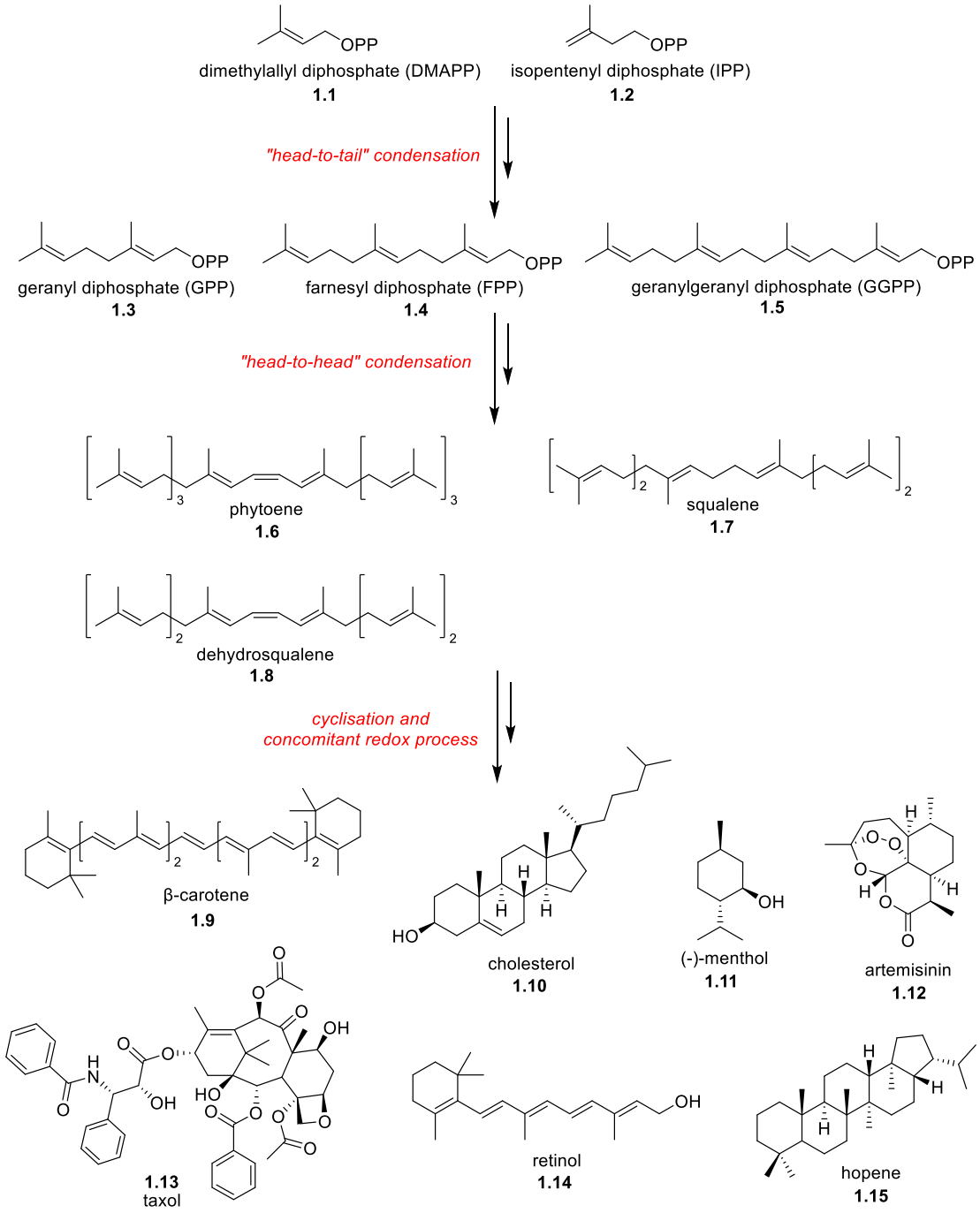
Biosynthetically, all terpenes are originated from, or at least partly from, the C_5-building block dimethylallyl diphosphate (DMAPP, **1.1**) and isopentenyl diphosphate (IPP, **1.2**). The DMAPP and IPP precursors are made in two distinct pathways: the mevalonate (MVA) pathway[3] and the methylerythritol phosphate (MEP) pathway (Scheme 1.1).[4] The MEP pathway is absent in higher animals and fungi, but in green plants the MEP and mevalonate pathways co-exist in separate cellular compartments.





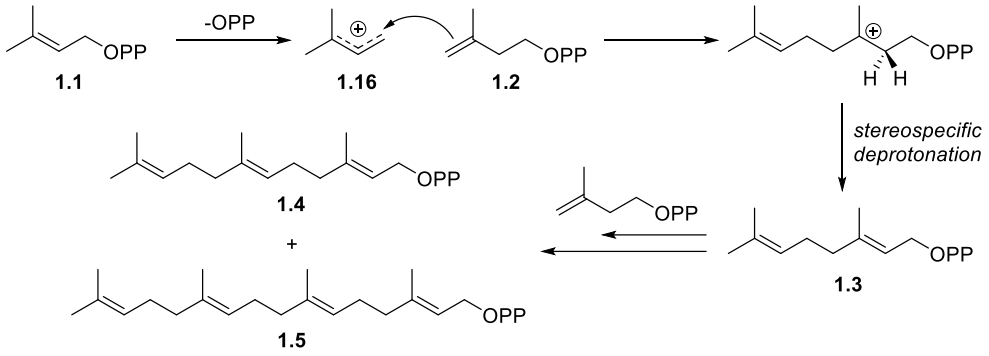
Scheme 1.1 Biosynthesis of C_5-terpene building block DMAPP and IPP *via* a) mevalonate (MVA) pathway; b) methylerythritol phosphate (MEP) pathway.

By enzymatic condensation of DMAPP with one or more IPP molecules in a "head-to-tail" fashion, higher linear terpenes *e.g.* C_{10}-geranyl diphosphate (GPP, **1.3**), C_{15}-farnesyl diphosphate (FPP, **1.4**) and C_{20}-geranylgeranyl diphosphate (GGPP, **1.5**) are produced.[5,6] Linear triterpenes (C_{30}) and tetraterpenes (C_{40}) are formed by "head-to-head" condensations between FPP **1.4** and GGPP **1.5**. This process produces phytoene **1.6**, squalene **1.7**, dehydrosqualene **1.8** and precursors to carotenoids (*e.g.* β-carotene **1.9**) and sterols (*e.g.*, cholesterol **1.10**).[7] Cyclisations of linear precursors and sequential enzymatic redox processes furnish myriad terpene natural products, for example C_{10}-monoterpenes such as menthol **1.11**, C_{15}-sesquiterpenes such as artemisinin **1.12**, C_{20}-diterpenes such as taxol **1.13** and retinol **1.14**, and C_{30}-triterpenes such as hopene **1.15** and cholesterol **1.10** (Scheme 1.2).



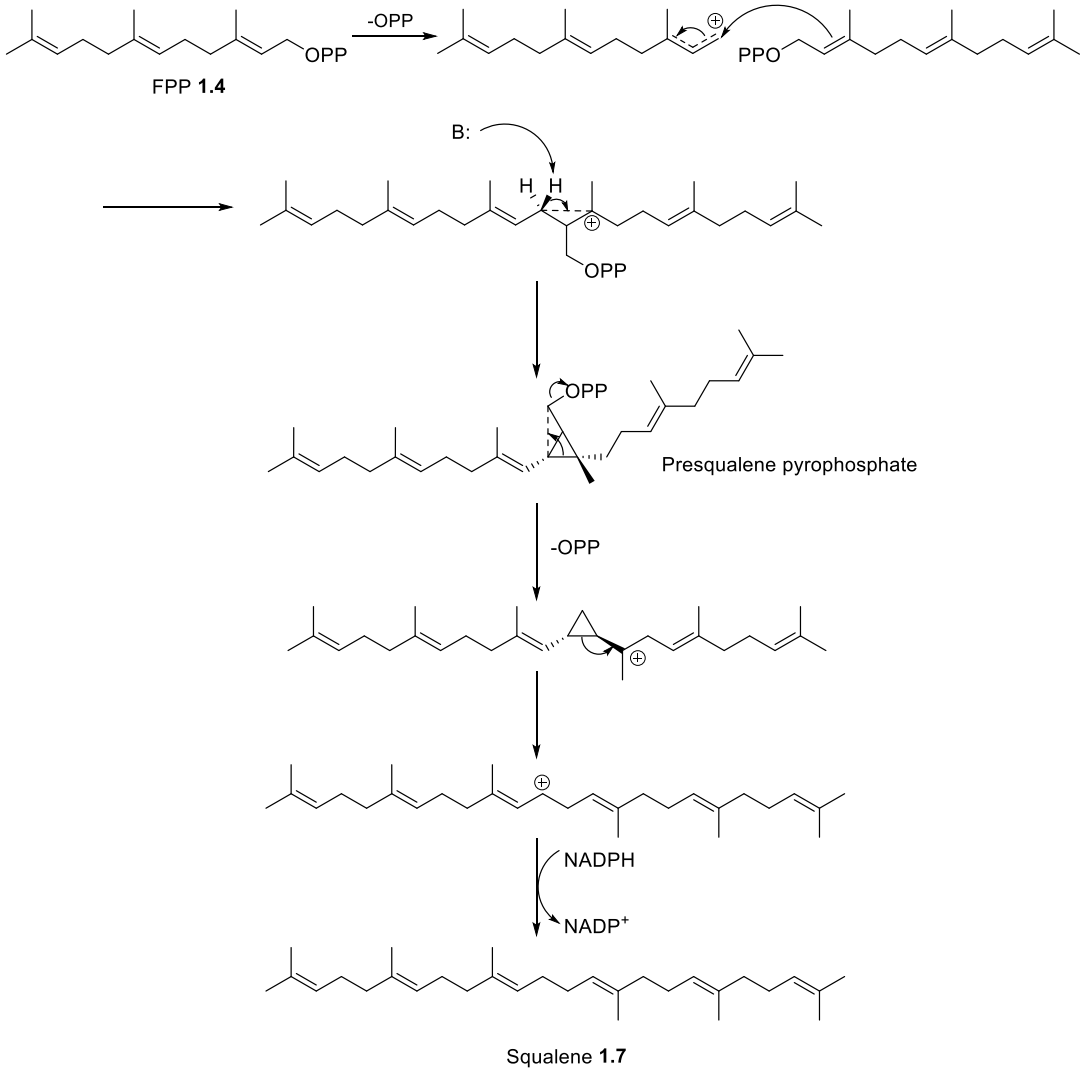
Scheme 1.2 Biosynthesis of terpene natural products, starting from C_5-building block DMAPP and IPP.

From a mechanistic point of view, the C_{10}-geranyl diphosphate **1.3** is produced *via* "head-to-tail" condensation between DMAPP and IPP involving the carbocation intermediate **1.16**, followed by a stereospecific deprotonation. Geranyl diphosphate **1.3** may react further with IPP **1.2** to produce higher linear terpene *e.g.*, farnesyl diphosphate **1.4** and geranylgeranyl diphosphate **1.5** (Scheme 1.3).



Scheme 1.3 "Head-to-tail" condensation of C_5-building block DMAPP **1.1** and IPP **1.2** to produce higher linear terpenes **1.4** and **1.5**.

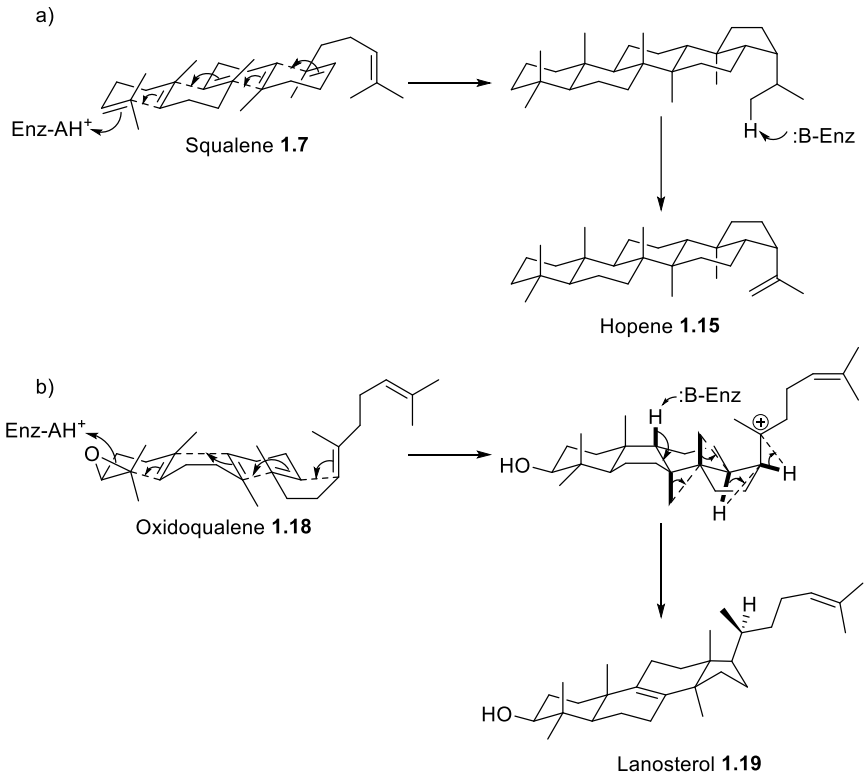
C_{15}-Farnesyl diphosphate **1.4** and C_{20}-geranylgeranyl diphosphate **1.5** are then linked "head-to-head" to give symmetrical C_{30}-squalene **1.6** (Scheme) and similarly C_{40}-phytofluene **1.17** (not shown).



Scheme 1.4 Squalene biosynthesis *via* "head-to-head" condensation of farnesyl diphosphate **1.4**.

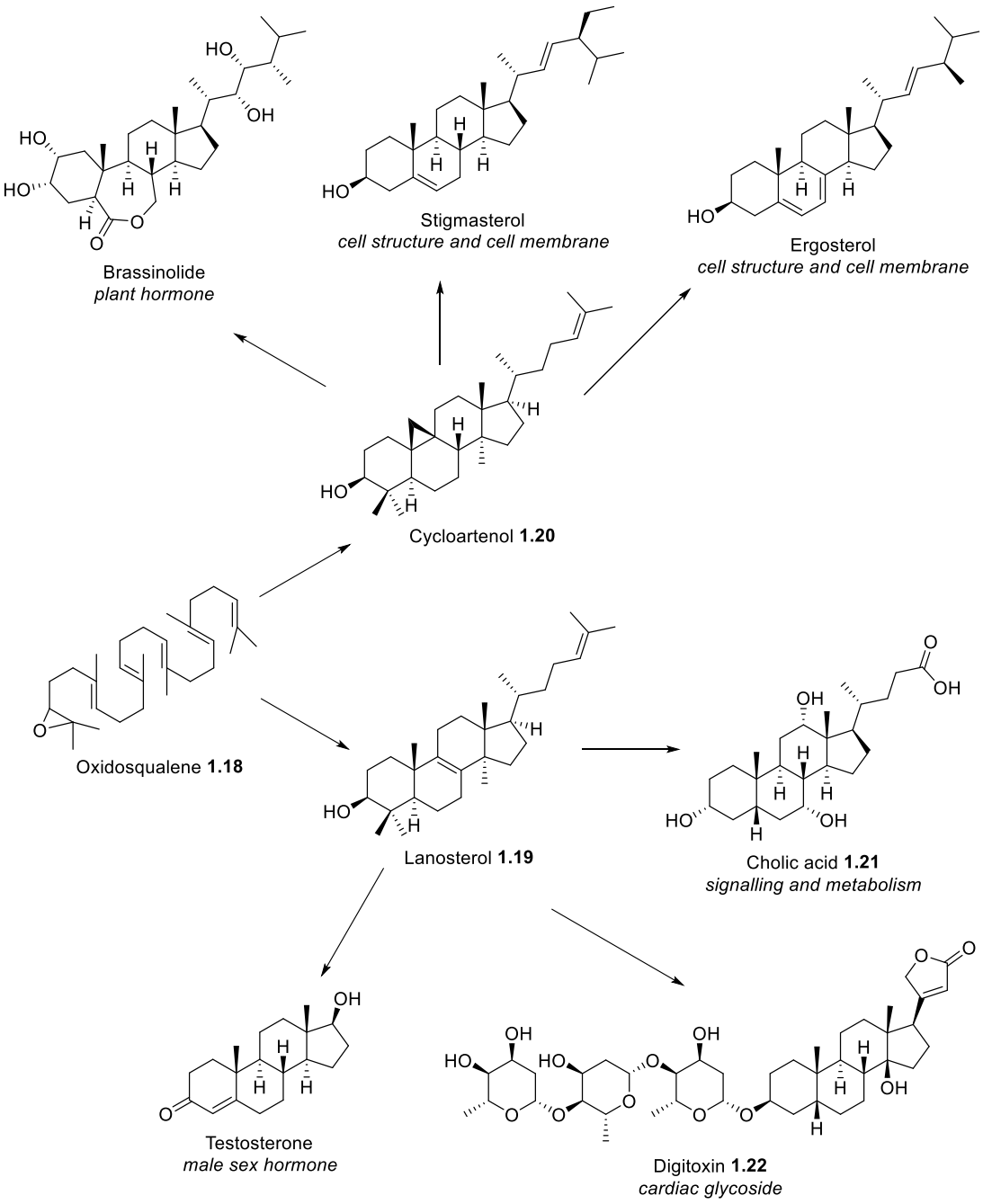
Enzymatic cyclisation of monoterpenes[8], sesquiterpenes[9,10], diterpenes[11,12] and triterpenes[13] has been extensively reviewed. In general, cyclisations of linear precursors begin with the formation of cationic species *via* protonation or dissociation of diphosphate, followed by stereospecific cationic cyclisation cascade and alkyl/hydride shifts in some cases, to construct the (poly)cyclic backbone.

For example, in the cyclisations of squalene **1.7** catalysed by squalene-hopene cyclase (SHC), initiated *via* stereospecific protonation, five C-C bonds are formed in a concerted manner to forge the pentacyclic backbone in one single step (Scheme 1.1a). Likewise, in the oxidosqualene-lanosterol cyclase catalysed (OSLC) cyclisation, cationic cyclisation cascade of oxidosqualene **1.18** forges the 6-6-6-5 tetracycle in one step, followed by sequential methyl shifts/deprotonation to furnish lanosterol **1.19** as the final product (Scheme 1.1b).



Scheme 1.1 Enzymatic cyclisation of squalene **1.7** by a) SHC and b) OSLC, to produce hopene **1.15** and lanosterol **1.19** correspondingly.

Lanosterol **1.19** serves as the starting point ofthe synthesis for fungi and animal steroids, while many plant steroids are biosynthetically originated from cycloartenol **1.20**.[14] Secondary metabolites of lanosterol **1.19** and cycloartenol **1.20** constitute the large family of steroids with diverse structures and bioactivities (Scheme 1.2).[15]



Scheme 1.2 Selected examples of natural occurring steroids derived from lanosterol **1.19** and cycloartenol **1.20** with various bioactivities.

While the polyene cyclisation process produces all *trans*-fused tetracyclic skeleton of steroids, it is noteworthy here that the cholic acid **1.21** and its derivatives possess *cis*-fused AB ring. This is the result of a selective reduction of the $\Delta^{5,6}$ olefin of cholesterol **1.10**.[16]

The biosynthesis of steroids serves as a good example for understanding the logic behind the natural assembly lines of terpenes. Although detailed discussion of biosynthetic pathways of various terpenes is beyond the scope of this document, understanding the biosynthesis process could be key to the development of chemical syntheses as many of them are based on biomimetic strategies.

1.2 Chemical synthesis of terpenes

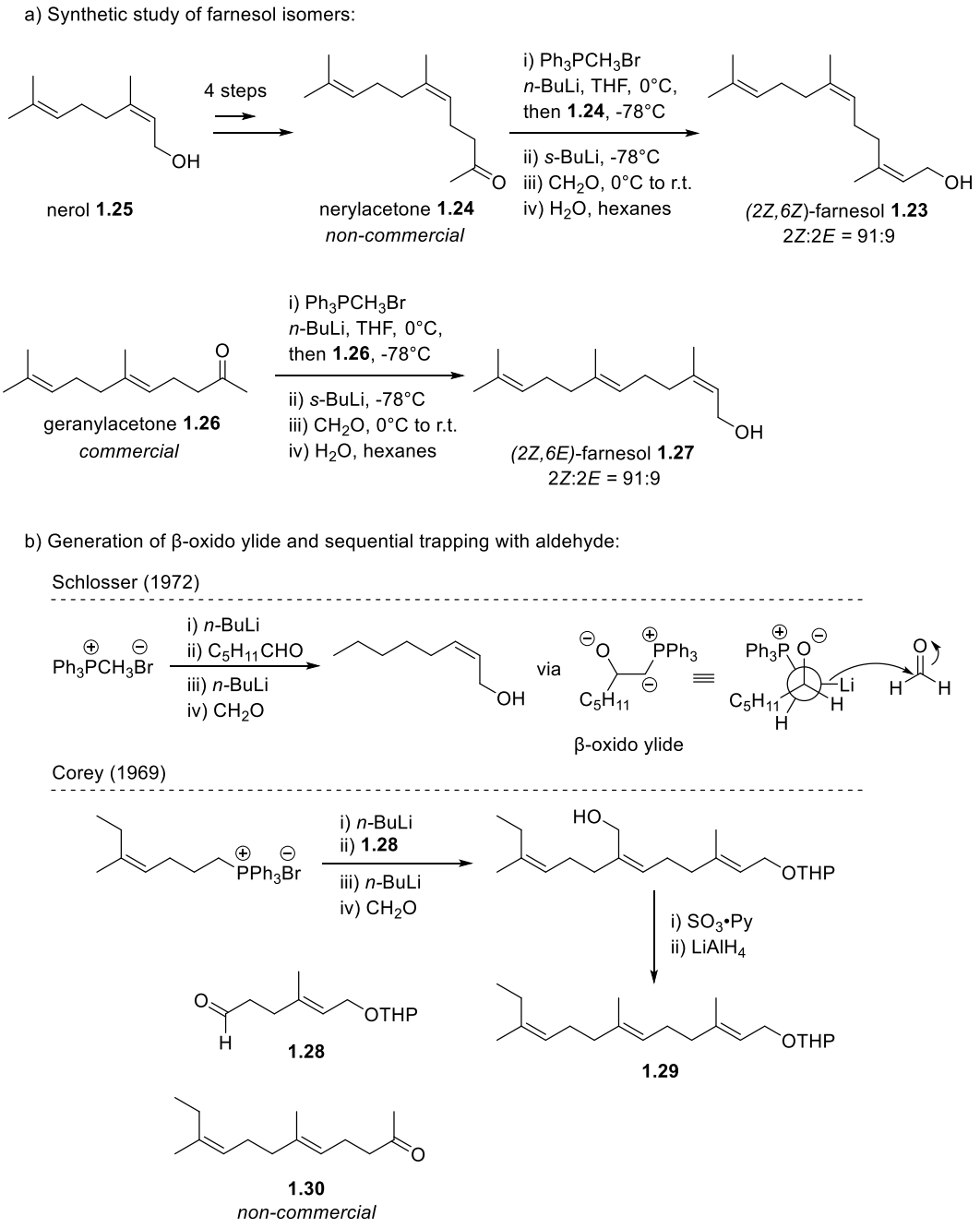
The structural complexity and the accompanying synthetic challenge of terpenes constantly spurs the innovation of new synthetic transformations. Due to the broadness of terpene chemistry, it is not possible to cover all aspects of their chemical synthesis. Therefore, the discussion is limited to C-C bond formation in the construction of "head-to-tail" arranged linear terpenes ($\geq C_{15}$) with defined olefin geometry, which is most relevant to the theme of this thesis.

1.2.1 Olefination approaches

The stereodefined trisubstituted olefin moiety is one of the most notable structural features of linear terpenes. However, there is no unified approach for the stereoselective formation of trisubstituted, *trialkyl* alkenes *via* olefination.

All-trans-polyprenols (up to C_{25}) can be readily accessed *via* Wittig/Horner-Wadsworth-Emmons (HWE) reactions.[17–20] In contrast, their corresponding *Z*-isomers can be difficult to access *via* these methods due to the lack of natural occurring/commercialised precursors.

This issue was encountered in the synthetic study of all four stereoisomers of farnesol *via* a modified Wittig reaction (Scheme 1.3a).[21] The modification was pioneered by Schlosser and Corey, utilising an aldehyde electrophile to trap the intermediate β-oxido ylide and *Z*-allylic alcohols can be obtained with good control of overall olefin geometry (Scheme 1.3b).[22–24]

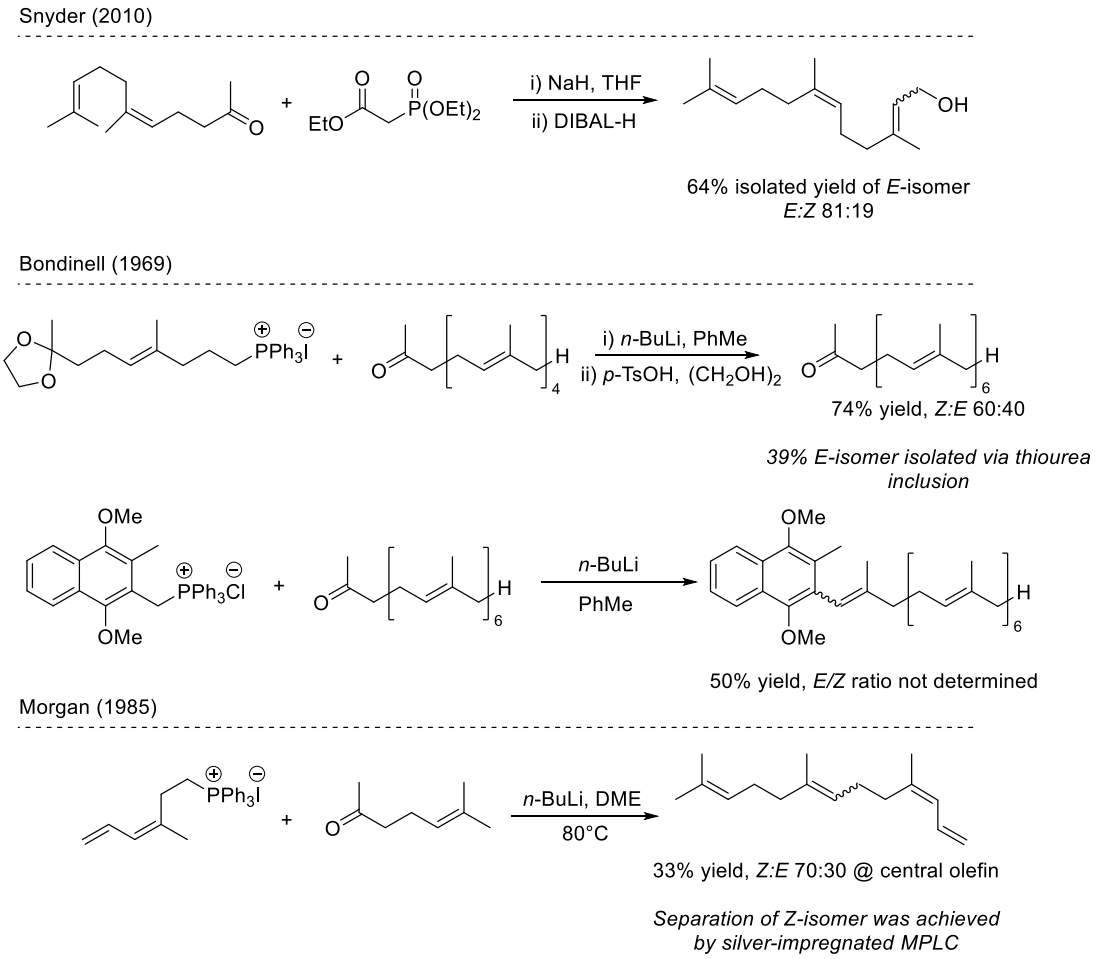


Scheme 1.3 a) Syntheses of farnesol isomers enabled by the modified Wittig reaction with formaldehyde as the electrophilic trap; b) Previous work on the generation of β-oxido ylide and following trapping with aldehydes.

(*2Z,6E)*-Farnesol **1.27** can be prepared directly from the commercially available geranylacetone **1.26** using the modified Wittig reaction. However, the non-commercial nerylacetone **1.24** needs four extra steps to be prepared from nerol **1.25**. Corey was targeting at a homologous farnesol derivative **1.29** with the choice of building the internal trisubstituted olefin, which is probably due to the lack of availability of the

corresponding ketone **1.30** (Scheme 1.3b, bottom). As a result, the preparation of aldehyde **1.28** and following deoxygenation requires extra manipulations.

In fact, preparing *Z*-terpenes *via* olefination is synthetically challenging. To the best of my knowledge, only a handful of linear *Z*-terpenes have been prepared using olefination reactions (Scheme 1.4).[17,21,25,26]



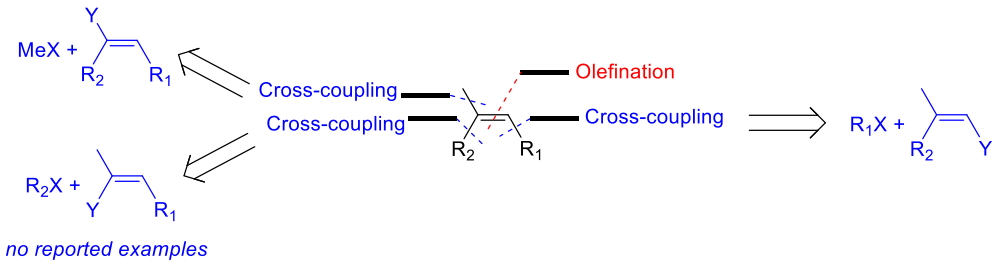
Scheme 1.4 Reported examples of linear *Z*-terpenes syntheses *via* olefination reactions.

Moreover, all of these syntheses involve only the construction of *one Z*-olefin unit and some of them gave mixtures of *E*- and *Z*-products which require careful separation by chromatographic methods.

1.2.2 Cross-coupling approaches

1.2.2.1 Negishi Coupling

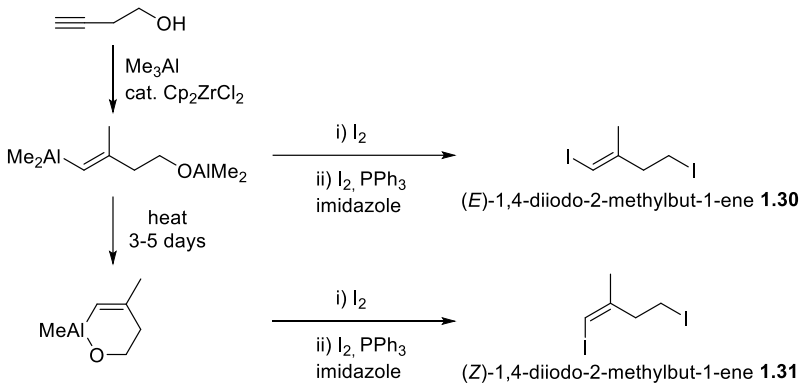
For the preparation of higher linear terpenes (≥ C_{20}) that contain *Z*-olefin moieties, finding suitable carbonyl precursors can be increasingly difficult. While direct olefination is no longer a suitable strategy, the development of cross-coupling chemistry provides alternative methods of disconnection for the syntheses of terpenes (Scheme 1.5).



Scheme 1.5 Alternative disconnections for the synthesis of trisubstituted olefin enabled by $C(sp^2)$-$C(sp^3)$ cross-coupling reaction for the syntheses of terpenes illustrated for the disconnection of *Z*-olefin.

Cross-coupling methods have been utilised for the development of iterative protocol for the preparation of linear terpenes (but not from terpenoid precursors). The major advantage of iterative processes is the potential of accessing any linear terpene with a unified approach. Negishi *et al.* reported the first iterative synthesis of linear terpenes with access to *all* stereoisomers, starting from the diiodo terpene building blocks **1.30** and **1.31** (Scheme 1.6a).[27]

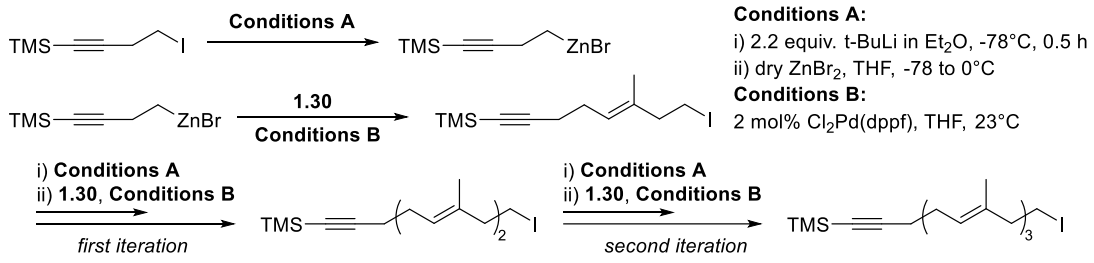
a) Preparation of *E*- and *Z*-alkenyl iodide via Zr catalysed carboalumination and sequential iodination



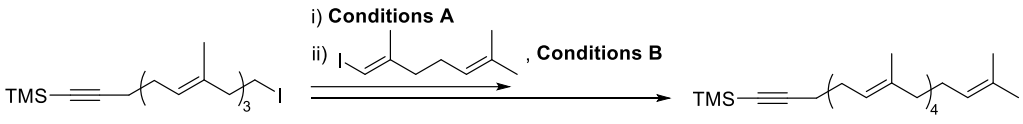
Scheme 1.6a) Preparation of *E*-and *Z*-alkenyl iodide **1.30** and **1.31** *via* Zr-catalysed carboalumination and sequential iodination reactions; b) Iterative Negishi coupling for chain extension; c) Capping of the primary iodide *via* Negishi coupling with suitable alkenyl iodide; d) Preparation of *(2E,6Z)*-farnesol **1.34**, *(2Z,6Z)*-farnesol **1.23** and *(2E,6Z,10E)*-geranylgeraniol **1.36** *via* Negishi coupling and stereoselective Zr-catalysed carbofunctionalisation reactions.

Iterative Negishi coupling with diiodide **1.30** or **1.31** furnished linear terpene with desired olefin geometry and chain length (Scheme 1.6b).

b) Generation of alkyl zinc reagent and iterative Negishi coupling with alkenyl iodide



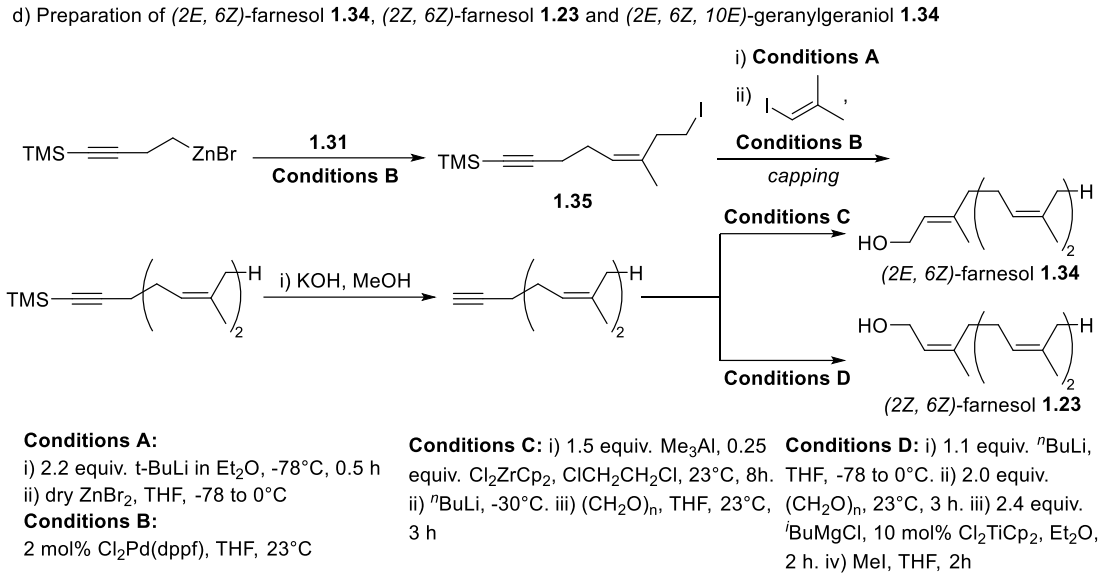
c) Capping of the primary iodide via Negishi coupling with alkenyl iodide



Scheme 1.7 b) Iterative Negishi coupling for chain extension; c) Capping of the primary iodide *via* Negishi coupling with suitable alkenyl iodide.

The primary iodide was then capped with a suitable alkenyl iodide *via* another Negishi coupling to furnish the terpene "head" (Scheme 1.6c). The terminal TMS-protected alkyne was deprotected and subject to the carboalumination reaction (Scheme 1.6d,

Conditions C) to give the *E*-alcohol.[28] The corresponding *Z*-alcohol can be accessed *via* alkyne hydroxymethylation-Ti catalyzed hydromagnesiation-methylation sequence (Scheme 1.6d, Conditions D).[29]



Scheme 1.8 d) Preparation of *(2E,6Z)*-farnesol **1.34**, *(2Z,6Z)*-farnesol **1.23** and *(2E,6Z,10E)*-geranylgeraniol **1.36** *via* Negishi coupling and stereoselective Zr-catalysed carbofunctionalisation reactions.

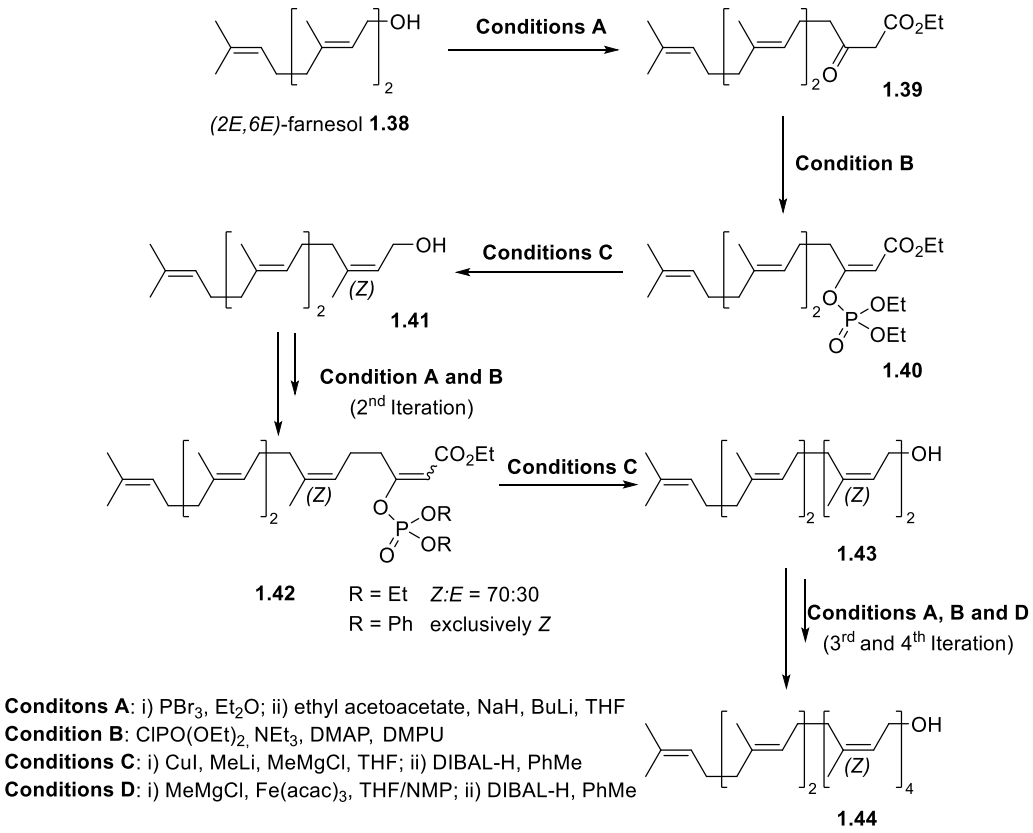
This method was exemplified in the preparation of (*2E,6Z*)-farnesol **1.34**, (*2Z,6Z*)-farnesol **1.23**, (*2E,6Z,10E*)-geranylgeraniol **1.36** (Scheme 1.8d) and coenzyme Q_{10} **1.37**.

1.2.2.2 Cu- and Fe-mediated cross-coupling

More recently, another protocol for the preparation of *Z*-polyprenols was established, featuring stereoselective enolisation and Cu-mediated cross-coupling.[30–32] This was applied iteratively to assemble polyprenols up to C_{35} with four consecutive *Z*-olefins (Scheme 1.9).[33]

In the synthesis of C_{35}-polyprenol **1.44**, *(2E,6E)*-farnesol **1.38** was first brominated and alkylated with ethyl acetoacetate to give β-keto ester **1.39** (Scheme 1.9, Conditions A), which was then enolised and trapped by diethyl chlorophosphate to yield vinyl phosphate **1.40** in a stereoselective manner (Scheme 1.9, Conditions B). The vinyl phosphate **1.40** was then methylated *via* a Cu-mediated cross-coupling reaction,

followed by ester reduction with DIBAL-H (Scheme 1.9, Conditions C) to furnish (*2Z,6E,10E*)-geranylgeraniol **1.41**. However, during the second iteration, treating **1.41** with the same conditions gave an *E/Z*-mixture of products **1.42**. Substituting diethyl phosphate with a bulkier diphenyl phosphate provides better stereochemical control and delivered C_{25}-polyprenol **1.43** with desired double bond geometry.



Scheme 1.9 Preparation of C_{35}-polyprenol **1.44** *via* iterative alkylation/cross-coupling sequence.

Presumably due to the failure of Cu-mediated cross-coupling reaction, the Fe-mediated cross-coupling conditions developed by Nakada *et al.et al.*. was employed (Scheme , Conditions D).[34] After another two iterations of this procedure, C_{35}-polyprenol **1.44** was obtained with an average yield of 7% from *(2E,6E)*-farnesol **1.38**.

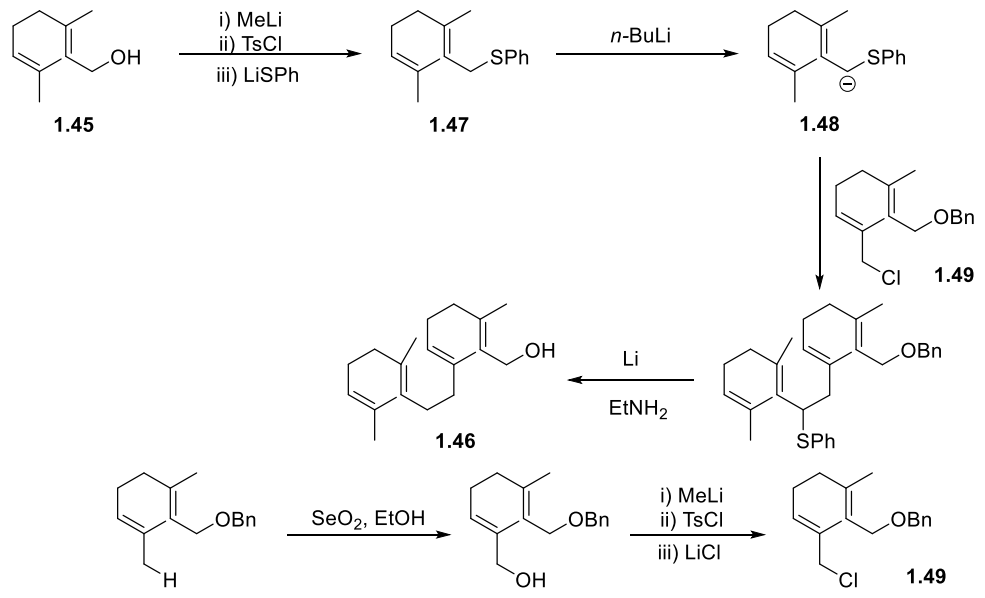
1.2.3. Allyl-allyl coupling approaches

1.2.3.1 Biellmann coupling

Before the emergence of Pd-catalysed cross-coupling chemistry, main-group organometallic reagents were used in the synthesis of linear terpenes. Several

examples utilise Biellmann coupling[35] and other allyl-allyl coupling methods (*e.g.,* organobarium chemistry) for the chain extension of terpenes. However, some of them suffer from by stereo- and regioisomerisation reactions (*e.g.,* allylic Grignard reagents are known to isomerise rapidly between *E*- and *Z*-isomers even at -80°C)[36] and in most examples only *E*-isomers are accessible (*vide infra*).

Altman *et al.* reported an early example of the assembly of (*2E,6E,10E*)-geranylgeraniol **1.46** *via* Biellmann coupling (Scheme 1.10).[37] Geranyl thiophenyl ether **1.47** can be readily prepared from geraniol **1.45** *via* tosylation and subsequent substitution with lithium thiophenolate. The stereochemical stability of the sulfur-stabilised carbanion **1.48** is crucial to the successful installation of the geranyl fragment. The cross-coupling partner 8-chlorogeranyl benzyl ether **1.49** can be accessed in two steps *via* selenium-mediated allylic oxidation of *O*-protected geraniol and tosylate displacement by chloride. The benzyl ether deprotection and the removal of allylic sulfide was achieved *via* Birch reduction, furnishing (*2E,6E,10E*)-geranylgeraniol **1.46** as the final product.

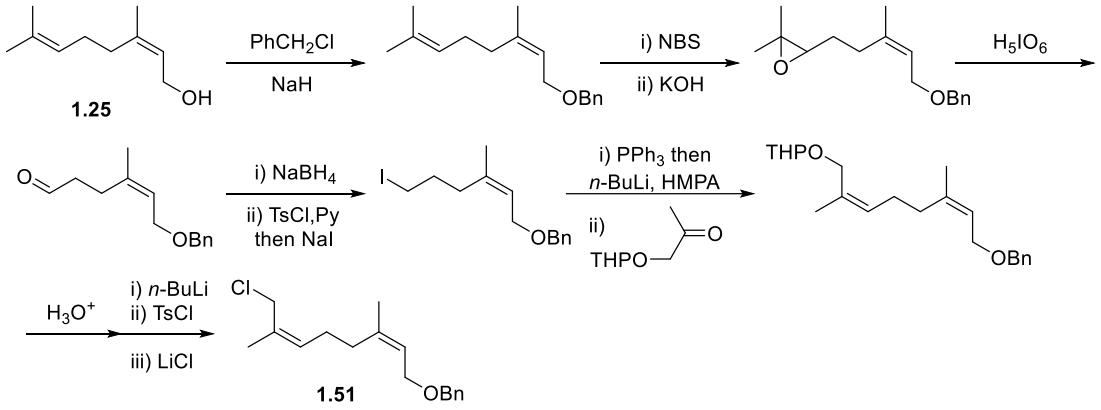


Scheme 1.10 Assembly of (*2E,6E,10E*)-geranylgeraniol **1.46** *via* Biellmann coupling between geranyl thiophenyl ether **1.47** and 8-chlorogeranyl benzyl ether **1.49**.

The downside of this method is the lack of access to the *Z*-terpenes as the selenium-mediated allylic oxidation is selective towards *E*-chloride **1.49**, which is the only product. Although neryl thiophenyl ether **1.50** (not shown) can be used instead of the

E-isomer **1.47** to install one *Z*-olefin unit, it is not possible to connect two consecutive *Z*-olefin units *via* this method.

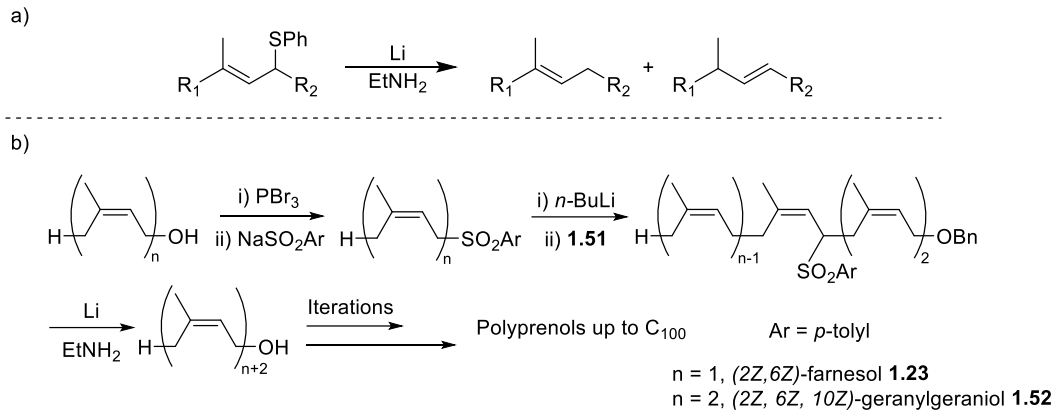
Thus, it is crucial to gain access to the *Z*-chloride **1.51**, which would be key to the access of *Z*-terpenes in general. In 1983, Sato *et al.* disclosed the preparation of the *Z*-chloride **1.51** from nerol **1.25**, utilising a Wittig reaction to install the desired olefin geometry (Scheme 1.11).[38]



Scheme 1.11 Preparation of 10-chloroneryl benzyl ether **1.51** from nerol **1.25**.

This 8-step sequence affords the *(Z,Z)*-C_{10} terpene building block **1.51** with 33% total yield and high stereoselectivity (up to 98:2 *Z:E* at the olefin allylic to chloride).

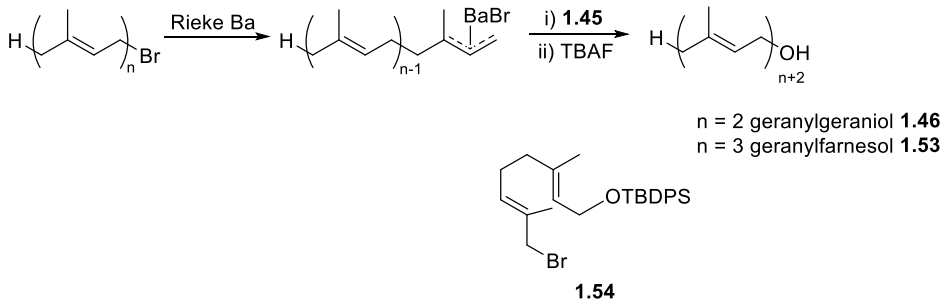
Further improvements were also made on Biellmann coupling where allylic sulfones are used instead of allylic sulfides, to provide superior yield and stereochemical outcome by avoiding double bond isomerisation observed in the reduction of allylic sulfides (Scheme 1.12a).[39,40] These modifications enabled the preparation of *all-Z*-polyprenols, including *(2Z,6Z)*-farnesol **1.23** and (*2Z,6Z,10Z*)-geranylgeraniol **1.52**, as demonstrated by Sato *et al.* (Scheme 1.12b).[38] This method was later applied iteratively in the preparation of various polyprenols (up to C_{50}) containing multiple *Z*-olefin units[40–42] and more recently in the syntheses of C_{60}- and C_{100}-dolichols.[43]



Scheme 1.12 a) Undesirable double bond isomerisation observed in the reductive desulfonylation of allylic sulfide b) Stereoselective syntheses of all-*Z*-polyprenols and polyprenols up to C_{50} *via* iteration of modified Biellmann coupling.

1.2.3.2 Stereodefined allylic metal reagents

The preparation of allylic barium reagents, pioneered by Yamamoto *et al.*, solved the problem of stereorandomisation of allylic metal reagents and provides an alternative allyl-allyl coupling method for the construction of 1,5-dienes.[44] This method was soon applied by Corey in the synthesis of all-*E*-polyprenols including geranylgeraniol **1.46** and geranylfarnesol **1.53** (Scheme 1.13).



Scheme 1.13 Preparation of all-*E*-polyprenols *via* allyl-allyl coupling with allylic barium reagents and allyl bromide **1.54**.

However, there is no report on the preparation of *Z*-allylic barium reagent and this method was not applied in the preparation of *Z*-polyprenols.

1.3 Summary and outlook

Among the pre-existing methods, olefination reactions are suitable for the stereoselective construction of linear polyprenols. The major limitations of olefination methods are the lack of synthetically/commercially available carbonyl precursors for higher terpenes ($\geq C_{20}$) and the poor *Z*-selectivity when forging internal trisubstituted olefin.

While cross-coupling methods are more contemporary and often high-yielding, the use of precious metal catalyst rendered the synthesis impractically expensive to scale up. In the case of in the abovementioned Negishi coupling (see Section 1.2.2.1), the dihalide reagent **1.30** and **1.31**, which are required for iterative procedure, need several steps to synthesise and are difficult to handle due to instability. Meanwhile, owing to the use of inexpensive metal catalyst, the abovementioned Cu/Fe-catalysed cross-coupling reaction (see Section 1.2.2.2) can be easily scaled-up. However, this method extends only one isoprene unit per iteration of procedure, which renders the synthesis of higher linear terpenes inefficient. The stereoselectivity of enolisation can also be difficult to control, particularly in the late stage of synthesis when stereochemical impact of the growing terpene chain becomes problematic.

In the assembly of C_{20} or higher linear terpenes, allyl-allyl coupling methods are often used. This is because multiple, stereodefined isoprene units, which are pre-installed, can be joined in a single step without the complication of double bond isomerisation. Thus, the synthesis of desired linear terpene is convergent, allowing separate preparation of individual precursors with fewer steps and higher yield.

Other methods reported for stereodefined trisubstituted olefin synthesis include, (metal-mediated) carbofunctionalisation of alkynes[45–47], selective 1,4-reduction of dienes[48–51] and olefin isomerisation[52–56]. While these are promising strategies for the construction of functionalised trisubstituted olefins, none of them are applicable for the construction of linear terpenes as the trisubstituted olefin units in linear terpenes are unfunctionalised. In addition, achieving desirable *E/Z*-selectivity remains to be challenging in many cases.

Despite the fact that linear terpenes up to C_{50} have been chemically synthesised with defined stereochemistry, it remains unclear if pre-existing methods can be reliably

applied for the assemblies of even higher linear terpenes. In previous examples of iterative syntheses, erosion of stereoselectivities and yields were observed with the growth of terpene chain. Thus, the assembly of higher linear terpenes still requires a modular, iterative and highly stereoselective method that takes into account the impact of the growing terpene chain.

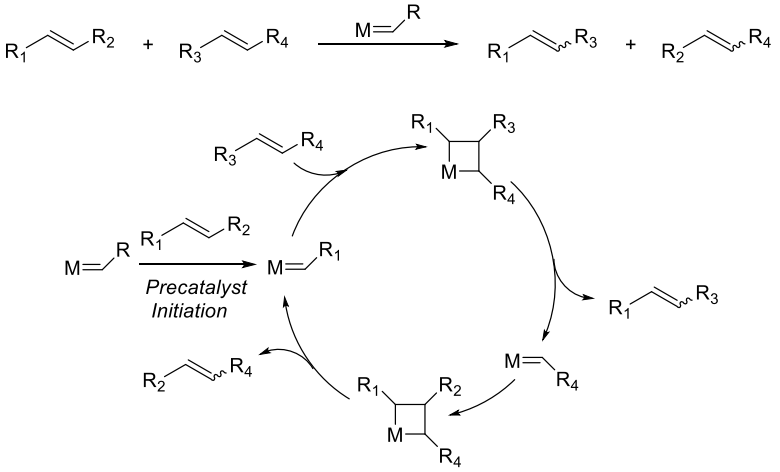
Chapter 2 Cross-metathesis reactions in the synthesis of trisubstituted olefins

2.1 General introduction to olefin metathesis chemistry

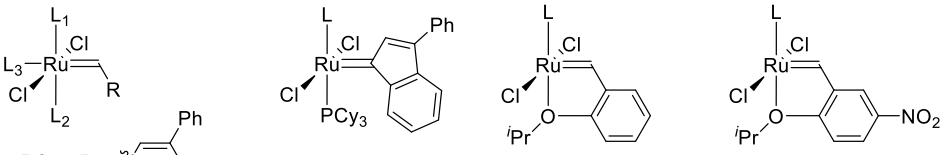
Since the first non-catalysed olefin metathesis reaction in 1931[57] and the first metal-catalysed reaction in 1955[58], olefin metathesis has become one of the most powerful tools for synthetic organic chemists to construct C-C double bonds.[59–61]

Based on the mechanistic understanding of recursive alkylidene-alkene exchange, different types of olefin metathesis reactions and various catalysts for different purposes were developed (Scheme 2.1).

a) Chauvin mechanism of olefin metathesis:



b) Selection of commonly used olefin metathesis precatalysts:

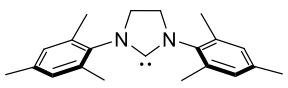
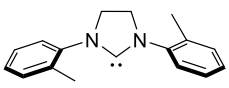
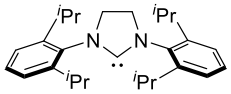


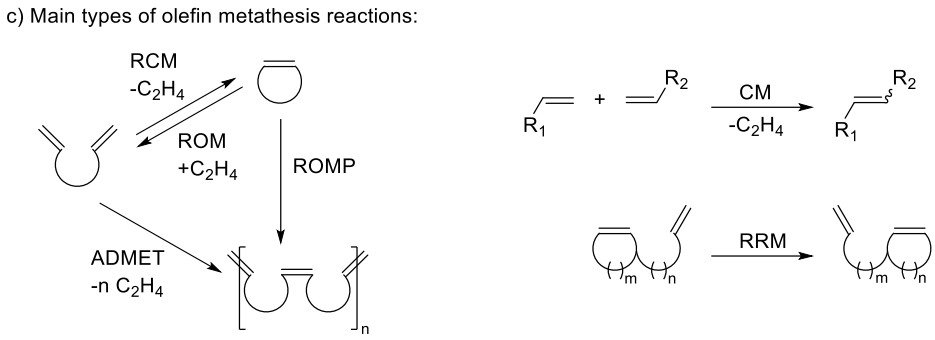
G0 $L_1 = L_2 = PCy_3$, R = Ph
GI $L_1 = L_2 = PCy_3$, R = Ph
GII L_1 = SIMes, $L_2 = PCy_3$, R = Ph
***i*PrGII** L_1 = SIPr, $L_2 = PCy_3$, R = Ph
TolGII L_1 = SITol, $L_2 = PCy_3$, R = Ph
GIII L_1 = SIMes, L_2 = L_3 = 4-bromopyridine, R = Ph

IndI L = PCy_3
IndII L = SIMes
IndSIPr L = SIPr

HGI L = PCy_3
HGII L = SIMes
HGSIPr L = SIPr
HGSITol L = SITol

GreI L = PCy_3
GreII L = SIMes
GreSIPr L = SIPr
GreSITol L = SITol

SIMes = 
SITol = 
SIPr = 



Scheme 2.1 Developments in olefin metathesis processes: a) Mechanism of olefin metathesis; b) Selection of commercially available Ru-based precatalysts; c) Major types of olefin metathesis reactions.

The Nobel prize in chemistry 2005, which was shared by Chauvin, Grubbs and Shrock for their contribution in the field of olefin metathesis, marked the great importance of the metathesis method in organic synthesis.[62]

Despite the overall development in olefin metathesis chemistry, syntheses of trisubstituted olefins are still challenging, particularly *via* cross-metathesis (CM) reactions. In this chapter, the application of cross-metathesis reactions targeting trisubstituted olefins will be reviewed, with the focus on the examples in the synthesis of terpenoid olefins.

2.2 Classification and reactivity of olefins in olefin metathesis reactions

To understand the challenges associated with producing trisubstituted olefins *via* CM reactions, the relative reactivities of different types of olefins needs to be discussed in the first place.

The initiation step, which is the metathesis event between substrate olefin and pre-catalyst, provides a scale for measuring both olefin reactivities and catalyst activities. In 1998, Grubbs *et al.* measured the second-order rate constants by tracing alkylidene concentration with proton NMR for metathesis reactions involving various alkyl-substituted olefins using **GI** (Figure 2.1).[63]

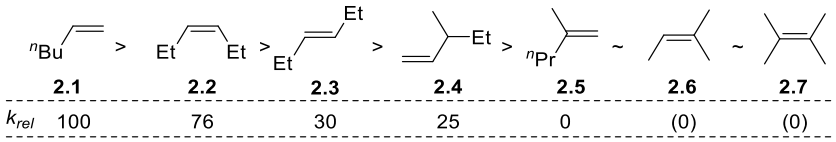


Figure 2.1 Relative initiation rate of olefin **2.1 – 2.7** with **GI** catalyst. Conditions: 3 mol% **GI**, C_6H_6, 35 °C. Number in parenthesis indicates the closest approximation of the observed value.

As shown above in Figure 2.1, it is clear that the initiation rate, as an estimation of olefin reactivity, decreases as the steric hinderance around the olefin increases. Highly substituted olefins, in this case 1,1-disubstituted olefin **2.5**, trisubstituted olefin **2.6** and tetrasubstituted olefin **2.7** cannot be initiated by **GI** complex. In the study of initiation rate of substituted styrenes, it is also noted that the observed trend in reactivity is closely related to the electronic nature of the olefin, typically the more electron-rich olefin possesses the higher reactivity in the initiation with **GI** complex.[63]

However, the trend of initiation rate only reflects the reactivity of olefins towards the pre-catalyst. Thus, this trend may not be extrapolated to real-world metathesis processes, which involves additional metathesis events between the olefin and the active catalyst (*i.e.,* the new propagating alkylidene generated during the initiation) and the kinetic profile of these steps should also be considered.[64]

The homodimerisation (also called self-metathesis) is the simplest, productive metathesis event that involves the fewest participants. Therefore, the tendency of given olefins towards homodimerisation can better reflect their reactivities in metathesis reactions. Based on different behaviours in homodimerisation, Grubbs *et al.* categorised olefins into four types (Table 2.1).[65]

Table 2.1 Outcomes of CM reactions between different olefin types

Olefin Type	Type I	Type II	Type III	Type IV
Type I (fast homodimerisation)	Statistical CM	Selective CM	Selective CM	No CM
Type II (slow homodimerisation)	Selective CM	Non-selective CM	Selective CM	No CM
Type III (no homodimerisation)	Selective CM	Selective CM	Non-selective CM	No CM
Type IV (spectators to CM)	No CM	No CM	No CM	No CM

Type I olefins are the most reactive olefins in CM reactions. They initiate rapidly and the resulting alkylidene unselectively metathesise with other Type I olefins or self-metathesise to give a mixture of all possible olefin isomers. These olefin products are also type I consumed in secondary metathesis processes, to eventually yield a *statistical* mixture of olefin isomers.

Type II olefins are less reactive, but reactive enough towards pre-catalysts for initiation. They homodimerises slowly, which allows controllable CM reactions with Type I olefins.

Type III olefins are even less reactive compared to Type II olefins and no homodimerisation occurs in this case. Type III olefins may react with Type I or Type II olefins to selectively form corresponding CM products.

Type IV olefins are completely inert in metathesis reactions—they do not participate, neither inhibit, metathesis reactions.

This classification allows the prediction of product distribution. CM reactions between two olefins of the same type (*i.e.,* two Type I olefins or two Type II olefins) are non-selective. This is due to the similar rates of homodimerisation and CM. On the other hand, CM reactions with two olefins of different types are selective. The rate

discrepancy between homodimerisation and CM allows the selective CM reaction to occur.

Due to the different activity between catalysts, this classification varies from catalysts. Thus, the activity of catalysts can be also compared, as more reactive catalysts are able to react with less reactive olefins. For example, olefins with perfluorinated alkyl substitution are spectator olefins (Type IV) for **GI**. However, they are Type II olefins for the more active **GII** complex.[65]

It should be noted that this classification based on homodimerisation rates only serves as a guideline for the estimation of olefin reactivity. Many exceptions have been reported, for example, dimerisation of isobutene (Type III) to give tetramethylethene using **GII** complex was observed.[66] To better evaluate the reactivity of olefins, it needs to be considered in conjunction with the reactivity of the propagating alkylidene species, which varies from reaction to reaction.

2.3 Cross-metathesis reactions in the construction of trisubstituted olefins

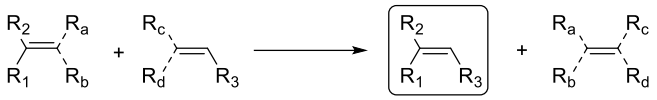
To construct a trisubstituted olefin *via* olefin metathesis, one may arbitrarily choose from any possible combination of suitable olefins. However, the outcome will largely depend on the choice of combination and the reactivity of olefins. There are in theory nine possible combinations based on the substitution pattern of both olefins. These combinations are ordered based on their substitution pattern and Grubbs classification with respect to **GII** complex in Table 2.2.

It is obvious that not all of listed combinations are practical or synthetically useful. For example, the combination of a trisubstituted olefin and a tetrasubstituted olefin is neither practical nor synthetically useful: they are Type III and Type IV olefins with minimum reactivity and preparation of one trisubstituted olefin from another trisubstituted olefin may not be synthetically attractive.

In fact, a general trend was observed that the combinations which involve more reactive olefins—hence olefins with fewer substitutions—also have more reported examples. Searching the most reactive olefin combination for the formation of trisubstituted olefin on Scifinder, which is the combination of a 1,1-disubstituted olefin and a terminal olefin, revealed over 3900 hits. The least reactive combination, which is the combination of a tetrasubstituted olefin and a trisubstituted olefin, has no reported example.

In the following part of this section, each olefin combination will be examined, and relevant examples will be discussed accordingly.

Table 2.2 Possible combinations of olefins for the synthesis of trisubstituted olefins *via* olefin metathesis



Olefin combination and classification with respect to **GII** complex	Olefin products	Hits on SciFinder[a]
1,1-disub. + terminal (Type III + Type I)	trisub. + ethylene	1915 hits Most explored olefin combination.
1,1-disub + disub. (Type III + Type II)	trisub. + terminal	64 hits
1,1-disub. + trisub. (Type III + Type III)	trisub. + 1,1-disub.	29 hits
trisub. + terminal (Type III + Type I)	trisub. + terminal	192 hits
trisub. + disub. (Type III + Type II)	trisub. + disub.	12 hits
trisub. + trisub. (Type III + Type III)	trisub. + trisub.	25 hits
tetrasub. + terminal (Type IV + Type I)	trisub. + 1,1-disub.	4 hits
tetrasub. + disub. (Type IV + Type II)	trisub. + trisub.	3 hits
tetrasub. + trisub. (Type IV + Type III)	trisub. + tetrasub.	No example found on Scifinder

[a] Results are acquired using the query as illustrated in Appendix I. This search is not exhaustive and only is used to reveal the general trend.

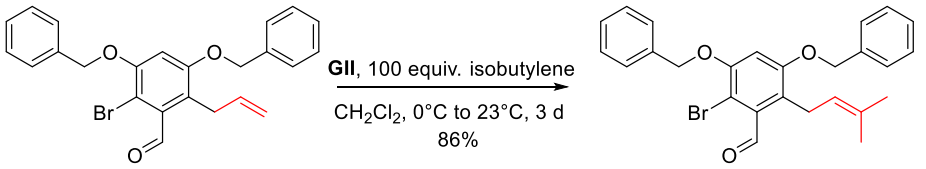
2.3.1 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a terminal olefin

The early examples using the combination of a 1,1-disubstituted olefin and a terminal olefin were RCM reactions that from relatively unstrained cyclic systems (typically 5-, 6-, 7 and 8-membered rings) using **GI** complex.[67–69] However, the corresponding CM examples were not reported until the more reactive **GII** complex was employed. Grubbs *et al.* disclosed the preparation of trisubstituted, functionalised olefins *via* CM reactions[70] and later the prenylation of terminal olefins *via* CM reactions with isobutylene **2.8** and 2-methyl-2-butene **2.9**.[66] These methods were soon adopted and now widely used in the syntheses of complex natural products (Scheme 2.2).[71–75]

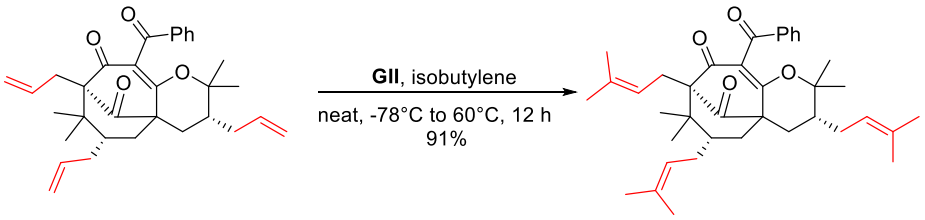
It should be noted that the CM between 1,1-disubstituted olefins and terminal olefins is intrinsically slow compared to the homodimerisation of terminal olefins. Thus, large excess of 1,1-disubstituted olefins is often required in these examples to achieve high yield. In extreme cases, the 1,1-disubstituted olefin can be used as a solvent to maximise its effective concentration.

Selected examples of CM prenylation of terminal olefins:

Arredondo (2019):

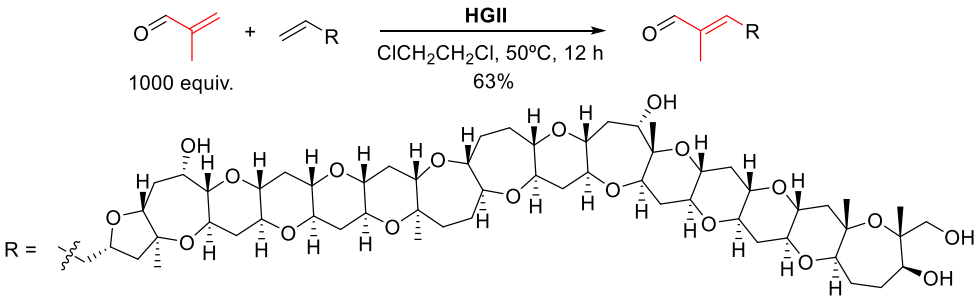


Boyce (2016):

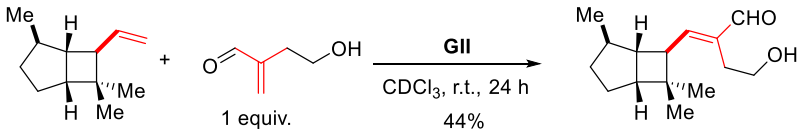


Selected examples of CM functionalisation of terminal olefins:

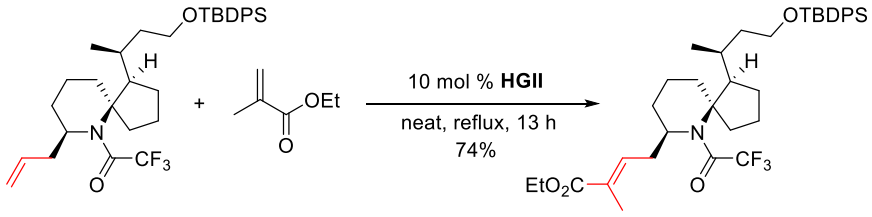
Jamison (2019):



Hurtley (2014):

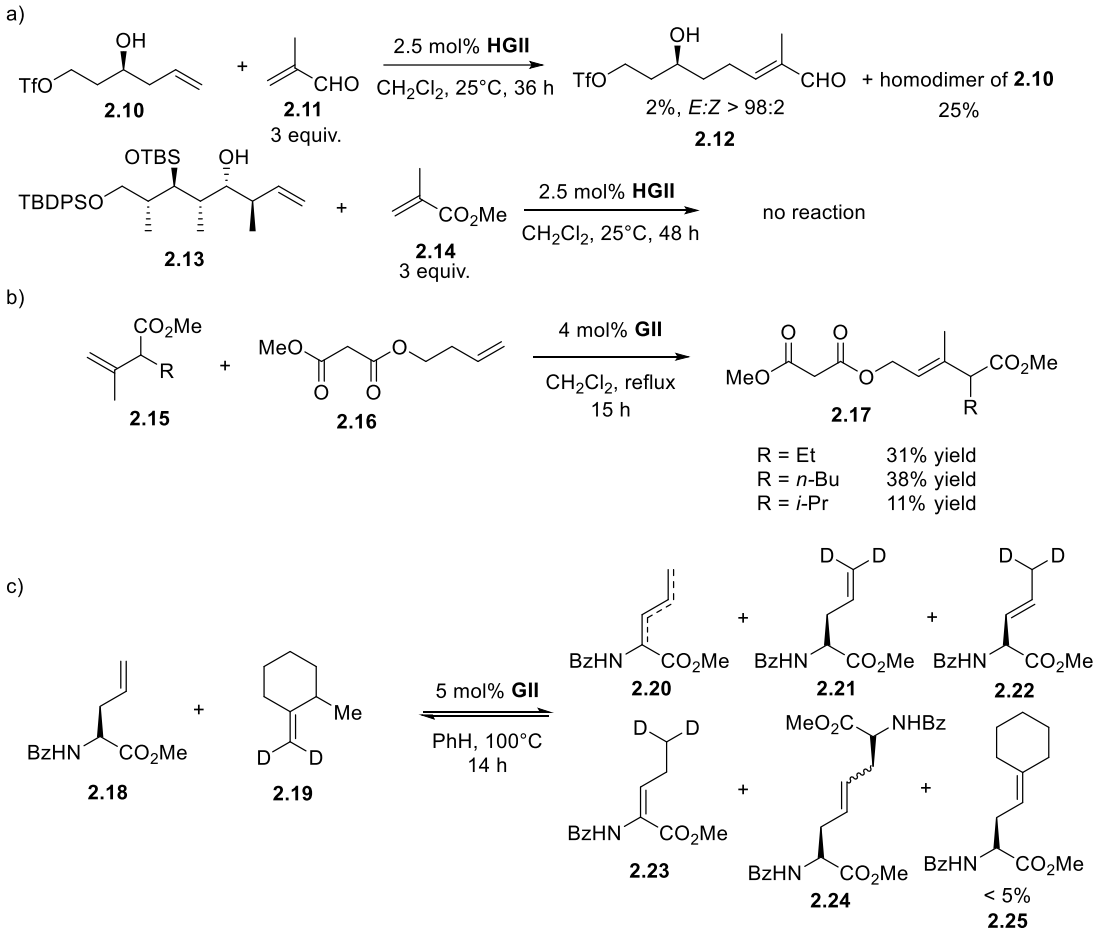


Xu (2007):



Scheme 2.2 Selected examples of CM between terminal olefins and 1,1-disubstituted olefins.

In contrast to the abovementioned prenylation and functionalisation protocols, there are also examples that CM reactions are low-yielding, which can be caused by various reasons. One of the common reasons is the homodimerisation of the terminal olefin outcompetes the desired CM, especially when the use large excess of CM partner becomes impractical. In the case of CM between **2.10** and **2.11**, significant amount of homodimer of terminal olefin **2.10** were observed, indicating a sluggish CM event compared to the homodimerisation (Scheme 2.3a).



Scheme 2.3 Selected examples of unsuccessful/low-yielding CM reactions between terminal olefins and 1,1-disubstituted olefins.

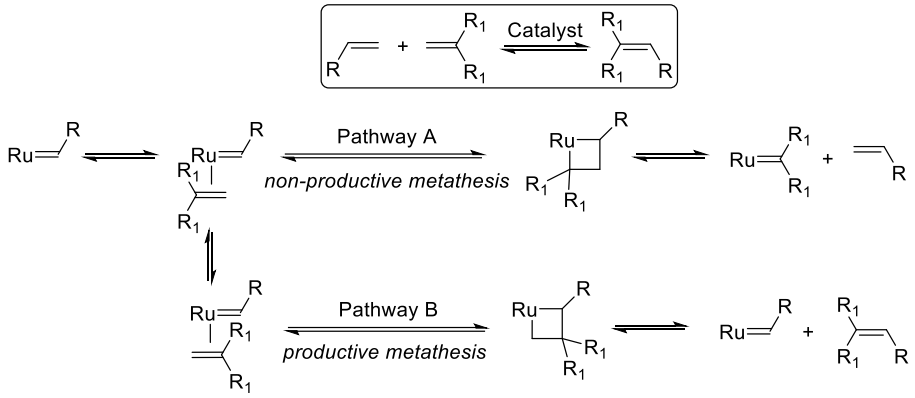
The risk of getting a low-yielding/unsuccessful CM reaction is also associated with the structural complexity of both olefin substrates (Scheme 2.3a).[76] In the CM reaction between **2.10** and **2.11**, trace amount of desired CM product and significant amount of homodimer **2.10a** was observed. The combination of **2.13** and **2.14,** however, gave no reaction due to their structural complexity (presumably β-branching in terminal olefin **2.13**).

Thus, the substitution pattern of olefin *substituents* (*e.g.*, β-branching) has to be considered. Formation of a trisubstituted olefin necessitates a sterically encumbered ruthenacycle intermediate with at least three substituents. As a result, the ruthenacycle is sensitive to additional steric hindrance and subtle changes of substitution on olefin substituents may have a great influence (Scheme 2.3b).[77] In the CM reaction between **2.15** and **2.16**, increasing the size of β-branching in **2.16** leads to significantly decreased yield.

The dual role of catalyst in these low-yielding reactions is worth mentioning. In addition to the catalyst activity, the catalyst lifetime is challenged in these sterically demanding CM reactions as the elevated temperature and extended reaction time are often employed to achieve satisfactory conversion. The problem associated with this olefin combination (*i.e.*, a 1,1-disubstituted olefin and a terminal olefin) is the generation of a reactive yet unstable ruthenium methylidene as the propagating species, which can lead to rapid catalyst decomposition and ruthenium hydrides formation.[78] Ruthenium hydrides are generally accepted as the main culprit behind the undesired olefin isomerisation in metathesis reactions.[79]

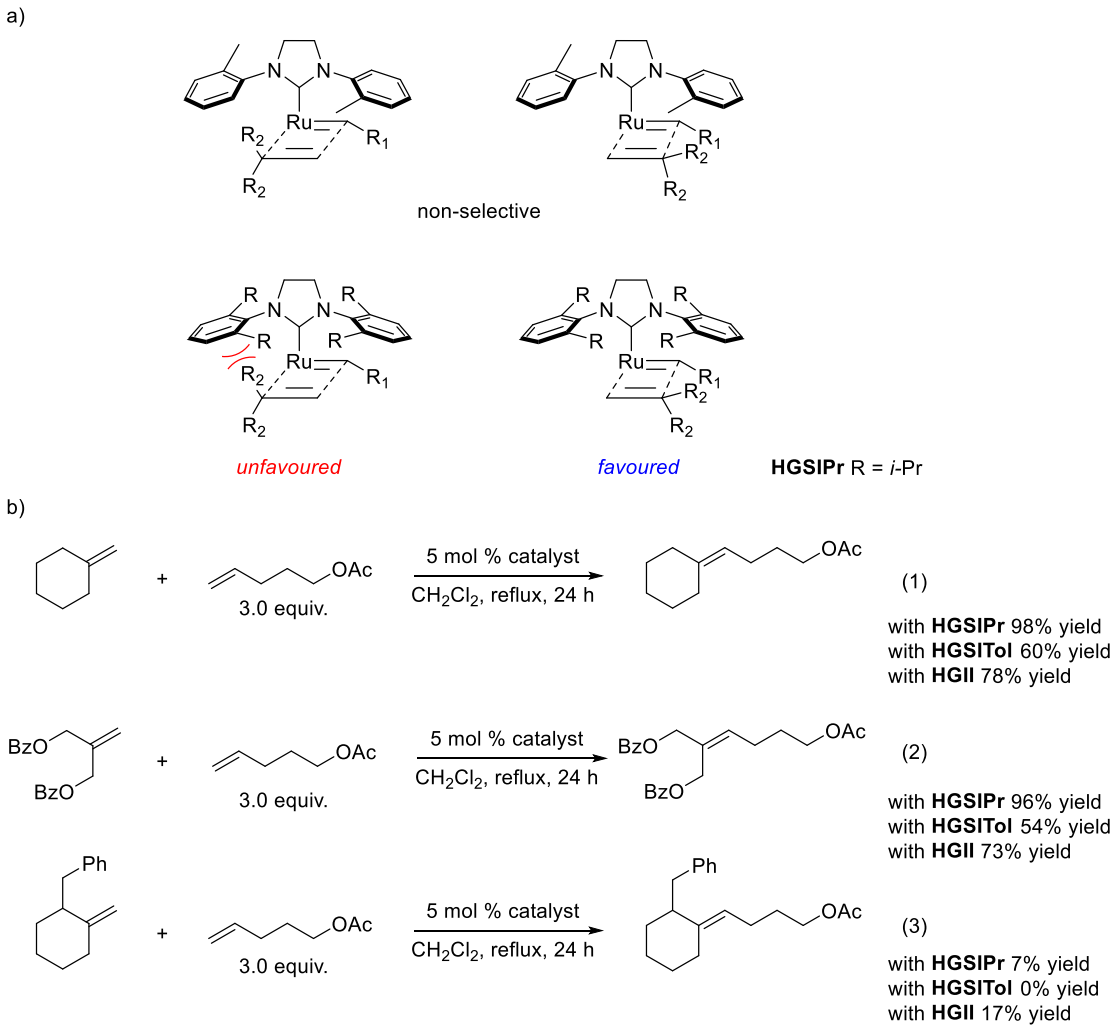
Robinson *et al.* encountered the undesired olefin isomerisation as well as the homodimerisation in their crossover experiment of a challenging CM reaction between a protected glycine derivative **2.18** and a deuterated 1,1-disubstituted olefin **2.19** with β-branching on its alkyl substituent. The reaction gave a mixture of deuterated and non-deuterated double bond isomers **2.20**-**2.23** and the homodimer **2.24** with a small amount (<5%) of desired CM product **2.24** (Scheme 2.3c). These observations are in line with a sluggish CM reaction that is not kinetically competitive against the rapid homodimerisation and catalyst decomposition/olefin isomerisation.

The inherent selectivity of non-productive metathesis over productive metathesis event may also lead to a low-yielding reaction (Scheme 2.4).



Scheme 2.4 Productive and non-productive metathesis events in CM reactions between terminal olefins and 1,1-disubstituted olefins.

For any given olefin metathesis reaction, there are two possible olefin orientations in the coordination step, which leads to the formation of two different metallacyclobutanes (mcb) that can collapse to give corresponding products (Scheme 2.4, pathway A and B). Unlike the productive metathesis pathway, the non-productive pathway does not produce desired CM product but still constitutes a catalyst turnover event. A kinetically favoured non-productive pathway may quickly deplete the catalyst and trigger undesired pathways induced by catalyst decomposition. Thus, it is not only catalyst activity and stability but also the selectivity of mcb formation that determine the efficiency of CM reactions. To improve the CM efficiency of sterically hindered olefins, Stewart *et al.* prepared a catalyst with a sizable NHC ligand baring *N*-2,6-diisopropylphenyl substitutions **HGSIPr** and a catalyst with a small NHC ligand baring *N*-tolyl substitutions **HGSITol**.[80] They hypothesised the catalyst with smaller NHC ligand **HGSITol** is non-selective towards productive metathesis while catalyst with larger NHC ligand **HGSIPr** favours productive metathesis by forcing olefin substituents away from ruthenium centre to avoid steric interaction with isopropyl substituents (Scheme 2.5a).



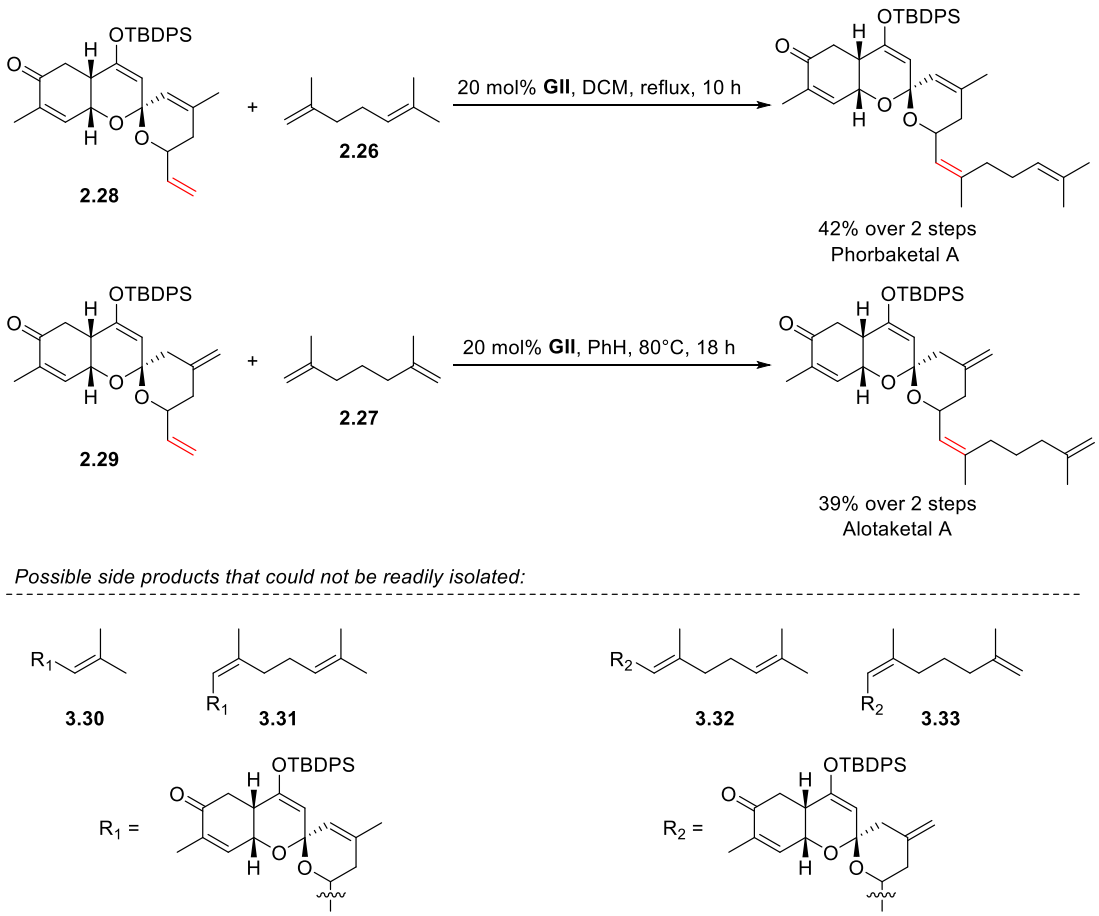
Scheme 2.5 a) Selectivity model of productive versus non-productive metathesis event with catalyst **HGSITol** and **HGSIPr** in the formation of trisubstituted olefins by CM. b) Comparison of CM efficiency between **HGII**, **HGSIPr** and **HGSITol** in the formation of trisubstituted olefins.

In support of this hypothesis, **HGSIPr** affords excellent yields which are higher than those with catalyst **HGII** and **HGSITol** (Scheme 2.5b, entry 1 and 2). However, **HGII** outperformed **HGSIPr** when a 1,1-disubsituted olefin with β-branching was employed, presumably due to the additional steric repulsions between isopropyl groups in **HGSIPr** and the β-branch (Scheme 2.5b, entry 3).

Despite numerous efforts made to increase the CM efficiency, a successful CM reaction requires extensive screening of reaction conditions and is often not guaranteed.

Unlike the well-established prenylation and functionalisation protocol, CM reactions are underdeveloped in the construction of terpenoid, trisubstituted olefin and only few examples were reported. Most of these examples involve the installation of a terpenoid side chain on various cyclic systems and these examples are summarised below.

Considering the geranylation of a terminal olefin using diene **2.26**, which seems to be a natural extension to the previously discussed prenylation reaction, the regioselectivity issue immediately emerges as there are two available sites for CM reaction. In the total syntheses of (-)-alotaketals A and (-)-phorbaketal A, the geranyl/isogeranyl side chains are installed *via* the CM reaction between diene **2.26** or **2.27** and the corresponding terminal olefin **2.28-2.29** (Scheme 2.6).[81]

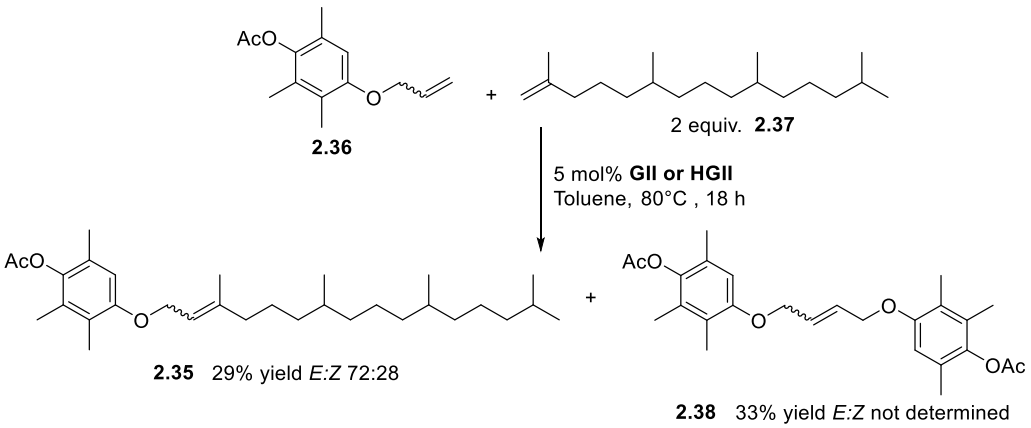


Scheme 2.6 Side chain installation *via* CM reactions in the total syntheses of (-)-Alotaketals A and (-)-Phorbaketal A.

Despite high catalyst loading and large excess of 1,1-disubstituted olefins **2.26** and **2.27** employed, the desired CM products were obtained in moderate yield. In the

reaction between **2.26** and **2.29**, identification of the prenylation product **3.30** indicates the CM reaction of **2.26** at the undesirable trisubstituted site. For comparison, when symmetrical diene **2.27** was used, comparable yield was obtained albeit no complication from regioselectivity. The identification of isomerised product **2.32**, however, suggests the catalyst decomposition and ruthenium hydride catalysed olefin isomerisation maybe responsible for the compromised yield.

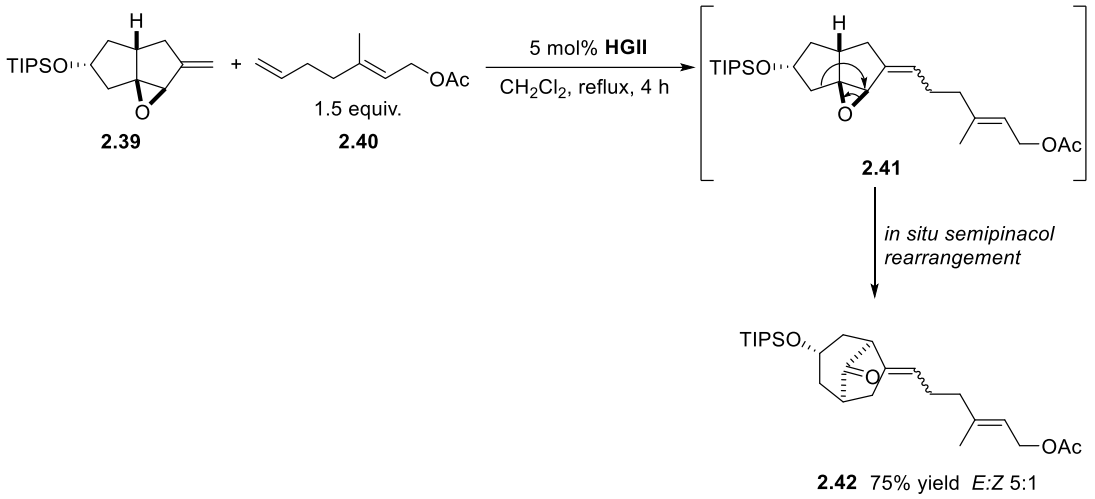
En route to the synthesis of vitamin E, the key precursor **2.35** was prepared *via* the CM between allyl ether **2.36** and 1,1-disubsituted olefin **2.37** which resembles the geometry of a linear terpene chain (Scheme 2.7).[82]



Scheme 2.7 Preparation of the key precursor to Vitamin E *via* CM.

The desired CM product **2.35** was isolated in 29% yield, accompanied with the homodimer of allyl ether **2.38** (33% yield) which was not consumed under reaction conditions. The catalyst (*e.g.,* **GII** or **HGII**), as well as the catalyst loading have no effect on the reaction. As previously discussed, dimerisation of the terminal olefin indicates either a sluggish CM event or the lack of selectivity towards productive metathesis versus non-productive metathesis. It should be noted that only small excess of partner olefin **2.37** was used in this reaction, presumably due to the synthetic availability. It is very likely that the small excess of **2.37** is not enough to shift the selectivity towards the desired CM reaction.

As part of the synthesis study of (iso)cyclocitrinol[83], the synthesis of a 6-alkylidenebicyclo[3.2.1]octan-8-one **2.42** was developed featuring a tandem CM/semipinacol rearrangement sequence (Scheme 2.8).[84]



Scheme 2.8 Tandem CM/semipinacol sequence as the key step in the synthesis of **2.42**.

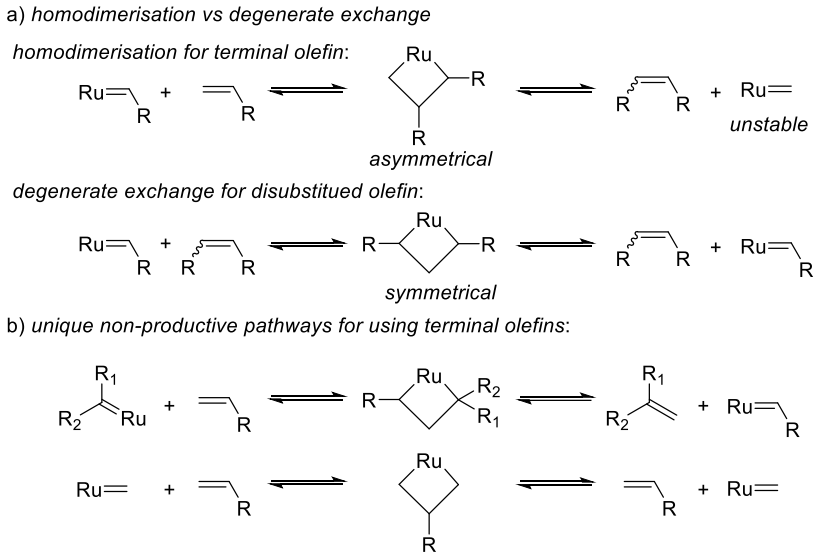
The CM reaction between **2.39** and **2.40** proceeded smoothly to give CM product **2.41** with high *E*-selectivity, which underwent concomitant semipinacol rearrangement under metathesis conditions to afford **2.42** in 75% yield. The Lewis acidic species catalysing the semipinacol rearrangement was proposed to be the ruthenium methylidene, which was present in a significant concentration after the completion of the CM reaction.[84]

2.3.2 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a disubstituted olefin

The combination of 1,1-disubstituted olefin and a disubstituted olefin is less often encountered in the construction of trisubstituted olefins. As introduced in the CM between 1,1-disubsituted olefins and terminal olefins, homodimers (*i.e.,* symmetrical disubstituted olefins) are less reactive compared to terminal olefins and are often not consumed under reaction conditions.

However, the reduced reactivity is sometimes beneficial to the CM efficiency and selectivity *(vide infra*). Compared to the use of terminal olefins, disubstituted olefins does not suffer from the complication of homodimerisation at low conversion, which generates unstable methylidene species that are susceptible to decomposition. Instead, the self-metathesis of symmetrical disubstituted olefins is traceless as no net reaction occurs during the formation and the collapse of a symmetrical mcb species (*i.e.,* degenerate exchange) (Scheme 2.9a). In addition, the use of symmetrical disubstituted

olefins avoids some non-productive metathesis events as there is only one orientation for symmetrical olefins in the olefin coordination step (Scheme 2.9b).

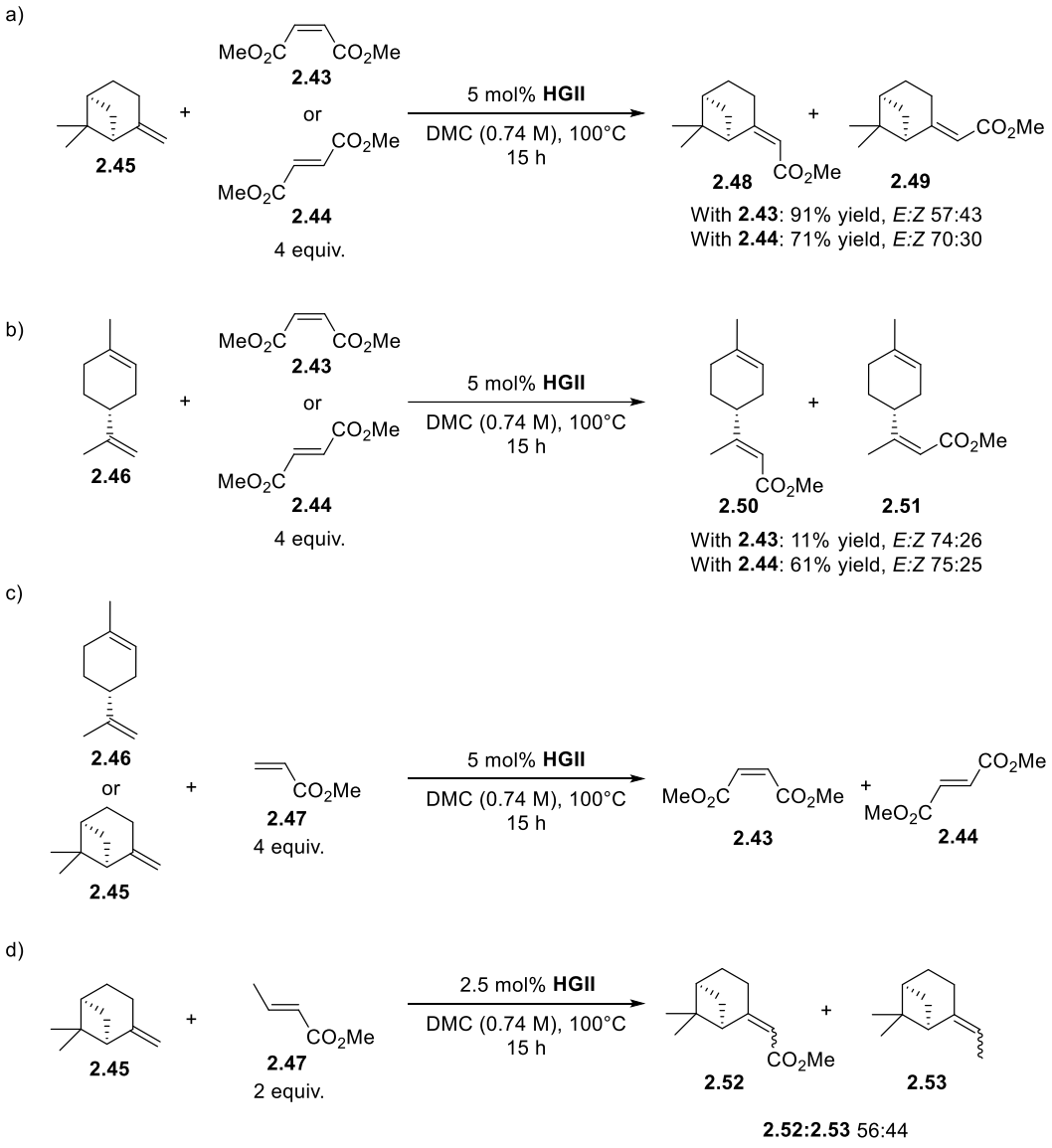


Scheme 2.9 Comparing the construction of trisubstituted olefin using the combination of 1,1-disubsituted olefin + terminal olefin and 1,1-disubstituted olefin + disubstituted olefin: a) homodimerisation of terminal olefins vs degenerate exchange of disubstituted olefins; b) unique non-productive pathways in the combination of 1,1-disubstituted olefin + terminal olefin.

The disubstituted olefin can be viewed as a reservoir of the more reactive terminal olefin, which is produced in a productive CM event. Thus, the concentration of terminal olefin remains low during the reaction, which slows down the rate of catalyst decomposition.

Bruneau *et al.* investigated the CM reaction between cyclic monoterpenes (*i.e.* β-pinene and limonene) and various disubstituted olefins.[85] Dimethyl maleate **2.43** and fumarate **2.44** metathesise smoothly with β-pinene **2.45** to give the corresponding CM products in good yields (Scheme 2.10a). Similar results were also observed in the CM reaction of maleate **2.43** and fumarate **2.44** with limonene **2.46** (Scheme 2.10b). However, both reactions of β-pinene **2.46** and limonene **2.46** with methyl acrylate **2.47** gave only homodimerisation products dimethyl maleate **2.43** and dimethyl fumarate **2.44** (Scheme 2.10c). These results indicated the rapid decomposition of catalyst *via* homodimerisation and non-productive metathesis of reactive terminal olefins prior to

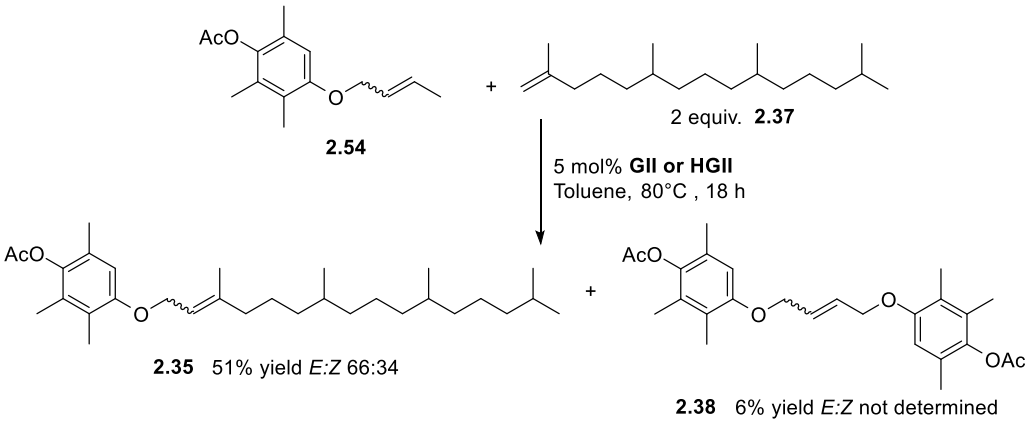
the productive CM event. The use of asymmetrical olefin suffers from regioselectivity issue and the desired regioisomers **2.52** are obtained in low yield (Scheme 2.10d).



Scheme 2.10 a) CM reaction of β-pinene **2.45** with dimethyl maleate **2.43** and dimethyl fumarate **2.44**; b) CM reaction of limonene **2.46** with dimethyl maleate **2.43** and dimethyl fumarate **2.44**; c) Unsuccessful CM reaction of β-pinene **2.45** and limonene **2.46** with methyl acrylate **2.47**; d) Complication of regioselectivity in the CM reaction of β-pinene **2.45** when asymmetrical disubstituted olefin **2.47** was used.

Another example is the aforementioned synthetic study of Vitamin E.[86] In the previous section, the key precursor **2.35** was prepared *via* the CM between allyl ether **2.36** and 1,1-disubsituted olefin **2.37** (see Scheme 2.7). However, by replacing the terminal

olefin **2.36** with its 'capped' surrogate **2.54**, better yield of **2.35** was obtained with a smaller amount of undesired homodimer **2.38**.

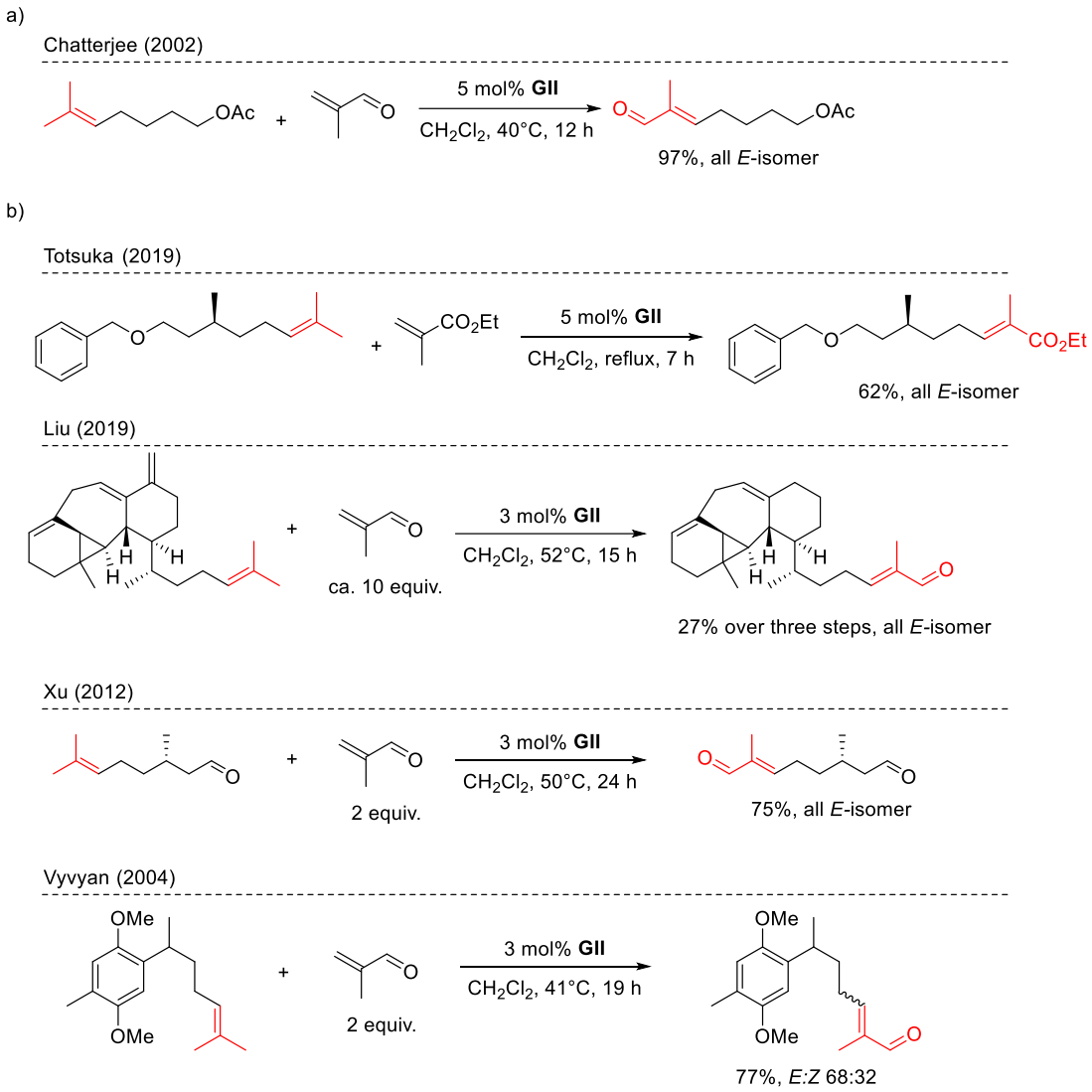


Scheme 2.11 Preparation of key intermediate **2.35** *via* CM between disubstituted olefin **2.54** and 1,1-disubsituted olefin **2.37**.

These examples indicate disubstituted olefins are often better CM partners than terminal olefins in the CM reaction with 1,1-disubstituted olefins due to their ability to suppress methylidene formation and non-productive CM events.

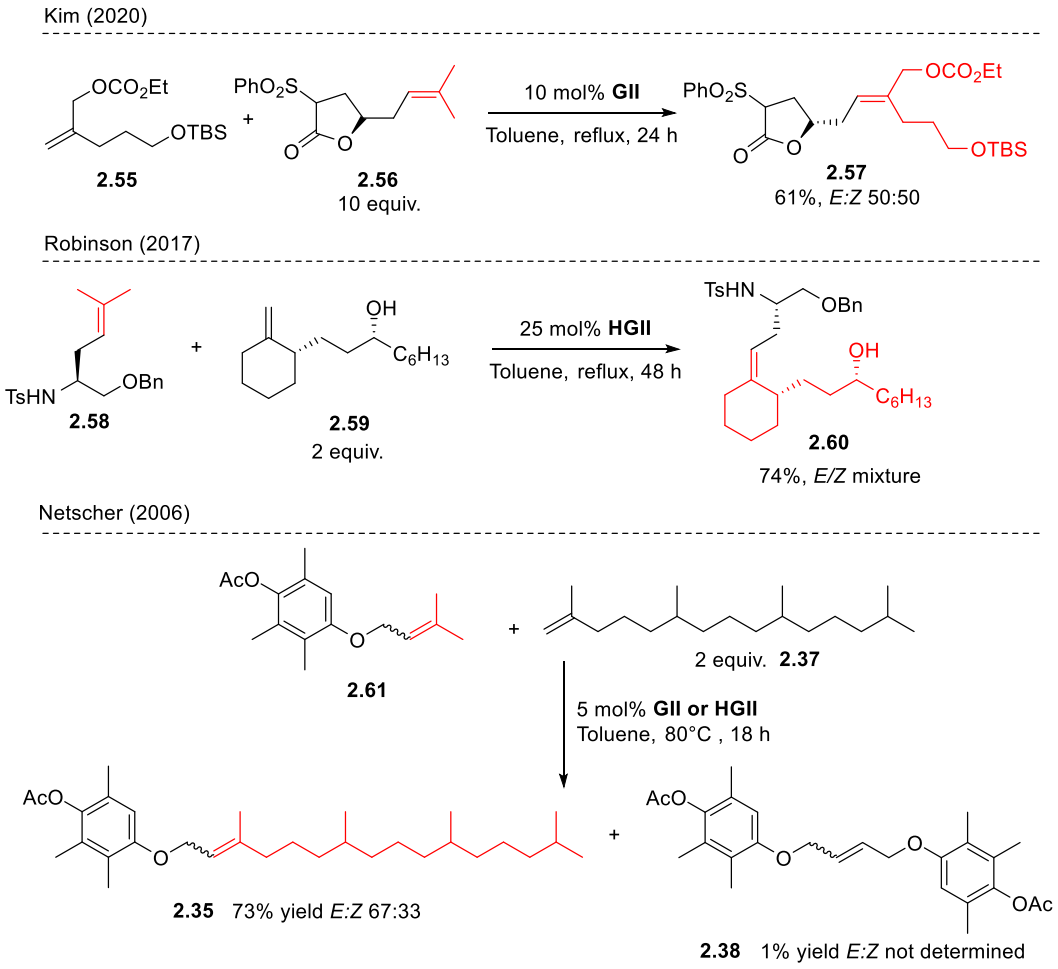
2.3.3 Formation of trisubstituted olefin from CM reactions between a 1,1-disubstituted olefin and a trisubstituted olefin

The combination of a 1,1-disubsituted olefin and a trisubstituted olefin is overlooked in CM reactions, presumably due to the apparent difficulty of combining two unreactive, sterically congested olefins. Despite being classified as Type III + Type III, this combination of olefin substrates was reported as early as 2002 in the functionalisation of trisubstituted olefins (Scheme 2.12a).[87] This method was soon adopted in many synthetic studies (Scheme 2.12b).[88–91]



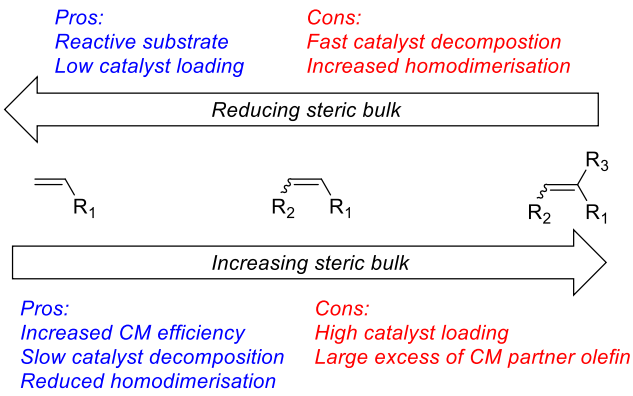
Scheme 2.12 a) Original protocol of functionalisation of trisubstituted olefin by CM reaction reported by Chatterjee *et al.*; b) Synthetic application of functionalisation of trisubstituted olefins *via* CM method.

Meanwhile, CM reaction between 1,1-disubstituted olefins and trisubstituted olefin partners other than acrylates/methacrylates are rare (Scheme 2.13).[92–94]



Scheme 2.13 Other examples of CM reactions involving structurally complex 1,1-disubstituted olefins and/or trisubstituted olefins.

In all these examples, the trisubstituted olefin products **2.59**, **2.60** and **2.38** are obtained in moderate to good yield. The most notable example is the CM reaction between **2.61** and **2.37**. Compared to other olefin combinations (Scheme 2.7 and 2.11), the combination of a 1,1-disubstituted olefin **2.37** and a trisubstituted olefin **2.61** produces highest yield of **2.35** with little dimerisation product **2.38**. These results are in agreement with the analysis of productive metathesis vs non-productive metathesis and the methylidene-induced catalyst decomposition. While increasing the steric bulk of partner olefin suppresses undesired catalyst decomposition and homodimerisation by reducing the methylidene formation, the CM efficiency is also improved as the productive CM reaction is more favourable. The only drawback is the reduced rate of productive CM reaction and higher catalyst loading are sometimes required (Scheme 2.14).

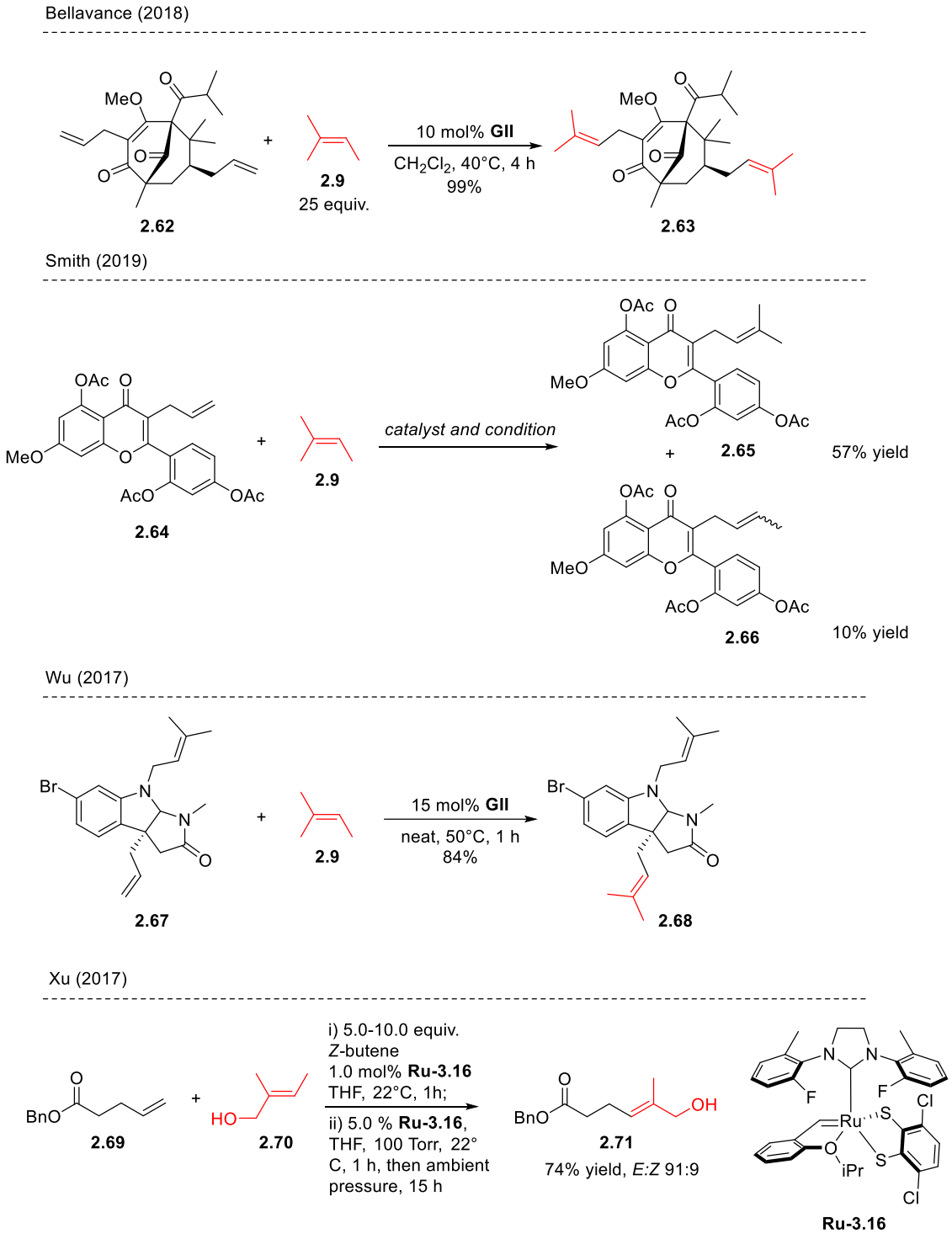


Scheme 2.14 Comparison of partner olefins employed in the CM reaction with 1,1-disubstituted olefin.

2.3.4 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and a terminal olefin

The combination of a trisubstituted olefin and a terminal olefin is frequently encountered in the construction of trisubstituted olefin *via* CM reaction. However, like abovementioned olefin combinations, most examples are based on the Grubbs prenylation/functionalisation protocol.[66,70] Some recent examples are listed below (Scheme 2.15).[95–98]

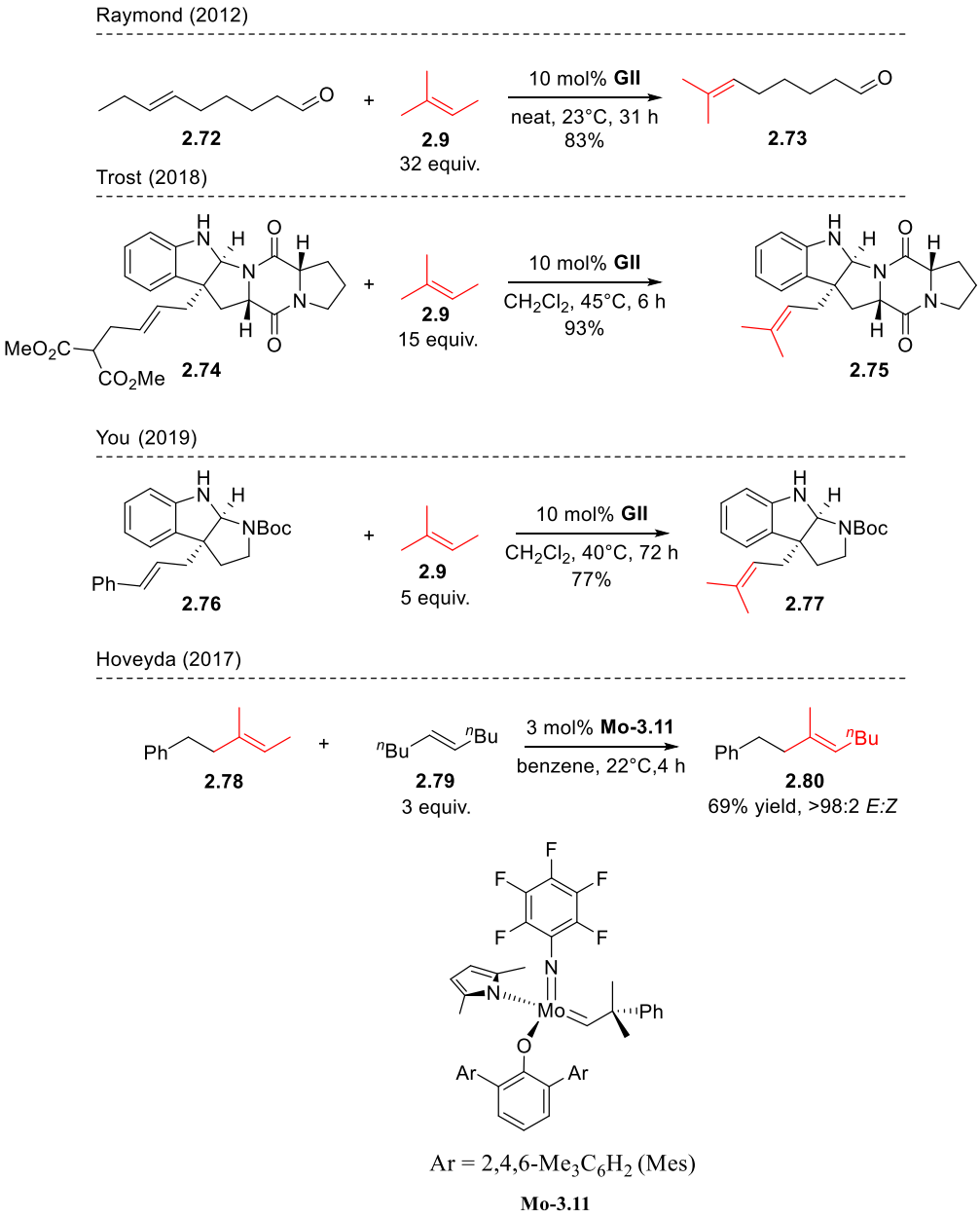
Although prenylation can be achieved using either isobutylene **2.8** or 2-methyl-2-butene **2.9** according to the protocol, 2-methyl-2-butene **2.9** (b.p. 38.5°C) is easier to handle than isobutylene **2.8** (b.p. -7°C). Large excess of **2.9** is required to drive the prenylation to completion in most cases but the yields are generally satisfactory. Smith *et al.* reported their attempt at prenylating a flavone derivative **2.64**, where they encountered a regioselectivity problem. The prenylated product **2.65** was obtained in 57% yield, accompanied with 10% of the undesired **2.66**. Although the experimental details are not reported, it is likely that the side product **2.66** can still metathesise with 2-methyl-2-butene **2.9** to give the desired product **2.65** if given enough time. Another noteworthy example is the stereoselective CM reaction between terminal olefin **2.69** and trisubstituted allylic alcohol **2.70**, which produces **2.71** in 74% yield and high stereoselectivity (*E:Z* 91:9). More discussion on the development of stereoselective metathesis can be found in Chapter 3 of this thesis.



Scheme 2.15 Selected examples of prenylation and functionalisation of terminal olefins *via* CM with trisubstituted olefin.

2.3.5 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and a disubstituted olefin

The combination of a trisubstituted olefin and a disubstituted olefin is rather rare in the construction of trisubstituted olefin *via* CM reaction and some notable examples are shown below (Scheme 2.16).[99–101]



Scheme 2.16 Selected examples of trisubstituted olefin syntheses *via* CM reactions between trisubstituted olefins and disubstituted olefins.

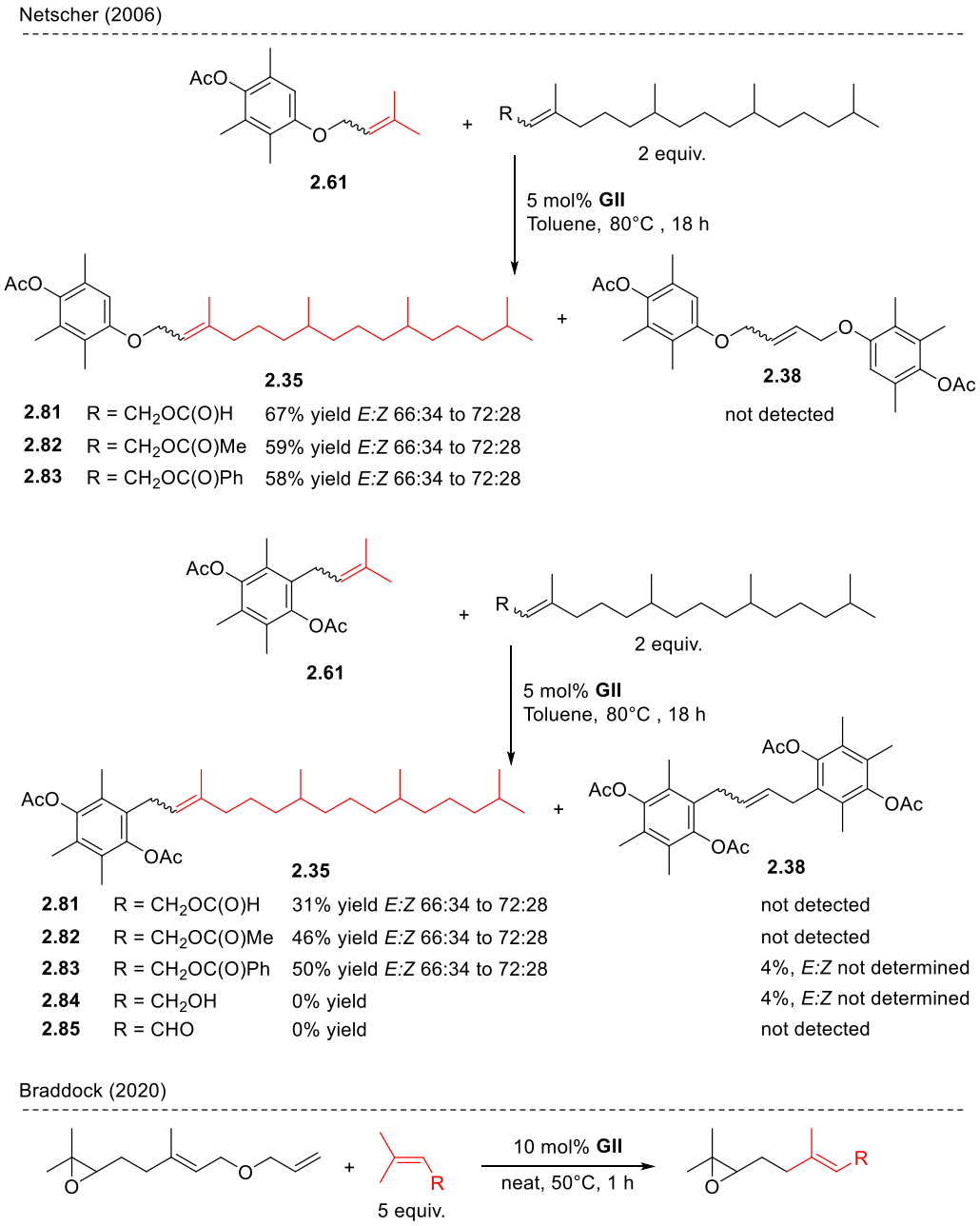
Prenylation of asymmetrical disubstituted olefins can be achieved by the treatment of **GII** catalyst and excess of 2-methyl-2-butene **2.9**. However, prolonged reaction time and high catalyst loading are required in order to achieve satisfactory conversion. Owing to the high activity of Mo-based catalyst, the stereoselective CM between **2.78** and **2.79** proceeds under mild conditions with relatively low catalyst loading.

2.3.6 Formation of trisubstituted olefin from CM reactions between a trisubstituted olefin and an another trisubstituted olefin

CM reactions between two different trisubstituted olefins are very rare. Netscher *et al.* reported several examples of CM reactions between two different trisubstituted olefins in their synthetic study of Vitamin E (Scheme 2.17, top).[82,94]

Recently, our group reported a series of CM reactions between relay-tethered monoterpenes and various trisubstituted olefins (Scheme 2.17, bottom). Detailed discussion can be found in Chapter 4 of this thesis.[102]

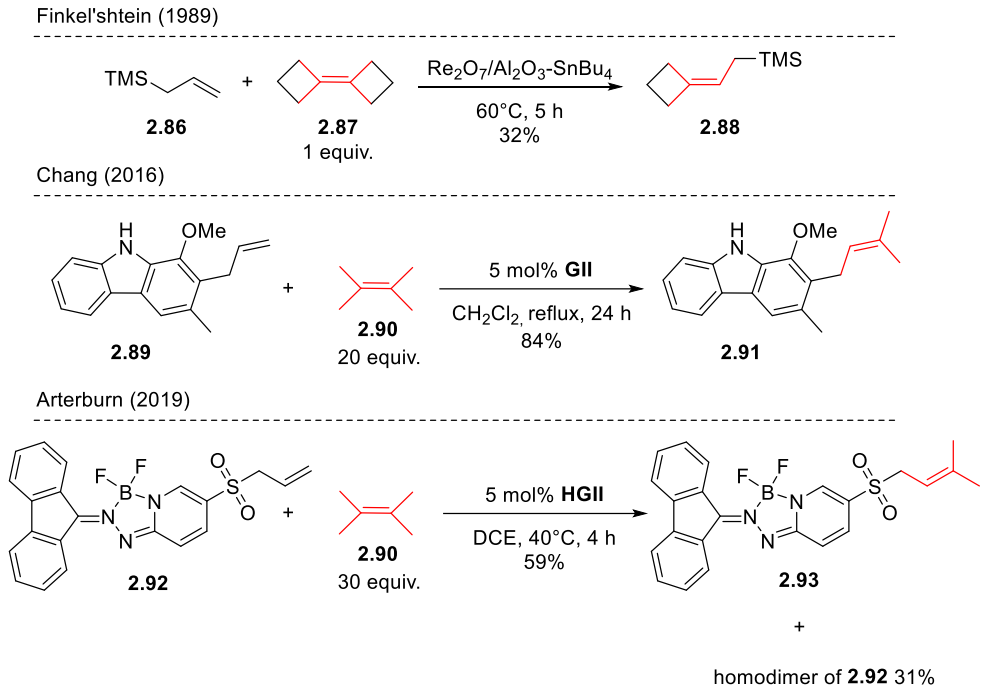
Overall, trisubstituted olefins are less common substrates compared to their 1,1-disubstituted equivalents in CM reactions as in most cases the use of trisubstituted olefin does not lead to superior outcome. In addition, the construction of a new trisubstituted olefin from a pre-existing trisubstituted olefin is less synthetically attractive than CM reactions that generates more substituted olefins from combining less substituted olefins.



Scheme 2.17 Construction of trisubstituted olefin from CM reactions between a trisubstituted olefin and an another trisubstituted olefin

2.3.7 Formation of trisubstituted olefin from CM reactions involving a tetrasubstituted olefin

Due to the steric bulk of four substituents, tetrasubstituted olefins are originally classified as a spectator (Type IV) olefin.[65] However, there are several examples of CM reactions between a tetrasubstituted olefin and a terminal olefin (Scheme 2.18).[103–105]



Scheme 2.18 Reported examples of trisubstituted olefin synthesis *via* CM reaction between tetrasubstituted olefins and terminal olefins.

It is surprising to see the CM reaction between allyltrimethylsilane **2.86** and tetrasubstituted olefin **2.87**, which is catalysed by an ill-defined, heterogeneous catalyst. Similar to previous prenylation protocols using isobutylene **2.8** and 2-methyl-2-butene **2.9**, the CM reaction between carbazole **2.89** and tetramethylethylene **2.90** proceeds smoothly to produce desired product **2.91** in high yield. Sulfone **2.92** also metathesises with **2.90** to yield the prenylated product **2.93** in moderate yield, accompanied with the homodimer of **2.92**

However, there is no reported example of CM reaction between tetrasubstituted olefin and disubstituted/trisubstituted olefins.

2.4 Summary and Outlook

In this chapter, CM reactions that produces trisubstituted olefins are reviewed based on the substitution pattern of olefin substrates employed. Correlating the number of substituents and the reactivity of different olefins in CM reactions revealed the general trend that less substituted, hence more reactive olefin combinations are more often used. However, the combination of most reactive olefins does not always produce better outcomes due to the complication of homodimerisation, methylidene-induced

catalyst decomposition and the subsequent isomerisation of product(s). On the other hand, the combination of more substituted olefins offers unique advantages including improved CM efficiency and catalyst lifetime, which are key to the success of CM reactions targeting at sterically congested, trisubstituted olefins.

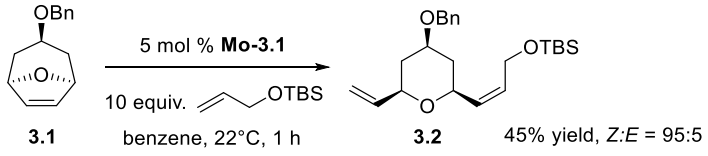
Overall, CM reactions are underexplored in the construction of trisubstituted olefins and the advantage of using more substituted olefin substrates has not been generally recognised. It is pleasing to see the increasing number of reported examples in synthetic studies which harness the advantages of using more substituted olefins in CM reactions. Improvements on catalyst design that further promotes CM efficiency between sterically congested olefins is another promising solution.

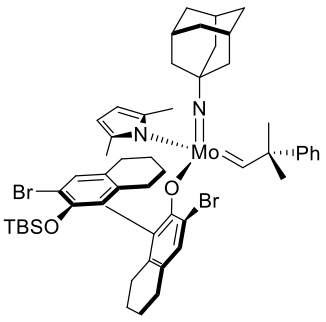
Chapter 3 Catalyst-Controlled Geometry-Selective Olefin Metathesis

3.1 *Z*-Selective olefin metathesis catalysed by molybdenum and tungsten complexes

Over the past decades, the catalyst-controlled geometry-selective olefin metathesis has been a fundamental yet long-standing conundrum. On the other hand, the value of such transformation—opening up an avenue for otherwise unreachable chemical space—is just great as its challenge.

In 2009, Schrock and Hoveyda provided the first solution to this conundrum. They reported the first example of catalyst-controlled *Z*-selective ring-opening/cross-metathesis (ROCM) reaction of oxabicycle **3.1** using a Mo-based monoaryloxide pyrrolide (MAP) catalyst **Mo-3.1** (Scheme 3.1). [106]

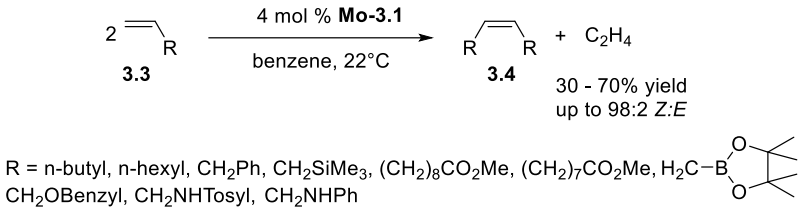




Mo-3.1

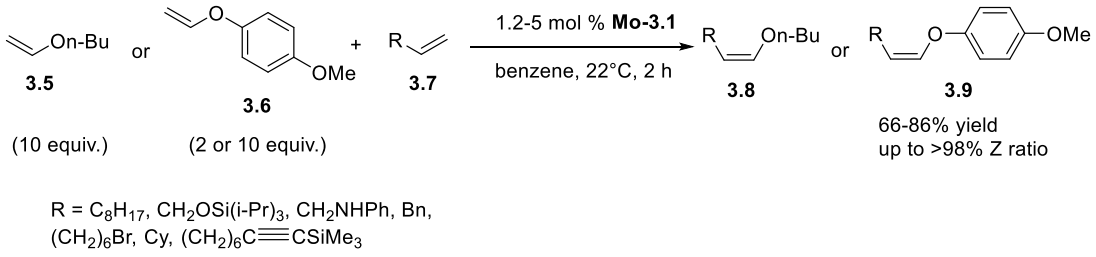
Scheme 3.1. First example of catalyst-controlled *Z*-selective ring-opening/cross-metathesis (ROCM) reaction using a Mo-based monoaryloxide pyrrolide (MAP) catalyst **Mo-3.1**.

Soon after this discovery, the same catalyst **Mo-3.1** and analogous W-MAP (not shown) catalysts found their use in cross metathesis. These catalysts catalysed the homocoupling of various *terminal* olefins (Scheme 3.2).[107]



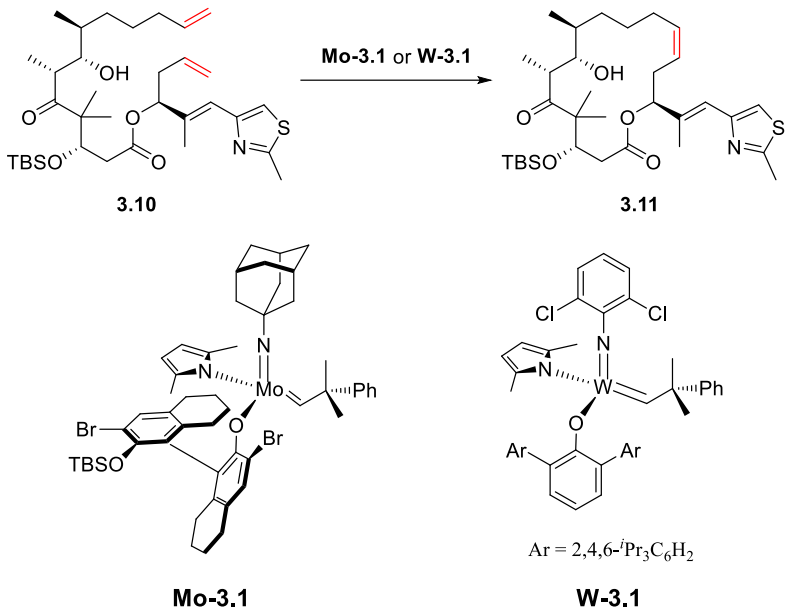
Scheme 3.2. *Z*-Selective homocoupling of *terminal* olefins with **Mo-3.1**.

Following previous success on the homocoupling of *terminal* alkenes, *Z*-selective cross metathesis of *terminal* enol ethers and allylic phthalimides with *terminal* olefins were reported using the same catalyst **Mo-3.1** (Scheme 3.3).[108] The *Z*-selective cross metathesis of *functionalised* olefins provides quick access to much valued synthetic intermediates that can be further manipulated. It is worth noting that the enol ethers and the allylic phthalimides are chosen to minimise undesired homocoupling of the terminal alkene.



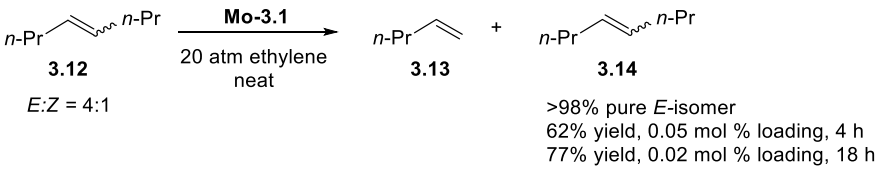
Scheme 3.3. *Z*-Selective homocoupling of *terminal* olefins with **Mo-3.1**.

In 2011, catalyst-controlled macrocyclic *Z*-selective ring-closing metathesis was reported as the key step in the total syntheses of epothilones C and A using the same Mo complex **Mo-3.1** and W-based MAP catalyst **W-3.1** (Scheme 3.4).[109] Subsequent syntheses of other natural products using similar *Z*-selective ring closing metathesis protocols, including yuzu lactone, ambrettolide, nakadomarin A, epothilone D, were also reported.[110]



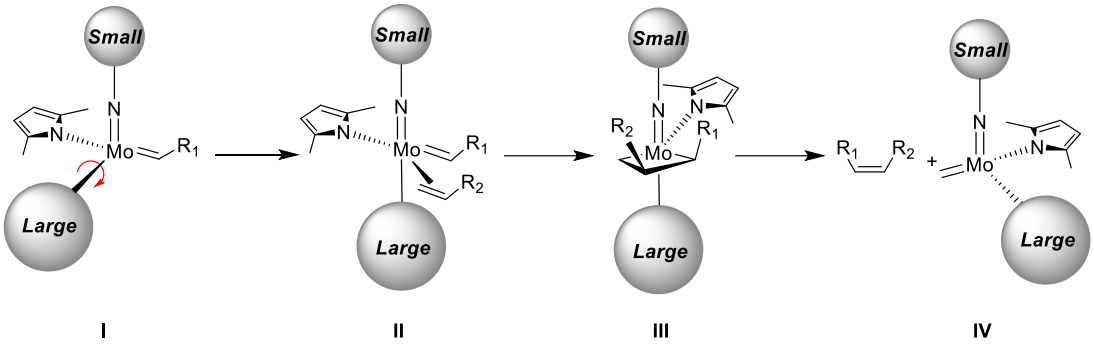
Scheme 3.4. *Z*-Selective macrocyclic ring-closing metathesis used in the stereoselective total syntheses of epothilones C and A with **Mo-3.1** and **W-3.1**.

In addition to the ability of generating *Z*-olefins, complex **Mo-3.1** can also catalyse ethenolysis to produce pure *E*-olefin from a geometrical mixture of *E*- and *Z*-isomers. As in ethenolysis, *Z*-olefins would preferentially coordinate and react with the catalyst, leaving predominantly unreacted *E*-olefin (Scheme 3.5).[111]



Scheme 3.5. *Z*-Selective ethenolysis of a geometrical mixture of 2-octenes **3.12** to produce geometrically enriched *(E)*-2-octene **3.14** using **Mo-3.1**.

The *Z*-selectivity of these Mo and W-based MAP catalysts is believed to arise from the sterically biased ligand sphere of the top and bottom side of the catalyst (Scheme 3.6). The sterically demanding, free rotating aryloxide ligand at the bottom side of the catalyst favours the *syn*-alkylidene isomer (**I**, R_1 *syn* to the smaller imido ligand) and forces the substituents on the mcb to adopt the *cis* geometry (**III**). The *cis*-mcb then collapses to give desired *Z*-olefin and the methylidene species as the products (**IV**).



Scheme 3.6. Rationale of the *Z*-selectivity in the MAP catalysts.

The major concern revealed by this model is that the catalyst-controlled generation of *trisubstituted* olefins and *E*-olefins, which necessitates the intermediacy of an *trans*-mcb, is highly disfavoured. The sterically demanding apical aryloxide and imido ligand offers excellent *Z*-selectivity, and at the same time, has minimal tolerance to the substitution pattern of olefins. Unsurprisingly for all aforementioned MAP catalysed transformations, both olefinic substrates are limited to *terminal* olefins. Therefore, the application of MAP catalysts is restricted to the construction of *(Z)*-1,2-disubstituted olefins.

In fact, developing *Z*-selective olefin metathesis reactions that forge trisubstituted olefins is non-trivial and represents a strategically distinct challenge. The ground state energy difference between *acyclic* trisubstituted *E*- and *Z*-olefins are relatively small compared to that in 1,2-disubstituted olefins. The energy gap is even smaller for those with *all aliphatic substitutents*.[112] Therefore, CM reactions that afford *acyclic trisubstituted olefins* are expected to display, in theory, a marginal selectivity arises from substrate-control. Despite ample examples of substrate-controlled *Z*-selective RCM reactions in *cyclic* systems, there is no universal and reliable protocol for such transformations. The *Z*-selectivity is often unpredictable while exhaustive catalyst screening and reaction optimisation are required to achieve the optimal result.

On the other hand, the design of a catalyst-controlled *Z*-selective metathesis reaction is hampered by the intermediacy of more hindered mcbs and smaller energy difference between *syn*- and *anti*-mcbs (which give *Z* and *E*-olefin correspondingly). The initial formation of this more hindered olefin requires higher catalytic activity. Moreover, a high level of selectivity requires effective differentiation between two substituents that

might be of similar size on one olefin carbon. Catalytic systems developed for the preparation of *(Z)*-1,2-disubstituted olefins have failed to date for *trisubstituted olefins.*

En route to the synthesis of epothilone B and D, Hoveyda group serendipitously discovered two Mo complexes (**Mo-3.2** and **Mo-3.3**) bearing two sizable aryloxide ligands, which are capable for macrocyclic RCM reactions (Figure 3.1).[113]

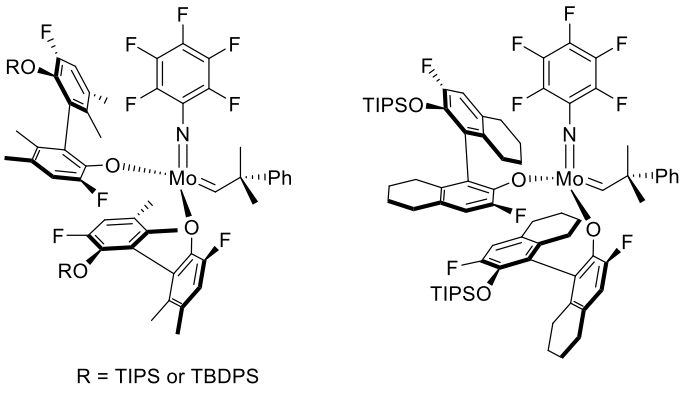
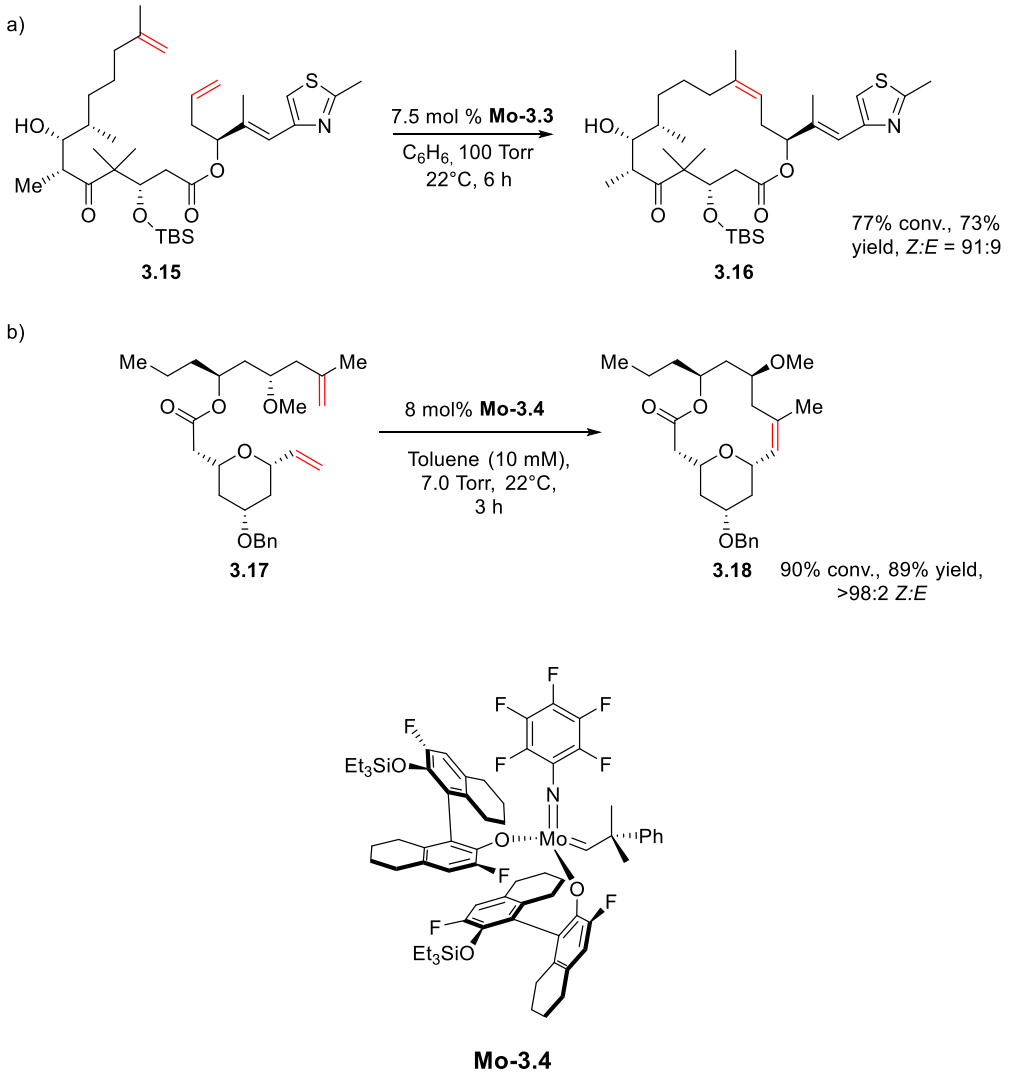


Figure 3.1 Catalysts bearing two aryloxide ligands for *Z*-selective macrocyclic RCM reactions.

These catalysts were used in the synthesis of a pivotal precursor towards epothilone D where a *Z*-selective RCM reaction is required to furnish the trisubstituted olefin. Although conventional Mo- and Ru-based catalysts are efficient to catalyse the ring closure (81 and 59% conv. respectively, with 20 mol% catalyst), the product is a mixture of both *E* and *Z* isomers (*Z:E* ~ 45:55). The Mo- and W-based MAP complexes, which successfully deliver various *(Z)*-1,2-disubstituted olefins, are ineffective at the RCM reaction here and afford low conversion with moderate *Z*-selectivity even at high catalyst loading (e.g. 17% conv. and 75 : 25 *Z:E* with 20 mol **Mo-3.1** in 24 h at 50 ◦C). Only with *bis*-aryloxide catalysts such as **Mo-3.3**, the desired *Z*-product **3.16** is generated in appreciable yield and high *Z*-selectivity (Scheme 3.7a).

In the total synthesis of (+)-neopeltolide, the *Z*-selective macrocyclic RCM reaction catalysed by **Mo-3.4** serves as a key step to the 12-membered intermediate (Scheme 3.7b).[114] It is noteworthy that other non-*Z*-selective catalysts give desired *Z*-product **3.18** with moderate yield (e.g. 49% and 54% yield, using 10 mol% **GII** and **HGII** catalyst respectively).



Scheme 3.7 a) *Z*-Selective macrocyclic RCM reaction catalysed by a bis-aryloxide Mo-complex as the key step in the synthesis of epothilone D. b) *Z*-Selective macrocyclic RCM reaction catalysed by a bis-aryloxide Mo-complex in the synthesis of (+)-neopeltolide.

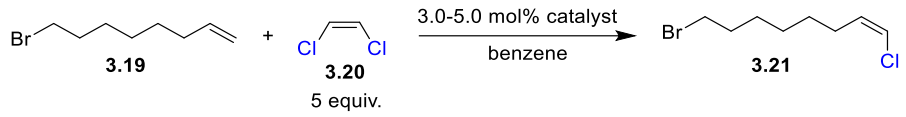
The basis for the high *Z*-selectivity of *bis*-aryloxide catalysts is congruent with the model shown in Scheme 3.6, as the imido and aryloxide ligands provide biased stereochemical environment that energetically differentiates the *cis*-mcb from *trans*-mcb. The pentafluorophenyl-imido ligand is even smaller in size compared to 2,6-diisopropylphenyl and adamantyl-imido ligand, and creates a larger size differential between apical imido and aryloxide ligands to provide better *Z*-selectivity. The small pentafluorophenyl-imido ligand is also required to accommodate a more sterically demanding *trisubstituted* mcb that formed in the course of metathesis.

However, the rationale of the finding that larger *bis*-aryloxide complexes are more effective than MAP alkylidenes is not straightforward, since complexes with sterically demanding ligands are expected to be less reactive, particularly for the preparation of sterically congested olefins.

It is suggested that higher activity requires the presence of two electron-withdrawing F-substituted aryloxy ligands, as opposed to the combination of a pyrrolide and an aryloxide, which are more electron-donating. The electron-deficient aryloxide lowers electronic repulsion that arises when the electron-donating alkyl ligands in the mcb reside opposite to a more electron-deficient aryloxide (i.e. better dipole–dipole minimisation).[113] The more sizeable aryloxy groups may also responsible for the improving the lifetime of the active complex, because they experience slower decomposition through dimerisation. The pentafluorophenyl-imido ligand while needed for high *Z*-selectivity due to its smaller size, likely facilitates the reaction by enhancing the Lewis acidity of the transition metal and stabilises the mcb through minimisation of the repulsive dipole-dipole interaction.

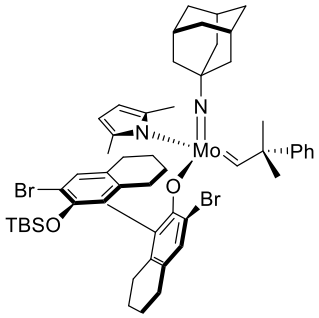
Although it took years before the *Z*-selective CM reaction that affords *trisubstituted* olefin was eventually developed, the valuable lessons learnt in the *Z*-selective RCM reactions guided the research of *Z*-selective CM reactions.

In particular, the unique electronic and steric properties of pentafluorophenyl-imido ligand were soon harnessed by a series of new catalysts. Catalysts bearing a pentafluorophenyl-imido ligand (**Mo-3.5** in this case) outperform conventional MAP catalysts, leading to a dramatic increase of yield in the CM reactions of terminal olefin **3.19** with *Z*-dichloroethylene **3.20** (Scheme 3.8). The same protocol can be applied to the synthesis of *Z*-alkenyl bromide and fluoride with moderate to good yield and high *Z*-selectivity.[115] It is noteworthy here that *Z*-alkenyl halides are inherently thermodynamically more favoured than their *E*-isomers.[116]

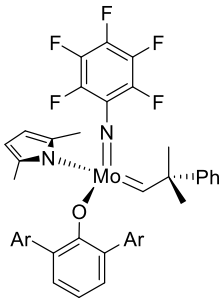


Entry	Catalyst; Loading (mol%)	Time (h); Temperature (°C)	Conversion (%); Yield (%)	*Z:E**
1	**Mo-3.1**; 5.0	4; 22	60; 27	>98:2
2	**Mo-3.5**; 3.0	4; 22	90; 75	>98:2
3	**Mo-3.6**; 5.0	4; 22	43; <5	n.d.

*n.d., not determined.

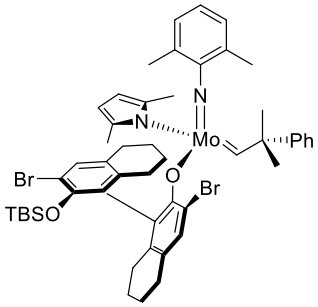


Mo-3.1



Ar = 2,4,6-$Et_3C_6H_2$

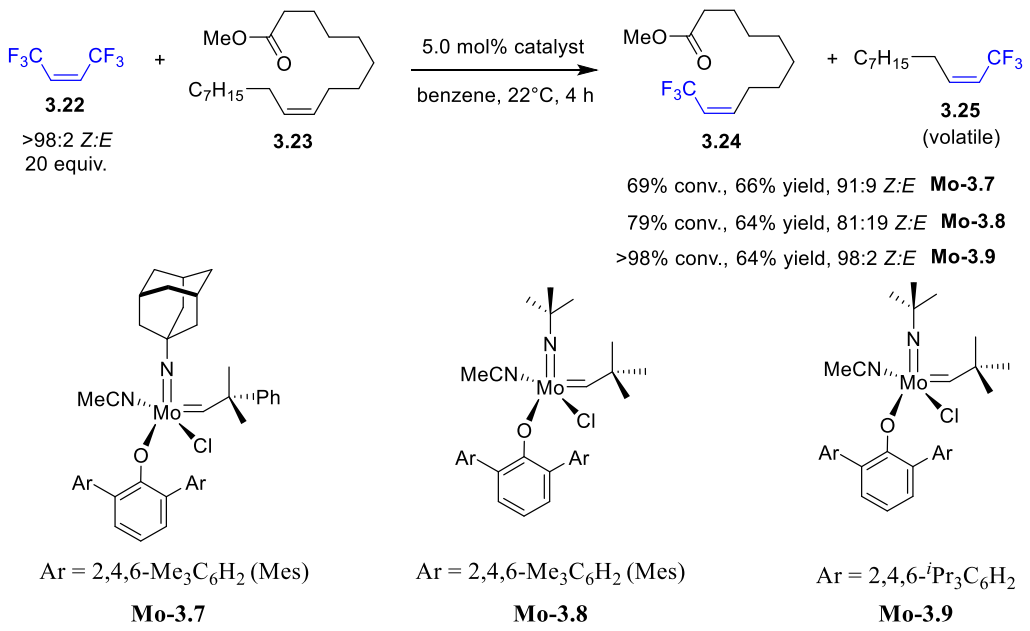
Mo-3.5



Mo-3.6

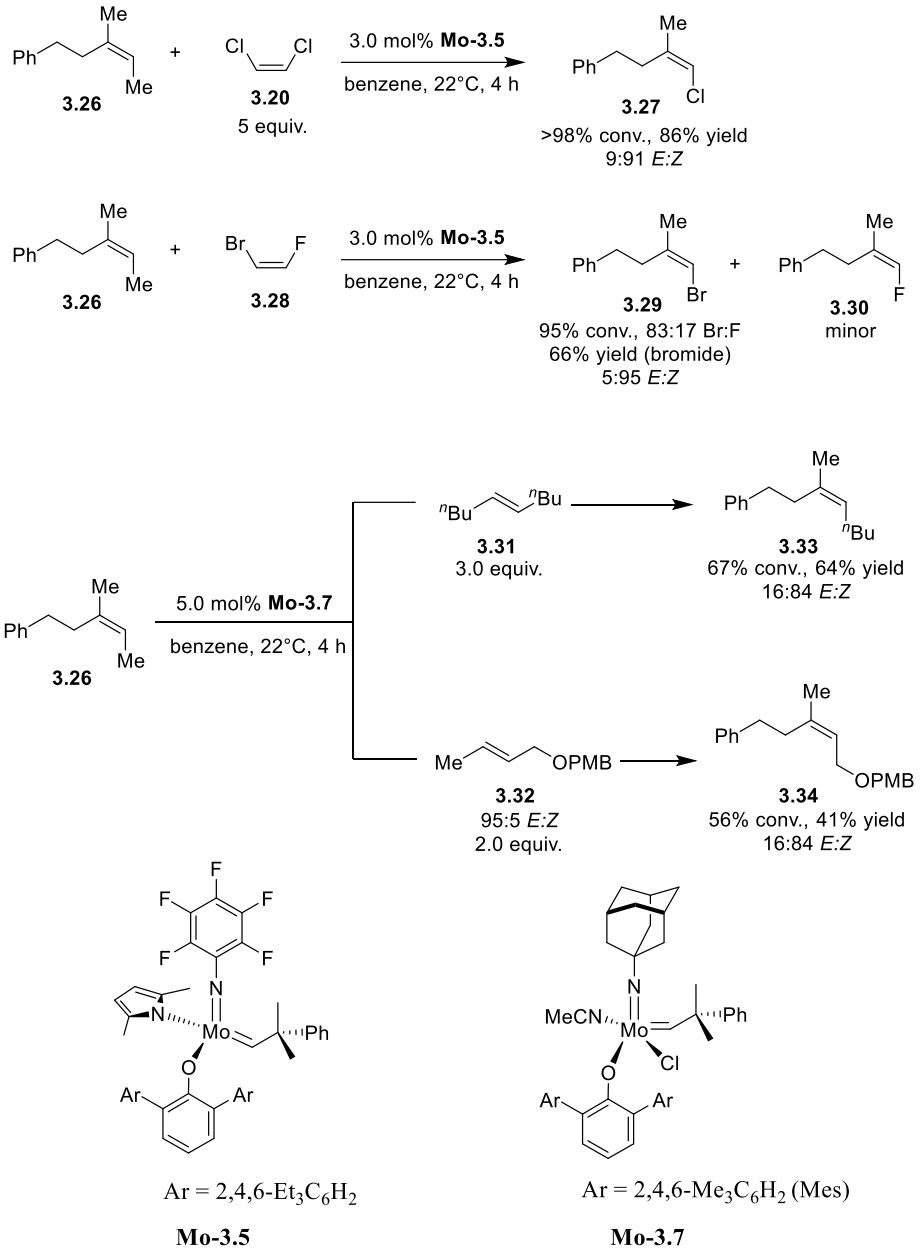
Scheme 3.8 *Z*-Selective CM reactions between a terminal olefin and *Z*-dichloroethylene to give *Z*-alkenyl chloride.

During the study of cross-metathesis that affords *Z*-alkenyl halides, a new class of catalysts bearing an addition chloride ligand, namely monoaryloxide chloride (MAC) catalysts, were also revealed. In addition to catalysing CM reactions that produce *Z*-alkenyl halides, **Mo-3.7**, **Mo-3.8** and **Mo-3.9** are capable to catalyse CM reactions that produce trifluoromethyl-substituted olefins (Scheme 3.9).[117]



Scheme 3.9 *Z*-Selective CM reaction catalysed by MAC catalysts to afford trifluoromethyl-substituted olefins.

With all these catalysts in hand, the stereoretentive CM reaction for the synthesis of *Z-trisubstituted* olefins were eventually developed. A variety of *Z*-trisubstituted olefins can be obtained, including alkenyl halides and more importantly all-alkyl-trisubstituted olefins (Scheme 3.10).[101]

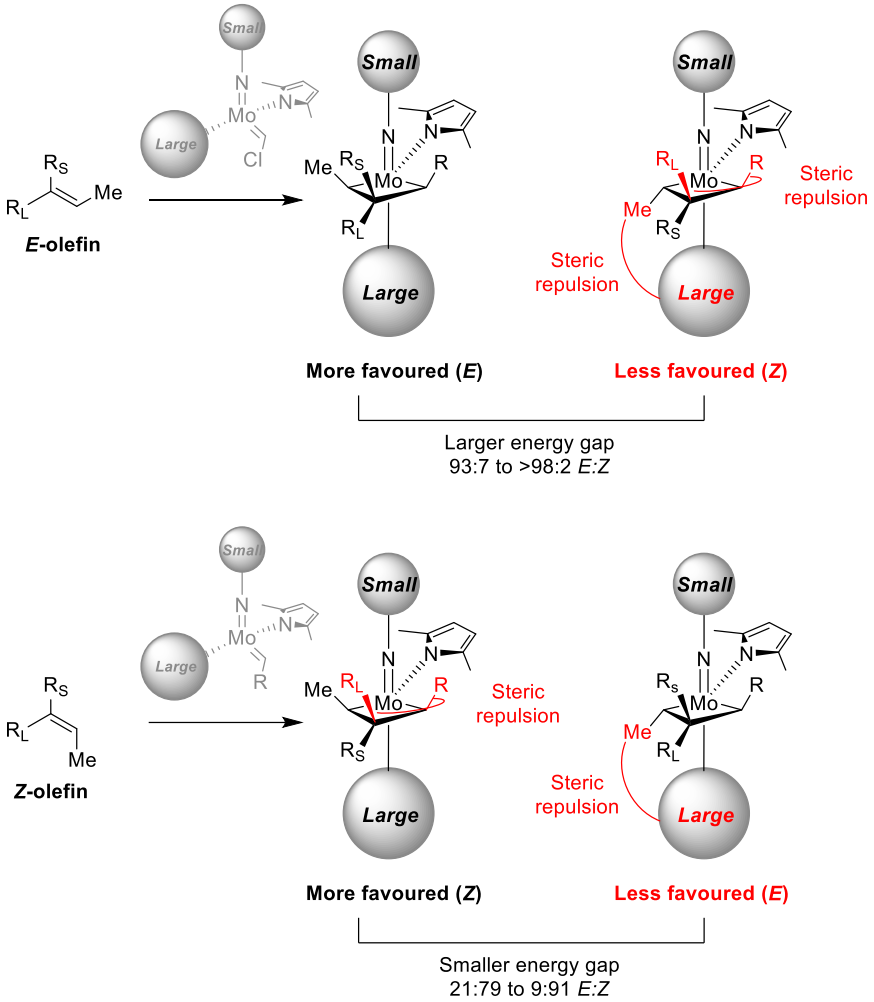


Scheme 3.10 Representative *Z*-selective CM reactions for the syntheses of trisubstituted alkenyl halides and trisubstituted olefins with alkyl chain.

Trisubstituted alkenyl halides were obtained in slightly reduced yield and selectivity using the same conditions disclosed in the previous synthesis of disubstituted alkenyl halides (see Scheme 3.8). As previously discussed, the all-alkyl trisubstituted olefins are among the most difficult targets for *Z*-selective CM reactions. Unsurprisingly, they were obtained in only moderate yield and reduced stereoselectivity.

The original stereochemical model for the *Z*-selective metathesis between terminal olefins failed to interpret the results. In the original model, the *cis*-mcb was favoured

by avoiding steric clash between aryloxide ligand and the adjacent substituent on mcb (Scheme 3.6). In the CM reactions involving disubstituted/trisubstituted olefinic substrates, the mcbs can no longer adopt all-*syn* geometry in some cases, due to the additional substituent on the β-carbon. For those cases, a stereoretentive model was proposed to rationalise the selectivity (Scheme 3.11)



Scheme 3.11 Proposed stereoretentive model for the formation of *E- and Z-*trisubstituted alkenyl halides.

In this model, the steric repulsions between α-substituent and the sizable aryloxide ligand are predominant for the stereoselectivity. The steric clashes between the α-substituents and the aryloxide ligand are highly unfavourable and always lead to unstable mcbs (Scheme 3.11, structures marked red). The level of stereoselectivity is further influence by the eclipsing interactions between substituents on the mcbs. In the *E*-selective case, a high level of stereoselectivity was observed because the energy gap

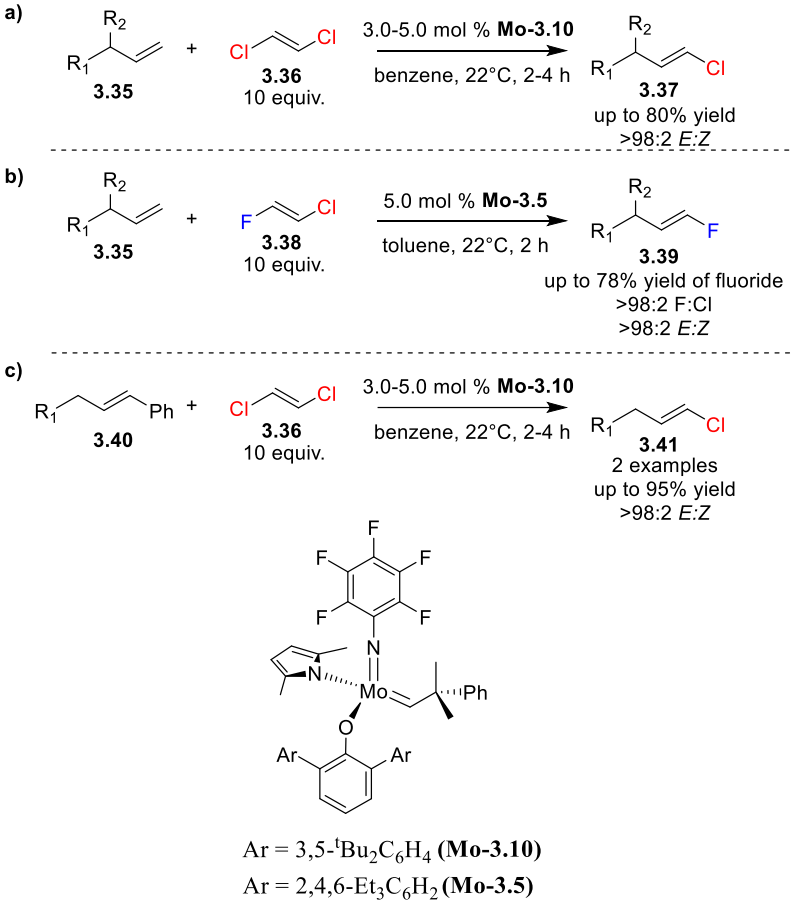
between the two possible mcbs is large, as the less favoured mcb is destabilised by both repulsive interactions while the more favoured mcb possesses none of these repulsions (Scheme 3.11, top). In the *Z*-selective case, the less favoured mcb was destabilised by the steric repulsion between the α-substituent and the aryloxide ligand while the more favoured mcb was destabilised by the eclipsing interactions between substituents on the mcb (Scheme 3.11, bottom). Thus, a smaller energy gap between these mcbs leads to a reduced stereoselectivity. Unlike the previous model (Scheme 3.6), the interaction between β-substituent and the aryloxide ligand is no longer the primary consideration, due to a longer distance between β-substituents and aryloxide ligand.[118]

Nevertheless, *Z*-selective olefin metathesis that generates *all-carbon trisubstituted* olefin using Mo- or W-based catalysts remains extremely scarce. To the best of my knowledge, the above-mentioned macrocyclic RCM reactions and stereoretentive CM reactions (*vide infra*) are the only examples that fall into this category.

3.2 *E*-Selective olefin metathesis catalysed by molybdenum and tungsten complexes

Despite the inherent thermodynamic stability over its *Z*-isomer in most cases, geometrically pure *E*-alkenes are not generally accessible *via* metathesis reactions, particularly *via* CM reactions. RCM reactions can sometimes deliver desired *E*-products in high geometric purity but often requires significant amount of catalyst screening and optimisation of the reaction conditions. CM reactions generally give a mixture of *E*- and *Z*-isomers although high level of selectivity can be achieved in some cases by careful choice of CM partner. It is noteworthy that the formation of *trisubstituted* olefins are less *E*-selective, presumably due to a smaller energy difference between the *E*- and *Z*-isomers. Thus, a kinetically controlled *E*-selective metathesis reaction is required for the preparation of geometrically pure *E*-alkenes.

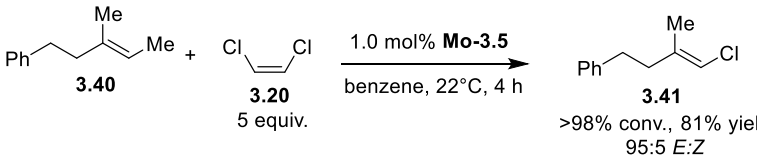
It turned out that development of such transformation is unexpectedly challenging. The early success of *Z*-selective metathesis reactions using Mo- and W-based catalysts provides little inspiration for the *E*-selective variant. It was not until the stereoretentive nature of Mo- and W-based catalyst was unveiled when the first *E*-selective CM reaction using MAP catalyst was reported (Scheme 3.12).[118]

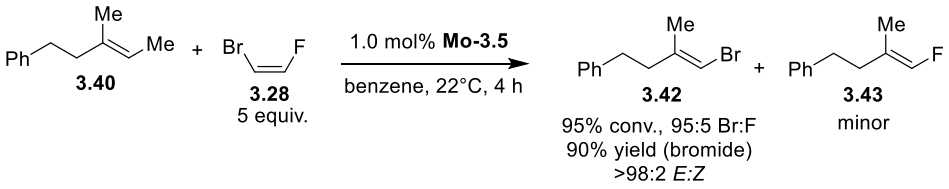


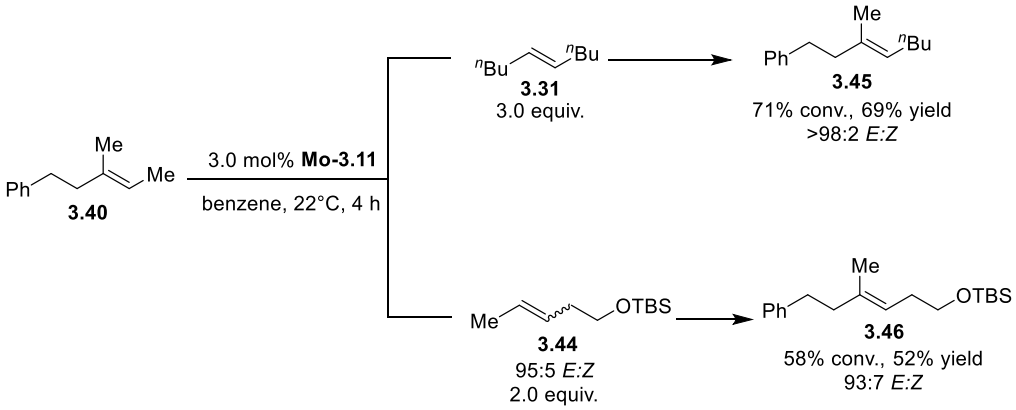
Scheme 3.12 *E*-Selective CM reactions for the preparation of 1,1-disubstituted alkenyl halides. a) Preparation of alkenyl halides **3.37** with α-branched terminal alkenes. b) Preparation of alkenyl fluorides **3.39** with α-branched, terminal alkenes. c) Preparation of unhindered alkenyl chloride **3.41** with 1,2-disubstituted alkenes **3.40**.

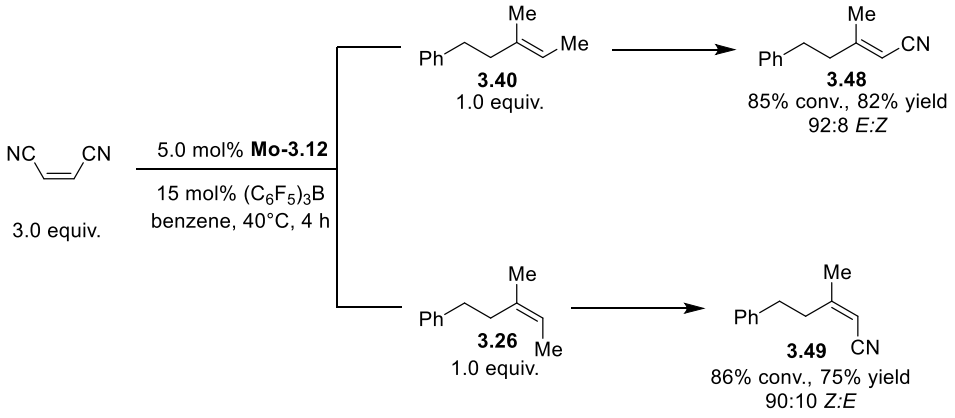
Various 1,2-disubstituted alkenyl chlorides and fluorides can be accessed with up to >98% *E*-selectivity by this method (Scheme 3.12a and 3.12b). For sterically unhindered alkenes with no α-branching, instead of a terminal alkene, a 1,2-disubstituted alkene was employed to supress the non-stereoselective homocoupling (and following isomerisation) processes that reduce *E/Z* selectivity (Scheme 3.12c). This also avoids the production of unstable and short-lived methylidene species when terminal alkenes are used (see below, Scheme 3.14).

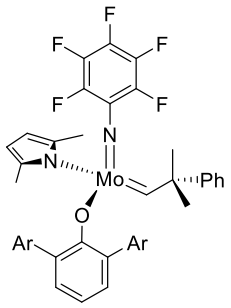
This method was then extended to the preparation of *E*-trisubstituted alkenyl chlorides, bromides, all-alkyl-trisubstituted alkenes and more recently alkenyl nitriles (Scheme 3.13).[119]



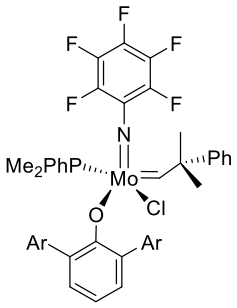








Ar = 2,4,6-$Et_3C_6H_2$ **(Mo-3.5)**
Ar = 2,4,6-$Me_3C_6H_2$ **(Mo-3.11)**

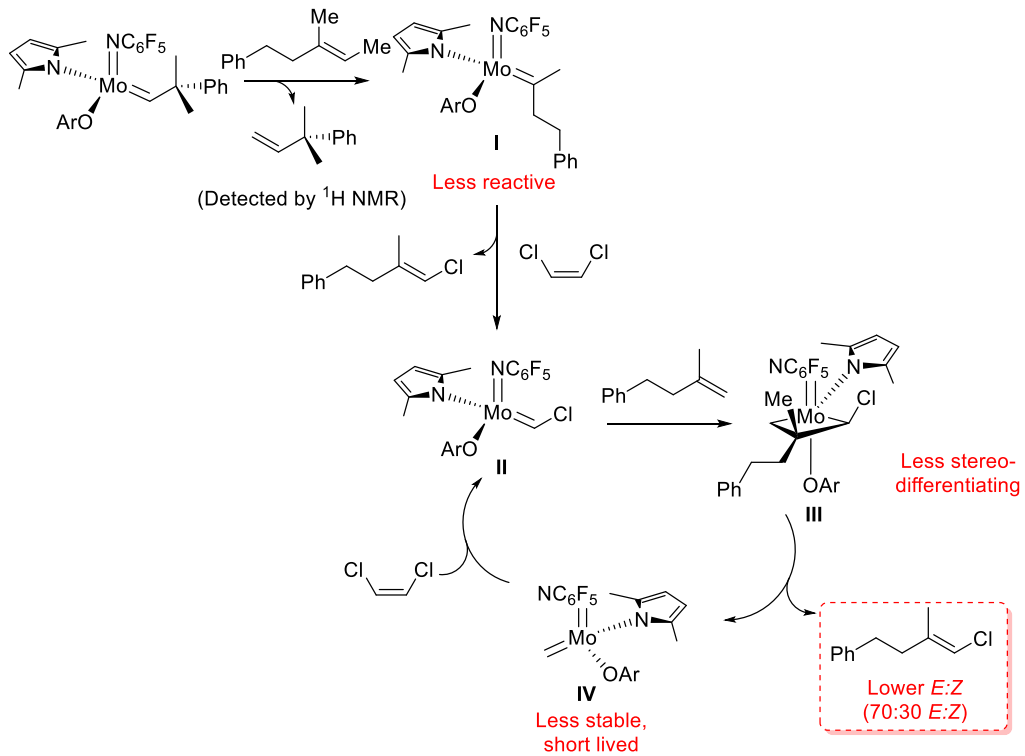


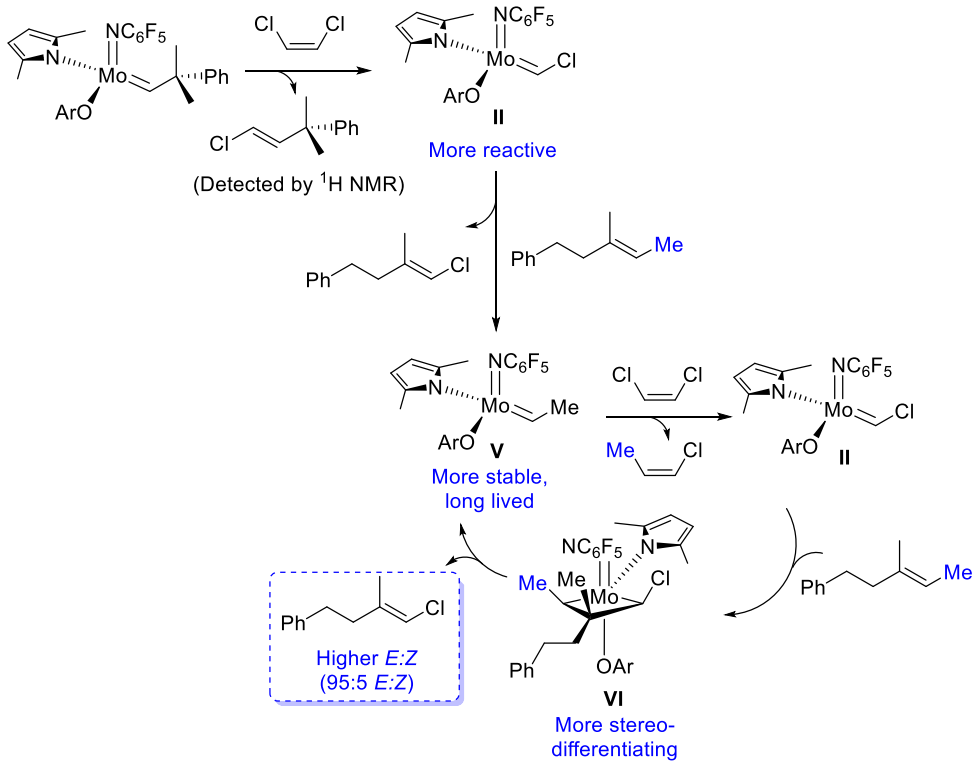
Ar = 2,4,6-$^{i}Pr_3C_6H_3$
Mo-3.12

Scheme 3.13 Representative *E*-selective CM reactions for the syntheses of trisubstituted alkenyl halides, nitriles and trisubstituted olefins with alkyl chain.

It is noteworthy that in the CM with 1,2-dichloroethylene, trisubstituted olefinic substrates deliver better stereochemical control over 1,1-disubstituted olefins (Scheme 3.14).

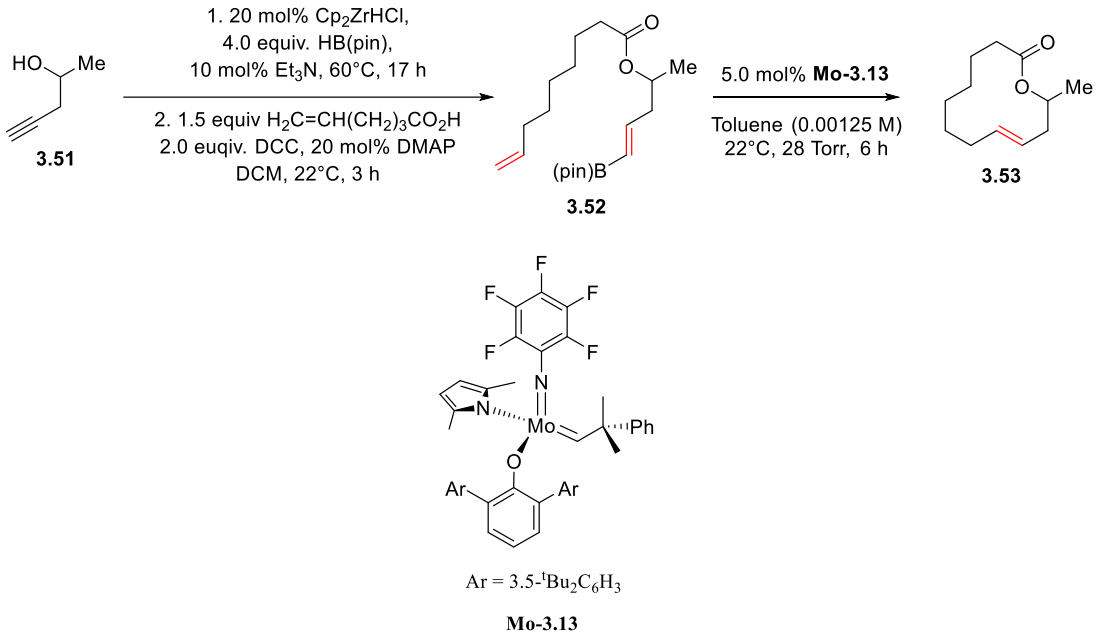
For trisubstituted alkenes, the catalyst initiates differently to form the chloromethylidene **II** (Scheme 3.14, bottom pathway). This chloromethylidene is more reactive than the sterically demanding 1,1-disubstituted alkylidene **I** formed by the initiation at a 1,1-disubstituted alkene. Metathesis of **II** with the trisubstituted alkene gives products in high stereoselectivity, owing to the formation of the more stereo-differentiating mcb **VI** with two α-substituents (compared to one α-substituent in mcb **III**). Collapse of mcb **VI** then generates ethylidene **V** that is more robust than the methylidene **IV** (MAP-based methylidenes are prone to bimolecular decomposition).[120] Although many combinations of olefinic substrates may produce desired products, the correct combinations of olefinic substrates can drastically change the reaction profile and lead to a superior outcome.





Scheme 3.14 Trisubstituted alkene triggered pathway leads to superior efficiency and stereoselectivity.

Soon after the breakthrough in the *E*-selective CM reactions, the *E*-selective macrocyclic RCM protocol was developed, and macrocyclic 1,2-disubsituted alkenes of different ring sizes can be accessed. The pre-installed *E*-alkenyl boropinacolate **3.62**, which is prepared *via* stereoselective hydrozirconation/boronate-trapping of terminal alkyne **3.51**, serves as the handle of stereochemical control. The synthetic utility was exemplified by the preparation of recifeiolide **3.53** (a 12-membered-ring antibiotic). The *E*-selective macrocyclic RCM step is highly *E*-selective (98:2 *E*:*Z*) with moderate yields (55% for recifeiolide).[121]



Scheme 3.15 Preparation of recifeiolide *via* an *E*-selective macrocyclic RCM between a terminal alkene and an alkenyl boropinacolate using **Mo-3.13**.

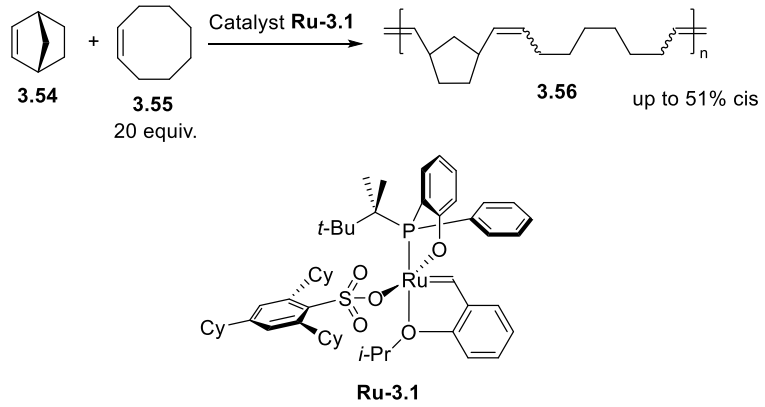
In summary, the *E*-selective olefin metathesis reactions using W- and Mo-based catalysts are still underdeveloped. Unlike *Z*-selective olefin metathesis reactions, the *E*-selective olefin metathesis operates in a stereoretentive manner for both 1,2-disubstituted and trisubstituted alkenes. A geometrically pure alkene is required to deliver the stereochemical control. Thus, the major difficulty for developing *E*-selective metathesis reactions is the preparation of a geometrically pure *E*-alkenyl substrate. This is rather difficult for RCM reactions as the *E*-alkene has to be pre-installed.

As Ru-based complexes are generally more functional group tolerant than W- and Mo-based complexes, the Ru-based complexes are potentially better platforms for developing *E*-selective olefin metathesis reactions. Indeed, we observed a growing number of geometry-selective olefin metathesis studies on Ru-based platforms in the recent years and major findings will be covered in the following section.

3.3 *Z*-selective and stereoretentive olefin metathesis catalysed by ruthenium complexes

The first designed, catalyst-controlled *Z*-selective olefin metathesis reaction catalysed by ruthenium complex is a *Z*-selective ROMP reported by Chen *et al.* in 2010.[122] A

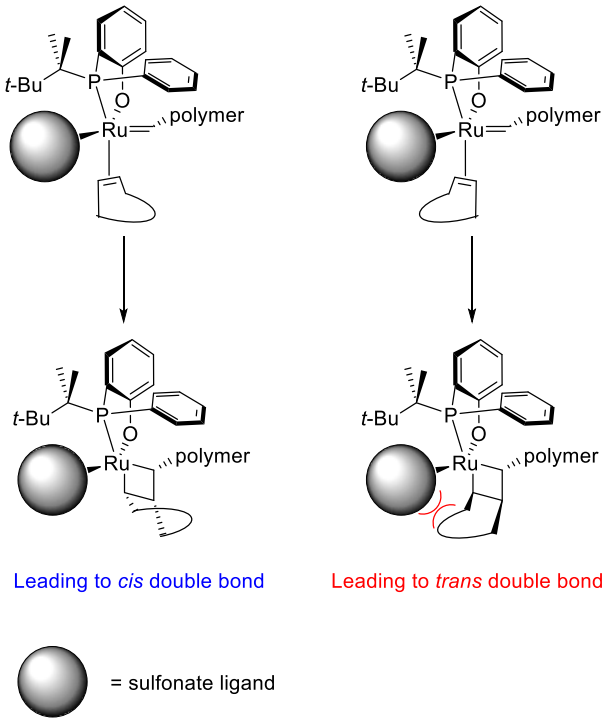
modified Grubbs 1st generation (**GI**) catalyst **Ru-3.1**, bearing a sizable sulfonate ligand and an asymmetric phosphine ligand, was employed to catalyse the copolymerisation of norbornene **3.54** and cyclooctene **3.55** to give a copolymer **3.56** with up to 51% *cis*-double bond content while commonly used **GI** produces polymers with only 10-20% *cis*-double bond content (Scheme 3.15).



Scheme 3.15 First ruthenium catalysed *Z*-selective ROMP using a modified Grubbs 1st generation catalyst **Ru-3.1**.

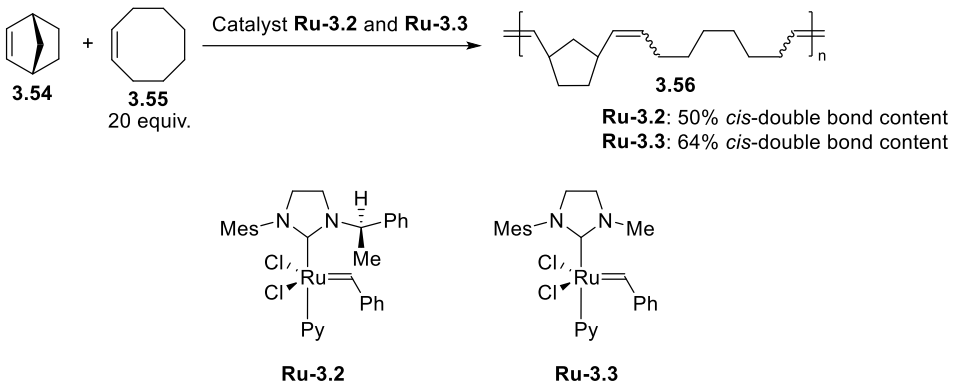
The asymmetric phosphine ligand provides a high degree of alternation in the copolymer, as the less-strained cyclooctene reacts cleanly at a competitive rate with only one diastereomeric form of the carbene, whereas norbornene shows the same high activity towards both.[123]

The *Z*-selectivity (*cis*-selectivity) is delivered by the sterically demanding sulfonate ligand, and the selectivity can be explained using the model illustrated in Scheme 3.16. The unfavourable steric clash between the bulky sulfonate ligand and the cyclic alkene destabilised the mcb which leads to a *trans* alkene (Scheme 3.16, right).



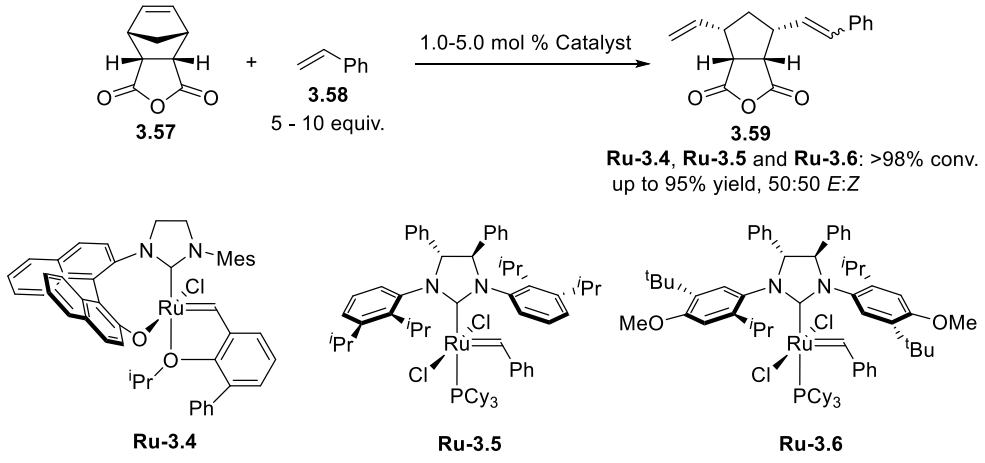
Scheme 3.16 Proposed model for the *Z*-selectivity in *Z*-selective ROMP reactions catalysed by **Ru-3.1**.

Blechert and Buchmeiser *et al.* reported a modified Grubbs 2nd generation catalyst **Ru-3.2** bearing an asymmetrical, chiral NHC ligand, catalysing the *Z*-selective copolymerisation of norbornene and cyclooctene to give the copolymer with 50% *cis*-double bond content.[124] An improved variant **Ru-3.3** was developed soon after with even higher *Z*-selectivity for the same transformation.[125] **Ru-3.2** and **Ru-3.1** offered comparable levels of *Z*-selectivity in the copolymerisation of norbornene and cyclooctene while **Ru-3.3** produced polymers with up to 64% *cis*-double bond content (Scheme 3.17). However, **Ru-3.2** and **Ru-3.3** were initially designed to catalyse enantioselective ROMP and no explanation was given for their *Z*-selectivity in these ROMP reactions.



Scheme 3.17 *Z*-selective ROMP of norbornene and cyclooctene catalysed by modified Grubbs 2nd generation catalysts **Ru-3.2** and **Ru-3.3**.

This unusual *Z*-selectivity of modified Grubbs catalyst bearing asymmetrical NHC ligands can be traced back to 2003, when Hoveyda *et al.* reported a stereogenic-at-Ru catalyst **Ru-3.4**, featuring an asymmetrical, bidentate aryloxide-NHC ligand.[126] They reported later a series of chiral catalysts (e.g. **Ru-3.5** and **Ru-3.6**) bearing a modified NHC backbone.[127] The chirality of these latter catalysts originate from the NHC backbone and the asymmetrically substituted aryl rings, which create a chiral C_2-symmetric environment around the metal centre. Despite showing appreciable levels of *Z*-selectivity, these catalysts were initially designed for the enantioselective ROCM reactions and no explanation for their *Z*-selectivity were given (Scheme 3.18).

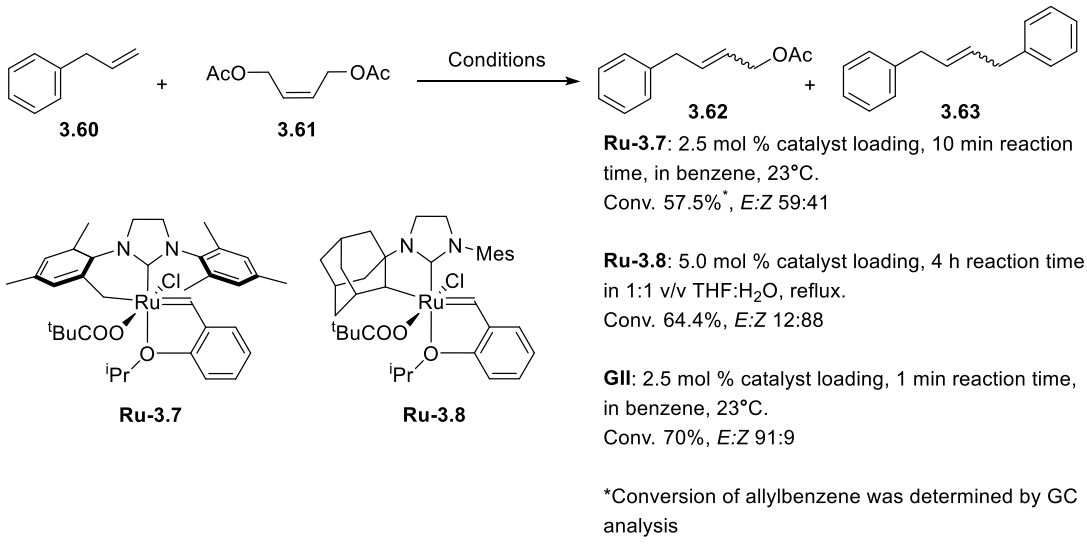


Scheme 3.17 *Z*-Selective ROCM of a bicyclic anhydride and styrene, catalysed by modified Grubbs 2nd generation catalysts **Ru-3.4**, **Ru-3.5** and **Ru-3.6**.

In 2011, Grubbs *et al.* reported their serendipitous discovery of a new catalyst **Ru-3.7**, bearing an asymmetrically substituted NHC. The asymmetry was introduced by an

unexpected C-H activation of a methyl proton on the mesityl group of a Grubbs 2nd generation catalyst. An improved catalyst **Ru-3.8** with better stability and activity was also reported, utilising the C-H activation of a methylene proton on the adamantyl group.[128] Although complexes bearing a chelating NHC ligand *via* C-H activation had previously been reported, but none of them were active as catalysts.[129]

Ru-3.7 and **Ru-3.8** catalysed the CM of allyl benzene and *cis*-1,4-diacetoxy-2-butene, showing high levels of *Z*-selectivity compared to the parent Grubbs 2nd generation catalyst (Scheme 3.18).



Ru-3.7: 2.5 mol % catalyst loading, 10 min reaction time, in benzene, 23°C.
Conv. 57.5%*, *E:Z* 59:41

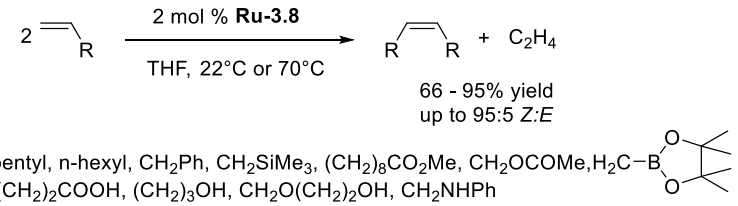
Ru-3.8: 5.0 mol % catalyst loading, 4 h reaction time, in 1:1 v/v THF:H_2O, reflux.
Conv. 64.4%, *E:Z* 12:88

GII: 2.5 mol % catalyst loading, 1 min reaction time, in benzene, 23°C.
Conv. 70%, *E:Z* 91:9

*Conversion of allylbenzene was determined by GC analysis

Scheme 3.18 *Z*-Selective CM of allyl benzene and *cis*-1,4-diacetoxy-2-butene catalysed by **Ru-3.7** and **Ru-3.8**, synthesised through intramolecular C-H activation.

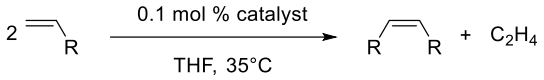
The substrate scope of **Ru-3.8** was demonstrated by homocoupling of various terminal olefins. In addition to substrates that are compatible with Mo-based catalysts (see Scheme 3.2), **Ru-3.8** also tolerates secondary and primary alcohols and carboxylic acids (Scheme 3.19).

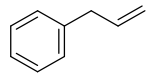
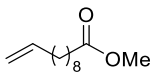
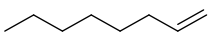
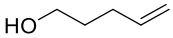


Scheme 3.19 *Z*-Selective homocoupling of terminal olefins catalysed by **Ru-3.8**.

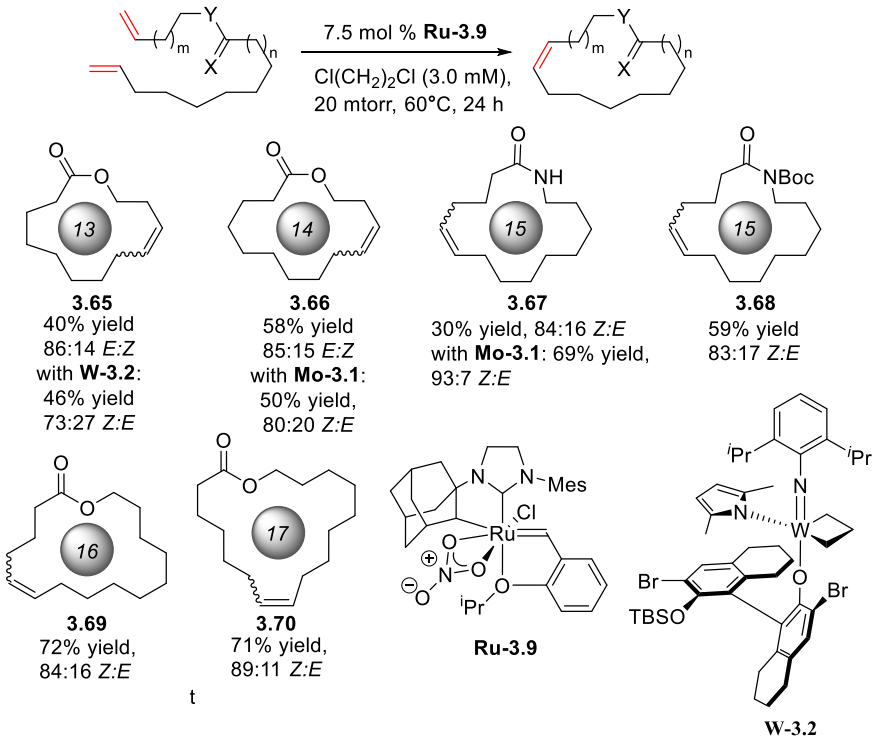
Further improvement of catalyst **Ru-3.8** involves the replacement of the anionic carboxylate ligand with a nitrate ligand. The nitrato catalyst **Ru-3.9** demonstrates superior *Z*-selectivity and reactivity which is showcased by homocoupling of various *terminal* olefin substrates (Table 3.1).[130]

Table 3.1 *Z*-Selective homocoupling of selected *terminal* olefin substrates catalysed by **Ru-3.8** and **Ru-3.9**.



Substrate	Catalyst;	Time (h)	Yield (%)	*Z:E**
	**Ru-3.8**	3	73	86:14
	Ru-3.9	3	91	92:8
	**Ru-3.8**	12	13	90:10
	Ru-3.9	12	85	91:9
	**Ru-3.8**	12	30	94:6
	Ru-3.9	12	83	92:8
	**Ru-3.8**	12	81	43:57
	Ru-3.9	12	67	81:19

Ru-3.9 also excels in macrocyclic RCM reactions and provides a powerful alternative to the Mo and W-based *Z*-selective catalysts (e.g. **Mo-3.1** and **W-3.2**). In some cases, **Ru-3.9** gave even better selectivity and/or yield (Scheme 3.20). *Z*-selective ethenolysis of geometric mixtures of macrocyclic products was also achieved to access pure *E*-macrocycles using the same catalyst **Ru-3.9**.[131]

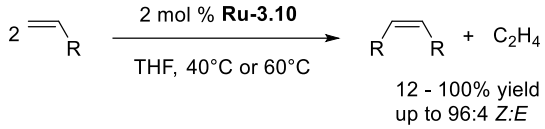


Scheme 3.20 Macrocyclic RCM reactions catalysed by **Ru-3.9** to produce macrocycles of various ring sizes with comparison to previously reported W and Mo-based *Z*-selective catalysts **Mo-3.1** and **W-3.2**.

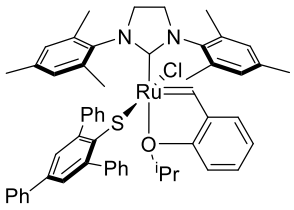
Despite delivering high *Z*-selectivity and moderate to good yields in most cases, the Grubbs *Z*-selective catalysts are less reactive than high-oxidation-state W and Mo-MAP catalysts. Their reduced reactivity is indicated by the elevated temperature and prolonged reaction time required to achieve satisfactory conversion. Furthermore, the bulky adamantyl substituent on the NHC significantly slows down the initiation rate and disfavours the coordination of more substituted olefin substrates for Hoveyda-type catalysts that are believed to initiate *via* associative/interchange mechanisms.[130] As a result, metathesis reactions catalysed Grubbs *Z*-selective complexes produce 1,2-disubstituted olefins only and both olefin substrates have to be *terminal* olefins.

Inspired by the stereogenic-at-Ru catalyst bearing sizable sulfonate ligand **Ru-3.1**, the *Z*-selective ruthenium catalyst **Ru-3.10**, bearing a bulky 2,4,6-triphenylbenzene thiolate ligand was developed by Jensen *et al.*.[132] Unlike sulfonates, thiolates coordinate to ruthenium centre more strongly and thus deliver better stereoselectivity. This catalyst displayed comparable *Z*-selectivity to previously reported Grubbs *Z*-

selective catalysts in various homocoupling reactions of terminal olefins (Scheme 3.21).



R =R = -$(CH_2)_5CH_3$, -$(CH_2)_3CH_3$, -$(CH_2)_8CO_2CH_3$, -$CH_2Si(CH_3)_3$, -$(CH_2)_2Ph$, -CH_2Ph,CH_2OCOCH_3, -CH_2NHPh, -$CH_2O(CH_2)_2OH$



Ru-3.10

Scheme 3.21 *Z*-Selective homocoupling of terminal alkenes using Ru thiolate catalyst **Ru-3.10**.

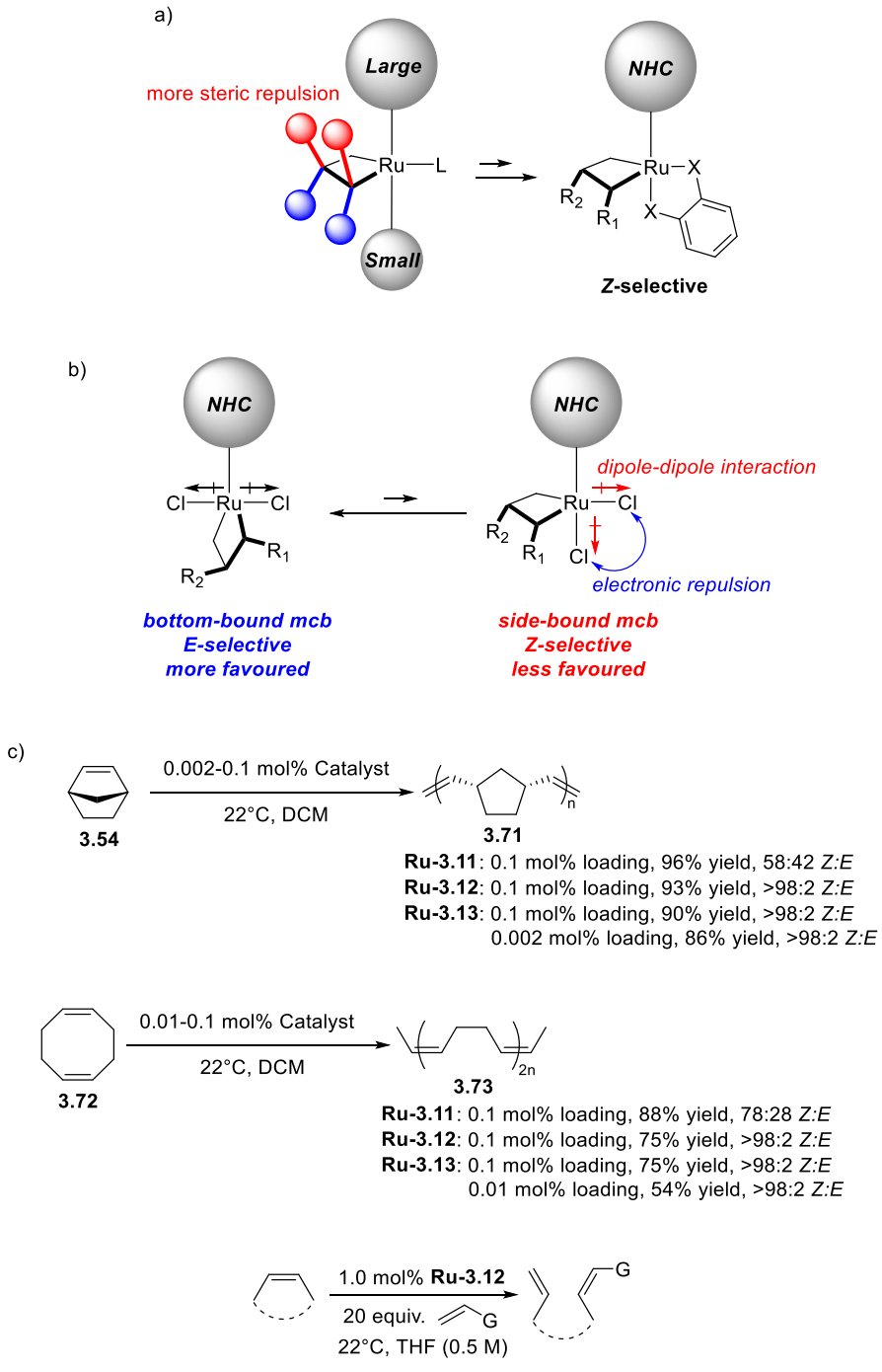
Despite its ease of preparation (1 step from **HGII**), **Ru-3.10** is incompatible with acidic functionalities and displays a short lifetime. Reduced *Z*-selectivity was observed at high conversions, indicating a catalyst decomposition which presumably involves ligand dissociation and thus leads to a non-selective catalyst.

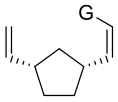
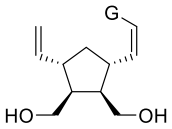
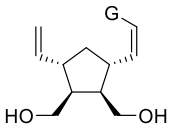
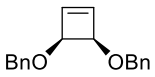
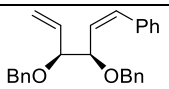
However, dithiolates were later found to be an important class of bidentate ligand in Ru-based metathesis catalysts. In 2013, Hoveyda *et al.* reported series of modified **HGII** catalysts bearing bidentate diolate/dithiolate ligands. Guided by the design principle of Mo-based stereoselective catalysts where stereoselectivity was introduced by the size differential of apical ligands, they investigated the possibility of replacing both X-type, chloride ligand in Hoveyda-Grubbs 2nd generation catalyst (**HGII)** with a suitable bidentate ligand. By replacing both chloride ligands with a bidentate ligand, the unfavourable dipole-dipole interaction and electronic repulsion between chlorides are minimised (Scheme 3.22b). In addition, the bidentate X-type ligand would be forced to adopt a *syn* orientation, thus the mcb must be side-bound in this case (Scheme 3.22a).

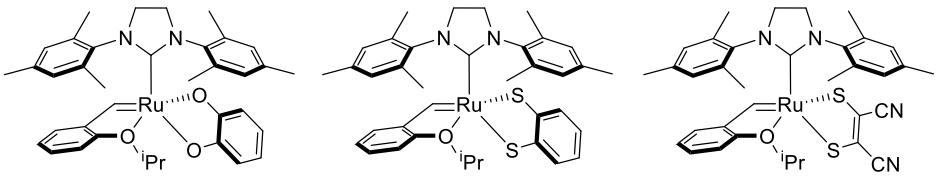
The catecholate substituted complex **Ru-3.11**, however, showed a minimal level of *Z*-selectivity in the ROMP reaction of norbornene and 1,5-cyclooctadiene. As revealed

by subsequent computational studies, it is likely due to an early transition state in the olefin coordination step where loosely coordinated olefin substrate is too distal for steric interactions to come into play.[133]

Nevertheless, dithiolate catalyst **Ru-3.12** and **Ru-3.13** displayed high level of *Z*-selectivity in various ROMP and ROCM reactions. In particular, **Ru-3.13** displays high turnover number (TON) in ROMP reactions (Scheme 3.22c).[134]



Entry	Substrate	G	Time (h)	Product	Yield (%)	*Z:E*
1		C_6H_5	1.0		75	98:2
2		Cy	2.0		59	>98:2
3		C_6H_5	1.0		92	97:3
4		*m*-FC_6H_4	1.0		93	96:4
5		*p*-$MeOC_6H_4$	1.0		82	98:2
6		Cy	8.0		61	>98:2
7		C_6H_5	12		63	93:7



Ru-3.11 **Ru-3.12** **Ru-3.13**

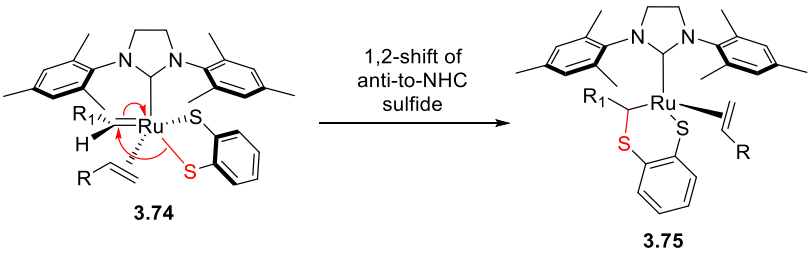
Scheme 3.22 a) Design principle and rationale for *Z*-selective Ru catalysts bearing X-type bidentate ligands. b) Structural features related to bottom-bound and side-bound mcb intermediates derived from common dichloride catalysts. c) Selected *Z*-selective ROMP and ROCM reactions catalysed by ruthenium complexes **Ru-3.11, Ru-3.12** and **Ru-3.13**, bearing bidentate diolate/dithiolate ligands.

Catalyst **Ru-3.12** was found more stable and functional group tolerant compared to **Ru-3.13** and was used in ROCM reactions that involves functionalised alkenes. Various functionalised alkenes can be incorporated as metathesis partners, including 1,3-diene, heteroaryl alkenes, *O*- and *S*-substituted alkenes as well as allylic and homoallylic alcohols.[135]

At this point, all three classes of distinct *Z*-selective catalysts have been covered: i) The Grubbs *Z*-selective catalysts (e.g. **Ru-3.9**) bearing asymmetric NHC ligands; ii) The Jensen *Z*-selective catalyst **Ru-3.10**, bearing a sizable thiolate ligand; iii) The Hoveyda *Z*-selective catalysts (e.g. **Ru-3.12**) bearing bidentate thiolate ligands.

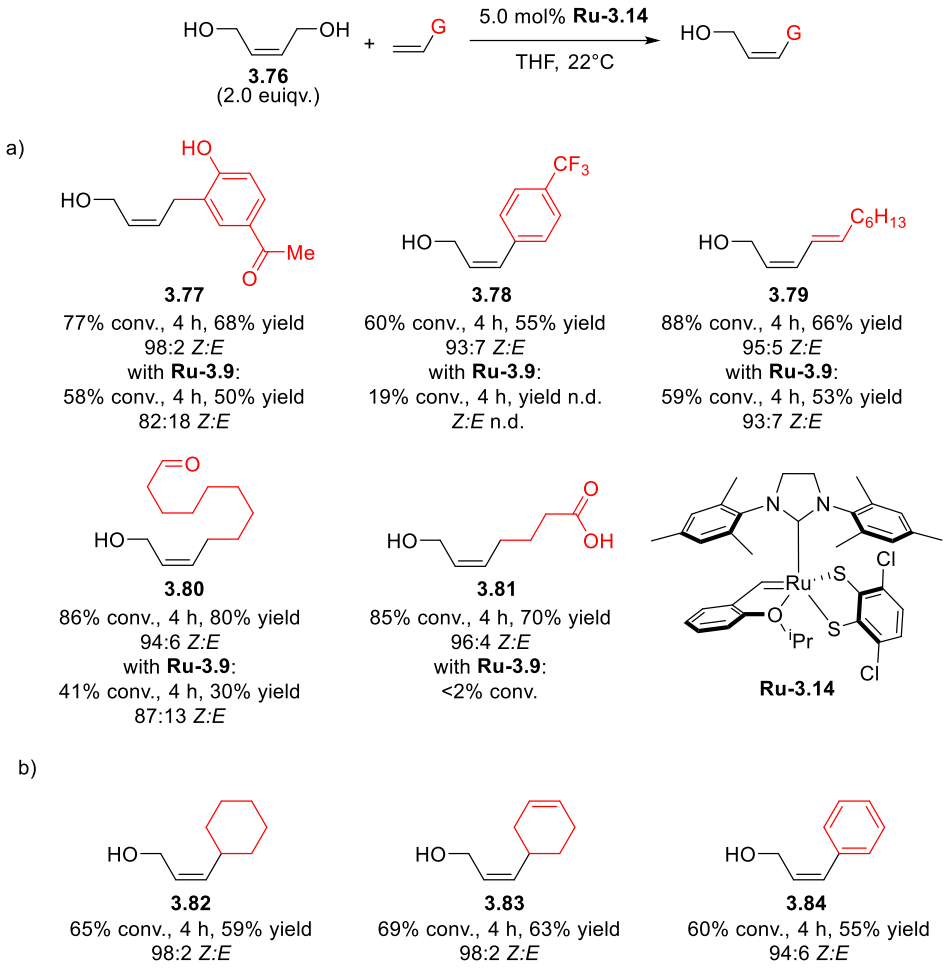
Among them, the thiocatecholate catalysts displayed superior stability and activity while the Grubbs *Z*-selective catalysts suffered from low reactivity due to the bulky *N*-adamantyl group, and the Jensen *Z*-selective catalyst was more prone to decomposition due to the loosely bound thiolate ligand. Unfortunately, for the Grubbs (e.g. **Ru-3.9**) and the Jensen *Z*-selective catalysts (e.g. **Ru-3.10**), their disadvantages were direct consequences of their sources of *Z*-selectivity and cannot be removed without a redesign or drastic change of their chemical structures. Thus, further developments of Ru-based stereoselective olefin metathesis were mainly focused on the thiocatecholate catalysts.

The performance of thiocatecholate catalyst **Ru-3.12** can be further improved by substituting the thiocatecholate ligand with a less electron-rich 2,5-dichlorothiocatecholate.[136] The resulting complex **Ru-3.14** possesses increased stability and activity. The chloro-substitution on the thiocatecholate also rendered a less electron-rich dithiolate ligand and thus slowed down the catalyst decomposition *via* a 1,2-sulfide shift pathway (Scheme 3.23).



Scheme 3.23 Decomposition pathway for *Z*-selective dithiolate catalysts *via* a 1,2-sulfide shift.

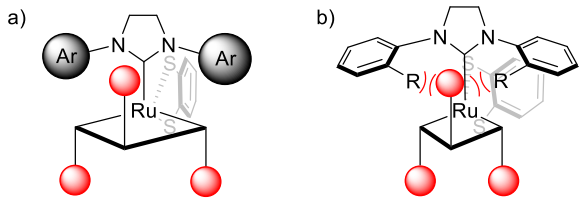
Catalyst **Ru-3.14** was successful for the challenging CM reaction between *Z*-2-butene-1,4-diol and various terminal olefins to produce allylic alcohols in high *Z*-selectivity (Scheme 3.24). In comparison, the Grubbs *Z*-selective catalyst **Ru-3.12** was less reactive for this transformation which involves *internal* olefins (Scheme 3.24a). Unlike thiolate-containing catalyst **Ru-3.10**, catalyst **Ru-3.14** tolerates acidic functionalities (e.g. carboxylic acids) and aldehydes well (Scheme 3.24a). In addition, **Ru-3.14** is less sterically restrained and tolerates more sterically demanding olefin substrate, for example, β-substituted alkenes and styrenes (Scheme 3.24b).



Scheme 3.24 a) Comparison of catalytic activity of **Ru-3.14** and Grubbs *Z*-selective catalyst **Ru-3.9** in *Z*-selective CM reactions of *Z*-2-butene-1,4-diol and terminal olefins. b) Selected examples of *Z*-selective CM reactions using sterically demanding, β-substituted olefins.

It was soon realised that the catalyst is actually operating in a stereoretentive manner. Grubbs *et al.* disclosed the preparation of various *E*-1,2-disubstituted alkenes by the *E*-selective CM reactions of *internal* olefins using **Ru-3.14** and its derivatives and the *E*-selectivity can be explained by the proposed stereoretentive model (Scheme 3.25a).[137]

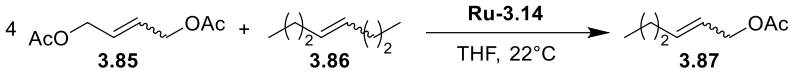
In this model, the β-substituent on the mcb can occupy the open space located in front of the plane of the NHC backbone, flanked by two *N*-aryl groups. Meanwhile, the α-substituents are forced by the repulsion of *N*-aryl groups, to take the opposite orientation to the β-substituent on the mcb.



Scheme 3.25 a) Proposed stereoretentive model for the *E*-selective CM reactions catalysed by dithiolate catalysts. b) Unfavourable steric repulsion between the β-substituent and the *ortho*-substituent of the *N*-aryl group in the mcb intermediate when *E*-olefins were used.

Despite showing excellent stereoretention, low conversions of *trans*-4-octene were observed in the CM reaction between 1,4-diacetoxy-2-butene **3.85** and 4-octene **3.86**, even when high catalyst loadings and prolonged reaction time were applied (Table 3.2). The discrepancy of reactivity between *Z*- and *E*-olefins can be attributed to the unfavourable steric repulsion between the β-substituent and the *ortho*-substituent of the *N*-aryl group (Scheme 3.25b).

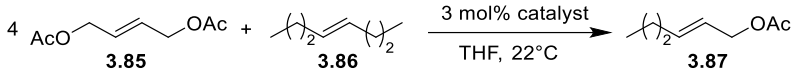
Table 3.2 Stereoretentive CM reaction between 1,4-diacetoxy-2-butene **3.85** and 4-octene **3.86** catalysed by **Ru-3.14**.



Entry	Catalyst Loading (%)	Geometry of 1,4-diacetoxy-2-butene /4-octene	Time (h)	Conversion (%)	Yield (%)	*Z:E*
1	3.0	*cis/cis*	0.25	54	49	>99:1
			1.5	94	91	>99:1
2	5.0	*trans/trans*	1	9	6	<1:99
			5	22	20	<1:99
			72	33	31	<1:99
3	7.5	*trans/trans*	1	15	11	<1:99
			5	33	31	<1:99
			72	50	47	<1:99

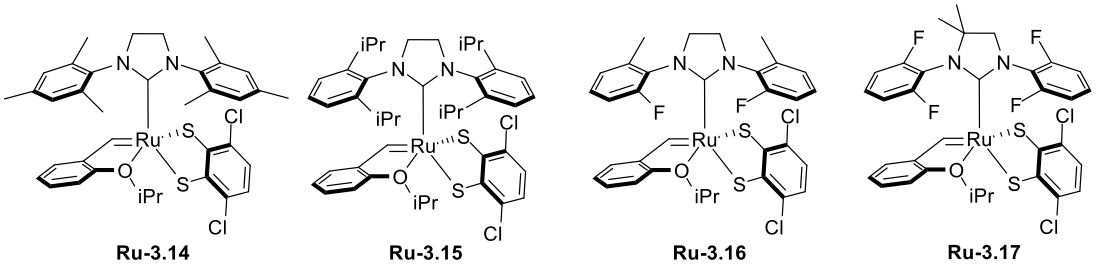
Tuning the size of open space by varying the *ortho*-substitution of the *N*-aryl groups leads to catalyst **Ru-3.15**, **Ru-3.16** and **Ru-3.17**. The latter two better accommodate β-substituents on the mcb intermediates, accordingly increased conversions were observed when they were used in the stereoretentive CM reactions between *trans*-4-octene and 1,4-diacetoxy-2-butene (Table 3.3).

Table 3.3 Improved catalyst performance in the *E*-selective CM reaction between *E*-1,4-diacetoxy-2-butene and *E*-4-octene by varying aryl substitutions.



3.85 **3.86** **3.87**

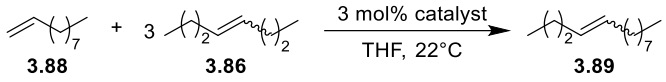
Entry	Catalyst	Time (h)	Conversion (%)	Yield (%)	*Z:E*
1	**Ru-3.14**	4	5	4	<1:99
		72	15	13	<1:99
2	**Ru-3.16**	2	5	5	<1:99
		4	12	11	<1:99
		72	25	24	<1:99
3	**Ru-3.17**	2	7	7	<1:99
		4	15	14	<1:99
		72	29	28	<1:99



Ru-3.14 **Ru-3.15** **Ru-3.16** **Ru-3.17**

However, in the more challenging CM reaction between an internal olefin and a terminal olefin using **Ru-3.14** to **Ru-3.17**, decomposition of methylidene *via* 1,2-sulfide shift became competitive for these catalysts. In the stereoretentive CM reaction between 4-octene and 1-decene, *trans*-octene reacted more slowly compared to *cis*-octene and homodimerisation of 1-decene predominated (Table 3.4).

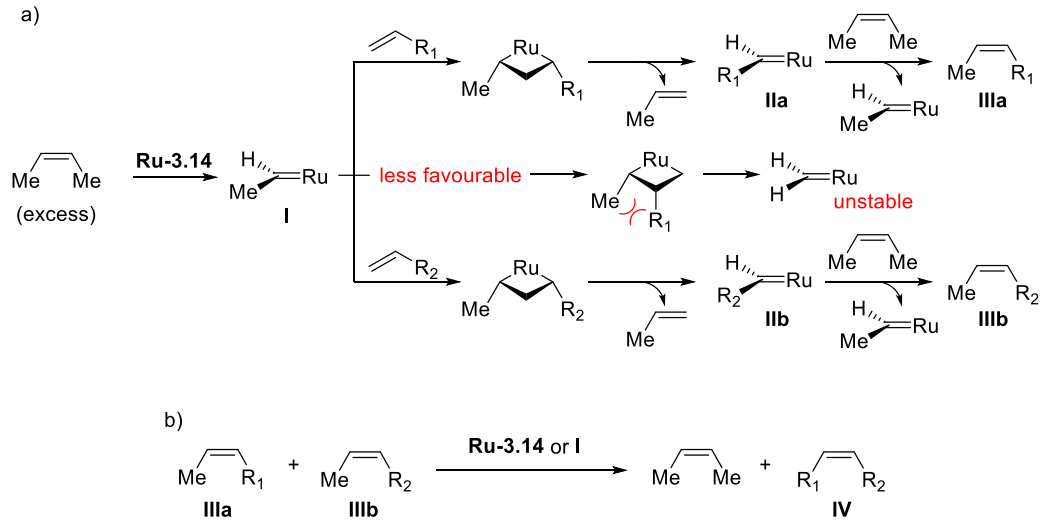
Table 3.4 *E*-Selective CM reaction between 4-octene and 1-decene catalysed by **Ru-3.14**, **Ru-3.15**, **Ru-3.16** and **Ru-3.17.**



3.88 **3.86** **3.89**

Entry	Catalyst	Isomer of 4-octene	Time (h)	Conversion (%)	Yield (%)	*Z:E*
1	**Ru-3.14**	*cis*	4	84	58	>99:1
2		*trans*	4	36	7	<1:99
3	**Ru-3.15**	*cis*	4	89	74	96:4
4		*trans*	4	92	4	13:88
5	**Ru-3.16**	*cis*	4	88	57	97:13
6		*trans*	4	53	29	<1:99
7	**Ru-3.17**	*cis*	4	79	54	>99:1
8		*trans*	4	53	31	<1:99

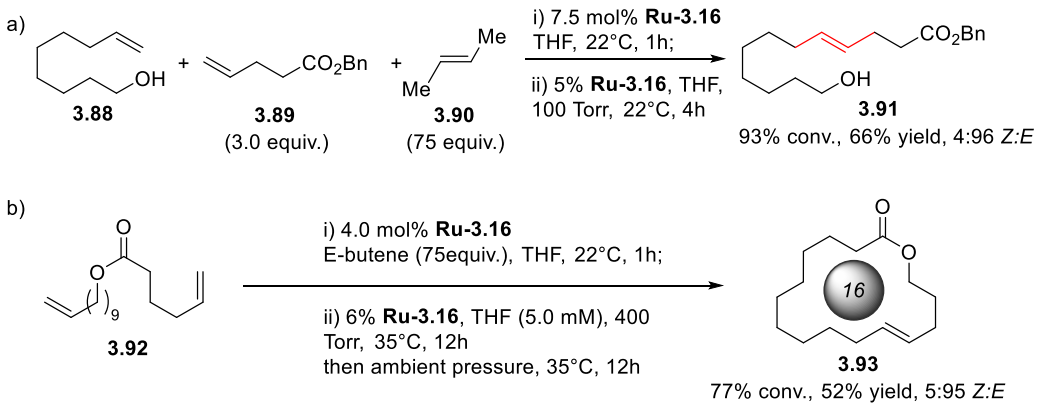
To solve the problem of catalyst decomposition *via* methylidene, Hoveyda *et al.* reported the *in situ* capping of methylidene-generating, *terminal* olefins using 2-butene, as a general strategy to avoid the methylidene generation in stereoretentive olefin metathesis reactions using thiocatecholate catalysts (Scheme 3.26).[138]



Scheme 3.26 a) Concept of in situ methylene capping in stereoretentive olefin metathesis. b) Stereoretentive metathesis of methylene-capped, *internal* olefins to generate product without complication of methylidene.

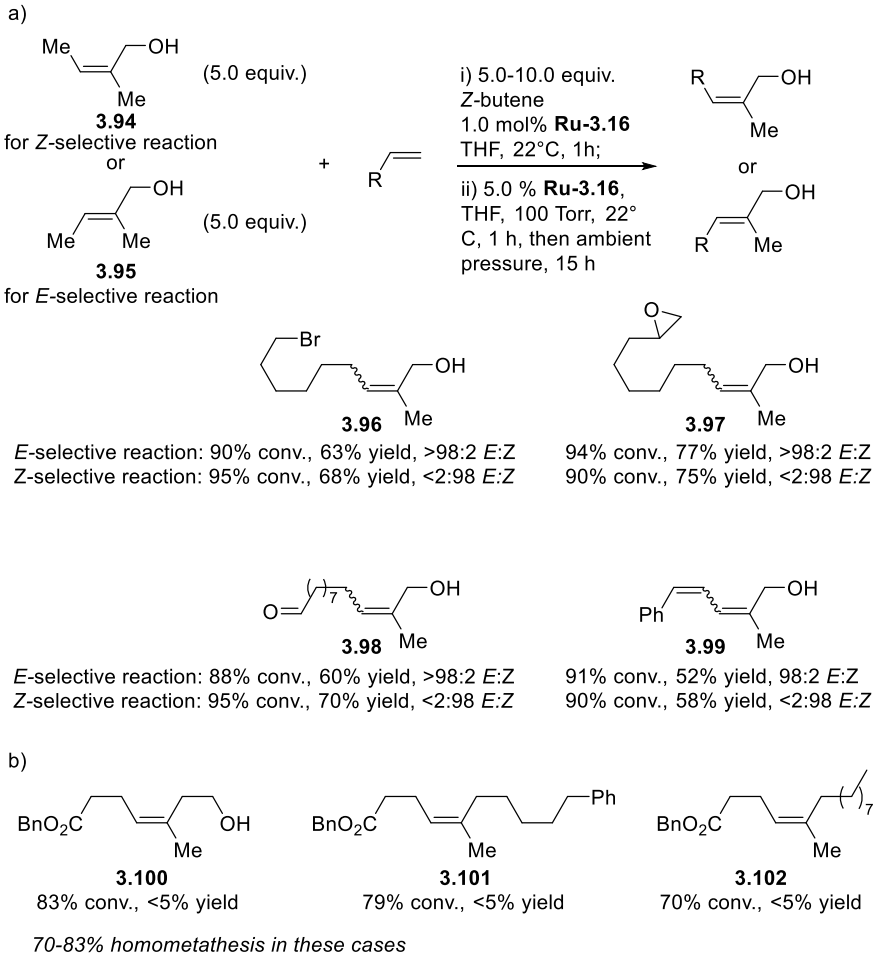
In stereoretentive CM reactions with methylene capping, the terminal olefins were first converted to the methylene-capped, 1,2-disubstituted olefins *via* a stereoretentive CM reaction with the capping reagent 2-butene, while generating a more stable, long-lived ethylidene **I** (Scheme 3.26a, top and bottom pathways). The resulting methylene-capped alkenes **IIa** and **IIb**, then participated a second stereoretentive CM (Scheme 3.26b) to yield the desired product **IV**.

Owing to the longevity of the ethylidene species, the efficiency of *E*-selective CM reactions was greatly improved (Scheme 3.27a, see Table 3.4 and 3.5 for comparisons) and the first, Ru-catalysed *E*-selective macrocyclic RCM reactions was developed (Scheme 3.27b).



Scheme 3.27 a) Efficient stereoretentive, *E*-selective CM reactions of *terminal* olefins *via in situ* methylene capping; b) First example of Ru-catalysed stereoretentive, *E*-selective macrocyclic RCM reaction *via in situ* methylene capping.

A more stable, ethylidene species is also crucial for the metathesis of *trisubstituted* olefins, which are sluggish to metathesise and require long-lived catalysts. Using the methylene capping strategy, *trisubstituted* allylic alcohols and ethers can be accessed *via* a stereoretentive CM reaction between a methylene-capped 1,2-disubstuted olefin and *trisubstituted* olefin (Scheme 3.28a).[98]

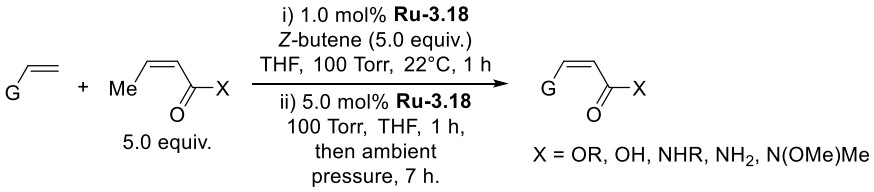


Scheme 3.28 a) Preparation of trisubstituted allylic alcohols *via* stereoretentive CM reactions between methylene-capped 1,2-disubstituted and trisubstituted olefins using **Ru-3.16**. b) All-alkyl trisubstituted olefins leads to inefficient CM reactions under otherwise the same conditions.

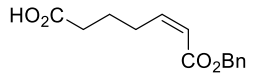
However, attempts at expanding the substrate scope to more general, all-alkyl trisubstituted olefins failed, emphasising the necessity of an allylic heteroatom (Scheme 3.28b). In those reactions, homometathesis of the terminal olefins (or their methylene-capped derivatives) predominated and little of desired CM products were observed (<5% yield). Those observations indicated trisubstituted olefins without allylic heteroatom are highly unreactive under the reaction conditions.

In addition to the methylene capping strategy, further efforts to improve catalyst stability was made by the incorporation of an unsaturated NHC ligand. The resulting catalyst **Ru-3.18** was used in the preparation of various *Z*-*α,β*-unsaturated carbonyl

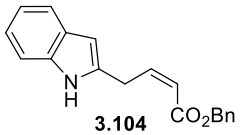
compounds, including esters, carboxylic acids, amides and Weinreb amides (Scheme 3.29).[139]



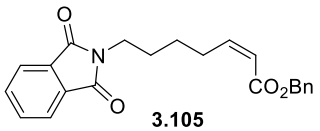
Selected examples of *Z*-α,β-unsaturated esters:



3.103
81% conv., 57% yield, >98:2 *Z:E*

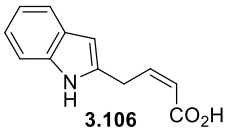


3.104
81% conv., 57% yield, >98:2 *Z:E*

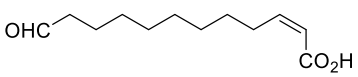


3.105
81% conv., 57% yield, >98:2 *Z:E*

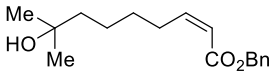
Selected examples of *Z*-α,β-unsaturated carboxylic acid:



3.106
86% conv., 52% yield, >98:2 *Z:E*

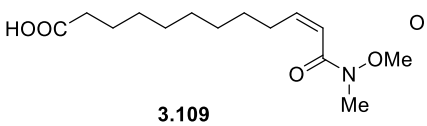


3.107
86% conv., 49% yield, >98:2 *Z:E*

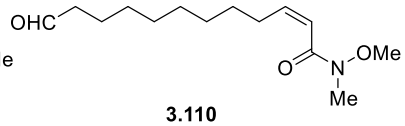


3.108
66% conv., 63% yield, >98:2 *Z:E*

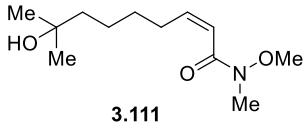
Selected examples of *Z*-α,β-unsaturated Weinreb amides:



3.109
88% conv., 54% yield, >98:2 *Z:E*

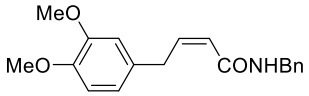


3.110
90% conv., 58% yield, >98:2 *Z:E*

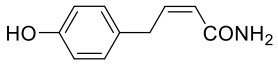


3.111
84% conv., 80% yield, >98:2 *Z:E*

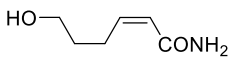
Selected examples of *Z*-α,β-unsaturated amides:



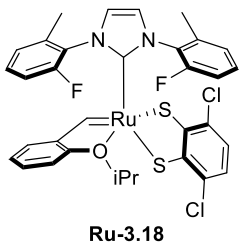
3.112
92% conv., 59% yield, 98:2 *Z:E*



3.113
77% conv., 61% yield, 98:2 *Z:E*



3.114
90% conv., 68% yield, >98:2 *Z:E*



Ru-3.18

Scheme 3.29 Preparation of *Z-α,β*-unsaturated carbonyl compounds *via Z*-selective CM reactions catalysed by **Ru-3.18**.

Although *Z*-selective CM reactions of *α,β*-unsaturated esters using Mo-based MAP catalysts (i.e. **Mo-3.6**) has been reported, only *tert*-butyl ester gave satisfactory yield, while carboxylic acid and amide substrates are not tolerated by Mo-based catalysts.[140]

3.4 Summary and outlook

We have now covered the major developments in stereoselective olefin metathesis with emphases on the development of new catalysts and related mechanistic insights/synthetic applications. In conclusion, the emergence of Ru-based stereoselective catalysts has greatly changed the landscape of stereoselective olefin metathesis. These catalysts offered complementary reactivity to Mo- and W-based catalysts, allowing a broader range of functionalities to be incorporated. Owing to the superior stability compared to Mo-based catalysts, Grubbs *Z*-selective catalyst (**Ru-3.9**) can be handled without the need of a glovebox and was commercialised. The commercially unavailable dithiolate catalysts, however, can be generated in situ with ease.[141] The much valued availability and practicality of Ru-based catalysts will continue to foster the development of new catalysts and synthetic applications.

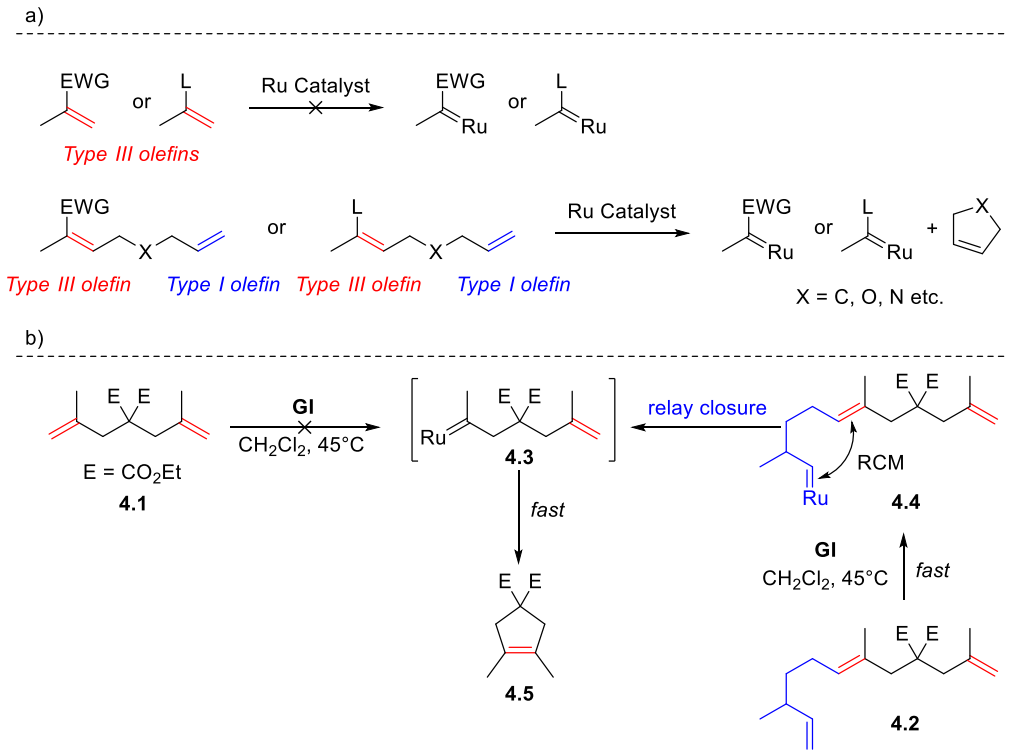
One of the major drawbacks of current Ru-catalysed stereoretentive olefin metathesis is the lack of a universal protocol for the generation of *trisubstituted* alkenes, in particular, all-alkyl *trisubstituted* alkenes. Although all-alkyl *trisubstituted* alkenes can be prepared using Mo-based catalysts (see Scheme 3.13), only limited examples were reported with moderate yield and selectivity. Further development of olefin metathesis catalysts may eventually solve this problem and leads to a broader application of stereoselective olefin metathesis.

Overall, the field of stereoselective olefin metathesis has been growing rapidly in the past decade. We have witnessed new breakthroughs in almost every year and there is no doubt that many more are yet to come.

Chapter 4 Relay cross-metathesis (ReXM) strategy in the synthesis of terpenoid, trisubstituted olefins

4.1 General introduction to relay strategy in olefin metathesis

To overcome the slow initiation process at sterically hindered or electronically deactivated olefin sites, Hoye *et al.* reported their application of relay strategy in RCM reactions.[142] Compared to conventional RCM reactions, relay ring-closing metathesis (RRCM) involves an extra RCM step to deliver the desired alkylidene species, which cannot form *via* direct initiation (Scheme 4.1a). A remarkable example of this strategy is the formation of a tetrasubstituted olefin *via* RRCM with relatively unreactive **GI** catalyst (Scheme 4.1b).

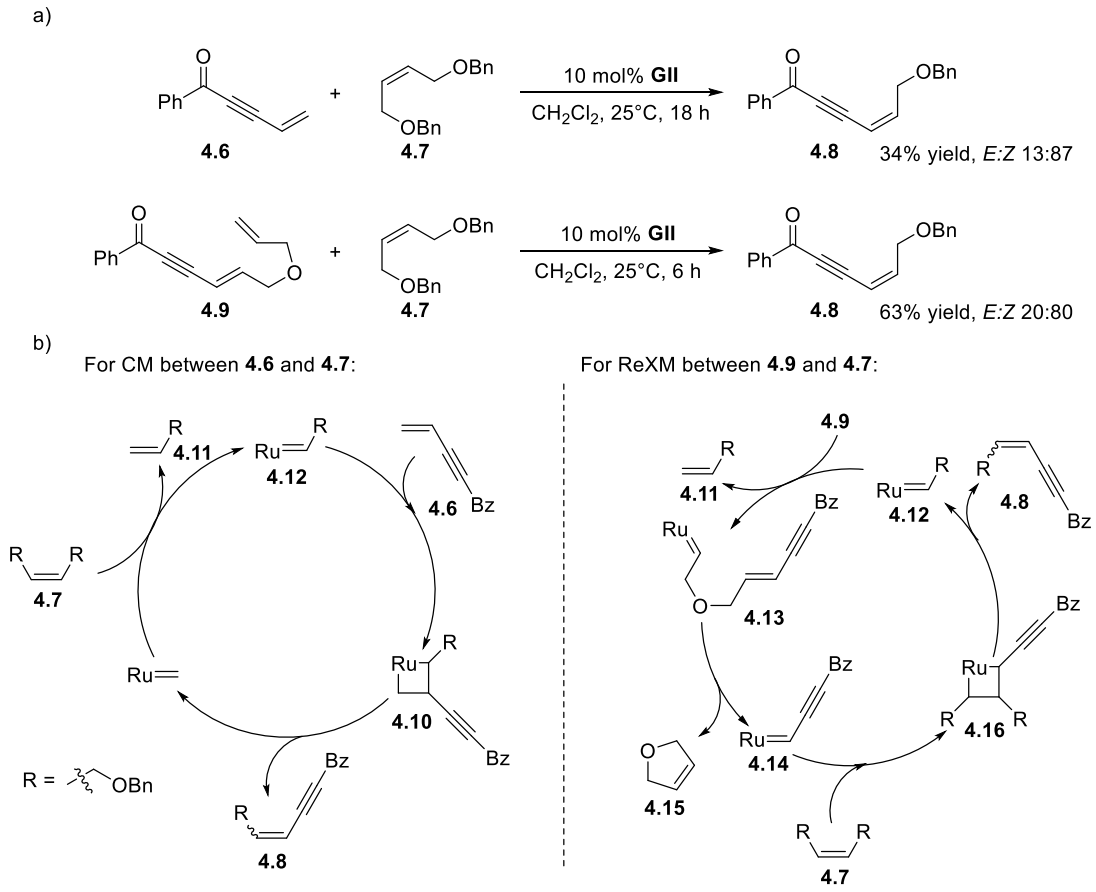


Scheme 4.1 a) Concept of relay-assisted initiation on sterically hindered/electronically deactivated olefin sites; b) Applying RRCM strategy in the formation of tetrasubstituted olefin.

As type III olefins are reluctant to initiate, the RCM between two 1,1-disubstituted olefins do not proceed. However, with the assistance from the relay, the initiation started at the most reactive type I olefin followed by the concomitant ring-closure to

give the desired alkylidene, which can then cyclise as per normal RCM reaction to form the desired product.

The relay strategy can also be applied in CM reactions to solve the initiation problem of sterically hindered/electronically deactivated olefins. Lee *et al.* reported the first examples of relay cross-metathesis (ReXM) where alkynyl alkylidene can be generated in the presence of more reactive, disubstituted olefin (Scheme 4.2).[143]

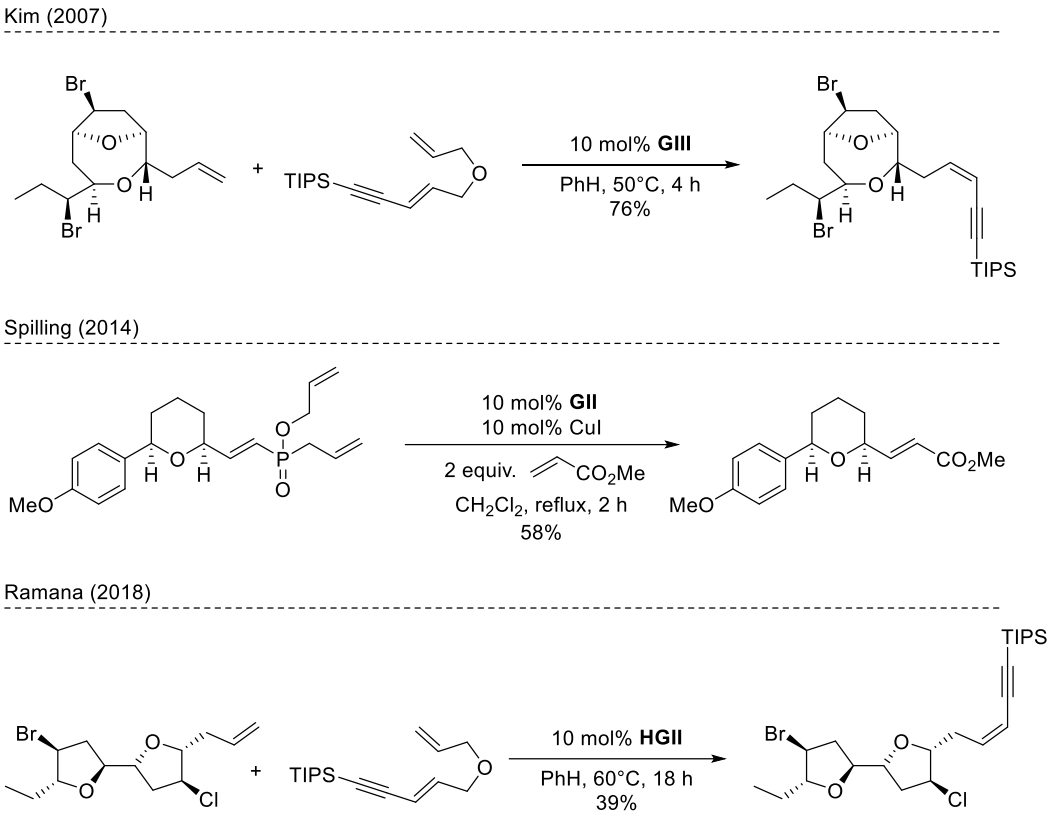


Scheme 4.2 a) Comparison between conventional CM reaction and ReXM reaction in the preparation of enyne **4.8**; b) Proposed catalytic cycle for the CM between **4.6** and **4.7** (left) and the ReXM between **4.9** and **4.7** (right).

The direct CM reaction between enyne **4.6** and disubstituted CM partner **4.7** (Scheme 4.2b, left) affords desired CM product **4.8** in only 34% yield. This is due to the selective initiation of **GII** catalyst onto the more reactive olefin **4.7**, which generates alkylidene **4.12**.

In contrast, relay-tethered **4.9** delivered the conjugated alkylidene **4.14** after initiation, which cannot be generated in direct CM reactions (Scheme 4.2b, right). Following the ring-closure of relay and the extrusion of dihydrofuran **4.15**, the conjugated alkylidene **4.14** metathesises with CM partner **4.7** to give mcb **4.16**, which then undergoes cycloreversion to give **4.8** as the final product. The difference of yield between these two reactions are believed to be the slower reaction between alkylidene **4.12** and enyne **4.6** compared to the reaction between conjugated alkylidene **4.14** and partner olefin **4.7**.

There are limited examples of ReXM and all of which provide *conjugated* olefins. These examples are summarised below in Scheme 4.3.[144–146]

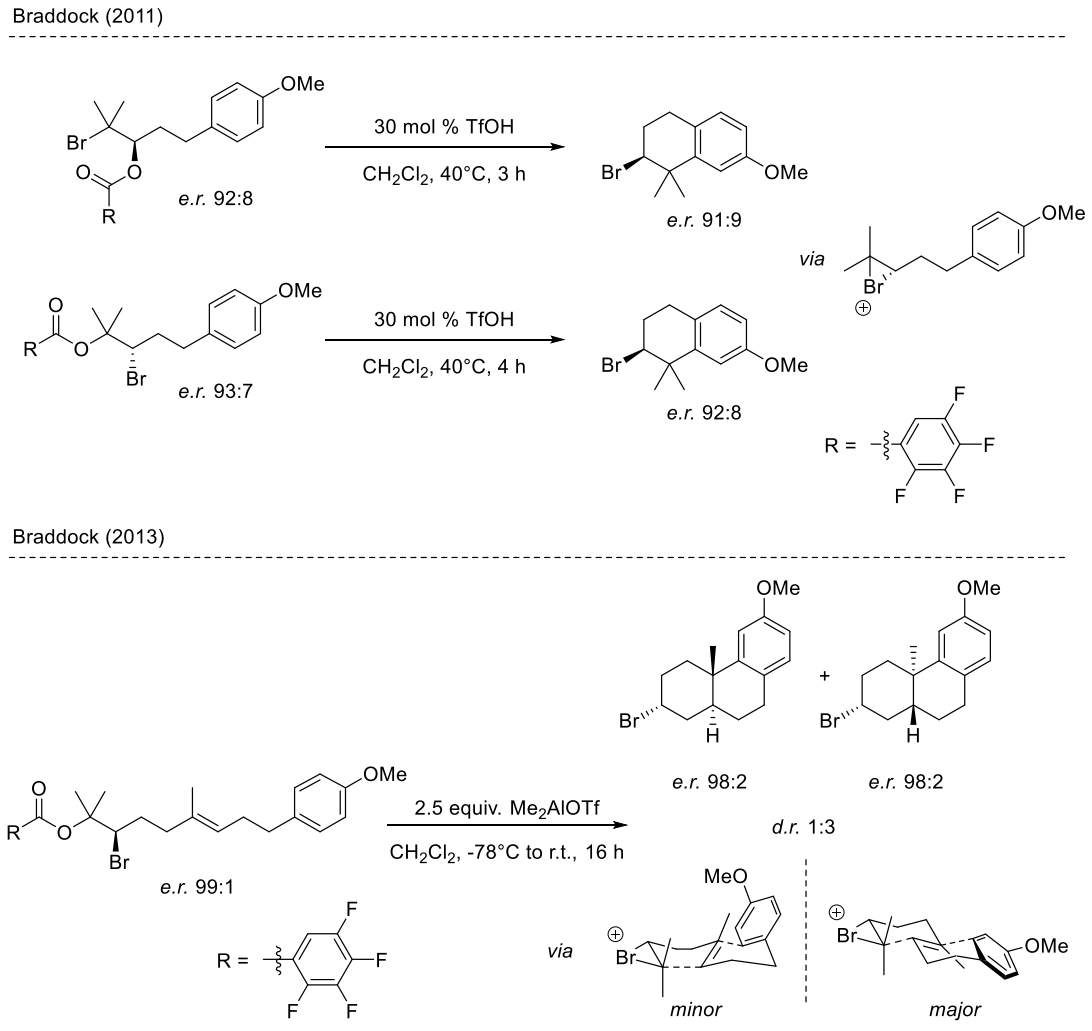


Scheme 4.3 Previous examples of preparation of conjugated olefins *via* ReXM reactions.

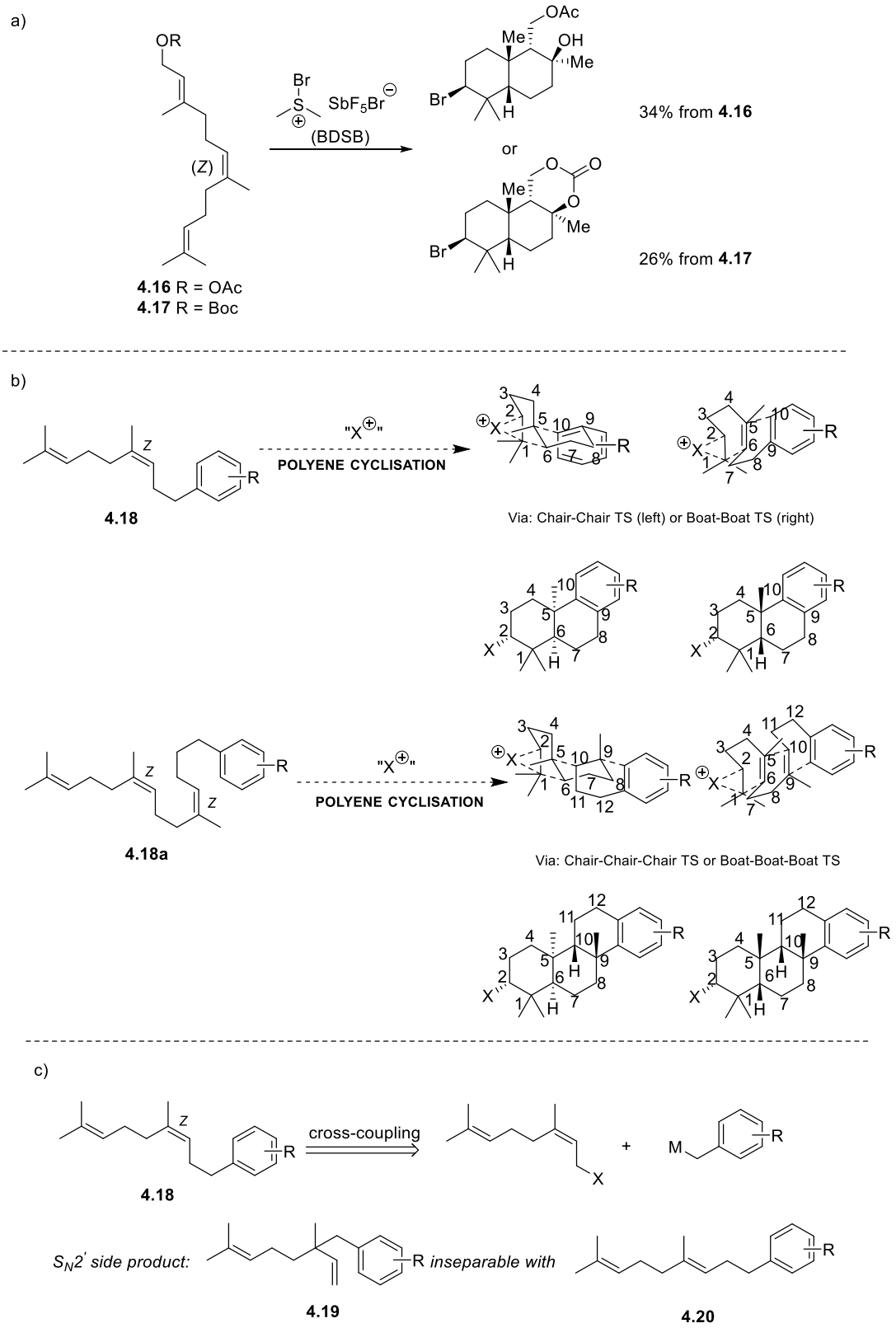
The above examples demonstrate the ability of relay strategy to direct the site of alkylidene formation, which leads to alkylidene species that cannot be accessed under conventional CM conditions. These alkylidene species in return, can alter the metathesis sequence and lead to the formation of otherwise inaccessible products.

4.2 Literature precedent for the cyclisation of *Z*-polyenes and proposed ReXM strategy for the synthesis of polyene precursors

Our group has a long-standing interest in the study of cationic polyene cyclisation processes (Scheme 4.4).[147,148] All these studies involve all-*E* polyene precursors which lead to the formation of fused ring systems with all-*trans* geometry.[72] In contrast to the well-explored polyene cyclisation of all-*E* polyenes[149,150], there is only very limited literature precedents on the cyclisation of *Z*-polyenes.[151–153]



Scheme 4.4 Enantiopure bromonium ion-initiated polyene cyclisation reported by Braddock group.



Scheme 4.5 a) Bromodiethylsulfonium bromopentachloroantimonate (BDSB) initiated cyclisation of *Z*-polyene **4.16** and **4.17**; b) Possible transition states for the cationic polyene cyclisation of diene **4.18**; c) Conventional retrosynthesis of diene **4.18** and side product **4.19**, which was found to be inseparable with diene **4.20**.

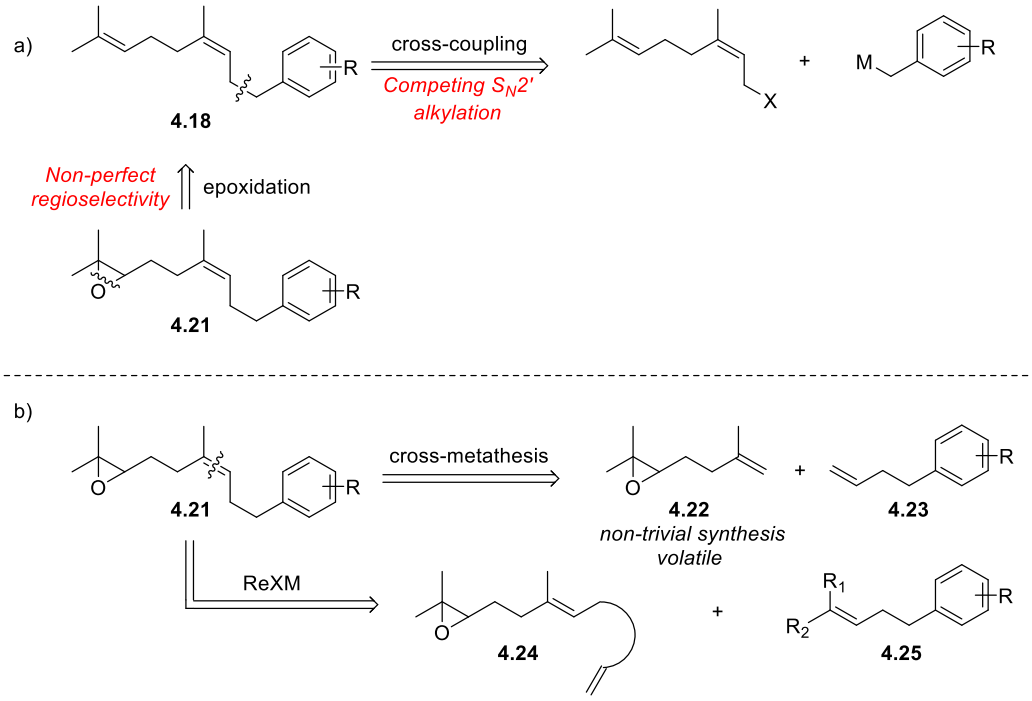
Inspired by the work of Snyder *et al.* on the bromonium ion induced cyclisation of *Z*-polyene (Scheme 4.5a),[153] we speculate the cyclisation of linear sesquiterpenes/diterpenes containing trisubstituted olefin with *Z*-geometry can be achieved under similar conditions (Scheme 4.5b). This would allow the access to *cis*-fused, steroidal ring systems and provide a mechanistic probe for the polyene cyclisation of *Z*-polyenes by the inspection of product distribution.

However, it is non-trivial to prepare the corresponding linear terpene precursor with high purity *via* conventional cross-coupling method. For example, the side product **4.19**, arises from the S_N2' trapping of the palladium π-allyl complex during the cross-coupling process, was found inseparable with all *trans*-diene **4.20** (R = *p*-methoxy) at all stages of synthesis (Scheme 4.5c).[148,154] As a result, the terminal alkene in impurity **4.19** may complicate the polyene cyclisation reaction.

These difficulties prompted us to investigate the synthesis of epoxypolyene **4.21** as an alternative substrate for polyene cyclisation. Epoxypolyenes of this type are conventionally assembled in a two-step sequence *via* a metal-catalysed cross-coupling reaction between an electrophilic geranyl species and a benzylic organometallic, prior to a regioselective epoxidation at the terminus of the geranyl chain.[155–158] This strategy usually suffers from two regioselectivity issues: the competing allylic S_N2' alkylation during the cross-coupling reaction and nonperfect regioselectivity during the epoxidation step (Scheme 4.6a).

To avoid these issues, alternative disconnection of **4.21** was proposed, utilising CM reaction to forge the *Z*-olefin (Scheme 4.6b). The pure *Z*-olefin can be accessed either by a *Z*-selective CM reaction or *via* a separation of the *E/Z*-product mixture when the *Z*-selectivity is absent.

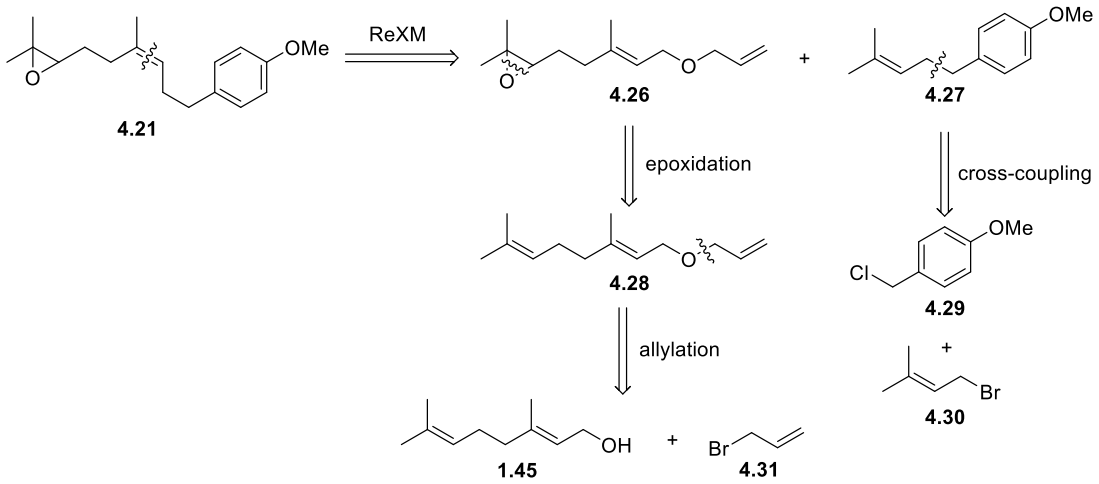
The intuitive disconnection revealed the 1,1-disubstituted olefin **4.22** and terminal olefin **4.23** as the substrates (Scheme 4.6b, top). However, the 1,1-disubstituted olefin **4.22** is a volatile compound and synthetically nonsimplified. Attention was then turned to more substituted olefins, based on the preliminary studies within our laboratory, [159] we proposed the ReXM reaction between a relay-tethered, trisubstituted olefin with a generic structure of **4.24** and an acceptor olefin **4.25** (Scheme 4.6b, bottom).



Scheme 4.6 a) Conventional retrosynthesis of terpene-related epoxypolyene and related problems; b) CM and ReXM approach to the preparation of epoxypolyene **4.21**.

Ideally, the two ReXM substrates **4.24** and **4.25** should be easily accessible from commercialised starting materials. It was recognised that diene **4.24** can be derived from a terpene, which is abundant and commercially available. As a result, $\Delta^{6,7}$-epoxy geranyl allyl ether **4.26**, which is accessible from geraniol **1.45** in two steps, was chosen as one substrate of the ReXM reaction. The allyl ether relay was previously reported to efficiently deliver α,α-disubstituted alkylidenes.[160,161]

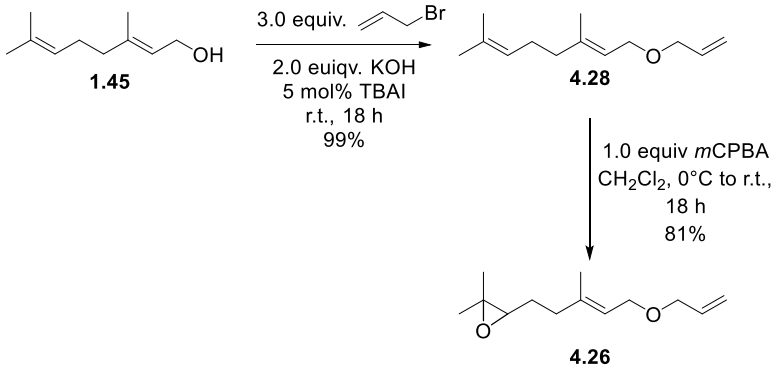
Considering the CM efficiency of different olefin combinations (see Chapter 2) and relevant examples reported by Robinson and Netscher *et al.*, a trisubstituted olefin acceptor **4.25** would suit best in this case.[94,162] The aromatic substituent R in **4.25** was elected to be an electron-donating, *p*-methoxy group, which would better stabilise the transition state of cationic polyene cyclisation. In addition, the symmetrical nature of the *p*-substituted phenyl group would reduce the potential regioisomers of tricycle product generated during the cyclisation cascade. Thus, *p*-homoprenylanisole **4.27**, which can be prepared from commercial materials in a single step, was elected as the acceptor olefin for the proposed ReXM reaction. The retrosynthetic analysis of epoxypolyene **4.21** is shown below in Scheme 4.7.



Scheme 4.7 Retrosynthetic analysis of epoxypolyene **4.21**.

4.3 Substrate preparation and optimisation of ReXM

With the synthetic plan in mind, the synthesis of substrate **4.26** and **4.27** was carried out. The multigram-scale allylation of geraniol **1.45** was achieved according to the protocol reported by Senthilkumar *et al.* to afford allyl ether **4.28** in 99% yield.[163] Treating the allyl ether **4.28** with dilute *m*CPBA solution is necessary to reduce unselective epoxidation, especially when the reaction was carried out in larger scales. The desired mono-epoxy product **4.26** was obtained in good yield (81%, Scheme 4.8).

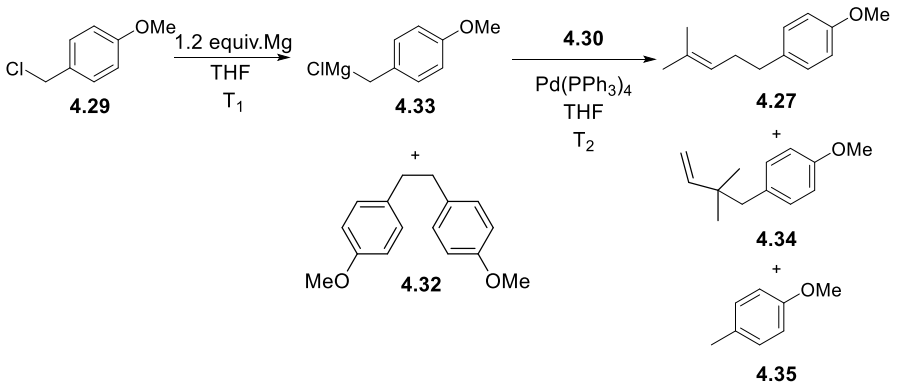


Scheme 4.8 Preparation of relay substrate **4.26**

However, the preparation of acceptor olefin **4.27** proved to be not straightforward. The initial attempt using the previously reported conditions,[148,164] where the benzylic Grignard reagent was generated in reflux THF, resulted the formation of significant amount of homocoupling product **4.32** (Table 4.1, entry 1). It was recognised that benzylic Grignard reagents can be generated at lower temperature where the adverse

homocoupling reaction was not observed.[165] Thus, the preparation of the benzylic Grignard reagent **4.33** was carried out at 0°C where small amount of homocoupling product **4.32** was easily separated (Table 4.1, entry 2). The reverse-prenylated product **4.34** and quenched Grignard reagent **4.35** were identified as the other by-products that cannot be separated from **4.27** *via* column chromatography. Various attempts were made to reduce the amount of quenched Grignard reagent **4.35**, including quenching the reaction with aprotic electrophile (Table 4.1, entry 3), using excess of prenyl bromide **4.30 (**Table 4.1, entry 4) and using freshly prepared prenyl bromide **4.30** to minimise the acid content from decomposition (Table 4.1, entry 5). Unfortunately, none of these efforts reduces the content of quenched Grignard reagent **4.35**. Fractional distillation was also known to fail to separate **4.35** from the product mixture.[148] Considering the subsequent ReXM step is compatible with methoxy-substituted arenes[68,166], attention was turned to reducing the content of the reverse-prenylated product **4.34**. The terminal olefin with quaternary allylic carbon (Type III olefin) in **4.34** could lead to undesired metathesis events. The stereoselectivity of prenylation remained unchanged in all attempts at 0°C (Table 4.1, entry 1-5). It is postulated that lowering the reaction temperature may shift the stereoselectivity. Gratifyingly, the reverse prenylation was minimised to effectively zero when the cross-coupling was carried out at -78°C (Table 4.1, entry 6).

Table 4.1 Optimisation of the preparation of acceptor olefin **4.27**



Entry	T_1 (°C)	**4.30** (equiv.)	T_2 (°C)	**4.27** Yield (%)[b]	**4.32** Yield (%)[c]	**4.34** Yield (%)[c]	**4.35** Yield (%)[c]
1	reflux	0.8	0	Trace	43	n.d.	n.d.
2	0	0.8	0	72	5	6	12
3[a]	0	0.8	0	69	3	5	10
4	0	1.2	0	65	6	4.5	14
5[e]	0	1.2	0	44	n.d.	5	13
6	0	1.2	-78	65	n.d.	Trace	13

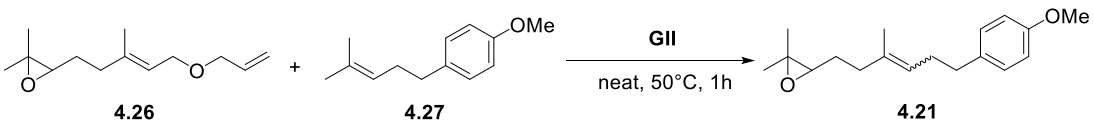
[a]T1, T2 are the temperatures under which Grignard reaction and Kumada coupling were carried out, n.d. = not determined. [b]Isolated yield. [c]Yield calculated based on ^{1}H NMR. [d]Benzaldehyde (0.3 equiv.) was used as a quench. [e]Freshly prepared 3,3-dimethylallylic bromide **4.30** was used.

With relay-tethered **4.26** and acceptor olefin **4.27** in hand, optimisation of the proposed ReXM was carried out. Treating the 1:5 mixture of **4.26** and **4.27** with 10 mol% **GII** catalyst under 50°C for one hour afforded the desired product **4.21** as a *E/Z*-mixture (Table 4.2, entry 1). A strong positive pressure of nitrogen, introduced by a needle inlet and outlet, was found necessary to remove volatiles (*i.e.* dihydrofuran **4.15** and isobutylene **2.8**) that may otherwise complicate the reaction. Different additives were then explored to improve the yield. While acetic acid was found as a useful additive for quenching the ruthenium hydride in the ReXM reaction between **4.26** and citral **4.36** (not shown),[159,167,168] addition of acetic acid (20 mol%) to the reaction mixture led to a significant erosion of the yield (Table 4.2, entry 2). CuI was previously reported as an dual-functional additive that accelerates the phosphine dissociation of the catalyst and scavenges ruthenium hydrides.[169,170] Indeed, improved yield was observed with the addition of 30 mol% of CuI (Table 4.2, entry 4).

As closer inspection of the reaction mixture revealed that **GII** catalyst is not fully dissolved, it is possible that the reaction could proceed with less catalyst. Reducing the catalyst loading to 5 mol% did not affect the overall yield and *E/Z*-selectivity (Table 4.2, entry 3). However, further reduction of the catalyst loading to 3 mol% (Table 4.2, entry 5-7) and 1 mol% (Table 4.2, entry 8-10) resulted reduced yields and difficult separations. Although employing large excess acceptor olefin **4.27** increases the yield to 31% with only 3 mol% catalyst (Table 4.2, entry 7), it is impractical to further

increase the excess of acceptor **4.27** as it became increasingly difficult to separate **4.27** from product **4.21** (Table 4.2, entry 9). Extending the reaction time is generally not necessary as full consumption of **4.27** is observed within 1 hour. In the cases with reduced catalyst loading, **4.27** was still present in the crude mixture after 1 hour. However, no further conversion of **4.27** was observed with increased reaction time, which possibly indicates the complete decomposition of the catalyst (Table 4.2, entry 10).

Table 4.2 Optimisation of the ReXM conditions



4.26 **4.27** **4.21**

Entry	**GII** (mol%)	**4.27** (equiv.)	*E*:*Z*[b]	**4.21** Yield (%)[a]
1	10	5	70:30	48
2	10	5	n.d.	29[c]
3	5	5	70:30	47
4	5	5	72:28	53[d]
5	3	2	n.d.	13
6	3	5	n.d.	14
7	3	7	67:33	31
8	1	2	n.d.	15
9	1	10	n.d.	14
10	1	5	n.d.	13[f]
11	10	5	67:33	63[e]
12	5	5	71:29	66[e]

[a]Isolated yield. [b] Ratio calculated based on ^{1}H NMR. [c]20 mol% acetic acid was added. [d]30 mol% CuI was added. [e]Compound **4.27** was free of reverse-prenylated by-product **4.34**. [f]2 h reaction. n.d. = not determined.

With the success on the stereoselective prenylation of **4.29**, **4.27** that is free from reverse-prenylated **4.34** was obtained. As predicted, improved yield of ReXM reaction was observed with pure **4.27** (Table 4.2, entry 11 and 12). It is noteworthy that the *E/Z*-selectivity of the ReXM reaction remained roughly unaffected across all entries (*ca. E:Z* 70:30).

4.4 Mechanism of ReXM reaction

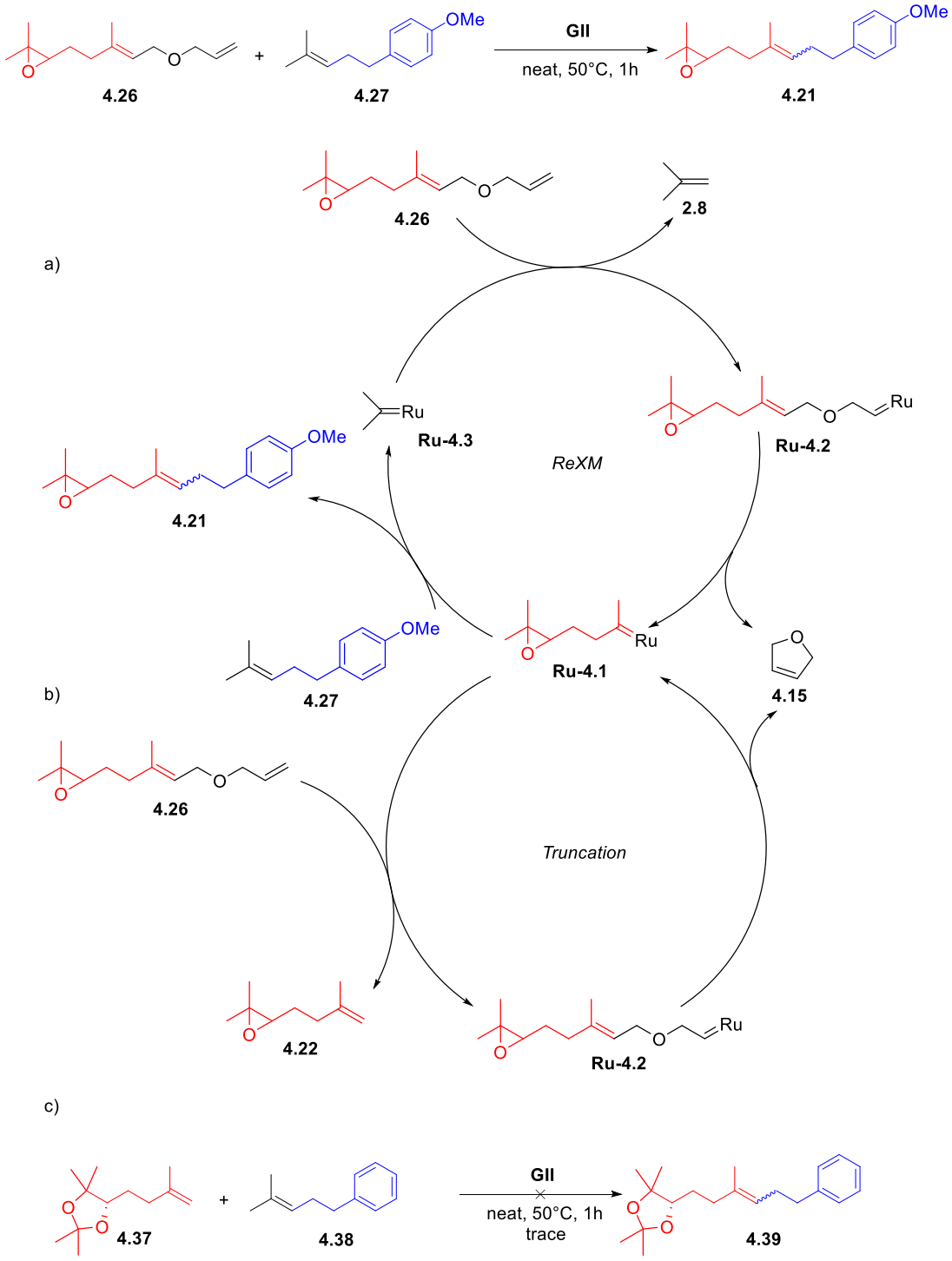
Based on Hoye's RRCM mechanism, the following catalytic cycle was proposed (Scheme 4.9a).

The catalyst initiation takes place at the most accessible and reactive terminal olefin in **4.26** to deliver the corresponding alkylidene **Ru-4.2**, which would undergo rapid RCM to give the desired 1,1-disubstituted alkylidene **Ru-4.1** and dihydrofuran **4.15**. The 1,1-disubstituted alkylidene **Ru-4.1** then metathesises with **4.27** to give the desired product **4.21** and isopropylidene **Ru-4.3**. The isopropylidene **Ru-4.3** reacts with the terminal olefin in **4.26** to give isobutylene **2.8** and alkylidene **Ru-4.3** to complete the cycle.

This mechanism is consistent with Hoye's proposal (see Scheme 4.1) where the catalyst initiation is at the terminal olefin in the relay component of the reaction. The product generation step that involves the combination of a 1,1-disubstituted alkylidene and a trisubstituted olefin has been proposed by Robinson *et al.*[162] to elucidate the outcomes of CM reactions between 1,1-disubstituted olefins and trisubstituted olefins.

Due to the similar reactivity between 1,1-disubstituted alkylidenes **Ru-4.1** and **Ru-4.4**, **Ru-4.1** may also compete to metathesise with the terminal olefin in **4.26** (Scheme 4.9b). This process leads to the net removal of the relay and was named truncation. In the truncation cycle, the metathesis between 1,1-disubstituted alkylidene **Ru-4.1** and the terminal olefin in **4.26** gives 1,1-disubstituted olefin **4.22** and 1,1-disubstituted alkylidene **Ru-4.3**, which undergoes rapid RCM to give dihydrofuran **4.15** and

regenerates 1,1-disubstituted alkylidene **Ru-4.1**. In the ReXM system, the generation of **4.22** is problematic and could dramatically reduce the yield.



Scheme 4.9 a) Proposed ReXM catalytic cycle with the metathesis of **Ru-4.1** with **4.27** as the product formation step; b) Undesired truncation cycle *via* the metathesis of **Ru-4.1** with **4.26**; c) Unsuccessful metathesis between 1,1-disubstituted olefin **4.30** and trisubstituted olefin **4.31**.

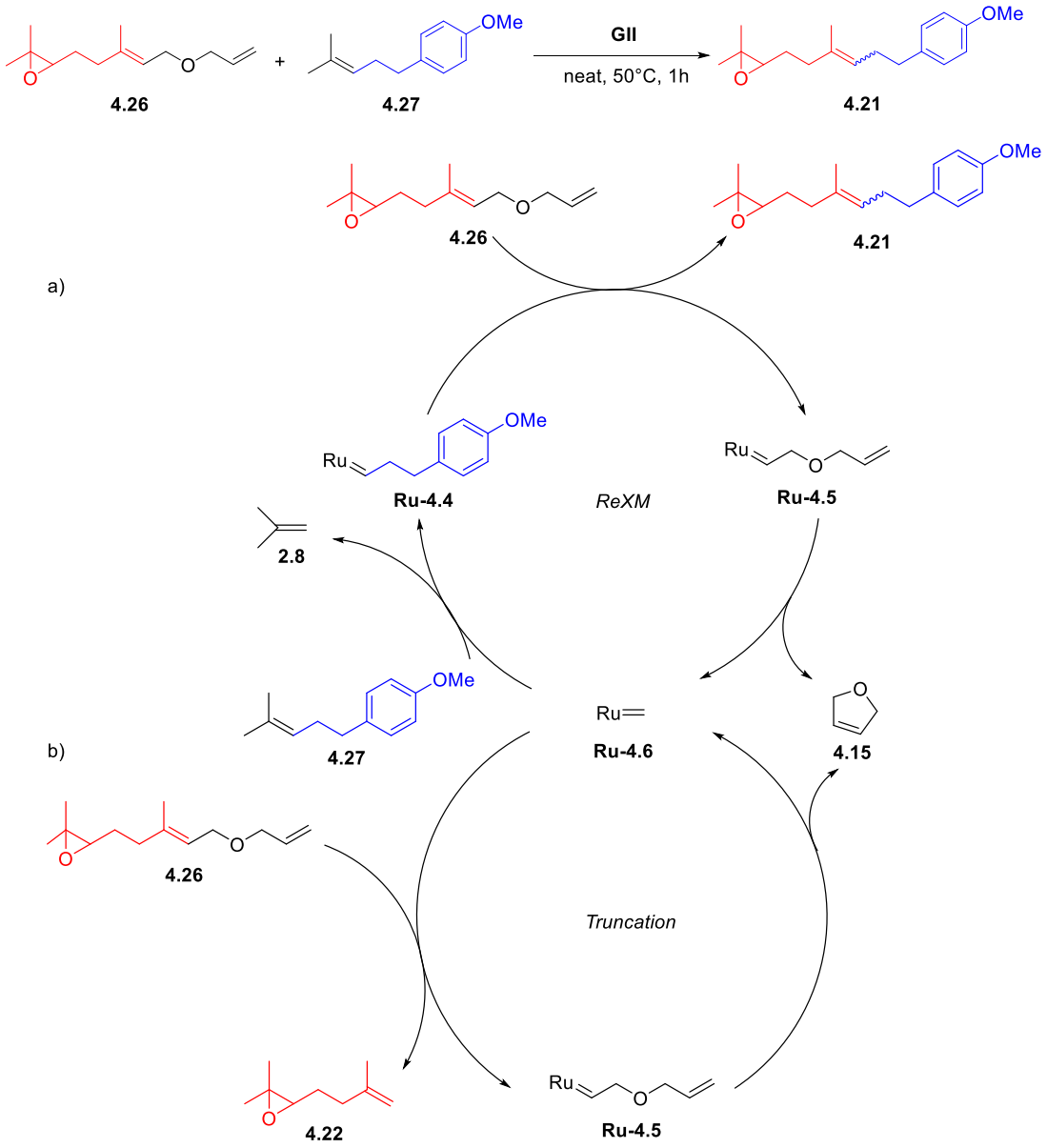
First of all, **4.22** was found to be volatile and could escape the reaction vessel under the ReXM conditions, which effectively removes substrate **4.26** from the reaction. Another problem with 1,1-disubstituted olefin **4.22** is the inefficient initiation by **GII** catalyst, which would impede the generation of **Ru-4.1** and prevent the product formation. Indeed, the direct CM reaction between trisubstituted olefin **4.38** and 1,1-disubstituted olefin **4.37**, which is analogues to **4.22**, was inefficient with only trace of product **4.39** observed in the reaction mixture (Scheme 4.9c). 1,1-Disubstituted olefin **4.22** was not used in this model reaction to avoid any complication from its volatile nature.

To attenuate this side reaction, the use of excess acceptor olefin **4.27** (5 equiv.) was required to compete with the undesired metathesis between **Ru-4.1** and the more reactive terminal olefin in **4.26**.

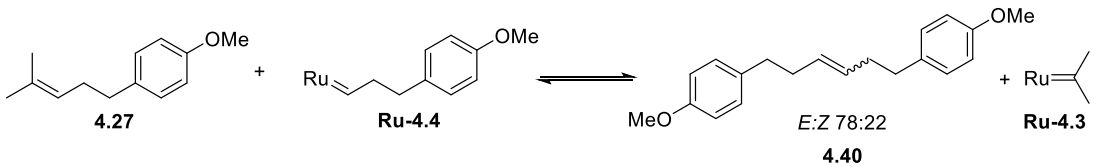
As the reaction progress, the concentration of **4.26** may dropped to a degree when catalyst initiation on trisubstituted olefin **4.27** becomes competitive. Thus, an alternative mechanism was proposed (Scheme 4.10a).

In this "reversed" ReXM cycle, where the ring-closure of the relay occurs after the product formation, alkylidene **Ru-4.4**, formed *via* the catalyst initiation at **4.27**, metathesises with the trisubstituted olefin in **4.26** to give **Ru-4.5**. The RCM of **Ru-4.5** would give dihydrofuran **4.15** and methylidene **Ru-4.6**, which may metathesise with **4.27** to produce 1,1-disubstituted olefin **4.22** (Scheme 4.10a). The truncation process is also possible *via* the metathesis between methylidene **Ru-4.6** and the trisubstituted olefin in **4.26** to give 1,1-disubstituted olefin **4.22** and alkylidene **Ru-4.5**, which gives dihydrofuran **4.15** and methylidene **Ru-4.6** *via* an RCM reaction (Scheme 4.10b).

The identification of by-product **4.40** in the ReXM reaction between **4.26** and **4.27** provided evidence supporting this mechanism. The generation of **Ru-4.3** must involve the metathesis between alkylidene **4.4** and another olefin, which is likely to be the most populated trisubstituted olefin **4.27** (Scheme 4.11).

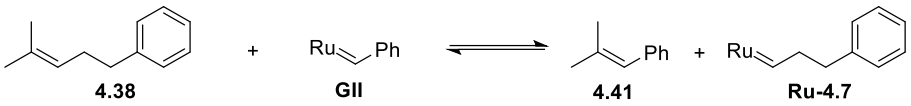


Scheme 4.10 a) Proposed ReXM catalytic cycle with the metathesis of **Ru-4.4** with **4.26** as the product formation step; b) Undesired truncation cycle *via* the metathesis of **Ru-4.6** with **4.26**.



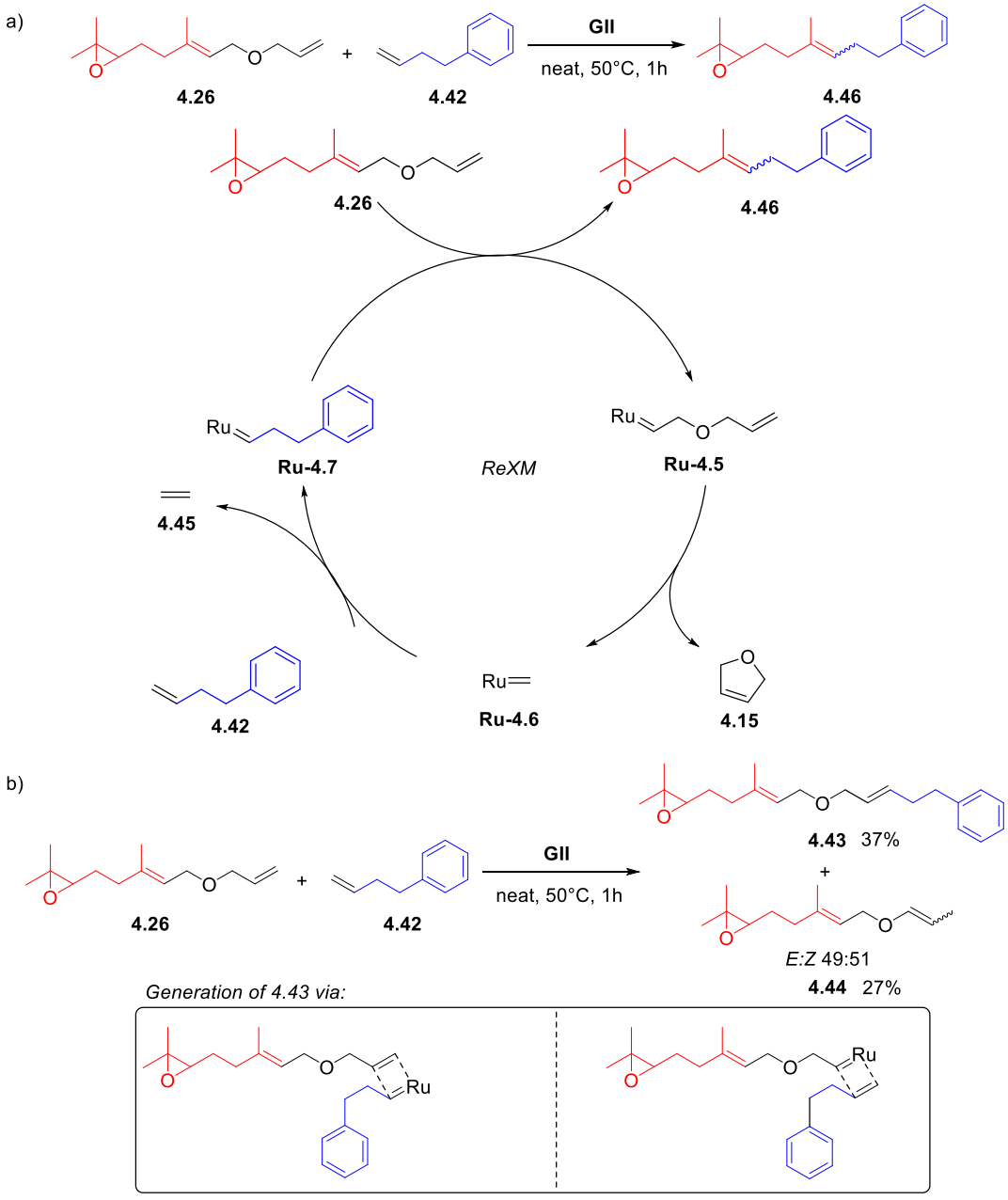
Scheme 4.11 Plausible mechanism for the generation of **4.40**.

The direct initiation of catalyst onto trisubstituted olefin **4.38**, which led to the generation of analogous **Ru-4.7**, was also observed *via* ^{1}H NMR (Scheme 4.12).[171]

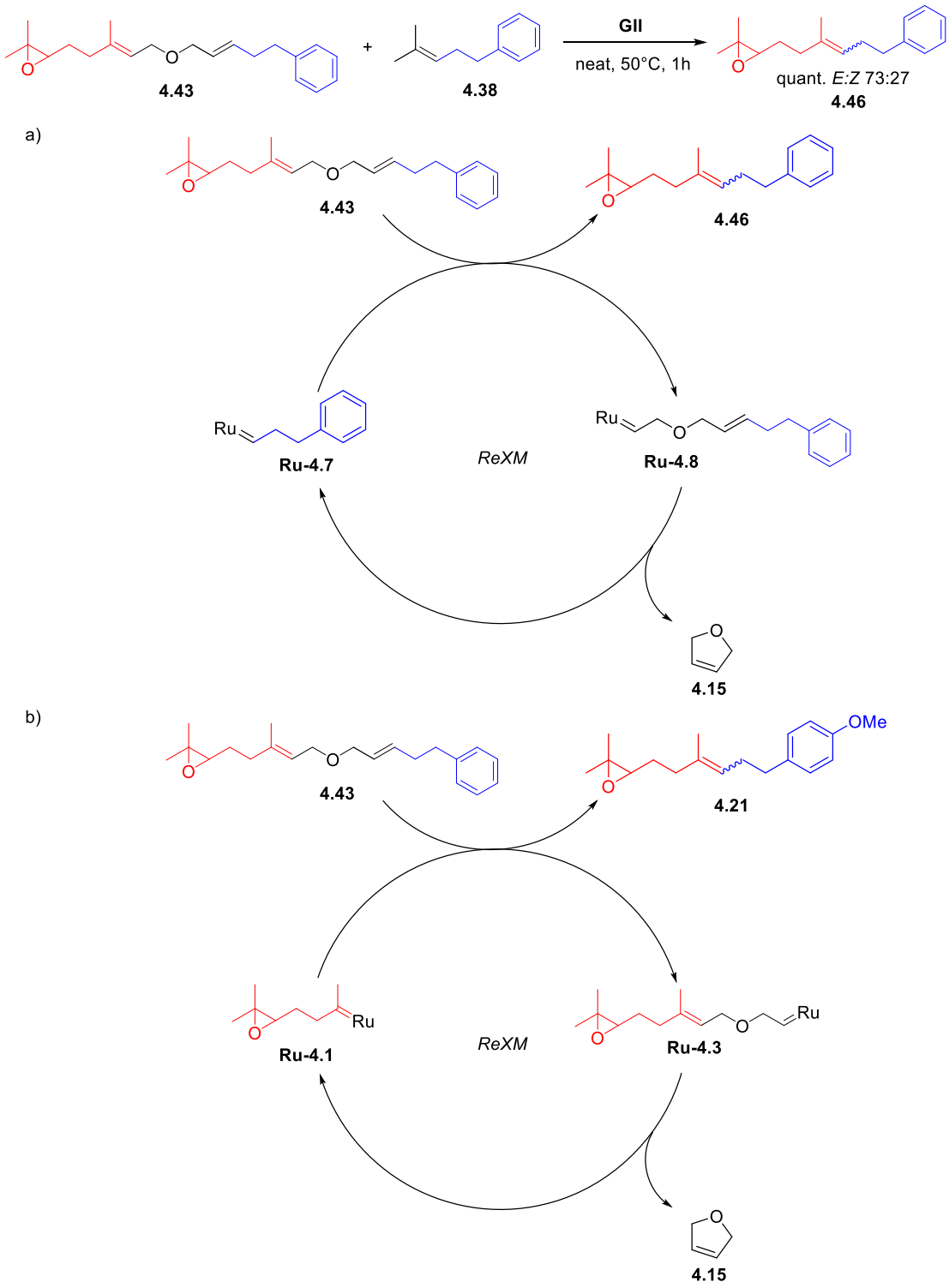


Scheme 4.12 Generation of **Ru-4.7** *via* catalyst initiation onto **4.27**.

To explore the possibility of **Ru-4.4** as the propagating species in the ReXM reaction, the terminal olefin **4.42**, which would generate **Ru-4.7** after initiation, was subjected to the ReXM conditions (Scheme 4.13a)



Scheme 4.13 a) Proposed cycle for the ReXM between **4.26** and **4.42**; b) Generation of **4.43** *via* CM and **4.44** *via* ruthenium hydride-induced isomerisation.



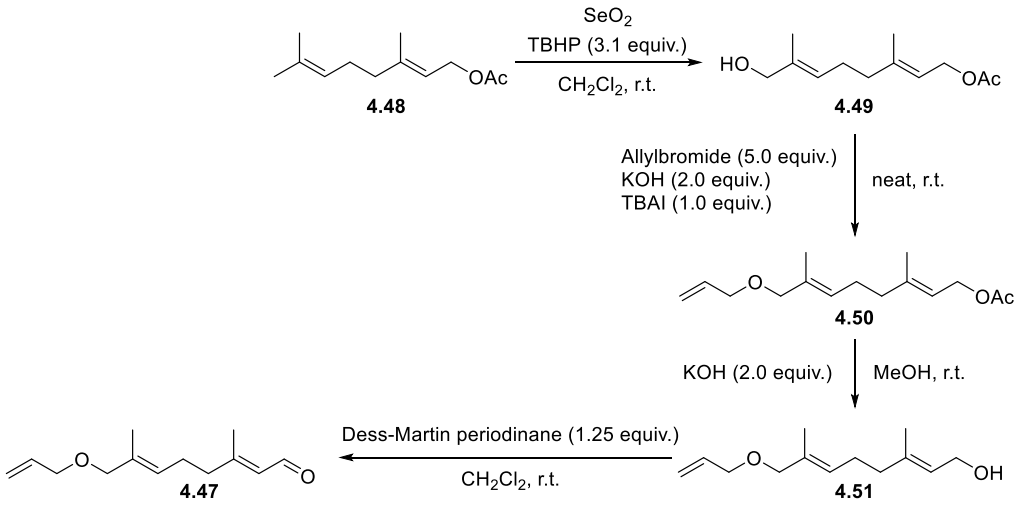
Scheme 4.14 a) Proposed catalytic cycle for the generation of **4.46** from **4.43** with **Ru-4.7** as the propagating alkylidene; b) Proposed catalytic cycle for the generation of **4.46** from **4.43** with **Ru-4.1** as the propagating alkylidene.

However, the major products are disubstituted olefin **4.43** and isomerised allyl ether **4.44**. The generation of **4.43** involves the metathesis either between **Ru-4.7** and **4.26**

or between **Ru-4.2** and **4.27**. The latter is less likely to occur due to the competitive ring-closure of **Ru-4.2** (Scheme 4.13b).

Resubmitting **4.43** to the ReXM conditions led to a clean conversion to the product **4.46**. Again, either **Ru-4.2** or **Ru-4.7** can be the propagating species (Scheme 4.14) The high yield may be attributed to the absence of truncation process, which is not possible due to the absence of terminal olefins.

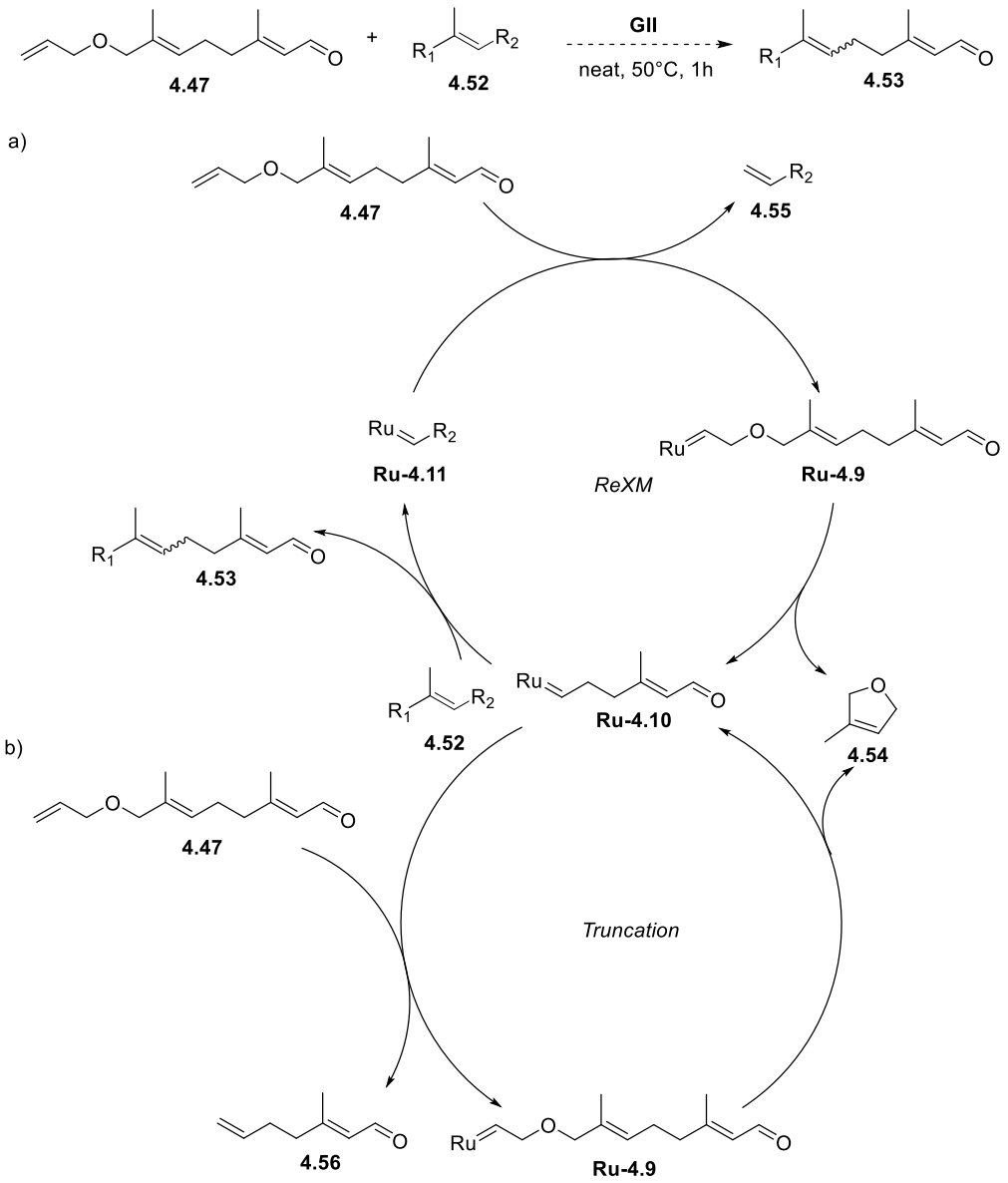
The possibility of relay-assisted generation of alkylidene was also investigated. The relay-tethered geranial **4.47** was prepared from geranyl acetate **4.48** in four steps with 29% overall yield (Scheme 4.15).



Scheme 4.15 Preparation of relay-tethered geranial **4.47**.

It was proposed that upon treating with **GII**, the ring-closure of the relay component in **4.47** would deliver the corresponding alkylidene **Ru-4.10**, which can metathesise with a terpene-derived, trisubstituted olefin **4.52** to form a new trisubstituted olefin **4.53** (Scheme 4.16a).

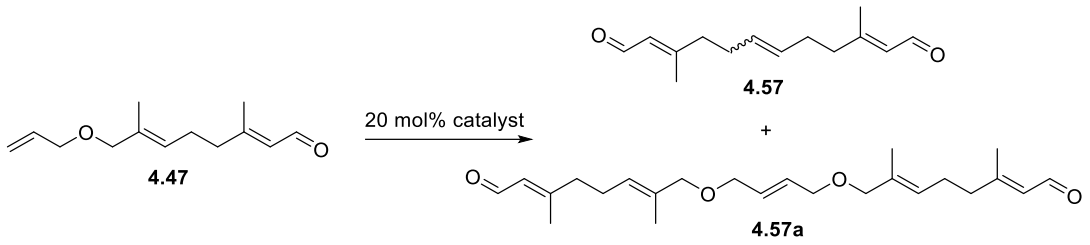
Unlike previously described, truncation is still possible but would be less problematic in this case as the truncated product **4.55** together with its homodimer (not shown) are supposedly involatile (Scheme 4.16b).



Scheme 4.16 a) Proposed catalytic cycle for the ReXM between **4.47** and **4.52**; b) Proposed truncation process for the ReXM between **4.47** and **4.52**.

Unfortunately, it turned out that the ring-closure of the relay component in **4.47** was unsuccessful (Table 4.3).

Table 4.3 Optimisation for the ReXM of **4.47**



Entry	Catalyst	Temperature (°C)	Time (h)	Solvent	Yield of **4.57** (%)[a]	Yield of **4.57a** (%)[a]
1[b]	GII	50	1 h	neat	n.d.	80%
2[c]	HGII	50	1 h	neat	n.d.	n.d.
3[c]	HGII	80	12 h	PhMe	n.d.	n.d.
4[d]	GII	80	12 h	PhMe	n.d.	n.d.

[a]n.d. = not detected. [b]Isolated yield. [c] Complex mixture was obtained after the reaction. [d]No reaction was observed based on ^{1}H NMR analysis.

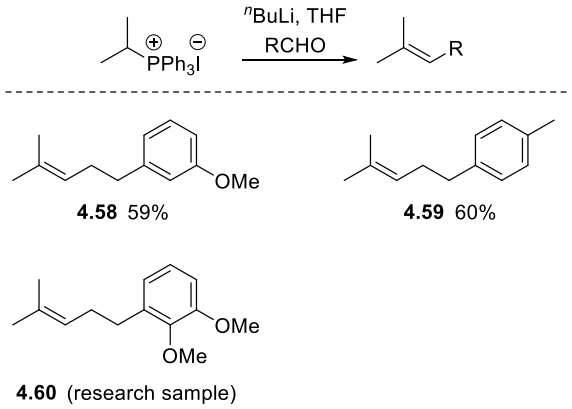
The homodimerisation of **4.47** occurred when treating **4.47** with **GII** to give **4.57a** in 80% yield (Table 4.3, entry 1). Switching to **HGII** catalyst resulted in the formation complex mixtures without detectable desired product **4.57** (Table 4.3, entry 2). No reaction was observed when toluene was used as the solvent after 12 h (Table 4.3, entry 4). These results prevented us from further exploring the ReXM reaction of this type.

Overall, the two catalytic cycles illustrated in Scheme 4.9a and Scheme 4.10a are not exclusive, and none can be proved or disproved based on our current experimental evidence.

4.5 Scope of ReXM reaction

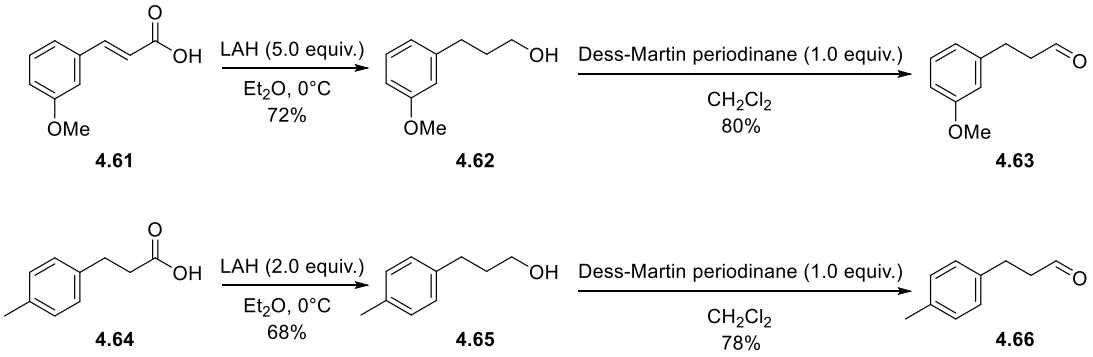
With the optimised conditions and relevant mechanistic understanding in mind, the scope of ReXM reaction was explored. This section focuses on introducing the examples that are suitable precursors for cationic polyene cyclisation. The complete list of examples can be found in our relevant publication.[102]

The non-commercial acceptor olefins were synthesised *via* Wittig reactions of corresponding aldehydes with isopropyltriphenylphosphonium iodide (Scheme 4.17)



Scheme 4.17 Preparation of trisubstituted olefins *via* Wittig reaction of aldehydes with isopropyltriphenylphosphonium iodide.

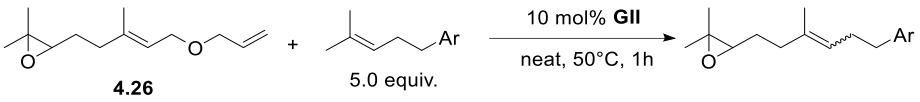
The non-commercial aldehydes were made from commercial carboxylic acids *via* lithium aluminium hydride (LAH) reduction and reoxidation by Dess-Martin periodinane (Scheme 4.18)



Scheme 4.18 Synthesis of aldehyde substrate **4.63** and **4.66** for the Wittig reaction with isopropyltriphenylphosphonium iodide **4.57**.

These trisubstituted olefins were subsequently tested in the ReXM reaction with **4.26** (Table 4.4).

Table 4.4 ReXM reaction of trisubstituted alkenes with **4.26**



Entry	Acceptor olefin	**4.26** (mmol)	Yield[a]	*E:Z*
1	**4.59**	0.25	67%	72:28
2	**4.58**	0.25	n.d.	n.d.
3	**4.58**	0.04	61%	72:28
4	**4.60**	0.25	n.d.	n.d.
5	**4.60**	0.036	n.d	n.d.

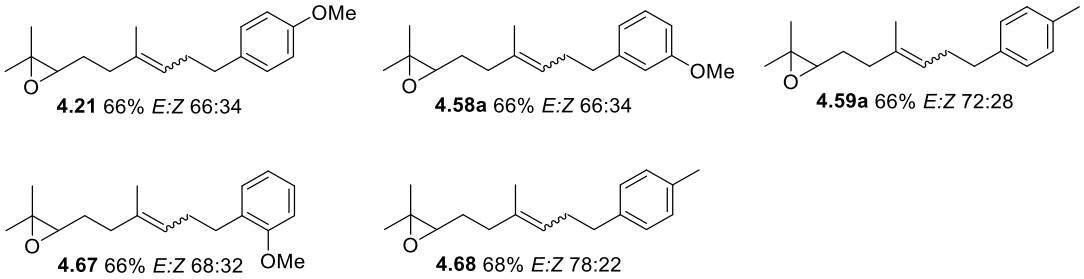
[a]Isolated yield; [b]n.d. = not determined. This is due to the formation of complex mixtures.

The ReXM reaction between **4.26** and **4.59** proceeded smoothly under the standard conditions (Table 4.4, entry 1). However, the ReXM reaction with **4.58** or **4.60** produced a complex mixture (Table 4.4, entry 2 and 4). Repeating the reaction in a smaller scale led to a better conversion of **4.58**, which may be the result of a more efficient removal of volatiles (Table 4.4, entry 3). Although the ReXM products derived from **4.60** were visible by ^{1}H NMR, the purification was unsuccessful (Table 4.4, entry 5).

Together with other examples in our publication,[102] various monosubstituted homoprenyl benzene derivatives can be accessed *via* ReXM protocol, which demonstrated the generality of this method (Scheme 4.19).

The *E/Z*-selectivities across examples, regardless of the nature of substrates, remained roughly unchanged (*i.e. E:Z* 70:30), which is directly comparable to those previously

reported for the generation of trisubstituted olefins *via* CM reactions using ruthenium precatalysts.[66,162,172]



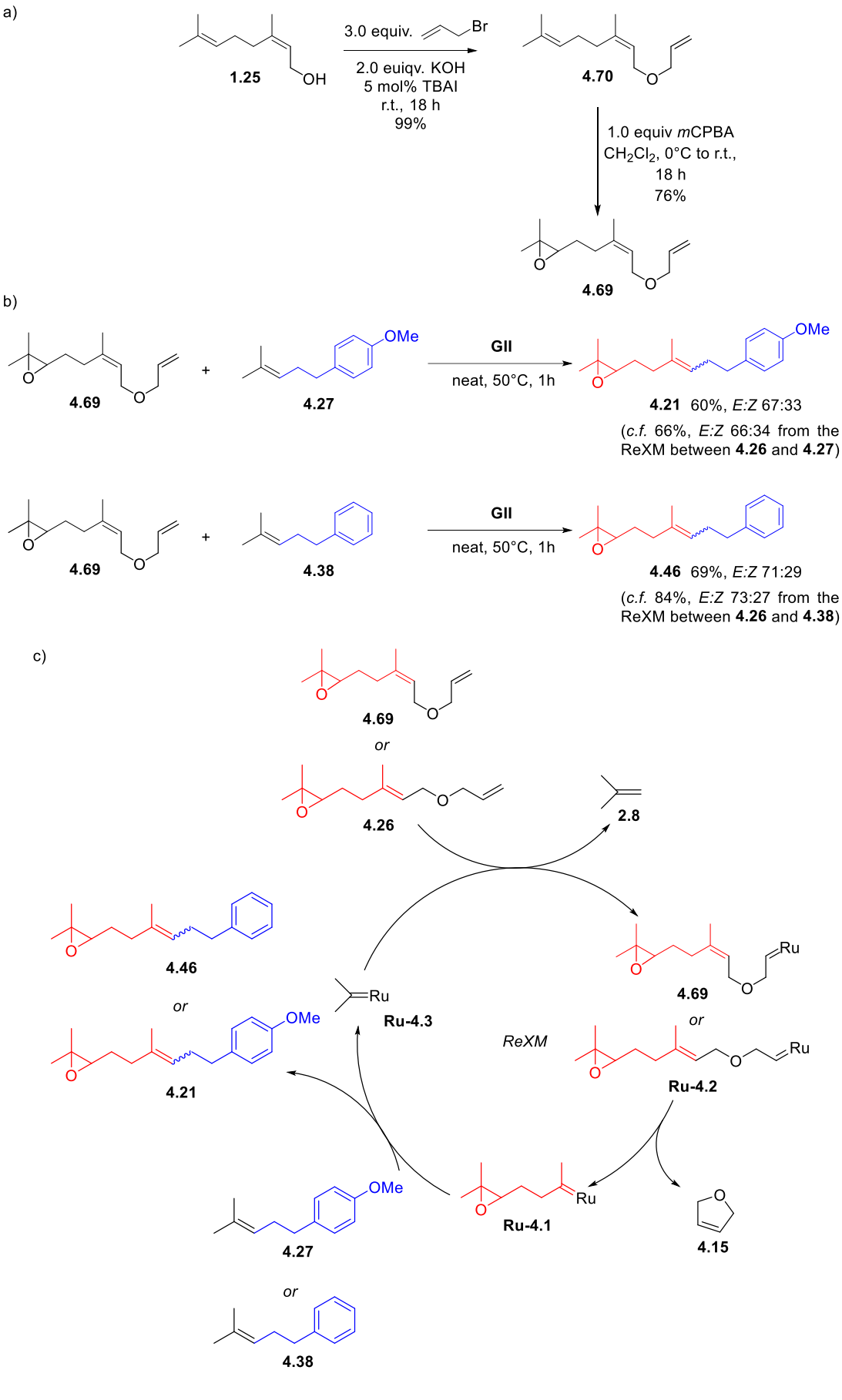
Scheme 4.19 Monosubstituted homoprenyl benzene derivatives synthesised *via* ReXM protocol.

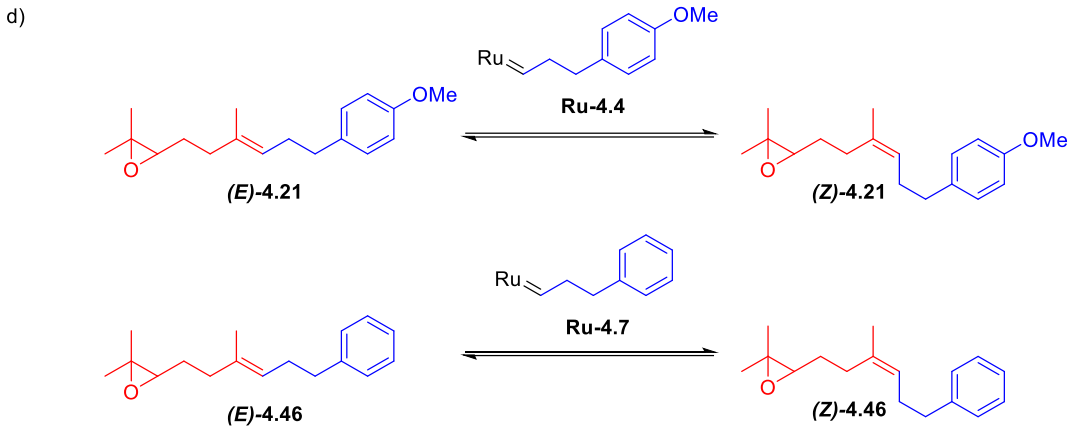
4.6 Attempts at altering the *E/Z*-selectivity in ReXM reactions

One of the major limitations of CM reaction in general is the lack of *E/Z*-selectivity. The trisubstituted olefin **4.69** with a *Z*-configured relay tether was then synthesised and tested under the ReXM conditions.

Similar to the preparation of **4.26**, trisubstituted olefin **4.69** was synthesised from nerol **1.25** in two steps (Scheme 4.20a). However, the *E/Z*-selectivity remained unchanged when **4.69** instead of **4.26** was used in the ReXM with **4.27** and **4.38** (Scheme 4.20b).

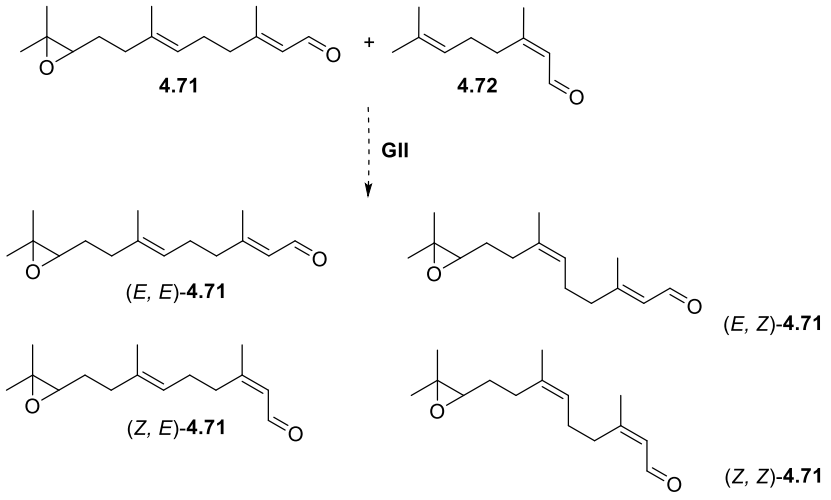
This may indicate the convergence of **4.26** and **4.69** to the same alkylidene **Ru-4.1** *via* RCM of the relay (Scheme 4.20c). The other possibility is the post-metathesis isomerisation of products *via* degenerative exchange with **Ru-4.4** (for **4.21**) or **Ru-4.7** (for **4.46**) (Scheme 4.20d).


a)
1.25
OH
3.0 equiv.
Br
2.0 euiqv. KOH
5 mol% TBAI
r.t., 18 h
99%
4.70
1.0 equiv mCPBA
CH2Cl2, 0°C to r.t.,
18 h
76%
4.69
b)
4.69
+
4.27
OMe
GII
neat, 50°C, 1h
4.21 60%, E:Z 67:33
(c.f. 66%, E:Z 66:34 from the ReXM between 4.26 and 4.27)
4.69
+
4.38
GII
neat, 50°C, 1h
4.46 69%, E:Z 71:29
(c.f. 84%, E:Z 73:27 from the ReXM between 4.26 and 4.38)
c)
4.69
or
4.26
2.8
4.46
or
4.21
OMe
Ru
Ru-4.3
ReXM
4.69
or
Ru-4.2
Ru
Ru-4.1
4.27
OMe
or
4.38
4.15



Scheme 4.20 a) Preparation of relay-tethered trisubstituted olefin **4.69**; b) Results of the ReXM between **4.69** and acceptor olefin **4.27**/**4.38**; c) Proposed mechanism for the concurrence of *E/Z*-selectivity *via* the convergence of **4.69** and **4.26** to the same alkylidene species **4.1**; d) Proposed mechanism for the concurrence of *E/Z*-selectivity *via* post-metathesis isomerisation with corresponding alkylidenes **Ru-4.4** and **Ru-4.7**.

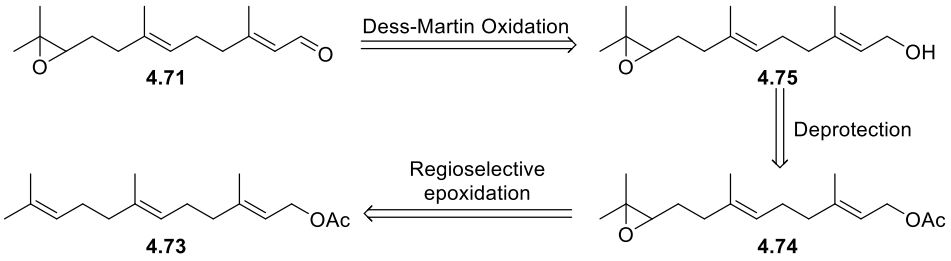
To evaluate the influence of post-metathesis isomerisation on the *E/Z*-distribution, the exchange experiment between a geometrically-pure trisubstituted olefin **4.71** and a trisubstituted olefin **4.72**, tagged with a *Z*-enal, was proposed (Scheme 4.21).



Scheme 4.21 Proposed post-metathesis isomerisation experiment between trisubstituted olefin **4.71** and trisubstituted olefin tagged with *Z*-enal **4.72**.

Neral **4.72** can be readily accessed from nerol **1.25** in one step. For the preparation of **4.71**, it is proposed that **4.71** can be accessed from farnesyl acetate **4.73** *via* a

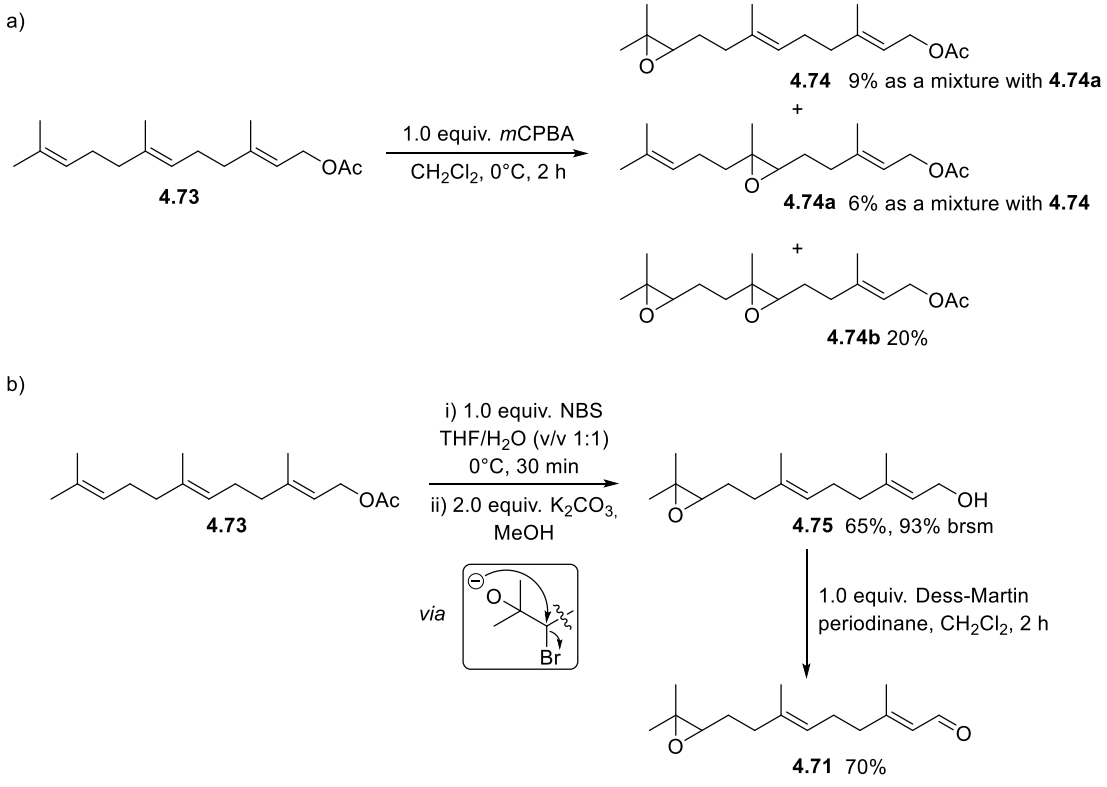
regioselective epoxidation at the terminal olefin, followed by deprotection and oxidation of alcohol to the corresponding aldehyde (Scheme 4.22).



Scheme 4.22 A retrosynthesis of substrate **4.71**.

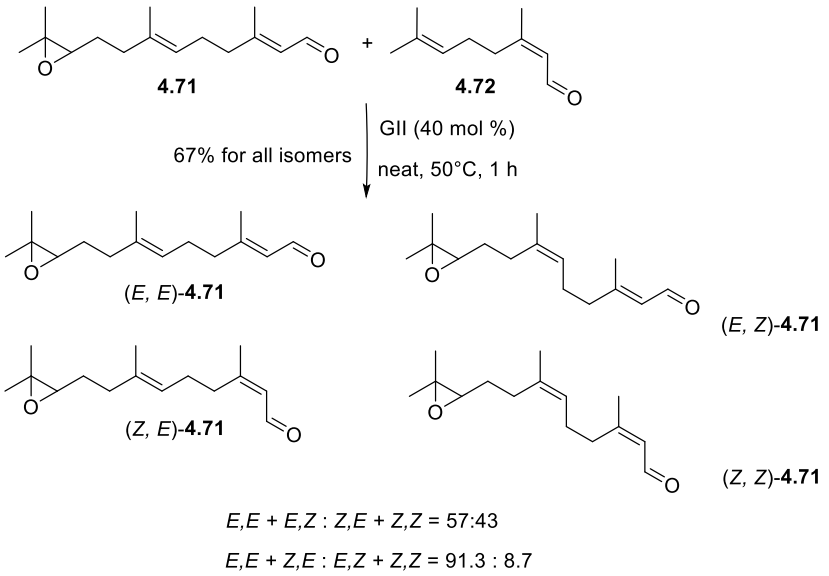
Initial attempts at epoxidation with *m*CPBA gave an inseparable mixture of both monoepoxide regioisomers **4.74** and **4.74a** with bisepoxide **4.74b** (Scheme 4.23a). Gratifyingly, regioselective bromohydration delivered the desired bromohydrin **4.76** in good yield (65%, 93% brsm). Further attempts at improving the yield failed as erosion of regioselectivity was observed when the reaction was allowed to complete.

Treating the bromohydrin with potassium carbonate in methanol afforded intermediate **4.75** *via* a one-pot bromide substitution and transesterification. Intermediate **4.75** was subsequently oxidised to give the desired product **4.71** (Scheme 4.23b).



Scheme 4.23 a) Attempted *m*CPBA epoxidation of farnesyl acetate **4.73**; b) Synthesis of **4.71** from farnesyl acetate **4.73**.

With both substrate **4.71** and **4.72** in hand, the CM reaction between **4.71** and **4.72**, mimicking the post-metathesis isomerisation in the ReXM system, was carried out under the same ReXM conditions with higher catalyst loading (Scheme 4.24).



Scheme 4.24 CM reaction between **4.71** and **4.72** mimicking the post-metathesis isomerisation event in ReXM reactions.

The incorporation of *Z*-enal moiety leads to the formation of *Z,E*- and *Z,Z*-isomers. Meanwhile, the isomerisation of the internal olefin leads to the formation of *E,Z*- and *Z,Z*-isomers. As a result, the ratio

$$Z,E + Z,Z : E,E + E,Z$$

represents the level of *Z*-enal incorporation. Similarly, the ratio

$$E,Z + Z,Z : E,E + Z,E$$

represents the level of internal olefin isomerisation.

The *E/Z*-enal ratio (*i.e.* the ratio $E,E + E,Z : Z,E + Z,Z$) can be obtained by comparing the integration of the resonance at δ9.98 (*E*-enal) and 9.89 (*Z*-enal). Due to the overlapping peaks, the C7-methyl resonances was not suitable for measurement of olefin isomerisation. Instead, the resonance of partially overlapping C11-methyl

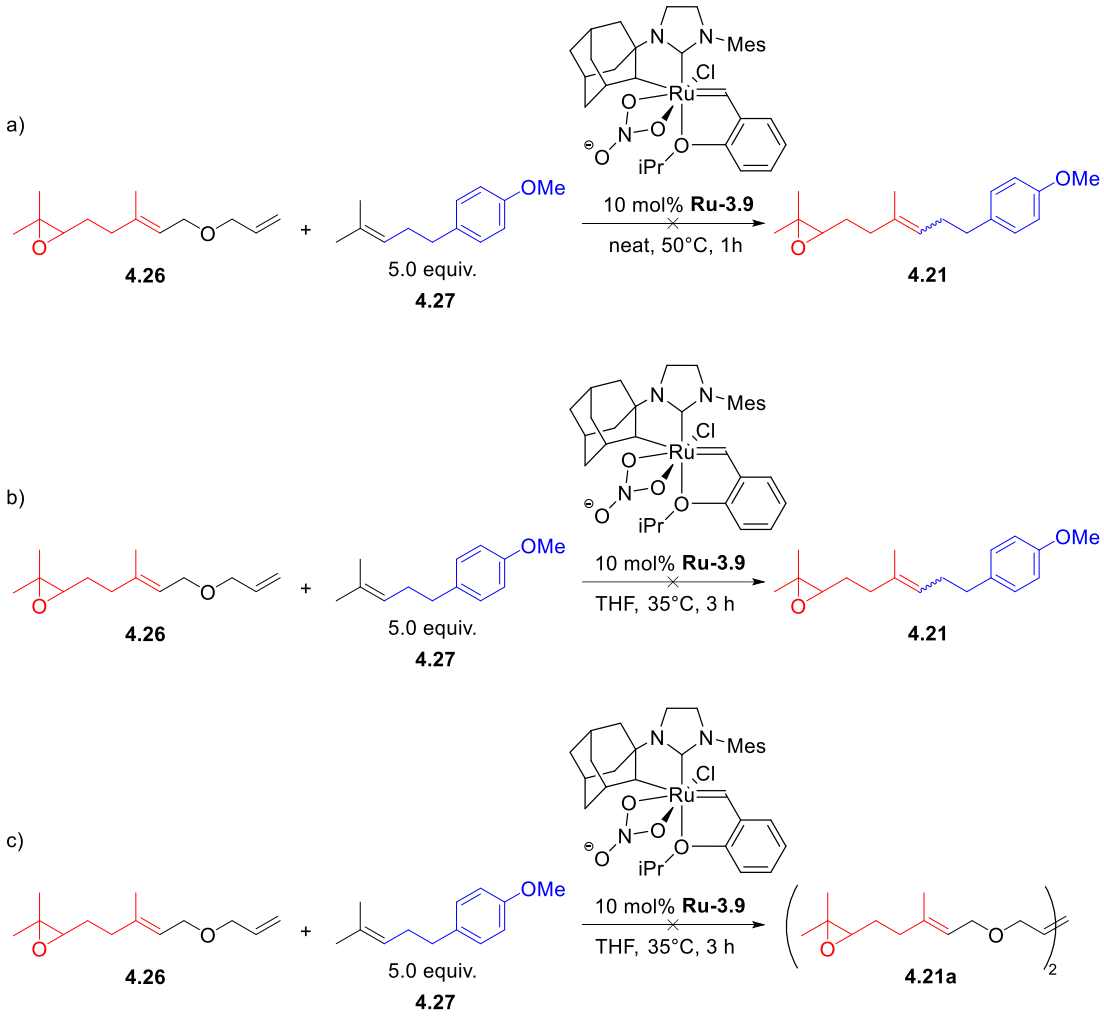
groups at δ1.32 (*Z*-olefin)/1.31 (*E*-olefin) and δ1.28 (*Z*-olefin)/1.27 (*E*-olefin) was resolved using the global spectral deconvolution algorithm integrated in Mestrenova software (see Appendix II).

A high level of *Z*-enal incorporation (43 out of 100) in one hour indicates the alkylidene exchange of trisubstituted olefin **4.71** is facile. More importantly, the initiation of trisubstituted olefin **4.71** and **4.72** must also be facile, which is somewhat counterintuitive as trisubstituted olefins are often considered unreactive towards initiation.[65]

This reaction also provides an opportunity to probe the intrinsic, kinetic *E/Z*-selectivity of ReXM as the *Z*-to-*E* isomerisation is negligible due to the low concentration of *Z*-olefin. Only 8.7% of trisubstituted olefin **4.71** isomerised to the *Z*-isomer in one hour, which corresponds to a kinetic *E/Z*-selectivity of *E:Z*= 83:17. This is more *E*-selective compared to the observed *E/Z*-selectivity in ReXM reactions, which is typically around *E:Z* = 70:30. This discrepancy of *E/Z*-selectivity strongly suggests the post-metathesis isomerisation is operating in our ReXM systems.

Knowing that post-metathesis isomerisation is the limiting factor of *E/Z*-selectivity, attention was turned to employing the *Z*-selective/stereoretentive catalysts in ReXM reactions.

The commercially available Grubbs *Z*-selective catalyst **Ru-3.9** was first tested under the standard ReXM conditions (Scheme 4.25a). However, no reaction occurred as indicated by the crude ^{1}H NMR. Using the original protocol[130] for the *Z*-selective CM reaction still gave no conversion (Scheme 4.25b).



Scheme 4.25 a) Attempted ReXM reaction between **4.26** and **4.27** with *Z*-selective catalyst **Ru-3.9** under standard ReXM conditions; b) Attempted ReXM reaction between **4.26** and **4.27** with *Z*-selective catalyst **Ru-3.9** using the original CM conditions; c) Undetected dimerisation of **4.26** in the ReXM reaction between **4.26** and **4.27**.

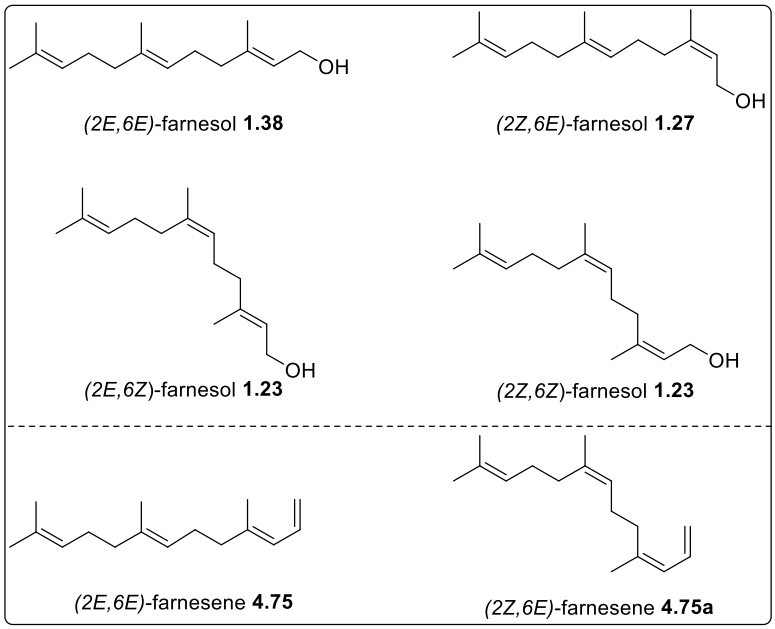
It was reasoned that the Grubbs *Z*-selective catalyst **Ru-3.9** is not active enough to catalyse the ring-closure between a terminal olefin and a trisubstituted olefin. The homodimerisation of **4.26** was neither observed (Scheme 4.25c), probably due to the low activity of **Ru-3.9** towards olefins with allylic substituents.[130] The ReXM reaction with thiocatecholate catalysts (*e.g.* **Ru-3.14 – Ru-3.17**) were not attempted as trisubstituted olefins without allylic heteroatoms cannot be obtained in useful amount.[98]

Overall, it has been established that the post-metathesis isomerisation of terpenoid, trisubstituted olefins prevents the substrate control over the *E/Z*-selectivity in ReXM systems. Thus, the development of a suitable stereoselective catalyst is left to be the only solution to the *E/Z*-selectivity conundrum in CM reactions targeting at all-alkyl trisubstituted olefins.

4.7 Attempts at separating *E*- and *Z*-products of ReXM reactions

As all the attempts at improving stereoselectivity in the ReXM systems failed, attention was then directed to the separation of *E*- and *Z*-isomers. Conventional flash chromatography and HPLC method were unable to separate geometric isomers of **4.21**.

Silver nitrate was widely used as a chromatographic support in the separation of various organic molecules including cyclic and acyclic terpenes.[173] Linear sesquiterpenes, including all four isomers of farnesol and (2*Z*,6*Z*)- and (2*Z*,6*E*)-farnesene, can be effectively partitioned (Scheme 4.26).

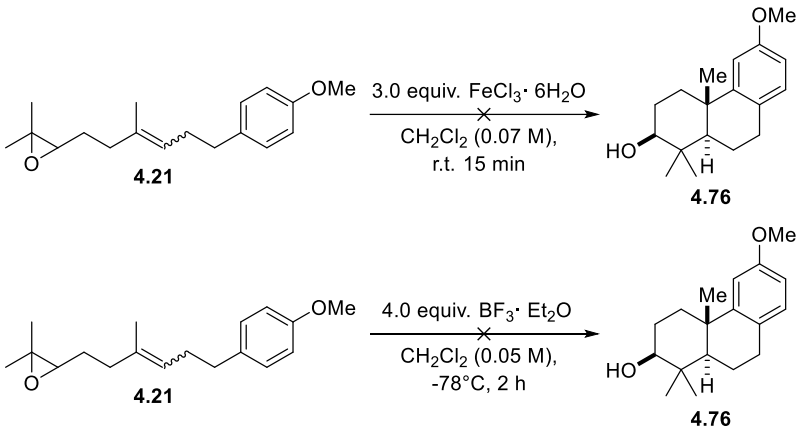


Scheme 4.26 Selection of sesquiterpenes separated *via* silver nitrate impregnated chromatography.

As silver nitrate impregnated TLC indicated partial separation of *E*- and *Z*-isomer of **4.21**, the separation of ReXM product **4.21** was attempted using flash chromatography

with silver nitrate impregnated silica gel (SNIS). Unfortunately, only partial separation was achieved *via* SNIS-flash chromatography.

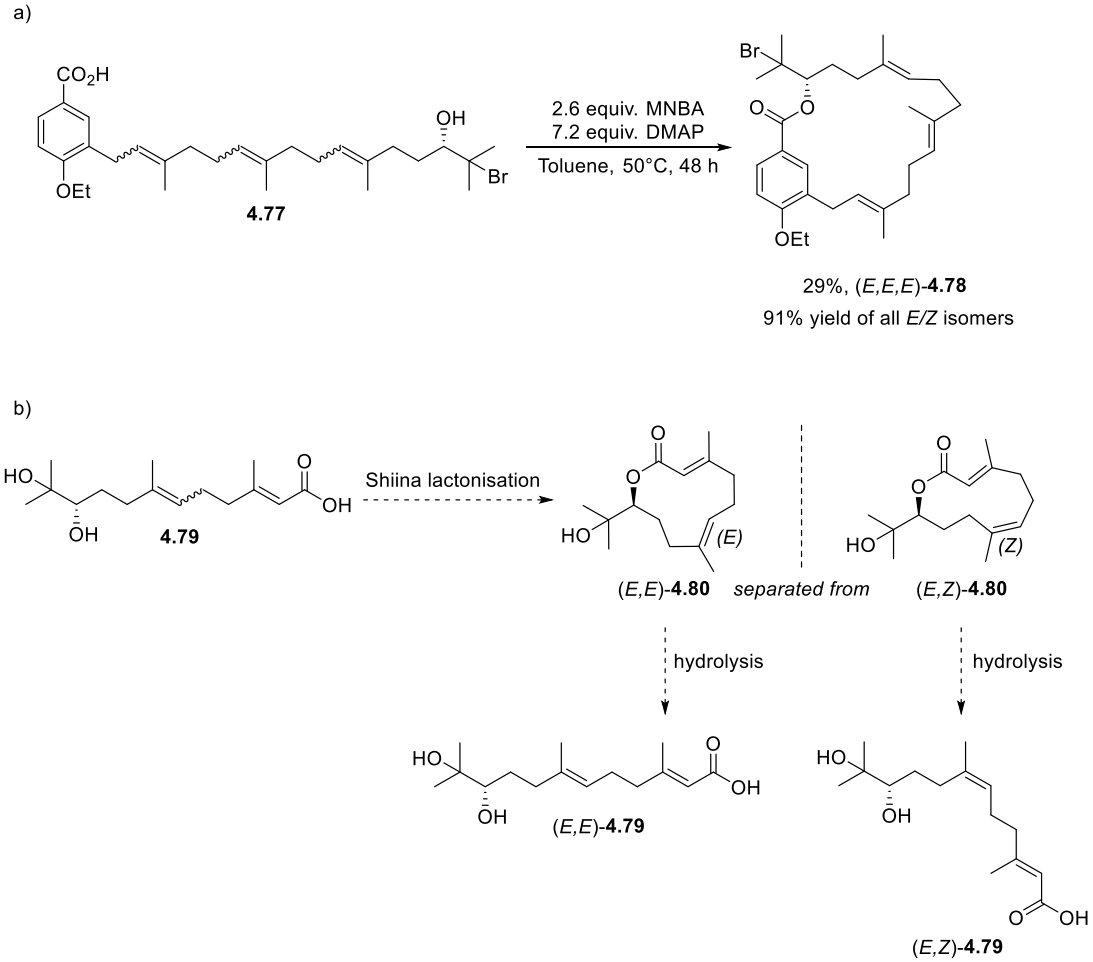
While physical separation of *E*- and *Z*-isomer of **4.21** was unsuccessful, attention was turned to the kinetic resolution/product separation of **4.21** *via* cyclisation reaction. Cationic polyene cyclisation of the *E/Z*-mixture of **4.21** provide the opportunity to explore not only the cyclisation chemistry of *Z*-olefin but also the separation of *E*- and *Z*-**4.21** *via* kinetic resolution. However, treating the mixture of *E*- and *Z*-**4.21** with boron trifluoride etherate or iron(III) chloride hexahydrate resulted in a complex mixture (Scheme 4.27).



Scheme 4.27 Unsuccessful cyclisations of **4.21** using boron trifluoride etherate or iron(III) chloride hexahydrate as Lewis acid promoters.

As the cyclisation of geometrically pure *E*-**4.21**[14] and its derivatives[154,155,174] has been demonstrated, it was reasoned that the *Z*-isomer of **4.21** complicated the polyene cyclisation.

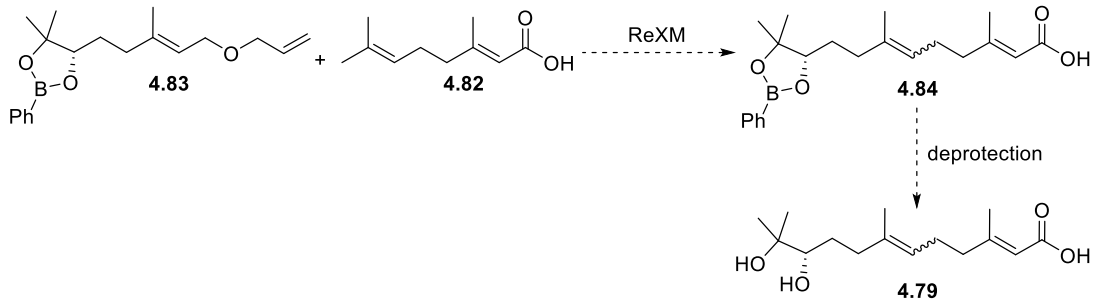
Inspired by the successful macrolactonisation of a geometric mixture of terpene precursor **4.77** in the synthetic study towards bromophycolide[175] (Scheme 4.28a), it was envisaged that the same strategy may be applied to the separation of *E*- and *Z*-isomers in iterative ReXM sequence (Scheme 4.28b).[175]



Scheme 4.28 a) Shiina lactonisation of polyene **4.77** resulted in the macrocyclic (*E,E,E*)-**4.78** that can be separated from other geometric isomers; b) Proposed separation of *E*- and *Z*-trisubstituted olefin **4.79** *via* the Shiina lactonisation-separation-hydrolysis sequence.

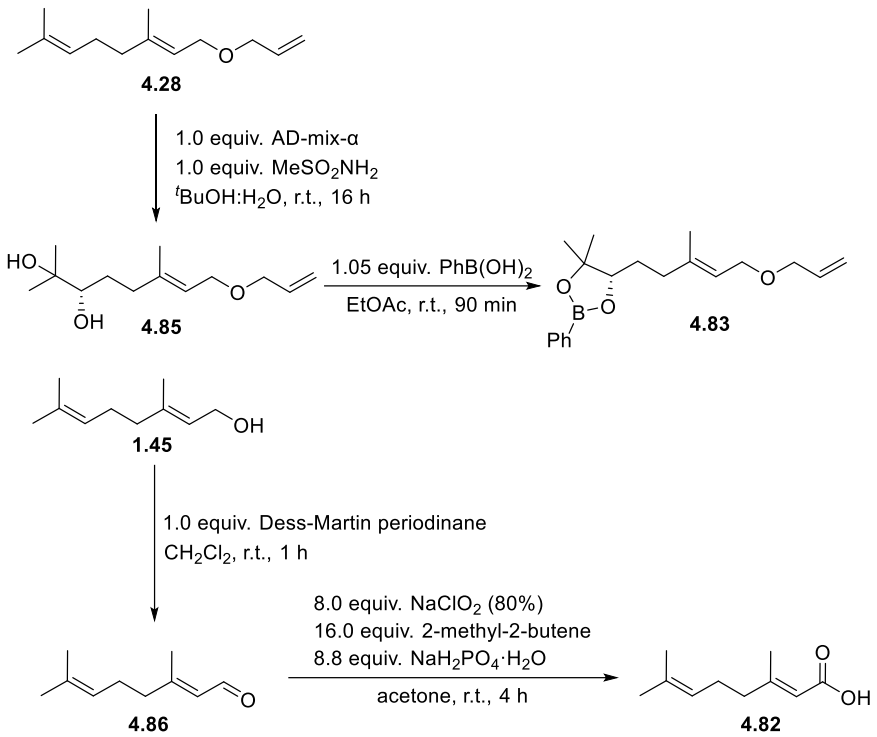
The Shiina lactonisation of *E*- and *Z*-**4.79** would produce corresponding cyclic product (*E,E*)- and (*E,Z*)-**4.80**, which are potentially separable. Hydrolysis of geometrically pure **4.80** isomers would give geometrically pure isomers of **4.79**.

The *E/Z*-mixture of **4.79** was proposed to be synthesised *via* the ReXM reaction between protected diol **4.82** and geranic acid **4.83**, followed by deprotection (Scheme 4.29).



Scheme 4.29 Proposed synthesis of **4.79** *via* ReXM between protected diol **4.82** and geranic acid **4.83**.

The protected diol **4.83** was prepared from the geranyl allyl ether **4.28** *via* Sharpless dihydroxylation and protection with phenylboronic acid. The partner olefin geranic acid **4.82** was prepared from geraniol **1.45** *via* sequential Dess-Martin oxidation and Pinnick oxidation (Scheme 4.30).



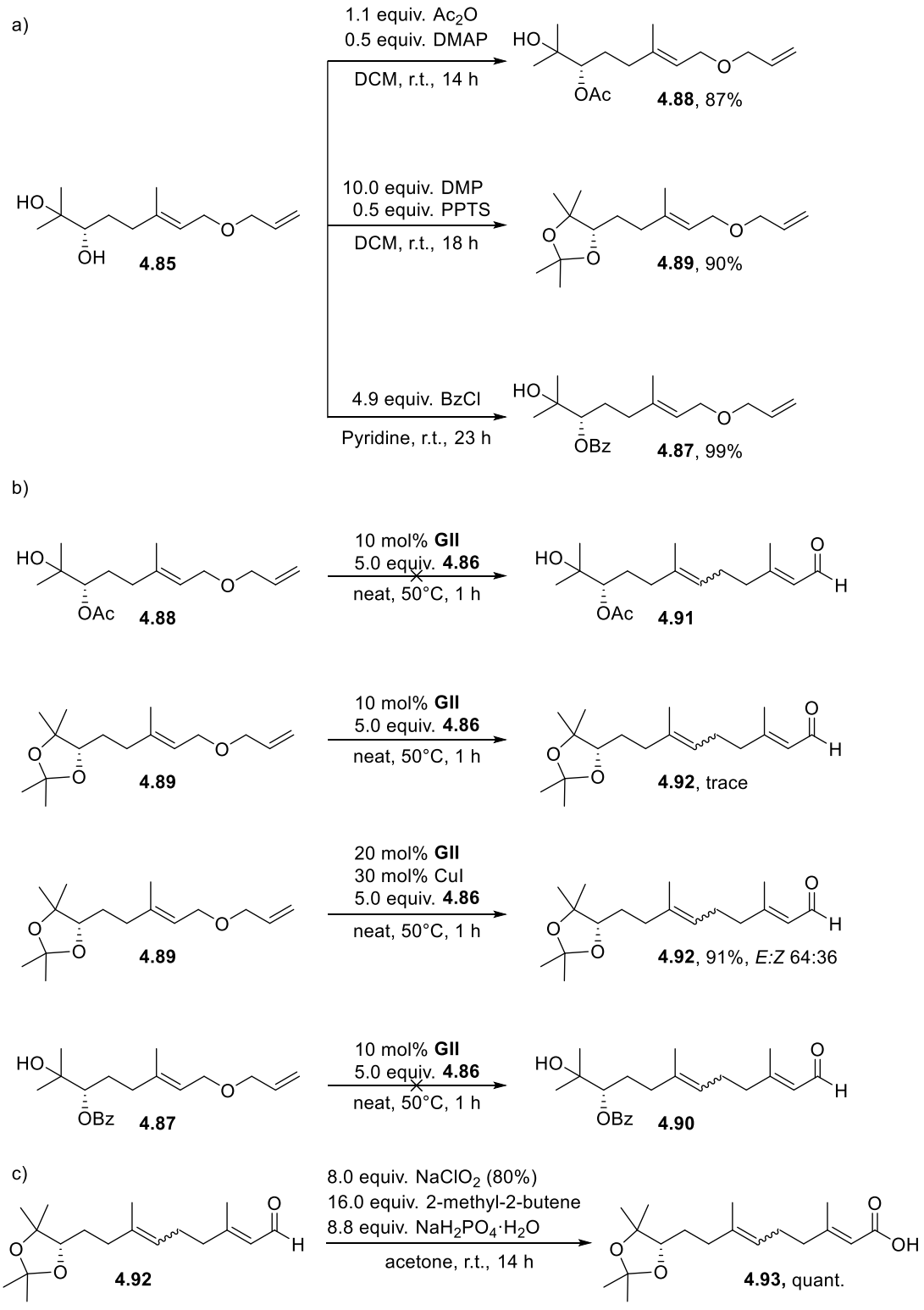
Scheme 4.30 Preparation of protected diol **4.83** and geranic acid **4.82** from geranyl allyl ether **4.28** and geraniol **1.45**.

Unfortunately, the ReXM reaction between **4.82** and **4.83** under standard conditions produced a complex mixture. The mixture was subjected to deprotection (pinacol in DCM) with hope to identify and separate potential products. However, this led to the decomposition of diol moiety as indicated by the disappearance of the characteristic resonance at δ4.08 (boronate)/δ3.36 (diol) on proton NMR.

As geranial **4.86** is known as a competent ReXM partner, it is proposed that the ReXM between protected diols and geranial **4.86,** followed by Pinnick oxidation would yield the desired precursors for lactonisation. Protected diols **4.87**-**4.89** was then synthesised and tested in the ReXM reaction with geranial **4.86** (Scheme 4.31a and 4.31b)

ReXM of geranial **4.86** with benzoate **4.87** and acetate **4.88** resulted in complex mixtures. However, the ReXM reaction with acetonide **4.88** under standard conditions yielded trace of desired product **4.92**. To improve the yield of **4.92**, higher catalyst loading (20 mol%) and phosphine scavenger copper(I) iodide was employed and **4.92** was obtained in 91% yield with a *E/Z* ratio of 64:36.

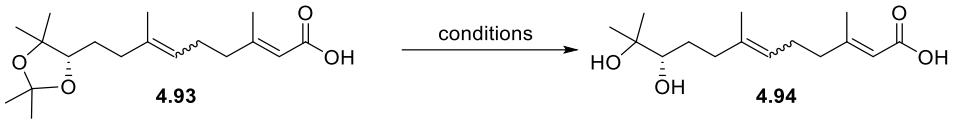
Despite multiple attempts were made, the Pinnick oxidation of **4.92** resulted desired **4.93** contaminated with unknown impurities. It was realised that the ruthenium residue from the previous ReXM may complicate the oxidation step. As a result, the ReXM product **4.92** was further purified by passing through a pad of silica. Gratifyingly, oxidation of the purified **4.92** afforded carboxylic acid **4.93** in quantitative yield (Scheme 4.31c).



Scheme 4.31 a) Synthesis of protected diols **4.89-4.92** from diol **4.85**; b) ReXM reactions between protected diol **4.89-4.92** and geranial **4.86**; c) Synthesis of carboxylic acid **4.93** *via* Pinnick oxidation of purified **4.92**

With carboxylic acid **4.93** in hand, the deprotection of the acetal moiety was then investigated. However, deprotection of the acetal moiety in **4.93** was non-trivial (Table 4.5).

Table 4.5 Attempted acetal deprotection of **4.93**



Entry	Conditions	Reaction outcome[a]
1	1 equiv. *p*-toluenesulfonic acid, 1:1 Et_2O/H_2O (0.5 M), 4 h	Complete decomposition
2	1 equiv. PPTS, 1:1 Et_2O/H_2O (0.5 M), overnight	No reaction
3	1 equiv. PPTS, 1:1 THF/H_2O (0.5 M), 48 h	No reaction
4	1 equiv. PPTS, MeOH (0.1 M), 16 h	Formation of methyl ester of **4.93**, no deprotection observed,
5	Water (0.33 M), reflux, overnight	Trace of **4.94**, contaminated with unknown impurities

[a]Monitored by ^{1}H NMR. No product was isolated in all cases.

Attempted acetal hydrolysis catalysed by PTSA led to complete decomposition as indicated by the disappearance of all ^{1}H NMR resonances in alkene region (entry 1, Table 4.5). The weakly acidic PPTS was not able to catalyse the hydrolysis in Et_2O/water or THF/water solvent system (entry 2 and 3, Table 4.5). Switching the solvent to methanol produced the corresponding methyl ester of **4.93** with no sign of deprotection based on ^{1}H NMR (entry 4, Table 4.5). Only trace of **4.94** was observed on ^{1}H NMR after 16 h reaction in refluxing water, together with unknown impurities

that potentially derived from acid-catalysed decomposition of **4.93**. It is proposed that a suitable Lewis acid may promote the acetal deprotection without triggering acid-catalysed decomposition of **4.93**.

Due to the impact of COVID-19 epidemic, the investigation on the deprotection of **4.93** and subsequent separation of *E*- and *Z*-product of ReXM reactions *via* lactonisation was interrupted.

4.8 Conclusion and future work

A concise synthesis of linear arene-capped monoterpenes, which are polyene cyclisation precursors to podocarpane-type terpenoids, using ReXM reactions between trisubstituted olefins was developed.

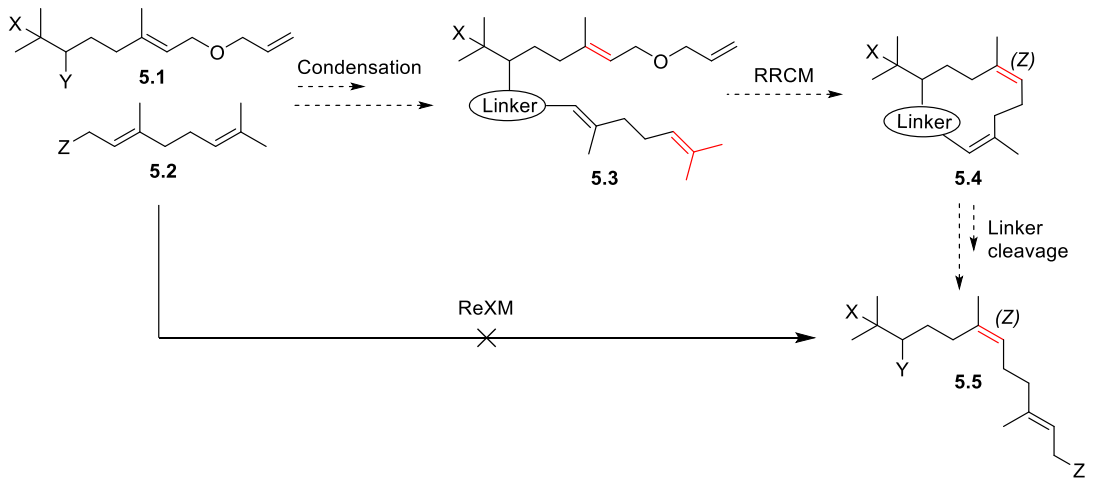
Various attempts were made to alter the *E/Z*-selectivity in ReXM reactions. The viability of substrate-control of *E/Z*-selectivity was explored and the post-metathesis isomerisation, which is surprisingly facile for trisubstituted olefins, was identified as the limiting factor for substrate-controlled, geometrically selective metathesis processes involving trisubstituted olefins. Commercially available Grubbs *Z*-selective catalyst was also tested in these ReXM reactions, and it was evident that a more active stereoselective catalyst is required for the challenging metathesis between trisubstituted olefins.

Finally, attempts were made to separate geometric isomers from the mixture. Silver nitrate impregnated chromatography methods were unsuccessful in the separation of products from ReXM reactions. The cationic polyene cyclisation reactions also failed to kinetically differentiate *E*- and *Z*-polyenes, potentially due to the complication from *Z*-polyenes. The lactonisation strategy, which was not fully investigated, is promising and worth exploring in the future.

Chapter 5 Relay ring-closing metathesis (RRCM) strategy in the synthesis of terpenoid, trisubstituted olefins

5.1 Proposed relay ring-closing metathesis for the stereoselective construction of terpenoid, trisubstituted olefins

Whereas the stereoselective formation of sterically-congested olefins (*i.e.* trisubstituted olefins) *via* ReXM protocol remained challenging (see Chapter 4), abundant examples of stereoselective RCM prompted us to investigate the RCM reactions as an alternative method. To overcome the slow initiation on trisubstituted olefins, an RRCM approach was proposed as described in Scheme 5.1.



Scheme 5.1. Proposed RRCM as an alternative approach to ReXM in the construction of terpenoid, trisubstituted olefins.

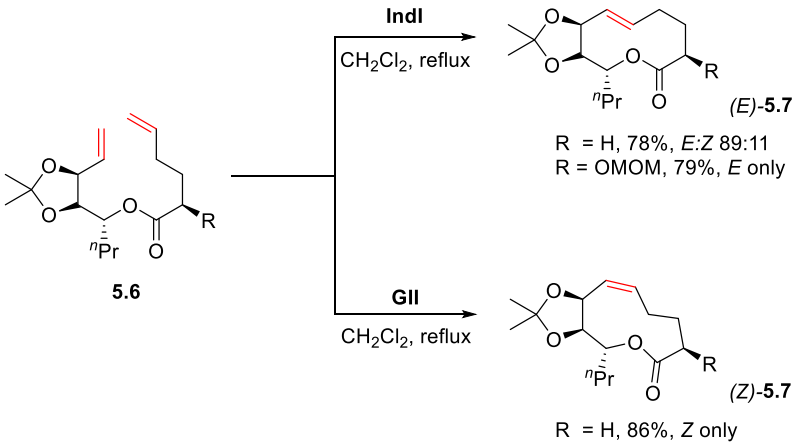
The RRCM precursor **5.3** was proposed to be prepared *via* condensation between functionalised diene **5.1** and geranyl derivatives **5.2**. After RRCM and linker cleavage, the acyclic diene **5.5** could be obtained as a single diastereomer, provided the ring-closure is highly stereoselective.

A survey of literature was then carried out to assess the validity of the proposed stereoselective RRCM approach. Relevant examples of stereoselective RCM/RRCM reactions and RCM reactions involving the combination of a trisubstituted olefin and a 1,1-disubstituted olefin are summarised in the following section.

5.2 Literature precedent for stereoselective (relay) ring-closing metathesis

There are ample examples describing highly *E/Z*-selective RCM processes to form a single diastereomer. The stereoselectivity could arise from stereoselective catalysts (see Chapter 3), from kinetically controlled RCM (*vide infra*) or simply from the thermodynamic bias towards one stereoisomer (*e.g.,* RCM reactions targeting at 5-7 membered rings give exclusively *Z*-products). Medium and macrocyclic rings can also be accessed *via* RCM with high *E/Z*-selectivity without the need of stereoselective catalysts. Selected examples of *E/Z*-selective formation of medium and macrocyclic rings will be discussed in this section to demonstrate the viability of accessing cyclic compounds with desired double bond geometry *via* RCM reactions.

Before the emergence of the more active Grubbs 2nd generation catalyst (**GII**), internal olefins were considered unreactive towards initiation by first generation ruthenium-based catalysts. Thus, the less active, first-generation catalysts enabled the kinetic control over RCM between two terminal olefins by preventing the backbiting of the kinetic product, which is a disubstituted olefin. Fürstner *et al.* demonstrated such kinetic control over product geometry in their synthetic study of herbarumin I (Scheme 5.2)[176]

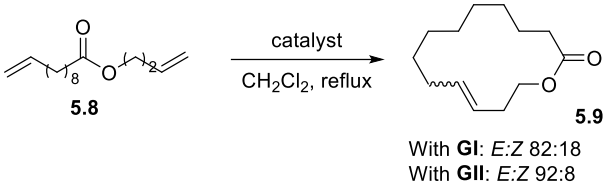


Scheme 5.2. Kinetic control over product geometry of **5.7** by employing less reactive **IndI** catalyst.

Computational study revealed that the undesired (*Z*)-**5.7** is ca. 3.5 kcal mol^{-1} more stable than the corresponding *E*-isomer. As expected, treating the diene **5.6** with a more reactive **GII** catalyst led to the exclusive formation of undesired (*Z*)-**5.7**. However,

when the less active **IndI** catalyst was used, the *E*-isomer was obtained in high stereoselectivity (*E:Z* 89:11). More importantly, this *E/Z* ratio does not change with reaction time, validating the kinetic control of catalyst over product geometry. Switching to the MOM-protected ether derivative of **5.6** led to the perfect *E*-selectivity under the same conditions.

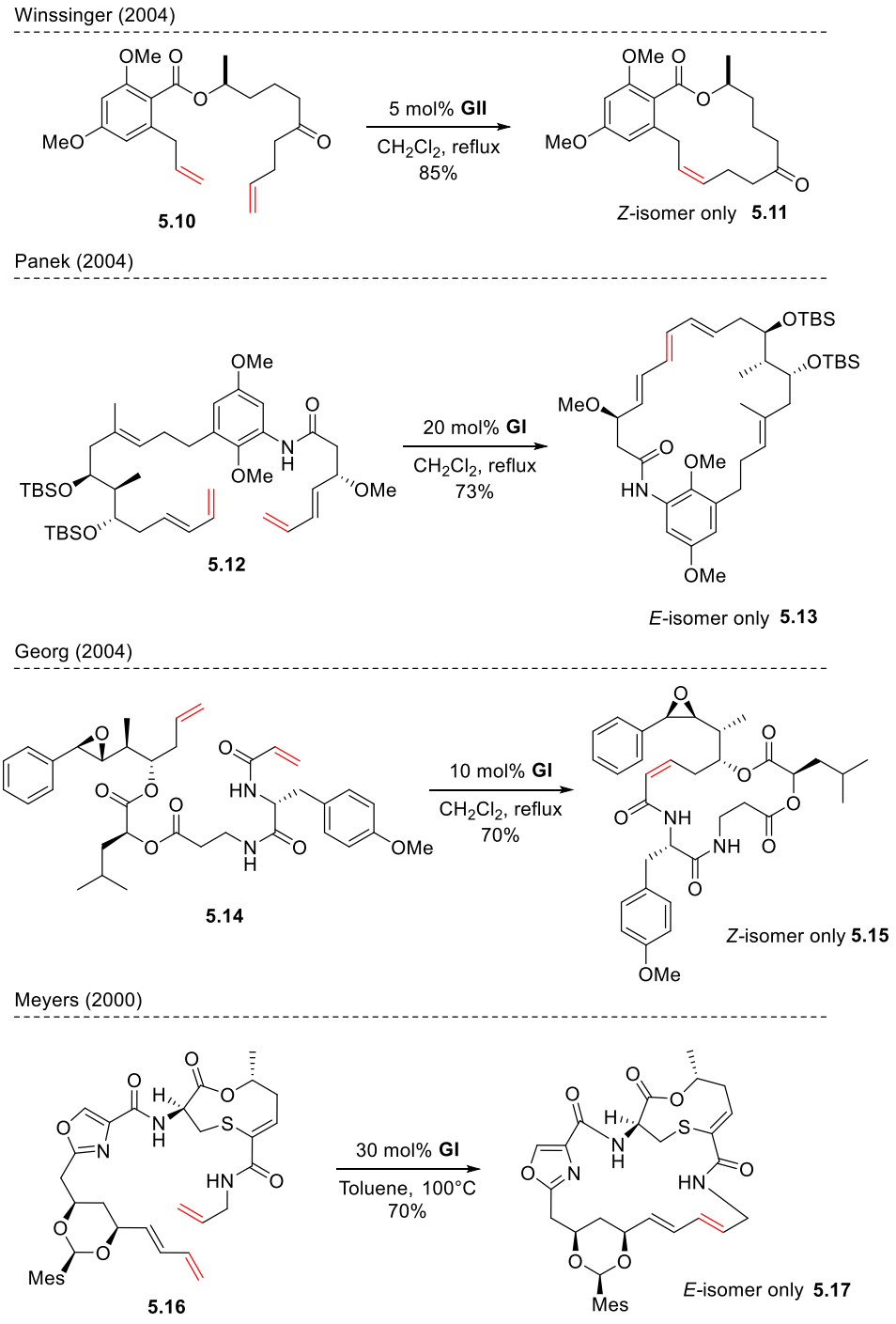
Similar effect was also observed by Grubbs *et al.* in their study of stereoselectivity in macrocyclic RCM reactions (Scheme 5.3).[177]



Scheme 5.3. Impact of catalyst on the stereoselectivity in macrocyclic RCM of diene **5.8**.

Treating diene **5.8** with less active **GI** catalyst afforded lactone **5.9** with a *E/Z* ratio of 82:18. The more active **GII** catalyst is more *E*-selective and yielded **5.9** with a *E/Z* ratio of 92:8. The high *E*-selectivity of **GII** catalysed RCM reaction was attributed to the post-metathesis isomerisation of *Z*-isomer towards the thermodynamically more stable *E*-isomer. Treating the *E/Z* mixture (*E:Z* 82:18) with **GII** led to the a *E:Z* 92:8 mixture, which has the same *E/Z*-ratio as the mixture obtained *via* the direct RCM of **5.8** with **GII**. This provided convincing evidence for the post-metathesis isomerisation.

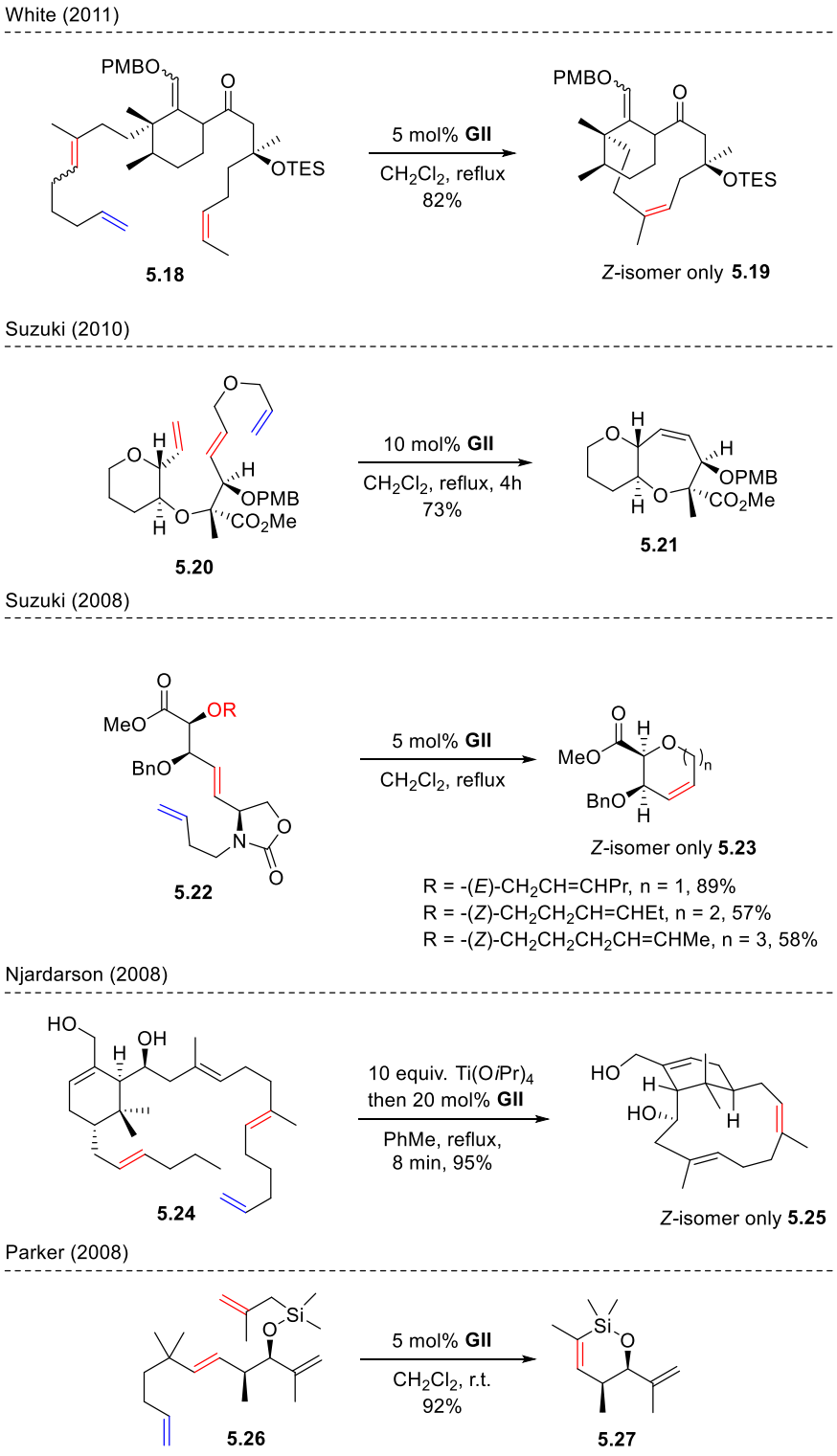
The majority of RCM reactions, when catalyst lifetime and activity permits, are considered operating under thermodynamic control. Although *E/Z*-mixtures were often obtained in the RCM reactions targeting at medium or macrocyclic compounds, it is possible to achieve reasonable stereoselectivity *via* optimisation of solvent choice,[178] temperature[179] and substrate substituents.[180–182] Selected examples of stereoselective formation of medium and macrocyclic rings *via* RCM reactions without using stereoselective catalysts were illustrated below in Scheme 5.4.[183–186] More examples can be found in the recent reviews regarding applications of RCM reactions in drug discovery and total synthesis.[187,188]



Scheme 5.4 Selected examples of stereoselective RCM for the formation of medium and macrocyclic rings.

Stereoselective RRCM reactions had also been reported and selected examples are summarised in Scheme 5.5.[189–193] A notable example is the preparation of *Z*-iodo olefins *via* RRCM reported by Parker *et al.*.[193] The *Z*-geometry of the trisubstituted olefin was established *via* a RRCM of acyclic silyl ether **5.26**, which afforded the six-membered cyclic silyl ether **5.27**. The ring cleavage of silyl ether **5.27** and subsequent

iodination furnished the desired *Z*-iodo olefin (not shown). This method demonstrated the possibility of a stereoselective RRCM- ring opening/functionalisation sequence for the formation of *Z*-trisubstituted olefin.



Scheme 5.5 Selected examples of stereoselective RRCM reactions.

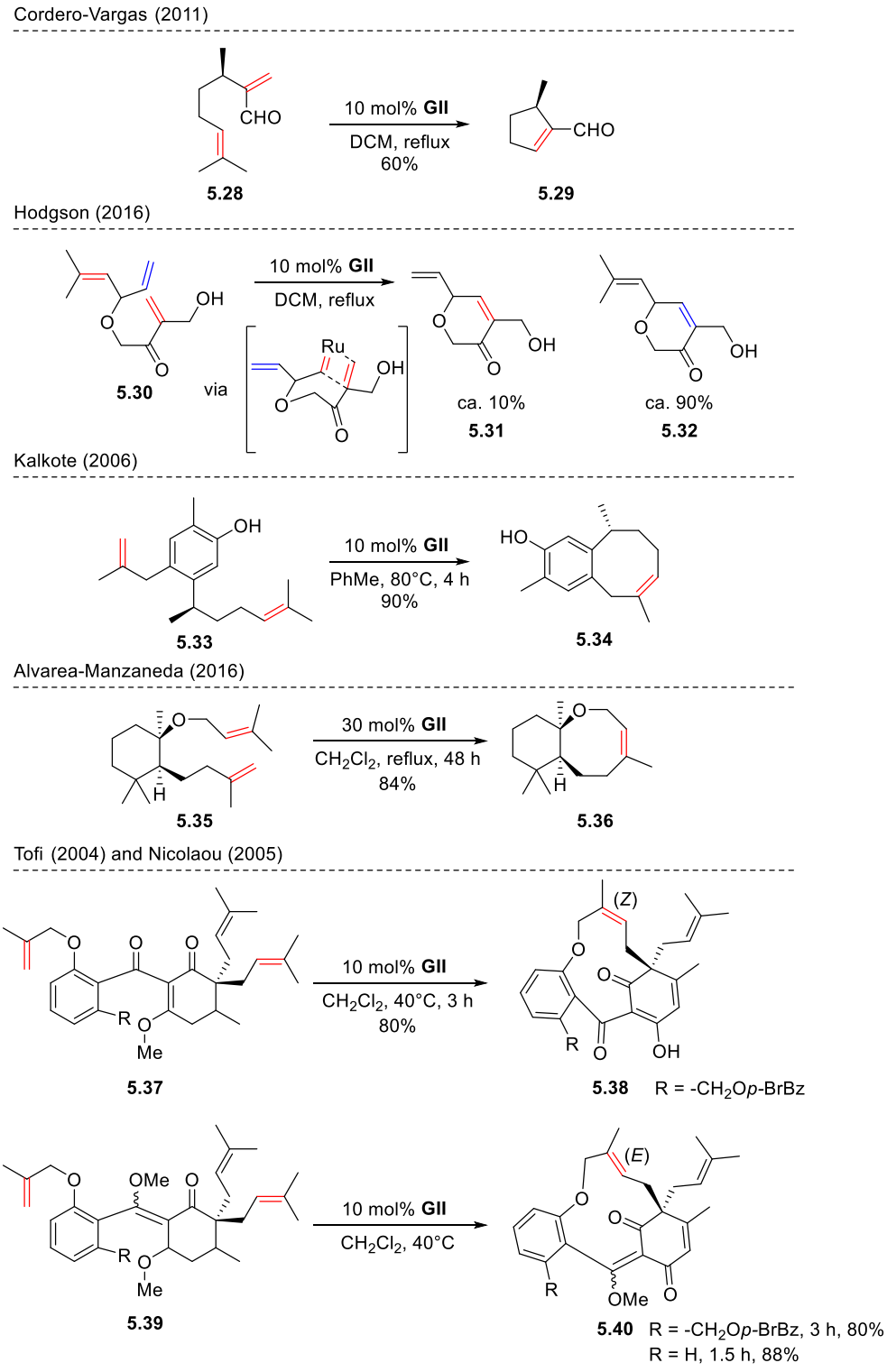
5.3 Literature precedent for the formation of cyclic trisubstituted olefin *via* ring-closing metathesis between a 1,1-disubstituted olefin and a trisubstituted olefin

Despite the broad application of RCM reactions in organic synthesis, the RCM reactions between two sterically congested olefins remains rare. A thorough survey of literature revealed a handful of examples of RCM reactions between 1,1-disubstituted olefins and trisubstituted olefins (Scheme 5.6).[194–199]

Various cyclic olefins of different ring sizes, including five-, six- and eight-membered rings, can be produced in good yields. A particularly noteworthy example is the Nicolaou's synthesis of coleophomone B, C and D, where the RCM reaction of **5.37** successfully forged the 11-membered ring with *Z*-trisubstituted olefin **5.38** (Scheme 5.6, bottom). The corresponding enolate **5.39**, however, produced *E*-olefin **5.40** in the RCM reaction.

It is also noteworthy that the RCM reaction of acrylate **5.30** reported by Hodgson *et al.*, provided strong evidence for the catalyst initiation onto the trisubstituted olefin site in the presence of a competitive terminal olefin site (Scheme 5.6).[195] This finding is mechanistically intriguing as trisubstituted olefins are generally considered inert towards catalyst initiation whilst catalyst initiation onto terminal olefins are often facile.

Overall, these examples demonstrated the viability of preparing trisubstituted olefins *via* RCM reactions between a 1,1-disubstituted olefin and a trisubstituted olefin.

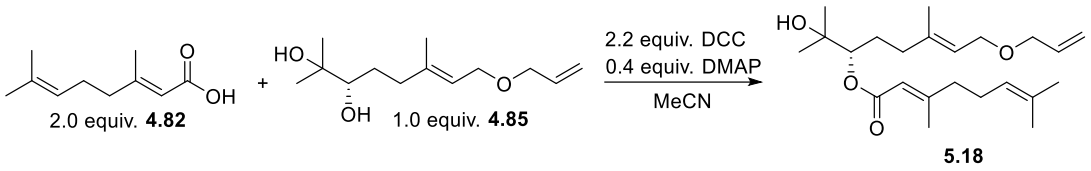


Scheme 5.6 Selected examples of RCM reactions between a 1,1-disubstituted olefin and a trisubstituted olefin.

5.4 Syntheses of RRCM precursors and attempted RRCM reactions

5.4.1 RRCM precursor with an ester linker

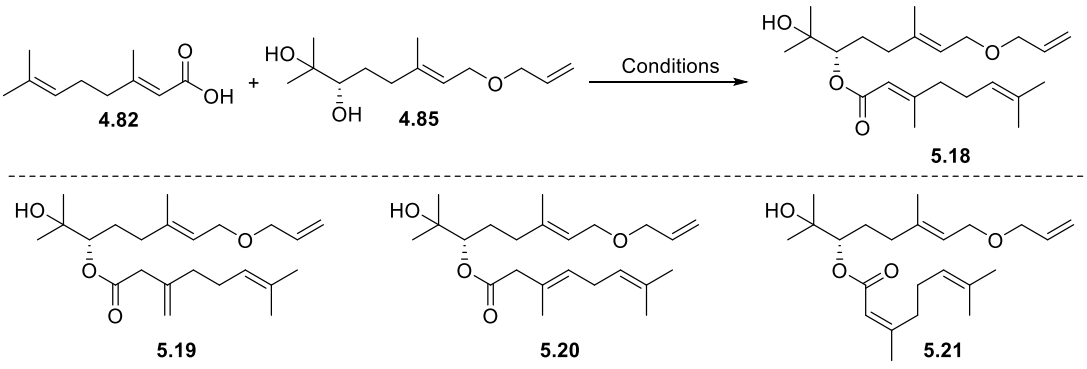
The RRCM precursor with an ester linker was initially proposed to be synthesised *via* the Steglich esterification between geranic acid **4.82** and diol **4.85** using DCC as the coupling reagent (Scheme 5.7).



Scheme 5.7 Preparation of RRCM precursor with an ester linker.

Despite significant amount of product **5.18** observed by proton NMR, the urea side product (not shown) was found inseparable with **5.18**, which is a common disadvantage of the Steglich esterification.[200] Thus, esterification using *N*-ethyl-*N*'-(3-dimethylaminopropyl)carbodiimide (EDC) was investigated as both EDC and its urea side product are water soluble and can be removed during the aqueous work-up. (Table 5.1)

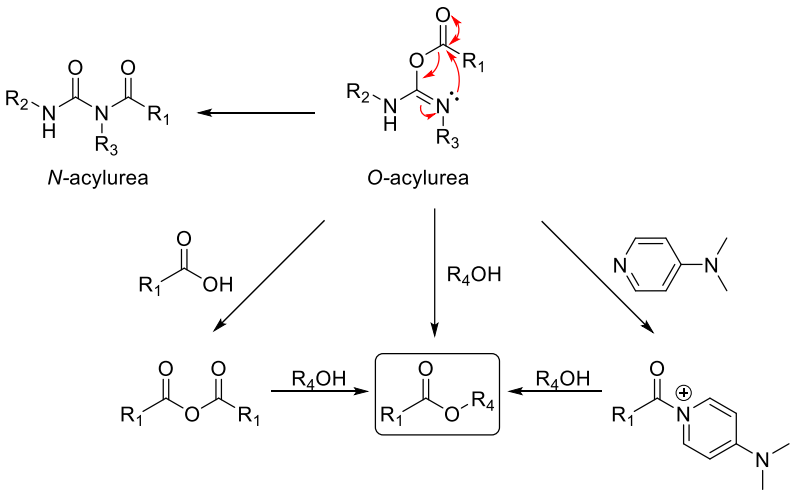
Table 5.1 Optimisation of EDC-mediated esterification between **4.82** and **4.85**



Entry	Conditions [a]	Yield of **5.18**[b]	Comments[c]
1	1.0 equiv. **4.82**, 2.0 equiv. **4.85**, 2.2 equiv. EDC, 0.4 equiv. DMAP, CH_2Cl_2 (0.1 M), 24 h	0%	Product was not observed by proton NMR.
2	1.0 equiv. **4.82**, 2.0 equiv. **4.85**, 2.2 equiv. EDC, 0.4 equiv. DMAP, CH_2Cl_2 (1 M), 24 h	Trace	Product not isolated
3	1.0 equiv. **4.82**, 2.0 equiv. **4.85**, 5.0 equiv. EDC, 0.4 equiv. DMAP, 0.4 equiv. CSA, neat, 24 h	3%	As an inseparable mixture with **5.19**, **5.20** and **5.21** (1:1:8, 32% combined yield)
4	1.1 equiv. **4.82**, 1.0 equiv. **4.85**, 5.0 equiv. EDC, 0.4 equiv. DMAP, neat, 24 h	5%	As an inseparable mixture with **5.19**, **5.20** and **5.21** (ca. 1:2:4, 15% combined yield)

[a]All reactions were carried at room temperature and EDC was used as its hydrochloride salt; [b]NMR yield; [c]The product ratio between compound **5.19-5.21** was not accurately determined due to the overlapping resonances on ^{1}H NMR.

Despite prolonged reaction, little product was observed under the initial conditions (Table 5.1, entry 1 and 2). It was reasoned that additional acid is required to protonate the *O*-acylurea, which would prevent the isomerisation to the unreactive *N*-acylurea (Scheme 5.8, top).[201] The *O*-acylurea can be trapped by the alcohol/DMAP/acid to form directly the ester product, or the activated esters that can be trapped by the alcohol to form the desired ester (Scheme 5.8, bottom). Thus, camphorsulfonic acid was chosen as the acid additive based on its successful application in carbodiimide-mediated esterification.[202,203] With additional CSA and extra equivalents of EDC, trace of the desired product **5.18** was isolated as a mixture with impurities, which were later identified as **5.19** – **5.21** (Table 5.1, entry 3). The structural assignment of **5.19** – **5.21** was based on the NMR analysis of the product mixture (Figure 5.1).



Scheme 5.8 Isomerisation of *O*-acylurea to the unreactive *N*-acylurea and ester formation pathways *via* nucleophilic trapping of *O*-acylurea.

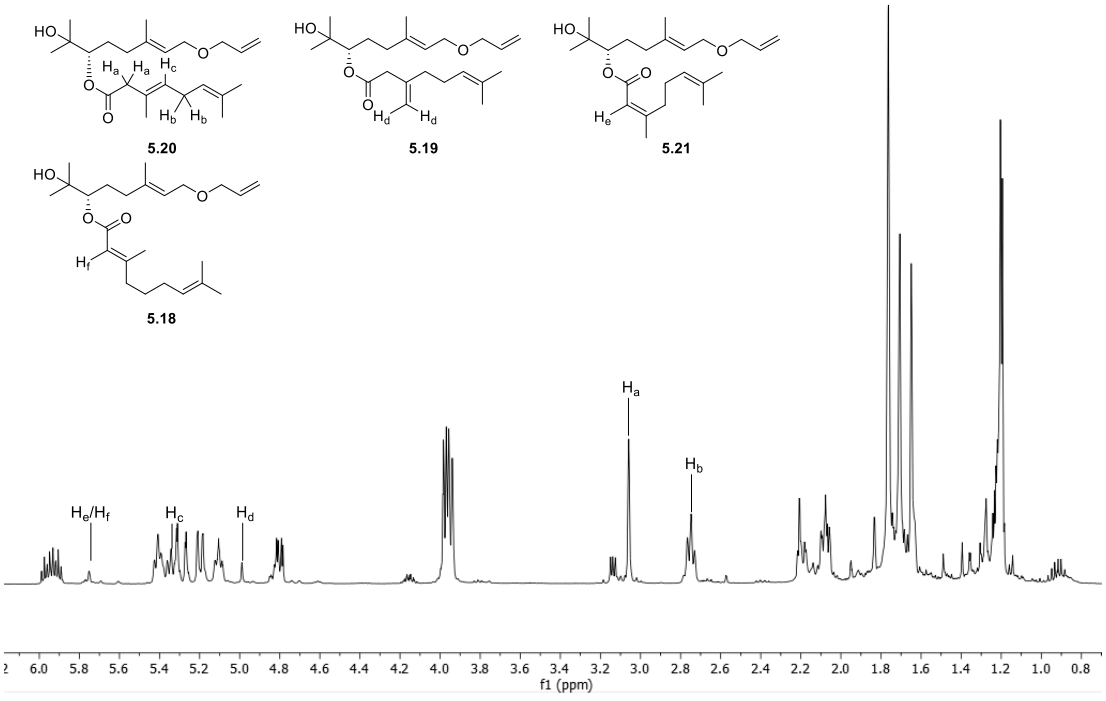
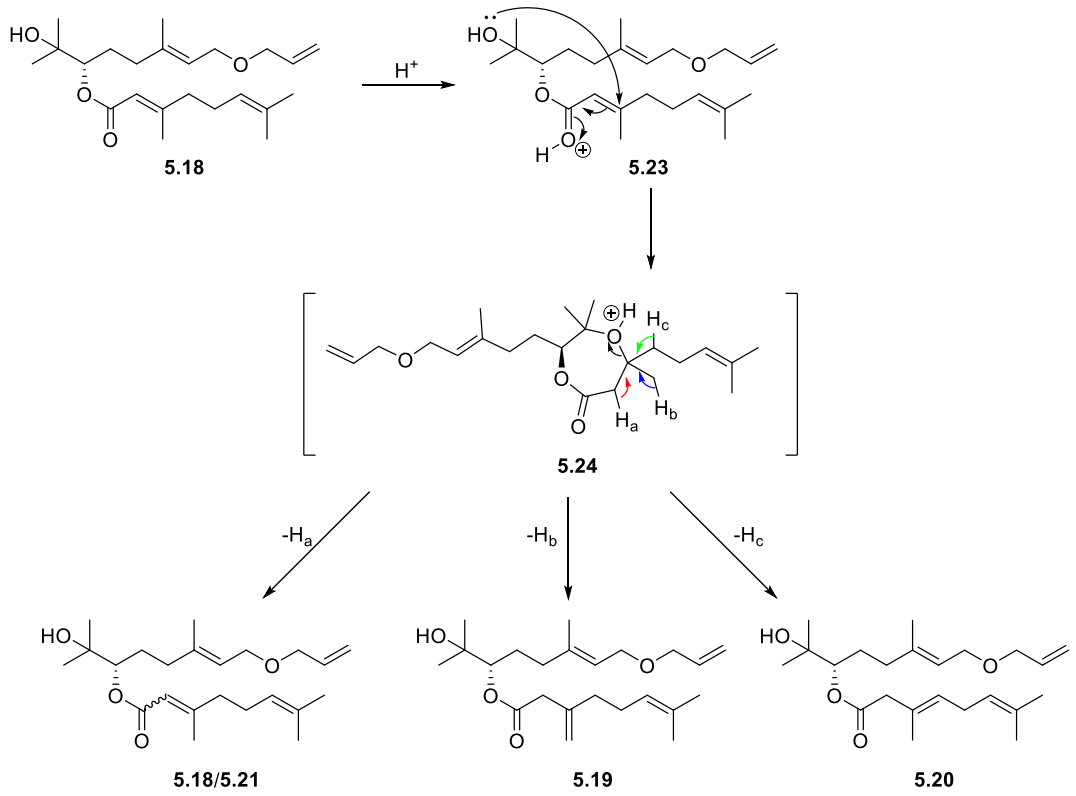


Figure 5.1 NMR assignment of the characteristic proton resonances in **5.19** – **5.21**.

The emergence of a new triplet at δ 5.34 ppm (H_c, Figure 5.1) indicated the formation of a new trisubstituted olefin. Together with the absence of the characteristic resonance of the α,β-unsaturated ester at ca. δ 6 ppm, a double bond isomerisation process was proposed. Identification of methylene protons at δ 3.06 and 2.74 ppm (H_a and H_b, Figure 5.1) by DEPT-135 experiment confirmed the hypothesis of double bond

isomerisation. The weak singlet at δ 4.99 (H_d, Figure 5.1) is characteristic for the methylene proton in 1,1-disubstituted olefins and was assigned to the other isomerised product **5.19**. The *E/Z*-isomerisation was also considered and the resonances at δ 5.74 and 5.75 ppm (H_e and H_f, Figure 5.1) were tentatively assigned to the α,β-unsaturated esters **5.18** and **5.21**. The isomerisation was proposed to proceed *via* an acid-catalysed intramolecular 1,4-addition of the tertiary alcohol to the α,β-unsaturated ester to produce intermediate **5.24**, which would undergo deprotonation pathways that give rise to isomerised product **5.19**, **5.20** and the *E/Z*-mixture of **5.18** and **5.21** (Scheme 5.9).

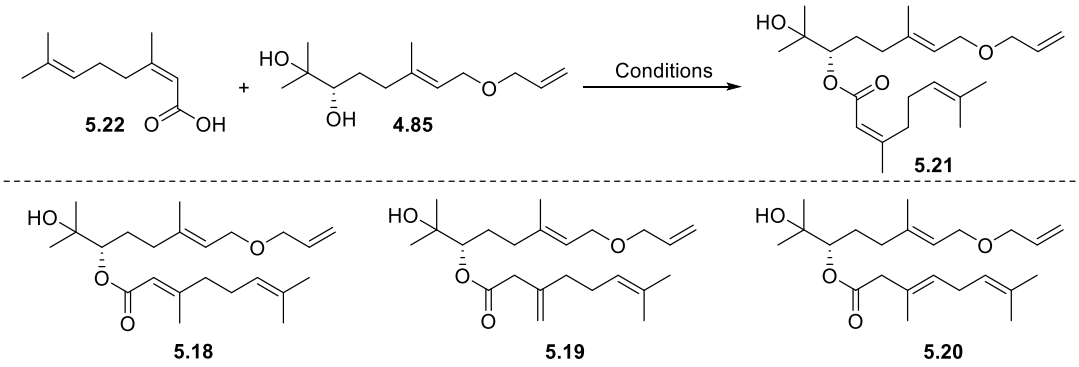


Scheme 5.9 Proposed mechanism for the acid-catalysed double bond isomerisation of ester **5.18**.

To verify the catalytic role of acid in the isomerisation process, the esterification was carried out without additional CSA (Table 5.1, entry 4). The content of ester **5.18/5.21** in the product mixture increased, indicating an acid-catalysed isomerisation process. However, the overall yield of ester products **5.18 – 5.21** reduced, which can be linked to the formation of unreactive *N*-acylurea.

The olefin isomerisation was also observed in the esterification between *Z*-acid **5.22** and diol **4.85** despite increased yield of isomerised products (Table 5.2).

Table 5.2 Optimisation of EDC-mediated esterification between **5.22** and **4.85**

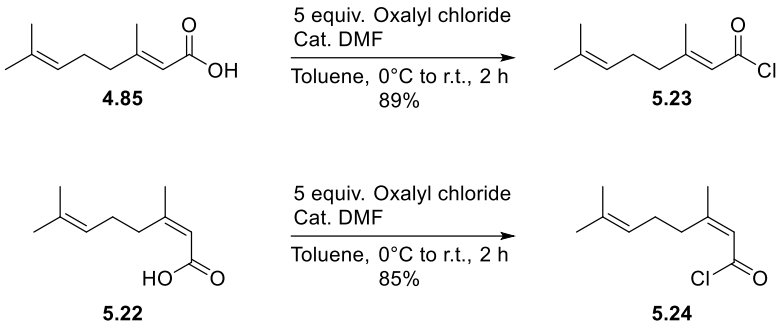


Entry	Conditions[a]	Yield of **5.21**[b]	Comments[c]
1	1.0 equiv. **5.21**, 2.0 equiv. **4.85**, 2.2 equiv. EDC, 0.4 equiv. DMAP, 0.4 equiv. CSA, neat	5%	As an inseparable mixture with **5.18**, **5.19** and **5.20** (ca. 2:3:15, 49% combined yield)
2	1.0 equiv. **5.21**, 2.0 equiv. **4.85**, 5.0 equiv. EDC, 0.4 equiv. DMAP, CH_2Cl_2 (0.1 M)	15%	As an inseparable mixture with **5.18**, **5.19** and **5.20** (ca. 1:1:2, 60% combined yield)

[a]EDC was used as its hydrochloride salt; [b]NMR yield; [c]The product ratio between compound **5.18-5.20** was not accurately determined due to the overlapping resonances in ^{1}H NMR.

Protection of the tertiary alcohol, which should prevent the intramolecular 1,4-addition in the isomerisation process, was also considered. However, no general strategy was available for the regioselective protection of the tertiary alcohol in the presence of a secondary alcohol. Thus, alternative syntheses of the acid-sensitive ester **5.18** and **5.21** *via* acid chlorides were investigated (Scheme 5.10).

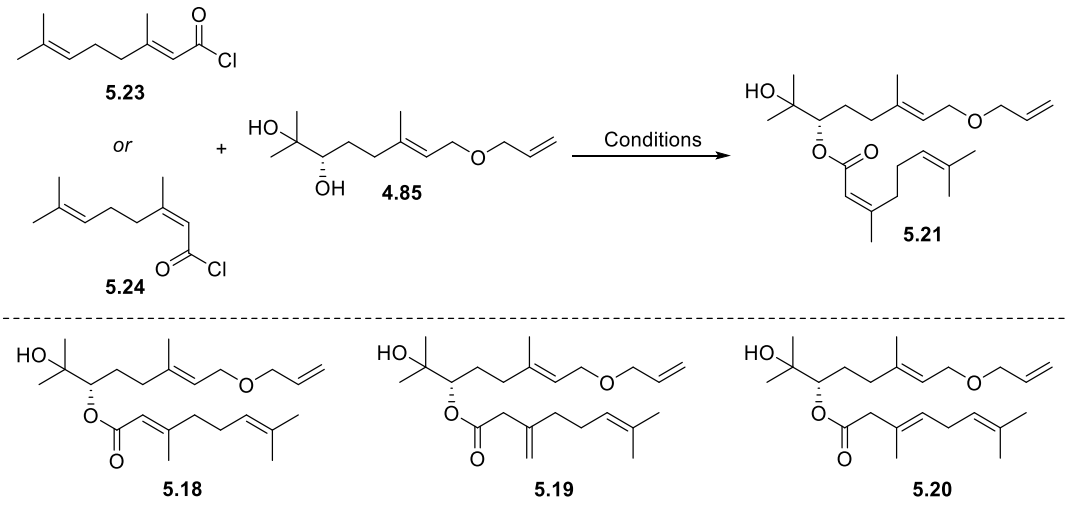
The corresponding acid chlorides of *E*- and *Z*-acid **4.85** and **5.22** were prepared by reacting the acids with the Vilsmeier reagent generated in situ by DMF and oxalyl chloride (Scheme 5.11).



Scheme 5.10 Preparation of acid chlorides **5.23** and **5.24**.

However, treating either of the acid chlorides **5.23/5.24** with diol **4.85** also led to a mixture of **5.18 – 5.21** (Table 5.3, entry 1 and 2).

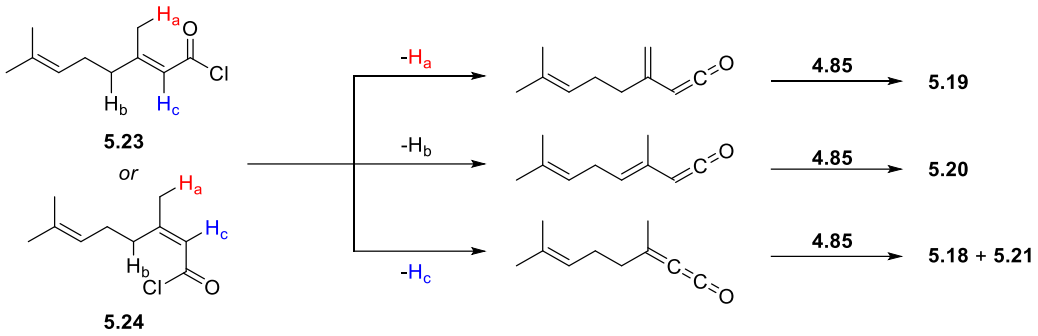
Table 5.3 Trapping of acid chloride **5.23/5.24** with diol **4.85**



Entry	Conditions	Yield of **5.21**[a]	Comments[b]
1	0.6 equiv. **5.23**, 1.0 equiv. **4.85**, 1.0 equiv. DMAP, Toluene, r.t., 24 h	21%	As an inseparable mixture with **5.18**, **5.19** and **5.20** (**5.18**:**5.19**:**5.20**:**5.21** ~ 5:1:1:21, 29% combined yield)
2	1.0 equiv. **5.24**, 1.0 equiv. **4.85**, 2.0 equiv. DMAP, Toluene, r.t., 24 h	15%	As an inseparable mixture with **5.18**, **5.19** and **5.20** (**5.18**:**5.19**:**5.20**:**5.21**~ 2:2:4:3, 60% combined yield)
3	1.0 equiv. **5.23**, 1.0 equiv. **4.85**, 1.0 equiv. DMAP, 8.0 equiv. K_2CO_3, Toluene, r.t., 24 h	36%	As an inseparable mixture with **5.18** (**5.18**:**5.21** ~ 1:9, 40% combined yield)

[a]NMR yield; [b]The product ratio between compound **5.18-5.20** was not accurately determined due to the overlapping resonances in ^{1}H NMR.

It is reasoned that the isomerisation proceeds *via* a ketene intermediate by deprotonation of the acid chloride, followed by the trapping of ketene with diol **4.85** (Scheme 5.11).

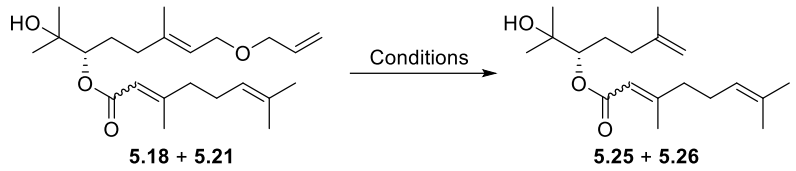


Scheme 5.11 Possible ketene intermediates generated *via* deprotonation of acid chlorides **5.23**/**5.24** and subsequent trapping by diol **4.85**.

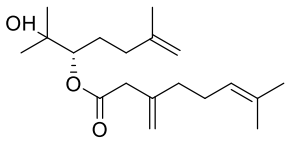
Indeed, the deprotonation and subsequent ketene formation of **4.85** was previously reported.[204] The combination of DMAP and potassium carbonate was found to provide the best result, producing only *E*/*Z*-mixture **5.18** and **5.21** without observable amount of **5.19** and **5.20** (Table 5.3, entry 3).

The mixture of *E*- and *Z*-ester **5.18** and **5.21** was then used to investigate the proposed RRCM chemistry (Table 5.4).

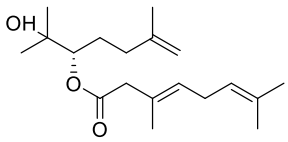
Table 5.4 Attempted RRCM of **5.18** and **5.21**



5.18 + 5.21 **5.25 + 5.26**



5.27

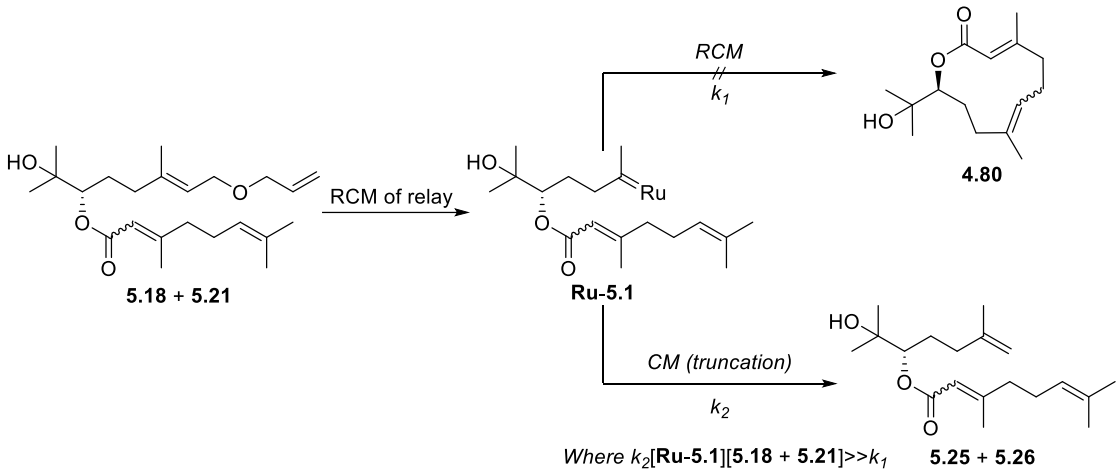


5.28

Entry	Conditions	Yield of **5.25** + **5.26**[a]	Comments
1	20 mol% **GII**, DCM (0.5 mM), reflux, 16 h	n.d.	As a mixture with unidentified impurities
2	20 mol% **GII**, Toluene (0.3 mM), reflux, 16 h	n.d.	As a mixture with **5.27**, **5.28** and other unidentified impurities
3	20 mol% **GII**, Toluene (0.5 mM), reflux, 48 h	n.d.	As a mixture with **5.27**, **5.28** and other unidentified impurities
4	20 mol% **GII**, 1 equiv. $Ti(O^iPr)_4$, Toluene (0.5 mM), reflux, 48 h	n.d.	As a complex mixture

[a]The methylene resonances of the 1,1-disubstituted olefin in **5.25**/**5.26** are detected at δ 4.71 and 4.67 in all entries. The yield was not determined due to the presence of unidentified impurities. N.d. = not determined.

The *E/Z*-esters were first subjected to the highly diluted RCM conditions in refluxing DCM (Table 5.4, entry 1). While the relay closure was operating as indicated by the disappearance of corresponding resonances on proton NMR, only truncated products **5.25** and **5.26** were detected. The generation of truncated products indicated that undesirable intermolecular CM kinetically outcompeted the desired intramolecular RCM (Scheme 5.12).



Scheme 5.12 Kinetically biased intermolecular CM pathway for the generation of truncation product.

In theory, RCM reactions could be conducted in even higher dilution, which would favour the formation of lactone **4.80**. The RRCM reaction was then attempted in refluxing toluene with higher dilution (Table 5.4, entry 2). Unfortunately, the identification of isomerised products **5.27** and **5.28** suggested ruthenium hydride formation *via* catalyst decomposition (Table 5.4, entry 2). It is reasoned that the RCM is too slow to compete catalyst decomposition in high dilution.

As truncation is inevitable even under high dilution conditions, attention was then turned to the RCM of the truncated products **5.25** and **5.26**. However, prolonged exposure of truncated products **5.25** and **5.26** to **GII** catalyst did not result the formation of detectable amount of lactone **4.80**. Instead, truncated products **5.25**/**5.26** and isomerised products **5.27/5.28** were observed (Table 5.4, entry 3). $Ti(O^iPr)_4$ was known as a mild Lewis acid additive to overcome the catalyst deactivation *via* chelation of carbonyl group.[205] Lewis acids was also known to shift the conformation preference of *α,β*-unsaturated esters.[206,207] Unfortunately, the use of $Ti(O^iPr)_4$ in RRCM led to a complex mixture (Table 5.4, entry 4).

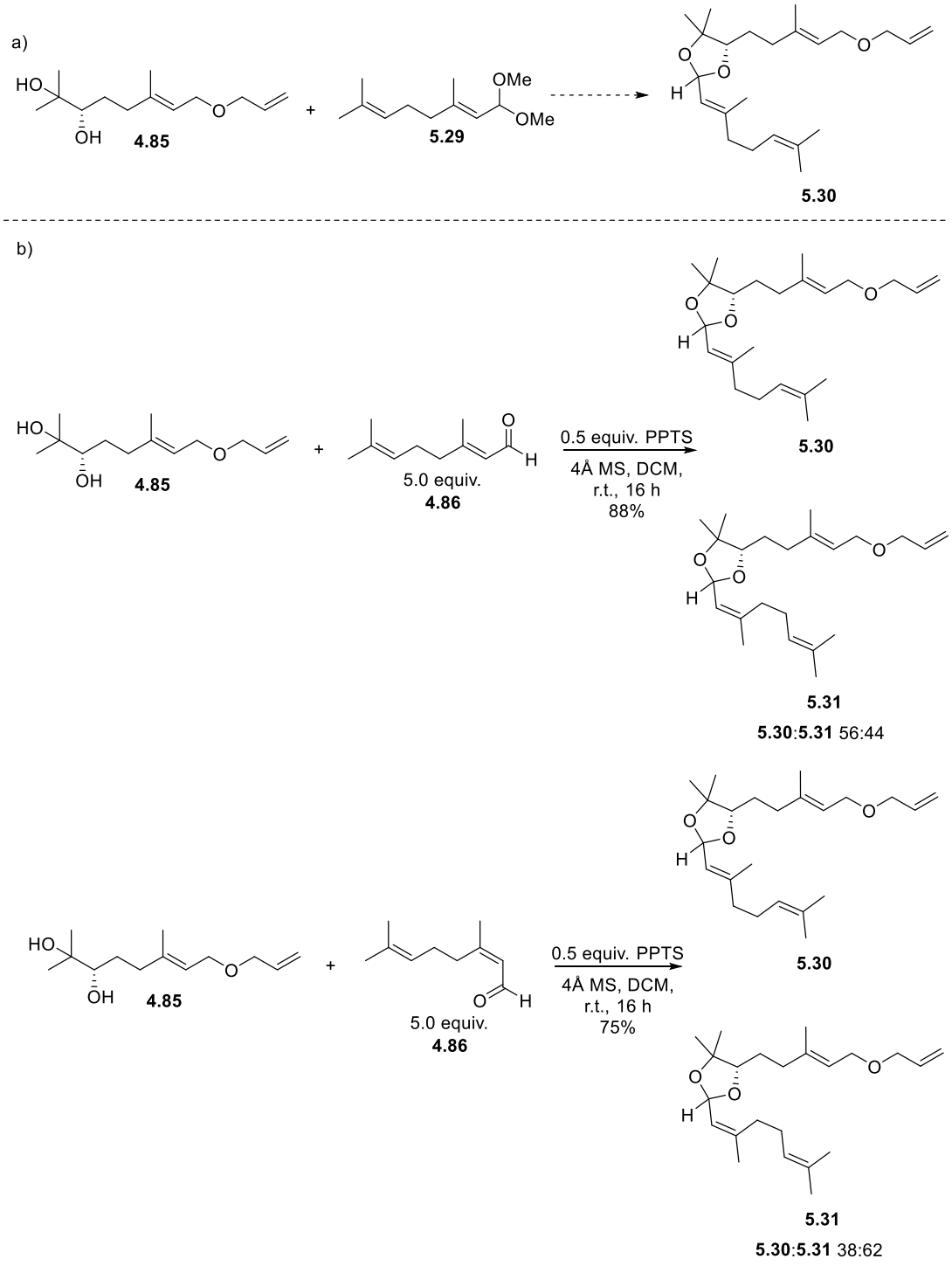
Due to the difficulty of the seemingly trivial esterification process, attention was turned to the preparation of the RRCM precursors bearing acetal linkers.

5.4.2 RRCM precursor with an acetal linker

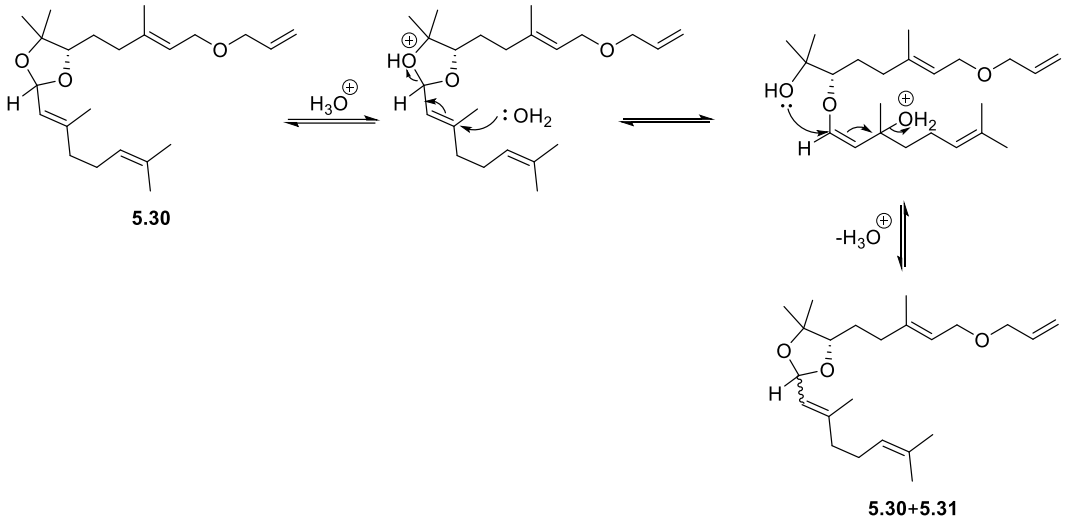
It was first proposed that the acetal-linked precursors can be prepared *via* the condensation between diol **4.85** and geranyl dimethyl acetal **5.29** (Scheme 5.13a). However, the literature conditions for Lewis acid catalysed acetalisation[208,209] failed to produce the desired acetal **5.29** in our hands.

Thus, the direct condensation between diol **4.85** and geranial **4.86** was investigated. Using conditions to the preparation of acetonide **4.89**, the condensation between diol **4.85** and geranial **4.86** proceeded smoothly to give *E*-acetal **5.30** and a significant amount of *Z*-acetal **5.31** as an inseparable mixture. The condensation between diol **4.85** and neral **4.72** also gave *Z*-acetal **5.31** with significant amount of *E*-acetal **5.30** (Scheme 5.13b). As considerable isomerisation of recovered geranial/neral **4.86/4.72** was detected, it is likely that the isomerisation of acetal proceeds *via* a reversible 1,4-addition pathway (Scheme 5.14).

The RRCM reaction of the acetal **5.30/5.31** was then investigated (Table 5.5).

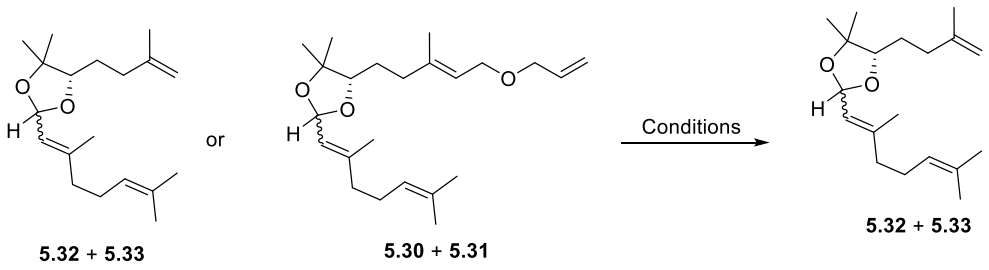


Scheme 5.13 a) Proposed synthesis of acetal **5.30** *via* condensation between diol **4.85** and geranyl dimethyl acetal **5.29**; b) Condensation between diol **4.85** and geranial/neral **4.86**/**4.72**.



Scheme 5.14. Acid-catalysed isomerisation *via* reversible 1,4-addition of **5.30** with water.

Table 5.5 Attempted RRCM/RCM acetal **5.30/5.31** and **5.32/5.33**



Entry	Conditions	Yield of **5.32** + **5.33**[a]	Comments
1	5 mol% **GII**, DCM (5 mM), reflux, 16 h	n.d.	Complex mixture with **5.32** and **5.33**. No RRCM products obtained.
2	20 mol% **GII**, DCM (6 mM), reflux, 16 h	80%	N/A
3	20 mol% **GII**, Toluene (6 mM), 80°C, 1.0 equiv. CuI, 24 h	65%	N/A

4	20 mol% **HGSIPr**, DCM (10 mM), reflux, 24 h	n.d.	Complex mixture with **5.32** and **5.33**.
5	20 mol% **GII**, neat, 50°C, under a positive flow of nitrogen	n.d.	Complex mixture with **5.32** and **5.33**.
6	20 mol% **HGSIPr**, neat, 50°C, under a positive flow of nitrogen	n.d.	Complex mixture with **5.32** and **5.33**.
7	20 mol% **TolGII**, neat, 50°C, under a positive flow of nitrogen	n.d.	Complex mixture with **5.32** and **5.33**.
8[b]	20 mol% **GII**, neat, 50°C, under a positive flow of nitrogen	n.d.	Trace of unidentified products with unreacted **5.32/5.33**
9[b]	20 mol% **HGSIPr**, neat, 50°C, under a positive flow of nitrogen	n.d.	Trace of unidentified products with unreacted **5.32/5.33**

[a]The yield was not determined due to the presence of unidentified impurities. No cyclic RRCM products was isolated in all entries. N.d. = not determined. [b]Reactions were carried out with truncated product **5.32/5.33** as the RCM substrate.

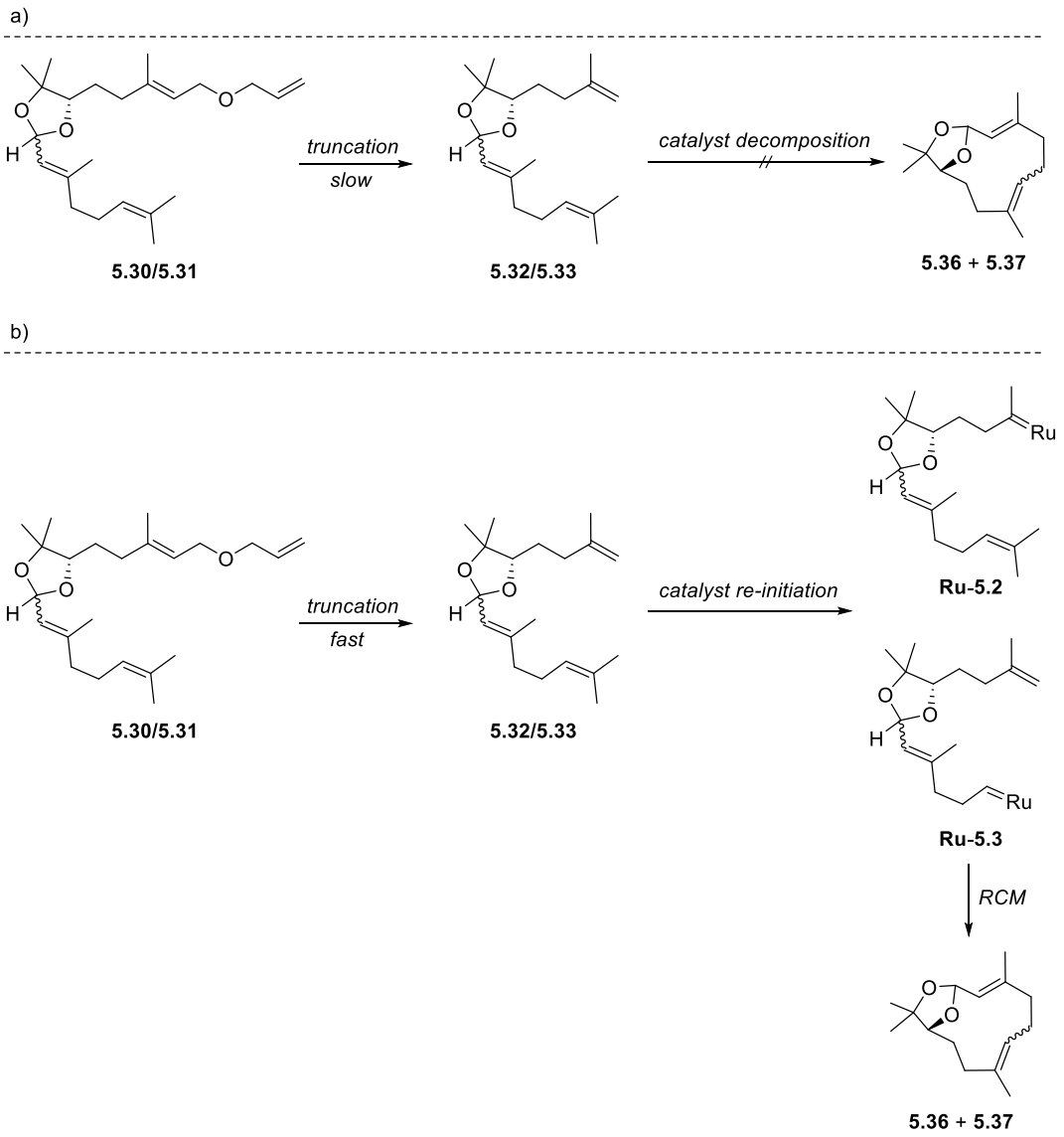
Employing low catalyst loading (5 mol%) under diluted conditions resulted incomplete relay closure as indicated by the unreacted starting material **5.30** and **5.31** after reaction (Table 5.5, entry 1). A high catalyst loading was found necessary to compete with catalyst decomposition, which afforded truncated products **5.32** and **5.33** in 80% yield (Table 5.5, entry 2). To facilitate the desired RCM, the reaction was carried out in toluene at elevated temperature. Unfortunately, no RRCM products was isolated from the reaction. The reduced yield of truncated products **5.32** and **5.33** may be the result of accelerated catalyst decomposition under elevated temperature (Table 5.5, entry 3). In order to promote the RCM between two sterically hindered olefins, catalyst **HGSIPr** was tested and a complex mixture containing truncated products **5.32** and **5.33** was obtained (Table 5.5, entry 4).

As all attempted RRCM reactions under standard, high dilution conditions failed, we wondered if RRCM of sterically hindered olefins could be carried out in higher concentrations. It is clear that the RCM is too slow compared to the catalyst decomposition and intramolecular truncation process in high dilution conditions. Increase of the concentration would at least allow the effective generation of truncated products **5.32** and **5.33**, which could be reinitiated to give **Ru-5.2**/**Ru-5.3** that undergo further RCM to afford the desired RCM products **5.35/5.36** (Scheme 5.15).

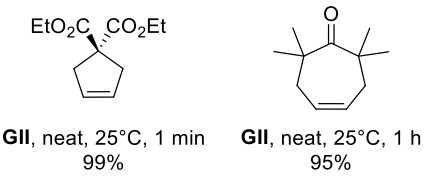
Although RCM reactions are generally benefited from high dilution by minimising the undesirable intermolecular oligomerisation/polymerisations, some RCM reactions can be carried out in much higher concentrations. One of the most notable examples is the RCM of diethyl diallyl malonate **5.34**, driven by the Thorpe-Ingold (gem-dialkyl) effect. This RCM reaction can be carried out neat to give the cyclic product in quantitative yield within 1 min. Likewise, seven-membered ketone **5.35** can be obtained in 95% yield without the need of solvents (Scheme 5.16).[210–212]

Unlike RCM reactions between two terminal olefins that liberate ethylene gas as the only volatile product, the RRCM system is complicated by the generation of dihydrofuran **4.15**. Dihydrofuran **4.15** is more reactive than the trisubstituted olefins in acetal **5.30/5.31** or the 1,1-disubstituted olefin in truncated product **5.32/5.33**. As a result, dihydrofuran **4.15** may complicate the RRCM reaction by backbiting to the catalyst and subsequent metathesis with other components in the reaction mixture. In fact, the effective removal of volatiles, including dihydrofuran **4.15**, by a constant flow of nitrogen is key to the success of the ReXM of two trisubstituted olefin (see Chapter 4).

Thus, the RRCM reactions were attempted in neat conditions with different catalysts (Table 5.5, entry 5-7). However, complex mixtures of truncated products **5.32/5.33** and other unidentified compounds were observed in all entries with no RRCM products isolated.



Scheme 5.15 a) Unsuccessful RRCM due to catalyst decomposition in high dilution reactions; b) Proposed generation and RCM of **5.32/5.33** in high concentration reactions.

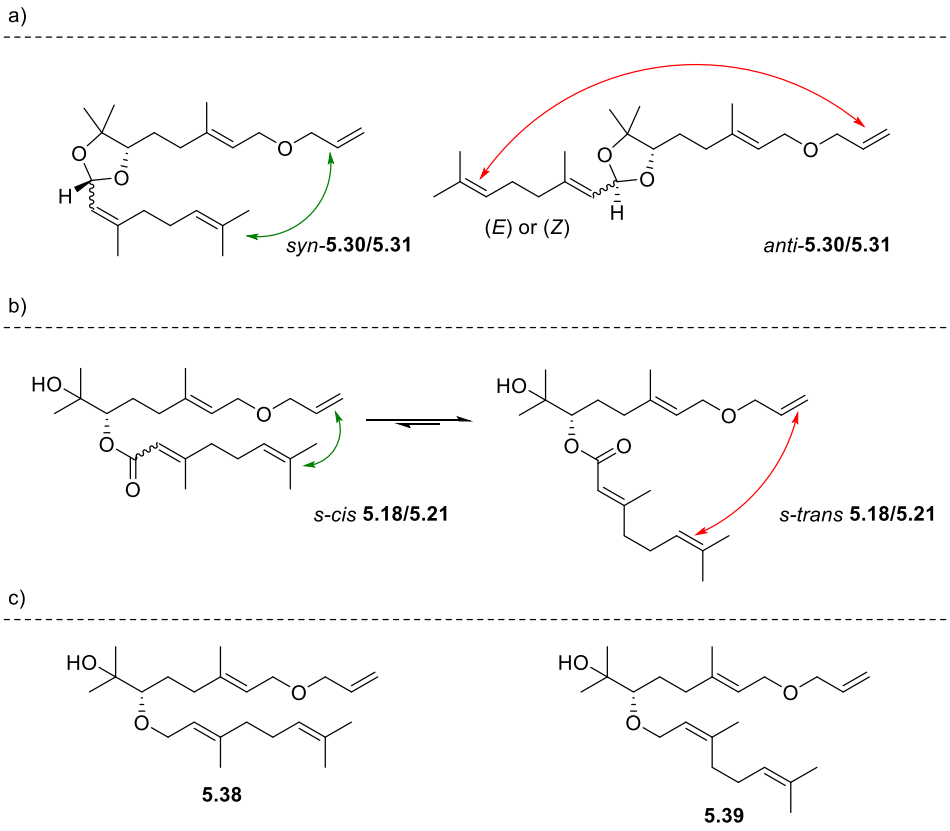


Scheme 5.16 Successful examples of RCM reactions carried out under neat conditions.

The truncated products **5.32/5.33** were also prepared and submitted to the metathesis conditions (Table 5.5, entry 8 and 9). Unfortunately, only unreacted starting material **5.32**/**5.33** and trace of unidentified olefin products, presumably oligomeric/polymeric

CM products were observed by ^{1}H NMR. Based on these results, it was concluded that either or both of the re-initiation of the truncated products **5.32/5.33** and the RCM of **Ru-5.2/Ru-5.3** are slow.

It was realised at this point that the slow RCM may be resulted from the different reactivities between the two diastereomers of acetal precursors **5.30** and **5.31** (Scheme 5.17a). The risk of having a substrate that is inert to RCM while reactive in unproductive metathesis events cannot be excluded. The same argument can be applied to the two ester conformers of *s-cis/ s-trans* **5.18/5.21** (Scheme 5.17b).

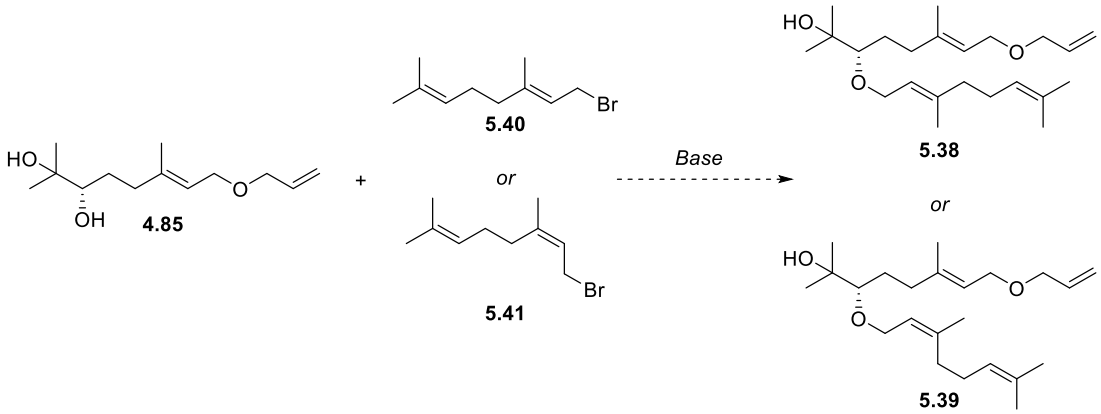


Scheme 5.17 Steric consideration of linear precursors in RRCM: a) Reactivity difference between *syn*- and *anti*-diastereomers of **5.30/5.31**; b) Reactivity difference between *s-cis/s-trans* conformers of ester precursors **5.18/5.21**.

Thus, a less sterically constrained RRCM precursor is required to improve the RRCM efficiency. Considering the synthetic difficulty of geometrically pure ester and acetal RRCM precursors, conformationally unstrained, ether-tethered RRCM precursors **5.38** and **5.39** were proposed as suitable RRCM precursors (Scheme 5.17c).

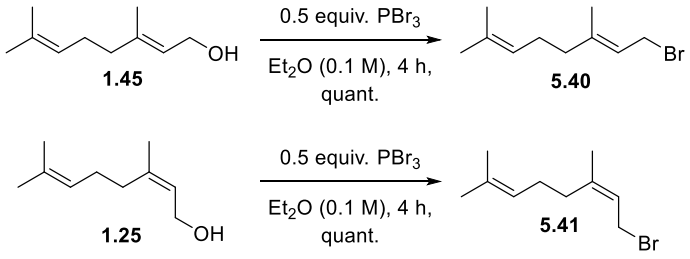
5.4.3 RRCM precursor with an ether linker

The *E*- and *Z*-ether **5.38** and **5.39** were proposed to be synthesised *via* Williamson reaction between diol **4.85** and corresponding geranyl/neryl bromide **5.40**/**5.41** (Scheme 5.18).



Scheme 5.18 Proposed Williamson ether synthesis of **5.38**/**5.39**.

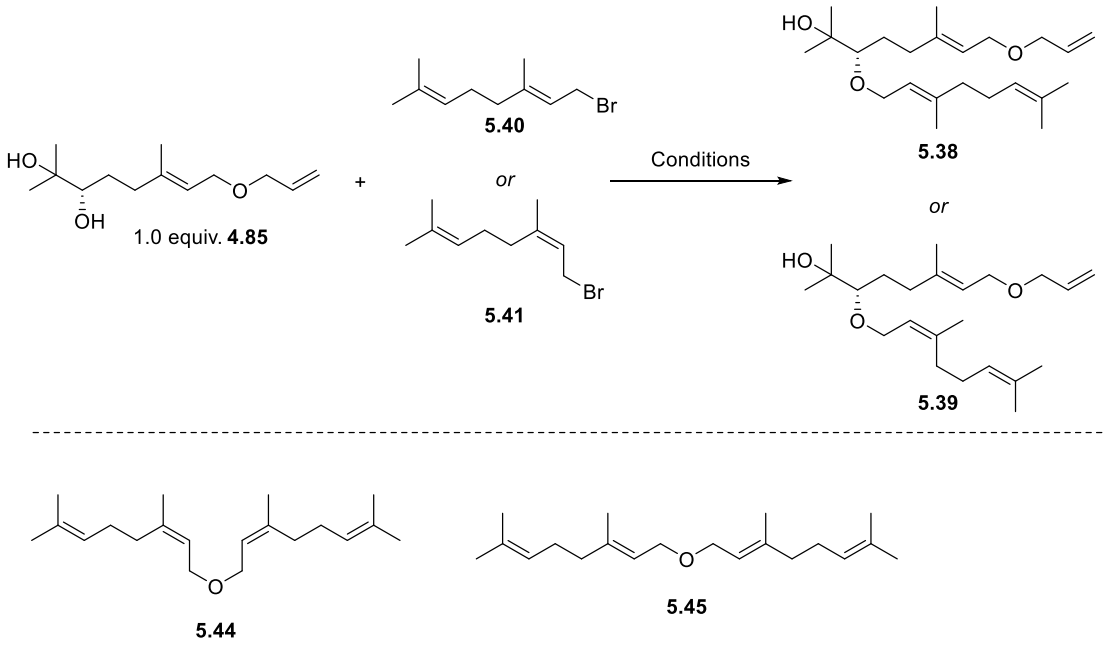
The geranyl and neryl bromide **5.40** and **5.41** were readily prepared in quantitative yield by reacting geraniol/nerol with phosphorous tribromide in diethyl ether (Scheme 5.19).



Scheme 5.19 Preparation of geranyl/neryl bromide **5.40/5.41**.

However, the etherification is unexpectedly low yielding, especially for the neryl bromide **5.41** even after optimisation (Table 5.6).

Table 5.6 Optimisation of Williamson synthesis of ether **5.38** and **5.39**



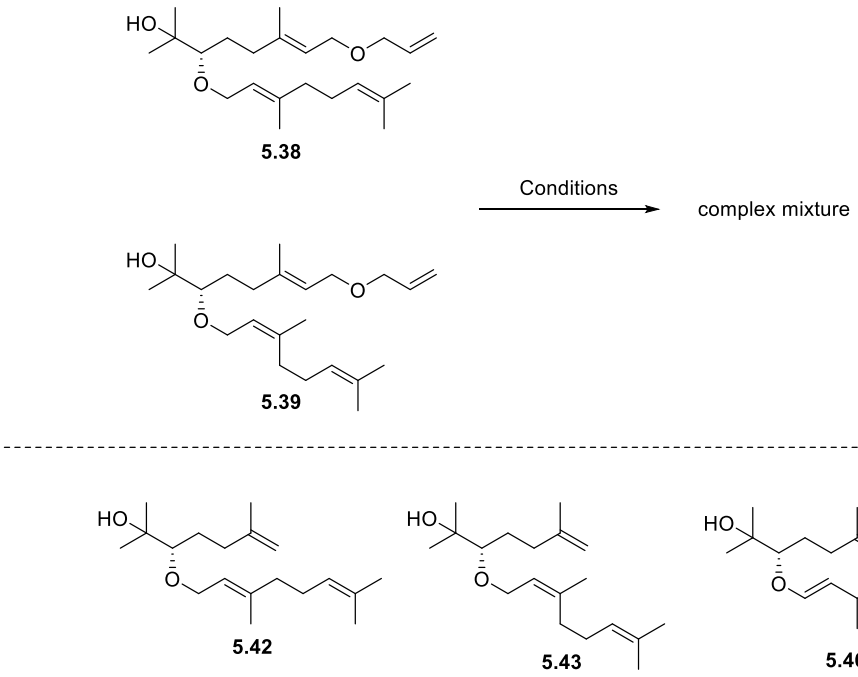
Entry	Conditions	Yield of **5.38** or **5.39**	Comments
1	5.0 equiv. **5.40**, KOH (2.0 equiv.), 10 mol% TBAI, neat, 16 h	34%	N/A
2	5.0 equiv. **5.40**, K_2CO_3 (8.0 equiv.), 10 mol% TBAI, neat, 24 h	n.d.	Reaction was not complete after 24 h
3	5.0 equiv. **5.41**, KOH (2 equiv.), 10 mol% TBAI, neat, 16 h	52%	As an inseparable mixture with dineryl ether **5.44**
4	1.1 equiv. **5.40**, 1.2 equiv. NaH, THF, -78°C to r.t., 16 h	60%	N/A
5	1.1 equiv. **5.41**, 1.2 equiv. NaH, THF, -78°C to r.t., 16 h	16%	N/A

6[a]	1.1 equiv. **5.40**, 1.2 equiv. NaH, THF, -78°C to r.t., 16 h	36%	N/A
7[a]	1.1 equiv. **5.41**, 1.2 equiv. NaH, THF, -78°C to r.t., 16 h	6%	40% of **4.85** was recovered after reaction
8	5.0 equiv. **5.40**, ^{t}BuOK (2.0 equiv.), 10 mol% TBAI, neat, 16 h	38%	N/A

[a]Reactions were carried out in larger scale (0.75 mmol **4.85**).

Nevertheless, with ether **5.38** and **5.39** in hand, a series of RRCM reactions were carried out under diluted or neat conditions (Table 5.7).

Table 5.7 Attempted RRCM reactions of **5.38**/**5.39**

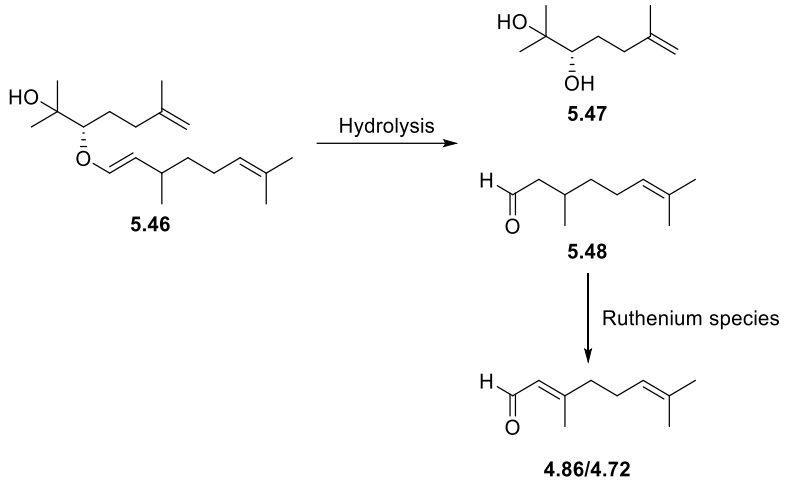


Entry	Conditions	Comments[a]
1	1.0 equiv. **5.38**, 5 mol% **GII**, DCM (2 mM), reflux, 16 h	Complex mixture of **5.42**, trace of **5.46** and other unidentified products

2	1.0 equiv. **5.39**, 5 mol% **GII**, DCM (2 mM), reflux, 16 h	Complex mixture of **5.43**, trace of **5.46** and other unidentified products
3	1.0 equiv. **5.39**, 10 mol% **HGIPr**, DCM (2 mM), reflux, 16 h	Complex mixture of **5.42** and other unidentified products
4	1.0 equiv. **5.38**, 10 mol% **GII**, neat, 50°C, under a positive flow of nitrogen	Complex mixture of **5.42**, **5.46** and other unidentified products
5	1.0 equiv. **5.39**, 10 mol% **GII**, neat, 50°C, under a positive flow of nitrogen	Complex mixture of **5.43**, **5.46** and other unidentified products

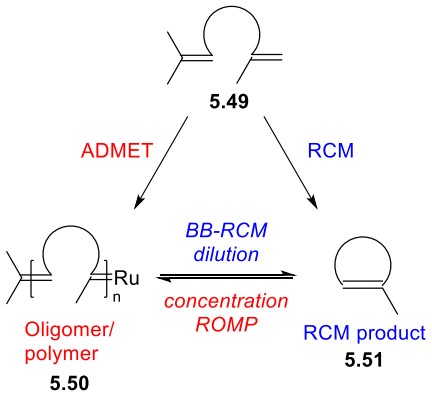
[a]No cyclic RRCM products were isolated in all entries.

The RRCM reactions in solution gave a complex mixture of truncated product **5.42/5.43** as the major component together with oligomerised/polymerised materials, indicated by the broadened peaks across the spectrum (Table 5.7, entry 1-3). Although no desired RRCM products were isolated, they might remain unidentified in the product mixture. The neat reactions produced majorly oligomeric/polymeric materials with **5.42/5.43** and **5.46** as the minor products. (Table 5.7, entry 4 and 5). The generation of enol ether **5.46** *via* ruthenium hydride induced isomerisation was indicated by the characteristic resonances around δ 6.3 ppm in proton NMR. Identification of the characteristic doublet of doublets of 1,2-diol at δ 3.30 ppm in crude mixture, together with the isolation of geranial/neral **4.86/4.72** mixture provided convincing evidence for the presence of enol ether **5.46** (Scheme 5.20).



Scheme 5.20 Possible mechanism for the decomposition of **5.46** and the generation of geranial/neral **4.86/4.72** and diol **5.47**.

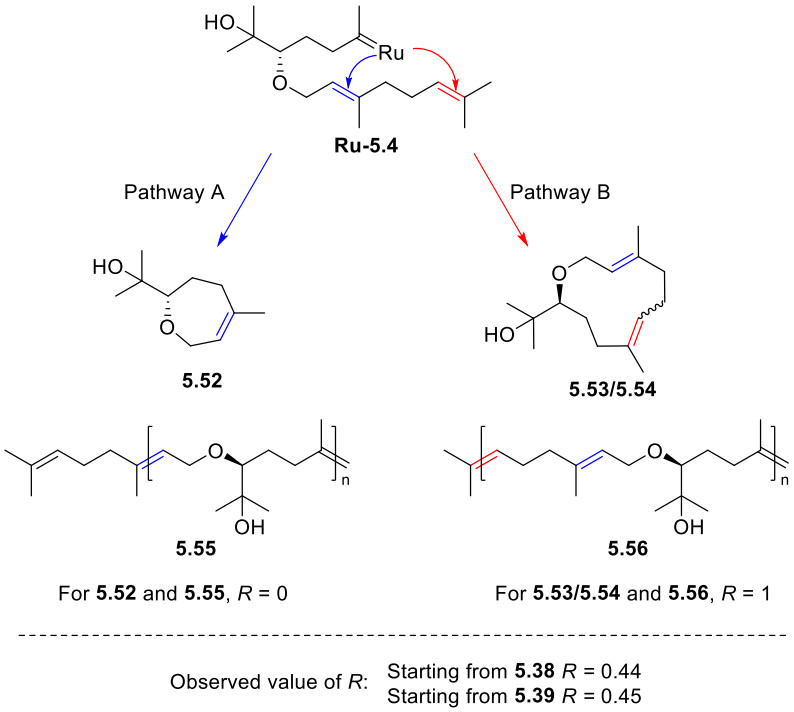
Although no desired RRCM product was isolated from the mixture, the emergence of oligomers/polymers *via* ADMET pathways presented the possibility of a backbiting-RCM (BB-RCM) strategy (Scheme 5.21).[60,213–215]



Scheme 5.21 Accessing RCM products **5.51** from oligomer/polymers **5.50** *via* equilibrium RCM reaction.

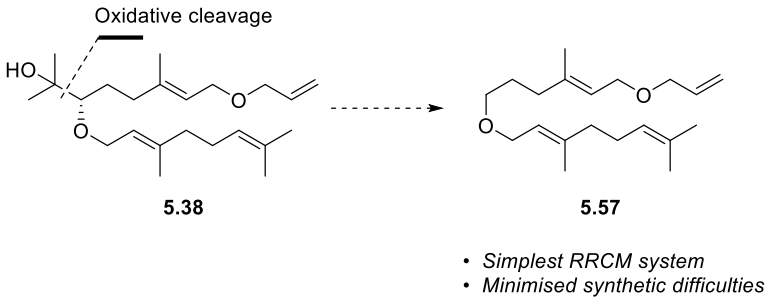
The ADMET-BB-RCM strategy is particularly useful when the catalyst reactivity or stability does not allow the conversion of diene **5.49** to the desired cyclic product **5.51** *via* RCM under conventional, high dilution conditions. The oligomeric/polymeric materials **5.50** can be produced *via* ADMET in high concentration, followed by equilibration in high dilution to access the desired RCM products.

However, due to the presence of multiple reactive olefins in the ether substrate **5.38/5.39** and truncated ether **5.42/5.43**, the control of regioselectivity became problematic. As indicated by the non-integer value of the ratio (denoted as *R*) between the integral of shielded olefin resonances at δ 5.17-5.05 ppm (aliphatic trisubstituted olefins) and deshielded olefin resonances δ 5.58-5.32 (trisubstituted olefins in allyl ether) in the reaction mixture, both pathway A and B (intra- and intermolecular) were operating (Scheme 5.22).



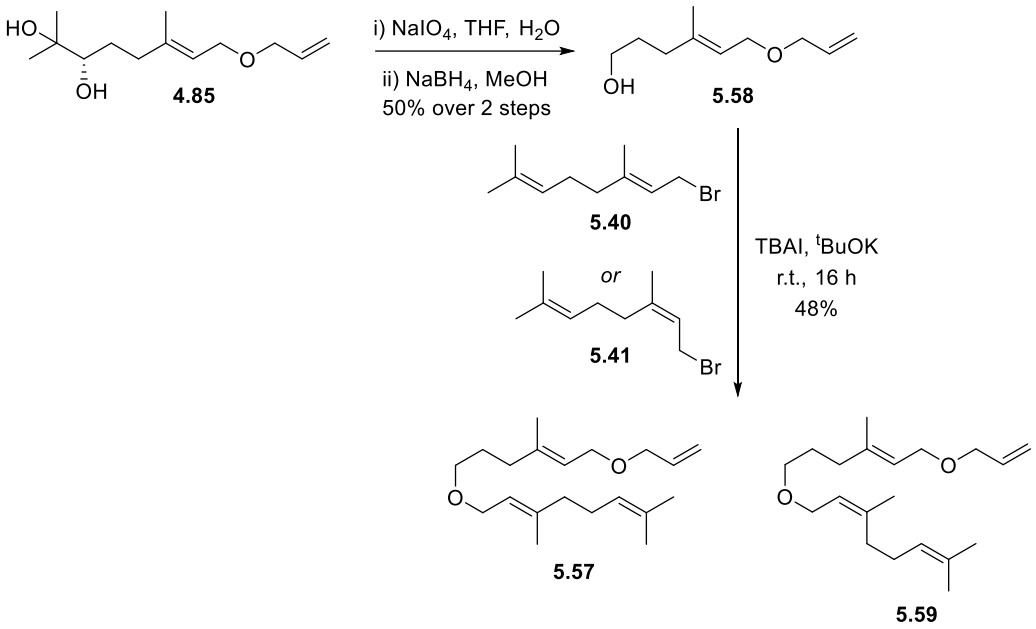
Scheme 5.22 Rationale for the observed ratio between the integral of allyl ether olefin (blue) and aliphatic trisubstituted olefin (red).

Thus, the oligomeric/polymeric materials produced in neat reactions were not suitable for testing the BB-RCM reaction targeting at **5.53/5.54**. As all attempted RRCM failed to produce the desired cyclic ether **5.53/5.54**, a structurally simplified ether **5.57** was proposed to promote the RRCM efficiency by removing the branched, tertiary alcohol functionality which potentially introduced conformational restraint to the RRCM system (Scheme 5.23).



Scheme 5.23 Proposed model substrate **5.57** for RRCM.

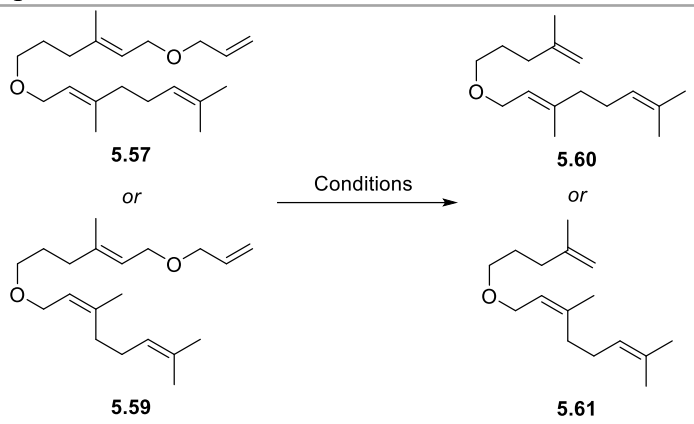
The geranyl ether **5.57** was prepared *via* Williamson reaction between geranyl bromide **5.40** and alcohol **5.58**, which was obtained by the oxidative cleavage of diol **4.85** by sodium periodate and subsequent sodium borohydride reduction. The corresponding neryl ether **5.59** were also prepared under the same conditions using neryl bromide **5.41** (Scheme 5.24).



Scheme 5.24 Preparation of ether **5.57**/**5.59** *via* Williamson reaction between geranyl/neryl bromide **5.40**/**5.41** and alcohol **5.58**.

The ether **5.57** and **5.59** were then subjected to RRCM conditions and the results are summarised in Table 5.8.

Table 5.8 Attempted RRCM of **5.57**/**5.59**



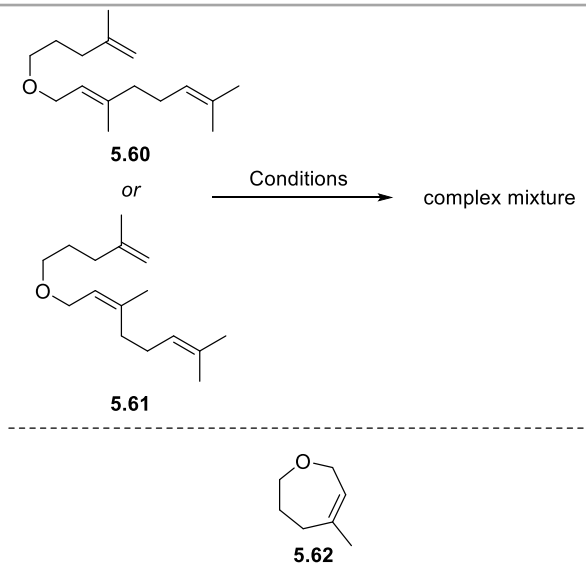
Entry	Conditions	Yield of **5.60** or **5.61**	Comments[a]
1	1.0 equiv. **5.57**, 10 mol% **GII**, DCM (10 mM), reflux, 16 h	94%	N/A
2	1.0 equiv. **5.57**, 10 mol% **GII**, Toluene (2 mM), 80°C, 16 h	53%	N/A
3	1.0 equiv. **5.57**, 10 mol% **GII**, neat, 50°C, 2.5 h	n.d.	Complex mixture
4	1.0 equiv. **5.57**, 10 mol% **HGII**, neat, 50°C, 16 h	99%	N/A
5	1.0 equiv. **5.59**, 10 mol% **GII**, Toluene (2 mM), 80°C, 16 h	72%	N/A
6	1.0 equiv. **5.59**, 10 mol% **GII**, neat, 50°C, 2.5 h	n.d.	Complex mixture

[a]No cyclic product was isolated in all entries.

The RRCM reactions of **5.57/5.59** in high dilution produced corresponding truncated products **5.60/5.61** (Table 5.8, entry 1,2 and 5) while RRCM reactions under neat conditions produced rapidly a complex mixture of oligomeric/polymeric materials (Table 5.8, entry 3 and 6).

The truncated ether **5.60**/**5.61** were subject to metathesis conditions. Full consumption of **5.60/5.61** was observed under neat conditions, producing oligomeric/polymeric materials as an inseparable mixture (Table 5.9).

Table 5.9 Attempted RCM truncated ether **5.60/5.61**



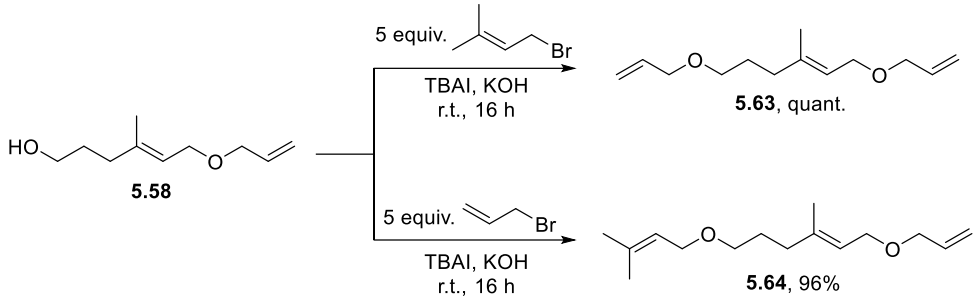
Entry	Conditions	Comments[a]
1	1.0 equiv. **5.60**, 10 mol% **GII**, neat, 50°C, 2.5 h	Complex mixture
2	1.0 equiv. **5.61**, 10 mol% **GII**, neat, 50°C, 2.5 h	Complex mixture
3[b]	1.0 equiv. **5.60**, 10 mol% **GII**, neat, 50°C, 2.5 h	Complex mixture
4[b]	1.0 equiv. **5.61**, 10 mol% **GII**, neat, 50°C, 2.5 h	Complex mixture

[a]Truncated ether **5.60/5.61** were fully consumed as indicate by ^{1}H NMR. [b]Volatiles were collected by a cold trap.

As the cyclic ether **5.62** may be generated but volatile enough to escape the reaction vial, an NMR tube containing deuterated chloroform in dry ice-acetone bath, was used as a cold trap to collect any volatile compounds (see Appendix III).

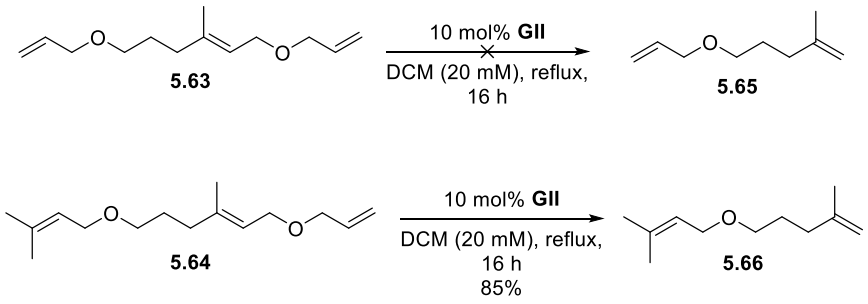
Only isobutylene **2.8** was observed by ^{1}H NMR from both reactions (Table 5.9, entry 3 and 4), confirming the metathesis reaction between the 1,1-disubsituted olefin and a trisubstituted olefin in ether **5.60/5.61**.

To obtain an authentic sample of **5.62** and study its formation *via* RRCM reaction, two model compounds were prepared as RRCM precursors (Scheme 5.25).



Scheme 5.25 Preparation of RRCM precursor **5.63** and **5.64**.

Allylation/prenylation of **5.58** with allyl bromide/prenyl bromide afforded **5.63** and **5.64** in excellent yields (Scheme 5.25). Allyl/prenyl ether **5.63/5.64** were subsequently tested under metathesis conditions (Scheme 5.26).



Scheme 5.26 Attempted RRCM of ether **5.63** and **5.64**.

Unfortunately, majority of ether **5.63** remained unreacted after 16 hours and trace of truncated product **5.65**, together with isomerised enol ether(s) were observed by ^{1}H NMR (Scheme 5.26, top). On the other hand, ether **5.64** underwent complete truncation under conventional RCM conditions (Scheme 5.26, bottom). As a result, it

remains unclear if the 7-membered cyclic ether **5.62** complicates the desired RRCM process.

5.5 Conclusion and future work

A systematic study of RRCM reactions in tethered, diterpene substrates was made to establish whether geometric-selective formation of trisubstituted olefins could be achieved *via* RRCM strategy.

Proposed substrates with ester/acetal linkers were obtained as mixtures of *E/Z*-isomers due to unexpected, acid-catalysed isomerisations. Under diluted conditions, all attempted RRCM reactions failed to yield cyclic products, which was attributed to the rapid truncation and catalyst decomposition. The truncated products were also considered as potential RCM precursors and were subjected to metathesis conditions. While no cyclic product was isolated, identification of oligomeric/polymeric materials in high concentration reactions suggested the metathesis reaction between a 1,1-disubstituted olefin and a trisubstituted olefin was operating, despite in an intermolecular manner.

Realisation of the conformational/constitutional constraints in ester/acetal system, which may complicate the cyclisation, led to the investigation of RRCM reactions in conformationally flexible ether system. RRCM reactions under conventional, high dilution conditions produced cleanly the corresponding truncated product. However, in high concentration, CM reaction of ether RRCM precursors and corresponding truncated products produced oligomeric/polymeric materials. As the allyl ether olefin was reactive towards CM reactions, the oligomeric/polymeric products were not suitable for further backbiting-RCM reaction.

Although RRCM is a powerful strategy to overcome the slow initiation of otherwise unreactive olefins, it does not guarantee a successful ring-closure. After all, we reached to the same conclusion as Hoye *et al.* drew from their unsuccessful RRCM attempts in the synthetic study of Callipeltoside A: “If the inherent rate of the crucial metathesis cyclisation event is slower than competing events (e.g., CM or [Ru] decomposition),

as is the case here, then the cyclisation will not be efficient regardless of the process by which the key ruthenium alkylidene intermediate is formed."[216]

While commercial **GII** catalyst provided a robust platform for the majority of metathesis reactions, the RRCM reaction involving highly substituted olefins requires a more reactive yet stable precatalyst. It is good to see new catalysts with higher activity, stability and tuneable functions emerge every year. With superior precatalysts, this RRCM approach to the geometrically selective synthesis of new terpenoid, trisubstituted olefins warrants further investigation.

Chapter 6 Experimental

General Experimental

Experimental Techniques: All reactions were carried out in oven-dried glassware. Air-sensitive reactions were performed under a positive pressure of nitrogen unless stated otherwise. Reaction temperatures other than room temperature were achieved with a dry-syn and heating mantle, ice/water bath or dry ice/acetone. 'Chromatographed' refers to flash column chromatography on silica gel 40−63 μm, unless otherwise stated. Analytical TLC was performed on Silica gel 60 F254 pre-coated aluminium-backed plates and visualised with either irradiation with UV light (254 or 350 nm) or potassium permanganate, vanillin or phosphomolybdic acid staining. Brine refers to a saturated aqueous NaCl solution. Work-up solutions are aqueous solutions unless otherwise stated.

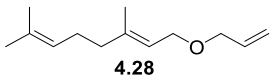
Characterisation: Fourier transform infrared (IR) spectra were recorded neat using an attenuated total reflection (ATR)-IR spectrometer and absorptions are reported to the nearest wavenumber. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DRX-400 or Bruker AV-400. Chemical shifts (δ) are expressed in parts per million (ppm) relative to the residual solvent peak. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 101 MHz. NMR acquisitions were performed at 298 K unless stated otherwise. Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; qu., quintet; m, multiplet. High-resolution mass spectrometry (HRMS) was conducted by the Imperial College Department of Chemistry Mass Spectrometry Service.

Reagents: Allyl bromide was distilled freshly before use; otherwise all reagents were obtained from commercial suppliers and used as received.

Solvents: All reactions were carried out in anhydrous solvents. HPLC grade CH_2Cl_2, THF, and EtOAc were dried by passing through a column of alumina beads. Extraction solvents, chromatography eluents (*n*-hexane, PE, pentanes, CH_2Cl_2, Et_2O, and EtOAc), and *t*-BuOH were used as received. "PE" refers to petroleum ether (40−60 °C). PE, EtOAc, CH_2Cl_2, and Et_2O were of GPR grade and pentanes were of HPLC grade.

Experimental for Chapter 4

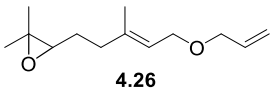
(*E*)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene (4.28)



4.28

Using a modified procedure of Rao,[163] to a mixture of neat geraniol **1.45** (5.30 mL, 30.0 mmol, 1.0 equiv.), allyl bromide (7.8 mL, 90 mmol, 3.0 equiv.) and TBAI (554 mg, 1.50 mmol, 5.0 mol%) was added crushed KOH pellets (3.37 g, 60.0 mmol, 2.0 equiv.) at room temperature and the mixture was stirred for 18 h. The crude reaction mixture was purified by loading directly onto a pad of silica gel and eluted with *n*-hexane, to give titled compound **4.28** (5.78 g, 29.7 mmol, 99%) as a colourless oil. R_f 0.60 (*n*-hexane); IR (ATR, neat) 2964, 2923, 2853, 1670, 1647, 1102, 1071 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.36 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.27 (dq, *J* = 17.3, 1.7 Hz, 1H), 5.18 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.13 – 5.06 (m, 1H), 4.00 (d, *J* = 6.8 Hz, 2H), 3.97 (dt, *J* = 5.7, 1.4 Hz, 2H), 2.16 – 1.96 (m, 4H), 1.68 (d, *J* = 1.3 Hz, 3H), 1.66 (s, 3H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.4, 135.2, 131.8, 124.2, 120.9, 117.1, 71.1, 66.7, 39.8, 26.5, 25.9, 17.8, 16.6; HRMS (EI^+) *m/z* calcd for $C_{13}H_{22}O$ $[M]^{\bullet+}$, 194.1671; found, 194.1682.

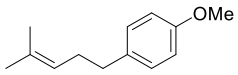
(*E*)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (4.26)



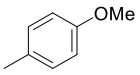
4.26

To a stirred solution of (*E*)-1-(allyloxy)-3,7-dimethylocta-2,6-diene **4.28** (1.41 g, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added dropwise a solution of *m*CPBA (1.63 g, 77%, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) over *ca.* 0.5 h at 0 °C. The mixture was allowed to warm to room temperature gradually. After a total reaction time of 18 h, the reaction mixture was concentrated under reduced pressure, dissolved in EtOAc (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), brine (100 mL), dried over Na_2SO_4, concentrated and chromatographed (20-50% Et_2O in pentanes), to afford the titled compound (1.71 g, 8.1 mmol, 81%) as a colourless oil. R_f 0.57 (30% EtOAc in pentanes); IR (ATR, neat) 3075, 2961, 2924, 2855, 1670, 1120, 1067 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.5, 10.5, 5.7 Hz, 1H), 5.43 – 5.36 (m, 1H), 5.26 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.5, 1.5 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.97 – 3.94 (m, 2H), 2.70 (t, *J* = 6.2 Hz, 1H), 2.26 – 2.07 (m, 2H), 1.68 (s, 3H), 1.67 – 1.62 (m, 2H), 1.29 (s, 3H), 1.25 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.4, 135.1, 121.5, 117.2, 71.3, 66.7, 64.2, 58.5, 36.4, 27.3, 25.0, 18.9, 16.7; HRMS (CI^+) calcd for $C_{13}H_{21}O_2$ $[M - H]^+$, 209.1536; found, 209.1535.

1-Methoxy-4-(4-methylpent-3-en-1-yl)benzene (4.27) and 1-Methoxy-4-methylbenzene (4.35)



4.27



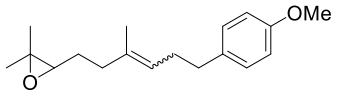
4.35

A solution of *p*-methoxybenzyl chloride **4.29** (2.26 mL, 16.6 mmol, 1.0 equiv.) in anhydrous THF (10 mL) was added dropwise over 20 min to magnesium turnings (0.478 g, 20.0 mmol, 1.2 equiv.) in anhydrous THF (10 mL) at 0°C. The reaction was warmed to room temperature and the mixture was stirred for 3 h. To the mixture was added dropwise a solution of tetrakis(triphenylphosphine)palladium(0) (0.226 g, 0.196 mmol, 1.5 mol%) and 1-bromo-3-methylbut-2-ene **4.30** (2.4 mL, 20.1 mmol, 1.0 equiv.) in THF (10 mL) at -78°C. The reaction mixture turned to green immediately and was stirred for an additional 3 h before warming to room temperature. The reaction mixture was stirred for further 16 h and quenched with ice water (20 mL), extracted with Et_2O (2 × 20 mL). The organics were washed with water (20 mL), brine (20 mL), dried over Na_2SO_4, concentrated reduced pressure and chromatographed (20% EtOAc in *n*-hexane) to give titled compound **4.27** (2.29 g, 12.3 mmol, 65%) as an inseparable mixture containing **4.35** (**4.35**:**4.27** = 16:84) and used for the synthesis of **4.21** without further purification. R_f 0.20 (10% EtOAc in *n*-hexane); IR (ATR, neat) 2960, 2907, 2851, 1610 cm^{-1}; ^1H NMR (for **4.27** only) (400 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.22 (t, *J* = 7.1, 1H), 3.84 (s, 3H), 2.63 (app. t, *J* = 7.8 Hz, 2H), 2.32 (app. q, *J* = 7.8 Hz, 2H), 1.74 (s, 3H), 1.62 (s, 3H). $^{13}C\{^1H\}$ NMR (for **4.27** only) (101 MHz, $CDCl_3$) δ 157.6, 134.5, 132.0, 129.3, 123.8, 113.6, 55.2, 35.2, 30.3, 25.7, 17.6; HRMS (ES^+) calcd for $C_{13}H_{17}O$ $[M - H]^+$, 189.1274; found, 189.1272.

General Procedure for ReXM reactions

To a neat mixture of relay compound **4.26** (0.25 mmol, 1.0 equiv) and partner olefin **4.27** (1.25 mmol, 5.0 equiv) was added ruthenium benzylidene **GII** (21 mg, 0.025 mmol, 10 mol %). The mixture was heated to 50 °C using an oil bath for 1 h under a strong positive pressure of nitrogen gas *via* a needle in/out to aid the removal of volatiles. The resulting mixture was loaded directly onto a column of silica gel and chromatographed.

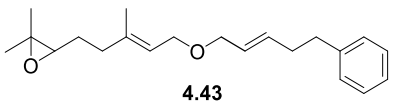
3-(6-(4-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (4.21)



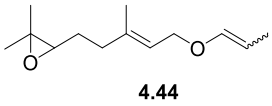
4.21

Following the general procedure for relay cross-metathesis using **4.26** or **4.69** (52.6 mg, 0.25 mmol, 1.0 equiv.) and **4.27** (250 mg, 1.25 mmol, 5.0 equiv.) gave **4.21** (45.1 mg, 0.17 mmol, 66%) as a brown oil from **4.26** or as a brown oil from **4.69** (41.0 mg, 0.15 mmol, 60%). The product was isolated as a mixture of *E*/*Z* geometrical isomers (*E*:*Z* 66:34 or 67:33 when using **4.26** and **4.69** as the substrate, respectively). R_f 0.35 (5% EtOAc in PE); IR (ATR, neat) 2952, 2918, 2851, 1610 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6, 2H), 5.25 (t, *J* = 7.2 Hz, 1H), 3.82 (s, 3H), 2.72 (t, *J* = 6.3 Hz, 1H), 2.61 (t, *J* = 8.4 Hz, 2H), 2.31 (q, *J* = 7.2 Hz, 2H), 2.23 – 2.06 (m, 2H), 1.73 (s, *J* = 1.3 Hz, *Z*-**4.21**, 1H), 1.60 (s, *E*-**4.21**, 2H), 1.82 – 1.47 (m, 2H), 1.33 (s, 3H), 1.29 (s, *E*-**4.21**, 2H), 1.28 (s, *Z*-**4.21**, 1H). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.60 ppm (major) and 1.73 ppm (minor); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8, 134.9, 134.5, 129.4, 125.3, 124.4, 113.8, 64.3, 64.2, 58.4, 55.4, 36.4, 35.5, 35.2, 30.3, 30.2, 28.6, 27.6, 27.5, 25.0, 23.5, 18.9, 18.8, 16.1. The major trisubstituted olefin was assigned as the *E*-isomer on the basis of a characteristic shielded methyl resonance at δ 16.1 vs 23.5 ppm for the minor *Z*-isomer; HRMS (ES^{+}) *m/z*: $[M + H]^{+}$ calcd for $C_{18}H_{27}O_2$, 275.2006; found, 275.2008.

((*E*)-6-(((*E*)-3,7-Dimethylocta-2,6-dien-1-yl)oxy)hex-4-en-1-yl)-benzene (4.43) and 2,2-Dimethyl-3-((3*E*)-3-methyl-5-(prop-1-en-1-yloxy)pent-3-en-1-yl)oxirane (4.44)



4.43



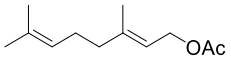
4.44

Following the general procedure for relay cross-metathesis using **4.26** (53 mg) and **4.42** (165 mg), gave **4.44** (14.3 mg, 0.07 mmol, 27%) as a colourless oil and a mixture of *E/Z* geometrical isomers (*E:Z* 49:51), and **4.43** (29.0 mg, 0.09 mmol, 37%) as a colourless oil.

For **4.43**: R_f 0.30 (10% EtOAc in pentanes); IR (ATR, neat) 3023, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 − 7.26 (m, 2H), 7.21 − 7.15 (m, 3H), 5.80 − 5.70 (m, 1H), 5.66 − 5.56 (m, 1H), 5.42 − 5.35 (m, 1H), 3.95 (d, J = 6.8, 2H), 3.91 (dd, J = 6.0, 0.9 Hz, 2H), 2.71 (m, 3H), 2.38 (m, 2H), 2.27 − 2.07 (m, 2H), 1.71 − 1.62 (m, 5H), 1.30 (s, 3H), 1.26 (s, 3H); $^{13}C\{1\ H\}$ NMR (101 MHz, $CDCl_3$): δ 141.9, 139.1, 133.7, 128.4, 128.3, 127.1, 125.8, 121.5, 70.8, 66.3, 64.0, 58.4, 36.2, 35.5, 34.1, 27.2, 24.9, 18.7, 16.5. HRMS (CI+) *m/z*: $[M + H]^+$ calcd for $C_{21}H_{31}O_2$, 315.2319; found, 315.2323.

For **4.44**: R_f 0.60 (10% EtOAc in pentanes); IR (ATR, neat) 1662 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 6.22 (dq, *J* = 12.5, 1.6 Hz, 0.51H, (*E*)-**4.44**), 5.96 (dq, J = 6.3, 1.7 Hz, 0.49H, (*Z*)-**4.44**), 5.41 (m, 1H), 4.79 (dq, *J* = 13.3, 6.7 Hz, 0.51H, (*E*)-**4.44**), 4.38 (appr. qu., *J* = 6.8 Hz, 0.49H, (*Z*)-**4.44**), 4.26 (d, *J* = 6.7 Hz, 1.02H, (*E*)-**4.44**), 4.18 (d, *J* = 6.7 Hz, 0.98H, (*Z*)-**4.44**), 2.70 (t, *J* = 6.3 Hz, 1H), 2.28−2.07 (m, 2H), 1.73 − 1.60 (m, 5H), 1.57 (dd, *J* = 6.8, 1.7 Hz, 1.53H, (E)-9a), 1.55 (dd, *J* = 6.7, 1.6 Hz, 1.47H, (*Z*)-**4.44**), 1.30 (s, 3H), 1.26 (d, *J* = 1.7 Hz, 3H). The *E/Z* ratio was determined by integration of the resonances at δ 4.26 ppm (major) and 4.18 ppm (minor); $13C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 146.2, 145.1, 139.8, 139.7, 128.5, 121.0, 120.4, 01.2, 98.8, 68.2, 65.7, 64.0, 58.4, 36.2, 36.2, 27.1, 24.9, 18.8, 16.6, 12.7, 9.3. HRMS (CI^+) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{23}O_2$, 211.1693; found, 211.1694.

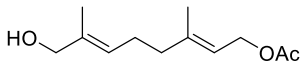
(*E*)-3,7-Dimethylocta-2,6-dien-1-yl acetate (4.48)



4.48

Using a modified procedure of Laschat[217], to a solution of geraniol 1.45 (2.00 g, 13.0 mmol, 1.0 equiv.) in CH_2Cl_2 (13 mL) was added Ac_2O (2.65 mL, 26.0 mmol, 2.0 equiv.) and DMAP (80 mg, 0.65 mmol, 5 mol%) and the mixture was stirred for 1h at room temperature. Methanol (5 mL) was then added, and the mixture was stirred for another 1 h. The mixture was taken up in *n*-hexane (30 mL), washed with deionised water (2 × 20 mL), saturated aqueous sodium bicarbonate solution (2 × 20 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (8% EtOAc in PE) to yield the titled compound as a colourless oil (2.44 g, 13.0 mmol, 99%). R_f 0.85 (10% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.36 (ddq, *J* = 7.1, 5.7, 1.3 Hz, 1H), 5.18 – 5.04 (m, 1H), 4.67 – 4.55 (m, 2H), 2.19 – 2.01 (m, 4H), 2.08 (s, 3H), 1.73 (d, *J* = 1.4 Hz, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.62 (d, *J* = 1.3 Hz, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 142.4, 132.0, 123.9, 118.3, 61.5, 39.7, 26.4, 25.8, 21.2, 17.8, 16.6. The spectroscopic data matches those previously reported.[218]

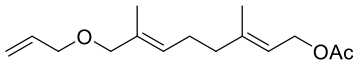
(2*E*,6*E*)-8-Hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate (4.49)



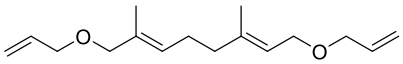
4.49

Using a modified procedure of Garg[219], to a solution of geranyl acetate **4.48** (991 mg, 5.09 mmol, 1.0 equiv.) in CH_2Cl_2 (25 mL) was added *tert*-butyl hydroperoxide (TBHP) (2.90 mL, 15.8 mmol, 3.1 equiv.). The reaction mixture was allowed to stir for 90 min and was added brine (10 mL) and saturated aqueous $NaHCO_3$ solution (10 mL). The mixture was then extracted with EtOAc (3 × 25 mL). The combined organics was dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (15% - 33% EtOAc in PE) to afford the titled compound (580 mg, 3.42 mmol, 57%) as a colourless oil. R_f 0.43 (33% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) 5.45 – 5.28 (m, 2H), 4.56 (d, J = 7.1 Hz, 2H), 3.98 (d, J = 4.7 Hz, 2H), 2.11 – 2.17 (m, 4H), 1.76 (s, 3H), 1.66 (s, 3H). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 171.3, 142.0, 135.7, 124.8, 119.6, 68.7, 61.3, 31.8, 26.0, 23.5, 21.1, 13.7. The spectroscopic data matches those previously reported.[219]

(*2E,6E*)-8-(Allyloxy)-3,7-dimethylocta-2,6-dien-1-yl acetate (4.50) and (*2E,6E*)-1,8-bis(allyloxy)-2,6-dimethylocta-2,6-diene (4.50a)



4.50

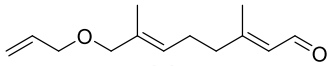


4.50a

To (2*E*,6*E*)-8-hydroxy-3,7-dimethylocta-2,6-dien-1-yl acetate **4.49** (210 mg, 1.0 mmol, 1.0 equiv.) was added allyl bromide (605 mg, 5.0 mmol, 5.0 equiv.), TBAI (370 mg, 1.0 mmol, 1.0 equiv.), KOH pellets (112 mg, 2.0 mmol, 2.0 equiv.) at room temperature. The mixture was allowed to stir overnight and loaded directly onto a pad of silica and eluted with *n*-hexane to afford the titled compound (203 mg, 0.80 mmol, 80%) as a mixture with bisallylated side product **4.50a** (37 mg, 0.75 mmol, 15%).

For **4.50** only: R_f 0.31 (10% EtOAc in PE); IR (ATR, neat) 3600-3100, 1726 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 5.94 (ddt, *J* = 17.3, 10.4, 5.6 Hz, 1H), 5.45 – 5.34 (m, 2H), 5.29 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.23 – 5.16 (m, 1H), 4.57 (d, *J* = 7.3 Hz, 2H), 3.94 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.87 (s, 2H), 2.21 – 2.13 (m, 4H), 2.07 (s, 3H), 1.79 (s, 3H), 1.67 (s, 3H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.1, 142.4, 135.0, 132.9, 127.0, 119.4, 116.8, 76.2, 70.6, 61.0, 31.8, 26.3, 23.5, 21.1, 13.9. HRMS (CI^+) *m/z:* $[M + H]^+$ calcd for $C_{15}H_{25}O_3$, 253.1798; found, 253.1799.

(*2E,6E*)-8-(Allyloxy)-3,7-dimethylocta-2,6-dienal (4.47)



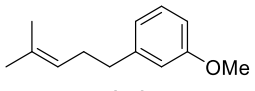
4.47

To the solution of (*2E,6E*)-8-(allyloxy)-3,7-dimethylocta-2,6-dien-1-yl acetate **4.50** and (*2E,6E*)-1,8-bis(allyloxy)-2,6-dimethylocta-2,6-diene **4.50a** (240 mg, **4.50**:**4.50a** 85:15) in MeOH (25 mL) was added KOH pellets (112 mg, 2.0 mmol) at room temperature and the mixture was allowed to stir for 1 h. The mixture was filtered and the filtrate was concentrated under reduced pressure. To the concentrated filtrate at room temperature was added CH_2Cl_2 (10 mL), Dess-Martin periodinane (424 mg, 1.0 mmol, 1.25 equiv.) in two portions and the mixture was allowed to stir for 90 min. The mixture was then quenched with saturated Na_2SO_3 solution (10 mL), saturated $NaHCO_3$ solution (10 mL) and allowed to stir for further 30 min. The biphasic mixture was separated and the aqueous was extracted with EtOAc (3 × 25 mL). The combined organic layer was washed with brine (25 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% EtOAc in PE) to afford the titled compound (177 mg, 0.85 mmol, 88%). R_f 0.31 (10% EtOAc in PE); IR (ATR, neat) 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 9.91 (d, J = 8.1 Hz, 1H), 5.97 – 5.83 (m, 2H), 5.44 – 5.35 (dt, J = 7.6, 1.3 Hz, 1H), 5.25 (dd, J = 17.2, 1.7 Hz, 1H), 5.16 (dd, J = 10.4, 1.6 Hz, 1H), 3.90 (dt, J = 5.6, 1.5 Hz, 2H), 3.83 (d, J = 1.2 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.35 – 2.24 (app. q, J = 7.6, 2H), 1.98 (d, J = 1.3 Hz, 3H), 1.64 (d, J = 1.3 Hz, 3H).. $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 190.8, 134.9, 134.4, 128.8, 125.3, 117.0, 77.5, 77.1, 76.8, 75.8, 70.9, 32.3, 26.8, 25.1, 14.3, 14.1. HRMS (EI^+) *m/z:* $[M + H]^+$ calcd for $C_{13}H_{20}O_2$, 209.1536; found, 209.1533.

General procedure for preparation of trisubstituted olefins 4.58 and 4.59 *via* Wittig olefination

To a suspension of $(CH_3)_2CHPPh_3I$ (7.8 g, 18 mmol, 1.8 equiv) in THF (20 mL) was added *n*-BuLi (11.25 mL, 1.6 M in hexanes, 18 mmol, 1.8 equiv) dropwise at 0 °C. After 30 min, aldehyde (1.0 equiv) was added dropwise and the mixture was stirred for 18 h. The mixture was quenched by addition of water (15 mL) and the THF was removed under reduced pressure. The mixture was diluted with diethyl ether (100 mL) and filtered through a pad of Celite. The combined organics were washed with water (3 × 20 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude material was purified by DCVC, eluting with pentanes, to give the desired trisubstituted alkene.

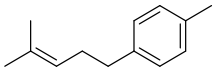
1-Methoxy-3-(4-methylpent-3-en-1-yl)benzene (4.58)



4.58

Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ (3.8 g, 8.8 mmol, 1.8 equiv.), THF (10 mL), *n*-BuLi (3.5 mL, 2.5 M in hexanes, 8.8 mmol, 1.8 equiv.), and 3-(3-methoxyphenyl)propanal (0.8 g, 4.9 mmol, 1.0 equiv.) gave the titled compound (0.55 g, 2.58 mmol, 59%) as a colourless oil. R_f 0.85 (10% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 − 7.15 (m, 1H), 6.82 − 6.77 (m, 1H), 6.76 − 6.72 (m, 2H), 5.23 − 5.12 (m, 1H), 3.80 (s, 3H), 2.71 − 2.57 (m, 2H), 2.29 (app. q, J = 7.6 Hz, 2H), 1.69 (d, J = 1.3 Hz, 3H), 1.58 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.7, 144.2, 132.2, 129.3, 123.8, 121.0, 114.3, 111.1, 55.2, 36.3, 30.0, 25.8, 17.8; HRMS (CI^+) *m/z:* $[M + H]^+$ calcd for $C_{13}H_{19}O$, 191.1430; found, 191.1430.

1-Methyl-4-(4-methylpent-3-en-1-yl)benzene (4.59)



4.59

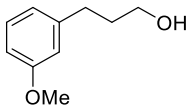
Following the general procedure for the formation of trisubstituted alkenes using $(CH_3)_2CHPPh_3I$ (2.5 g, 5.8 mmol, 1.2 equiv), THF (10 mL), *n*-BuLi (2.3 mL, 2.5 M in hexanes, 5.8 mmol, 1.2 equiv.), and 3-(4-methylphenyl)propanal (0.72 g, 4.9 mmol, 1.0 equiv.) gave the titled compound (0.51 g, 2.95 mmol, 60%) as a colourless oil. R_f 0.93 (10% EtOAc in petrol); IR (ATR, neat) 3042 cm^{-1} ;^1H NMR (400 MHz, $CDCl_3$): δ 7.10 (app. s, 4H), 5.26−5.12 (m, 1H), 2.66−2.56 (m, 2H), 2.33 (s, 3H), 2.29 (app. q, J = 7.7 Hz, 2H), 1.70 (s, 3H), 1.59 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 139.5, 135.2, 132.2, 129.1, 128.4, 124.0, 35.8, 30.3, 25.8, 21.2, 17.8; HRMS (EI^+) *m/z:* $[M]^{\bullet+}$ calcd for $C_{13}H_{18}$, 174.1409; found, 174.1411.

General procedure for the preparation of aldehyde substrate 4.63 and 4.66 *via* sequential reduction-oxidation reactions of corresponding carboxylic acids

To a solution of carboxylic acid (20.0 mmol, 1.0 equiv.) in diethyl ether (200 mL) at 0°C was added lithium aluminium hydride (LAH) powder (100.0 mmol, 5.0 equiv.) in two portions. The reaction was allowed to stir for 10 min and monitored by TLC. Upon completion, the reaction was quenched by addition of water (50 mL), diluted aqueous H_2SO_4 (100 mL). The mixture was allowed to stir for further 30 min and was separated. The aqueous was extracted with EtOAc (3 × 50 mL) and the combined organics were washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure to afford the required alcohol and used in the following step without further purification.

The alcohol was immediately dissolved in CH_2Cl_2 (50 mL) and was added Dess-Martin periodinane (1.0 equiv.). The mixture was stirred for 2 h and monitored by TLC. Upon completion, the reaction was quenched with saturated Na_2SO_3 aqueous solution (100 mL), saturated aqueous $NaHCO_3$ aqueous solution (100 mL) and allowed to stir for further 30 min. The mixture was separated and the aqueous was extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed to afford the corresponding aldehydes.

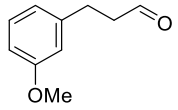
3-(3-Methoxyphenyl)propanol (4.62)



4.62

Following the general procedure of preparing aldehydes from corresponding carboxylic acids, using (*E*)-3-(3-methoxyphenyl)acrylic acid (3.56 g, 20.0 mmol, 1.0 equiv.), lithium aluminium hydride (LAH) powder (3.80 g, 100.0 mmol, 5.0 equiv.), afforded the titled compound as a pale yellow oil (2.40 g, 14.4 mmol, 72%) and was used in the following step without further purifications. R_f 0.20 (20% EtOAc in petrol); IR (ATR, neat) 3073 cm^{-1} ;^{1}H NMR (400 MHz, $CDCl_3$): 7.23 (td, *J* = 7.6, 0.9 Hz, 1H), 6.87 – 6.71 (m, 3H), 3.82 (s, 3H), 3.70 (t, *J* = 6.4 Hz, 2H), 2.71 (dd, *J* = 8.6, 6.8 Hz, 2H), 1.98 – 1.85 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 159.7, 143.5, 129.4, 120.9, 114.2, 111.2, 62.3, 55.2, 34.1, 32.1; HRMS (CI^+) *m/z:* $[M + H]^+$ calcd for $C_{10}H_{15}O_2$, 167.2275; found, 167.2273.

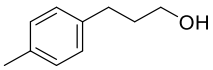
3-(3-Methoxyphenyl)propanal (4.63)



4.63

Following the general procedure of preparing aldehydes from corresponding carboxylic acids, using 3-(3-methoxyphenyl)propanol 4.62 (2.40 g, 14.4 mmol, 1.0 equiv.) and Dess-Martin periodinane (6.10 g, 14.4 mmol, 1.0 equiv.), afforded the titled compound (2.14 g, 13.0 mmol, 90%) as a colourless oil. R_f 0.60 (20% EtOAc in petrol); IR (ATR, neat) 3073, 1728 cm^{-1} ;^1H NMR (400 MHz, $CDCl_3$): δ 9.81 (t, J = 1.4 Hz, 1H), 7.20 (t, J = 8.2 Hz, 1H), 6.84 – 6.63 (m, 3H), 3.79 (s, 3H), 2.92 (d, J = 7.5 Hz, 2H), 2.83 – 2.68 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.6, 159.9, 142.1, 129.7, 120.7, 114.3, 111.7, 55.3, 45.3, 28.3; HRMS (EI^+) *m/z:* $[M + H]^+$ calcd for $C_{10}H_{13}O_2$, 165.2115; found, 165.2115.

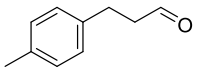
3-(*p*-Tolyl)propan-1-ol (4.65)



4.65

Following the general procedure of preparing aldehydes from corresponding carboxylic acids, using 3-(*p*-tolyl)propanoic acid (3.28 g, 20.0 mmol, 1.0 equiv.), lithium aluminium hydride (LAH) powder (3.80 g, 100.0 mmol, 5.0 equiv.), afforded the titled compound as a pale yellow oil (2.05 g, 13.6 mmol, 68%) and was used in the following step without further purifications. R_f 0.23 (20% EtOAc in PE); IR (ATR, neat) 3032 cm^{-1} ;^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 4H), 3.70 (t, J = 6.4 Hz, 2H), 2.78 – 2.60 (m, 2H), 2.35 (s, 3H), 1.97 – 1.83 (m, 2H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 138.8, 135.5, 129.2, 128.4, 62.5, 34.5, 31.8, 21.1; HRMS (CI^+) *m/z:* $[M + H]^+$ calcd for $C_{10}H_{15}O$, 151.2285; found, 151.2286.

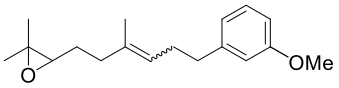
3-(*p*-Tolyl)propanal (4.66)



4.66

Following the general procedure of preparing aldehydes from corresponding carboxylic acids, using 3-(3-methoxyphenyl)propanol **4.65** (1.50 g, 10.0 mmol, 1.0 equiv.) and Dess-Martin periodinane (4.24 g, 10.0 mmol, 1.0 equiv.), afforded the titled compound (1.17 g, 7.80 mmol, 78%) as a colourless oil. R_f 0.66 (20% EtOAc in PE); IR (ATR, neat) 3032, 1730 cm^{-1} ;^1H NMR (400 MHz, $CDCl_3$): δ 9.84 (t, J = 1.5 Hz, 1H), 7.18 – 7.01 (m, 4H), 2.95 (t, J = 7.5 Hz, 2H), 2.84 – 2.73 (m, 2H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 201.8, 137.2, 135.9, 129.3, 128.2, 45.4, 27.7, 21.0; HRMS (EI+) *m/z:* $[M]^{\bullet+}$ calcd for $C_{10}H_{14}O$, 150.2205; found, 150.2205.

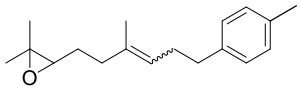
3-(6-(3-Methoxyphenyl)-3-methylhex-3-en-1-yl)-2,2-dimethyloxirane (4.58a)



4.58a

Following the general procedure for relay cross-metathesis using **4.26** (9.5 mg, 0.04 mmol, 1.0 equiv.) and **4.58** (44 mg, 0.23 mmol, 5.0 equiv.) and **GII** catalyst (3.4 mg, 0.004 mmol, 10 mol %) afforded the titled compound (7.5 mg, 61%) as a colourless oil. The product was isolated as a mixture of *E*/*Z* geometrical isomers (*E:Z* 72:28). R_f 0.45 (10% EtOAc in pentanes); IR (ATR, neat) 2952, 2918, 2851, 1610 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.14 (m, 1H), 6.80−6.76 (m, 1H), 6.74 (d, *J* = 1.4 Hz, 1H), 6.75−6.70 (m, 1H), 5.31−5.12 (m, 1H), 3.80 (s, 3H), 2.72−2.66 (m, 1H), 2.65−2.59 (m, 2H), 2.37−2.27 (m, 2H), 2.22−2.03 (m, 2H), 1.70 (d, *J* = 1.3 Hz, 0.84H, *Z*-**4.58a**), 1.66−1.54 (m, 2H), 1.58 (d, *J* = 1.2 Hz, 2.16H, *E*-**4.58a**), 1.30 (s, 3H), 1.26 (s, 2.16H, *E*-**4.58a**), 1.25 (s, 0.84H, *Z*-**4.58a**). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.58 (major) and 1.70 (minor) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.7, 144.1, 135.0, 129.3, 125.2, 124.3, 121.0, 114.4, 111.1, 64.3, 64.2, 58.5, 55.3, 36.5, 36.2, 29.9, 28.7, 27.6, 25.0, 23.5, 18.9, 16.1. The *E*-isomer was identified as the major isomer on the basis of its shielded methyl resonance at δ 16.1 ppm versus 23.5 ppm for the minor *Z*-isomer; HRMS (ES^{+}) *m/z:* calcd for $C_{18}H_{27}O_2$ $[M + H]^{+}$, 275.2006; found, 275.2008.

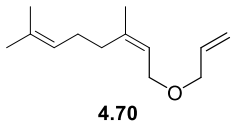
2,2-Dimethyl-3-(3-methyl-6-(p-tolyl)hex-3-en-1-yl)oxirane (4.59a)



4.59a

Following the general procedure for relay cross-metathesis using **4.26** (53 mg, 0.25 mmol, 1.0 equiv.) and **4.58** (218 mg, 1.25 mmol, 5.0 equiv.) afforded the titled compound (43 mg, 0.16 mmol, 65%) as a colourless oil. The product was isolated as a mixture of *E*/*Z* geometrical isomers (*E:Z* 72:28). R_f 0.45 (10% EtOAc in pentanes); IR (ATR, neat) 2952, 2918, 2851, 1610 cm $^{-1}$; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 4H), 5.29−5.21 (m, 1H), 2.74−2.67 (m, 1H), 2.65−2.58 (m, 2H), 2.36−2.27 (m, 2H), 2.33 (s, 3H), 2.23−2.04 (m, 2H), 1.72 (d, *J* = 1.4 Hz, 0.84H, *Z*-**4.59a**), 1.72−1.51 (m, 2H), 1.62 (s, 2.16H, *E*-**4.59a**), 1.34 (s, 3H), 1.30 (s, 2.16H, *E*-**4.59a**), 1.29 (s, 0.84H, *Z*-**4.59a**). The *E*:*Z* ratio was determined by integration of the resonances at δ 1.62 (major) and 1.72 (minor) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 139.3, 139.2, 135.2, 135.2, 134.8, 129.1, 129.0, 128.4, 125.3, 124.5, 64.2, 64.2, 58.4, 36.4, 35.9, 35.7, 30.2, 30.1, 28.6, 27.5, 27.5, 25.0, 25.0, 23.4, 21.1, 18.9, 18.8, 16.1. The *E*-isomer was identified as the major isomer on the basis of a characteristic shielded methyl resonance at 16.1 versus 23.4 ppm for the minor *Z*-isomer; HRMS (ES^{+}) *m/z:* [M + H]$^{+}$ calcd for $C_{18}H_{27}O$, 259.2062; found, 259.2056.

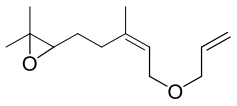
(*Z*)-1-(Allyloxy)-3,7-dimethylocta-2,6-diene (4.70)



4.70

Using a modified procedure of Rao,[163] to a mixture of neat nerol **1.25** (5.30 mL, 30 mmol, 1.0 equiv.), allyl bromide (7.8 mL, 90 mmol, 3.0 equiv.) and TBAI (554 mg, 1.50 mmol, 5 mol%) was added crushed KOH pellets (3.37 g, 60.0 mmol, 2.0 equiv.) at room temperature and the mixture was stirred for 18 h. The crude reaction mixture was purified by loading directly onto a pad of silica gel and eluted with *n*-hexane, to give titled compound **4.28** (5.81 g, 29.9 mmol, 99%) as a colourless oil. R_f 0.65 (*n*-hexane); IR (ATR, neat) 3091, 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.3, 5.6 Hz, 1H), 5.41−5.32 (m, 1H), 5.30−5.24 (m, 1H), 5.21−5.13 (m, 1H), 5.14−5.04 (m, 1H), 4.00−3.92 (m, 4H), 2.12−2.02 (m, 4H), 1.75 (d, *J* = 1.2 Hz, 3H), 1.68 (s, 3H), 1.60 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 140.4, 135.1, 131.9, 123.9, 121.8, 116.8, 71.0, 66.3, 32.3, 26.7, 25.7, 23.5, 17.6; HRMS (ES^+) *m/z:* $[M]^+$ calcd for $C_{13}H_{22}O$, 194.1671; found, 194.1670.

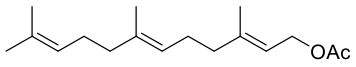
(*Z*)-3-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2-dimethyloxirane (4.69)



4.69

To a solution of (*E*)-1-(allyloxy)-3,7-dimethylocta-2,6-diene **4.69** (1.41 g, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) was added dropwise a solution of *m*CPBA (1.63 g, 77%, 7.28 mmol, 1.0 equiv.) in CH_2Cl_2 (30 mL) over *ca.* 0.5 h at 0 °C. The mixture was allowed to warm to room temperature gradually. After a total reaction time of 18 h, the reaction mixture was concentrated reduced pressure, dissolved in EtOAc (100 mL) and washed with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL), brine (100 mL), dried over Na_2SO_4, concentrated and chromatographed (20-50% Et_2O in pentanes), to give **3a** (1.60 g, 7.6 mmol, 76%) as a colourless oil. R_f 0.25 (10% EtOAc in pentanes); IR (ATR, neat) 3075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.46−5.38 (m, 1H), 5.27 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.03−3.93 (m, 4H), 2.70 (t, *J* = 6.3 Hz, 1H), 2.29−2.15 (m, 2H), 1.76 (d, *J* = 1.2 Hz, 3H), 1.71−1.54 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.5, 134.9, 122.4, 117.0, 71.2, 66.2, 63.9, 58.4, 28.9, 27.5, 24.9, 23.4, 18.7; HRMS (ES^+) *m/z:* $[M - H]^+$ calcd for $C_{13}H_{21}O$, 209.1542; found, 209.1547.

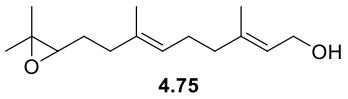
(2*E*,6*E*)-3,7,11-Trimethyldodeca-2,6,10-trien-1-yl acetate (4.73)



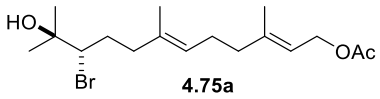
4.73

To a solution of (*E,E,E*)-farnesol (444 mg, 2.0 mmol, 1.0 equiv.) in CH_2Cl_2 (2 mL) was added acetic anhydride (408 mg, 4.0 mmol, 2.0 equiv.) and DMAP (12 mg, 0.1 mmol, 0.05 equiv.) under room temperature. The mixture was allowed to stir for 2 hours and was added methanol (5 mL). The mixture was further stirred for 1 hour and was concentrated under reduced pressure and chromatographed (10% EtOAc in PE), to give the titled compound (501 mg, 1.88 mmol, 94%) as a colourless oil. R_f 0.45 (10% EtOAc in pentanes); IR (ATR, neat) 3075, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.1 Hz, 1H), 5.16 – 5.07 (m, 2H), 4.61 (d, *J* = 7.1 Hz, 2H), 2.18 – 2.04 (m, 6H), 2.08 (s, 3H), 2.03 – 1.97 (m, 2H), 1.73 (s, 3H), 1.70 (s, 3H), 1.63 (s, 3H), 1.62 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 142.3, 135.5, 131.4, 124.3, 123.6, 118.2, 61.4, 39.7, 39.5, 26.7, 26.2, 25.7, 21.1, 17.7, 16.5, 16.0; The spectroscopic data matches those previously reported.[220]

(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dien-1-ol (4.75)



4.75



4.75a

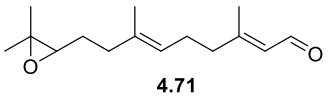
To a solution of acetate **4.73** (210 mg, 0.70 mmol, 1.0 equiv.) in THF/H_2O (1:1, 5 mL) at 0°C was added dropwise cold *N*-bromosuccinimide (116 mg, 0.7 mmol, 1.0 equiv.) solution in THF/H_2O (1:1, 5 mL) over 20 min. The mixture was allowed to stir for another 10 min and was then diluted with chloroform (10 mL) and separated. The organics were washed with brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% EtOAc in PE) to afford the bromohydrin **4.75a** (235 mg, 0.46 mmol, 66%) as a colourless oil.

The bromohydrin **4.75** was then dissolved in methanol (2 mL), added KOH (65 mg, 1.1 mmol, 2.0 equiv.) and was allowed to stir for 2 hours. The mixture was concentrated and chromatographed (30% EtOAc in PE) to afford the titled compound (155 mg, 0.46 mmol, 66% over two steps) as a colourless oil.

4.75a: R_f 0.6 (20% EtOAc in PE); IR (ATR, neat) 3470, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.37 (t, *J* = 7.2 Hz, 1H), 5.21 (t, *J* = 6.8 Hz, 1H), 4.62 (d, *J* = 7.2 Hz, 2H), 3.99 (d, *J* = 11.4, 1H), 2.36 – 2.28 (m, 1H), 2.24 (s, 1H), 2.19 – 2.06 (m, 5H), 2.08 (s, 3H), 2.04 – 1.95 (m, 1H), 1.81 – 1.76 (m, 1H), 1.73 (s, 3H), 1.62 (s, 3H), 1.37 (s, 3H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 171.2, 142.0, 133.6, 125.4, 118.4, 72.5, 70.8, 61.4, 39.4, 38.1, 32.0, 26.6, 26.1, 25.8, 21.1, 16.5, 15.9. The spectroscopic data matches those previously reported.[221]

4.75: R_f 0.2 (30% EtOAc in PE); IR (ATR, neat) 3470, 1737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.43 (dq, *J* = 6.9, 1.3 Hz, 1H), 5.18 (dq, *J* = 6.9, 1.3 Hz, 1H), 4.17 (d, *J* = 6.9 Hz, 2H), 2.73 (t, *J* = 6.2 Hz, 1H), 2.22 – 2.03 (m, 6H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.68 – 1.62 (m, 2H), 1.64 (s, 3H), 1.33 (s, 3H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 139.4, 134.4, 124.5, 123.6, 64.2, 59.4, 58.4, 39.4, 36.3, 27.3, 26.1, 24.9, 18.8, 16.2, 16.0. HRMS (CI^+) *m/z:* $[M - OAc]^+$ calcd for $C_{15}H_{25}O$, 221.1900; found, 221.1900.

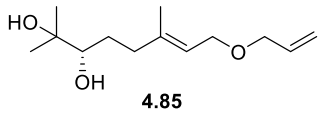
(2*E*,6*E*)-9-(3,3-Dimethyloxiran-2-yl)-3,7-dimethylnona-2,6-dienal (4.71)



4.71

To a solution of **4.73** (120 mg, 0.5 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added Dess-Martin periodinane (212 mg, 0.5 mmol, 1.0 equiv.). The reaction was allowed to stir for 2 hours and monitored by TLC. Upon completion, the reaction was quenched with saturated Na_2SO_3 aqueous solution (5 mL), saturated $NaHCO_3$ aqueous solution (5 mL) and allowed to stir for further 30 min. The mixture was separated and the aqueous was extracted with EtOAc (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (10% EtOAc in PE) to afford the titled compound (85 mg, 70%) as a pale-yellow oil. R_f 0.2 (10% EtOAc in PE); IR (ATR, neat) 1670 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 10.01 (d, J = 8.1 Hz, 1H), 5.90 (d, J = 8.1 Hz, 1H), 5.15 – 5.09 (m, 1H), 2.71 (td, J = 6.2, 1.9 Hz, 1H), 2.31 – 2.21 (m, 4H), 2.19 (s, 3H), 2.17 – 2.05 (m, 2H), 1.72 – 1.59 (m, 2H), 1.65 (s, 3H), 1.32 (s, 3H), 1.28 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 191.4, 163.8, 135.9, 127.6, 123.2, 64.2, 58.5, 40.6, 36.4, 27.5, 25.7, 25.0, 18.9, 17.7, 16.2. HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{15}H_{25}O_2$, 237.1849; found, 237.1845.

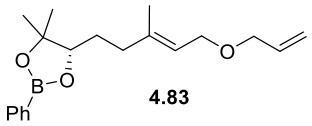
(*S*,*E*)-8-(Allyloxy)-2,6-dimethyloct-6-ene-2,3-diol (4.85)



4.85

Using a modified procedure of Sharpless,[222] to a vigorously stirred solution of AD-mix-α (7.0 g, 1.4 g mol^{-1}) in *t*-BuOH (75 mL) and H_2O (75 mL) at room temperature was added $MeSO_2NH_2$ (476 mg, 5.0 mmol, 1.0 equiv.) followed by **4.28** (972 mg, 5.0 mmol, 1.0 equiv). The reaction mixture was allowed to stir for 16 h. The mixture was quenched by the addition of a 20% Na_2SO_3 aqueous solution (150 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, concentrated, and chromatographed (40% EtOAc in PE), to afford the titled compound (632 mg, 2.8 mmol, 55%) as a colourless oil. R_f 0.36 (40% EtOAc in *n*-hexane); $[\alpha]_D^{20}$ −26.1 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3600−3100, 3075, 1666 cm^{-1} ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.47−5.37 (m, 1H), 5.28 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.19 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.03−3.93 (m, 4H), 3.36 (dd, *J* = 10.5, 2.0 Hz, 1H), 2.31 (ddd, *J* = 14.7, 9.7, 5.2 Hz, 1H), 2.16−2.06 (m, 1H), 1.99− 1.81 (br s, 2H), 1.68 (s, 3H), 1.66−1.56 (m, 1H), 1.51−1.39 (m, 1H), 1.20 (s, 3H), 1.16 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 140.1, 134.9, 121.2, 117.1, 78.1, 73.1, 71.2, 66.5, 36.6, 29.5, 26.5, 23.2, 16.5; HRMS (ES$^+$) *m/z:* [M + Na]$^+$ calcd for $C_{13}H_{24}O_3Na$ 251.1623; found, 251.1631. The enantiomeric excess was established by HPLC measurement of its benzoate derivative **4.87** as 92%.

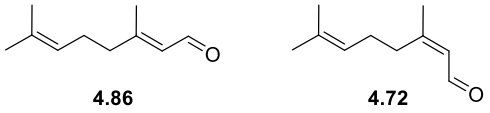
(*S,E*)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-4,4-dimethyl-2-phenyl-1,3,2-dioxaborolane (4.83)



4.83

Phenylboronic acid (315 mg, 2.63 mmol, 1.05 equiv.) was added to a solution of diol **4.85** (570 mg, 2.5 mmol, 1.0 equiv) in EtOAc (10 mL) at room temperature. After 90 min, the reaction mixture was concentrated, loaded onto a pad of silica and chromatographed (15% EtOAc in PE) to afford the titled compound (775 mg, 2.50 mmol, 99%) as a pale beige oil. R_f 0.85 (15% EtOAc in PE); $[\alpha]_D^{25}$ −17.1 (*c* 1.0, $CHCl_3$); IR (ATR, neat) 3600−3100, 3075, 1666 cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (d, *J* = 7.1 Hz, 2H), 7.51−7.42 (m, 1H), 7.41−7.33 (m, 2H), 6.00−5.89 (m, 1H), 5.46 (t, *J* = 6.6 Hz, 1H), 5.28 (d, *J* = 17.2 Hz, 1H), 5.19 (d, *J* = 10.3 Hz, 1H), 4.06 (dd, *J* = 10.3, 3.4 Hz, 1H), 4.02 (d, *J* = 6.7 Hz, 2H), 3.99 (d, *J* = 5.7 Hz, 2H), 2.48−2.38 (m, 1H), 2.23−2.12 (m, 1H), 1.81−1.69 (m, 1H), 1.73 (s, 3H), 1.68−1.59 (m, 1H), 1.44 (s, 3H), 1.29 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 139.6, 135.0, 134.8, 131.3, 127.8, 121.2, 117.1, 85.3, 82.1, 71.2, 66.6, 36.4, 29.9, 28.8, 23.5, 16.7; HRMS (EI^+) *m/z:* $[M]^{\bullet+}$ calcd for $C_{19}H_{27}{}^{11}BO_3$, 314.2053; found, 314.2062.

(*E*)-3,7-dimethylocta-2,6-dienal (4.86) and (*Z*)-3,7-dimethylocta-2,6-dienal (4.72)



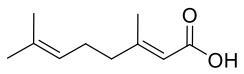
4.86 **4.72**

To geraniol **1.45** or nerol **1.25** (1.00 g, 6.5 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) at room temperature was added Dess-Martin periodinane (1.51 g, 3.6 mmol, 1.1 equiv.) and the reaction was allowed to stir for 2 h. The reaction was quenched with saturated Na_2SO_3 aqueous solution (30 mL), saturated $NaHCO_3$ aqueous solution (30 mL) and allowed to stir for further 30 min. The mixture was separated and the aqueous was extracted with EtOAc (3 × 30 mL). The combined organics were washed with brine (30 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (10% EtOAc in PE) to afford **4.86** (905 mg, 5.85 mmol, 90%) or **4.72** (875 mg, 5.72 mmol, 88%) using **1.45**/**1.25** respectively as a colourless oil.

For **4.86**: R_f 0.65 (10% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.02 (d, *J* = 8.1 Hz, 1H), 5.91 (dq, *J* = 8.1, 1.3 Hz, 1H), 5.13 – 5.06 (m, 1H), 2.31 – 2.21 (m, 4H), 2.19 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.4 Hz, 3H), 1.63 (d, *J* = 1.4 Hz, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 191.5, 164.0, 133.1, 127.5, 122.7, 40.7, 25.9, 25.8, 17.8, 17.7. The spectroscopic data matches those previously reported.[223]

For **4.72**: R_f 0.65 (10% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.92 (d, *J* = 8.3 Hz, 1H), 5.90 (dd, *J* = 8.3 1.4 Hz, 1H), 5.12 (tdt, *J* = 7.3, 2.8, 1.4 Hz, 1H), 2.61 (t, *J* = 7.5 Hz, 2H), 2.26 (q, *J* = 7.5 Hz, 2H), 2.01 (d, *J* = 1.3 Hz, 3H), 1.71 (d, *J* = 1.2 Hz, 3H), 1.62 (s, 3H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 190.9, 163.9, 133.7, 128.7, 122.3, 32.6, 27.1, 25.7, 25.1, 17.7. The spectroscopic data matches those previously reported.[223]

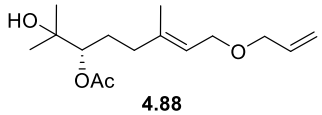
(*E*)-3,7-Dimethylocta-2,6-dienoic acid (4.82)



4.82

To a solution of geranial **4.86** (1.00 g, 6.5 mmol, 1.0 equiv.) and 2-methyl-2-butene (11.0 mL, 100 mmol, 16.0 equiv.) in acetone (20 mL) at room temperature was added a solution of 80% $NaClO_2$ (5.35 g, 52.0 mmol, 8.0 equiv.) and $NaH_2PO_4 \bullet H_2O$ (8.58 g, 55.0 mmol, 8.8 equiv.) in water (25 mL) *via* a dropping funnel over *ca.* 40 min. The reaction was allowed to stir for 4 h. The mixture was extracted with EtOAc (3 × 50 mL) and the combined organics were washed with brine (50 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% – 50% EtOAc in PE) to afford the titled compound (973 mg, 5.78 mmol, 89%) as a colourless oil. R_f 0.20 (20% EtOAc in PE); IR (ATR, neat) 3600 – 3100, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.77 – 5.62 (m, 1H), 5.10 (ddt, J = 5.4, 3.8, 1.8 Hz, 1H), 2.21 (s, 3H), 2.20 (d, J = 1.3 Hz, 4H), 1.71 (s, 3H), 1.63 (d, J = 1.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 172.6, 163.1, 132.8, 122.9, 115.4, 41.3, 26.1, 25.8, 19.3, 17.8; The spectroscopic data matches those previously reported.[224,225]

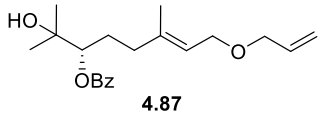
(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl acetate (4.88)



4.88

To a solution of diol **4.85** (228 mg, 1.0 mmol, 1.0 equiv.) in CH_2Cl_2 (5 mL) at room temperature was added acetic anhydride (112 mg, 1.1 mmol, 1.1 euiqv.) and DMAP (61 mg, 0.5 mmol, 0.5 equiv.). The reaction was allowed to stir for 14 h. The mixture was washed with a saturated aqueous solution of $NaHCO_3$ (3 × 10 mL) and extracted with EtOAc (3 × 50 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% – 50% EtOAc in PE) to afford the titled compound (235 mg, 0.87 mmol, 87%) as a colourless oil. R_f 0.40 (40% EtOAc in PE); IR (ATR, neat) 3600–3100, 1733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.89 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.35 – 5.29 (m, 1H), 5.27 – 5.20 (m, 1H), 5.14 (dq, *J* = 10.3, 1.4 Hz, 1H), 4.76 (dd, *J* = 10.3, 2.6 Hz, 1H), 3.98 – 3.90 (m, 4H), 2.07 (s, 3H), 2.00 – 1.95 (m, 2H), 1.80 – 1.64 (m, 2H), 1.63 (d, *J* = 1.4 Hz, 3H), 1.16 (s, 3H), 1.15 (s, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 171.4, 139.4, 135.1, 121.3, 117.2, 79.7, 72.5, 71.2, 66.6, 36.1, 27.7, 26.7, 25.0, 21.2, 16.7; HRMS (CI^+) *m/z:* $[M + Na]^+$ calcd for $C_{15}H_{26}O_4Na$, 293.1729; found, 293.1724.

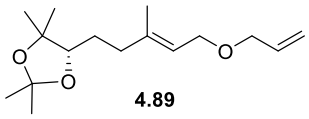
(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl benzoate (4.87)



4.87

To a solution of diol **4.85** (100 mg, 0.44 mmol, 1.0 equiv.) in pyridine (4 mL) was added benzoyl chloride (64 μL, 0.56 mmol, 1.3 equiv.). The reaction was allowed to stir for 18 h. Then additional benzoyl chloride (132 μL, 1.1 mmol, 2.6 equiv.) was added and the mixture was allowed to stir for an additional 5 h. The mixture was diluted with EtOAc (100 mL) and washed with a 1 M aqueous solution of HCl (3 × 50 mL) then with a saturated aqueous $NaHCO_3$ solution (3 × 50 mL). The combined organics were washed with brine (100 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% EtOAc in PE) to afford the titled compound (140 mg, 0.43 mmol, 97%) as a colourless oil. R_f 0.41 (40% EtOAc in PE); IR (ATR, neat) 3600–3100, 3064 1715 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.11−8.02 (m, 2H), 7.63−7.54 (m, 1H), 7.50−7.42 (m, 2H), 5.91 (ddt, *J* = 17.3, 10.4, 5.7 Hz, 1H), 5.38−5.30 (m, 1H), 5.30−5.22 (m, 1H), 5.20− 5.14 (m, 1H), 5.07 (dd, *J* = 9.6, 3.3 Hz, 1H), 4.01−3.86 (m, 4H), 2.13−2.03 (m, 2H), 1.98−1.74 (m, 3H), 1.65 (s, 3H), 1.27 (s, 6H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 166.8, 139.4, 135.1, 133.3, 130.2, 129.8, 128.6, 121.4, 117.1, 80.4, 72.8, 71.2, 66.6, 36.1, 27.9, 26.7, 25.3, 16.7; HRMS (ES^+) *m/z:* $[M + Na]^+$ calcd for $C_{20}H_{28}O_4Na$, 355.1885; found, 355.1894. HPLC (CHIRALCEL OD; 10% IPA in *n*-hexane; 0.5 mL/min) t_R = 10.1 min (major), 10.9 min (minor) (96:4).

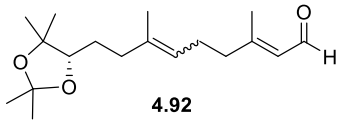
(*S,E*)-5-(5-(Allyloxy)-3-methylpent-3-en-1-yl)-2,2,4,4-tetramethyl1,3-dioxolane (4.89)



4.89

To a solution of diol **4.85** (1.05 g, 4.59 mmol, 1.0 equiv.) in CH_2Cl_2 (9 mL) at room temperature was added 2,2-dimethoxypropane (5.60 mL, 45.9 mmol, 10.0 equiv.) and pyridinium *p*-toluenesulfonate (577 mg, 2.30 mmol, 0.5 equiv.). The reaction was allowed to stir for 18 h. The mixture was concentrated under reduced pressure and chromatographed (10% EtOAc in PE) to afford the titled compound (1.11 g, 90%) as a colourless oil. R_f 0.41 (40% EtOAc in PE); R_f 0.20 (10% EA in PE); ^{1}H NMR (400 MHz, $CDCl_3$) 6.02 – 5.83 (ddt, *J* = 17.2, 10.4, 6.8, 1H), 5.39 (q, *J* = 1.4 Hz, 1H), 5.27 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dd, *J* = 10.4, 1.6 Hz, 1H), 3.99 (d, *J* = 6.8 Hz, 2H), 3.96 (dt, *J* = 5.7, 1.5 Hz, 2H), 3.65 (dd, *J* = 9.5, 3.3 Hz, 1H), 2.26 (s, 1H), 2.06 (s, 1H), 1.71 – 1.62 (m, 4H), 1.49 (m, 1H), 1.41 (s, 3H), 1.32 (s, 3H), 1.23 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 135.0, 121.1, 117.0, 106.5, 82.9, 80.1, 71.1, 66.5, 36.7, 28.6, 27.5, 26.9, 26.1, 22.9, 16.6; HRMS (EI^+) *m/z:* $[M]^{\cdot+}$ calcd for $C_{16}H_{28}O_3^+$, 268.2038; found, 268.2050.

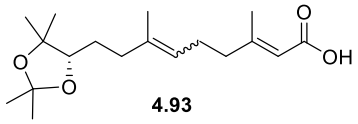
(2*E*)-3,7-Dimethyl-9-((*S*)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienal (4.92)



4.92

Following the general procedure for relay-cross-metathesis using (*S,E*)-5-(5-(allyloxy)-3-methylpent-3-en-1-yl)-2,2,4,4-tetramethyl-1,3-dioxolane **4.89** (29.3 mg, 0.11 mmol, 1.0 equiv.) and geranial **4.86** (83.7 mg, 0.55 mmol, 5.0 equiv.) afforded the titled compound (31 mg, 0.09 mmol, 91%, *E:Z* 64:36) as a pale-pink oil. R_f 0.20 (10% EA in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (d, *J* = 8.1 Hz, 1H), 5.86 (dq, *J* = 8.1, 1.2 Hz, 1H), 5.23 – 5.03 (m, 1H), 3.61 (m, 1H), 2.26 – 2.10 (m, 5H), 2.15 (d, *J* = 1.34 Hz, 3H), 2.08 – 1.92 (m, 1H), 1.67 (d, *J* = 1.4 Hz, 1H, *Z*-**4.92**), 1.61 (d, *J* = 1.4 Hz, 2H, *E*-**4.92**), 1.63 – 1.51 (m, 1H), 1.48 – 1.36 (m, 1H), 1.39 (s, 3H), 1.30 (s, 3H), 1.22 (s, 3H), 1.07 (d, *J* = 1.9 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 191.3, 163.7, 136.0, 135.9, 127.5, 127.4, 124.0, 122.9, 106.6, 106.5, 82.8, 82.5, 80.1, 80.0, 40.8, 40.5, 36.7, 28.9, 28.6, 28.6, 27.7, 27.5, 26.9, 26.9, 26.0, 26.0, 25.6, 25.4, 23.2, 22.9, 17.6, 17.6, 16.1; HRMS (ES^-) *m/z:* $[M - H + HCOOH]^-$ calcd for $C_{19}H_{31}O_5^+$, 339.2171; found, 339.2170.

(2*E*)-3,7-Dimethyl-9-((S)-2,2,5,5-tetramethyl-1,3-dioxolan-4-yl)nona-2,6-dienoic acid (4.93)

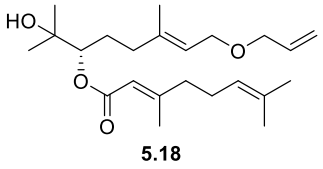


4.93

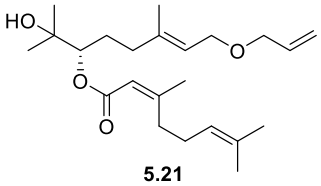
To a solution of **4.92** (39.0 mg, 0.13 mmol, 1.0 equiv.) and 2-methyl-2-butene (0.60 mL, 5.4 mmol, 41.5 equiv.) in acetone (2 mL) was added a solution of 80% $NaClO_2$ (105 mg, 1.1 mmol, 8.5 equiv.) and $NaH_2PO_4 \bullet H_2O$ (134 mg, 0.91 mmol, 7.0 equiv.) in water (2 mL) *via* a dropping funnel over *ca.* 40 min. The reaction was allowed to stir for 4 h. The mixture was extracted with EtOAc (3 × 5 mL) and the combined organics were washed with brine (5 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% – 50% EtOAc in PE) to afford the titled compound (41 mg, quant.) as a colourless oil. R_f 0.20 (40% EtOAc in PE); IR (ATR, neat) 3600 – 3200, 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.76 – 5.68 (m, 1H), 5.23 (tq, *J* = 7.2, 1.4 Hz, 1H), 3.75 – 3.61 (m, 1H), 2.74 – 2.58 (m, 2H), 2.31 – 2.14 (m, 4H), 2.10 – 1.99 (m, 1H), 1.95 (d, *J* = 1.3 Hz, 3H), 1.72 (d, *J* = 1.3 Hz, 0.63H, *Z*-4.93), 1.70 – 1.57 (m, 1H), 1.66 (d, *J* = 1.3 Hz, 2.33H, *E*-4.93), 1.54 – 1.45 (m, 1H), 1.44 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.12 (s, 1.95H, *E*-4.93), 1.11 (s, 1.05H, *Z*-4.93); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 170.8, 163.3, 135.4, 123.7, 115.6, 106.5, 82.9, 80.1, 36.7, 33.6, 28.6, 27.7, 26.9, 26.7, 26.1, 25.7, 22.9, 16.0; HRMS (CI^+) *m/z:* $[M + Na]^+$ calcd for $C_{18}H_{30}O_4Na^+$, 333.2042; found, 333.2040.

Experimental for Chapter 5

(*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl (*E*)-3,7-dimethylocta-2,6-dienoate (5.18) and (*S*,*E*)-8-(Allyloxy)-2-hydroxy-2,6-dimethyloct-6-en-3-yl (*Z*)-3,7-dimethylocta-2,6-dienoate (5.21)



5.18



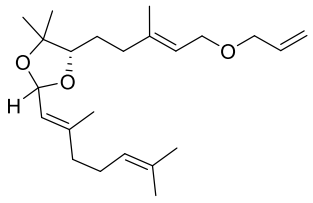
5.21

To a solution of geranic acid **4.83** (202 mg, 1.2 mmol, 1.0 equiv.) in toluene (10 mL) at 0°C was added dropwise oxalyl chloride (0.508 mL, 6.0 mmol, 5.0 equiv.) over *ca.* 15 min. The mixture was allowed to warm to room temperature and was stirred for 2 h. The mixture was concentrated under reduced pressure to give crude acid chloride **5.23** (204 mg, 89%). The crude acid chloride was immediately used without further purifications.

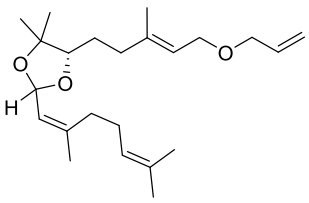
To a solution of diol **4.85** (137 mg, 0.60 mmol, 1.0 equiv.) in toluene (10 mL) at room temperature was added DMAP (73.3 mg, 0.60 mmol, 1.0 equiv.), potassium carbonate (663 mg, 4.8 mmol, 8.0 equiv.) and freshly prepared acid chloride **5.23** (112 mg, 0.60 mmol, 1.0 equiv.). The reaction was allowed to stir for 16 h. The reaction was quenched with a saturated aqueous solution of NH_4Cl (20 mL). The organic was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (20% – 50% EtOAc in PE) to afford an inseparable mixture of **5.18** and **5.21** (142 mg, 0.53 mmol, 88%, **5.18**:**5.21** 58:42). The diastereomeric ratio was measured by the integration of characteristic resonance at δ 2.70 – 2.59 (CH_2, **5.21**) and 1.91 (CH_3, **5.18**). R_f 0.25 (20% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) 5.96 – 5.83 (m, 1H), 5.74 – 5.70 (m, 0.58H, **5.18**), 5.70 – 5.66 (m, 0.42H, **5.21**), 5.40 – 5.33 (m, 1H), 5.24 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.18 – 5.12 (m, 1H), 5.10 – 5.01 (m, 1H), 4.85 – 4.73 (m, 1H), 3.99 – 3.85 (m, 4H), 2.70 – 2.59 (m, 0.84H, **5.21**), 2.21 – 2.13 (m, 7H), 2.10 – 2.03 (m, 2H), 1.91 (d, *J* = 1.4 Hz, 1.16H, **5.21**), 1.76 – 1.63 (m, 2H), 1.73 (s, 3H), 1.68 – 1.66 (m, 3H), 1.77 – 1.64 (m, 1H), 1.60 (s, 3H), 1.19 (s, 3H), 1.18 (s, 1.74H, **5.18**), 1.18 (s, 1.26H, **5.21**); ^{13}C NMR (101 MHz, $CDCl_3$) δ171.4, 167.0, 162.9, 161.4, 140.2, 135.1, 132.8, 132.7, 123.6, 123.0, 122.9, 122.2, 117.1, 115.9, 115.3, 115.2, 78.8, 78.7, 72.7, 71.2,

66.3, 41.3, 41.2, 31.7, 29.0, 28.4, 26.9, 26.8, 26.2, 26.1, 25.8, 25.1, 23.5, 19.2, 19.1, 17.8; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{23}H_{41}O_3^+$, 365.3050; found, 365.3043.

(5*S*)-5-((*E*)-5-(Allyloxy)-3-methylpent-3-en-1-yl)-2-((*E*)-2,6-dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-1,3-dioxolane (5.30) and (5*S*)-5-((*E*)-5-(Allyloxy)-3-methylpent-3-en-1-yl)-2-((*Z*)-2,6-dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-1,3-dioxolane (5.31)



5.30



5.31

To a solution of diol **4.85** (100 mg, 0.44 mmol, 1.0 equiv.) in CH_2Cl_2 (4.3 mL) at room temperature was added geranial **4.86** or neral **4.72** (333 mg, 2.19 mmol, 5.0 equiv.), pyridinium *p*-toluenesulfonate (55 mg, 0.22 mmol, 0.5 equiv.) and activated 4 Å molecular sieves. The reaction was allowed to stir for 16 h. The mixture was concentrated under reduced pressure and chromatographed (10% EtOAc in PE) to afford an inseparable mixture of **5.30** and **5.31** (142 mg, 0.39 mmol, 88%, **5.30**:**5.31** 56:44, *syn*:*anti* ~ 2:13) using geranial **4.86** or (121 mg, 75%, 0.33 mmol, **5.30**:**5.31** 38:62) as a colourless oil. The ratio of **5.30**:**5.31** was determined by integrating the acetal proton at δ 5.78/5.61 (**5.30)** and 5.74/5.58 (**5.31**). The minor diastereomers were tentatively assigned as *syn*-isomers due to transannular interactions. R_f 0.20 (20% EA in PE); IR (ATR, neat) 1673, 1375, 1051 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.96 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.78 (d, *J* = 7.7 Hz, 0.09H, *syn*-**5.30**), 5.74 (d, *J* = 7.8 Hz, 0.05H, *syn*-**5.31**), 5.61 (d, *J* = 7.6 Hz, 0.54H, *anti*-**5.30**), 5.58 (d, *J* = 7.7 Hz, 0.35H, *anti*-**5.31**), 5.46 – 5.38 (m, 1H), 5.30 (dq, *J* = 17.2, 1.8 Hz, 1H), 5.26 – 5.18 (m, 2H), 5.18 – 5.07 (m, 1H), 4.09 – 3.96 (m, 4H), 3.65 – 3.60 (m, 0.14H, *syn*-**5.30** and *syn*-**5.31**), 3.59 – 3.51 (m, 0.86H, *anti*-**5.30** and *anti*-**5.31**), 2.40 – 2.27 (m, 1H), 2.22 – 2.01 (m, 6H), 1.81 – 1.76 (m, 3H), 1.74 – 1.68 (m, 7H), 1.65 – 1.60 (m, 3H), 1.30 (s, 1.68H, **5.30**), 1.29 (s, 1.32H, **5.31**), 1.16 (s, 1.68H, **5.30**), 1.15 (s, 1.32H, **5.31**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 139.7, 135.1, 124.0, 123.9, 123.3, 122.2, 121.2, 117.2, 98.0, 97.7, 85.0, 79.6, 71.2, 66.7, 39.7, 36.8, 32.7, 27.9, 27.1, 26.2, 25.8, 25.5, 23.8, 23.6,

17.8, 17.0, 16.7; HRMS (CI^+) *m/z:* $[M + H]^+$ calcd for $C_{23}H_{39}O_3^+$, 363.2899; found, 363.2909.

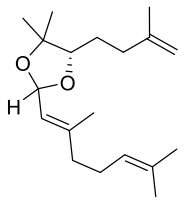
General procedure for RRCM reactions under diluted conditions

To the RRCM substrate was added degassed solvent (by purging with nitrogen) and catalyst. The reaction mixture was under vigorous stirring to promote the removal of volatiles and heated if required using an oil bath. Upon completion of the reaction, the mixture was concentrated under reduced pressure and chromatographed.

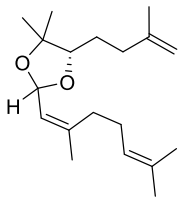
General procedure for RRCM reactions under neat conditions

Similar to the procedure of ReXM reactions. To the neat mixture of RRCM substrate was added catalyst. The mixture was heated to 50°C using an oil bath under a strong positive pressure of nitrogen gas *via* a needle inlet/outlet setup to aid the removal of volatiles. Upon completion of the reaction, the mixture was loaded directly onto a column of silica gel and chromatographed.

(5*S*)-2-((*E*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-5-(3-methylbut-3-en-1-yl)-1,3-dioxolane (5.32) and (5*S*)-2-(*Z*)-2,6-Dimethylhepta-1,5-dien-1-yl)-4,4-dimethyl-5-(3-methylbut-3-en-1-yl)-1,3-dioxolane (5.33)



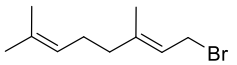
5.32



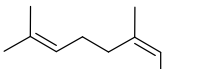
5.33

Following the general procedure of RRCM reaction under diluted conditions using a solution of **5.30/5.31** (36.0 mg, 0.10 mmol, 1.0 equiv. **5.30**:**5.31** 56:44) in CH_2Cl_2 (20 mL) and **GII** catalyst (17.0 mg, 0.020 mmol, 0.2 equiv.) afforded an inseparable mixture of **5.32**/**5.33** (23.4 mg, 80%, **5.32**:**5.33** 60:40) as a pale-brown oil. The ratio of **5.30**:**5.31** was determined by integrating the acetal proton at δ 5.78/5.62 ppm (**5.32**) and 5.74/5.58 ppm (**5.33**). The minor diastereomers were tentatively assigned as *syn*-isomers due to unfavourable transannular interactions. R_f 0.20 (20% EA in PE); IR (ATR, neat) 1666, 1375, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.78 (d, *J* = 7.7 Hz, 0.09H, *syn*-**5.32**), 5.74 (d, *J* = 7.8 Hz, 0.06H, *syn*-**5.33**), 5.61 (d, *J* = 7.6 Hz, 0.52H, *anti*-**5.32**), 5.58 (d, *J* = 7.7 Hz, 0.34H, *anti*-**5.33**), 5.28 – 5.24 (m, 0.12H, *syn*-**5.32** and *syn*-**5.33**), 5.24 – 5.18 (m, 0.86H, *anti*-**5.32** and *anti*-**5.33**), 5.15 – 5.07 (m, 1H), 4.79 – 4.68 (m, 2H), 3.65 – 3.60 (m, 0.15H, *syn*-**5.32** and *syn*-**5.33**), 3.59 – 3.50 (m, 0.85H, *anti*-**5.32** and *anti*-**5.33**), 2.31 – 2.21 (m, 1H), 2.22 – 1.97 (m, 5H), 1.78 – 1.72 (m, 6H), 1.71 – 1.63 (m, 4H), 1.61 – 1.50 (m, 4H), 1.28 (s, 1.80H, **5.32**), 1.26 (s, 1.20H, **5.33**), 1.14 (s, 1.80H, **5.32**), 1.13 (s, 1.20H, **5.33**); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.3, 144.7, 144.5, 131.9, 124.0, 123.9, 123.3, 122.2, 110.2, 98.0, 97.6, 84.9, 84.9, 79.6, 39.7, 35.0, 32.7, 29.8, 27.8, 27.1, 26.2, 25.8, 25.5, 23.8, 23.6, 22.7, 17.8, 17.0; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{19}H_{33}O3^+$, 293.2475; found, 293.2468.

(*E*)-1-Bromo-3,7-dimethylocta-2,6-diene (5.40) and (*Z*)-1-Bromo-3,7-dimethylocta-2,6-diene (5.41)



5.40



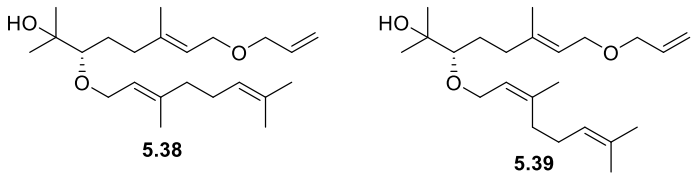
5.41

To a solution of geraniol **1.45** or nerol **1.25** (1.00 g, 6.5 mmol, 1.0 equiv.) in Et_2O (6.5 mL) at 0°C was added dropwise PBr_3 (1.51 g, 3.6 mmol, 0.5 equiv.) and the reaction was allowed to stir for 4 h. The reaction was quenched with a saturated $NaHCO_3$ solution (10 mL) and allowed to stir for further 30 min. The mixture was separated and the aqueous phase was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure to afford 5.40 (1.41 g, 6.50 mmol, quant.) or 5.41 (1.41 g, 6.50 mmol, quant.) using 1.45/1.25 respectively as a colourless oil. The bromide 5.40/5.41 were used immediately without further purification in subsequent reactions.

For **5.40**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (tq, *J* = 8.4, 1.3 Hz, 1H), 5.10 (m, 1H), 4.06 (d, *J* = 8.4 Hz, 2H), 2.19 – 2.05 (m, 4H), 1.75 (s, 3H), 1.71 (s, 3H), 1.63 (d, *J* = 1.3 Hz, 3H). The spectroscopic data matches those previously reported.[226]

For **5.41**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.56 (td, *J* = 8.5, 1.6 Hz, 1H), 5.14 (m, 1H), 4.04 (d, *J* = 8.5 Hz, 2H), 2.22 – 2.07 (m, 4H), 1.81 (d, *J* = 1.4 Hz, 3H), 1.72 (s, 3H), 1.65 (d, *J* = 1.4 Hz, 3H). The spectroscopic data matches those previously reported.[227]

(*S*,*E*)-8-(Allyloxy)-3-(((*E*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-2,6-dimethyloct-6-en-2-ol (5.38) and (*S*,*E*)-8-(allyloxy)-3-(((*Z*)-3,7-dimethylocta-2,6-dien-1-yl)oxy)-2,6-dimethyloct-6-en-2-ol (5.39)



5.38 5.39

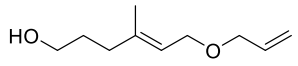
To a solution of diol **4.85** (100 mg, 0.44 mmol, 1.0 equiv.) in THF (1 mL) at -78°C was added NaH (12.6 mg, 0.52 mmol, 1.2 equiv., 60% in paraffin oil) and the solution was allowed to stir for 1 hour. Freshly prepared bromide **5.40**/**5.41** (104 mg, 0.48 mmol, 1.1 equiv.) was then added and the mixture was allowed to warm to room temperature and stirred for further 16 h. The reaction was quenched with water (20 mL) and THF was removed under reduced pressure. The aqueous was extracted with Et_2O (3 × 20 mL), washed with brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (10% Et_2O in PE) to afford **5.38** (96 mg, 0.26 mmol, 60%) or **5.39** (25 mg, 0.073 mmol, 16%) as a colourless oil, using **5.40** and **5.41** respectively.

For **5.38**: R_f 0.15 (10% Et_2O in PE); IR (ATR, neat) 1670, 1066 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.5, 10.5, 5.7 Hz, 1H), 5.45 – 5.34 (m, 2H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.19 – 4.04 (m, 2H), 4.02 – 3.91 (m, 4H), 3.04 (dt, *J* = 8.6, 4.3 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.13 – 2.01 (m, 5H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.70 – 1.52 (m, 2H), 1.67 (s, 6H), 1.59 (d, *J* = 1.4 Hz, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.1, 139.9, 135.0, 131.7, 123.9, 121.1, 121.0, 117.0 (2 carbons), 86.5, 73.2, 71.1, 69.7, 66.5, 39.6, 36.9, 29.5, 26.6, 26.4, 25.7, 24.5, 17.7, 16.6; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{23}H_{41}O_3^+$, 365.3056; found, 365.3054.

For **5.39**: R_f 0.20 (10% Et_2O in PE); ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.5, 10.5, 5.7 Hz, 1H), 5.45 – 5.34 (m, 2H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.19 – 4.04 (m, 2H), 4.02 – 3.91 (m, 4H), 3.04 (dt, *J* = 8.6, 4.3 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.13 – 2.01 (m, 5H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.70 – 1.52 (m, 2H), 1.67 (s, 6H), 1.59 (d, *J* = 1.4 Hz, 3H), 1.18 (s, 3H), 1.14 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 140.2, 135.1, 132.1, 123.8,

122.1, 121.2, 117.1, 86.6, 73.3, 71.2, 69.5, 66.7, 37.0, 32.4, 29.6, 26.8, 26.7, 25.8, 24.7, 23.6, 17.8, 16.7; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{23}H_{40}O_3Na^+$, 387.2875; found, 387.2872.

(*E*)-6-(Allyloxy)-4-methylhex-4-en-1-ol (5.58)

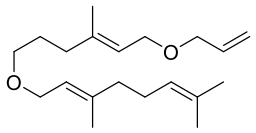


5.58

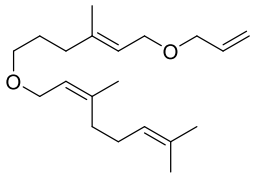
To a solution of diol **4.85** (274 mg, 1.2 mmol, 1.0 equiv.) in THF/H_2O (7 mL, 1:1 THF:H_2O) at 0°C was added sodium periodate (471 mg, 2.2 mmol, 1.83 equiv.) and the reaction was stirred for 20 h. The reaction was quenched by addition of a saturated aqueous solution of Na_2SO_3 (20 mL). THF then was removed under reduced pressure and the aqueous was extracted with Et_2O (3 × 20 mL). The combined organics were washed with brine (20 mL), dried over $MgSO_4$, concentrated under reduced pressure to afford the crude aldehyde (160 mg, 0.95 mmol, 78%) as a colourless oil.

The crude aldehyde was immediately dissolved in methanol (5 mL) at room temperature and sodium borohydride (73 mg, 1.8 mmol, 2.5 equiv.) was added in three portions. The reaction was stirred for 30 min and quenched by addition of a saturated aqueous solution of NH_4Cl (5 mL). Methanol was removed under reduced pressure and the aqueous was extracted with Et_2O (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over $MgSO_4$, concentrated under reduced pressure and chromatographed (10% EtOAc in PE) to afford the titled compound (102 mg, 0.60 mmol, 50% over two steps) as a colourless oil. R_f 0.30 (10% EtOAc in PE); IR (ATR, neat) 3600 – 3200, 1070 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 5.95 (ddt, *J* = 17.2, 10.3, 5.7 Hz, 1H), 5.42 (tq, *J* = 6.8, 1.3 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.21 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.06 – 3.96 (m, 4H), 3.67 (t, *J* = 6.5 Hz, 2H), 2.14 (t, *J* = 7.7 Hz, 2H), 1.81 – 1.71 (m, 2H), 1.71 (d, *J* = 1.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 138.0, 134.8, 121.8, 117.2, 71.2, 66.4, 62.1, 41.8, 31.5, 16.7; HRMS (ES^+) *m/z:* $[M]^{\bullet+}$ calcd for $C_{10}H_{18}O_2^+$, 169.1229; found, 169.1221.

(*E*)-1-(((*E*)-6-(Allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.57) and (*Z*)-1-(((*E*)-6-(allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.57)



5.57



5.59

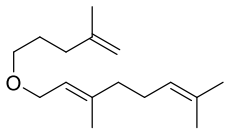
To alcohol **5.58** (100 mg, 0.59 mmol, 1.0 equiv.) at 0°C was added *t*-BuOK (80.6 mg, 0.72 mmol, 1.2 equiv.) and the mixture was allowed to stir for 1 hour. Freshly prepared bromide **5.40**/**5.41** (148 mg, 0.72 mmol, 1.2 equiv.) and tetrabutylammonium iodide (111 mg, 0.30 mmol, 0.5 equiv.) was then added. The mixture was allowed warm to room temperature and stirred for further 16 h. The mixture was directly loaded onto a column of silica gel and chromatographed (10% – 20% EtOAc in PE) to afford **5.57** (85 mg, 0.29 mmol,48%) or **5.39** (84 mg, 0.29 mmol, 48%) as a colourless oil, using **5.40** and **5.41** respectively.

For **5.57**: R_f 0.25 (10% Et_2O in PE); IR (ATR, neat) 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.5, 10.5, 5.7 Hz, 1H), 5.45 – 5.34 (m, 2H), 5.27 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.5 Hz, 1H), 5.12 – 5.03 (m, 1H), 4.19 – 4.04 (m, 2H), 4.02 – 3.91 (m, 2H), 3.04 (dt, *J* = 8.6, 4.3 Hz, 1H), 2.34 – 2.24 (m, 1H), 2.13 – 2.01 (m, 5H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.70 – 1.52 (m, 2H), 1.67 (s, 3H), 1.59 (d, *J* = 1.4 Hz, 3H), 1.18 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 135.2, 131.7, 124.2, 121.2, 121.1, 117.0 (2 carbons), 71.1, 69.9, 67.4, 66.7, 39.7, 36.2, 27.9, 26.5, 25.8, 17.8, 16.6, 16.5; HRMS (ES^+) *m/z:* $[M + Na]^+$ calcd for $C_{20}H_{34}O_2Na^+$, 329.4257; found, 329.2466.

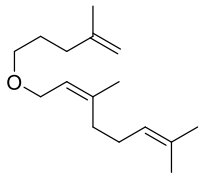
For **5.59**: R_f 0.33(10% Et_2O in PE); IR (ATR, neat) 1640, 1096 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.92 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.39 – 5.31 (m, 2H), 5.26 (dq, *J* = 17.2, 1.6 Hz, 1H), 5.17 (dq, *J* = 10.4, 1.4 Hz, 1H), 5.13 – 5.05 (m, 1H), 4.03 – 3.90 (m, 6H), 3.38 (t, *J* = 6.7 Hz, 2H), 2.16 – 1.99 (m, 7H), 1.76 – 1.71 (m, 4H), 1.66 (dd, *J* = 7.2, 1.3 Hz, 7H), 1.60 (d, *J* = 1.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 140.0, 135.2, 132.0, 124.0, 122.2, 121.1, 117.1, 71.1, 70.0, 67.1, 66.7, 36.2, 32.4, 27.9,

26.9, 25.8, 23.6, 17.8, 16.5; HRMS (ES^+) *m/z:* $[M + Na]^+$ calcd for $C_{20}H_{34}O_2Na^+$, 329.4257; found, 329.2463.

(*E*)-3,7-Dimethyl-1-((4-methylpent-4-en-1-yl)oxy)octa-2,6-diene (5.60) and (*Z*)-1-(((*E*)-6-(allyloxy)-4-methylhex-4-en-1-yl)oxy)-3,7-dimethylocta-2,6-diene (5.61)



5.60



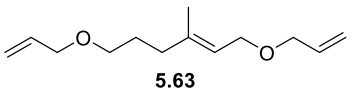
5.61

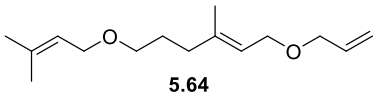
Following the general procedure of RRCM under diluted conditions using **5.57** or **5.59** (25 mg, 0.083 mmol, 1.0 equiv.), **GII** catalyst (7.0 mg, 0.0083 mmol, 0.10 equiv.) and toluene (50 mL) under 80°C for 16 h, afforded **5.60** (10.0 mg, 0.042 mmol, 53%) or **5.61** (13.6 mg, 0.058 mmol, 72%) as a colourless oil, using **5.60** and **5.61** respectively.

For **5.60**: R_f 0.25 (10% EtOAc in PE); ^1H NMR (400 MHz, $CDCl_3$) δ 5.39 – 5.31 (m, 1H), 5.13 – 5.03 (m, 1H), 4.69 (d, *J* = 8.4 Hz, 2H), 3.97 (dd, *J* = 6.7, 1.0 Hz, 2H), 3.41 (t, *J* = 6.7 Hz, 2H), 2.14 – 1.99 (m, 6H), 1.78 – 1.70 (m, 5H), 1.68 (s, 3H), 1.66 (d, *J* = 1.3 Hz, 3H), 1.60 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 145.6, 139.9, 131.7, 124.1, 121.2, 110.0, 69.9, 67.4, 39.7, 34.4, 27.9, 26.5, 25.8, 22.5, 17.8, 16.6; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{16}H_{29}O^+$, 237.2213; found, 237.2209.

For **5.61**: R_f 0.33(10% EtOAc in PE); ^1H NMR (400 MHz, $CDCl_3$) 5.44 – 5.30 (m, 1H), 5.20 – 5.06 (m, 1H), 4.81 – 4.65 (m, 2H), 4.06 – 3.91 (m, 2H), 3.44 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 6H), 2.11 (s, 2H), 1.78 (d, *J* = 1.3 Hz, 3H), 1.75 (s, 1H), 1.72 (d, *J* = 1.6 Hz, 4H), 1.64 (d, *J* = 1.6 Hz, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.7, 135.1, 134.9, 131.4, 127.9, 121.3, 117.2, 85.5, 82.2, 71.3, 66.7, 36.5, 30.0, 28.9, 23.6, 16.8; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{16}H_{29}O^+$, 237.2213; found, 237.2212.

(*E*)-1,6-Bis(allyloxy)-3-methylhex-2-ene (5.63) and (*E*)-1-(allyloxy)-3-methyl-6-((3-methylbut-2-en-1-yl)oxy)hex-2-ene (5.64)


5.63


5.64

To alcohol **5.58** (100 mg, 0.59 mmol, 1.0 equiv.) at room temperature was added KOH pellets (67.3 mg, 1.2 mmol, 2.0 equiv.) and the mixture was allowed to stir for 1 hour. To the mixture was then added allyl bromide (0.26 mL, 3.0 mmol, 5.0 equiv.) or prenyl bromide (447 mg, 3.0 mmol, 5.0 equiv.) and tetrabutylammonium iodide (111 mg, 0.30 mmol, 0.5 equiv.). The mixture was allowed to stir for further 16 h. Excessive allyl bromide or prenyl bromide was removed under reduced pressure. The resulting mixture was directly loaded onto a column of silica gel and chromatographed (10% EtOAc in PE) to afford **5.63** (124 mg, 0.59 mmol, quant.) or **5.64** (129 mg, 0.57 mmol, 96%) as a colourless oil, using allyl bromide and prenyl bromide respectively.

For **5.63**: R_f 0.35 (10% EtOAc in PE); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.01 – 5.81 (m, 2H), 5.43 – 5.32 (m, 1H), 5.32 – 5.22 (m, 2H), 5.22 – 5.10 (m, 2H), 4.06 – 3.91 (m, 6H), 3.41 (t, *J* = 6.6 Hz, 2H), 2.13 – 2.05 (m, 2H), 1.76 – 1.68 (m, 2H), 1.66 (d, *J* = 1.3 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.9, 135.1, 121.1, 117.1, 116.8, 110.1, 71.9, 71.1, 70.0, 66.7, 36.1, 27.9, 16.5; HRMS (ES^+) *m/z:* $[M + H]^+$ calcd for $C_{13}H_{23}O_2^+$, 211.1688; found, 211.1681.

For **5.64**: R_f 0.35 (10% EtOAc in PE); IR (ATR, neat) 1640, 1096 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.2, 10.4, 5.7 Hz, 1H), 5.38 – 5.30 (m, 2H), 5.25 (dq, *J* = 17.2, 1.7 Hz, 1H), 5.16 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.01 – 3.87 (m, 6H), 3.38 (t, *J* = 6.7 Hz, 2H), 2.13 – 2.01 (m, 2H), 1.73 (d, *J* = 1.3 Hz, 3H), 1.71 – 1.66 (m, 2H), 1.67 – 1.60 (m, 6H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.6, 136.5, 134.8, 121.1, 120.8, 116.7, 70.7, 69.6, 67.0, 66.3, 35.9, 27.6, 25.6, 17.8, 16.2; HRMS (ES^+) *m/z:* $[M]^{\bullet+}$ calcd for $C_{15}H_{26}O_2^+$, 238.1928; found, 238.1928.

References

(1) Firn, R. *Nature's Chemicals*; Oxford: Biology, 2010.

(2) Arroo, R. Eberhard Breitmaier. Terpenes—Flavors, Fragrances, Pharmaca, Pheromones. Wiley-VCH, 2006, 214 Pp ISBN 3-527-31786-4. *Appl. Organomet. Chem.* **2007**, *21*.

(3) Miziorko, H. M. Enzymes of the Mevalonate Pathway of Isoprenoid Biosynthesis. *Arch. Biochem. Biophys.* **2011**, *505*, 131–143.

(4) Rohmer, M. From Molecular Fossils of Bacterial Hopanoids to the Formation of Isoprene Units: Discovery and Elucidation of the Methylerythritol Phosphate Pathway. *Lipids* **2008**, *43*, 1095–1107.

(5) Thulasiram, H. V.; Erickson, H. K.; Poulter, C. D. Chimeras of Two Isoprenoid Synthases Catalyze All Four Coupling Reactions in Isoprenoid Biosynthesis. *Science (80-.).* **2007**, *316*, 73–76.

(6) Liang, P.-H.; Ko, T.-P.; Wang, A. H.-J. Structure, Mechanism and Function of Prenyltransferases. *Eur. J. Biochem.* **2002**, *269*, 3339–3354.

(7) Oldfield, E.; Lin, F. Y. Terpene Biosynthesis: Modularity Rules. *Angew. Chem. Int. Ed.* **2012**, *51*, 1124–1137.

(8) Croteau, R. Biosynthesis and Catabolism of Monoterpenoids. *Chem. Rev.* **1987**, *87*, 929–954.

(9) Christiansont, D. W. Managing and Manipulating Carbocations in Biology : Terpenoid Cyclase Structure and Mechanism Charles A Lesburg *, Jonathan M Carutherst , Chiana M Paschallt And. *Curr. Opin. Struct. Biol.* **1998**, *8*, 695–703.

(10) Cane, D. E. Enzymic Formation of Sesquiterpenes. *Chem. Rev.* **1990**, *90*, 1089–1103.

(11) Dickschat, J. S. Bacterial Diterpene Biosynthesis. *Angew. Chem. Int. Ed.* **2019**, *58*, 15964–15976.

(12) Minami, A.; Ozaki, T.; Liu, C.; Oikawa, H. Cyclopentane-Forming Di/Sesterterpene Synthases: Widely Distributed Enzymes in Bacteria, Fungi, and Plants. *Nat. Prod. Rep.* **2018**, *35*, 1330–1346.

(13) Abe, I. Enzymatic Synthesis of Cyclic Triterpenes. *Nat. Prod. Rep.* **2007**, *24*, 1311.

(14) Behrman, E. J.; Gopalan, V. Cholesterol and Plants. *J. Chem. Educ.* **2005**, *82*, 1791.

(15) Schaller, H. The Role of Sterols in Plant Growth and Development. *Prog. Lipid Res.* **2003**, *42*, 163–175.

(16) Russell, D. W.; Setchell, K. D. R. Bile Acid Biosynthesis. *Biochemistry* **1992**, *31*, 4737–4749.

(17) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Simple Reagents for Direct Halonium-Induced Polyene Cyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

(18) Citron, C. A.; Rabe, P.; Barra, L.; Nakano, C.; Hoshino, T.; Dickschat, J. S. Synthesis of Isotopically Labelled Oligoprenyl Diphosphates and Their Application in Mechanistic Investigations of Terpene Cyclases. *Eur. J. Org. Chem.* **2014**, *2014*, 7684–7691.

(19) Zhang, Q.; Tiefenbacher, K. Sesquiterpene Cyclizations inside the Hexameric Resorcinarene Capsule: Total Synthesis of δ-Selinene and Mechanistic Studies. *Angew. Chem. Int. Ed.* **2019**, *58*, 12688–12695.

(20) Rinkel, J.; Lauterbach, L.; Dickschat, J. S. Spata-13,17-Diene Synthase—An Enzyme with Sesqui-, Di-, and Sesterterpene Synthase Activity from Streptomyces Xinghaiensis. *Angew. Chem. Int. Ed.* **2017**, *56*, 16385–16389.

(21) Yu, J. S.; Kleckley, T. S.; Wiemer, D. F. Synthesis of Farnesol Isomers *via* a Modified Wittig Procedure. *Org. Lett.* **2005**, *7*, 4803–4806.

(22) Corey, E. J.; Yamamoto, H. Simple, Stereospecific Syntheses of C17- and C18-Cecropia Juvenile Hormones (Racemic) from a Common Intermediate. *J. Am.*

Chem. Soc. **1970**, *92*, 6636–6637.

(23) Corey, E. J.; Yamamoto, H. Modification of the Wittig Reaction to Permit the Stereospecific Synthesis of Certain Trisubstituted Olefins. Stereospecific Synthesis of α-Santalol. *J. Am. Chem. Soc.* **1970**, *92*, 226–228.

(24) Schlosser, M.; Christmann, K. F. Trans-Selective Olefin Syntheses. *Angew. Chem. Int. Ed.* **1966**, *5*, 126–126.

(25) Bondinell, W. E.; Snyder, C. D.; Rapoport, H. Synthesis of Chlorobiumquinone. *J. Am. Chem. Soc.* **1969**, *91*, 6889–6891.

(26) Morgan, E. D.; Thompson, L. D. Synthesis of (Z,E)- and (Z,Z)-α-Farnesenes and -Homofarnesenes. *J. Chem. Soc., Perkin Trans. 1* **1985**, *63*, 399–404.

(27) Negishi, E. I.; Liou, S. Y.; Xu, C.; Huo, S. A Novel, Highly Selective, and General Methodology for the Synthesis of 1,5-Diene-Containing Oligoisoprenoids of All Possible Geometrical Combinations Exemplified by an Iterative and Convergent Synthesis of Coenzyme Q10. *Org. Lett.* **2002**, *4*, 261–264.

(28) Okukado, N.; Negishi, E. ichi. One-Step Conversion of Terminal Acetylenes into Terminally Functionalized (E)-3-Methyl-2-Alkenes *via* Zircomium-Catalyzed Carboalumination. A Simple and Selective Route to Terpenoids. *Tetrahedron Lett.* **1978**, *19*, 2357–2360.

(29) Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato, M. Specific Hydromagnesiation of Prop-2-Ynylic Alcohols. A Simple and Specific Route to Terpenoids. *J. Chem. Soc. Chem. Commun.* **1981**, No. 14, 718–720.

(30) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Simple Reagents for Direct Halonium-Induced Polyene Cyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

(31) Brown, R. C. D.; Bataille, C. J.; Hughes, R. M.; Kenney, A.; Luker, T. J. Permanganate Oxidation of 1,5,9-Trienes: Stereoselective Synthesis of Tetrahydrofuran-Containing Fragments. *J. Org. Chem.* **2002**, *67*, 8079–8085.

(32) Xie, H.; Shao, Y.; Becker, J. M.; Naider, F.; Gibbs, R. A. Synthesis and Biological Evaluation of the Geometric Farnesylated Analogues of the A-Factor Mating Peptide of Saccharomyces Cerevisiae. *J. Org. Chem.* **2000**, *65*, 8552–8563.

(33) Gampe, C. M.; Tsukamoto, H.; Wang, T. S. A.; Walker, S.; Kahne, D. Modular Synthesis of Diphospholipid Oligosaccharide Fragments of the Bacterial Cell Wall and Their Use to Study the Mechanism of Moenomycin and Other Antibiotics. *Tetrahedron* **2011**, *67*, 9771–9778.

(34) Hayashi, N.; Nakada, M. Asymmetric Total Synthesis of MK8383: The Iron-Mediated Coupling Reaction Is the Only Effective Method for the Construction of the (Z)-Trisubstituted Side-Chain Alkene. *Tetrahedron Lett.* **2009**, *50*, 232–235.

(35) Biellmann, J. F.; Ducep, J. B. Synthese Du Squalene Par Couplage Queue a Queue. *Tetrahedron Lett.* **1969**, *10*, 3707–3710.

(36) Hutchison, D. A.; Beck, K. R.; Benkeser, R. A.; Grutzner, J. B. Concerning the Structure of Allylic Grignard Reagents. *J. Am. Chem. Soc.* **1973**, *95*, 7075–7082.

(37) ALTMAN, L. J.; ASH, L.; MARSON, S. A New, Highly Stereoselective Synthesis of All Trans -Geranylgeraniol. *Synthesis (Stuttg).* **1974**, *1974*, 129–131.

(38) Sato, K.; Miyamoto, O.; Inoue, S.; Furusawa, F.; Matsuhashi, Y. STEREOSELECTIVE SYNTHESIS OF A CISOID C10 ISOPRENOID BUILDING BLOCK AND SOME ALL- CIS -POLYPRENOLS. *Chem. Lett.* **1983**, *12*, 725–728.

(39) Grieco, P. A.; Masaki, Y. General 1,5-Diene Synthesis. Application to the Synthesis of Squalene. *J. Org. Chem.* **1974**, *39*, 2135–2136.

(40) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. Synthesis of Ubiquinones. Elongation of the Heptaprenyl Side-Chain in Ubiquinone-7. *J. Chem. Soc. Perkin Trans. 1* **1978**, No. 10, 1101.

(41) Yu, X.; Wang, S.; Chen, F. Solid-Phase Synthesis of Solanesol. *J. Comb. Chem.* **2008**, *10*, 605–610.

(42) Liu, F.; Vijayakrishnan, B.; Faridmoayer, A.; Taylor, T. A.; Parsons, T. B.; Bernardes, G. J. L.; Kowarik, M.; Davis, B. G. Rationally Designed Short Polyisoprenol-Linked PglB Substrates for Engineered Polypeptide and Protein N-Glycosylation. *J. Am. Chem. Soc.* **2014**, *136*, 566–569.

(43) Hirao, K.; Ono, R.; Manabe, Y.; Masui, S.; Atomi, H.; Fukase, K. Total Syntheses of C60- And C100-Dolichols. *J. Org. Chem.* **2020**, *85*, 11549–11559.

(44) Yanagisawa, A.; Habaue, S.; Yamamoto, H. Direct Insertion of Alkali (Alkaline-Earth) Metals into Allylic Carbon-Halogen Bonds Avoiding Stereorandomization. *J. Am. Chem. Soc.* **1991**, *113*, 5893–5895.

(45) G. Suero, M.; D. Bayle, E.; S. L. Collins, B.; J. Gaunt, M. Copper-Catalyzed Electrophilic Carbofunctionalization of Alkynes to Highly Functionalized Tetrasubstituted Alkenes. *J. Am. Chem. Soc.* **2013**, *135*, 5332–5335.

(46) Lv, W.; Liu, S.; Chen, Y.; Wen, S.; Lan, Y.; Cheng, G. Palladium-Catalyzed Intermolecular Trans-Selective Carbofunctionalization of Internal Alkynes to Highly Functionalized Alkenes. *ACS Catal.* **2020**, *10*, 10516–10522.

(47) Trost, B. M.; Ball, Z. T. Addition of Metalloid Hydrides to Alkynes: Hydrometallation with Boron, Silicon, and Tin. *Synthesis (Stuttg).* **2005**, No. 6, 853–887.

(48) Chen, T. A.; Shon, Y. S. Alkanethiolate-Capped Palladium Nanoparticles for Selective Catalytic Hydrogenation of Dienes and Trienes. *Catal. Sci. Technol.* **2017**, *7*, 4823–4829.

(49) Nakayama, T.; Kanai, H. Selective Hydrogenation of Conjugated Dienes Catalyzed By Thiocyanatotris(Triphenylphosphine)Cobalt(I). *Bulletin of the Chemical Society of Japan*. 1985, pp 16–22.

(50) Lee, J. T.; Alper, H. Regioselective Hydrogenation of Conjugated Dienes Catalyzed by Hydridopentacyanocobaltate Anion Using .Beta.-Cyclodextrin as

the Phase Transfer Agent and Lanthanide Halides as Promoters. *J. Org. Chem.* **1990**, *55*, 1854–1856.

(51) Li, D.; Park, Y.; Yoon, W.; Yun, H.; Yun, J. Asymmetric Synthesis of 1-Benzazepine Derivatives *via* Copper-Catalyzed Intramolecular Reductive Cyclization. *Org. Lett.* **2019**, No. Ii, 7–11.

(52) Metternich, J. B.; Gilmour, R. A Bio-Inspired, Catalytic e → Z Isomerization of Activated Olefins. *J. Am. Chem. Soc.* **2015**, *137*, 11254–11257.

(53) Chen, C.; Dugan, T. R.; Brennessel, W. W.; Weix, D. J.; Holland, P. L. Z -Selective Alkene Isomerization by High-Spin Cobalt(II) Complexes. *J. Am. Chem. Soc.* **2014**, *136*, 945–955.

(54) Gauthier, D.; Lindhardt, A. T.; Olsen, E. P. K.; Overgaard, J.; Skrydstrup, T. In Situ Generated Bulky Palladium Hydride Complexes as Catalysts for the Efficient Isomerization of Olefins. Selective Transformation of Terminal Alkenes to 2-Alkenes. *J. Am. Chem. Soc.* **2010**, *132*, 7998–8009.

(55) Erdogan, G.; Grotjahn, D. B. Mild and Selective Deuteration and Isomerization of Alkenes by a Bifunctional Catalyst and Deuterium Oxide. *J. Am. Chem. Soc.* **2009**, *131*, 10354–10355.

(56) Larsen, C. R.; Grotjahn, D. B. Stereoselective Alkene Isomerization over One Position. *J. Am. Chem. Soc.* **2012**, *134*, 10357–10360.

(57) Schneider, V.; Frolich, P. K. Mechanism of Formation of Aromatics from Lower Paraffins. *Ind. Eng. Chem.* **1931**, *23*, 1405–1410.

(58) Anderson, A. W.; Merckling, M. G. Polymeric Bicyclo[2.2.1]Hept-2-Ene. *Chem.Abstr.* **1955**, *50*, 3008.

(59) *Handbook of Metathesis*; Grubbs, R. H., Wenzel, A. G., O'Leary, D. J., Khosravi, E., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2015; Vol. 2.

(60) Monfette, S.; Fogg, D. E. Equilibrium Ring-Closing Metathesis. **2009**, No. section 3, 3783–3816.

(61) Zukowska, K.; Grela, K. *Cross Metathesis*; Elsevier Ltd., 2014; Vol. 5.

(62) Ahlberg, P. Development of the metathesis method in organic synthesis https://www.nobelprize.org/prizes/chemistry/2005/prize-announcement/.

(63) Ulman, M.; Grubbs, R. H. Relative Reaction Rates of Olefin Substrates with Ruthenium(II) Carbene Metathesis Initiators. *Organometallics* **1998**, *17*, 2484–2489.

(64) Nelson, D. J.; Manzini, S.; Urbina-Blanco, C. A.; Nolan, S. P. Key Processes in Ruthenium-Catalysed Olefin Metathesis. *Chem. Commun.* **2014**, *50*, 10355–10375.

(65) Chatterjee, A. K.; Choi, T. L.; Sanders, D. P.; Grubbs, R. H. A General Model for Selectivity in Olefin Cross Metathesis. *J. Am. Chem. Soc.* **2003**, *125*, 11360–11370.

(66) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. Synthesis of Symmetrical Trisubstituted Olefins by Cross Metathesis. *Org. Lett.* **2002**, *4*, 1939–1942.

(67) Maier, M. E.; Langenbacher, D.; Rebien, F. Synthetic Routes to 1,4-Difunctionalized Cycloheptenes. *Liebigs Ann.* **1995**, *1995*, 1843–1848.

(68) Chang, S.; Grubbs, R. H. A Highly Efficient and Practical Synthesis of Chromene Derivatives Using Ring-Closing Olefin Metathesis. *J. Org. Chem.* **1998**, *63*, 864–866.

(69) Kirkland, T. A.; Grubbs, R. H. Effects of Olefin Substitution on the Ring-Closing Metathesis of Dienes. *J. Org. Chem.* **1997**, *62*, 7310–7318.

(70) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. Synthesis of Functionalized Olefins by Cross and Ring-Closing Metatheses. *J. Am. Chem. Soc.* **2000**, *122*, 3783–3784.

(71) Arredondo, V.; Roa, D. E.; Yan, S.; Liu-Smith, F.; Van Vranken, D. L. Total Synthesis of (±)-Pestalachloride C and (±)-Pestalachloride D through a Biomimetic Knoevenagel/Hetero-Diels-Alder Cascade. *Org. Lett.* **2019**, *21*, 1755–1759.

(72) Boyce, J. H.; Eschenbrenner-Lux, V.; Porco, J. A. Syntheses of (+)-30-Epi-, (-)-6-Epi-, (±)-6,30-Epi-13,14-Didehydroxyisogarcinol and (±)-6,30-Epi-Garcimultiflorone A Utilizing Highly Diastereoselective, Lewis Acid-Controlled Cyclizations. *J. Am. Chem. Soc.* **2016**, *138*, 14789–14797.

(73) Sittihan, S.; Jamison, T. F. Total Synthesis of the Marine Ladder Polyether Gymnocin B. *J. Am. Chem. Soc.* **2019**, *141*, 11239–11244.

(74) Hurtley, A. E.; Lu, Z.; Yoon, T. P. Cycloaddition of 1,3-Dienes by Visible Light Photocatalysis. *Angew. Chem. Int. Ed.* **2014**, *53*, 8991–8994.

(75) Xu, S.; Arimoto, H.; Uemura, D. Asymmetric Total Synthesis of Pinnaic Acid. *Angew. Chem. Int. Ed.* **2007**, *46*, 5746–5749.

(76) Cossy, J.; BouzBouz, S.; Hoveyda, A. H. Cross-Metathesis Reaction. Generation of Highly Functionalized Olefins from Unsaturated Alcohols. *J. Organomet. Chem.* **2001**, *624*, 327–332.

(77) Barile, F.; Bassetti, M.; D'Annibale, A.; Gerometta, R.; Palazzi, M. Cross-Metathesis Reactions of Homoallyl Methyl Malonates with Sterically Hindered Allylic Esters. *Eur. J. Org. Chem.* **2011**, No. 32, 6519–6526.

(78) Soon, H. H.; Wenzel, A. G.; Salguero, T. T.; Day, M. W.; Grubbs, R. H. Decomposition of Ruthenium Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2007**, *129*, 7961–7968.

(79) Schmidt, B. Catalysis at the Interface of Ruthenium Carbene and Ruthenium Hydride Chemistry: Organometallic Aspects and Applications to Organic Synthesis. *Eur. J. Org. Chem.* **2004**, 1865–1880.

(80) Stewart, I. C.; Douglas, C. J.; Grubbs, R. H. Increased Efficiency in Cross-Metathesis Reactions of Sterically Hindered Olefins. *Org. Lett.* **2008**, *10*, 441–444.

(81) Cheng, H.; Zhang, Z.; Yao, H.; Zhang, W.; Yu, J.; Tong, R. Unified Asymmetric Total Syntheses of (−)-Alotaketals A–D and (−)-Phorbaketal A. *Angew. Chem. Int. Ed.* **2017**, *56*, 9096–9100.

(82) Netscher, T. Preparation of Trialkyl-Substituted Olefins by Ruthenium Catalyzed Cross-Metathesis. *J. Organomet. Chem.* **2006**, *691*, 5155–5162.

(83) Plummer, C. W.; Wei, C. S.; Yozwiak, C. E.; Soheili, A.; Smithback, S. O.; Leighton, J. L. Design, Development, Mechanistic Elucidation, and Rational Optimization of a Tandem Ireland Claisen/Cope Rearrangement Reaction for Rapid Access to the (Iso)Cyclocitrinol Core. *J. Am. Chem. Soc.* **2014**, *136*, 9878–9881.

(84) Plummer, C. W.; Soheili, A.; Leighton, J. L. A Tandem Cross-Metathesis/Semipinacol Rearrangement Reaction. *Org. Lett.* **2012**, *14*, 2462–2464.

(85) Sarmento Fernandes, L.; Mandelli, D.; Carvalho, W. A.; Fischmeister, C.; Bruneau, C. Functionalization of (-)-β-Pinene and (-)-Limonene *via* Cross Metathesis with Symmetrical Internal Olefins. *Catal. Commun.* **2020**, *135*, 105893.

(86) Netscher, T.; Malaisé, G.; Bonrath, W.; Breuninger, M. A New Route to Vitamin E Key-Intermediates by Olefin Cross-Metathesis. *Catal. Today* **2007**, *121*, 71–75.

(87) Chatterjee, A. K.; Grubbs, R. H. Formal Vinyl C-H Activation and Allylic Oxidation by Olefin Metathesis. *Angew. Chem. Int. Ed.* **2002**, *41*, 3171–3174.

(88) Totsuka, Y.; Yasuno, Y.; Shinada, T. First Synthesis of All-Trans-Polyprenol with 100 Carbons. *Chem. Lett.* **2019**, *48*, 491–494.

(89) Liu, X.; Liu, J.; Wu, J.; Huang, G.; Liang, R.; Chung, L. W.; Li, C. C. Asymmetric Total Synthesis of Cerorubenic Acid-III. *J. Am. Chem. Soc.* **2019**, *141*, 2872–2877.

(90) Xu, J.; Caro-diaz, E. J. E.; Trzoss, L.; Theodorakis, E. A. Nature-Inspired Total Synthesis of (−)-Fusarisetin A. **2012**, 1–4.

(91) Vyvyan, J. R.; Loitz, C.; Looper, R. E.; Mattingly, C. S.; Peterson, E. A.; Staben, S. T. Synthesis of Aromatic Bisabolene Natural Products *via* Palladium-

Catalyzed Cross-Couplings of Organozine Reagents. *J. Org. Chem.* **2004**, *69*, 2461–2468.

(92) Kim, H. S.; Park, H.; Lim, J.; Lim, C.; Kim, T.; Lee, S.; Hur, J.; Sim, J.; Choi, H. J.; Suh, Y. G. Collective Syntheses of Guaiane Sesquiterpenes: Stereoselective Syntheses of (+)-Dysodensiol F, (+)-10β,14-Dihydroxy- Allo-Aromadendrane, and (-)-Dendroside C Aglycon. *J. Org. Chem.* **2020**, *85*, 13779–13792.

(93) Burnley, J.; Wang, Z. J.; Jackson, W. R.; Robinson, A. J. Cross-Metathesis Approach to the Tricyclic Marine Alkaloids (-)-Fasicularin and (-)-Lepadiformine A. *J. Org. Chem.* **2017**, *82*, 8497–8505.

(94) Netscher, T.; Malaisé, G.; Bonrath, W.; Breuninger, M. A New Route to Vitamin E Key-Intermediates by Olefin Cross-Metathesis. *Helv. Chim. Acta* **2007**, *121*, 71–75.

(95) Bellavance, G.; Barriault, L. Modular Total Syntheses of Hyperforin, Papuaforins A, B, and C *via* Gold(I)-Catalyzed Carbocyclization. *J. Org. Chem.* **2018**, *83*, 7215–7230.

(96) Smith, R. J.; Hawkins, B. C. Synthetic Strategies towards the Synthesis of Oxyisocyclointegrin. *Eur. J. Org. Chem.* **2019**, *2019*, 6847–6854.

(97) Wu, K.; Du, Y.; Wang, T. Visible-Light-Mediated Construction of Pyrroloindolines *via* an Amidyl Radical Cyclization/Carbon Radical Addition Cascade: Rapid Synthesis of (±)-Flustramide B. *Org. Lett.* **2017**, *19*, 5669–5672.

(98) Xu, C.; Liu, Z.; Torker, S.; Shen, X.; Xu, D.; Hoveyda, A. H. Synthesis of Z- or E-Trisubstituted Allylic Alcohols and Ethers by Kinetically Controlled Cross-Metathesis with a Ru Catechothiolate Complex. *J. Am. Chem. Soc.* **2017**, *139*, 15640–15643.

(99) Hart-Cooper, W. M.; Clary, K. N.; Toste, F. D.; Bergman, R. G.; Raymond, K. N. Selective Monoterpene-like Cyclization Reactions Achieved by Water Exclusion from Reactive Intermediates in a Supramolecular Catalyst. *J. Am.*

Chem. Soc. **2012**, *134*, 17873–17876.

(100) Trost, B. M.; Bai, W. J.; Hohn, C.; Bai, Y.; Cregg, J. J. Palladium-Catalyzed Asymmetric Allylic Alkylation of 3-Substituted 1 H-Indoles and Tryptophan Derivatives with Vinylcyclopropanes. *J. Am. Chem. Soc.* **2018**, *140*, 6710–6717.

(101) Nguyen, T. T.; Koh, M. J.; Mann, T. J.; Schrock, R. R.; Hoveyda, A. H. Synthesis of E- and Z-Trisubstituted Alkenes by Catalytic Cross-Metathesis. *Nature* **2017**, *552*, 347–354.

(102) Bahou, K. A.; Braddock, D. C.; Meyer, A. G.; Savage, G. P.; Shi, Z.; He, T. A Relay Strategy Actuates Pre-Existing Trisubstituted Olefins in Monoterpenoids for Cross-Metathesis with Trisubstituted Alkenes. *J. Org. Chem.* **2020**, *85*, 4906–4917.

(103) Finkel'shtein, E. S.; Portnykh, E. B.; Antipova, I. V.; Vdovin, V. M. Extension of the Hydrocarbon Chains of A-Olefins by Their Cometathetical Reaction with Trimethylallylsilane. *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1989**, *38*, 1240–1243.

(104) Liu, Y.; Guo, Y.; Ji, F.; Gao, D.; Song, C.; Chang, J. Divergent Syntheses of Carbazole Alkaloids Clausenapin, Indizoline, Claulansine M, and Clausenaline D. *J. Org. Chem.* **2016**, *81*, 4310–4315.

(105) Sapkota, R. R.; Jarvis, J. M.; Schaub, T. M.; Talipov, M. R.; Arterburn, J. B. Bimolecular Cross-Metathesis of a Tetrasubstituted Alkene with Allylic Sulfones. *ChemistryOpen* **2019**, *8*, 201–205.

(106) Ibrahem, I.; Yu, M.; Schrock, R. R.; Hoveyda, A. H. Highly Z- And Enantioselective Ring-Opening/Cross-Metathesis Reactions Catalyzed by Stereogenic-at-Mo Adamantylimido Complexes. *J. Am. Chem. Soc.* **2009**, *131*, 3844–3845.

(107) Jiang, A. J.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. Highly Z-Selective Metathesis Homocoupling of Terminal Olefins. *J. Am. Chem. Soc.* **2009**, *131*, 16630–16631.

(108) Meek, S. J.; O'Brien, R. V; Llaveria, J.; Schrock, R. R.; Hoveyda, A. H. Catalytic Z-Selective Olefin Cross-Metathesis for Natural Product Synthesis. *Nature* **2011**, *471*, 461–466.

(109) Yu, M.; Wang, C.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. Synthesis of Macrocyclic Natural Products by Catalyst-Controlled Stereoselective Ring-Closing Metathesis. *Nature* **2011**, *479*, 88–92.

(110) Wang, C.; Yu, M.; Kyle, A. F.; Jakubec, P.; Dixon, D. J.; Schrock, R. R.; Hoveyda, A. H. Efficient and Selective Formation of Macrocyclic Disubstituted Z Alkenes by Ring-Closing Metathesis (RCM) Reactions Catalyzed by Mo- or W-Based Monoaryloxide Pyrrolide (MAP) Complexes: Applications to Total Syntheses of Epilachnene, Yuzu Lactone, Ambretto. *Chem. Eur. J.* **2013**, *19*, 2726–2740.

(111) Marinescu, S. C.; Levine, D. S.; Zhao, Y.; Schrock, R. R.; Hoveyda, A. H. Isolation of Pure Disubstituted e Olefins through Mo-Catalyzed Z-Selective Ethenolysis of Stereoisomeric Mixtures. *J. Am. Chem. Soc.* **2011**, *133*, 11512–11514.

(112) Cuvigny, T.; Hervé du Penhoat, C.; Julia, M. Isomérisation Cis Trans Régiosélective de Doubles Liaisons Trisubstituées. *Tetrahedron Lett.* **1980**, *21*, 1331.

(113) Wang, C.; Haeffner, F.; Schrock, R. R.; Hoveyda, A. H. Molybdenum-Based Complexes with Two Aryloxides and a Pentafluoroimido Ligand: Catalysts for Efficient z-Selective Synthesis of a Macrocyclic Trisubstituted Alkene by Ring-Closing Metathesis. *Angew. Chem. Int. Ed.* **2013**, *52*, 1939–1943.

(114) Yu, M.; Schrock, R. R.; Hoveyda, A. H. Catalyst-Controlled Stereoselective Olefin Metathesis as a Principal Strategy in Multistep Synthesis Design: A Concise Route to (+)-Neopeltolide. *Angew. Chem. Int. Ed.* **2015**, *54*, 215–220.

(115) Koh, M. J.; Nguyen, T. T.; Zhang, H.; Schrock, R. R.; Hoveyda, A. H. Direct Synthesis of Z-Alkenyl Halides through Catalytic Cross-Metathesis. *Nature* **2016**, *531*, 459–465.

(116) Wiberg, K. B.; Wang, Y. G.; Petersson, G. A.; Bailey, W. F. Intramolecular Nonbonded Attractive Interactions: 1-Substituted Propenes. *J. Chem. Theory Comput.* **2009**, *5*, 1033–1037.

(117) Koh, M. J.; Nguyen, T. T.; Lam, J. K.; Torker, S.; Hyvl, J.; Schrock, R. R.; Hoveyda, A. H. Molybdenum Chloride Catalysts for Z-Selective Olefin Metathesis Reactions. *Nature* **2017**, *542*, 80–85.

(118) Nguyen, T. T.; Koh, M. J.; Shen, X.; Romiti, F.; Schrock, R. R.; Hoveyda, A. H. Kinetically Controlled E -Selective Catalytic Olefin Metathesis. *Science (80-.).* **2016**, *352*, 569–575.

(119) Mu, Y.; Nguyen, T. T.; Koh, M. J.; Schrock, R. R.; Hoveyda, A. H. E- and Z-, Di- and Tri-Substituted Alkenyl Nitriles through Catalytic Cross-Metathesis. *Nat. Chem.* **2019**, *11*, 478–487.

(120) Schrock, R. R.; Hoveyda, A. H. Molybdenum and Tungsten Imido Alkylidene Complexes as Efficient Olefin-Metathesis Catalysts. *Angew. Chem. Int. Ed.* **2003**, *42*, 4592–4633.

(121) Shen, X.; Nguyen, T. T.; Koh, M. J.; Xu, D.; Speed, A. W. H.; Schrock, R. R.; Hoveyda, A. H. Kinetically E-Selective Macrocyclic Ring-Closing Metathesis. *Nature* **2017**, *541*, 380–385.

(122) Torker, S.; Müller, A.; Chen, P. Building Stereoselectivity into a Chemoselective Ring-Opening Metathesis Polymerization Catalyst for Alternating Copolymerization. *Angew. Chem. Int. Ed.* **2010**, *49*, 3762–3766.

(123) Bornand, M.; Torker, S.; Chen, P. Mechanistically Designed Dual-Site Catalysts for the Alternating ROMP of Norbornene and Cyclooctene. *Organometallics* **2007**, *26*, 3585–3596.

(124) Vehlow, K.; Wang, D.; Buchmeiser, M. R.; Blechert, S. Alternating Copolymerizations Using a Grubbs-Type Initiator with an Unsymmetrical, Chiral n-Heterocyclic Carbene Ligand. *Angew. Chem. Int. Ed.* **2008**, *47*, 2615–2618.

(125) Lichtenheldt, M.; Wang, D.; Vehlow, K.; Reinhardt, I.; Kühnel, C.; Decker, U.; Blechert, S.; Buchmeiser, M. R. Alternating Ring-Opening Metathesis Copolymerization by Grubbs-Type Initiators with Unsymmetrical N-Heterocyclic Carbenes. **2009**, 9451–9457.

(126) Van Veldhuizen, J. J.; Garber, S. B.; Kingsbury, J. S.; Hoveyda, A. H. A Recyclable Chiral RU Catalyst for Enantioselective Olefin Metathesis. Efficient Catalytic Asymmetric Ring-Opening/Cross Metathesis in Air. *J. Am. Chem. Soc.* **2002**, *124*, 4954–4955.

(127) Berlin, J. M.; Goldberg, S. D.; Grubbs, R. H. Highly Active Chiral Ruthenium Catalysts for Asymmetric Cross- and Ring-Opening Cross-Metathesis. *Angew. Chem. Int. Ed.* **2006**, *45*, 7591–7595.

(128) Endo, K.; Grubbs, R. H. Chelated Ruthenium Catalysts for Z -Selective Olefin Metathesis. *J. Am. Chem. Soc.* **2011**, *133*, 8525–8527.

(129) Trnka, T. M.; Morgan, J. P.; Sanford, M. S.; Wilhelm, T. E.; Scholl, M.; Choi, T. L.; Ding, S.; Day, M. W.; Grubbs, R. H. Synthesis and Activity of Ruthenium Alkylidene Complexes Coordinated with Phosphine and N-Heterocyclic Carbene Ligands. *J. Am. Chem. Soc.* **2003**, *125*, 2546–2558.

(130) Keitz, B. K.; Endo, K.; Patel, P. R.; Herbert, M. B.; Grubbs, R. H. Improved Ruthenium Catalysts for Z-Selective Olefin Metathesis. *J. Am. Chem. Soc.* **2012**, *134*, 693–699.

(131) Marx, V. M.; Herbert, M. B.; Keitz, B. K.; Grubbs, R. H. Stereoselective Access to Z and e Macrocycles by Ruthenium-Catalyzed Z-Selective Ring-Closing Metathesis and Ethenolysis. *J. Am. Chem. Soc.* **2013**.

(132) Occhipinti, G.; Hansen, F. R.; Törnroos, K. W.; Jensen, V. R. Simple and Highly Z-Selective Ruthenium-Based Olefin Metathesis Catalyst. *J. Am. Chem. Soc.* **2013**, *135*, 3331–3334.

(133) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. Reactivity and Selectivity Differences between Catecholate and Catechothiolate Ru Complexes. Implications Regarding Design of Stereoselective Olefin Metathesis Catalysts.

J. Am. Chem. Soc. **2014**, *136*, 14337–14340.

(134) Khan, R. K. M.; Torker, S.; Hoveyda, A. H. Readily Accessible and Easily Modifiable Ru-Based Catalysts for Efficient and Z-Selective Ring-Opening Metathesis Polymerization and Ring-Opening/Cross- Metathesis. *J. Am. Chem. Soc.* **2013**, *135*, 10258–10261.

(135) Koh, M. J.; Khan, R. K. M.; Torker, S.; Hoveyda, A. H. Broadly Applicable Z- and Diastereoselective Ring-Opening/Cross-Metathesis Catalyzed by a Dithiolate Ru Complex. *Angew. Chem. Int. Ed.* **2014**, *53*, 1968–1972.

(136) Koh, M. J.; Khan, R. K. M.; Torker, S.; Yu, M.; Mikus, M. S.; Hoveyda, A. H. High-Value Alcohols and Higher-Oxidation-State Compounds by Catalytic Z-Selective Cross-Metathesis. *Nature* **2015**, *517*, 181–186.

(137) Johns, A. M.; Ahmed, T. S.; Jackson, B. W.; Grubbs, R. H.; Pederson, R. L. High Trans Kinetic Selectivity in Ruthenium-Based Olefin Cross-Metathesis through Stereoretention. *Org. Lett.* **2016**, *18*, 772–775.

(138) Xu, C.; Shen, X.; Hoveyda, A. H. In Situ Methylene Capping: A General Strategy for Efficient Stereoretentive Catalytic Olefin Metathesis. The Concept, Methodological Implications, and Applications to Synthesis of Biologically Active Compounds. *J. Am. Chem. Soc.* **2017**, *139*, 10919–10928.

(139) Liu, Z.; Xu, C.; Del Pozo, J.; Torker, S.; Hoveyda, A. H. Ru-Based Catechothiolate Complexes Bearing an Unsaturated NHC Ligand: Effective Cross-Metathesis Catalysts for Synthesis of (Z)-α,β-Unsaturated Esters, Carboxylic Acids, and Primary, Secondary, and Weinreb Amides. *J. Am. Chem. Soc.* **2019**, *141*, 7137–7146.

(140) Yu, E. C.; Johnson, B. M.; Townsend, E. M.; Schrock, R. R.; Hoveyda, A. H. Synthesis of Linear (Z)-α,β-Unsaturated Esters by Catalytic Cross-Metathesis. The Influence of Acetonitrile. *Angew. Chem. Int. Ed.* **2016**, *55*, 13210–13214.

(141) Müller, D. S.; Curbet, I.; Raoul, Y.; Le Nôtre, J.; Baslé, O.; Mauduit, M. Stereoretentive Olefin Metathesis Made Easy: In Situ Generation of Highly Selective Ruthenium Catalysts from Commercial Starting Materials. *Org. Lett.*

2018, *20*, 6822–6826.

(142) R. Hoye, T.; S. Jeffrey, C.; A. Tennakoon, M.; Wang, J.; Zhao, H. Relay Ring-Closing Metathesis (RRCM): A Strategy for Directing Metal Movement Throughout Olefin Metathesis Sequences. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211.

(143) Hansen, E. C.; Lee, D. Efficient and Z-Selective Cross-Metathesis of Conjugated Enynes. *Org. Lett.* **2004**, *6*, 2035–2038.

(144) Malla, R. K.; Ridenour, J. N.; Spilling, C. D. Relay Cross Metathesis Reactions of Vinylphosphonates. *Beilstein J. Org. Chem.* **2014**, *10*, 1933–1941.

(145) Kim, H.; Lee, H.; Lee, D.; Kim, S.; Kim, D. Asymmetric Total Syntheses of (+)-3-(Z)-Laureatin and (+)-3-(Z)-Isolaureatin by "Lone Pair−Lone Pair Interaction-Controlled" Isomerization. *J. Am. Chem. Soc.* **2007**, *129*, 2269–2274.

(146) Senapati, S.; Das, S.; Ramana, C. V. Total Synthesis of Notoryne. *J. Org. Chem.* **2018**, *83*, 12863–12868.

(147) Braddock, D. C.; Marklew, J. S.; Thomas, A. J. F. 062a. Enantiospecific Bromonium Ion Generation and Intramolecular Capture: A Model System for Asymmetric Bromonium Ion-Induced Polyene Cyclisations. *Chem. Commun.* **2011**, *47*, 9051–9053.

(148) Braddock, D. C.; Marklew, J. S.; Foote, K. M.; White, A. J. P. An Enantiospecific Polyene Cyclization Initiated by an Enantiomerically Pure Bromonium Ion. *Chirality* **2013**, *25*, 692–700.

(149) Yoder, R. A.; Johnston, J. N. A Case Study in Biomimetic Total Synthesis: Polyolefin Carbocyclizations to Terpenes and Steroids. *Chem. Rev.* **2005**, *105*, 4730–4756.

(150) Barrett, A. G. M.; Ma, T. K.; Mies, T. Recent Developments in Polyene Cyclizations and Their Applications in Natural Product Synthesis. *Synthesis (Stuttg).* **2019**, *51*, 67–82.

(151) Snowden, R. L.; Eichenberger, J. C.; Linder, S. M.; Sonnay, P.; Vial, C.; Schulte-Elte, K. H. Internal Nucleophilic Termination in Biomimetic Acid Mediated Polyene Cyclizations: Stereochemical and Mechanistic Implications. Synthesis of (.+-.)-Ambrox and Its Diastereoisomers. *J. Org. Chem.* **1992**, *57*, 955–960.

(152) Smit, W. A.; Semenovsky, A. V.; Kucherov, V. F. Stereospecific Cyclization of Isoprenoids. The Cyclization of Farnesylacetone Stereoisomers and Their Monocyclic Analogs. *Tetrahedron Lett.* **1964**, *5*, 2299–2306.

(153) Snyder, S. A.; Treitler, D. S.; Brucks, A. P. Simple Reagents for Direct Halonium-Induced Polyene Cyclizations. *J. Am. Chem. Soc.* **2010**, *132*, 14303–14314.

(154) Zhao, J.-F.; Zhao, Y.-J.; Loh, T.-P. Indium Tribromide-Promoted Arene-Terminated Epoxy Olefin Cyclization. *Chem. Commun.* **2008**, *1*, 1353.

(155) Cherney, E. C.; Green, J. C.; Baran, P. S. Synthesis of Ent-Kaurane and Beyerane Diterpenoids by Controlled Fragmentations of Overbred Intermediates. *Angew. Chem. Int. Ed.* **2013**, *52*, 9019–9022.

(156) Lang, M.; Steglich, W. An Effective Method for the Synthesis of 13C-Labeled Polyprenylhydroxybenzoic Acids. *Synthesis (Stuttg).* **2005**, *2005*, 1019–1027.

(157) Rosales, V.; Zambrano, J. L.; Demuth, M. Regioselective Palladium-Catalyzed Alkylation of Allylic Halides with Benzylic Grignard Reagents. Two-Step Synthesis of Abietane Terpenes and Tetracyclic Polyprenoid Compounds. *J. Org. Chem.* **2002**, *67*, 1167–1170.

(158) Gansäuer, A.; Justicia, J.; Rosales, A.; Rinker, B. Efficient and Stereoselective Synthesis of Precursors for Epoxypolyene Cyclizations *via* Allylic Substitutions. *Synlett* **2005**, No. 12, 1954–1956.

(159) Bahou, K. PhD Studies, Imperial College London, 2016.

(160) Bahou, K. A.; Braddock, D. C.; Meye, A. G.; Savage, G. P. Kinetic Benchmarking Reveals the Competence of Prenyl Groups in Ring-Closing

Metathesis. *Org. Lett.* **2017**, *19*, 5332–5335.

(161) Fujioka, K.; Yokoe, H.; Yoshida, M.; Shishido, K. Total Synthesis of Penostatin B. *Org. Lett.* **2012**, *14*, 244–247.

(162) Wang, Z. J.; Jackson, W. R.; Robinson, A. J. An Efficient Protocol for the Cross-Metathesis of Sterically Demanding Olefins. *Org. Lett.* **2013**, *15*, 3006–3009.

(163) Rao, H. S. P.; Senthilkumar, S. P. A Convenient Procedure for the Synthesis of Allyl and Benzyl Ethers from Alcohols and Phenols. *J. Chem. Sci.* **2001**, *113*, 191–196.

(164) Snyder, S. A.; Treitler, D. S. Et2SBr.SbCl5Br: An Effective Reagent for Direct Bromonium-Induced Polyene Cyclizations. *Angew. Chem. Int. Ed.* **2009**, *48*, 7899–7903.

(165) Baker, K. V.; Brown, J. M.; Hughes, N.; Skarnulis, A. J.; Sexton, A. Mechanical Activation of Magnesium Turnings for the Preparation of Reactive Grignard Reagents. *J. Org. Chem.* **1991**, *56*, 698–703.

(166) Ferré-Filmon, K.; Delaude, L.; Demonceau, A.; Noels, A. F. Stereoselective Synthesis of (E)-Hydroxystilbenoids by Ruthenium-Catalyzed Cross-Metathesis. *Eur. J. Org. Chem.* **2005**, *2005*, 3319–3325.

(167) Hong, S. H.; Sanders, D. P.; Lee, C. W.; Grubbs, R. H. Prevention of Undesirable Isomerization during Olefin Metathesis. *J. Am. Chem. Soc.* **2005**, *127*, 17160–17161.

(168) Higman, C. S.; Plais, L.; Fogg, D. E. Isomerization During Olefin Metathesis: An Assessment of Potential Catalyst Culprits. *ChemCatChem* **2013**, *5*, 3548–3551.

(169) Schulz, M. D.; Atkinson, M. B. J.; Elsey, R. J.; Thuo, M. M. Copper(I) Halides Inhibit Olefin Isomerized by-Products from Phosphine-Based Grubbs' Metathesis Catalysts in Polar Protic Solvents. *Transit. Met. Chem.* **2014**, *39*, 763–767.

(170) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. Rate Enhanced Olefin Cross-Metathesis Reactions: The Copper Iodide Effect. *J. Org. Chem.* **2011**, *76*, 4697–4702.

(171) Berheci, D.; Braddock, D. The Ru-Catalysed Degenerate Exchange of Isopropylidene Groups and Its Application in Labelling Natural Compounds, Imperial College London, 2020.

(172) Chatterjee, A. K.; Grubbs, R. H. Synthesis of Trisubstituted Alkenes *via* Olefin Cross-Metathesis. *Org. Lett.* **1999**, *1*, 1751–1753.

(173) Williams, C. M.; Mander, L. N. Chromatography with Silver Nitrate. *Tetrahedron* **2001**, *57*, 425–447.

(174) Yu, L. G.; Ni, T. F.; Gao, W.; He, Y.; Wang, Y. Y.; Cui, H. W.; Yang, C. G.; Qiu, W. W. The Synthesis and Antibacterial Activity of Pyrazole-Fused Tricyclic Diterpene Derivatives. *Eur. J. Med. Chem.* **2015**, *90*, 10–20.

(175) Bahou, K. A.; Braddock, D. C.; Meyer, A. G.; Savage, G. P. Relay Cross Metathesis for the Iterative Construction of Terpenoids and Synthesis of a Diterpene-Benzoate Macrolide of Biogenetic Relevance to the Bromophycolides. *Org. Lett.* **2020**, *22*, 3176–3179.

(176) Fürstner, A.; Radkowski, K.; Wirtz, C.; Goddard, R.; Lehmann, C. W.; Mynott, R. Total Syntheses of the Phytotoxic Lactones Herbarumin I and II and a Synthesis-Based Solution of the Pinolidoxin Puzzle. *J. Am. Chem. Soc.* **2002**, *124*, 7061–7069.

(177) Lee, C. W.; Grubbs, R. H. Stereoselectivity of Macrocyclic Ring-Closing Olefin Metathesis. *Org. Lett.* **2000**, *2*, 2145–2147.

(178) Nakashima, K.; Ito, R.; Sono, M.; Tori, M. Olefin Metathesis Reactions of Some Aromatic Dienes with Ortho- and Meta- Disubstitution. Formation of 10-, 12-, 14-, and 17-Membered Cyclic Compounds and Isomerization of an Allylic Alcohol. *Hetrocycles* **2000**, *53*, 301–314.

(179) Arisawa, M.; Kato, C.; Kaneko, H.; Nishida, A.; Nakagawa, M. Concise

Synthesis of Azacycloundecenes Using Ring-Closing Metathesis (RCM). *J. Chem. Soc. Perkin Trans. 1* **2000**, No. 12, 1873–1876.

(180) Furstner, A.; Thiel, O. R.; Blanda, G. Asymmetric Synthesis of the Fully Functional Macrolide Core of Salicylihalamide: Remote Control of Olefin Geometry during RCM. *Org. Lett.* **2000**, *2*, 3731–3734.

(181) Nicolaou, K. C.; Ninkovic, S.; Sarabia, F.; Vourloumis, D.; He, Y.; Vallberg, H.; Finlay, M. R. V.; Yang, Z. Total Syntheses of Epothilones A and B *via* a Macrolactonization-Based Strategy. *J. Am. Chem. Soc.* **1997**, *119*, 7974–7991.

(182) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. Remote Effects in Macrolide Formation through Ring-Forming Olefin Metathesis: An Application to the Synthesis of Fully Active Epothilone Congeners. *J. Am. Chem. Soc.* **1997**, *119*, 2733–2734.

(183) Barluenga, S.; Lopez, P.; Moulin, E.; Winssinger, N. Modular Asymmetric Synthesis of Pochonin C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3467–3470.

(184) Evano, G.; Schaus, J. V.; Panek, J. S. A Convergent Synthesis of the Macrocyclic Core of Cytotrienins: Application of RCM for Macrocyclization. *Org. Lett.* **2004**, *6*, 525–528.

(185) Tripathy, N. K.; Georg, G. I. RCM Approach for the Total Synthesis of Cryptophycin-24 (Arenastatin A). *Tetrahedron Lett.* **2004**, *45*, 5309–5311.

(186) Dvorak, C. A.; Schmitz, W. D.; Poon, D. J.; Pryde, D. C.; Lawson, J. P.; Amos, R. A.; Meyers, A. I. The Synthesis of Streptogramin Antibiotics: (−)-Griseoviridin and Its C-8 Epimer. *Angew. Chemie* **2000**, *112*, 1730–1732.

(187) Hughes, D.; Wheeler, P.; Ene, D. Olefin Metathesis in Drug Discovery and Development - Examples from Recent Patent Literature. *Org. Process Res. Dev.* **2017**, *21*, 1938–1962.

(188) Cheng-Sánchez, I.; Sarabia, F. Recent Advances in Total Synthesis *via* Metathesis Reactions. *Synthesis (Stuttg).* **2018**, *50*, 3749–3786.

(189) Schwartz, K. D.; White, J. D. Synthesis of the Cyclohexane Core of Phomactins and a New Route to the Bicyclo[9.3.1]Pentadecane Diterpenoid Skeleton. *Org. Lett.* **2011**, *13*, 248–251.

(190) Fujiwara, K.; Tanaka, K.; Katagiri, Y.; Kawai, H.; Suzuki, T. Model Studies for the Stereoselective Construction of the BC-Ring of Armatol F Based on Ireland-Claisen Rearrangement and Relay Ring-Closing Olefin Metathesis. *Tetrahedron Lett.* **2010**, *51*, 4543–4546.

(191) Sato, D.; Fujiwara, K.; Kawai, H.; Suzuki, T. Concise Stereoselective Synthesis of Cis-3-Alkoxy-2-Carbomethoxy Medium-Ring Oxacycles from (R)-3-(3-Butenyl)-4-Propynoyloxazolidin-2-One. *Tetrahedron Lett.* **2008**, *49*, 1514–1517.

(192) McGrath, N. A.; Lee, C. A.; Araki, H.; Brichacek, M.; Njardarson, J. T. An Efficient Substrate-Controlled Approach towards Hypoestoxide, a Member of a Family of Diterpenoid Natural Products with an inside-out [9.3.1]Bicyclic Core. *Angew. Chem. Int. Ed.* **2008**, *47*, 9450–9453.

(193) Xie, Q.; Denton, R. W.; Parker, K. A. A Relay Ring-Closing Metathesis Synthesis of Dihydrooxasilines, Precursors of (Z)-Lodo Olefins. *Org. Lett.* **2008**, *10*, 5345–5348.

(194) Basante-Avendaño, A.; Guerra-Ayala, V. E.; Sánchez-Eleuterio, A.; Cordero-Vargas, A. A Free-Radical and Protecting-Group-Free Approach to (-)-Boschnialactone and γ-Lycorane. *Synthesis (Stuttg).* **2019**, *51*, 2207–2213.

(195) Ribaucourt, A.; Hodgson, D. M. Total Synthesis and Structural Revision of the Cytotoxin Aruncin B. *Org. Lett.* **2016**, *18*, 4364–4367.

(196) Chavan, S. P.; Thakkar, M.; Jogdand, G. F.; Kalkote, U. R. First Enantiospecific Synthesis of (−)-Parvifoline and (−)-Curcuquinone. *J. Org. Chem.* **2006**, *71*, 8986–8988.

(197) Torres, A.; Gutierrez, P.; Alvarez-Manzaneda, R.; Chahboun, R.; Alvarez-Manzaneda, E. Preparation of Oxocene Terpenes. the First Enantiospecific Synthesis of Cytotoxic Arenaran A. *Org. Biomol. Chem.* **2016**, *14*, 9836–9845.

(198) Vassilikogiannakis, G.; Margaros, I.; Tofi, M. Olefin Metathesis: Remote Substituents Governing the Stereoselectivity of 11-Membered-Ring Formation. *Org. Lett.* **2004**, *6*, 205–208.

(199) Nicolaou, K. C.; Montagnon, T.; Vassilikogiannakis, G.; Mathison, C. J. N. The Total Synthesis of Coleophomones B, C, and D. *J. Am. Chem. Soc.* **2005**, *127*, 8872–8888.

(200) El-Faham, A.; Albericio, F. Peptide Coupling Reagents, More than a Letter Soup. *Chem. Rev.* **2011**, *111*, 6557–6602.

(201) Hegarty, A. F.; McCormack, M. T.; Ferguson, G.; Roberts, P. J. Isolation and Reactivity of a Model for the Carbodiimide-Carboxylic Acid Adduct. O-Benzoyl-N,N-Dimethyl-N'-(N-Methyl-2,4-Dinitroanilino)Isourea. *J. Am. Chem. Soc.* **1977**, *99*, 2015–2016.

(202) Yokokawa, F.; Sameshima, H.; Shioiri, T. Total Synthesis of Lyngbyabellin A, a Potent Cytotoxic Metabolite from the Marine Cyanobacterium Lyngbya Majuscula. *Tetrahedron Lett.* **2001**, *42*, 4171–4174.

(203) Yokokawa, F.; Sameshima, H.; Katagiri, D.; Aoyama, T.; Shioiri, T. Total Syntheses of Lyngbyabellins A and B, Potent Cytotoxic Lipopeptides from the Marine Cyanobacterium Lyngbya Majuscula. *Tetrahedron* **2002**, *58*, 9445–9458.

(204) Kulkarni, Y. S.; Niwa, M.; Ron, E.; Snider, B. B. Synthesis of Terpenes Containing The Bicyclo[3.1.1]Heptane Ring System by the Intramolecular [2 + 2] Cycloaddition Reaction of Vinylketenes with Alkenes. Preparation of Chrysanthenone, β-Pinene, β-Cis-Bergamotene, β-Trans-Bergamotene, β-Copaene, and β-Yla. *J. Org. Chem.* **1987**, *52*, 1568–1576.

(205) Fürstner, A.; Langemann, K. Total Syntheses of (+)-Ricinelaidic Acid Lactone and of (-)-Gloeosporone Based on Transition-Metal-Catalyzed C-C Bond Formations. *J. Am. Chem. Soc.* **1997**, *119*, 9130–9136.

(206) Shida, N.; Kabuto, C.; Niwa, T.; Ebata, T.; Yamamoto, Y. Studies on S-Cis/s-Trans Preference of Acyclic α,β-Unsaturated Esters. Reactions, Supersonic Jet

Spectroscopy, NOEs, and X-Ray Analysis. *J. Org. Chem.* **1994**, *59*, 4068–4075.

(207) Loncharich, R. J.; Schwartz, T. R.; Houk, K. N. Theoretical Studies of Conformations of Acrolein, Acrylic Acid, Methyl Acrylate, and Their Lewis Acid Complexes. *J. Am. Chem. Soc.* **1987**, *109*, 14–23.

(208) Velusamy, S.; Punniyamurthy, T. Cobalt(II)-Catalyzed Chemoselective Synthesis of Acetals from Aldehydes. *Tetrahedron Lett.* **2004**, *45*, 4917–4920.

(209) Tumma, N.; Jacolot, M.; Jean, M.; Chandrasekhar, S.; Van De Weghe, P. Synthetic Studies towards Stachybotrin C. *Synlett* **2012**, *23*, 2919–2922.

(210) Gatti, M.; Vieille-Petit, L.; Luan, X.; Mariz, R.; Drinkel, E.; Linden, A.; Dorta, R. Impact of NHC Ligand Conformation and Solvent Concentration on the Ruthenium-Catalyzed Ring-Closing Metathesis Reaction. *J. Am. Chem. Soc.* **2009**, *131*, 9498–9499.

(211) Forbes, M. D. E.; Myers, T. L.; Maynard, H. D.; Schulz, G. R.; Patton, J. T.; Smith, D. W.; Wagener, K. B. Solvent-Free Cyclization of Linear Dienes Using Olefin Metathesis and the Thorpe-Ingold Effect. *J. Am. Chem. Soc.* **1992**, *114*, 10978–10980.

(212) Dinger, M. B.; Mol, J. C. High Turnover Numbers with Ruthenium-Based Metathesis Catalysts. *Adv. Synth. Catal.* **2002**, *344*, 671–677.

(213) Conrad, J. C.; Eelman, M. D.; Duarte Silva, J. A.; Monfette, S.; Parnas, H. H.; Snelgrove, J. L.; Fogg, D. E. Oligomers as Intermediates in Ring-Closing Metathesis. *J. Am. Chem. Soc.* **2007**, *129*, 1024–1025.

(214) Bailey, G. A.; Foscato, M.; Higman, C. S.; Day, C. S.; Jensen, V. R.; Fogg, D. E. Bimolecular Coupling as a Vector for Decomposition of Fast-Initiating Olefin Metathesis Catalysts. *J. Am. Chem. Soc.* **2018**, *140*, 6931–6944.

(215) Sytniczuk, A.; Dabrowski, M.; Banach, Ł.; Urban, M.; Czarnocka-Śniadała, S.; Milewski, M.; Kajetanowicz, A.; Grela, K. At Long Last: Olefin Metathesis Macrocyclization at High Concentration. *J. Am. Chem. Soc.* **2018**, *140*, 8895–8901.

(216) Hoye, T. R.; Danielson, M. E.; May, A. E.; Zhao, H. Total Synthesis of (-)-Callipeltoside A. *J. Org. Chem.* **2010**, *75*, 7052–7060.

(217) Heidt, T.; Baro, A.; Köhn, A.; Laschat, S. Synthesis of Cembranoid Analogues through Ring-Closing Metathesis of Terpenoid Precursors: A Challenge Regarding Ring-Size Selectivity. *Chem. Eur. J.* **2015**, *21*, 12396–12404.

(218) Débieux, J. L.; Cosandey, A.; Helgen, C.; Bochet, C. G. Photoacylation of Alcohols in Neutral Medium. *Eur. J. Org. Chem.* **2007**, No. 13, 2073–2077.

(219) Ippoliti, F. Synthesis of 8-Hydroxygeraniol. *Org. Synth.* **2019**, *96*, 586–598.

(220) Oikawa, M.; Hashimoto, R.; Sasaki, M. Asymmetric Synthesis and in Vivo Biological Inactivity of the Right-Hand Terpenoid Fragment of Terpendole E. *Eur. J. Org. Chem.* **2011**, No. 3, 538–546.

(221) Hanzlik, R. P. SELECTIVE EPOXIDATION OF TERMINAL DOUBLE BONDS: 10,11-EPOXYFARNESYL ACETATE. *Org. Synth.* **1977**, *56*, 112.

(222) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M. The Osmium-Catalyzed Asymmetric Dihydroxylation: A New Ligand Class and a Process Improvement. *J. Org. Chem.* **1992**, *57*, 2768–2771.

(223) Masuda, T.; Odaka, Y.; Ogawa, N.; Nakamoto, K.; Kuninaga, H. Identification of Geranic Acid, a Tyrosinase Inhibitor in Lemongrass (Cymbopogon Citratus). *J. Agric. Food Chem.* **2008**, *56*, 597–601.

(224) Valentine, D.; Johnson, K. K.; Priester, W.; Sun, R. C.; Toth, K.; Saucy, G. Rhodium Chiral Monophosphine Complex Catalyzed Hydrogenations of Terpenic and α-(Acylamino)-Substituted Acrylic Acids. *J. Org. Chem.* **1980**, *45*, 3698–3703.

(225) Wang, Y.; Wu, Z.; Yu, H.; Han, S.; Wei, Y. Highly Efficient Oxidation of Alcohols to Carboxylic Acids Using a Polyoxometalate-Supported Chromium(Iii) Catalyst and CO2. *Green Chem.* **2020**, *22*, 3150–3154.

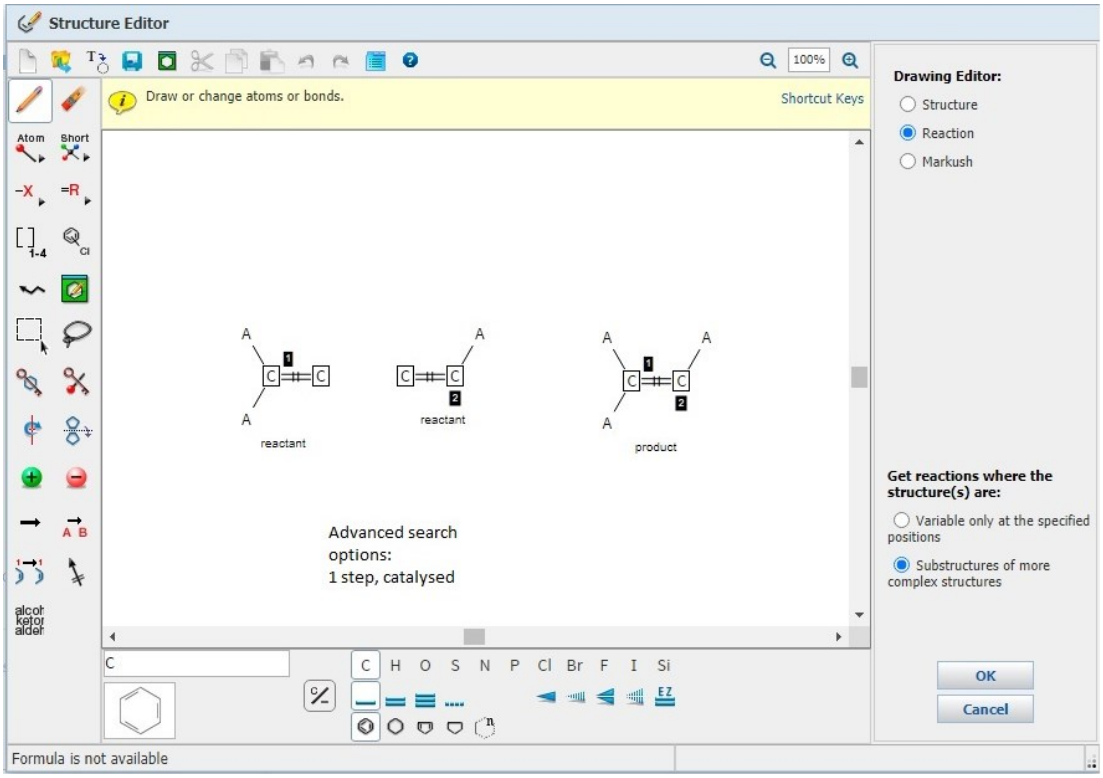
(226) Kobayashi, S.; Ando, A.; Kuroda, H.; Ejima, S.; Masuyama, A.; Ryu, I. Rapid

Access to 6-Bromo-5,7-Dihydroxyphthalide 5-Methyl Ether by a CuBr2-Mediated Multi-Step Reaction: Concise Total Syntheses of Hericenone J and 5′-Deoxohericenone C (Hericene A). *Tetrahedron* **2011**, *67*, 9087–9092.

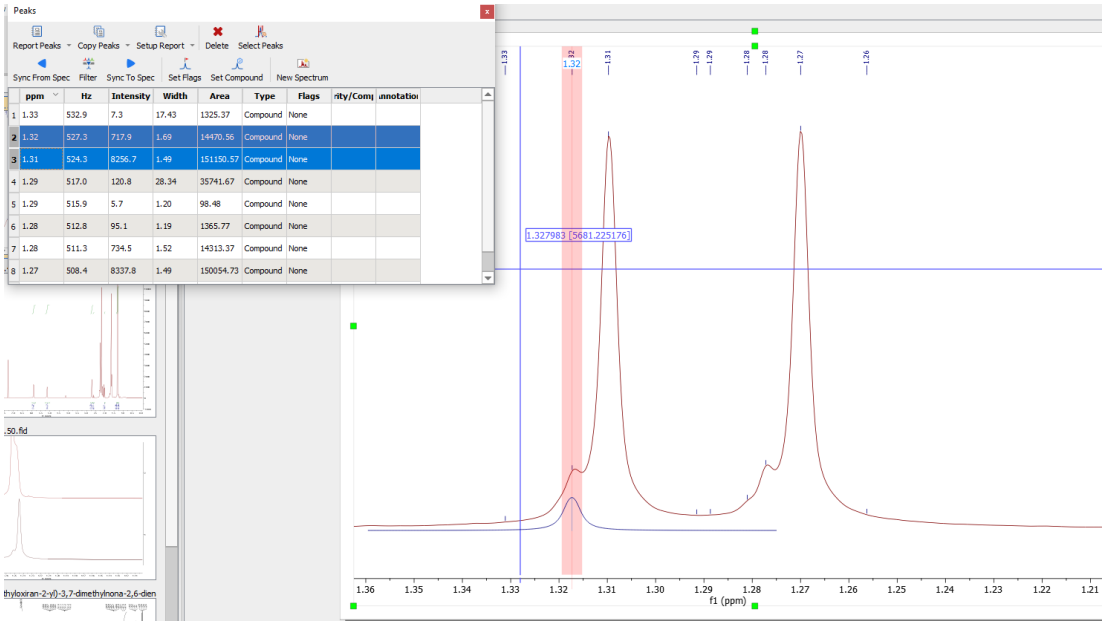
(227) Sakane, S.; Fujiwara, J.; Maruoka, K.; Yamamoto, H. Chiral Leaving Group: Asymmetric Synthesis of Limonene and Bisabolene. *Tetrahedron* **1986**, *42*, 2193–2201.

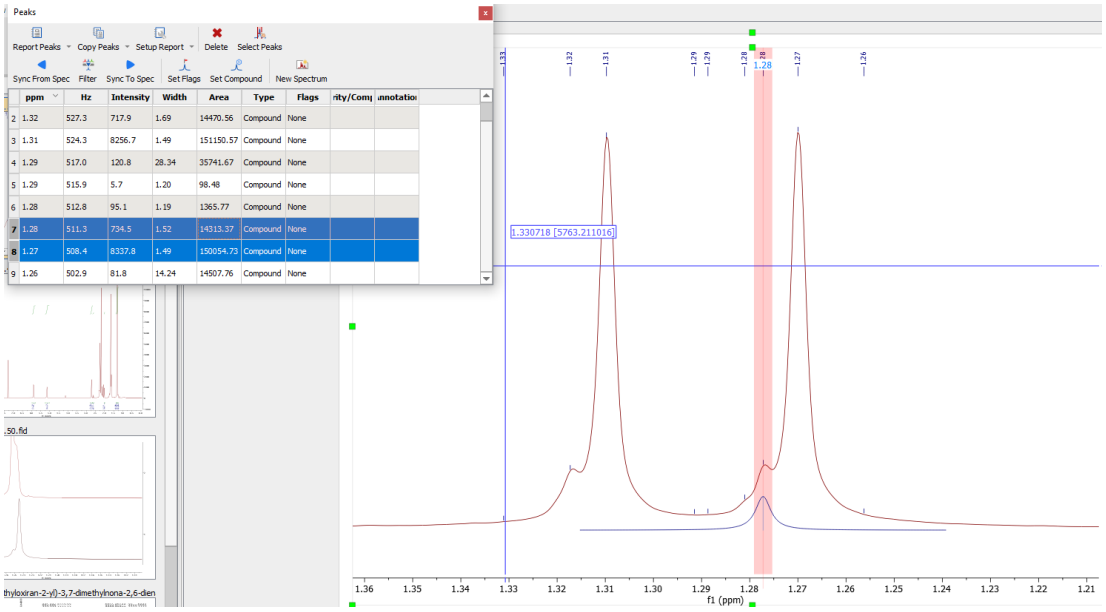
Appendices

Appendix I – Query used for searching different olefin combinations used in the synthesis of trisubstituted olefin *via* metathesis reactions.



Appendix II – Determination of *E/Z*-ratio of the internal olefin of 4.71 *via* global spectral deconvolution





Appendix III – Setup for the gas collection experiments

The gas outlet of the reaction vial was connected to the NMR tube *via* a cannula. The NMR tube was filled with deuterated chloroform and was immersed in the dry ice-acetone bath. Upon completion of the reaction, the cannula was rinsed with deuterated chloroform before removal from the NMR tube. The NMR tube was then sealed for NMR experiments.

