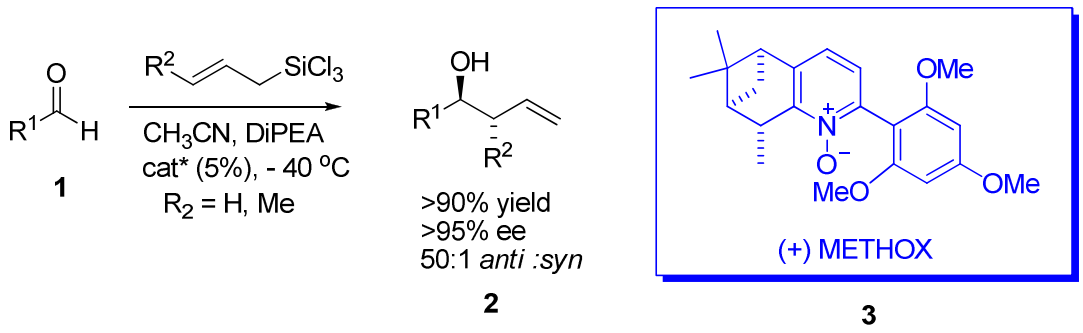
A thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

Asymmetric Synthesis of Homoallylic Alcohols and their Applications

Maciej Ł. Barłóg

Thesis Abstract

Herein it is presented a further development of the well-established catalytic asymmetric allylation of aldehydes **1** leading to enantiopure homoallylic alcohols **2** (Scheme1).

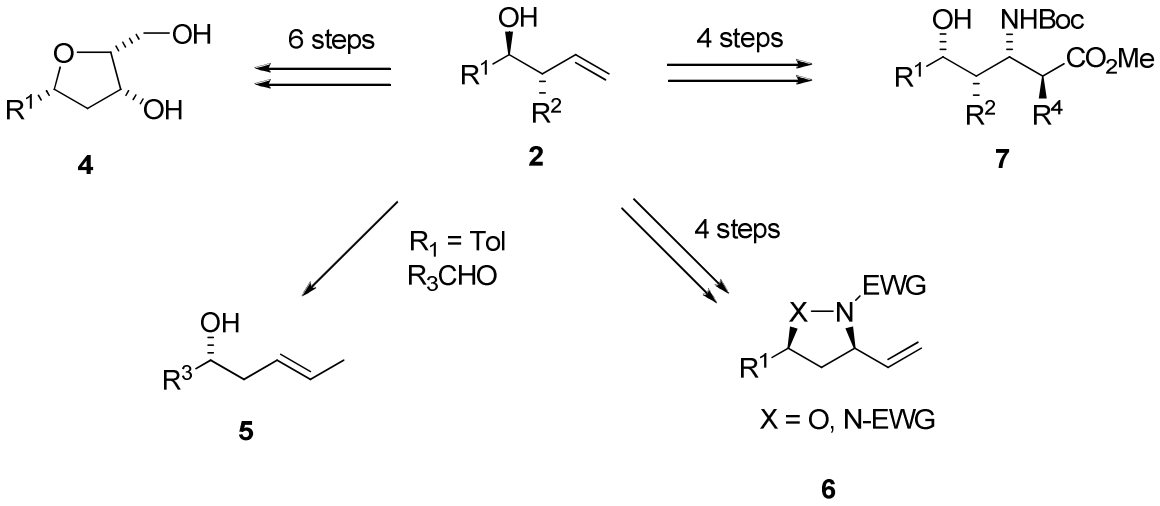


1 **2** **3**

Scheme 1

Stereogenic centre(s) served as the foundation for synthesis of a variety of other advanced intermediates and building blocks with multiple chiral centres (Scheme 2).

- New approaches to homoallylic alcohols **5** were dementrated with excellent control of chiral centers
- Biologically relevant carbohydrate analogues **4** were synthesised in four possible configurations using singlet oxygen raction as the key step
- δ-hydroxy-*β*-amino acids **7** were synthetised diastereoselectively using Pd catalysis as the key step.
- A novel approach to synthesis of isoxazolidines and pyrazolidines **6** was demonstrated



4 **2** **7** **5** **6**

Scheme 2

Acknowledgements

I would like to thank my supervisors Prof. Pavel Kočovský and Prof. Andrei Malkov for giving me the opportunity to join the group and for the intersting project. I am indebted for all the support, guidance and ideas given to me throughout duration of this project.

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Finally, last but not least, I would like to thank my parents because they made me the man I am and completing this work is much because of their effort. Most of my acknowledgements go to my wife Karina for being here with me and supporting me with all her love and kindness. I could not imagine accomplishing all the work herein on this thesis without beloved person sharing with me all the successes as well as failures.

Abbreviations and Acronyms

Ac	-	Acetyl
AcOH	-	Acetic acid
aq	-	Aqueous
Bn	-	Benzyl
Bu	-	Butyl
^{o}C	-	Degrees centigrade
Cat, cat*	-	Catalyst, chiral catalyst
Cy	-	Cyclohexyl
DCM	-	Dichloromethane
DIPEA	-	Hünig's base, *N,N*-Diisopropylethylamine
DMAP	-	4-Dimethylaminopyridine
DMF	-	Dimethylformamide
DMSO	-	Dimethylsulfoxide
dr	-	Diastereoisomeric ratio
ee	-	Enantiomeric excess
Et	-	Ethyl
Equiv	-	Equivalents
EWG	-	Electron withdrawing group
HMPA	-	Hexamethylphosphoramide
i-, *iso*-	-	Isomeric (branched alkyl chain)
L, L*	-	Ligand, chiral ligand
LA, LA*	-	Lewis acid, chiral Lewis acid
LB, LB*	-	Lewis base, chiral Lewis base
M	-	Metal
m-CPBA	-	*meta*-chloroperoxybenzoic acid
Me	-	Methyl
MeCN	-	Acetonitrile
mmol	-	Millimole
n-	-	Normal (linear alkyl chain)
Napht	-	Naphthyl
NHPI	-	*N*-Hydroxyphthalimide

Nu	-	Nucleophile
[ox]	-	Oxidising agent, oxidation, oxidative conditions
Ph	-	Phenyl
Pr	-	Propyl
Py	-	Pyridine
[red]	-	Reducing agent, reduction, reductive conditions
RT	-	Room temperature
s-, sec-	-	Secondary (branched alkyl chain)
sat	-	saturated
TBHP	-	*tert*-Butyl hydroperoxide
t-, tert-	-	Tertiary (branched alkyl chain)
TBDMS	-	tert-Butyldimethylsilyl
TFA	-	Trifluoroacetic acid
TfOH	-	Trifluoromethanesulfonic acid
TMS	-	Trimethylsilyl
p-Tol	-	*p*-Toluyl, *p*-methylphenyl

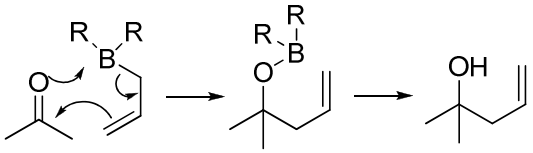
Content

1. Enantioselective Allylation and Allyl Transfer

1.1 Literature Review

1.1.1 Stoichiometric Asymmetric Allylation of Aldehydes with Boranes

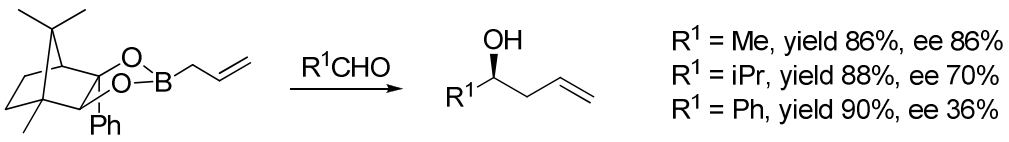
Allylation of the carbonyl group is one of the fundamental reactions for creating a new carbon-carbon bond. Since the pioneering work by Grignard[1a] and Barbier[1b] over a hundred years ago, the allylating reagents continued to evolve. Allylation of carbonyls with organometallics (B,[2h,2i] Si,[2j-m] Sn,[2n] Cr,[2o,2p] Ti,[2q] etc.[2a-g]) remains a powerful strategic reaction that creates up to two chiral centers. In the 1970s, the pursuit of an asymmetric version of this reaction began. The earliest attempts of borane allylation were reported by Mikhailov and Bubnov,[3] who introduced triallyl boranes **10** as the first reagents capable of stereoselective S_E2' reaction on carbonyl compounds **9** resulting in a wide range of homoallylic alcohols **12** (Scheme 3).



9 **10** **11** **12**

Scheme 3

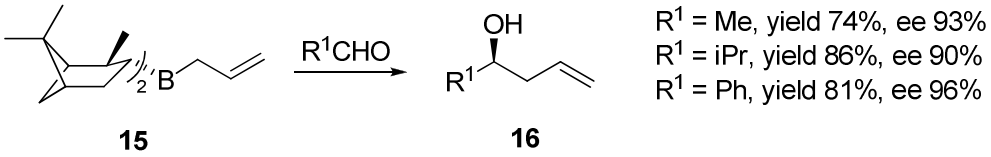
Several years later, Hoffman and Herold published an asymmetric version of this type of reaction.[4] They used modified camphor **13** to introduce a stereogenic centre to a series of secondary homoallylic alcohols **14** with moderate to good levels of enantioselectivity (Scheme 4).



13 **14**

Scheme 4

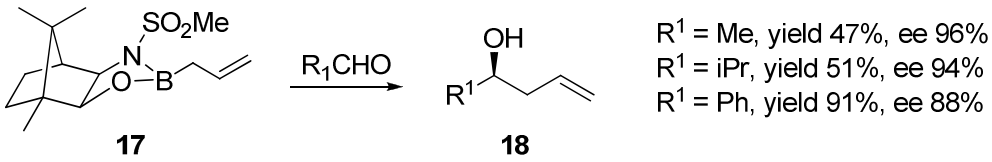
This methodology was followed by Brown and Jadhav who used naturally occurring α-pinene and in a series of reactions built a highly stereoselective chiral matrix **15**. This allowed them to obtain homoallylic alcohols **16** with excellent enantioselectivity (Scheme 5).[5]



15 **16**

Scheme 5

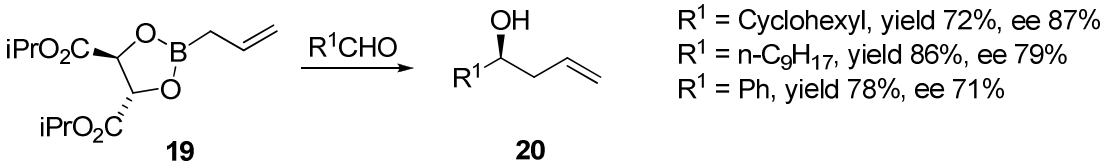
The high yields and excellent enantioselectivity shown by β-allyldiisopinocampheylborane ($Ipc_2BCH_2CH{=}CH_2$) **15** ensured that it remains till the present day among the most widely used asymmetric allylating reagents. Following on the work of Hoffman and Brown, a few years later Reetz introduced the nitrogen derivatisation of camphor and its application as a chiral auxiliary for allylboranes (Scheme 6).[6]



17 **18**

Scheme 6

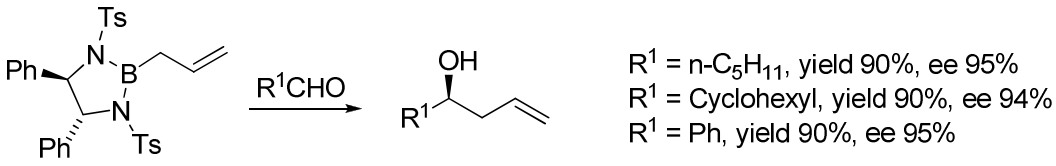
Another interesting approach to enantioselective allylation was developed by Roush and co-workers.[7] In 1985, they reported on DIPT (diisopropyl tartrate) as a chiral auxiliary to derivatise allyl boronates **19** in order to prepare a series of enantioenriched alcohols **20** (Scheme 7).



19 **20**

Scheme 7

This idea was further developed by Corey and coworkers, who used the tosyl amide of readily available 1,2-diamino-1,2-diphenylethane **21** which can be obtained in both *S,S* and *R,R* forms (Scheme 8).[8]

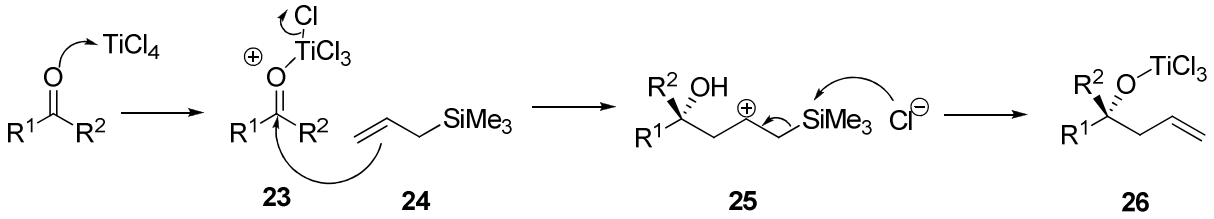


21 **22**

Scheme 8

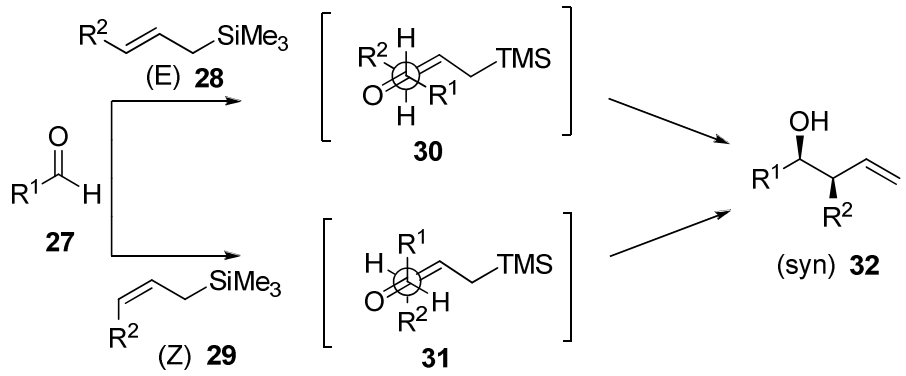
1.1.2 Asymmetric allylation of aldehydes catalysed by Lewis acids

The next milestone in the synthesis of homoallylic alcohols was set by Sakurai and Hosomi, who used Lewis acid catalysts for facilitating the nucleophilic attack of allyl silane (Scheme 9).[9] The reaction is initiated e.g, by $TiCl_4$, which coordinates to the carbonyl oxygen **23**, thereby increasing its electrophilicity. Nucleophilic attack by allylsilane **24**, followed by cleavage of TMS group **25**, furnishes the product **26**. High reactivity of allyl silanes toward carbonyls in this reaction can be explained by σ (Si-C)-π conjugation, known as the β-silicon effect.[10]



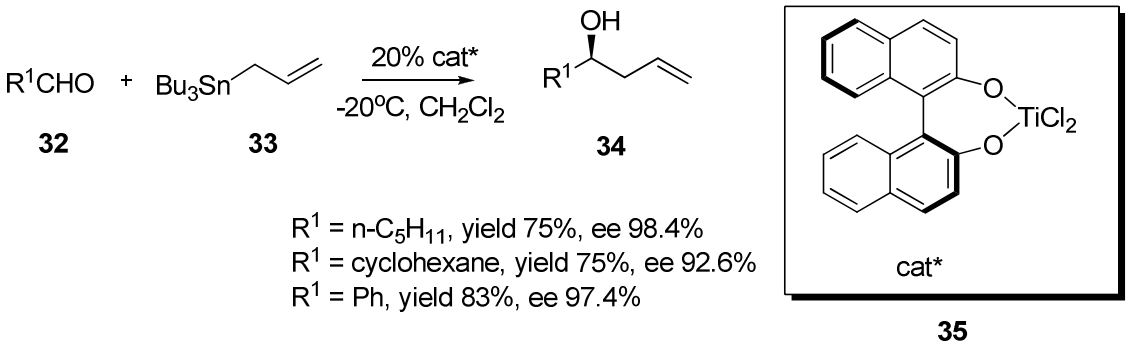
Scheme 9

The reaction proceeds presumably through an open transition state: when C3 substituted allylsilanes (e.g. crotyl trimethylsilane) are submitted to the reaction, the major product is the *syn* disastereoisomer for both the *E* **28** and *Z* **29** isomers of the starting silanes (Scheme 10).[11,12] However, the *E* isomer produces practically pure *syn* product **32** while the *Z* configuration gives a 2:1 mixture of alcohols.



Scheme 10

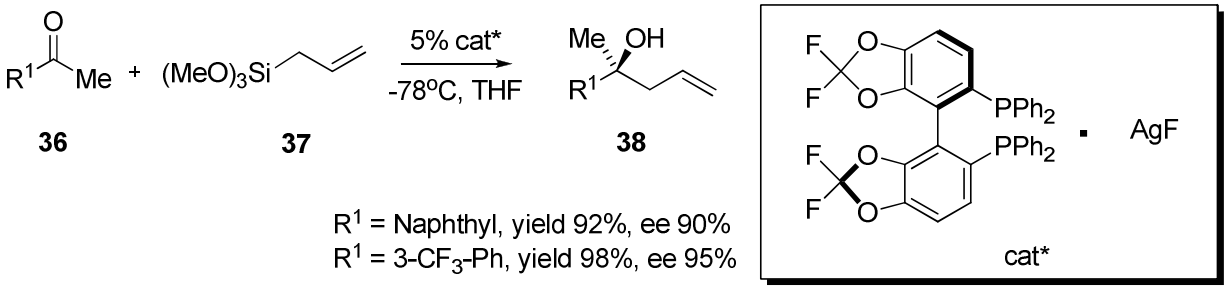
There are known catalytic versions of this reaction that employ other transition metal catalysts.[13] In the last two decades, examples of the asymmetric Sakurai allylation of ketones and aldehydes regularly appear in the literature. Metals like Ti[14] (**35**, Scheme 11), Ag[15] (**39**, Scheme 12), Sc[16] (**43**, Scheme 13) are commonly used in catalyst molecules but other Lewis acids are also known to be very effective.[17]



32 **33** **34** **35**

R^1 = n-C_5H_{11}, yield 75%, ee 98.4%
R^1 = cyclohexane, yield 75%, ee 92.6%
R^1 = Ph, yield 83%, ee 97.4%

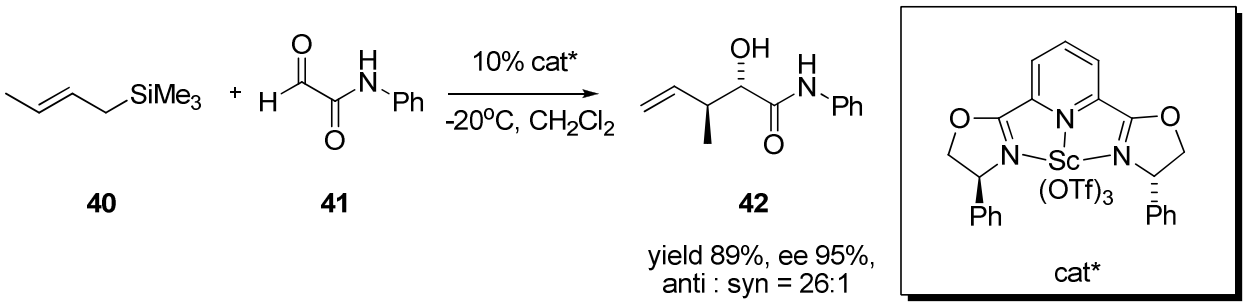
Scheme 11



36 **37** **38** **39**

R^1 = Naphthyl, yield 92%, ee 90%
R^1 = 3-CF_3-Ph, yield 98%, ee 95%

Scheme 12



40 **41** **42** **43**

yield 89%, ee 95%,
anti : syn = 26:1

Scheme 13

1.1.3 Allylation Of Aldehydes Catalysed By Lewis Bases

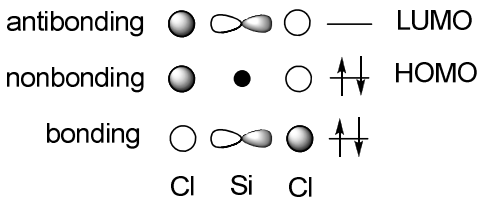
The mechanism by which chiral Lewis bases promote asymmetric allylation is conceptually different from the one presented for Lewis acids (vide supra). The reactions catalysed by Lewis bases, however, offer a range of novel and synthetically useful transformations.[18] Use of Lewis base catalyst changes the chemical reactivity of the organometallic reagents in a number of ways. It can increase the nucleophilicity or electrophilicity of the reagents by modulation of the electronic properties.[19] Lewis base-catalysed processes employing non-metallic reagents are not very common in organic synthesis. The main reason is the lack of target Lewis acidic sites in the carbon based molecules and no possibility of valence expansion on carbon atoms. On the other hand, the silicon atom is known to create hypervalent bonding systems and thus Lewis base catalysts have been successfully utilised in reactions with organosilicon compounds.

Silicon normally engages in bonding with only four other atoms, which completes the electronic requirement for an outer-shell octet. In SiL_4, the molecule has a tetrahedral geometry, and therefore the central silicon atom displays sp^3 hybridization.[18] The ability of silicon to expand its coordination shell, which is similar to phosphorus and antimony, has been intensively exploited only during the last two decades. [20] However, simple silicon compounds with coordination number higher than four were known since early 19th century (**44, 45** Figure 1). [2]

44 **45**

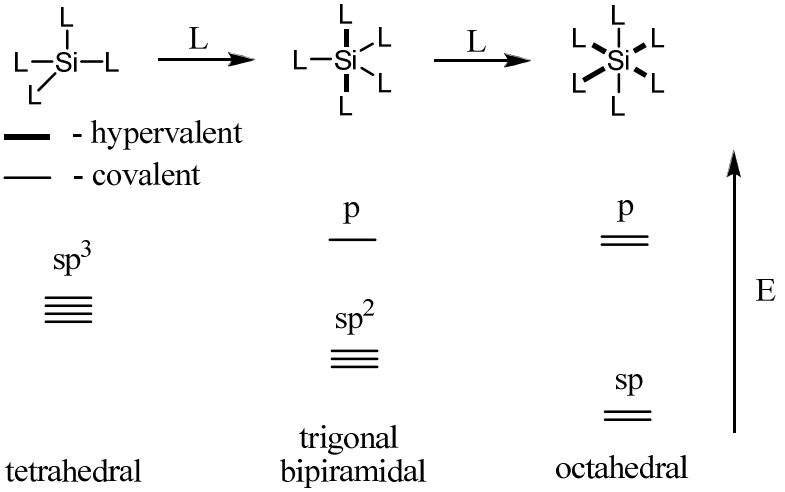
Figure 1

Expansion of the SiL_4 species to a pentacoordinate silicon complex (SiL_5) requires a p orbital to engage in hypervalent three-centre four-electron (3c-4e) bonding. The latter bonding type results in more electron density located at the peripheral ligands and electron deficiency at the central atom. This can be explained through a molecular orbital diagram (Scheme 14).



Scheme 14

The trigonal bipyramidal structure of silicon pentavalent complexes employs sp^2 hybridization of the central silicon atom. Further expansion of the coordination sphere to an octahedral, hexacoordinate complex (SiL_6), requires a second p orbital to engage in hypervalent bonding, and the silicon atom to be formally sp hybridized. According to Bent's rule, highly electronegative elements, which are usually hypervalently bonded (F, Cl, OR), prefer p-character bond (Scheme 15).[24] The formation of hypervalent p-symmetry orbitals effectively lowers the energy of the hybrid orbitals involved in covalent bonding by increasing the proportion of "s character" in these orbitals, leaving nonbonding p-MO for extra valency.[18,23]

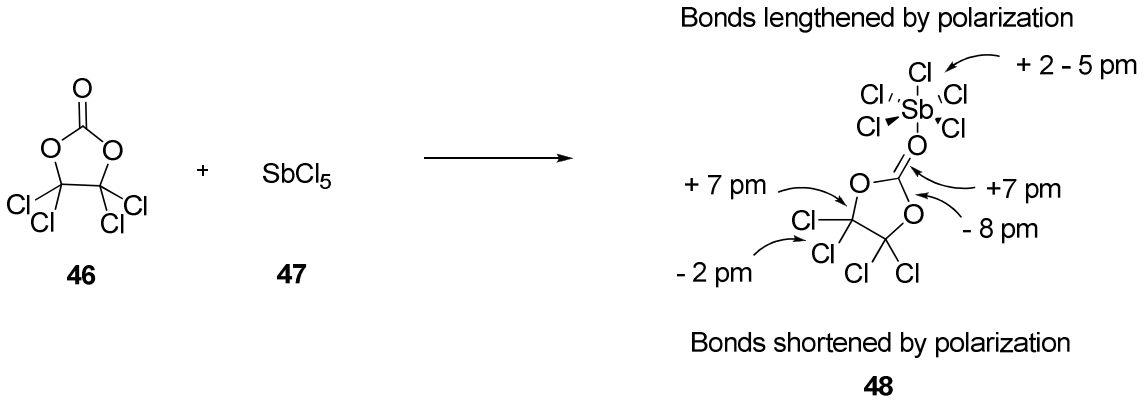


Scheme 15

The changes in bond order induced by adduct formation allow for the simultaneous enhancement of nucleophilic and electrophilic character dependent on bond polarizability during acid-base interactions.[18] The behaviour of hypervalent species and why this often leads to novel forms of reactivity is best understood through Gutmann's empirical analysis of acid–base interactions.[22] Formation of an acid–base adduct leads to an overall increase in the electron density in the acceptor fragment of the adduct, but the distribution of this electron density is not equal among the atoms.

Redistribution of electron density has noticeable consequences on the bond lengths. These observations became the basis of Gutmann's four empirical rules of molecular adduct. Application of the rules can be illustrated by changes in antimony pentachloride **47** X-ray structure upon Lewis base **46** binding (Scheme 16).[22]

- The smaller the intramolecular distance between the donor (D) and the acceptor (A), the greater the induced lengthening of the peripheral bonds (A-X)
- The longer the bond between D and A, the greater the degree of polarization of electron density across that bond
- When the coordination number of an atom increases, so do the lengths of all the bonds originating from that coordination centre.
- The bonds adjacent to D and A will either contract or elongate to compensate for the changes in electron density at D and A.

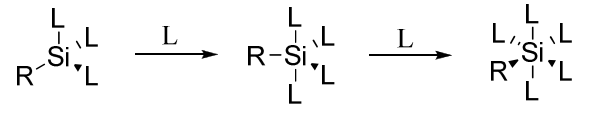


46 **47** **48**

Scheme 16

Induction of noticeable changes in the bond lengths throughout the complex is a clear manifestation of both the first and fourth rules.[18]

Changing valency and electronics of the silicon centre has a direct impact on the nucleophile (R) transfer in Lewis base catalysed reactions (Scheme 17).[25a]



4-coordinate 5-coordinate 6-coordinate

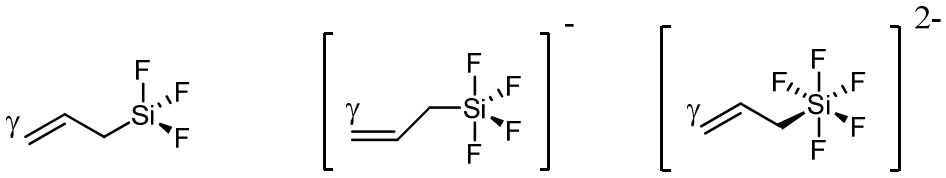
49 **50** **51**

L - Cl^-, F^-, RO^-, DMF, HMPA
R - eg. allyl

Scheme 17

Tetra-coordinate organosilicon compound **49** is a weak Lewis acid and has poor ability for nucleophilic transfer of R. Pentavalent state **50** is reached by attack of neutral or negatively charged nucleophile (e.g., DMF, HMPA, F^-) on the silicon centre. The resulting complex is more Lewis acidic and R-nucleophilic as hypervalency causes an increase of the positive charge on silicon and negative charge on its ligands (Scheme 17). Attachment of the next ligand to form a hexacoordinate species **51** is usually the rate determining step. At this point the silicon atom reaches it highest positive charge and the R group is transferred. [25b]

Kira and coworkers conducted computational studies over a series of fluorosilicon compounds which showed how fluorine ligation impacts both electrophilicity and nucleophilicity of the molecule.[25c]

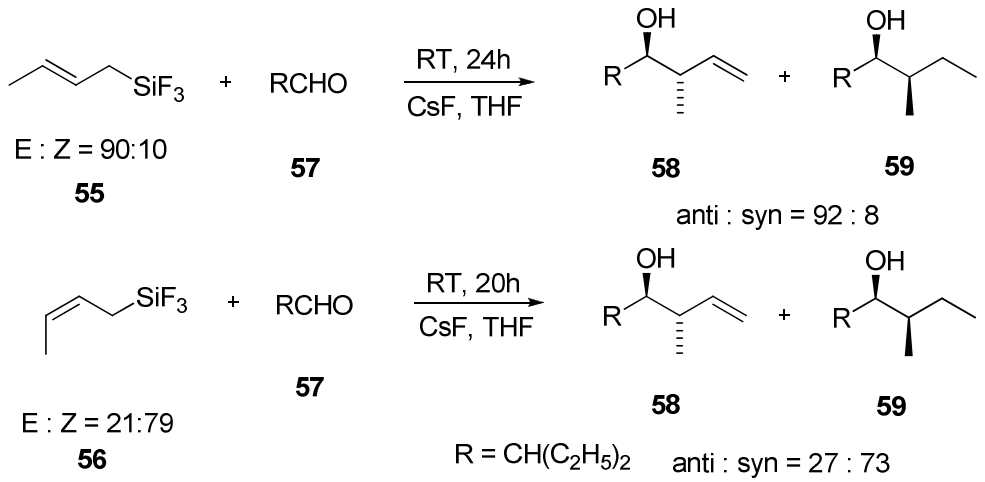


4-coordinate	5-coordinate	6-coordinate
52	**53**	**54**
q(Si) = 1.37	q(Si) = 1.35	q(Si) = 1.51
$q(C_\gamma)$ = -0.26	$q(C_\gamma)$ = -0.31	$q(C_\gamma)$ = -0.38
Si-C = 1.85Å	Si-C = 1.90Å	Si-C = 1.99Å

Scheme 18

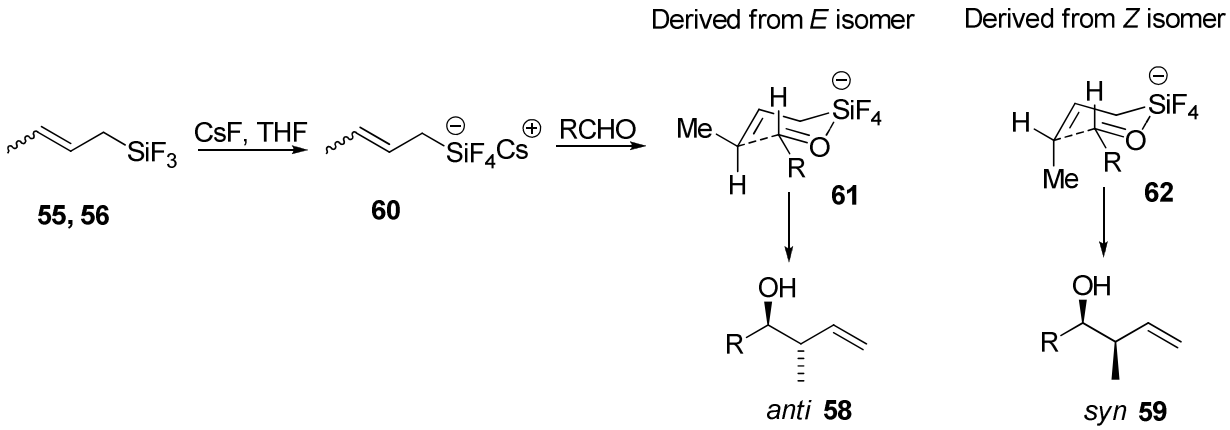
The most important is the increasing polarity of the molecule as electron density rises on the nucleophilic γ carbon and drops on silicon (Scheme 18).

The first use of fluorine ions as the Lewis-basic catalyst for allylation with allyltrifluorosilane (**55** and **56**) was presented by Kira and Sakurai.[26] The reaction showed different *syn/anti* selectivity than Lewis acid catalysis and the ratio of alcohols (**58** and **59**) obtained in identical conditions was entirely based on the *E : Z* ratio of the starting crotylsilanes (Scheme 19).



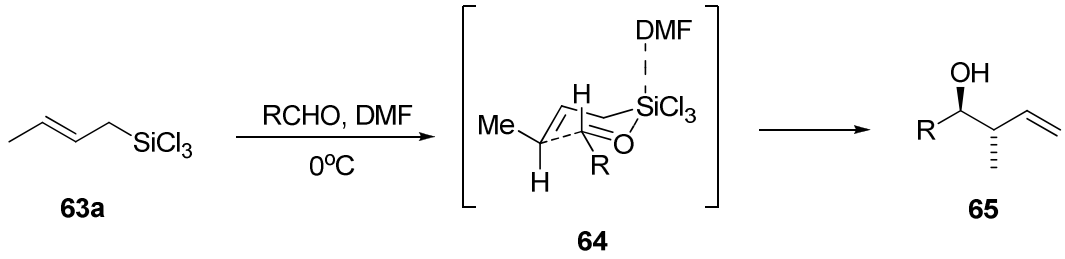
Scheme 19

The results were completely different from previous protocols that employ Lewis acid catalysts indicating that another mechanism must be involved. The authors suggested that enhanced Lewis acidity of the pentacoordinated silicon fluoride **60** is capable to attract carbonyl oxygen and activate it for nucleophilic attack. Increased electrophilicity of the carbonyl group coordinated to silicon triggers the allyl transfer.[26] The high diastereoselctivity observed in this case was attributed to the six-memebered cyclic transition states **61** and **62** (Scheme 20).



Scheme 20

The idea of activation of organotrichlorosilanes with Lewis bases was further developed by Kobayashi and Nishio.[27] They discovered that common organic solvents, such as DMF and HMPA, are highly efficient and selective initiators for reactions with trichlorosilanes **63**. Excellent regio and stereoselectivity, which mirrored the geometrical *E*/*Z* purity of the starting material, lend further credence to the operation of the six memebered cyclic transition state **64** concept (Scheme 21).



63a **64** **65**

Scheme 21

To confirm that the hypervalent silicate is the key intermediate in this reaction, Kobayashi and Nishio conducted ^{29}Si NMR experiments.[27] Dramatic changes in the chemical shifts of crotyltrichlorosilane were attributed to coordination of certain solvents to the silicon atom (Table 1).

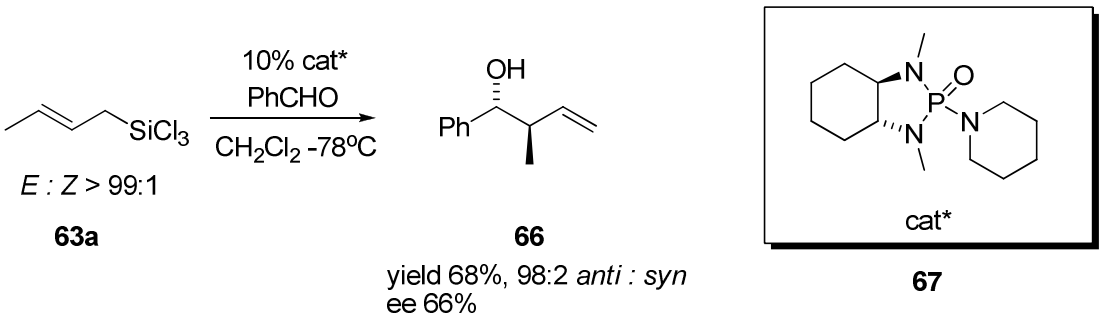
Table 1. Crotyl trichlorosilane ^{29}Si NMR chemical shift in various solvents.[27]

No	Solvent	Chemical shift (ppm)
1	$CDCl_3$	+8.0
2	CD_3CN	+8.6
3	C_6D_6	+7.9
4	THF-d_8	+8.5
5	DMF-d_7	-170
6	HMPA	-22

1.1.4 Asymmetric Lewis-basic catalysts

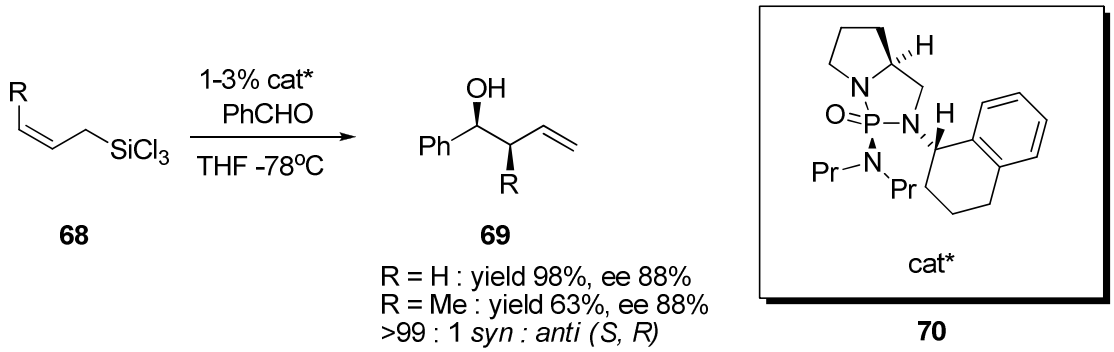
These experiments set the foundation for the modern Lewis base mediated asymmetric allylations. Chiral analogues of both DMF and HMPA were developed, and the field is continuously evolving.

The undisputed pioneer in the HMPA-derived chiral Lewis basic catalysis is Denmark, whos group first reported an enantioselective variant of this reaction.[28] They obtained excellent *anti/syn* selectivity for alcohols **66** with moderate yield and ee (Scheme 22).



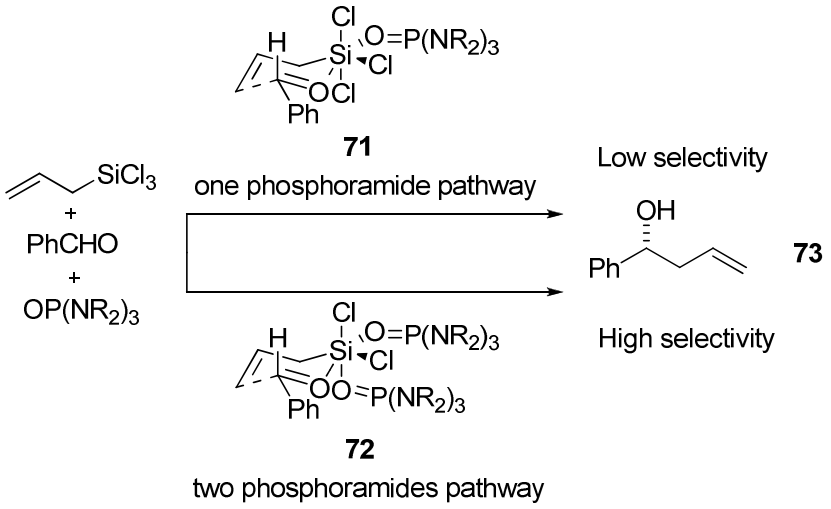
Scheme 22

Shortly after, Iseki and Kobayashi and coworkers came up with the proline based chiral HMPA derivative **70**.[29a] In the course of optimisation supported by *PM-3* calculations, their catalysts (Scheme 23) exhibited better selectivity, yields and TON than the original Denmark molecule.[29b]



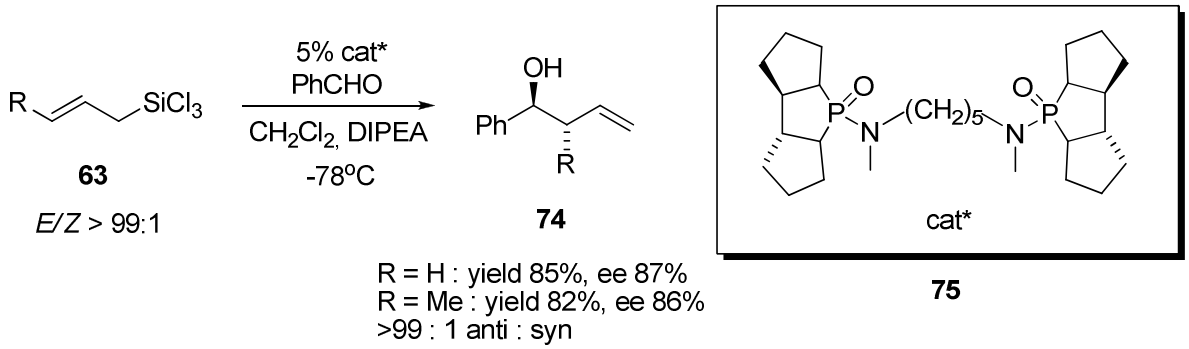
Scheme 23

Detailed mechanistic studies were conducted by Denmark and Fu, who concluded that dependence of enantioselectivity on catalyst loading might be caused by two phosphoramide pathways. Coordination of either one **71** or two **72** catalyst molecules leads to homoallylic alcohols **73** of low or high enantioselectivity respectively (Scheme 24).[30]



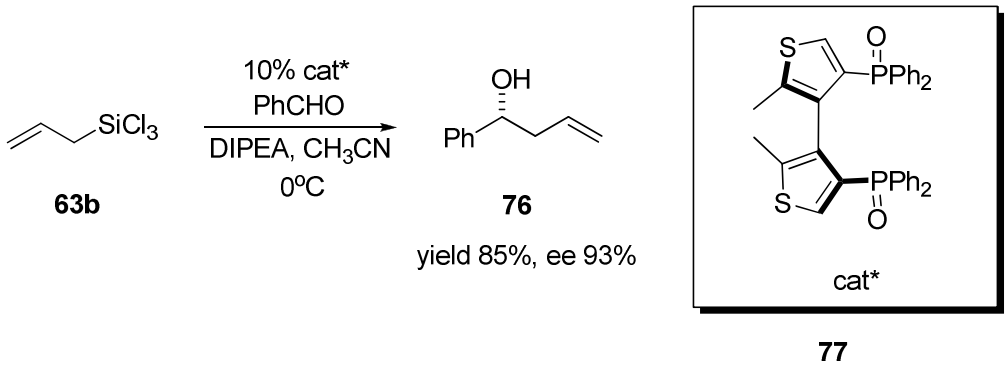
Scheme 24

Based on these findings, they synthesised a series of bidentate phosphoramides, among which the most selective was the dimeric catalyst with a five-carbon linker **75** (Scheme 25).[30]



Scheme 25

Other examples of the phosphorus-based Lewis-basic chiral catalysts include diphosphine oxides, which are also able to coordinate trichlorosilyl derivatives and generate hypervalent silicate structures. Initial experiments by Nakajima and coworkers yielded only moderate enantioselectivity but brought the idea to the further development.[31] The axially chiral biheteroaryl-diphosphine oxide **77** reported by Simoni and coworkers provided excellent selectivity, especially with electron-poor aromatic aldehydes (Scheme 26).[32]

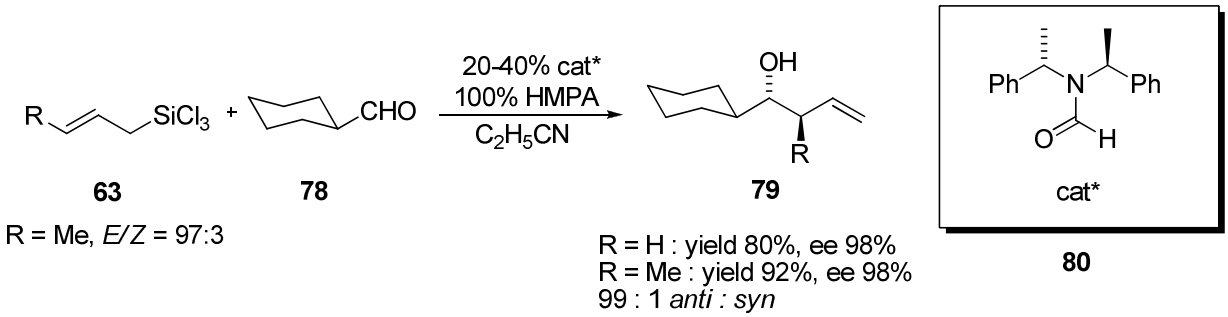


63b **76** **77**

yield 85%, ee 93%

Scheme 26

An interesting class of Lewis base catalyst are chiral derivatives of DMF **80**. Iseki et al[33] reported asymmetric allylation of aliphatic aldehydes **78** with excellent yields and ees. Remarkably, the selectivity was very high for simple aliphatic aldehydes, but it decayed for aromatic and conjugated ones. A dramatic increase of selectivity was observed after addition of a stoichiometric amount of HMPA (Scheme 27).



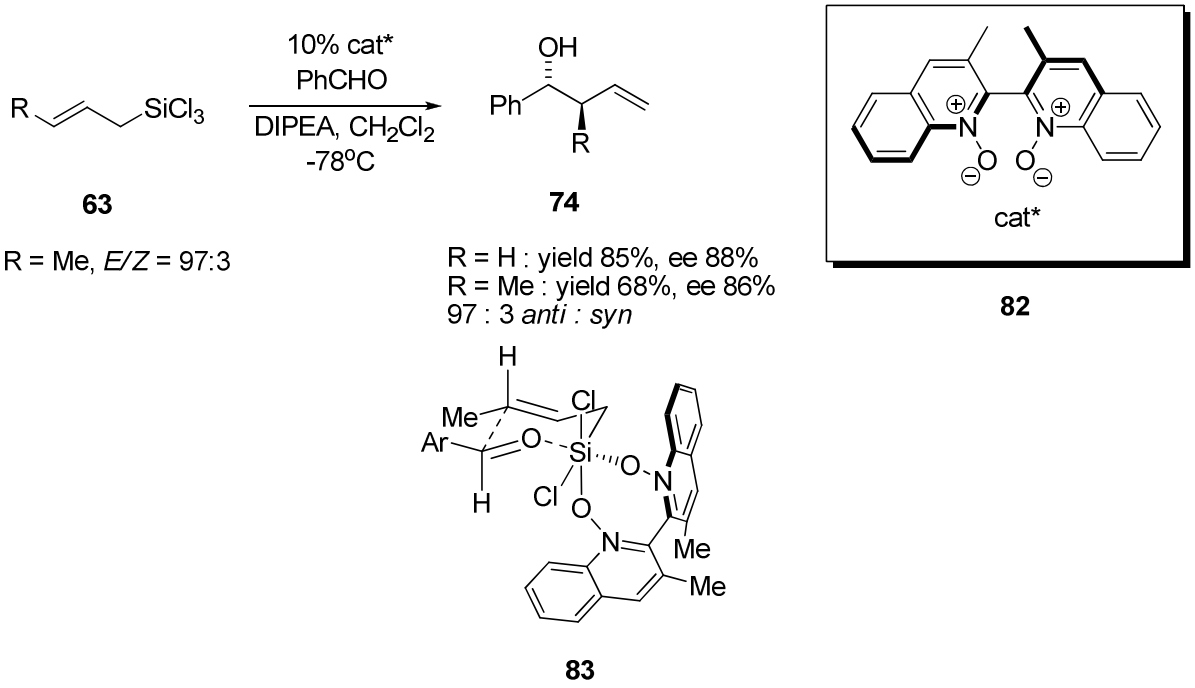
63 **78** **79** **80**

R = Me, *E/Z* = 97:3

R = H : yield 80%, ee 98%
R = Me : yield 92%, ee 98%
99 : 1 *anti : syn*

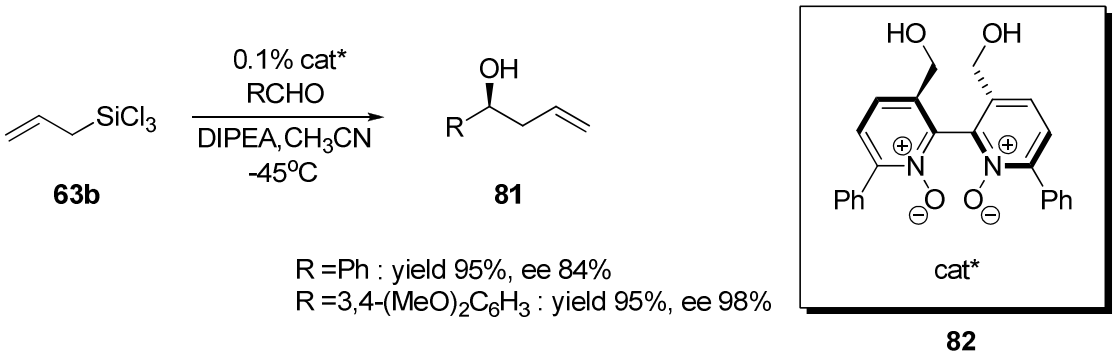
Scheme 27

Heteroaromatic *N*-oxides possess an electron pair with high donating properties. The strong Lewis basicity of the oxygen, combined with high affinity for silicon, represents a perfect candidate for development of a new class of Lewis-basic catalysts.[34] In 1998, Nakajima and coworkers reported on the first use of the axially chiral biquinoline *N,N'*-dioxides **82** for asymmetric allylation of aldehydes and proposed a cyclic chair-like transition structure, where electron pairs from both *N*-oxides are involved in hypervalent coordination to silicon **83** (Scheme 28).[35]



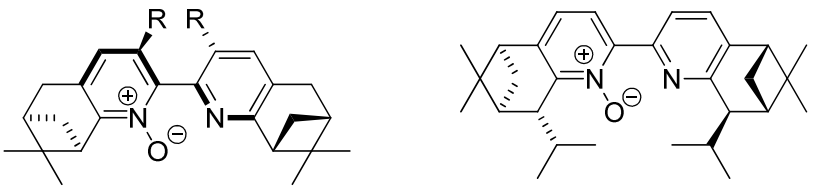
Scheme 28

This work was followed by Hayashi's group who introduced catalysts based on substituted bipyridine *N*-oxide **82**. They reported impressive level of enantioselectivity, up to 98% ee, accompanied with a very low catalyst loading and a short reaction time (Scheme 29).[36]



Scheme 29

Prior to Hayashi's publication, Malkov, Kočovský and coworkers reported on a series of catalysts derived from terpene-based bipyridine *N*-monoxides.[37] Enantiopurities in the case of Me_2PINDOX **83** and iso-PINDOX **84** reached 98% and 97% respectively, which can be attributed to the impact of both central and axial chirality present in the molecule (Figure 2). The substancial steric hindrance, however, may be the reason of lower activity, so that 10 mol% catalyst loading was required. Very high selectivity was explained by analogus double chelation mechanism via O and N atoms.[38]



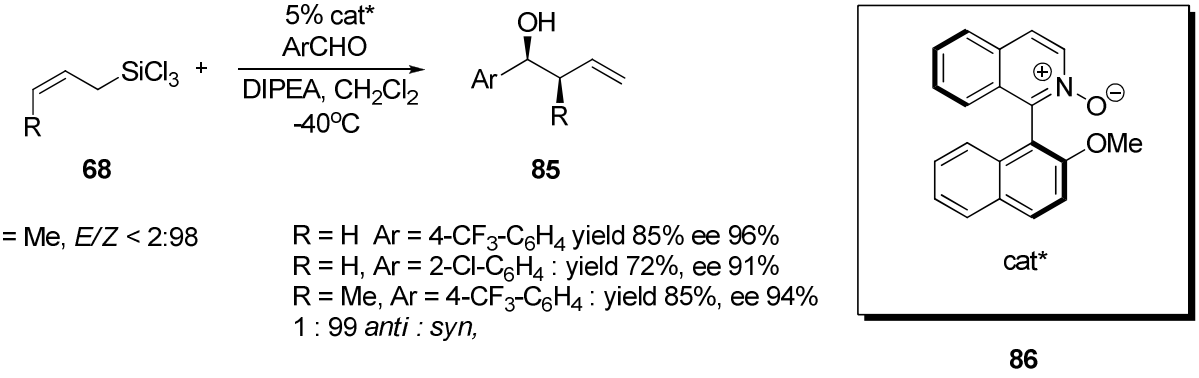
83 **84**

R = H (S, 90%ee)
R = Me (S, 98%ee)

S, 97%ee

Figure 2

Another type of asymmetric Lewis-basic catalyst reported by Malkov Kočovský and coworkers was QUINOX **86**. This catalysts selectivity was based solely on axial chirality. Under optimised conditions, it provided alcohols **85** with excellent enantioselectivity, especially for aldehydes with electron withdrawing groups, and (*Z*)-crotyl trichlorosilane **68**.[39] On the other hand, using this catalyst for highly electron rich aldehydes (e.g., 4-MeO-PhCHO) produced only 16% ee (Scheme 30).



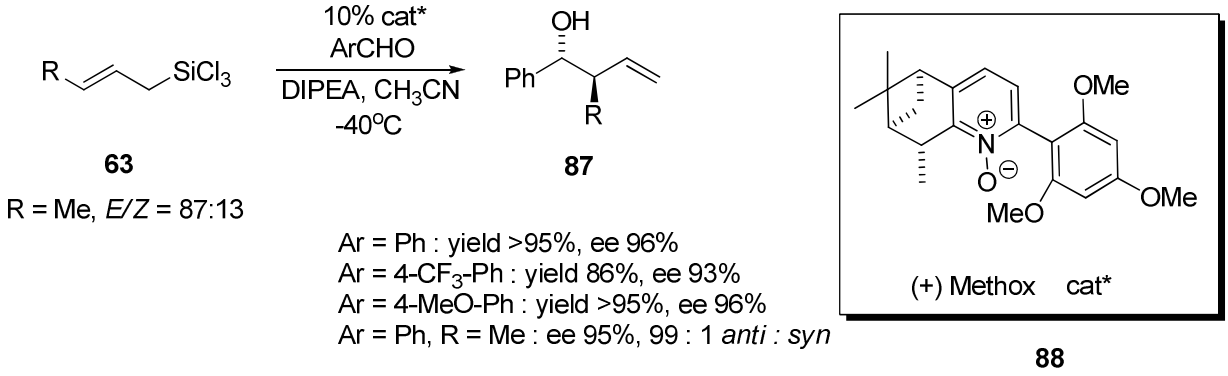
68 **85** **86**

R = Me, *E/Z* < 2:98

R = H Ar = 4-CF_3-C_6H_4 yield 85% ee 96%
R = H, Ar = 2-Cl-C_6H_4 : yield 72%, ee 91%
R = Me, Ar = 4-CF_3-C_6H_4 : yield 85%, ee 94%
1 : 99 *anti : syn,*

Scheme 30

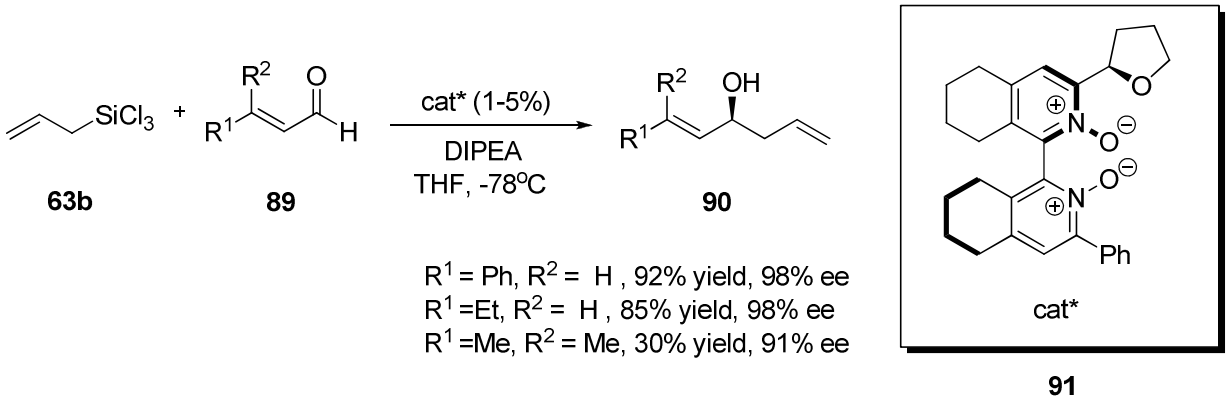
In 2005 the Malkov and Kočovský group reported on the synthesis and application of yet another type of *N*-oxide Lewis-base catalyst.[40] The molecule named METHOX **88** shows unmatched enantioselectivity at reasonable catalyst loading for both electron-poor and electron-rich aromatic aldehydes (Scheme 31). Another interesting feature of the catalyst is its high selectivity over a wide range of temperatures. Numerous experiments showed drop from 96% ee at -40°C to respectable 87% ee at RT with constant, nearly quantitive yields. High kinetic preference for the (*E*)-isomer of crotyl trichlorosilane **63** allows the reaction with technical grade starting material to give pure *anti* diatereoisomer with excellent ee and dr.



Scheme 31

Allylation of aliphatic and conjugated aldehydes has not been extensively investigated. In all the publications overviewed so far, selectivity of the catalyst was demonstrated with use of aromatic aldehydes. In reports, where cinnamyl aldehyde was employed, a dramatic drop of the ee was usually observed.[28,36b] This severely limits the scope of alcohols and the practical use of this asymmetric allylation methodology as a key, chirality introducing step.

Development of a novel *N,N*-dioxide **91** catalyst was reported recently by Kotora and coworkers.[41] The catalyst exhibits high enantioselectivity **90** (up to 98% ee) for a series of multisubstituted α,β-unsaturated aldehydes **89** (Scheme 32).



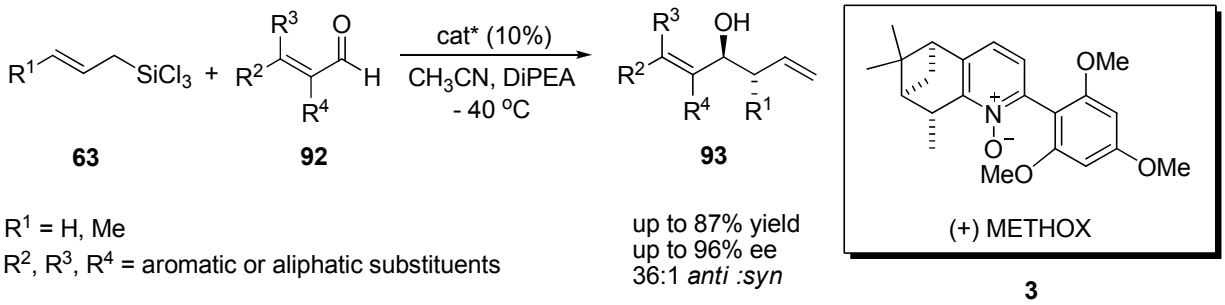
Scheme 32

1.2 Methox-catalysed allylation of the aliphatic aldehydes

The project was completed with the assistance of final year undergraduate student **Yvonne Jewkes** and Erasmus exchange student **Jiří Mikušek**

1.2.1 Abstract

A highly enantio- and diastereo-selective protocol for the allylation of conjugated unsaturated aldehydes **92** catalysed by Methox **3** has been developed. The respective homoallylic alcohols were obtained in good yields and good-to-excellent ee (up to 96%) (Scheme 33).



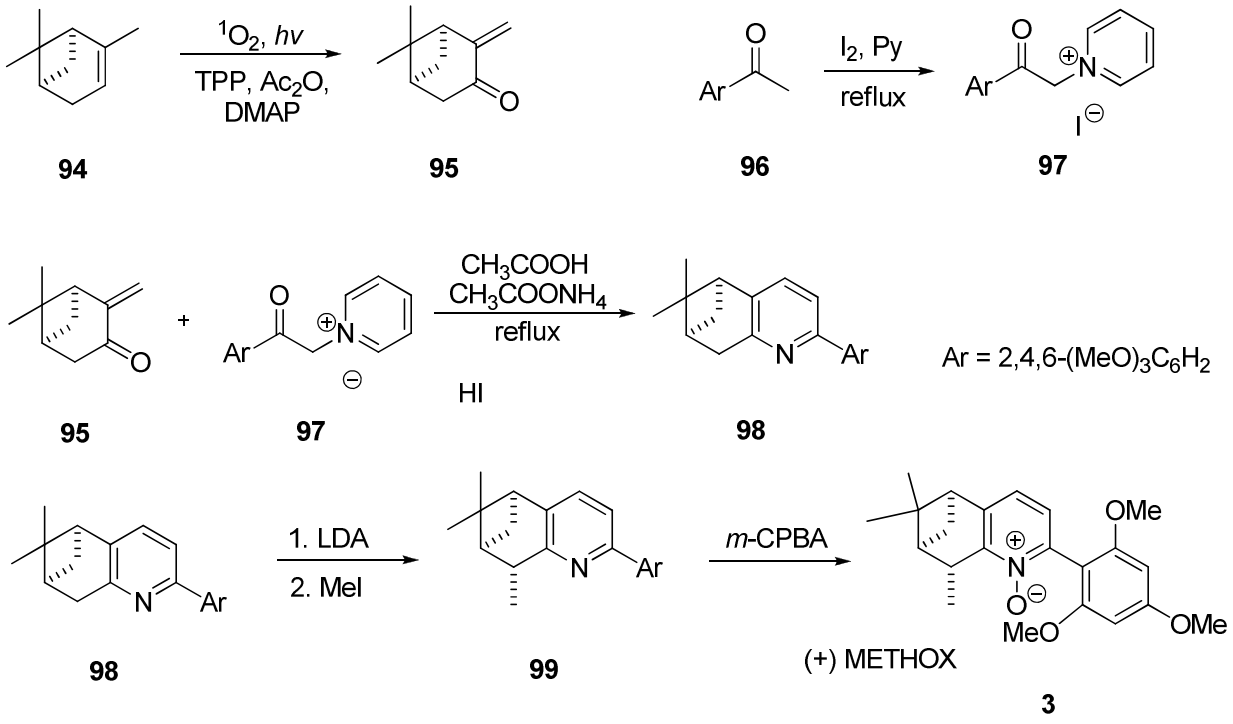
Scheme 33

1.2.2 Project aim

Methox proved to be effective and universal catalyst for asymmetric allylations and demonstrated high selectivity for a range of aromatic aldehydes. The initial experiments with Methox-catalysed allylation of cinnamyl aldehyde showed ee as high as 88%, while most of the catalysts presented in the preceding introduction section proved less efficient, except for mono-*N*-oxide **84** (Figure 2).[37b] Encouraged by this success, we became interested in the expansion of Methox's scope. Most of the previously mentioned catalysts proved ineffective when aliphatic aldehydes were used as an electrophile. On the other hand, Kobayashi's formamide,[33] although achieving very good results for aliphatic aldehydes was rather inefficient in the case of their aromatic congeners. We felt that it would be advantageous to prove that Methox can be an effective catalyst for both aromatic and aliphatic aldehydes. Previous studies of the Methox catalysed allylations focused mainly on the influence of ring substitution in aromatic aldehydes. Now, we will focus on a wide range of non-aromatic unsaturated aldehydes. This project aimed to open a new and simple route towards a series of homoallylic alcohols that have not been synthesised before by this method.

1.2.3 Synthesis of Methox – chiral Lewis base catalyst

Methox can be synthesised in several relatively simple steps (Scheme 34).[40] The synthesis starts with inexpensive natural α-pinene **94**, which affords pinocarvone **95** by ene reaction with singlet oxygen.[42] Singlet oxygen reactions will be discussed in more detail in Chapter 3. This approach allows the use of both enantiomers of the naturally occurring α-pinene (Scheme 34). Pinocarvone acts as the Michael acceptor for the Kröhnke salt **97** prepared from pyridine, iodine and the appropriate acetophenone **96**.[43] The two components are refluxed together with ammonium acetate in acetic acid. Michael reaction, followed by amination of both carbonyls leads to the chiral pyridine derivative **98**.[43] The pyridine is then deprotonated with LDA and the methyl group is introduced distaereoselectively **99**. The final step is oxidation of the pyridine nucleus into *N*-oxide, followed by recrystallisation to upgrade the enantiopurity of Methox **3** to 99% ee.



Scheme 34

1.2.4 Results and discussion

Previous catalysts developed in our group, such as Quinox and Pindox, exhibit moderate to good enantioselectivity for conjugated aldehydes.[37a,37b] Enantioselectivity of 96% ee was obtained for cinnamyl aldehyde with *iso*-Pindox but a low yield of 25% and complicated catalyst synthesis limit its practical use. Reaction with cinnamyl aldehyde gave 51% ee with Quinox but only after lowering the temperature to –90 ^{o}C, which inevitably affected the reaction rate and yield. Allylation of its saturated analogue: 3-phenylpropanal gave only 49% ee, highlighting the importance of the conjugation for attaining good enantioselectivity. High selectivities obtained for α,β unsaturated aldehydes, comparable with aromatic substrates, were attributed to lowered electrophilicity of carbonyl in the conjugated system.[55] Aliphatic aldehydes, due to higher reactivity, are reversibly consumed in the formation of a 1-chloro-1-silyloxy derivative. Chlorinated product is favoured in the equilibrium therefore no allylation product is observed.

In the course of our study we examined several commercially available conjugated aldehydes and a few more synthesised by methods leading to either α- or β-substituted products (Figure 3).

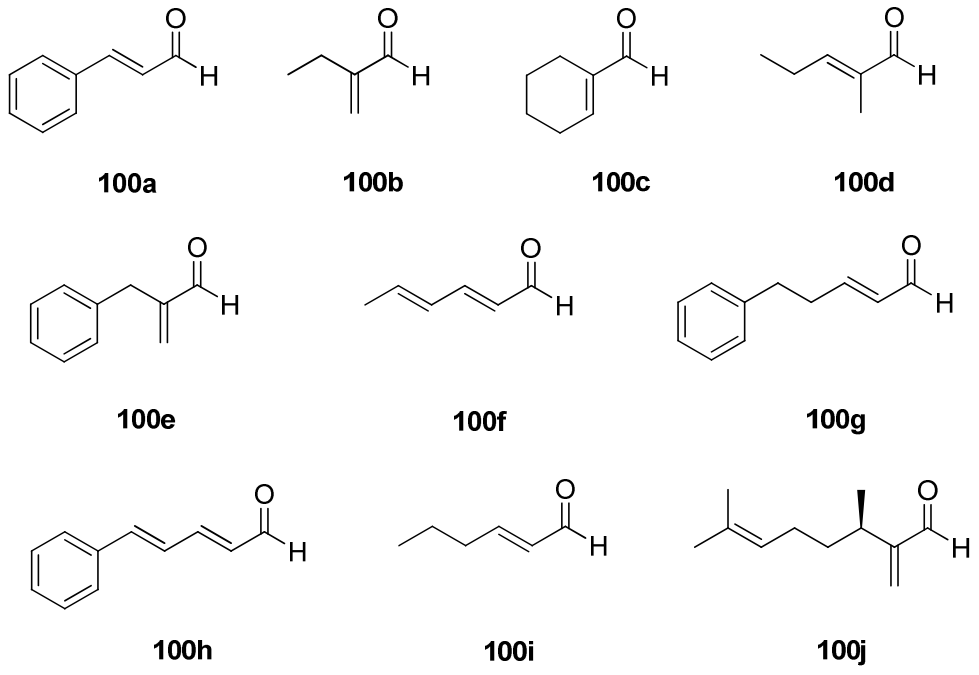
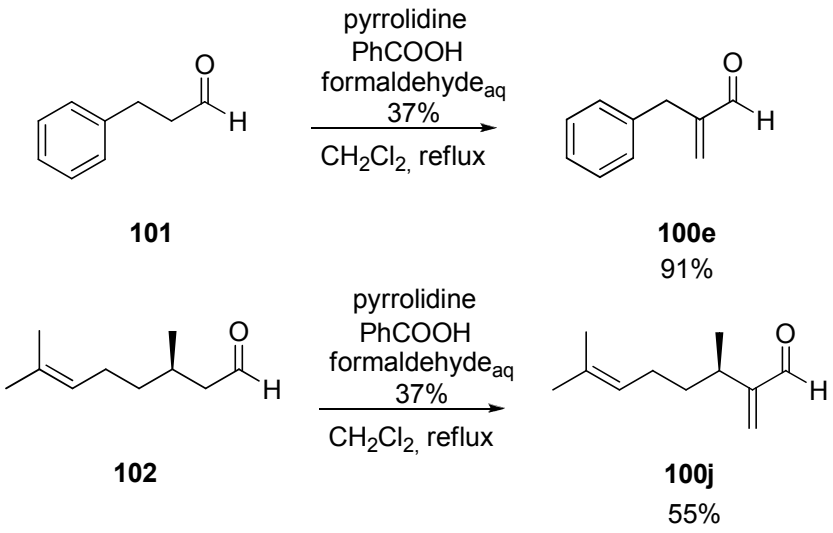


Figure 3

1.2.5 Synthesis of starting α,β-unsaturated aldehydes

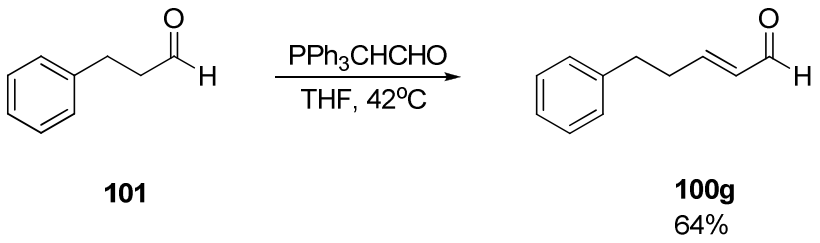
In order to examine Methox in the allylation of conjugated aldehydes we used commercially available compounds with a variety of α- and β-substitution patterns. To further extend the range of substrates, we employed two different methods to convert saturated aldehydes **101** and **102** into the desired starting materials **100e** and **100j**.

Two of α–substituted unsaturated aldehydes were prepared by Mannich-type condensation of aldehyde with aqueous formaldehyde in the presence of pyrrolidine and benzoic acid (Scheme 35).[44] The reported method also allows a self condensation of aldehydes.



Scheme 35

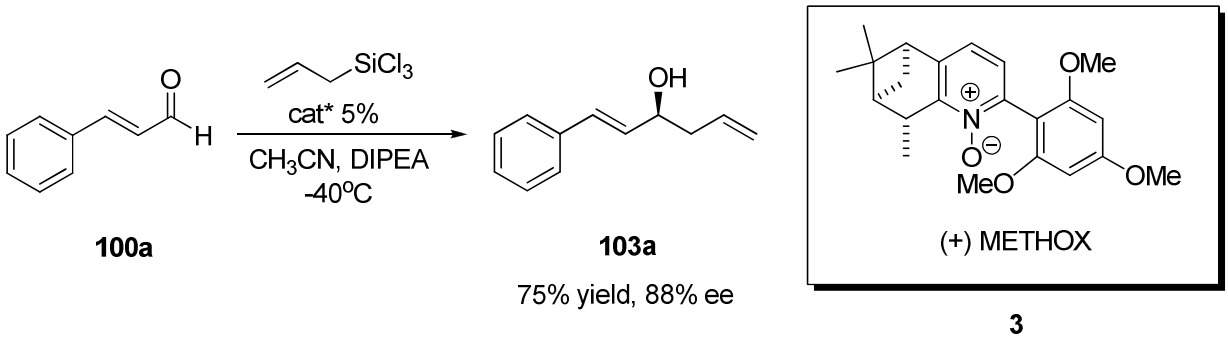
β- Substituted acrolein derivative **100g** was synthesised using Horner-Wadsworth-Emmons chemistry by the procedure reported by Lee and coworkers (Scheme 36).[45] The reaction of dihydrocinnamyl aldehyde **101** with (triphenylphosphoranylidene)acetaldehyde gave the desired product in good yield.



Scheme 36

1.2.6 Allylation of α,β-unsaturated aldehydes

To probe the potential of unsaturated aldehydes for the enantioselective allylation, we first carried out the reaction with cinnamaldehyde **100a**, which is both an aromatic and α,β-unsaturated aldehyde. This aldehyde also represents a breaking point in means of enantioselectivity in publications where reported, allylated either by chiral *N*-oxides and HMPA derivatives.[28,30b,36b] Allyl trichlorosilane was added to a mixture of cinnamyl aldehyde **100a**, DIPEA and 5% of Methox at –40 °C. The reaction was usually completed after 3 days (Scheme 37). The desired product **103a** was isolated in good yield; and the HPLC analysis showed high enantioselectivity (88% ee). Encouraged by these results, we prepared a series of highly enantioenriched homoallylic alcohols and summarized the outcome in Table 2.

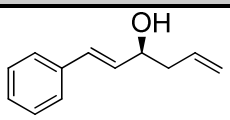
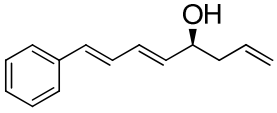
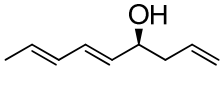
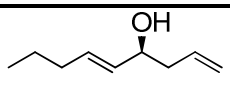


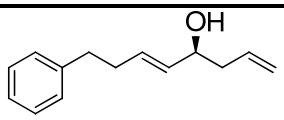
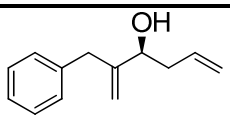
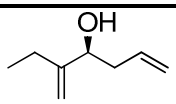
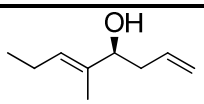
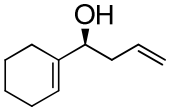
100a **103a** **3**

75% yield, 88% ee

Scheme 37

Table 2. Enantioselective allylation of α,β-unsaturated aldehydes.

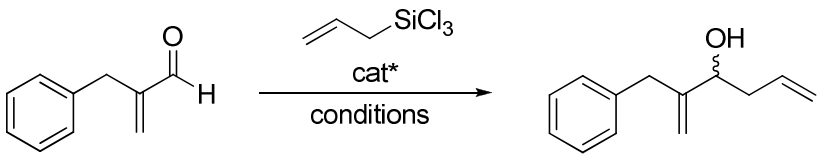
Entry	103	Alcohol	Yield [%]	ee [%]	Chiral analysis
1[a]	**a**		75	88	HPLC
2[ae]	**b**		73	88	HPLC
3[ae]	**c**		42	>86[c]	Mosher's ester ^{19}F NMR
4[ae]	**d**		68	86	Mosher's ester ^{19}F NMR

5[bf]	**e**		49	88	HPLC
6[bf]	**f**		46	70	GC
7[ae]	**g**		48[d]	89	GC
8[a]	**h**		65	93	GC
9[ae]	**i**		37	83	Mosher's ester ^{19}F NMR

[a] Reaction at –40 °C, [b] Reaction in –30 °C, [c]Minor enantiomer, signal overlapping with traces of stereoisomer, [d] Product extremely volatile. [e] Obtained by Yvonne Jewkes, [f] Obtained by Jiří Mikušek

All the synthesised alcohols showed good to high enantioselectivity, the absolute values were only slightly lower than those obtained for aromatic aldehydes with the same catalyst.[40] Methox catalysed allylation is also tolerant to a variety of substitution pattern. Unexpected drop of enantioselectivity observed for alcohol **103e** (entry 6) was further investigated.

In order to bring enantioselectivity in line with the rest of the series, we optimised conditions for this aldehyde (Scheme 38). Lowering the reaction temperature to –45 °C for Methox **3** and also use of *R*-(+)-Quinox **86**, another highly enantioselective Lewis base catalyst developed in our group, we obtained 88 and 80% ee respectively. Both enantiomers of the product were successfully prepared. Details are summarised in Table 3.



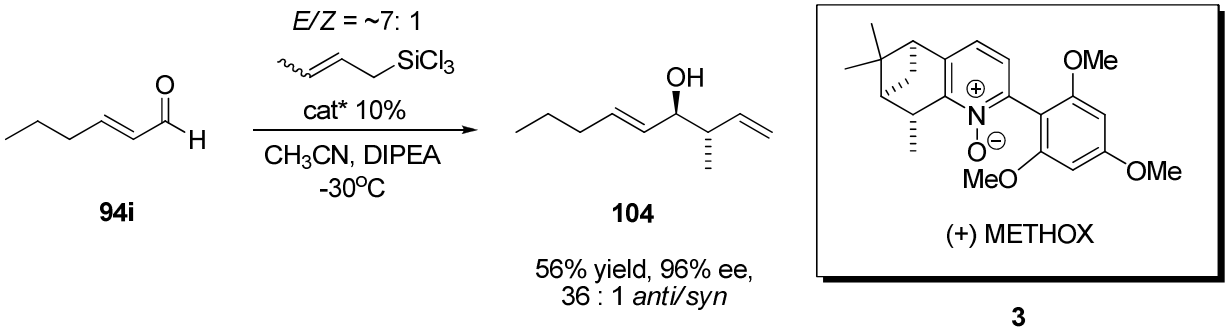
100e **103f**

Scheme 38

Table 3. Allylation – optimising conditions

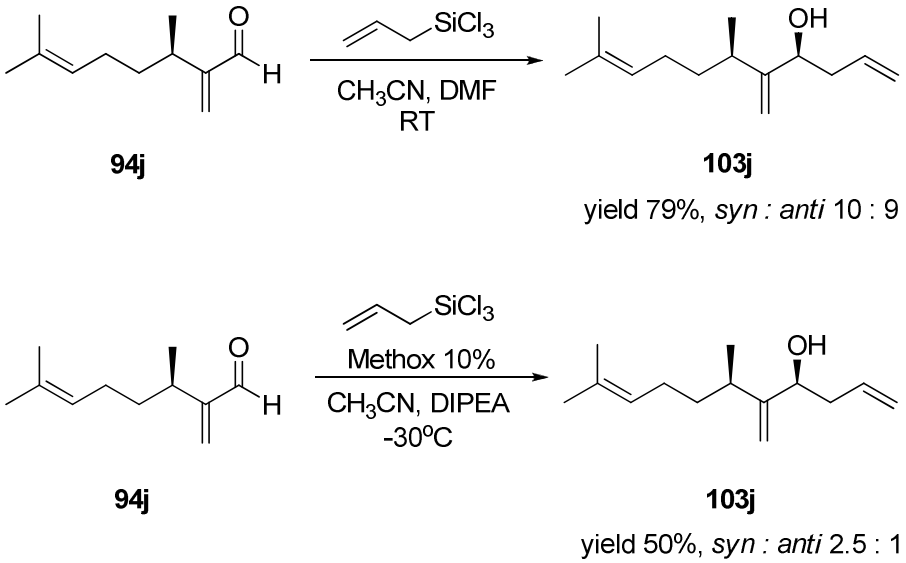
Entry	Catalyst	Catalyst loading [%]	Solvent	Temperature [°C]	Yield [%][a]	ee [%]
1	Methox	10	CH_3CN	-30	46	70 (*S*)
2	Methox	10	CH_3CN	-45	23	88 (*S*)
3	*R*-Quinox	5	CH_2Cl_2	-30	20	80 (*R*)

Methox exhibits high kinetic preference for *E* crotyl trichlorosilane, which allows the use of technical grade crotyl chloride as a starting material.[40] The desired branched homoallylic alcohol was obtained in excellent ee and diastereoselectivity (Scheme 39).



Scheme 39

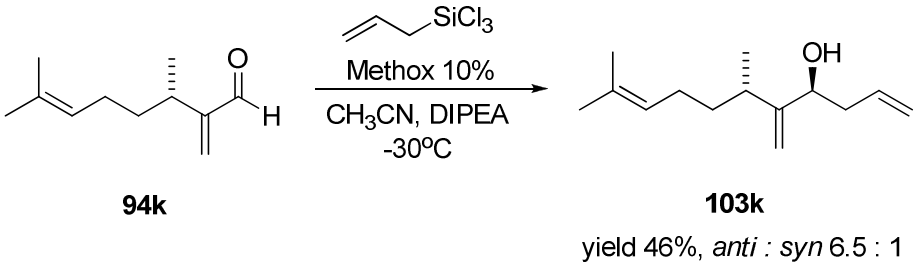
Finally, we decided to investigate the influence of chirality in the aliphatic side chain of the substrate aldehyde. Methylenated citronellal features a chiral centre proximal to the aldehyde. In the reaction catalysed by DMF the chirality present in the molecule had little effect on the newly formed stereogenic centre, giving an almost equimolar mixture of *anti/syn* diastereoisomers. Methox-catalysed allylation of the enantiomers of citronellal was expected to create two pairs of aldehyde-catalyst systems. Matching and mismatching pair should differ substantially in diastereoselectivity (Scheme 40).



Scheme 40

The room temperature reaction, catalysed by DMF, produced both diastereoisomers in nearly equimolar ratio. The later experiment with Methox **3** only slightly improved the selectivity to 2.5 : 1, revealing a mismatching relationship of the substrate-catalyst.

In order to find the matching pair, the opposite enantiomer of citronellal was methylenated and submitted for Methox catalysed allylation. The *S* enantiomer of the methylenated citronellal gave substantially higher diastereoselectivity of allylation. The main product is assumed to have absolute configuration of *S,S* (anti) (Scheme 41). Overall low enantioselectivity is similar to aldehyde 6, Table 2 and can be assigned to the presence of a large substituent in α position.



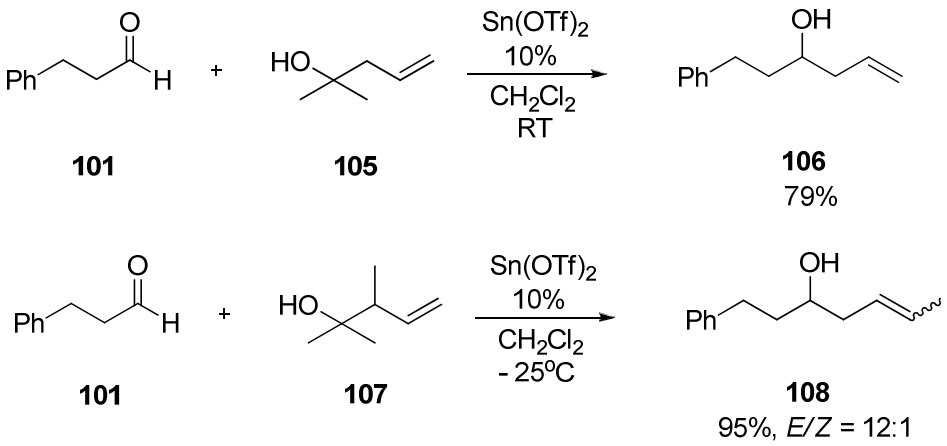
Scheme 41

1.3 Allyl transfer as a new method to synthesize linear homoallylic alcohols

The project was completed under supervision and in collaboration with **Dr. Mikhail Kabeshov.**

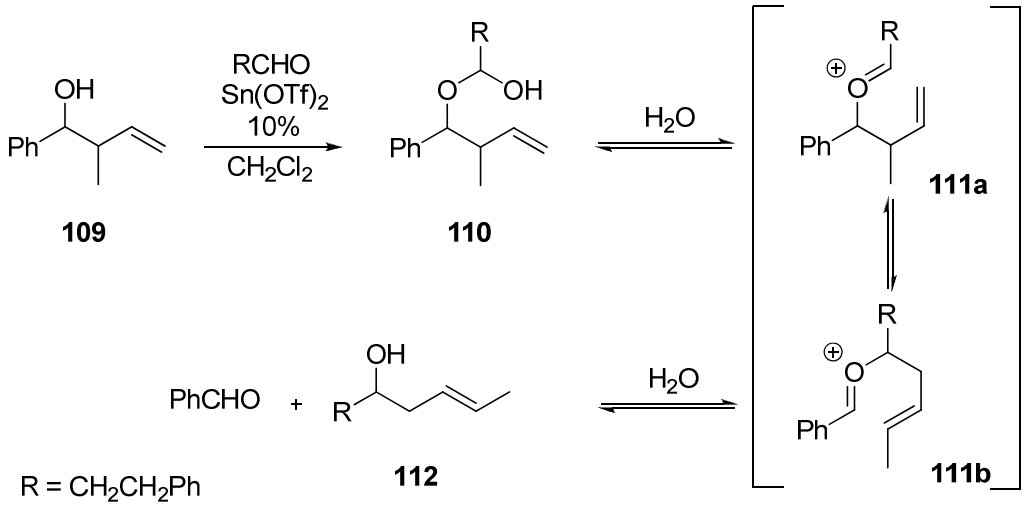
1.3.1 Introduction

In 1998 Nokami and coworkers reported on a conceptually new method of allylation of aldehydes.[46a] Allylic functionality was transferred from homoallylic alcohol **105** to the aldehyde **101** in the presence of $Sn(OTf)_2$ as catalyst. Initial experiments showed good results for allyl transfer from simple homoallylic alcohol. The same conditions applied to dihydrocinnamyl aldehyde **101** and branched alcohol **107** gave the desired linear product **108** in excellent yield and *E/Z* ratio up to 12:1 (Scheme 42).



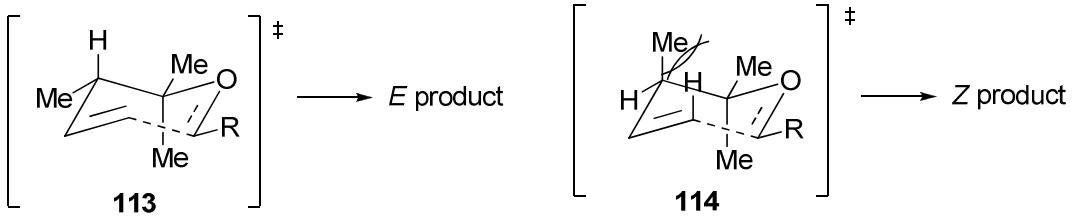
Scheme 42

Nokami suggested a mechanism according to which the Lewis acid catalyses reaction of chiral racemic homoallylic alcohol **109** with external aldehyde, to create hemiacetal **110**.[46b] Oxycarbenium species **111** formed by displacement of hydroxyl undergoes 2-oxonia [3,3]-sigmatropic rearrangement as shown on Scheme 43. The reaction is driven towards forming the most stable cationic intermediate, featuring less sterically hindered and thermodynamically more stable internal alkene **111b**.[46]



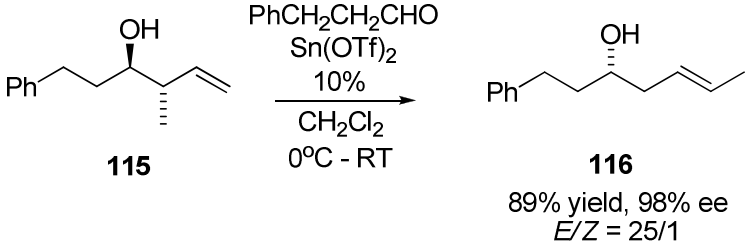
Scheme 43

Significant preference for the *E* isomer was rationalised by cyclic chairlike transition-state models (Scheme 44). Transition state **113** leading to *E* product is more favourable than **114** due to minimisation of 1,3-diaxial repulsion between the methyl substituent and the hydrogen atom of the alkene.[46a]



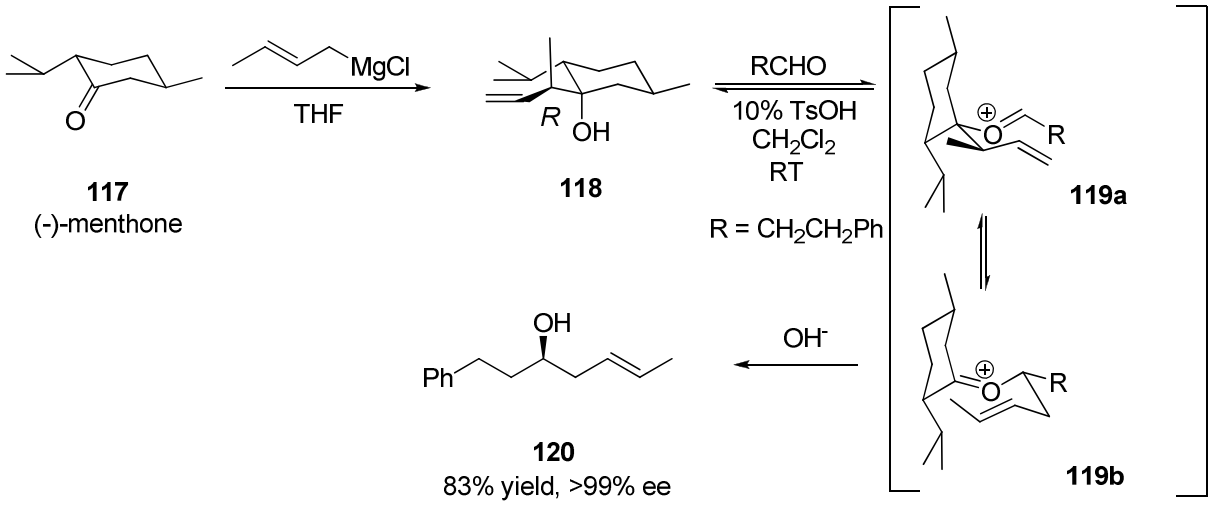
Scheme 44

The first enantioselective version of this reaction was demonstrated by Sumida and Nokami two years later.[46b] Alcohol **115** was isolated as a pure *3R,4S* enantiomer and submitted to the allyl transfer mediated by $Sn(OTf)_2$. The desired product **116** was isolated as a pure *S* enantiomer in high yield (Scheme 45). The reaction proceeds with complete inversion of the stereogenic centre and exhibits kinetic preference for the *anti* diastereoisomer.



Scheme 45

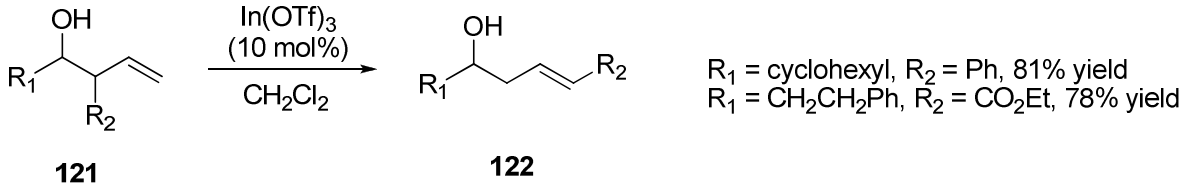
In 2001 Nokami reported on asymmetric crotylation reaction of aldehyde via acid-catalysed allyl-transfer reaction from the branched homoallylic alcohol **118**.[47a] (–)-Menthone **117** derived from natural (–)-menthol was used as a source of chirality. The reaction proceeded via the six-membered cyclic transition state **119** and gave *E*-alkene selectively **120**, while preserving high enantiomeric purity of 99% (Scheme 46).



Scheme 46

This method was further optimised, allowing employment of various allylation reagents with multifunctionalised allyl moiety.[47b] The use of (-)-menthone allowed Nokami to prepare a series of enantiopure, *E*-configured alkenols.[47c] All the products obtained in this manner were isolated as single enantiomers.

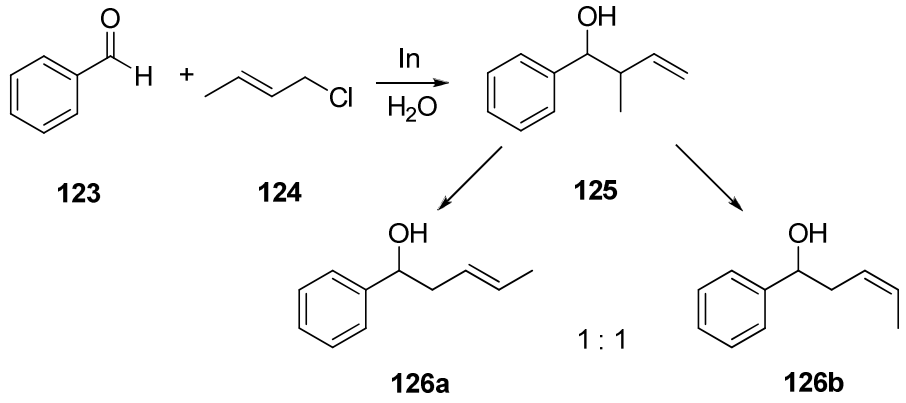
Loh and coworkers used $In(OTf)_3$ as a Lewis acid catalyst and showed that the presence of an external aldehyde is not necessary for the formation of the linear homoallylic alcohol **122**.[48] The indium salt catalysed a full conversion of the branched isomer **121** (Scheme 47). Monitoring the aldehyde proton by NMR of the crude mixture indicated generation of the free aldehyde *in situ*. When a mixture of *syn/anti* diastereoisomers was submitted to the reaction, their ratio was virtually mirrored by the *E/Z* ratio of the linear products.



Scheme 47

1.3.2 Results and discussion

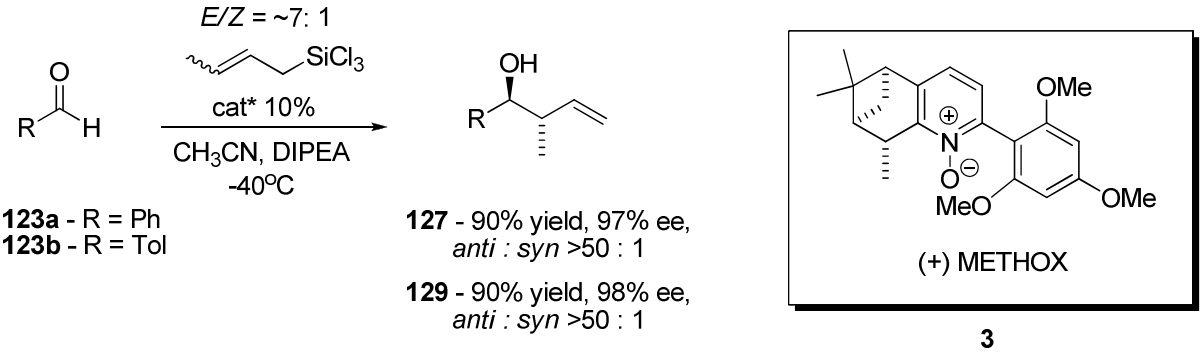
The initial aim of the project was to develop a robust protocol for the synthesis of a series of linear homoallylic alcohols with an internal double bond and submit them to oxidation with singlet oxygen. In order to prepare racemic material, we used the procedure reported by Loh and coworkers utilising metallic indium.[49] The first step is the metal-mediated Barbier-type crotylation of benzaldehyde **123** resulting in the branched alcohol **125** as an intermediate. Alcohol **125** subsequently undergoes a Lewis acid allyl transfer reaction to yield the linear isomer as a single product (Scheme 48).



Scheme 48

Unfortunately, the linear alcohols were obtained almost quantitatively but as an equimolar, inseparable mixture of *E* **126a** and *Z* **126b** isomers as revealed by NMR spectroscopy. The result indicates that the *syn* and *anti* diastereoisomers of **125** were formed in an equimolar ratio due to the lack of control in the first step.

To investigate the rearrangement, alcohols **127** and **129** were synthesized by the Methox-catalysed allylation as single *S*,*S* enantiomer in excellent yields and selectivity (Scheme 49).



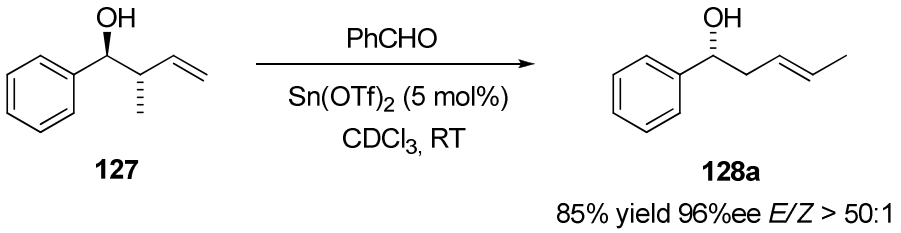
123a - R = Ph
123b - R = Tol

127 - 90% yield, 97% ee, *anti* : *syn* >50 : 1

129 - 90% yield, 98% ee, *anti* : *syn* >50 : 1

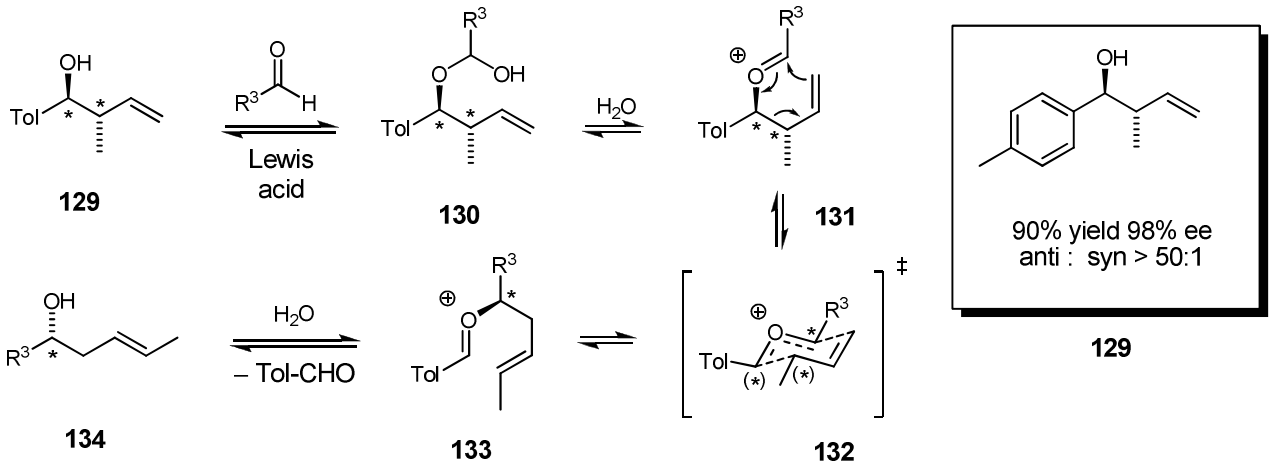
Scheme 49

An equimolar mixture of **127** and benzaldehyde **123** was treated with $Sn(OTf)_2$, and the reaction progress was monitored by ^1H NMR. The reaction was complete after 20 minutes and the linear homoallylic alcohol **128** was isolated as a pure *E* isomer with complete inversion of the benzylic stereo centre (Scheme 50).



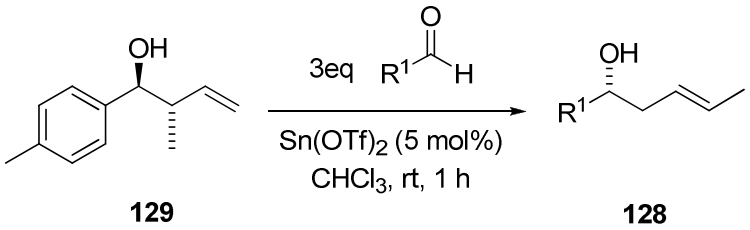
Scheme 50

During optimisation, we found $Sn(OTf)_2$ to be the most effective Lewis acid, whereas the more electron-rich *p*-tolyl derivative **129** emerged as the best allyl donor. The high reactivity of **129** is assumed to result from its enhanced capability to stabilise the positive charge in transition state **133** compared to the phenyl analogue in **127** (Scheme 50), thus disfavouring the reverse reaction. As an additional benefit of **129**, the reduced electrophilic character of *p*-tolualdehyde, released during the reaction, makes it less competitive with the receptor aldehyde in the allyl-transfer process, thereby avoiding the formation of the corresponding α-adduct. Herein we adopted the mechanism proposed by Nokami, where the driving force for the key oxonia-Cope rearrangement (**131** → **133** via the transition state **132**) is the formation of the more stable cation **133.**[46b] Predicted chair-like transition state **132** with all equatorial substituents provides excellent *E/Z* ratio of >>50:1 of the product with a complete preservation of the stereochemical information (Scheme 51).



Scheme 51

Alcohol **129** was employed in the crotylation of a wide range of receptor aldehydes (Scheme 52, Table 4). The reaction proved to be very efficient in every instance, with good yields and high enantioselectivity, essentially irrespective of the nature of aldehyde. The only drawback observed was the inability to introduce an allyl group to pyridine- and furan-derived aldehydes. This was rationalised by high Lewis basisity of the heterocycles, competing for the Lewis acid catalyst with the substrate aldehyde.



Scheme 52

Table 4. The scope of the enantioselective allyl-transfer reaction.

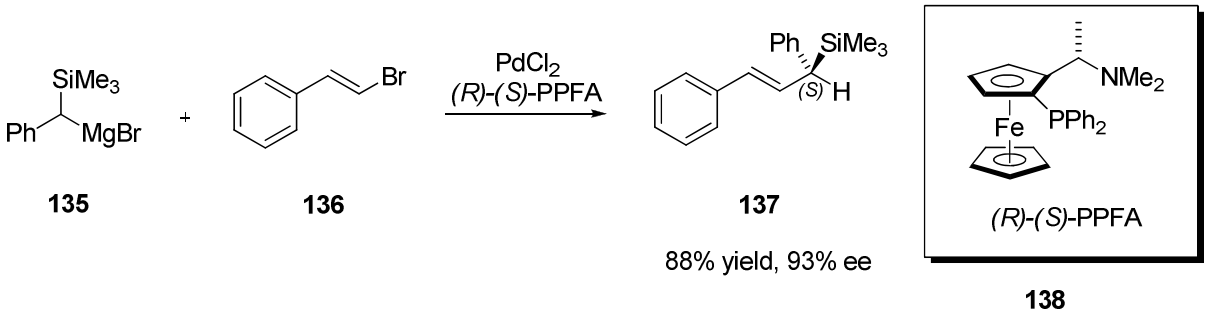
Entry	128	R^1	Yield, % [b,c]	ee, %	Chiral analysis
1	**a**	Ph	85	96	GC
2	**b**	4-$NO_2C_6H_4$	75	98	HPLC
3	**c**	$PhCH_2$	82	96	HPLC
4	**d**	*t*Bu	60	93	Mosher's ester ^{19}F NMR
5	**e**	*c*C_6H_{11}	80	97	GC
6	**f**	Et_2CH	83	≥95	GC
7	**g**	*n*C_6H_{11}	85	≥97	Mosher's ester ^{19}F NMR
8	**h**	$MeS(CH_2)_2$	72	≥97	Mosher's ester ^{19}F NMR
9	**i**	$PhCH_2CH_2$	85	97	GC

[a] The reactions were carried out with 1 mmol of **1** and 3 mmol of R^1CHO in $CHCl_3$ (15 mL), [b] Isolated yield. [c] In all cases the (*E/Z*) ratio was >100:1.

1.4. Kinetic resolution of chiral allyltrichlorosilanes

Allylic silanes were shown to be useful synthetic reagents that readily react with electrophiles to give a wide variety of multifunctionalised compounds. When a chiral controller is used, the method becomes an excellent tool for the synthesis of enantiopure building blocks. Allyl trichlorosilanes used in previous sections were all non chiral and the chirality was introduced to the product by the catalyst. However, in the experiments with the chiral citronellal derivative (Scheme 40 and 41), we have demonstrated that selectivity in the formation of the new C-C bond depends on the matched/mismatched relationship in the pair aldehyde-catalyst.

Development of chiral allylsilanes was pioneered by Hayashi and co-workers, who used the predefined stereogenic centre for the synthesis of enantioenriched alcohols.[50a] Initial investigation focused on the asymmetric synthesis of allyl TMS derivatives **137** and their further development.[50] In one of the practical protocols, they used palladium-catalysed asymmetric Grignard cross-coupling of **135** and **136** in the presence of the ferrocenylphosphine ligand **138** (Scheme 53).[51]



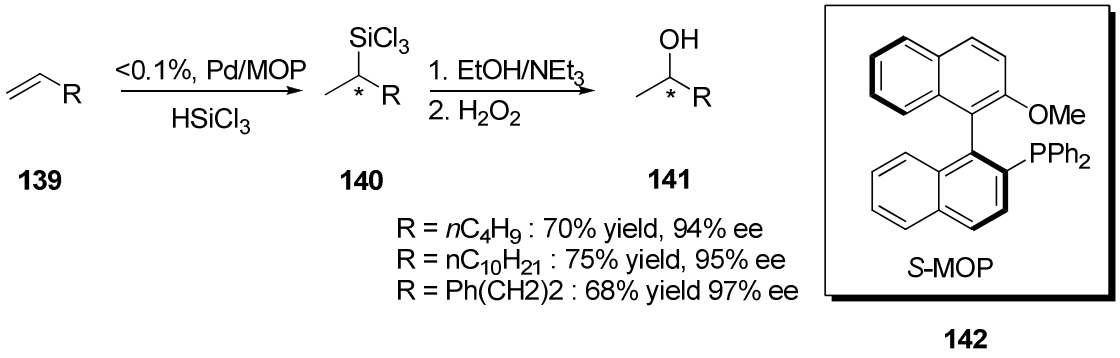
135 **136** **137**

88% yield, 93% ee

138

Scheme 53

The transmetallation methodology was also applied to the synthesis of enantioenriched trichlorosilanes **140**. These useful intermediates were obtained in high enantioselectivity from the corresponding alkenes **139** by palladium catalysed asymmetric *S*-MOP **142** catalysed hydrosilylation. These intermediates were converted into enantiopure aliphatic alcohols **141** (Scheme 54).[52]

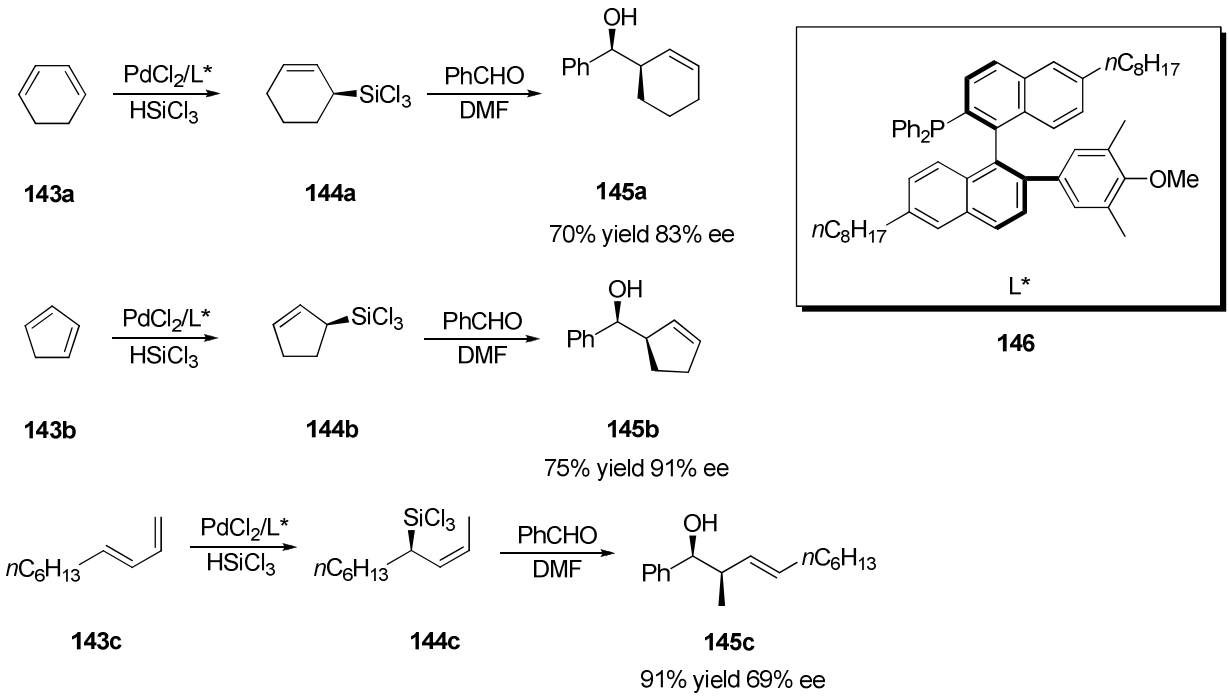


139 **140** **141** **142**

R = nC_4H_9 : 70% yield, 94% ee
R = $nC_{10}H_{21}$: 75% yield, 95% ee
R = Ph(CH2)2 : 68% yield 97% ee

Scheme 54

Synthesis of chiral allyltrichlorosilanes can also be considered as an alternative route to chiral homoallylic alcohols widely discussed in this chapter. The palladium-MOP complex has been identified as a successful catalyst for the enantioselective hydrosilylation of 1,3-dienes **143**. Enantioenriched allyltrichlorosilanes **144** reacted with aldehydes in the presence of achiral DMF as a catalyst to yield the respective homoallylic alcohols **145**. The best results were obtained with chiral triphenylphosphine ligand **146** featuring long aliphatic chains to overcome solubility issues (Scheme 55).[53]



143a **144a** **145a**
70% yield 83% ee

143b **144b** **145b**
75% yield 91% ee

143c **144c** **145c**
91% yield 69% ee

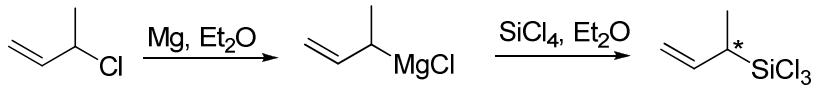
146

Scheme 55

1.4.1. Results and discussion

To develop a more straightforward approach to linear homoallylic alcohols of type **15**, we started an investigation on the use of chiral racemic allyltrichlorosilanes for the asymmetric allylation. We reasoned that chiral *N*-oxide catalysts[34] developed in our group might be able to kinetically resolve the racemic allyltrichlorosilane **149.**

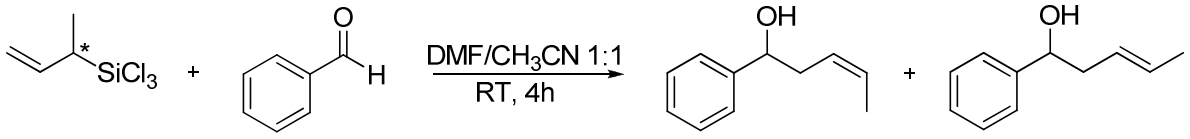
The simplest chiral trichlorosilane **149** was prepared from the corresponding halide **147** by first converting it into Grignard reagent **148** in ether followed by reaction with silicon tetrachloride (Scheme 56).[54] It is worth noting that a commercially available solution of the Grignard reagent in THF was used initially, however, it proved extremely difficult to separate the resulting solution from $MgCl_2$. Trichlorosilane **149** appears to be unusually stable for manipulation and storage but has to be distilled under low pressure. Attempts to use temperatures over 60 ^{o}C resulted in the formation of gel-like residues, probably due to polymerisation.



147 **148** **149**

Scheme 56

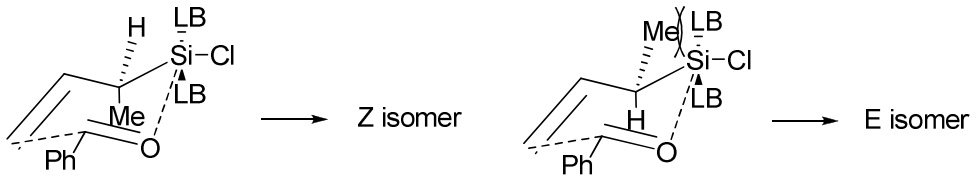
With the chiral racemic silane **149** in hand, the initial experiments were conducted in the presence of DMF as a Lewis-basic catalyst to obtain a reference sample of two isomeric alcohols **126b** and **126a** (Scheme 57). The reaction was complete in just over 4 h to give a 3:2 mixture of **126b** and **126a** as racemates in 75% isolated yield.



149 **123** **126b** **126a**

Scheme 57

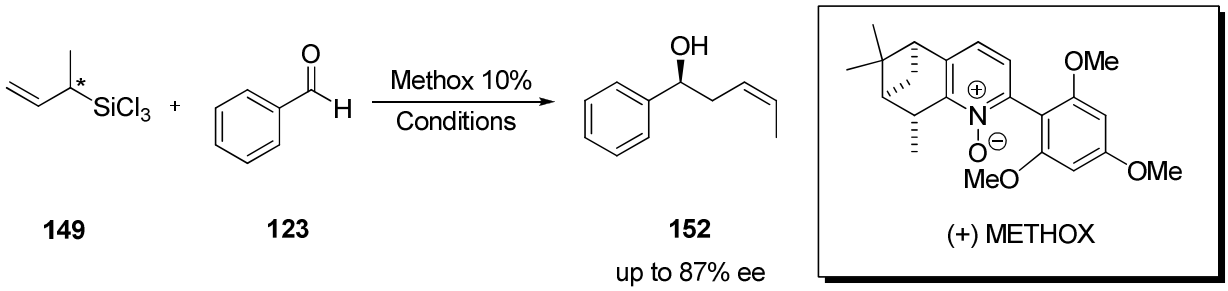
This result can be rationalised by considering transition structures **150** and **151** leading to *Z* and *E* isomers, respectively (Scheme 58). The sterically bulky Si moiety with coordinated Lewis base appears to favour the conformation, where the methyl group at the stereogenic centre is forced into axial position. We reasoned that use of chiral Lewis base may also provide a bias to discriminate between the enantiomers.



150 **151**

Scheme 58

As a proof of concept, three equivalents of racemic trichlorosilane **149** were reacted with benzaldehyde in the presence of Methox **3**, chiral Lewis base, under various conditions (Scheme 59). The results are summarised in Table 5.



149 **123** **152** up to 87% ee **3**

Scheme 59

Table 5. Kinetic resolution of chiral racemic allyltrichlorosilane **149** with Methox.

Entry	Methox Loading (%)	Reaction time (days)	Solvent	Temperature [°C]	Isolated yield of 152 (%)	*Z/E* ratio	ee (%)[c]
1	10	14	[a]	-30	35	6:1	56
2	10	14	[b]	-30	46	6:1	59
3	10	5	CH_3CN	-40	14	9:1	68
4	10	30	propionitrile	-80	5	>20:1	82
5	10	30	CH_2Cl_2	-80	5	>20:1	87

[a] - CH_3CN:DIPEA : 2 : 0.5, [b] - CH_3CN:DIPEA : 0.5 : 2, [c] – ee confirmed by HPLC analysis

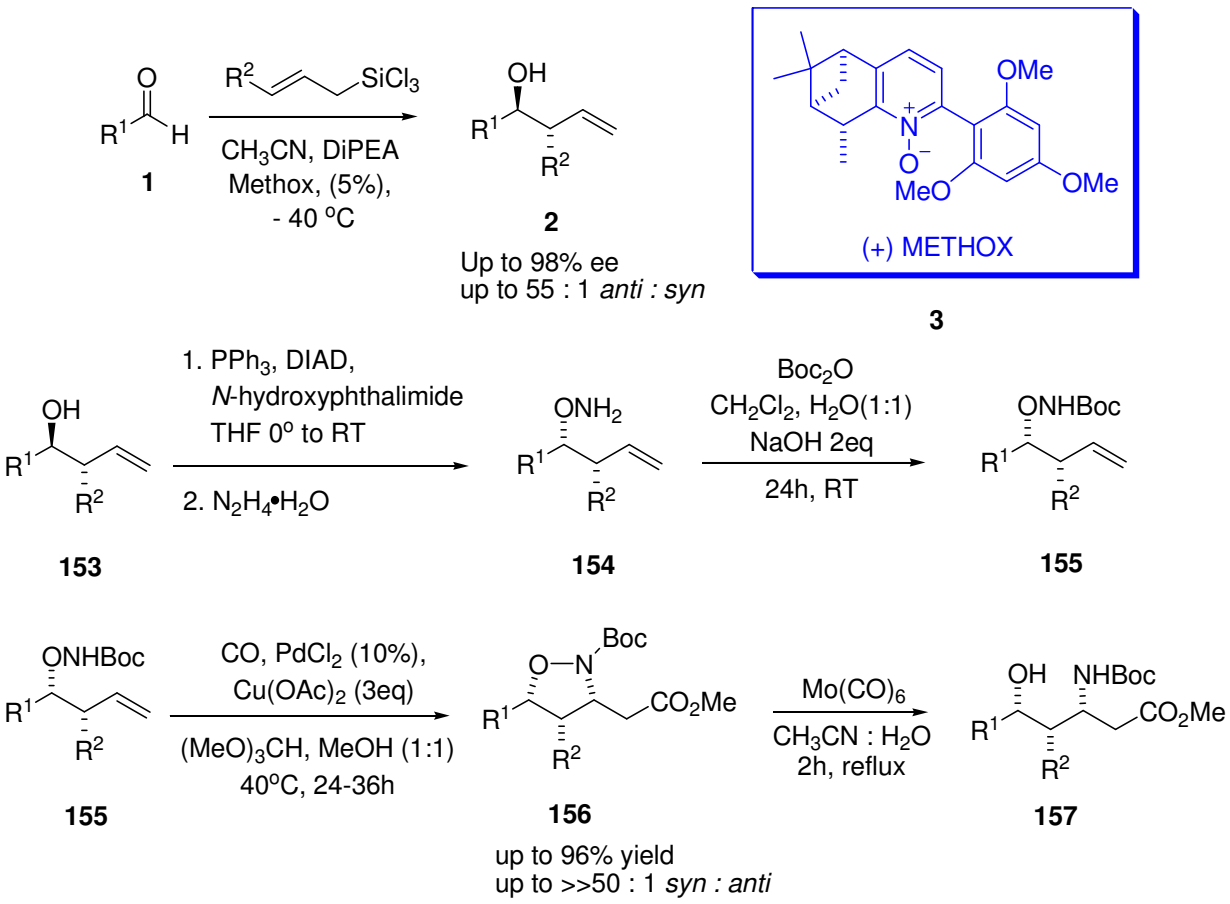
Reactions at sub-zero temperatures gave expected preference for allylation with one enantiomer of **152**. Lowering temperature had a dramatic impact on the reaction rates: at −80 ^{o}C only small quantities of the product were isolated. Another drawback of the reactions at low temperatures is the formation of branched isomer of the desired alcohol in up to equimolar quantities with the product. Despite the yield, the good level of enantioselectivity in this reaction is encouraging. It is clear that further optimisation of the reaction conditions, including use of other chiral Lewis bases, is required.

2. Synthesis of β-Amino-δ-Hydroxy Esters via a Stereoselective Palladium-Catalysed Functionalisation of Homoallylic Alcohols.

The project was completed with assistance of the Erasmus exchange student **Lucie Potucká**

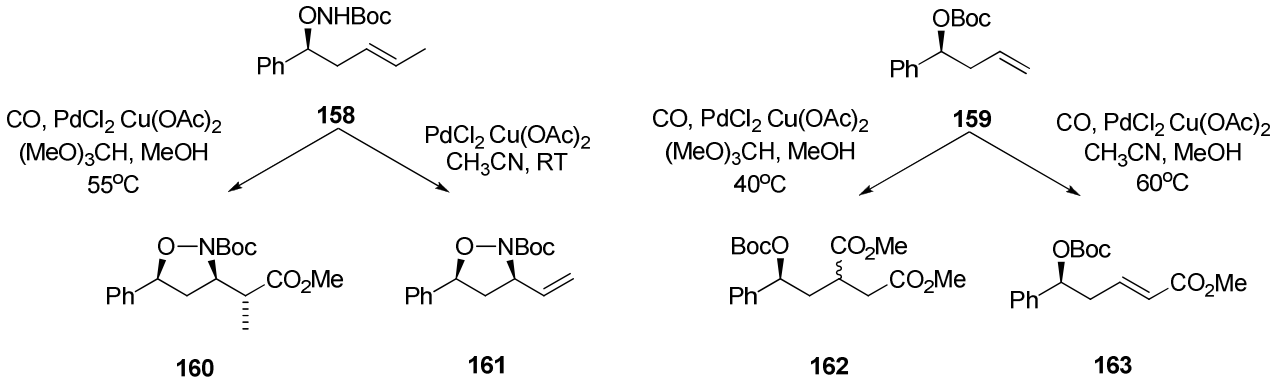
2.1 Abstract

We report a practical procedure for synthesis of multifunctionalised enantioenriched heterocyclic compounds employing chiral homoallylic alcohols obtained by asymmetric allylation. In a series of a few standard synthetic steps, we gain access to valuable β-amino-δ-hydroxy esters **157** building blocks from readily available or commercial materials (Scheme 60). High yields, excellent diastereoselectivity and simple purification protocols make this approach attractive from an industrial point of view.



Scheme 60

In the course of the research, we developed several novel palladium catalysed transformations. A diverse range of products **160**-**163** was obtained from same starting materials **158**, **159** by adjusting reactions conditions (Scheme 61).



Scheme 61

2.2 Literature review

Transformations of unsaturated hydrocarbons catalysed by transition metal complexes continue to constitute a very important field of organic chemistry. The past 30 years have witnessed a considerable effort to achieve selective multiple C-C bond couplings by means of transition metal complexes. The activation of an unsaturated carbon-carbon bond can be induced by its coordination to the metal, which makes the bond susceptible to addition of a nucleophile. Many of these reactions are catalysed by palladium, perhaps the most versatile and widely used transition metal, which can exist in three easily interconvertible oxidation states: Pd(0), Pd(II), and Pd(IV).[56]

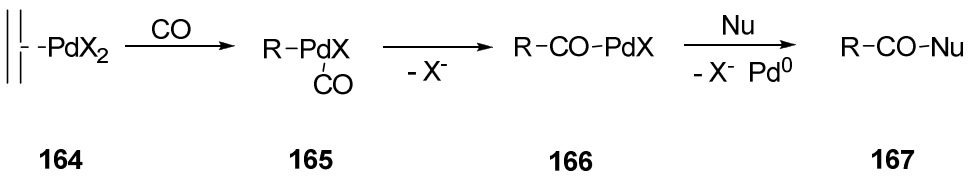
The unique properties of palladium derive from its ability to form both d^8 and d^{10} complexes at 0 and +2 oxidations states. The empty orbitals in the valence-shell provide Lewis acidic or electrophilic sites, one of which would serve as the LUMO (i.e., lowest unoccupied molecular orbital). Filled nonbonding orbitals provide Lewis basic or nucleophilic sites, one of which would act as HOMO.[57] Palladium can therefore readily participate in a variety of concerted reactions of relatively low activation energies. Tunable coordination abilities make this metal a versatile vehicle. Palladium catalysis is well-established for named C-C cross couplings, a variety of C-O and C-N transformations, polymerisations, rearrangements and hydrogenation. The ability to form stable complexes with a variety of ligands makes palladium-based species also a powerful tool for modern asymmetric synthesis.[57]

2.2.1 Alkoxycarbonylation

One of the undisputed milestones in palladium catalysed functionalisation of the double bond is the oxidation of ethylene to acetaldehyde in water called the Wacker process.[59] Oxidative conditions of Pd^{2+}/Pd^{0} reoxidised by the Cu^{2+}/Cu^{+} system were successfully applied to a variety of organic processes.

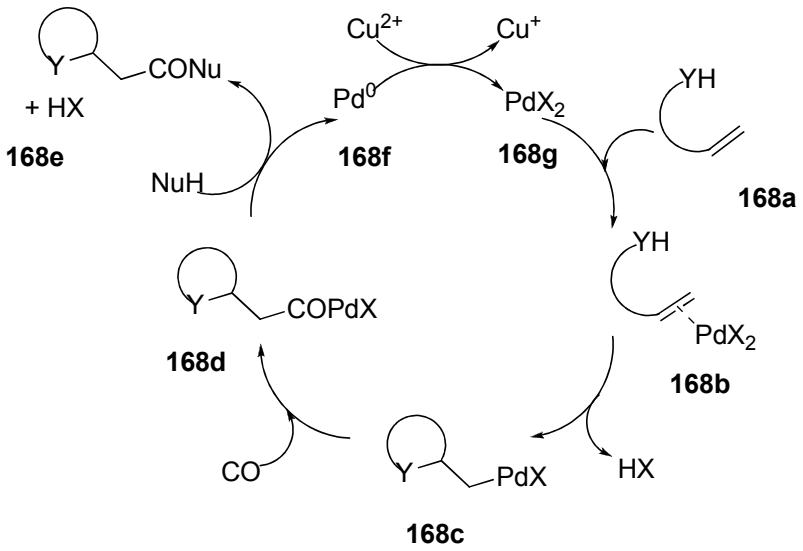
Carbon monoxide (CO) is a chemically reactive and inexpensive carbon source. It also provides versatile access to ^{13}C labelled compounds.[68] Therefore, oxidative carbonylations constitute an important class of Pd(II)-mediated reactions.[63] Other transition metals like cobalt and molybdenum, which exhibit high affinity for carbon monoxide, are also known for carbonylation reactions.[58] However, the high toxicity of $Co_2(CO)_8$ and $Mo(CO)_6$ complexes and their stoichiometric use severely limit their application. Relatively stable acyl-palladium complexes were found to be versatile intermediates in the synthesis of a variety of heterocycles and carbonyl derivatives .[56b,57]

There are two major pathways to generate C-Pd active species. The first one assumes oxidative insertion of a palladium complex into a carbon halogen bond followed by various C-C couplings, like Heck or Suzuki reactions. When organopalladium species are generated in the presence of carbon monoxide, it inserts into C-Pd bond to form an acyl palladium derivative, which can be further attacked by N or O nuclephiles.[69] The second mechanism of oxidative carbonylation starts with electrophilic attack of Pd^{2+} on the olefinic double bond to form the active π-Pd complex **164**. An exchange of ligand for CO is followed by oxidative insertion to create a new C-C bond **166**. Nucleophilic attack on the carbonyl causes displacement of palladium, releasing the stable carbonyl product **167** (e.g., ester or amide) (Scheme 62).[56b] This type of reaction is the main scope of this chapter and will be discussed in detail.



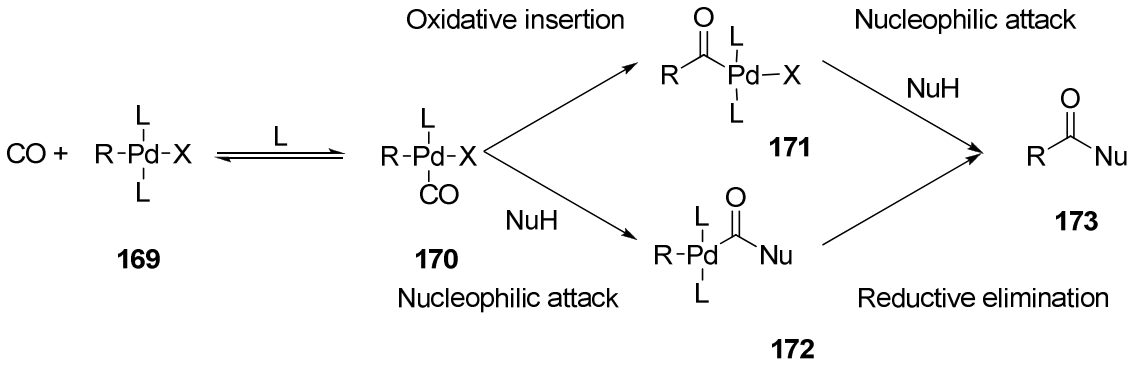
Scheme 62

To avoid using stoichiometric amounts of palladium, the catalytic cycle is completed by excess of copper(II) salt or oxygen to regenerate Pd(II) species **168g** (Scheme 63).



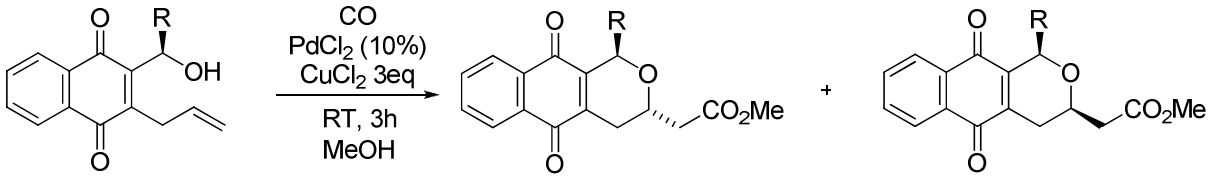
Scheme 63

Although the general mechanism is known, there are two possible pathways describing the actual formation of an ester (or amide). In the majority of the literature data, the nucleophile attacks the acyl-palladium complex, displacing the Pd^0 species.[61a] However, kinetic studies by Yamamoto's group with *trans*-Pd(COPh)I$(PPh)_2$ suggest that an alternative route is in operation,[61b] namely that the acetoxyester-palladium intermediate **172** undergoes subsequent reductive elimination of metal to form product **173** (Scheme 64).



Scheme 64

When carbonylation is performed on unsaturated substrates having a nucleophilic function in a suitable position, an intramolecular nucleophilic attack on the alkene Pd(II) complex is favoured. This type of reaction was intensively studied in the 1970s by grups of Stille, Fenton and others to find similar results and form mechanistic conclusions.[60] Semmelhack and co-workers used this methodology for the total synthesis of naphthoquinone antibiotics: nanaomycin A (**174**) and desoxyfrenolicin (**175**). An intramolecular alkoxy-carbonylation reaction yielded the desired product but with poor diastereocontrol.[62] (Scheme 65)



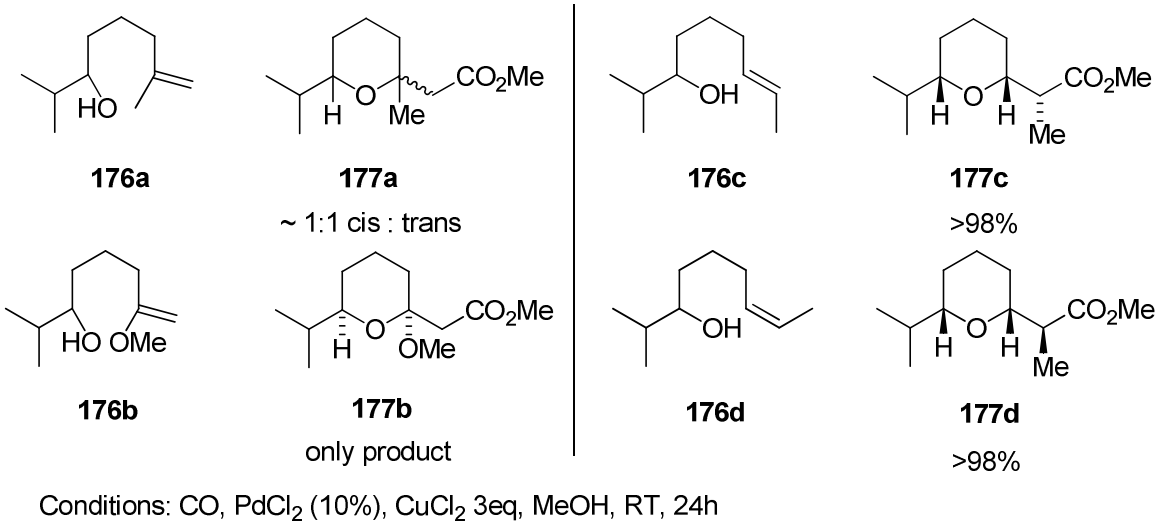
173 **174** **175**

R = nPr - Deoxyfrenolicin: 70% yield, 3 : 1 *trans : cis*
R = Me - Nanaomycin A: 75% yield, 2 : 3 *trans : cis*

Scheme 65

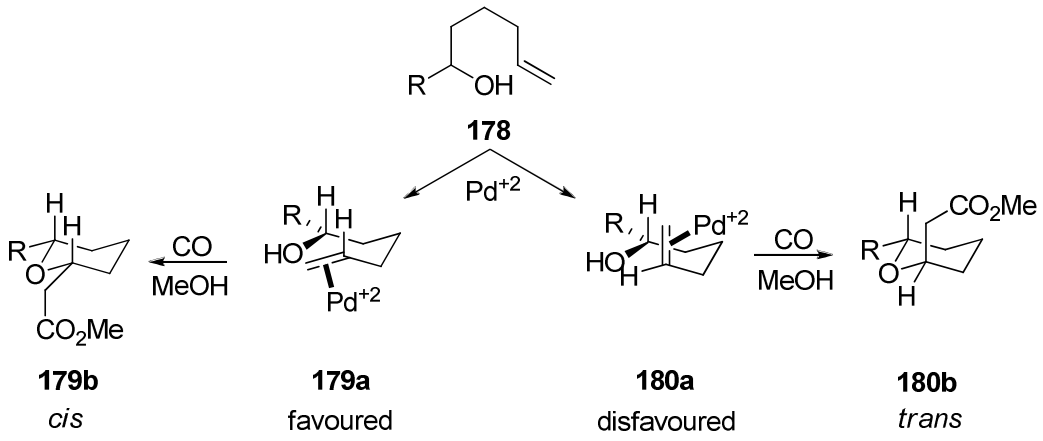
Access to diastereoselective formation of substituted tetrahydrofurans and pyrans is vital for the total synthesis of many natural products. Palladium-catalysed 1,2-alkoxycarbonylation leading to these structures was further investigated by Semmelhack and coworkers.[63]

Initial results showed a strong dependence of the six-membered ring geometry on the double bond substitution pattern. While the 1,2-substitued alkenes strongly prefer a *cis* arrangement **177c**, **177d**, the selectivity generated by 1,1-disubstituted isomers remains poor **177a**. It was explained by repulsive axial interactions experienced by the methyl substituent in the cyclic arrangement (Scheme 67). However, a methoxy group in that position has a stabilising influence driving *cis* ring closure exclusively to **177b**. The latter stereoselectivity can be further aided by the substituent anomeric effect (Scheme 66).[63b]



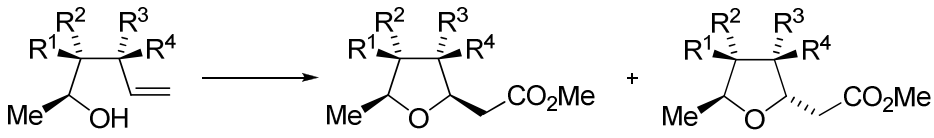
Scheme 66

Formation of the *cis*-2,6 arrangement of substituents was rationalised by pseudo chair conformations in the transition state for nucleophilic attack **179a** and **180a**. The *trans* stereochemistry **180b** is disfavoured because it would require the alkene-Pd(II) moiety to adopt an energetically higher pseudoaxial position (Scheme 67).[63b]



Scheme 67

Palladium-catalysed intramolecular alkoxycarbonylation of analogous substituted 5-hydroxy-l-pentenes **181** was also investigated by Semmmelhack.[64] The reaction produces 2,5-disubstituted tetrahydrofurans in good yields with *cis/trans* ratio highly dependent on the substitution pattern. With a methyl group at C-4, 1:l or 2:l mixtures of *cis:trans* products **182a** and **182b** were obtained, depending on the relative configuration of the Me. With a methyl or phenyl group at C-3, the selectivity improved, producing either *cis*-2,5- or *trans*-2,5-disubstituted furans in >9:1 selectivity (Scheme 68 and Table 6). [64]



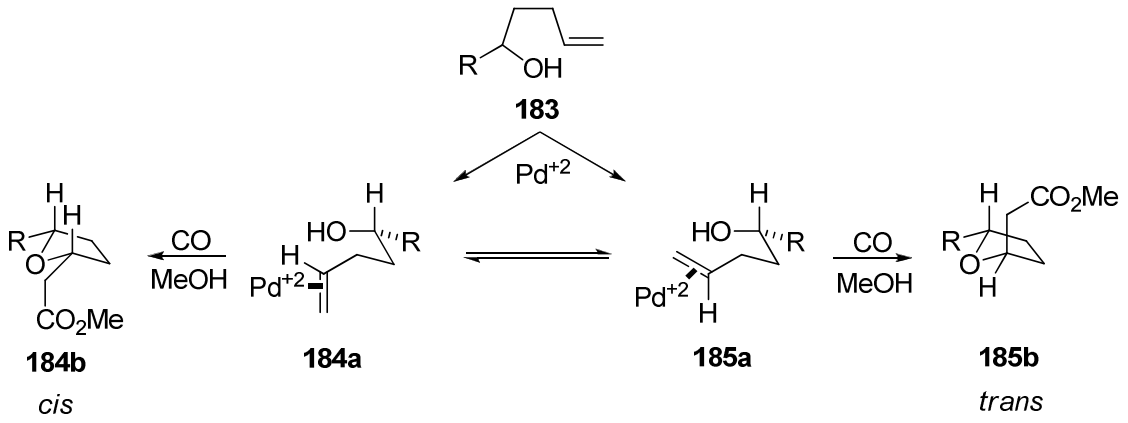
181 **182a** **182b**

Scheme 68

Table 6. Diastereoselectivity of THF ring formation.

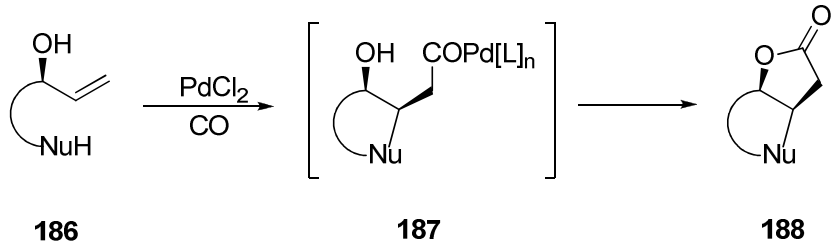
Entry	R^1	R^2	R^3	R^4	*cis : trans* ratio
1	Me	H	H	H	**38 : 62**
2	H	Me	H	H	**50 : 50**
3	H	H	Me	H	**10 : 90**
4	H	H	Ph	H	**0 : 100**
5	H	H	H	Me	**87 : 13**
6	H	H	H	Ph	**93 : 7**

The results were rationalised by steric interactions in the appropriate transition structures (Scheme 69). Two five-membered competing transition states **184a** and **185a** leading to the *cis* and the *trans* products **184b** and **185b** are assumed to be of comparable energy.[57] Therefore, the authors suggested that transition states arising from conformations with minimum nonbonded interactions would be more favoured. The effect is reinforced by the position, configuration and size of the substituent.[64]



Scheme 69

When an additional hydroxyl group is appropriately placed as in the substrate **186**, the Pd-acyl intermediates **187** can be trapped in an intramolecular fashion to furnish the *cis*-fused lactones **188** (Scheme 70).[65a]



Scheme 70

Palladium catalysed cascade of double cyclisations was soon appreciated as a simple and a straightforward route toward pyran and tetrahydrofuran lactones. Fused heterocyclic γ-lactones are important structural motifs in many natural products, such as kalafugin **189**, granaticin **190**, and frenolicin B **191** (Figure 4).[63a,66]

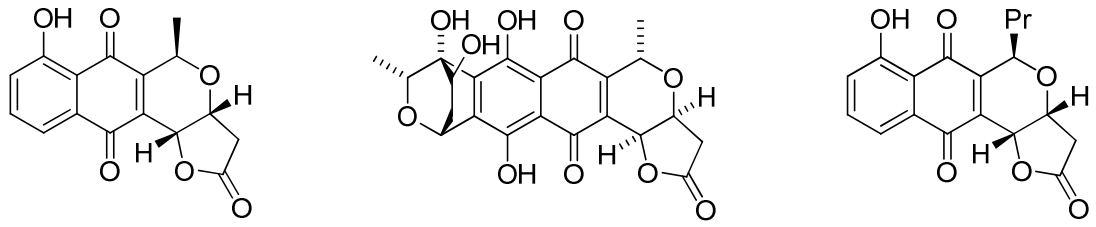
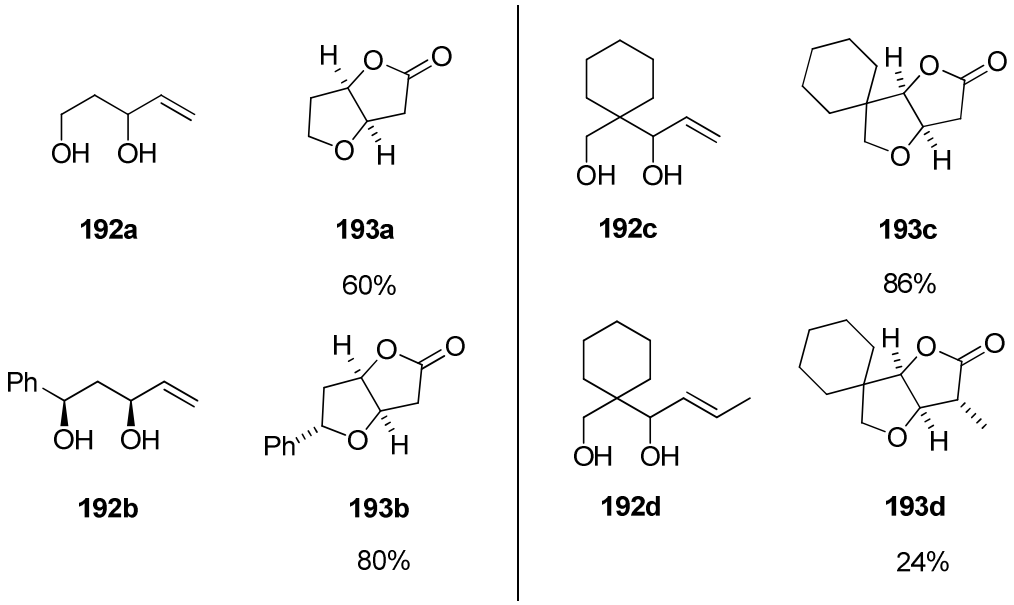


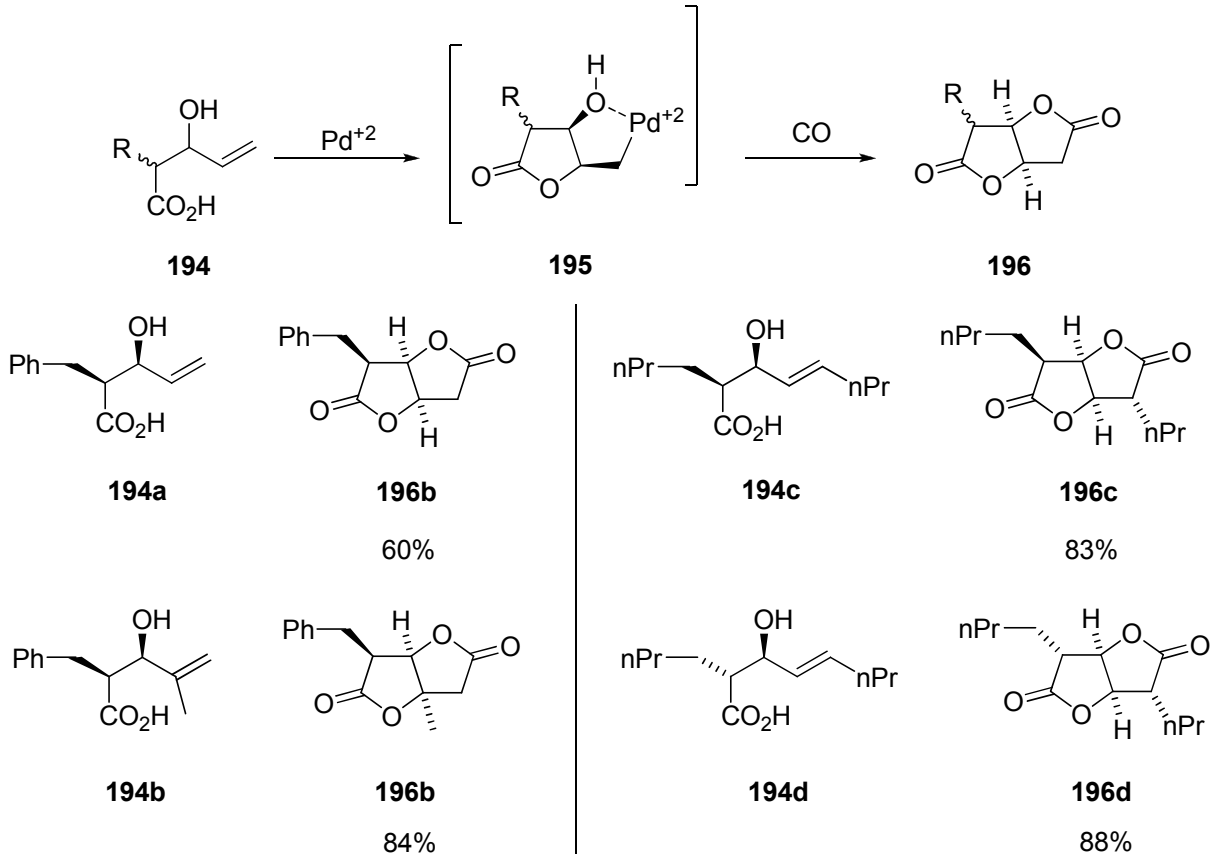
Figure 4

This type of reaction was pioneered by Tamaru and coworkers.[65a] In the mid-1980s, the group investigated a cascade closure of fused cyclic tetrahydrofurans and γ-lactones, as well as double lactonisation (Scheme 71). Reactions reported by Yoshida and Tamaru proceed with high yields, regio- and stereo-selectivity.



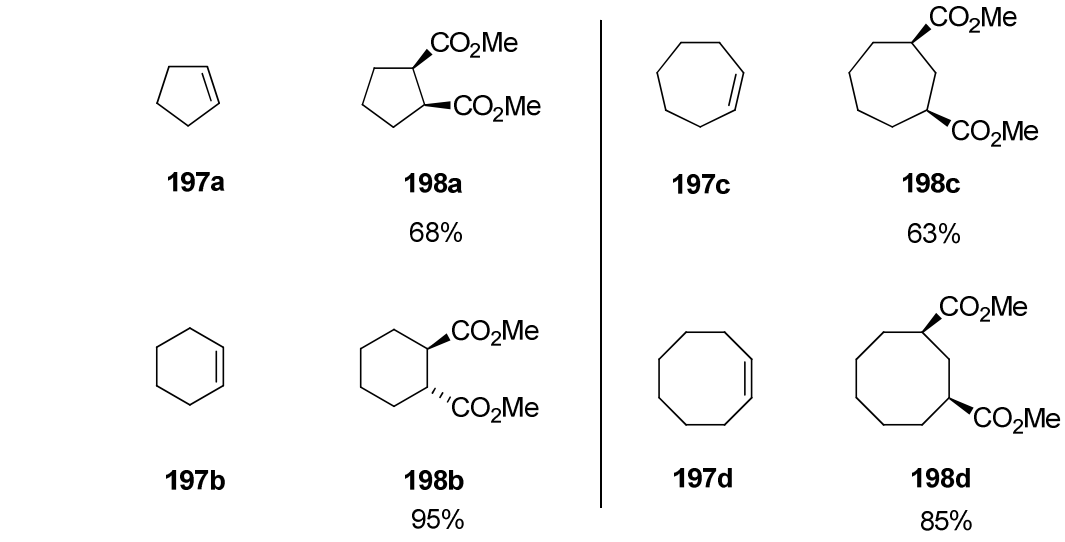
Scheme 71

Cyclization of 3-hydroxy-2-pentenoic acids **194** to bis-lactones **196** also yielded products as single diastereoisomers. Formation of exclusively *cis*-lactones was attributed to the directing effect of the free allylic hydroxyl group (Scheme 72).[65b]



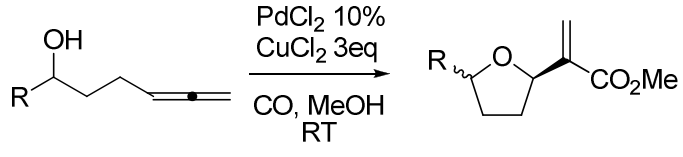
Scheme 72

Although the cascade ring closure, furnished by alkoxylation of metal-carbonyl intermediate, was the major aspect of the palladium-catalysed reactions discussed here, its scope is much broader. In 1976 Stille and coworkers reported the double carbonylations of the double bonds in a series of cyclic olefins **197** (Scheme 73).[60c]



Scheme 73

Highly reactive allene derivatives **199** react at room temperature with carbon monoxide in the presence of palladium by 5-exo cyclisation to form THF derivatives **200** as mixtures of *cis/trans* isomers. (Scheme 74).[67]



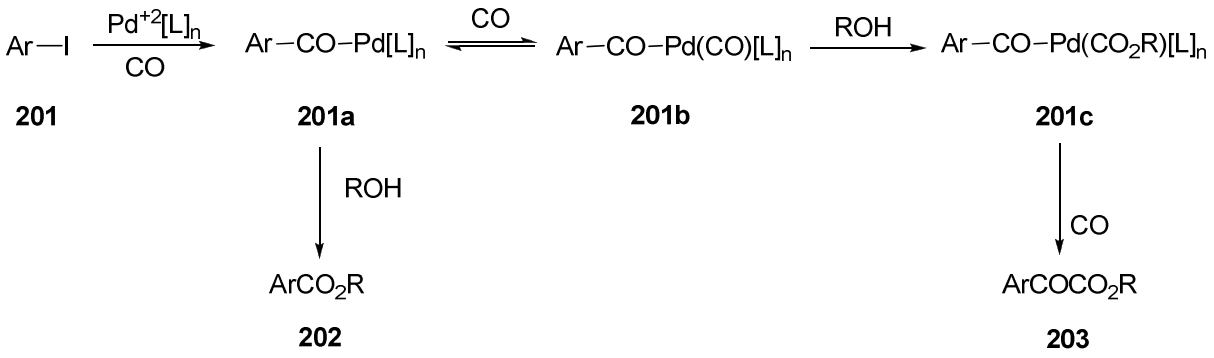
199 **200**

up to 92% yield

R = H, Me, CH_2COCH_3, CH_2COtBu, $CH_2(OH)CH_3$

Scheme 74

Yamamoto and coworkers examined carbonylation of various aryl iodides into α-keto esters and esters catalysed by palladium. Reaction with alcohols was carried out in the presence of Et_3N and phosphine ligands. Adjusting the CO pressure, ligand types, basicity, and solvent allowed switching between the two products (Scheme 75).[61b]



201 **201a** **201b** **201c**

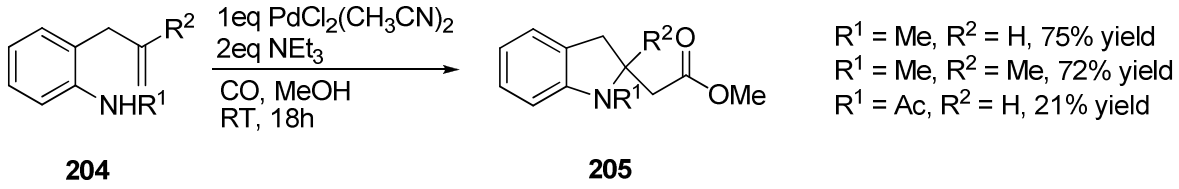
202 **203**

Scheme 75

2.2.2 Aminocarbonylation

Palladium-catalysed ether ring closures, followed by lactonisation or furnishing methyl esters, were recognised as a powerful tool for synthesising many useful heterocycles. The reactions discussed in the previous paragraphs were also successfully employed in the synthesis of nitrogen analogues. Urethane and indole motifs appear commonly in natural products molecules. Polyfunctionalised nitrogen heterocyclic intermediates for the syntheses of pyrrolidine alkaloids are easily available via Pd catalysed reactions.[70,56b]

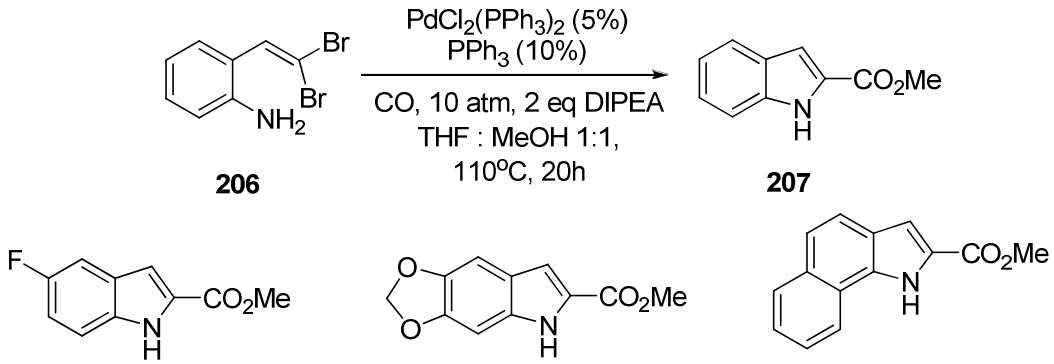
The first palladium-assisted aminocarbonylation of *o*-allylanilines was demonstrated by Hegedus et al.[71] The desired dihydroindolacetates were obtained in good yields under mild conditions (Scheme 76).



204 **205**

Scheme 76

This approach was further extended to the synthesis of fully aromatic indole derivatives **207**. The palladium-catalysed N,C-coupling/carbonylation sequence, as a route to 2-carboxyindoles, required higher temperatures and 10 bar pressure (Scheme 77).[72]

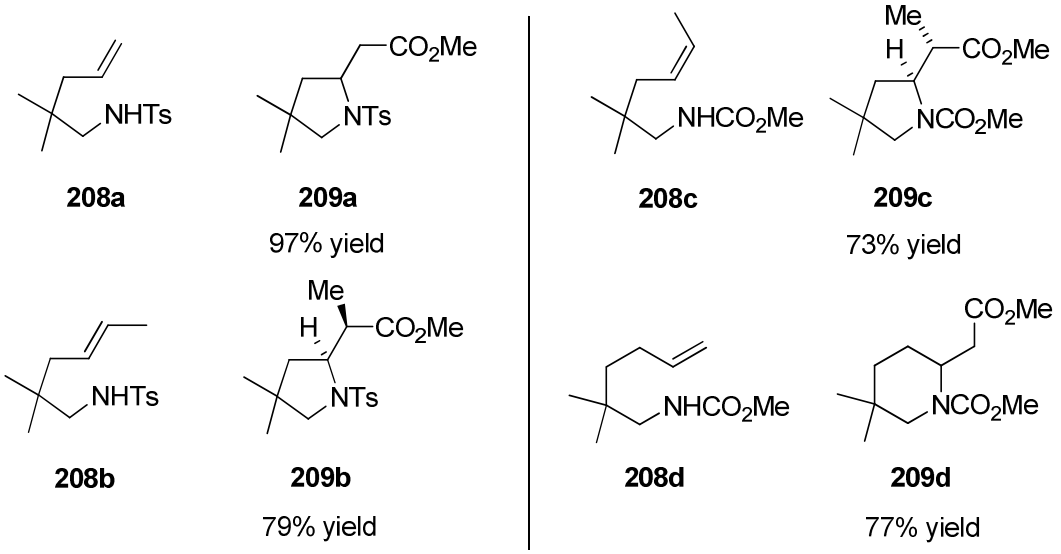


206 **207**

207a 78% yield **207b** 67% yield **207c** 60% yield

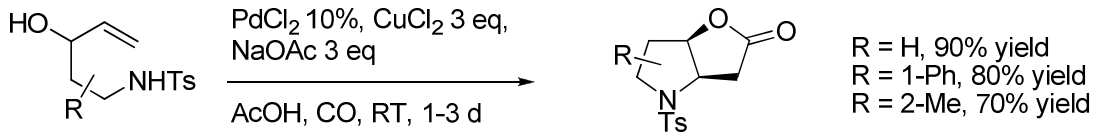
Scheme 77

Yoshida and Tamaru were investigating cyclisation of tosylamides **208**, affording pyrrolidine and piperidine derivatives **209** in analogy to the formation of tetrahydrofurans **182** and pyrans **177** discussed in earlier sections. Closures of five and six-membered rings under the Wacker conditions, similar to those presented in Scheme 77, were reported to proceed in good yields and selectivity (Scheme 78).[75]



Scheme 78

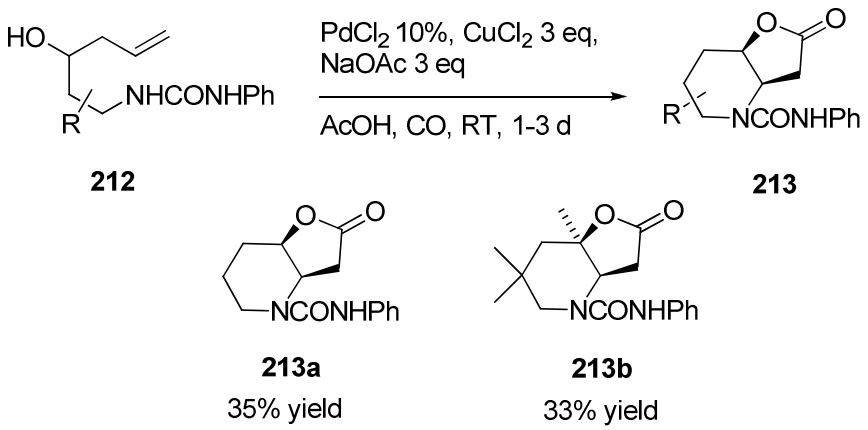
These reactions can be followed by intramolecular N or O nucleophilic attack. Thus, stereoselective, intramolecular aminocarbonylation of 3-hydroxypent-4-enylamides **210**, catalysed by palladium, provides the *cis*-3-hydroxy pyrrolidine lactones **211** in good to excellent yields (Scheme 79).[63a]



210 **211**

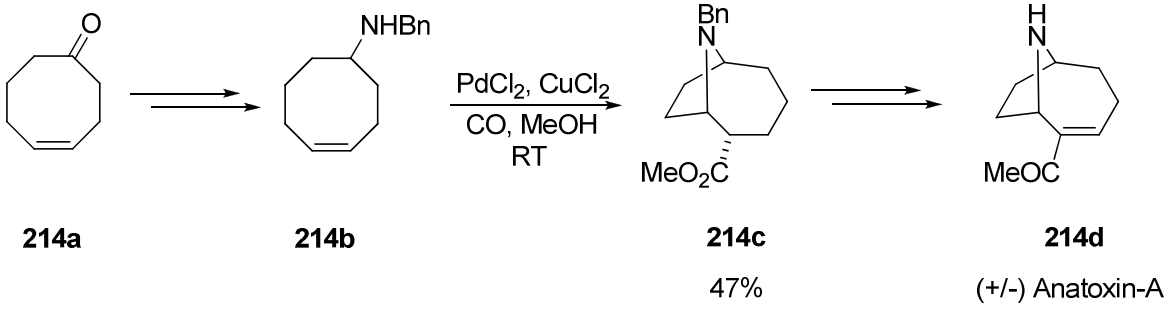
Scheme 79

The scope of this reaction was further extended for cyclisation of *N*-protected amino hydroxy-olefins **212** to produce *cis*-3-hydroxypiperidineacetic derivatives **213** with high diastereoselectively under the same conditions but in considerably lower yields (Scheme 80).[73b]



Scheme 80

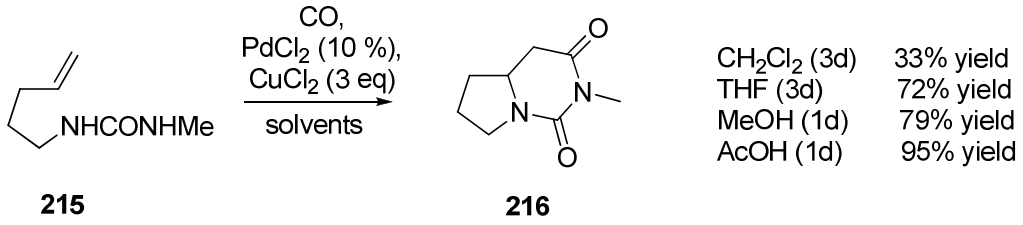
Intramolecular palladium catalysed aminocarbonylation was utilised as a key step in the total synthesis of racemic anatoxin **214d** (Scheme 81),[74] which mimics acetylcholine functions and is used for neurotransmission research.



Scheme 81

Tamaru, Yoshida, and co-workers expanded the scope of this methodology by employing urea and oxazolidinone derivatives, which are known as nucleophiles.[75] These fragments are very common in modern drug structures (Befloxatone, Ritonavir, Toloxatone) and represent easily available intermediates for the synthesis of diamino and hydroxyaminoacids.[76] Tandem cyclisation can be moderated by different types of urea or carbamate as well as by the choice of solvent. Depending on the conditions, formation of the first ring can be followed by amidation or esterification. Tamaru and coworkers found urea to be the most reactive towards the intramolecular aminopalladation reaction, whereas carbamate was more reactive than tosylamide. Benzamide was by far the least reactive. The best results for the double cyclisation were obtained with *N*-methylurea moiety.

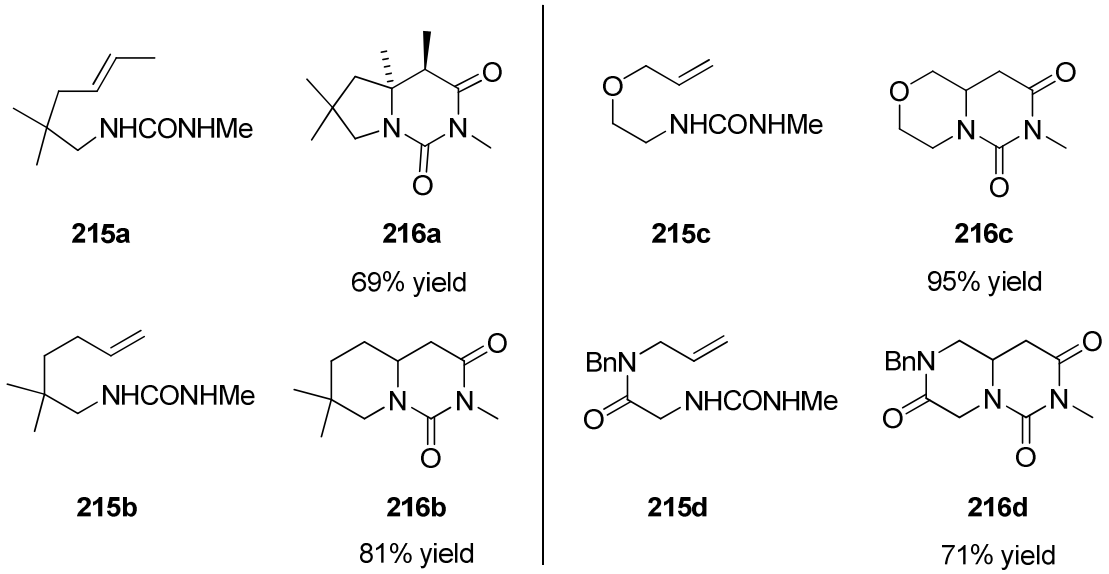
Acetic acid with 3 equivalents of AcONa was the solvent of choice for the reaction. It was rationalised by proposed solvation of chloride ion of $PdCl_2$, via hydrogen bonding, which results in the exposure of Pd^{2+} to the coordination to the olefin. Dichloromethane appeared to be the worst solvent for the reaction, resulting in low yields of **216** and 3 days reaction time (Scheme 82).[75]



215 **216**

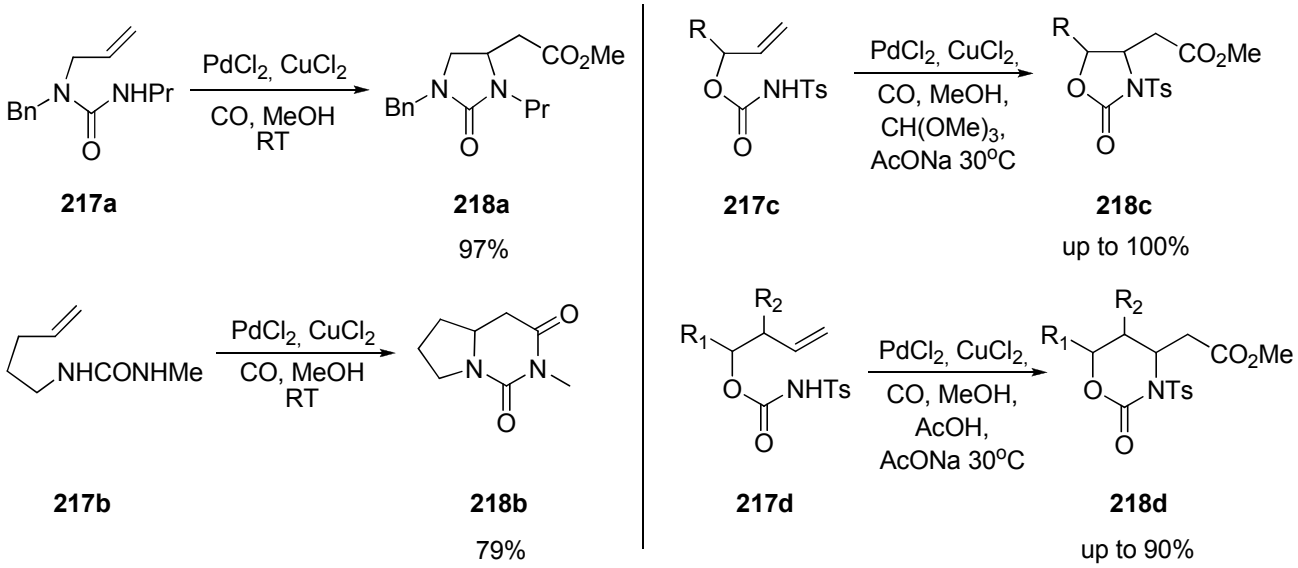
Scheme 82

Under the optimised conditions, Tamaru and coworkers synthesised a series of cyclic ureas fused with another heterocycle (Scheme 83).[75]



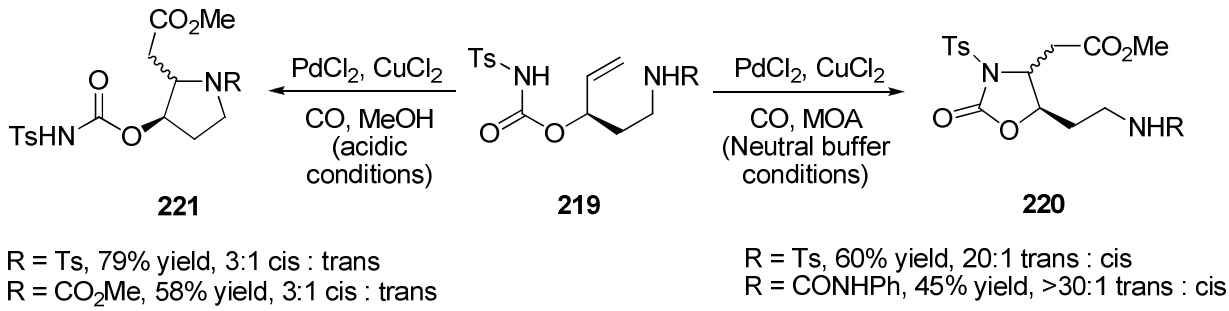
Scheme 83

Further studies showed that nitrogen nucleophiles, depending on their structure, display completely different reaction behaviour in the Wacker-type intramolecular aminocarbonylation.[77] Recognised differences in the reactivity towards ring closure were assigned to the type of the nitrogen nucleophile present and the size of the closing ring. (Scheme 84). Endo-6 ring closure of carbamates **217d** proved to be most difficult, which was rationalised by molecular orbital overlapping models.[77]



Scheme 84

Palladium-assisted ring closure of **219** proceeds chemoselectively in either direction, depending on whether acidic or buffered neutral conditions are applied. Methyl orthoacetate (MOA), methyl orthoformate (MOF), 2,2-dimethoxypropane, or propylene oxide were successfully used as HCl scavengers, producing methanol and ester as neutral byproducts. Only in the presence of orthoacetates do the cyclisations proceed in high *trans*-stereoselectivity (Scheme 85).[77]



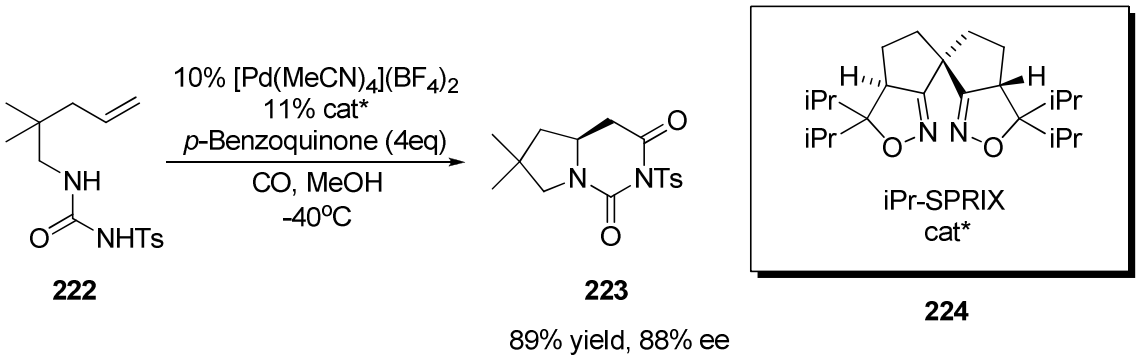
221 **219** **220**

R = Ts, 79% yield, 3:1 cis : trans
R = CO_2Me, 58% yield, 3:1 cis : trans

R = Ts, 60% yield, 20:1 trans : cis
R = CONHPh, 45% yield, >30:1 trans : cis

Scheme 85

The recent report by Sasai and coworkers[78] shows that intramolecular *exo*-carbonylation of achiral urea **222** can be performed with good enantioselectivity. The use of a chiral spiro-bis(isoxazoline) ligand (SPRIX) **224** furnished the desired product **223** in good yield and enantiopurity, opening an efficient synthetic method for the preparation of optically active cyclic β-aminoacid derivatives (Scheme 86).

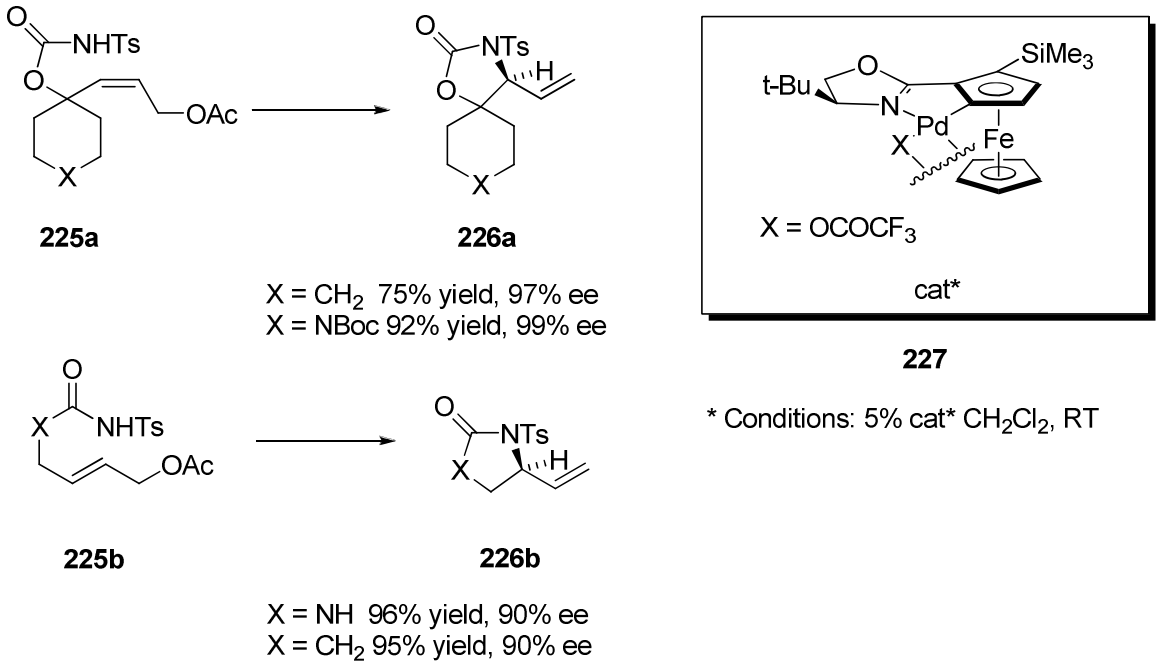


222 **223** **224**

89% yield, 88% ee

Scheme 86

When nucleophilic attack on the palladium π-complex is followed by elimination of a leaving group instead of carbonylation, heterocycles with an allylic moiety **226** are formed. The use of chiral ferrocenyloxazoline palladacycles **227** as catalysts for enantioselective intramolecular aminopalladation of the double bond to form allylic amides was reported.[79] A series of oxazolidinones, imidazolidinones, and pyrrolidinones were prepared by this methodology (Scheme 87).



225a **226a**

X = CH_2 75% yield, 97% ee
X = NBoc 92% yield, 99% ee

227

* Conditions: 5% cat* CH_2Cl_2, RT

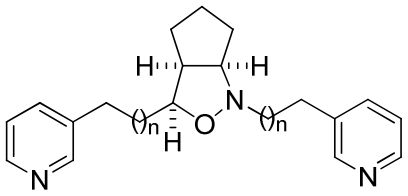
225b **226b**

X = NH 96% yield, 90% ee
X = CH_2 95% yield, 90% ee

Scheme 87

2.2.3 Synthesis of isoxazolidines and their applications

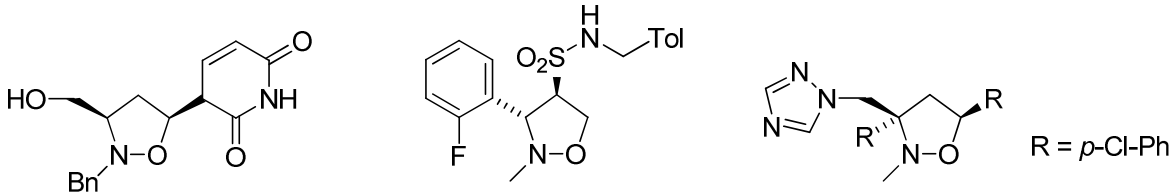
Nitrogen-containing heterocycles and their derivatives have a broad application in organic and biological chemistry and, as a result, their synthesis and reactivity is subject of considerable interest. The isoxazolidine structure is present in a number of naturally occurring molecules, such as pyrinodemins - potent cytotoxic alkaloids **228** isolated from the Okinawan marine sponge *Amphimedon sp* (Figure 5).[80]



228

Figure 5

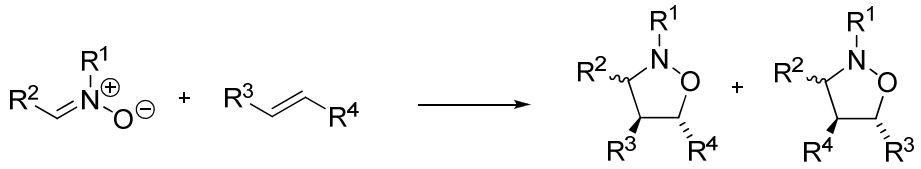
Even more important are the commercial and pharmaceutical uses of these compounds as modern drugs or their precursors. The current trends for designing new drug molecules are largely based on mimicking naturally occurring structures (e. g., nucleosides). Alterations can take place in both the aglycon and carbohydrate moieties resulting in high anti-HIV (carbovir) and antifungal (polyoxins) activity.[81] Demand for enantiopure N and O containing five-membered heterocycles, isoxazolidines and isoxazolines, triggered rapid development of methods for their synthesis. Many recently described compounds containing this motif were recognized for their potential antiviral and antimicrobial properties **229a-c** (Figure 6).[82]



229a **229b** **229c**

Figure 6

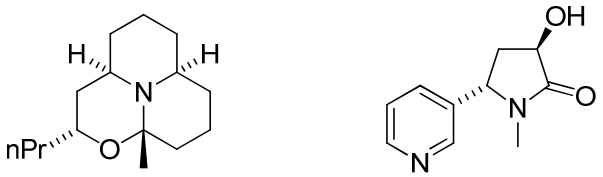
Isoxazolines and isoxazolidines are typically generated via [3+2] cycloaddition of a nitrone **230** to an alkene **231**.[83] Intramolecular nitrone-olefin cycloaddition leads to the formation of a new C-C bond and a new C-O bond. The [3+2] cycloaddition itself is a concerted, pericyclic process whose regiochemistry is controlled by steric factors and orbital interactions of the nitrone (the dipole) and the dipolarophile. The cycloaddition is stereospecific with respect to the configuration of the alkene (Scheme 88).[84]



230a **231** **232a** **232b**

Scheme 88

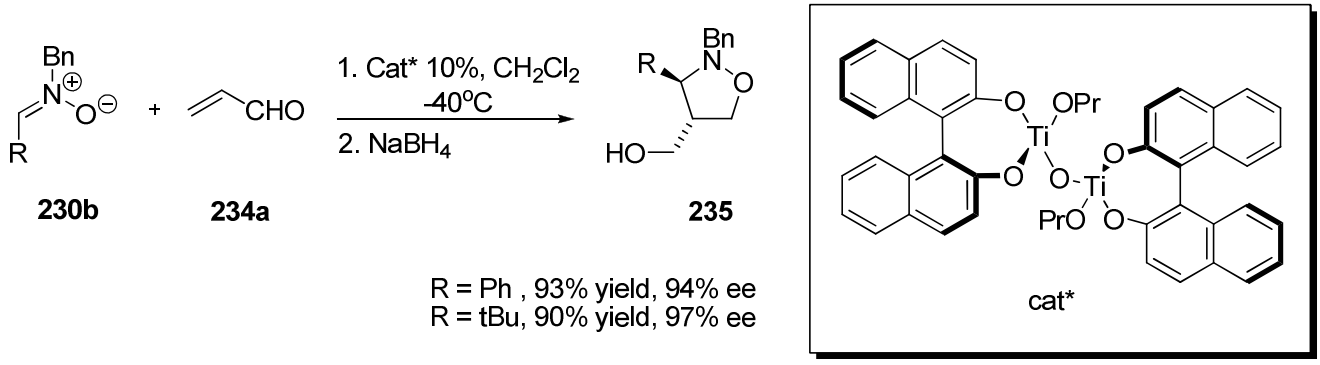
Enantiomerically pure isoxazolidines are direct precursors to numerous biologically active compounds, such as chiral 1,3-amino alcohols and alkaloids, e.g., (+)-porantheridine **233a** or (+)-hydroxycotinine **233b** (Figure 7).[188]



233a **233b**

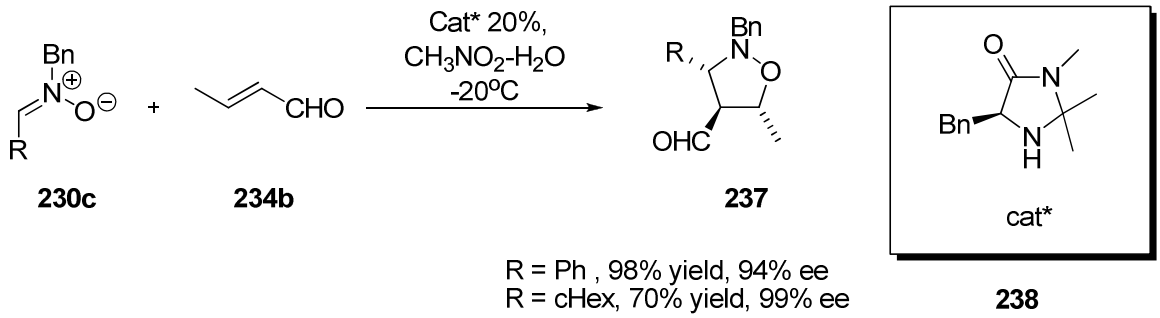
Figure 7

Effective methods for controlling up to three contiguous stereogenic centres were intensively studied in the last decade. There are known protocols for the enantioselective 1,3-dipolar cycloaddition reaction between nitrones **230** and alkenes **234** directed by either metal-based Lewis acids **236** (Scheme 89) or by organocatalysts **238** (Scheme 90).[85]



230b **234a** **235** **236**

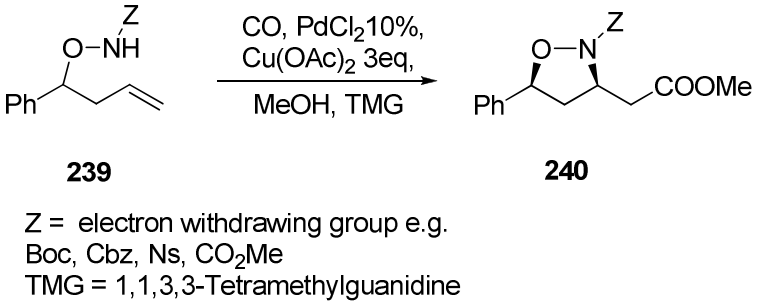
Scheme 89



Scheme 90

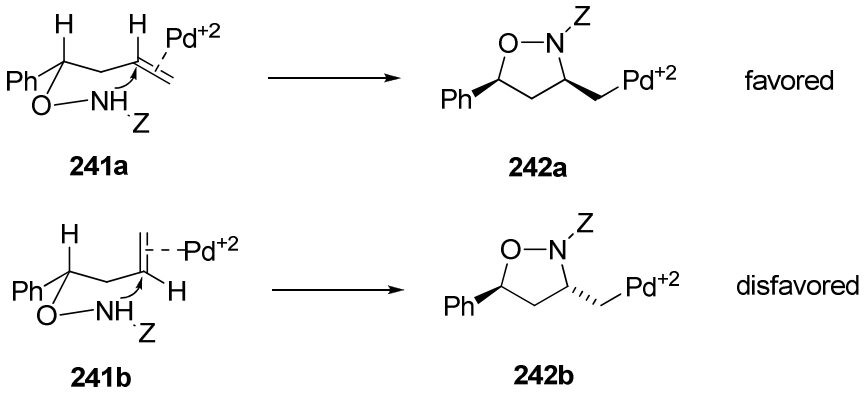
2.2.4 Formation of an isoxazolidine ring in the diastereoselective cyclization of *N*-protected-*O*-alkoxyamines

A conceptually new and straightforward strategy for a diastereoselective synthesis of 3,5-disubstituted isoxazolidines was developed by Bates and coworkers.[86] Treatment of *O*-homoallylhydroxylamines **239** with catalytic palladium(II) and co-oxidant, e.g., copper(II), in the presence of a strong base, methanol, and carbon monoxide results in the formation of isoxazolidines **240** in good yields. An electron-withdrawing group on the hydroxylamine nitrogen proved to be essential. Bates also observed that in the case of carbamate derivatives the products are exclusively formed as *cis*-isomers, which was confirmed by nOe experiments (Scheme 91).



Scheme 91

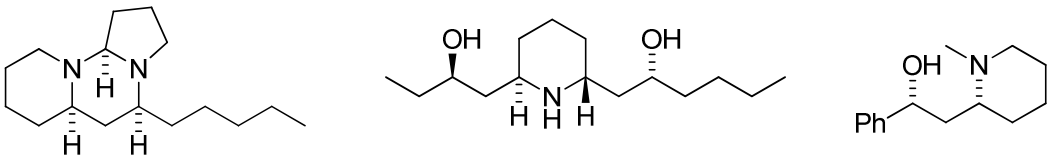
The predominant formation of the *cis*-isomer was explained by an envelope-like reactive conformation, similar to those shown in Schemes 68 and 70, in which **241a** is favoured over **241b** due to the less crowded alkene-palladium moiety (Scheme 92).[86]



241a **242a** **241b** **242b**

Scheme 92

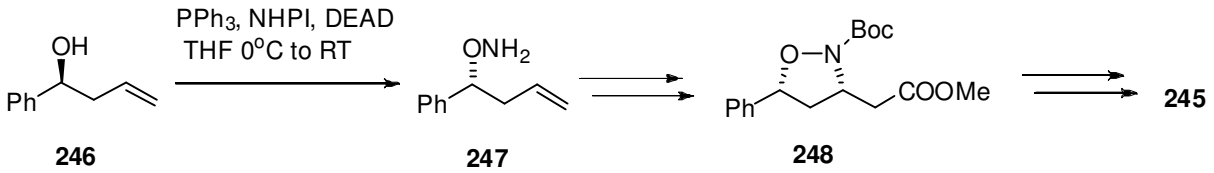
Enantiopure, multisubsituted isoxazolidnes are valuable intermediates in the total synthesis of natural products of Sedum alkaloid family. All these molecules possess either a 1,3-aminoalcohol or a 1,3-diamine moiety in addition to nitrogen heterocycle and are interesting synthetic targets. Selected compounds, such as andrachamine **243**, tetraponerine-8 **244** and sedamine **245** presented on Figure 8, were all synthesised using isoxazolidine intermediates.[87]



243 **244** **245**

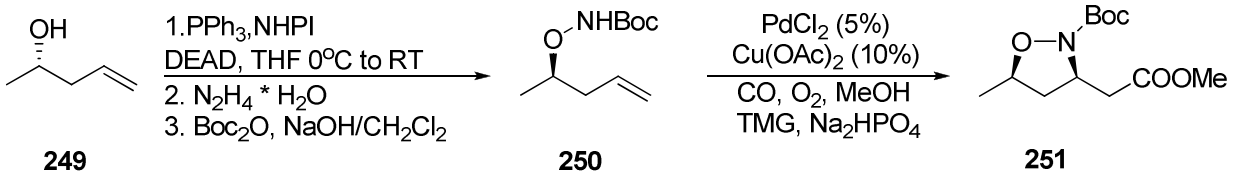
Figure 8

Successful application of palladium-mediated ring-closure/carbonylation as the key step was reported for the synthesis of the alkaloid sedamine **245**.[88] This compound is the best known of a large group of piperidine alkaloids that have been isolated from Sedum and other species. The initial (*S*)-stereogenic centre was introduced in alcohol **246** via chiral Lewis acid catalysed asymmetric allylation of benzaldehyde to obtain homoallylic alcohol in 95% ee. Complete inversion of the stereogenic centre took place in the next Mitsunobu product **247**. Cyclisation of the *N*-Boc protected alkoxyamine into five-membered isoxazolidine **248** was followed by five more steps to furnish the desired natural product **245** (Scheme 93).



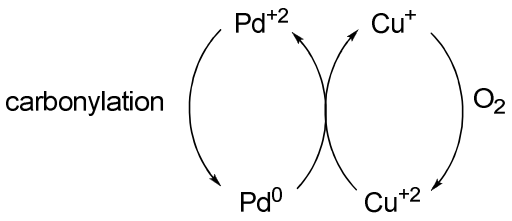
Scheme 93

This procedure was further explored by Dongol and co-workers who synthesised a series of aromatic isoxazolidines.[89] Addition of TMG (1,1,3,3-tetramethylguanidine) and Na_2HPO_4 at room temperature were found optimal for the reaction. *N*-Boc protected derivative **250** of commercially available (*S*)-(+)-4-pentenol **249** was used in synthesis of the enantiopure isoxazolidine **251**. GC analysis of the product confirmed complete inversion of the chiral centre and maintained 99% ee (Scheme 94).



Scheme 94

Another important aspect of this method is the reoxidation of the palladium species, which is being reduced during the catalytic process. Dongol and coworkers reported on complete formation of isoxazolidine under an atmosphere of CO and O_2 as copper reoxidant.[89] This modification introduced by Åkermark and coworkers reduces substantially the amount of the metal-based waste and makes the whole process more suitable for large scale operations (Scheme 95).[90]

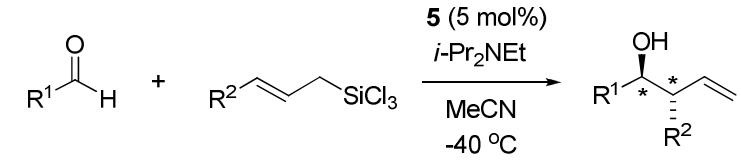


Scheme 95

2.3 Results and discussion

2.3.1 Synthesis of starting materials

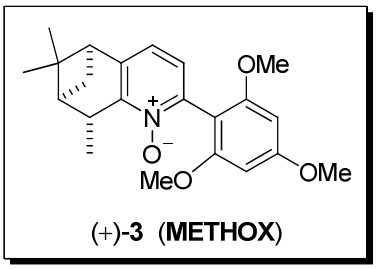
Synthesis of chiral homoallylic alcohols similar to those shown in Schemes 93 and 94 is a well established process in our group.[37,39,40] In this work we have demonstrated further development and synthetic applications of this class of compounds. Two top catalysts found in our laboratory, Methox and Quinox, provide access to enantiopure homoallylic alcohols with up to two stereogenic centres in either *syn* or *anti* configuration.[39,40] These substrates with predefined chirality are ideal starting materials for the synthesis of more complex building blocks with multiple stereogenic centres. A series of enantiopure homoallylic alcohols with a wide range of electronic and steric properties was prepared (Table 7, Scheme 96).



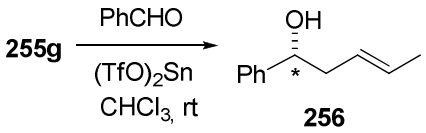
253, R^2 = H
254, R^2 = Me

252a, R^1 = C_6H_5
252b, R^1 = 4-MeO-C_6H_4
252c, R^1 = 4-F-C_6H_4
252d, R^1 = 4-Br-C_6H_4
252e, R^1 = 4-NO_2-C_6H_4
252f, R^1 = 3-MeO-C_6H_4

255a, R^1 = C_6H_5, R^2 = H
255b, R^1 = 4-MeO-C_6H_4, R^2 = H
255c, R^1 = 4-F-C_6H_4, R = H
255d, R^1 = 4-Br-C_6H_4, R^2 = H
255e, R^1 = 4-NO_2-C_6H_4, R^2 = H
255f, R^1 = 3-MeO-C_6H_4, R^2 = H
255g, R^1 = C_6H_5, R^2 = Me
255h, R^1 = 4-F-C_6H_4, R^2 = Me
255i, R^1 = C_6H_5-CH=CH, R^2 = H



(+)-**3** (**METHOX**)



256

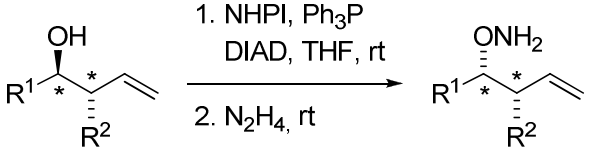
Scheme 96

Table 7. Synthesis of enantiopure homoallylic alcohols

Entry	alcohol[a]	yield[d] %	ee[b] %	de[c]
1	(±)-**255a**	93	racemic[f]	n/a
2	(*S*)-(–)-**255b**	70	96	n/a
3	(*S*)-(–)-**255c**	75	95	n/a
4	(*S*)-(–)-**255d**	91	91	n/a
5	(*S*)-(–)-**255e**	72	92	n/a
6	(*S*)-(–)-**255f**	82	94	n/a
7	(1*S*,2*S*)-(–)-**255g**	87	95	55 : 1
8	(1*S*,2*S*)-(–)-**255h**	52	98	35 : 1
9	(*S*)-(–)-**255i**	75	88	n/a
10	(*R*)-(+)-**256**	76	92	n/a

[a] The absolute configuration of the starting alcohols **255** has either been established previously or is inferred by analogy, based on the fact that the allylation of aromatic aldehydes catalysed by (+)-METHOX (**3**) is known to produce (*S*)-alcohols[40]. [b] The enantiomeric purity of the starting alcohols was established by chiral HPLC or GC. [c] Established by ^{1}H NMR (or ^{19}F NMR, where applicable) spectroscopy. [d] Isolated yield after purification; note that conversions were practically quantitative. [f] – racemic alcohol was prepared via DMF catalysed reaction.

There are two different methods for the conversion of an alcohol into the corresponding alkoxyamine (R-ONH$_2$), one involving the Mitsunobu substitution, in which a new C-O bond is formed with inversion of the original configuration,[86,91,93] and another proceeding with net retention, where the O-N bond is constructed instead, leaving the chiral centre unaffected.[92] According to the former approach, alcohols **255a-i** were treated with *N*-hydroxyphthalimide (NHPI) in the presence of diisopropyl diazodicarboxylate (DIAD) and triphenylphosphine under the standard Mitsunobu conditions[86,91,93] and the resulting phthalimides were deprotected on reaction with hydrazine to afford the required alkoxyamines **257a-i** in good yields (Scheme 97 and Table 8).



NHPI = *N*-hydroxyphthalimide;
DIAD = diisopropyl diazodicarboxylate;

257a, $R^1 = C_6H_5$, $R^2 = H$
257b, $R^1 = 4\text{-MeO-}C_6H_4$, $R^2 = H$
257c, $R^1 = 4\text{-F-}C_6H_4$, R = H
257d, $R^1 = 4\text{-Br-}C_6H_4$, $R^2 = H$
257e, $R^1 = 4\text{-}NO_2\text{-}C_6H_4$, $R^2 = H$
257f, $R^1 = 3\text{-MeO-}C_6H_4$, $R^2 = H$
257g, $R^1 = C_6H_5$, $R^2 = Me$
257h, $R^1 = 4\text{-F-}C_6H_4$, $R^2 = Me$
257i, $R^1 = C_6H_5\text{-CH=CH}$, $R^2 = H$

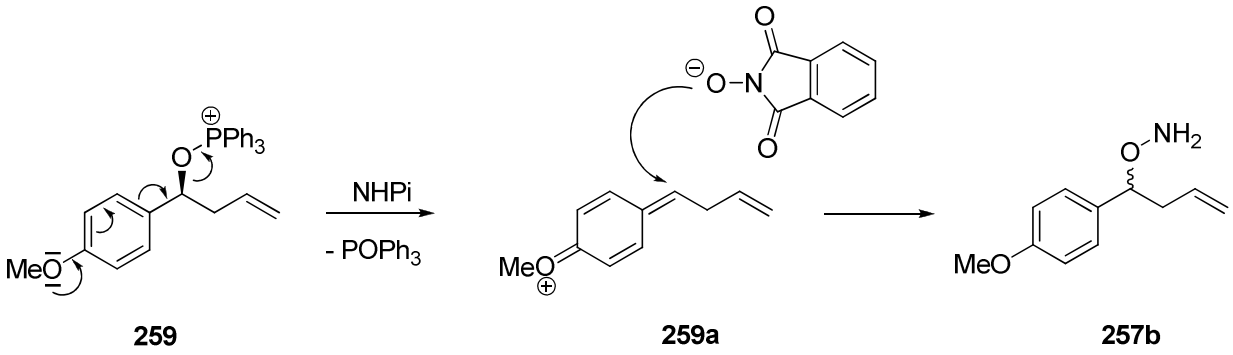
Scheme 97

Table 8. Synthesis of alkoxyamines

Entry	**alkoxyamine**	**yield**[a] **%**	**ee**[b] **%**	**de**[c]
1	(±)-**257a**	85	racemic	n/a
2	(*R*)-(+)-**257b**	74	~10	n/a
3	(*R*)-(+)-**257c**	78	90	n/a
4	(*R*)-(+)-**257d**	86	90	n/a
5	(*R*)-(+)-**257e**	84	92	n/a
6	(*R*)-(+)-**257f**	91	88	n/a
7	(1*R*,2*S*)-(+)-**257g**	89	95[d]	35 : 1[e]
8	(1*R*,2*S*)-(+)-**257h**	54	98[d]	28 : 1[f]
9	(*S*)-(–)-**257i**	64	~40[g]	n/a
10	(S)-(–)-**258**	81	90	n/a

[a] Isolated yield after purification; note that conversions were practically quantitative. [b] The enantiomeric purity was inferred from the ^{19}F NMR spectra of the corresponding Mosher derivatives. [c] Established by ^1H NMR spectroscopy for **257g** (by integration of the signals of the benzylic protons of the crude products) and by ^{19}F NMR for **257h**. [d] The enantiomeric purity is assumed to be identical to that of the starting material, as the second chiral centre remained unchanged. [e] Increased to 55:1 purity by chromatography. [f] The conversion was ~70%. The *syn/anti* ratio could not be accurately established due to the overlap of the relevant signals in the ^1H NMR spectrum of the crude product with those of the unreacted starting material; the 28:1 ratio corresponds to the product after purification. [g] Isolated as 2 : 1 ratio mixture with S_N2' product **260**.

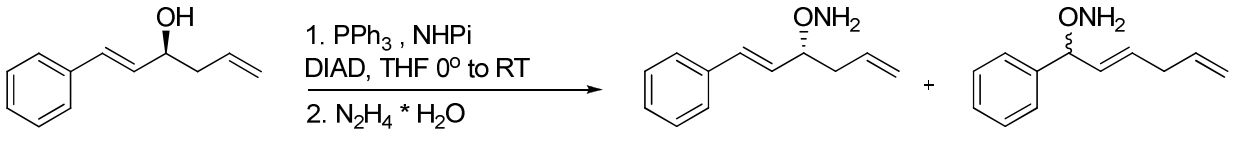
In all cases, except two (entry 2 and 9), the inversion of configuration was almost perfect (with very little loss in the stereochemical integrity if any). All noted losses in the range of 3-5% ee were assigned to insufficient accuracy of the Mosher amide detection method compared to the enantiopurity of alcohols confirmed by HPLC and GC. However, the *p*-methoxy derivative **255b** (96% ee) produced the corresponding alkoxyamine **257b**, which turned out to be almost racemic (~10% ee). We assume this was a result of the strong electron donating effect **259** of the methoxy group at the *p*-position, which led to participation of cationic intermediate **259a** stabilised by resonance. The strong S_N1 component in this reaction renders the product **257b** nearly racemic (Scheme 98).



259 **259a** **257b**

Scheme 98

Another example where we have encountered a similar problem was Mitsunobu reaction of the alcohol **255i,** derived from cinnamyl aldehyde. Product **260** was formed as a result of the competing S_N2' reaction in 1:2 ratio with the desired *O*-alkoxyamine **257i** (Scheme 99).[91b]



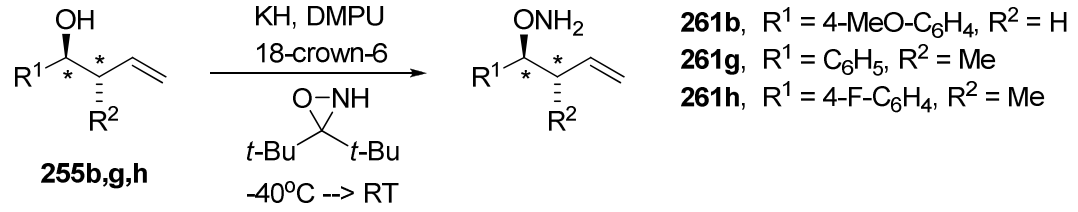
255i **257i** **260**

2 : 1

Scheme 99

Mosher amide analysis of the products revealed ca. 40% enantiopurity of **257i** (loss from 88%) and **260** was obtained as a racemate. This was again rationalised by the high stability of the cation in the conjugated system which enabled S_N2, S_N2' and S_N1 reactions to compete. This result represents a serious blow to the general belief in the Mitsunobu reaction[93] as a means of clean inversion and will deserve further investigation.

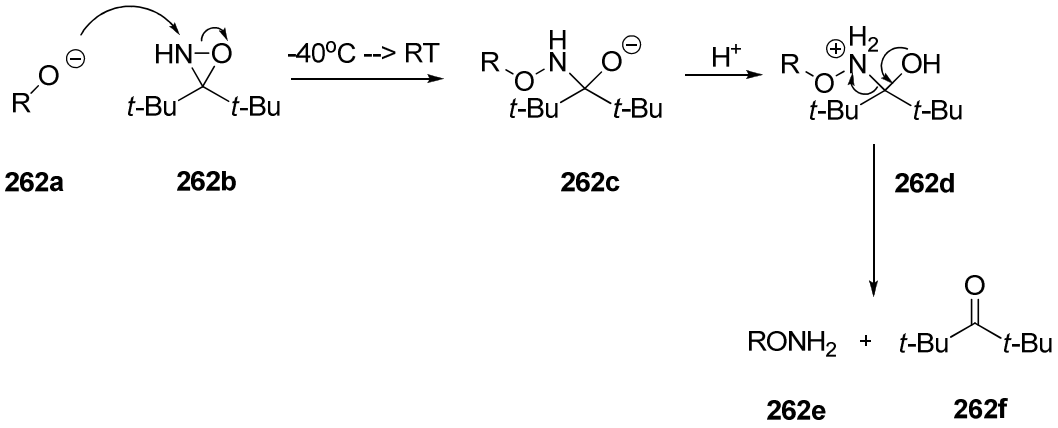
One of the possibilities to avoid racemisation is to install the alkoxyamine moiety without affecting the chiral centre. The retention pathway (Scheme 100) is based on the construction of the O-N bond via the reaction of the corresponding alkoxide (generated in situ) with 3,3'-di-*tert*-butyloxaziridine, which involves a nucleophilic substitution at the oxaziridine nitrogen.[94] According to this scenario, alcohols **255b,g,h** were deprotonated with potassium hydride in the presence of the potassium-specific 18-crown-6 ether and the resulting alkoxides were allowed to react with 3,3'-di-*tert*-butyloxaziridine to produce **261b** (88%), **261g** (65%), and **261h** (33%); these experiments were conducted by the Erasmus exchange student **Lucie Potucká**.



DMPU = 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone

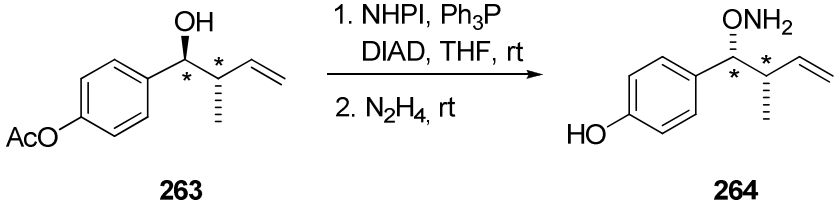
Scheme 100

The mechanism of oxaziridine **262b** reaction proposed by Ellman resembles opening of the epoxide with an alkoxide **262a**. When temperature is increased, a more stable alkoxide **262c** is preferred and O-N bond is being formed. Protonation of the product **262c** leads to the collapse of the molecule **262d** and formation of alkoxyamine **262e** and an unreactive byproduct **262f** (Scheme 101). Bulky *t*-Bu groups prevent nucleophilic attack on carbonyl as well as it enolisation.[92]



Scheme 101

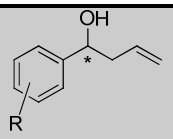
Another approach (performed by the project student Colin Robinson) to prevent racemisation of the electron-rich starting alcohols in the Mitsunobu step was to decrease the electron donating effect of the substituents by replacing OMe with OAc. Alcohol **263** was synthesised in 96% ee and with 28:1 *anti* : *syn* diastereopurity using Methox crotylation under standard conditions. Mitsunobu reaction of the latter alcohol, followed by hydrazinolysis gave the product **264** with pure inversion with only minor decay of diastereopurity (25:1 *syn* : *anti*). The acetate group was then cleaved by hydrazine hydrate (Scheme 102).



Scheme 102

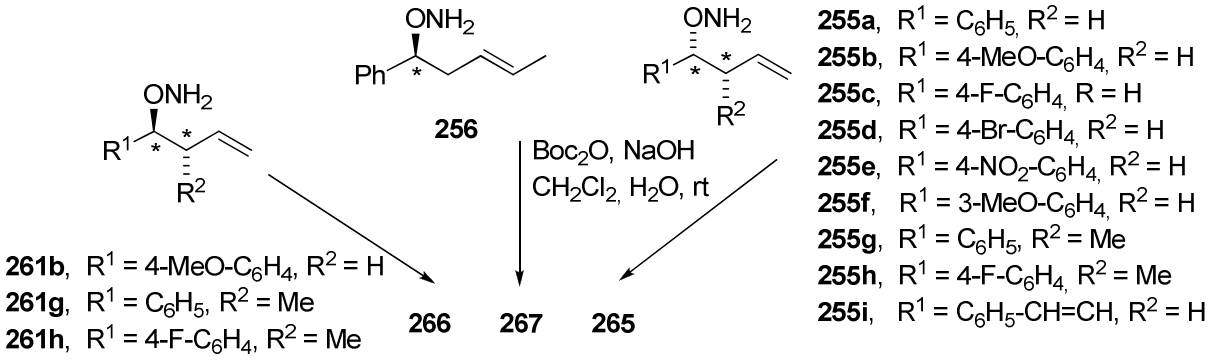
This result clearly indicates the existence of a borderline of the mechanism, which determines the scope of the Mitsuobu method. Computational analysis of the stability of benzylic cations and vulnerability of the respective alcohols to racemisation was carried out by Dr Mikhail Kabeshov (Table 9). DFT calculations were carried out at B3LYP{1}/6-31g(d,p) level with the CPCM{2} solvation model.

Table 9. Relative stability of benzylic cations

Entry		stability to racemisation
1	4-NO_2	11.5
2	4-CN	9.3
3	4-Ac	5.2
4	4-F	0.2
5	3-MeO	0.1
6	**Ph**	**0**
7	3-NHAc	-0.3
8	4-AcO	-2.8
9	4-Me	-4.7
10	4-NHAc	-8.2
11	4-MeO	-10.5
12	3,4-diMeO	-12.1
13	4-NH_2	-20

The results shown in Table 9 estimate the resistance of the selected homoallylic alcohols to racemisation during the Mitsunobu reaction. The greater the number the lower the stability of the benzylic cation and the more suppressed S_N1 reaction. Simple phenyl group was set as a reference point. The results from Table 9 perfectly mirror the experimental data. With a 4-MeO substituent, almost complete racemisation was observed while a 4-OAc group was sufficient to prevent it.

A series of *O*-alkoxyamines were submitted to *N*-derivatisation with an electron withdrawing group. Derivatisation with EWG is crucial for the ring closing aminocarbonylation to occur, as free NH_2 proved unreactive.[86] *tert*-Butyloxycarbonyl (Boc) was employed as the group of choice, since it is much easier to remove than, e.g., acetate, and is beneficial to diastereoselectivity. Boc-derivatisation of **257**, **258**, and **261** was carried out under the standard Schotten-Bauman-type conditions using di-*tert*-butyl dicarbonate (Boc-anhydride) and NaOH in a two-phase system, and afforded the model alkoxycarbamates **265**, **267**, and **266** in high isolated yields (Scheme 103, table 10).



Scheme 103

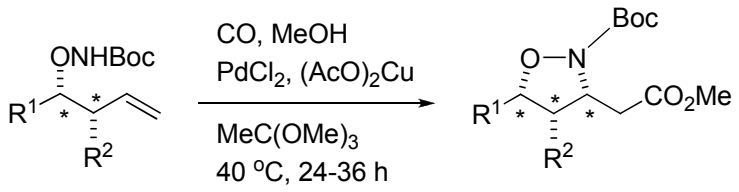
Table 10. Synthesis of *N*-Boc protection of alkoxyamines (Scheme 103).

Entry	*N*-Boc alkoxyamine	yield %	ee %	de
1	(*R*)-(+)-**265a**	99	racemic	n/a
2	(*R*)-(+)-**265b**	85	~10	n/a
3	(*R*)-(+)-**265c**	92	90	n/a
4	(*R*)-(+)-**265d**	82	90	n/a
5	(*R*)-(+)-**265e**	77	92	n/a
6	(*R*)-(+)-**265f**	97	88	n/a
7	(1*R*,2*S*)-(+)-**265g**	98	95	35 : 1
8	(1*R*,2*S*)-(+)-**265h**	76	98	28 : 1
9	(*S*)-(–)-**266b**	79	96	n/a
10	(1*S*,2*S*)-(–)-**266g**	69	95	55 : 1
11	(1*S*,2*S*)-(–)-**266h**	69	98	35 : 1
12	(S)-(–)-**267**	91	90	n/a

2.3.2 Ring-Closing Carboamination of the Boc-Protected Alkoxyamines.

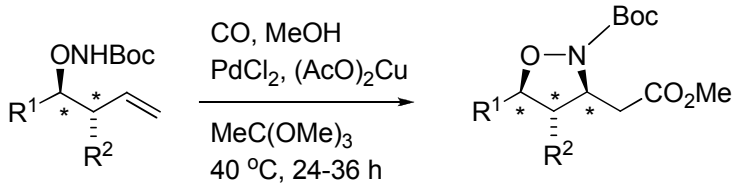
Treatment of the unsaturated Boc protected alkoxycarbamates **265a-h** with methanol and carbon monoxide at atmospheric pressure in the presence of $PdCl_2$ as catalyst (10 mol%) and $(AcO)_2Cu$ (2-3 equiv) to reoxidise the palladium, was expected to result in the formation of isoxazolidines **268a-h** (Scheme 104 and Table 11). However, the first attempts with just methanol as a solvent and reactant were rather disappointing: thus, at 0 ^oC or at room temperature, there was practically no reaction detected, whereas at 30 ^oC, especially in the presence of a base, such as K_2CO_3, Et_3N, AcONa, $PhCO_2Na$, or tetramethylguanidine, etc., precipitation of Pd-black was observed within ~10 min, apparently as a result of the stoichiometric oxidation of CO and/or MeOH at the expense of Pd(II).[86] Finally, after much experimentation, we were able to identify a 1:1 mixture of methanol and methyl orthoacetate as the medium of choice, with no additional base required. Here, the role of the orthoacetate is to "mop up" the Brønsted acid generated during the reaction; the latter process also produces MeOH, which is present anyway, and one equivalent of the innocuous AcOMe. Significantly, under these neutral conditions, the reduction of Pd(II) by CO/MeOH was suppressed, so that the desired carboamination could proceed to completion.

The cyclisation of **265a-f** and **266b**, i.e., terminal olefins lacking another substituent (R^2 = H), proceeded with very high diastereoselectivity (24:1 to >50:1; Table 2, entries 1-6 and 9). The cyclisation of their homologues with an additional methyl (R^2 = Me) exhibited dependence on the configuration. Thus, the *syn*-configured alkoxycarbamates **265g,h** produced the less stereochemically pure *syn,syn*-isozaxolidines **268g,h** (entries 7 and 8), whereas the *anti*-configured analogues **266g,h** afforded the *anti,anti*-isoxazolidines **269g,h** of high diastereoisomeric purity (entries 10 and 11).



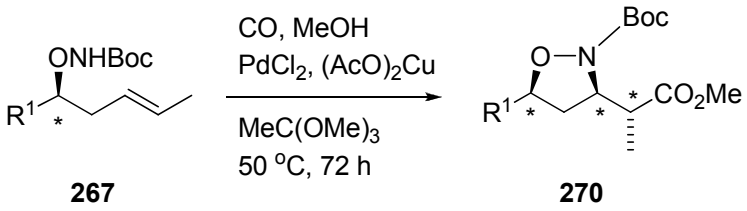
265a, $R^1 = C_6H_5$, R^2 = H
265b, R^1 = 4-MeO-C_6H_4, R^2 = H
265c, R^1 = 4-F-C_6H_4, R = H
265d, R^1 = 4-Br-C_6H_4, R^2 = H
265e, R^1 = 4-NO_2-C_6H_4, R^2 = H
265f, R^1 = 3-MeO-C_6H_4, R^2 = H
265g, $R^1 = C_6H_5$, R^2 = Me
265h, R^1 = 4-F-C_6H_4, R^2 = Me

268a, $R^1 = C_6H_5$, R^2 = H
268b, R^1 = 4-MeO-C_6H_4, R^2 = H
268c, R^1 = 4-F-C_6H_4, R = H
268d, R^1 = 4-Br-C_6H_4, R^2 = H
268e, R^1 = 4-NO_2-C_6H_4, R^2 = H
268f, R^1 = 3-MeO-C_6H_4, R^2 = H
268g, $R^1 = C_6H_5$, R^2 = Me
268h, R^1 = 4-F-C_6H_4, R^2 = Me



266b, R^1 = 4-MeO-C_6H_4, R^2 = H
266g, $R^1 = C_6H_5$, R^2 = Me
266h, R^1 = 4-F-C_6H_4, R^2 = Me

269b, R^1 = 4-MeO-C_6H_4, R^2 = H
269g, $R^1 = C_6H_5$, R^2 = Me
269h, R^1 = 4-F-C_6H_4, R^2 = Me



267 **270**

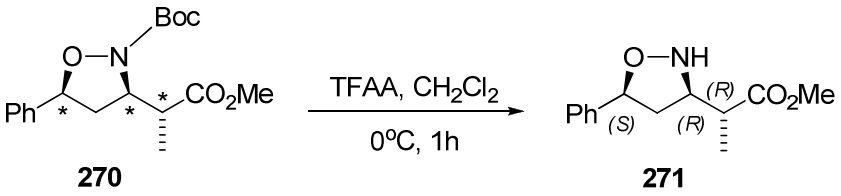
Scheme 104

Table 11. Palladium-catalysed ring-closing carbonylation of *N*-Boc alkoxyamines.

Entry	*N*-Boc alkoxyamine	ee %	de	isoxazolidine	yield[a] (%)	de[b]
1	(*R*)-(+)-**265a**	racemic	n/a	**268a**	93	>50 : 1
2	(*R*)-(+)-**265b**	10	n/a	**268b**	80	>50 : 1
3	(*R*)-(+)-**265c**	90	n/a	**268c**	76	20 : 1[c,d]
4	(*R*)-(+)-**265d**	90	n/a	**268d**	93	>50 : 1
5	(*R*)-(+)-**265e**	92	n/a	**268e**	73	25 : 1
6	(*R*)-(+)-**265f**	88	n/a	**268f**	96	>50 : 1
7	(1*R*,2*S*)-(+)-**265g**	95	35 : 1	**268g**	69	4.5 : 1[e,f]
8	(1*R*,2*S*)-(+)-**265h**	98	28 : 1	**268h**	60	5.7 : 1[f]
9	(*S*)-(–)**266b**	96	n/a	**269b**	54	>25 : 1[e]
10	(1*S*,2*S*)-(–)-**266g**	95	55 : 1	**269g**	71	>20 : 1[e,f]
11	(1*S*,2*S*)-(–)-**266h**	98	35 : 1	**269h**	66	17 : 1[e,f]
12	(S)-(–)-**267**	90	n/a	**270**	55	22 : 2 : 1[g]

[a] Isolated yield after purification; note that conversions were practically quantitative. [b] Established for the crude product by ^{1}H NMR spectroscopy (by integrating the signals of the benzylic protons). [c] The ^{19}F NMR spectrum of the crude product showed a 16:1 ratio. [d] Increased to ≥40:1 by chromatography. [e] Increased to >50:1 by chromatography. [f] In principle, three diastereoisomers could be formed here. However, the third isomer could not be detected, presumably because its concentration was below the detection limit of the NMR spectroscopy. [g] Increased to 40:2.5:1 by chromatography.

It is frequently pointed out that the presence of another substituent at the olefinic double bond causes serious deterioration of the palladium(II)-catalysed cyclisation. Two main factors seem to contribute to this: one is the decrease of the stability of the intermediate olefin-palladium complex due to the increased steric hindrance. Another factor is the inhibition of an approach of a nucleophile to the sterically crowded electrophilic center.[75] Homologue **267**, with a more sterically hindered disubstituted double bond, required slightly higher temperature and extended reaction time to produce **270** as an almost pure diastereoisomer (entry 12). The relative configuration of **270** was established by NMR spectroscopy and confirmed by X-ray crystallography of the deprotected isoxazolidine (Scheme 105, Figure 9).



270 **271**

Scheme 105

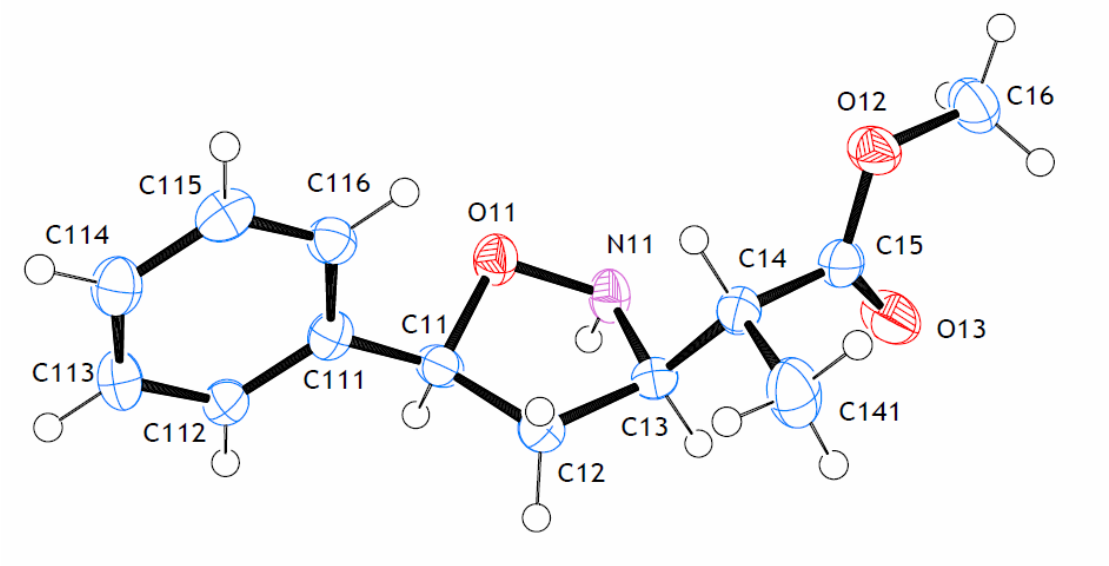
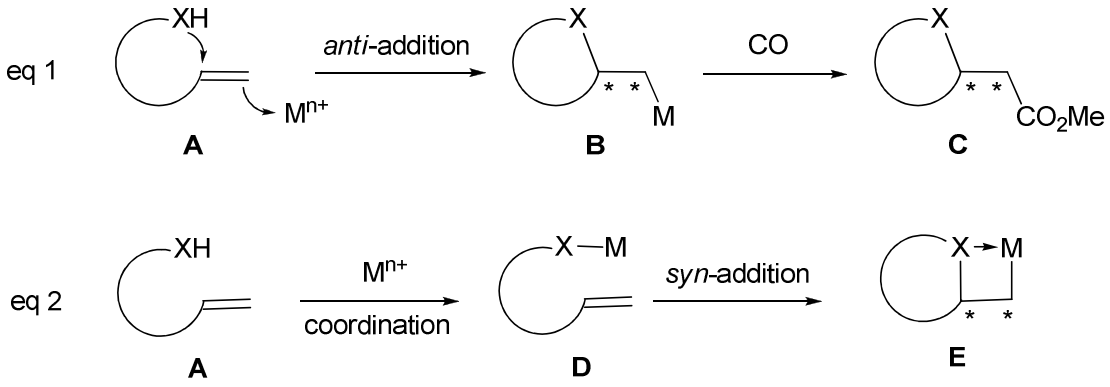


Figure 9. An ORTEP diagram for **271**.

There are two major mechanisms describing stereocontrolled electrophilic additions across a C=C bond. When metals, such as Pd[190] or Hg,[190,191] are employed as the electrophilic triggers of the reaction, the initially formed organometallic product **B** can be utilized in a subsequent reaction that would allow the construction of a new C-C bond from the C-M bond. The overall result would then be the formation of a C-X and C-C bond, where X is introduced as a nucleophile, and the new C-substituent formally as an electrophile (**C**).[57,63,190a,192]

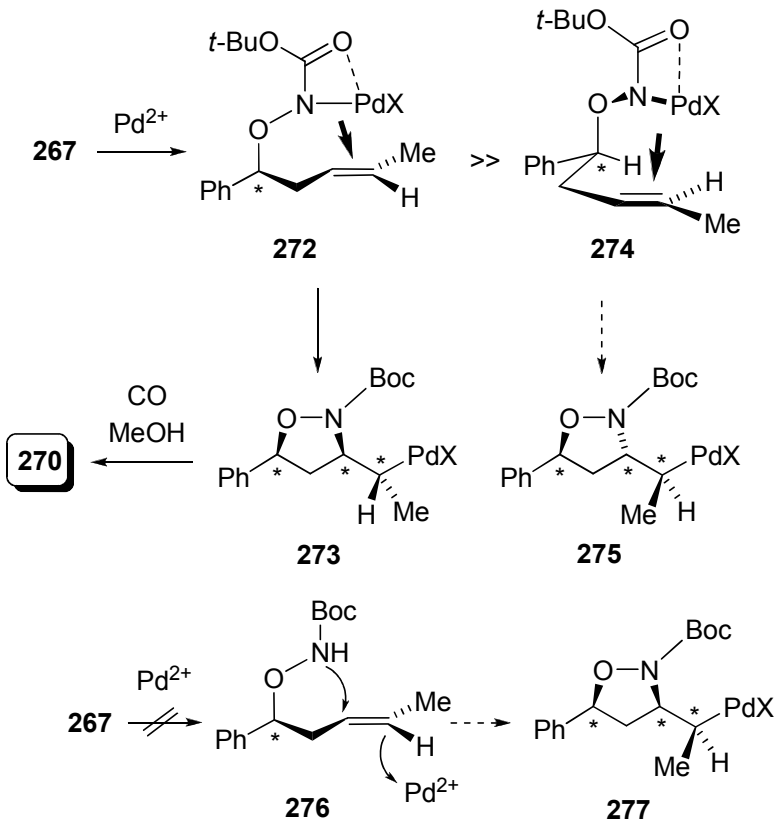
In his seminal paper, Semmelhack[63] had shown that olefinic alcohols can be readily cyclised in a stereocontrolled manner by Pd^{2+} (eq 1, X = O) and the resulting organopalladium intermediate **B** would then undergo carbonylation (with retention of configuration) to produce the corresponding ester (M = CO_2Me).[62-64,193] Semmelhack had also developed a catalytic cycle, in which the Pd(0) resulting from the reaction is re-oxidized by Cu(II).[63,193] The latter reaction was formulated as an *anti*-addition of Pd^{2+} and the alkoxy group across the double bond (eq 1),[63,193] which is in line with the mechanism of the Bäckvall oxidation, where the initially generated η^4-Pd(II)-complex of a conjugated diene is attacked by a nucleophile from the face opposite to Pd,[194] and with the mechanism of Pd(II)-catalysed amination of ethylene, thoroughly investigated by Åkermark.[195]

Aside from the *anti*-mechanism (eq 1), the *syn*-addition (eq 2) may also operate, especially if the XH group (-OH or -NHR) is deprotonated with a base prior to the reaction,[196] so that it can easily pre-coordinate the metal and steer its approach to the C=C bond. Numerous examples of the latter mechanism have been reported for the catalytic cyclisations with nitrogen or oxygen as internal nucleophile and the Ar-[Pd] species by groups of Wolfe and others.[196,197] In fact, Wolfe[198a] , Hartwig[198b] and collaborators have been able to prepare the N-Pd complexes (**D**, X = NR) from the corresponding amines via deprotonation followed by treatment with Pd(II), and elucidate the mechanism with the aid of deuterium labelling.



Scheme 106

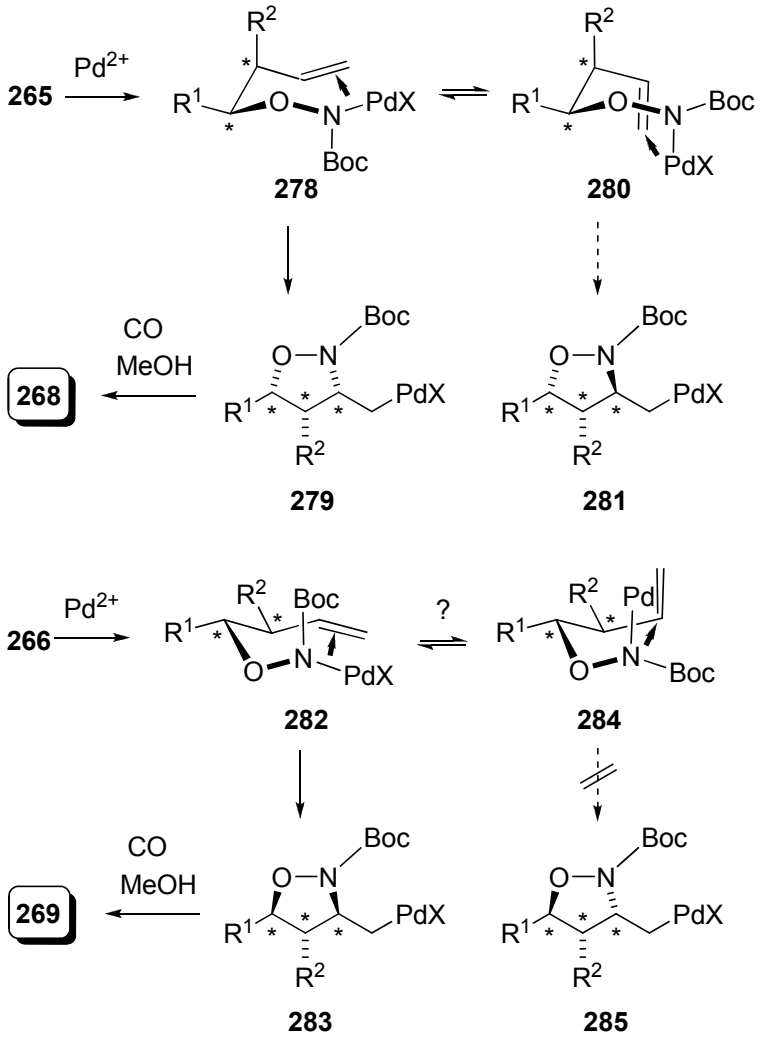
The experiment with **267** was of key importance for establishing the stereochemistry of the Pd-catalysed cyclisation: here, the formation of diastereoisomer **270** corresponds to a *syn*-addition (eq 2 in Scheme 106) of Pd and the nitrogen across the C=C bond. Apparently, the carbamate group is capable of coordinating the Pd(II) catalyst (Scheme 107), presumably by nitrogen upon its deprotonation (**272**), followed by a *syn*-addition across the neighbouring C=C bond, to generate the palladium species **273**, whose carbonylation (with retention of configuration) gives rise to ester **270**. This mechanism mirrors the findings by Wolfe[95] and Hartwig,[96] research groups who first deprotonated model amines with a strong base prior to the addition of a palladium complex (typically Ar-PdX). The *syn*-attack on the opposite face of the double bond, as in **274**, would generate 1,3-strain, so that the corresponding Pd intermediate **275** is apparently not generated in any appreciable amount. By contrast, the *anti*-pathway (**276** → **277**) would give rise to yet another diastereoisomer of **270**, whose formation was not observed. These findings show that carbamates stand in stark contrast to alcohols, which prefer the *anti*-pathway in the carbonylative cyclisation (Scheme 108).[63]



Scheme 107

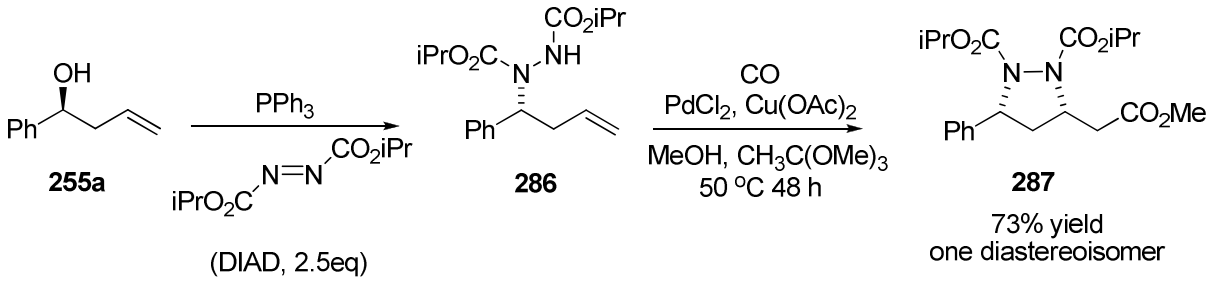
Similar mechanistic arguments can be applied to the remaining members of the series, i.e., **265** and **266** (Scheme 108). Thus, carbamates **265** apparently prefer the pathway involving the palladium complexes **278** and **279** to give **268**; by analogy, carbamates **266** can be assumed to react via **282** and **283**, giving rise to **269**. In the case of the *syn*-configured carbamates **266**, the reactive intermediate **278** is more congested than the analogous species **282** arising from the *anti*-configured carbamate **266**, which can account for the clean formation of one diastereoisomer in the latter instance (**269**) and the less stereochemically homogeneous reaction in the former (**268**); compare entries 10 and 11 with 7 and 8 with in Table 10.

In the absence of the R^2 substituent (i.e., R^2 = H), the diastereoselectivity was high in all instances (Table 11, entries 1-6 and 9).



Scheme 108

In order to expand the scope of the reaction, a nitrogen analogue of the *N*-Boc alkoxyamine was synthesised from homoallylic alcohol **255a** by a modified Mitsunobu reaction.[97] In the absence of a suitable reagent, azodicarboxylate serves as an *N*-nucleophile to furnish the hydrazine derivative **286** (Scheme 109) .

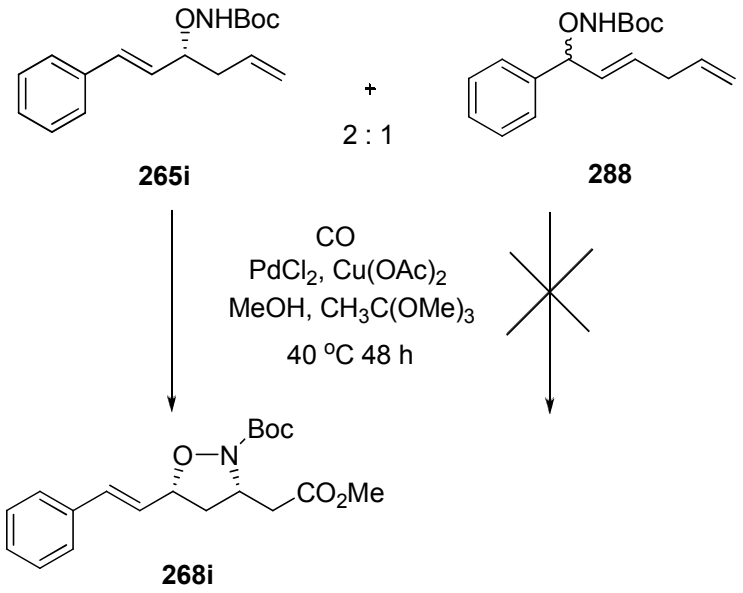


Scheme 109

Product **286** was submitted to palladium-catalysed carbonylation under standard conditions with slightly increased temperature to cleanly furnish pyrazolidine **287** (Scheme 109). The product was obtained as a single diastereoisomer, presumably of *syn* configuration according to the proposed mechanism (Scheme 108). Attempts to close the pyrazolidine ring with Boc protected hydrazine failed and gave only 25% of impure product after 7 days at 60 ^{o}C. This reaction requires further investigation. To the best of our knowledge, this is the first example of asymmetric synthesis of pyrazolidines by aminocarbonylation.

The reactions described above demonstrate the high level of diastereoselectivity in closing 5-membered isoxazolidine rings. Closing six- and seven-membered ring was unsuccessful, as reported by Bates and Sa-Ei.[86]

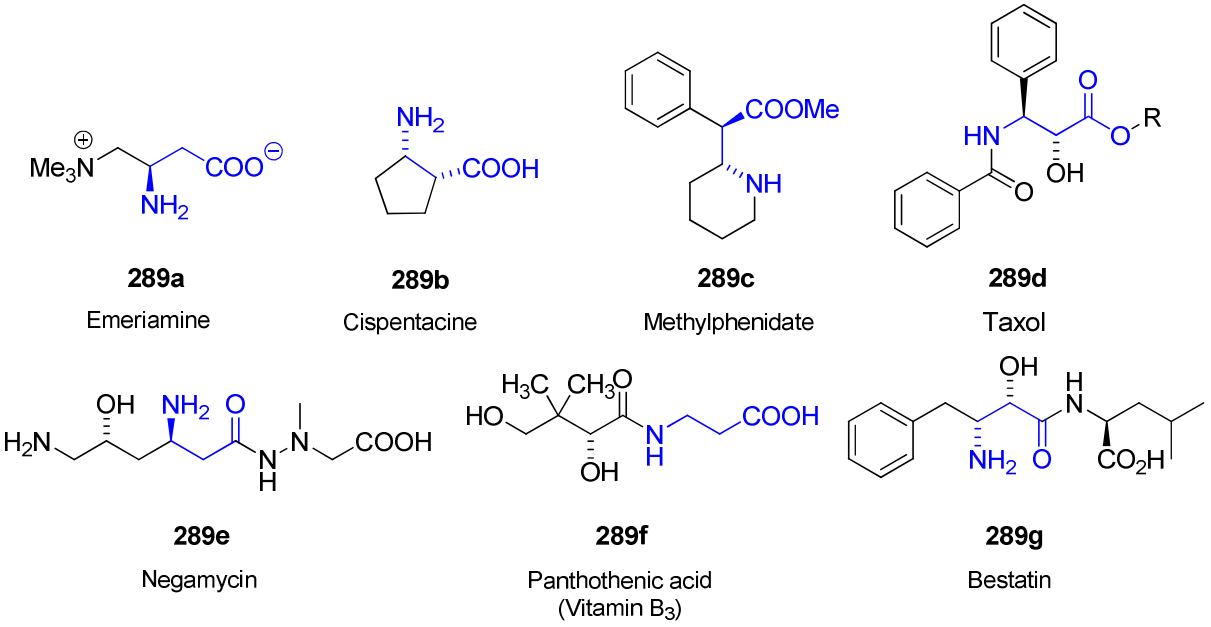
An inseparable 2:1 mixture of alkoxyamines **257i** and **260** shown in Scheme 99, after protection with Boc, was carbonylated under standard conditions. Only alkoxyamine derivative **265i** underwent cyclisation and the product **268i** was easily isolated in 87% yield as a single diastereoisomer, while **288** was recovered unchanged (Scheme 110).



Scheme 110

2.3.3 Synthetic Application of Isoxazolidines

During the last decade, synthesis of optically active β-amino acids attracted considerable attention due to their biologically important properties, their occurrence in natural products and as potential precursors to many other molecules, such as β-lactams.[98] This structural motif is very common in nature and has been successfully reproduced by chemists (Figure 10). Furthermore, β-amino acids and their derivatives show interesting and useful pharmacological properties.[99]



289a Emeriamine

289b Cispentacine

289c Methylphenidate

289d Taxol

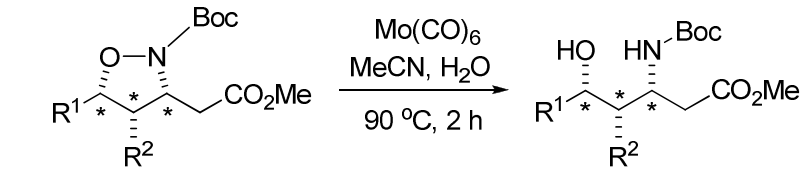
289e Negamycin

289f Panthothenic acid (Vitamin B_3)

289g Bestatin

Figure 10

Although methods for the synthesis of γ- and δ-substituted β-aminoacids are known, there is only a limited number of asymmetric variants.[100] Therefore, the synthetic pathway presented here represents an important contribution to this methodology. The cleavage of the O-N bond in the *N*-Boc-protected isoxazolidines **268** and similarly in the related isoxazolidines **269** and **270**, would open an interesting access to β-amino-δ-hydroxy acids, with an optional substituent (R^2) at the γ-position. Up to three stereogenic centres can be controlled using this methodology. Of the existing methods for the O-N bond cleavage, we chose the protocol of Cicchi and coworkers that employed $Mo(CO)_6$, as this reagent appears to be tolerant to the *N*-Boc group.[101] Indeed, on treatment with a stoichiometric amount of $Mo(CO)_6$ at 90 °C (Scheme 111), the selected *N*-Boc protected isoxazolidines **268c,f,g** afforded the expected *N*-Boc-protected β-amino-δ-hydroxy acids **290c** (65%), **290f** (86%), and **290g** (77%).



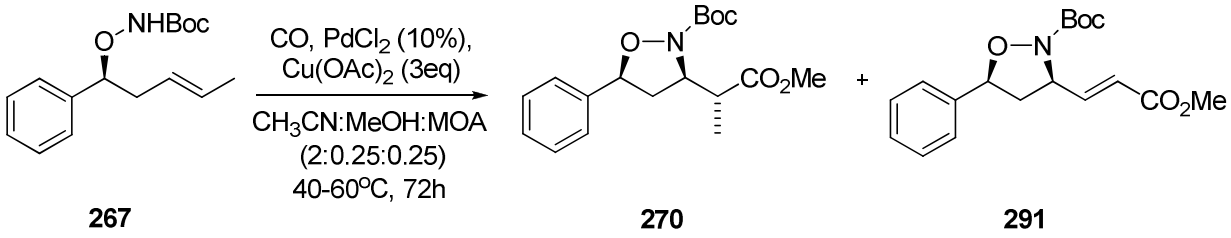
268c, R^1 = 4-F-C_6H_4, R^2 = H
268f, R^1 = 3-MeO-C_6H_4, R^2 = H
268g, R^1 = Ph, R^2 = Me

290c, R^1 = 4-F-C_6H_4, R^2 = H
290f, R^1 = 3-MeO-C_6H_4, R^2 = H
290g, R^1 = Ph, R^2 = Me

Scheme 111

2.3.4 Unexpected Palladium Catalysed Transformations

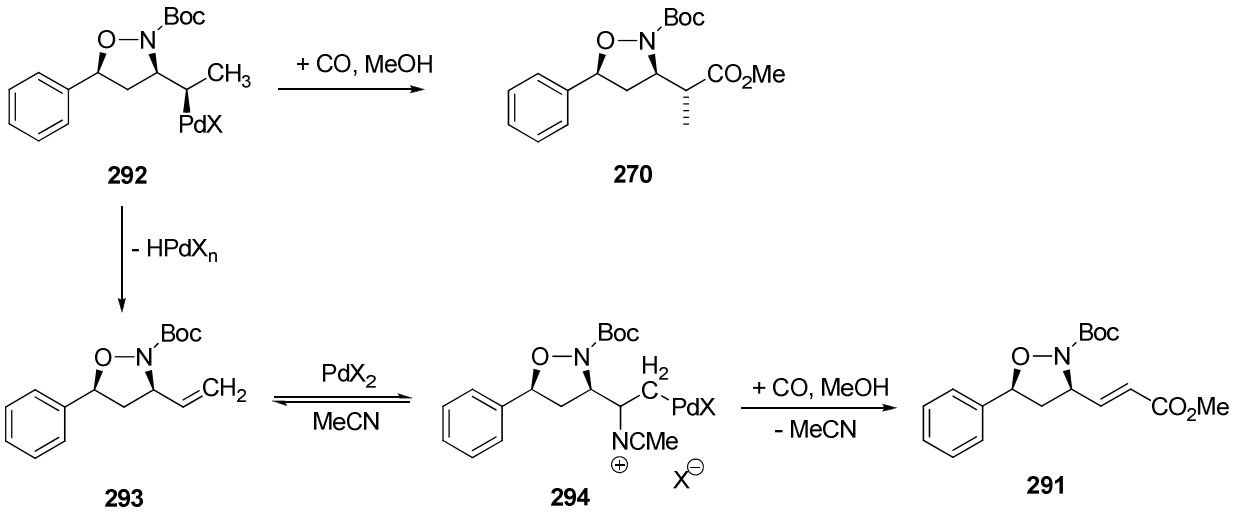
While optimising the conditions for the carbonylative cyclisation of **267** into **270** (Scheme 105), the solvent composition of MeCN/$(MeO)_3CH$/MeOH 8:1:1) gave a 1:1 mixture of **270** and an unexpected unsaturated product **291** bearing an isoxazolidine moiety. Analysis of the isolated product **291** confirmed the structure shown in Scheme 112.



267 **270** **291**

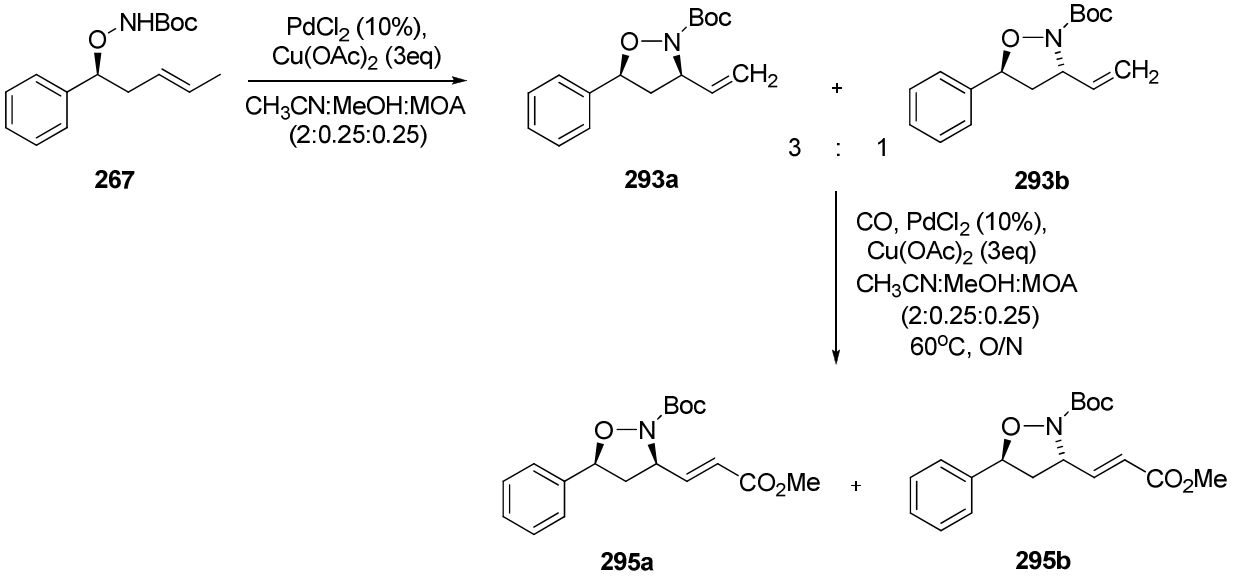
Scheme 112

Compound **291** has never been described in the literature. We assumed that products **270** and **291** are formed by two different manifolds (Scheme 113). In the first pathway, organopalladium species **292** can be trapped with CO to give the expected ester **270**. In the second route, acetonitrile is known as a good coordinating solvent which may trigger competing β-hydride elimination of the stabilised palladium species.[102] This would produce intermediate **293**. Next, addition of the palladium-acetonitrille complex across the double bond may result in the formation of the organopalladium species **294**, which would then undergo carbonylation followed by elimination of acetonitrile to produce **291** (Scheme 113).



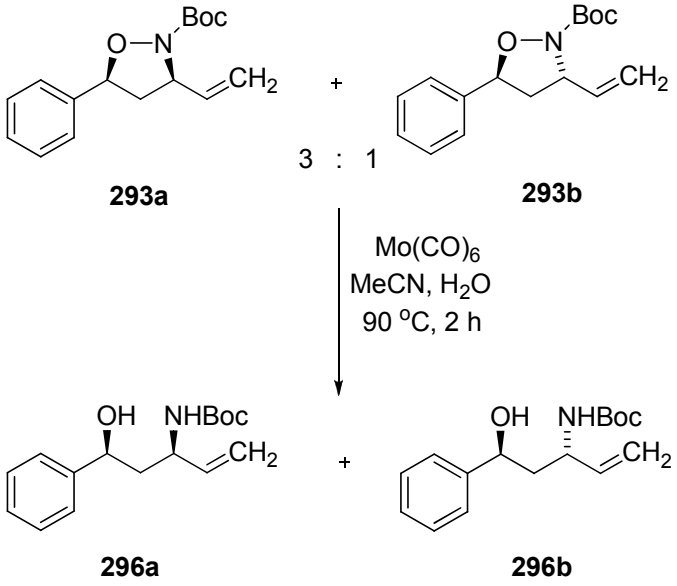
Scheme 113

In order to confirm this hypothesis, *N*-Boc protected alkoxyamine **267** was submitted to the standard conditions used in the Pd-catalysed carbonylation (as in Scheme 112), except this time under argon atmosphere, i.e., lacking CO. As expected, the reaction resulted in a clean conversion of **267** into an inseparable 3:1 mixture of *syn*/*anti* vinyl isoxazolidines **293a** and **293b** (Scheme 114). The mixture was then submitted to carbonylation under the carbon monoxide atmosphere to give a full conversion overnight into the corresponding α,β-unsaturated esters **295a** and **295b** in 75% isolated yield.



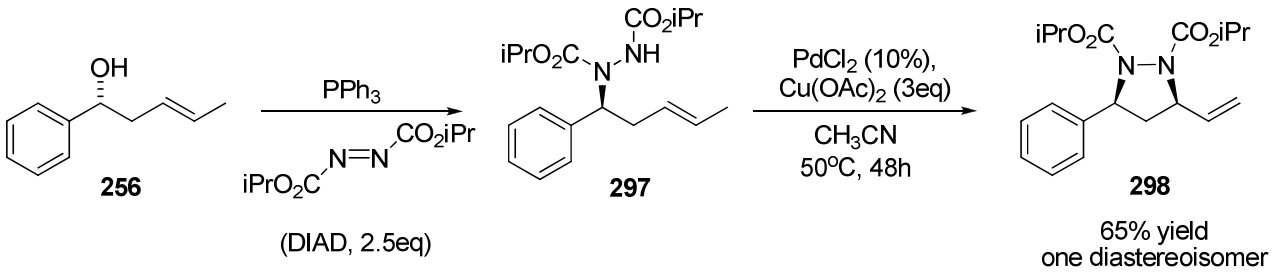
Scheme 114

Further experiments showed that the 3-3.5:1 ratio of diastereoisomers remained constant for a variety of solvent compositions and temperatures and was accompanied by full conversions and 80-90% isolated yields. The best diastereoselectivity was obtained in the presence of 2 eq of PPh_3 to give 11:1 *syn/anti* ratio but only in 25% isolated yield. A mixture of vinyl isoxazolidines was submitted to N-O bond cleavage by $Mo(CO)_6$ and the diastereoisomeric *N*-Boc protected amino alcohols **296a** and **296b** were isolated by chromatography in good yields (Scheme 115).



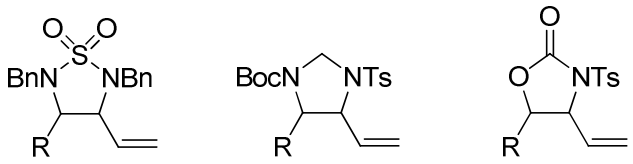
Scheme 115

In order to expand the scope of this reaction, the nitrogen analogue **297** was synthesized and cyclised to afford the enantiopure pyrazolidine vinyl derivative **298** as a single diastereoisomer (Scheme 116).



Scheme 116

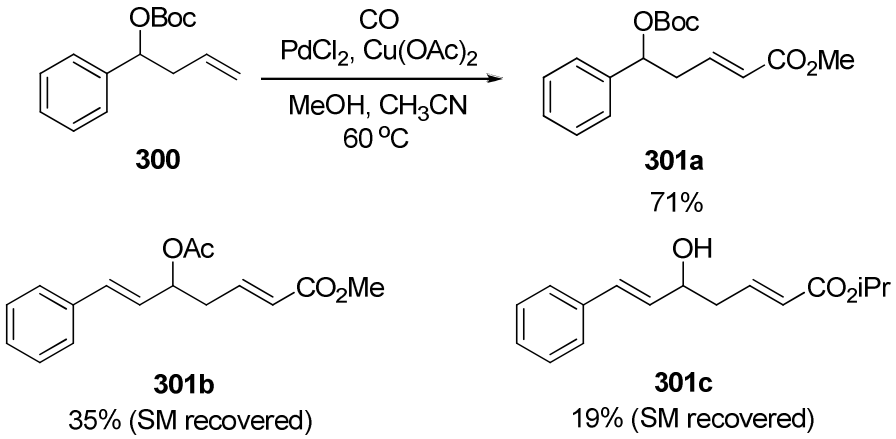
Formation of the multisubstituted izoxazolidines, pyrazolidines, and imidazolidines **299** has been intensively investigated by White, Stahl and others (Figure 11).[103] The methodology presented in this work provides a complementary contribution towards these highly sought after chiral heterocycles.



299a **299b** **299c**

Figure 11

Other interesting developments were observed when the alcohol derivative cannot form five- or six-membered rings. When terminal olefin is heated to 60 ^{o}C in the presence of Pd^{2+} in a mixture of acetonitrile and methanol under an atmosphere carbon monoxide, formation of α,β-unsaturated esters took place. The product was identical to the one that can be obtained by ruthenium-catalysed cross metathesis with methyl acrylate. This reaction was attempted with several other substrates (Scheme 117). Boc protected alcohol appeared to be the best but the reaction is poorly reproducible at this stage and will require more research and optimisation.

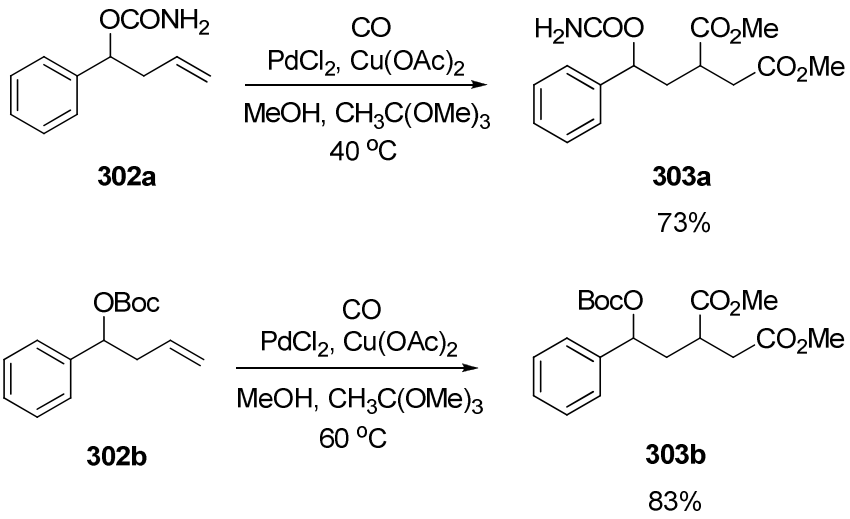


300 **301a** 71%

301b 35% (SM recovered) **301c** 19% (SM recovered)

Scheme 117

When substrates that are unable to cyclise were submitted to the reaction in methanol and methyl orthoacete, the double bond of the olefin was doubly carbonylated. This type of transformation was previously reported by Stille and Ishii, where the compounds were obtained as part of complex mixtures.[60c,104] In our case, the products were formed as nearly equimolar mixtures of *syn* and *anti* diastereoisomers with no other by-products present (Scheme 118).



Scheme 118

Palladium is well known for participating in a variety of complexes with phosphines, *N*-heterocyclic carbenes, amines, DMF, carbon monoxide, nitriles and isocynanates. Application of these ligands leads to dramatic changes in the catalyst activity and may switch the reaction pathways.[57] The initial results presented in Scheme 117 and 118 are encouraging and give warrant for further investigation.

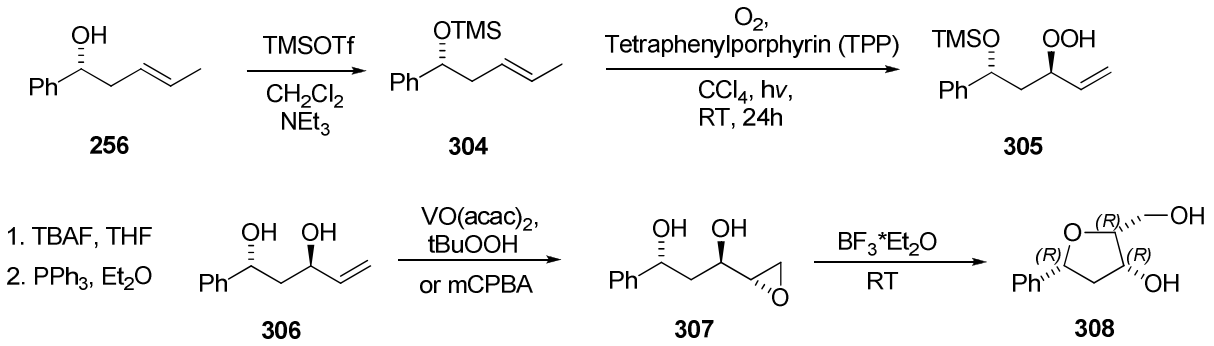
Conclusions

An efficient, chemo- and diastereo-selective methodology for the synthesis of chiral isoxazolidines and β-amino-δ-hydroxy esters was developed. Optimised reaction conditions were applied to the synthesis of a series of enantiopure compounds in consistently high isolated yields. In the course of the experiments, mechanistic probes shed light on the probable mechanism of diastereoselective aminocarbonylation. The scope of the reaction was expanded to hydrazines and substrates with internal double bonds. We developed a convenient method for the synthesis of vinyl substituted isoxazolidines and pyrazolidines. In addition, we have accomplished some preliminary work on the synthesis of α,β-unsaturated esters from terminal olefins and double carbonylation of the terminal double bond.

3. Oxidation of linear homoallylic alcohols with singlet oxygen as a versatile route to diastereo and enantiopure 2-deoxypentose derivatives.

3.1 Abstract

Reported herein is a conceptually new synthetic route to enantiopure 2-deoxypentose derivatives using readily available non chiral starting materials and gaseous oxygen in the key step. Enantiopure alcohol **256** was prepared by the rearrangement developed by us and described in previous chapters, followed by TMS protection. The silyl ether **304** was then submitted to oxidation to yield hydroperoxide **305** as the main product. Further deprotection and reduction provided access to diastereopure diol **306,** which was epoxidised in the next step. Treatment of **307** with a catalytic amount of a Lewis acid resulted in the epoxide opening to furnish 1-C substituted β-deoxyribose **308** (Scheme 119).



Scheme 119

The method developed by us has many advantages. The starting alcohol can be prepared in both enantiopure versions and the phenyl group can be replaced by most of the aliphatic and aromatic groups via an allyl transfer reaction.

3.2 Introduction (Literature Review)

3.2.1 Physical Properties of Singlet Oxygen

Singlet oxygen ($^1O_2$) is a higher energy state of molecular oxygen species. It is one of the most active intermediates involved in chemical and biochemical reactions.[115] Singlet oxygen is an attractive oxidant due to its high reactivity, simple apparatus and procedures and that it grants an easy access to a variety of oxygen-containing products, e.g., alcohols, epoxides, etc. Allylic photo-oxygenation represents a useful and operationally simple process. Introduction of the oxygen functionality into alkenes by an ene reaction (Schenck reaction) may serve as a very useful, multi-purpose synthetic method.[116] Increasing demand for stereoselective synthesis boosts its synthetic potential but the issues of stereo- and regio-selectivity of singlet oxygen reactions require more detailed investigation.

Oxygen is a triplet in its ground state, so it has two degenerated LUMOs containing one unpaired electron each. In this state oxygen exhibits diradical properties, however, is unreactive towards most organic compounds.[117] The reason is that the substrates are usually in a singlet form, which makes the reaction with triplet oxygen spin-forbidden. That is why the reactions with oxygen in its ground form are kinetically blocked, despite having great thermodynamic potential.[118] One way to make the oxygen react is to put it into an excited state. Oxygen has two major excited states and both are singlets. Table 12 shows the main physical properties of the singlet oxygen species.

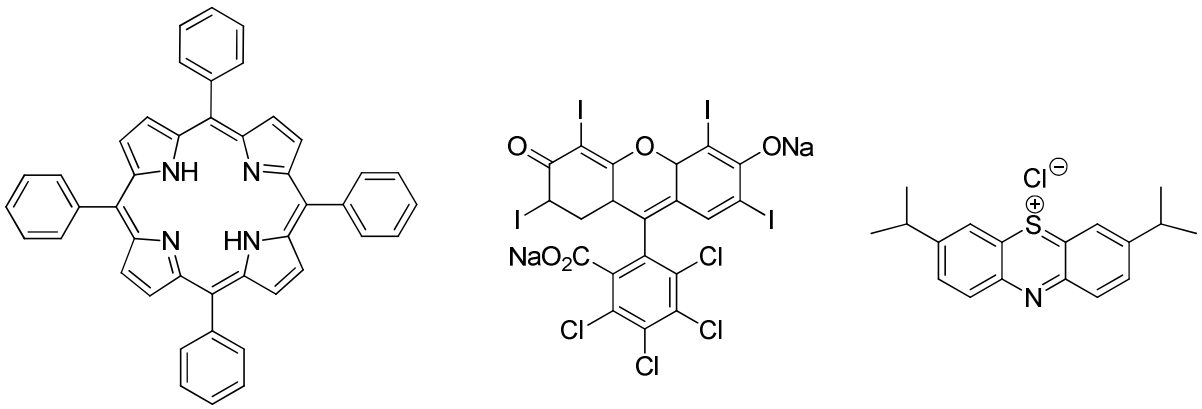
Table 12. Molecular oxygen excited states and lifetimes

States of the oxygen molecule	Occupancy of highest orbitals	Energy above ground state [kcal/mol]	Lifetime
Second excited state ($^1\Sigma g^+$)	↑ ↓	37	10^{-12} s
First excited state ($^1\Delta g$)	↑↓	22.4	10^{-4} s
Ground state ($^3\Sigma g^-$)	↑ ↑	-	stable

Briefly, the following processes are involved in the generation of singlet oxygen. [119]

Sen (S_0) + hν → Sen (S_1)
Sen (S_1) → Sen (T_1) (intersystem crossing)
Sen (T_1) + $^3O_2$ → $^1O_2$ + Sen (S_0)

First, the photosensitiser (Sen) is excited from the ground singlet state to the excited singlet state. Then it undergoes an intersystem crossing to a longer-lived excited triplet state. When the photosensitiser and an oxygen molecule are in proximity, an energy transfer can take place that allows the photosensitiser to relax to its ground singlet state and create an excited singlet state oxygen molecule. The structures of dyes most commonly used as sensitisers are shown in Figure 12.



309a
Tetraphenylporphyrin (TPP)

309b
Rose Bengal

309c
Methylene blue

Figure 12. Popular photosensitisers

Most of the known photosensitisers are deeply coloured because their main absorption bands lie within the visible area. Visible light sources are convenient to apply and the energy of the photons is higher than for IR bands, which makes visible light more effective. On the other hand, it delivers considerably less energy than UV radiation, thus avoiding free radical side reactions in chlorinated solvents. Absorption spectra of the two commonly used photosensitisers are shown in Figure 13.[131]

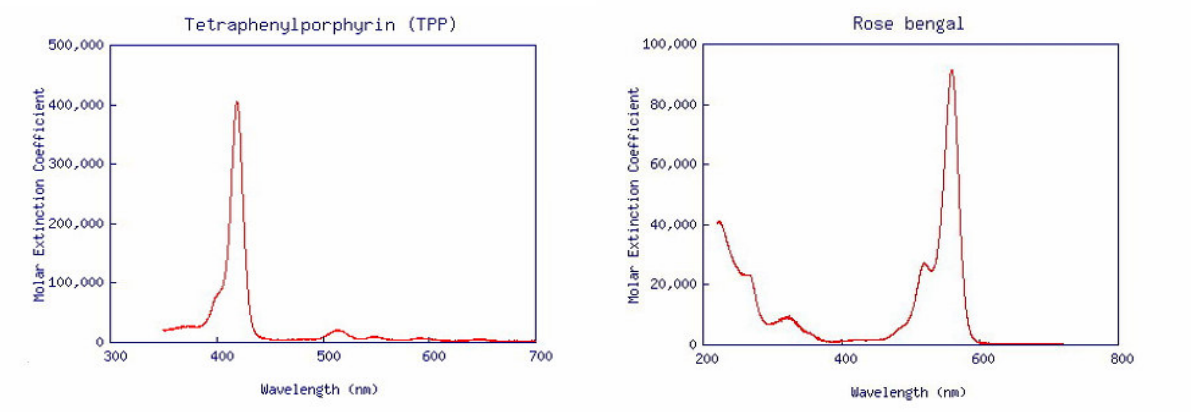


Figure 13. Absorption bands for popular photosensitisers

The key characteristic of a photosensitising agent is its *quantum yield* (Φ_Δ).[122] The singlet oxygen quantum yield defines the number of molecules of $^1O_2$ generated for each photon absorbed by the photosensitiser (Table 13). The higher the value of Φ_Δ the more efficient the energy transfer. This is why not all of the compounds which exhibit an absorption in the desired area can be used as sensitisers in the singlet oxygen generation.

Table 13. Quantum yields (Φ_Δ) and triplet state energies (E_T) of the most common sensitisers.[123]

Sensitiser	Bengal rose	Methylene blue	TPP	Fullerene
Φ_Δ	0.76	0.52	0.58	1.00
E_T (kJ/mol)	165	142	137	151

The singlet oxygen molecule is relatively stable in the gas phase (up to several minutes) because its quenching is a slow, spin-forbidden radiative deactivation. Singlet oxygen luminescence was established in the gas and condensed phases where it decays to triplet state.[124]

$^1O_2 \rightarrow {}^3O_2 + h\nu$ (1268 nm)

$2\ ^1O_2 \rightarrow 2\ ^3O_2 + h\nu$ (634 and 701 nm)

In the liquid phase, perturbations of the electronic structure of singlet oxygen caused by collisions with solvent molecules quench the $^1O_2$ species. Radiationless process acquires partially allowed character, leading to enhancement of the variety of transitions in which $^1O_2$ decays. The decay rate constant increases exponentially with rising the vibration energy of the deactivating bond stretching in the solvent molecules in the series: C-Cl > C-D > O-D > C-H > O-H. [125] Dramatic change of quenching rate constants for different types of bonds in relation to the two exited oxygen states is illustrated in Table 14.

Table 14. Singlet oxygen quenching in liquid phase

Type of bond	$^1\Delta g$ quenching $M^{-1}s^{-1}$	$^1\Sigma g^+$ quenching $M^{-1}s^{-1}$
O-H	2900	1.5×10^9
N-H	1530	4.7×10^8
$C\text{-}H_{aromatic}$	494	1.1×10^8
C-H	309	1.0×10^8
O-D	132	2.7×10^8
$C\text{-}D_{aromatic}$	21.7	5.3×10^7
C-D	10.4	3.3×10^7
C=S	0.35	1.6×10^6
$C\text{-}F_{aromatic}$	0.62	1.5×10^6
C-F	0.05	5.6×10^5
C-Cl	0.18	1.6×10^5

Table 15. Singlet oxygen quenching in gas phase

collider	$^1\Sigma g^+$ quenching $M^{-1}s^{-1}$
He	<0.6
Ne	~ 0.6
N_2	7.8
O_2	9.0
Ar	10.2
Kr	21.6
SF_6	26.4
SO_2	31.8
Xe	46.8
PCl_3	252

By contrast, the quenching rate constants in the gas phase are up to eight folds lower (Table 15).[126] As a consequence, this results in an enormous solvent dependence, including a large isotope and heavy atom effect, on the lifetime of the O_2 ($^1\Delta_g$) species. Variation in the lifetime for the typical solvents extends over five orders of magnitude, as illustrated in Table 16.[127]

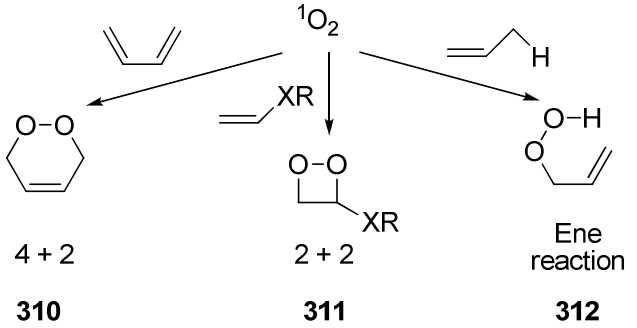
Table 16. Singlet oxygen lifetime in popular solvents

Solvent	Singlet oxygen lifetime (μs)	Solvent	Singlet oxygen lifetime
H_2O	3.1	Ethanol-D	230 μs
Ethanol	12	CD_3CN	600 μs
Benzene	28	Acetone-D	690 μs
Acetone	51	Benzene-D	700 μs
CH_3CN	56	$(C_2F_2)_2O$	1.1 ms
CH_2Cl_2	59	$CDCl_3$	3.6 ms
D_2O	71	C_6F_6	9.4 ms
CD_2Cl_2	120	CCl_4	31 ms
$CHCl_3$	166	perfluorodecalin	300 ms

3.2.2 Synthetic Applications of Singlet Oxygen – The Ene Reaction

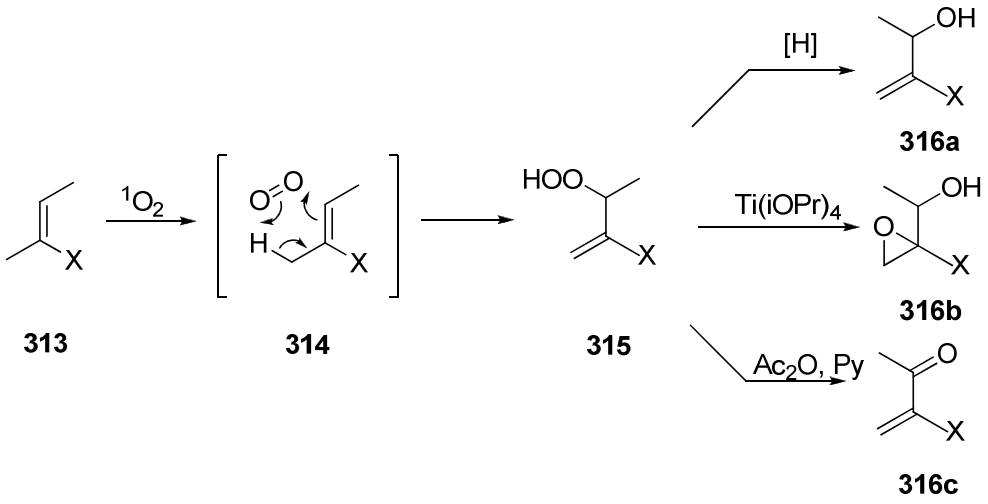
Most of the known reactions of singlet oxygen with alkenes can be divided into three main categories (Scheme 120).[128]

- Conjugated dienes form 4+2 cycloaddiction products **310**
- Electron-rich olefins prefer 2+2 cycloaddition **311**
- Other alkenes undergo an ene reaction to give allylic hydroperoxides **312**



Scheme 120

Due to the direct relevance to our research programme, the chapter is mainly focused on the singlet oxygen ene reaction. It was first reported by Schenck in 1943[129] and is generally called the Schenck reaction. In some sources it is also referred to as an indirect substitutive addition[115] Allylic hydroperoxides **312** resulting from the ene reaction serve as versatile intermediates for further transformations (Scheme 121).

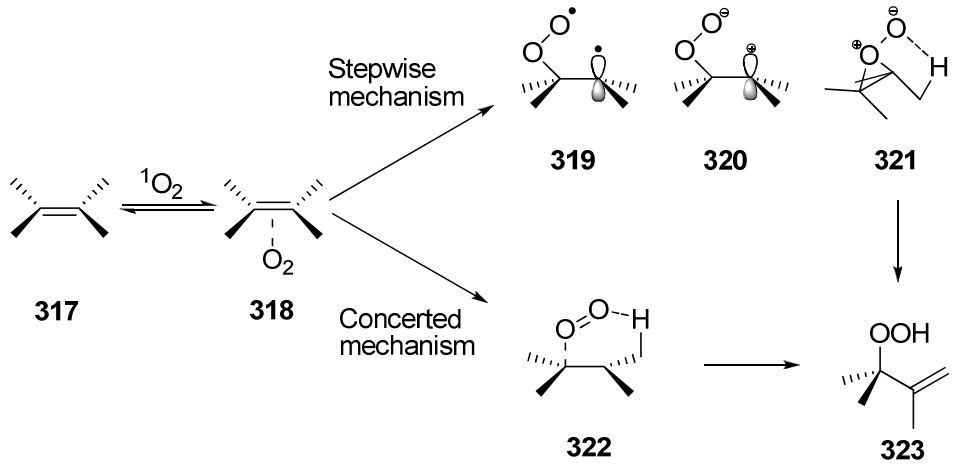


Scheme 121. Application of the ene reaction products

Alkene **313** reacts with singlet oxygen via the cyclic mechanism **314** and then forms allylic hydroperoxides **315** that can further undergo the following reactions:

- Reduction of allylic peroxides leading to allylic alcohols **316a**
- Ti(IV) catalysed epoxidation furnishing epoxy alcohols **316b**
- Dehydration leading to enones **316c**

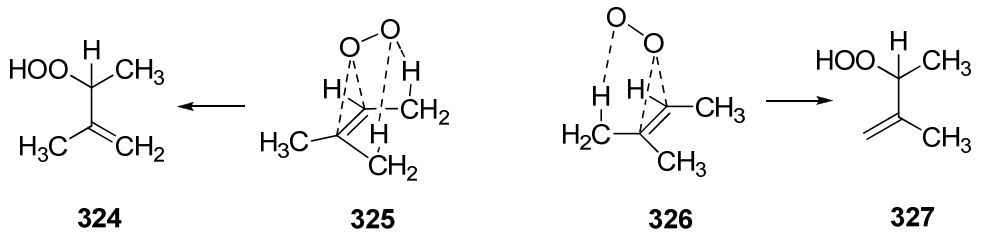
There are several hypotheses regarding the ene reaction mechanism involving different transition states and pathways of the transformation.[115] Two major theories consider either a concerted pathway via a six-membered pericyclic transition state **322**[130] or a stepwise mechanism via perepoxide-like **321**[131] or biradical **319**[132] intermediates. Kinetic data[133] clearly support the stepwise mechanism but the absence of the Markovnikov directing effect[134] contradicts the biradical or zwitterionic **320** intermediates (Scheme 122).



Scheme 122. Possible ene reaction mechanisms

Since singlet oxygen is a highly reactive oxidant that easily undergoes reactions with a wide range of substrates, selectivity control in these transformations is essential for practical synthesis applications. The major problem of the Schenck reaction is its poor regioselectivity. When a given substrate has several allylic protons available, abstraction usually takes place at all possible sites leading to complex mixtures of isomeric products. This problem has been studied intensively over the past years and several empirical rules have been proposed to predict the regioselectivity of the reactions for a variety of substrates.[115]

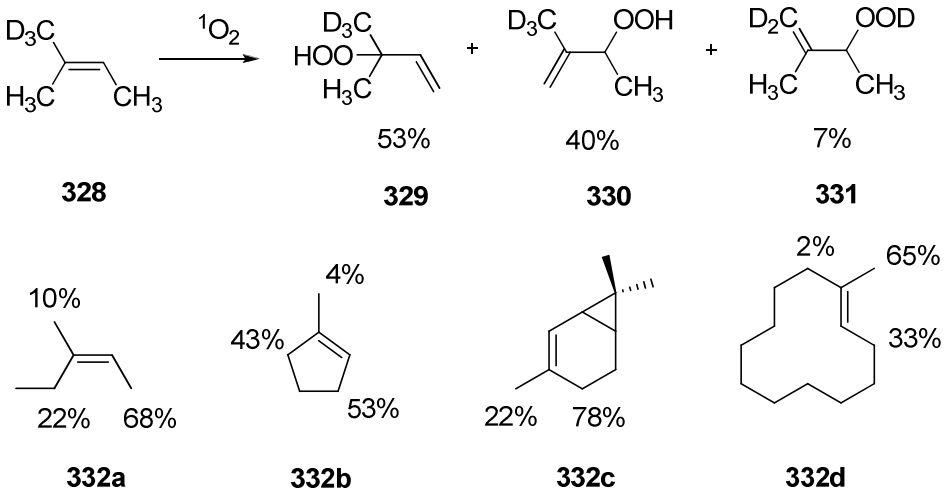
The preference for hydrogen abstraction from the *cis*-positioned groups in trisubstituted alkenes is usually called the "cis effect". It was interpreted as a consequence of the concerted rather than the stepwise diradical mechanism.[135] To understand the reasons for this behaviour, two possible transition structures for the attack of $^1O_2$ on the substituted alkene should be considered. Mechanistic investigation by Singleton and co-workers[136] suggested that the transition state leading to the reaction of one of the initially *cis*-methyl groups **325** is preferred over **326** for a number of reasons (Scheme 123). Attachment of the singlet oxygen to the olefinic carbons is synchronous with coordination to both methyl protons. The double bonds are perpendicular to each other and the transition state **325** is highly symmetric. By contrast, in the alternative TS structure **326** the oxygen interaction with the *trans*-methyl group is less favourable. The transition state **326** is an analogue to the later stage of *cis*-protons attack represented by structure **325.** Lack of symmetry in structure **326** makes it eventually higher in energy by 2.8 kcal/mol compared to **325**.



324 **325** **326** **327**

Scheme 123. "Cis effect" rationalisation

The simplest example of this "cis effect" is the reaction of deuterated alkene **328** (Scheme 124), where 93% of the products result from the proton abstraction from the initially *cis*-methyl groups (**329** and **330**), while formation of **331** is clearly disfavoured (Note, that the H/D isotope effect in the singlet oxygen ene reaction is negligible because the rate limiting step is the formation of the intermediate peroxyepoxide).[137] Scheme 124 also gives examples of how the structure of the substrate determines the site of hydrogen abstraction in more complex molecules.[138] The percentage value indicates the position where protos is abstracted from, while peroxy group is formed on the opposite side of the double bond.

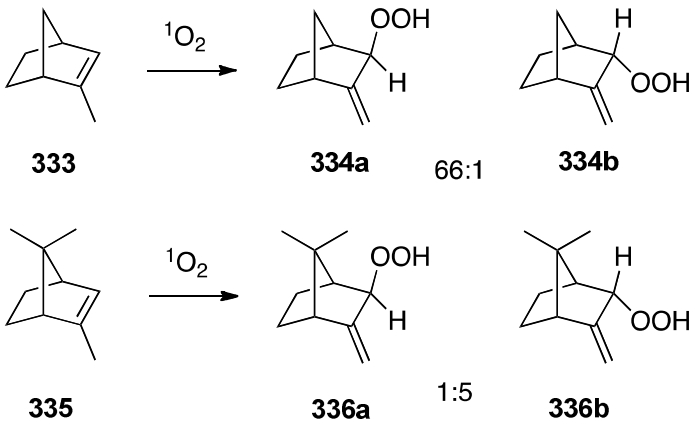


328 **329** **330** **331**

332a **332b** **332c** **332d**

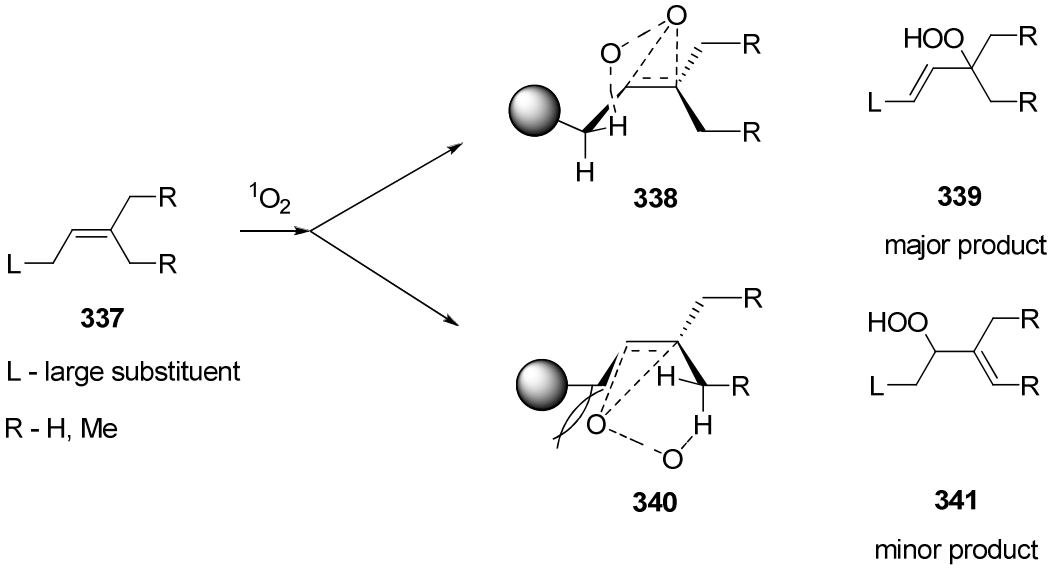
Scheme 124. Examples of the "cis effect".

Steric properties of the substrate are another important factor that affects the selectivity of the singlet oxygen ene reactions. Thus, Jefford and co-workers reported that the ratio of *exo/endo* hydroperoxides **334** and **336** formed by the photooxidation of 2-methylnorborn-2-ene **333** is reversed in the case of more bulky 7,7-dimethyl derivative **335** (Scheme 125).[139]



Scheme 125. Sterically controlled ene reaction

The regioselectivity in the photooxygenation of trisubstituted alkenes **337** with large geminal groups in favour of hydroperoxide **339** suggests that the allylic protons next to the bulky alkyl substituent are more reactive. The regioselectivity was explained by examining the possible transition states **338** and **340** (Scheme 126).[140] In the TS **340**, which leads to the minor product, the repulsive non-bonding interactions between the oxygen atom and the large group also remain in the final structure **341**. In the TS **338**, where the hydrogen is removed from the carbon next to the large group, the repulsive interactions are weaker and product **339** is formed preferentially.



Scheme 126. Large group effect - rationale

Several further examples of singlet oxygen ene reaction where regioselectivity is controlled by steric properties of the substituents are presented in Figure 14.[138]

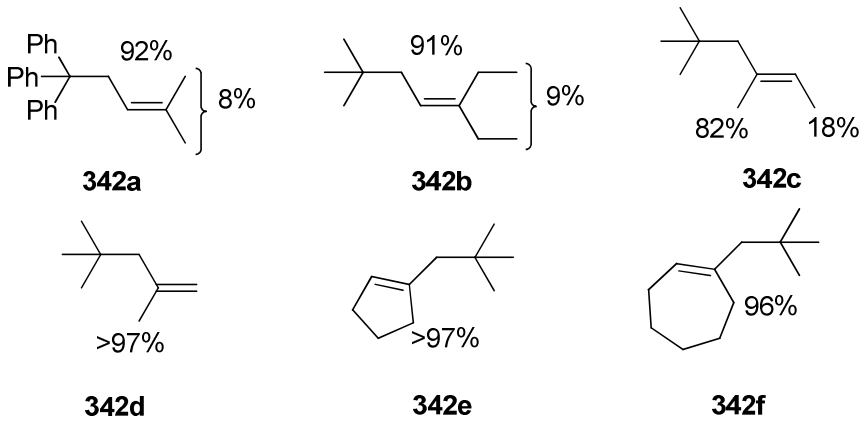


Figure 14. Large substituent effect – examples.

The regiochemistry of the ene reaction is also influenced by the electronic properties of substituents. Thus, electrophilic heteroatoms favour hydrogen abstraction from the same side of the double bond (Figure 15).

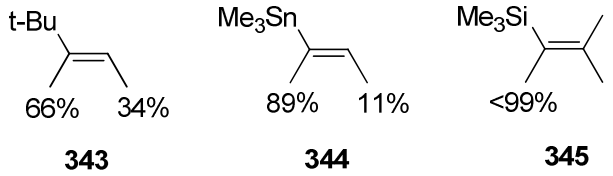


Figure 15. Directing effect of electrophilic heteroatoms.

The regioselectivity in photooxygenation of vinylsilanes **345** and vinylstannanes **344** can be explained by the interaction between the negatively charged oxygen of the peroxyepoxide and the heteroatom bearing a partial positive charge.[141] In the case of **344** and **345** the proton abstraction site is mainly influenced by the electronic factors (Figure 16), whereas the effect of the *tert*-butyl group in **343** is of steric origin (Scheme 126).

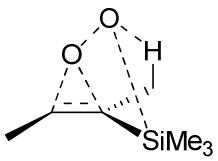
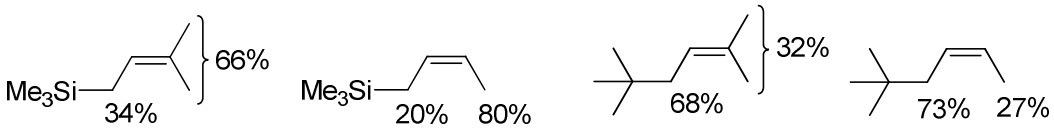


Figure 16. Directing effect of silicon.

For the *t*-Bu, Me_3Si-, and Me_3Sn- substituents, steric and stereoelectronic effects are working in opposite directions, as follows:

- Steric Effects: Me_3Sn- < Me_3Si- < *t*-Bu-
- Electronic Effects: Me_3Sn- > Me_3Si- >> *t*-Bu-

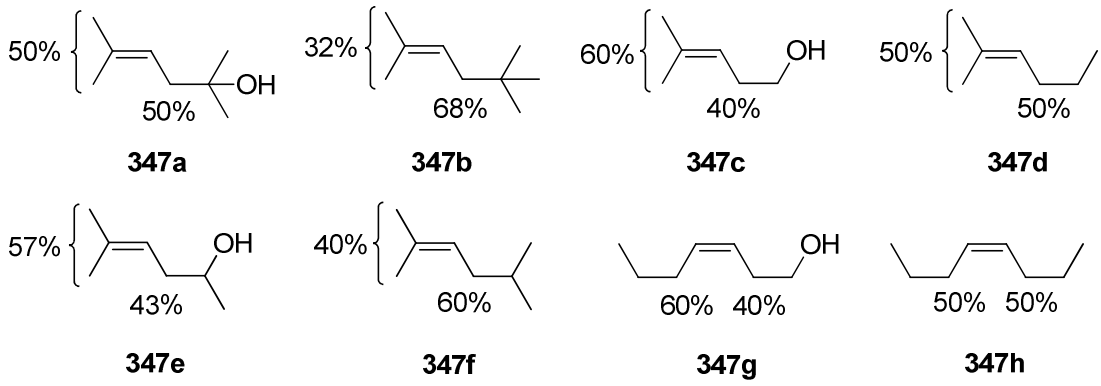
Further evidence of the electronic nature of the directing effect of the TMS group was obtained by reducing its steric influence by inserting an additional CH_2 group (Figure 17). Thus, replacing *t*-butyl with TMS group led to the predicted reversal of regioselectivity in the ene reaction.[116]



346a **346b** **346c** **346d**

Figure 17. Directing effect of *t*-Bu and TMS groups in the allylic position.

Stratakis and coworkers compared both the steric and electronic effects of the substituents in the homoallylic position.[138] Increased distance between the double bond and the directing group dramatically diminished regioselectivity. The electronic influence of the hydroxy group in the remote position is rather weak, though some differences in the regioselectivity still remain compared with the corresponding alkenes (Figure 18).

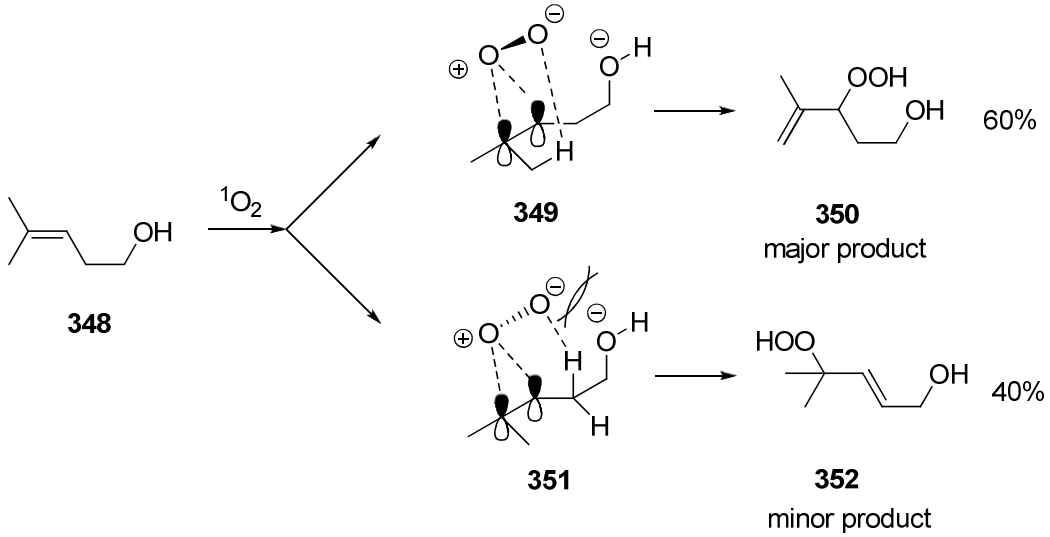


347a **347b** **347c** **347d**

347e **347f** **347g** **347h**

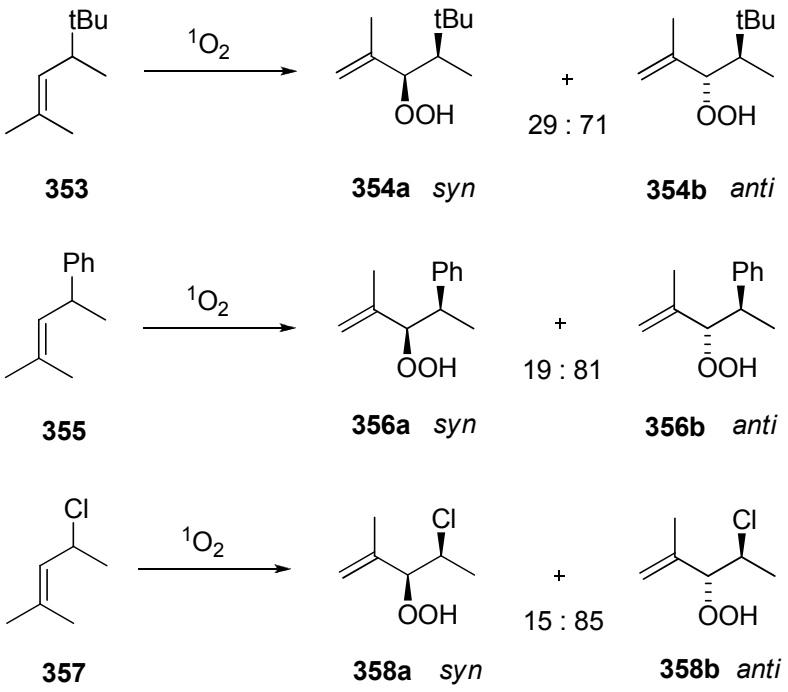
Figure 18. Directing effect in homoallylic position.

Thus, in the ene reaction of homoallylic alcohol **348** with singlet oxygen, the electronic repulsion between the hydroxyl group and the oxygen atom of the peroxyepoxide in the TS **351** disfavours the formation of product **352**.[138] On the other hand, such a repulsive interaction is not present in the transition structure **349** leading to the major product **350** (Scheme 127).



Scheme 127. Ene reaction regioselectivity controlled by O-O repulsion.

Diastereoselectivity is another important factor in the singlet oxygen ene reaction. In the allylic systems, the stereoelectronic effects of the substituent combined with the 1,3-allylic strain, e.g., in the case of a (*Z*)-methyl group, often gives rise to good *anti* diastereoselectivity.[142] The repulsive effect can be either of steric or electronic origin. Diastereoselectivity controlled by steric effects is illustrated in Scheme 128.



Scheme 128. Ene reaction controlled by steric factors.

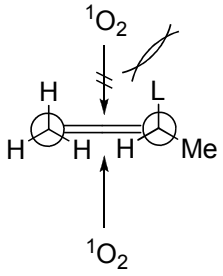
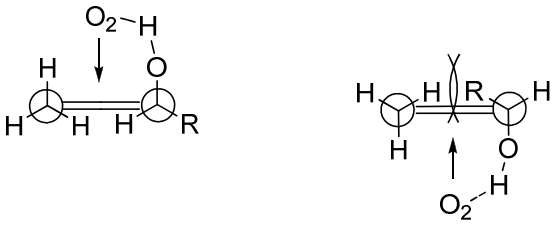


Figure 19. Steric interactions in the ene reaction.

This selectivity can be rationalized in the Newman projection (Figure 17). The steric bias in the most favourable conformer blocks the oxygen approach from the upper face, resulting in the formation of the *anti* product. Nevertheless, steric control alone leads to only moderate disatereoselectivity.

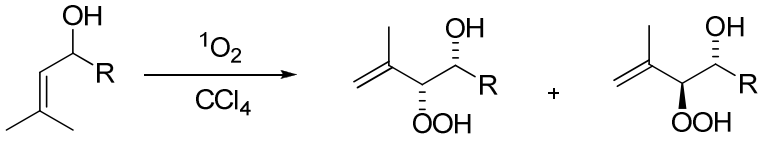
High diastereoselectivity was observed in the oxygenation of allylic alcohols. It was rationalised by the combined effect of hydrogen bonding and 1,3 allylic strain (Figure 20).[115] Here, the approach of the oxygen molecule is assisted by the OH group, while the steric strain determines the conformational preference.



359 **360**

Figure 20. Ene reaction controlled by hydrogen bond.

Adam and coworkers investigated the photo-oxygenation of a series of chiral (*Z*)-allylic alcohols and amines in order to shed more light on the origin of the observed high *syn* selectivity. Thorough examination of all the steering factors led to a series of conclusions**:** The size of the aliphatic substituent at the stereogenic centre does not affect the reaction diastereoselctivity (Scheme 129).[144]

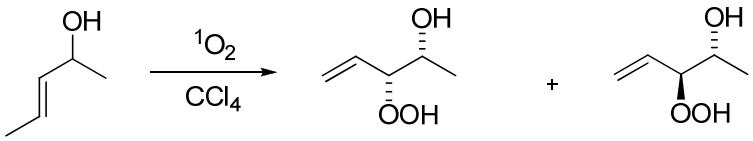


361 **362a** **362b**

R = Me: *syn / anti* = 93 : 7
R = tBu: *syn / anti* = 95 : 5

Scheme 129. *Syn*-selectivity of ene reaction of allylic alcohols

The presence of the 1,3-allylic strain is crucial for the selective oxidation of allylic alcohols. In the case of *E* double bond, as in substrate **363**, where the strain is absent, both disatereoisomers are generated in the nearly equimolar ratio (Scheme 130).[114b]

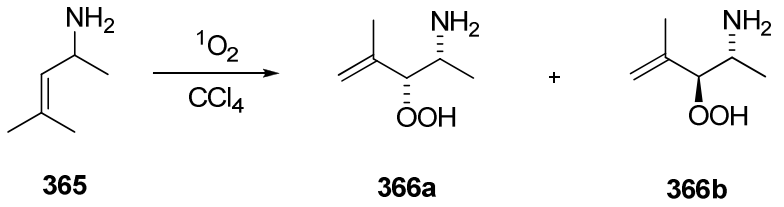


363 **364a** **364b**

syn / anti = 54 : 46

Scheme 130. Non-selective ene reaction of *E* allylic alcohols.

High *syn* preference applies also to other substituents capable of hydrogen-bonding with the approaching oxygen (Scheme 131).

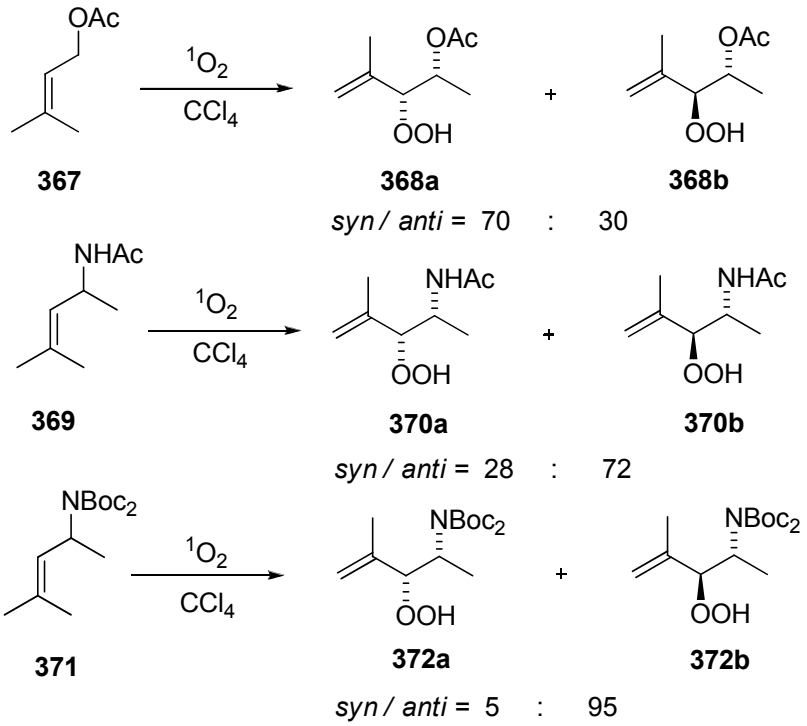


365 **366a** **366b**

syn / anti = 95 : 5

Scheme 131. Ene reaction controlled by hydrogen bonding.

Removing the possibility of forming H-bonds by acetylation of both alcohol **367** and amine **369** led to a dramatic loss of selectivity (Scheme 132). In the extreme case, when the amine was derivatised with two bulky groups **371**, the π-facial selectivity was reversed and the *anti* product **372b** was isolated almost exclusively. In the absence of electronic interactions the stereoselectivity is controlled by steric factors (Figure 19).



367 **368a** **368b**

syn / anti = 70 : 30

369 **370a** **370b**

syn / anti = 28 : 72

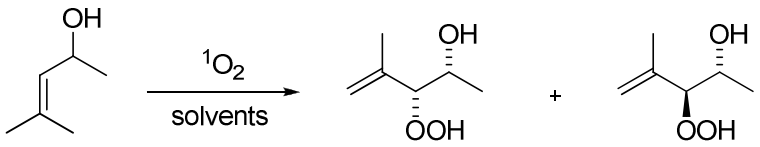
371 **372a** **372b**

syn / anti = 5 : 95

Scheme 132. Impact of derivatisation on selectivity of the ene reaction of allylic amines and alcohols.

Solvent effect is another factor to influence the facial preference. High *syn*-selectivity for the allylic alcohols **373** is only achieved in the nonpolar chlorinated solvents (Table 17, entries 1-3). However, in polar and protic solvents (entries 4 and 5), a significant loss of diastereoselectivity is observed. It is likely that the solvents capable of hydrogen bonding provide alternative stabilisation of the negatively charged oxygen atom in the intermediate peroxyepoxide, preventing the allylic hydroxyl group from the internal complexation.[144]

Table 17. Solvent effect.

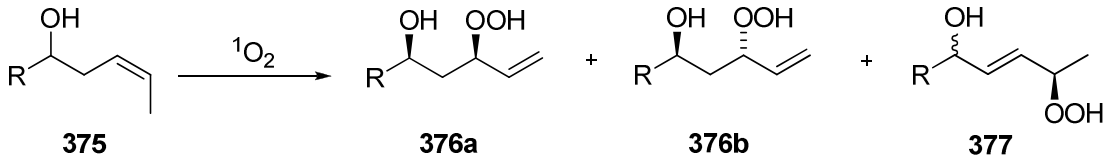


373 **374a** **374b**

Entry	Solvent	*Syn* 374a	*Anti* 374b
1	CCl_4	93	7
2	$CHCl_3$	92	8
3	CH_2Cl_2	90	10
4	CH_3CN	76	24
5	CH_3OH	73	27

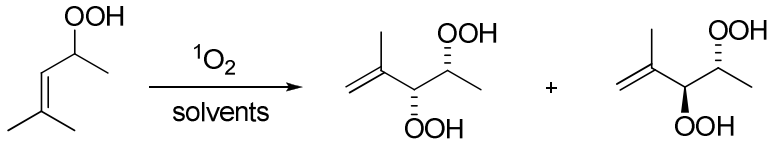
Taking into account the significant steering influence of the allylic hydroxyl group on the regio- and diastereo-selectivity of the ene reaction, the respective homoallylic analogues were also examined.[138] However, the placing the extra carbon between the hydroxy group and the double bond had a negative effect on selectivity. Homoallylic alcohols **375** exhibited regioselectivities similar to simple alkenes in non-polar solvents (Figure 18). Substituent R at the stereogenic centre had little effect on the product distribution (Table 18).[143,145] A similar drop of selectivity was observed for allylic hydroperoxides **378** (Scheme 133).[143]

Table 18. Ene reaction of α-homoallylic alcohol



375 **376a** **376b** **377**

R	Diastereoselectivity 376a : 376b	Regioselectivity 376 : 377
Me	56 : 44	56 : 44
Et	44 : 56	51 : 49
t-Bu	49 : 51	58 : 42
Ph	45 : 55	63 : 37

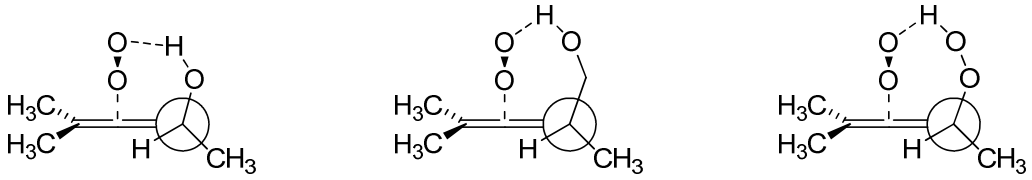


378 **379a** **379b**

in CCl_4 - *syn*/*anti* = 34:66
in acetone-d - *syn*/*anti* = 30:70

Scheme 133

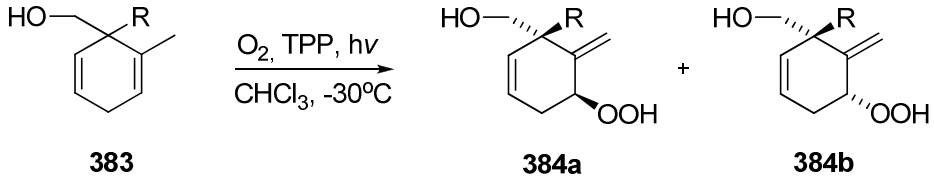
The observed low regio- and diastereo-selectivities for homoallylic substrates can be explained by the lack of the allylic strain and loss of the directing effect typical for the allylic alcohols. The remote homoallylic position of the OH in both the homoallylic alcohols and allylic hydroperoxides, provides no appreciable bias in the π-facial attack. The lack of stereocontrol can also be rationalised in terms of the reversible formation of perepoxide-like diastereoisomeric exciplexes **380-382** during the oxyfunctionalisation step (Figure 21).[143] In these intermediates, formation of the 6-membered structure with the incoming singlet oxygen is essential for the high diastereoselectivity that is observed in the allylic systems (**380**, Figure 21,), whereas in the exciplexes **381** and **382** coordination of the incoming oxygen proceeds via more flexible seven-membered transient species, thus reducing the steering control exercised by the OH group in hydroperoxides and homoallylic alcohols. This rationalisation is a direct analogy to the diastereoselectivity of the epoxidation process with use of both Sharpless and peroxyacids protocols (Scheme 148 and 149).



380 **381** **382**

Figure 21

The only known example of diastereoselective oxidation of homoallylic alcohols **383** with singlet oxygen was reported by Linker and Frohlich[146] (Scheme 134). Exclusive formation of the *anti*-product **384b** was possible in the case of sterically demanding substituents R. High selectivity was rationalised by the directing effect of the hydroxyl group supported by the repulsive steric interactions from the opposite face.



383 **384a** **384b**

R = Me - *syn*/*anti* = 39:61
R = Et - *syn*/*anti* = < 4:96
R = iPr - *syn*/*anti* = < *4:96*

Scheme 134

Conclusion

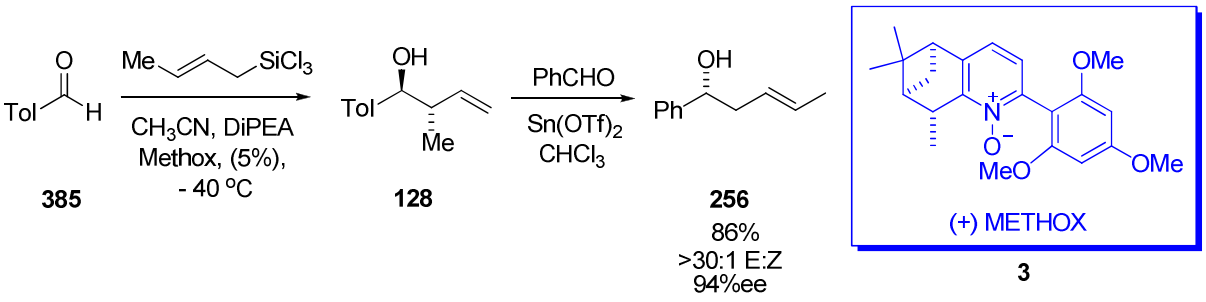
Singlet oxygen is regarded as powerful and versatile tool in organic synthesis. Numerous ways of controlling the selectivity of ene reaction of allylic systems were presented herein. Nevertheless its synthetic applications are severely limited when the directing group is in the more remote homoallylic position. Therefore development of a methodology for selective oxidation of homoallylic alcohols constitutes an interesting challenge.

3.3 Results and Discussion

The aim of this project was to develop an efficient method for generating singlet oxygen and investigate stereoselective oxygenation of homochiral allylic and homoallylic alcohols by the Schenk ene reaction. As a secondary objective, we intended to employ the enantiopure intermediates obtained by this method in the synthesis of important carbohydrate analogues.

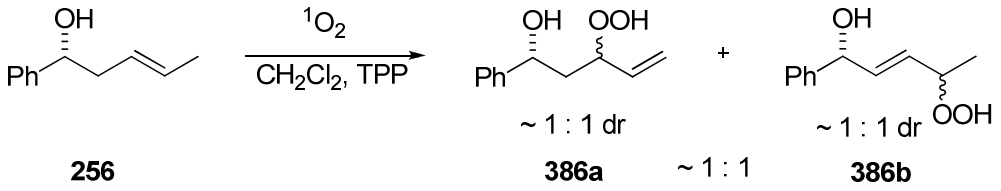
3.3.1 Optimisation of the Ene Reaction

According to the literature data,[143] alcohols in both free and protected form, may serve as an efficient steering group to control regio- and stereo-selectivity of the singlet oxygen ene reaction. Therefore, chiral homoallylic alcohols with an (*E*)-internal double bond **256** were selected as model substrates for our investigation. They can be easily obtained in good yields and high enantioselectivity via the allyl-transfer reaction[164] described in the previous chapters. This universal method provides access to a wide range of homoallylic alcohols with excellent enantiopurity (Scheme 135). Another advantage of this methodology is the possibility to synthesise both *R* and *S* alcohols selectively just by switching between Methox enantiomers.



Scheme 135

Alcohol **256** was subjected to an ene reaction with singlet oxygen. The experiment was conducted in dichloromethane with a 150W medium pressure mercury UV lamp as a light source and tetraphenylporphyrine (TPP) as photosensitiser.[42] Irradiation for 36 h at room temperature afforded an inseparable mixture of all four possible peroxyalcohols **386a** and **386b** in equimolar quantities (Scheme 136). This outcome mirrored the results reported by Adam[165] for the analogous oxygenation of the isomeric (*Z*)-homoallylic alcohols.



Scheme 136

In addition, we observed that UV irradiation was triggering numerous side reactions, resulting in the formation of unidentified by-products. It also led to an increased acidification of the reaction mixture over the time. The latter effect was manifested in the change of colour from purple to bright green, which could be rationalised by photodegradation of the chlorinated solvent under UV light to generate HCl.[166] The green colour was assigned to the protonated form of the photosensitser, which appears to be inactive in this state.

Therefore, to minimize decomposition, we switched to the generation of singlet oxygen under milder visible light irradiation.[120] Importantly, the visible light sources are also safer and more convenient from the operational point of view. A sodium lamp, with the main band in the yellow light area (570-590 nm), was successfully used by Adam[144b] in various photooxidation reactions. Taking into account that TPP has its main absorption band in the blue and violet light area of the spectrum with wavelengths around 400-450 nm (Figure 11), a white light source should serve as a reasonable alternative to UV irradiation, delivering sufficient energy in the desired bandwidth. Indeed, irradiation of pinene, which was selected as a benchmark substrate, with a white light source under standard reaction conditions led to a quantitavive formation of pinocarvone (Scheme 34). Several different light sources were investigated and the results can be summarised as follows:

- A sodium 400W lamp, a powerful light source, proved very efficient, however, it generated the amount of heat that was difficult to cope with. For this reason, it was not suitable for singlet oxygen reaction at sub-zero temperatures. However, it offered considerable advantages for large-scale preparations at ambient or elevated temperatures.
- A high intensity discharge (HID) lamp benefits from very high luminous efficiency at low wattage. Low heat output makes it a perfect choice for low temperature

experiments. Reactions can be conducted at −20 °C, albeit at the expense of the reaction rate. Selectivity of the reaction shown in Scheme 137 remained poor even at −20 °C.

- A portable 500W halogen lamp is a reliable, easy to use source of white light. It is characterised by a broad range of wavelengths emitted at high power output. This type of lamp is designed for continuous work avoiding overheating problems during long time irradiation without external cooling systems.
- A panel of light-emitting diodes (LED), a light source presented by our collaborators from the University of Bath, exhibited superior performance in terms of reaction time, power efficiency and scaling up possibilities. At later stages, it was incorporated into the design of a flow reactor for generation of singlet oxygen.

In further optimisation of the reaction conditions, the solvent was changed from dichloromethane to carbon tetrachloride. According to Table 16, in CCl_4 the lifetime of singlet oxygen increased almost 500 times. Also, higher boiling point of CCl_4 reduced solvent losses from the reaction vessel by evaporation, whereas its non-polar character does not disrupt any polar interactions that may develop between the reacting species (Table 16).

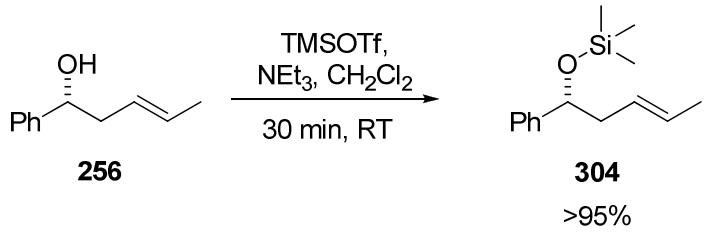
The results shown in Scheme 136 indicate that the hydroxyl in the homoallylic position has little effect on product distribution. Therefore, we next considered derivatisation of the hydroxyl group to order to tune its directing effect. The choice of protecting group had to take into account the following factors:

- Selectivity: The protecting group should favour a selective formation of 1,3 peroxyalcohol isomer with preference for one diastereoisomer.
- Separability: The resulting mixture of peroxyalcohol derivatives should be separable by standard laboratory techniques, e.g. flash chromatography.
- Stability: The protecting group should be stable to oxidation under the reaction conditions and be a poor leaving group.
- Solubility: As the reaction takes place in nonpolar solvents, ionic groups are excluded.
- Easy protection/deprotection: The group must be easy to install and to remove, avoiding the use of any harsh conditions (temperature, acids) due to the presence of the benzylic stereogenic centre prone to racemisation.
- Detectability: The group has to have a minimum footprint in ^{1}H NMR spectroscopy to allow monitoring of the reaction and determining product ratios in crude product.

Taking into account a proven steering effect of the trimethylsilyl group (Figure 15, 16, 17, Scheme 127), we decided to investigate silyl ethers as possible protecting groups to improve the selectivity of the ene reaction. In the published examples, the ability of the silicon atom to direct singlet oxygen in the ene reaction is either of electronic origin[163] or an interplay of steric and stereoelectronic factors.[141b]

3.3.2 Oxygenation of TMS protected homoallylic alcohol

We envisioned that the chiral silyl ether groups may enhance the regio- or diastereo-selectivity of the singlet oxygen reaction. Bulky protecting groups were expected to work in two different ways. Firstly, it may serve as a bulky substituent and, secondly, may interact via the electropositive silicon atom. Trimethylsilyl ether of the homoallylic alcohol **304** was obtained quantitatively by treatment of alcohol **256** with trimethylsilyl trifluoromethanesulfonate (Scheme 137).[167] TMSCl can be also used but reaction is much slower and gives lower yields.

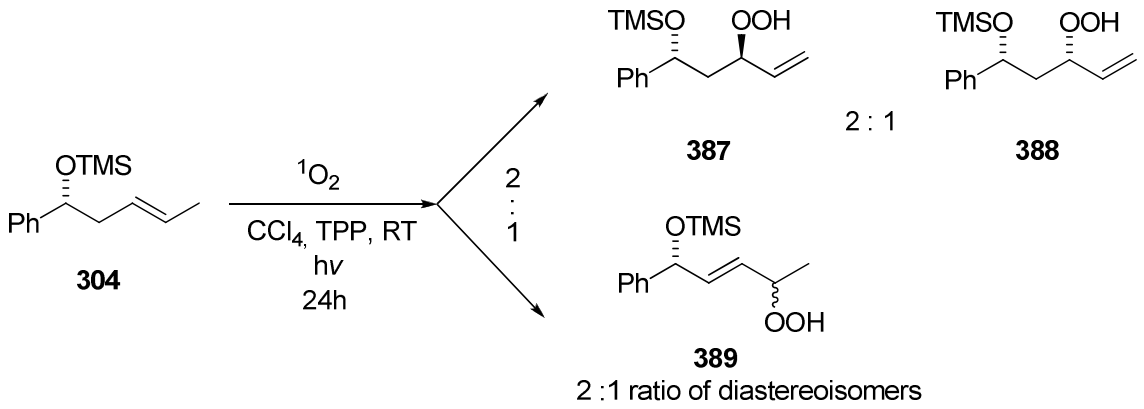


256 **304** >95%

Scheme 137. TMS protection of alcohol.

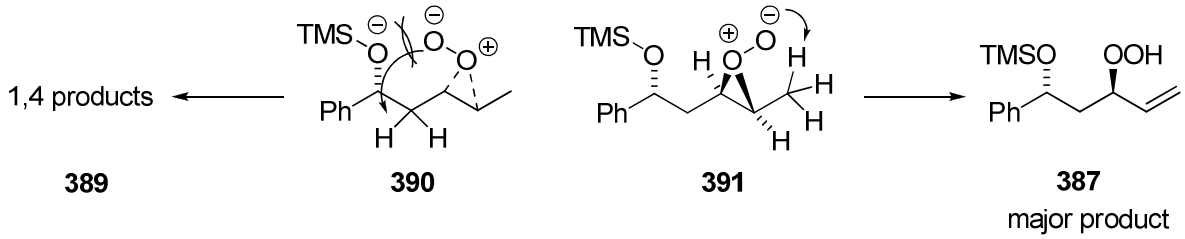
An aliquot of TMS derivative **304** was deprotected with TBAF/THF and the resulting alcohol was analysed by chiral HPLC to confirm that no deterioration of enantiopurity was taking place.

TMS derivative **304** was photooxidised at room temperature using a portable 500W halogen lamp (Scheme 138). A clean conversion was observed after 20-24h and the products were isolated in 85% overall yield. Analysis of the product mixture by ^{1}H NMR spectroscopy revealed that regio and diastereoselectivity of the reaction improved substantially compared to the oxidation of the unprotected alcohol (Scheme 136). The product was identified as a mixture of 1,3- and 1,4-isomers, two diastereoisomers each, with a clear preference toward the *anti* product with the terminal double bond **387** (Scheme 138). The relative configuration of the 1,3-regioisomers was later determined by the X-ray crystallographic analysis of their respective derivatives (*vide infra*).



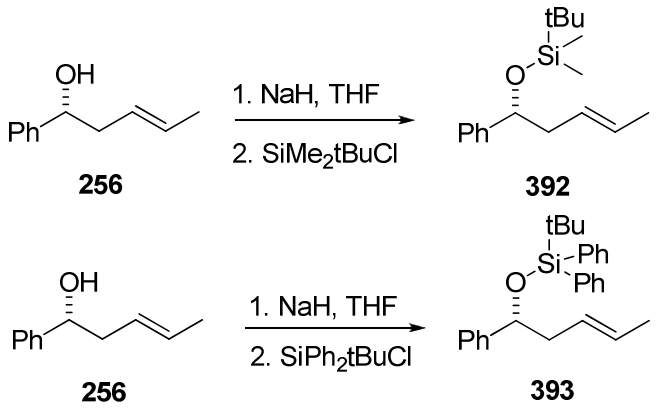
Scheme 138. Oxygenation of TMS protected homoallylic alcohol.

With the TMS protection in place, 1,3-diastereoisomers **387** and **388** were readily separable by flash chromatography on silica, whereas the pair of 1,4-diastereoisomers were eluted as an inseparable mixture of **389**. The selectivity towards 1,3-regioisomers can be rationalised as follows (Scheme 139). A high degree of polarisation of the Si-O bond in the TMS protected alcohol places a large partial negative charge on the oxygen atom. As a result, repulsive interactions with the oxygen atom of peroxyepoxide **390** disfavour hydrogen abstraction from position 2 leading to a minor isomer. The same repulsion may also favour the approach of the singlet oxygen molecule from the opposite π face leading to preference for the *anti* diastereoisomer **387**. See also Schemes 126 and 127.



Scheme 139. Mechanistic rationalisation of 1,3 –anti product preference.

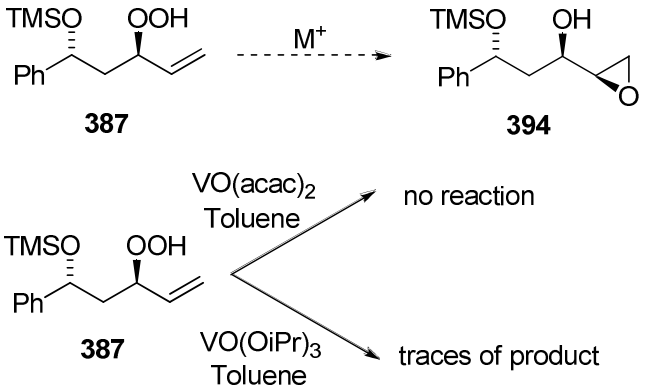
In order to assess the influence of the steric factor on the product ratio, we synthesised a series of silyl ethers with bulkier substituents **392** (dimethyltertbutylsilane) and **393** (diphenyltertbutylsilane) (Scheme 140).



Scheme 140. Synthesis of sterically more demanding silyl ethers.

However, the use of the more bulky substituents had little effect on the selectivity but led to substantial reduction in the rate of photooxygenation. These results may serve as evidence that it is the electronic rather than steric factors that play the major role in regio- and stereoselectivity. In addition, synthesis of the two bulky silyl ethers also proved more difficult giving slow conversion and low yields

In our initial experiments we aimed at exploring the atom-economic approach utilising the existing peroxyalcohol as a source of oxygen to form epoxyalcohol **394** diastereoselectively (Scheme 141). Intramolecular epoxidation of this type, mediated by complexes of Ti and V, was reported by Adam,[178] who also observed high diastereoselectivity in the oxygen transfer.

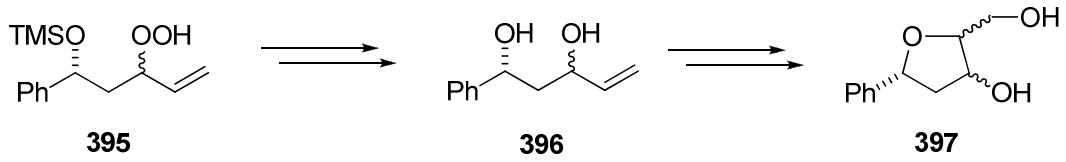


Scheme 141. Attempted intramolecular metal catalysed epoxidation.

In our case, no reaction took place when $VO(acac)_2$ was employed as a catalyst, whereas the use of $VO(O\textit{i}Pr)_3$ gave a complex mixture with only traces of the desired product (Scheme 141).

3.3.3 Synthesis and epoxidation of allylic diols

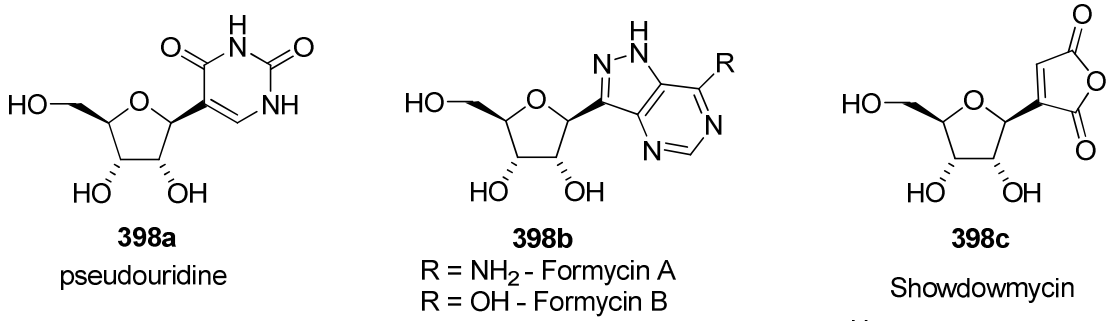
As a potential synthetic application of the 1,3-allylic diols **396**, we focused on the development of a synthetic approach towards a series of enantiomerically pure sugar derivatives **397** (Scheme 142).



395 **396** **397**

Scheme 142.

Asymmetric synthesis of unnatural *C*-nucleosides represents an interesting and timely challenge. There has been considerable interest in various analogues of *C*-nucleosides, because most of them show a broad spectrum of biological activity.[105] Some of the naturally occurring *C*-nucleosides were recognized as antibiotic, antiviral and antitumor agents (Figure 22).[106]



398a pseudouridine

398b R = NH_2 - Formycin A; R = OH - Formycin B

398c Showdowmycin

398d Pyrazomycin

398e Oxazinomycin

Figure 22

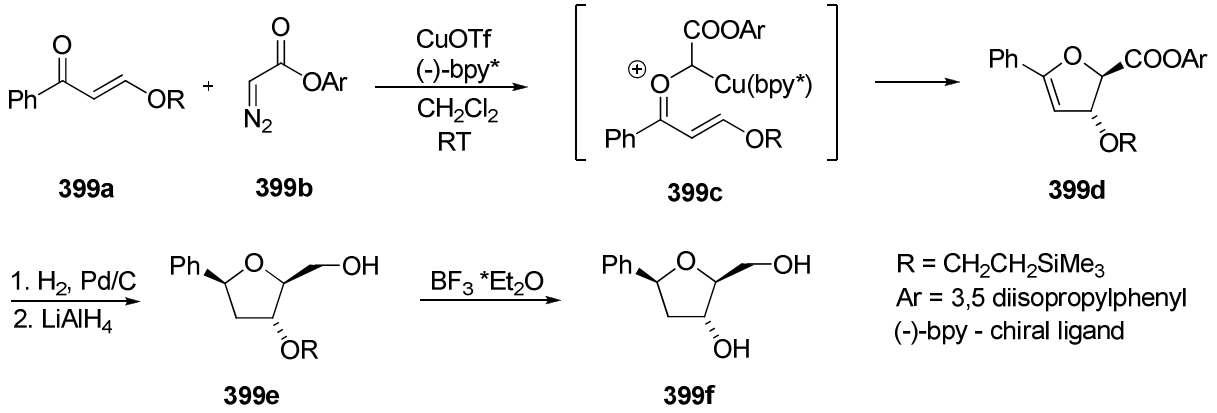
These compounds mimic the action of regular nucleosides; however, the replacement of a C-N with a C-C linkage in *C*-nucleosides provides these compounds with impressive therapeutic lifetimes. *C*-Nucleosides appear to resemble their respective counterparts uridine or adenosine, which explains their activity. The C-C linkage, on the other hand, provides resistance towards the enzymatic degradation and therefore the half-life of these compounds is far greater than that of *N*-nucleosides.[107]

A large array of synthetic strategies toward *C*-nucleosides has been developed to date, and the compounds were used in a wide range of applications. In a recent review, Kočovský[108] summarised all synthetic approaches with their pros and cons, including an assessment of their applications and future prospects. According to this survey, the synthetic strategies fall in one of the five categories:

(a) Connection of an appropriate functional group to the anomeric position of a preformed carbohydrate moiety, followed by construction of the aglycon unit;
(b) connection of an appropriate functional group to a preformed aglycon, followed by construction of the carbohydrate moiety;
(c) a direct coupling of a preformed carbohydrate moiety with an aglycon;
(d) modification of an existing *C*-nucleoside; and
(e) modular approaches.

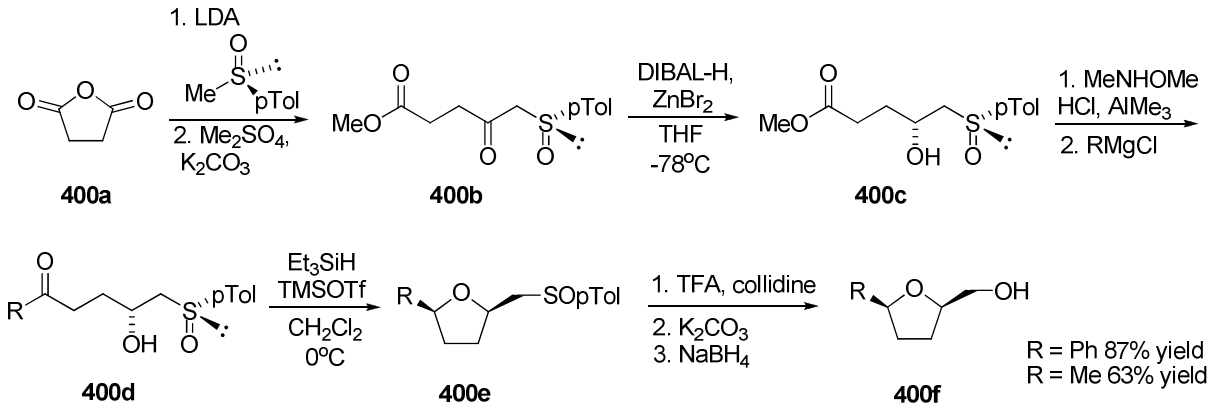
Synthesis of a carbohydrate moiety on the predefined aglycon, which is at the heart of our strategy (Scheme 143), clearly falls into the category (b) approach. These strategies are not very common, as they require construction of up to four contiguous stereogenic centres. Therefore, most of the known protocols describe synthesis of the racemic material or include a step where a chiral moiety is incorporated into the molecule.[174]

An interesting carbene cycloaddition approach was developed recently by Fu and coworkers.[112] Asymmetric copper-catalysed cycloaddition of diazoester **399b** to enone **399a** leads to the dihydrofuran derivative **399d** (Scheme 143). Reduction of the compound **399d** affords sugar **399f** in 90% de



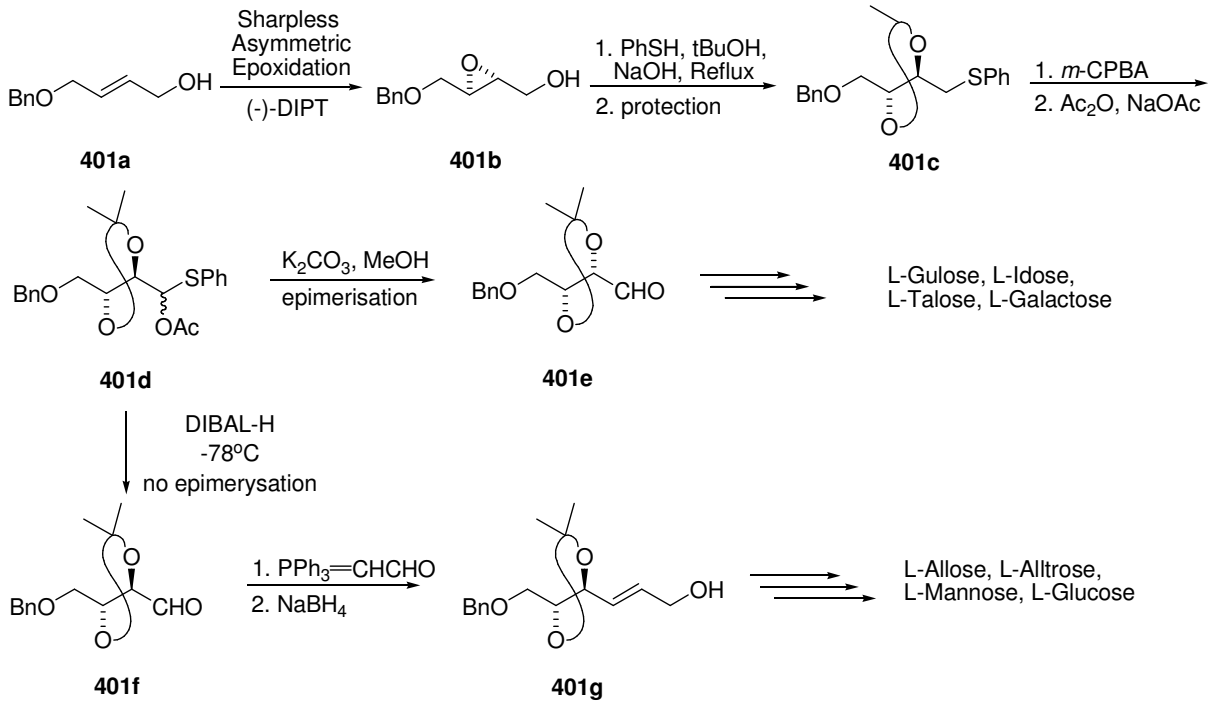
Scheme 143

Stereoselective synthesis of tetrahydrofurans (and tetrahydropyrans) that can be regarded as a blueprint for the synthesis of dideoxy ribose derivative was developed by Carren (Scheme 144).[175] In this approach, succinic anhydride **400a** was first opened with enantiopure (*R*)-methyl-*p*-tolylsulfoxide, followed by esterification of the resulting acid. A highly diastereoselective reduction of **400b** gave the hydroxysulfinyl ester in 98% de. Ester **400c** was then transformed into ketone **400d** via Weinreb amide, followed by reductive cyclization to afford the β-*C*-nucleoside structure **400f**.



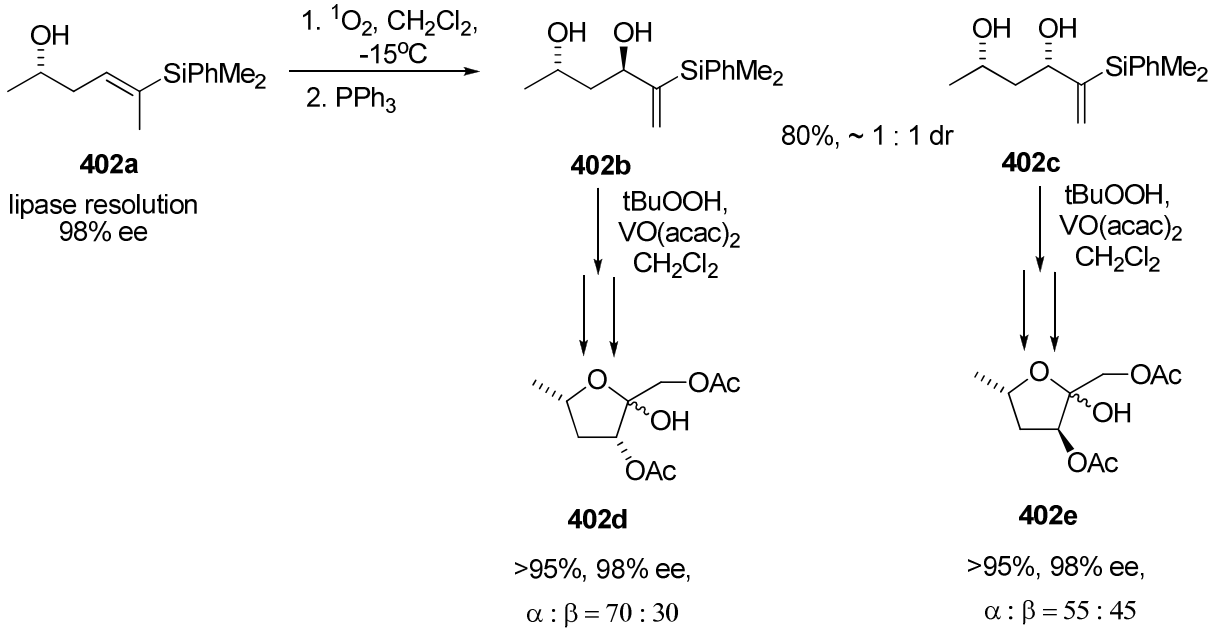
Scheme 144

Sharpless asymmetric epoxidation was successfully used in the synthesis of a series of unnatural L-hexoses.[161] Sharples, Matsamune and coworkers used a reagent-controlled strategy employing four key reactions to obtain monosaccharides in eight possible configurations. The use of the opposite tartrate enantiomers and the presence of diverging intermediates provides a perfect control over all the stereogenic centres (Scheme 145).



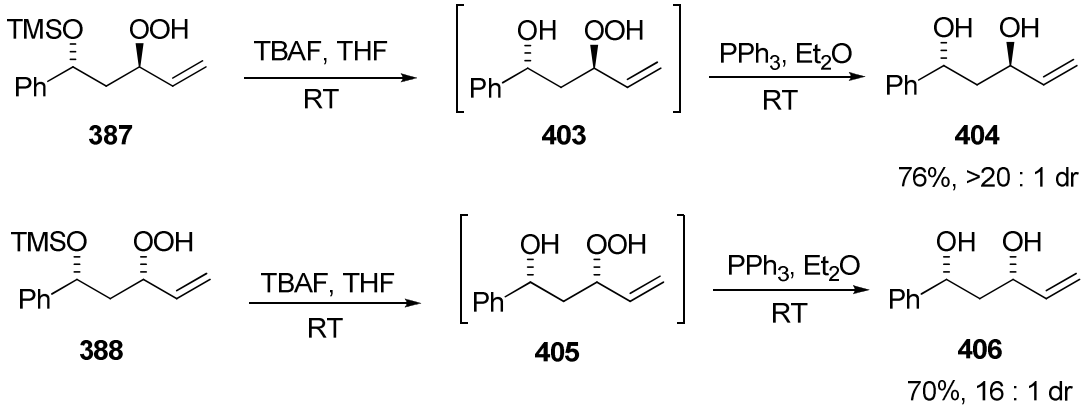
Scheme 145

A synthetic approach to carbohydrates using singlet oxygen chemistry was reported by Adam and co-workers: the ene reaction followed by epoxidation and opening of the epoxides furnished diastereoisomeric furans **402d** and **402e** (Scheme 146).[164] The enantiopure starting homoallylic alcohol **402a** was obtained by a lipase catalysed resolution of the racemates. Singlet oxygen reaction gave an equimolar mixture of diastereoisomers **402b** and **402c**, which were separated by chromatography at the diol stage.



Scheme 146

In our strategy, removal of the TMS ether group in hydroperoxides **387** and **388** was followed by reduction of the peroxide moiety. Standard TBAF/THF deprotection of the silyl ether produced a mixture of peroxyalcohol **403** and reduced diol **404**.[168] The crude mixture was than treated with a triphenylphosphine (Scheme 147).[165] Both reactions can be monitored by TLC and were found to proceed cleanly, without any by-product formation.

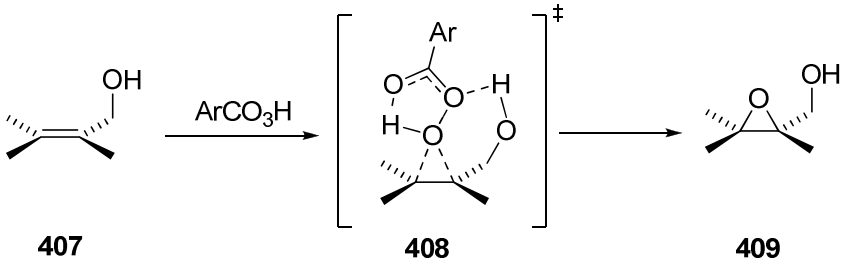


Scheme 147

Diols **404** and **406** were isolated in 76% and 70% yields over 2 steps as >20:1 and 16:1 dr, respectively. Discarding the mixed fractions after chromatography allowed us to substantially increase dr, compared with the starting compounds, with little loss of the product. ^{1}H NMR data of these diols were in good agreement with the literature.[165]

Asymmetric epoxidation is a very useful methodology for introducing new stereogenic centres in the synthesis of chiral compounds. In our case, diols **404** and **406** already have a set of stereogenic centres. Therefore, we focused on a diastereoselective epoxidation employing non-chiral reagents. For the allylic alcohols, the most widely used reagents are *m*-CPBA and complexes of transition metals (Ti, V) with an external oxidant. High diastereoselectivity in the epoxidation of allylic alcohols has been shown to be due to participation of the hydroxyl group in shaping up the transition structures, which ensure the epoxide is delivered from a single π face.[189]

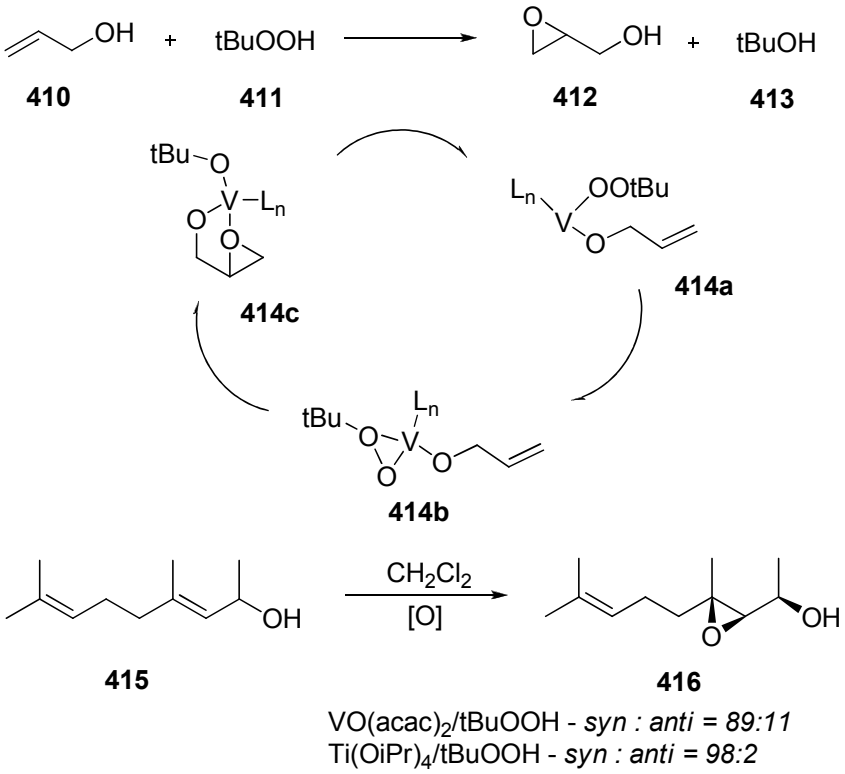
For the organic peroxyacids, the selectivity is rationalised by a transition structure largely based on the "butterfly" mechanism proposed by Bartlett.[151] The transition state involves the interaction of the electron-rich alkene **407** with an electrophilic peroxyacid. Formation of the hydrogen bond between the alcohol and the oxygen of the incoming oxidising reagent was proposed as the stereocontrolling factor. Peroxyacid is directed by the hydroxyl group and the six-memebered ring structure **408** provides its delivery to the *syn* face of the alkene (Scheme 148).



407 **408** **409**

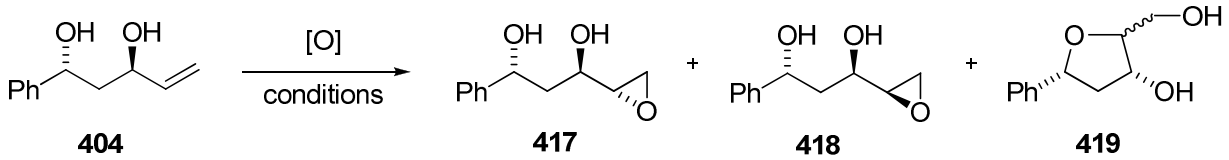
Scheme 148

Numerous transition metals complexes were used as catalysts for epoxidations of a variety of alkenes by organic hydroperoxides. Very good results were also obtained with allylic alcohols.[156] Transition metal catalysis exhibited exceptional reactivity combined with high regio- and diastereo-selectivity. It has been rationalised by coordination of the metal cation by both allylic alcohol and peroxide in the transition state. High reactivity towards an allylic moiety was demonstrated by Adam and Wirth in the epoxidation of 1-methylgeraniol.[157] The metal catalysed epoxidation gave exclusively the 3,4-epoxide while *m*-CPBA resulted in almost equimolar mixture of the products from the reactions occurring at the both double bonds (Scheme 149).



Scheme 149

In our project, both diols were epoxidised using the V(IV)/TBHP system and with *m*-CPBA in a toluene and dichloromethane respectively (Scheme 150). The best results of the epoxidation of the major *anti* diastereoisomer **404** are summarised in Table 19.



Scheme 150

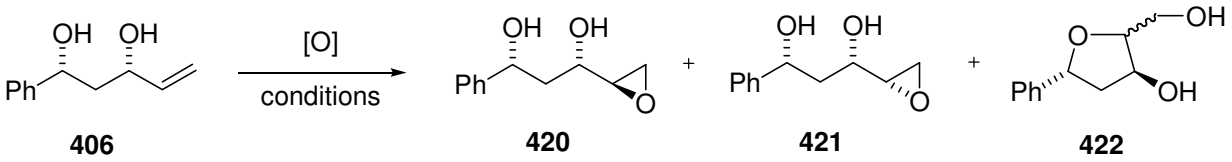
Table 19. Epoxidation of *anti* diol (404)[a]

Entry	Epoxidising reagent	Solvent	Crude product 417:418	Epoxide combined yield %[a]	419 Yield %[c]
1	$VO(acac)_2$/TBHP	Toluene	3 : 1	63	11
2	$VO(acac)_2$/TBHP	CH_2Cl_2	4 : 1	58	10
3	*m*-CPBA	CH_2Cl_2	1 : 1	66	6

[a]The absolute configuration was deduced from the X-ray analysis of the cyclised products. [b]Isolated yield. [c]The same ratio of diastereoisomers as for the epoxides.

In all cases, epoxidation was complete overnight. The crude reaction mixture contained only traces of the cyclised THF products **419** but their amount increases during chromatographic purification on silica. Similar opening of epoxides by Lewis acidic silica gel was also observed by Adam and coworkers.[163,169]

The results of the epoxidation of the *syn* diastereoisomer **406** (Scheme 151) are summarized in Table 20.



406 **420** **421** **422**

Scheme 151

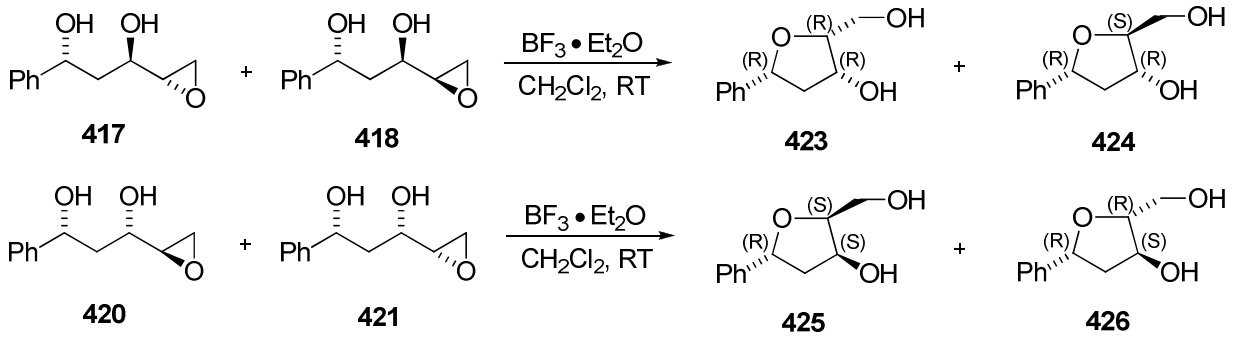
Table 20. Epoxidation of *syn* diol[a]

Entry	Epoxidising agent	Solvent	Crude product 420:421	Epoxide combined Yield %[b]	422 Yield %[c]
1	$VO(acac)_2$/TBHP	Toluene	3 : 1	38[d]	8
2	*m*-CPBA	CH_2Cl_2	1 : 2	48[g]	26

[a] – absolute configuration deduced from the X-ray analysis of the cyclised products; [b] – yield of the isolated product; [c] - the same ratio of diastereoisomers as for the epoxides, [d] – pure 420 was isolated in 10% yield, [e] – pure 421 was isolated in 16% yield.

3.3.4 Intramolecular epoxide opening with a Lewis acid

The epoxides were submitted to an intramolecular cyclisation mediated by a Lewis acid (Scheme 152, Table 21).[170] The reaction proceeds smoothly and cleanly under mild conditions. The use of catalytic amount of BF_3•Et_2O as a Lewis acid in 30 minutes produced the desired products of 5-*exo* cyclisation. Desired product was obtained in good yields as mixtures of 1-phenyl deoxyribose diastereoisomers. Product composition reflected the ratio of the diastereoisomeric epoxydiols submitted for the reaction. We were able to isolate and identify all four configurational isomers of the 3-hydroxy-tetrahydrofurans (Scheme 152).



Scheme 152

Table 21. Intramolecular cyclisation

Entry	Epoxide mixture	Epoxides ratio	Overall yield (%)	Products after chromatography		
				Pure product 1 (%)	Pure product 2 (%)	Remaining mixture (%)[b]
1	**417** + **418**	3 : 1	69	**423** (49)	- [a]	2 : 1 (20)
2	**417** + **418**	1 : 1	71	**423** (19)	**424** (14)	1 : 1 (38)
3	**420** + **421**	4 : 1	80	**425** (20)	**426** (7)	2.5 : 1 (53)
4	**420** + **421**	1 : 3	68	**425** (9)	**426** (25)	1 : 3 (34)

[a]Traces of **424** were detected but the isomer could not be isolated in a pure form. [b]Submitted to further purification by recrystalisation.

In order to probe the suggested configurations for the products, we compared the ^{1}H NMR pattern of our compounds with 3-hydroxy-tetrahydrofurans reported by Tamaru and coworkers.[171] By recrystallisation from hexane and dichloromethane, we were also able to obtain X-ray quality crystals for the cyclic products **423** and **425**. X-Ray crystallographic analysis, carried out by Dr Louis Farrugia, established the structures of **423** and **425** as (+)-*R,R,R* (Figure 23) and (+)-*R,S,S* (Figure 24), respectively. These results also confirmed the structures of both starting diols. Diastereoisomer **426** (Scheme 152) was found to be identical to L-configured 1-phenyl-deoxyriboside, reported by Fu and co-workers,[112] (Figures 25, 26), while the NMR spectra or the remaining structure **424** is considerably different (Figure 27).

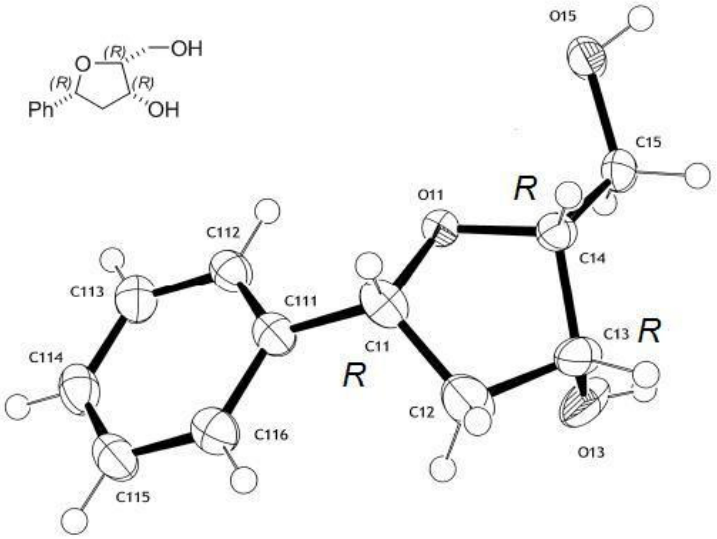


Figure 23. An ORTEP diagram for 423

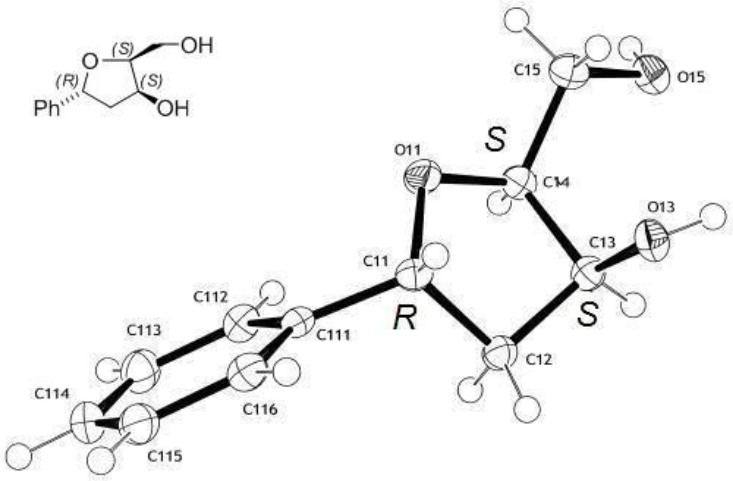


Figure 24. An ORTEP diagram for 425

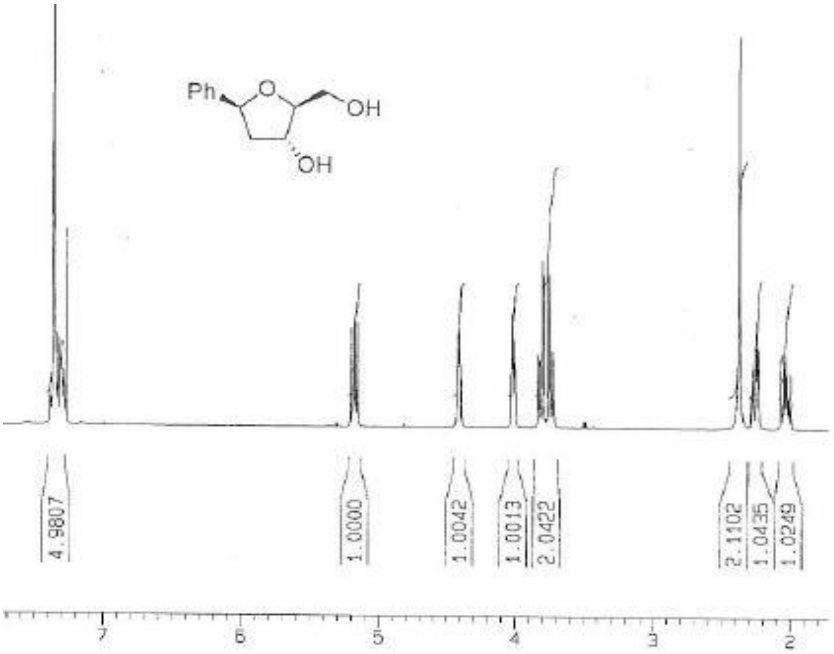


Figure 23. L-deoxyribose derivative reported by Fu.

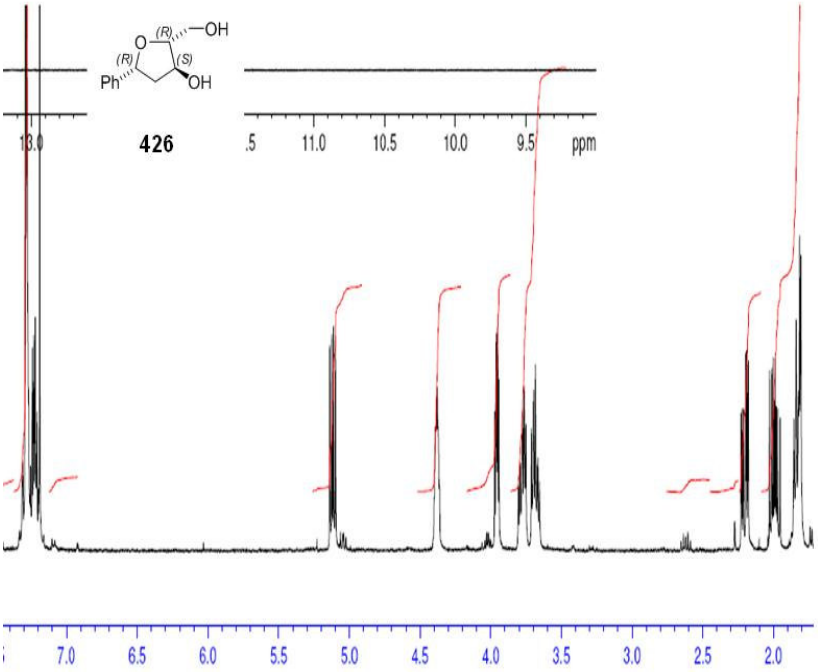


Figure 24. D-deoxyribose derivative 426 – this work.

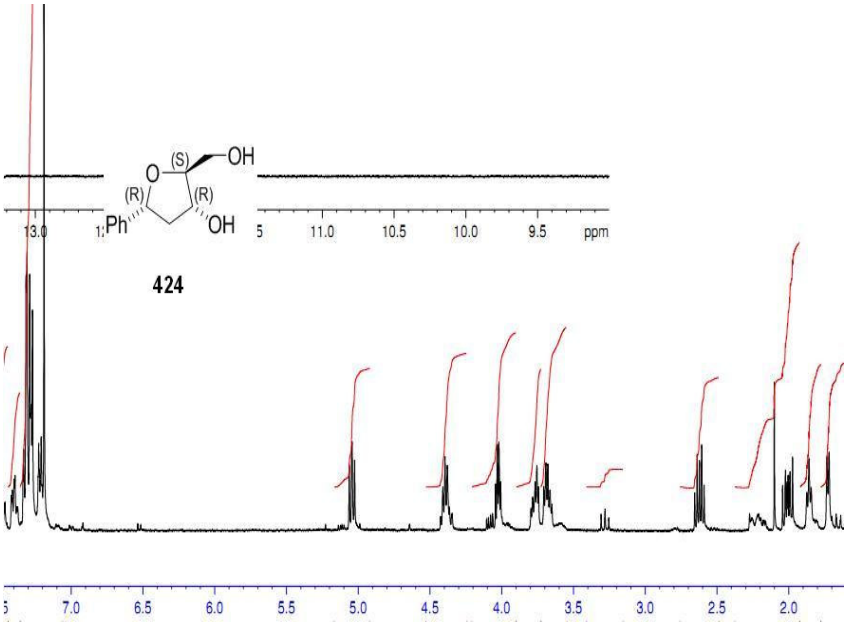
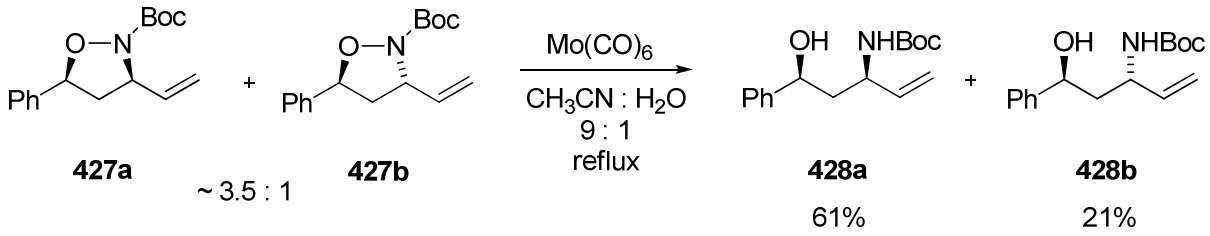


Figure 27. L-deoxyribose derivative 424

3.3.5 Synthesis of 3-NHBoc THF derivative

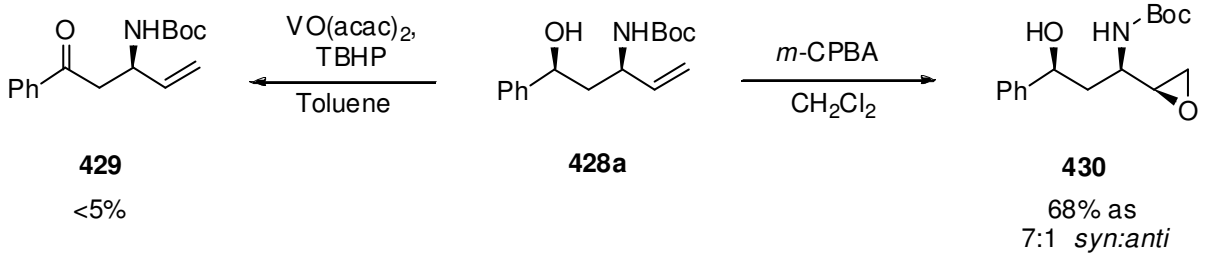
Unnatural *C*-nucleosides and sugars can be synthesised in a variety of configurations, as shown in the previous section. Herein, we report an alternative route to transform an α-homoallylic alcohol into 1,3-difunctionalised terminal alkenes, which can be further used to build a 3-amino-tetrahydrofuran framework.

In the previous chapter (Schemes 115 and 116), we described the palladium catalysed cyclisation of *N*-Boc alkoxyamines into the corresponding isoxazolidines, which can be formally viewed as a C-H activation (Scheme 115). Cleavage of the O-N bond in the 3.5:1 mixture of **427a** and **427b** produced a mixture of the respective 1,3-aminoalcohols **428a** and **428b**, which can be separated by flash chromatography (Scheme 154).



Scheme 154

Epoxidation of the major *syn* isomer with the V(IV)/TBHP system proved unsuccessful, leading only to a small amount of conjugated ketone. On the other hand, epoxidation with *m*-CPBA is known to be controlled by carbamate and amide groups.[172] Desired product **430** was obtained in good yield and dr (Scheme 155). Only traces of the cyclised tetrahydrofuran were formed under the reaction conditions.



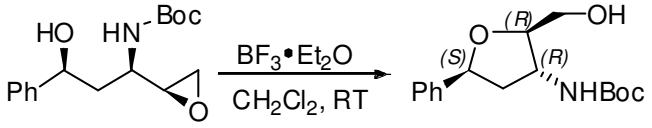
429 <5%

428a

430 68% as 7:1 *syn:anti*

Scheme 155

The mixture was then submitted to the standard Lewis acid catalysed cyclisation (Scheme 156). After flash chromatography on silica, the major diastereoisomer **431** was isolated in 43% yield along with 29% of a 1:1 mixture with the minor isomer. Its configuration was confirmed by ^{1}H NMR spectroscopy.



430 **431**

Scheme 156

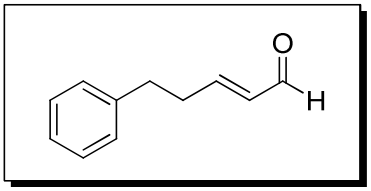
Conclusions

The singlet oxygen reagent was successfully applied to the oxidation of enantiopure homoallylic alcohols. A reasonable level of stereo and diasteroselectivity was achieved, accompanied by good yields and good separability of the products. Our initial studies showed a conceptually new route to highly enantioenriched, valuable 1-substituted sugars and possible C-nucleosides. The simplicity of the method and the ability to produce all four possible diasteroisomers, deriving from a single chiral centre, are highly encouraging. Nevertheless some optimisations are clearly required.

4. Experimental

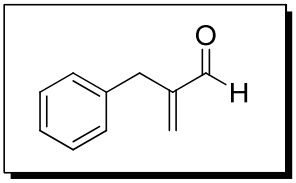
General Methods. Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded on automatic polarimeter RUDOLPH RESEARCH ANALYTICAL APV-6W, in $CHCl_3$ at 25 °C unless otherwise indicated with an error of <±0.1. The $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. The NMR spectra were recorded on a BRUKER ULTRASHIELD 400 NMR spectrometer in $CDCl_3$, ^1H at 400 MHz, ^{13}C at 100.6 MHz and ^{19}F at 376 MHz with chloroform-d_1 (δ 77.0, ^{13}C), tetramethylsilane (δ 0.00, ^1H), and trichlorofluoromethane (δ 0.00, ^{19}F) as internal standards unless otherwise indicated. The IR spectra were recorded for $CHCl_3$ solutions on a SHIMADZU FTIR-8400S spectrophotometer. The mass spectra (EI and/or CI) were measured on a dual sector JEOL JMS-700 mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free argon in oven-dried glassware twice evacuated and filled with the argon. Solvents and solutions were transferred by syringe-septum and cannula techniques. Solvents for the reactions were of reagent grade and were dried; acetonitrile was distilled immediately before use from calcium hydride, THF was obtained from Pure-Solv™ Solvent Purification System (Innovative Technology) and DMPU was dried with molecular sieves (4Å) which were activated at 300 °C. The enantiomeric purity was determined by using chiral HPLC (HP AGILENT 1100 SERIES) and GC (HP GC SYSTEM 6890 SERIES) techniques (for alcohols) and by ^{19}F or ^1H NMR measurements of Mosher derivatives.

Method A: Synthesis of β-substituted conjugated aldehydes.[45] Water (2 mL) was added to a solution of (triphenylphosphoranylidene)acetaldehyde (1.33 g, 4.37 mmol) in THF (15 mL) and the solution was stirred at room temperature for 40 min. Dihydrocinnamaldehyde (418 mg, 3.12 mmol) was then added dropwise and the solution was subsequently heated at 42 ºC and stirred for 18 h. The reaction was quenched with satd aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic solution was dried with Na_2SO_4 and evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 2 cm) with a mixture of petroleum ether and ethyl acetate (97:3).

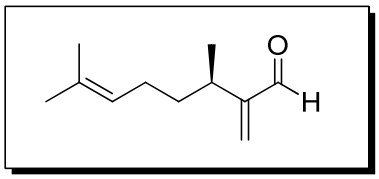


(*E*)-5-Phenylpent-2-enal (100g). Yellowish oil (326 mg, 64%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.56-2.62 (m, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 6.06 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 6.77 (dt, *J* = 15.6, 6.7 Hz, 1H), 7.10-7.25 (m, 5H), 9.41 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.1 (CH_2), 34.2 (CH_2), 126.4 (CH), 128.4 (CH), 128.6 (CH), 133.4 (CH), 140.3 (C), 157.3 (CH), 194.0 (CH); **MS** (EI) *m/z* (%) 161 (M^+, 22), 130 (17), 117 (87), 105 (18), 91 (100), 83 (55), 65 (52); **HRMS** (EI) 160.0887 ($C_{11}H_{12}O^+$ requires 160.0888).

Method B: Synthesis of α-substituted conjugated aldehydes.[44] A 37% aqueous solution of formaldehyde (5.47 mmol) and the appropriate aldehyde (6.02 mmol) were added consecutively to a solution of pyrrolidine (0.55 mmol) and benzoic acid (1.1 mmol) in CH_2Cl_2 (4 mL) at room temperature. The mixture was then heated rapidly to 45 ºC and stirred for 2 h at this temperature. The reaction was quenched with satd aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 20 mL), and the organic solution was dried with Na_2SO_4 and evaporated. The crude product was purified by chromatography on a column of silica gel (15 × 2 cm) with a mixture of petroleum ether and ethyl acetate (99:1).

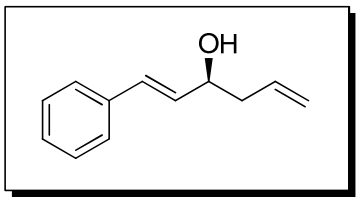


2-Benzylacrylaldehyde (100e). Colourless oil (722.5 mg, 91%)**: ^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.49 (s, 2H), 5.99 (s, 1H), 6.03 (s, 1H), 7.10-7.24 (m, 5H), 9.53 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.2 (CH_2), 126.5 (CH), 128.6 (CH), 129.2 (CH), 135.2 (CH_2), 138.2 (C), 149.8 (C), 194.0 (CH); **IR** ν 3055, 1689, 1427, 1265, 956, 705 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 147 [$(M+H)^+$, 10], 113 (5), 89 (100), 85 (21), 69 (27); **HRMS** (CI/isobutane) 147.0807 ($C_{10}H_{10}O$ + H^+ requires 147.0810).

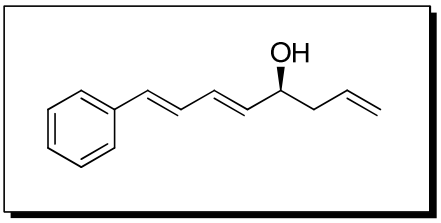


(*R*)-(-)-3,7-Dimethyl-2-methyleneoct-6-enal (100j). Colourless oil (164 mg, 55%): **$[\alpha]_D$** -5.9 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.9 Hz, 3H), 1.31 (ddt, *J* = 13.4, 9.0, 6.9 Hz, 1H), 1.41-1.50 (m, 1H), 1.49 (s, 3H), 1.59 (s, 3H), 1.76-1.93 (m, 2H), 2.63 (sext, *J* = 6.9 Hz, 1H), 5.03-5.7 (m, 1H), 5.91 (s, 1H), 6.15 (s, 1H), 9.50 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.6 (CH_3), 25.7 (CH_2), 25.8 (CH_3), 31.0 (CH), 35.6 (CH_2), 124.2 (CH), 131.7 (C), 133.1 (CH_2), 155.5 (C), 194.7 (CH); **MS** (CI/isobutane) *m/z* (%) 167 [$(M+H)^+$, 100], 149 (30), 123 (26), 109 (42), 81 (39), 69 (59); **HRMS** (CI/isobutane) 167.1440 ($C_{11}H_{18}O + H^+$ requires 167.1436)

Method C: General Procedure for the Reaction of Allyltrichlorosilane and Crotyltrichlorosilane with Aldehydes. An oven-dried flask was filled with argon and charged with (+)-Methox or (*R*)-(+)-Quinox (0.075 mmol), followed by acetonitrile (5 mL, in the case of Methox) or dichloromethane (5 mL in the case of Quinox), diisopropylethylamine (478 mg, 3.7 mmol), and aldehyde (0.75 mmol). The mixture was then cooled to -45 ºC and allyltrichlorosilane or crotyltrichlorosilane (1.10 mmol) was added dropwise. The mixture was stirred at -45 ºC for 4 h and then it was kept in a freezer at -30 ºC for 5 days. The reaction was quenched with satd aqueous $NaHCO_3$, the product was extracted with ethyl acetate and the organic solution was dried with $MgSO_4$ and evaporated The crude product was purified by chromatography on a column of silica gel (15×1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5). In all cases the conversions were ≥95%, as revealed by GC and NMR analysis of the crude mixtures. The isolated yields of alcohols and ee are given in Table 7. The enantiopurity of the resulting alcohol was determined by chiral GC, or HPLC, or by Mosher derivatization (see below).

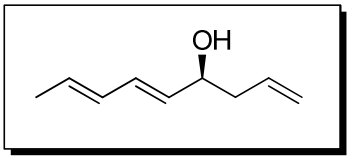


(*S*,*E*)-(-)-1-Phenylhexa-1,5-dien-3-ol (103a). Method C, starting from cinnamyl aldehyde, afforded **103a** as a yellowish oil (445 mg, 75%): $[\alpha]_D$ -25.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.72 (br d, *J* = 4.0 Hz, 1H), 2.27-2.41 (m, 2H), 4.29 (m, 1H), 5.08-5.15 (m, 2H), 5.74-5.84 (dddd, *J* = 17.1, 10.2, 7.4, 6.9 Hz, 1H), 6.17 (dd, *J* = 15.9 and 6.3 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 7.15-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 42.0 (CH_2), 71.7 (CH), 118.5 (CH_2), 126.5 (2 × CH), 127.7 (CH), 128.6 (2 × CH), 130.4 (CH), 131.6 (CH), 134.1 (CH), 136.7C); **IR** ν 3371, 3070, 3026, 2926, 2850, 1495, 1449, 1217, 1030, 997, 966, 916, 748 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 157 (M - OH, 100), 133 (24); **HRMS** (CI/isobutane) 157.1016 ($C_{12}H_{13}$ requires 157.1017), all identical to the data of an authentic sample of the (+)-enantiomer;[37a] **HPLC** analysis (Chiralcel IB column, hexane/2-propanol = 97:3, 0.75 mL min^{-1}) showed 88% ee (t_R = 18.5 min, t_S = 27.7 min).

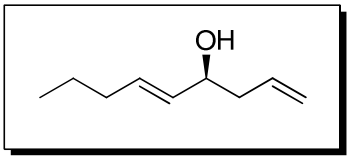


(4*S*,5*E*,7*E*)-(-)-8-Phenyl-1,5,7-octatrien-4-ol (103b). Method C, starting from (2*E*,4*E*)-5-phenylpenta-2,4-dienal, afforded **103b** as a yellowish oil (183.7 mg, 73%): $[\alpha]_D$ -23.6 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.65 (d, *J* = 4.0 Hz, 1H), 2.23-2.37 (m, 2H), 4.19-4.25 (m, 1H), 5.08-5.14 (m, 2H), 5.72-5.82 (m, 2H), 6.35 (dd, *J* = 15.2, 10.5 Hz, 1H), 6.47 (d, *J* = 15.7 Hz, 1H), 6.70 (dd, *J* = 15.5, 10.6 Hz, 1H), 7.13-7.36 (m, 5H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 42.0 (CH_2), 71.4 (CH), 118.5 (CH_2), 126.4 (2 × CH), 127.6 (CH), 128.2 (CH) 128.6 (2 × CH), 130.8 (CH), 132.8 (CH), 134. 0 (CH), 135.6 (CH), 137.2 (C); **IR** ν 3364, 3078, 3024, 2905, 1641, 1492, 1447, 1297, 1071, 1026, 986, 914, 746, 691 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 183 (M – OH, 100), 159 (10), 107 (15), 81 (10), 73 (10); **HRMS** (CI/isobutane) 183.1172 ($C_{14}H_{14}$ + H^+ requires 183.1168), all in accordance with the literature data given for the

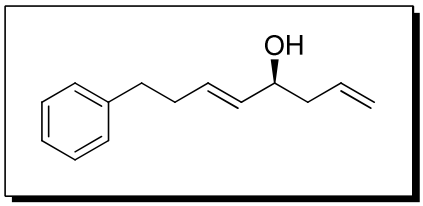
racemate;[179] **HPLC** analysis (Chiralcel OD-H column, hexane/ 2-propanol 96:4, 0.75 mL min^{-1}) showed 88 % ee t_R= 18.54 min, t_S = 22.78 min).



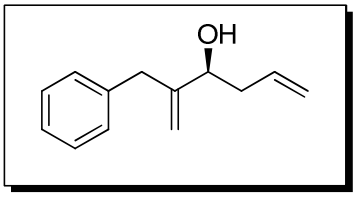
(4*S*,5*E*,7*E*)-(–)-1,5,7-Nonatrien-4-ol (103c). Method C, starting from (2*E*,4*E*)-hexa-2,4-dienal, afforded **103c** as a yellowish oil (151 mg, 42%): $[\alpha]_D$ -7.7 (*c* 1.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.67 (d, *J* = 3.9, 1H), 1.76 (dd, *J* = 6.7, 1.2 Hz, 3H), 2.25-2.38 (m, 2H), 4.16-4.22 (m, 1H), 5.11-5.17 (m, 2H), 5.57 (dd, *J* = 15.2, 6.6 Hz, 1H). 5.71 (dd, *J* = 15.0, 6.8 Hz, 1H), 5.80 (dddd, *J* = 17.0, 10.3, 7.4, 6.8 Hz, 1H), 6.04 (ddd, *J* = 15.1, 10.5, 1.5 Hz, 1H), 6.20 (dd, *J* = 15.1, 10.4 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 18.2 (CH_3), 42.0 (CH_2), 71.5 (CH), 118.3 (CH_2), 130.2 (CH), 130.7 (CH), 131.0 (CH), 132.3 (CH), 134.2 (CH); IR ν 3362, 3078, 3018, 2916, 1435, 1261, 1025, 985, 913 cm^{-1}; **MS** (EI^+) m/z (%) 138 (M^+, 23), 97 (100), 79 (41); **HRMS** (EI^+) 138.1048 ($C_9H_{14}O$ requires 138.1045), in agreement with the literature;[181] **^{19}F NMR** of the corresponding Mosher ester showed ≥86% ee (δ_R = -71.47, δ_S = -71.53).



(4*S*,5*E*)-(-)-1,5-Nonadien-4-ol (103d). Method C, starting from (*E*)-hex-2-enal, afforded **103d** as a yellowish oil (244 mg, 68%): $[\alpha]_D$ -14.1 (*c* 1.00, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 1.40 (sext, *J* = 7.4 Hz, 2H), 1.63 (br s 1H), 1.95 (q, *J* = 7.1 Hz, 2H), 2.23-2.36 (m, 2H), 4.12 (q, *J* = 6.3 Hz, 1H), 5.10-5.16 (m, 2H), 5.48 (ddd, *J* = 15.4, 6.7, 1.4 Hz, 1H), 5.61 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.80 (dddd, *J* = 17.1, 10.4, 7.4, 6.8 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 13.7 (CH_3), 22.3 (CH_2), 34.3 (CH_2), 42.1 (CH_2), 71.9 (CH), 118.0 (CH_2), 132.1 (CH), 132.2 (CH), 134.5 (CH); **IR** ν 3433, 3414, 3333, 2960, 2930, 2911, 2873, 1436, 1261, 1027, 995, 968, 914 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 123 (M - OH, 100), 113 (5), 99 (45), 81 (20), 67 (10); **HRMS** (CI/isobutane) 123.1160 (C_9H_{15} requires 123.1174), in agreement with the literature;[180] **^{19}F NMR** of the corresponding Mosher ester showed 87% ee (δ_R = -71.46, δ_S = -71.51).

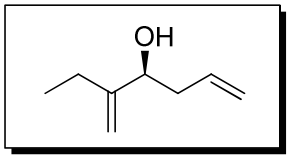


(*S*,*E*)-(-)-8-Phenylocta-1,5-dien-4-ol (103e). Method C, starting from (*E*)-5-phenylpent-2-enal, afforded **103e** as a light yellow oil (78 mg, 49%): $[\alpha]_D$ -12.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.13-2.25 (m, 2H), 2.24-2.31 (m, 2H), 2.62 (dd, *J* = 8.1, 7.4 Hz, 2H), 4.03 (br q, *J* = 6.3 Hz, 1H), 5.02-5.07 (m, 2H), 5.42 (tdd, *J* = 15.4, 6.7, 1.3 Hz, 1H), 5.63 (dtd, *J* = 15.4, 6.7, 0.9 Hz, 1H), 5.70 (dddd, *J* = 18.0, 10.6, 7.3, 6.8 Hz, 1H), 7.09-7.13 (m, 3H), 7.17-7.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 32.9 (CH_2), 34.5 (CH_2), 40.9 (CH_2), 70.7 (CH), 117.1 (CH_2), 124.8 (CH), 127.3 (2 × CH), 127.4 (2 × CH), 130.1 (CH), 131.8 (CH), 133.3 (CH), 140.7 (C); **IR** ν 3315, 3055, 2932, 1435, 1265, 972, 918, 708 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 185 (M - OH, 100), 161 (43), 142 (81), 117 (19), 91 (16), 81 (9); **HRMS** (CI/isobutane) 185.1327 ($C_{14}H_{17}$ requires 185.1330); **HPLC** analysis (Chiralcel OJ-H column, hexane/isopropanol 95:5, 0.75 mL min^{-1}) showed 89% ee (t_R = 14.8 min, t_S = 17.1 min).

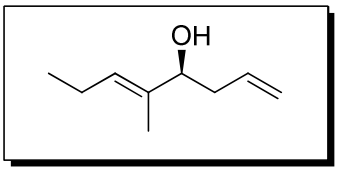


(*S*)-(-)-2-Benzylhexa-1,5-dien-3-ol (103f). Method C, starting from **100e**, afforded **103f** as a colourless oil (68 mg, 46%): $[\alpha]_D$ -3.2 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 3.8 Hz, 1H), 2.23 (dt, *J* = 14.2, 7.7 Hz, 1H), 2.32-2.38 (m, 1H), 3.27 (d, *J* = 15.6 Hz, 1H), 3.41 (d, *J* = 15.6 Hz, 1H), 4.04-4.08 (m, 1H), 4.73 (d, *J* = 1.2 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 5.05 (br s, 1H), 5.07-5.10 (m, 1H), 5.09 (d, *J* = 1,2 Hz, 1H), 5.67-5.77 (m, 1H), 7.12-7.25 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 39.2 (CH_2), 40.4 (CH_2), 73.2 (CH), 112.4 (CH_2), 118.4 (CH_2), 126.4 (CH), 128.5 (2 × CH), 129.3 (2 × CH), 134.6 (CH), 139.3 (C), 150.6 (C); **IR** ν 3321, 3055, 2924, 1435, 1265, 910, 740 cm^{-1}; **MS** (CI/isobutane) m/z (%) 171 (M – OH, 47), 129 (20), 113 (21), 97 (27); **HRMS** (CI/isobutane) 171.1177 ($C_{13}H_{15}$ requires 171.1174); chiral GC analysis (Supelco β-DEX 120 column, oven at 100 °C for 2 min then 1 ^oC min^{-1}) showed 88% ee for the Methox experiment carried out at -45 ^oC, 70% ee for the Methox experiment

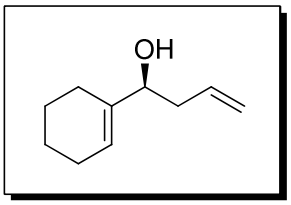
carried out at -30 °C, and 80% ee (opposite enantiomer) for the (*R*)-(+)-Quinox experiment carried out at -30 °C (t_R = 50.14 min, t_S = 50.49 min).



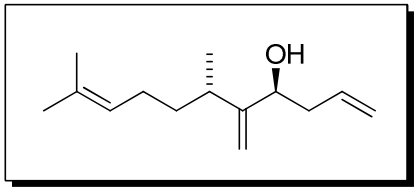
(*S*)-(-)-2-Ethyl-1,5-hexadien-3-ol (103g). Method C, starting from 2-methylenebutanal, afforded **103g** as a yellowish oil (215 mg, 48%): $[\alpha]_D$ -30.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.08 (t, *J* = 7.4 Hz, 3H), 1.68 (d, *J* = 3.9 Hz, 1H), 2.02 (dq, *J* = 16.5, 7.4 Hz, 1H), 2.13 (dq, *J* = 16.3, 7.5 Hz, 1H), 2.28 (dt, *J* = 14.2, 7.7 Hz, 1H), 2.37-2.44 (m, 1H), 4.12-4.16 (m, 1H), 4.87 (d, *J* = 1.4 Hz, 1H), 5.05 (t, *J* = 1.1 Hz, 1H), 5.11-5.18 (m, 2H), 5.80 (dddd, *J* = 17.1, 10.2, 7.4, 6.8 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 12.2 (CH_3), 24.4 (CH_2), 40.4 (CH_2), 74.0 (CH), 108.5 (CH_2), 118.1 (CH_2), 134.7 (CH), 152.7 (C); **IR** ν 3380, 3078, 3025, 2931, 1641, 1434, 1297, 989, 915, 748, 692 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 1109 (M - OH, 100), 95 (19), 85 (30); **HRMS** (CI/isobutane) 109.1019 (C_8H_{13} requires 109.1017); **GC** analysis (Supelco γ-DEX 120 column, oven: 50 °C for 2 min, then 0.5 °C min^{-1} to 70 °C) showed 89% ee (t_R = 36.06 min, t_S = 36.44 min).



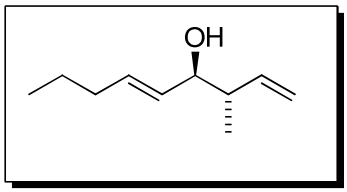
(4*S*,5*E*)-(-)-5-Methyl-1,5-octadien-4-ol (103h). Method C, starting from (*E*)-2-methylpent-2-enal, afforded **103h** as a colourless oil (196 mg, 65%): $[\alpha]_D$ -11.6 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.96 (t, *J* = 7.5 Hz, 3H), 1.61 (s, CH_3 and OH), 2.03 (quintet, *J* = 7.4 Hz, 2H), 1.99-2.38 (m, 2H), 4.01-4.05 (m, 1H), 5.07-5.15 (m, 2H), 5.40 (dt, *J* = 7.1, 1.1 Hz, 1H), 5.76 (dddd, *J* = 17.2, 10.2, 7.3, 6.9 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 11.5 (CH_3), 14.0 (CH_3), 20.8 (CH_2), 39.9 (CH_2), (CH), 117.6 (CH_2), 128.5 (CH), 134.9 (CH), 135.7 (C); **IR** ν 3369, 2963,2934, 2874, 1641, 1125, 1066 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 123 (M - OH, 100), 99 (15), 81 (10), 69 (10); **HRMS** (CI/isobutane) 123.1167 (C_9H_{15} requires 123.1168); **GC** analysis (Supelco γ-DEX 120 column, oven: 70 °C, then 0.5 °C min^{-1} to 90 °C) showed 93% ee (t_R = 32.52 min, t_S = 33.62 min).



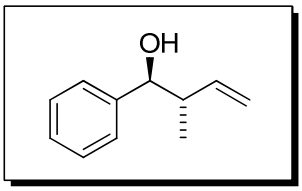
(*S*)-(-)-(1'-Cyclohexen-1'-yl)but-3-en-1-ol (103i). Method C, starting from cyclohex-1-enecarbaldehyde, afforded **103i** as a colourless oil (73 mg, 37%): **$[\alpha]_D$** -17.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.50-1.71 (m, 4H + 1H (OH)), 1.89–1.96 (m, 1H)], 1.98-2.11 (m, 3H), 2.25-2.38 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 1H), 5.02-5.08 (m, 2H), 5.61 (br s, 1H), 5.72 (dddd, *J* = 17.1, 10.2, 7.4, 6.8 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 22.62 (CH_2), 22.63 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 39.9 (CH_2), 75.2 (CH), 117.7 (CH_2), 123.1 (CH), 135.0 (C), 139.2 (CH); **IR** ν 3347, 2926 2858, 2837, 1641, 1298, 1269, 1137, 1030 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 135 (M - OH, 35), 113 (57), 107 (90), 97 (40), in agreement with the literature;[182] **^{19}F NMR** of the corresponding Mosher's ester showed 83 % ee (δ_R = -71.32 ppm and δ_S = -71.57 ppm).



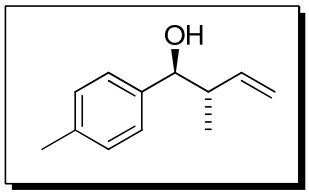
(4*S*,6*S*)-(+)-6,10-Dimethyl-5-methyleneundeca-1,9-dien-4-ol (103k). Method C, starting from (*S*)-3,7-dimethyl-2-methyleneoct-6-enal, afforded **103k** as a colourless oil (55 mg, 57%): $[\alpha]_D$ +7.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$, main diastereoisomer) δ 1.08 (d, *J* = 6.9 Hz, 3H), 1.30-1.40 (m, Hz, 1H), 1.49 (ddt, *J* = 15.7, 8.9, 6.7 Hz, 1H), 1.59 (s, 3H), 1.69 (br s, 4H), 1.84-1.92 (m, 2H), 2.02 (sxt, *J* = 6.9 Hz, 1H), 2.18 (br pent, *J* = 6.9 Hz, 1H), 2.31-2.38 (m, 1H), 4.01-4.05 (m, 1H), 4.85 (s, 1H), 5.00-5.12 (m, 4H), 5.75 (dddd, *J* = 17.0, 10.3, 7.5, 6.8 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$; δ 17.7 (CH_3), 20.7 (CH_3), 25.7 (CH_3), 25.9 (CH_2), 35.4 (CH), 37.4 (CH_2), 40.8 (CH_2), 73.3 (CH), 107.8 (CH_2), 118.1 (CH_2), 124.4 (CH), 131.6 (C), 134.8 (CH), 157.1 (C); **IR** ν 3389, 3077, 2965, 2916, 2857, 1642, 1452, 1437, 1377, 1109, 1047, 901 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 209 [$(M+H)^+$, 9], 191 (M-OH, 100), 167 (16) 149 (24), 135 (58), 124 (15), 109 (31), 95 (41), 81 (28); **HRMS** (CI/isobutane) 209.1901 ($C_{14}H_{25}O$ requires 209.1905).



(3*S*,4*R*,*E*)-(-)-3-Methylnona-1,5-dien-4-ol (104). Method C, starting from (*E*)-hex-2-enal, afforded **104** as a colourless oil (103 mg, 67%): $[\alpha]_D$ -3.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 3H), 0.98 (d, *J* = 6.9 Hz, 3H), 1.34-1.47 (m, 2H), 1.73 (br s, 1H), 1.96-2.10 (m, 2H), 2.17-2.26 (m, 1H), 3.79 (t, *J* = 7.3 Hz, 1H), 5.05-5.10 (m, 2H), 5.42 (tdd, *J* = 15.4, 7.5, 1.3 Hz, 1H), 5.60 (dt, *J* = 15.4, 6.7, 1H), 5.69 (ddd, *J* = 16.7, 10.8, 8.2 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 13.8 (CH_3), 16.3 (CH_3), 22.4 (CH_2), 34.5 (CH_2), 44.7 (CH), 76.5 (CH), 116.5 (CH_2), 130.8 (CH), 133.8 (CH), 140.8 (CH); **IR** ν 3385, 2957, 2925, 2855, 1639,1260, 1015 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 137 (M - OH, 35), 91 (49), 69 (100); **HRMS** (CI/isobutane) 137.1307 ($C_{10}H_{17}$ requires 137.1330); **GC** analysis (Supelco α-DEX 120 column, oven: 50 ºC, then 1 ºC min^{-1}) showed 36:1 dr and 96% ee for the major enantiomer ($t_{3S,4R}$ = 43.21 min, $t_{3R,4S}$ = 43.62 min).

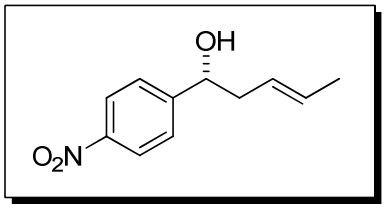


(1*S*,2*S*)-(-)-2-Methyl-1-phenyl-but-3-en-1-ol (127). Method C, starting from benzaldehyde, afforded **127** as a yellowish liquid (146 mg, 90%): $[\alpha]_D$ -120.3 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.79 (d, *J* = 6.8 Hz, 3H), 2.15 (br.s., 1H), 2.35-2.45 (m, 1H), 4.26 (d, *J* = 7.8 Hz, 1H), 5.07-5.14 (m, 2H), 5.72 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 7.16-7.29 (m, 5H, Ph); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 46.2 (CH), 77.8 (CH), 116.7 (*C*H_2), 126.8 (2 × CH), 127.6 (CH), 128.2 (2 × CH), 140.6 (*C*H), 142.4 (C); **MS** (CI/isobutane) *m/z* (%) 145 (M – OH, 100), 129 (11), 107 (13), 85 (24); **HRMS** (CI/isobutane) 145.1016 ($C_{11}H_{13}$ requires 145.1017), in agreement with the literature;[183] **IR** ν 3684, 3422, 2975, 2875, 1455, 1260, 1019, 914, 799, 761, 701 cm^{-1}; **GC** analysis (Supelco γ-DEX 120 column, oven for 2 min at 100 °C, then 0.5 ºC min^{-1}) showed 97% ee (t_{SS} = 37.3 min, t_{RR} = 37.0 min).

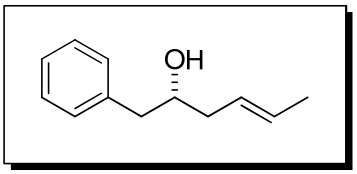


(1*S*,2*S*)-(-)-2-Methyl-1-*p*-tolyl but-3-en-1-ol (129). Method C, starting from 4-methylbenzaldehyde, afforded **129** as a colourless oil (237 mg, 90%): $[\alpha]_D$ -99.5 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.86 (d, *J* = 6.8 Hz, 3H), 2.11 (d, *J* = 2.6 Hz, 1H), 2.35 (s, 3H), 2.42-2.52 (m, 1H), 4.32 (dd, *J* = 8.0, 2.6 Hz, 1H), 5.16-5.24 (m, 2H), 5.81 (ddd, *J* = 17.2, 10.3, 8.2 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.22 (d, *J* = 8.0 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.6 (CH_3), 21.1 (CH_3), 46.2 (CH), 77.7 (CH), 116.7 (CH_2), 126.7 (2 × CH), 128.9 (2 × CH), 137.3 (C), 139.4 (C), 140.8 (*C*H); **IR** ν 3652, 3420, 2976, 2927, 2870, 1637, 1514, 1456, 1417, 1374, 1261, 1179, 1103, 1017, 914, 813, 760, 722, 677 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 159 (M - OH, 100), 121 (40); **HRMS** (CI/isobutane) 159.1172 ($C_{12}H_{15}$ requires 159.1174); **GC** analysis (Supelco γ-DEX 120 column, oven for 2 min at 100 °C, then 0.5 °C min^{-1}) showed 98% ee (t_{RR} = 49.5 min, t_{SS} = 50.0 min).

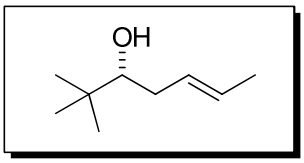
Method D: General Procedure for the $(TfO)_2Sn$-Catalysed Allyl Transfer. Tin(II) triflate (21 mg, 0.05 mmol) was added in one portion to a solution of the alcohol **129** (1 mmol) and respective aldehyde (3 mmol) in $CHCl_3$ (15 mL; passed through a pad of basic Al_2O_3 before use) at room temperature. The reaction mixture was stirred at room temperature and monitored by TLC. After full consumption of the starting alcohol the mixture was diluted with ethyl acetate (150 mL) and washed with the saturated $NaHCO_3$ solution (2×100 mL). The organic layer was dried over sodium sulfate and the solvents were removed in vacuum. The product was purified on a column of silica gel (2.5 × 15 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 80:20).



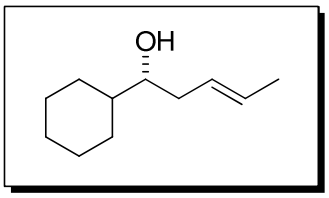
(*R,E*)-(+)-1-(4-nitrophenyl)-pent-3-en-1-ol (128b). Method D, starting from 4-nitrobenzaldehyde, afforded **128b** as a yellowish liquid (155 mg, 75%): $[\alpha]_D$ +61.5 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.68-1.72 (br d, *J* = 6.3 Hz, 3H), 2.25 (d, *J* = 3.2 Hz, 1H), 2.30-2.40 (m, 2H), 2.45-2.54 (m, 1H), 4.76-4.82 (m, 1H), 5.35-5.45 (m, 1H), 5.57-5.67 (m, 1H), 7.50-7.54 (m, 2H), 8.18 – 8.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 42.9 (CH_2), 72.3 (CH), 123.6 (2 × CH), 125.5 (CH), 126.5 (2 × CH), 130.9 (CH), 147.2 (C), 151.3 (C); **IR** ν 3565, 2940, 2357, 1715, 1605, 1520, 1437, 1347, 1107, 1050, 1013, 969, 854, 751, 701 cm^{-1}; **MS** (CI) *m/z* (%) 208 [$(M + H)^+$, 100], 190 (10), 152 (10); **HRMS** (CI) 208.0972 ($C_{11}H_{14}NO_3$ requires 208.0974); **HPLC** analysis (Chiracel OJ-H column, hexane/2-propanol = 96:4, 0.75 mL min^{-1}) showed 98% ee (t_R = 39.7 min, t_S = 36.9 min).



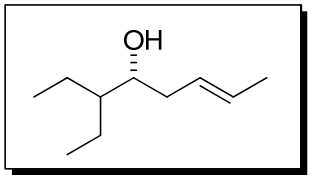
(*R,E*)-(-)-1-phenyl hex-4-en-2-ol (128c). Method D, starting from 2-phenylacetaldehyde, afforded **128c** as a colourless liquid (144 mg, 82% yield): $[\alpha]_D$ -4.5 (*c* 1.0, MeOH); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.60-1.67 (m, 4H, O*H* and CH_3), 2.07 (dt, *J* = 14.7, 7.6 Hz, 1H), 2.15-2.25 (m, 1H), 2.65 (dd, *J* = 13.6, 7.8 Hz, 1H), 2.72 (dt, *J* = 13.6 Hz, 5.0 Hz, 1H), 3.72-3.82 (m, 1H), 5.35-5.45 (m, 1H), 5.48-5.58 (m, 1H), 7.12-7.27 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 40.0 (CH_2), 43.2 (CH_2), 72.0 (CH), 126.4 (CH), 126.9 (CH), 128.5 (2 × CH), 129.1 (CH), 129.4 (2 × CH), 138.5 (C); **MS** (EI) *m/z* (%) 176 (M^+, 7), 121 (80), 92 (100); **HRMS** (EI) 176.1199 ($C_{12}H_{16}O$ requires 176.1201), in agreement with the literature; [184] **HPLC** analysis (Chiracel IB column, hexane/2-propanol = 98:2, 0.75 mL min^{-1}) showed 96% ee (t_R = 11.9 min, t_S = 10.3 min).



(*R,E*)-(+)-2,2-dimethylhept-5-en-3-ol (128d). Method D, starting from pivalaldehyde, afforded **128d** as a yellowish liquid (85 mg, 60%): $[\alpha]_D$ +12.0 (*c* 5.0, MeOH; **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.90 (s, 9H), 1.67-1.71 (br d, *J* = 6.5 Hz, 3H), 1.85-1.95 (m, 1H), 2.24-2.32 (m, 1H), 3.17-3.21 (m, 1H), 5.39-5.62 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0 (3 × CH_3), 25.7 (CH_3), 34.5 (C), 35.2 (CH_2), 78.3 (CH), 128.6 (CH), 128.7 (CH), in agreement with the literature;[184] **^{19}F NMR** of the corresponding Mosher ester showed 93% ee (δ_R = -71.51 ppm and δ_S = -71.15 ppm).

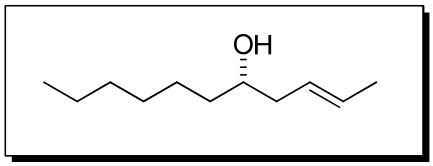


(*R,E*)-(+)-1-cyclohexyl-pent-3-en-1-ol (128e). Method D, starting from cyclohexanecarbaldehyde, afforded **128e** as a colourless liquid (134 mg, 80% yield): $[\alpha]_D$ +7.6 (*c* 2.5, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.80-1.35 (m, 6H, Cy and O*H*), 1.55-1.70 (m, 7H, Cy and CH_3), 1.75-1.82 (m, 1H), 1.92-2.02 (m, 1H), 2.15-2.25 (m, 1H), 3.22-3.28 (m, 1H), 5.32-5.42 (m, 1H), 5.45-5.55 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 37.5 (CH), 42.3 (CH_2), 74.9 (CH), 127.6 (CH), 128.9 (CH); **IR** ν 3362, 2925, 2857, 1449, 1261, 1027, 969 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 151 (M - OH, 100), 113 (15), 95 (25); **HRMS** (CI/isobutane) 151.1485 ($C_{11}H_{19}$ requires 151.1487; **GC** analysis (Supelco α-DEX 120 column, oven for 30 min at 105 °C, then °C min^{-1}) showed 97% ee (t_R = 30.1 min, t_S = 31.0 min).

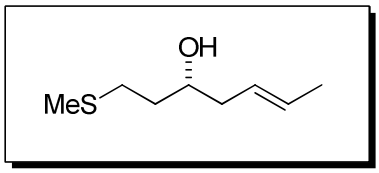


(*R,E*)-(+)-3-ethyl oct-6-en-4-ol (128f). Method D, starting from 2-ethylbutanal, afforded **128f** as a colourless liquid (130 mg, 83% yield): $[\alpha]_D$ +4.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz;

$CDCl_3$) δ 0.90 (t, *J* = 7.4 Hz, 6H), 1.22-1.50 (m, 6H), 1.65-1.72 (br d, *J* = 6.6 Hz, 3H), 2.01-2.11 (m, 1H), 2.18-2.26 (m, 1H), 3.52-3.60 (m, 1H), 5.38-5.48 (m, 1H), 5.51-5.61 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 11.7 (CH_3), 18.1 (CH_3), 21.3 (CH_2), 21.9 (CH_2), 37.5 (CH), 46.0 (CH_2), 72.1 (CH), 127.9 (CH), 128.8 (CH), in agreement with the literature;[47a] **GC** analysis (Supelco α-DEX 120 column, oven for 2 min at 65 °C, then 0.5 ºC min^{-1}) showed 95% ee (t_R = 36.0 min, t_S = 36.6 min).

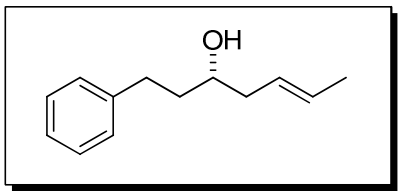


(*S,E*)-(-)-undec-2-en-5-ol (128g). Method D, starting from heptanal, afforded **128g** as a colourless liquid (145 mg, 85% yield): $[\alpha]_D$ -1.5 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.87 (t, *J* = 7.0 Hz, 3H), 1.22-1.45 (m, 10H, $(CH_2)_5$), 1.52 (d, *J* = 3.9 Hz, 1H), 1.65-1.72 (br. d, *J* = 6.4 Hz, 3H), 1.97-2.07 (m, 1H), 2.15-2.25 (m, 1H), 3.52-3.60 (m, 1H), 5.37-5.47 (m, 1H), 5.50-5.60 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 18.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 36.8 (CH_2), 40.7 (CH_2), 71.0 (CH), 127.2 (CH), 128.9 (CH); **IR** ν 3360, 3021, 2957, 2928, 2857, 1456, 1378, 1260, 1034, 967, 800 cm^{-1}; **MS** (CI) *m/z* (%) 153 (M - OH, 100), 97 (50), 71 (60); **HRMS** (CI) 153.1642 ($C_{11}H_{21}$ requires 153.1643); **^{19}F NMR** of the corresponding Mosher ester showed 97% ee (δ_R = -71.31 ppm and δ_S = -71.35 ppm).

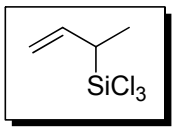


(*R,E*)-(-)-1-(methylthio)-hept-5-en-3-ol (128h). Method D, starting from 3-(methylthio)propanal, afforded **128h** as a colourless liquid (115 mg, 72% yield): $[\alpha]_D$ -14.5 (*c* 0.5, $CHCl_3$);); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.67-1.77 (m, 5H), 1.92 (d, *J* = 3.9 Hz, 1H), 2.05-2.15 (m, 4H), 2.17-2.27 (m, 1H), 2.57-2.67 (m, 2H), 3.67-3.77 (m, 1H), 5.37-5.47 (m, 1H), 5.52-5.62 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 18.1 (CH_3), 30.8 (CH_2), 35.6 (CH_2), 40.7 (CH_2), 70.1 (CH-O), 126.7 (CH), 129.2 (CH); **IR** ν 3734, 3375, 3025, 2915, 1437, 1260, 1016, 968, 800 cm^{-1}; **MS** (CI) *m/z* (%) 143 (M - OH, 100), 102 (40); **HRMS** (CI)

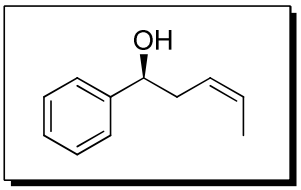
143.0892 ($C_8H_{15}S$ requires 143.0894); **^{19}F NMR** of the corresponding Mosher ester showed 97% ee (δ_R = -71.24 ppm and δ_S = -71.22 ppm).



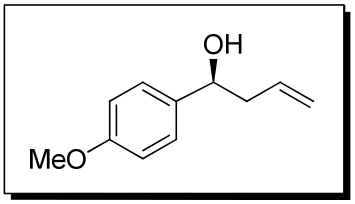
(*S,E*)-(-)-1-phenylhept-5-en-3-ol (128i). Method D, starting from 3-phenylpropanal, afforded **128i** as a colourless liquid (162 mg, 85% yield): $[\alpha]_D$ -15.7 (*c* 0.7, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.57 (br s, 1H), 1.62 (br d, *J* = 6.3 Hz, 3H), 1.66-1.74 (m, 2H), 2.01-2.04 (m, 1H), 2.13-2.22 (m, 1H), 2.61 (dt, *J* = 13.8, 8.0 Hz, 1H), 2.74 (dt, *J* = 13.8, 7.5 Hz, 1H), 3.50-3.60 (m, 1H), 5.30-5.40 (m, 1H), 5.45-5.55 (m, 1H), 7.08-7.25 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 32.1 (CH_2), 38.4 (CH_2), 40.8 (CH_2), 70.1 (CH), 125.7 (CH), 126.8 (CH), 128.3 (2 × CH), 128.4 (2 × CH), 129.3 (CH), 142.1 (C); **IR** ν 3654, 3374, 3062, 3025, 2929, 2856, 1603, 1495, 1454, 1377, 1261, 1045, 968, 746, 699 cm^{-1}; **MS** (CI) *m/z* (%) 191 [$(M + H)^+$, 5], 173 (100), 134 (30), 117 (40); **HRMS** (CI) 191.1426 ($C_{13}H_{19}O$ requires 191.1436), in agreement with the literature;[47a] **GC** analysis (Supelco γ-DEX 120 column, oven for 2 min at 120 °C, then 0.5 °C min^{-1}) showed 97% ee (t_R = 40.9 min, t_S = 41.3 min).



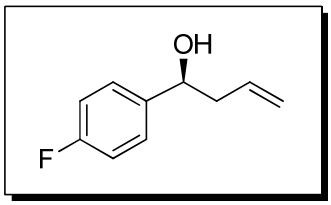
But-3-en-2-yl-trichlorosilane (149).[54] 2-Butenyl chloride (14.3g, 0.159 mol) was added dropwise to magnesium turnings (11.6 g, 0.48 mol) in dry ether (10 mL) under an argon atmosphere. The resulting Grignard reagent was transferred to a syringe and added dropwise to a vigorously stirred solution of $SiCl_4$ (30.4g (0.18 mol) in dry ether (100 mL). The mixture was stirred for 5 h, over which period a white precipitate was formed. The precipitated salts were removed by filtration under argon and the product was distilled under reduced pressure (45-50 °C at 26 mm Hg) to afford **149** (11.2 g, 37% overall) as a colourless liquid: **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.33 (d, *J* = 7.3 Hz, 3H), 2.32-2.39 (m, 1H), 5.18 (dt, *J* = 17.1, 1.2Hz, 1H), 5.22 (dt, *J* = 10.4, 1.0 Hz, 1H), 5.84 (ddd, *J* = 17.1, 10.4, 7.3 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 12.3 (CH_3), 34.0 CH_2), 117.2 (CH_2), 134.0 (CH).



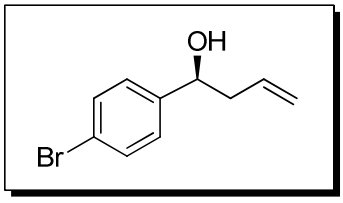
(1*S*,*Z*)-(-)-1-phenylpent-3-en-1-ol (151). Method C, starting from benzaldehyde and **149**, afforded **151** as a colourless oil (9 mg, 14% yield): $[\alpha]_D$ -44.7 (*c* 0.6, $CHCl_3$, for 68% ee, 9:1 *Z/E*); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.62 (d, *J* = 6.3 Hz, 3H), 2.01 (br s, 1H), 2.25-2.40 (m, 2H), 4.59-4.62 (m, 1H), 5.32-5.40 (m, 1H), 5.53 (dq, *J* = 15.2, 6.4 Hz, 1H), 7.17-7.29 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.0 (CH_3), 36.9 (CH_2), 73.8 (CH), 125.6 (CH), 125.8 (2 × CH), 127.5 (CH), 127.7 (CH), 128.4 (2 × CH), 144.1 (C); **IR** ν 3363, 3024, 2920, 2857, 1492, 1452, 1325, 1255, 1197, 1115, 1045, 1015, 910, 874, 758 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 145 (M - OH, 60), 133 (13), 113 (23), 97 (24) ; **HRMS** (CI/isobutane) 145.1015 ($C_{11}H_{13}$ requires 145.1017); **HPLC** analysis (Chiralcel OD-H column, hexane/2-propanol - 98:2, 0.75 mL min^{-1}) showed 87 % ee (t_R = 19.2 min, t_S = 25.0 min).



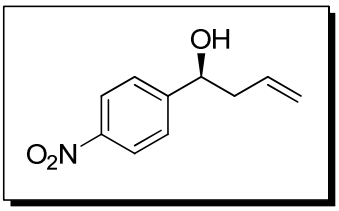
(*S*)-(–)-1-(4'-Methoxyphenyl)-3-buten-1-ol (255b). Method C, starting from 4-methoxybenzaldehyde, afforded **255b** as a pale yellow oil (636 mg, 70%): $[\alpha]_D$ -32.5 (*c*, 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.97 (s, 1H), 2.43 (t, *J* = 6.4 Hz, 2H), 3.73 (s, 3H), 4.64 (t, *J* = 5.6 Hz, 1H), 5.05-5.11 (m, 2H), 5.83 (ddt, *J* = 17.2, 10.1, and 7.1 Hz, 1H), 6.81 (d, *J* = 8.8 Hz, 2H), 7.22 (d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 43.7 (CH_2), 55.3 (CH_3), 73.0 (CH), 113.8 (2 × CH), 118.0 (CH_2), 127.1 (2 × CH), 134.7 (CH), 136.1 (C), 159.0 (C); **IR** ν 3422, 2958, 2928, 2835, 1621, 1512 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 179 [$(M + H)^+$, 5], 161 (M – OH, 100), 151 (20), 137 (15); **HRMS** (CI/isobutane) 161.0965 ($C_{11}H_{14}O_2$ - OH requires 161.0966), in agreement with the literature;[39] HPLC analysis (Chiralcel OD-H column, hexane/2-propanol 97:3, 1 mL min^{-1}) showed 96% ee (t_R = 14.80 min, t_S = 17.30 min).



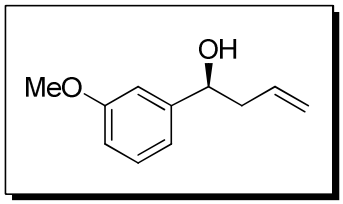
(S)-(-)-1-(4'-fluorophenyl)-but-3-en-1-ol (255c). Method C, starting from 4-fluorobenzaldehyde, afforded **255c** as a yellowish oil (560 mg, 75% yield: $[\alpha]_D$ -42.2 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.05 (br s, 1H), 2.33-2.47 (m, 2H), 4.62-4.66 (m, 1H), 5.08 (dd, *J* = 18.1, 10.9 Hz, 2H), 6.95 (t, *J* = 8.7 Hz, 2H), 7.24 (dd, *J* = 8.7, 5.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 44.0 (CH_2), 72.6 (CH), {115.1 (CH), 115.3 (CH, *J* = 21.3 Hz), 118.7 (CH_2), 127.5 (2 x CH, $J_{C,F}$ = 8.0 Hz), 134.2 (CH), 139.5 (C, $J_{C,F}$ = 3.1Hz), 162.1 (C, $J_{C,F}$ = 245.2 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ -115.14; **MS** (CI/ISO) *m/z* (%) 167 [$(M + H)^+$, 29], 149 (100), 125 (23), 107 (16), 85 (32); **HRMS** (CI/ISO) (M - OH) 149.0765 ($C_{10}H_{10}F$ requires 149.0767); **HPLC** analysis (Chiralcel OD-H column , hexane/2-propanol 98.5:1.5, 0.75 mL min^{-1}) showed 95% ee (t_R = 19.62 min, t_S = 20.56 min).



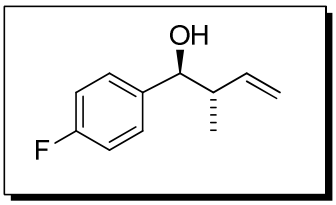
(S)-(-)-1-(4'-bromophenyl)-but-3-en-1-ol (255d). Method C, starting from 4-bromobenzaldehyde, afforded **255d** as a yellowish liquid (344 mg, 82%): $[\alpha]_D$ -50.9 (*c*, 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (br d, *J* = 2.4 Hz, 1H), 2.33-2.47 (m, 2H), 4.64 (dd, *J* = 7.2 and 5.2 Hz, 1H), 5.07-5.12 (m, 2H), 5.65-5.76 (dddd, *J* = 17.5, 10.9, 7.6, and 6.6 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 2H), 7.40 (d, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9 (CH_2), 72.6 (CH), 119.0 (CH_2), 121.3 (C), 127.6 (2 × CH), 131.5 (2 × CH), 133.9 (CH), 142.8 (C); MS; IR ν 3374, 3077, 2932, 2907, 1641, 1593, 1489, 1431, 1404, 1070, 1011, 918, 826 cm^{-1}; (EI^+) *m/z* (%) 226 (M^+, 4), 187 (100), 157 (30), 77 (96); HRMS (EI^+) 225.9989 ($C_{10}H_{11}{}^{79}BrO$ requires 225.9993). **HPLC** analysis (Chiracel OJ-H column, hexane/2-propanol 96:4, 0.5 mL min^{-1}) showed 91% ee (t_S = 27.29 min major, t_R= 29.61 min minor).



(S)-(-)-1-(4'-nitrophenyl)-but-3-en-1-ol (255e). Method C, starting from 4-nitrobenzaldehyde, afforded **255e** as a yellow oil (416 mg, 81% yield): $[\alpha]_D$ -56.3 (*c* 1.9, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.19 (br s, 1H), 2.43-2.51 (m, 1H), 2.54-2.61 (m 1H), 4.88 (dd, *J* = 7.7, 4.8 Hz, 1H), 5.21 (m, 2H), 5.80 (dddd, *J* = 17.0 , 10.4, 7.8, 6.5 Hz, 1H), 7.54 (d, *J* = 8.8 Hz, 2H), 8.21 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 43.9 (CH_2), 72.2 (CH), 119.7 (CH_2), 123.6 (2 × CH), 126.6 (2 × CH), 133.2 (CH), 147.3 (C), 151.1 (C); **MS (CI)** *m/z* (%) 194 [$(M + H)^+$, 100], 178 (9), 164 (11), 146 (33), 113 (15); **HRMS** (CI) 194.0820 ($C_{10}H_{11}O_3N + H^+$ requires 194.0817), in agreement with the literature;[39] **HPLC** analysis (Chiralcel IB column, hexane/2-propanol 99:1, 0.75 mL min^{-1}) showed 92% ee (t_R = 81.21 min, t_S = 83.06 min).



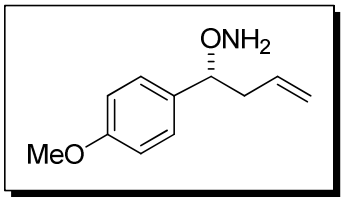
(S)-(-)-1-(3'-methoxyphenyl)-but-3-en-1-ol (255f). Method C, starting from 3-methoxybenzaldehyde, afforded **255f** as a colourless liquid (315 mg, 89%): $[\alpha]_D$ -42.5 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz $CDCl_3$) δ 2.12 (br s, 1H), 2.47-2.59 (m, 2H), 3.84 (s, 3H), 4.73 (dd, *J* = 7.0, 5.6 Hz, 1H), 5.16–5.22 (m, 2H), 5.79–5.89 (dddd, *J* = 17.2, 10.2, 7.4, 7.0 Hz, 1H), 6.84 (dd, *J* = 8.1, 2,5 Hz, 1H), 6.96 (m, 2H), 7.29 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 43.8 (CH_2), 55.2 (CH_3), 73.2 (CH), 111.3 (CH), 113.0 (CH), 118.1 (CH), 118.5 (CH), 129.5 (CH), 134.4 (CH), 143.6 (C), 159.7 (C); **MS** (EI^+) *m/z* (%) 178 (M^+, 12), 137 (98), 109 (100), 94 (31); **HRMS** (EI^+) 178.0993 ($C_{11}H_{14}O_2$ requires 178.0994), all in agreement with the data for an authentic sample of the (*R*)-(+)-enantiomer;[39] **HPLC** analysis (Chiracel OD-H column, hexane/2-propanol 96:4, 1 mL min^{-1}) showed 94% ee (t_R = 19.76 min, t_S = 24.65 min).



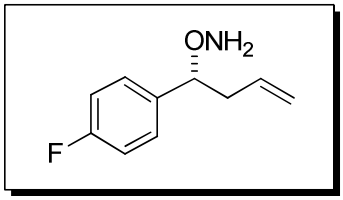
(1*S*,2*S*)-(–)-1-(4'-Fluorophenyl)-2-methyl-3-buten-1-ol (255h). Method C, starting from 4-fluorobenzaldehyde, afforded **255f** as a pale yellow liquid: (824 mg, 52%): $[\alpha]_D$ -67.6 (*c*, 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.79 (d, *J* = 6.8 Hz, 3H), 2.05 (s, 1H), 2.31-2.41 (m, 1H), 4.27 (d, *J* = 7.9 Hz, 1H), 5.11-5.16 (m, 2H), 5.71 (ddd, *J* = 17.0, 10.5, and 8.2 Hz, 1H), 6.93-6.99 (m, 2H), 7.20-7.29 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 46.5 (CH), 77.2 (CH), 115.0 (2 x CH, $J_{C,F}$ = 21.4 Hz), 117.15 (CH_2), 128.41 (2 x CH, $J_{C,F}$ = 7.8 Hz), 138.10 (C, $J_{C,F}$ = 2.9 Hz), 140.5 (CH), 161.0 (C, $J_{C,F}$ = 247.5 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -115.0 (1F); IR ν 3412, 2966, 2931, 2874, 1604, 1456 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 163 (M – OH, 100), 137 (28); **HRMS** (CI/isobutane) 163.0925 ($C_{11}H_{13}F$ - OH requires 163.0917), in agreement with the literature;[185] **GC** analysis (Supelco γ-DEX 120 column, oven for 2 min at 80 °C, then 0.5 °C min^{-1}) showed 98% ee ($t_{1R,2R}$ = 77.35 min, $t_{1S,2S}$ = 78.22 min) and the ratio of diastereoisomers 35:1.

Method E: General Procedure for the Synthesis of Alkoxyamines with Inversion of Configuration via Mitsunobu Reaction.[93] Triphenylphosphine (1.2 mmol) and *N*-hydroxy-phthalimide (1.2 mmol) were added to a solution of the respective alcohol (1 mmol) in freshly distilled THF (10 mL) under argon at 0 °C and the mixture was stirred for 2 min. Diisopropyl azodicarboxylate (1.2 mmol) was then added dropwise over a period of 30 min and the resulting solution was stirred at room temperature under argon for 2 h. Hydrazine hydrate (100% $N_2H_4 \bullet H_2O$, 0.1 mL) was then added and the reaction stirred at room temperature for 30 min. The reaction was quenched with dematerialized water (5 mL) and the mixture was diluted with a mixture of ethyl acetate and petroleum ether (1:1; 10 mL). The organic layer was separated and the aqueous layer was extracted with a mixture of ethyl acetate and petroleum ether (1:1; 3×15 mL). The combined organic fractions were dried over Na_2SO_4 and the solvents were removed in vacuum. The product was purified on a column of silica gel (1.5×20 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). The enantiomeric and diastereoisomeric purity was established for both the crude product and the purified material

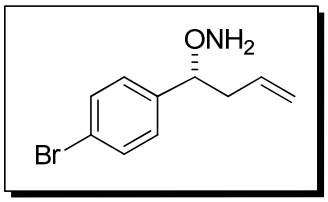
Method F: General Procedure for the Preparation of Mosher Amides from *N*-Alkoxyamines.[187] (*R*)-(+)-3,3,3-Trifluoro-2-methoxy-2-phenylpropionyl chloride (150 mg, 0.6 mmol), prepared in situ from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (99% ee from Sigma-Aldrich), was added to a solution of the alkoxyamine (0.5 mmol) and triethylamine (0.6 mmol) in CH_3CN (1 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was then removed in vacuo and the resulting oil was dissolved in ether (20 mL). The ethereal solution was washed with 1M HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4) and concentrated in vacuo to give an oil, which was analyzed by ^{19}F and ^{1}H NMR spectroscopy.



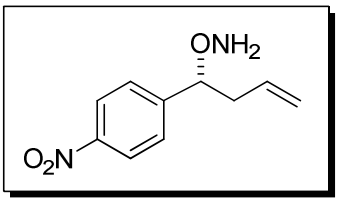
(*R*)-(+)-*O*-(1-(4'-Methoxyphenyl)but-3-enyl)hydroxylamine (257b). Method E, starting from pure (*S*)**-255b** (96% ee), afforded **257b** (314 mg, 74%) as a pale yellow oil: $[\alpha]_D$ +2.8 (*c*, 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28-2.36 (m, 1H), 2.48-2.56 (m, 1H), 3.74 (s, 3H), 4.42 (t, *J* = 6.8 Hz, 1H), 4.93-5.01 (m, 2H), 5.11 (s, 2H), 5.67 (ddt, *J* = 17.3, 10.2, and 7.2 Hz, 1H), 6.82 (br d, *J* = 8.7 Hz, 2H), 7.18 (br d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.3 (CH_2), 55.3 (CH_3), 86.2 (CH), 113.9 (2 × CH), 117.0 (CH_2), 128.1 (2 × CH), 133.2 (C), 134.6 (CH), 159.3 (C); **IR** ν 3319, 2933, 1607, 1585, 1509, 1247 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 194 [$(M + H)^+$, 37], 177 (100), 161 (98); **HRMS** (CI/isobutane) 194.1180 ($C_{11}H_{15}NO_2$ + H^+ requires 194.1181). The enantiopurity was not accurately determined but the optical rotation (+2.8) was rather low compared to that of the (*S*)-enantiomer **261b** obtained via the oxaziridine method (Method G), which showed $[\alpha]_D$ -33.7. Therefore, the enantiopurity of the product must be very low (5-10% ee).



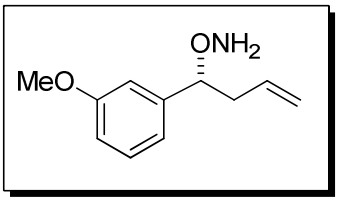
(*R*)-(+)-*O*-[1-(4'-Fluorophenyl)-3-buten-1-yl]hydroxylamine (257c). Method E, starting from (*S*)-**255c** (95% ee), afforded **257c** (316 mg, 78%) as a yellowish oil: $[\alpha]_D$ +48.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.31 (ddd, *J* = 14.4, 7.8, and 6.7 Hz, 1H), 2.51 (m, 1H), 4.47 (t, *J* = 6.7 Hz, 1H), 4.89-5.09 (br m, 4H), 5.65 (ddd, *J* = 17.2, 10.2, and 7.0 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.22 (dd, *J* = 8.7 and 5.5 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.5 (CH_2), 85.9 (CH), 115.4 (2 × CH, $J_{C,F}$ = 21.4 Hz), 117.3 (CH_2), 128.4 (2 × CH, $J_{C,F}$ = 8.0 Hz), 134.1 (CH), 137.1 (C, $J_{C,F}$ = 3.3 Hz), 162.4 (C, $J_{C,F}$ = 245.6 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ -114.7; **IR** ν 3321, 3078, 2908, 1641, 1604, 1510, 1418, 1223, 1157, 989, 912, 835 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 182 [$(M + H)^+$, 100], 165 (47), 149 (100), 137 (82), 121 (23); **HRMS** (CI/isobutane) 182.0979 ($C_{10}H_{12}FNO + H^+$ requires 182.0981). **^{19}F NMR** of the corresponding Mosher amide (Method F) showed 90% ee [δ_R -69.17 (minor) and δ_S -69.11 (major)].



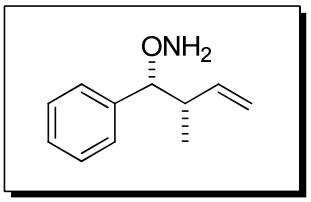
(*R*)-(+)-*O*-[1-(4'-Bromophenyl)-3-buten-1-yl]hydroxylamine (257d). Method E, starting from (*S*)-**255d** (91% ee), afforded **257d** (275 mg, 86%) as a colourless oil: $[\alpha]_D$ +34.8 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.30 (m, 1H), 2.48 (m, 1H), 4.54 (t, *J* = 6.8 Hz, 1H), 4.97 (m, 2H), 5.19 (br s, 2H), 5.59-5.70 (dddd, *J* = 17.2, 10.2, 7.0, 6.8 Hz, 1H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.4 (CH_2), 85.9 (CH), 117.5 (CH_2) 121.6 (C), 128.5 (2 × CH), 131.6 (2 × CH), 133.9 (CH), 140.6 (C); **IR** ν 3321, 3078, 2920, 1643, 1589, 1485, 1431, 1404, 1342, 1296, 1265, 1180, 1069, 1007, 991, 952, 914, 817, 779, 737 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 242 [$(M + H)^+$,100], 209 (42), 185 (8), 113 (13); **HRMS** (CI/isobutane) 242.0181 ($C_{10}H_{12}{}^{79}BrNO + H^+$ requires 242.0177). **^{19}F NMR** spectrum of the Mosher derivative (Method F) showed 90% ee [δ_S -69.02 (minor) and δ_R -69.14 (major)].



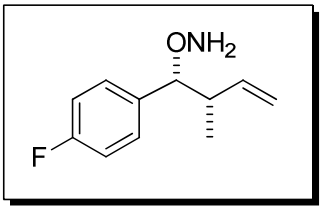
(*R*)-(+)-*O*-[1-(4'-Nitrophenyl)-3-buten-1-yl]hydroxylamine (257e). Method E, starting from (*S*)-**257e** (92% ee), afforded **257e** (236 mg, 84%) as a yellow oil: $[\alpha]_D$ +34.8 (*c*, 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.34 (m, 1H), 2.50 (m, 1H), 4.63 (t, *J* = 6.7 Hz, 1H), 4.97 (m, 2H), 5.32 (br s, 2H), 5.60-5.70 (dddd, *J* = 17.5, 10.5, 7.1, 6.9 Hz, 1H), 7.41 (d, *J* = 8.8 Hz, 2H), 8.16 (d, *J* = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.3 (CH_2), 85.4 (CH), 118.0 (CH_2), 123.7 (2 × CH), 127.5 (2 × CH), 133.2 (CH), 147.5 (C), 149.4 (C); **IR** ν 3321, 3078, 2935, 2909, 1642, 1601, 1518, 1344, 1282, 1080, 991, 918, 854 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 209 [(M + H)$^+$, 100], 194 (22), 146 (5); **HRMS** (CI/isobutene) 209.0923 [($C_{10}H_{12}N_2O_3$ + H^+) requires 209.0926]. **^{19}F NMR** spectrum of the Mosher derivative (Method F) showed 92% ee [δ_S -69.01 (minor), and δ_R -69.15 (major)].



(*R*)-(+)-*O*-[1-(3'-Methoxyphenyl)-3-buten-1-yl]hydroxylamine (257f). Method E, starting from (*S*)-**255f** (94% ee), afforded **257f** (256 mg, 91%) as a colourless oil: $[\alpha]_D$ +35.2 (*c*, 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.29-2.37 (m, 1H), 2.46-2.54 (m, 1H), 3.75 (s, 3H), 4.46 (dd, *J* = 7.6, 6.0 Hz, 1H), 4.95-5.03 (m, 2H), 5.19 (br s, 2H), 5.64-5.75 (ddd, *J* = 17.1, 10.2, 7.0 Hz, 1H), 6.75-6.85 (m, 2H), 7.21 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.6 (CH_2), 55.2 (CH_3), 86.6 (CH), 112.1 (CH), 113.3 (CH), 117.1 (CH), 119.12 (CH), 129.6 (CH), 134.4 (CH), 143.1 (C), 159.8 (C); **IR** ν 3316, 3074, 2936, 1641, 1599, 1586, 1489, 1454, 1435, 1286, 1256, 1255, 1040, 993, 914, 872, 783 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 194 [(M + H)$^+$, 70], 177 (22), 161 (100), 137 (24); **HRMS** (CI//isobutene) 194.1178 ($C_{10}H_{11}NO_3$ + H^+ requires 194.1181). **^{1}H NMR** spectrum of the Mosher derivative (Method F) showed ≥88% ee [δ_S 3.16 (MeO, minor) and δ_R 3.10 (MeO, major); the ^{19}F signals were poorly resolved, so that the analysis of the Mosher ester could only be done with the proton signals of the MeO group.

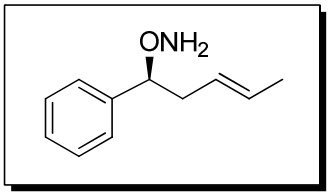


(1*R*,2*S*)-(+)-*O*-[1-Phenyl-2-methyl-3-buten-1-yl]hydroxylamine (257g). Method E, starting with (1*S*,2*S*)-**255g** (95% ee; 55:1 *anti/syn* ratio), afforded a crude product (35:1 *syn/anti* ratio as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to afford pure **257g** (388 mg, 89%) (a 35:1 mixture of *syn/anti* diastereoisomers, as evidenced by ^{1}H NMR) as a colourless oil: $[\alpha]_D$ +43.4 (*c* 0.93, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.10 (d, *J* = 6.8 Hz, 3H), 2.61 (m, 1H), 4.38 (d, *J* = 6.8 Hz, 1H), 4.93 (m, 1H), 4.96 (m, 1H), 5.24 (br s, 2H), 5.63-5.71 (ddd, 17.5, 10.1, and 7.6 Hz, 1H), 7.28-7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8 (CH_3), 42.8 (CH), 91.1 (CH), 114.8 (CH_2), 127.5 (2 × CH), 127.7 (CH), 128.2 (2 × CH), 140.01 (CH), 140.03 (C); **IR** ν 3318, 3082, 2967, 2928, 2882, 1640, 1582, 1493, 1454, 1416, 1370, 1180, 1103, 1072, 991, 914, 756, 702 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 178 [(M + H)$^+$, 100], 161 (19), 145 (78), 122 (10), 107 (27); **HRMS** (CI/isobutane) 178.1230 ($C_{11}H_{15}NO$ + H^+ requires 178.1232).



(1*R*,2*S*)-(+)-*O*-[1-(4'-Fluorophenyl)-2-methyl-3-buten-1-yl]hydroxylamine (257h). Method E, starting with pure (1*S*,2*S*)-**255h** (98% ee; 35:1 *anti/syn* ratio), afforded a crude product at ~80% conversion (≥20:1 *syn/anti* ratio as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to afford pure **257h** (112 mg, 54%) as a pale yellow oil: $[\alpha]_D$ +31.6 (*c*, 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.8 Hz, 3H), 2.41-2.56 (m, 1H), 4.26 (d, *J* = 7.0 Hz, 1H), 4.80-4.89 (m, 2H), 5.53 (ddd, *J* = 17.2, 10.6, and 7.5 Hz, 1H), 6.95-7.01 (m, 2H), 7.17-7.23 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.9 (CH_3), 42.8 (CH), 90.3 (CH), 114.5 (CH_2), 115.1 (2 x CH, $J_{C,F}$ = 21.4 Hz), 129.5 (2 x CH, $J_{C,F}$ = 8.3 Hz), 134.7 (C, $J_{C,F}$ = 3.4 Hz), 139.01 (CH), 162.60 (C, $J_{C,F}$ = 8.3 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$)

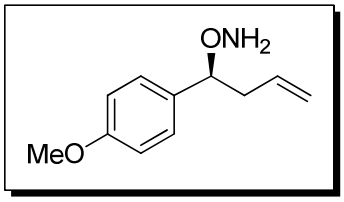
δ -114.9 (1F); **IR** ν 3500, 3018, 2965, 2916, 2849, 2359, 1602, 1508, 1222 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 195 [$(M + H)^+$, 70], 163 (100), 125 (28); **HRMS** (CI/isobutane) 196.1142 [$(C_{11}H_{14}FNO + H^+)$] requires 196.1132); ^{19}F NMR spectrum showed ≥30:1 *syn/anti* ratio (δ_{major} -114.98, δ_{minor} -114.82).



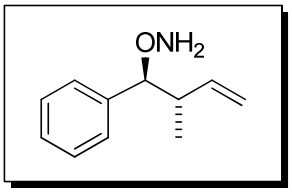
(*S*)-(–)-*O*-(1-Phenyl-3-penten-1-yl)hydroxylamine (258). Method E, starting from (*R*)-**256** (92% ee), afforded **258** (220 mg, 81%) as a colourless liquid: $[\alpha]_D$ -30.9 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.67 (dd, *J* = 6.1, 1.3 Hz, 3H, 2.32-2.39 (m, 1H), 2.49-2.57 (m, 1H), 4.53 (dd, *J* = 7.6, 6.0 Hz, 1H), 5.24 (br s, 2H), 5.36-5.44 (m, 1H), 5.46-5.55 (m, 1H), 7.30-7.42 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 39.5 (CH_2), 87.2 (CH), 126.77 (2 × CH), 126.8 (CH), 127.72 (CH), 127.76 (CH), 128.5 (2 × CH), 141.6 (C); **IR** ν 3314, 3028, 2916, 2855, 1581, 1495, 1452, 1362, 1175, 1001, 966, 914 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 178 [$(M + H)^+$, 100], 161 (13), 145 (65); **HRMS** (CI//isobutene) 178.1231 ($C_{10}H_{15}NO + H^+$ requires 178.1232). Mosher amide (Method F) ^{1}H NMR showed 90% ee [δ_S = 3.14 (major), and δ_R = 3.08 (minor)].

Method G: General Procedure for the Synthesis of Alkoxyamines with Retention of Configuration. The respective alcohol (1.0 mmol), 18-crown-6 ether (0.2 mmol), and KH (1.2 mmol), obtained by rinsing its oil suspension with hexane, were added consecutively to 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU; 1.5 mmol) and the mixture was stirred at room temperature for 1 h under Ar. The resulting mixture was then added dropwise to a solution of 3,3-di-tert-butyl-oxaziridine (1.2 mmol) in DMPU (1.5 mL) at -40 °C and the resulting mixture was stirred first at –40 °C, then slowly allowed to warm to room temperature over a period 2 h (the reaction starts at ca –20 °C; if heated too fast, the mixture tends to overflow from the flask). The reaction was quenched with brine (5 mL) and the mixture was diluted with a mixture of ethyl acetate and petroleum ether (1:1; 10 mL). The organic layer was separated and the aqueous layer was extracted with an ethyl acetate-petroleum ether mixture (1:1; 3×15 mL). The combined organic fractions were dried over Na_2SO_4 and the solvent was removed in vacuum. The product was purified on a column of silica gel (1.5×20 cm), using a

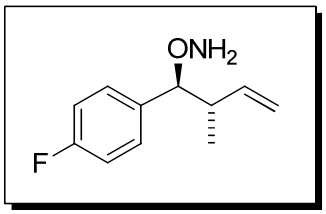
gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). The enantiomeric and diastereoisomeric purity was established for both the crude product and the purified material.



(*S*)-(–)-*O*-[1-(4'-Methoxyphenyl)-3-buten-1-yl]hydroxylamine (261b). Method G, starting with pure (*S*)-**255b** (96% ee) afforded **261b** (236 mg, 88%) as a pale yellow oil: $[\alpha]_D$ -33.7 (*c*, 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.28-2.35 (m, 1H), 2.48-2.56 (m, 1H), 3.73 (s, 3H), 4.41 (t, *J* = 7.1 Hz, 1H), 4.92-5.01 (m, 2H), 5.67 (ddt, *J* = 17.1, 10.2, and 7.0 Hz, 1H), 6.83 (br d, *J* = 8.7 Hz, 2H), 7.18 (br d, *J* = 8.6 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 40.4 (CH_2), 55.3 (CH_3), 86.3 (CH), 113.9 (2 × CH), 117.0 (CH_2), 128.1 (2 × CH), 133.2 (C), 134.5 (CH), 159.3 (C); **IR** ν 3318, 2936, 1611, 1585, 1512, 1245 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 194 [$(M + H)^+$, 37], 177 (100), 161 (98); **HRMS** (CI/isobutane) 194.1185 ($C_{11}H_{15}NO_2 + H^+$ requires 194.1181); the enantiomeric purity should correspond to that of the starting alcohol i.e., 96% ee. The product was identical with its almost racemic version **257b** (except for the optical rotation).



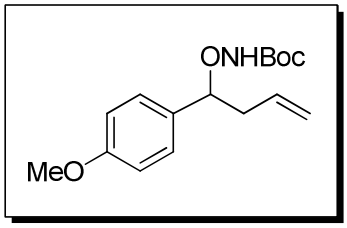
(1*S*,2*S*)-(–)-*O*-[2-Methyl-1-phenyl-3-buten-1-yl]hydroxylamine (261g). Method G, starting with pure (*1S,2S*)-**255g** (95% ee; 55:1 *anti/syn* ratio), afforded **261g** (169 mg, 65%) as a pale yellow oil: $[\alpha]_D$ -88.3 (*c*, 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.77 (d, *J* = 6.8 Hz, 3H), 2.41-2.51 (m, 1H), 4.25 (d, *J* = 7.8 Hz, 1H), 4.95-5.00 (m, 2H), 5.81 (ddt, *J* = 17.6, 10.0, and 7.7 Hz, 1H), 7.18-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 43.1 (CH), 90.2 (CH), 114.4 (CH_2), 127.4 (2 × CH), 127.7 (CH), 128.3 (2 × CH), 140.2 (C), 141.0 (CH); **IR** ν 3318, 3028, 2966, 2881, 1639, 1581, 1454 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 178 [$(M + H)^+$, 22], 161 (20), 145 (50), 137 (100), 121 (80); **HRMS** (CI/isobutane) 178.1228 ($C_{11}H_{15}NO + H^+$ requires 178.1232); the stereochemical purity corresponds to that of the starting alcohol, i.e., 95% ee and ~40:1 dr (by ^{1}H NMR).



(1*S*,2*S*)-(–)-*O*-[1-(4'-Fluorophenyl)-2-methyl-3-buten-1-yl]hydroxylamine (261h). Method G, starting with pure (*1S,2S*)**-255h** (98% ee; 35:1 *anti/syn* ratio), afforded **261h** (97 mg, 33%) as a colourless oil: $[\alpha]_D$ -49.6 (*c*, 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.7 Hz, 3H), 2.30-2.40 (m, 1H), 4.25 (d, *J* = 7.7 Hz, 1H), 5.10-5.14 (m, 2H), 5.74-5.82 (m, 1H), 6.93-6.99 (m, 2H), 7.14-7.20 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 43.1 (CH), 90.4 (CH), 115.0 (CH_2), 115.2 (2 x CH, $J_{C,F}$ = 21.4 Hz), 129.31 (2 x CH, $J_{C,F}$ = 8.3 Hz), 134.8 (C, $J_{C,F}$ = 2.9 Hz), 140.8 (CH), 162.6 (C, $J_{C,F}$ = 245.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.8 (1F); **IR** ν 3500, 3017, 2970, 2360, 2330, 1604, 1512, 1219 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 195 [$(M + H)^+$, 70], 163 (100), 125 (28); **HRMS** (CI/isobutane) 196.1145 ($C_{11}H_{14}FNO$ + H^+ requires 196.1132); ee and de correspond to those of the starting alcohol (vide supra): 98% ee and >30:1 dr by ^{1}H NMR.

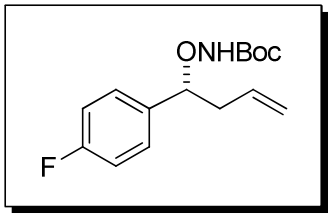
Method H: General Procedure for the Synthesis of *N*-Boc Derivatives of Alkoxyamines

A solution of the respective alkoxyamine (1.0 mmol) and $(Boc)_2O$ (2.0 mmol) in CH_2Cl_2 (15 mL) was added to a solution of NaOH (2.0 mmol) in deionized water (5 mL) and the resulting two-phase mixture was stirred at room temperature for 24 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (3×25 mL). The combined organic extracts were dried over Na_2SO_4 and the solvent was removed in vacuum. The product was purified on a column of silica gel (1.5×20 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 85:15).

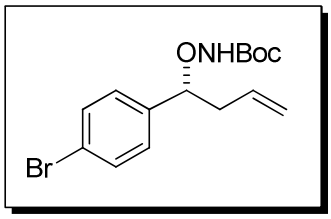


***tert*-Butyl (±)-{[1-(4'-Methoxyphenyl)-3-buten-1-yl]oxy}carbamate (265b).** Method H, starting with racemic **257b**, afforded **(±)-265b** (193 mg, 85%) as a colourless oil: **^{1}H NMR**

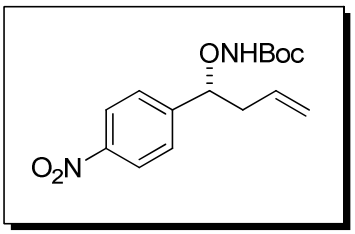
(400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2,37-2.44 (m, 1H), 2.63-2.70 (m, 1H), 3.74 (s, 3H), 4.67 (t, *J* = 6.9 Hz, 1H), 4.95-5.05 (m, 2H), 5.71 (ddd, *J* = 17.0, 10.0, and 6.9 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.18 (d, *J* = 7.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 39.5 (CH_2), 55.3 (CH_3), 81.6 (C), 86.6 (CH), 113.9 (2 × CH), 117.4 (CH_2), 128.6 (2 × CH), 131.7 (C), 134.0 (CH), 156.4 (C), 159.6 (C); **IR** ν 3372, 2978, 2254, 1735, 1697, 1612, 1512, 1250 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 161 [$(M\text{-}ONHBoc)^+$, 100]; **HRMS** (CI/isobutene) 161.0963 [$(C_{11}H_{13}O)^+$ requires 161.0966]; note that the MS could only detect the benzylic cation, which is much more stable than the molecular peak. The product was identical with its almost enantiopure version (-)-**261b** (except for the optical rotation).



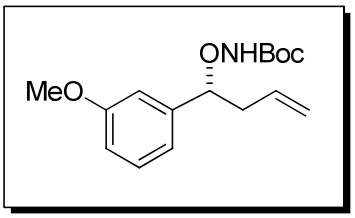
***tert*-Butyl (*R*)-(+)-{[1-(4'-Fluorophenyl)-3-buten-1-yl]oxy}carbamate (265c).** Method H, starting with (*S*)-**257c** (90% ee), afforded **265c** (329 mg, 92%) as a colourless oil: $[\alpha]_D$ +108.6 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.40 (ddd *J* = 14.2, 6.9, 6.8 Hz, 1H), 2.66 (ddd, *J* = 14.2, 7.2, 7.0 Hz, 1H), 4.71 (t, *J* = 7.0 Hz, 1H), 4.96-5.04 (dd, *J* = 17.1, 10.2 Hz, 2H), 5.69 (dddd, *J* = 17.1, 10.2, 7.0, 6.9 Hz, 1H), 6.81 (br s, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.23 (dd, *J* = 8.7, 5.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 39.6 (CH_2), 81.8 (C), 86.4 (CH), 115.4 (2 × CH, $J_{C,F}$ = 21.4 Hz), 117.74 (CH_2), 129.0 (2 × CH, *J* = 8.1 Hz), 133.5 (CH), 135.6 (C, $J_{C,F}$ = 3.2 Hz), 156.5 (C), 162.6 (C, $J_{C,F}$ = 246.4 Hz); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ -113.9 (1F); **IR** ν 3302, 2978, 2931, 1736, 1705, 1604, 1512, 1443, 1366, 1227, 1165, 1103, 1003, 918, 833 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 282 [$(M + H)^+$, 16], 226 (29), 150 (100), 138 (14), 110 (12); **HRMS** (FAB+) 282; ($C_{15}H_{20}FNO_3 + H^+$ requires 282.1505).



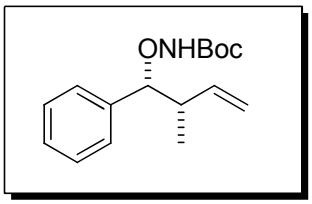
***tert*-Butyl (*R*)-(+)-{[1-(4'-Bromophenyl)-3-buten-1-yl]oxy}carbamate (265d).** Method H, starting with (*S*)-**257d** (90% ee), afforded **265d** (246 mg, 82%) as a colourless oil: $[\alpha]_D$ +124.5 (*c* 0.83, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 2.48 (m, 1H), 2.73 (m, 1H), 4.79 (t, *J* = 6.9 Hz, 1H), 5.09 (m, 2H), 5.73-5.83 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 6.91 (br s, 1H), 7.23 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 39.5 (CH_2), 81.8 (C), 86.4 (CH), 117.9 (CH_2), 122.2 (C), 129.0 (2 × CH), 131.6 (2 × CH), 133.3 (CH), 138.9 (C), 156.4 (C); **IR** ν 3289, 2980, 2924, 1743, 1697, 1604, 1490, 1368, 1250, 1163, 1100, 1011, 920, 820 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 342 $[(M + H)^+$ 15], 286 (22), 209 (100), 131 (38), 130 (18); **HRMS** (FAB+) 342.0709 ($C_{15}H_{22}{}^{79}BrO_3N + H^+$ requires 342.0705).



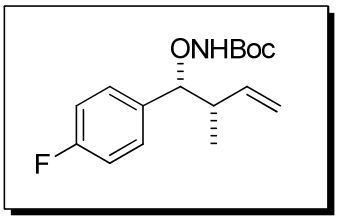
***tert*-Butyl (*R*)-(+)-{[1-(4'-Nitrophenyl)-3-buten-1-yl]oxy}carbamate (265e).** Method H, starting with (*S*)-**257e** (92% ee), afforded **265e** (248 mg, 77%) as a yellowish oil: $[\alpha]_D$ +113.4 (*c* 1.2, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.42 (m, 1H), 2.65 (m, 1H), 4.85 (t, *J* = 6.8 Hz, 1H), 4.99 (m, 2H), 5.63-5.73 (ddd, *J* = 16.7, 9.7, 7.0 Hz, 1H), 7.10 (br s, 1H), 7.44 (d, *J* = 8.7 Hz, 2H), 8.14 (d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.1 (3 × CH_3), 39.6 (CH_2), 82.1 (C), 86.1 (CH), 118.4 (CH_2), 123.6 (2 × CH), 128.0 (2 × CH), 132.6 (CH), 147.6 (C), 147.7 (C), 156.6 (C); **IR** ν 3306, 3080, 2980, 2930, 1719, 1697, 1607, 1520, 1456, 1368, 1344, 1248, 1161, 1103, 1013, 920, 854, 799, 775 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 309 $[(M + H)^+$, 7], 253 (88), 194 (37), 176 (100), 162 (22), 146 (82), 134 (41), 118 (28) ; **HRMS** (CI/isobutene) 309.1454 ($C_{15}H_{20}N_2O_5 + H^+$ requires 309.1450).



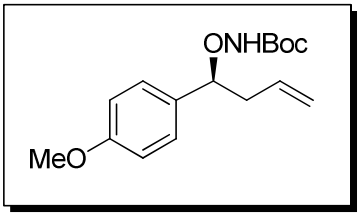
***tert*-Butyl (*R*)-(+)-{[1-(3'-Methoxyphenyl)-3-buten-1-yl]oxy}carbamate (265f).** Method H, starting with (*S*)-**257f** (88% ee), afforded **265f** (294 mg, 97%) as a colourless oil: $[\alpha]_D$ +142.9 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 2.40 (m, 1H), 2.63 (m, 1H), 3.75 (s, 3H), 4.70 (t, *J* = 6.9 Hz, 1H), 4.96l-5.06 (m, 2H), 5.68-5.80 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 6.77-6.86 (m, 4H), 7.21 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 39.8 (CH_2), 55.2 (CH_3), 81.6 (C), 87.0 (CH), 112.6 (CH), 113.6 (CH), 117.5 (CH_2), 119.5 (CH), 129.6 (CH), 133.8 (CH), 141.6 (CH), 156.4 (C), 159.8 (C); **IR** ν 3310, 2980, 2926, 1740, 1701, 1605, 1456, 1437, 1368, 1258, 1248, 1161, 1103, 1043, 1013, 918, cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 294 [$(M + H)^+$, 11], 238 (27), 162 (100); **HRMS** (FAB+) 294.1710 [($C_{16}H_{23}NO_4 + H^+$) requires 294.1705].



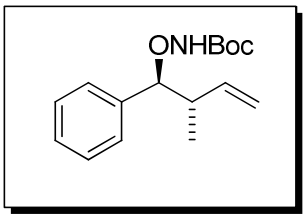
***tert*-Butyl (1*R*,2*S*)-(+)-[(1-Phenyl-2-methyl-3-buten-1-yl)oxy)carbamate (265g).** Method H, starting with pure (1*R*,2*S*)-**257g** (95% ee; 35:1 *syn/anti* ratio), afforded **265g** (521 mg, 98%) as a colourless oil: $[\alpha]_D$ +165.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.13 (d, *J* = 6.8 Hz, 3H), 1.37 (s, 9H), 2.60 (dd, *J* = 7.4, 6.8 Hz, 1H), 4.49 (d, *J* = 7.4 Hz, 1H), 4.85 (m, 2H), 5.54 (ddd, *J* = 17.2, 10.2, 7.4 Hz, 1H), 6.80 (br s, 1H), 7.17-7.30 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.1 (CH_3), 28.2 (3 × CH_3), 42.5 (CH), 81.5 (C), 91.3 (CH), 115.2 (CH_2), 127.8 (2 × CH), 128.0 (CH), 128.2 (2 × CH), 138.9 (C), 139.3 (CH), 159.3 (C); **IR** ν 3302, 2978, 2932, 1705, 1451, 1437, 1366, 1250, 1165, 1096, 1003, 918, 849, 756, 702 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 278 [$(M + H)^+$, 6], 222 (15), 145 (100); **HRMS** (FAB) 278.1755 ($C_{16}H_{23}NO_3 + H^+$) requires 278.1756).



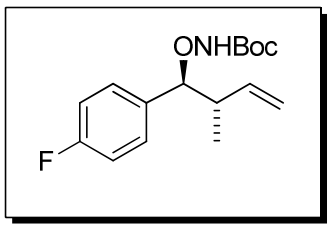
***tert*-Butyl (1*R*,2*S*)-(+)-{[1-(4'-Fluorophenyl)-2-methyl-3-buten-1-yl]oxy}carbamate (265h).** Method H, starting with pure (1*R*,2*S*)-**257h** (98% ee; 28:1 *syn/anti* ratio), afforded **265h** (140 mg, 76%,) as a pale yellow oil: $[\alpha]_D$ +138.5 (*c*, 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.12 (d, *J* = 6.8 Hz, 3H), 1.38 (s, 9H), 2.53-2.63 (m, 1H), 4.47 (d, *J* = 7.5 Hz, 1H), 4.82-4.86 (m, 2H), 5.51 (ddt, *J* = 17.1, 10.5, and 7.5 Hz, 1H), 6.77 (s, 1H), 6.94-6.99 (m, 2H), 7.14-7.19 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.2 (CH_3), 27.2 (3 × CH_3), 41.4 (CH), 80.7 (C), 89.6 (CH), 115.1 (2 x CH, $J_{C,F}$ = 21.9 Hz), 115.9 (CH_2), 129.5 (2 x CH, $J_{C,F}$ = 7.8 Hz), 134.7 (C, $J_{C,F}$ = 3.4 Hz), 138.0 (CH), 156.3 (C), 162.5 (C, $J_{C,F}$ = 246.4 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.2 (1F); **IR** ν 3300, 3020, 2980, 2361, 2343, 1734, 1701, 1602, 1510, 1224 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 296 [$(M + H)^+$, 5], 240 (15), 163 (100); **HRMS** (FAB+) 296.1664 ($C_{16}H_{22}FNO_3 + H^+$ requires 296.1656).



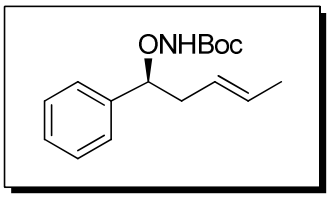
***tert*-Butyl (*S*)-(–)-{[1-(4'-Methoxyphenyl)-3-buten-1-yl]oxy}carbamate (266b).** Method H, starting with pure (*S*)-**261b** (96% ee), afforded **266b** (215 mg, 79%,) as a colourless oil: $[\alpha]_D$ -139.1 (*c*, 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 2.36-2.44 (m, 1H), 2.62-2.70 (m, 1H), 3.73 (s, 3H), 4.67 (t, *J* = 7.1 Hz, 1H), 4.94-5.04 (m, 2H), 5.71 (ddt, *J* = 17.1, 10.2, and 7.0 Hz, 1H), 6.79 (s, 1H), 6.82 (br d, *J* = 8.7 Hz, 2H), 7.18 (br d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 39.5 (CH_2), 55.3 (CH_3), 81.5 (C), 86.3 (CH), 113.9 (2 × CH), 117.4 (CH_2), 128.6 (2 × CH), 131.7 (C), 133.9 (CH), 156.4 (C), 159.6 (C); **IR** ν 3372, 2978, 2254, 1735, 1697, 1612, 1512, 1250 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 161 [$(M-ONHBoc)^+$, 100]; **HRMS** (CI/isobutene) 161.0963 [($C_{11}H_{13}O^+$ requires 161.0966]; The product was identical with its racemic version **265b** (except for the optical rotation).



***tert*-Butyl (1*S*,2*S*)-(–)-{[2-Methyl-1-phenyl-3-buten-1-yl]oxy}carbamate (266g).** Method H, starting with pure (1*S*,2*S*)-**261g** (95% ee; 55:1 *anti/syn* ratio), afforded **266g** (185 mg, 69%,) as a colourless oil: $[\alpha]_D$ -149.4 (*c*, 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 9H), 2.49-2.58 (m, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.98-5.03 (m, 2H), 5.90-5.99 (m, 1H), 6.81 (s, 1H), 7.19-7.30 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 28.2 (3 × CH_3), 42.5 (CH), 81.4 (C), 91.3 (CH), 114.7 (CH_2), 127.6 (2 × CH), 128.1 (CH), 128.3 (2 × CH), 138.9 (C), 140.4 (CH), 156.2 (C); **IR** ν 3300, 3019, 2982, 1740, 1695, 1635, 1215 cm^{-1}; MS (FAB/NOBA) *m/z* (%) 278 [$(M+H)^+$, 8], 222 (18), 145 (100); HRMS (FAB) 278.1753 ($C_{16}H_{23}NO_3 + H^+$) requires 278.1756).



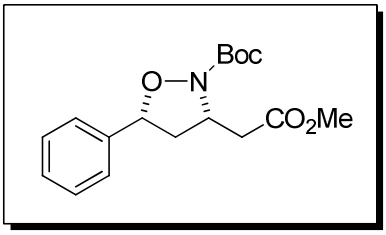
***tert*-Butyl (1*S*,2*S*)-(–)-{[1-(4'-Fluorophenyl)-2-methylbut-3-en-1-yl]oxy}carbamate (266h).** Method H, starting with pure (1*S*,2*S*)-**261h** (98% ee; 35:1 *anti/syn* ratio), afforded **266h** (185 mg, 69%) as a colourless oil: $[\alpha]_D$ -150.6 (*c*, 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.80 (d, *J* = 7.0 Hz, 3H), 1.36 (s, 9H), 2.49-2.58 (m, 1H), 4.50 (d, *J* = 7.8 Hz, 1H), 4.98-5.03 (m, 2H), 5.87-5.96 (m, 1H), 6.78 (s, 1H), 6.95-7.00 (m, 2H), 7.16-7.21 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 16.4 (CH_3), 28.2 (3 × CH_3), 42.6 (CH), 81.7 (C), 90.7 (CH), 116.0 (CH_2), 115.2 (2 x CH, $J_{C,F}$ = 21.4 Hz), 129.3 (2 x CH, $J_{C,F}$ = 8.3 Hz), 134.8 (C, $J_{C,F}$ = 8.3 Hz), 140.3 (CH), 156.3 (C), 162.5 (C, $J_{C,F}$ = 8.3 Hz); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.1 (1F); **IR** ν 3300, 3021, 2980, 2365, 1740, 1694, 1606, 1511cm^{-1}; MS (FAB+) *m/z* (%) 296 [$(M+H)^+$, 6], 240 (16), 163 (100); HRMS (FAB+) 296.1665 ($C_{16}H_{22}FNO_3 + H^+$ requires 296.1662).



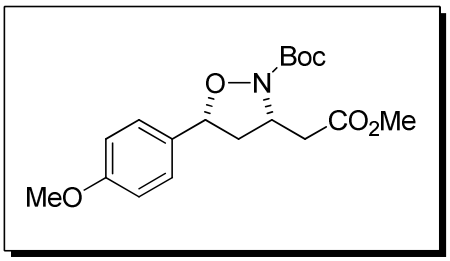
***tert*-Butyl (*S,E*)-(–)-[(1-Phenyl-3-penten-1-yl)oxy]carbamate (267).** Method H, starting from **(*R*)-256 (90% ee), afforded 267 (285** mg, 91%) as a colourless oil: $[\alpha]_D$ -155.5 (*c* 0.75, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.38 (s, 9H), 1.54 (d, *J* = 6.2 Hz, 3H), 2.35 (m, 1H), 2.59 (m, 1H), 4.67 (t, *J* = 6.9 Hz, 1H), 5.27-5.47 (m, 2H), 6.79 (br s, 1H), 7.22-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 28.2 (3 × CH_3), 38.5 (CH_2), 81.5 (C), 87.6 (CH), 126.1 (CH), 127.3 (2 × CH), 128.1 (CH), 128.2 (CH), 128.5 (2 × CH), 140.0 (C), 156.4 (C); **IR** ν 3322, 2982, 2932, 1740, 1709, 1454, 1393, 1370, 1265, 1246, 1161, 1103, 1011, 968, 849, 799, 733, 698 cm^{-1}; **MS** (FAB+) *m/z* (%) 278 [$(M+H)^+$ 18], 254 (37), 222 (53), 146 (100), 118 (17); **HRMS** (FAB+) 278.1753 ($C_{16}H_{23}NO_3 + H^+$ requires 278.1756).

Method I: General Procedure for the Palladium-Catalysed Cyclization/Carbonylation

A round-bottom flask was charged with $PdCl_2$ (0.1 mmol) and $(AcO)_2Cu.2H_2O$ (3.0 mmol) and flushed with CO. The flask was then connected to a CO balloon (atmospheric pressure). Methyl orthoacetate (10 mL) was added and the resulting solution was stirred at room temperature for 30 min. A solution of the respective Boc-protected alkoxyamine (1.0 mmol) in MeOH (10 mL) was added in one portion and the mixture was stirred at 40 °C until completion of the reaction (monitored by TLC), typically 48 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (5 mL), the mixture was diluted with deionized water (5 mL) and extracted with ethyl acetate (4×10 mL). The combined organic phase was dried over Na_2SO_4 and the solvent was evaporated in vacuum. The product was purified by chromatography on a column of silica gel (1.5×10 cm) using a gradient of petroleum ether and ethyl acetate (100:0 to 90:10).

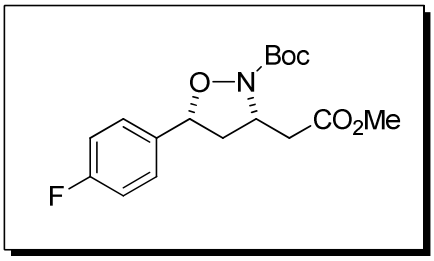


(3*S,5*R**)-(±)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-phenylisoxazolidine (268a).** Method I, starting with (±)-**265a**,[86] afforded a crude product (a >50:1 mixture of *syn/anti* diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to afford pure **268a** (108 mg, 93%) as a colourless dense oil, in which the opposite diastereoisomer could not be detected by NMR: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.54 (s, 9H), 2.04 (ddd, *J* = 12.6, 9.0, and 6.1 Hz, 1H), 2.64 (dd, *J* = 15.9 and 8.8 Hz, 1H), 2.94-3.0 (m, 2H), 3.71 (s, 3H), 4.72 (m, 1H), 4.92 (dd, *J* = 9.9 and 6.6 Hz, 1H), 7.32-7.45 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 40.7 (CH_2), 43.2 (CH_2), 51.8 (CH_3), 57.4 (CH), 82.2 (CH), 82.8 (CH), 126.6 (CH), 128.5 (CH), 128.6 (CH), 137.1 (C), 157.4 (C), 171.2 (C) in accordance with the literature data;[86] **IR** ν 2978, 1735, 1707, 1740, 1709, 1437, 1367, 1318, 1255, 1161, 1064. 968 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 322 [$(M + H)^+$, 5], 266 (100), 222 (45); **HRMS** (CI/isobutane) 322.1652 ($C_{17}H_{23}NO_5 + H^+$ requires 322.1654).

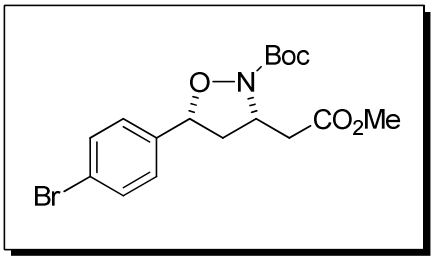


(3*S,5*R**)-(±)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(4'-methoxyphenyl) isoxazolidine (268b).** Method I, starting with (±)-**265b**, afforded a crude product (a 22:1 mixture of *syn/anti* diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to afford pure **268b** (149 mg, 80%) as a pale yellow oil: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.94 (ddd, *J* = 12.6, 10.1, and 6.3 Hz, 1H), 2.56 (dd, *J* = 15.8 and 8.8 Hz, 1H), 2.83 (ddd, *J* = 12.6, 8.2, and 6.4 Hz, 1H), 2.88 (dd, *J* = 15.8 and

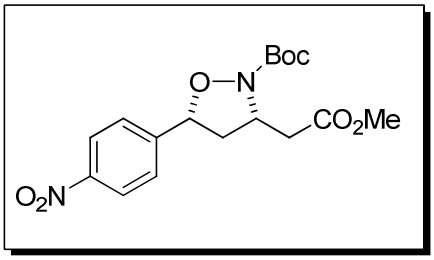
5.5 Hz, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.58-4.65 (m, 1H), 4.77 (dd, *J* = 10.1, 6.4 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 2H), 7.25 (d, *J* = 8.5 Hz, 2H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 40.7 (CH_2), 42.9 (CH_2), 51.8 (CH), 55.3 (CH_3), 57.5 (CH_3), 82.2 (C), 82.7 (CH), 113.9 (2 × CH), 128.2 (2 × CH), 128.7 (C), 157.4 (C), 159.8 (C), 171.3 (C); **MS** (CI/isobutane) *m/z* (%) 352 [$(M+H)^+$, 8], 296 (100), 252 (94), 219 (76), 137 (92); **HRMS** (CI/isobutane) 352.1758 ($C_{18}H_{25}NO_6$ + H^+ requires 352.1760). The diastereoisomeric purity was >50:1 as the *anti*-isomer could not be detected ^{1}H NMR spectroscopy. The product was identical with its enantiopure version (-)-**269b** (except for the optical rotation).



(3*S*,5*R*)-(–)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(4'-fluorophenyl) isoxazolidine (268c). Method I, starting with (*R*)-**265c** (90% ee), afforded a crude product (a 16:1 mixture of diastereoisomers, as evidenced by ^{19}F NMR) (20:1 by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268c** (128 mg, 76%) (>40:1 by both ^{1}H and ^{19}F NMR), followed by a 3:1 mixture of **268c** and the *anti*-diastereoisomer (15 mg, 9%). **268c:** viscous, colourless oil: $[\alpha]_D$ -4.2 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.93 (ddd, *J* = 12.6, 10.0, and 6.2 Hz, 1H), 2.56 (dd, *J* = 15.8 and 8.8 Hz, 1H), 2.83-2.90 (m, 2H), 3.63 (s, 3H), 4.58-4.65 (m, 1H), 4.80 (dd, *J* = 10.0 and 6.4 Hz, 1H), 6.98 (t, *J* = 8.7 Hz, 2H), 7.29 (dd, *J* = 8.7 and 5.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH), 40.7 (CH_2), 43.2 (CH_2), 51.8 (CH), 57.5 (CH_3), 82.2 (CH), 82.4 (C), 115.5, (2 × CH, $J_{C,F}$ = 21.6 Hz), 128.5 (2 × CH, $J_{C,F}$ = 8.3 Hz), 132.8 (C, $J_{C,F}$ = 3.1 Hz), 157.3 (C), 163.3 (C, $J_{C,F}$ = 247.0 Hz), 171.2 (C); **^{19}F NMR** (376.5 MHz, $CDCl_3$) δ -113.2; **IR** ν 2954, 2923, 2853, 1734, 1608, 1514, 1457, 1438, 1369, 1327, 1301, 1258, 1227, 1157, 1064, 834, 758 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 340 [$(M + H)^+$, 46], 284 (100) 240 (90), 239 (71), 207 (21), 155 (17), 119 (37); **HRMS** (CI/isobutane) 340.1559 [($C_{17}H_{22}FNO_5$ + H^+) requires 340.1560).

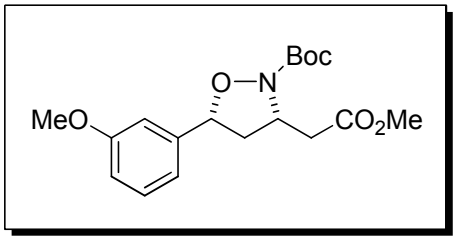


(3*S*,5*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(4'-bromophenyl) isoxazolidine (268d). Method I, starting with (*R*)-**265d** (90% ee), afforded a crude product (a >50:1 mixture of diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268d** (229 mg, 93%) as a colourless dense oil: $[\alpha]_D$ +8.5 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.89 (ddd, *J* = 12.6, 9.9, and 6.1 Hz, 1H), 2.52 (dd, *J* = 15.9 and 8.8 Hz, 1H), 2.86 (m, 2H), 3.61 (s, 3H), 4.60 (m, 1H), 4.79 (dd, *J* = 9.8 and 6.6 Hz, 1H), 7.18 (d, *J* = 8.3 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.1 (3 × CH_3), 40.6 (CH_2), 43.1 (CH_2), 51.8 (CH_3), 57.5 (CH), 82.0 (CH), 82.4 (C) 122.4 (CH), 128.2 (2 × CH), 131.7 (2 × CH), 136.3 (C), 157.2 (C), 171.1 (C); **IR** ν 2978, 1732, 1593, 1489, 1438, 1370, 1300, 1254, 1200, 1157, 1069, 1011, 953, 899, 845, 818, 752 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 400 [$(M+H)^+$, 17], 344 (100) 300 (16), 266 (13); **HRMS** (CI/isobutane) 400.0753 [($C_{17}H_{22}{}^{79}BrNO_5$ + H^+) requires 400.0760].

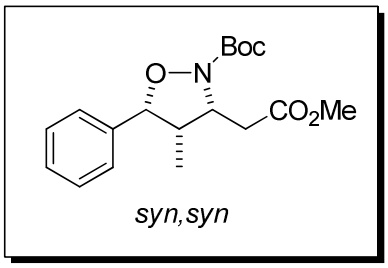


(3*S*,5*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(4'-nitrophenyl) isoxazolidine (268e). Method I, starting with (*R*)-**265e** (92% ee), afforded a crude product (a 25:1 mixture of diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268e** (160 mg, 73%) as a yellowish oil (>50:1 dr): $[\alpha]_D$ +14.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.93 (ddd, *J* = 12., 9.7, 6.0 Hz, 1H), 2.52 (dd, *J* = 15.9 and 8.8 Hz, 1H), 2.87 (dd, *J* = 15.9 and 5.4 Hz, 1H),

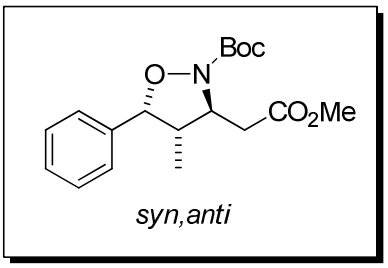
2.97 (ddd, J = 12.6, 8.2, and 6.8 Hz, 1H), 3.62 (s, 3H), 4.63 (m, 1H), 4.95 (dd, J = 9.7 and 6.8 Hz, 1H), 7.49 (d, J = 8.4 Hz, 2H), 8.15 (d, J = 8.8 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 40.5 (CH_2), 43.3 (CH_2), 51.8 (CH_3), 57.6 (CH), 81.2 (CH), 82.8 (C), 123.8 (2 × CH), 127.1 (2 × CH), 144.8 (C), 147.8 (C), 157.1 (C), 170.9 (C); **IR** ν 2982, 1732, 1604, 1524, 1454, 1439, 1370, 1346, 1300 1254, 1200, 1157, 1107, 1015, 853, 748 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 367 [(M + H)$^+$, 9], 337 (19), 311 (100), 281 (96), 267 (35), 237 (22), 204 (20), 160 (27), 122 (36), 113 (38); **HRMS** (CI/isobutane) 367.1510 ($C_{17}H_{22}N_2O_7$ + H^+ requires 367.1505).



(3*S*,5*R*)-(–)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(3'-methoxyphenyl) isoxazolidine (268f). Method I, starting with (*R*)-**265f** (88% ee), afforded a crude product (as a pure diastereoisomer; the *anti*-diastereoisomer could not be detect by ^{1}H NMR), which was further purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268f** (182 mg, 96%) as a colourless oil: $[\alpha]_D$ -1.8 (*c* 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.45 (s, 9H), 1.93 (ddd, J = 12.6, 9.8, 6.0 Hz, 1H), 2.54 (dd, J = 15.8, 8.8 Hz, 1H), 2.87 (m, 2H), 3.62 (s, 3H), 3.74 (s, 3H), 4.62 (m, 1H), 4.81 (dd, J = 9.8, 6.6 Hz, 1H), 6.79 (m, 1H), 6.88 (m, 2H), 7.20 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 40.7 (CH_2), 43.2 (CH_2), 51.8 (CH_3), 55.3 (CH_3), 57.4 (CH), 82.3 (C), 82.6 (CH), 111.9 (CH), 114.1 (CH), 118.8 (CH), 129.6 (CH), 138.8 (C), 157.4 (C), 159.8 (C), 171.2 (C); **IR** ν 2978, 2955, 2931, 1734, 1703, 1605, 1587, 1456, 1437, 1370, 1321, 1258, 1159, 1064, 850 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 352 [(M + H)$^+$, 7], 296 (100), 252 (49), 154 (17), 137 (22), 124 (19),113 (15); **HRMS** (CI/isobutane) 352.1761 ($C_{18}H_{25}NO_6$ + H^+ requires 352.1760).

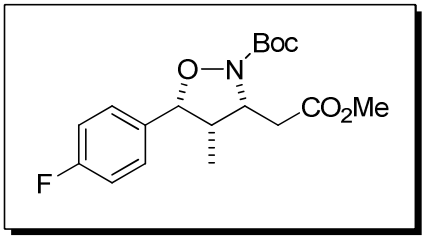


(3*R*,4*S*,5*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-4-methyl-5-phenylisoxazolidine **(268g)** (*syn,syn*). Method I, starting with (1*R*,2*S*)-**265g** (95% ee; 55:1 *syn/anti* ratio), afforded a crude product (a 4.5:1 mixture of *syn,syn* and *syn,anti* diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268g** (89 mg, 69%) as a lipophilic component and its *syn,anti*-diastereoisomer (21 mg, 16%) as a more polar component. Pure (+)-**268g** (50:1 *syn,syn/syn,anti*): a colourless oil; $[\alpha]_D$ +11.2 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.56 (d, *J* = 7.3 Hz, 3H), 1.45 (s, 9H), 2.54 (dd, *J* = 16.6 and 9.2 Hz, 1H), 2.86-2.99 (m, 2H), 3.63 (s, 3H), 4.61 (ddd, *J* = 9.2, 7.0, and 6.0 Hz, 1H), 5.07 (d, *J* = 5.9 Hz, 1H), 7.19-7.33 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 10.8 (CH_3), 28.2 (3 × CH_3), 35.6 (CH_2), 42.6 (CH), 51.8 (CH_3), 61.0 (CH), 82.2 (C), 84.7 (CH), 126.2 (2 × CH), 127.7 (CH), 128.2 (2 × CH), 135.6 (C), 158.0 (C), 171.7 (C); **IR** ν 2978, 2951, 1736, 1701, 1454, 1439, 1370, 1330, 1292, 1254, 1169, 1092, 1030, 991, 960, 852, 702 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 336 [$(M + H)^+$, 11], 280 (100), 236 (77); **HRMS** (CI/isobutane) 336.1812 ($C_{18}H_{25}NO_5 + H^+$ requires 336.1811).

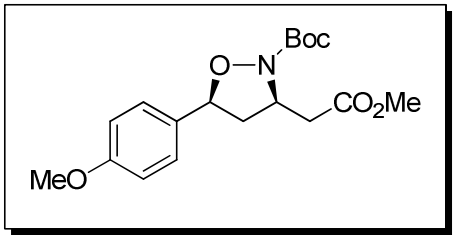


Pure *syn,anti*-diastereoisomer 268g' (27:1 dr by ^{1}H NMR). Obtained by chromatography along with **268g** as the more polar component (29 mg, 23%): a colourless oil; $[\alpha]_D$ +34.2 (*c* 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.65 (d, *J* = 7.2 Hz, 3H), 1.47 (s, 9H), 2.59 (m, 1H), 2.64 (dd, *J* = 15.8 and 9.2 Hz, 1H), 2.88 (dd, *J* = 15.8 and 4.9 Hz, 1H), 3.66 (s, 3H), 4.28 (ddd, *J* = 9.2, 4.9, and 2.3 Hz, 1H), 5.26 (d, *J* = 5.9 Hz, 1H), 7.18-7.31 (m, 5H); **^{13}C NMR** (100 MHz,

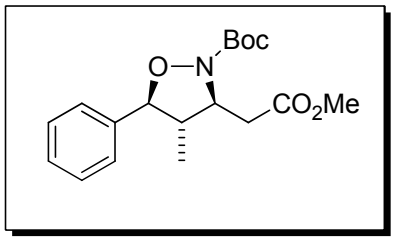
$CDCl_3$) δ 14.9 (CH_3), 28.3 (3 × CH_3), 38.7 (CH_2), 45.2 (CH), 51.8 (CH_3), 63.6 (CH), 82.1 (C), 83.1 (CH), 126.3 (2 × CH), 127.7 (CH), 128.2 (2 × CH), 136.1 (C), 155.9 (C), 171.2 (C); **IR** ν 2970, 2931, 2859, 1736, 1705, 1605, 1454, 1370, 1343, 1312, 1261, 1169, 1088, 1022, 752 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 336 [$(M + H)^+$, 32], 280 (61), 236 (100), 118 (55); **HRMS** (FAB) 336.1807 [($C_{18}H_{25}NO_5 + H^+$) requires 336.1811].



(3*R*,4*S*,5*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-4-methyl-5-(4'-fluorophenyl)isoxazolidine (268h). Method I, starting with (1*R*,2*S*)-**265hh** (98% ee; 28:1 *syn/anti* ratio),), afforded a crude product (a 5.7:1 mixture of diastereoisomers, as evidenced by ^{19}F NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **268h** (116 mg, 60%) as a pale yellow oil: $[\alpha]_D$ +10.9 (*c*, 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.55 (d, *J* = 7.3 Hz, 3H), 1.44 (s, 9H), 2.54 (dd, *J* = 16.4 and 9.2 Hz, 1H), 2.87 (dd, *J* = 16.5 and 5.9 Hz, 1H), 2.88-2.96 (m, 1H), 3.63 (s, 3H), 4.59 (ddd, *J* = 9.1, 7.0, and 6.1 Hz, 1H), 5.05 (d, *J* = 6.1 Hz, 1H), 6.94-7.00 (m, 2H), 7.16-7.21 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 10.2 (CH_3), 28.2 (3 × CH_3), 35.5 (CH_2), 42.6 (CH), 51.8 (CH_3), 61.0 (CH), 82.4 (C), 83.1 (CH), 115.2 (2 × CH, $J_{C,F}$ = 21.9 Hz), 127.9 (2 × CH, $J_{C,F}$ = 7.8 Hz), 131.3 (C, $J_{C,F}$ = 2.9 Hz), 157.8 (C), 162.2 (C, $J_{C,F}$ = 245.93 Hz), 171.5 (C); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.3 (1F); **IR** ν 3020, 2981, 2354, 1733, 1712sh, 1513 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 354 [$(M + H)^+$, 12], 298 (100), 254 (100); **HRMS** (CI/isobutane) 354.1721 ($C_{18}H_{24}FNO_5 + H^+$ requires 354.1711); ^{19}F NMR showed 37:1 dr.

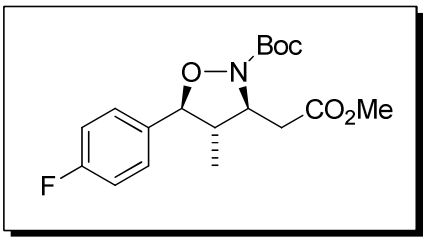


(3*R*,5*S*)-(–)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(4'-methoxyphenyl) isoxazolidine (269b). Method I, starting with (*S*)-**266b** (96% ee), afforded a crude product (a ≥25:1 mixture of diastereoisomers, as revealed by the ^{1}H NMR spectrum), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **269b** (193 mg, 78%) as a colourless oil: $[\alpha]_D$ -2.7 (*c*, 1.6, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.94 (ddd, *J* = 12.6, 10.1, and 6.2 Hz, 1H), 2.56 (dd, *J* = 15.8 and 8.8 Hz, 1H), 2.82 (ddd, *J* = 12.6, 8.3, and 6.3 Hz, 1H), 2.88 (dd, *J* = 15.7 and 5.5 Hz, 1H), 3.62 (s, 3H), 3.73 (s, 3H), 4.58-4.64 (m, 1H), 4.77 (dd, *J* = 10.1 and 6.4 Hz, 1H), 6.82 (br d, *J* = 8.8 Hz, 2H), 7.24 (br d, *J* = 8.7 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3×CH_3), 40.7 (CH_2), 42.9 (CH_2), 51.7 (CH_3), 55.3 (CH_3), 57.4 (CH), 82.2 (C), 82.7 (CH), 114.0 (2×CH), 128.2 (2×CH), 128.8 (C), 157.8 (C), 159.9 (C), 171.2 (C); **IR** ν 2979, 2358, 2336, 1736, 1702sh, 1517 cm^{-1}; **MS** (FAB+) *m/z* (%) 352 [$(M+H)^+$, 40], 296 (100), 252 (70), 219 (100); **HRMS** (CI/isobutane) 352.1763 ($C_{18}H_{25}NO_6$ + H^+ requires 352.1755); ^{1}H NMR showed >50:1 dr. The product was identical with its racemic version **268b** (except for the optical rotation).

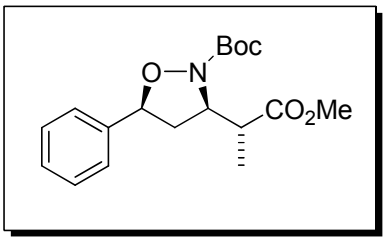


(3*S*,4*S*,5*S*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(Methoxycarbonylmethyl)-4-methyl-5-phenyl-isoxazolidine (269g). Method I, starting with (1*S*,2*S*)-**266g** (95% ee; 55:1 *anti/syn* ratio), afforded a crude product (a >20:1 mixture of diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish pure **269g** (193 mg,

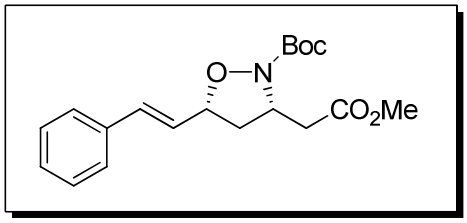
71%) as a colourless oil: $[\alpha]_D$ +12.2 (*c*, 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.09 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H), 2.22-2.31 (m, 1H), 2.62 (dd, *J* = 15.3 and 8.1 Hz, 1H), 2.83 (dd, *J* = 15.3 and 5.6 Hz, 1H), 3.62 (s, 3H), 4.20 (ddd, J_1 = 8.1 Hz, $J_2 = J_3$ = 5.6 Hz, 1H), 4.35 (d, *J* = 8.8 Hz, 1H), 7.24-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.8 (CH_3), 28.2 (3×CH_3), 39.9 (CH_2), 51.8 (CH), 51.9 (CH), 64.6 (CH_3), 82.2 (C), 89.9 (CH), 126.8 (2×CH), 128.6 (2×CH), 128.7 (CH), 136.5 (C), 157.4 (C), 171.2 (C); **IR** ν 3020, 2984, 2364, 2337, 1734, 1516 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 336 [$(M + H)^+$, 5], 280 (100), 236 (53); **HRMS** (CI/isobutane) 336.1821 ($C_{18}H_{26}NO_5 + H^+$ requires 336.1805); ^{1}H NMR showed >50:1 dr.



(3*S*,4*S*,5*S*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(Methoxycarbonylmethyl)-4-methyl-5-(4'-fluorophenyl)isoxazolidine (269h). Method I, starting with (1*S*,2*S*)-**266h** (98% ee; 35:1 *anti/syn* ratio), afforded a crude product (a 17:1 mixture of diastereoisomers, as evidenced by ^{19}F NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish **269h** (98 mg, 66%) as a colourless oil: $[\alpha]_D$ +12.1 (*c*, 1.4, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.8 Hz, 3H), 1.45 (s, 9H), 2.21-2.29 (m, 1H), 2.62 (dd, *J* = 15.3 and 8.1 Hz, 1H), 2.82 (dd, *J* = 15.3 and 5.6 Hz, 1H), 3.62 (s, 3H), 4.18 (ddd, *J* = 8.0, 5.7, and 5.7 Hz, 1H), 4.34 (d, *J* = 9.1, 1H), 6.95-7.01 (m, CH), 7.27-7.31 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 28.2 (3×CH_3), 39.9 (CH_2), 51.69 (CH), 51.73 (CH), 64.5 (CH_3), 82.3 (C), 89.1 (CH), 115.5 (2 × CH, $J_{C,F}$ = 21.9 Hz), 128.6 (2 × CH, $J_{C,F}$ = 8.3 Hz), 132.1 (C, $J_{C,F}$ = 3.4 Hz), 157.2 (C), 162.9 (C, $J_{C,F}$ = 245.9 Hz), 171.0 (C); **^{19}F NMR** (376 MHz, $CDCl_3$) δ -114.1 (1F); **IR** ν 3020, 2984, 2358, 2340, 1735, 1707sh, 1515 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 354 [$(M + H)^+$, 12], 298 (100), 254 (100); **HRMS** (CI/isobutane) 354.1714 ($C_{18}H_{24}FNO_5 + H^+$ requires 354.1711); ^{19}F NMR showed 50:1 dr.



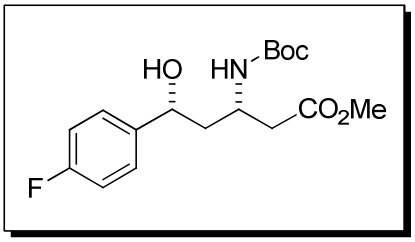
(3*R*,5*S*,1'*R*)-(–)-*N*-*tert*-Butoxycarbonyl-3-{[2'-(Methoxycarbonyl)-1'-methyl]-1'-ethyl}-5-phenyl-isoxazolidine (3*R*,5*S*,1'*R*)-(-)-(270). Method I, starting with (*S*)-**267** (90% ee) and heating at 55 °C for 96 h, afforded a crude product (a 22:2:1 mixture of diastereoisomers, as evidenced by ^{1}H NMR) as a viscous oil, which was purified by chromatography on a column of silica gel (1×10 cm), using a gradient of petroleum ether and ethyl acetate as eluent (20:1 to 10:1) to afford pure **270** (33 mg, 55%) as a dense colourless oil: $[\alpha]_D$ -18.5 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.18 (d, *J* = 7.0 Hz, 3H), 1.45 (s, 9H), 2.05 (ddd, *J* = 12.6, 10.4, and 6.8 Hz, 1H), 2.66 (ddd, *J* = 12.6, 8.5, and 6.2 Hz, 1H), 2.88 (t, *J* = 6.8 Hz, 1H), 4.57 (ddd, *J* = 8.5, 6.7, and 6.6 Hz, 1H), 4.76 (*J* = 10.4 and 6.2 Hz, 1H), 7.23-7.34 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 11.8 (CH_3), 28.2 (3×CH_3), 39.5 (CH_2), 43.6 (CH), 51.8 (CH_3), 62.2 (CH), 82.2 (C), 83.0 (CH), 126.6 (2×CH), 128.5 (CH), 128.6 (2×CH), 137.0 (C), 157.8 (C), 174.2 (C); **IR** ν 2978, 1736, 1458, 1327, 1258, 1165, 1072, 756 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 336 [(M + H)$^+$, 58], 280 (89), 236 (100), 203 (33), 149 (75), 133 (75) ; **HRMS** (FAB+) 336.1808 ($C_{18}H_{25}NO_5$ + H^+ requires 336.1811); ^{1}H NMR showed 40:2.5:1 dr.



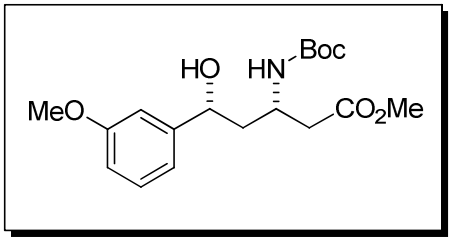
(3*S*,5*R*)-(+)-*N*-*tert*-Butoxycarbonyl-3-(methoxycarbonylmethyl)-5-(2'-phenylethen-1'yl)isoxazolidine (268i). Method I, starting with (*S*)-**265i** [40% ee, as revealed by the analysis of the alkoxyamine **257i**), contaminated by **288** (2:1 ratio), afforded a crude product (a >20:1 mixture of diastereoisomers, as evidenced by ^{1}H NMR), which was purified by chromatography on a column of silica gel (1.5×20 cm), using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10) to furnish **268i** (211 mg, 87%) as a colourless oil (with de >>50:1 – opposite not visible on HNMR) unreacted **288** as less polar compound was isolated completely

on the collumn: $[\alpha]_D$ + 5.9 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.82 (ddd, *J* = 12.6, 9.4, and 5.2 Hz, 1H), 2.51 (dd, *J* = 15.8 and 8.8 Hz, 1H), 2.69 (ddd, *J* = 12.6, 8.1, and 6.8 Hz, 1H), 2.84 (dd, *J* = 15.8 and 5.5 Hz, 1H), 3.63 (s, 3H), 4.48 (m, 1H), 4.57 (m, 1H), 6.08 (dd, *J* = 16.0 and 7.3 Hz, 1H), 6.63 (d, *J* = 16.0 Hz, 1H), 7.17-7.37 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (3 × CH_3), 40.5 (CH_2), 41.3 (CH_2), 51.8 (CH_3), 57.3 (CH), 81.9 (CH), 82.2 (C), 124.9 (CH), 126.7 (2 × CH), 128.3 (CH), 128.6 (2 × CH), 134.8 (CH), 136.0 (C), 157.3(C), 171.2 (C); **MS** (CI/isobutene) *m/z* (%) 348 [$(M + H)^+$, 12], 292 (100), 248 (44), 215 (43), 134 (56), 113 (46). **HRMS** (CI/isobutane) 348.1815 ($C_{19}H_{25}NO_5 + H^+$ requires 348.1811).

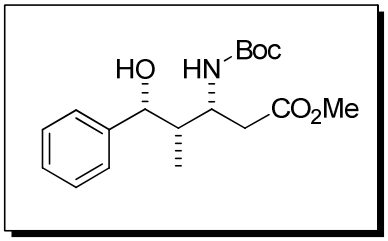
Method J: General Procedure for the Reduction of the Cyclization Products with $Mo(CO)_6$.[101] A solution of the respective isoxazolidine (0.1 mmol) in a 9:1 mixture of CH_3CN and H_2O (2.5 mL) was added to $Mo(CO)_6$ (0.5 mmol) and the resulting solution was heated to reflux (~90 ^oC) for 2 h, during which time the colour had changed from white to black. The mixture was then cooled to room temperature, filtered through Celite, and the filtrate was evaporated. The residue was purified by chromatography on a column of silica gel (1×7 cm), using a gradient of petroleum ether and ethyl acetate from 9:1 to 2:1.



Methyl-(3*S*,5*R*)-(+)-3-(*tert*-Butoxycarbamoyl)-5-hydroxy-5-(4'-fluorophenyl)valerate (290c). Method J, starting with **268c**, produced **290c** (53 mg, 65%) as a viscous colourless oil: $[\alpha]_D$ +15.0 (*c* 2.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.79 (dt, *J* = 14.2, 5.3 Hz, 1H), 1.97 (dt, *J* = 14.2, 8.1 Hz, 1H), 2.46-2.56 (m, 2H), 2.95 (br s, 1H), 3.60 (s, 3H), 3.93 (br s, 1H), 4.68-4.70 (m, 1H), 5.20 (br d, *J* = 7.2 Hz, 1H), 6.95 (t, *J* = 8.7 Hz, 2H), 7.25 (dd, *J* = 8.6, 5.4 Hz, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.3 (3 × CH_3), 39.0 (CH_2), 43.7 (CH_2), 45.6 (CH), 51.8 (CH_3), 55.2 (CH_3), 72.3 (CH), 115.3 (2 × CH, $J_{C,F}$ = 21.3 Hz), 127.5 (2 × CH, $J_{C,F}$ = 8.1 Hz), 139.9 (C), 155.5 (C), 162.2 (C, $J_{C,F}$ = 245.4 Hz), 172.1 (C); **MS** (FAB+) *m/z* (%) 342 [$(M + H)^+$, 74], 286 (12), 268 (100), 207 (67), 176 (16), 147 (18); **HRMS** (FAB+) 342.1719 ($C_{18}H_{24}FNO_5 + H^+$ requires 342.1717).

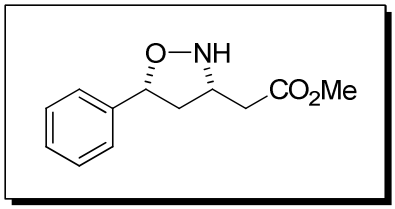


Methyl (3*S*,5*R*)-(+)-3-(*tert*-Butoxycarbamoyl)-5-hydroxy-5-(3'-methoxyphenyl)valerate (290f). Method J, starting with **268f**, produced **290f** (39 mg, 86%) as a viscous colourless oil: $[\alpha]_D$ +10.1 (*c* 1.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.82 (dt, *J* = 14.2, 5.1 Hz, 1H), 1.97 (dt, *J* = 14.2, 8.1 Hz, 1H), 2.43-2.58 (m, 2H), 2.74 (br s, 1H), 3.60 (s, 3H), 3.73 (s, 3H), 3.97 (br s, 1H), 4.68 (dd, *J* = 8.0, 5.0 Hz, 1H), 5.20 (br d, *J* = 5.6 Hz, 1H), 6.72-6.75 (m, 1H), 6.84-6.86 (m 2H), 7.15-7.20 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 39.1 (CH_2), 43.5 (CH_2), 45.8 (CH), 51.7 (CH_3), 55.2 (CH_3), 72.3 (CH), 79.6 (C), 111.2 (CH), 113.2 (CH), 118.1 (CH), 129.6 (CH), 145.9 (C), 155.5 (C), 159.8 (C), 172.1 (C); **IR** ν 3360, 2974, 2931, 1709, 1690, 1601, 1508, 1493, 1454, 1439, 1366, 1316, 1254, 1211, 1165, 1045, 860, 787 cm^{-1}; **MS** (FAB+) *m/z* (%) 354 [$(M + H)^+$, 38], 280 (76), 219 (62), 188 (24), 146 (31). **HRMS** (FAB+) 354.1919 ($C_{18}H_{27}NO_6 + H^+$ requires 354.1917).

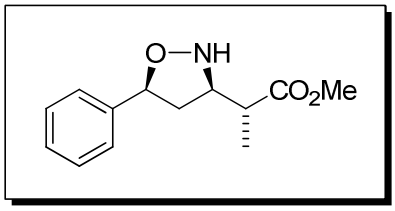


Methyl (3*S*,4*S*,5*R*)-(+)-3-(*tert*-Butoxycarbamoyl)-5-hydroxy-3-methyl-5-(phenyl)valerate (290g). Method J, starting with **268g**, produced **290g** (31 mg, 77%) as a viscous colourless oil: $[\alpha]_D$ +26.0 (*c* 1.7, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.76 (d, *J* = 6.5 Hz, 3H), 1.37 (s, 9H), 1.88-1.97 (m, 1H), 2.51 (dd, *J* = 15.6, 6.5. Hz 1H), 2.58–2.64 (m, 2H), 3.60 (s, 3H), 4.02 (br s, 1H), 4.79 (br s, 1H), 4.95 (br d, *J* = 5.8 Hz, 1H), 7.16-7.28 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 8.2 (CH_3), 28.4 (3 × CH_3), 38.2 (CH_2), 43.7 (CH), 50.7 (CH), 51.8 (CH_3), 75.1 (CH), 79.7 (C), 125.8 (2 × CH), 127.2 (CH), 128.2 (2 × CH), 143.4 (C), 155.8 (C), 172.2 (C); **IR** ν 3430, 3380 2978, 1694, 1504, 1454, 1439, 1366, 1250, 1165, 1018, 995, 856, 737, 702 cm^{-1};

MS (CI/isobutane) *m/z* (%) 338 [(M + H)$^+$, 60], 282 (74), 264 (54), 250 (100), 189 (23), 132 (31); **HRMS** (CI/isobutane) 338.1971 ($C_{18}H_{27}NO_5$ + H^+ requires 338.1967).

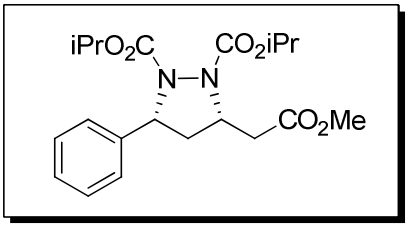


(3*S,5*R**)-(±)-3-(Methoxycarbonylmethyl)-5-(phenyl)isoxazolidine (432).** Trifluoroacetic acid (2 mL) was added slowly to a solution of (±)-**268a** (279 mg, 0.87 mmol) in CH_2Cl_2 (2 mL) at 0 ^oC and reaction mixture was stirred in this temperature for 1 h. The reaction was quenched slowly with a cold saturated aqueous $NaHCO_3$ until basic pH and the product was extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, dried over Na_2SO_4, and the solvent was evaporated. The crude product was practically pure but was further purified by flash chromatography on a column of silica gel (5×1 cm) with a mixture of petroleum ether and AcOEt (80:20 to 70:30) to afford (±)-**432** (174 mg, 90%) as white crystals: mp 73-74 ^oC (AcOEt-petroleum ether); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.80 (ddd, *J* = 12.6, 8.7, 5.7 Hz, 1H), 2.46 (dd, *J* = 16.0, 6.5 Hz, 1H), 2.70 (dd, *J* = 16.0, 7.6 Hz, 1H), 2.81 (dt, *J* = 12.6, 7.8 Hz, 1H), 3.61 (s, 3H), 3.92-3.99 (m, 1H), 4.82 (t, *J* = 8.2 Hz 1H), 5.30 (br s, 1H), 7.19 – 7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 39.7 (CH_2), 43.9 (CH_2), 51.8 (CH_3), 57.6 (CH), 84.7 (CH), 126.2 (2 × CH), 127.0 (CH), 128.6 (2 × CH), 139.5 (C), 171.9 (C); **IR** ν 3250, 3032, 2953, 1732, 1495, 1437, 1375, 1263, 1206, 1157, 1045, 910, 758, 731 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 222 [(M + H)$^+$ 100], 107 (13); **HRMS** (CI/isobutane) 222.1127 ($C_{12}H_{15}NO_3$ + H^+ requires 222.1130).

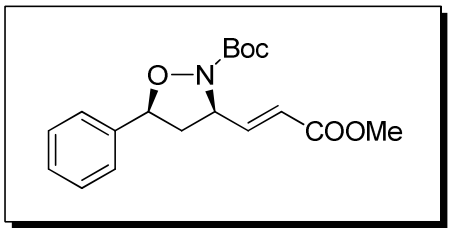


(3*R*,5*S*,1'*R*)-(-)-3-{[2'-(Methoxycarbonyl)-1'-methyl]-eth-1'-yl}-5-phenyl-isoxazolidine (271). Treatment of **270** (30 mg) under the same conditions as described for the preparation of **432**, afforded **271** (18 mg, 88%) as long colourless needles: mp 73-74 ^oC (from hexane); $[\alpha]_D$ -

47.9 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.19 (d, *J* = 7.1 Hz, 3H), 1.90 (ddd, *J* = 12.5, 9.3, 6.7, 1H), 2.68 (dq, *J* = 9.2, 7.2 Hz, 1H), 2.77 (ddd, *J* = 12.5, 7.8, 7.2 Hz, 1H), 3.70 (s, 3H), 3.80-3.86 (m, 1H), 4.87 (br s, 1H), 5.79 (br s, 1H), 7.27-7.41 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 13.4 (CH_3), 28.7 (CH_2), 40.9 (CH_2), 50.8 (CH_3), 62.2 (CH), 84.0 (CH), 125.17 (2 × CH), 127.0 (CH), 127.5 (2 × CH), 138.3 (C), 174.6 (C); **MS** (FAB+) *m/z* (%) 236 [(M + H)$^+$, 12], 233 (9), 268 (100), 207 (22), 147 (27); **HRMS** (FAB+) 236.1284 [($C_{13}H_{17}NO_3$ + H^+) requires 236.1287].

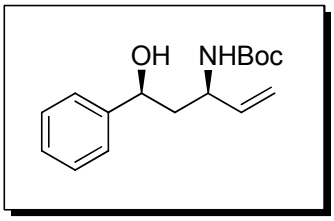


(3*S,5*R**)-(±)-*N,N*'-Biisopropoxycarbonyl-3-(Methoxycarbonylmethyl)-5-phenylpyrazolidine (287).** Method I, starting with **286**, produced **287** (85 mg, 73%) as a viscous colourless oil; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.15 (d, *J* = 6.3 Hz, 3H), 1.17 (d, *J* = 6.4 Hz, 3H), 1.19 (d, *J* = 3.9 Hz, 3H), 1.20 (d, *J* = 3.8 Hz, 3H), 2.30-2.47 (m, 3H), 2.78 (dd, *J* = 15.9, 5.3 Hz, 1H), 3.63 (s, 3H), 4.54-4.60 (br. m, 1H), 4.84-4.99 (m, 2H), 5.34 (dd, *J* = 8.0, 5.1 Hz, 1H), 7.15-7.32 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 21.91 (CH_3), 21.94 (CH_3), 21.95 (CH_3), 21.98 (CH_3), 38.4 (CH_2) 39.9 (CH_2), 51.8 (CH_3), 55.5 (CH), 61.9 (CH), 70.0 (CH), 70.2 (CH), 125.9 (2 × CH), 127.3 (CH), 128.5 (2 × CH), 140.3 (C), 156.0 (C), 157.1 (C), 170.9 (C); **MS** (FAB/NOBA) *m/z* (%) 393 [(M + H)$^+$, 100], 307 (48), 306 (67), 261 (10), 219 (31), 189 (10), 154 (10), 145 (17), 117 (20), **HRMS** (FAB+) 393.2022 ($C_{20}H_{28}O_6N_2$ + H^+) requires 393.2026.

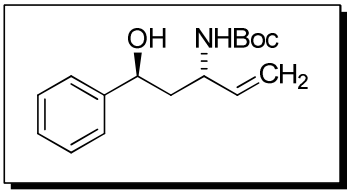


(3*R*,5*S*,*E*)-(–)-*N*-*tert*-Butoxycarbonyl-3-[1'-(Methoxycarbonyl)-ethen-2'-yl]-5-phenyl-isoxazolidine (291). Modified Method I, starting with **267**, produced **291** (36 mg, 45%) as a

viscous colourless oil: $[\alpha]_D$ -6.8 (*c* 0.8, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 2.06 (ddd, *J* = 12.4, 10.0, 6.9 Hz, 1H), 2.94 (ddd, *J* = 12.4, 8.8, 6.2 Hz, 1H), 3.76 (s, 3H), 4.90 (dd, *J* = 10.0, 6.2 Hz, 1H), 4.92-4.98 (m, 1H), 6.13 (dd, *J* = 15.5, 1.4 Hz, 1H), 6.95 (dd, *J* = 15.5, 6.0 Hz, 1H), 7.30-7.41 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.2 (CH_3), 43.2 (CH_2), 51.7 (CH_3), 60.9 (CH), 82.6 (C), 82.9 (CH), 121.0 (CH), 126.8 (2 × CH), 128.6 (2 × CH), 128.8 (CH), 136.4 (C), 146.5 (CH), 157.3 (C), 166.7 (C); **IR** ν 2956, 2923, 2854, 1723, 1459, 1369, 1308, 1260 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 334 [$(M + H)^+$, 20], 307 (31), 278 (100), 233 (41), 201 (22), 174 (32), 155 (39), 139 (41), 105 (15); **HRMS** (FAB) 334.1658 ($C_{18}H_{24}NO_5$ requires 334.1654).

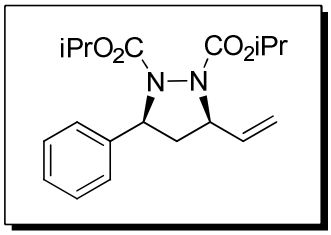


***tert*-Butyl (3*R*,5*S*)-(-)-5-Hydroxy-5-phenylpent-1-en-3-ylcarbamate (296a).** Method J, starting with **293a**, produced **296a** (92 mg, 61% yield) as a viscous colourless oil: $[\alpha]_D$ -23.8 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.43 (s, 9H), 1.80-1.92 (br. m, 1H), 1.98 (dt, J = 14.1, 8.1 Hz, 1H), 2.67 (br. s, 1H), 4.25 (br. s, 1H), 4.65-4.75 (br. m, 1H), 4.78 (dd, *J* = 8.4, 4.8 Hz, 1H), 5.12 (d, *J* = 10.4 Hz, 1H), 5.20 (d, *J* = 17.2 Hz, 1H), 5.74-5.82 (m, 1H), 7.23-7.40 (m, 5H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 44.3 (CH_2), 51.3 (CH), 72.2 (CH), 79.6 (C), 115.0 (CH_2), 125.8 (2 × CH_2), 127.7 (CH), 128.6 (2 × CH_2), 138.6 (CH), 144.4 (C), 155.5 (C); **IR** ν 3404, 3339, 2977, 2927, 1692, 1504, 1250, 1170 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 278 [$(M + H)^+$, 32], 204 (84), 148 (23), 144 (22); **HRMS** (FAB^+) 278.1754; ($C_{16}H_{23}NO_3 + H^+$ requires 278.1756).

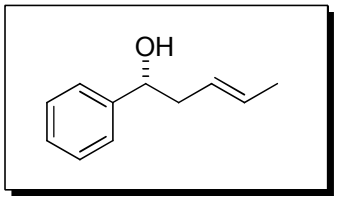


***tert*-Butyl (3*S*,5*S*)-(+)-5-Hydroxy-5-phenylpent-1-en-3-ylcarbamate (296b).** Method J, starting with **293b**, produced **296b** (32 mg, 21% yield) as a viscous colourless oil: $[\alpha]_D$ +0.7 (*c*

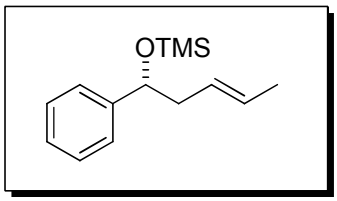
1.7, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.41 (s, 9H), 1.63 (ddd, *J* = 14.0, 10.3, 2.6 Hz, 1H), 1.89 (ddd, *J* = 14.1, 10.9, 3.3 Hz, 1H), 3.82 (br. s, 1H), 4.45 (br. s, 1H), 4.69 (br. d, *J* = 10.7 Hz, 1H), 4.83 (br. d, *J* = 8.7 Hz, 1H), 5.08 (d, *J* = 10.5 Hz, 1H), 5.15 (d, *J* = 17.3 Hz, 1H), 5.80 (ddd, *J* = 17.3, 10.5, 6.7 Hz, 1H), 7.16-7.21 (m, 1H), 7.25-7.32 (m, 4H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 45.4 (CH_2), 49.7 (CH), 70.2 (CH), 80.1 (C), 114.8 (CH_2), 125.6 (2 × CH), 127.3 (CH), 128.4 (2 × CH), 138,1 (CH), 144.1 (C), 156.7 (C); **IR** ν 3400, 3342, 3064, 2924, 2854, 1691, 1502, 1454, 1365, 1250, 1168, 1024, 996, 758 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 278 [$(M + H)^+$, 57], 222 (16), 204 (100), 144 (14), 101 (90); **HRMS** (FAB^+) 278.1761; ($C_{16}H_{23}NO_3 + H^+$ requires 278.1756).



(3*S*,5*R*)-(-)-*N,N*'-Bisisopropoxycarbonyl-3-vinyl-5-phenylpyrazolidine (298). Modified Method I, starting with **297**, produced **298** (31.5 mg, 65%) as a viscous colourless oil: $[\alpha]_D$ -19.3 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.22 (d, *J* = 6.2 Hz, 3H), 1.26 (d, *J* = 6.3 Hz, 3H), 1.263 (d, *J* = 6.3 Hz, 3H), 1.29 (d, *J* = 6.3 Hz, 3H), 2.33 (ddd, *J* = 12.7, 7.5, 6.6 Hz, 1H), 2.37 (ddd, *J* = 12.7, 7.9, 4.0 Hz, 1H), 4.78 (br. s, 1H), 4.93 (septet, *J* = 6.3 Hz, 2H), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H). 5.19 (t, *J* = 7.2 Hz, 1H), 5.35 (dt, *J* = 17.2, 1.5 Hz), 5.71 (ddd, *J* = 17.2, 10.4, 4.6 Hz, 1H), 7.15-7.30 (m, 5H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 21.96 (CH_3), 21.98 (2 × CH_3), 22.02 (CH_3), 40.7 (CH_2), 60.7 (CH), 62.0 (CH), 69.98 (CH), 70.05 (CH), 115.9 (CH_2), 125.9 (2 × CH), 127.2 (CH), 128.5 (2 × CH), 135.6 (CH), 140.8 (C); **IR** ν 2980, 2936, 1697, 1373, 1303, 1103, 920, 756 cm^{-1} ; **MS** (EI) *m/z* (%) 346 (M^+, 9), 260 (37), 218 (54), 215 (13), 173 (100), 129 (21), 104 (13), 83 (22); **HRMS** (EI) 346.1896; ($C_{19}H_{26}O_4N_2^+$ requires 346.1893).



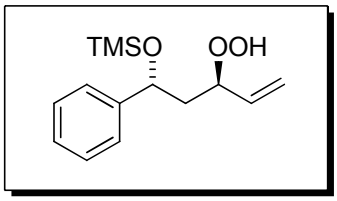
(*R*,*E*)-(+)-1-Phenylpent-3-en-1-ol (256). Method D, starting with benzalehyde, produced **256** (131 mg, 81% yield) as colourless oil: $[\alpha]_D$ +64.9 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.57 (br d, *J* = 6.4 Hz,, 3H,), 2.23-2.37 (m, 3H,), 4.52 (dd, *J* =5.1 Hz, *J* = 7.8 Hz, 1H), 5.25-5.35 (m, 1H), 5.41-5.52 (m, 1H), 7.12-7.26 (m, 5H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 18.0 (CH_3), 42.6 (CH_2), 73.4 (CH), 125.7 (2 × CH), 126.7 (CH), 127.2 (CH), 128.2 (2 ×CH), 129.1 (CH), 144.0 (C); **IR** ν 3650, 3360, 3027, 2963, 2916, 1493, 1453, 1270, 1026, 912, 872, 799, 758, 700 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 145 (M - OH, 100), 107 (93); **HRMS** (CI//isobutene) 145.1022 ($C_{11}H_{12}$ + H^+) requires 145.1017, in agreement with literature;[173] HPLC analysis (Chiralcel OD-H column, hexane/2-propanol 98:2, 0.75 mL/min) showed 94% ee (t_R = 17.43min, t_S = 24.59 min).



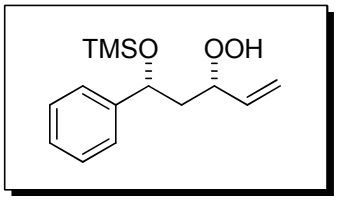
(*R*,*E*)-(+)-1-Phenyl-1-trimethylsilyloxy-pent-2-ene (304).[199] Trimethylsilyl trifluoromethanesulfonate (880 mg, 3.96 mmol) was added dropwise to a solution of the alcohol **256** (584 mg, 3.6 mmol) and triethylamine (550 mg, 5.4 mmol) in dry dichloromethane (10 mL) at room temperature and the resulting mixture was stirred at this temperature for 1 h. The reaction was quenched with a saturated aqueous solution of sodium hydrogen solution (10 mL) and the product was extracted into dichloromethane (3 × 10 mL). The organic solution was dried over magnesium sulfate and the solvent was evaporated in vacuo. The residue was purified by chromatography on a column of silica gel (3 × 10 cm), using a mixture of petroleum ether and ethyl acetate (99:1) to afford **304** as a colourless oil (888 mg, 95%): $[\alpha]_D$ +33.4 (*c* 1.5, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.0 (s, 9H), 1.60 (d, *J* = 5.7 Hz, 3H), 2.34-2.39 (m, 2H), 4.58 (dd, *J* = 7.6, 5.4 Hz, 1H), 5.21-5.48 (m, 2H), 7.17-7.31 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0 (3 × CH_3), 17.4 (CH_3), 43.7 (CH_2), 75.1 (CH), 125.7 (2 × CH), 126.7 (CH),

127.2 (CH), 127.7 (CH), 127.9 (2 × CH), 144.9 (C); **MS** (FAB) *m/z* (%) 145 (M - OTMS, 100) (as with alcohol **256**, no molecular peak could be observed).

Method K: Singlet oxygen ene reaction.[145] A pink solution of the TMS ether **304** (888 mg, 3.8 mmol) and TPP (Tetraphenylporphyrin) (0.6 mg, 10^{-3} mmol) in CCl_4 (10 mL) were added to a transparent glass reaction vessel fitted with an oxygen diffuser and a stirrer. The reaction flask was placed in a water cooling jacket and a moderate stream of dry oxygen was run through the system, while stirring vigorously for the best oxygen dispersion. A portable 500W halogen lamp was used to irradiate the reaction mixture, and the reaction was monitored by H^1 NMR every 4 h. The reaction takes typically 20-24 h. After completion, CCl_4 was evaporated and the oily residue analysed by NMR spectroscopy. In optimised condions a mixture of 2 : 1 of 1,3 and 1,4 diols was obtained. 2 : 1 ratio of *anti*/*syn* 1,3 diols was observed. The mixture was purified by chromatography on a column of silica gel (2.5 × 25 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 90:10). *Syn* and *anti* 1,3 diols were isolated in low yields of 17 and 27% respectively followed by an inseparable mixture of 1,4 diols (21%).



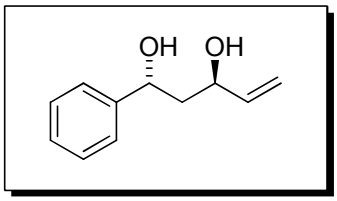
(1*R*,3*R*)-(+)-3-Hydroperoxy-1-phenyl-1-trimethylsilyloxy-pent-4-ene (387). Method K, starting with **304**, produced **387** (254 mg, 27%) as a viscous colourless oil: $[\alpha]_D$ + 33.9 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.0 (s, 9H), 1.82 (ddd, *J* = 14.8, 8.7, 3.1 Hz, 1H), 1.92 (ddd, *J* = 14.8, 9.2, 3.9 Hz, 1H), 4.48-4.53 (m, 1H), 4.85 (dd, 9.2, 3.1 Hz, 1H), 5.21 (dd, *J* = 10.5, 1.2 Hz, 1H), 5.27 (dd, *J* = 17.4, 1.2 Hz, 1H), 5.79 (ddd, *J* = 17.4, 10.5, 6.9 Hz, 1H), 7.11-7.27 (m, 5H), 8.42 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0 (3 × CH_3), 43.1 (CH_2), 71.1 (CH), 82.7 (CH), 118.4 (CH_2), 125.7 (2 × CH), 127.2 (CH), 128.3 (2 × CH), 136.6 (CH), 144.6 (C); **IR** ν 3348, 2955, 1420, 1366, 1257, 840 cm^{-1}; **MS** (FAB/NOBA) *m/z* (%) 267 [(M + H)$^+$,14], 253 (36), 179 (100), 147 (70); **HRMS**. (FAB+) 267.1410 ($C_{14}H_{23}O_3Si$ + H^+ requires 267.1416).



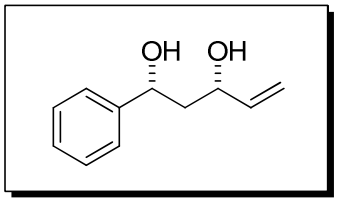
(1*R*,3*S*)-(+)-3-Hydroperoxy-1-phenyl-1-trimethylsilyloxy-pent-4-ene (388). Method K, starting with **304**, produced **388** (169 mg, 17% yield) as a viscous colourless oil: $[\alpha]_D$ +51.0 (*c* 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 0.0 (s, 9H), 1.74 (ddd, *J* = 14.3, 6.4, 4.9, 1H), 2.25 (ddd, *J* = 14.3, 8.7, 7.8 Hz, 1H), 4.39 (q, *J* = 7.0 Hz, 1H), 4.76 (dd, *J* = 8.7, 4.4 Hz, 1H), 5.29-5.33 (m, 2H), 5.88 (ddd, *J* = 17.5, 10.5, 7.1 Hz, 1H), 7.24-7.35 (m, 5H), 8.35 (s, 1H);); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 0.0 (3 × CH_3), 42.7 (CH_2), 72.5 (CH), 84.3 (CH), 118.7 (CH_2), 125.9 (2 × CH), 127.4 (CH), 128.2 (2 × CH), 136.8 (CH), 144.4 (C); **IR** ν 3348, 2955, 1420, 1366, 1257, 840 cm^{-1} ; **MS** (CI/isobutane) *m/z* (%) 249 (M - OH, 20), 179 (100), 159 (59), 149 (30); **HRMS** (CI//isobutene) 249.1307 ($C_{14}H_{21}O_2Si^+$ requires 249.1311).

Method L. Deprotection of TMS alkoxy peroxides. TBAF/THF (1M solution, 1 mL, 1 mmol) was added slowly to a solution of the TMS alkoxy peroxides (0.9 mmol) in THF (8 mL) at 0 ^oC and the reaction mixture was stirred at room temperature, while monitored by TLC/$KMnO_4$. After completion (3-4 h), the excess of THF was slowly evaporated and a saturated $NaHCO_3$ solution (5 mL) was added. The product was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic extracts were dried over Na_2SO_4. The ^{1}H NMR spectrum of the crude mixture usually showed a partial reduction of the peroxide. The crude mixture was submitted for the reduction step without further purifications.

Method M. Reduction of peroxy alcohols.[164] PPh_3 (350 mg, 1.35 mmol) was added in one portion to a solution of the peroxy alcohol/diol (0.9 mmol) in diethyl ether (30 mL) under argon and the mixture was stirred overnight at room temperature. After 16 h the solvent was evaporated and the ^{1}H NMR spectrum of the crude product confirmed full conversion. The oily residue was purified on a column of silica gel (2.5 × 15 cm) using a gradient of petroleum ether and ethyl acetate as eluent (5:1 to 1:1).



(1*R*,3*R*)-(+)-1-Phenylpent-4-ene-1,3-diol (404). Method L followed by Method M, starting with **387**, produced **404** (112 mg, 76% yield) as a viscous colourless oil: $[\alpha]_D$ +22.6 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.90 (ddd, *J* = 14.6, 7.7, 3.2 Hz, 1H), 2.04 (ddd, *J* = 14.6, 8.7, 3.5 Hz, 1H), 2.60 (br d, *J* = 4.3 Hz, 1H), 2.93 (br d, *J* = 3.5 Hz, 1H), 4.10 (br s, 1H), 5.04 (dt, *J* = 8.5, 2.9Hz, 1H), 5.16 (dt, *J* = 10.5, 1.4, 1H), 5.30 (dt, *J* = 17.2, 1.5 Hz, 1H), 5.95 (ddd, *J* = 17.2, 10.5, 5.4 Hz, 1H), 7.25-7.41 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 44.3 (CH_2), 70.6 (CH), 71.7 (CH), 114.7 (CH_2), 125.0 (2 × CH), 125.6 (CH), 128.5 (2 × CH), 140.4 (CH), 144.3 (C); **IR** ν 3373, 2960, 2859, 1718, 1427, 1269, 1111, 924 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 161 (M - OH, 20), 145 (54), 105 (100); **HRMS** (CI//isobutene) 161.0965 ($C_{11}H_{13}O^+$ requires 161.0966. In agreement with the literature.[165]

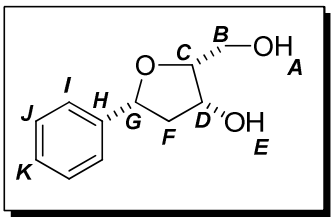


(1*R*,3*S*)-(+)-1-Phenylpent-4-ene-1,3-diol (406). Method L followed by Method M, starting with **387**, produced **406** (78 mg, 70% yield) as a viscous colourless oil: $[\alpha]_D$ +38.0 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.85 (dt, *J* = 14.6, 3.1 Hz, 1H), 1.95 (dt, *J* = 14.6, 9.8 Hz, 1H), 2.89 (br d, *J* = 2.4 Hz, 1H), 3.20 (br d, *J* = 1. Hz, 1H), 4.45 (br s, 1H), 4.91 (dd, *J* = 9.0, 3.0 Hz, 1H), 5.04 (dt, *J* = 10.4, 1.2 Hz, 1H), 5.21 (dt, *J* = 17.2, 1.3Hz, 1H), 5.89 (ddd, *J* = 17.2, 10.4, 5.9, 1H), 7.26-7.39 (m, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 45.3 (CH_2), 73.5 (CH), 74.8 (CH), 114.7 (CH_2), 125.7 (2 × CH), 127.7 (CH), 128.6 (2 × CH), 140.4 (CH), 144.3 (C); **IR** ν 3383, 2926, 2857, 1455, 1266, 1062, 911 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 161 (M - OH,12), 145 (7), 105 (100); **HRMS** (CI//isobutene) 161.0962 ($C_{11}H_{13}O^+$ requires 161.0966). In agreement with the literature.[165]

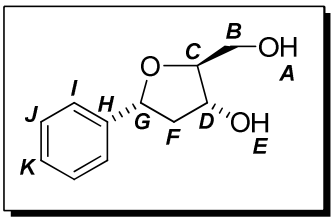
Method N. Epoxidation of the allylic diols.[176] $VO(acac)_2$ (1.8 mg, 0.007 mmol) was added in one portion to a solution of the respective diol (0.14 mmol) in toluene or CH_2Cl_2 (0.5 mL) at 0

^{o}C. Subsequently, a solution TBHP (0.16 mmol), prepared by diluting of its 6M solution in nonane (27 μL) with toluene or CH_2Cl_2 (0,.5 mL). The reaction mixture was stirred at this temperature for 1 h and then at room temperature overnight. Full consumption of the starting material was confirmed by TLC analysis by then. A saturated $NaHCO_3$ solution (1 mL) was added and the product was extracted into CH_2Cl_2 (3 × 5 mL). Combined organic fractions were dried over sodium sulfate and the solvents were removed in vacuum. The product was purified by chromatography on a column of silica gel (1 × 7 cm) using a gradient of petroleum ether and ethyl acetate as eluent (5:1 to 1:1) to collect the epoxide, followed by 100% AcOEt to collect the corresponding tetrahydrofurane derivatives.

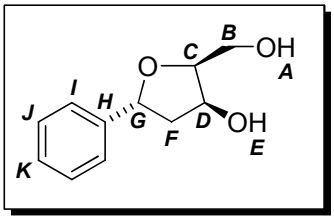
Method O. Intramolecular opening of the epoxides.[177] A solution of BF_3•Et_2O (0.008 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to solution of the respective epoxide (0.08 mmol) in CH_2Cl_2 (0.5 mL) and the reaction mixture was stirred at room temperature for 30 min, by which time a full conversion was confirmed by TLC analysis. Saturated $NaHCO_3$ solution (1 mL) was added and the product was extracted into CH_2Cl_2 (3 × 5 mL). Combined organic extracts were dried over sodium sulfate and the solvents were removed in vacuum. The product was purified by chromatography on a column of silica gel (1 × 7 cm) using a gradient of petroleum ether and ethyl acetate as eluent (3:1, 2:1, 1:1, 1:2, 1:3) for the best separation of the diastereoisomers.



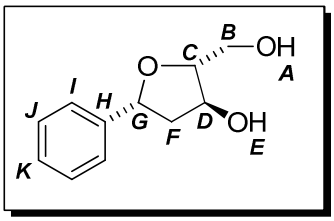
(2*R*,3*R*,5*R*)-(+)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ol (423). Method N, starting with **417**, produced **423** (30 mg, 49%) as colourless needles, mp: 63-64^{o}C (CH_2Cl_2/hexane); $[\alpha]_D$ +7.0 (*c* 0.9, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.96 (***F***, ddd, *J* = 13.4, 8.3, 4.6 Hz, 1H), 2.27 (***A***, dd, *J* = 7.2, 5.3 Hz, 1H), 2.73 (***F***, dt, *J* = 13.4, 7.0 Hz, 1H), 2.81 (***E***, d, *J* = 6.9 Hz, 1H), 3.97-4.10 (***B* + *C***, m, 3H), 4.60-4.66 (***D***, m, 1H), 4.88 (***G***, t, *J* = 7.7 Hz, 1H), 7.26-7.44 (***I* + *J* + *K***, m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 44.5 (***F***, CH_2), 61.9 (***B***, CH_2), 74.0 (***D***, CH), 79.1 (***G***, CH), 81.2 (***C***, CH), 126.3 (***I***, 2 × CH), 127.9 (***K***, CH), 128.6 (***J***, 2 × CH), 141.6 (***H***, C); **IR** ν 3379, 2924, 2862, 1450, 1257, 1034 cm^{-1}; **MS** (EI$^+$) *m/z* (%) 194 (M^+, 15), 163 (5), 145 (10), 117 (23), 105 (23); **HRMS**. (EI$^+$) 194.0941 ($C_{11}H_{14}O_3^+$ requires 194.0943).



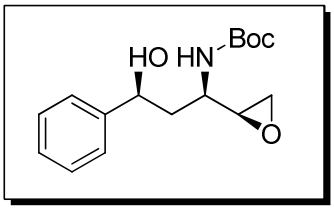
(2*S*,3*R*,5*R*)-(+)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ol (424). Method N, starting with **418**, produced **424** (3 mg, 14%) as a colourless solid: $[\alpha]_D$ +8.0 (*c* 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.80 (***E***, d, *J* = 5.4 Hz, 1H), 1.93 (***A***, t, *J* = 5.5 Hz, 1H), 2.08 (***F***, ddd, *J* = 12.7, 8.2, 7.1 Hz, 1H), 2.70 (***F***, dt, *J* = 12.7, 6.7 Hz, 1H), 3.75 (***B***, dt, *J* = 11.6, 5.3 Hz, 1H), 3.84 (***B***, dt, *J* = 11.6, 4.4 Hz, 1H), 4.09 (***C***, td, *J* = 5.1, 4.3 Hz, 1H), 4.43-4.49 (***D***, m, 1H), 5.11 (***G***, dd, *J* = 7.9, 7.1 Hz, 1H), 7.34 – 7.41 (***I* + *J* + *K***, m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 43.7 (***F***, CH_2), 62.8 (***B***, CH_2), 73.3 (***D***, CH), 79.6 (***G***, CH), 85.4 (***C***, CH), 125.6 (***I***, 2 × CH), 127.6 (***K***, CH), 128.6 (***J***, 2 × CH), 142.6 (***H***, C); **IR** ν 3379, 2924, 2854, 1442, 1087, 1034 cm^{-1}; **MS** (CI//isobutene) *m/z* (%) 195 [$(M + H)^+$, 53], 177 (100), 159 (23), 129 (28), 105 (18); **HRMS** (CI//isobutene) 195.1023 ($C_{11}H_{14}O_3$ +H^+ requires 195.1021).



(2*S*,3*S*,5*R*)-(+)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ol (425). Method N, starting with **420**, produced **425** (3 mg, 20% yield) as colourless shining plates: mp: 75-76 °C; $[\alpha]_D$ +56.2 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 2.07 (***F***, ddd, *J* = 13.3, 10.1, 4.6 Hz, 1H), 2.35 (***A***, dd, *J* = 6.9, 5.6 Hz, 1H), 2.44 (***F***, ddd, *J* = 13.3, 5.8, 1.4 Hz, 1H), 3.36 (***E***, d, *J* = 4.2 Hz, 1H), 3.98-4.10 (***B***, m, 2H), 4.24 (***C***, dd, *J* = 7.9, 3.9 Hz, 1H), 4.67 (***D***, t, *J* = 3.8 Hz, 1H), 5.33 (***G***, dd, *J* = 10.1, 5.8 Hz, 1H), 7.23-7.40 (***I* + *J* + *K,*** m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 45.3 (***F***, CH_2), 62.1 (***B***, CH_2), 74.9 (***D***, CH), 80.0 (***G***, CH), 81.4 (***C***, CH), 125.6 (***I***, 2 × CH), 127.6 (***K***, CH), 128.5 (***J***, 2 × CH), 142.4 (***H***, C); **IR** ν 3379, 2924, 2854, 1450, 1257, 1033 cm^{-1}; **MS** (EI+) *m/z* (%) 194 (M^+, 32), 145 (15), 117 (36), 105 (41); **HRMS**. (EI^+) 194.0948 ($C_{11}H_{14}O_3^+$ requires 194.0943).

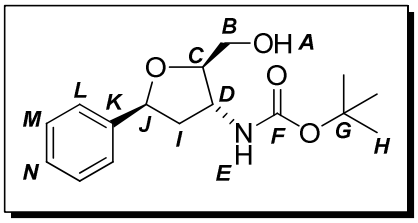


(2*R*,3*S*,5*R*)-(+)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ol (426). Method N, starting with **421**, produced **426** (8 mg, 25%) as a colourless solid: $[\alpha]_D$ + 42.8 (*c* 0.4, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.81 (***E***, br d, *J* = 4.0 Hz, 1H), 1.84 (***A***, t, *J* = 6.3 Hz, 1H), 1.99 (***F***, ddd, *J* = 13.3, 10.3, 6.3 Hz, 1H), 2.20 (***F***, ddd, *J* = 13.3, 5.7, 2.0 Hz, 1H), 3.63 (***B***, ddd, *J* = 11.5, 6.5, 5.0 Hz, 1H), 3.78 (***B***, ddd, *J* = 11.5, 5.5, 4.2 Hz, 1H), 3.96 (***C***, ddd, *J* = 4.8, 4.2, 3.0, Hz, 1H), 4.35 - 4.41 (***D***, m, 1H), 5.19 (***G***, dd, *J* = 10.3, 5.6 Hz, 1H), 7.28 -7.38 (***I* + *J* + *K***, m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 44.1 (***F***, CH_2), 63.5 (***B***, CH_2), 73.8 (***D***, CH), 80.1 (***G***, CH), 87.3 (***C***, CH), 126.0 (***I***, 2 × CH), 127.9 (***K***, CH), 128.6 (***J***, 2 × CH), 141.1 (***H***, C); **IR** ν 3356, 2924, 1450, 1257, 1087, 1041 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 195 [$(M + H)^+$, 35], 177 (86), 159 (27), 129 (37); **HRMS** (CI//isobutene) 195.1019 ($C_{11}H_{14}O_3 + H^+$ requires 195.1021).



***tert*-Butyl (1*S*,3*R*,4*S*)-(+)-1-Phenyl-4,5-epoxy-1-hydroxy-pentan-3-yl Carbamate (430).**[172a] *m*-Chloroperoxybenzoic acid (44 mg, 0.25 mmol) was added in one portion to a solution of **296a** (64 mg, 0.23 mmol) in dichloromethane (2 mL) at 0 °C. The reaction mixture was stirred at this temperature for 2 h and than at room temperature overnight. The reaction was quenched with a saturated aqueous solution of sodium hydrogen carbonate solution (2 mL), the product was extracted into dichloromethane (3 × 3 mL), the organic solution was dried over sodium sulfate and the solvent was evaporated in vacuo. The residue was purified by chromatography on a column of silica gel (1 × 7 cm), using a gradient of petroleum ether and ethyl acetate as eluent (9:1 to 2:1) to afford **430** (46 mg, 68%) as a viscous colourless oil: $[\alpha]_D$ -28.0 (*c* 1.3, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.43 (s, 9H), 1.97–2.11 (m, 2H), 2.52 (br s, 1H), 2.61 (dd, *J* = 4.7, 2.7 Hz, 1H), 2.75 (dd, *J* = 4.6, 4.1 Hz, 1H), 3.09 (dt, *J* = 4.0, 2.6 Hz, 1H), 4.01 (br s, 1H), 4.59 (br s, 1H), 4.87 (ddd, *J* = 7.6, 5.9, 3.5 Hz, 1H), 7.26-7.39 (m, 5H); **^{13}C NMR** (100

MHz, $CDCl_3$) δ 28.3 (3 × CH_3), 42.4 (CH_2), 44.5 (CH_2), 47.4 (CH), 53.5 (CH), 72.0 (CH), 79.8 (C), 125.8 (2 × CH), 127.8 (CH), 128.6 (2 × CH), 144.1 (C), 156.8 (C); **IR** ν 3428, 3331, 2978, 2931, 1691, 1506, 1367, 1166, cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 294 [$(M + H)^+$, 20], 238 (100), 220 (76); **HRMS** (CI//isobutene) 294.1706 ($C_{16}H_{23}O_4N + H^+$ requires 294.1705).



tert*-Butyl (2*R*,3*R*,5*S*)-(-)-2-(Hydroxymethyl)-5-phenyltetrahydrofuran-3-ylcarbamate (431).** Method N, starting with **430**, produced **431** (9 mg, 43%) as a viscous colourless oil: $[\alpha]_D$ -7.9 (*c* 0.6, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.46 (H***, s, 9H), 2.13-2.27 (***I***, m, 2H), 2.83 (***A***, br s, 1H), 3.77-3.85 (***B***, m, 2H), 3.88 (***C***, dd, *J* = 9.5, 4.9, 1H), 4.08-4.18 (***D***, br m, 1H), 4.82 (***E***, br s, 1H), 5.05 (***J***, dd, *J* = 8.3, 6.9 Hz, 1H), 7.27-7.35 (***L* + *M* + *N***, m, 5H); **^{13}C NMR** (100.6 MHz, $CDCl_3$) δ 28.4 (***H***, 3 × CH_3), 41.2 (***I***, CH_2), 53.0 (***D***, CH), 63.6 (***B***, CH_2), 79.6 (***J***, CH), 80.4 (***G***, C), 86.3 (***C***, CH), 125.9 (***L***, 2 × CH), 127.9 (***N***, CH), 128.6 (***M***, 2 × CH), 141.3 (***K***, C), 156.9 (***F***, C); **IR** ν 3426, 3330, 2979, 2930, 2879, 1684, 1525, 1367, 1287, 1254, 1168, 1050 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 294 [$(M + H)^+$, 7], 257 (25), 238 (48); **HRMS** (CI//isobutene) 294.1703 ($C_{16}H_{23}O_4N + H^+$ requires 294.1705).

5. References

1. (a) Grignard, V. *Compt. Rend.* **1900,** *130*, 1322. (b) Barbier, P. *Compt. Rend.* **1899,** *128,* 110.
2 For leading reviews, see: (a) Hoffmann, R. W. *Angew. Chem. Int. Ed.* **1987**, *26*, 489-503. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Denmark, S. E.; Stavenger, R. A. *Acc. Chem. Res.* **2000**, *33*, 432. (d) Denmark, S. E.; Fu, J. P. *Chem. Commun.* **2003**, 167; (e) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (f) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (g) Denmark, S. E.; Almstead, N. G. *J. Mex. Chem. Soc.* **2009**, *53*, 174. For allylboron reagents, see: (h) Roush, W. R. In *Comprehensive Organic Synthesis* (Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.); Pergamon: Oxford 1991; Vol 2, p 1. (i) Hall, D. G.; Lachance, H. *Org. React.* **2008**, *73*, 1. For allylsilanes, see: (j) Sakurai, H. *Pure Appl. Chem.* **1982**, *54*, 1. (k) Hosomi, A. *Acc. Chem. Res.* **1988**, *21*, 200. (l) Fleming, I.; Dunogués, J.; Smithers, R. *Org. React.* **1989**, *37*, 57. (m) Fleming, I.; Barbero, A.; Walter, D. **1997**, *97*, 2063. (n) Gung, B. W. *Org. React.* **2004**, *64*, 1. (o) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991. (p) Hargaden, G. C.; Guiry, P. I. *Adv. Synth. Catal.* **2007**, *349*, 2407. (q) Duthaler, R. O.; Hafner, A. *Chem. Rev*. **1992**, *92*, 807.
3. Mikhailov, B. M.; Bubnov, Y. N. *Izv. Akad. Nauk SSSR Ser. Khim*. **1964**, 1874.
4. (a) Herold, T.; Hofmann, R. W. *Angew. Chem. Int. Ed. Engl.* **1978**. *17*, 768. (b) Hoffmann, R. W.; Herold T. *Chem. Ber.* **1981,** *114*, 375.
5. Brown, H. C.; Jadhav, P. K. *J. Am. Chem. Soc*. **1983**, *105*, 2092.
6. Reetz, M. T. *Pure Appl. Chem.* **1988**, *60*, 1607.
7. Roush, W. R.; Walts, A. E.; Hoong L. K. *J. Am. Chem. Soc.* **1985**, *107*, 8186.
8. Corey, E. J.; Yu, C. M.; Kim, S. S. *J. Am. Chem. Soc.* **1989**, *1*, 5495.
9. (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett*. **1976**, 1295. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, 941.
10. (a) Schweig, A.; Weidner, U.; Manuel, G. *J. Organomet. Chem*. **1974**, *67*, C4. (b) Hartman, G. D.; Traylor, T. G. *Tetrahedron Lett*. **1975**, *11*, 939.
11. Hayashi, T.; Kabeta, K.; Hamachi, I.; Kumada, M. *Tetrahedron Lett*. **1983**, *24*, 2865.
12. Denmark, S. E.; Weber, E. J. *Helv. Chim. Acta* **1983**, *66*, 1655.
13. (a) Lee, P. H.; Lee, K.; Sung, S.; Chang, S. *J. Org. Chem.* **2001**, *66,* 8646. (b) Hollis, K. H.; Robinson, N. P.; Whelan, J.; Bosnich, B. *Tetrahedron Lett*. **1993**, *34*, 4309.

14. Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi A. *J. Am. Chem. Soc.* **1993***, 115,* 7001.
15. Wadamoto, M.; Yamamoto, H. *J. Am. Chem. Soc,* **2005**, *127*, 14556.
16. Evans, D. A.; Aye Y.; Wu, J. *Org. Lett*. **2006,** *8*, 2071.
17. (a) Ishihara, K.; Mouri, M.; Gao, Q.; Maruyama, T.; Furuta, K.; Yamamoto, H. *J. Am. Chem. Soc.* **1993**, *115*, 1490. (b) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, *68*, 5593. (c) Shizuka, M.; Snapper, M. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 5049 (d) Yanagisawa, A.; Nakashima, H.; Ishiba, A.; Yamamoto H. *J. Am. Chem. Soc.* **1996**, *118,* 4723. (e) Yu, C. M.; Choi, H. S.; Jung W. H.; Kim, H. J.; Lee, J. K. *Bull. Korean Chem. Soc*. **1997**, *18*, 471.
18. Denmark, S. E.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2003,** *47***,** 1560.
19. (a) van Leeuwen, P.W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741. (b) Tolman, C. A. *Chem. Rev.* **1977**, *77*, 313.
20. (a) Gutmann, V. *Coord. Chem. Rev.* **1975**, *15*, 207. (b) Holmes, R. R. *Chem. Rev*. **1996**, 96, 927.
21 (a) Gay-Lussac, J. L. Thénard, L. J. *Mémories de physique et de chimie de la Société d'Arcueil*, **1809**, *2*, 317. (b) Davy, J. *Phil Trans Roy London,* **1812**, *102*, 352.
22. (a) Gutmann, V. *The Donor-Acceptor Approach to Molecular Interactions*, Plenum, New York, **1978**, Chapter 1. (b) Jensen, W. B. The Lewis Acid-Base Concepts, Wiley-Interscience, New York, **1980**, 135.
23. Tandura, S. N.; Voronkov, M. G.; Alekseev, N. V. *Top. Curr. Chem*. **1986**, *131*, 99.
24. (a) Bent, H. A. *Chem. Rev.* **1961**, *61*, 275. (b) Jonas, V.; Boehme, C.; Frenking, G. *Inorg. Chem*. **1996**, *35*, 2097.
25. (a) Orito, Y.; Nakajima, M. *Synthesis*, **2006**, *9*, 1391. (b) Corriu, R. J. P. *J. Organomet. Chem*. **1990**, *400*, 81. (c) Kira, M.; Sato, K.; Sakurai, H.; Hada, M.; Izawa, M.; Ushio, J. *Chem. Lett.* **1991**, 387.
26. Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett*, **1987**, *28*, 4081.
27. (a) Kobayashi, S.; Nishio, K. *Tetrahedron Lett*. **1993**, *34*, 3453. (b) Kobayashi, S. Nishio, K. *J. Org. Chem*. **1994**, *59*, 6620.
28. Denmark. S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161.
29. (a) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kobayashi, Y. *Tetrahedron Lett*. **1996**, *37*, 5149. (b) Iseki, K.; Kuroki, Y.; Takahashi, M.; Kishimoto, S.; Kobayashi, Y. *Tetrahedron*, **1997**, *5*3, 3513.

30. (a) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc*. **2000**, *122*, 12021. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc*. **2001**, *123*, 9488.
31. Kotani, S.; Hashimoto, S.; Nakajima, M. *Tetrahedron* , **2007** , *63* , 3122.
32. Simonini, V.; Benaglia, M.; Benincori, T. *Adv. Synth. Catal.* **2008**, *350*, 561.
33. Iseki, K.; Mizuno, S.; Kuroki, Y.; Kobayashi, Y. *Tetrahedron*, **1999,** *55*, 977.
34. Malkov, A. V.; Kočovský, P. *Eur. J. Org. Chem.* **2007**, 29.
35. Nakajima, M.; Saito, M.; Shiro, M.; Hashimoto, S. *J. Am. Chem. Soc*. **1998,** *120*, 6419.
36. (a) Shimada, T.; Kina, A.; Ikeda, S.; Hayashi, T. *Org. Lett*. **2002**, *4*, 2799. (b) Shimada, T.; Kina, A.; Hayashi, T. *J. Org. Chem.* **2003**, *68*, 6329.
37 (a) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kočovský P. *Org. Lett.* **2002**, *4*, 1047. (b) Malkov, A. V.; Bell, M.; Orsini, M.; Pernazza, D.; Massa, A.; Herrmann, P.; Meghani, P.; Kočovský, P. *J. Org. Chem.* **2003**, *68*, 9659.
38. Malkov, A.V.; Bell, M.; Vassieu1, M.; Bugatti, V.; Kočovský, P. *J. Mol. Catal.* **2003**, *196*, 179.
39. (a) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kočovský, P. *Angew. Chem. Int. Ed.* **2003**, *42*, 3674. (b) Malkov, A. V.; Ramírez-López, P.; Biedermannová, L.; Rulíšek, L.; Dufková, L.; Kotora, M.; Zhu, F.; Kočovský, P. *J. Am. Chem. Soc*. **2008**, *130*, 5341.
40. Malkov, A. V.; Bell M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219.
41. Kadlčíková, A.; Valterová, I.; Ducháčková, L.; Roithová, J.; Kotora, M. *Chem. Eur. J.* **2010**, *16*, 9442.
42. Mihelich, E. D.; Eickhoff, D. J.; *J. Org. Chem*. **1983**, *48*, 4135.
43. Kröhnke, F. *Synthesis*, **1976**, 1.
44. Erkkila, A.; Pihko, P. M. *Eur. J. Org. Chem*. **2007**, 4205
45. Hon, Y. S.; Sheu, T. R.; Lee, C. F. *Synth. Commun.* **2000**, *30*, 97.
46. (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S.-I. *J. Am. Chem. Soc*. **1998**, *120*, 6609. (b) Sumida, S.-I.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310.
47. (a) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka K. *J. Am. Chem. Soc*. **2001**, *123*, 9168. (b) Nokami, J.; Nomiyama, K,; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem. Int. Ed*. **2003**, *42*, 1273. (c) Nokami, J.; Nomiyama, K.; Shafi, S. M.; Kataoka, K. *Org. Lett*. **2004**, *6*, 1261.
48. (a) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Angew. Chem.* **2001**, *113*, 3005. (b) *Angew. Chem. Int. Ed.* **2001**, *40*, 2921.

49. Tan, K.-T.; Chan, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc*. **2003**, *125*, 2958.

50. (a) Hayashi, T.; Konishi, M.; Kumada, M. J. *Am. Chem. Soc.* **1982**, *104*, 4963. (b) Suginome, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chem. Eur. J.* **2005**, *11*, 2954. (c) Hayashi, T.; Konishi, M.; Kumada, M. *J. Chem. Soc., Chem. Commun.* **1983**, 736.

51. Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

52. Hayashi, T; Uozumi, Y. *Pure Appl. Chem.* **1992**, *64*, 1911.

53. (a) Hayashi, T.; Han, J. W.; Takeda, A.; Tang, J.; Nohmi, K.; Mukaide, K.; Tsuji, H.; Uozumi, Y. *Adv. Synth. Catal.* **2001**, *343*, 279. (b) Han, J. W.; Hayashi, T. *Tetrahedron: Asymmetry* **2002**, *13*, 325.

54. Hwang, R.; Gaspar, P. P. *J. Am. Chem. Soc.* **1978**, *100*, 6626.

55. Denmark, S. E.; Fu, J.; Lawler, M. J. *J. Org. Chem.* **2006**, 71, 1523.

56. (a) Beccalli, E. M.; Broggini, G. Martinelli, M. Sottocornola, S. Chem. Rev. **2007**, 107, 5318. (b) Zeni, G.; Larock, R. C. *Chem. Rev.* **2004**, 104, 2285.

57. Negishi, E. *Organopalladium Chemistry for Organic Synthesis*; J. Wiley: New York, 2002.

58. (a) Giannoccaro, P.; Nobile, C. F.; Mastrorilli, P.; N. Ravasio, *J. Organomet. Chem*., **1991**, 251. (b) Funk, J. K.; Yennawar, H.; Sen, A. *Helv. Chim. Acta.* **2006**, *89*, 1687. (c) Ren, W. Yamane, M. *J. Org. Chem,* **2010**, *75*, 8410.

59. Smidt, J.; Hafner, W.; Jira, R.; Sedlmeier, J.; Sieber, R.; Rüttinger, R.; Kojer, H. *Angew. Chem.* **1959**, *71*, 176.

60. (a) Fenton, D. M.; Steinwand, P. J. *J. Org. Chem.* **1972**, *37*, 2034. (b) Stille, Y. K.; James, D. E.; Hines, L. F. *J. Am. Chem. Soc.* **1973**, *95*, 5062. (c) James, D. E.; Hines, L. F.; Stille, J. K. *J. Am. Chem. Soc.* **1976**, *98*, 1810. (d) Yukawa T.; Tsutsumi, S. *J. Org. Chem.* **1969**, *34*, 738.

61. (a) Schoenberg, A.; Bartoletti, I.; Heck, R. F. *J. Org. Chem.* **1974**, *39*, 3318. (b) Ozawa, F.; Kawasaki, N.; Okamoto, H.; Yamamoto, T.; Yamamoto, A. *Organometallics*, **1987**, *6*, 1640.

62. Semmelhack, M. F.; Bozell, J. J.; Sato, T.; Wulff, W.; Spiess, E.; Zask, A. *J. Am. Chem. Soc.* **1982**, *104*, 5850.

63. (a) Semmelhack, M. F.; Bodurow, C. *J. Am. Chem. Soc.* **1984**, *106*, 1496. (b) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035.

64. Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483.

65. (a) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Hojo, M.; Yoshida, Z. *Tetrahedron Lett.* **1985**, *26*, 3207. (b) Tamaru, Y.; Higashimura, H.; Naka, K.; Hojo, M.; Yoshida, Z. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1045.

66. Kraus, G. A.; Li, J. *J. Am. Chem. Soc.* **1993**, *115*, 5859.

67. Walkup, R. D.; Park, G. *Tetrahedron Lett.* **1987**, *28*, 1023.

68. Eriksson, J.; Åberg, O.; Långström, B. *Eur. J. Org. Chem.* **2007**, 455.

69. (a) Yamamoto, A.; Ozawa, F.; Osakada, K.; Huang, L.; Son, T.; Kawasaski, N.; Doh, M.-K. *Pure Appl. Chem.* **1991**, *63*, 687. (b) Barnard, C. F. J. *Organometallics*, **2008**, *27*, 5402.

70. (a) Liptrot, D.; Alcaraz, L.; Roberts, B. *Adv. Synth. Catal*. **2010**, *352*, 2183. (b) Wolfe, J. P. *Eur. J. Org. Chem.* **2007**, 571.

71. (a) Hegedus, L. S.; Allen, G. F.; Olsen, D. J. *J. Am. Chem. Soc.*, **1980**, *102*, 3583. (b) Hegedus, L. S.; McKearin, J. M. *J. Am. Chem. Soc*. **1982**, *104*, 2444.

72. Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899.

73. (a) Tamaru, Y.; Kobayashi, T.; Kawamura, S.; Ochiai, H.; Yoshida, Z. *Tetrahedron Lett.*, **1985**, *26*, 4479. (b) Tamaru, Y.; Hojo, M.; Yoshida, Z. *J. Org. Chem.* **1988**, *53*, 5731.

74. Oh, C.-Y.; Kim, K.-S.; Ham, W.-H. *Tetrahedron Lett.* **1998**, *39*, 2133.

75. Tamaru, Y.; Hojo, M.; Higashimura, H.; Yoshida, Z. *J. Am. Chem. Soc.* **1988**, *110*, 3994.

76. (a) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *J. Am. Chem. Soc.* **1985**, *107*, 1797; (b) Hirama, M.; Shigemoto, T.; Yamazaki, Y.; Ito, S. *Tetrahedron Lett.* **1985**, *26*, 4133.

77. Harayama, H.; Abe, A.; Sakado, T.; Kimura, M.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem*. **1997**, *62*, 2113.

78. Tsujihara, T.; Shinohara, T.; Takenaka, K.; Takizawa, S.; Onitsuka, K.; Hatanaka, M.; Sasai. H. *J. Org. Chem.* **2009**, 9274.

79. Overman, L. E.; Remarchuk, T. P. *J. Am. Chem. Soc.* **2002**, *124*, 12.

80. Hirano, K.; Kubota, T.; Tsuda, M.; Mikami, Y.; Kobayashi, J. *Chem. Pharm. Bull.* **2000**, *48*, 974.

81. (a) Evina, C. M.; Guillerm, and G. *Tetrahedron Lett.*, **1996**, *37*, 163. (b) Asami, M.; Takahashi, J.; Inoue, S.; *Tetrahedron: Asymmetry.* **1994**, *5*, 1649.

82. (a) Chiacchio, U.; Gumina, G.; Rescifina, A.; Romeo, R. Uccella, N.; Casuscelli, F.; Piperno, A.; Romeo, G. *Tetrahedron,* **1996**, *52*, 8889. (b) Loh, B.; Vozzolo1, L.; Mok, B. J.; Lee, C. C.; Fitzmaurice, R. J.; Caddick, S.; Fassati, A. *Chem. Biol. Drug Des.* **2010** , *75*, 461. (c) Palmer, G. C.; Ordy, M. J.; Simmons, R. D.; Strand, J. C.; Radov, L. A.; Mullen, G. B.; Kinsolving, C. R.; Georgiev, V. S.; Mitchell, J. T., Allen, S. D. *Antimicrob. Agents Chemother.* **1989**, *33*, 895.

83. (a) Huisgen, R., *Angew. Chem. Int. Ed.*, **1963**, *2*, 633. (b) Huisgen, R., *Angew. Chem. Int. Ed.*, **1963**, *2* , 565. (c) Confalone, P. N.; Huie, E. M. *Org. React.* **1988**, *36*, 1.

84. Jones, R. C. F.; Martin, J. N. *Nitrones, Chem. Heterocycl. Compd.,* **2002***, 59,* 1.

85. (a) Kano, T.; Hashimoto, T.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 11926. (b) Jen, S. W.; Wiener, J. J. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2000**, *122*, 9874.

86. Bates, R. W.; Sa-Ei, K. *Org. Lett.* **2002**, *4*, 4225.

87. Bates, R. W.; Sa-Ei, K. *Tetrahedron* **2002**, *58*, 5957.

88. Bates, R. W.; Boonsombat, J. *Org. Biomol. Chem.* **2005**, *3*, 520.

89. Dongol, K. G.; Tay, B. Y.; Xiang, K. *Synth. Commun.* **2006,** *36*, 1247.

90. Byström, S. E.; Larsson, E. M.; Åkermark, B. *J. Org. Chem.* **1990**, *55*, 5674.

91. (a) Janza, B.; Studer, A. *J. Org. Chem.* **2005**, *70*, 6991. (b) Ishikawa, T.; Kawakami, M., Fukui, M.; Yamashita, A.; Urano, J.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 7734.

92. (a) Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 6528. (b) Foot, O. F.; Knight, D. W. *Chem. Commun.* **2000**, 975.

93. (a) Mitsunobu, O.; Yamada, Y. *Bull. Chem. Soc. Japan* **1967**, *40*, 2380. (b) Mitsunobu, O. *Synthesis* **1981**, 1. (c) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

94. Choong, I. C.; Ellman, J. A. *J. Org. Chem.* **1999**, *64*, 6528.

95. (a) Wolfe, J. P. *Synlett* **2008**, 2913. (b) Wolfe, J. P.; Rossi, M. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (c) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099. (d) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (e) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793. (f) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 6276.

96. Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302.

97. Di Grandi, M. J.; Tilley, J. W. *Tetrahedron Lett*. **1996**, *37*, 4327.

98. Juaristi, E. (Ed.) *Enantioselective Synthesis of β-Amino Acid*s; Wiley–VCH: New York, **1997.**

99. (a) Shinagawa, S.; Kanamaru, T.; Harada, S.; Asai, M.; Okazaki, H. *J. Med. Chem.* **1987**, *30*, 1458. (b) Shih, C.; Gossett, L. S.; Gruber, J. M.; Grossman, C. S.; Andis, S.

L.; Schultz, R. M.; Worzalla, J. F.; Corbett, T. H.; Metz, J. T. *Biorg. Med. Chem. Lett*. **1999**, *9*, 69. (c) Tamura, S.; Kuyama, S.; Kodaira, Y.; Higashikawa, S. *Agric. Biol. Chem*. **1964**, *28*, 137. (d) Morel, E.; Paıs, M.; Turpin, M.; Guyot, M. *Biomed. Pharmacother*. **1983**, *37*, 184. (e) Schmidt, U.; Langner, J. *J. Chem. Soc., Chem. Commun*. **1994** , 2381.

100. (a) Hirama, M.; Shigemoto, T.; Ito, S. *J. Org. Chem.* **1987**, *52*, 3342. (b) Arrowsmith, R. J.; Carter, K.; Dann, J. G.; Davies, D. E.; Harris, C. J.; Morton, J. A.; Lister, P.; Robinson, J. A.; Williamsd, D. J. *J. Chem. Soc., Chem. Comm.* **1986**, 755. (c) Guanti, G.; Moro, A.; Narisano E. *Tetrahedron Lett*. **2000**, *41*, 3203. (d) Di Felice, P.; Porzi, G.; Sandri, S. *Tetrahedron: Asymmetry* **1999**, *10*, 2191.
101. Cicchi, S.; Goti, A.; Brandi, A.; Guarna, A.; De Sarlo, F.; *Tetrahedron Lett.* **1990**, *31*, 3351.
102. Tijani, J.; Suleiman R.; El Ali, B. *Appl. Organometal. Chem.* **2008**, *22*, 553.
103. (a) Fraunhoffer, K. J.; White, M. C. *J. Am. Chem. Soc.* **2007,** *129***,** 7274. (b) McDonald, R. I., Stahl, S. S. *Angew. Chem. Int. Ed.* **2010**, *49*, 5529. (c) van Benthem, R. A. T. M.; Hiemstra, H.; Longarela, G. R.; Speckamp, W. N. *Tetrahedron Lett.* **1994**, *35*, 9281.
104. Yokota, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **2002**, *67*, 5005.
105. Poll, R.; Wijayaratne, T. *Tetrahedron Lett.* **1991**, *32*, 4831.
106. (a) Gerzon, K.; Delong, D. C.; Cline, J. C.; *Symposium on Antibiotics*, Ste Marguerite, Quebec, Canada, 1–3 March **1971**, (b) Marquez, V. E.; Lim, M.; *Med. Res. Rev.* **1986**, *6*, 1.
107. (a) Calter, M. A.; Zhu, C. *J. Org. Chem.* **1999**, *64*, 1415. (b) Mishra, R. C.; Katiyar, D.; Tewari, N.; Tripathi, R. P. *Nucleosides, Nucleotides & Nucleic Acids*, **2004**, *23*, 531.
108. Štambaský, J; Hocek, M.; Kočovský, P. *Chem. Rev.* **2009***, 109,* 6729.
109. Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem*. **1997**, *62*, 3453.
110. Guianvarc'h, D.; Fourrey, J. L.; Tran-Huu-Dau, M. E.; and Guerineau, V. *J. Org. Chem*. **2002**, *67*, 3724.
111. Adlington, R. M.; Baldwin, J. E.; Pritchard, G. J.; Spencer, K. C. *Tetrahedron Lett.* **2000**, *41*, 575.
112. Son, S.; Fu, G. C. *J. Am. Chem. Soc*. **2007**, *129*, 1046.
113. Joubert, N.; Pohl, R.; Klepetářová, B.; Hocek, M. *J. Org. Chem*. **2007**, *72*, 6797.
114. Kalvoda, L.; Farkaš, J.; Šorm, F. *Tetrahedron Lett.* **1970**, *26*, 2297.
115. Prein, M.; Adam, W. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 477.

116. Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595.

117. (a) Schenck, G. O.; Ziegler, K. *Naturwissenschaften* **1954** , *32,* 1576. (b) Foote, C. S., *Acc. Chem. Res*. **1968**, *1*, 104.

118. Kappock, T. J.; Caradonna, J. P. *Chem. Rev*. **1996**, *96*, 2659.

119. Foote, S. C. *Active Oxygen in Chemistry;* Chapman & Hall: New York, **1995.**

120. Gandra, N.; Aaron, T. F. *Tetrahedron* **2006**, *62,* 10771. (b) Wilkinson, F.; Brummer, J. G. *J. Phys. Chem. Ref. Data,* **1981**, *10*, 809.

121. Du, H.; Fuh, R. A.; Li, J.; Corkan, A.; Lindsey, J. S. *Photochem. Photobiol.* **1998**, *68,* 141.

122. Wilkinson, F.; Helman, W. P.; Ross, A. B. *J. Phys. Chem. Ref. Data*, **1993**, *22,* 113.

123. Ma, L. C.; Qian, S. P.; Han, Z. H. *Chinese Chem. Lett.* **2003**, *14,* 962.

124. (a) Krasnovskii, A. A. *Biofizika* **1976**, *21*, 748. (b) Khan, A. U.; Kasha, M. *Proc. Nat. Acad. Sci. U.S.A*. **1979**, *76*, 6047.

125. Schweitzer, C.; Schmidt, R. *Chem. Rev*. **2003**, *103*, 1685.

126. Fink, E. H.; Setzer, K. D.; Wildt, J.; Ramsay, D. A.; Vervloet, M. *Int. J. Quantum Chem.* **1991**, *39*, 287.

127. (a) Jenny, T. A.; Turro, J. N. *Tetrahedron Letters*, **1982**, *23,* 2923. (b) Ogilby, P. R.; Foote, C. S. *J. Am. Chem. Soc*. **1983**, *105*, 3423. (c) Schmidt, R. *J. Am. Chem. Soc*. **1989,** *111*, 6983.

128. (a) Wassermann, H. H.; Ives, J. L. *Tetrahedron*, **1981**, *37*, 1825. (b) Gorman, A. A.; Rodgers, M. A. *J. Chem. Soc. Rev.* **1981**, *10*, 205.

129. Schenck, G. O. **1943**, *DE-B*, *933925.*

130. (a) Yamaguchi, K.; Yabushita, S.; Fueno, T.; Houk, K. N. *J. Am. Chem. Soc.* **1981**, *103*, 5043. (b) Davies, A. G.; Schiesser, C. H. *Tetrahedron,* **1991**, *47*, 1707.

131. Inagaki, S.; Fujimoto, H.; Fukus, K. *J. Am. Chem. Soc.* **1975**, *97*, 7480.

132. Harding, L. B.; Goddart, W. D. *J. Am. Chem. Soc.* **1980**, *102*, 439.

133. Orfanopoulos, I.; Smonou, C. S. *J. Am. Chem. Soc.* **1990**, *112,* 3607.

134. Stephenson, L. M.; McClure, D. E.; Sysak, P. K. *J. Am. Chem. Soc.* **1973**, *95*, 7888.

135. Houk, K. N.; Williams, J. C.; Mitchell, P. A.; Yamaguchi, K. *J. Am. Chem.Soc.* **1981**, *103*, 949.

136. Singleton, D. A.; Hang, C.; Szymanski, M. J. *J. Am. Chem. Soc*. **2003**, *125*, 1319.

137. Orfanopoulos, M.; Grdina, M. J.; Stephenson, L. M. *J. Am. Chem. So*c. **1979**, *101*, 275.

138. Stratakis, M.; Orfanopoulos, M. *Tetrahedron,* **2000**, *56,* 1595.

139. Jefford, C. W.; Laffer, M. H.; Boschung, A. F. *J. Am. Chem. Soc.* **1972**, 94, 8904.

140. Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* **1989**, *30*, 4875.

141. (a) Dubac, J.; Laporterie, A. *Chem. Rev.* **1987**, *87*, 319. (b) Adam, W.; Schwarm M. *J. Org. Chem.* **1988**, *53*, 3129.

142. Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

143. Adam, W.; Brunker, H. G.; Kumar, A. S.; Peters, E. M.; Peters, K.; Schneider, U.; von Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899.

144. (a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1992**, *114*, 6549. (a) Adam, W.; Nestler, B. *J. Am. Chem. Soc.* **1993**, *115*, 5041.

145. Adam, W.; Saha-Moller, C. R.; Schambony, S. B.; Schmid, K. S.; Wirth, T. *Photochem. Photobiol.* **1999**, *70*, 476.

146. Linker, T.; Frohlich, L. *J. Am. Chem. Soc.* **1995** , *117*, 2694.

147. (a) Jørgensen K. A. *Chem. Rev.* **1989**, *89,* 431. (b) Hoveyda, A. H.; Evans, D. A.; Fu G. C. *Chem. Rev.* **1993**, *93*, 1307.

148. (a) Kamata, K.; Hirano, T.; Kuzuya, S.; Mizuno, N. *J. Am. Chem. Soc*. **2009**, *131*, 6997. (b) Johnson, M. R.; Kishi, Y. *Tetrahedron Lett.* **1979**, *45*, 4747. (c) Adam, W.; Smerz, A. K. *Tetrahedron* **1995**, *51*, 13039.

149. (a) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc*. **1983**, *105*, 3123. (b) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H. *J. Am. Chem. Soc*. **1996**, *118*, 7004.

150. Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1959**, 1958.

151. Bartlett, P. D. *Rec. Chem. Prog*. **1950**, *11*, 47.

152. (a) McKittrick, B. A.; Ganem, B. *Tetrahedron Lett.* **1985***, 26,* 4895. (b) Kočovský, P. *Tetrahedron Lett.* **1988**, *2*, 2475. (c) Chamberlain, P.; Roberts, M. L.; Whitham, G. H. *J. Chem. Soc*. **1970**, 1374. (d) Hasegawa, A.; Sable, H. Z. *J. Org. Chem*. **1966**, *31*, 4149.

153. Prilezhaev, N. A. *Ber*. **1909**, *42*, 4811.

154. Ewins*,* R. C.; Henbest*,* H. B.; McKarvey, M. A. *J. Chem. Soc., Chem. Commun*. **1967***,* 1085.

155. (a) Tu, Y.; Wang, Z.-X.; Shi. Y. *J. Am. Chem. Soc*. **1996**, *118,* 9806. (b) Wang, Z.-X.; Tu, Y.; Frohn, M.; Zhang, J.-R; Shi Y. *J. Am. Chem. Soc*. **1997**, *119,* 11224. (c)) Z.-X., Wang; Tu, Y.; Frohn, M.; Shi Y. *J. Org. Chem.* **1997**, *62,* 2328.

156. Sheng, M. N.; Zajcek, J. G. *J. Org. Chem*. **1970**, *35*, 1839.

157. Adam, W.; Wirth, T. *Acc. Chem. Res*. **1999**, *32*, 703.

158. Bailey, M.; Markó, I. E; Oflis, W. D. *Tetrahedron Lett.* **1991**, *32*, 2687.

159. (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta*, **1979**, *12*, 63. (b) Malkov, A. V.; Czemerys, L.; Malyshev, D. A. *J. Org. Chem.* **2009**, *74*, 3350.

160. (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) Williams, I. D.; Pedersen, S. F.; Sharpless, K. B.; Lippard, S. J. *J. Am. Chem. Soc.* **1984**, *106*, 6430. (c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103,* 6237.

161. (a) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed, L. A.; Sharpless, K. B.; Walker, F. J. *Science,* 1983, *220*, 949. (b) Ko, S. Y.; Lee, A. W. M.; Masamune, S.; Reed III, L. A.; Sharpless, K. B.; Walker, F. J. *Tetrahedron* **1990**, *46*, 245.

162. (a) Payne, G. B. *J. Org. Chem.* **1962***, 27,* 3819. (b) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1974**, *96*, 4280.

163. Adam, W.; Saha-Moller, C. R.; Schmid, K. S. *J. Org. Chem.* **2001**, *66,* 7365.

164. Malkov, A. V.; Kabeshov, M. A.; Barłóg, M.; Kočovský, P. *Chem. Eur. J.* **2009**, *15*, 1570.

165. Adam, W.; Saha-Moller, C. R.; Schmid, K. S. *J. Org. Chem.* **2000**, *65,* 1431.

166. Shirayama, H.; Tohezo, Y.; Taguchi, S. *Water Res.* **2001**, *35*, 1941.

167. Margio, M.; Wabnitz, T. C. *Angew. Chem.* **2005**, *117*, 804.

168. Crouch, R. D. *Tetrahedron* **2004**, *60,* 5833.

169. Vilotijevic, I.; Jamison, T. F. *Marine Drugs* **2010**, *8*, 763.

170. (a) Narayan, R. S., Sivakumar, M.; Bouhlel, E.; Borhan, B. *Org. Lett*. **2001**, 3, 2489. (b) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517. (c) Morimoto, Y.; Nishikawa, Y.; Ueba, C.; Tanaka T. *Angew. Chem. Int. Ed.* **2006**, *45*, 810.

171. Tamaru, Y.; Hojo, M.; Kawamura, S.; Sawada, S.; Yoshida Z. *J. Org. Chem.* **1987**, *52*, 4063.

172. (a) Kočovský, P.; Starý, I. *J. Org. Chem*, **1990**, *55*, 3236 (b) Katsuki, T.; Martin, V. *Organic Reactions*, **2004**, *48*, 1. (c) Jensen, A. J.; Luthmanl, K. *Tetrahedron Lett.* **1998**, *39*, 3213.

173. Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc*. **2001**, *123*, 9168.

174. (a) Calter, M. A.; Sugathapala, P. M.; Zhu, C. *Tetrahedron Lett.* **1997**, *38*, 3837. (b) Gudmundsson, K. S.; Drach, J. C.; Townsend, L. B. *J. Org. Chem.* **1998**, *63*, 984.

175. Carreno, M. C.; Des Mazery, R.; Urbano, A.; Colobert, F.; Solladie, G. *J. Org. Chem.* **2003**, *68*, 7779.

176. Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

177. Prestat, G.; Baylon, C.; Heck, M. P.; Mioskowski, C. *Tetrahedron Lett.* **2000**, *41*, 3829.

178. Adam, W.; Peters, K.; Renz, M. *J. Org. Chem*. **1997**, *62*, 3183.

179. Kostikov, R. R. *Zh. Org. Khim*. **1971**, *7*, 2297.

180. (a) Mukaiyama, T.; Harada, T.; Shoda, S. *Chem. Lett.* **1980**, *9*, 1507. (b) Kubota, K.; Leighton, J. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.

181. Georgy, M.; Lesot, P.; Campagne, J. *J. Org. Chem.* **2007**, *72*, 3543.

182. Kimura, M.; Shimizu, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron* **2005**, *61*, 3709.

183. Hafner, A.; Duthaler, R.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.*, **1992**, *114*, 2321.

184. Loh, T.-P.; Lee, C.-L. K.; Tan, K.-T. *Org. Lett*. **2002**, *4*, 2985.

185. Bandini, M.; Cozzi, P.-G.; Umani-Ronchi, A. *Tetrahedron* **2001**, *57*, 835**.**

186. Ishikawa, T.; Kawakami, M., Fukui, M.; Yamashita, A.; Urano, J.; Saito, S. *J. Am. Chem. Soc.* **2001**, *123*, 7734.

187. Iwagami. H.; Yatagai, M.; Nakazawa, M.; Orita, H.; Honda, Y.; Ohnuki, T.; Yukawa, T. *Bull. Chem. Soc. Jpn*. **1991**, *64*, 175.

188. (a) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460. (b) Jacob, P.; Shulgin, A. T., Benowitz, N. L. *J. Med. Chem.* **1990**, *33*, 1888.

189. Freccero, M.; Gandolfi, R.; Sarzi-Amade, M.; Rastelli A. *J. Org. Chem.* **2000**, *65*, 2030.

190. (a) Kočovský, P. Electrophilic Additions to C=X Bonds In *Chemistry of Functional Groups; Supp. A3: The Chemistry of Double-Bonded Functional Groups* (S. Patai, Ed.); J. Wiley & Sons: Chichester, 1997, p 1135. (b) Kočovský, P.; Pour, M. *J. Org. Chem.* **1990**, *50*, 5580.

191. (a) Walkup, R. D.; Par, G. *Tetrahedron Lett.* **1987**, *28*, 1023. (b) Reitz, A. B.; Nortey, S. O.; Maryanoff, B. E. *J. Org. Chem.* **1987**, *52*, 4191. (c) Takahata, H.; Banba, Y.; Tajima, M.; Momose, T. *J. Org. Chem.* **1991**, *56*, 240. (d) Kočovský, P. *Organometallics* **1993**, *12*, 1969. (e) Kočovský, P.; Šrogl, J.; Gogoll, A.; Hanuš, V.; Polášek, M. *J. Chem. Soc., Chem. Commun.* **1992**, 1086. (f) Kočovský, P.; Šrogl, J.; Pour, M.; Gogoll, A. *J. Am. Chem. Soc.* **1994**, *116*, 186. (g) Kočovský, P.; Grech, J. M.; Mitchell, W. L. *J. Org. Chem.* **1995**, *60*, 1482. (h) Kočovský, P.; Grech, J. M.; Mitchell, W. L. *Tetrahedron Lett.* **1996**, *37*, 1125. (i) Kočovský, P.; Dunn, V.; Grech, J. M.; Šrogl, J.; Mitchell, W. L. *Tetrahedron Lett.* **1996**, *37*, 5585. (j) Hornberger, K. R.; Hamblett, C. L.; Leighton, J. L. *J. Am. Chem. Soc.* **2000**, *122*, 12894. For a related

reaction employing Tl(III), see: (k) Michael, J. P.; Ting, P. C.; Bartlett, P. A. *J. Org. Chem.* **1985**, *50*, 2416. (l) Kočovský, P.; Langer, V.; Gogoll, A. *J. Chem. Soc., Chem. Commun.* **1990**, 1026. (m) Kočovský, P.; Baines, R. S. *J. Org. Chem.* **1994**, *59*, 5439.

192. Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley: Chichester, 1995.

193. (a). Semmelhack, M. F.; Zask, A. *J. Am. Chem. Soc.* **1983**, *105*, 2034. (b) Semmelhack, M. F.; Bodurow, C.; Baum, M. *Tetrahedron Lett*. **1984**, *25*, 3171. (c) Semmelhack, M. F.; Zhang, N. *J. Org. Chem.* **1989**, *54*, 4483. (d) Semmelhack, M. F.; Kim, C. R.; Bobler, W.; Meier, M. *Tetrahedron Lett*. **1989**, *30*, 4925. (e) Semmelhack, M. F.; Kim, C.; Zhang, N.; Bodurow, C.; Sanner, M.; Dobler, W.; Meier, M. *Pure Appl. Chem.* **1990**, *62*, 2035. (f) Semmelhack, M. F.; Epa, W. R. *Tetrahedron Lett*. **1993**, *34*, 7205.

194. (a) Bäckvall, J.-E. *Acc. Chem. Res.* **1983**, *16*, 335. (b) Bäckvall, J.-E. *Pure Appl. Chem.* **1992**, *64*, 429. (c) Andersson, P. G.; Bäckvall, J.-E. C-O and C-N Bond Formation Involving Conjugated Dienes and Allylpalladium Intermediates In *Organopalladium Chemistry for Organic Synthesis* (E. Negishi, Ed.); J. Wiley & Sons: New York **2002**; Vol 2, p 1859.

195. Åkermark, B.; Bäckvall, J.-E.; Hansén, K. S.; Sjöberg, K.; Zetterberg, K. *Tetrahedron Lett*. **1974**, *15*, 1363.

196. (a) Wolfe, J. P.; Rossi, M. *J. Am. Chem. Soc.* **2004**, *126*, 1620. (b) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099. (c) Hay, M. B.; Wolfe, J. P. *J. Am. Chem. Soc.* **2005**, *127*, 16468. (d) Hay, M. B.; Wolfe, J. P. *Tetrahedron Lett.* **2006**, *47*, 2793. (e) Nakhla, J. S.; Kampf, J. W.; Wolfe, J. P. *J. Am. Chem. Soc.* **2006**, *128*, 2893.

197. (a) Starý, I.; Kočovský, P. *J. Am. Chem. Soc.* **1989**, *111*, 4981. (b) Starý, I.; Zajíček, J.; Kočovský, P. *Tetrahedron* **1992**, *48*, 7229. (c) Farthing, C. N.; Kočovský, P. *J. Am. Chem. Soc.* **1998**, *120*, 6661. (d) Jamieson, A. G.; Sutherland, A.; Willis, C. L. *Org. Biomol. Chem*. **2004**, *2*, 808 and references therein. (e) Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem*. **2005**, *3*, 735.

198. (a) Neukom, J. D.; Perch, N. S.; Wolfe, J. P. *J. Am. Chem. Soc* **2010**, *132*, 6276. (b) Hanley, P. S.; Marković, D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 6302.

199. Kocienski, P. J., *Protecting Groups*; Georg Thieme Verlag: New York **1994.**

6. Appendix