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

Functionalised Trichlorosilanes in the Asymmetric Allylation

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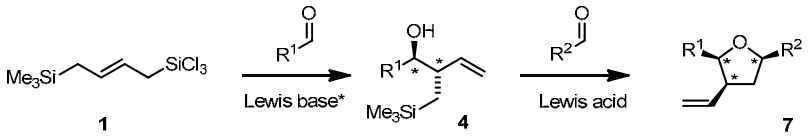
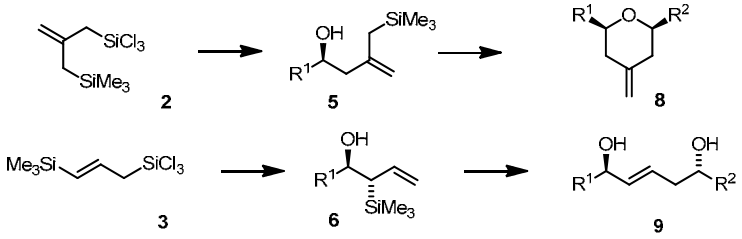
Thesis Abstract

Herein we present a synthetic route to the homoallylic alcohols **4**, using the well-established asymmetric organocatalysed allylation of aldehydes. Alcohols **4** were transformed in one step into the substituted tetrahydrofurans **7** in the presence of achiral Lewis acids, forming three chiral centres from two (**Scheme 1**).[1]



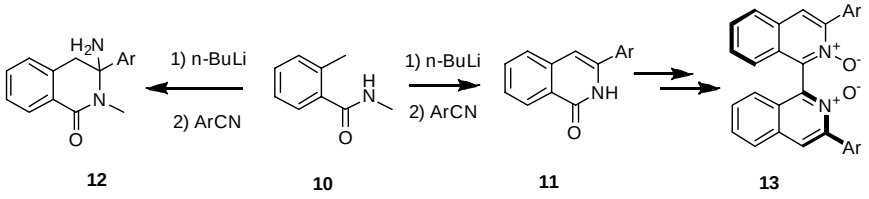
Scheme 1: Synthesis of the substituted tetrahydrofurans.

A synthetic route towards analogous homoallylic alcohols **5** and **6** and substituted tetrahydropyrans **8** or diols **9** respectively, has also been developed (**Scheme 2**).



Scheme 2: Synthesis of substituted tetrahydropyrans and 1,5-diols.

During the synthesis of the organocatalyst **13** an unexpected side reaction was observed. Since the transformation of **10** into **11** is a well established route in the synthesis of many compounds of pharmaceutical importance, yet the literature has been reporting notoriously low yields without further attempts at optimalization, we studied this reaction in detail to shed light on the formation of the unexpected byproduct **12** (**Scheme 3**).



Scheme 3: Synthesis of the novel organocatalyst 13.

In the last part of the project, we synthesized amino acid-based sulfonamide catalysts, and applied them in the total synthesis of the natural product *Speranskatine A*. We also investigated the mechanism of the cross-aldol reaction of ketones catalyzed by leucinol; the experimental results were backed-up by the quantum calculations.

Author's Declaration

This thesis represents the original work of Ondřej Kysilka unless explicitly stated otherwise in the text. The research was carried out at the University of Glasgow under the supervision of Prof. Pavel Kočovský and Prof. Andrei V. Malkov during the period of October 2008 to August 2012.

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And last but not least to **Kristýna,** for keeping me sane during the final stages of writing-up.

Orbitals are for mathematicians, organic chemistry is for those who like to cook.
- Alexander Shulgin

Abbreviations and Acronyms

Ac	Acetyl
AcOH	Acetic acid
aq.	Aqueous
BSA	Benzenesulfonic acid
Bn	Benzyl
Bu	Butyl
^{o}C	Degrees centigrade
cat, cat*	Catalyst, chiral catalyst
CSA	Camphorsulfonic acid
Cp	Cyclopentyl
Cy	Cyclohexyl
DCM	Dichloromethane
DHP	3,4-Dihydro-2H-pyran
DIBAL	Diisobutylaluminium hydride
DIPEA	Hünig's base, *N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess–Martin periodinane
DMPU	3-Dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone
DMS	Dimethylsulfide
DMSO	Dimethylsulfoxide
DNBSA	2,4-Dinitrobenzenesulfonic acid
dr	Diastereoisomeric ratio
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric excess
Et	Ethyl
eq.	Equivalents
EWG	Electron withdrawing group
HMPA	Hexamethylphosphoramide

HOBt	Hydroxybenzotriazole
HWE	Horner–Wadsworth–Emmons
i-, *iso-*	Isomeric (branched alkyl chain)
IBX	2-Iodoxybenzoic acid
L, L*	Ligand, chiral ligand
LA, LA*	Lewis acid, chiral Lewis acid
LAH	Lithium aluminium hydride
LB, LB*	Lewis base, chiral Lewis base
LDA	Lithium diisopropylamide
M	Metal
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	Methyl
MeCN	Acetonitrile
mmol	Millimole
n-	Normal (linear alkyl chain)
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
Nu	Nucleophile
[ox]	Oxidising agent, oxidation, oxidative conditions
PicAm	2-benzyl-3-phenyl-1-(pyridin-2-yl)propan-1-amine
Ph	Phenyl
PPTS	Pyridinium *p*-toluenesulfonate
Pr	Propyl
PTSA	*p*-toluenesulfonic acid
Py	Pyridine
[red]	Reducing agent, reduction, reductive conditions
RT	Room temperature
s-, *sec-*	Secondary (branched alkyl chain)
sat.	Saturated
tart	Tartarate
TBAF	Tetrabutylammmonium fluoride
TBCO	2,4,4,6-Tetrabromocyclohexa-2,5-dienone
t-, *tert-*	Tertiary (branched alkyl chain)
TBDMS	*tert*-butyldimethylsilyl

TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
TMS	Trimethylsilyl
p-Tol	*p*-tolyl, *p*-methylphenyl

Contents

1 Organocatalysis

Organocatalysis by definition is a metal-free form of catalysis which uses small organic molecules rather then metals and metal complexes. Organocatalysis is in many ways similar to the enzyme catalysis, i.e., the kinetics of the organocatalysed reaction often follow the Michaelis-Menten equation, describing the reversible formation of a catalyst (enzyme)-substrate complex. If the catalyst-substrate complex is reactive enough, no achiral background reaction is taking place and if the catalyst dissociates from the substrate with a sufficient rate, only a catalytic amount of the activator is required.

Transition metal complexes transfer the chirality from their chiral ligands through an organised transition state resulting from the strong interaction between the central metal atom of the catalyst and the reactants. Organocatalysts, like enzymes typically rely on weaker interactions, usually hydrogen bonding and π-π stacking.

Although organocatalysis is often not as enantioselective as the enzyme reactions, organocatalysts are usually not strictly substrate specific and thus more versatile. Some organocatalysts are quite 'picky'; others, such as cinchona alkaloids, amino acids, amino acid derivatives or oligopeptides, have a very broad spectrum of applications.

Furthermore, organocatalysts are usually more robust and insensitive to oxygen and air moisture and do not involve the toxicity and pollution issues or high price of the metal. They lack problems involving leaching of the toxic metals into the products, which is especially important in pharmaceutical industry.

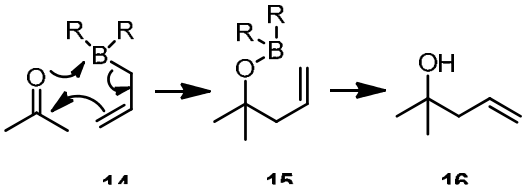
Although organocatalysed reactions have been known for more than a century, the term 'organocatalysis' was introduced by MacMillan in 2001 describing enantioselective synthesis using 'organic catalysts'.[2] However, the first records of organocatalysts go back as far as to the 1908 when Bredig and Rosenthaler described the hydrocyanation of benzaldehyde using quinine or quinidine respectively.[3] In 1974 Hajos published a remarkably simple intramolecular aldol reaction catalysed by proline (3 mol %), yielding the Hajos–Parrish ketone with 93% ee.[4] The proline catalyst had then been forgotten for almost 30 years, as the attempts to establish the highly enantioselective intermolecular version of this reaction failed.

Enantioselective organocatalysis was revived by the Barbas, MacMillan, List, Denmark, and Kobayashi groups as well as our own group and others, and now represents a robust and powerful tool in organic synthesis.

2 Asymmetric Allylations

2.1 Chiral auxiliaries vs. organocatalysts

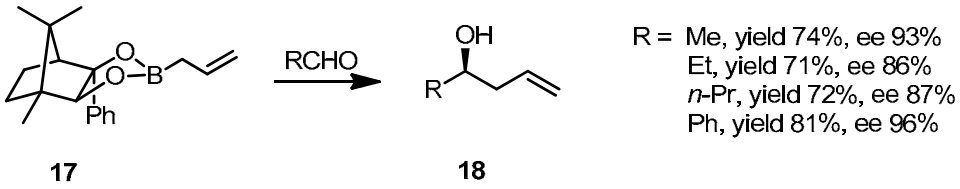
For a long time the classic approach to asymmetric allylations was based on the use of optically active Lewis acid complexes, such as tin(II) triflate complexes with various chiral diamines.[5] Another type of Lewis acid, boranes, were first introduced in the 1970s by Mikhailov who used triallyl boranes **14** to make the homoallylic alcohols **16**.



14 15 16

Scheme 4: Allylation with triallyl boranes.

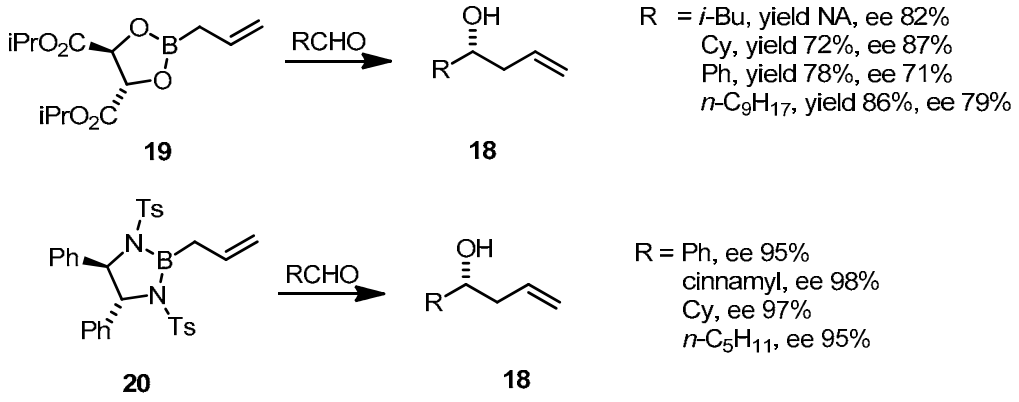
In the eighties, Herold & Hoffmann and Brown & Jadhav used asymmetric boranes such as **17** with the camphor or α-pinene moiety respectively, to make homoallylic alcohols **18** (**Scheme 5**).[6]



17 18

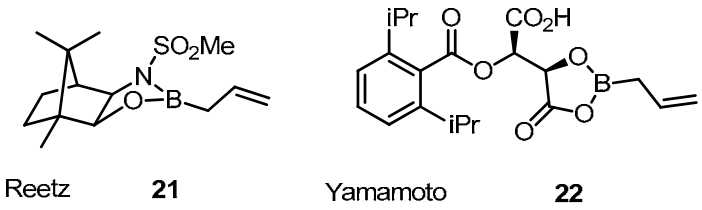
Scheme 5: Camphor chiral borane auxiliary.

Roush and Corey employed the diisopropyl tartarate and 1,2-diamino-1,2-diphenylethane respectively to obtain homoallylic alcohols **18** with moderate to excellent enantioselectivities (**Scheme 6**).[7]



Scheme 6: Roush's and Corey's chiral auxiliaries.

In contrast to these chiral auxiliaries, Reetz introduced a sulfonamide derivative of camphor **21**, which he used in a catalytic amount to furnish the homoallylic alcohols with up to 96% ee.[8] In 1991, Yamamoto reported on allylation of various aldehydes with substituted allylsilanes catalysed by chiral borane **22** with enantioselectivities up to 66 % ee.[9]



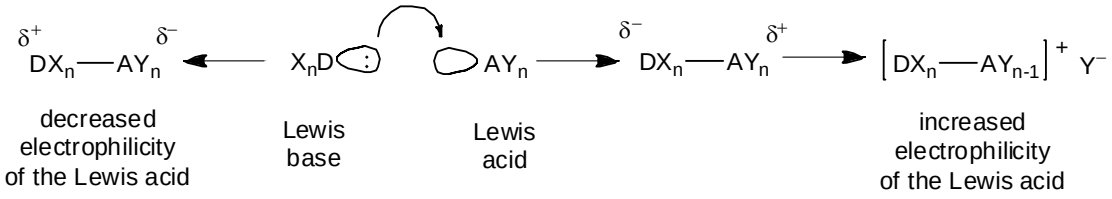
Scheme 7: Reetz's and Yamamoto's catalysts.

Metals, such as Ti or Sc (which bind to the carbonyl oxygen, thus increasing the electrophilicity of the carbonyl carbon), complexed with a chiral ligand have also been commonly used by Costa or Evans group and by others.[10]

Rather than increasing the reactivity of the carbonyl group with a Lewis acid, coordination of a Lewis base to the nucleophile does further increase its nucleophilicity, promoting the addition reaction. Assuming that only the activated nucleophile-Lewis base complex will react, the activator (Lewis base) can be used just in a catalytic amount, provided it is released readily after the reaction and returned into the catalytic circle.[11]

A Lewis acid - Lewis base complex, as the product of the neutralisation reaction is in general expected to have increased thermodynamic stability and thus decreased reactivity. The complexation of a Lewis base to the electrophile will decrease the overall electron density at the electrophile (Lewis acid) centre, but reactivity-wise, it is more important to consider how the electrons are distributed over the molecule. Obviously, in general, it is desirable to enhance the electrophilicity of the Lewis acidic centre, rather than make the reactants to quench each other's reactivity.

Although the main electron transfer in this 'neutralisation' reaction is from the donor (Lewis base) to the acceptor (Lewis acid), in complex species the electrons are redistributed over the peripheral ligands of the acceptor, which results in the overall decrease of the electron density of the central atom of the electrophile (**Scheme 8**).



Scheme 8: Lewis base - Lewis acid reaction.

The important consequence of this fact is the activation of the electrophile, as its central atom becomes more Lewis acidic and electrophilic (and its ligands of course more nucleophilic). The peripheral bonds compensate for the changes of the electron density and also, the higher the coordination number, the longer the peripheral bonds are and the more electrophilic the central atom becomes.

The bond lengths for SiF_4, SiF_5^- and SiF_6^{2-} for example are 1.56, 1.66(ax)/1.62(eq) and 1.69 Å, respectively, i.e., the bonds become longer and the silicon atom becomes more electrophilic/Lewis acidic with the increasing number of ligands.[12] This facilitates the activation of the electrophile by coordinating the non-bonding lone pair of a functional group of the electrophile (aldehyde, ketone, imine, etc.).

Silicon usually forms bonds with only four other atoms, completing the electronic requirement for an outer-shell octet. Thus the central silicon atom displays sp^3 hybridization and the molecule assumes a tetrahedral geometry. The ability of silicon to expand its coordination shell (similarly to phosphorus and antimony) has been intensively studied only during the last decades.[13] Silicon's ability to coordinate beyond the octet rule was originally

explained by involving the 3d orbitals in the hybridization, as in the case of transition metals. It was later concluded however, that the d orbitals are too diffuse to participate in the hybridization and currently, the theory of the three centred four electrons bond (3c-4e) is widely accepted. The tetravalent silicon is sp^3 hybridized, the pentavalent silicon is formally sp^2 hybridized (trigonal bipyramid with the axial bonds slightly longer due to the Jahn-Teller effect), and the hexavalent silicon is formally sp hybridized (tetragonal bipyramid).

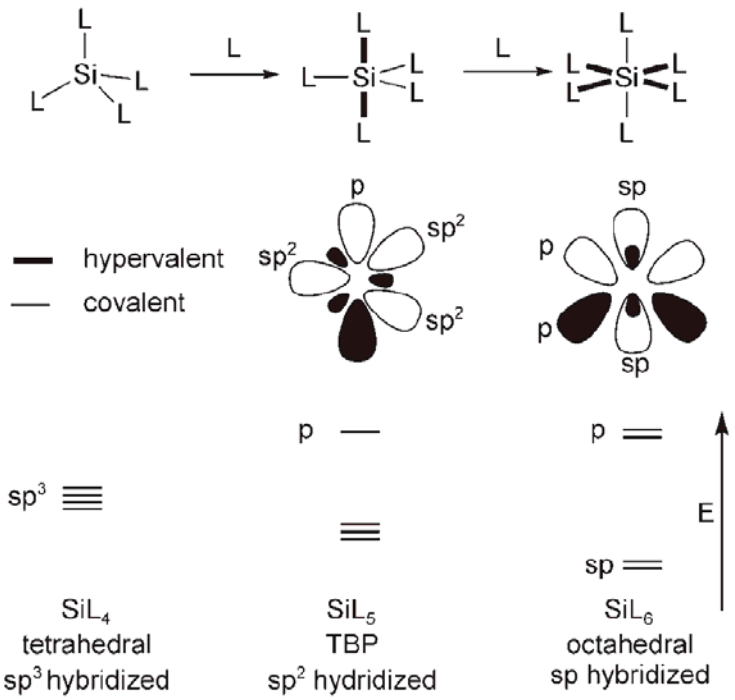
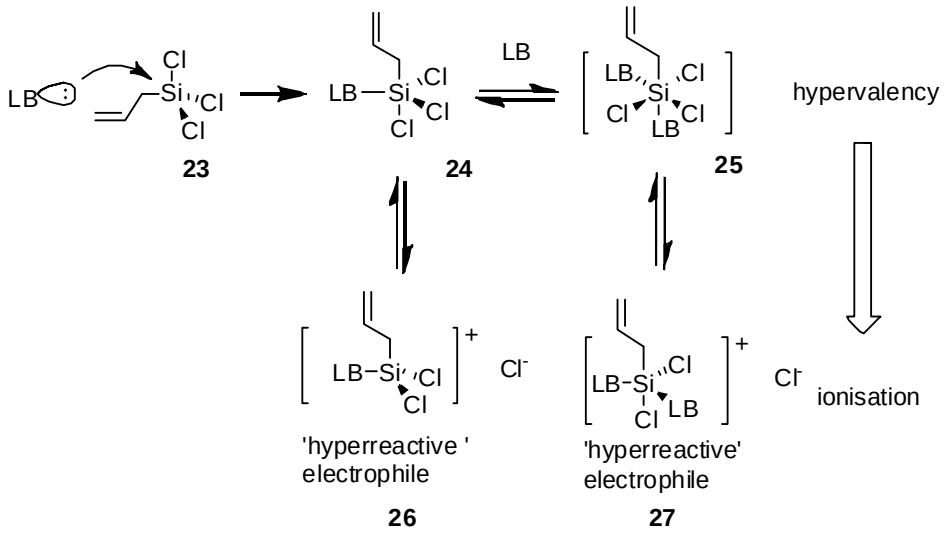


Figure 1. Tetra-, penta- and hexavalent silicon species.

The hypervalent bonds (the penta and hexavalent species) are electron rich at the ligands and electron deficient at the central silicon atom – hence the overall increased electrophilicity and affinity towards the carbonyl oxygen. The synthetic consequences are as follows: The tetracoordinated silicon (for example the allyl trichlorosilane **23**) is a weak Lewis acid and not reactive enough for the nucleophilic transfer of the allyl moiety (**Scheme 9)**. The pentavalent species **24** is formed with either negatively charged (Cl^-, F^-) or neutral (HMPA, DMF, DMPU, DMSO) Lewis base coordinated to the central atom. The carbon-silicon bond becomes longer and weaker and the allyl moiety is more prone to be transferred to the corresponding carbonyl or similar group. Coordination of another ligand generates the hexacoordinated species **25** and further increases the carbon bond length and thereby the reactivity towards the acceptor. Depending on how nucleophilic the Lewis base is, the ligand(s) around the central silicon atom (i.e., chloride in the case of trichlorosilanes) may or

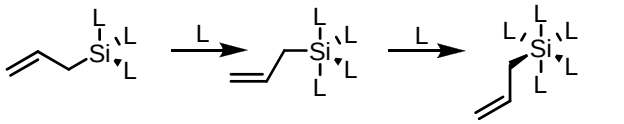
may not dissociate from the hypervalent species **24** or **25** to form 'hyperreactive' ionic pairs **26** or **27** (**Scheme 9)**.



Scheme 9: Activation of allyltrichlorosilane with the Lewis base.

To further confirm that the hypervalent silicates are the key intermediates and active species in the allylation reaction, Kobayashi conducted a series of ^{29}Si NMR experiments, and dramatic changes in the chemical shifts of the crotyl trichlorosilane were observed in various solvents (for example +8 ppm in $CDCl_3$ and -170 ppm in d_7-DMF for the allyltrichlorosilane, i.e., almost 180 ppm difference), confirming the extensive coordination of the polar aprotic solvents to the silicon atom.[14]

The mechanism of the silicon activation with fluoride anions is based on the rapid bonding of fluoride onto the silicon atom (the average Si-F bond energy is about 570 kJ/mol). The silicon species forms a pentacoordinated silicate, which itself is already an active allyl donor, however in the presence of Lewis basic solvent coordinates another molecule of the Lewis base to form a hexacoordinated silicate (**Scheme 10**). This one undergoes an allyl transfer to the carbonyl compound and the resulting alkoxide is trapped by the silicate regenerating the fluoride anion and the neutral Lewis base.



L = Cl^-, F^-, RO^-, DMF, HMPA, DMSO, DMPU

Scheme 10: Further activation of the tetracoordinated Si species.

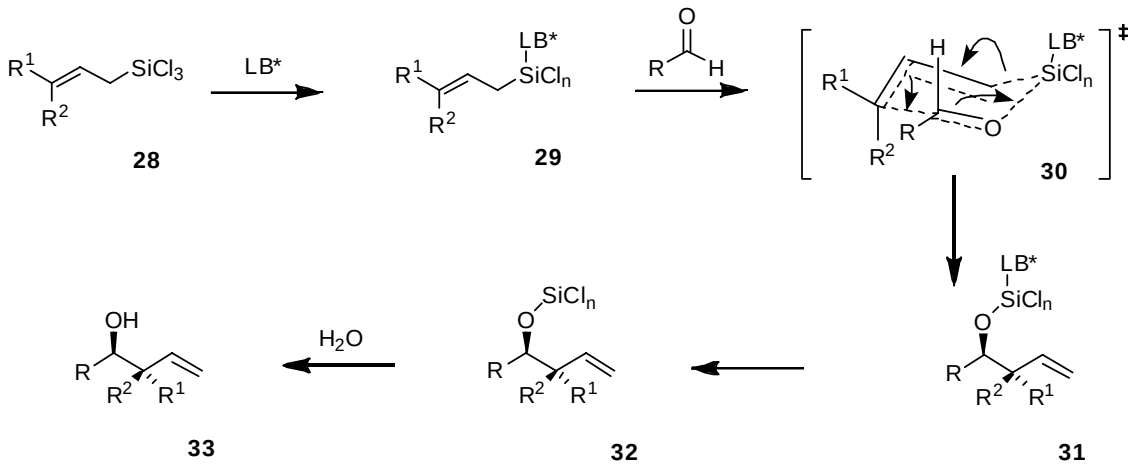
The realisation of the fact that not only anions, such as Cl^-, F^-, but also the neutral Lewis bases (i.e., common polar aprotic solvents, e.g., DMF or DMSO), can activate the tetracoordinated silanes, set ground for developing new mild methods of organocatalysis and chiral modifications of the organocatalysts. The electrophilicity of the hypervalent silicon species increases almost 300 times after the first coordination and almost 10 000 time for the hexacoordinated complexes compared to the original sp^3 hybridized species.[15] The overall reactivity can be tuned by a careful choice of the catalyst (halides or various neutral Lewis bases) and the silane (polyalkyl-, polyalkoxyl-, polyhalo-silanes).

The reduction potential of silanes has been extensively studied for many years now and the silicon complexes with fluorides (penta- and hexavalent fluorosilicates) were the first species to be used in the allylation reactions, especially since introduction of TBAF and its congeners (which are soluble in organic solvents and replaced the previously used inorganic fluorides).[16]

A large variety of catalysts have been developed for the enantioselective allylation of aldehydes, e.g., optically active phosphoramides, formamides, imines, and *N*-oxides amongst the most common ones. The scope, limitations and selectivities of various catalysts differ remarkably.[11]

The mechanism by which chiral Lewis bases activate the allyl trichlorosilanes **28** starts with the coordination of the chiral Lewis base to the silicon atom (**Scheme 11**). The complex **29** thus formed coordinates to the aldehyde and the resulting ternary complex of the allylation reagent, aldehyde, and chiral Lewis base reacts through a six-membered chair transition state **30** where both diastereo- and enantioselectivity are controlled and the chirality of the chiral Lewis base is translated to the intermediate **31**. Dissociation of the Lewis base from the trichlorosilyl ether **31**, followed by hydrolysis, gives the chiral homoallylic alcohol **33**.

In the crotylation reaction for example, assuming the reaction proceeds through the cyclic transition state organised around the hypervalent silicon, (*E*)-alkene produces a homoallylic alcohol with the *anti* configuration whereas (*Z*)-alkene then naturally gives the *syn* product (**Scheme 11**).



R^1, R^2 = Me, H

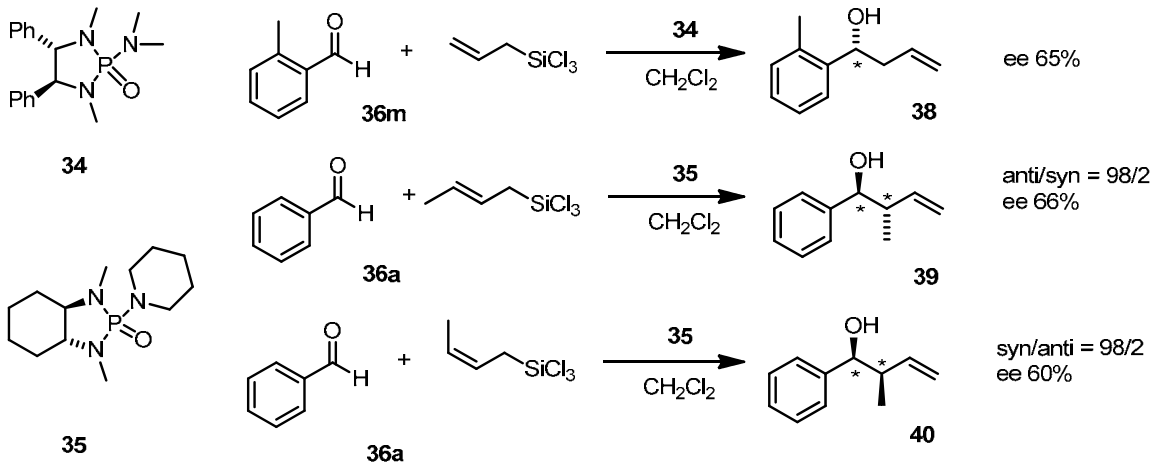
Scheme 11: Crotylation of aldehydes.

2.1.1 Chiral Phosphoramides as Organocatalysts in the Asymmetric Allylation

The first example of enantioselective allylation catalysed by chiral phosphoramide, which was also the first enantioselective Lewis base-catalysed allylation published, was reported nearly 20 years ago by Denmark.[17] It was shown that HMPA efficiently catalyses the allylation of benzaldehyde and Denmark first investigated the use of a stochiometric amount of chiral phosphoramide, achieving moderate enantioselectivities, while the reaction was highly diastereoselective (for the addition of crotylsilanes). Subsequent investigation of optically active phosphoramides showed that the Lewis base **34** is an efficient organocatalyst applicable for a wide range of substrates and the reaction of allyltrichlorosilane and various aldehydes led to the desired homoallylic alcohols (**Scheme 12**). Similar results were obtained for the crotylations of benzaldehyde with (*E*)- and (*Z*)-crotyltrichlorosilanes, with excellent diastereoisomeric ratios. *Anti* diastereoisomers were obtained preferentially from (*E*)-substrates, whereas *syn* diastereoisomer was formed when (*Z*)-crotyltrichlorosilane was

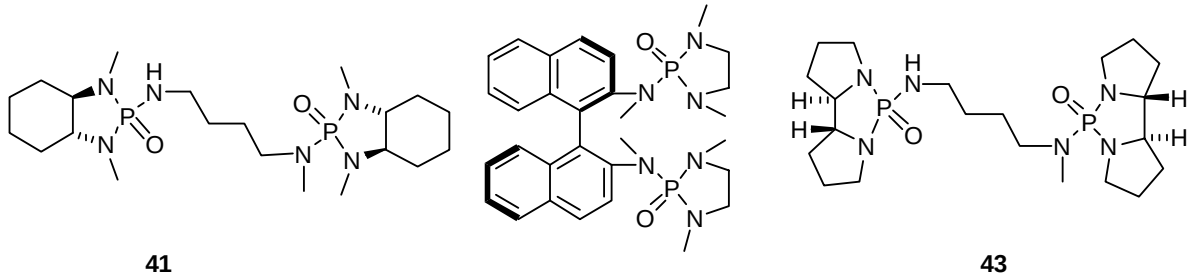
employed. However both yields and enantioselectivities were moderate (up to 66 % ee) and high catalyst loading was required (25 mol% or more).

The rate and selectivity of allylation were dependant on the nature of the aromatic aldehyde used, both electron-donating and electron-withdrawing substituents dramatically reduced the selectivity, as well as substitution in the *ortho* position.



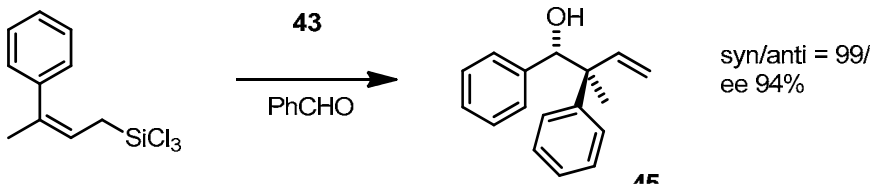
Scheme 12: Denmark's chiral phosphoramides.

Later, the structure of this type of catalysts was improved by using the bidentate bisphosphoramides (**41**, **42** and **43**) (it was shown that when the monodentate catalyst concentration is very low, the reaction proceeds with only one molecule of the phosphoramide coordinated to the silicon atom, jeopardizing the enantioselectivity of the reaction) capable of chelation of silicon in the transition state of the allylation reaction (**Scheme 13**).[18] Typical catalyst loadings were 5-10 mol% and the reaction reached full conversion in a span of few hours.



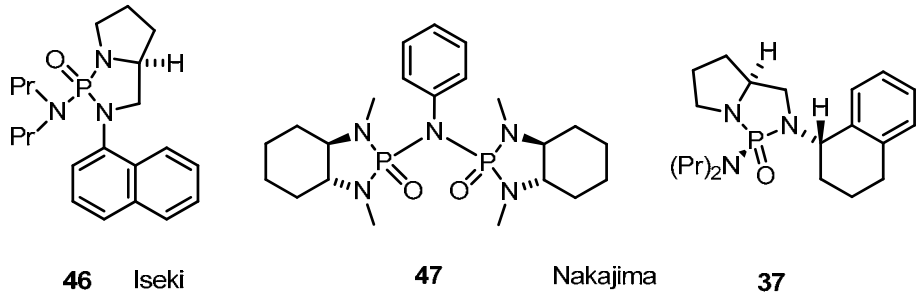
Scheme 13: Denmark's bisphosphoramide catalysts.

This type of catalysts can even be used for the construction of quarternary stereogenic centres (**Scheme 14**), thus the intermediate in the synthesis of serotonin antagonist **45** was prepared with high diastereoselectivity and enantioselectivity.



Scheme 14: Allylation on the sterically hindered reaction center.

Several other phosphoramides, such as **46** or **47**, have been developed by Iseki and other groups giving up to 90% ee (**Scheme 15**).[19] Employing the catalyst **46** or **47** resulted in good yields and moderate to good enantioselectivities, however extended reaction times (up to 7 days) were required.

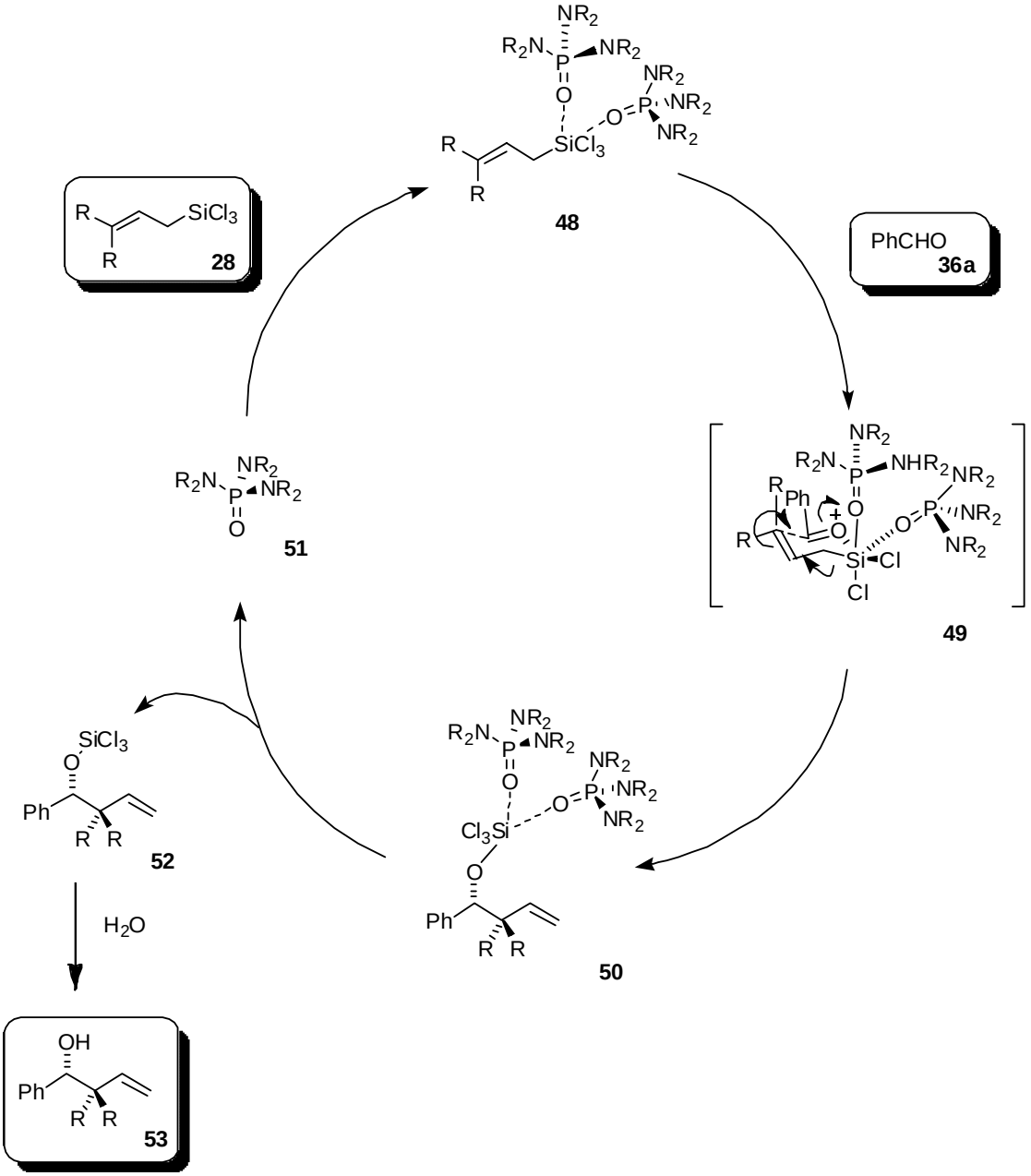


Scheme 15: Other phosphoramide catalysts.

Optimized procedure for the allylation reaction employed the *N*,*N*-diisopropylethylamine (Hünig's base) as an additive and proton scavenger; surprisingly this one was superior to the other ones used, such as triethyl amine. Nakajima postulated that the Hünig's base increases the rate of the catalyst turnover by facilitating the cleavage of the catalyst-silicon bond.

The mechanism of the phosphoramide-catalysed allylation has been investigated, particularly by the Denmark group (**Scheme 16**). For some of the studies, instead of silicon, Denmark used the complexes with tin, which exhibit almost the same coordination properties as silicon but much stronger bonding, which allowed detailed NMR and crystallographic studies that were then extrapolated to Si. The key step is the complexation of the allylsilane

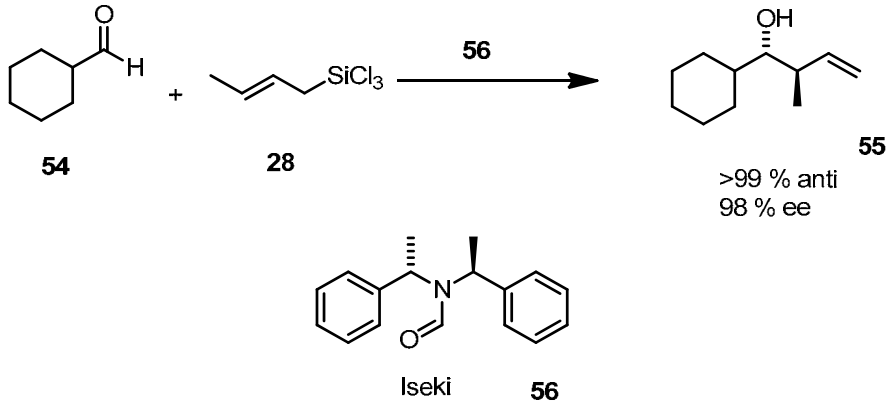
28 with the Lewis base catalyst to form the hypercoordinated reactive silicon species **48**. This intermediate reacts with the electrophilic aldehyde **36a** forming the homoallylic alcohol. The aldehyde is also coordinated to the silicon intermediate in the transition state **49.** Two molecules of the catalyst are involved in the complex with both substrates (the reaction was found to be following first order kinetics towards both silane and aldehyde and a second order towards the monodentate phosphoramide promoter), this dual activation leads to the high diastereo- and enantioselectivity (**Scheme 16**).[20]



Scheme 16: Activation of allyltrichlorosilane with phosphoramides.

2.1.2 Chiral Formamides as Organocatalysts in the Asymmetric Allylation

Following on the original observations made by Nishio and Kobayashi, that DMF as a solvent promoted the allylation of aldehydes with trichlorosilanes,[21] it was not surprising that chiral formamides were found to be versatile organocatalysts for the asymmetric allylation of aldehydes. Iseki and Kobayashi developed the catalyst **56,** which catalysed allylation and crotylation of various aldehydes with enantioselectivities up to 98%.[22] (*E*)-crotyltrichlorosilane gave predominantly the corresponding *anti* homoallylic alcohol **55** with 99% selectivity, whereas the reaction with the (*Z*)-isomer was extremely sluggish (**Scheme 17**). Formamides of this type however need at least 20 mol% loading to work efficiently and require the HMPA presence as a co-catalyst. The reaction is also rather sluggish, requiring up to two weeks to achieve full conversion. However, interestingly **56** is one of the few catalysts reported to the date, that give excellent enantioselectivies for aliphatic aldehydes (and interestingly giving almost racemic products for the aromatic ones).[23]

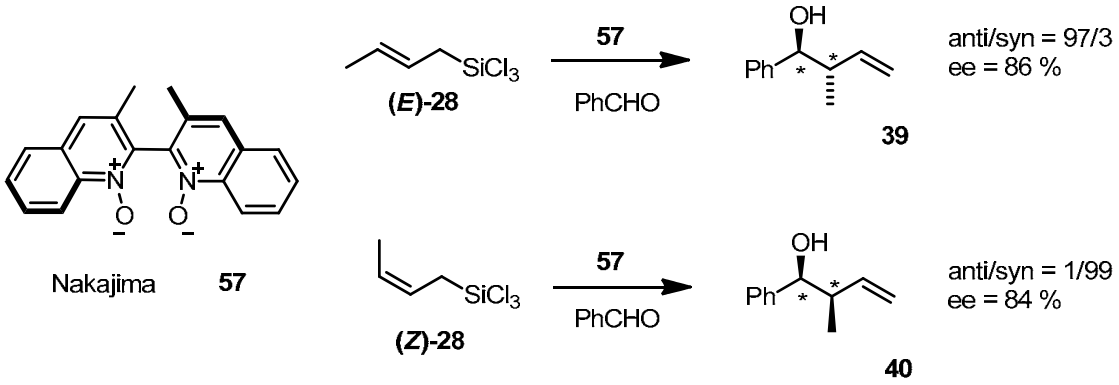


Scheme 17: Iseki's formamide catalyst.

2.1.3 Chiral N-Oxides as Organocatalysts in the Asymmetric Allylation

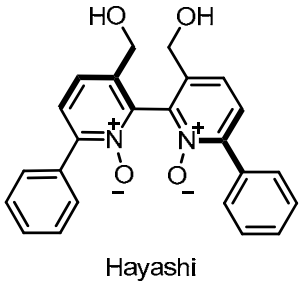
Chiral *N*-oxides,[24] which possess significant nucleophilicity toward the silicon atom, were first used as catalysts in enantioselective allylation ten years ago by Nakajima. He developed the Lewis basic *bis*-oxide **57** with axial chirality. **57** catalysed the reaction of a range of aromatic, aliphatic and α,β-unsaturated aldehydes with allyltrichlorosilane (**Scheme**

18).[25] 10 mol % loading of the catalyst was typically used and enantioselectivities up to 92% were obtained for the aromatic substrates, whereas enantioselectivities in the reactions of aliphatic aldehydes were in general quite poor. The use of diisopropylethylamine as an achiral additive was found to be crucial because of the acceleration of the reaction, especially at low temperatures (conducting reactions at low temperatures improved the asymmetric induction considerably). Again, allylation using (*E*)-crotyltrichlorosilanes gave *anti*-diastereoisomers (such as **39**) whereas use (*Z*)-crotyltrichlorosilanes led to *syn*-homoallylic alcohols (such as **40**).



Scheme 18: Nakajima's N-oxide catalyst.

Hayashi reported that catalyst **60** can be used with loading as low as 0.01 mol % without loss of enantioselectivity (although the reaction time were longer and the yields somewhat lower).[26]

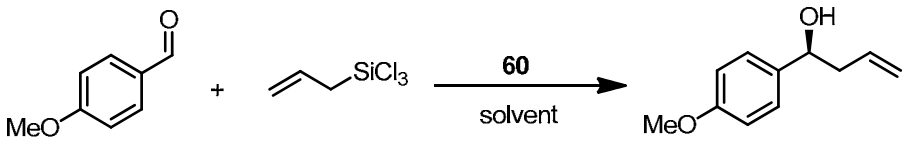


60

Scheme 19: Hayashi's bipyridine catalyst.

This 2,2'-bipyridine-*N*,*N*'-dioxide **60**, whose chirality originates from the biaryl axial chirality, was prepared in 9 steps from 2,9-diphenylphenanthroline.[27] This catalyst was found to have high catalytic activity as well as high enantioselectivity for the asymmetric allylation of aromatic aldehydes with allyltrichlorosilane. With catalyst loading of 0.1 mol%, the

reaction was complete within 2.5 hours, which stands in a remarkable contrast to the much lower catalytic activity of most of the other chiral Lewis bases, where at least 1-10 mol % loading is usually required. The activity of the catalyst decreased rapidly when the phenyl groups were substituted by methyl, hydrogen or *tert*-butyl groups respectively. The high catalytic activity was attributed mainly to the π-π stacking between the phenyl groups and the aromatic ring of the aldehyde which probably enhances the activity as well as enantioselectivity. Some of Hayashi's results are summarized in **Table 1**.



Scheme 20: Allylation of anisaldehyde catalysed by 60.

Table 1: Hayashi's catalyst 60.

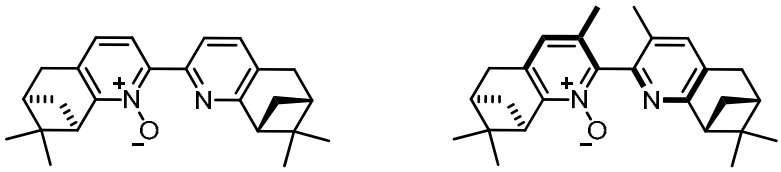
entry	catalyst loading (%)	solvent	T (°C)	time (h)	Yield (%)	ee (%)
1	1	CH_3CN	-45	0.25	96	94
2	0.1	CH_3CN	-45	2.5	96	94
3	0.01	CH_3CN	-45	12	68	94
4	0.5	CH_2Cl_2	-78	2.5	90	78
5	0.1	CH_2Cl_2	-45	2.5	91	76

Crotylation of benzaldehyde catalysed by Hayashi's catalyst **60** gave the usual *syn* or *anti* γ-allylated homoallylic alcohols respectively (depending on the configuration of the double bond) with high diastereoselectivities but moderate enantioselectivities (around 70%). Enantioselectivities were strongly dependent on the nature of the aromatic ring of the aldehyde, giving the best results for the electron rich systems. Aliphatic aldehydes gave inferior results, showing both poor reactivity and enantioselectivity.

Hayashi developed a synthetic route to the ligands of type **60** and a broad range of catalysts with various substituents in the 2,2'-positions have been prepared by his group.[28] However, the original structure **60** has shown the best results.

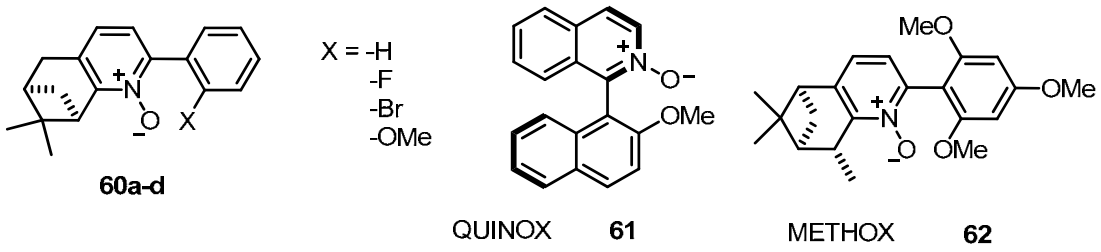
In 2002, prior to Hayashi's paper, the chiral bipyridine *N*-monoxide PINDOX (**58a**) and its dimethyl analogue **58b** were introduced by Kočovský and Malkov, which catalysed allylation of various aromatic aldehydes with allyltrichlorosilane at up to 98% ee.[29] Again, the saturated aldehydes showed only poor asymmetric induction, highlighting the importance

of π-conjugation. Interestingly, the corresponding *N,N'*-dioxide gave both lower yield and enantioselectivity than the *N*-oxide. It was suggested that while one N-O group of **58** coordinates to the silicon atom of the allyl silane (increasing its nucleophilicity), the other nitrogen stabilizes the intermediate by chelation and thus reducing the number of other diastereoisomeric transition states, which results in high enantioselectivity.



Scheme 21: PINDOX and its dimethyl analogue.

Other weakly coordinating groups with affinity to silicon could mimic the behaviour of the second pyridine nitrogen and thus a range of new catalysts was prepared, where the pyridine moiety was replaced by a substituted benzene ring (compounds **60a-d**, **Scheme 22**).[30] However, all of them showed lower activity than their bipyridine counterpart. Relatively high asymmetric induction in the case of both methoxy-substituted and unsubstituted derivative in comparison with their fluoro- and bromo-substituted counterparts suggested that electronic properties of the phenyl ring may play a more important role than coordination.



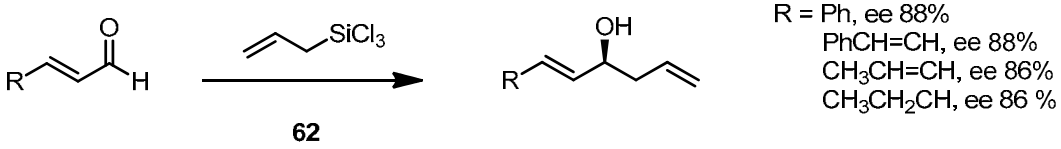
Scheme 22: Other *N*-oxide catalysts.

In 2003, synthesis of quinoline-type *N*-oxide catalyst QUINOX (**61**) was published by Kočovský and Malkov.[31] QUINOX catalysed allylation of benzaldehyde with allyltrichlorosilane with 87% ee, enantioselectivity was not altered even if the catalyst loading was decreased to 1 mol%. However, whereas electron rich aldehydes (such as *p*-methoxybenzaldehyde) gave almost racemic products, electron poor aldehydes (such as *p*-trifluoromethylbenzaldehyde) reacted with 96% enantioselectivity. This was compatible with the hypothesis of the arene-arene interactions of the catalyst with the aldehyde substrate.

Allylation with the crotyltrichlorosilane were also examined, both PINDOX (**58a**) and QUINOX (**61**) produced mainly *anti* homoallylic alcohol when (*E*)-isomer of the starting material was used. Interestingly, QUINOX catalysed the reaction of (*Z*)-crotyltrichlorosilane with higher rate, which represents a reversal of the trend commonly observed with other *N*-oxide catalysts, which usually show preference for the (*E*)-isomer.

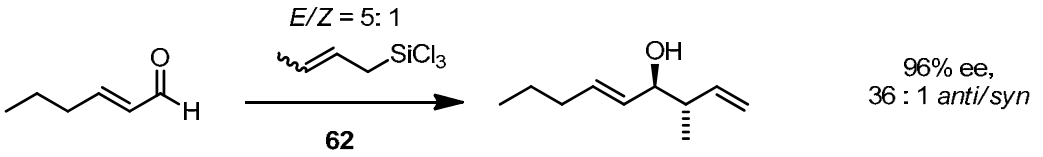
In 2005 Kočovský and Malkov introduced another pyridine-type *N*-oxide METHOX (**62**), where the benzene ring is substituted by three methoxy groups. METHOX catalysed allylation of aromatic benzaldehydes with high enantioselectivities (up to 96% ee) and confirmed the hypothesis that methoxy groups effects are of electronic rather than steric origin (decreasing the electron density in the ring by introducing electron withdrawing substituents, such as fluorine, had a detrimental effect on both conversion and enantioselectivity). The nature of the aldehyde seemed to have little effect on the outcome, i.e., both electron-rich and electron-poor aldehydes reacted with both high conversion and enantioselectivities. Increasing the steric hindrance around the carbonyl group (i.e., introducing the *ortho* substituents onto the aldehydic aromatic ring) had a detrimental effect on the reaction. Reducing the catalyst loading had no effect on enantioselectivity, though the reaction slowed down. Rising the temperature from the original -40°C to room temperature (during the reaction of benzaldehyde with allyltrichlorosilane) led to a decrease to the 87% ee from the original 96% ee, thus as usual, the low temperature is a prerequisite for achieving good enantioselectivities.

METHOX was also proven to be the catalyst of a choice in the allylation and crotylation of conjugated aliphatic and aromatic aldehydes.[32]



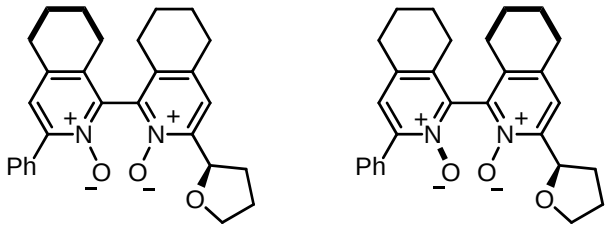
Scheme 23: Allylation of aldehydes with METHOX.

As METHOX exhibits high kinetic preference for the (*E*)-crotyltrichlorosilane, technical grade crotyl chloride (*E*/*Z* = 5 : 1) is sufficient as a starting material.



Scheme 24: Crotylation of aldehydes with METHOX.

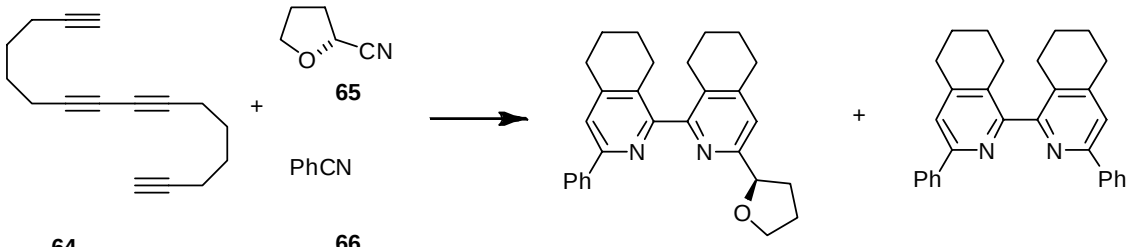
A few years ago Kotora introduced the bis(tetrahydroisoquinoline) *N*,*N*'-dioxides (*R*,*R*)-**63** and (*S*,*R*)-**63** and demonstrated their application in the allylation of a range of aromatic and aliphatic aldehydes.[33]



(*R*,*R*)-**63** (*S*,*R*)-**63**

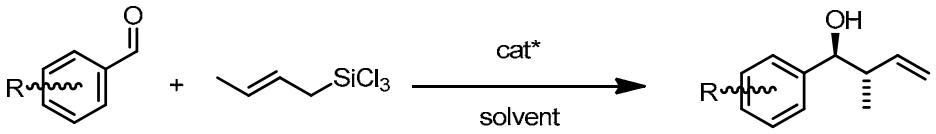
Scheme 25: Kotora's dioxide catalysts.

Both dioxides were prepared by the cyclotrimerization of the tetrayne **64** with (*R*)-tetrahydrofurannitrile **65** and benzonitrile **66**. Interestingly, the one-pot cyclotrimerization of all three components in the presence of $CpCo(CO)_6$ under the microwave irradiation in THF afforded **67** in an acceptable 28% yield (as a mixture of two diastereoisomers), contaminated with 20% of the undesired **68**.



Scheme 26: Synthesis of Kotora's catalyst.

Oxidation of **67** by *m*CPBA gave a mixture of *N*,*N*'-dioxides **(*R*,*R*)-63** and **(*S*,*R*)-63**, which were separated by column chromatography of silica gel. Several aldehydes were screened; for selected examples see **Table 2**. Enantioselectivities showed to be strongly solvent dependent, with best results being obtained in THF and PhCl.



Scheme 27: Crotylation of aromatic aldehydes catalysed by Kotora's catalyst.

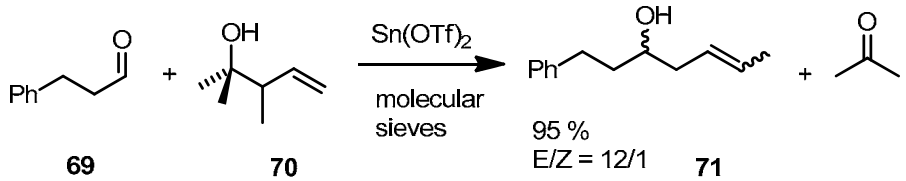
Table 2: Some of Kotora's results for various aldehydes.

Entry	R	Solvent	(*R*,*R*)		(*S*,*R*)	
			Yield (%)	ee (%)	Yield (%)	ee (%)
1	H	MeCN	99	53 (S)	99	44 (*R*)
2	H	PhCl	99	93 (R)	99	94 (*S*)
3	H	THF	99	93 (R)	98	96 (*S*)
4	4-MeO	THF	99	86 (R)	90	91 (*S*)
5	4-CF_3	THF	76	95 (R)	91	87 (*S*)
6	2-Cl	THF	45	46 (R)	42	14 (*S*)

Aliphatic α,β-unsaturated aldehydes react with a lower rate, however the allylation of crotonaldehyde proceeded with 85% ee for both diastereoisomers of the catalyst, aldehydes with longer aliphatic chains gave the homoallylic alcohols with excellent >95% enantioselectivities. Reactions typically reached full conversion in several hours, catalyst loading varied from 1 mol % to 5 mol %.

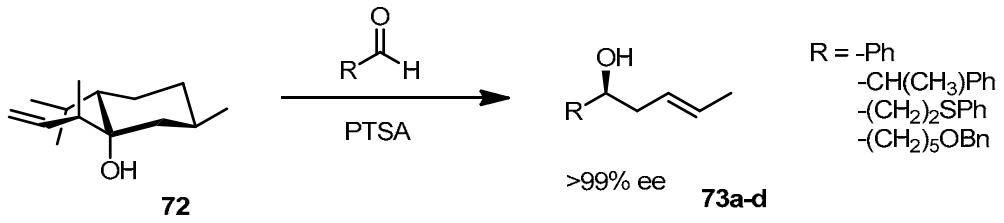
2.1.4 The Allyl Transfer

In the presence of an acid, the allylic functionality can be stereoselectively transferred from γ-homoallylic alcohol (**70**) to an aldehyde to obtain the respective α-homoallylic alcohol (**71**) (**Scheme 28**). Nokami assumed that the allyl transfer reaction proceeds in the direction giving a sterically less hindered homoallylic alcohol and thermodynamically more stable olefin.[34] Addition of powdered molecular sieves 4Å to the reaction medium led to improved yields as did a lower reaction temperature (-25 °C). Several catalysts were investigated ($Zn(OTf)_2$, AgOTf, $PhSO_2NHOH$); the best results were obtained with tin(II) triflate.



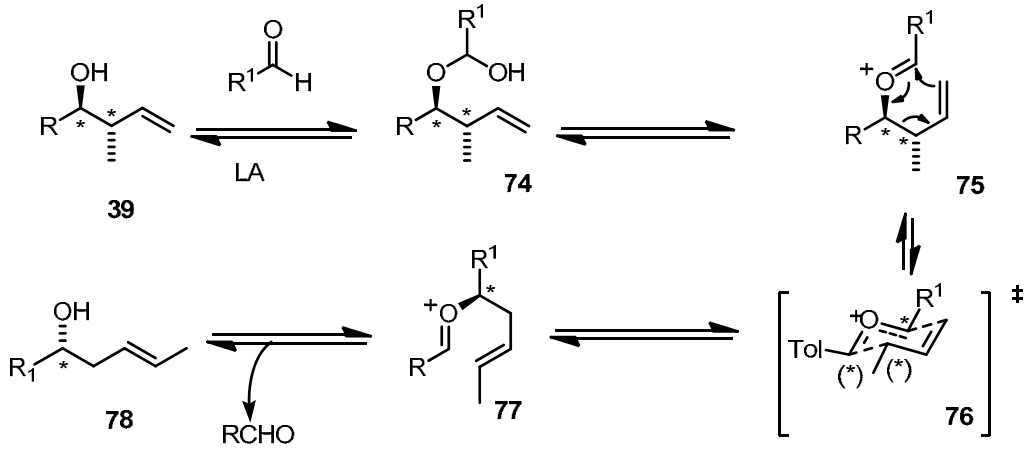
Scheme 28: Allyl transfer.

The first general enantioselective allyl transfer reaction was developed by Nokami in 2001.[35] As a source of chirality, Nokami used (-)-menthone which was subjected to the crotylation reaction with the corresponding Grignard reagent to give the homoallylic alcohol **72**. This reacted readily with a number of aldehydes with no loss of enantiopurity in all cases (**Scheme 29**). From several catalysts investigated (PTSA, CSA, BSA, $Sn(OTf)_2$), PTSA gave the best results.



Scheme 29: Allyl transfer with menthone-derived chiral auxiliary.

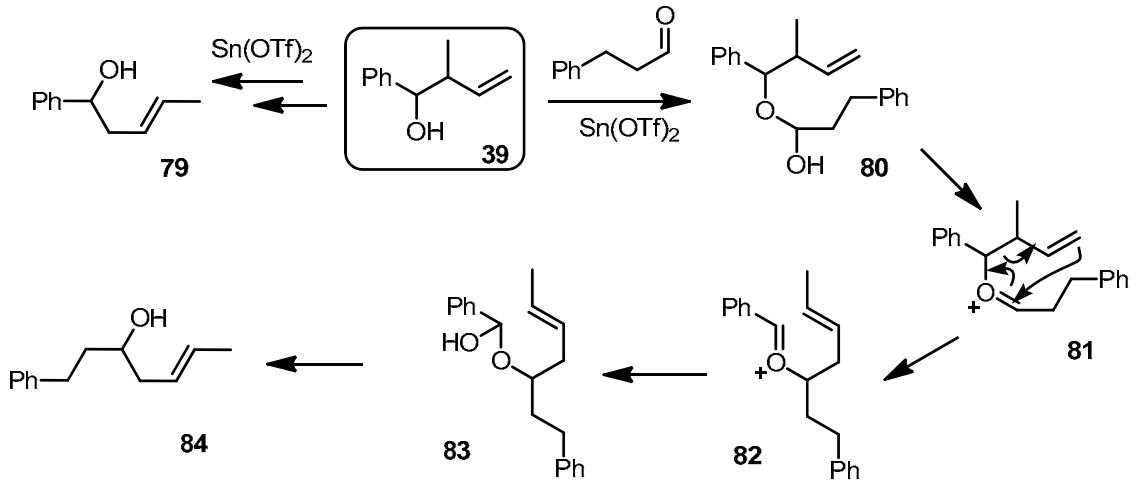
Nokami and Sumida proposed the following mechanism for the allyl transfer (**Scheme 30**).[36] The reaction proceeds via hemiacetal **74**, derived from an aldehyde and the homoallylic alcohol **39**, oxycarbenium ion **75**, followed by a [3.3] sigmatropic rearrangement in the presence of a suitable acid.



Scheme 30: Allyl transfer mechanism.

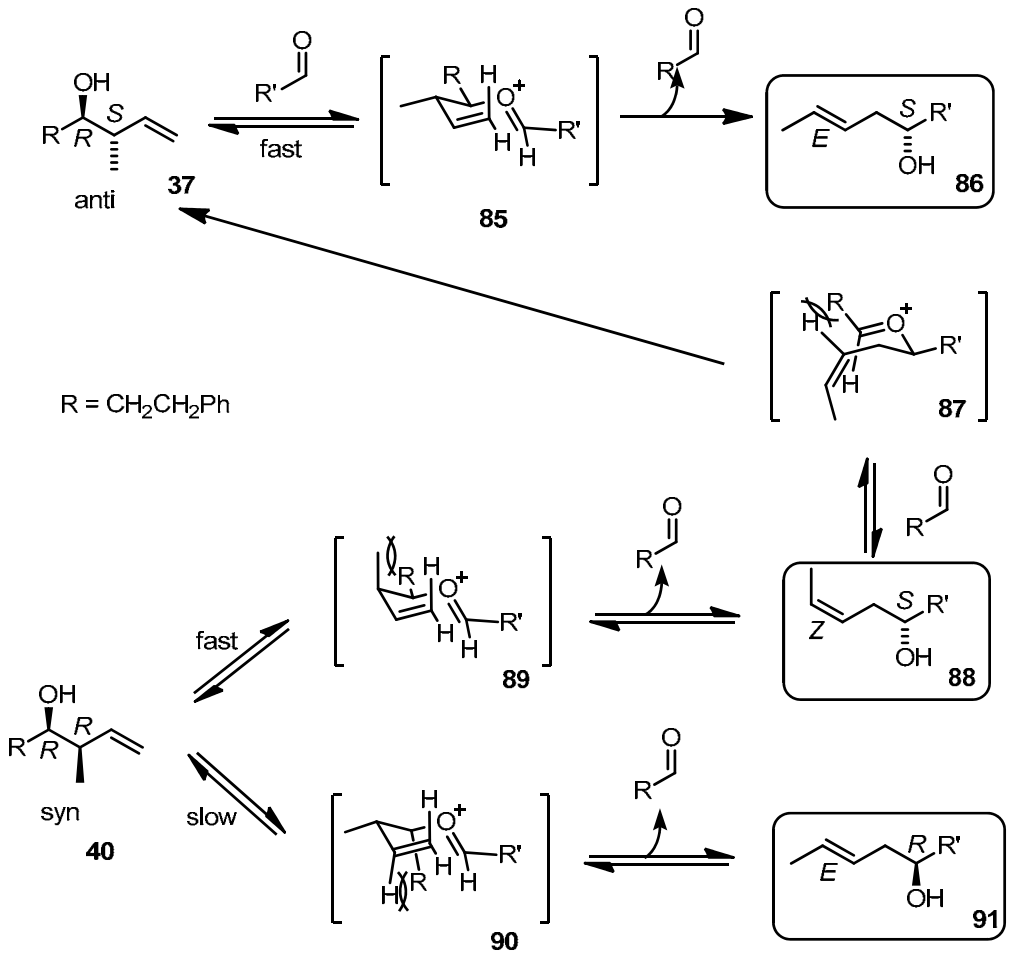
Nokami also investigated the allyl transfer using compound **39** as an allyl donor. The reaction of **39** and dihydrocinnamaldehyde gave **84** as a major product but a substantial amount of byproduct **79** was isolated. Formation of the byproduct **79** suggested that

benzaldehyde, formed during the reaction of **39** with dihydrocinnamaldehyde, reacts with **39** competitively.



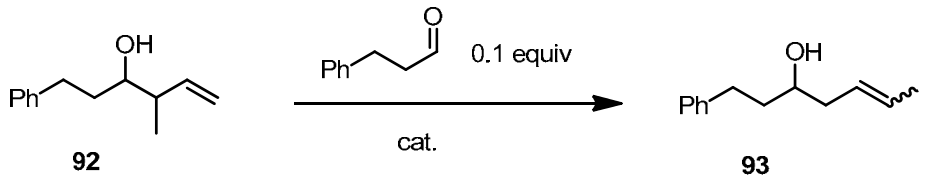
Scheme 31: Side reactions during the allyl transfer.

Chirality in both *syn* and *anti* γ-adduct was stereospecifically transferred to the corresponding α-adduct. *Anti* isomers gave exclusively (*E*) α-homoallylic alcohols with inversion of configuration at the chiral centre. Reaction of the *syn* isomers was less stereospecific, nevertheless giving (*Z*) configuration of the double bond predominantly (*Z*/*E* ratio being between 18/1 – 7/1 according to the Nokami's report). The difference in the selectivity between *syn* and *anti* can be rationalized by the six-membered transition state model (**Scheme 32**).



Scheme 32: Mechanism of the byproducts formation during the allyl transfer.

Nokami also explored alternative catalysts and found that many acids as well as simple hydrogen chloride catalysed the isomerization of γ-homoallylic alcohol **92** to its α-isomer **93** (**Scheme 33** and **Table 3**).



Scheme 33: Screening of Lewis acids in Nokami's allyl transfer.

Table 3: Conversion of γ-adducts to α-adducts.

entry	catalyst[a]	*anti/syn* ratio of 92	t (h)	*E*/*Z* ratio of 93	yield of 93 (%)
1	$Sn(OTf)_2$	23/1	2	25/1	88
2	$Cu(OTf)_2$	19/1	4	20/1	80
3	$Zn(OTf)_2$	17/1	48	25/1	72
4	AgOTf	23/1	95	25/1	83
5	$AlCl_3$	25/1	6	50/1	51
6	$SnCl_4$	33/1	8	23/1	77
7	$BF_3.Et_2O$	1/1	24	1/1	73
8	TfOH	18/1	2	17/1	89
9	HCl[b]	100/1	4	100/1	84

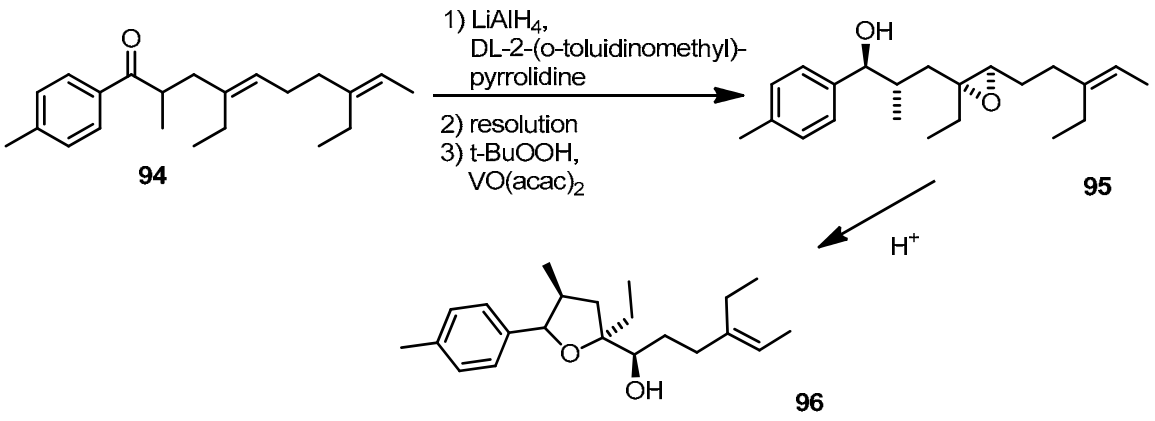
[a]10 mol% of catalyst used unless stated otherwise [b]1 eq. of HCl used in a form of anhydrous 1M solution in diethyl ether (commercial from Aldrich)

Nokami concluded that the actual nature of the catalyst for the allyl transfer reaction is not completely clear. The Brønsted acid HCl served as a good catalyst, and could be created from a Lewis acid *in situ* with alcohol or trace of moisture.

2.2 Methods of Preparation of Substituted Tetrahydrofurans

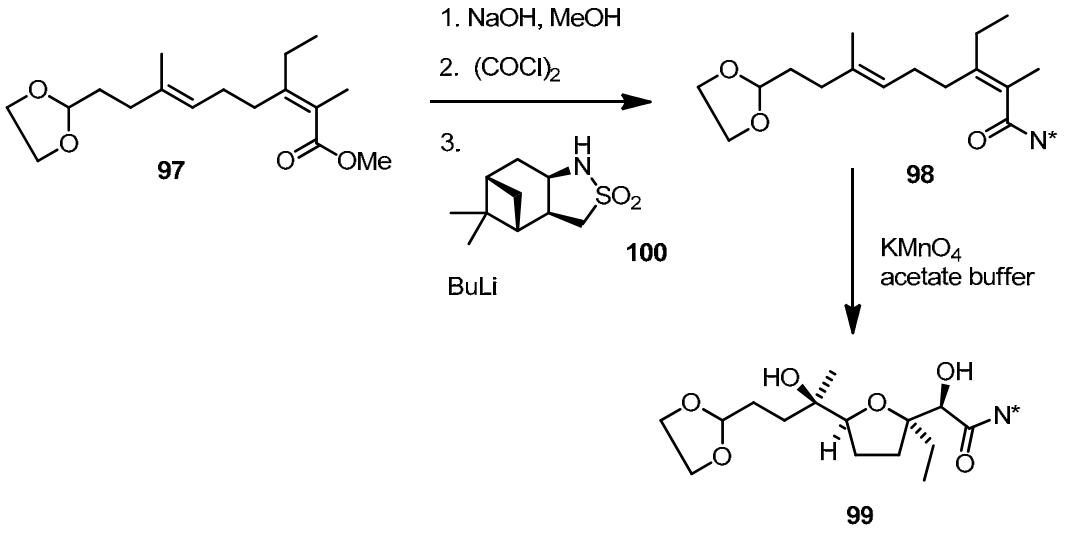
Substituted tetrahydrofurans are featured in a large number of antibiotics,[37] polyene mycotoxins and other biologically important natural products, such as Galbacin,[38] Aplydilactone,[39] Mupirocin,[40] Annoreticuin,[41] Bullatalicin,[42] Gigantecin,[43] amongst others.[44] The polyether antibiotics are a class of compounds isolated from fermentation cultures of *Streptomyces* and characteristically contain 3-5 oxygen atoms serving as ligands for the complexation of metal cations. The framework of these molecules is dominated by the presence of substituted tetrahydrofurans, tetrahydropyrans, and spiroketal systems. Their structural complexity and diversity (as well as commercial value of many of them) continue to challenge synthetic organic chemists for more than three decades after the landmark syntheses of *Lasalocid A* or *Monensin* were reported.[45] Construction of polyether antibiotics is, to a large extent, an exercise in the enantioselective preparation of substituted tetrahydrofurans and tetrahydropyrans. Hence, considerable attention has been focussed on the development of efficient and stereocontrolled routes to these key structural fragments. Several methods have been developed to address the problem of stereoselective synthesis of the core tetrahydrofuran ring of these molecules. There have been three major approaches: resolution of racemates, use of chiral auxiliaries and taking advantage of stereochemistry already set up in previous steps.

In the synthesis of *Lasalocid A*, Kishi and co-workers used reduction of ketone **94** by $LiAlH_4$ in the presence of (±)-2-(*o*-toluidinomethyl)pyrrolidine followed by resolution of the racemate, epoxidation of the double bond followed by the epoxide opening giving **96** in 75% yield and 8:1 ratio of diastereoisomers (**Scheme 34**).



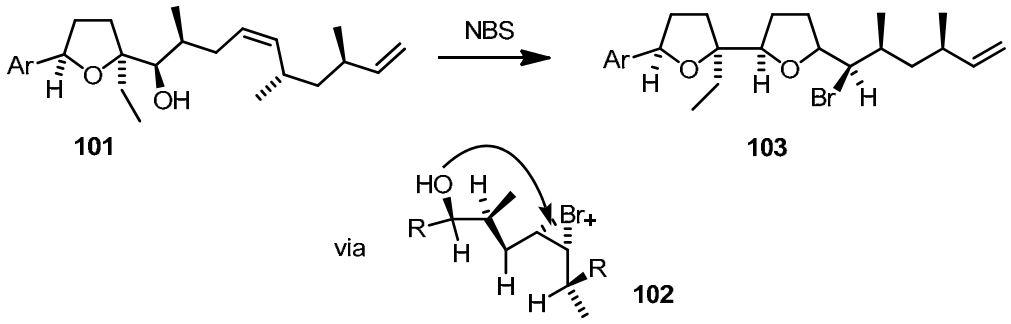
Scheme 34: Synthesis of tetrahydrofuran fragment of Lasalocid A.

In the synthesis of *Salinomycin*, Kocieński used (2*S*)-bornane-10,2-sultam **100** (Oppolzer's chiral auxiliary) to prepare chiral diene **98.**[46] Oxidative cyclization afforded the desired tetrahydrofuran **99** in 54 % yield as a 6:1 mixture of diastereoisomers (**Scheme 35**).



Scheme 35: Synthesis of tetrahydrofuran fragment of *Salinomycin.*

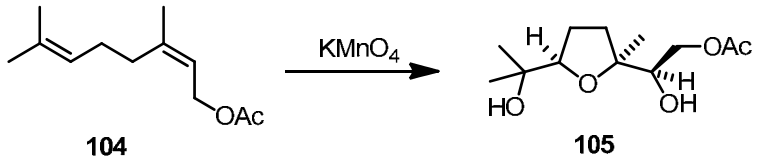
In the synthesis of *Monensin*, Kishi took advantage of the fact that bromination of the olefin **101** occurs selectively from one face, being assisted by the neighbouring group participation. Opening of the bromonium ion provided tetrahydrofuran **103** in 57% yield (**Scheme 36**).[47]



Scheme 36: Synthesis of tetrahydrofuran fragment of Monensin.

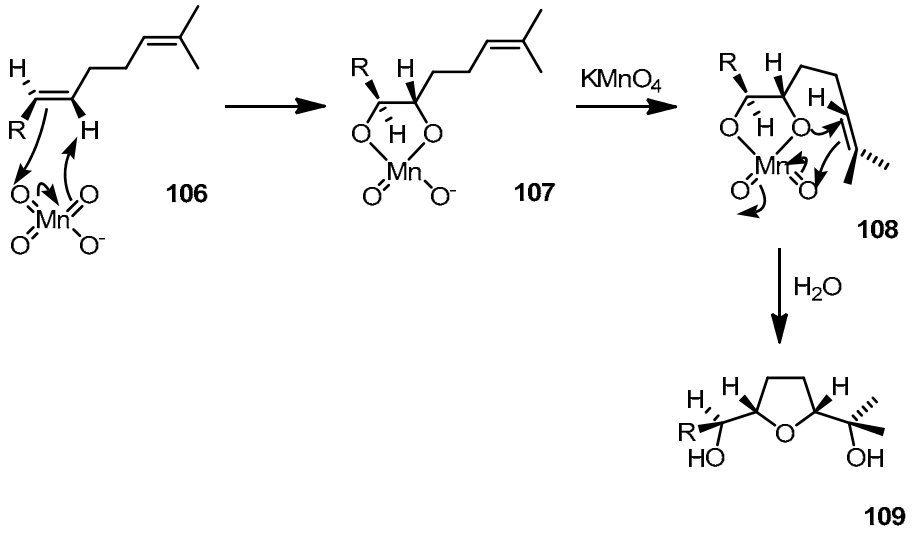
2.2.1 Oxidative Cyclization of 1,5-Dienes

In 1965 Klein reported that 1,5-dienes can be converted into tetrahydrofurans when treated with potassium permanganate under mildly alkaline conditions.[48] Years later, when interest in polyether antibiotics had developed, the synthetic possibilities of this pioneering work were extended. The reaction is general, and *cis*-2,5-bis(hydroxymethyl)-tetrahydrofurans (such as **105**) can be generated from the appropriate dienes with complete stereocontrol (**Scheme 37**).



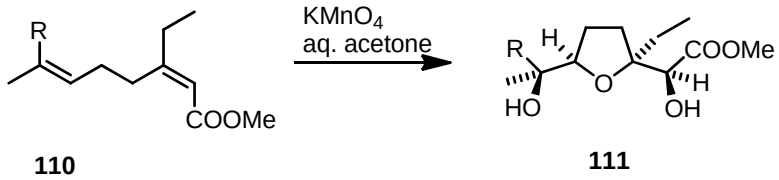
Scheme 37: Oxidative cyclization.

The mechanism suggested by Baldwin[49] (**Scheme 38**) involves an initial [3+2] cycloaddition of MnO_4^- to one of the diene double bonds and the resulting ester **107** is oxidized by another molecule of permanganate to the Mn(VI) diester **108**. This species then undergoes an intramolecular cycloaddition to the remaining double bond producing *cis* tetrahydrofuran **109** on hydrolysis.



Scheme 38: Mechanism of the oxidative cyclization.

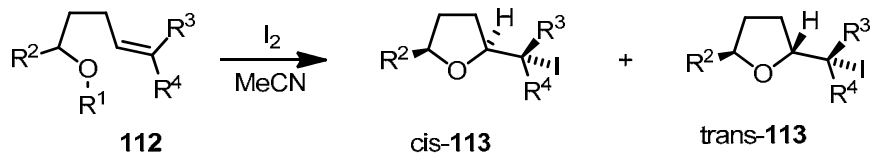
Oxidative cyclization of 1,5-dienes has been employed in a synthesis of the (racemic) ring system of *Monensin* (**Scheme 39**).



Scheme 39: Synthesis of the tetrahydrofuran fragment of *Monensin.*

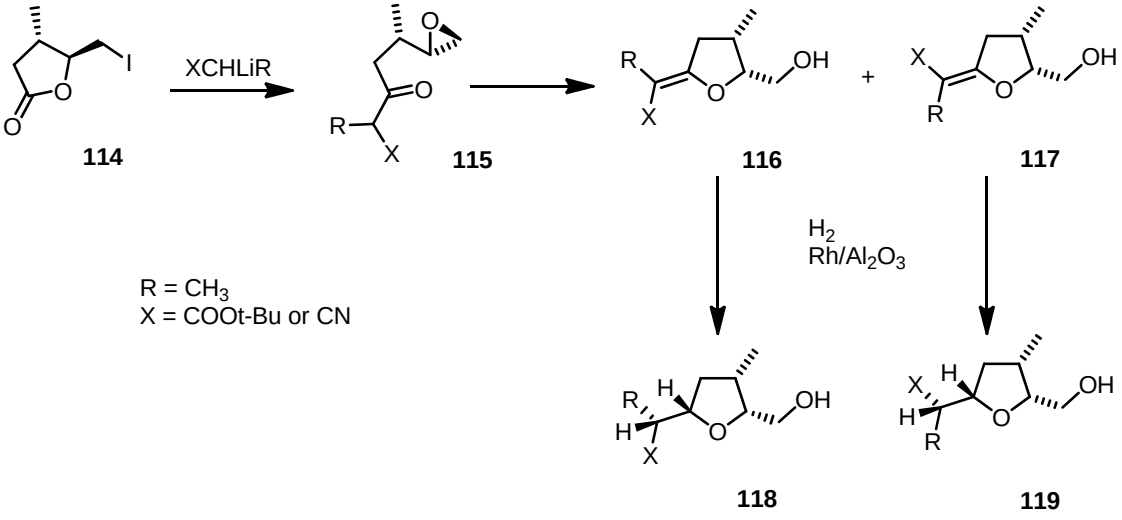
2.2.2 Halocyclization

A different approach to 2,5-disubstituted tetrahydrofurans has been developed by Bartlett.[50] This method involves the use of unsaturated alcohols or the corresponding ethers which undergo electrophilic cyclization with iodine in acetonitrile (**Scheme 40**). It was found that formation of *trans*-2,5-disubstituted tetrahydrofurans (*trans*-**113**) predominates when free alcohols are used, and that *cis* isomers (*cis*-**113**) are the major products from the corresponding ethers.



Scheme 40: Halocyclization.

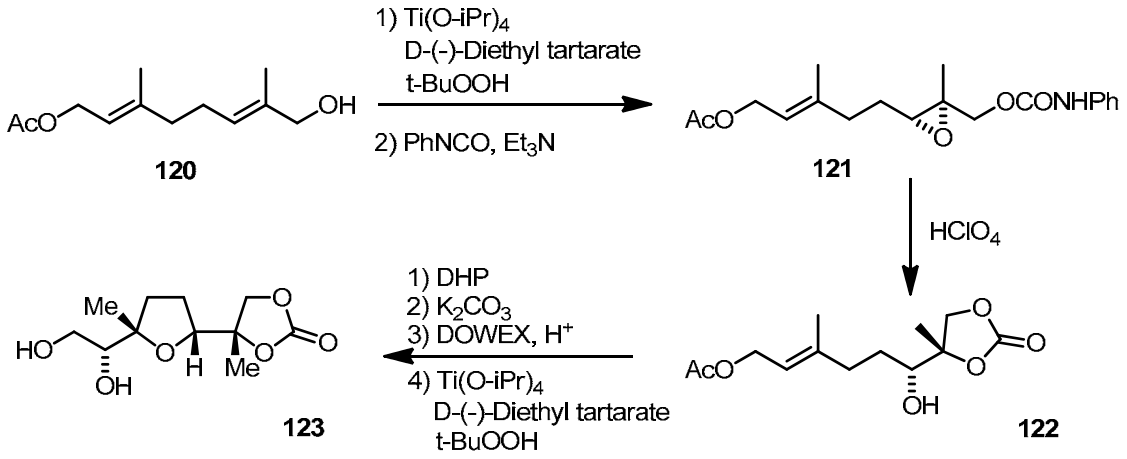
Halocyclization has also been applied, in the present context, to unsaturated acids. Iodolactonization of unsaturated acids with iodine in acetonitrile provides mainly the thermodynamically favoured lactone with high selectivity[51] that are convertible into tetrahydrofurans.[52] Iodolactone **114** was prepared in an enantiomerically pure form from the corresponding carboxylic acid and treated with stabilized carbanions to give the epoxide **115**, which undergoes, under the reaction conditions, a ring closure to afford tetrahydrofurans **116** and **117** with the exocyclic double bond. A mixture of (*E)* and (*Z)* isomers is usually obtained, their ratio depends on the nature of the carbanion used. The (*Z*) isomer can be also converted into the (*E*) isomer on treatment with sodium alkoxide in ethanol. Tetrahydrofurans, such as **116** or **117**, can be hydrogenated from the less hindered face, giving products **118** or **119** respectively (**Scheme 41**).



Scheme 41: Iodolactonization in the synthesis of substituted tetrahydrofurans.

2.2.3 Epoxidation-Cyclization

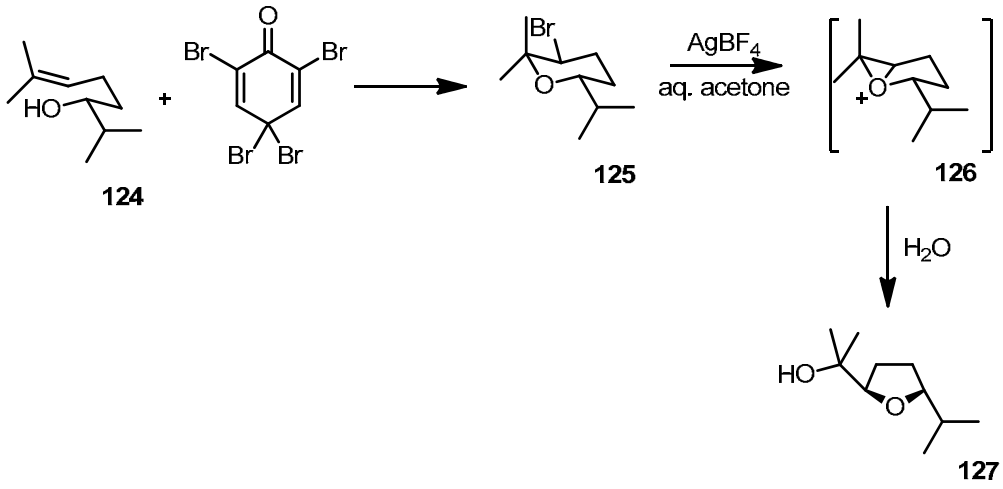
The epoxidation approach has been used to generate the tetrahydrofuran fragment of *Ionomycin*.[53] Asymmetric epoxidation of **120** and the reaction with phenyl isocyanate gave phenylurethane **121** which was treated with the perchloric acid to afford the cyclic carbonate **122**. Hydroxyl group protection, base-catalysed hydrolysis of the acetate, and deprotection set the stage for a second asymmetric epoxidation. The intermediate epoxide was not isolated and the Lewis acid-catalysed cyclization involving the free hydroxyl occurred spontaneously, forming tetrahydrofuran **123**.



Scheme 42: Synthesis of the tetrahydrofuran fragment of *Ionomycin*

2.2.4 Ring Contraction of Tetrahydropyrans

Bartlett investigated the formation of 2,5-disubstituted tetrahydrofurans by the ring contraction of appropriately substituted tetrahydropyrans.[54] The approach is based on the fact that the 1,3-asymmetric induction is more easily attained in a 6- rather than in a 5-membered ring. The unsaturated alcohol **124** was treated with TBCO to generate the desired tetrahydropyran **125** as the major cyclic ether. Tetrahydropyran **125** was then treated with silver(I) tetrafluoroborate in aqueous acetone, and the 2,5-disubstituted tetrahydrofuran **127** was isolated in a good yield. According to the authors, the ring contraction takes place via intermediate formation of a bridged oxonium ion **126**. Nucleophilic capture of this carbocation by solvent yields the observed product **127**.

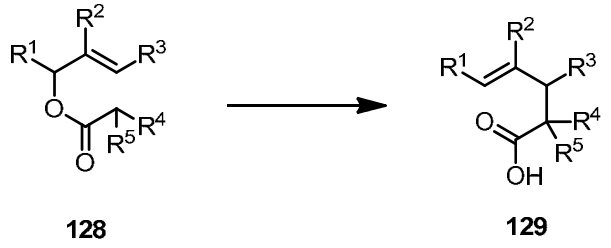


Scheme 43: Tetrahydropyran ring contraction

It is possible to improve the ring contraction methodology by using thallium(III) ions as electrophiles instead of bromine.[55] Treatment with thallium(III) converted unsaturated alcohols into the substituted tetrahydrofurans in a single step (lifetime of the thalliated intermediate appears to be extremely short).

2.2.5 Ester Enolate Claisen-Ireland Rearrangement

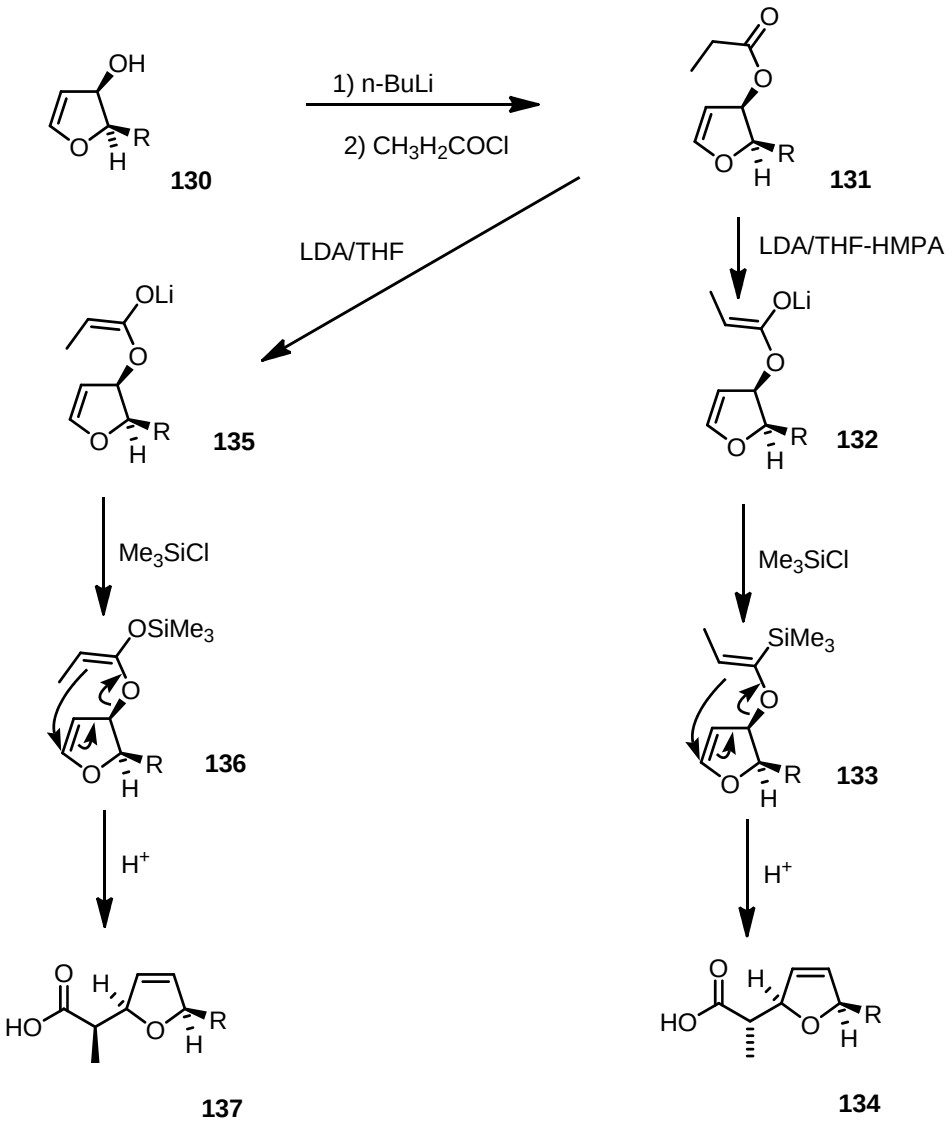
The Claisen-Ireland ester enolate rearrangement constitutes another route to tetrahydrofurans.[56] Ireland reported that stereochemical control was possible through the stereoselective enolate formation. They showed that [3,3] sigmatropic rearrangement of a number of allylic esters **128** in the form the enolate ions produces γ,δ-unsaturated acids **129** (**Scheme 44**).



Scheme 44: Claisen-Ireland rearrangement.

It was demonstrated that kinetic enolization with LDA gives selectively the enolates in which the geometry is solvent dependent, when using THF, formation of a (*Z*)-enolate was favoured, while a mixture of THF and HMPA gives mainly the (*E*)-enolate isomer.

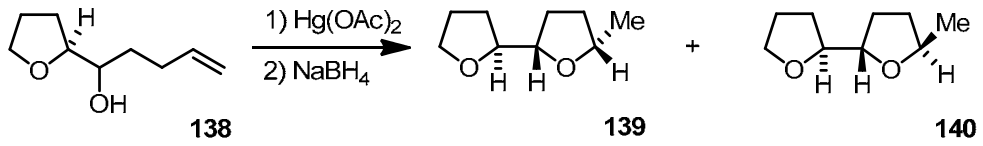
These results have been applied to the tetrahydrofuran chemistry as follows (**Scheme 45**): Transformation of glycal **130** into ester **131** (required for Claisen-Ireland rearrangement) prior to enolate formation is achieved simply by reaction of the lithium alcoholate with the requisite acid chloride.[57] Next, ester enolate of appropriate geometry must be generated. Ireland reported that kinetic enolization using lithium diisopropylamide in THF at -78°C affords predominantly (90% of the total) the *Z*-enolate **135**, while the use of LDA in THF containing HMPA gives the *E*-enolate **132** (as 80-90% of the total). The [3,3] sigmatropic rearrangement is triggered by warming either the lithium enolates **135**, **132** or the corresponding silyl enolates **136, 133** to room temperature. After hydrolysis, the functionalized dihydrofurans **137** or **134** are isolated. Hydrogenation then gives the corresponding substituted tetrahydrofurans. This ester enolate rearrangement has been used frequently in the synthesis of polyether antibiotic.



Scheme 45: Claisen-Ireland rearrangement in the synthesis of tetrahydrofurans (after hydrogenation).

2.2.6 Mercuricyclization

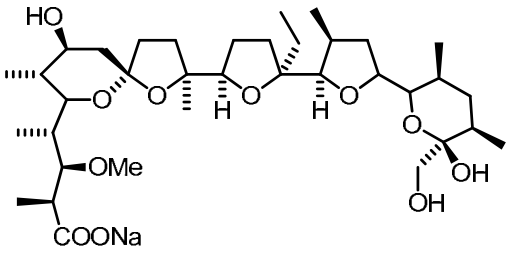
Mercuricyclization of unsaturated alcohols has been used to generate 2,5-disubstituted tetrahydrofuranyl systems (mainly *trans* substituted rings formed). In the last step of the process the mercury group is removed by the borohydride reduction. The mercuricyclization route has been used mainly to make *bis*-tetrahydrofurans (**Scheme 46**).[58]



Scheme 46: Mercuricyclization

2.2.7 Cyclization of 1,4-Diols

The cyclization of a 1,4-diol system was used by Still in the synthesis of *Monensin* to construct the central tetrahydrofuran ring in 67% yield.[59] In this protocol the diol is usually converted into the monomesylate, followed by the stereospecific ring closure.

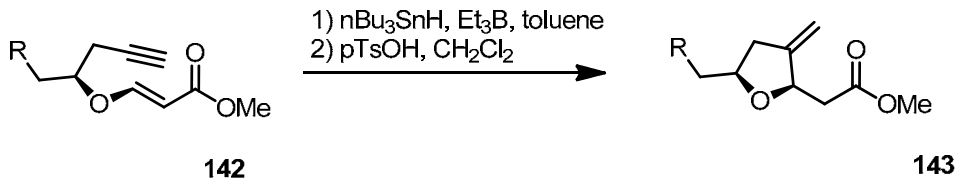


Monensin **141**

Scheme 47: Structure of Monensin.

2.2.8 Radical Cyclization

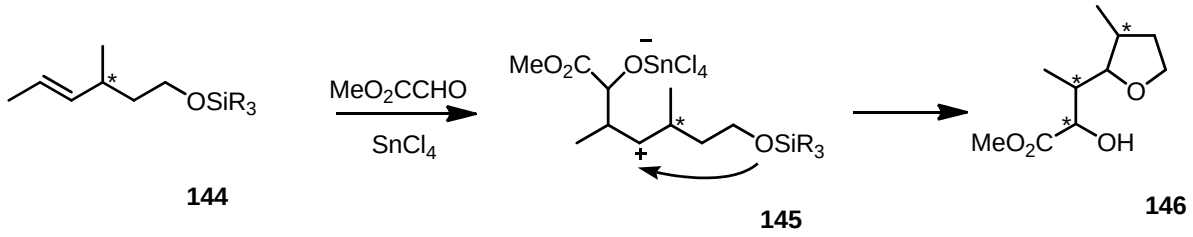
Radical-mediated cyclizations have also been extensively used for the construction of oxygen-containing ring systems.[60] Thus, for instance, radical cyclization in the presence of tributylstannane and triethylborane was employed in the total synthesis of *(-)-Amphidinolide K*.[61] The reaction gave mainly (16:1) the *cis*-2,5-disubstituted oxolane intermediate **143** after acidic destannylation (**Scheme 48**).



Scheme 48: Synthesis of the tetrahydrofuran fragment of *Amphidinolide K*.

2.2.9 Lewis Acid-Promoted Prins Cyclization

In 1996, Mikami and Shimizu unexpectedly obtained the substituted tetrahydrofuran **146** in an attempted glyoxylate-ene reaction of silyl ether **144**, presumably via the Prins reaction to form a carbon-carbon bond, followed by intramolecular reaction and an attack of the siloxy group onto the cationic intermediate to form the tetrahydrofuran **146**.[62]



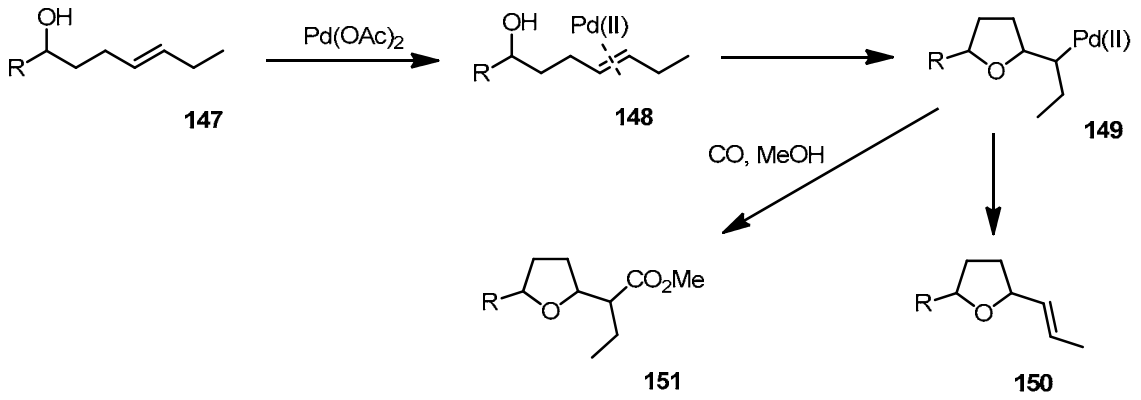
Scheme 49: The Prins reaction.

Mikami and Shimizu screened several silyl groups and the less bulky but relatively stable dimethyl-*iso*-propylsilyl protecting group was found to be the best choice.[62] This method is suitable for mono- and disubstituted furan rings, its drawback have been relatively low yields.

2.2.10 Oxy-Palladation

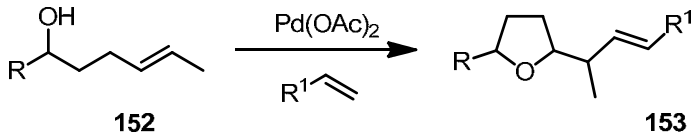
Oxy-palladation reactions of 1,4-hydroxy-alkenes lead to the formation of tetrahydrofuranyl Pd(II) intermediates **149** through the attack of the -OH group on an alkene-Pd complex **148** (**Scheme 50**).[63] By trapping with CO/MeOH, the organo-Pd intermediate is readily converted into the cyclic ester **151**. The intermediate **149** has not been detected but it

was proposed to undergo a β-hydride elimination in the absence of CO to give the alkene **150**.



Scheme 50: Oxy-palladation.

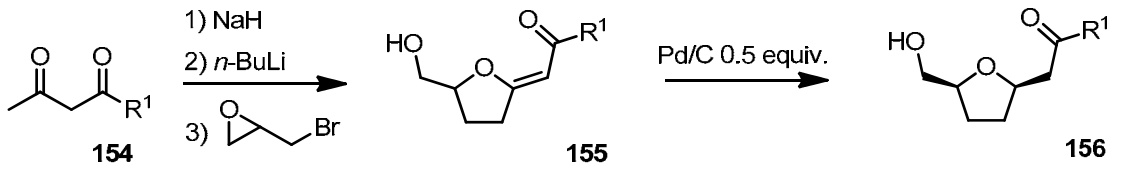
Substrates which are unable to eliminate β-hydride can undergo vinylation (via Heck reaction) i.e. one-pot ring closure and extension of the side chain (**Scheme 51**).



Scheme 51: reaction in the synthesis of tetrahydrofurans.

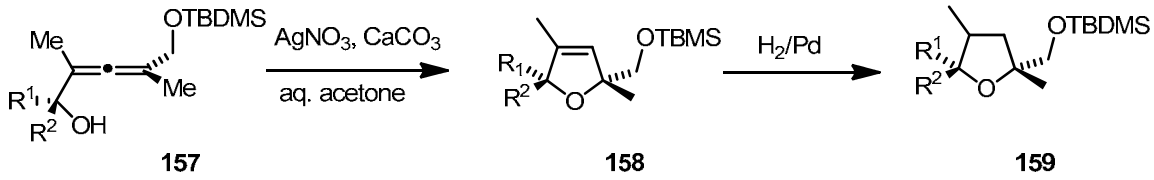
2.2.11 Miscellaneous methods

Freifeld and co-workers prepared 2-alkylidene tetrahydrofurans **155** which can serve as building blocks in the synthesis of many natural products and can be converted into substituted tetrahydrofurans by simple hydrogenation.[64] Intermediate **155** was prepared by the $LiClO_4$ mediated cyclization of dilithiated diketone **154** with epibromohydrin. The hydrogenation of **155** afforded tetrahydrofuran **156**. The stereoselectivity of the latter reaction is dependent on the nature of the substituent R and reaction conditions and is usually strongly in favour of the formation of *cis* disatereoisomer (**Scheme 52**).



Scheme 52: The epoxide ring opening.

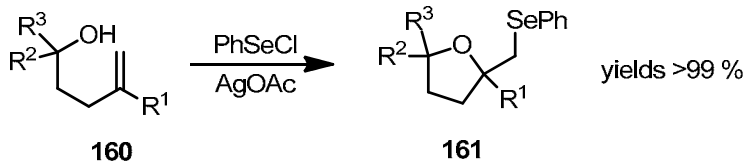
Allenes have become popular in the metal-catalysed addition reactions, they closely parallel the behaviour of alkynes in their reactivity toward Ag(I)-mediated nucleophilic additions. However, unlike alkyne substrates, allenes offer the potential of axial chirality to allow enantio- and diastereoselective reactions.[65] Nearly 30 years ago Olsson and Claesson reported that tetrahydrofurans, such as **159**, can be prepared by the 5-*endo*-*trig*-cyclization of allenic alcohols **157** (Scheme 21).[66]



Scheme 53: Allenes in the synthesis of tetrahydrofurans.

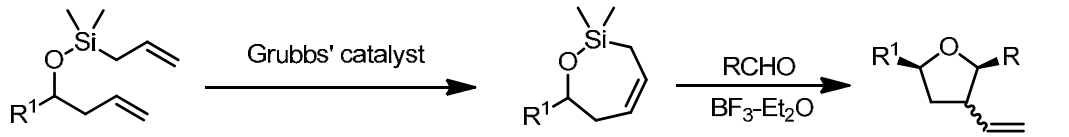
In 2004, this approach was used by Fürstner in the synthesis of *Amphidinolide*, where enantiopure allenes were obtained first and then treated with $AgNO_3/CaCO_3$ in acetone to afford the corresponding tetrahydrofurans with excellent chirality transfer.[67]

Seleno-cyclizations are another route to the oxygen heterocycles, especially tetrahydrofurans (**Scheme 54**); this method gives almost quantitative yields under extremely mild reaction conditions.[68]



Scheme 54: Seleno-cyclization.

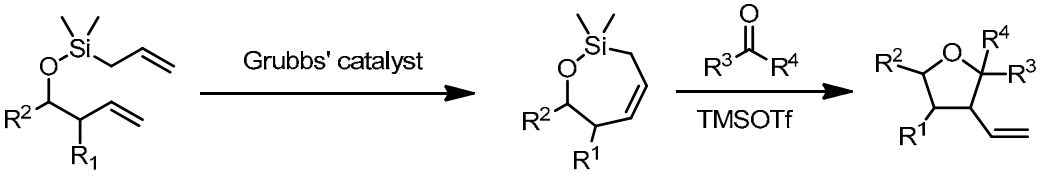
Marsden and Cossy simultaneously developed a novel method for the preparation of functionalized tetrahydrofurans via cyclic allylsiloxanes. Marsden used homoallylic silanes **162** with Grubbs' catalyst to produce the cyclic allylsilanes **163** in good yields, which reacted with various aldehydes in the presence of boron trifluoride etherate to afford substituted tetrahydrofurans **164** (**Scheme 55**).[69]



162 **163** **164**

Scheme 55: Approach to the trisubstituted tetrahydrofurans by Marsden and co-workers.

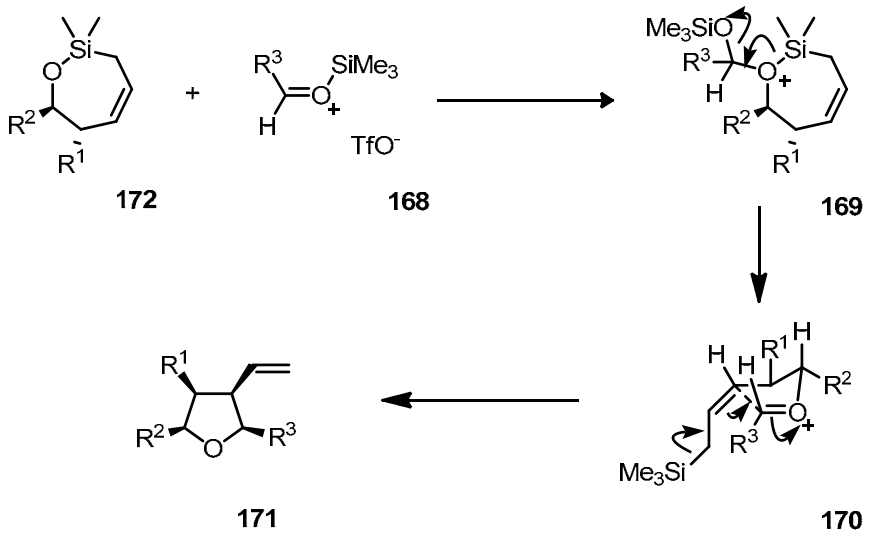
Cossy converted homoallylic silanes **165** with Grubbs' catalyst into cyclic allylsilanes **166**, which reacted with aldehydes, ketones or ketals to give substituted tetrahydrofurans **167** with high diastereoselectivity (**Scheme 56**).[70]



165 **166** **167**

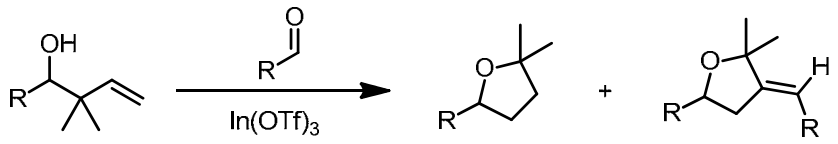
Scheme 56: Approach to the trisubstituted tetrahydrofurans by Cossy and co-workers.

Cossy interprets the formation of tetrahydrofurans by the following mechanism (**Scheme 57**).[70] Reaction of the silylether moiety of the cyclic allylsiloxanes **172** with the electrophiles **168** (carbonyl compounds or their acetals activated by the Lewis acid TMSOTf) generates oxonium ions **169** which can be trapped intramolecularly by the allylsilane, thus generating the oxygenated heterocycle **171**. A chairlike transition state, in which the substituents preferentially occupy pseudo-equatorial positions, can account for the stereochemical outcome of this reaction.



Scheme 57: Proposed mechanism of the ring contraction.

There have been plenty of approaches to the synthesis of heterocycles using indium chemistry.[71] A few years ago, Loh reported on the formation of tetrahydrofurans from homoallylic alcohols catalysed by $In(OTf)_3$.[72] The reaction of homoallylic alcohols (**173**) with aldehydes gave an unexpected mixtures of compounds **174** and **175** (**Scheme 58**). The **82** : **83** ratio depends strongly on reaction conditions,[73] on the ratio of starting materials, and the nature of the aldehyde and homoallylic alcohol used. Some of Loh's results are summarized in **Table 4**.



173 **174** **175**

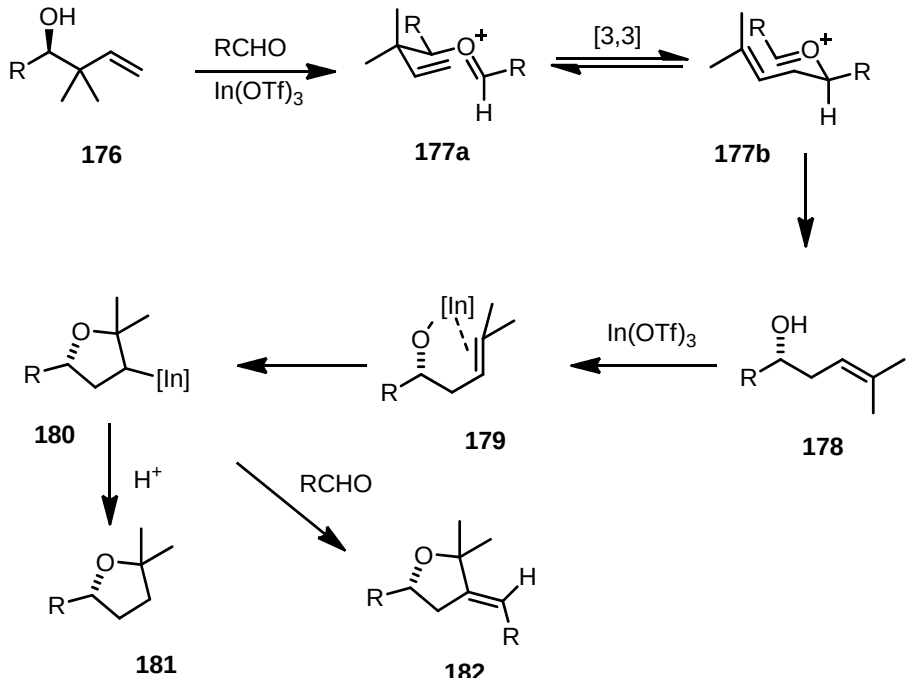
Scheme 58: Indium chemistry in the synthesis of tetrahydrofurans.

Table 4: Outcome of Loh's "allyl transfer" reaction (Scheme 58) depending on reaction conditions.

entry	**R**	**$In(OTf)_3$ eq.**	**RCHO eq.**	**T /°C**	**time/h**	**yield/% (ratio of 174:175)**
1	$PhCH_2CH_2$	0.1	0.1	25	240	54 (81:19)
2	$PhCH_2CH_2$	0.2	0.1	25	192	70 (59:41)
3	$PhCH_2CH_2$	0.1	0.1	40	14	56 (70:30)
4	$PhCH_2CH_2$	0.1	1.0	40	14	60 (3:97)
5	Ph	0.1	0.1	40	14	28(72:28)
6	Ph	0.1	1.0	40	14	66 (3:97)
7	$CH_3(CH_2)_7$	0.1	0.1	40	14	59 (75:25)
8	$CH_3(CH_2)_7$	0.1	1.0	40	14	58 (7:93)

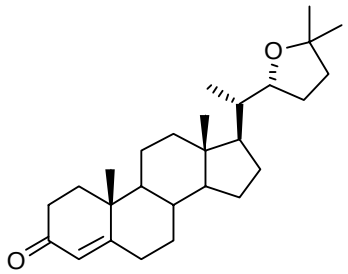
Interestingly, when the reaction was performed in the presence of a catalytic amount of indium triflate (0.1 equiv) and aldehyde (0.1 equiv), product **174** was formed preferentially with the selectivity up to 81%. On the other hand, upon increasing the amount of aldehyde, compound **175** became the major product with selectivity up to 97%. The double bond in product **175** always had (*E*) geometry.

Loh suggested a reaction mechanism which involves first an $In(OTf)_3$ promoted conversion of the homoallylic alcohol **176** into the corresponding intermediate **177b** via a [3,3]-sigmatropic rearrangement. This step is followed by an additive incorporation of an oxygen and indium across the double bond to give the tetrahydrofuranyl-indium species **180**. Trapping of **180** with a proton source would form **181** while an alternative nucleophilic attack at the parent aldehyde would form **182** after elimination (**Scheme 59**).



Scheme 59: The mechanism postulated by Loh.

No cyclization was observed with 1-alkyl-2-methyl-3-butenols and 1-alkyl-3-butenols, and only the allyl transfer was observed.



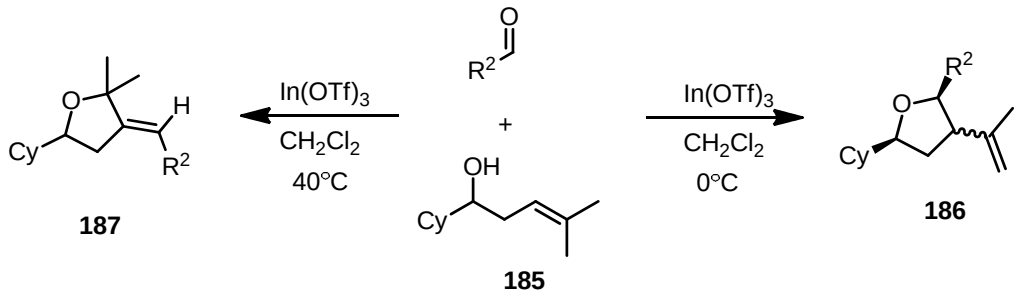
Shidasterone

183

Scheme 60: Structure of Shidasterone.

Loh demonstrated practical use of this method in the synthesis of Shidasterone,[74] a steroid with recently discovered antitumor activity.

Loh and Cheng have further reported that when the cyclization was conducted at 0 °C, the reaction took a completely different turn to afford the tetrahydrofuran product **186** instead of **187**, which can be viewed as a result of an exocyclic Oppolzer's type III cyclization.[75,76] Temperature appears to function as the key switch in alteration of the reaction pathway.

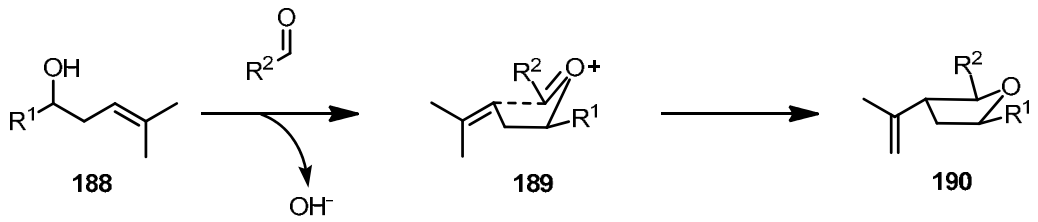


Scheme 61: Temperature influence in Loh's cyclizations.

Table 5. Some of Loh and Cheng's results which show the influence of the temperature and different substituents (Scheme 61).

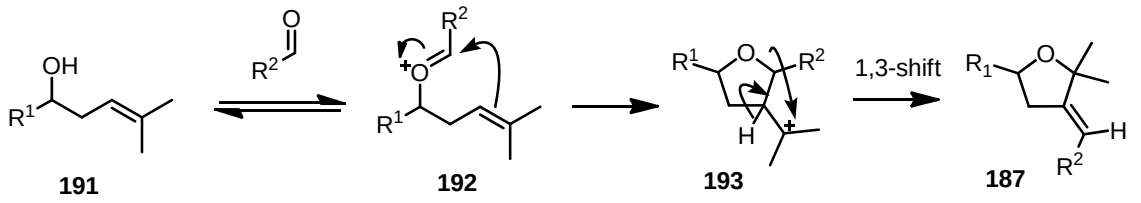
entry	R^2	T/°C	yield of the main product (%)
1	$PhCH_2CH_2$	40	65
2	$PhCH_2CH_2$	0	95
3	$CH_3(CH_2)_7$	40	81
4	$CH_3(CH_2)_7$	0	69
5	Ph	40	97
6	Ph	0	72
7	cyclohexyl	40	75
8	cyclohexyl	0	77

All reactions proceeded smoothly to afford various five-membered cyclic ethers but not with a very good stereoselectivity. This can be accounted for by the relatively non-rigid five-membered transition state **189** (**Scheme 62**).



Scheme 62: Proposed mechanism of the cyclization.

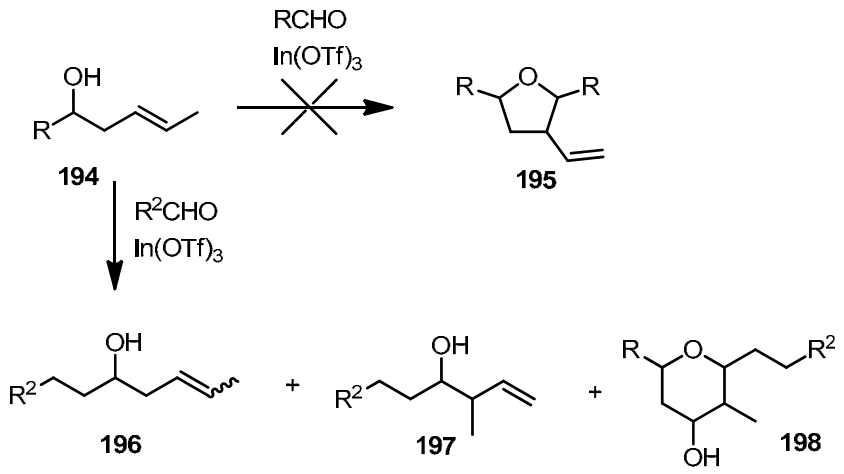
Another mechanism was proposed for the formation of **187**. It involves an oxonium-ene type cyclization to afford the carbocation intermediate **192**, prior to the 1,3-shift, rearranging to the thermodynamic product **187** under thermal conditions (**Scheme 63**).



Scheme 63: Proposed mechanism of the formation of thermodynamic product 187.

This mechanism is supported by the fact that **190** is converted into **187** upon refluxing in dichloromethane in the presence of indium triflate. However, when the experiment was carried out in the presence of a 2,6-di-*tert*-butyl-4-methylpyridine, no reaction took place and only starting material was isolated. Furthermore, trifluoromethanesulfonic acid also catalyses the same transformation of **190** to **187**. The latter observations indicate that a complex protic acid is formed in the reaction system, which catalysed the *in situ* generation of a carbocation, triggering the postulated thermodynamic 1,3-shift.

Loh and Tan reported that no desired tetrahydrofuran product **195** was obtained when monosubstituted homoallylic alcohol **194** was subjected to the same reaction conditions (**Scheme 64**), apparently disubstitution at the distal end of the double bond is essential to this oxonium-ene type cyclization. Here, instead of the furan **195**, α-adduct **196** was isolated as a main product together with a small amount of γ-adduct **197** and traces of Prins cyclization product **198** (**Scheme 64** and **Table 6**).

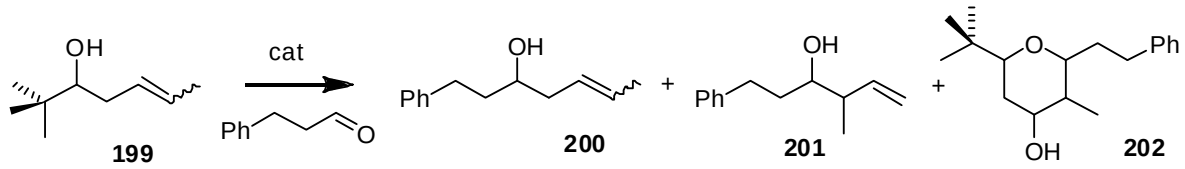


Scheme 64: Homoallylic alcohols with the monosubstituted double bond at the distal end under "Loh's conditions".

Table 6: Some of Loh and Tan's results which show the influence of different substituents.

entry	R	R^2	yield/%	ratio of products 196/197formed
1	Cy	$PhCH_2CH_2$	25	>95 : 5
2	$(CH_3)_2CH$	$PhCH_2CH_2$	23	>95 : 5
3	*n*-C_8H_{17}	$PhCH_2CH_2$	25	76 : 24
4	Ph	$PhCH_2CH_2$	45	>95 : 5
5	Cy	$PhCH_2CH_2$	49	>95 : 5
6	*t*-Bu	$PhCH_2CH_2$	69	>95 : 5

Loh and Tan also explored various catalysts in the reaction of alcohol **199** with dihydrocinnamaldehyde (**Scheme 65**). Whereas CSA, PTSA, $InBr_3$, $Ag(OTf)_3$, $La(OTf)_3$, and $Lu(OTf)_3$ did not work at all, $Yb(OTf)_3$, $Cu(OTf)_2$, $Sc(OTf)_3$, $Sn(OTf)_2$, and $In(OTf)_3$ gave different ratios of products **200**, **201** and **202** (**Table 7**).

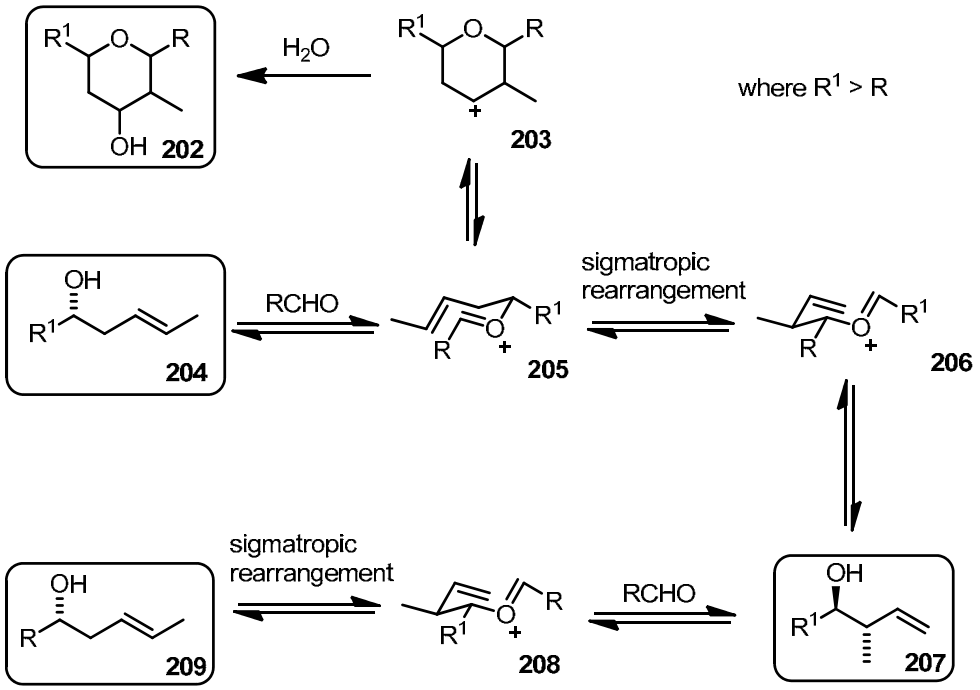


Scheme 65: Influence of the Lewis acid.

Table 7: Screening of various Lewis acids.

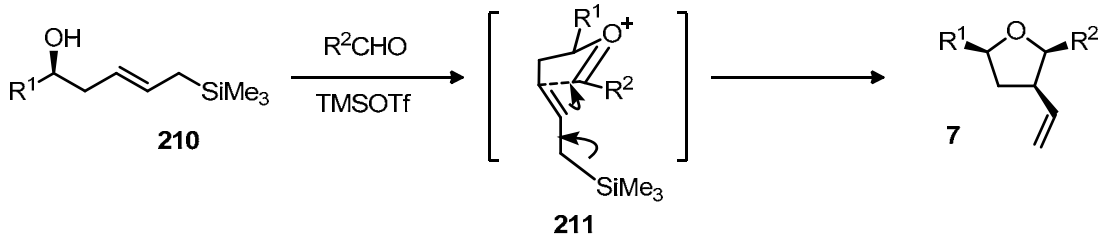
entry	catalyst	yield of 200 (%)	yield of 201 (%)
1	$Yb(OTf)_3$	15	5
2	$Cu(OTf)_2$	22	3
3	$Sc(OTf)_3$	40	28
4	$Sn(OTf)_2$	55	23
5	$In(OTf)_3$	69	10

The following mechanism of the formation α-adducts, γ-adducts and Prins cyclizaton products were suggested (**Scheme 66**). The α-adduct **209** was generated from the $In(OTf)_3$ promoted allyl transfer reaction of the γ-adduct **207**. Thus, alcohol **207** underwent a thermodynamic conversion to the preferred linear regioisomer **209**. The stereochemistry was retained after the allyl transfer from the original homoallylic alcohol **204**. The steric effect is very important, and the whole rearrangement process was driven by the difference in steric bulk of the two substrates. The cyclic Prins product **202** was derived from the oxonium ion **205** which can cyclize to give a stable cation **203** which reacts further to give the six membered ring **202**.



Scheme 66: Proposed mechanism.

In 2006 Peng and Hall reported on the synthesis of homoallylic alcohols **210** containing a trimethylsilyl moiety, which upon treatment with aldehydes gave all-syn trisubstituted tetrahydrofurans **7** with high diastereo- and enantioselectivity (**Scheme 67** and **Table 8**).[1] The diastereoselectivity is explained by the pseudo-diequatorial arrangement of R^1 and R^2 in the transition state **211**.

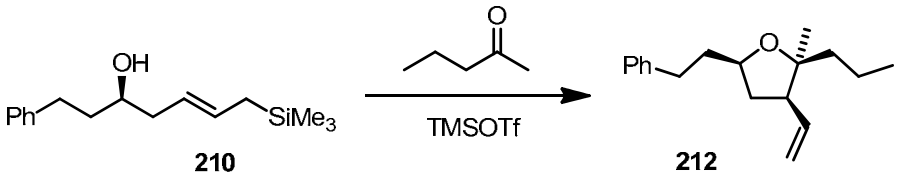


Scheme 67: Peng & Hall's cyclization.

Table 8: Examples of Peng & Hall's cyclizations.

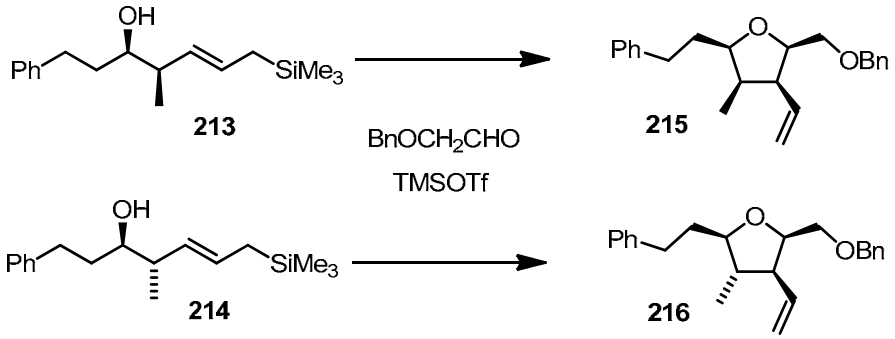
Entry	R^1	R^2	yield (%)	ee (%)
1	$PhCH_2CH_2$	Ph	75	93
2	$PhCH_2CH_2$	*n*-C_7H_{15}	82	95
3	Ph	$PHCH_2OCH_2$	72	91

Remarkably, the use of ketones instead of aldehydes in this reaction provides 1,1,2,4-tetrasubstituted furans **212** in high yields (**Scheme 68**).



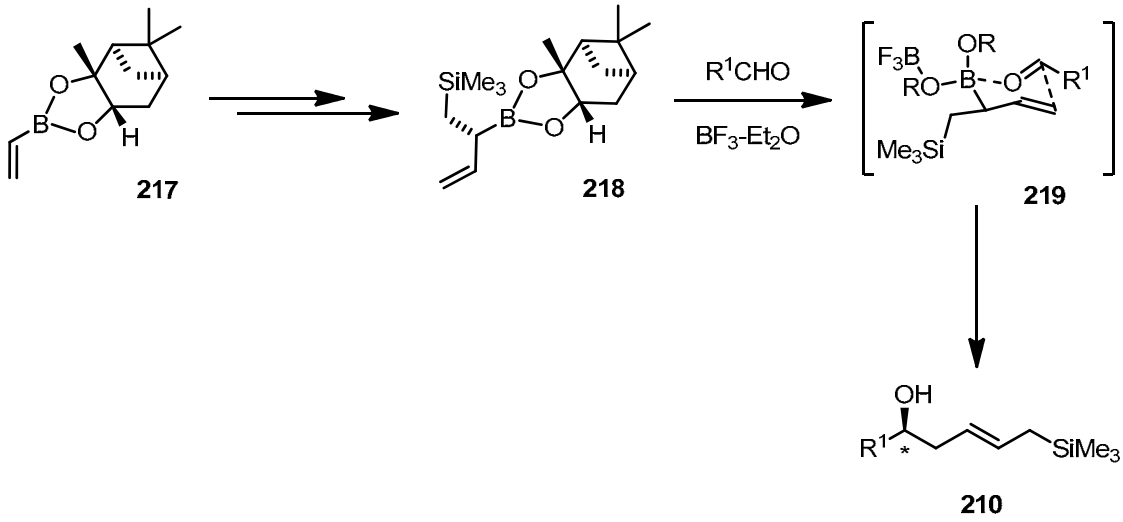
Scheme 68: Ketones in the Peng & Hall's cyclization.

Also, both *syn* and *anti* crotyl reagents **213** and **214** were prepared and their reactions with aldehyde gave the corresponding tetrasubstituted tetrahydrofurans **215** and **216**.



Scheme 69: A way to prepare the tetrasubstituted tetrahydrofurans.

Enantiopure starting materials (homoallylic alcohols) for those reactions were prepared using the pinanediol chiral auxiliary. From pinanedioxy ethyleneboronic ester **217**, intermediate **218** was prepared in two steps. Intermediate **218** adds onto aldehydes with very good *E*/*Z* selectivity and enantioselectivities forming the homoallylic alcohol **210** (**Scheme 70**).



Scheme 70: Enantioselective version with the chiral auxiliary.

As depicted in transition structure **219**, the enantioselectivity is controlled by the configuration of the reagent's α-carbon centre and the preference for a pseudo-equatorial orientation of the substituent.

An obvious drawback of this method is the need of one equivalent of an expensive chiral auxiliary, which cannot be recovered from the reaction (5g of (+)-vinylboronic acid pinanediol ester currently costs £158.00 at Aldrich).

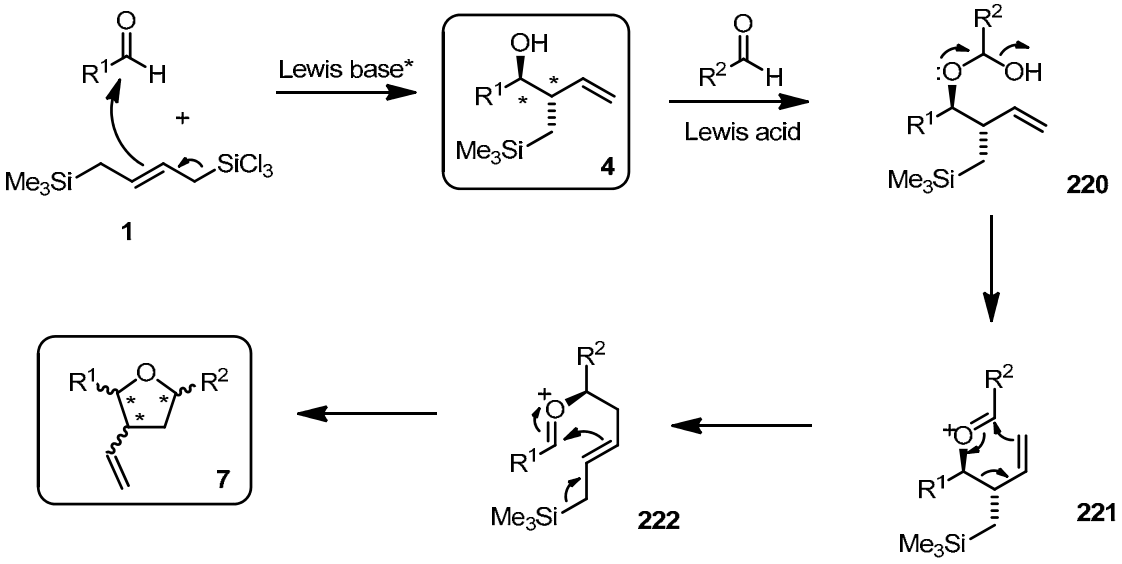
Homoallylic alcohols can be prepared enantioselectively by an allylation reaction from the corresponding trichlorosilanes by using a catalytic amount of chiral catalyst (which can be later recovered from the reaction mixture).[77]

2.3 Results and discussion

2.3.1 Project Aim

Lewis base-catalysed enantioselective allylation of aldehydes has become a powerful tool for the C-C bond formation, providing a robust alternative to the boron chemistry, using allyl boranes and a stoichiometric amount of chiral auxiliaries. It has been demonstrated recently that the homoallylic alcohols, products of the allylation of aldehydes with allyltrichlorosilanes, are themselves powerful allylating agents, which broadened the scope of the method even more. Further advancement can be achieved by decorating the allyltrichlorosilane with another functionality which would enable further synthetic development.[78]

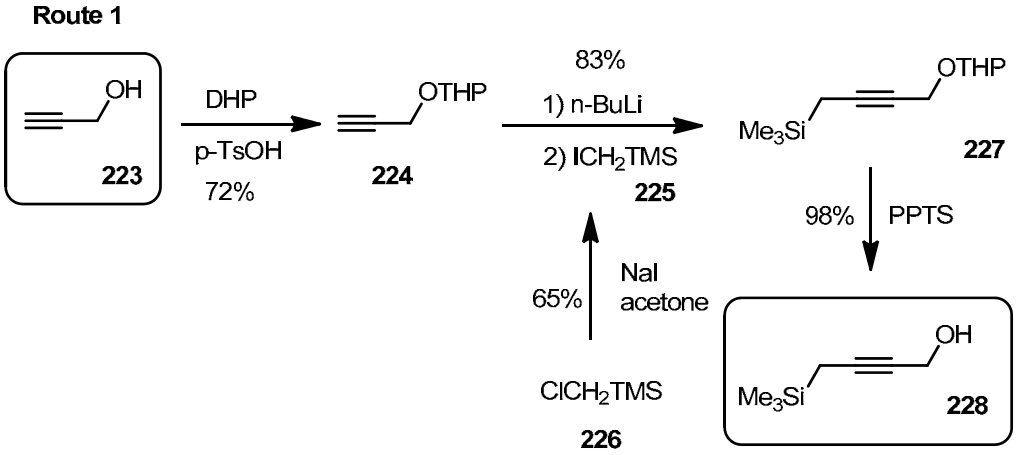
We envisioned that the bifunctional allyldisilane **1** would allow a stereoselective triple allylation of aldehydes, resulting in a stereocontrolled construction of trisubstituted tetrahydrofurans. Interestingly, the two silicon groups in the disilane have in fact orthogonal reactivities. Allytrimethylsilane requires Lewis acid catalysis to undergo the transformation, whereas allyltrichlorosilyl reagents are activated by the Lewis bases. With the bifunctional disilane **1**, the key stereogenic centres are constructed in the first allylation step and the subsequent diastereoselective cyclization cascade then requires just a non-chiral Lewis acid. The first steps of the cascade mirrors the analogous cross-crotylation. The key difference is that the alcohol **4** has a latent allylsilane functionality, which is unmasked by the [3.3] sigmatropic rearrangement (**221** → **222**), and the five-membered ring **7** is closed by the intramolecular allylation (**Scheme 71**).



Scheme 71: The reaction cascade towards the substituted tetrahydrofurans.

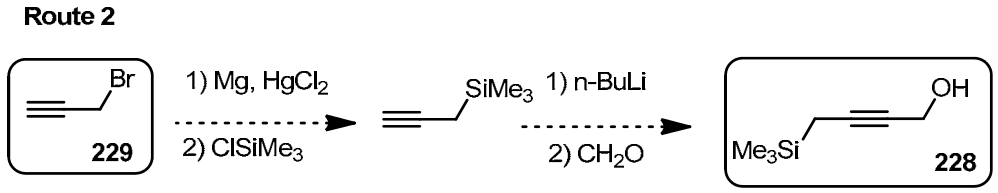
2.3.2 Synthesis of the Disilane

There are at least two feasible ways to prepare the intermediate **228** (**Scheme 72** and **73**) from the corresponding propargyl-based starting material.



Scheme 72: Synthesis of the intermediate 228 from the propargylic alcohol.

Route 2 (**Scheme 73**) is somewhat shorter, and looks more feasible at the first glance. However, **Route 1** (**Scheme 72**) was explored first, taking into account the cost of the starting materials, low published yields of the Grignard step and last but not least the use of the toxic mercury(II) chloride suggested in this transformation involved in **Route 2**.



Scheme 73: Synthesis of the intermediate 228 from the propargylic bromide.

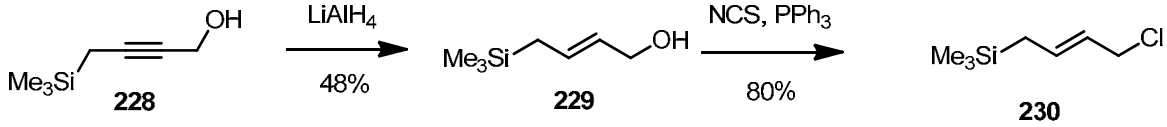
Propargylic alcohol **223** was protected as a tetrahydropyranyl ether **224**,[79] which was deprotonated with *n*-butyllithium, and treated with (chloromethyl)trimethylsilane using the published conditions.[80] However, only poor conversion (~6%) was observed, due to the poor electrophilicity of the (chloromethyl)trimethylsilane. The more reactive (iodomethyl)trimethylsilane and (trifluoromethansulfonylmethyl)trimethylsilane are commercially available but considerably more expensive. (Iodomethyl)trimethylsilane **227** was therefore prepared by the Finkelstein reaction of **225** with an excess of sodium iodide in acetone and reacted readily with the deprotonated propargylic alcohol to give intermediate **227** in good yield.[81]

Surprisingly, the deprotection step turned out to be quite tricky. The published method using PTSA in methanol gave disappointingly low yields and a lot of undesired byproducts. We investigated alternative deprotection protocols involving AcOH in THF,[82] $MgBr_2$[83], PPTS[84] and few others and identified PPTS in aqueous ethanol at an elevated temperature as an optimal method, see **Table 9** for details.

Table 9: Deprotection of 227.

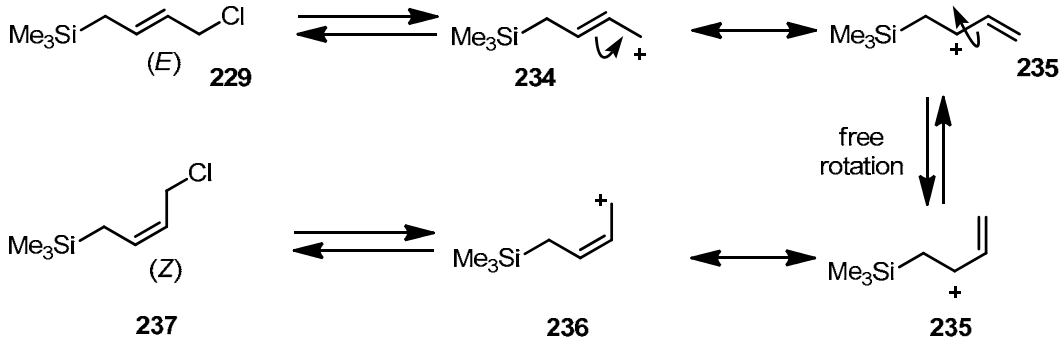
Entry	Reagent	Reaction conditions	Yield %
1	PTSA, aq. MeOH solution	0°C, then 20h at 20 °C	60
2	AcOH, THF, water (vol. ratio 14:2:1)	24 h at 20 °C	0
3	$MgBr_2$, Et_2O	24 h at 20 °C	0
4	PPTS, aq. EtOH solution	24 h at 20 °C	88
5	PPTS, aq. EtOH solution	24 h at 55 °C	98

Reduction of the triple bond by lithium aluminium hydride (**228** to **229**) proceeded uneventfully, and the (*E*)-isomer was formed exclusively as expected (**Scheme 74**).



Scheme 74: Synthesis of the chloride 230.

The conversion of alcohol **229** into chloride **230** proved to be quite problematic and required a great deal of optimization. The published procedure using an excess of thionyl chloride at low temperatures failed completely, giving just a complex mixture of products.[85] Surprisingly, by using thionyl chloride and an excess of amine base in dichloromethane we obtained a mixture of (*E*) and (*Z*) isomers of allylic chloride. We assumed that the allylic rearrangement of **229** took place and the resulting carbocation **235** (stabilized by the silicon in β-position) allowed the isomerisation of the double bond and formation of **237** to occur (**Scheme 75**). Unfortunately, the (*Z*)-isomer (which was always formed preferentially despite varying reaction conditions) is unsuitable for further enantioselective allylation using METHOX as a catalyst.



Scheme 75: Isomerization of the allylic chloride 230.

After this failure we switched to procedures that utilize milder chlorinating reagents. Lithium chloride in the presence of methanesulfonyl chloride and lutidine or collidine in DMF was reported to be selectively converting allylic alcohols into chlorides.[86] However, using the reported conditions (typically at 0 °C), we isolated just starting materials, whereas at elevated temperatures we obtained a complex mixture of products, probably due to the nucleophilic attack onto the double bond. Another mild method that has been claimed not to

give any allylic rearrangement products involved a treatment with *N*-chlorosuccinimide and DMS at low temperatures.[87] However, we obtained only a complex mixture, again with none of the desired product present.

We switched to the methods employing triphenylphosphine and various chlorinating agents. The reaction with triphenylphosphine in tetrachloromethane appeared promising and the desired allylic chloride was formed (although the conversion was poor even after prolonged time under reflux).[88] Finally, the reaction with triphenylphosphine and hexachloroacetone or *N*-chlorosuccinimide gave the desired allylic chloride with full conversion.[89]

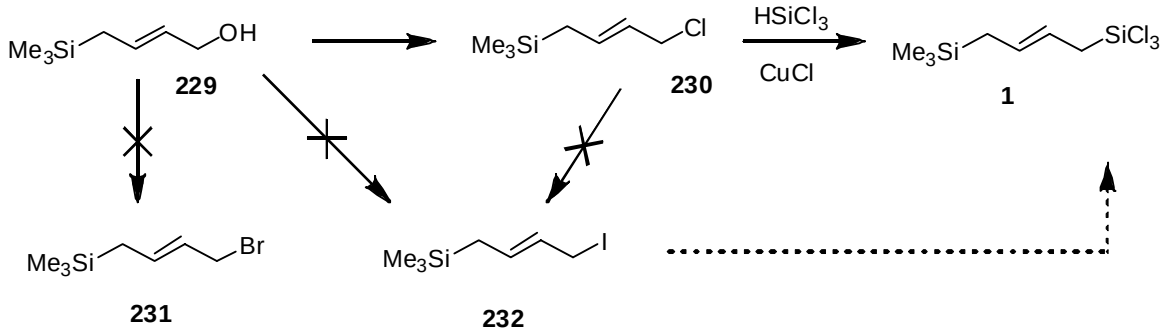
However, this reaction is typically carried out at 0 °C in order to prevent the side reactions and requires excess (usually at least 2 equivalents) of triphenylphosphine in order to reach reasonable conversion under those conditions. Unfortunately, due to the sensitive nature of the product, the crude reaction mixture cannot be purified by column chromatography, which leads to decomposition (even when basic silica gel or alumina treated with triethylamine are employed). Upon heating, the nucleophilic substitution on the allylic chloride with the remaining triphenylphosphine took place, giving rise to the phosphonium salt, distillation was therefore not an option as a purification method. With just one equivalent of the triphenylphosphine present, the reaction became too slow at 0 °C, on the other hand upon warming up to room temperature, too many byproducts were formed. We tried to oxidise the remaining triphenylphosphine carefully with a slight excess of hydrogen peroxide at low temperature to get triphenylphospine oxide (which is insoluble in diethyl ether and non-polar solvents, hence easy to separate), however the product decomposed under those conditions. We observed a similar degradation of the product when methylation of the excess triphenylphosphine was attempted with iodomethane in order to produce an insoluble phosphonium salt, which could be filtered off from the reaction mixture.

In conclusion, the best method found was leave the reaction mixture at 5-10 °C with one equivalent of triphenylphosphine and *N*-chlorosuccinimide, while monitoring the progress by TLC carefully. When quenched in time, this method gave full conversion, typically after several hours, and almost no byproducts detected in the crude mixture. The chlorination methods used are summarized in **Table 10**.

Table 10: Chlorination of 229.

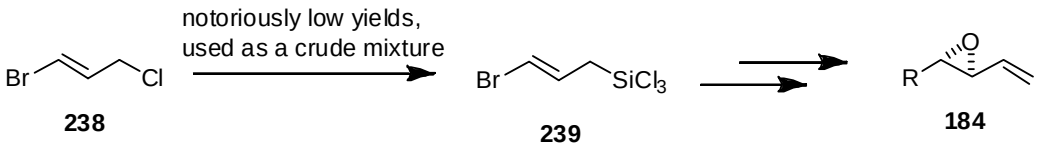
Entry	Reagent	T (°C)	Result
1	$SOCl_2$	0	complex mixture
2	$SOCl_2/Et_3N/CH_2Cl_2$	0	predominantly *cis* allyl chloride
3	$SOCl_2$/Hünig's base/CH_2Cl_2	0	predominantly *cis* allyl chloride
4	LiCl/MsCl/DMF	0	0 % conversion
5	LiCl/MsCl/DMF	RT	decomposition
6	NCS/DMS	-30	decomposition
7	Ph_3P/CCl_4	RT	6 % conversion
8	Ph_3P/hexachloroacetone	5	>99% conversion
9	Ph_3P/NCS	5	>99% conversion

Trichlorosilylation reaction, using the optimised conditions for the allyl/crotyl chloride substrate analogues (i.e., room temperature, cat. amount of Cu(I) chloride, amine base as a proton scavenger, 2-3 hours to reach the full conversion) proceeded slowly, giving very low conversion <10% even after prolonged reaction time and no changes were observed even upon raising the temperature (which, not surprisingly, also led to the decomposition of the sensitive trichlorosilane after a few hours). Employing the more active Cu(I) bromide or iodide instead of chloride as a catalyst had no effect, increasing the catalyst loading up to 10% had no effect either. Attempts were therefore made to synthesize more reactive starting material, i.e. bromide (with NBS a CBr_4), iodide and triflate. However, procedures using various brominating and iodinating agents to convert **229** into **231** or **232** failed, as well as the Finkelstein procedure, giving usually just a complex mixture of products.



Scheme 76: Synthesis of the disilane.

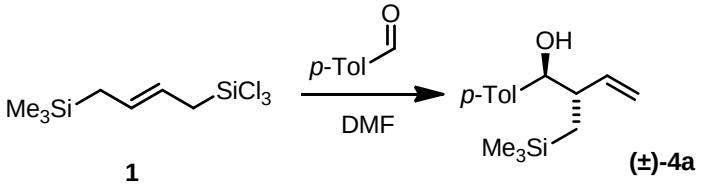
It was however found that upon increasing the amount of the copper "catalyst" to at least one equivalent, full conversion was achieved within a few hours (similarly to the allyl/crotyl chloride substrate analogue). This observation may actually solve the problems connected with the synthesis of the analoguous trichlorosilane **239**, where similar conversion issues were encountered in our group several years ago; this hypothesis has not been tested yet however (**Scheme 77**).[90]



Scheme 77: Problems connected with the synthesis of analogous trichlorosilane previously in our group.

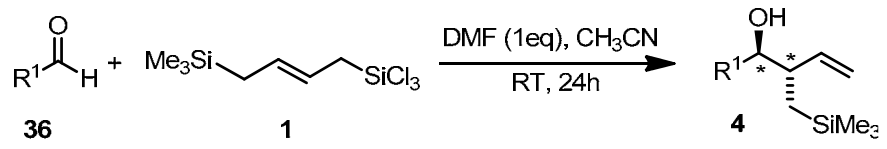
2.3.3 Allylation of Aldehydes

As a model reaction, racemic homoallylic alcohol **4a** bearing the trimethylsilane moiety was prepared by from *p*-tolualdehyde by allylation with trichlorosilane **1** and DMF as a Lewis base catalyst (**Scheme 78**).[21] As in the case of simple crotylation, the reaction gave exclusively the *anti*-configured product (as expected from the 6-membered chair transition state), which was confirmed by the NMR spectroscopy and X-ray crystallography.



Scheme 78: Model allylation of p-tolualdehyde.

A series of racemic homoallylic alcohols **4** was then prepared by allylation of aldehydes **36** with the bifunctional allyldisilane **1**, again using DMF as an achiral Lewis base (**Scheme 79**). Results are summarized in **Table 11**.

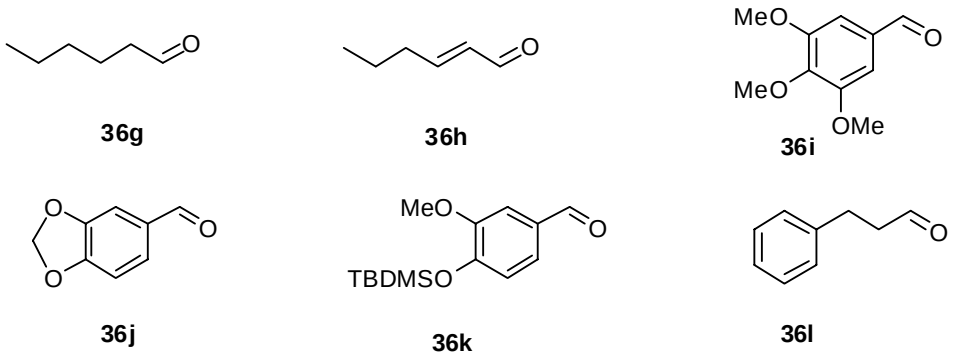


Scheme 79: Allylation of aldehydes with the disilane 1.

Table 11: Allylation of various aldehydes.

Entry	R^1	Aldehyde[a]	Product 4	Yield [%][b]
1	Ph	**36a**	**4a**	88
2	4-MeC_6H_4	**36b**	**4b**	92
3	4-FC_6H_4	**36c**	**4c**	85
4	4-$CF_3C_6H_4$	**36d**	**4d**	90
5	4-$NO_2C_6H_4$	**36e**	**4e**	91
6	3-$MeOC_6H_4$	**36f**	**4f**	80
7	*n*C_5H_{11}	**36g**[c]	**4g**	79
8	*n*PrCH=CH	**36h**[c]	**4h**	90
9	3,4,5-$(MeO)_3C_6H_2$	**36i**[c]	**4i**	71
10	2-MeO-3-OTBDMS-C_6H_3	**36j**[c]	**4j**	75
11	piperonyl	**36k**[c]	**4k**	67
12	PhC_2H_4	**36l**[c]	**4l**	77

[a]The reactions were carried out with 0.5 mmol of aldehyde, 0.4 mmol of disilane and 0.5 mmol of DMF. [b]Isolated yield; all products were diastereoisomerically pure (>99:1 dr), as evidenced by ^{1}H NMR spectroscopy. [c]See **Scheme 80** for the structures of the selected aldehydes.

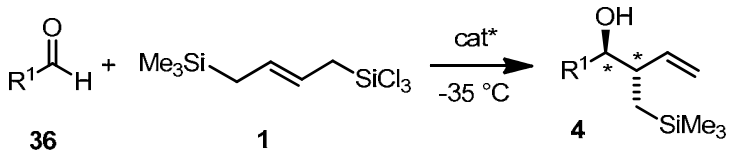


Scheme 80: Some of the model aldehydes used in the allylation reaction.

Aldehydes were selected mostly according to their electronic properties to explore the scope and limitations of the reaction. The piperonal-, vanillin- and gallic-like moieties of aldehydes **36j**, **36k** and **36i** are also a common motif in several natural products.

2.3.4 Asymmetric Allylation of Aldehydes

Next, we endeavoured to prepare these homoallylic alcohols enantioselectively. A whole range of organocatalysts have been developed by our group in recent years including chiral *N*-oxides, amides and others (**Scheme 82**) and several of them were tested in the allylation reaction with the above mentioned disilane. (**Scheme 81** and **Table 12**).

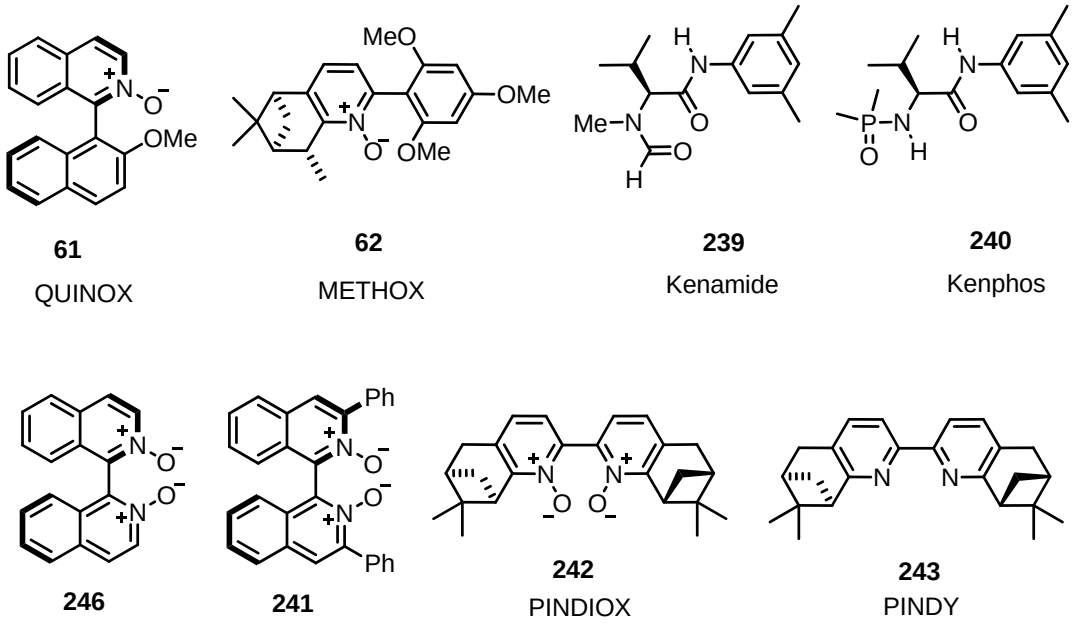


Scheme 81: The enantioselective allylation of 36.

Table 12: Screening of various catalysts.

Entry	Aldehyde 36, R^1 [a]	Catalyst[g]	Loading [mol%]	Solvent [b]	*t* [c]	Yield of 4 [%][d]	ee of 4 [%][e]
1	**36a**, Ph	**62**	20	CH_3CN	7d	52	93
2	**36a**, Ph	**62**	10	CH_3CN	11d	23	10[f]
3	**36c,** 4-FC_6H_4	**62**	15	CH_3CN	7d	45	97
4	**36d**, 4-$CF_3C_6H_4$	**62**	15	CH_3CN	7d	55	90
5	**36e**, 4-$NO_2C_6H_4$	**62**	20	CH_3CN	7d	46	94
6	**36f**, 3-$MeOC_6H_4$	**62**	15	CH_3CN	7d	41	96
7	**36c**, 4-FC_6H_4	**61**	50	DCM	10d	47	89
8	**36d**, 4-$CF_3C_6H_4$	**61**	20	DCM	9d	50	99
9	**36a**, Ph	**244**	10	THF	12h	80	90
10	**36d**, 4-$CF_3C_6H_4$	**244**	5	THF	12h	73	97
11	**36f**, 3-$MeOC_6H_4$	**244**	5	THF	12h	73	77
12	**36i**, *n*-C_5H_{11}	**244**	5	THF	12h	80	73
13	**36k**, *n*-PrCH=CH	**244**	5	THF	12h	83	98
14	**36a**, Ph	**245**	10	THF	12h	82	96
15	**36a**, Ph	**245**	1	THF	24h	70	91
16	**36d**, 4-$CF_3C_6H_4$	**245**	5	THF	12h	79	94
17	**36f**, 3-$MeOC_6H_4$	**245**	5	THF	12h	71	87
18	**36l**, PhC_2H_4	**245**	5	THF	12h	85	30

[a]The reactions were carried out with 0.5 mmol of aldehyde and 0.4 mmol of disilane at -35 °C. [b]The solvent was optimized for each catalyst previously.[91] [c]Reaction time: d - days, h - hours. [d]Isolated yield; all products were diastereoisomerically pure (>99:1 dr), as evidenced by ^{1}H NMR spectroscopy. [e]Determined by chiral HPLC or GC. The relative configuration was established by ^{1}H NMR spectroscopy. [f]Reaction at room temperature. [g]See **Scheme 82** and **Scheme 83**.



Scheme 82: Some of the organocatalysts developed in our group.

However, the early experiments involving METHOX (**62**), our most successful allylation catalyst to date, were not very promising. Whilst allylation and crotylation reactions of aldehydes catalysed by METHOX are usually complete within hours, when using the disilane **1** we did not observe any notable conversion even after 48 hours at -40°C.[77] Upon increasing the temperature the sensitive starting material eventually decomposed.

It had been demonstrated that bulky trichlorosilanes react considerably more slowly and require higher catalyst loading and longer reaction time.[92] We screened several organocatalysts under various reaction conditions and whereas at room temperature the starting material usually decomposed before the allylation could have taken place, at lowered temperatures the reaction became very sluggish. Pyridine-based catalyst **243** (PINDY) did not work at all, *N*,*N*-dioxide **246** showed moderate enantioselectivity but with low yield, with **239** (Kenamide) and **240** (Kenphos) the yields increased but at the expense of enantioselectivity. Finally, **61** (QUINOX) gave good 89% ee in the allylation of *p*-fluorobenzaldehyde and excellent 99% ee in the allylation of *p*-trifluoromethylbenzaldehyde (**Table 12**, **entries 7** and **8**). The reaction was very slow though and usually took several days to complete and thus the yields were low to moderate, most likely due to the decomposition of the starting material during this long reaction time.

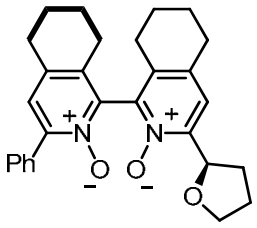
Encouraged by these results, we turned back to METHOX, this time allowing the reaction to run for several days at -35 °C in the freezer. Conversion was checked in the

intervals of 2-3 days to minimize the damage to the sensitive starting material. Allylation of various aldehydes with trichlorosilane **1** catalysed by METHOX gave homoallylic alcohols with ees over 90% (**Table 12**, entries **1** - **6**).

Organocatalyst **241** gave full conversion, in a period of few hours, unfortunately this catalyst was not available in an enantiopure form (as attempts for its resolution, e.g., by crystallization with BINOL,[31] failed, and this catalyst was therefore abandoned for the time being).[93] The results were however suggesting the *N*,*N*'-dioxides, such as **241** or PINDIOX, **242** could be the catalysts of choice. Efforts were made to prepare an analogue of the *N*-dioxide catalyst **241** (see **Chapter 3.2.1.** for details).

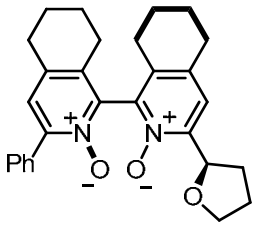
We eventually turned to the *N*,*N*'-dioxide catalysts **244** and **245**, which gave us both excellent conversion and enantioselectivities in just several hours (**Scheme 83** and **Table 12,** entries **9**-**18**).[33] These catalysts worked even with aliphatic aldehydes and we got moderate 73% ee for the functionalization of hexanal and excellent 98% for allylation of hex-2-enal. This is to the best of our knowledge the first example of an effective addition of an allyl trichlorosilane to an aliphatic aldehyde, which are notoriously difficult substrates, and with the exception of Kobayashi's chiral formamide, most of other organocatalysts do not work for this type of reaction at all.[11]

We were also able to lower the catalyst loading to 5 mol% without any loss of enantioselectivity or notable loss of the reaction rate. Upon decreasing the catalyst loading to 1 mol%, full conversion was reached after 24 hours, with ee still over 90%.



244

ANET-RR



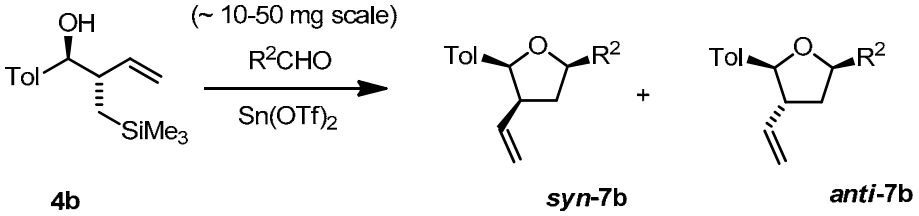
245

ANET-SR

Scheme 83: The most active dioxide catalysts.

2.3.5 The Intramolecular Cascade Allylation

Alcohol **4b** was reacted with another aldehyde in the presence of a Lewis acid to give rise to a mixture of diastereoisomers (**Scheme 84**). Both products were in ~ 1:1 ratio, depending on the reaction conditions and the nature of the starting aldehyde, ***syn*-7b** (bearing all the substituents on the same side of the ring) and ***anti*-7b** (with the vinyl group on the opposite side). Upon decreasing the temperature, the disatereoisomeric ratio changed in favour of product ***syn*-7b** (**Scheme 84** and **Table 13**), therefore compound ***syn*-7b** will be referred to as a *syn* tetrahydrofuran (or kinetic) product from now on in the text, compound ***anti*-7b** will be referred to as an *anti* product. Configuration was established by extensive NOE analysis (see the experimental part for details).



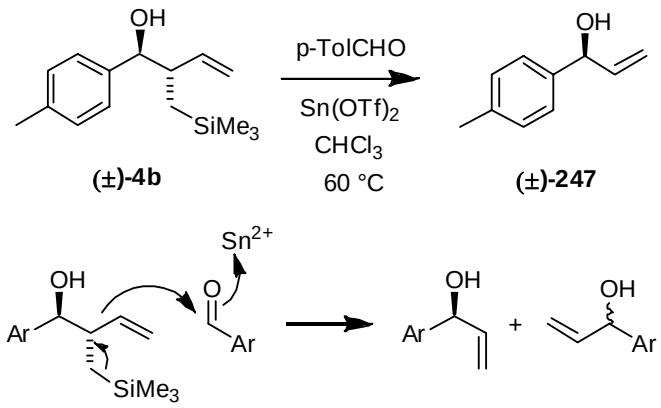
Scheme 84: Intramolecular allyl transfer to form tetrahydrofurans 7b.

Table 13: Intramolecular allyl transfer (Scheme 84).

entry	R^2	T/°C	solvent	ratio of *syn*-7b : *anti*-7b
1	$PhCH_2CH_2$	20	$CHCl_3$	1 : 1.5
5	p-Tol	60	$CHCl_3$	1 : 1[a]
2	p-Tol	20	$CHCl_3$	1.2 : 1
3	p-Tol	-50	$CHCl_3$	1.7 : 1
4	p-Tol	-90	CH_2Cl_2[b]	5:1

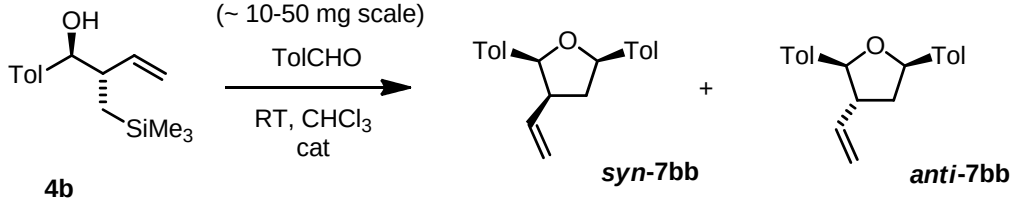
[a]Only traces of the cyclic products **7b**, compound **247** was observed as a major product. [b]Dichloromethane used as a solvent, as chloroform freezes at -63 °C

When the reaction temperature was decreased to -90 °C, we were able to obtain a mixture of ***syn*-7b** and ***anti*-7b** in 5 : 1 ratio (**Table 13**, **entry 4**). However, attempts to obtain the *anti* diastereoisomer ***anti*-7b** selectively by increasing the reaction temperature failed as yields dropped drastically and the alcohol **247** was identified as the main product of the reaction, presumably via the mechanism shown in the **Scheme 85**.



Scheme 85: The unexpected product 247 and a possible mechanism of its formation.

Several Lewis acids were screened in the reaction of the homoallylic alcohol **4b** with *p*-tolualdehyde; the results are summarized in (**Scheme 86** and **Table 14**). All reactions were carried out at room temperature in $CHCl_3$ as a solvent.



Scheme 86: LA screening.

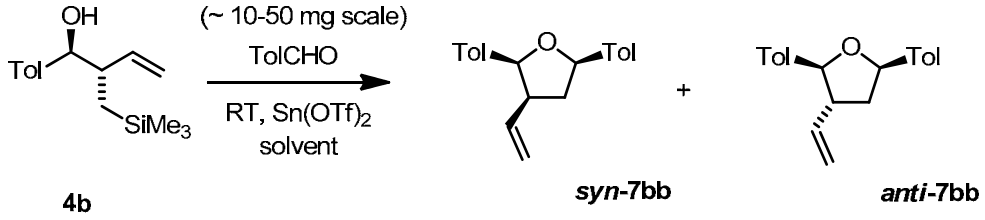
Table 14: Results of the LA screening.

entry	catalyst	conversion	ratio of *syn-7bb* and *anti-7bb*
1	$Sn(OTf)_2$	full	1.2 : 1
2	$Cu(OTf)_2$	full	2.6 : 1
3	$Ag(OTf)_2$	full	N/A[a]
4	ZnI_2	full	N/A[b]
5	$SnCl_2$	full	N/A[b]
6	$AlCl_3$	full	N/A[c]
7	Ph_3SiCl	0 %	N/A[d]
8	TMSOTf	full	1 : 1[e]
9	TfOH	full	N/A[f]

[a]No trace of desired cyclic products **7**, unknown byproduct. [b]Compound **247** as the only product. [c]Starting material decomposed. [d]No reaction, only starting material isolated. [e]Only traces of the cyclic products **7**, compound **247** was observed as a major product. Reaction was repeated at -40°C, giving 30% of compounds ***syn*-7bb** and ***anti*-7bb** in 1:1 ratio and 70% of compound **247**. [f]Compound **247** as the only product. Reaction was repeated at -40°C with the same result.

As can be seen from **Table 14**, if one wishes to obtain the tetrahydrofuran products, tin(II) triflate and copper(II) triflate are the catalysts of choice. Catalyst loading was varied from 5-50 mol % and did not have any notable effect on the outcome of the reaction or ratio of the tetrahydrofuran diastereoisomers.

Early experiments were run in chloroform as a solvent, as this proved to be the best choice for the 'standard' allyl transfer reaction. However, several solvents were screened in the model reaction of the homoallylic alcohol **36b** with *p*-tolualdehyde; the results are summarized in **Table 15**. All reactions were carried out at room temperature with 50 mol% loading of tin(II) triflate as a catalyst.



4b ***syn*-7bb** ***anti*-7bb**

Scheme 87: Solvents screening.

Table 15: Results of the solvents screening.

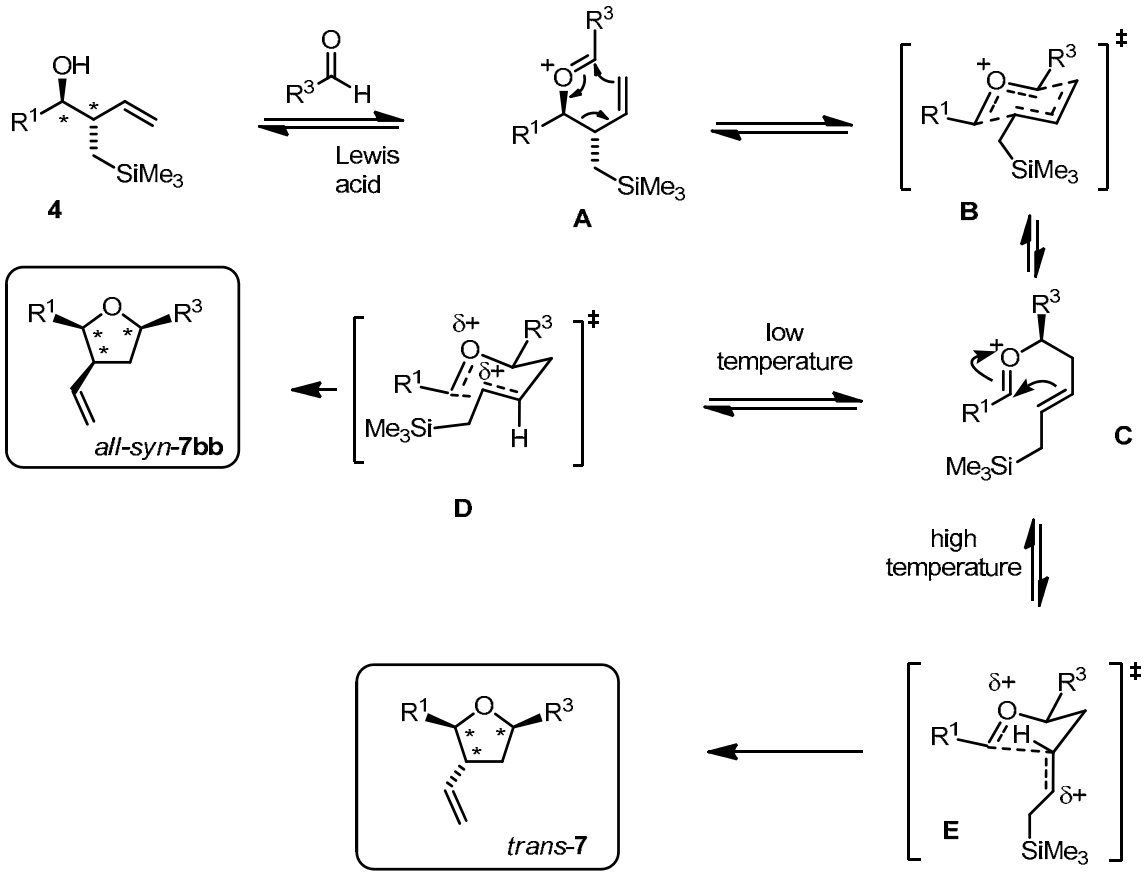
entry	solvent	conversion	ratio of *syn-7bb* and *anti-7bb*
1	dichloromethane	full	1.9 : 1
2	chloroform	full	1.2 : 1
3	tetrachloromethane	full	1 : 1.4
4	diethyl ether	full	5.7 : 1
5	tetrahydrofuran	full	**9.9 : 1**
6	hexane	full	N/A[a]
7	benzene	full	N/A[a]
8	methanol	full	9.4 : 1
9	ethyl acetate	full	9.1 : 1
10	dimethylformamide	0 %	N/A[b]
11	dimethylsulfoxide	0 %	N/A[b]
12	acetonitrile	full	N/A[a]

[a]Compound **247** as the only product. [b]No conversion, only starting material isolated.

It seems that polar (**entry 8**) and etheric solvents (**entries 4, 5**) enhance the diastereoisomeric ratio in favour of the kinetic product. Non-polar solvents (**entries 6, 7**) as well as elevated temperature promote the formation of **247**. In polar aprotic solvents (**entries 10, 11**) no reaction took place. THF emerged as the solvent of choice then, with methanol and

ethyl acetate following closely behind. On the other hand, in chlorinated solvents (**entries 1-3**), the reaction was not diastereoselective, giving an almost equimolar ratio of *syn* and *anti* products.

Taking into account these results, we carried out reaction of **4b** with *p*-tolualdehyde at -90 °C in tetrahydrofuran, obtaining a mixture of products ***syn*-7bb** and ***anti*-7bb** in 21:1 ratio. Rationale behind the temperature influence is as follows (**Scheme 88**):



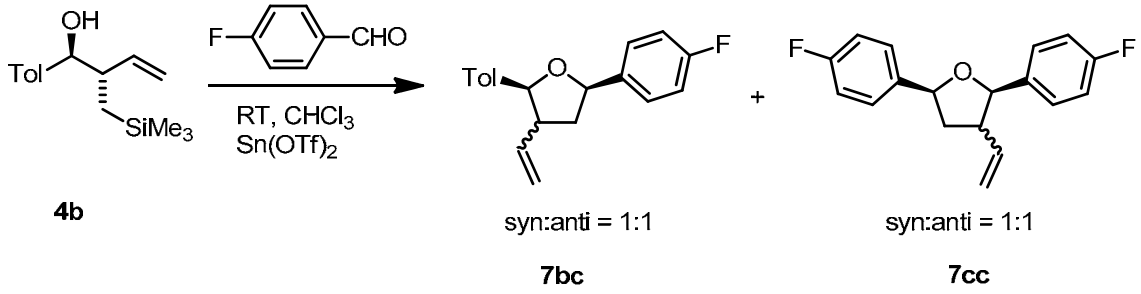
Scheme 88: Mechanism of formation of the *syn* and *anti* tetrahydrofuran product.

The major products formed under the kinetic conditions (low temperature) are the *all-syn* substituted tetrahydrofurans. The first steps of the cyclization (**Scheme 88**, **4** → **B**) were expected to mirror the analogous cross-crotylation,[94] however, the key difference between alcohols **4** and the non-functionalized analogues of **4** (i.e., homoallylic alcohols without the trimethylsilyl moiety), is that **4** has a latent allylsilane functionality, which is unmasked by the oxonia-Cope rearrangement (**4** → **A**): the intermediate **C,** arising from **A** via TS **B** contains both the activated carbonyl fragment and the allylsilane moiety. This intermediate is

then set for yet another intramolecular allylation (**C** → *all-syn* **7** or **C** → *trans* **7**). In this final allylation, low temperature favors TS **D**, affording the all-*syn* product, as the trimethylsilyl chain is already prearranged in the equatorial position from the previous sigmatropic rearrangement. Higher temperature on the other hand would tend to allow for the competing pathway to operate to some extent (**C** → **E** → *anti* **7**), to give the anti product (**Scheme 88**).

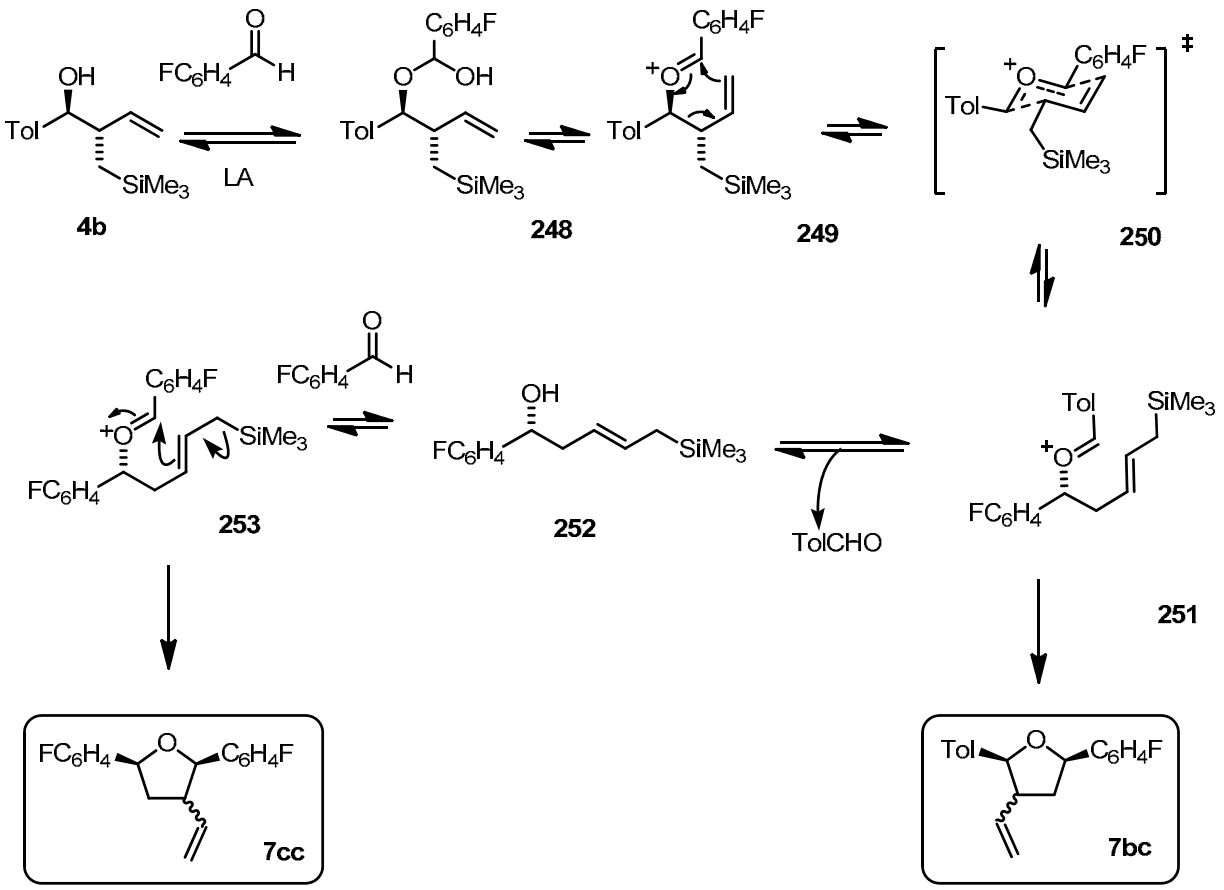
2.3.6 Scope and Limitations

Homoallylic alcohol **4b** was reacted with several aldehyde representatives containing electron rich and poor aromatic rings and aliphatic moiety to explore the scope of the reaction. With *p*-fluorobenzaldehyde (**Scheme 89**), a mixture of **7bc** and the unexpected byproduct **7cc** in ~ 1 : 1 ratio was obtained, two diastereoisomers of each in 1:1 ratio.



Scheme 89: Unwanted byproducts during the cyclization.

p-Fluorobenzaldehyde was used in a slight excess (1.2 eq), and both *p*-fluorobenzaldehyde and *p*-tolualdehyde were observed in the crude reaction mixture despite the fact that the latter aldehyde was not present before. This observation, as well as the formation of **7cc**, can be rationalized by the following mechanism (**Scheme 90**).

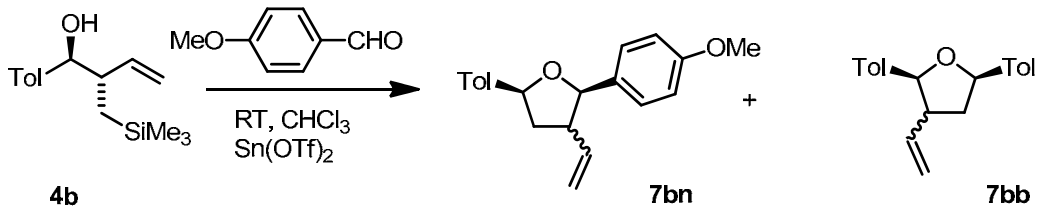


Scheme 90: Formation of the byproduct 7cc.

Homoallylic alcohol **2** reacts with *p*-fluorobenzaldehyde, forming the intermediate **251** via the oxonia-Cope rearrangement. Then, either cyclization (intramolecular allyl transfer) can take place as outlined before, forming **7bc** as the previously expected product. Alternatively, *p*-tolualdehyde is released forming the γ-homoallylic alcohol **252** as a product of "standard" allyl transfer. Alcohol **252** then reacts further with *p*-fluorobenzaldehyde (as it is more electrophilic than *p*-tolualdehyde) forming **7cc**.

One could expect that the intramolecular transformation of **251** into **7bc** is much faster than the formation of **252**. However, the relatively electron-rich tolyl moiety is decreasing reactivity of the adjacent carbonyl group, so that one could expect that when a more electron deficient aryl moiety is used instead of tolyl, formation of **7cc** will be suppressed.

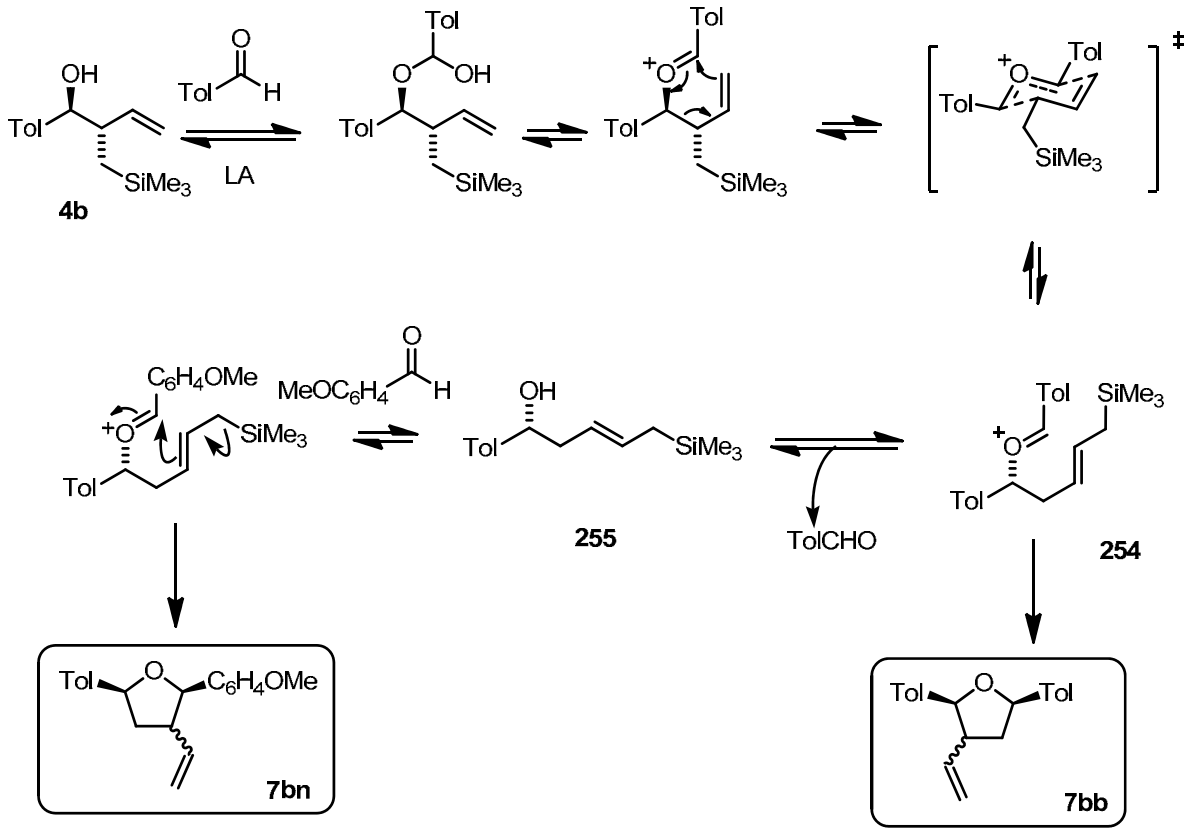
A different result was attained when we used *p*-methoxybenzaldehyde as a substrate (**Scheme 91**). A mixture of the expected **7bn** as well as the undesired **7bb** was obtained in ratio 1 : 3.5. The side product had the aryl moieties of the original homoallylic alcohol on both "sides" of the tetrahydrofuran ring. Both *p*-methoxybenzaldehyde and *p*-tolualdehyde were detected in the crude mixture.



4b **7bn** **7bb**

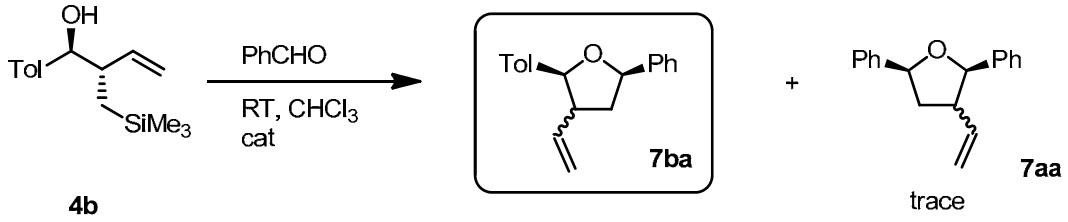
Scheme 91: Unwanted byproducts during the cyclization.

This result can also be rationalized by the mechanism similar to that above (**Scheme 92**), taking into account the fact that this time, *p*-tolualdehyde is the most reactive aldehyde present in the system. Intermediate **254** undergoes either the 'standard' allyl transfer giving the γ-homoallylic alcohol **255** and eventually the tetrahydrofuran **7bn** or undergoes the cyclization giving the 'unexpected' product **7bb**.



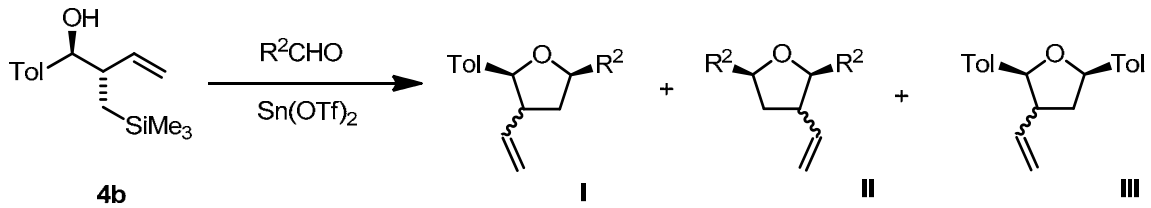
Scheme 92: Formation of the byproduct 7bb.

Reaction of **4b** with benzaldehyde gave the expected product **7ba** with just a trace of the byproduct **7aa** (**Scheme 92**).



Scheme 93: Reaction of 4b and 36a.

For summary of the results see **Scheme 94** and **Table 16**.



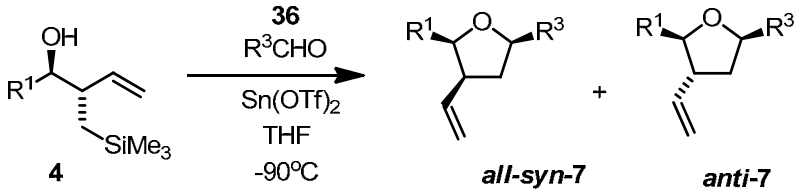
Scheme 94: The cyclization and the unwanted byproducts.

Table 16: Products distribution depending on the electron properties of the aldehyde.

entry	R^2	solvent	T/°C	product(s), (ratio)	ratio of the *syn* : *anti* diastereoisomers
1	$PhCH_2CH_2$	$CHCl_3$	20	**I** only	1 : 1.5
2	Ph	$CHCl_3$	20	**I** : **II** (1: 1)	1.4 : 1
3	p-F-C_6H_4	$CHCl_3$	20	**I** : **II** (1 : 1)	1 : 1
4	p-F-C_6H_4	THF	-90	**I** : **II** (1 : 2)	6.2 : 1
5	*p*-MeO-C_6H_4	$CHCl_3$	20	**I**: **III** (1 : 2.5)	1.2 : 1
6	*p*-MeO-C_6H_4	THF	-90	**I** : **III** (1 : 3.5)	4.3 : 1
7	$CH_3CH=CH$	THF	-90	no reaction	N/A

Racemic homoallylic alcohols **4** were subjected to the allyl-transfer reaction with aldehydes **36**, catalysed by the Lewis acid (**Scheme 95**). For this allylation sequence, the reaction conditions were optimized to give preferentially kinetic product ***all-syn*-7**. The results are summarized in **Table 17**. Most of the cyclizations were carried out with racemic alcohols **4**, however preservation of the enantiointegrity during the cyclization cascade was illustrated by employing the enantioenriched **4** (**entries 1**, **9**, **11** and **20**). As mentioned before, low temperature was found to be a prerequisite for achieving high diastereoselectivity; at room temperature, it dropped considerably (compare **entries 6** and **7**).

The reaction offers a diverse substrate scope: apart from the representative aromatic aldehydes **36** (**entries 1-15**), it also proved to work well with aliphatic **(entries 16**, **17**, **20**, **21**), α,β-unsaturated (**entry 18**, **19**, **23** and **24**), and heteroaromatic aldehyde (**entry 25**).

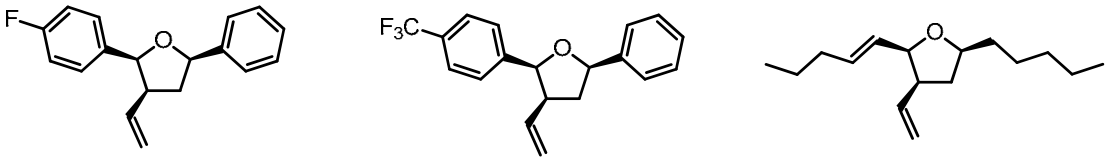


Scheme 95: Cyclizations at optimized conditions.

Table 17: Examples of the intramolecular allyl transfer.

Entry	Alcohol 4, R^1 [a]	Aldehyde 36, R^3	Tetrahydrofuran 7	Yield [%][b]	Dr [c] (*all-syn*-7/*anti*-7) (ee [%])
1	**4a**, Ph	**36a**, Ph	**7aa**	95	> 25:1 (90)[d]
2	**4a**, Ph	**36b**, 4-MeC_6H_4	**7ab**	90	> 25:1
3	**4a**, Ph	**36d**, 4-$CF_3C_6H_4$	**7ad**	80	20:1
4	**4a**, Ph	**36g**, 4-ClC_6H_4	**7ag**	94	21:1
5	**4a**, Ph	**36h**, 3-BrC_6H_4	**7ah**	87	> 25:1
6	**4b**, 4-MeC_6H_4	**36b**, 4-MeC_6H_4	**7bb**	85	> 25:1
7[e]	**4b**, 4-MeC_6H_4	**36b**, 4-MeC_6H_4	**7bb**	86	10:1
8[f]	**4b**, 4-MeC_6H_4	**36b**, 4-MeC_6H_4	**7bb**	88	1.2:1
9	**4c**, 4-FC_6H_4	**36a**, Ph	**7ca**	92	> 25:1 (87, 95)[g]
10	**4c**, 4-FC_6H_4	**36g**, 4-ClC_6H_4	**7cg**	90	23:1
11	**4d**, 4-$CF_3C_6H_4$	**36a**, Ph	**7da**	79	> 25:1 (90)[i]
12	**4e**, 4-$NO_2C_6H_4$	**36a**, Ph	**7ea**	90	> 25:1
13	**4e**, 4-$NO_2C_6H_4$	**36b**, 4-MeC_6H_4	**7eb**	89	> 25:1
14	**4e**, 4-$NO_2C_6H_4$	**36g**, 4-ClC_6H_4	**7eg**	92	> 25:1
15	**4a**, Ph	**36o,** 3-BrC_6H_4	**7ao**	89	> 25:1
16	**4a**, Ph	**36i**, nC_5H_{11}	**7ai**	88	10:1
17	**4a**, Ph	**36j**, cC_6H_{11}	**7aj**	85	10:1
18	**4e**, 4-$NO_2C_6H_4$	**36k**, nPrCH=CH	**7ek**	91	> 25:1
19	**4e**, 4-$NO_2C_6H_4$	**36l**, $Me(CH=CH)_2$	**7el**	80	7:1
20	**4k**, nPrCH=CH	**36i**, nC_5H_{11}	**7ki**	92	9:1 (95)[j]
21	**4a**, Ph	**36j**, Et	**7aj**	25	10:1
22	**4a**, Ph	**36k**, iPr	**7ak**	0	n/a
23	**4a**, Ph	**36l**,cyclohexenyl	**7al**	55	15:1
24	**4a**, Ph	**36m**, cinnamyl	**7am**	49	12:1
25	**4a**, Ph	**36n**, furyl	**7an**	45	9:1
26	**4c**, 4-FC_6H_4	**36b**, p-Me-C_6H_4	**7ch**	91	15:1
27	**4k**, nPrCH=CH	**36a**, Ph	**7ka**	82	20:1

[a]The reactions were carried out with 0.5 mmol of aldehyde and 0.4 mmol of disilane using 10-50 mol% of $Sn(OTf)_2$ at -90 ^oC. [b]Isolated yield. [c]Dr was determined by NMR spectroscopy, ee was determined by chiral HPLC or GC [d]The starting alcohol **4a** was of 93% ee. [e]The reaction was carried out at RT. [f]$CHCl_3$ was used as a solvent (at RT). [g]The starting alcohol 4c was of 89% ee and 97% ee, respectively. [i]The starting alcohol **4d** was of 90% ee. [j]The starting alcohol **4k** was of 98% ee.



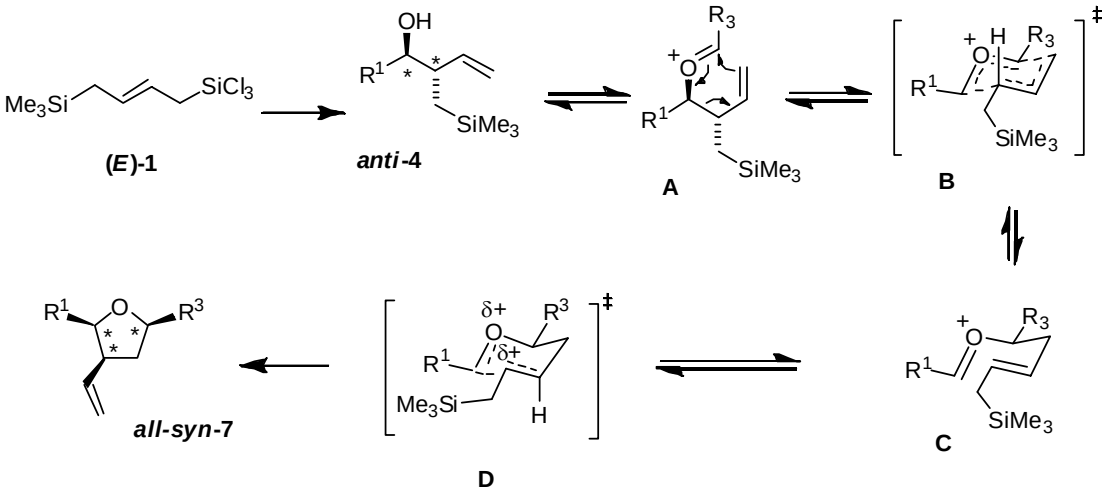
94%
95% ee (from 97% ee)
7ca

95%
90% ee (from 90% ee)
7da

92%
95% ee (from 98% ee)
7ki

Scheme 96: Examples of enantiopure tetrahydrofurans made.

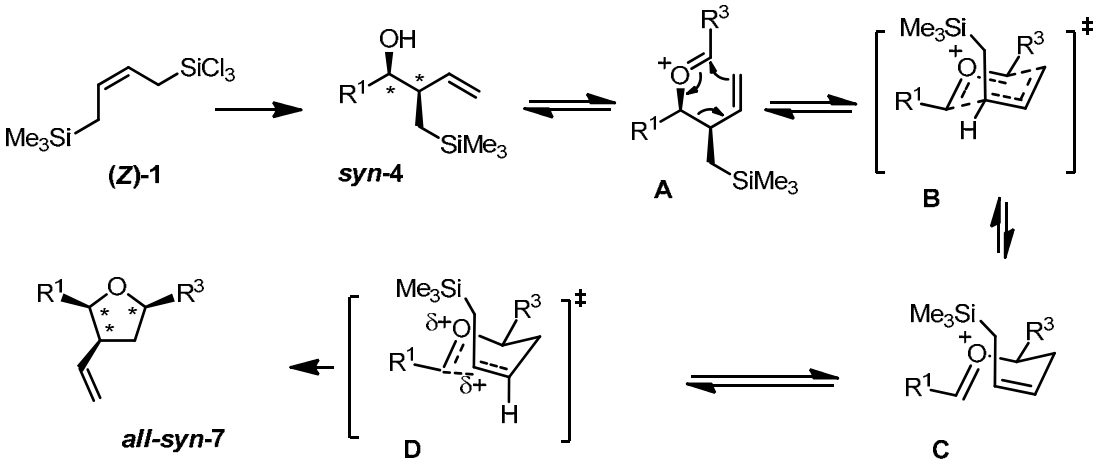
When the homoallylic aliphatic alcohol **4k** was employed as a substrate for the cyclization, either with benzaldehyde or pentanal, only the expected tetrahydrofurans (as a mixture of diastereoisomers, see **Scheme 96**) were observed in the crude reaction mixture (**Table 17,** entries **20**, **27)**. This implies that the aliphatic homoallylic alcohol **4k** is sufficiently reactive and no isomerisation takes place.



Scheme 97:The intramolecular allylation sequence for the (*E*)-trichlorosilane.

As mentioned before, silanes with the *E* configuration of the double bond give *anti* configured homoallylic alcohols with (**Scheme 97**). Trichlorosilanes with the *cis* configuration of the double bond (which give the *syn* homoallylic alcohols) are not suitable for the allylation reaction catalysed by METHOX, which we expected to be the catalyst of choice during the early experiments. However, with respect to the configuration of the final

tetrahydrofuran product, the configuration of the homoallylic alcohol (*syn* or *anti*) and thus the configuration of the double bond of the starting trichlorosilane **1**, is actually immaterial.

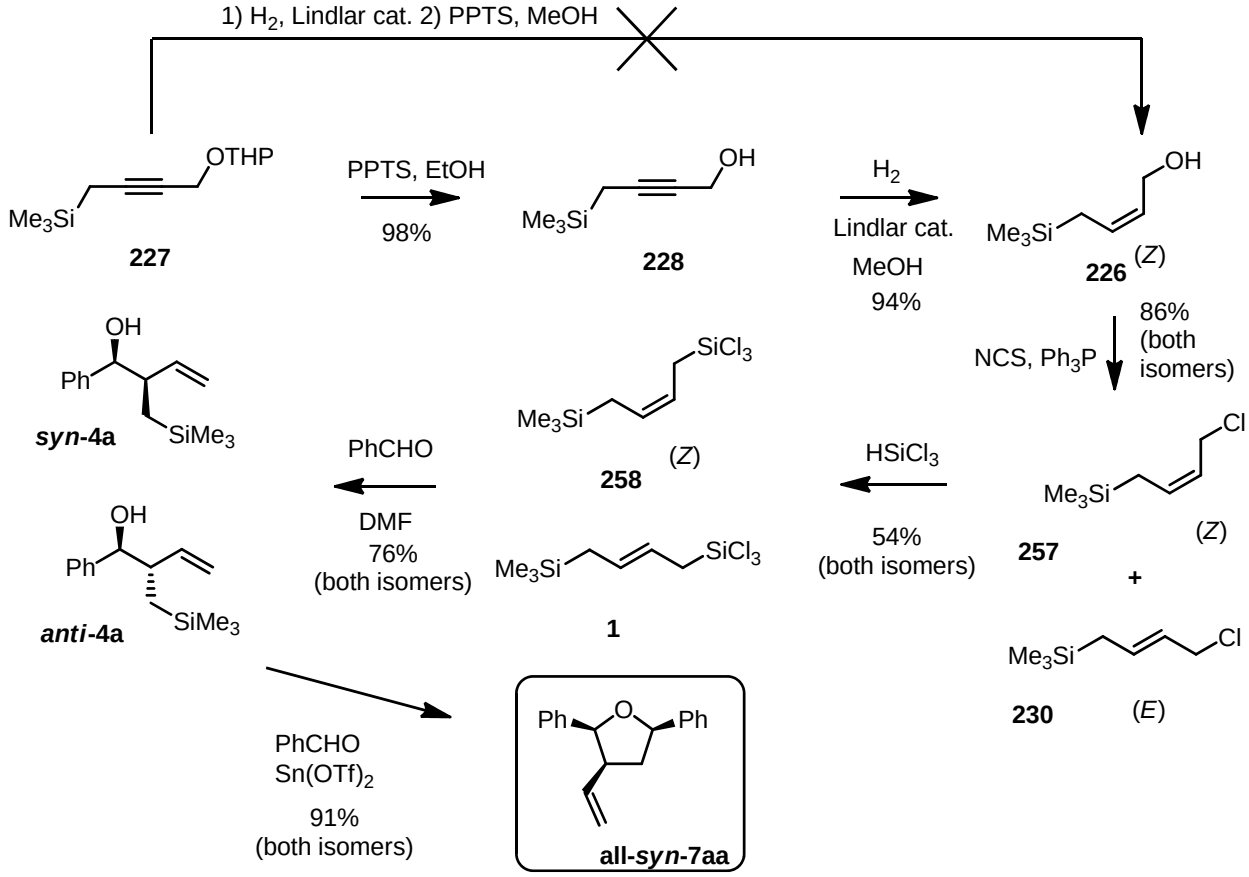


Scheme 98: The intramolecular allylation sequence for the (*Z*)-trichlorosilane.

Hence, in general, it is not important how stereoselective the reduction of the triple bond or chlorination are because both isomers yield the same all-*syn* tetrahydrofuran product in the end, even if we use the mixture of two isomers as a starting material, as long as the catalyst we use in the allylation reaction is not as stereospecific as METHOX.

To prove this concept, alcohol **228** was hydrogenated in the presence of the Lindlar catalyst, giving alkene **226** with *Z* configuration on the double bond exclusively (**Scheme 98**). A one-pot reaction to convert **227** into **256** was attempted, however no conversion of **227** was observed even after several days. Chlorination of **256** using the same procedure as for *E* isomer gave surprisingly a 1:1 mixture of *Z* and *E* chlorides **257** and **230**, trichlorosilylation of this mixture then gave a 1:1 mixture of the corresponding *E* and *Z* trichlorosilanes **258** and **1**, which afforded a mixture of *syn* and *anti* diastereoisomers of alcohol **4**, again in approximate 1:1 ratio.

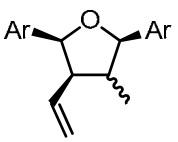
This mixture of *syn* and *anti* homoallylic alcohols **4** (inseparable on the column) gave only one diastereoisomer (*all-syn*) of **7aa** when treated with benzaldehyde in the presence of Lewis acid (**Scheme 99**).



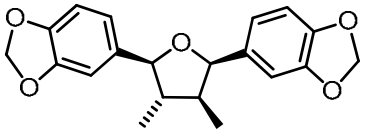
Scheme 99: Allylation with the *E* and *Z* disilane.

2.3.7 Tetrasubstituted Tetrahydrofurans

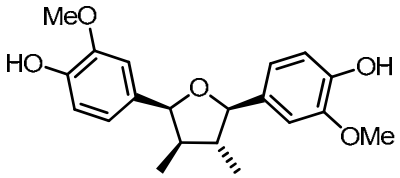
As the next logical step in the tetrahydrofuran project, we used the methodology developed in the synthesis of tetrasubstituted tetrahydrofurans to make the tetrasubstituted tetrahydrofurans. This would open an easy synthetic pathway towards a whole range of relatively simple natural products with the tetrahydrofuran core **259,** such as Galbacin **260**, Verrucosin **261** or Beilschmin **262** and others (**Scheme 100**). Note the piperonyl-, vanillin- and gallic-like aryl moiety, which are a common motif of relatively simple natural products.



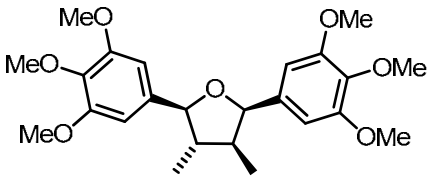
259



260 Galbacin



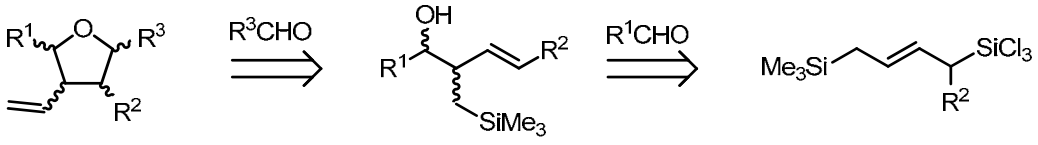
261 Verrucosin



262 Beilschmin

Scheme 100: Some of the simple natural products with the tetrahydrofuran core.

As the first approach towards this type of compounds we decided to redecorate the starting disilane **1** in order to obtain the corresponding homoallylic alcohols **264** with a substituent on the other side of the double bond (**Scheme 101**). These alcohols, when exposed to the optimized allyl-transfer conditions in the presence of a Lewis acid were expected to undergo the cyclization, forming the tetrasubstituted tetrahydrofurans **263**.

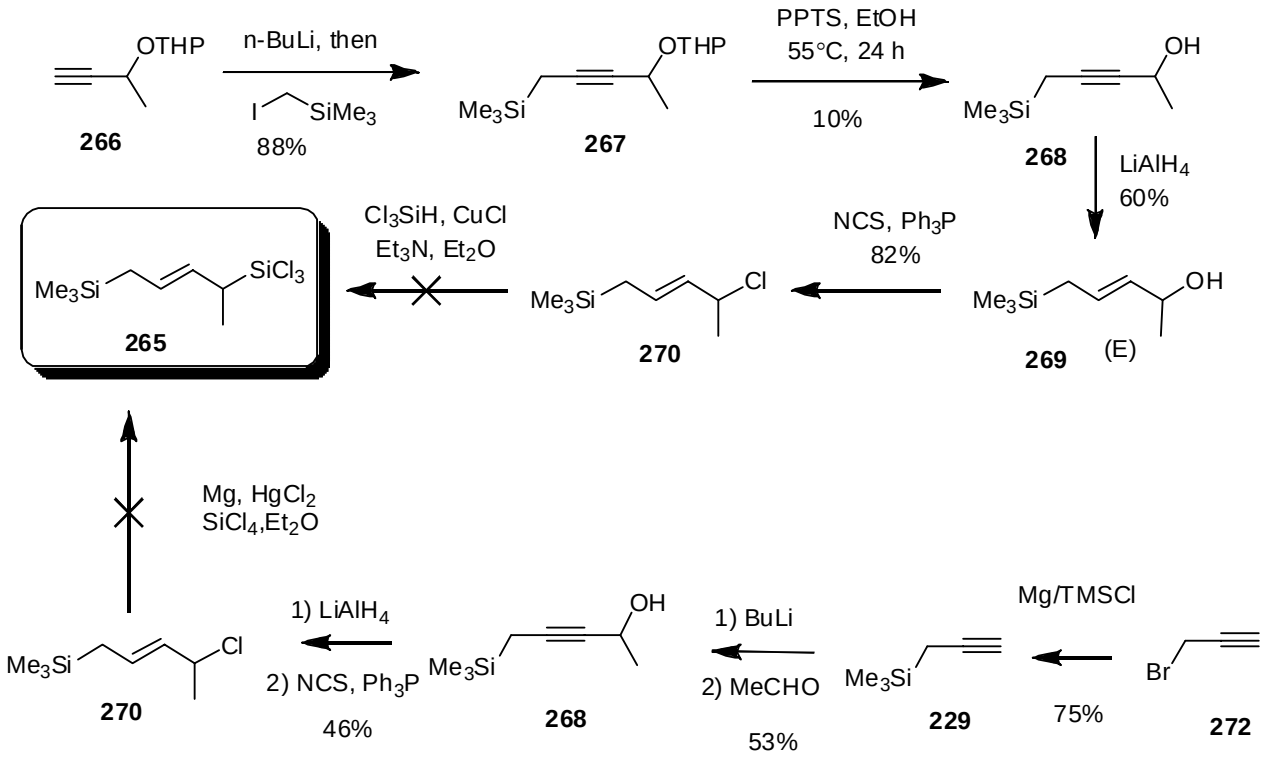


263 **264** **265**

Scheme 101: Route to the tetrasubstituted tetrahydrofurans.

Therefore, we attempted to synthesize the analogue of the bifunctional allyldisilane **1** using a modification of the original reaction sequence (**Scheme 102**). We started off with the

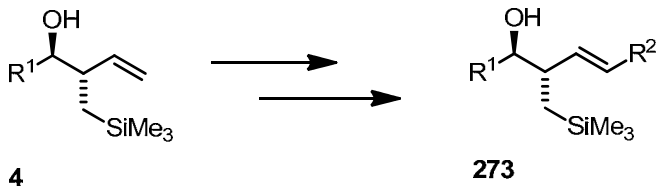
but-3-yn-2-ol (rather than propargylic alcohol), protected as THP ether (**266)**, and introduced the trimethylsilyl moiety. The deprotection step turned out to be rather troublesome however, giving poor yields. Attempts at protecting the but-3-yn-2-ol with various silyl groups also proved to be an exercise in futility as the subsequent deprotection was not particularly selective with respect to the trimethylsilyl moiety. Reduction of the triple bond of **268** and the subsequent chlorination of alcohol **269** using the previously optimized conditions worked well, however attempts to introduce the trichlorosilyl group onto the secondary carbon of **270** using the standard trichlorosilane-based procedure failed despite several attempts.



Scheme 102: Attempted synthesis of the modified disilane.

Choosing a different approach towards the modified disilane, we started with the propargylic bromide **229**, introduced the trimethylsilyl moiety first, and then obtained the intermediate **268** by the nucleophilic addition of the deprotonated **272** onto the acetaldehyde (**Scheme 102**). After reduction of the triple bond and chlorination, we attempted the Grignard chemistry this time, in order to introduce the trimethylsilyl moiety and failed again however, getting only a complex mixture of products.

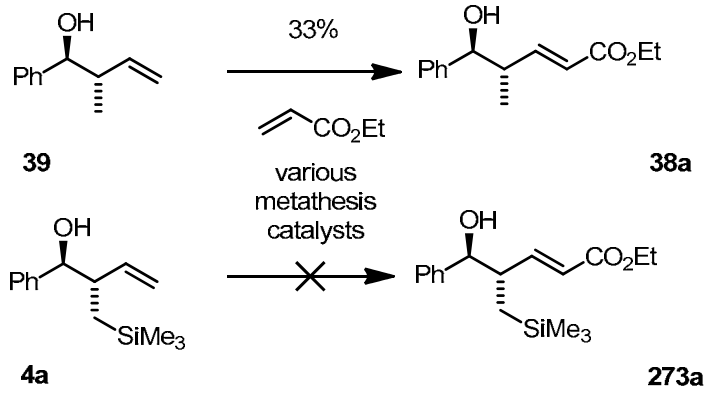
We then chose a different strategy, and rather then making the allyldisilane **265**, we attempted to modify the homoallylic alcohols of type **4**, which we previously made (**Scheme 103**).



4 **273**

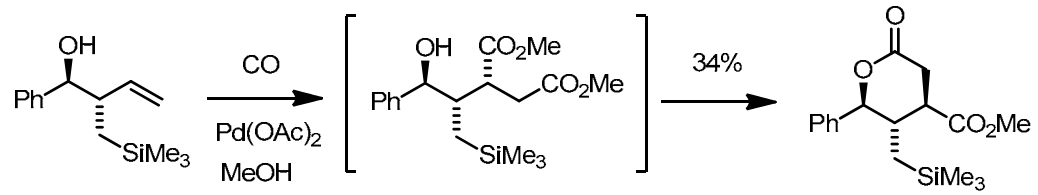
Scheme 103: Attempted modification of the original homoallylic alcohol 4.

Grubbs chemistry (Grubbs catalyst 1st and 2nd generation and Grubbs-Hoveyda catalyst, see the Experimental part for details) was attempted first, however the alcohols failed to react and even after tedious optimizations attempts, protection of the alcohol functionality and increasing the temperature/reaction time, we were able to obtain only traces of the desired product **273a** (**Scheme 104**). This failure apparently stems from the steric hindrance in the substrate-catalyst complex caused by bulky trimethylsilyl moiety, as the model metathesis reactions on the simple homoallylic alcohols without the trimethylsilyl moiety worked fine.[95]



Scheme 104: Attempted metathesis.

Another transformation, carbopalladation of alcohol **4a**, under the atmosphere of carbon monooxide in the presence of Pd^{2+} catalyst, was successfully applied for similar substrates in our group before. For the alcohol **4a** we however isolated lactone **275** as the only product, as a result of double carbonylation of the double bond followed by lactonization (**Scheme 105**).[96]

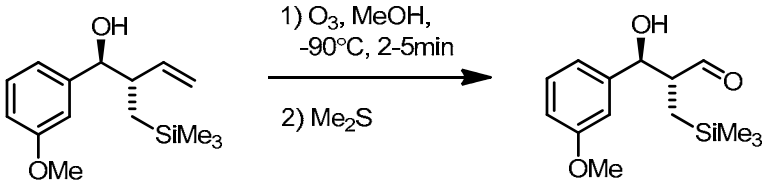


4a **274** **275**

Scheme 105: Carbopalladation of the homoallylic alcohol.

We decided to switch from metathesis to traditional Wittig chemistry, and in order to do so, homoallylic alcohol **4f** was subjected to ozonolysis first, to obtain the corresponding aldehyde. Early experiments resulted only in decomposition of the starting material, probably due to the oxidation of the silicon moiety. However, after decreasing the temperature to -90 °C and careful monitoring the progress of the reaction and immediate quenching, we reached full conversion just after 2-5 minutes.

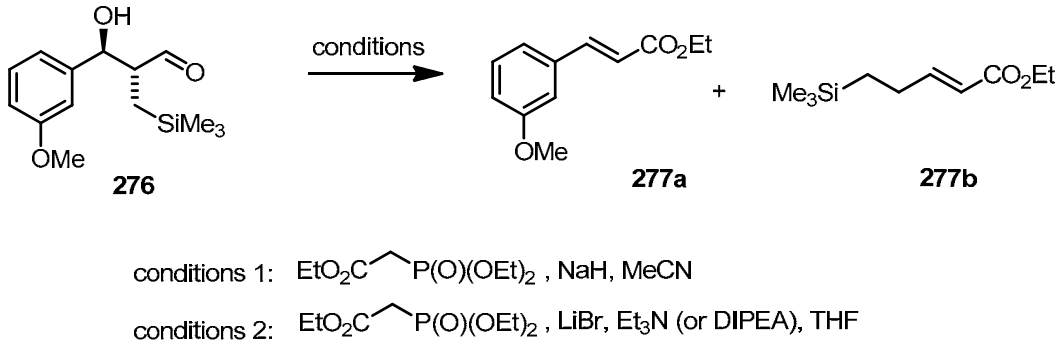
The aldehyde **276f** decomposes readily on the column of silicagel or alumina, but can be readily used as a crude material, as the ozonolysis at the low temperatures typically gave a practically pure product (**Scheme 106**).



4f **276f**

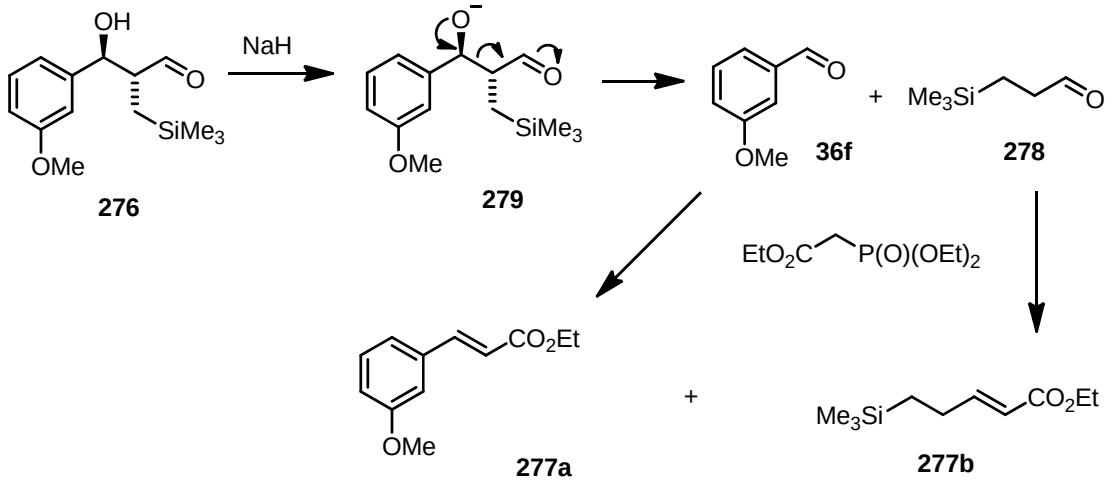
Scheme 106:Ozonolysis of the homoallylic alcohol.

Several Wittig and HWE conditions were then explored in order to get the ester (**Schemes 107** and **108**).



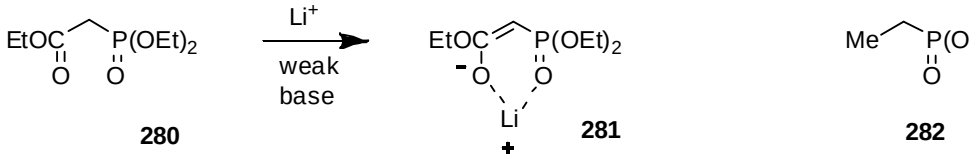
Scheme 107: The HWE reaction.

Disappointingly, following the published conditions, HWE reagent in the presence of the strong base (NaH) gave just the cinnamic-like ester **310** and conjugated ester **311**, as products of the retro aldol mechanism, followed by the HWE reaction of the undesired substrates.



Scheme 108: Formation of the unwanted products..

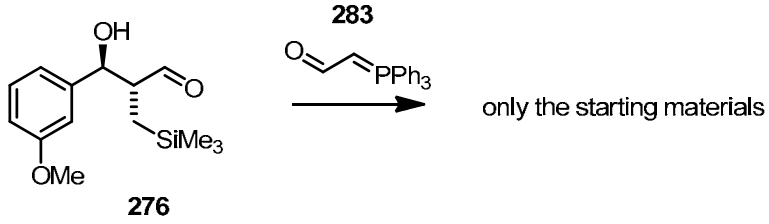
In order to avoid the strongly basic conditions and thus the retro-aldol pathway, the HWE reagent was treated with lithium chloride and deprotonated with weaker triethyl amine and/or Hünig's base respectively (**Scheme 109**).



Scheme 109: HWE reaction in the presence of LiCl.

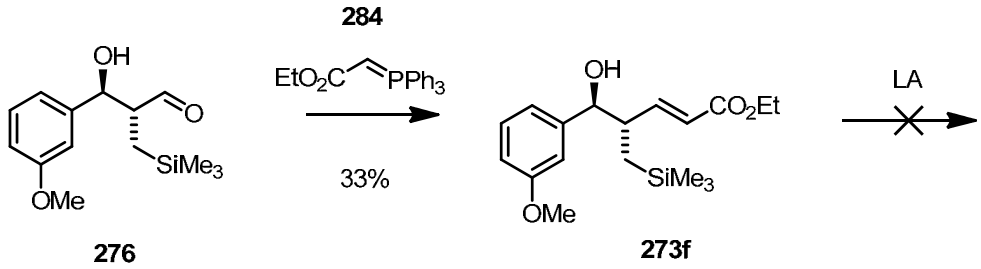
Upon mixing the lithium enolate **281** with the aldehyde, we obtained the same pair of undesired products **277a** and **277b**. The same outcome was observed using the HWE reagent **282** (**Scheme 109**).

With the Wittig reagent **283** no reaction took place, despite varying the reaction conditions and increasing the temperature and reaction time (**Scheme 110**).



Scheme 110: Attempted Wittig reaction.

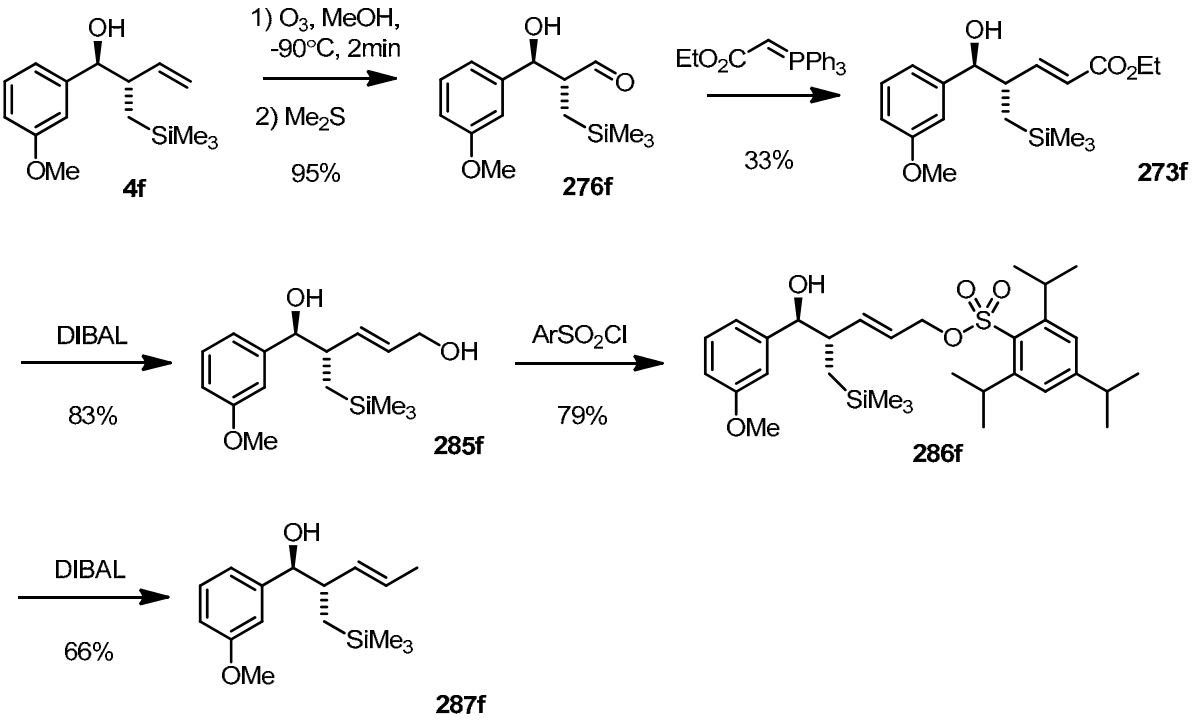
Finally, using the Wittig reagent **284**, the desired ester was obtained in **85%** yield (**Scheme 111**).[97]



Scheme 111: Successful Wittig reaction.

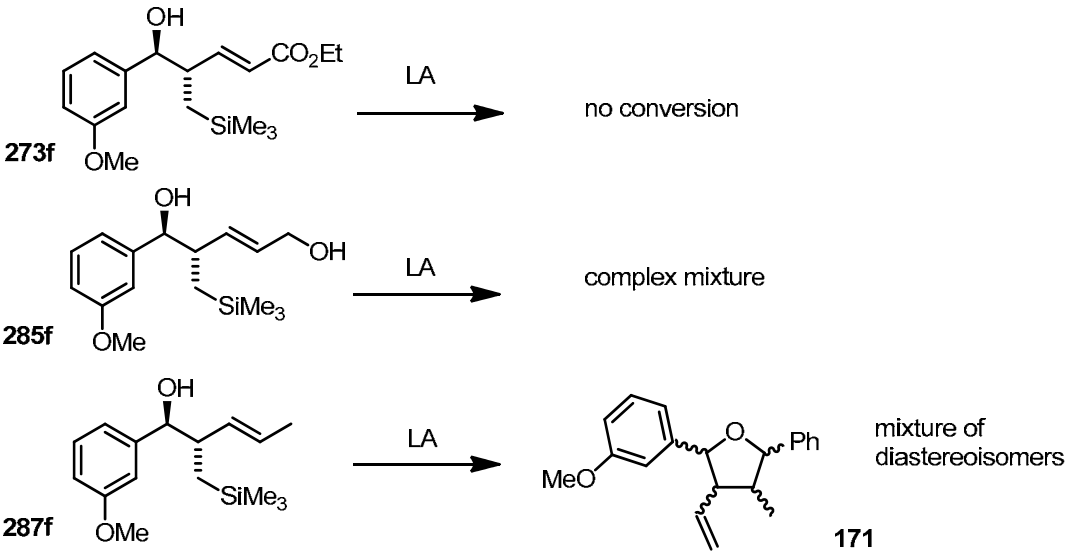
Ester **284** however did not undergo the cyclization under the Lewis acidic conditions, as the conjugated double bond is apparently too electronically poor to undergo the oxonia-Cope rearrangement. Ester **284** was therefore reduced to alcohol with DIBAL and cyclization

of the resulting alcohol **285f** was attempted in the presence of LA. This reaction however gave a complex mixture of products under the cyclization conditions (not surprisingly, taking into account the two alcohol moieties present in the substrate).



Scheme 112: Reaction sequence towards the substituted homoallylic alcohol 321.

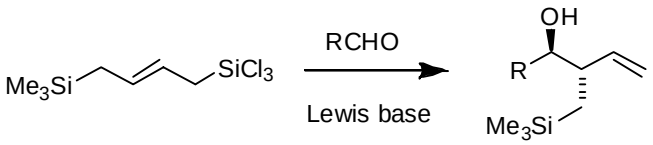
Alcohol **285f** was then transformed into sulfonate **286f** and reduced with DIBAL in the final attempt to produce a suitable homoallylic alcohol substrate for the cyclization reaction. The reduced product **287f** reacted readily when exposed to the Lewis acidic conditions (although more slowly than the unsubstituted analogue), giving however a complex mixture of various diastereoisomers, unseparable by chromatography. Attempts to get at least one of them preferentially, by varying the reaction conditions failed (see **Scheme 113** for the summary of results).



Scheme 113: Results of the attempted cyclizations.

2.3.8 Other Bifunctional Disilanes

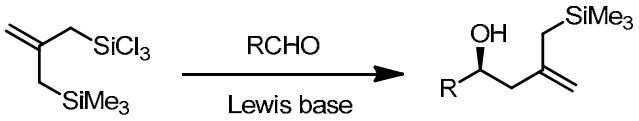
We used the methodology developed during the synthesis of the original disilane **1** in the synthesis of another novel disilane **2** (**Scheme 114**).



1 **4**

Scheme 114: Allylation with the original disilane 1.

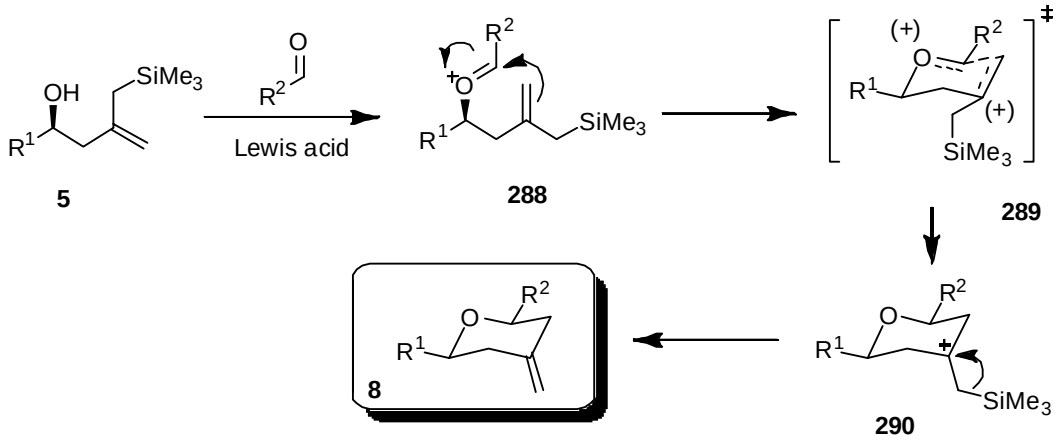
We envisioned that **2**, when used in the allylation of aldehydes, would give the homoallylic alcohols **5** with the (methylene)trimethylsilyl moiety at the β-position to the alcohol (**Scheme 115**)..



2 **5**

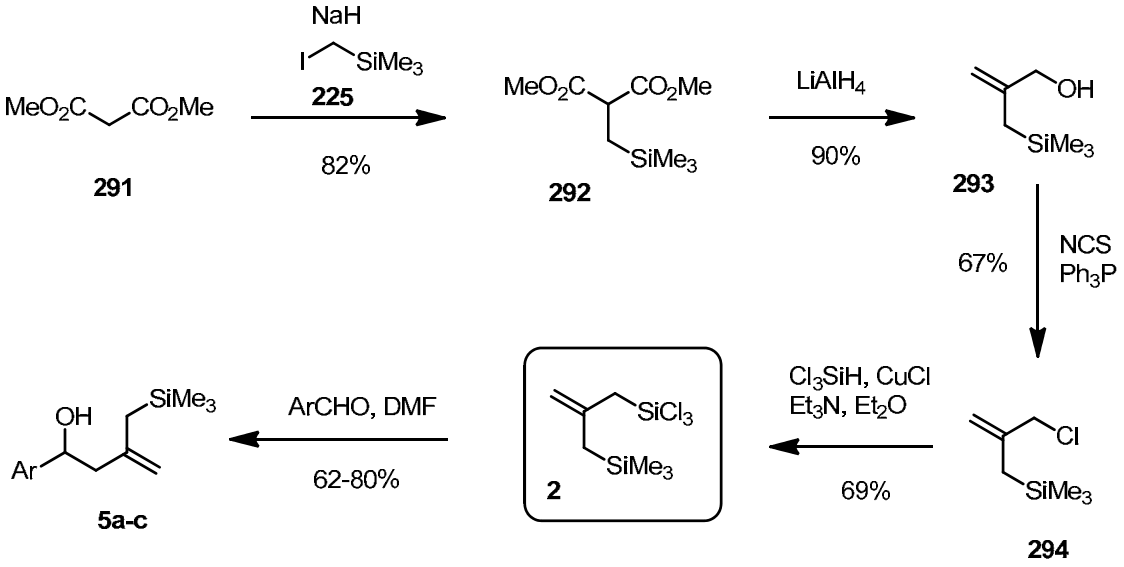
Scheme 115: Allylation with the analogous disilane 2.

We further expected that these alcohols, in the presence of the aldehyde and Lewis acid, would cyclize to afford the substituted tetrahydropyrans **8** with the exocyclic double bond (**Scheme 116**). The mechanism was anticipated to be similar to that outlined before in the synthesis of tetrahydrofurans, however this time no [3.3] sigmatropic rearrangement can take place and after the nucleophilic attack onto the activated carbonyl (**Scheme 116**, intermediate **288**), a stable 6-membered ring would be formed.



Scheme 116: Intramolecular allylation to form the substituted tetrahydropyrans.

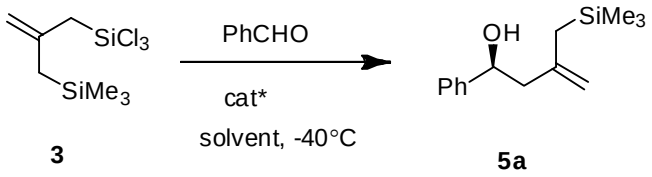
Disilane **2** was synthesized from the malonate **291** in four steps as follows (**Scheme 117**): Dimethylmalonate **291** was deprotonated by sodium hydride and alkylated by (iodomethyl)trimethylsilane. Alkylation with the cheaper (chloromethyl)trimethylsilane was also attempted, however with poor conversion even after prolonged reaction time. The more reactive iodide **225** was then prepared, using the Finkelstein procedure (*vide supra*). Reduction with $LiAlH_4$ gave the alcohol **293**, which was transformed into the chloride **294** and then to trichlorosilane **2** using the protocols previously developed for the analogous disilane **1**. Disilane **2**, when treated with benzaldehyde in the presence of a Lewis base (DMF), afforded the expected racemic homoallylic alcohol **5a**, in a good yield.



Ar = Ph, *p*-$CH_3C_6H_4$, *p*-$CF_3C_6H_4$

Scheme 117: Synthesis of the homoallylic alcohols 5.

As the next step, we explored the enantioselective version of this transformation. We first used the *N*-oxide **62** (METHOX) as a chiral catalyst, and obtained the alcohol **5a** with 33% ee. Other organocatalyst were also screened, all of them however worked with low enantioselectivities (**Scheme 118** and **Table 18**). Monooxide QUINOX (**Table 18**, entry **2**) gave almost racemic product and dioxides **244** and **245** gave poor enantioselectivities around 30% even after optimalization.



3 **5a**

Scheme 118: The enantioselective version.

Table 18 Enantioselective allylations of benzaldehyde with the trichlorosilane 2.

Entry	Catalyst	Solvent	Yield (%)	ee (%)
1	METHOX (**62**)	MeCN	80	33
2	QUINOX (**61**)	DCM	67	7
3	(S,R)-ANET (**244**)	THF	55	30
4	(R,R)-ANET (**245**)	THF	62	31

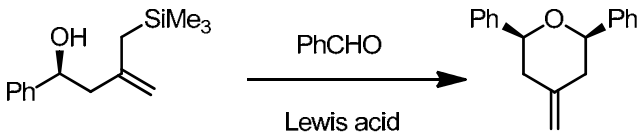
Low enantioselectivies are probably caused by the steric clash between the molecule of the catalyst and the bulky trimethylsilyl group in the six-membered transition state of the allylation step (**Scheme 119**). This would force the reaction to proceed through the less hindered linear transition state, where the chirality of the catalyst is not transferred effectively.

cyclic TS open-chain TS

295 **296**

Scheme 119: Cyclic and linear transition state.

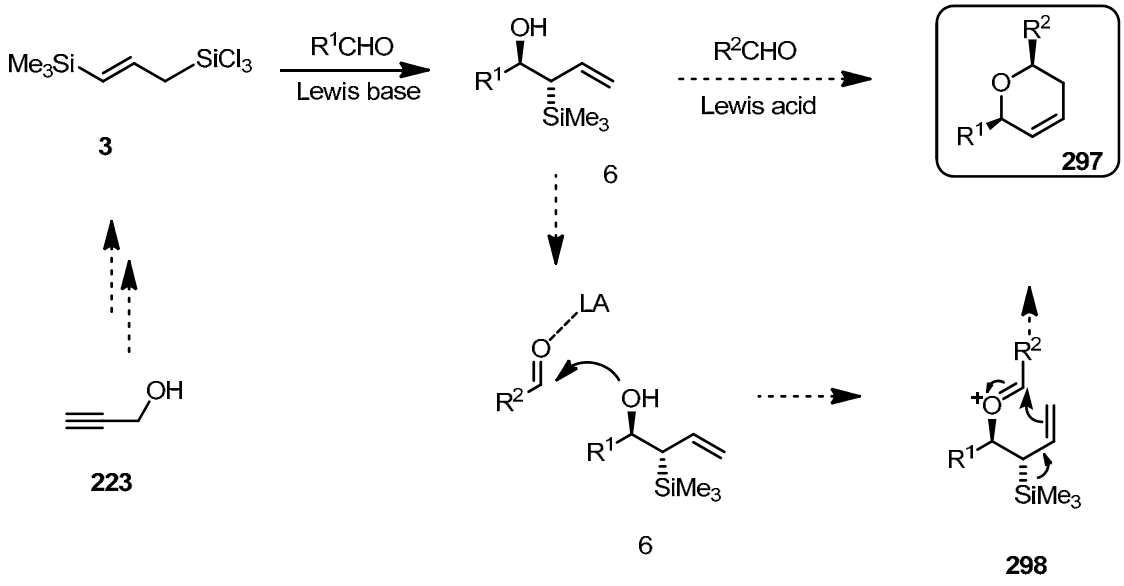
As expected, after treatment with another portion of benzaldehyde in the presence of Lewis acid, alcohol **5a** gave the substituted tetrahydropyran **8aa** with the *syn* configuration of the phenyl substituents (**Scheme 120**).



5a 45% **8aa**

Scheme 120: Intramolecular allylation.

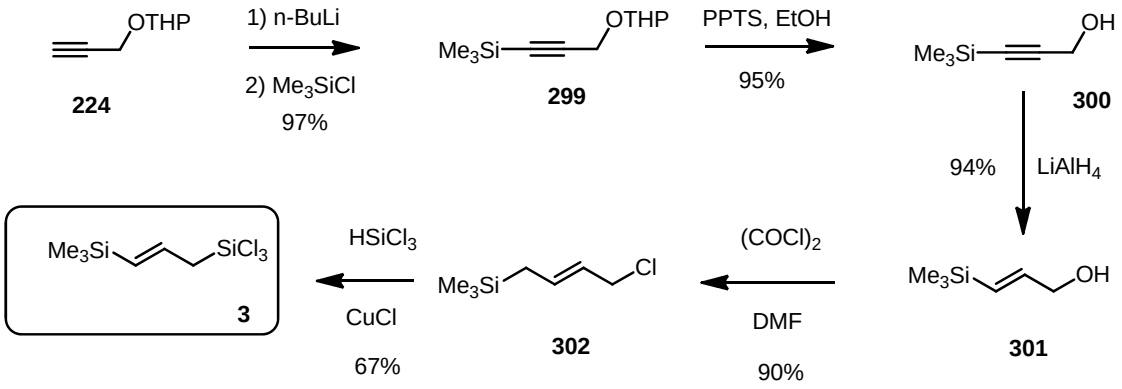
Another disilane **3** was prepared from propargyl alcohol in several steps (*vide infra*), using a slightly modified procedure previously developed during the synthesis of the original disilane **1**. The vinylsilane **3** is a close analogue of the disilane **1**, however one carbon shorter and was expected to give the homoallylic alcohols of type **6** on reaction with aldehydes. These homoallylic alcohols were expected to undergo cyclization in the presence of a Lewis acid and another portion of aldehyde, to form the dihydropyrans **329** (**Scheme 121**).



Scheme 120: Allylation with the disilane 3.

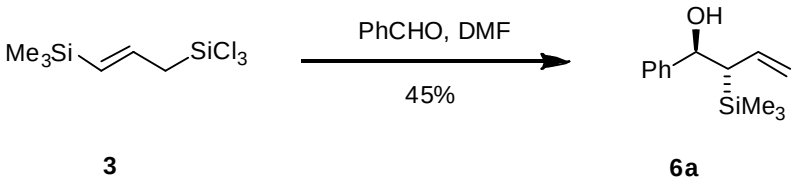
The vinylsilane **3** was synthesized as follows: Propargyl alcohol was protected as a THP ether **224**, deprotonated, and alkylated with chlorotrimethylsilane (**Scheme 121**). After

deprotection, the triple bond was reduced with lithium aluminium hydride, giving the alkene **301.** After screening of several methods, oxalyl chloride in the presence of DMF was found to be the chlorinating agent of choice to produce the allyl chloride **302**. Trichlorosilylation of the latter derivative with an excess of trichlorosilane and in the presence of one equivalent of copper(I) chloride furnished the desired disilane **3**.



Scheme 121: Synthesis of the disilane 3.

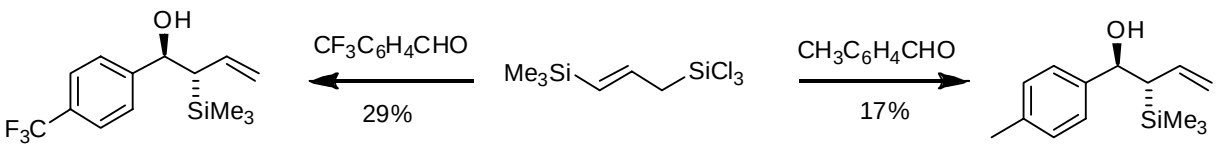
The disilane **3** was then used in the allylation of benzaldehyde. When treated with benzaldehyde in the presence of an achiral Lewis base (DMF), the expected homoallylic alcohol **6a** was obtained in moderate yield as pure *anti* stereoisomer (**Scheme 122**).



3 **6a**

Scheme 122: Allylation of benzaldehyde with the disilane 3.

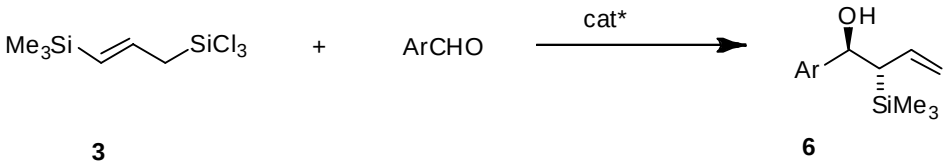
Two other examples of the homoallylic alcohol were prepared, with the electron poor and electron rich aromatic moiety, by the allylation of *p*-tolualdehyde and *p*-trifluoromethyl benzaldehyde respectively to form **6b** and **6d** (**Scheme 123**).



6b **3** **6d**

Scheme 123: Allylation of the electron rich and electron poor aldehyde with disilane 3.

In the enantioselective version of the allylation of aldehydes with **3**, we tried three organocatalysts that proved to be most successful with the analogous trichlorosilane **1**. We obtained moderate enantioselectivities but very low yields, which we were not able to optimalize (**Scheme 124** and **Table 19**).



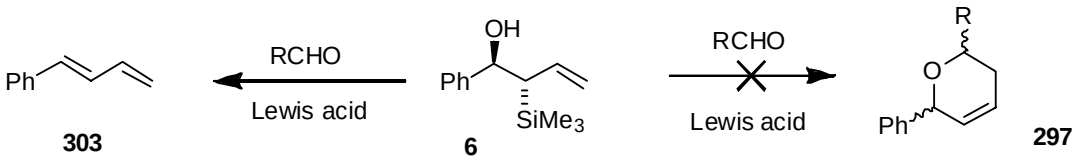
3 **6**

Scheme 124:Enantioselective version of the allylation.

Table 19: Enantioselective allylations of aldehydes with the trichlorosilane (3).

Entry	Catalyst	Ar	Yield (%)	ee (%)
1	METHOX (**62**)	Ph	10	45
2	QUINOX (**61**)	Ph	9	32
3	METHOX (**62**)	p-$CH_3C_6H_4$	15	63
4	QUINOX (**61**)	p-$CH_3C_6H_4$	8	23
5	QUINOX (**61**)	p-$CF_3C_6H_4$	10	35
6	(S,R)-ANET (**245**)	p-$CF_3C_6H_4$	11	56

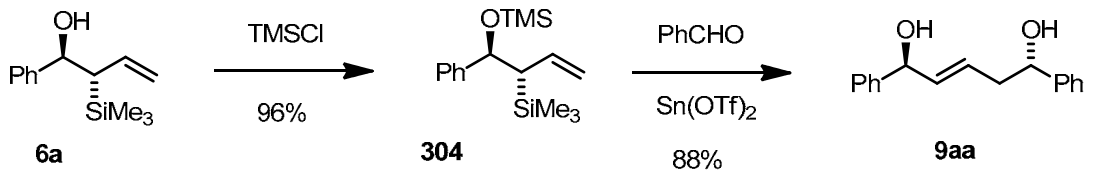
Alcohol **6a**, disappointingly, upon treating with tin(II) triflate as a Lewis acid did not give the expected dihydropyran **297** but just a product of a Peterson olefinaton **303** (**Scheme 125**).



303 **6** **297**

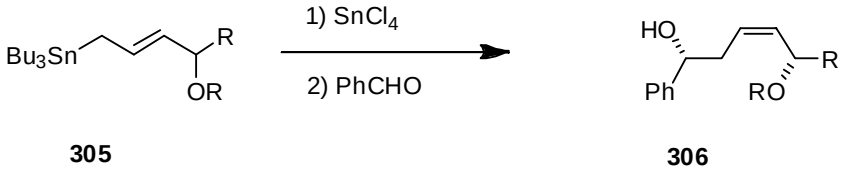
Scheme 125: Intramolecular allylation of aldehyde 6a.

We then protected the alcohol moiety of **6a** as a TMS ether to prevent the S_N1 elimination during the "cyclization" conditions. In the presence of tin(II) triflate, nucleophilic attack at the aldehyde carbonyl took place to furnish the diol **9aa**. (**Scheme 126**).



Scheme 126: Allylation with the TMS protected homoallylic alcohol 6a.

This is the same class of diols as those made by Roush,[98] using a boron chiral auxiliary or Thomas,[99] (**Scheme 127**) using allylation of aldehydes with organostannanes (he further used the diols in the synthesis of natural products - patulolides). We however avoided both the use of expensive chiral auxiliaries or toxic organotin compounds.



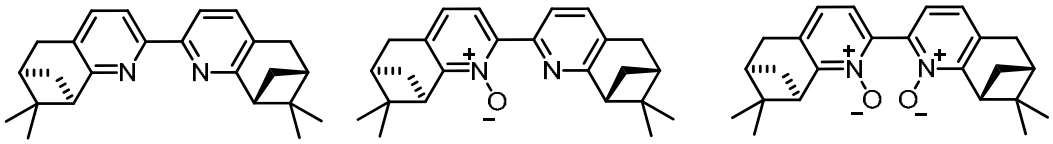
Scheme 127: E. J. Thomas's chemistry.

3 Development of a Novel N,N'-Dioxide Catalyst

3.1 N-Oxide Catalysts With the Axial Chirality

The application of chiral *N*-oxides in catalysis can be roughly divided into two groups. They can serve as chiral ligands for the transition metals, or especially in organosilicon chemistry, as organocatalysts themselves. The high nucleophilicity of the *N*-oxide oxygen, together with its affinity to silicon, represents an ideal combination of properties to serve as activators/chiral ligands for the organo-silicon reagents. [100]

A large number of *N*-oxide organocatalysts have been developed in our group in the past few years.[31] Some of them rely purely on axial chirality or central chirality, others on a combination of both. Differences in the reactivities and enantioselectivities of chiral pyridines and their *N*-monooxides a *N*,*N*'-dioxides can be demonstrated in the series of three catalysts, PINDY, PINDOX, PINDIOX (**Scheme 128**). The monooxide can be selectively made by oxidation of the bipyridine **243** with one equivalent of *m*CPBA (as there is unrestricted rotation about the py-py axis, it can be assumed that the electron density on the other ring will be reduced after introducing the first oxygen, due to conjugation between the aromatic rings, although weak).[101]

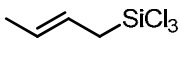


PINDY **243** | **PINDOX** **307** | **PINDIOX** **242**

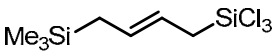
Scheme 128: The PINDY-derived catalyst series.

Although the allylation of aldehydes with the crotyl trichlorosilane (*E*)-**28** (**Scheme 129**) was much faster with the dioxide, it was found to be much less enantioselective. It was proposed that the coordination of the second nitrogen to the silicon atom plays an important role in the transition state.

However, in the case of bulky trichlorosilanes, such as **1**, it was found necessary to use the dioxide catalyst, as both PINDY and PINDOX failed to catalyse the reaction with appreciable rate.



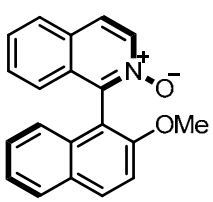
(*E*)-28



1

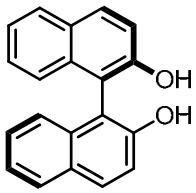
Scheme 129: Crotyltrichlorosilane and the novel disilane.

Catalysts, relying solely on axial chirality, such as QUINOX (**Scheme 130**), are usually synthesized as racemates and co-crystallized with an enantiopure partner (usually BINOL), and separated by crystallization or on a column.[31]



(*R*)-**QUINOX**

61



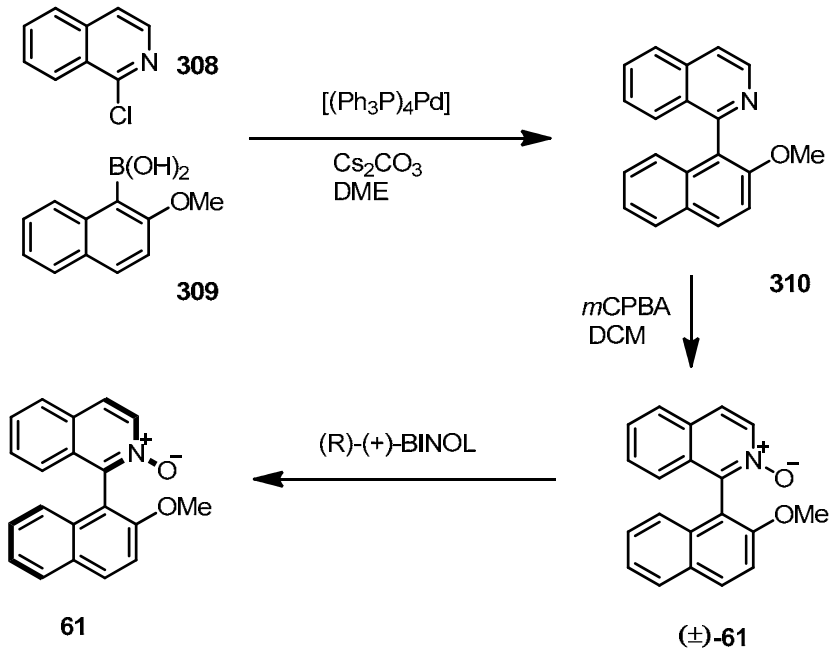
(*R*)-**BINOL**

308

Scheme 130: QUINOX and BINOL.

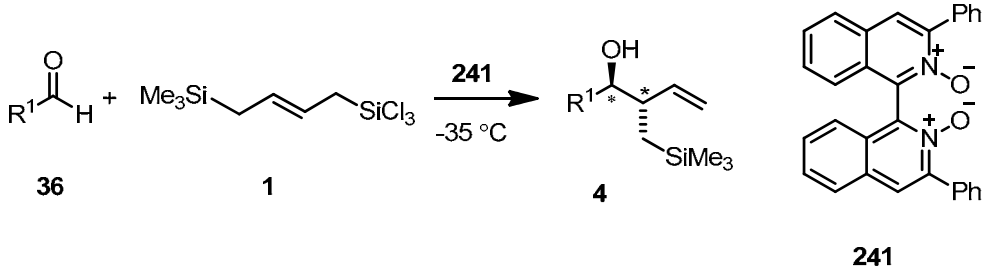
QUINOX, is prepared in two steps from the commercially available 1-chloro-isoquinoline **308** and 2-methoxy-1-naphthylboronic acid **309**, which in turn is prepared from 1-bromo-2-methoxy naphthalene by lithiation with *n*-BuLi in THF, followed by a reaction with $(MeO)_3B$ and subsequent hydrolysis of the intermediate boronate ester with HCl.[31] The biaryl intermediate **310** is prepared by the Suzuki-Miyaura coupling of 1-chloro-isoquinoline **308** with the corresponding boronic acid **309** in DME in the presence of cesium carbonate and a catalytic amount of palladium triphenylphosphine. Treatment of **246** with *m*CPBA then provides the *N*-oxide **61** in almost quantitative yield (**Scheme 131**).

The *N*-oxide is resolved by co-crystallization with (*R*)-(+)-BINOL from CH_2Cl_2. The crystals contain the molecular compound (*R*)-BINOL·(*R*)-QUINOX. Flash chromatography of the latter material gives (*R*)-(-)-QUINOX (> 99% ee) and the recovered (*R*)-(+)-BINOL. The mother liquor provides the enantiomerically enriched (*S*)-(+)-QUINOX, which can be purified by co-crystallization with (*S*)-(-)-BINOL to produce (*S*)-(+)-QUINOX (>99.8% ee after a single crystallization).



Scheme 131: Synthesis of QUINOX.

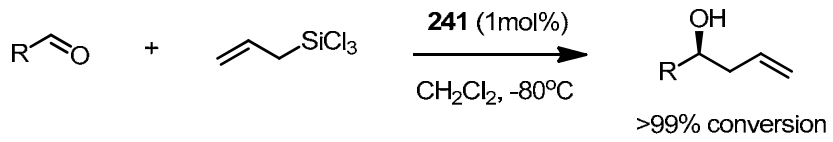
In the process of screening the chiral catalysts for the allylation of aldehydes with the bulky disilane **1**, we came across the *N*,*N*'-dioxide **241**, which afforded the full conversion of the starting disilane **1** in a few hours, in contrast to METHOX or QUINOX, which typically took days in order to take the reaction to the completion (*vide supra*).



36 **1** **4** **241**

Scheme 132: Allylation with the bulky disilane 1.

The bisisoquinoline catalyst **241**, was synthesized in our group several years ago and was shown to be highly active and gave moderate to good enantioselectivities for most of the substrates (**Scheme 133** and **Table 20**).

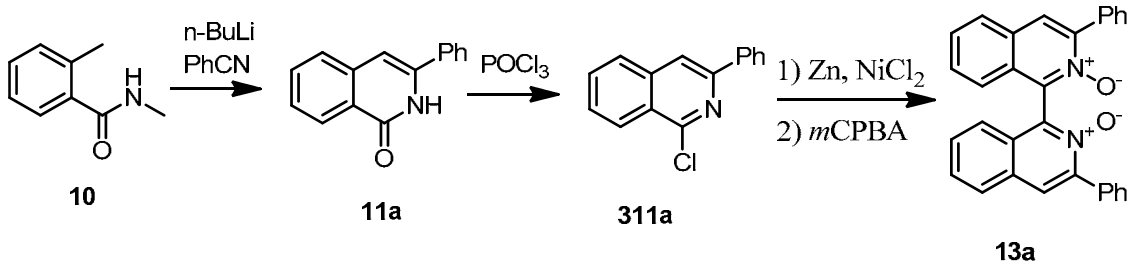


Scheme 133: Allylation of aldehydes catalysed by the dioxide 241.

Table 20: Results of the allylation of aldehydes catalysed by the dioxide 241.

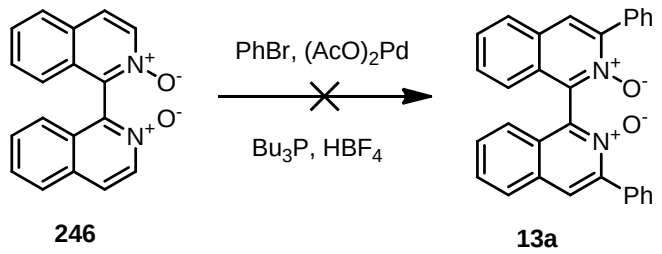
Entry	R	Time (h)	ee(%)
1	Ph	18	81
2	4-MeC_6H_4	18	69
3	3,5-$Me_2C_6H_3$	18	71
4	4-ClC_6H_4	30	76
5	4-$MeOC_6H_4$	18	2
6	3,4-$(MeO)C_6H_3$	18	10

Racemic dioxide **13a** was prepared (similarly to QUINOX) in four steps from the commercially available *o*-methylbenzamide (**Scheme 134**).



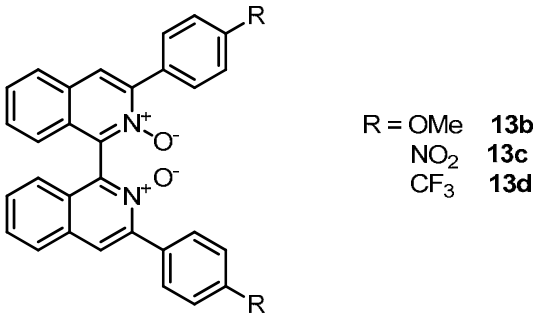
Scheme 134: Synthetic path towards 241.

Racemic dioxide **13a** however resisted a number of attempts at classical resolution and was eventually resolved by chiral HPLC on a very small scale. Attempted synthesis of **13a** via **246** (which in turn can be prepared enantiomerically pure) via coupling with PhBr, was unsuccessful (**Scheme 135**).[102]



Scheme 135: Alternative attempted synthesis of 13a.

We envisaged that a catalyst like **13b-d**, bearing additional moiety on the phenyl rings might crystallize more easily with BINOL, while retaining the activity of the original compound.



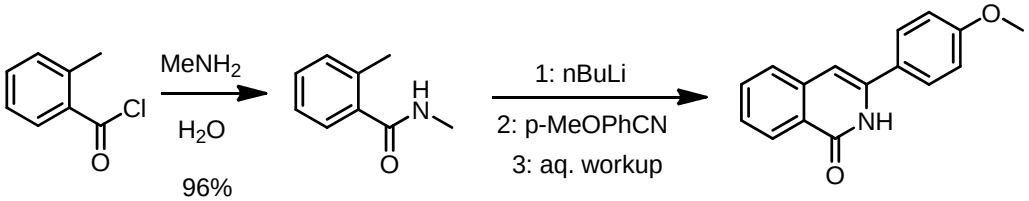
Scheme 136: Analogues of the dioxide 241.

3.2 Results and Discussion

*This part of the project was completed in the cooperation with the undergraduate Erasmus exchange student **Michal Májek**.*

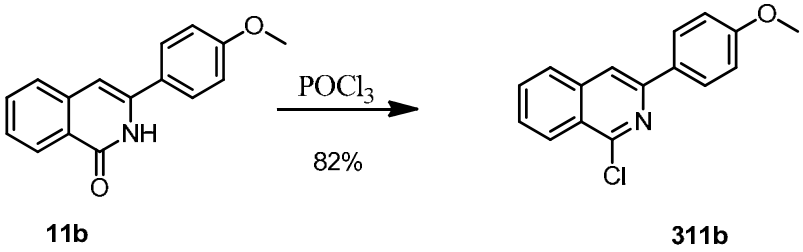
3.2.1 Synthesis of the Catalyst

o-Methylbenzamide **10** was prepared from the corresponding chloride **1** by reaction with excess of methylamine. The cyclic amide **11b** was then prepared by the annulation with p-methoxybenzonitrile mediated by an excess of butyllithium in THF **(Scheme 137)**.



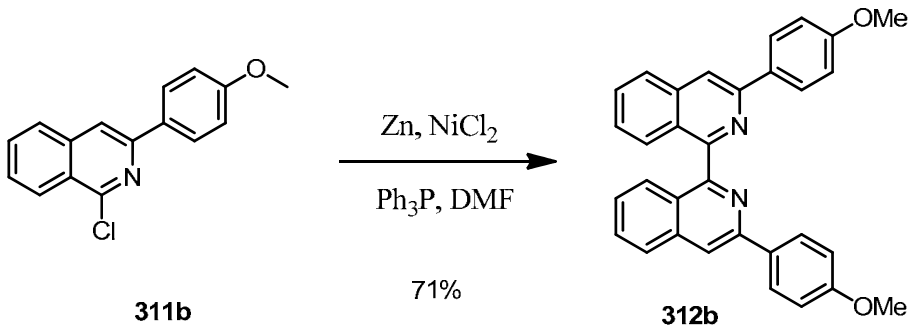
Scheme 137: Synthesis of the intermediate 11b.

11b was treated with $POCl_3$ at high temperatures, giving the chloroisoquinoline **311b** (**Scheme 138**).



Scheme 138: Chlorination of 11b.

The latter derivative then underwent the dimerization, mediated by the in situ generated $(Ph_3P)_2NiCl_2$ in the presence of zinc in DMF affording the biaryl **312b** (**Scheme 139**).

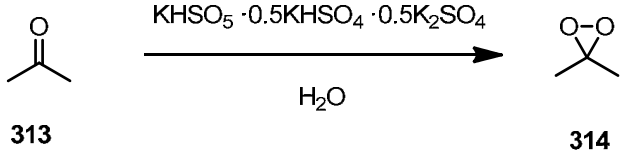


311b **312b**

Scheme 139: The coupling reaction.

The oxidation step turned out to be rather troublesome. We screened several oxidising reagents: hydrogen peroxide,[103] peroxyacetic acid,[104] DMDO[105] and *m*CPBA.[106] Peroxyacetic acid in acetic acid was found not to be reactive enough at room temperature, no *N*-oxide was formed from **312b** even after several days, and upon heating, inseparable mixtures were formed.

DMDO was formed *in situ* from oxone and acetone (**Scheme 140**), however in this case we encountered solubility problems. Since oxone is insoluble in acetone, mixtures of acetone and water are needed, otherwise no DMDO is generated. **314** is very poorly soluble in acetone, and addition of water induced immediate precipitation of **314** and no reaction took place.

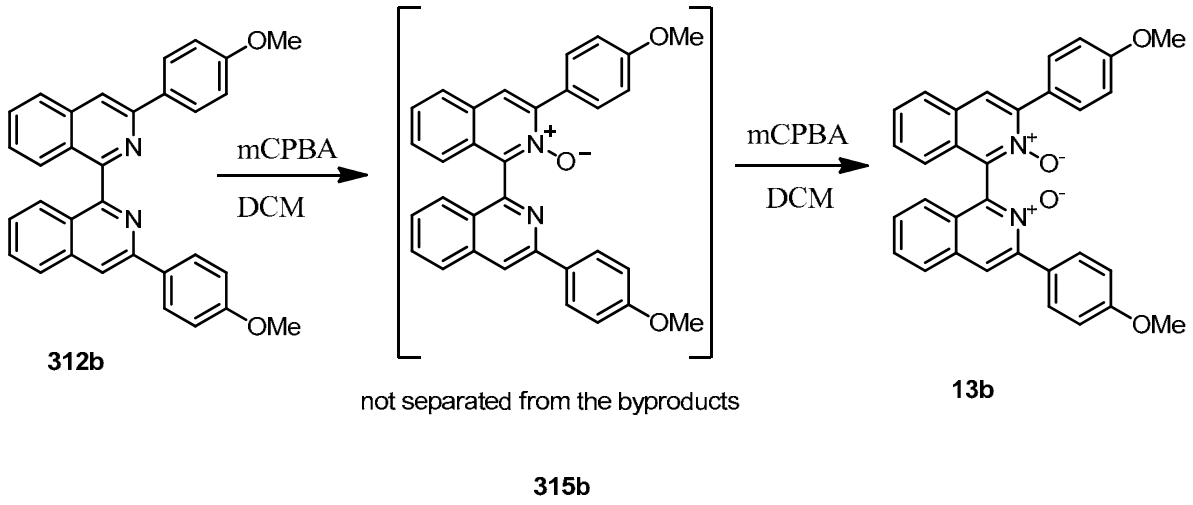


313 **314**

Scheme 140: Synthesis of oxone.

*m*CPBA was selected in the end as the oxidant of choice, although it is far from being an ideal reagent. Oxidation of **312b** with *m*CPBA in DCM at room temperature first led to the monoxide **315b**, but various oxidation byproducts are also formed, that could not be separated from the monoxide by chromatography. Further oxidation did not proceed smoothly, since the steric congestion already increased significantly after the first oxidation. A large excess of *m*CPBA, and long reaction times were needed (10 eq, 7 days at RT) in order to form the desired bis-isoquinoline dioxide. When we tried to speed up the reaction of reaction by elevating the temperature, the quantity of byproducts increased sharply (**Scheme 141**).

We were not able to separate enantiomers of **13b** by co-crystallization with BINOL. As in the case of its predecessor, solubility was the main problem. Solvents usually used in this operation are DCM, toluene and benzene as well as binary solvents mixtures: DCM with *n*-hexane, *n*-heptane, and cyclohexane failed completely. In all cases, either viscous oils, or crystals of racemic *N*,*N'*-dioxide **13b** were obtained from the mother liquors. We were able to efficiently resolve **13b** only by chiral HPLC on a milligram scale. Co-crystallisation of the monooxide **315b** with BINOL might be more feasible, as the solubility of the catalyst decreases sharply with increasing number of *N*-oxides units in the molecule. Therefore the monooxide **315b** might have comparable solubility to BINOL, however the limiting problem is the poor availability of the monoxide, as our attempts to purify it either by crystallization or by chromatography failed.



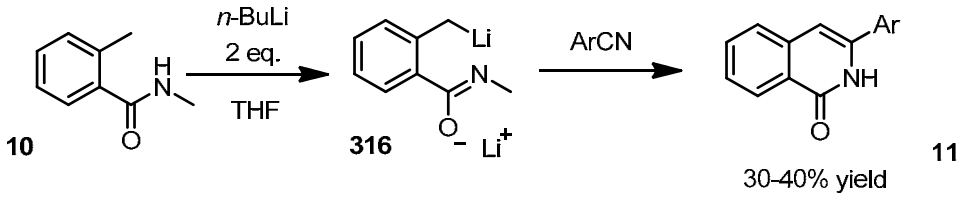
Scheme 141: The oxidation step.

This part of the project was then unsuccessful. However, during the course of synthesis, we observed some interesting behaviour of the intermediate **316** (**Scheme 142**)**.**

3.2.2 Mechanism of the Cyclization Step

Transformation of tolylamides **10** into the isoquinolines of type **11** is a reaction that has been known for more than 30 years (**Scheme 142**). This reaction is often used in the synthesis of pharmacologically interesting targets and, according to the literature, is known to

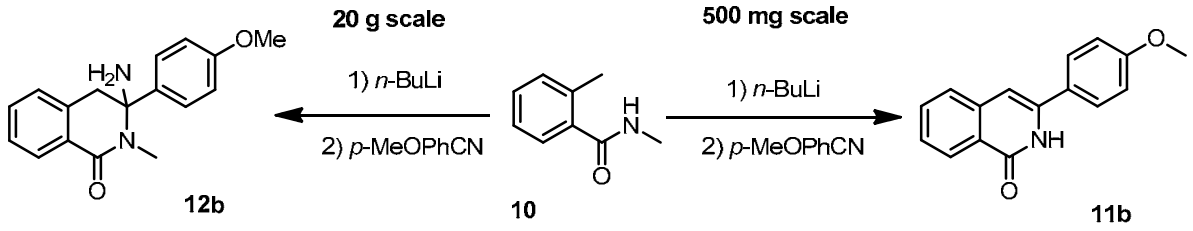
give notoriously low yields.[107] However, we did not come across any study addressing this problem in detail. Similar to the published procedures, we typically got yields between 30-40%. The mechanism of this transformation and the loss of the *N*-methyl group is discussed on the page 109.



Scheme 142: The annulation step.

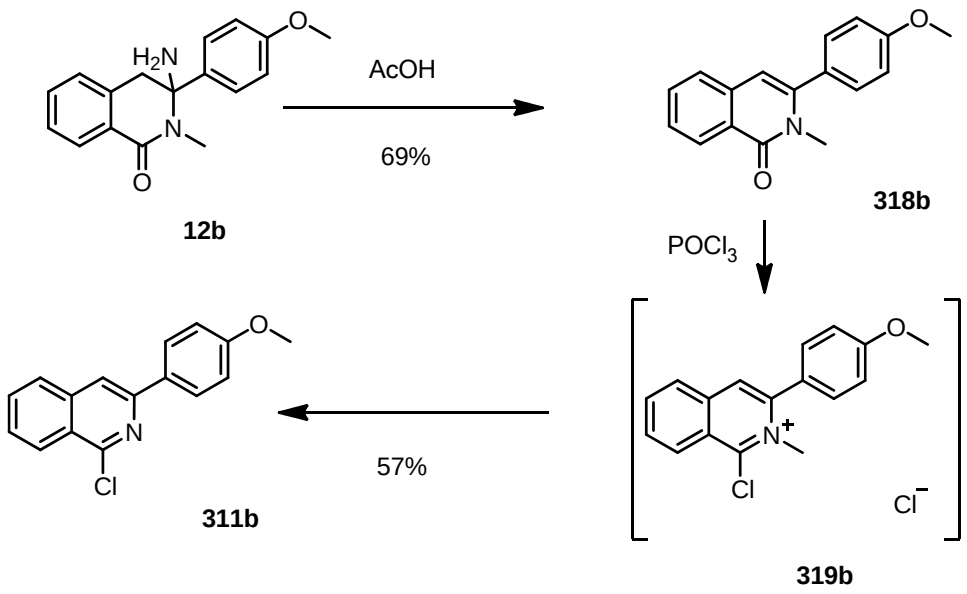
The lithium cation is coordinated to the imine nitrogen, which facilitates the deprotonation of the adjacent methyl group by the second equivalent of BuLi, by a similar principle as in directed ortho methalation (DoM).

After the initial experiments we decided to scale up from the initial 500 mg scale to about 20 g scale. We followed the reaction sequence, and we isolated the product in 65% yield, which however to our surprise turned out to be amine **12b** rather than the expected isoquinolone **11b**, as was also proven by X-ray analysis.



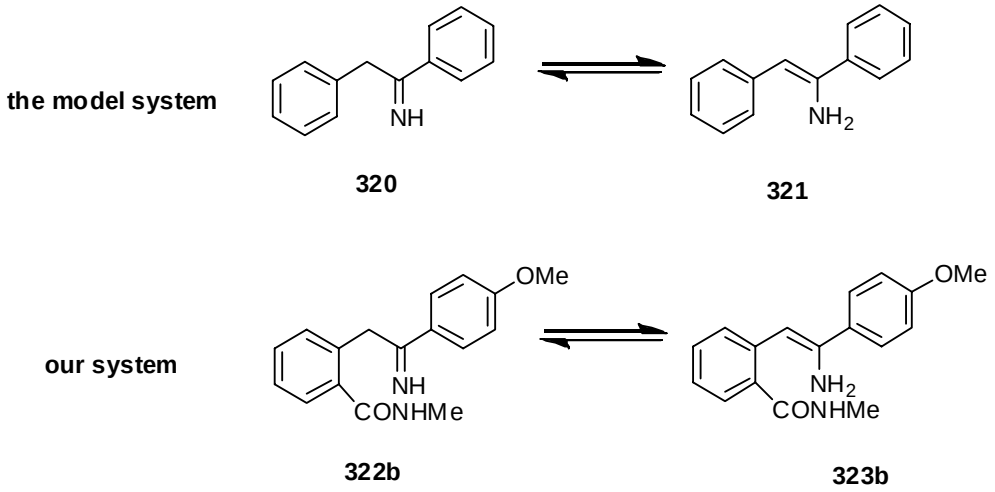
Scheme 143: Unexpected outcome of the reaction after scale-up.

However, we managed to convert the amine **12b** into the chloride **311b** (**Scheme 144**). If **12b** is heated up to 80 °C in AcOH, elimination of ammonia takes place, and **318** is formed. **318** was chlorinated to form the salt **319b**. It was reported before that similar systems undergo dealkylation under acidic conditions.[108] It turns out that **319b** is a strong alkylating agent, and that it loses the methyl in the presence of $POCl_3$ under reflux. Therefore, it is possible to get the desired product **311b** in one step from **318b**.



Scheme 144: Transformation of the unwanted aminal 12b into the chloride intermediate 311b.

However, we were wondering why the unexpected aminal **12b** was formed during the same reaction conditions we used before and we decided to investigate this reaction further. The protonated form of the intermediate formed by the reaction of **316** with the nitrile (**Scheme 145**, compound **322b**), has a structure similar to the known compound **320**. According to the literature,[109] the equilibrium between **320** and **321** is strongly influenced by the dielectric constant of the solvent (**Scheme 145** and **Table 21**) and thus we expected a similar behaviour for our system and the equilibrium between **322b** and **323b**.

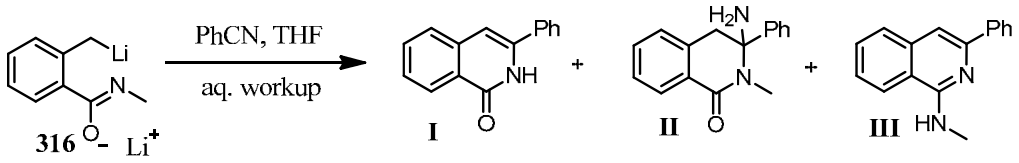


Scheme 145: The imine-enamine equilibrium.

Table 21: Published ratio of imine 320 : enamine 321 depending on the solvent.

Solvent	Dielectric constant	Ratio of 320 : 321
chloroform	4.8	2.9
nitrobenzene	34.8	0.5
DMSO	46.7	0.3

We tried to verify the hypothesis about the influence of the solvent by a set of experiments. (**Scheme 146** and **Table 22**). We created the intermediate **316** in THF, reacted it with benzonitrile, and the resulting solution was diluted by a large volume of other solvent (toluene, MeCN or DMF; at this point the lithium anion was fully consumed and hence there was no competing reaction between benzonitrile and acetonitrile e.g.), and then quenched by adding water dropwise into the mixture (**method G**, as it was called for the needs of this experiment). Nearly no difference in the product distribution was found - a majority of the lactam (product of **type I**, see **Scheme 146**) was formed in all cases, i.e. the solvent did not have any influence on the outcome of the reaction. See **Scheme 146** and **Table 22**, entries **1**, **2**, and **3** for the results. This means, that either no equilibrium is formed (all **322b** stays as imine), or that the cyclization to form the lactam is very fast under the given conditions.



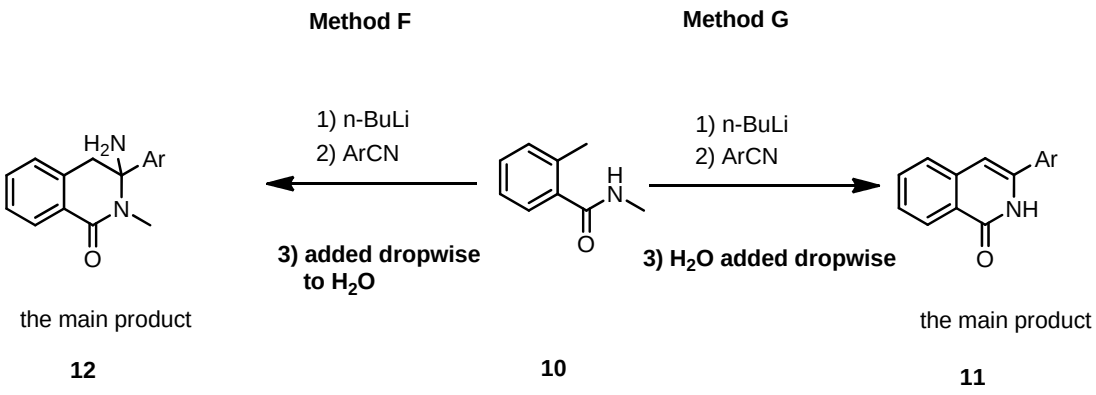
method F = adding the reaction mixture into the water/NH_4Cl solution
method G = adding the water/NH_4Cl solution in the reaction mixture

Scheme 146: Different method of quenching the reactive intermediate.

Table 22: Various methods of quenching the reactive intermediate.

Entry	Solvent	Quenching medium	Method	Type I product	Type II product	Type III product
1	toluene	H_2O	G	70%	2%	7%
2	DMF	H_2O	G	78%	5%	3%
3	MeCN	H_2O	G	76%	4%	1%
4	THF	H_2O	F	12%	56%	8%
5	THF	10 vol. % H_2O in THF	F	21%	44%	4%
6	THF	1 vol. % H_2O in THF	F	33%	37%	7%

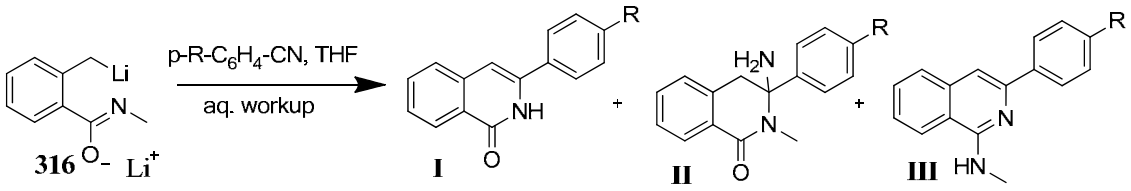
In another set of experiments we used the quenching **method F** (the lithium salt is added dropwise to the quenching medium), but besides of using pure water, we also used solutions of water in THF (10 vol. % and 1 vol. % water in THF, **Table 22**, entries **4**, **5**, and **6**). A difference in the product distribution was now observed: with decreasing concentration of water in the quenching medium, the ratio of the aminal (**type II** product) to the isoquinoline (**type I** product) changed from 5 : 1 (when pure water is used for quenching), to almost 1 : 1 (when 1% water in THF is used).



Scheme 147: Different outcome of the reaction depending on the quenching method.

The more intuitive way of quenching the reactive intermediate is adding the reaction mixture slowly to water (so that in every moment there is an excess of water). We observed that using this method, the formation of the undesired aminal **12** is promoted. However, if we reverse the operation and add water to the reaction mixture we obtained **11** as the main product (**Scheme 147**).

We also found out that the nature of the nitrile plays a role only when the reaction mixture is added to water (**method F**), in the other case, when the reaction is quenched by adding water to the reaction mixture (**method G**), the influence of the electronic nature of the nitrile is negligible. (**Scheme 148** and **Table 22**). The original literature[107] also suggested using the saturated solution of NH_4Cl as a quenching medium, however we did not find any notable difference when water was used.



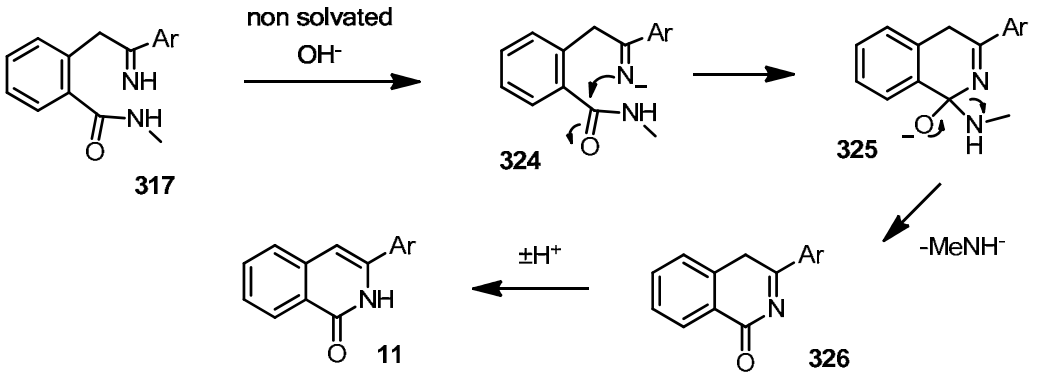
method F = adding the reaction mixture into the water/NH_4Cl solution
method G = adding the water/NH_4Cl solution in the reaction mixture

Scheme 148: Cyclization with various nitriles.

Table 22. Products distribution depending on the quenching method and nature of the nitrile.

Entry	R	Quenching medium	Method	Product I (%)	Product II (%)	Product III (%)
1	H	NH_4Cl	F	8%	65%	12%
2	H	NH_4Cl	G	73%	4%	13%
3	H	H_2O	F	12%	56%	8%
4	H	H_2O	G	85%	5%	7%
5	OMe	NH_4Cl	F	5%	40%	6%
6	OMe	NH_4Cl	G	41%	1%	12%
7	CF_3	NH_4Cl	F	14%	33%	-
8	CF_3	NH_4Cl	G	35%	2%	-

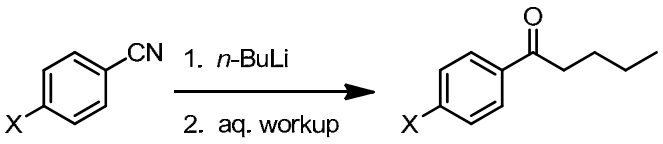
When we decrease the concentration of water immediately available to solvate the OH^- ions (which are created by reaction of water and lithium salt) then naked OH^- can act as a strong base, deprotonating the nitrogen atom of imine **317**, which results in an immediate cyclization (**Scheme 149**).



Scheme 149: Mechanism of formation of lactam 11.

The key step in this mechanism is the deprotonation of the imine. According to the literature,[110] pK_a values of this type of imines are around 26. The nature of the nitrile does not affect the formation of product **11**, because the aromatic moiety cannot stabilize the negative charge on the nitrogen. The process depends only on the concentration of water in the system. Low concentration of water allows the deprotonation of imine by the non-solvated OH^- ions, which would not be possible in the aqueous medium. This also explains, why the same ratio of products was observed in all experiments in different solvents, when **method G** (water added to the reaction mixture) was employed. Toluene, THF, MeCN, and DMF are all very poor in anion solvation, therefore the naked OH^- immediately deprotonated the imine, which quickly cyclized. On the other hand, if water is used as a bulk solvent (**method F**), then the OH^- ions are solvated, and unable to effectively abstract the hydrogen from imine. Using NH_4Cl solution for the workup, as suggested by the original literature,[107] is then in fact contra-productive. It only further decreases the pH of the solution, and we saw that high pH is crucial for high yields of the desired amide product. The likely reason, why saturated NH_4Cl solution was used in original literature, was an attempt to suppress the hydrolysis of imine intermediate **317** to the ketone. But as we found, this hydrolysis reaction is slower than the cyclization of imine **317** anion to lactam **11** – the corresponding ketone was never isolated from the reaction mixture. Therefore, there is no reason why NH_4Cl solution should be used for the workup.

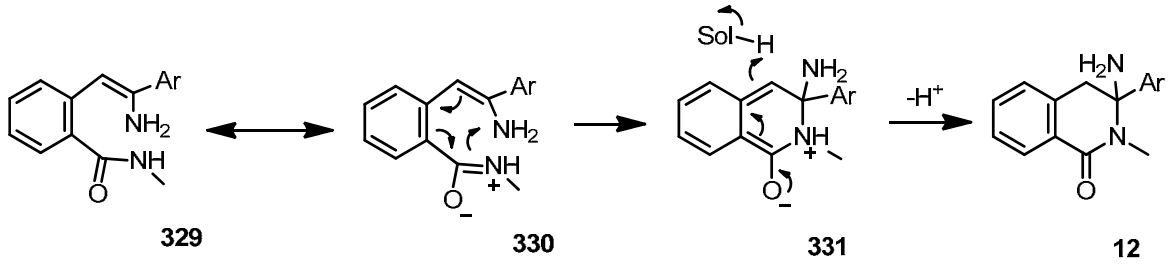
When excess of *n*-butyllithium was used, as the original literature suggests, the substituted valerophenones **328** were always isolated. (**Scheme 150**) Apparently, the excess of nitrile is then only an expensive trap for the organolithium and exactly two equivalents of n-BuLi should be used.



327 **328**

Scheme 150: A side reaction of the nitrile with the BuLi.

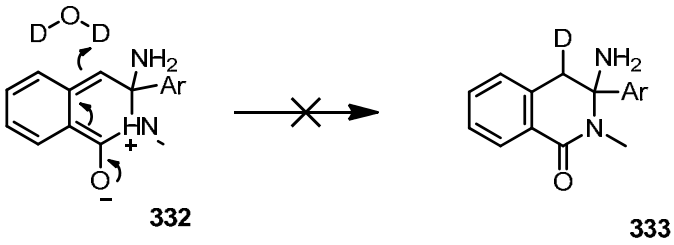
The aminal **12** could be formed by the sigmatropic rearrangement as follows (**Scheme 151**):



Scheme 151: Possible mechanism of the formation of aminal 12.

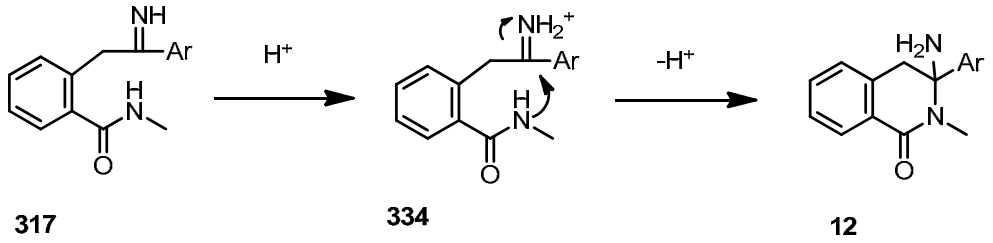
However, the key step in this mechanism is the imino/enamine tautomerism, which would generate the enamine. The enamine itself can undergo the electrocyclic reaction (**Scheme 151**). This tautomeric equilibrium should be strongly influenced by the dielectric constant of the solvent, which was not observed. Furthermore, precedents for this type of eletrocyclic reactions usually exist at temperatures above 150 °C, whereas our reaction was complete at room temperature in a few seconds.

We decided to model the transition state of this reaction (DFT, PBE1PBE 6-311G(d)), getting $\Delta E^{\neq}$ = 170 kJ mol^{-1}, which is too high for the reaction to proceed at the room temperature. To rule this mechanism out beyond doubt, we worked up the reaction with deuterated water (added the reaction mixture dropwise to the deuterated water). Should this mechanism be taken into an account, we would have detected the deuterium in the final product, however none of this was observed (**Scheme 152**).



Scheme 152: Quenching of intermediate 332 by adding the mixture into the deuterated water.

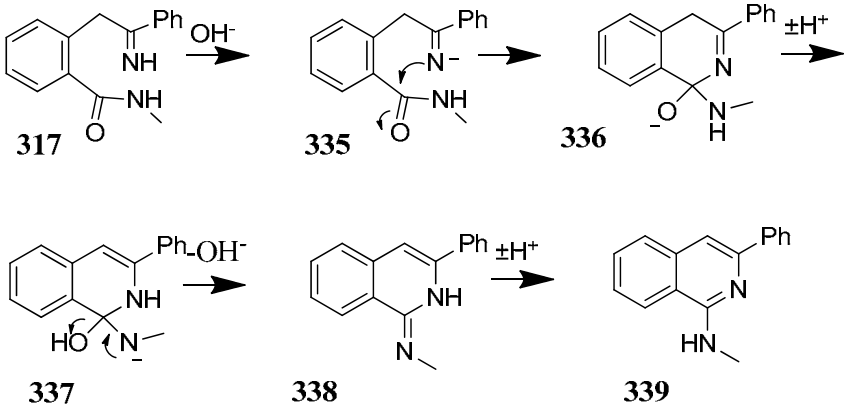
In the other mechanism we proposed, the key step in the formation of the product **12** is the protonation of the imine:



Scheme 153: Proposed mechanism of the formation of aminal 12.

According to the literature,[111] the pK_{aH} of this kind of imines are around 7, hence the protonation can occur in the aqueous medium. Dielectric constant of the solvent does not affect the formation of **12**. The important factor is the concentration of water in the system, enabling the protonation of the imine, which we did observe. The substituents on the aromatic ring of the nitrile can stabilize/destabilize the cation intermediate **334** and thus influence the formation of **12**, which was observed too (**Table 22**). The ratio of products **12**/**11** is decreasing in the order of $MeOC_6H_4$>Ph>$CF_3C_6H_4$ (the electron withdrawing groups are destabilizing the cation **334** and thus disfavouring the formation of the product **12**).

In most cases, independent of the method of quenching used (**F**,**G**), the byproducts of type **339** were formed (**Scheme 154**). The mechanism for their formation is quite straightforward: after the nucleophilic attack of the imine anion onto the amide, instead of elimination of the methylamine (which would result in type **I** products), hydroxide is eliminated, and **339** (type **III** product) is formed (**Scheme 154**).



Scheme 154: Proposed mechanism for the formation of the byproduct 339.

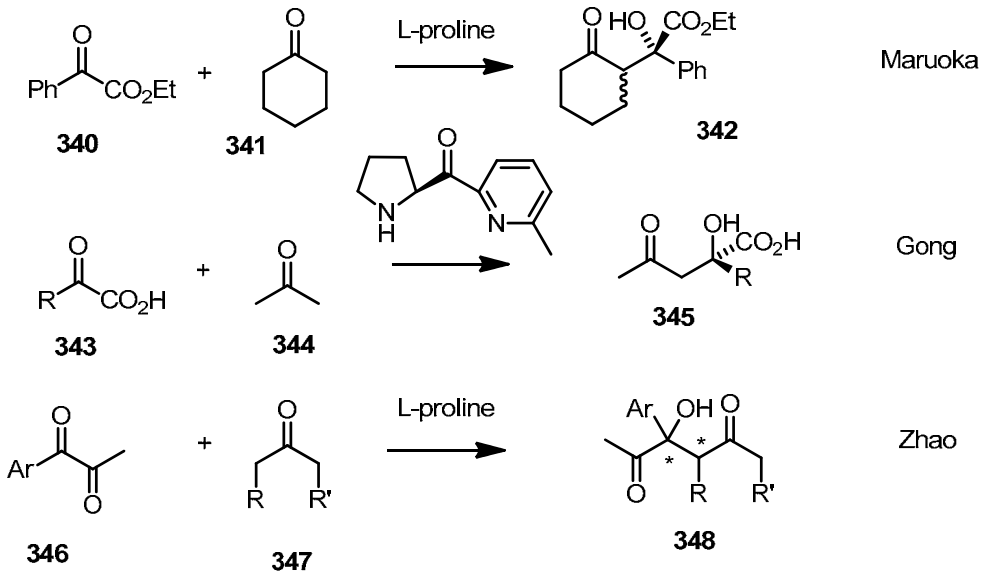
To conclude, we have shown that if the formation of the lactam **11** is to be promoted, the reactive intermediate has to be quenched by carefully adding water (not ammonium chloride) into the mixture, and not the other way round. Electron donating groups further promote the formation of **11**. The aminal byproducts **12**, which have not been previously described in the literature and which, most likely were the reason for low yields of the cyclization reactions, were isolated and characterized.

4 Asymmetric Aldol Reactions

4.1 Recent Development in the Asymmetric Aldol Reactions

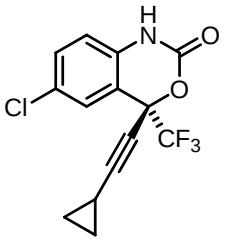
The asymmetric intermolecular cross-aldol reactions between aldehydes and aldehydes or aldehydes and ketones have proved to be an important tool for C-C bond formation, which has been extensively explored for the construction of chiral β-hydroxy aldehydes or β-hydroxy ketones in synthetic organic chemistry. By contrast, enantioselective intermolecular cross-aldol reaction between ketones, which produces 3-substituted-3-hydroxy ketones with quaternary stereogenic centres, is much more challenging, especially in the organocatalytic realm.[112] The key position amongst the organocatalysts catalysing aldol reaction has been held for a long time by proline and its derivatives, which is partly related to the key function of proline carboxyl group in steering the reactants by hydrogen bonding.[113] In contrast to the great success in the field of aldehyde-ketone reactions, the selective ketone-ketone reactions are more rare. With non-symmetrical ketones, four possible enamines can be generated in the equilibrium, which can form four possible products, each one then in a form of different stereoisomers. A successful and selective reaction between two ketone partners must be then designed in a way where one of the components in non enolizable (i.e., has no α protons) and reacts as an electrophilic acceptor. Furthermore, to prevent the self aldolization of the nucleophilic partner, the non enolizable ketone should be much more reactive, i.e., should contain an activated carbonyl group.

For example, Maruoka reported on high enantio- and diastereoselectivities for the reaction of aromatic α-ketoesters with cyclohexanone (96-99% ee, ≥20:1 dr), catalysed by L-proline (30 mol% loading) (**Scheme 155**).[114] Gong has shown that the related reaction of acetone with the free α-ketoacids, catalysed by the *N*-(α-pyridyl)proline amide (20-30 mol%) at 0 ^{o}C, can give the aldol products with ≤98% ee.[115] Zhao has found the reaction of acetone with α-diketones, catalysed by L-proline (50 mol%), affords the corresponding aldol products in ≤85% ee.[116]



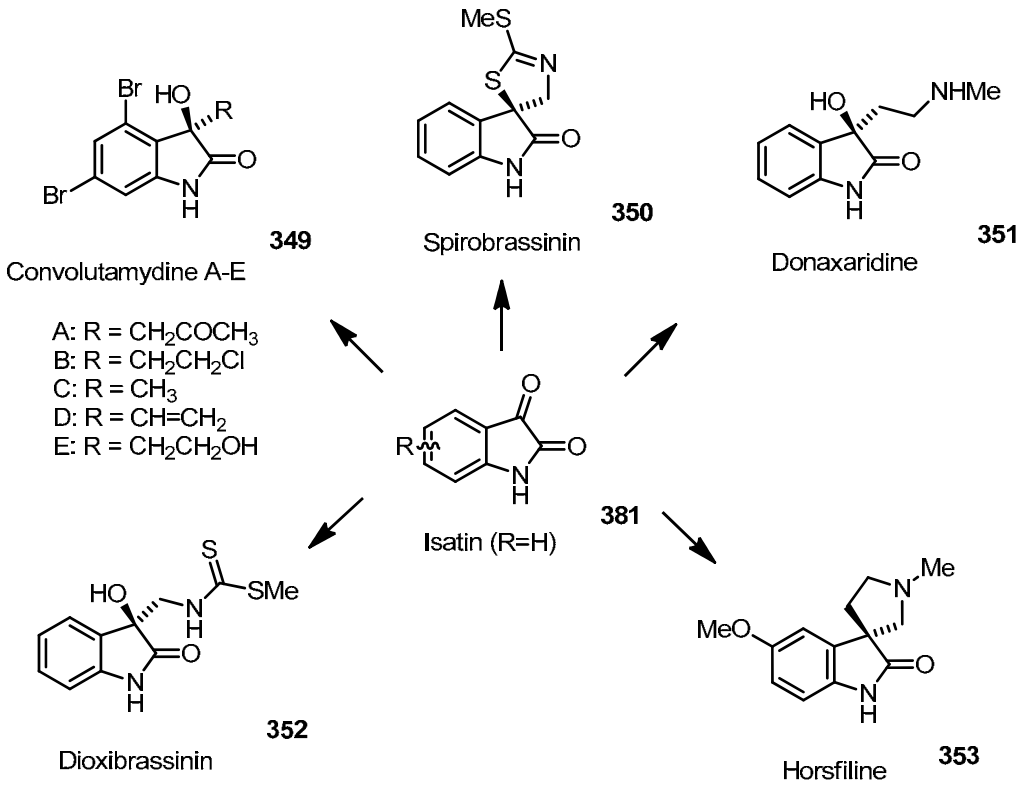
Scheme 155: Examples of enantioselective aldol reactions.

Besides ketoesters and diketones, ketones with α-CCl_3 and CF_3 group are also suitable candidates for the selective ketone-ketone aldol reaction. α-Trifluoromethyl tertiary alcohols and their derivatives are vital structural motifs in anticonvulsants, anaesthetics, Merck's anti-HIV agent Efavirenz and other pharmaceuticals, some also find application in LCD materials.[117] Amino acid-catalysed asymmetric aldol reaction between methyl ketones and aryl trifluoromethyl ketones was reported by Zhang and co-workers but only moderate enantioselectivities were obtained.[118] Wang and co-workers were using proline-derived *N*-sulfonamides for the reaction of methyl ketones with α,β-unsaturated trifluoromethyl ketones (with 59-94% ee for various sulfonamide-based catalysts) but otherwise this field remains largely unexplored.[119]



Efivarenz

Aldol reaction provides an easy access to chiral tertiary alcohols, and in particular, the utilization of isatins (see **Scheme 156**) as electrophiles has drawn much attention. This reaction affords chiral 3-hydroxy-2-oxyindole derivatives, an important structural motif in a number of biologically active compounds (**Scheme 156**).[120]



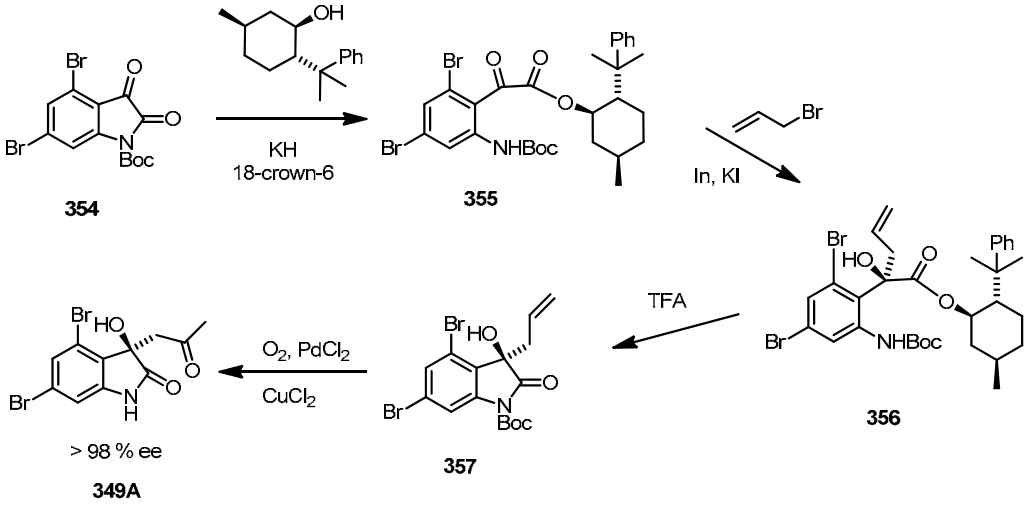
Scheme 156: Some of the nature products derived from the isatine.

Aldol reaction of isatins with, e.g., acetone fulfils the criteria for a selective reaction described above. Isatins cannot enolize, C-3 isatin carbonyl is activated and much more reactive than that of acetone, and acetone as a symmetrical ketone can form only one type of enamine.

Convolutamydines are a family of alkaloids that were isolated from the marine bryozoan *Amathia Convulata* in 1995. All of them bear a common 4,6-dibromo-3-hydroxyindole skeleton and contain a tertiary alcohol at C-3; the individual *Convolutamydines* (A-E) then differ in the side chain moiety at this center. All of them exhibit interesting biological activities, *Convolutamydine A* for an example has a potent inhibitory activity towards the differentiation of the human HL-60 promyelocytic leukaemia cells.[121]

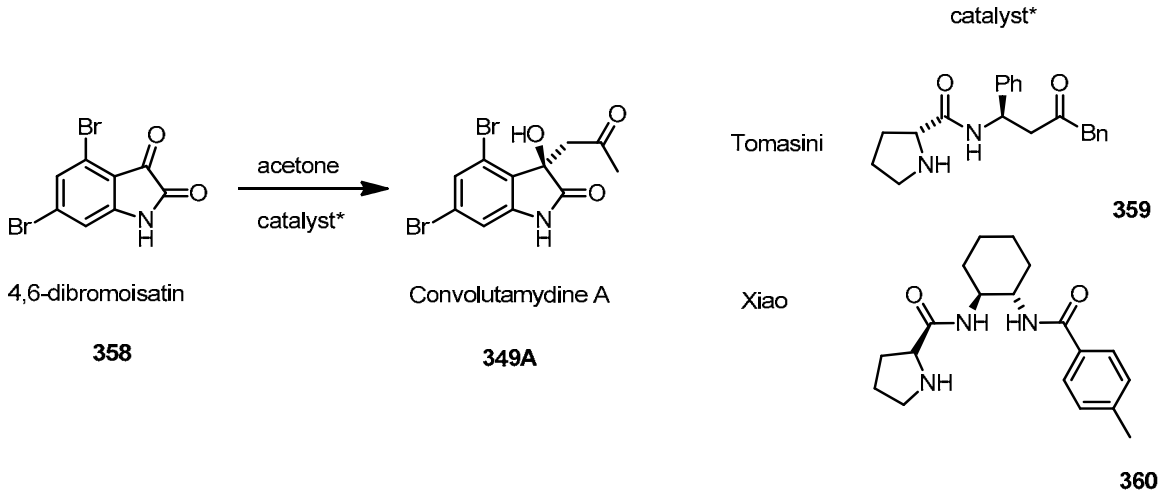
The first enantioselective synthesis of *Convolutamydine A* was reported in 2006 by Tomasini, through a direct aldol reaction of 4,6-dibromoisatine with acetone, using peptidic catalysts, having proline at the *N*-terminus (94% ee), proline itself gave only inferior results (**Scheme 157**).[122] Shortly after that, Stazi published a longer but more selective synthesis of

enantiopure *Convolutamydine A*.[123] The key steps of the latter synthesis were the In-catalysed diastereoselective allylation[72] of the ketoester **355** and Wacker oxidation of **35**.[123]



Scheme 157: Synthesis of Convolutamydine A by Tomasini.

In 2007, Xiao reported another aldol reaction of isatin with acetone, this time catalysed by the chiral bisamide **360**, derived from a chiral diamine and L-proline (64% ee).[124]

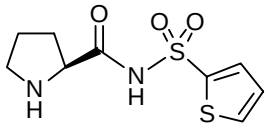


Scheme 158: Synthesis of Convolutamydine A from 4,6-dibromoisatine.

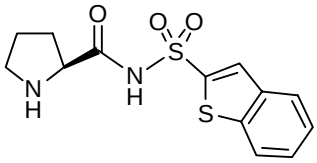
Hao showed that simple proline can catalyse the aldol reaction of *N*-substituted isatins with acetone with moderate to good enantioselectivities, however with poor results for unsubstituted isatin.[125] Interestingly, substitution at position 4 of the isatin, reverses the enantioselectivity of the reaction and the opposite enantiomer becomes the major product.

Our group reported on the synthesis of Convolutamydine A, using D-leucinol as a catalyst (94 % ee).[94] We have demonstrated that the simple vicinal aminoalcohols, derived from common α-amino acids act as superior catalysts in the cross-aldol reaction of isatins with ketones and leucinol was identified as the catalyst of a choice. However, although readily available from α-amino acids and therefore relatively cheap, high loading (20 mol % of the catalyst) was still needed. High catalyst loading is in general a common problem of organocatalysed aldol reactions, typically over 10 mol % and sometimes even up to 50 mol % of the catalyst is needed. Therefore the design and development of new organocatalysts aimed at lowering the loading and improving the turnover and recovery of the catalyst is required.

In 2008, Nakamura and co-workers reported on the sulfonamide catalysts **360**, which they used in the synthesis of convolutamydines, using 2 mol % and lower loading.[126] The most active of the sulfonamide catalysts screened were those with 2-thienyl **360** and 2-benzothienyl moiety **361** (Scheme **159**).



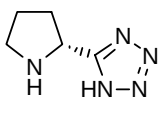
360



361

Scheme 159: Nakamura's catalysts.

Prior to this, sulfonamide derivates were known already to catalyse the aldol reaction, Ley and co-workers in 2004 developed the proline-based catalysts **362** and **363**,[127] Berkessel and co-workers reported that acylsulfonamides, such as **364** or **365**, catalysed the aldol reaction between acetone and *p*-nitrobenzaldehyde with enantioselectivity up to 98% and with just 5 mol % of catalyst loading.[128] The improved selectivity of these acylsulfonamide catalyst was attributed to a better shielding of one of the enantiotopic faces of the aldehyde by the aryl ring or by tighter hydrogen bonding in the List-Houk transition state.[129]



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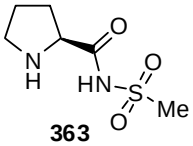

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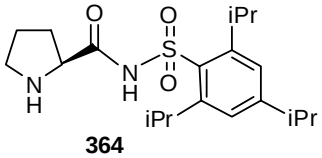

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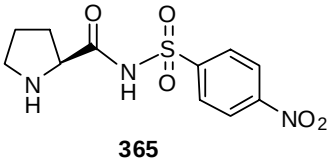
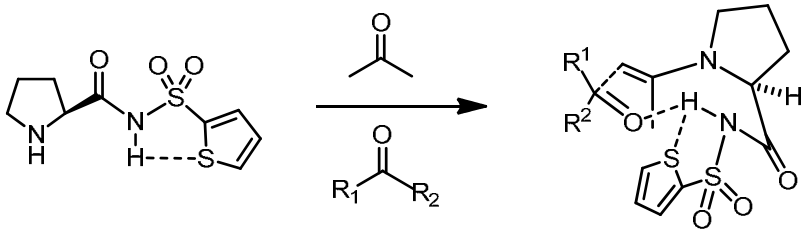


365

Ley **Berkessel**

Scheme 159: Ley's and Berkessel's sulfonamide catalysts.

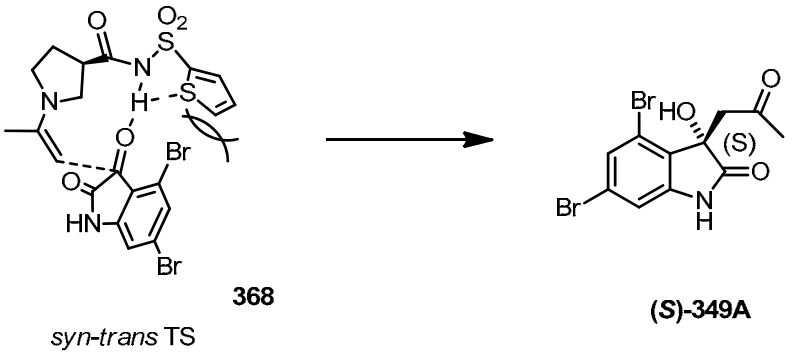
To overcome the difficulty of the enantioselective reaction between isatins as the ketone acceptors and acetone, Nakamura and co-workers designed heteroarylsulfonylprolinamides, where the transition state **367** is controlled by the intramolecular hydrogen bonding between the NH group of the sulfonamide and the heteroatom (sulfur or oxygen) of the heteroaryl group (**Scheme 161**). The NH proton is quite acidic (with pKa similar to that of carboxylic acids) and coordinates strongly to the carbonyl group of the electrophile.



360 **367**

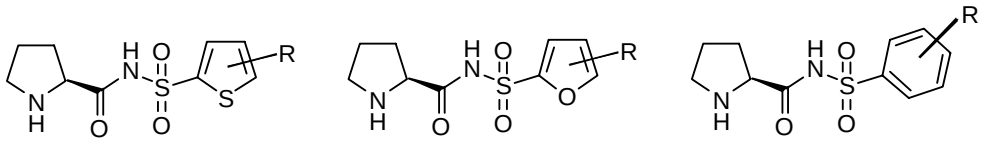
Scheme 161: Proposed transition state.

In accordance with the conclusions made by Tomasini and co-workers and based on DFT calculations, Nakamura suggested two plausible transition states: *anti-trans* and *syn-trans* (**Scheme 162**).[130]



Scheme 162: Proposed transition states.

The reaction using the thienyl catalyst **366** preferentially proceeds through the *anti-trans* TS to give (*R*)-**349**, because the other transition state, i.e., *syn-trans* (which naturally would give the opposite enantiomer) is destabilized by the steric repulsion between the 4-bromo and 2-thienyl groups. Experiments clearly showed that the organocatalyst bearing thienyl (**366**) or furyl (**369**) moiety were superior to those with aryl (**370**), where such hydrogen bonding and thus this case of steric repulsion do not exist.



Scheme 163: Examples of the sulfonamide catalysts.

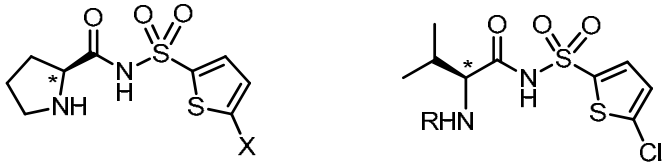
Nakamura's catalyst **360** exhibited high activity even at loading as low as 0.5%. This catalyst is now commercially available but very expensive. Solubility of these catalysts in common organic solvents is also an issue. Efficient recovery of the homogenous catalyst is

still a practical problem and there has not been much success in the development of aldol reaction organocatalysts anchored to a solid support, without a dramatic loss of their reactivity. However, Toru recently managed to entrap the *N*-sulfonamides in Montmorillonite by a cation exchange method. Although the reactivity slightly decreased, the catalyst still afforded convolutamydines with >90% ee even at 2 mol % loading.[131]

4.2 Results and Discussion

4.2.1 The Sulfonamide Catalysts

Inspired by Toru and Nakamura's *N*-sulfonamide methodology, we aimed at applying their catalysts and their analogues in the total synthesis of *Speranskatine A*, a natural product we prepared (*vide infra*), using the leucinol as a catalyst in the enantioselective step. We proved earlier that valine- and leucine-derived catalysts can often produce similar or even higher enantioselectivities than their proline-derived congeners or the more complex analogues with additional chiral centres.[132] Therefore, it was of interest to find out if this was the case here as well, by employing the valine analogues of Nakamura's proline *N*-sulfonamide catalysts. Hence, besides making the analogue of the original **371**, we set out to investigate the efficiency of sulfonamides **372** and **373**. Since Nakamura and Toru have shown that the additional substituent of the thiophene moiety of the catalysts **360** did not affect the catalytic capability, we resolved to use α-halogenated (Cl or Br) thiophene unit, partly because the starting material was considerably cheaper and partly because the halogen represents a handle for possible future anchoring of the catalyst to a polymeric support or polyfluorinated tag.

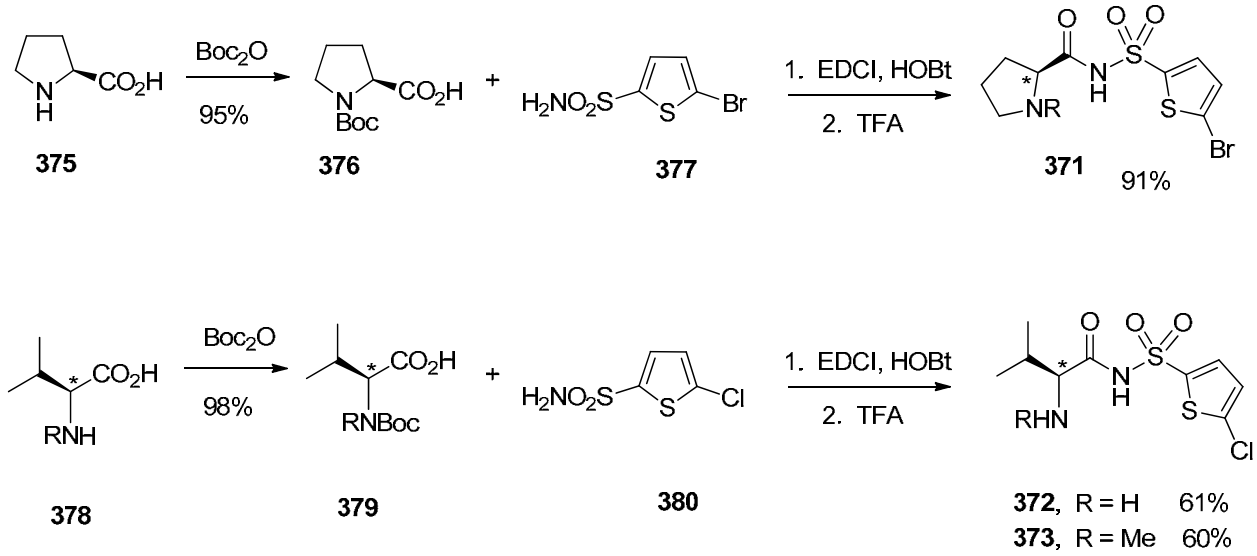


360, X = H (Nakamura)
371, X = Br

372, R = H,
373, R = Me

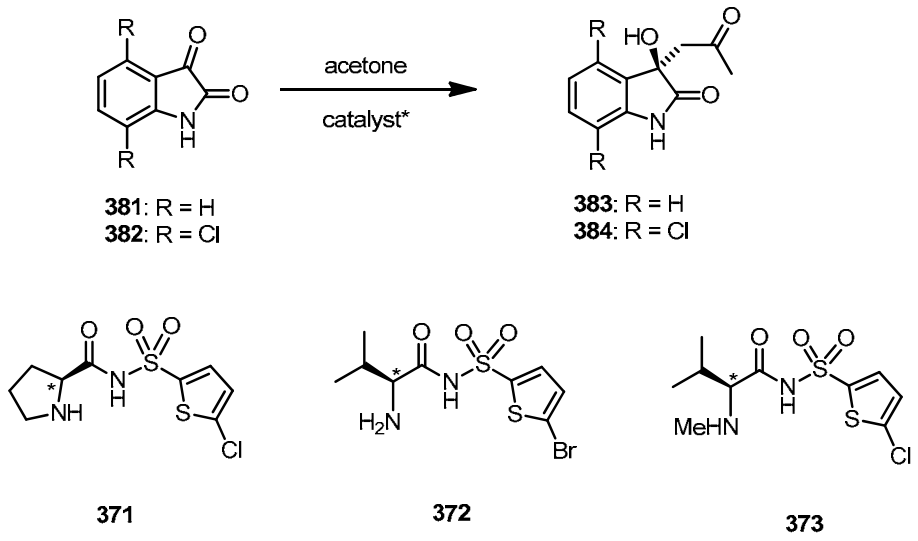
Scheme 164: Our analogues of the Nakamura's catalyst.

The new catalysts were synthesized in a straightforward manner from proline, valine, and *N*-methylvaline respectively, via Boc protection of the amino group and amidation with the corresponding sulfonamide, followed by Boc deprotection (**Scheme 165**).



Scheme 165: Synthesis of the sulfonamide catalysts.

We first applied the catalyst in the aldol reaction of isatins. Both the original proline catalyst 360 (or its halogenated analogue) **371** and its valine analogue **372** worked well, giving 94% and 95% ee, respectively, in the reaction of isatins with acetone (**Scheme 166** and **Table 23**). The *N*-methyl catalyst **373** gave only 35% ee and interestingly of the opposite enantiomer (in spite of the fact that, like the proline derivatives, the *N*-methyl valine catalyst is a secondary amine). This behaviour indicates fundamental differences in the transitions state.



Scheme 166: Aldol reaction of isatins with acetone, catalysed by the sulfonamide catalysts.

Table 23: Results of the aldol reaction of isatins with acetone, catalysed by the sulfonamide catalysts.

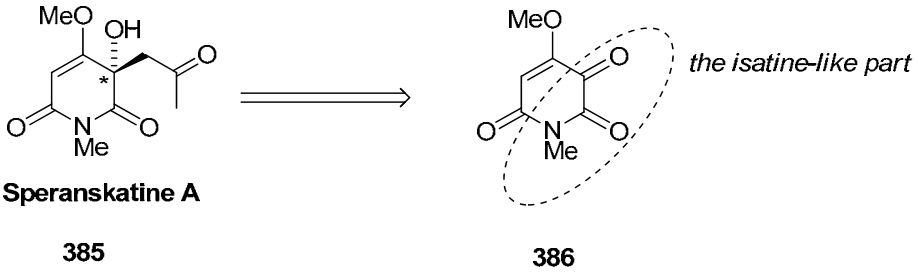
Entry	Catalyst	Isatin	Conversion (%)	Product (% ee)[a]
1	**371**•TFA	**381**	99	(*R*)-(+)-**383** (94)
2	**371**•TFA	**382**	98	(*R*)-(+)-**384** (95)
3	**372**•TFA	**382**	99	(*R*)-(+)-**384** (94)
4	**373**•TFA	**382**	53	(*S*)-(–)-**384** (35)

[a]Determined by chiral HPLC.

4.2.2 Synthesis of Speranskatine A

We then applied this methodology in the final step of the synthesis of *Speranskatine A*, an alkaloid isolated in 1995 from *Speranskia tuberculata*,[133] a Chinese plant, whose extracts are being used for the treatment of rheumatic arthritis, and inflammatory diseases,[134] and whose synthesis has not been reported to date.

As seen in the **Scheme 167**, the stereogenic centre can be constructed by an aldol reaction of ketone **386** with acetone. It is obvious that the amidic part and the activated keto group of compound **386** are quite similar to the isatine system and therefore could be expected that the organocatalysts successfully employed in the synthesis of convolutamydines could also be effective here.

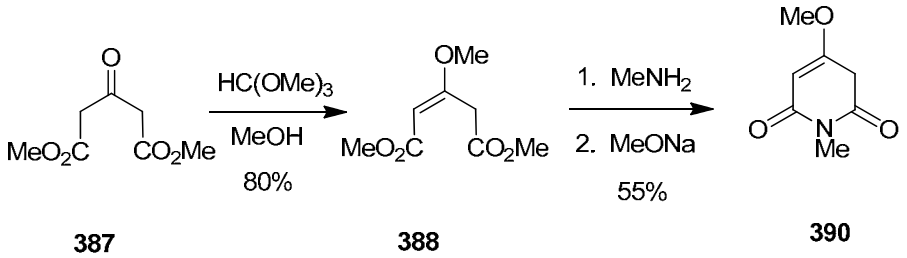


Speranskatine A

385 **386**

Scheme 167: Speranskatine can be made by aldol reaction of 386 with acetone.

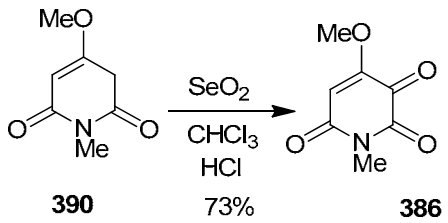
The starting ketone **386** was synthesized as follows: dimethyl oxoglutarate **387** was treated with trimethyl orthoformate to produce the enol ether **388**, and the ring was closed on by reaction with methylamine, according to the published procedure.[134] The diketone **390** was prepared from **388** in a good yield (60% overall).



387 388 390

Scheme 168: Synthesis of the intermediate 390.

The subsequent step required a great deal of optimization, as we run into difficulties trying to oxidize the diketone **390**. Selenium dioxide, usually the catalyst of a choice for oxidation of allylic methylene groups did not seem to work at all at first, using published conditions for similar systems. Various other oxidizing reagents, such as $KMnO_4$, HNO_3, $PhI(OAc)_2$, DMP, IBX, $(AcO)_4Pb$, and $K_2S_2O_8$, also failed to give the desired product too. Finally, it was discovered by serendipity that oxidation with SeO_2, carried out at room temperature in chloroform acidified with a trace of concentrated hydrochloric acid, afforded the desired ketone in 73% yield after purification (**Scheme 169**).

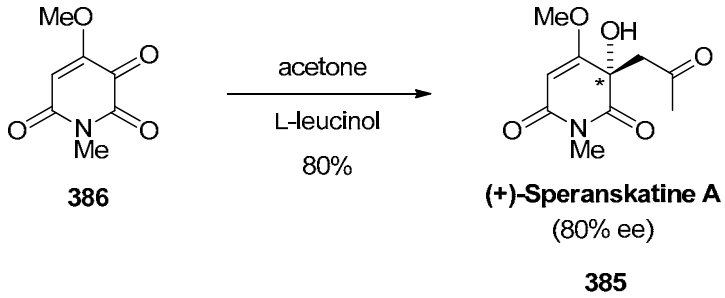


390 386

Scheme 169: Successful oxidation of 390.

Not surprisingly, proline failed to catalyse the aldol reaction completely, and only the starting material was isolated. On the other hand, our first attempts to perform the aldol reaction of ketone **386** with acetone, using the conditions previously optimized for isatins (20 mol% of L-leucinol as a catalyst, dichloromethane with a trace of water as a solvent, 20 °C) resulted in a complete conversion of the starting activated ketone into the aldol product with 66% ee (**Scheme 170**). Upon decreasing the temperature, enantioselectivity did not improve and conversion dropped drastically. When the temperature was increased up to 37 ^oC, 72% ee was attained after 1 day. In the next attempt, rather than adding the catalyst to the solution of ketone **386** in the solvent, a solution of ketone **386** in CH_2Cl_2 was added dropwise over a period of 2 h to a mixture of L-leucinol, acetone, and CH_2Cl_2 in the presence of a trace amount of water and the results turned out to be rather surprising: One hour after the

dropwise addition, the analysis of an aliquot showed 28% ee (20% conversion). After 6 h, the ee increased to 58% (45% conversion) and finally reached 80% ee within 36 h (98% conversion). These observations are discussed in detail in the chapter **4.2.4.**

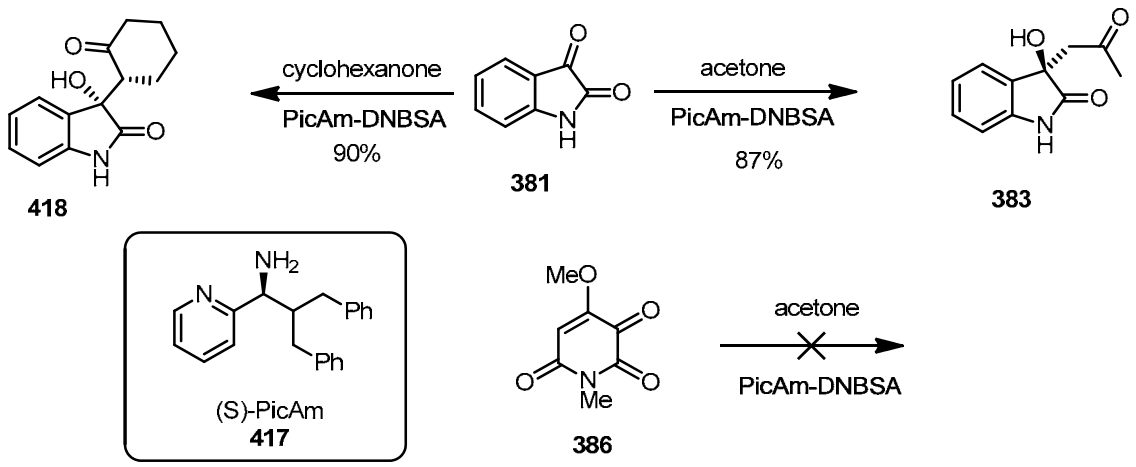


Scheme 170: The aldol reaction to form the Speranskatine A.

Toru and Nakamura's sulfonamides, although being very enantioselective in the aldol reaction with isatins**,** catalysed the reaction of ketone **386** to afford *Speranskatine A* efficiently but exhibited much lower enantioselectivities (**371** and **372** gave 30% ee each at room temperature, which was increased to 53% ee at –20 ^{o}C, at the expense of conversion). The *N*-methylvaline catalyst **373** then gave practically racemic product (3% ee). Further decreasing the temperature did not have any effect on the enantioselectivity.

The tripeptide catalyst H-Pro-Pro-Asp-NH_2, developed by Wennemers,[135] afforded the non-natural enantiomer of *Speranskatine A* with 41% ee at room temperature. Upon lowering the temperature to 0 or -20 ^{o}C, respectively, no reaction took place.

Finally, the salt of (*S*)-PicAm (**417**) and 3,5-dinitrobenzenesulfonic acid (DNBSA), recently developed by Nugent as a new organocatalyst with a primary amino group, [136] catalysed the reaction of isatin with acetone, affording (*S*)-**383** (62% ee), whereas the reaction of isatin with cyclohexanone, catalysed by **417**•DNBSA, produced (3*S*,2'*R*)-(-)-**418** (44% ee) as a single diastereoisomer (all at room temperature, **Scheme 171**). However, treatment of **386** with acetone to afford the *Speranskatine A* did not give any notable conversion.



Scheme 171: Reaction of isatine with acetone and cyclohexanone catalysed by PicAm.

These findings leave L-leucinol as a superior catalyst in the enantioselective step of synthesis of *Speranskatine A*, not only because it exhibited the highest enantioselectivity but also as one which promotes the formation of the natural *(+)-Speranskatine A*.

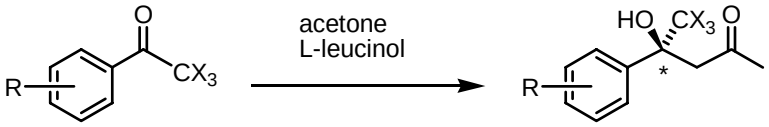
The absolute configuration of *Speranskatine A* has been deduced to be (*S*)-(+)-**385** from the way of its formation in relation to Convolutamydine A.

4.2.3 α-Trifluoromethyl Ketones in Aldol Reactions

As we stated at the beginning of the chapter, in a successful aldol reaction, one of the partners should be non-enolizable, and bear an activating group, such as CF_3. And because of the medicinal importance of tertiary alcohols with CF_3 substituents, and to further explore the applicability of aminoalcohols in this catalytic ketone-ketone aldol reaction, we screened the reactivity of acetone with a set of non-enolizable ketones bearing the activating trifluoromethyl group; in all cases, L-leucinol (20 mol%) was employed as a catalyst (**Scheme 172**). High yields and good enantioselectivities were attained, however, a slightly higher temperature (37 ^{o}C) was required to accelerate the reaction to a practical level. Under the same conditions, the thiophene derivative **403** underwent the reaction with good enantioselectivity, whereas the corresponding pyrrole analogue afforded only an a complex polymeric mixture. 3-Trifluoroacetyl indole did not react (~1% conversion). It was therefore acetylated in order to further decrease the electron density and increase reactivity towards the nucleophilic attack. Indeed, the corresponding acetyl derivative **404** afforded the tertiary alcohol **407** with 46% ee.

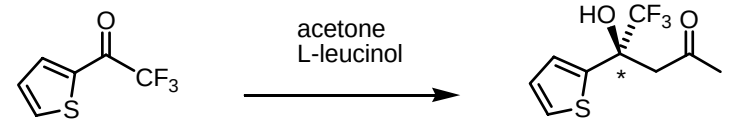
By contrast, enolizable aromatic ketones ArCOMe (Ar = Ph and 4-$NO_2C_6H_4$) proved practically inert, whereas the $PhCH_2COCF_3$ was fully converted into the corresponding aldol product, which however turned out to be racemic.

The absolute configuration of the tertiary alcohols **397**-**402** and **406**-**408**, has not been established by X-ray crystallography, it has only been deduced to be as drawn in the **Scheme 172**, from the way of their formation in relation to the analogous reaction of acetone with isatins.

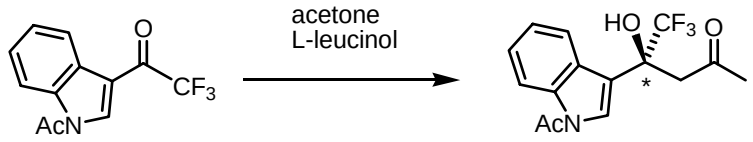


391 R = H, X = F
392 R = H, X = Cl
393 R = 4-F, X = F
394 R = 3-F, X = F
395 R = 4-Cl, X = F
396 R = 3-MeO, X = Cl

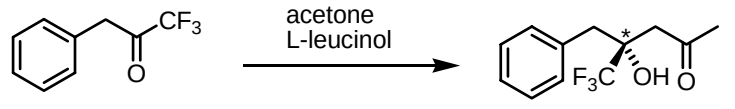
397 (85%, 77% ee)
398 (70%, 64% ee)
399 (86%, 82% ee)
400 (86%, 73% ee)
401 (84%, 78% ee)
402 (72%, 66% ee)



403 → **406** (79%, 82% ee)



404 → **407** (76%, 46% ee)



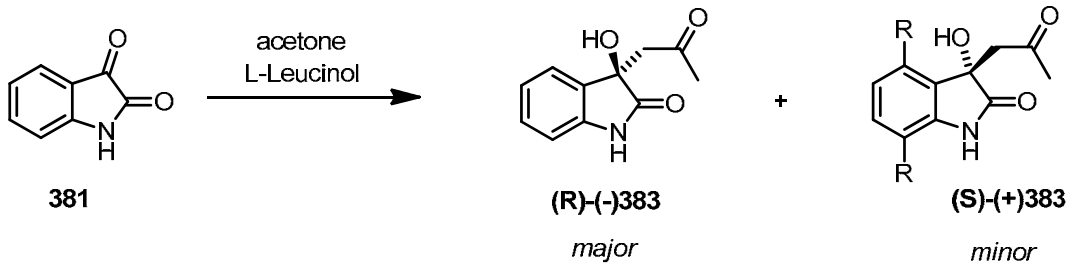
405 → **408** (72%, 0% ee)

Scheme 172: α-Trifluoromethyl ketones in aldol reactions.

4.2.4 The Unusual Enantioselectivity Build-up During Leucinol-Catalysed Aldol Reactions

*This part of the project was completed with the assistance of **Dr. Mikhail Kabeshov**, who performed the quantum calculations.*

Intrigued by the unusual enantioselectivity build-up in the aldol reaction of acetone with isatins (in the synthesis of *Convolutamydine A*) and ketone **386** (in the synthesis of *Speranskatine A*) we set to investigate this transformation in more detail, using isatin and acetone as model substrates (**Scheme 173**).



Scheme 173: Model reaction for the mechanistic studies.

At the initial stage of the reaction, the both enantiomers were formed approximately with the same rate, only after 20-30 minutes, one of the enantiomers began to dominate, whereas the concentration of the other one remained unchanged from that point (**Figure 1**).

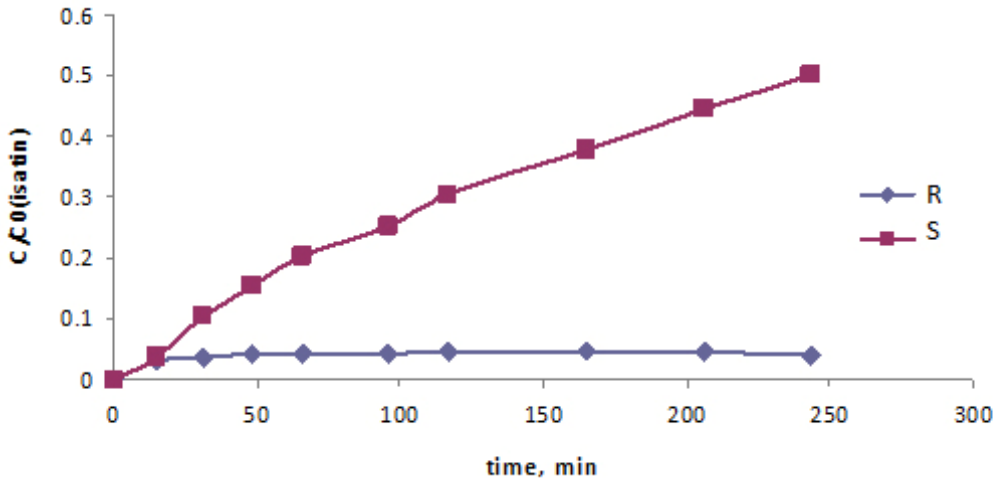
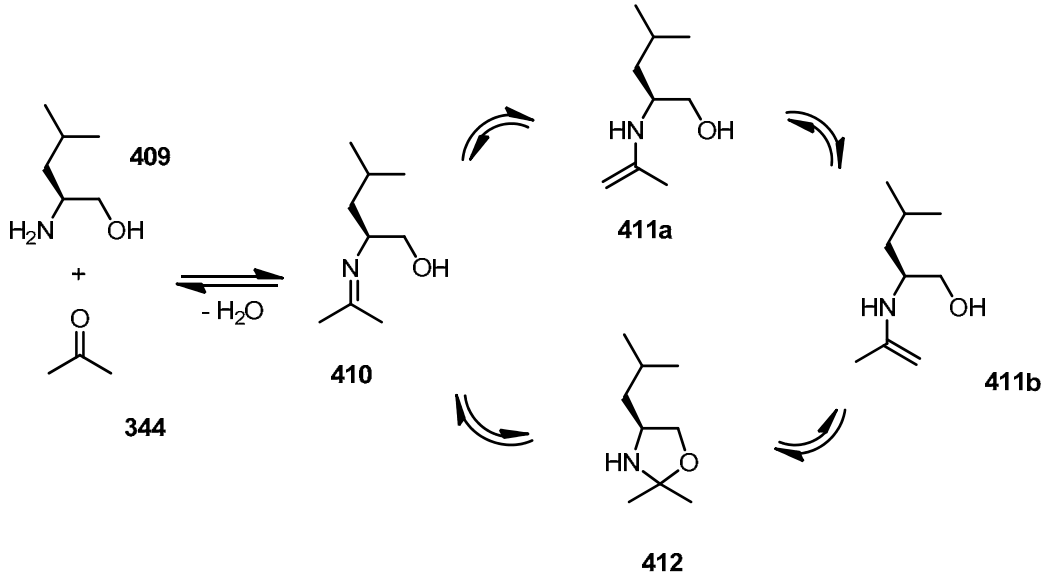


Figure 1: Relative concentration of *R* and *S* enantiomer of 383, depending on the reaction time.

The aldol reaction of isatin **381** with acetone in the presence of L-leucinol (**409**) (20 mol%) has been found by us to be first-order in **381**.[132] We have also demonstrated the key importance of the primary amino group and the hydroxyl and have shown the linear correlation between the enantiopurity of leucinol and that of the product **383** (after full conversion), which indicates that only one molecule of the catalyst is likely to be involved in the stereo-discriminating step.[132] Furthermore, formation of species **410-412** was proposed by us as a result of mixing acetone and leucinol in $CDCl_3$ and monitoring the mixture by NMR (**Scheme 174**).[132] This study revealed a gradual disappearance of leucinol at the expense of a concomitant build-up of oxazolidine **412**, reaching completion within 2 h at 37 ^oC; no other species could be detected during this process.



Scheme 174: Possible products of the reaction of leucinol with acetone.

Isatin **381** was found to catalyze the latter formation of oxazolidine **412**, which was then complete within several minutes at room temperature. On the other hand, the isolated oxazolidine **412** proved to be unstable in the absence of an excess of acetone, as its solution in wet $CDCl_3$ slowly decomposed back to acetone and leucinol, presumably via enamines **411** and/or imine **410** (ca 50 % conversion within 24 h).

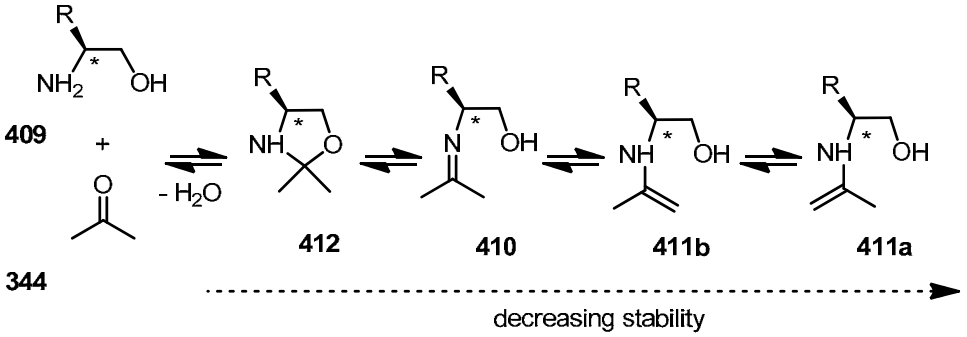
Oxazolidine **412** was found to catalyze the aldol reaction of isatin **381** with acetone in $CHCl_3$ at 37 °C as effectively as leucinol, with the same rate constant (at 20 mol% catalyst loading). This observation is in a full agreement with the Gschwind study,[137] in which she

showed that the analogous oxazolidinone (derived from proline) generates the reactive enamine.

In CH_2Cl_2, the reaction catalysed by oxazolidine **412** proved to be 10 times slower than that in $CHCl_3$, and 3 times slower when catalyzed by leucinol **409**. This effect was attributed to the dependence of the rate of the equilibration **411** ⇆ **412**, which is apparently higher in $CHCl_3$ than that in CH_2Cl_2.[132] Nevertheless, the final enantiomeric excess of the product turned out to be unaffected.

Autocatalysis by the product **383** was ruled out by a control experiment, carried out in the presence of (*S*)-(-)-**383** (20 mol%), added at the onset of the reaction. The latter additive neither catalysed the reaction nor it altered the enantiomeric ratio of the gradually produced **383** when L-leucinol was also added to the mixture.[132]

To further corroborate experimental observation and obtain a complementary information, we studied the mechanism of the latter aldol reaction by DFT calculations using Gaussian 09.[138,139] The quantum chemical calculations revealed the energies of the individual molecules involved along the multistep sequence (**Scheme 175**): thus, oxazolidine **412** was identified as the most stable species, whereas imine **410** was predicted to be less stable by ~5 kcal mol^{-1}. Most significantly, the *syn*-enamine **411b** was found be more stable than the *anti*-rotamer **411a** by ~2 kcal mol^{-1}.*



Scheme 175: Relative stability of the species formed from the reaction of leucinol and acetone.

The calculations further suggested that a molecule of water is required for the formation of the enamine **411**, as no energetically accessible transition state could be found in

*Geometries of all structures were optimized in vacuum at the B3LYP/6-31g(d,p) level. IRC analysis was performed to unambiguously assign located transition states to the reaction pathways studied. Electronic energies were obtained by performing single point calculations at the TPSSh/cc-PVTZ level with CPCM/UAKS solvation model. Enthalpies are reported as Δ*E* + zero point vibrational energy (ZPVE) corrections at 0 K + thermal corrections at 298 K and Gibbs free energies were obtained as Δ*G* = Δ*H* – TΔ*S* at 298 K (Kabeshov, M. unpublished results).

its absence (see **Scheme 176**, transition states **414** and **415)**. Thus, transition states **414** and **415** were identified for the conversion of oxazolidine **412** into enamines **411b** and **411a**, respectively, where the former species (*syn* rotamer) is lower in energy by 1.8 kcal mol^{-1} (**Scheme 174**). Furthermore, the transitions state **414**, leading to **6**, is preferred kinetically, as the activation energy for its formation is lower by 2.9 kcal mol^{-1} than that of **415**.

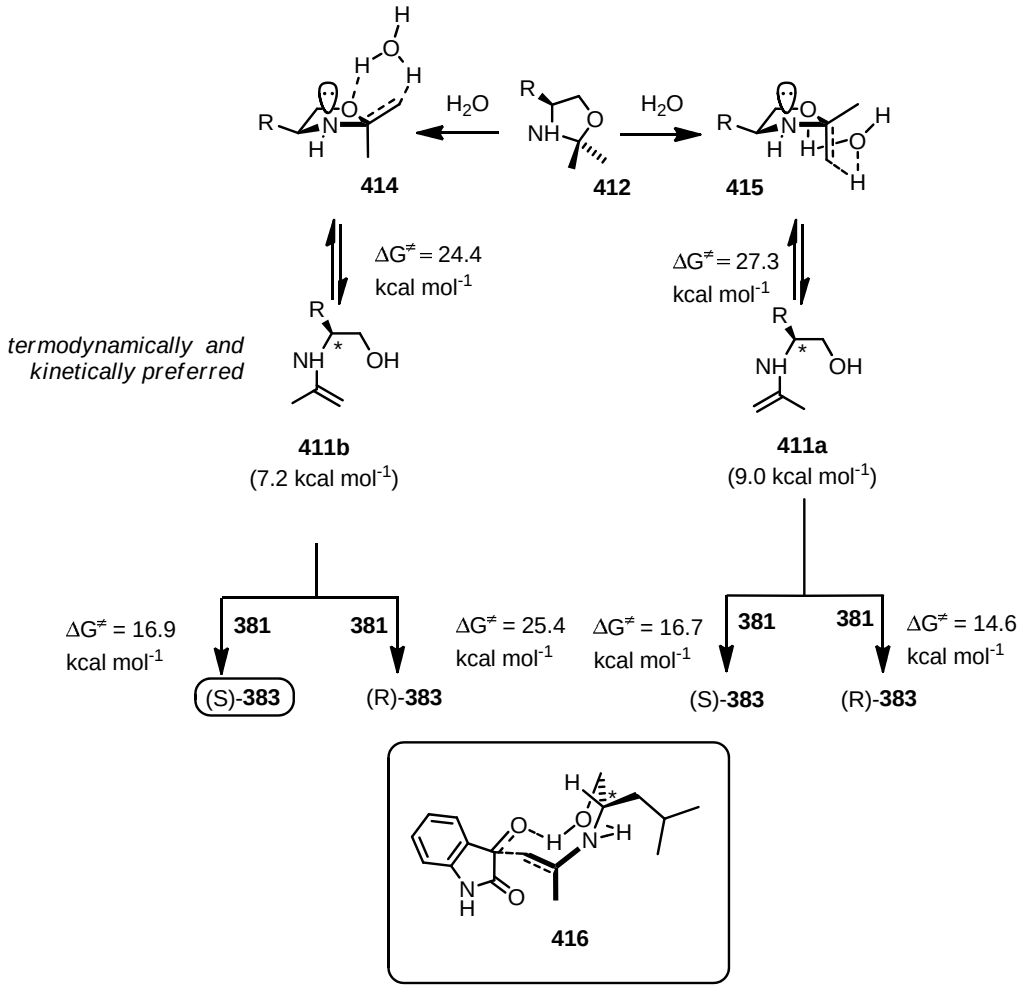
Based on these results, enamine formation can be expected to proceed with very high selectivity in favour of **411b**. Furthermore, the reaction of **411b** with isatin (**381**) should proceed via TS **416**, giving rise to (*S*)-**383**, since the pathway toward its enantiomer from the same enamine would require overcoming an activation barrier that is higher by 8.5 kcal mol^{-1}.

By contrast, the *anti*-enamine **411a** (disfavoured both kinetically and thermodynamically) would predominantly produce (*R*)-**383**, as the corresponding transition state is preferred by 2.1 kcal mol^{-1} over that generating (*S*)-**383**. In other words, the *syn*-enamine **411b** should produce mainly (*S*)-**383**, whereas its *anti*-rotamer **411a** would predominantly afford (*R*)-**2a**. This shows that selective formation of syn-enamine **411b** over its counterpart **411a** plays a crucial role in the catalytic system.

Furthermore, the temperature effect, observed for the analogous formation of *Speranskatine A* (+)-**385** from ketone **386** also supports this scenario: here, at 20 ^{o}C, the enantioselectivity was lower (66% ee) than that at the optimal 37 ^{o}C (72% ee; *vide supra*), which is compatible with the faster established equilibration at higher temperature (a prerequisite for the thermodynamic control).

This analysis can also account for the experimentally observed initial formation of a nearly racemic product, resulting from a different catalytic process (possibly using free leucinol as an amine base). As soon as all the leucinol is consumed by conversion into oxazolidine **412**, the reaction follows the scenario shown in **Scheme 176**, and (*S*)-**383** is produced almost exclusively.

A substantial kinetic isotope effect[140] (k_H/k_D = 2.7) was observed for the reaction of isatin **381** with d_6-acetone, implying that the enamine formation is featured in the kinetic law. This is in line with the calculations, which predict a significantly higher activation energy for the formation of the *syn/anti*-enamines **411** than that for their subsequent reaction with isatine **381** (24.4 kcal mol^{-1} and 27.3 kcal mol^{-1} vs 16.9 kcal mol^{-1} and 14.6 kcal mol^{-1}, respectively; see **Scheme 176**).



Scheme 176: Proposed mechanism for the formation of 383.

In conclusion, L-leucinol **409**, a primary amino alcohol, has been shown to serve as an efficient, enantioselective organocatalyst for the cross-aldol reaction of isatin **381** (an activated, non-enolizable ketone) with acetone (an enolizable, less electrophilic ketone). The reaction proceeds at room temperature with a trace of water in CH_2Cl_2, at 10-20 mol% catalyst loading. Mechanistic and computational studies allowed to identify oxazolidine **412** as the resting state of the catalyst and demonstrated the key role of water in its conversion into the reactive enamine. Calculations further suggest that the *syn*-enamine **411b** is generated preferentially and then reacts with isatin (**381**) to afford the aldol product (*S*)-(-)-**383** via TS **416**.

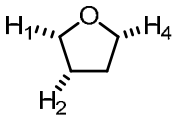
It is pertinent to note that the preferential formation of the *syn*-enamine **411a** stands in sharp contrast to the well established *anti*-enamine generation from proline and could thus be regarded as a characteristic feature of primary amino alcohols.

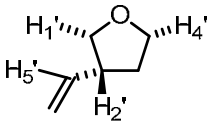
5 Experimental Part

5.1 General Methods.

Melting points were determined on a Kofler block and are uncorrected. Optical rotations were recorded in $CHCl_3$ unless otherwise indicated, with an error of $\leq \pm 0.1$. The $[\alpha]_D$ values are given in 10^{-1} deg cm^3 g^{-1}. The NMR spectra were recorded in $CDCl_3$, ^1H at 400 MHz, ^{19}F at 377 MHz and ^{13}C at 101 MHz with chloroform-*d*$_1$ (δ 7.26, ^1H; δ 77.16, ^{13}C) and chlorotrifluoromethane (δ 0.00, ^{19}F) as internal standards, unless stated otherwise. Various 2D-techniques, DEPT and NOE experiments were used to establish the structures and to assign the signals. The IR spectra were recorded in NaCl disc, the mass spectra (EI, CI or FAB) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation unless otherwise indicated. All reactions were performed under an atmosphere of dry argon in oven-dried glassware. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR spectra. The enantiomeric excesses were determined by HPLC equipped with diode array detector, or by GC. The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures.

All solvents and reagents for the reactions were of reagent grade and were dried and distilled under argon immediately before use as follows: chloroform from phosphorus pentoxide, Hünig's base and acetonitrile from calcium hydride, THF and diethyl ether from sodium. Petroleum ether refers to the fraction boiling in the range 40-60 °C. Dichloromethane was obtained from the Pure-Solv™ Solvent Purification System (Innovative Technology).





Individual NMR spectra of substituted tetrahydrofurans were obtained from the mixture of syn and anti forms in $CDCl_3$ using a selective 1D TOCSY experiment, which, together with a traditional 2D COSY and HMQC, provided an unambiguous assignment of the NMR signals. Of particular interest was the stereochemistry of the protons H_1, H_2 and H_4 and H_1', H_2' and H_4', in each molecule. A series of selective 1D NOESY experiment identified clear through-space NOE correlations which allowed assignment of the relative stereochemistry.

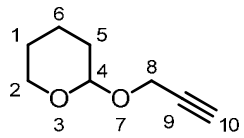
A clear NOE from H_1' to H_4' and H_5'(alkene) showed that H_1' and H_4' are *syn*-orientated, and that H_1' and the alkene are also *syn*, a small asymmetric signal for H_2' indicated an indirect NOE to H_2', thus H_2' must be anti to both H_1' and H_4'. This arrangement was confirmed by selective irradiation of H_2', which produced an asymmetric indirect NOE response for H_4'. A clear NOE from H_2 to H_1 showed that H_2 and H_1 are *syn*-configured. A clear NOE from H_4 to H_1 showed that H_4 and H_1 are *syn*-related.

The chemical shift differences of H_1/H_1' and H_2/H_2' in the *syn* and *anti* forms are larger than for any other protons in the molecules and this provides circumstantial evidence that suggests that the difference in stereochemistry may be located in this part of the molecule. The multiplets of each proton in the two forms are remarkably similar, which indicates a particularly well known difficulty of applying the Karplus curve to 5-membered rings, where the pseudo-*trans*(H_1'-H_2') and pseudo-*gauche*(H_1-H_2) arrangement of protons can produce similar couplings.

Selective 1D TOCSY. Using the "selmlgp" pulse program, the NMR signal of H_2 was selectively irradiated using a 40 ms 180° Gauss1.1 shaped-pulse of 70 dB, a M-LEV-17 mixing time of 200 ms was sufficient to allow the propagation of the $^3J_{H\text{-}H}$ couplings to all multiplets within the molecule. The NMR signal of H_2' was selectively irradiated using a 40 ms Gauss1.1 pulse of 70 dB, a M-LEV-17 mixing time of 200 ms was sufficient to allow the propagation of the $^3J_{H\text{-}H}$ couplings to all multiplets within the molecule. Zero-quantum coherences were suppressed.

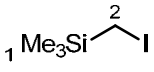
Selective 1D NOESY. The "selnogp" pulse program was used, with a selective Gauss5 profile, using a 40 ms 180° pulse of 70 dB with single pulsed-field-gradient echo, a mixing time of 0.4 s allowed NOE transfer, with purge gradients used to remove transverse magnetisation.

5.2 Asymmetric Allylations



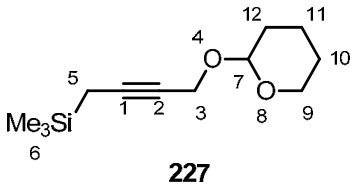
223

(223). Propargyl alcohol (40.79 g, 0.73 mol) was added in one portion to 3,4-dihydro-2*H*-pyran (64.20 g, 0.73 mol) at 0 °C, followed by *p*-toluenesulfonic acid (4.31 g, 0.02 mol) in small portions over the period of 20 min while stirring vigorously. The reaction mixture was stirred at 0 °C for 2h, then diluted with petroleum ether (100 mL), and washed with a saturated $NaHCO_3$ solution (2 x 50 mL) and brine (2 x 50 mL) and dried ($MgSO_4$). Petroleum ether was evaporated *in vacuo* and the crude product was purified by distillation at a reduced pressure (88-92 °C / 60 torr) to give **223** (73.43 g, 72%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.40-1.82 (m, 6H, H-1, H-5, H-6), 2.35 (s, 1H, H-10), 3.42-3.52 (m, 1H, H-2), 3.74-3.82 (m, 1H, H-2), 4.16 (d, $^2J_{H\text{-}H}$ = 15.4 Hz, 1H, H-8), 4.24 (d, $^2J_{H\text{-}H}$ = 15.4 Hz, 1H, H-8), 4.74-4.78 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_2, C-6), 24.3 (CH_2, C-1), 29.2 (CH_2, C-5), 53.0 (CH_2, C-6), 61.0 (CH_2, C-2), 73.0 (CH, C-10), 78.8 (C, C-9), 95.83 (CH, C-4) consistent with the literature data.[141]



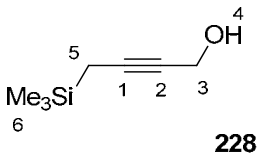
225

(225). (Chloromethyl)trimethylsilane (4.54 g, 37.03 mmol) was added in one portion to a solution of sodium iodide (15.00 g, 100.1 mmol) in a freshly distilled acetone (100 mL) an the reaction mixture was stirred at ambient temperature for 24 h under Ar. Almost immediately, a white precipitate of NaCl was formed that thickened over time, eventually hindering agitation. The cooled mixture was filtered through a medium-porosity fritted funnel and the solid material was washed with acetone (200 mL). Acetone was then removed from the filtrate by fractionation through a 20 cm Vigreaux column. The apparatus was then cooled and pentane (50 mL) and water (100 mL) were poured down the Vigreaux column into the distillation flask. The mixture was transferred into a separating funnel, using 100 mL of water and 200 mL of pentane, shaken and separated. The aqueous layer was extracted with pentane (3 x 50 mL) and the combined organic layers were washed with 10 % aqueous sodium thiosulfate (1 x 50 mL) to remove free iodine, and then with brine (1 x 50 mL). The pentane solution was dried ($MgSO_4$), filtered, and concentrated *in vacuo* using a room-temperature bath. The residue was distilled (20 cm Vigreaux column, b.p. 138–140 °C) to give **225** (5.18 g, 65%) as colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (s, 9H, H-1), 2.00 (s, 2H, H-2); ^{13}C NMR (100 MHz, $CDCl_3$) δ -18.3 (CH_2, C-1), 2.0 (CH_3, C-2) consistent with the literature data.[142]



227

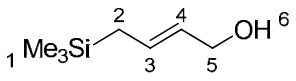
(227). An oven-dried 250 mL round bottom flask was charged with 2-(2-propynyl)tetrahydro-2*H*-pyran (**9**) (1.49 g, 10.61 mmol) and dry THF (50 mL) and the mixture was cooled to -30 °C under argon. *n*-BuLi (1.6M solution in hexane, 7.30 mL, 11.68 mmol) was then added dropwise over a period of 30 min while stirring and the mixture was stirred at the same temperature for an additional 15 min and then at 0 °C for another 20 min. (Iodomethyl)trimethylsilane (2.50 g, 11.68 mmol) was then added slowly *via cannula* over a period of 5 min and the mixture was stirred at 0 °C for another 10 minutes. The reaction vessel was then wrapped in an aluminium foil and heated to 55 °C for 3 h under reflux under an argon atmosphere. The mixture was then diluted with hexane (150 mL) and ethyl acetate (50 mL) and washed with water (1 × 50 mL) and brine (1 × 50 mL). The solvents were evaporated to give crude **227** (2.00 g, 83%) as a yellow oil, which was submitted to the next step without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 9H, H-6), 1.50 (t, $^{5}J_{H\text{-}H}$ = 2.5 Hz, 2H, H-5), 1.50-1.64 (m, 4H, H-10, H-11), 1.68-1.88 (m, 2H, H-12), 3.47-3.56 (m, 1H, H-9), 3.81-3.87 (m, 1H, H-9), 4.21 (dt, $^{2}J_{H\text{-}H}$ = 15.5 Hz, $^{5}J_{H\text{-}H}$ = 2.5 Hz, 1H, H-3), 4.28 (dt, $^{2}J_{H\text{-}H}$ = 15.5 Hz, $^{5}J_{H\text{-}H}$ = 2.5 Hz, 1H, H-3), 4.84 (t, $^{3}J_{H\text{-}H}$ = 3.5 Hz, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.9 (CH_3, C-6), 7.4 (CH_2, C-5), 19.4 (CH_2, C-11), 25.6 (CH_2, C-10), 30.5 (CH_2, C-12), 54.9 (CH_2, C-3), 62.2 (CH_2, C-9), 74.7 (C, C-2), 84.7 (C, C-1), 96.5 (CH, C-7) consistent with the literature data.[80]



228

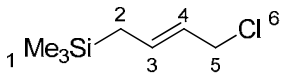
(228). A solution of PTSA (22.7 mg, 0.12 mmol) and pyridine (9.4 mg, 0.12 mmol) in ethanol (4 mL) was added in one portion to a solution of trimethyl(4-tetrahydro-2*H*-pyran-2-yloxy-2-butynyl)silane (**228**) (135 mg, 0.60 mmol) in a mixture of ethanol (2 mL) and water (1.2 mL) while stirring and the reaction mixture was stirred at 55 °C for 24 h. Ethanol was then evaporated *in vacuo*, the residue was diluted with petroleum ether (20 mL) and thoroughly washed with half-saturated brine (4 × 10 mL) and then with brine (1 × 10 mL). The organic solution was dried (Na_2SO_4) and evaporated to afford 4-(trimethylsilyl)-2-butyn-1-ol (83 mg, 98%) as a viscous yellowish oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 9H, H-6), 1.48 (t, $^{5}J_{H\text{-}H}$= 2.7 Hz, 2H, H-5), 4.22 (t, $^{5}J_{H\text{-}H}$= 2.7 Hz, 2H, H-

3); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.0 (CH_3, C-6), 6.5 (CH_2, C-5), 52.0 (CH_2, C-3), 77.0 (C, C-2), 82.6 (C, C-3) consistent with the literature data.[143]



229

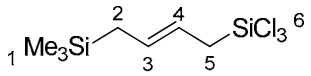
(229). A solution of 4-(trimethylsilyl)-2-butyn-1-ol (1.90 g, 13.35 mmol) in dry THF (10 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (1.52 g, 40.05 mmol) in dry THF (10 mL) at 0 °C under argon and the resulting mixture was stirred for another 10 min and then refluxed for 3 h. The mixture was then cooled with an ice-water bath, cold water (5 mL) was added dropwise, and then a 20 % NaOH aqueous solution (5 mL) and another portion of water (15 mL). The mixture was filtered through a short plug of sand and Celite, diluted with water (20 mL) and extracted with dichloromethane (5 × 50 mL). The organic phase was washed with brine (1 × 50 mL), dried ($MgSO_4$), and evaporated *in vacuo* to furnish a yellowish oil. The crude product was purified by distillation at reduced pressure (89-92 °C / 26 torr) to afford **229** (923 mg, 48 %) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H, H-1), 1.49 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, H-2), 4.06 (d, $^3J_{H\text{-}H}$ = 5.1 Hz, 2H, H-5), 5.44-5.56 (m, 1H, H-3), 5.64-5.74 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.9 (CH_3, C-1), 22.9 (CH_2, C-2), 64.1 (CH_2, C-5), 127.7 (CH, C-3), 130.3 (CH, C-4) consistent with the literature data.[144]



230

(230). A suspension of *N*-chlorosuccinimide (1.95 g, 14.6 mmol) in dichloromethane (10 mL) was added to a solution of 4-(trimethylsilyl)-2-buten-1-ol (**11**) (1.39 g, 12.2 mmol) and triphenylphosphine (3.20 g, 12.2 mmol) in dry dichloromethane (20 mL) at 0 °C and the mixture was stirred at 5 °C under Ar and monitored by TLC (the reaction typically took several hours). The reaction mixture was then allowed to warm up to ambient temperature and then passed through a short plug of sand and Celite. Dichloromethane was carefully evaporated from the filtrate *in vacuo* without heating and the residue was diluted with dry ether (10 mL). This process induced the formation of a white precipitate, which was removed by filtration through a short plug of sand and Celite, and the filtrate was evaporated, again without heating. The crude product was purified by distillation at a reduced pressure (50-54 °C / 10 torr) to afford **229** (851 mg, 80%) as a colourless oil: ^{1}H

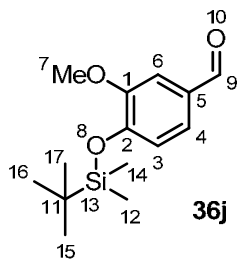
NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 9H. H-1), 1.44 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 2H, H-2), 3.97 (d, $^3J_{H\text{-}H}$ = 7.3 Hz, 2H, H-5), 5.35-5.44 (m, 1H, H-3), 5.66-5.76 (m, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.12 (CH_3, C-1), 22.8 (CH_2, C-2), 46.1 (CH_2, C-5), 124.1 (CH, C-3), 130.9 (CH, C-4); MS (CI-isobutane) *m/z* (%) 163/165 ($M+H^+$, 100/32), 127 (20); HRMS (CI-isobutane) *m/z* 162.0630 ($C_7H_{15}{}^{35}ClSi$, $M+H^+$, requires 162.0630).



1

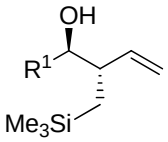
(1). A suspension of CuCl (1.00 g, 10.00 mmol) and powdered 4Å molecular sieves (2.00 g) in a mixture of dry Hünig's base (1690 mg, 13.1 mmol) and dry ether (200 mL) in an oven-dried flask was cooled to 0 °C under argon. (*E*)-1-Chloro-4-(Trimethylsilyl)-2-buten **(230)** (850 mg, 5.2 mmol) was added as a solution in diethyl ether (100 mL) *via cannula* in one portion, followed by a dropwise addition of trichlorosilane (1330 mg, 10.0 mmol) over a period of 20-30 min with vigorous stirring. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature until completion (ca 2 h). The progress of the reaction was monitored by ^{1}H NMR spectroscopy.[†] After completion, the precipitate was removed by filtration under argon, the filtrate was transferred into a micro-distillation apparatus, and ether was distilled off under an inert atmosphere. The distillation residue was usually dissolved in an appropriate solvent and used in the next step as such immediately. Alternatively, the crude product was purified by distillation under reduced pressure (90-92 °C / 8 torr) to give **1** as a colourless liquid (860 mg, 63%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.01 (s, 9H, H-1), 1.49 (dd, $^3J_{H\text{-}H}$ = 8.1 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 2H, H-2), 2.26 (dd, $^3J_{H\text{-}H}$ = 7.6 Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 2H, H-5), 5.18 (dtt, $^3J_{H\text{-}H}$ = 15.2 and 7.6 Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 1H, H-3), 5.57 (dtt, $^3J_{H\text{-}H}$ = 15.1 and 8.2 Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.8 (CH_3, C-1), 23.6 (CH_2, C-2), 29.4 (CH_2, C-5), 115.9 (CH, C-3), 132.4 (CH, C-4); MS (FAB-NOBA) *m/z* (%) 261 ($M+H^+$, 18), 228 (60), 226 (100), 221 (45); HRMS (FAB-NOBA) *m/z* 260.9849 ($C_7H_{16}{}^{35}Cl_3Si_2$, $M+H^+$, requires 260.9856).

[†] The conversion was checked using the following procedure: 0.05-0.1 mL of the crude reaction mixture was transferred *via cannula* into an oven dried NMR tube under a stream of argon, dry $CDCl_3$ was added and the ^{1}H NMR spectrum was recorded immediately.



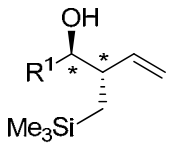
36j

(36j). Hünig's base (8.11 g, 110 mmol) was added to a solution of vanillin (7.61g, 50 mmol) in dry DMF (30 mL) and the resulting orange solution was stirred at room temperature for 5 min. TBDMSCl (8.29 g, 55 mmol) was added portion-wise in the course of 30 min and the mixture was stirred for another hour. The lemon-yellow reaction mixture was then cooled to 0° C and ice-cold water (100 mL) was added slowly and then diethyl ether (200 mL) and the mixture was stirred for 5 min. The organic layer was separated and the aqueous phase was extracted with diethyl ether (2×50 mL). The organic phases were combined and washed with a 10% aqueous solution of lithium chloride (2×50mL), saturated $NaHCO_3$ solution (2×50 mL) and finally brine (1×100 mL). The organic phase was dried ($MgSO_4$) and the solvent was evaporated *in vacuo* to afford the product **36j** as an yellowish oil, which was used without further purification (12.77 g, 96%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.19 (s, 6H, H-12, 14), 0.95 (s, 9H, H-15, 16, 17), 3.86 (s, 3H, H-7), 6.95 (d, $^3J_{H\text{-}H}$ = 7.7Hz, 1H, H-3), 7.35 (dd, $^3J_{H\text{-}H}$ = 7.8, 1.9 Hz, 1H, H-4), 7.40 (d, $^4J_{H\text{-}H}$ = 1.9 Hz, 1H, H-6), 9.89 (s, 1H, H-9); ^{13}C NMR (400 MHz, $CDCl_3$) δ -4.7 (CH_3, C-12, 14), 18.50 (C, C-11), 25.59 (CH_3, C-15, 16, 17), 55.44 (CH_3, C-7), 110.10 (CH, C-6), 120.71 (CH, C-3), 126.23 (CH, C-4), 130.94 (C, C-5), 151.34 (C, C-2), 151.63(C, C-1), 191.01 (C, C-8) in accordance with the literature data.[145]



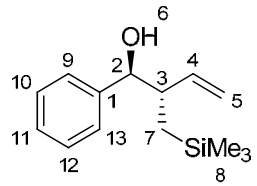
4

Method A: General procedure for the synthesis of racemic homoallylic alcohols 4a-k. DMF (280 mg, 3.8 mmol), Hünig's base (150 mg, 1.2 mmol), and the corresponding aldehyde (0.5 mmol) were added consecutively in this order to a solution of (*E*)-trimethyl[4-(trichlorosilyl)-2-butenyl]silane (**1**) (100 mg, 0.4 mmol) in MeCN (10 mL) at –20 °C and the reaction mixture was stirred at the same temperature overnight. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) at -20 °C and left to warm up to room temperature. The solid residue was filtered off, MeCN was evaporated, and the residue was dissolved in ether (40 mL) and the solution was washed with a saturated $NaHCO_3$ solution (1 × 30 mL) and brine (1 × 30 mL) and dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on a column of silica gel (2 × 25 cm) with a mixture of petroleum ether and AcOEt (98:2).



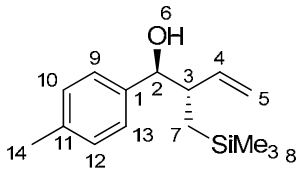
4

Method B: General procedure for the synthesis of enantio-enriched homoallylic alcohols 4a-4k. A solution of the chiral catalyst in an appropriate solvent (1 mL, see **Table 12** for details), Hünig's base (300 mg, 2.4 mmol), and the corresponding aldehyde (0.5 mmol) were added consecutively in this order to a solution of allyldisilane **1** (100 mg, 0.4 mmol) in the appropriate solvent (10 mL) at -78 °C. The reaction mixture was then transferred to a freezer (-35 °C). Upon reaching the full conversion (monitored by NMR spectroscopy), the reaction was quenched with a saturated aqueous $NaHCO_3$ solution (1 mL) and left to warm up to room temperature. The solid residue was removed by filtration, the solvent was evaporated, and the residue was dissolved in ether (40 mL) and the solution was washed with a saturated $NaHCO_3$ solution (1 × 30 mL) and brine (1 × 30 mL) and dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on a column of silica gel (2 × 25 cm) with a mixture of petroleum ether and AcOEt (98:2).



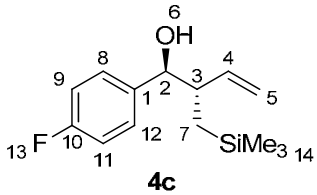
4a

4a was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F = 0.18, stains visualized by UV and PMA) to afford **4a** (88%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ −52.5 (*c* 1.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.09 (s, 9H, H-8), 0.43 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-7), 0.49 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 10.5 Hz, 1H, H-7), 2.25 (d, $^3J_{H\text{-}H}$ = 2.2 Hz, 1H, H-6), 2.37-2.47 (m, 1H, H-3), 4.30 (dd, $^3J_{H\text{-}H}$ = 7.8 Hz, $^2J_{H\text{-}H}$ = 2.1 Hz, 1H, H-2), 5.20 (dd, $^3J_{H\text{-}H}$ = 6.2 Hz, $^2J_{H\text{-}H}$ = 1.8 Hz, 1H, H-5), 5.22-5.25 (m, 1H, H-5), 5.63 (ddd, $J_{H\text{-}H}$ = 15.7, 9.3, and 6.2 Hz, 1H, H-4), 7.27-7.38 (m, 5H, H-9, 10, 11, 12, 13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.7 (CH_3, C-8), 18.2 (CH_2, C-7), 49.0 (CH,C-3), 78.8 (CH, C-2), 118.2 (CH_2, C-5), 127.4 (CH, C-11), 127.8 (CH, C-9, 13), 128.3 (CH, C-10, 12), 141.3 (C, C-1), 142.3 (CH, C-4); IR ν 3548, 3019, 2955, 2895, 2401, 1248, 1216 cm^{-1}; MS (CI-isobutane) *m/z* (%) 217 ($M+H^+$-H_2O, 100), 187 (10), 179 (18), 149 (5), 128 (10); HRMS (CI-isobutane) *m/z* 217.1414 ($C_{14}H_{21}Si$, $M+H^+$-H_2O, requires 217.1413); chiral HPLC (Chiracel IB column, hexane/2-propanol = 99.5:0.5, 1 mL/min) showed 93% ee (t_{major} = 13.5 min, t_{minor} = 15.9 min).



4b

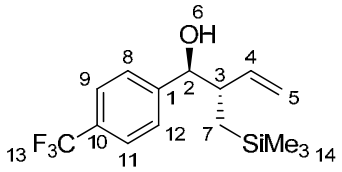
4b was prepared by method **A** / **B**. The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F = 0.23, stains visualized by UV and PMA) to afford **4b** (92%, >99% of *anti* diastereoisomer) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.09 (s, 9H, H-8), 0.40-0.51 (m, 2H, H-7), 2.20 (s, 1H, H-6), 2.35 (s, 3H, H-14), 2.37-2.47 (m, 1H, H-3), 4.25 (d, $^3J_{H-H}$ = 7.3 Hz, 1H, H-2), 5.17-5.21 (m, 1H, H-5), 5.23 (dd, $^3J_{H-H}$ = 7.2 Hz, $^2J_{H-H}$ = 2.7 Hz, 1H, H-5), 5.63 (ddd, $^3J_{H-H}$ = 17.6, 9.4, and 7.3 Hz, 1H, H-4), 7.14 (d, 2H, $^3J_{H-H}$ = 7.8 Hz, 2H, H-10, 12), 7.20 (d, $^3J_{H-H}$ = 7.8 Hz, 2H, H-9, 13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.6 (CH_3, C-8), 18.2 (CH_2, C-7), 21.3 (CH_3, C-14), 48.9 (CH, C-3), 78.7 (CH, C-2), 118.1 (CH_2, C-5), 127.3 (CH, C-10, 12), 129.0 (CH, C-9, 13), 137.3 (C, C-11), 139.3 (C, C-1), 141.5 (CH, C-4); IR ν 3550, 3020, 2954, 2895, 2401, 1248 cm^{-1}; MS (CI-isobutane) *m/z* (%) 231 ($M+H^+-H_2O$, 100), 159 (42), 141 (17), 121(14); HRMS (CI-isobutane) *m/z* 231.1574 ($C_{15}H_{23}Si$, $M+H^+-H_2O$, requires 231.1569).



4c

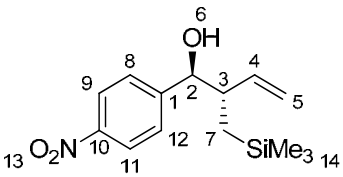
4c was prepared by method **A** / **B**. The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.11, stains visualized by UV and PMA) to afford **4c** (85%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ +44.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.08 (s, 9H, H-14), 0.39 (dd, $^2J_{H-H}$ = 14.5 Hz, $^3J_{H-H}$ = 3.4 Hz, 1H, H-7), 0.47 (dd, $^2J_{H-H}$ = 14.5 Hz, $^3J_{H-H}$ = 11.1 Hz, 1H, H-7), 2.36 (d, $^3J_{H-H}$ = 2.0 Hz, 1H, H-6), 2.32-2.42 (m, 1H, H-3), 4.27 (dd, $^3J_{H-H}$ = 7.9 and 2.0 Hz, 1H, H-2), 5.21 (dd, $^3J_{H-H}$ = 16.7 Hz, $^2J_{H-H}$ = 1.8 Hz, 1H, H-5), 5.25 (dd, $^3J_{H-H}$ = 10.4 Hz, $^2J_{H-H}$ = 1.8 Hz, 1H, H-5), 5.62 (ddd, $^3J_{H-H}$ = 16.7, 10.4, and 9.4 Hz, 1H, H-4), 7.03 (m, 2H, H-8, 12), 7.29 (dd, $^3J_{H-F}$ = 8.7 Hz, $^3J_{H-H}$ = 8.4 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.7 (CH_3, C-14), 18.2 (CH_2, C-7), 49.3 (CH, C-3), 78.1 (CH, C-2), 115.1 (d, $^2J_{C-F}$ = 21.3 Hz, CH, C-9, 11), 118.6 (CH_2, C-5), 129.0 (d, $^3J_{C-F}$ = 8.2 Hz, CH, C-8, 12), 137.9 (d, $^4J_{C-F}$ = 3.2 Hz, C, C-1), 141.2 (CH, C-4), 162.4 (d, $^1J_{C-F}$ = 245.2 Hz, C, C-10); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.0 (tt, $^3J_{H-F}$ = 8.7 Hz, $^4J_{H-F}$ = 5.5 Hz, 1F); IR ν 3547, 3019, 2952, 2896, 2400, 1249, 1217 cm^{-1}; MS (CI-isobutane) *m/z* (%) 235 ($M+H^+-H_2O$, 100), 205 (10), 125 (15), 113 (20); HRMS (CI-isobutane) *m/z* 235.1319

($C_{14}H_{20}FSi$, $M+H^+-H_2O$, requires 235.1318); chiral HPLC (Chiracel IB column, hexane/2-propanol = 99.5:0.5, 0.75 mL/min) showed 97% ee (t_{major} = 16.6 min, t_{minor} = 17.4 min).



4d

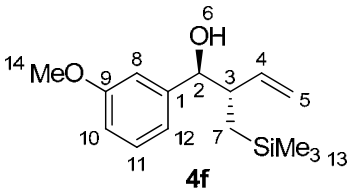
4d was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F = 0.13, stains visualized by UV and PMA) to afford **4d** (90%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ +32.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.08 (s, 9H, H-14), 0.41 (dd, $^2J_{H-H}$ = 14.5 Hz, $^3J_{H-H}$ = 3.3 Hz, 1H, H-7), 0.51 (dd, $^2J_{H-H}$ = 14.5 Hz, $^3J_{H-H}$ = 11.4 Hz, 1H, H-7), 2.32 (d, $^3J_{H-H}$ = 2.1 Hz, 1H, H-6), 2.35-2.46 (m, 1H, H-3), 4.36 (dd, $^3J_{H-H}$ = 7.5 Hz, $^3J_{H-H}$ = 2.1 Hz, 1H, H-2), 5.23 (dd, $^3J_{H-H}$ = 17.1 Hz, $^2J_{H-H}$ = 1.7 Hz, 1H, H-5), 5.23-5.25 (m, 1H, H-5), 5.63 (ddd, $^3J_{H-H}$ = 17.1, 10.1, and 7.3 Hz, 1H, H-4), 7.44 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, H-8, 12), 7.60 (d, $^3J_{H-H}$ = 8.3 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.7 (CH_3, C-14), 18.1 (CH_2, C-7), 49.1 (CH, C-3), 78.2 (CH, C-2), 118.9 (CH_2, C-5), 124.3 (q, $^1J_{C-F}$ = 272.0 Hz, CF_3, C-13), 125.2 (q, $^3J_{C-F}$ = 3.7 Hz, CH, C-9, 11), 127.7 (CH, C-8, 12), 129.9 (q, $^2J_{C-F}$ = 32.3 Hz, C, C-10), 140.6 (CH, C-4), 146.3 (C, C-4); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4 (s, 3F); IR ν 3548, 3020, 2956, 2897, 1250, 1216 cm^{-1}; MS (CI-isobutane) *m/z* (%) 285 ($M+H^+-H_2O$, 42), 193 (100), 175 (10), 113 (25); HRMS (CI-isobutane) *m/z* 285.1282 ($C_{15}H_{20}F_3Si$, $M+H^+-H_2O$, requires 285.1286); chiral GC (Supelco β-DEX 120 column, oven for 1 min at 80 °C, then increase at 0.5 deg min^{-1}) showed 90% ee (t_{major} = 105.6 min, t_{minor} = 106.7 min).



4e

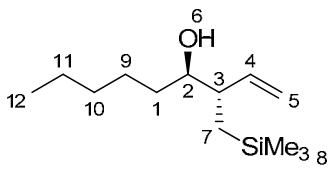
4e was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (gradient of 98:2 and 90:10) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.05, stains visualized by UV and PMA) to afford **4e** (91%, >99% of *anti* diastereoisomer) as a white crystalline solid: mp 64-67 °C; $[\alpha]_D$ -45.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.08 (s, 9H, H-14), 0.40 (dd, $^2J_{H-H}$ = 14.4 Hz, $^3J_{H-H}$ = 3.2 Hz, 1H, H-7), 0.55 (dd, $^2J_{H-H}$ = 14.4 Hz, $^3J_{H-H}$ = 11.5 Hz, 1H, H-7), 2.33-2.48 (m, 1H, H-3), 2.46 (d, $^3J_{H-H}$ = 2.0 Hz, 1H, H-6), 4.42 (dd, $^3J_{H-H}$ = 7.2 Hz, $^3J_{H-H}$ = 2.0

Hz, 1H, H-2), 5.17 (dd, $^3J_{H\text{-}H}$ = 17.1 Hz, $^2J_{H\text{-}H}$ = 1.6 Hz, 1H, H-5), 5.23 (dd, $^3J_{H\text{-}H}$ = 10.0 Hz, $^2J_{H\text{-}H}$ = 1.6 Hz, 1H, H-5), 5.58 (ddd, $^3J_{H\text{-}H}$ = 17.1, 10.0, and 10.0 Hz, 1H, H-4), 7.49 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 2H, H-8, 12), 8.19 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.7 (CH_3, C-14), 18.2 (CH_2, C-7), 49.3 (CH, C-3), 77.9 (CH, C-2), 119.2 (CH_2, C-5), 123.5 (CH, C-9, 11), 128.2 (CH, C-8,12), 140.0 (CH, C-4), 149.7 (C, C-10), 149.8 (C, C-1); IR ν 3549, 3020, 2954, 2896, 1523, 1348, 1250, 1216 cm^{-1}; MS (CI-isobutane) *m/z* (%) 280 (M+H$^+$, 25), 262 (35), 250 (30), 232 (100) 122 (80); HRMS (CI-isobutane) *m/z* 280.1365 ($C_{14}H_{22}NO_3Si$, M+H$^+$, requires 280.1369); chiral HPLC (Chiracel OD-H column, hexane/2-propanol = 99.5:0.5, 1 mL/min) showed 94% ee (t_{minor} =35.3 min, t_{major} = 42.8 min).



4f

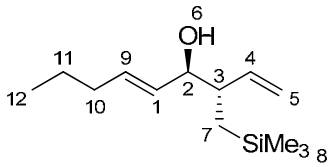
4f was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (gradient of 98:2 and 96:4) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.29, stains visualized by UV and PMA) to afford **4f** (91%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ -41.4 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.08 (s, 9H, H-13), 0.44-0.52 (m, 2H, H-7), 2.23 (d, $^3J_{H\text{-}H}$= 2.2 Hz, 1H, H-6), 2.43 (dddd, $^3J_{H\text{-}H}$ = 9.3, 7.7, 7.5 and 4.8 Hz, 1H, H-3), 3.82 (s, 3H, H-14), 4.27 (dd, $^3J_{H\text{-}H}$ = 7.7 and 2.2 Hz, 1H, H-2), 5.20 (dd, $^3J_{H\text{-}H}$ = 5.3, $^2J_{H\text{-}H}$ = 1.6, 1H, H-5), 5.23-5.26 (m, 1H, H-5), 5.59-5.70 (m, 1H, H-4), 6.83 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 1H, H-12), 6.89-6.93 (m, 2H, H-10, 11), 7.25 (m, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.6 (CH_3, C-13), 18.2 (CH_2, C-7), 48.8 (CH, C-3), 55.4 (CH_3, C-14), 78.8 (CH, C-2), 112.9 (CH_2, C-5), 113.3 (CH, C-10), 118.2 (CH, C-8), 119.9 (CH, C-12), 129.3 (CH, C-11), 141.3 (CH, C-4), 144.0 (C, C-1), 159.7 (C, C-9); IR ν 3551, 3018, 2954, 2894, 2400, 1248, 1216 cm^{-1}; MS (FAB-NOBA) *m/z* (%) 247 (M+H$^+$-H_2O, 65), 226 (62), 209 (20), 137 (135), 109 (10), 74 (100); HRMS (FAB-NOBA) *m/z* 247.1517 ($C_{15}H_{23}OSi$, M+H$^+$-H_2O, requires 247.1518); chiral HPLC (Chiralpak IB-3 column, hexane/2-propanol = 98:2, 1 mL/min) showed 96% ee (t_{major} =15.0 min, t_{minor} = 25.7 min).



4g

4g was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1

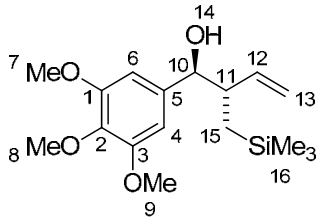
mixture; R_F = 0.40, stains visualized by PMA) to afford **4g** (79%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ -9.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.04 (s, 9H, H-8), 0.61 (dd, $^2J_{H\text{-}H}$ = 14.5 Hz, $^3J_{H\text{-}H}$ = 10.6 Hz, 1H, H-7), 0.70 (dd, $^2J_{H\text{-}H}$ = 14.5 Hz, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-7), 0.89 (t, $^3J_{H\text{-}H}$ = 6.9 Hz, 3H, H-12), 1.25-1.36 (m, 6H, H-9, 10, 11), 1.41-1.54 (m, 2H, H-1), 1.61 (d, $^3J_{H\text{-}H}$ = 3.8 Hz, 1H, H-6), 2.10-2.19 (m, 1H, H-3), 3.29-3.36 (m, 1H, H-2), 5.09 (dd, $^3J_{H\text{-}H}$ = 17.2 Hz, $^2J_{H\text{-}H}$ = 2.1 Hz, 1H, H-5), 5.13 (dd, $^3J_{H\text{-}H}$ = 10.5 Hz, $^2J_{H\text{-}H}$ = 2.0 Hz, 1H, H-5), 5.13 (ddd, $J_{H\text{-}H}$ = 17.11, 10.1 and 9.4 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.53 (CH_3, C-8), 14.2 (CH_3, C-12), 18.6 (CH_2, C-11), 22.8 (CH_2, C-7), 25.6 (CH_2, C-9), 32.1 (CH_2, C-10), 34.2 (CH_2, C-1), 46.7 (CH, C-3), 75.8 (CH, C-2), 117.2 (CH_2, C-5), 140.9 (CH, C-4); IR ν 3555, 3023, 2921, 2895, 1263, 1215 cm^{-1}; MS (CI-isobutane) *m/z* (%) 211 ($M+H^+-H_2O$, 100), 185 (8), 173 (9), 128 (10), 85 (10); HRMS (CI-isobutane) *m/z* 211.1887 ($C_{13}H_{27}OSi$, $M+H^+-H_2O$, requires 211.1877); chiral GC (Supelco β-DEX 120 column, oven for 1 min at 80 °C, then increase at 0.25 deg min^{-1}) showed 73% ee (t_{major} = 91.0 min, t_{minor} = 92.3 min).



4h

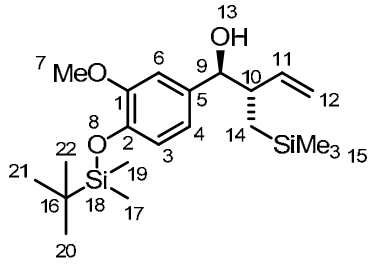
4h was prepared by method **A** / **B.** The crude product was purified by chromatography on a column of silica gel with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.34, stains visualized by PMA) to afford **4h** (90%, >99% of *anti* diastereoisomer) as a colourless oil: $[\alpha]_D$ +13.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 9H, H-8), 0.48 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 11.3 Hz, 1H, H-7), 0.73 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 3.9 Hz, 1H, H-7), 0.91 (t, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, H-12), 1.42 (ddq, $^3J_{H\text{-}H}$ = 9.7, 9.5, and 7.6 Hz, 2H, H-11), 1.80 (s, 1H, H-6), 1.98-2.10 (m, 2H, H-10), 2.11-2.20 (m, 1H, H-3), 3.72 (dd, $^3J_{H\text{-}H}$ = 7.7 and 7.7 Hz, 1H, H-2), 5.14 (dd, $^3J_{H\text{-}H}$ = 9.8 Hz, $^2J_{H\text{-}H}$ = 1.7 Hz, 1H, H-5), 5.16-5.18 (m, 1H, H-5), 5.38 (ddd, $^3J_{H\text{-}H}$ = 15.4, 7.7 and 1.5 Hz, 1H, H-4), 5.58 (dd, $^3J_{H\text{-}H}$ = 15.7 and 9.2 Hz, 1H, H-1), 5.66 (ddd, $^3J_{H\text{-}H}$ = 15.0, 9.8 and 9.4 Hz, 1H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.58 (CH_3, C-8), 13.8 (CH_3, C-12), 18.1 (CH_2, C-11), 22.4 (CH_2, C-7), 34.6 (CH_2, C-10), 47.4 (CH, C-3), 77.4 (CH, C-2), 117.6 (CH_2, C-5), 130.7 (CH, C-1), 134.5 (CH, C-9), 141.3 (CH, C-4); IR ν 3599, 3019, 3030, 2947, 2409, 1300, 1199 cm^{-1}; MS (CI-isobutane) *m/z* (%) 209 ($M+H^+-H_2O$, 100), 171 (8), 135 (6), 99 (12); HRMS (CI-isobutane) *m/z* 209.1723 ($C_{13}H_{25}Si$, $M+H^+-H_2O$, requires 209.1720); chiral

GC (Supelco β-DEX 120 column, oven for 1 min at 80 °C, then increase at 0.5 deg min^{-1}) showed 98% ee (t_{major} = 73.9 min, t_{minor} = 76.8 min).



4i

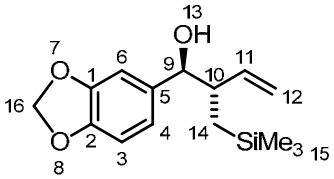
4i was prepared by method **A** / **B.** The crude homoallylic alcohol was purified by chromatography on a column of silica gel (15g) with a mixture of petroleum ether and AcOEt (98:2 to 80:20) (TLC in a petroleum ether-AcOEt 80:20 mixture; R_F = 0.29, stains visualized by UV and PMA) to afford **4i** (810 mg, 75%, >99% of *anti* diastereoisomer) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 9H, H-16), 0.43 (dd, $^2J_{H-H}$ = 14.6 Hz, $^3J_{H-H}$ = 4.2 Hz, 1H, H-15), 0.47 (dd, $^2J_{H-H}$ = 14.6 Hz, $^3J_{H-H}$ = 10.3 Hz, 1H, H-15), 2.41 (d, $^3J_{H-H}$ = 2.0 Hz, 1H, H-14), 2.35-2.46 (m, 1H, H-11), 3.84 (s, 3H, H-8), 3.87 (s, 6H, H-7, H-9), 4.20 (dd, $^3J_{H-H}$ = 8.1 Hz, $^2J_{H-H}$ = 1.4 Hz, 1H, H-10), 5.22-5.29 (m, 2H, H-13), 5.65 (ddd, J_{H-H} = 16.8, 10.6, and 9.3 Hz, 1H, H-12), 6.56 (s, 2H, H-4, 6); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.7 (CH_3), 18.0 (CH_2, C-15), 48.7 (CH, C-11), 56.0 (CH_3, C-7, 9), 60.8 (CH_3, C-8), 78.9 (CH, C-10), 104.3 (CH, C-4, 6), 106.7 (CH, C-12), 118.2 (CH_2, C-13), 137.7 (C), 141.5 (C), 153.1 (C); IR ν 3550, 3022, 2895, 2786, 2418, 1190 cm^{-1}; MS (CI-isobutane) *m/z* (%) 325 ($M+H^+$, 50), 307 (65), 197 (100); HRMS (CI-isobutane) *m/z* 325.1833 ($C_{17}H_{29}O_4Si$, $M+H^+$, requires 325.1830).



4j

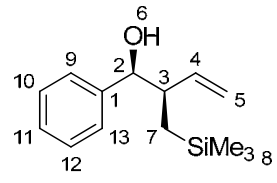
4j was prepared by method **A** / **B.** The crude homoallylic alcohol was purified by chromatography on a column of silica gel (20g) with a mixture of petroleum ether and AcOEt (98:2 to 92:8) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.30, stains visualized by UV and PMA) to afford **4j** (990 mg, 75%, >99% of *anti* diastereoisomer) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.08 (s, 9H, H-15), 0.16 (s, 3H, H-17), 0.17 (s, 3H, H-19), 0.39 (dd, $^2J_{H-H}$ = 14.6 Hz, $^3J_{H-H}$ = 3.3 Hz, 1H, H-14), 0.45 (dd, $^2J_{H-H}$ = 14.6 Hz, $^3J_{H-H}$ = 10.9 Hz, 1H, H-14), 1.02 (s, 9H, H-21, 22, 23); 2.32 (d, $^3J_{H-H}$ = 1.4 Hz, 1H, H-13), 2.35-2.44 (m, 1H, H-10), 3.84 (s, 3H, H-7), 4.21 (dd, $^2J_{H-H}$ = 8.2.6 Hz, $^2J_{H-H}$ = 1.6 Hz, 1H, H-9), 5.21-5.24 (m, 1H, H-12), 5.26 (dd, $^3J_{H-H}$ = 9.3 Hz, $^2J_{H-H}$ = 1.5 Hz, 1H, H-12), 5.67 (ddd, J_{H-H} = 17.0, 10.2, and 9.4 Hz, 1H, H-11), 6.78 (dd, $^3J_{H-H}$ = 8.1 Hz, $^4J_{H-H}$ = 2.2 Hz, 1H, H-4), 6.83 (d, $^3J_{H-H}$ = 8.3 Hz, 1H, H-3), 6.87 (d,

$^{3}J_{H\text{-}H}$ = 1.9 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.6 (C, C-16), -0.85 (CH_3, C-15), 0.5 (CH_3, C-17, 19), 18.1 (CH_2, C-14), 25.7 (CH_3, C-20, 21, 22), 49.0 (CH, C-10), 55.5 (CH_3, C-7), 78.6 (CH, C-9), 110.7 (CH_2, C-12), 117.9 (CH, C-6), 120.1 (CH, C-4), 120.4 (CH, C-3), 135.6 (CH, C-11), 141.6 (C, C-5), 144.4 (C, C-2), 150.9 (C, C-1); IR ν 3549, 3025, 2890, 2795, 2435, 1248, cm^{-1}; MS (CI-isobutane) *m/z* (%) 395 ($M+H^+$, 30), 377 ($M+H^+-H_2O$, 92), 267 (100), 209 (10), 127 (8); HRMS (CI-isobutane) *m/z* 395.2440 ($C_{21}H_{39}O_3Si_2$, $M+H^+$, requires 395.2432).



4k

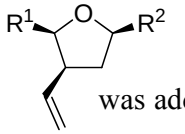
4k was prepared by method **A** / **B.** The crude homoallylic alcohol was purified by chromatography on a column of silica gel (35g) with a mixture of petroleum ether and AcOEt (98:2 to 92:8) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.22, stains visualized by UV and PMA) to afford **4k** (1.91g, 71%, >99% of *anti* diastereoisomer) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 9H, H-15), 0.43-0.49 (m, 2H, H-14), 2.34 (d, $^{3}J_{H\text{-}H}$ = 1.6 Hz, 1H, H-14), 2.35-2.44 (m, 1H, H-10), 4.22 (dd, $^{3}J_{H\text{-}H}$ = 8.0 Hz, $^{4}J_{H\text{-}H}$ = 1.0 Hz, 1H, H-9), 5.21-5.24 (m, 1H, H-12), 5.25-5.28 (m, 1H, H-12), 5.65 (ddd, $^{3}J_{H\text{-}H}$ = 16.3, 10.0, and 9.5 Hz, 1H, H-11), 5.98 (s, 1H, H-16), 5.99 (s, 1H, H-16), 6.78-6.82 (m, 2H, H-3, 4), 6.85-6.88 (m, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.8 (CH_3, C-15), 18.1 (CH_2, C-14), 49.0 (CH, C-10), 78.5 (CH, C-9), 100.9 (CH_2, C-16), 107.4 (CH, C-6), 107.8 (CH, C-3), 118.1 (CH_2, C-12), 120.9 (CH, C-4), 136.1 (CH, C-11), 141.2 (C, C-5), 146.9 (C, C-1), 147.6 (C, C-2); IR ν 3558, 3015, 2799, 2442, 1198, cm^{-1}; MS (CI-isobutane) *m/z* (%) 261 ($M+H^+-H_2O$, 35), 151 (100), 81 (5); HRMS (CI-isobutane) *m/z* 261.1312 ($C_{15}H_{21}O_2Si$, $M+H^+-H_2O$, requires 261.1305).



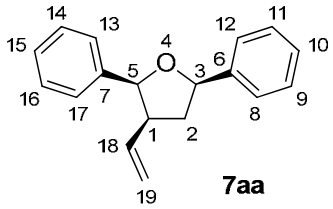
***syn*-4a**

A 1:1 mixture of ***syn*-4a** and ***anti*-4a** was prepared by method **A** from the 1:1 mixture of the corresponding *E* and *Z* disilane**.** The crude mixture was purified by chromatography on a column of silica gel (2g) with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.46, stains visualized by UV and PMA) to afford ***syn*-4a** as a colourless oil (55 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.02 (s, 9H, H-8), 0.53 (dd, $^{2}J_{H\text{-}H}$ = 14.5 Hz, $^{3}J_{H\text{-}H}$ = 11.7 Hz, 1H, H-7), 0.81 (dd, $^{2}J_{H\text{-}H}$ = 14.5 Hz, $^{3}J_{H\text{-}H}$ = 2.8 Hz, 1H, H-7), 2.09 (d, $^{3}J_{H\text{-}H}$ = 5.0 Hz, 1H,

H-6), 2.54-2.65 (m, 1H, H-3), 4.58 (t, $^{3}J_{H-H}$ = 5.1 Hz, 1H, H-2), 5.01-5.11 (m, 2H, H-5), 5.57 (ddd, J_{H-H} = 17.0, 10.3, and 9.2 Hz, 1H, H-4), 7.25-7.45 (m, 5H, H-9, 10, 11, 12, 13); ^{13}C NMR (100 MHz, $CDCl_3$) δ -6.0 (CH_3, C-8), 11.5 (CH_2, C-7), 42.1 (CH, C-3), 73.4 (CH, C-2), 111.3 (CH_2, C-5), 121.5 (CH, C-11), 122.0 (CH, C-9, 13), 122.6 (CH, C-10, 12), 135.0 (CH, C-4), 136.9 (C, C-2); IR ν 3543, 3010, 2960, 2480, 1260 cm^{-1}; MS (CI-isobutane) *m/z* (%) 217 ($M+H^+-H_2O$, 100), 187 (22), 179 (25), 128 (10); HRMS (CI-isobutane) *m/z* 217.1420 ($C_{14}H_{21}Si$, $M+H^+-H_2O$, requires 217.1413).



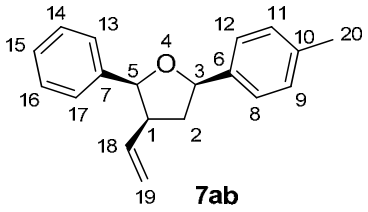
Method C: General method for the intramolecular cascade allylation (intramolecular allyl transfer). The aldehyde (0.05 mmol) was added via a Hamilton syringe to a solution of the corresponding homoallylic alcohol **4** (0.04 mmol) in dry THF (1 mL) at room temperature under argon. The solution was stirred at -90 °C for 10 min, then a suspension of tin(II) triflate (8 mg, 0.02 mmol) in THF (0.5 mL) was added slowly *via cannula* on the wall of the reaction vessel (in order to cool it to -90 °C before reaching the reactants) while stirring vigorously. The reaction mixture was stirred at –90 °C overnight and then allowed to warm to room temperature over 4-5 h. The solvent was evaporated at reduced pressure and the crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1).



7aa

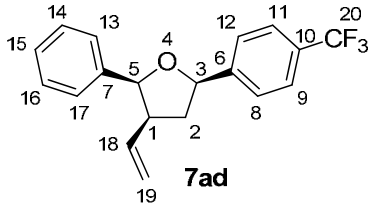
7aa was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.23, stains visualized by UV and PMA) to afford **7aa** (95%, >25:1 de) as a colourless oil: $[\alpha]_D$ −50.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.92 (ddd, $^{2}J_{H-H}$ = 12.5 Hz, $^{3}J_{H-H}$ = 9.4 and 9.2 Hz, 1H, H-2), 2.57 (ddd, $^{2}J_{H-H}$ = 12.6 Hz, $^{3}J_{H-H}$ = 7.9, and 6.0 Hz, 1H, H-2), 3.30-3.41 (m, 1H, H-1), 4.78 (dd, $^{3}J_{H-H}$ = 10.2 Hz, $^{2}J_{H-H}$ = 1.6, 1H, H-19), 4.92 (ddd, $^{3}J_{H-H}$ = 17.0 Hz, $^{2}J_{H-H}$ = 1.7 Hz, $^{4}J_{H-H}$ = 0.8 Hz, 1H, H-19), 5.10 (dd, $^{3}J_{H-H}$ = 9.6 and 5.9 Hz, 1H, H-3), 5.23 (ddd, $^{3}J_{H-H}$ = 17.2, 10.1 and 8.2 Hz, 1H, H-18), 5.24 (d, $^{3}J_{H-H}$ = 8.2 Hz, 1H, H-5), 7.25-7.52 (m, 10H, H-13-17 and 8-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.8 (CH_2, C-2), 49.2 (CH, C-1), 80.5 (CH, C-3), 83.8 (CH, C-5), 115.9 (CH_2, C-19), 126.0 (CH, C-10), 127.0 (CH, C-15), 127.2 (CH,

C-9, 10), 127.5 (CH, C-14, 16), 128.1 (CH, C-8,12), 128.6 (CH, C-13,17), 138.4 (CH, C-18), 140.3 (C, C-3), 142.0 (C, C-5); IR ν 3019, 2399, 2361, 1510, 1216 cm^{-1}; MS (CI-isobutane) *m/z* (%) 251 ($M+H^+$, 42), 233 (25), 137 (100), 121 (54), 69 (50); HRMS (CI-isobutane) *m/z* 251.1440 ($C_{18}H_{19}O$, $M+H^+$, requires 251.1436); (Chiralpak IA-3 column, hexane/2-propanol = 95:5, 0.5 mL/min) showed 90% ee (t_{minor} = 10.0 min, t_{major} = 13.5 min).



7ab

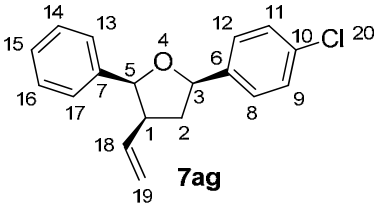
7ab was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F = 0.49, stains visualized by UV and PMA) to afford **7ab** (90%, de > 25:1) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (ddd, $^2J_{H-H}$ = 12.5 Hz, $^3J_{H-H}$ = 9.3 and 9.3 Hz, 1H, H-2), 2.38 (s, 3H, H-20), 2.57 (ddd, $^2J_{H-H}$ = 12.6 Hz, $^3J_{H-H}$ = 7.9 and 6.1 Hz, 1H, H-2), 3.51-3.65 (m, 1H, H-1), 4.79 (dd, $^3J_{H-H}$ = 10.2 Hz, $^2J_{H-H}$ = 1.6, 1H, H-19), 4.90 (ddd, $^3J_{H-H}$ = 16.9 Hz, $^2J_{H-H}$ = 1.7 Hz, $^4J_{H-H}$ = 0.8 Hz, 1H, H-19), 5.11 (dd, $^3J_{H-H}$ = 9.5 and 5.9 Hz, 1H, H-3), 5.24 (ddd, $^3J_{H-H}$ = 17.2, 10.1, and 8.2 Hz, 1H, H-18), 5.24 (d, $^3J_{H-H}$ = 8.2 Hz, 1H, H-5), 7.25-7.52 (m, 9H, H-13-17 and 8-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (CH_3, C-20), 40.8 (CH_2, C-2), 49.2 (CH, C-1), 80.6 (CH, C-3), 83.9 (CH, C-5), 116.0 (CH_2, C-19), 126.2 (CH, C-9,11), 127.1 (CH, C-15), 127.2 (CH, C-14, 16), 128.1 (CH, C-8,12), 128.6 (CH, C-13, 17), 134.0 (C, C-10), 138.4 (CH, C-18), 140.3 (C, C-6), 142.0 (C, C-7); IR ν 3019, 2399, 2375, 2362, 1510, 1216, 1014 cm^{-1}; MS (CI-isobutane) *m/z* (%) 265 ($M+H^+$, 45), 247 (58), 151 (100); HRMS (CI-isobutane) *m/z* 265.1570 ($C_{19}H_{21}O$, $M+H^+$, requires 265.1592).



7ad

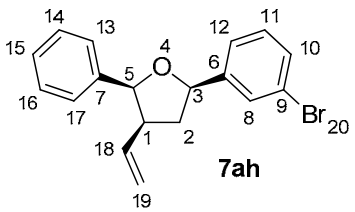
7ad was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.25, stains visualized by UV and PMA) to afford **7ad** (80%, 20:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.86 (ddd, $^2J_{H-H}$ = 12.5 Hz, $^3J_{H-H}$ = 9.4 and 8.9 Hz, 1H, H-2), 2.60 (ddd, $^2J_{H-H}$ = 12.6 Hz, $^3J_{H-H}$ = 7.3 Hz and 6.2 Hz, 1H, H-2), 3.30-3.39 (m, 1H, H-1), 4.76 (ddd, $^3J_{H-H}$ = 10.1 Hz, $^2J_{H-H}$ = 1.7, $^4J_{H-H}$ = 0.6, 1H, H-19), 4.90 (ddd, $^3J_{H-H}$ = 17.0 Hz, $^2J_{H-H}$ = 1.7 Hz, $^4J_{H-H}$ = 0.9 Hz, 1H, H-19), 5.12 (dd, $^3J_{H-H}$ = 9.5 and 6.3 Hz, 1H, H-3), 5.19 (ddd, $^3J_{H-H}$

= 17.0, 10.0 and 8.9, 1H, H-18), 5.24 (d, $^{3}J_{H\text{-}H}$ = 8.1, 1H, H-5), 7.20-7.38 (m, 5H, H-13,14,15,16,17), 7.54-7.68 (m, 4H, H-8,9,11,12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2, C-2), 49.1 (CH, C-1), 79.7 (CH, C-5), 83.9 (CH, C-3), 115.7 (CH_2, C-19), 125.5 (q, $^{3}J_{C\text{-}F}$ = 3.9 Hz, CH, C-9,11), 124.1 (q, $^{1}J_{C\text{-}F}$ = 271.0 Hz, CF_3, C-20), 126.1 (CH, C-8,12), 126.9 (CH, C-14,16), 127.4 (CH, C-15), 128.1 (CH, C-13.17), 129.6 (q, $^{2}J_{C\text{-}F}$ = 32.3 Hz, C, C-10), 137.9 (CH, C-18), 139.9 (C, C-7), 146.3 (C, C-6); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.3 (s, 3F); IR ν 3019, 2400, 2361, 1510, 1250, 1217, 1015 cm^{-1}; MS (CI-isobutane) *m/z* (%) 319 ($M+H^+$, 100), 301 (60), 205 (35), 129 (37); HRMS (CI-isobutane) *m/z* 319.1305 ($C_{19}H_{18}F_3O$, $M+H^+$, requires 319.1310).



7ag

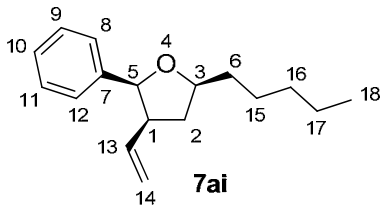
7ag was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.49, stains visualized by UV and PMA) to afford **7ag** (94%, >25:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (ddd, $^{2}J_{H\text{-}H}$ = 12.4 Hz, $^{3}J_{H\text{-}H}$ = 10.1 and 6.2 Hz, 1H, H-2), 2.57 (ddd, $^{2}J_{H\text{-}H}$ = 12.6 Hz, $^{3}J_{H\text{-}H}$ = 7.3 and 6.1 Hz, 1H, H-2), 3.28-3.40 (m, 1H, H-1), 4.78 (dd, $^{3}J_{H\text{-}H}$ = 10.0 Hz, $^{2}J_{H\text{-}H}$ = 1.7, 1H, H-19), 4.91 (ddd, $^{3}J_{H\text{-}H}$ = 17.0 Hz, $^{2}J_{H\text{-}H}$ = 1.7 Hz, $^{4}J_{H\text{-}H}$ = 0.7 Hz, 1H, H-19), 5.06 (dd, $^{3}J_{H\text{-}H}$ = 9.7 Hz, $^{3}J_{H\text{-}H}$ = 6.9 Hz, 1H, H-3), 5.15-5.26 (m, 1H, H-5), 5.20 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, H-18), 7.22-7.46 (m, 9H, H-13-17 and 8,9,11,12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.7 (CH_2, C-2), 49.1 (CH, C-1), 79.8 (CH, C-5), 83.9 (CH, C-3), 115.6 (CH_2, C-19), 126.9 (CH, C-15), 127.4 (CH, C-14, 16), 127.5 (CH, C-8,12), 128.1 (CH, C-9, 11), 128.7 (CH, C-13, 17), 133.2 (C-10), 138.1 (CH, C-18), 140.1 (C-7), 140.7 (C, C-6); IR ν 3020, 2398, 2361, 1510, 1215, 1199 cm^{-1}; MS (CI-isobutane) *m/z* (%) 285/287, 285 ($M+H^+$, 48/17), 269 (13), 267 (20), 178 (10), 137 (80), 69 (100); HRMS (CI-isobutane) *m/z* 285.1042 ($C_{18}H_{18}{}^{35}ClO$, $M+H^+$, requires 285.1046).



7ah

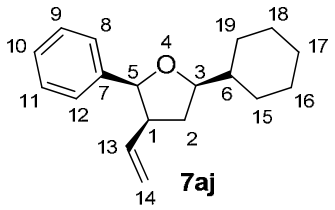
7ah was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.43,

stains visualized by UV and PMA) to afford **7ah** (87%, >25:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (ddd, $^{2}J_{H\text{-}H}$ = 12.5 Hz, $^{3}J_{H\text{-}H}$ = 9.1 and 9.1 Hz, 1H, H-2), 2.58 (ddd, $^{2}J_{H\text{-}H}$ = 12.6 Hz, $^{3}J_{H\text{-}H}$ = 8.0, and 6.1 Hz, 1H, H-2), 3.32 (m, 1H, H-1), 4.78 (dd, $^{3}J_{H\text{-}H}$ = 10.1 Hz, $^{2}J_{H\text{-}H}$ = 1.9, $^{4}J_{H\text{-}H}$ = 0.5 Hz, 1H, H-19), 4.91 (ddd, $^{3}J_{H\text{-}H}$ = 17.0 Hz, $^{2}J_{H\text{-}H}$ = 1.8 Hz, $^{4}J_{H\text{-}H}$ = 0.8 Hz, 1H, H-19), 5.05 (dd, $^{3}J_{H\text{-}H}$ = 9.2 and 6.1 Hz, 1H, H-3), 5.21 (dd, $^{3}J_{H\text{-}H}$ = 17.0, 10.0, and 8.3 Hz, 1H, H-18), 5.22 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, H-5), 7.22-7.38 (m, 7H, H-13-17 and 11,12), 7.44 (dd, $^{3}J_{H\text{-}H}$ = 7.7 Hz, $^{4}J_{H\text{-}H}$ = 1.5 Hz, 1H, H-10), 7.64 (t, $^{4}J_{H\text{-}H}$= 1.4 Hz, 1H, H-8); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2, C-2), 49.1 (CH, C-1), 79.7 (CH, C-5), 83.9 (CH, C-3), 115.6 (CH_2, C-19), 122.7 (C, C-9), 124.6 (CH, C-10), 126.9 (CH, C-15), 127.4 (CH, C-14, 16), 128.1 (CH, C-13, 17), 129.0 (CH, C-10), 130.2 (CH, C-11), 130.5 (CH, C-8), 138.0 (CH, C-18), 139.9 (C, C-7), 144.5 (C, C-6); IR ν 3019, 2400, 2361, 1515, 1253, 1215, 1199 cm^{-1}; MS (CI-isobutane) *m/z* (%) 331/329 (M+H^{+}, 19/20), 313 (10), 311 (11), 187 (14), 185 (15), 137 (45), 69 (100); HRMS (CI-isobutane) *m/z* 329.0534 ($C_{18}H_{18}{}^{79}BrO$, M+H^{+}, requires 329.0514).



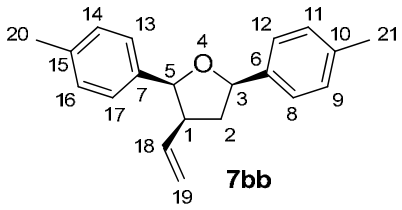
7ai

7ai was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.54, stains visualized by UV and PMA) to afford **7ai** (92%, 10:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, $^{3}J_{H\text{-}H}$ = 7.4, 3H, H-18), 1.29-1.55 (m, 8H), 1.80-1.91 (m, 1H, H-2), 2.20 (ddd, $^{2}J_{H\text{-}H}$ = 12.6, $^{3}J_{H\text{-}H}$ = 7.3 and 5.5 Hz, 1H, H-2), 3.11-3.23 (m, 1H, H-1), 4.02 (dtd, $^{3}J_{H\text{-}H}$ = 9.6, 6.3 and 5.7 Hz, 1H, H-3), 4.75 (ddd, $^{3}J_{H\text{-}H}$ = 10.1 Hz, $^{2}J_{H\text{-}H}$ = 2.0, $^{4}J_{H\text{-}H}$ = 0.5, 1H, H-14), 4.90 (ddd, $^{3}J_{H\text{-}H}$ = 17.0 Hz, $^{2}J_{H\text{-}H}$ = 2.0 Hz, $^{4}J_{H\text{-}H}$ = 0.8 Hz, 1H, H-14), 5.04 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 1H, H-5), 5.17 (ddd, $^{3}J_{H\text{-}H}$ = 17.1, 10.0 and 9.0, 1H, H-13), 7.19-7.36 (m, 5H, H-8, 9, 10, 11, 12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2 (CH_3, C-18), 22.8 (CH_2, C-17), 26.3 (CH_2, C-15), 32.1 (CH_2, C-16), 35.7 (CH_2, C-6), 38.5 (CH_2, C-2), 49.1 (CH, C-1), 79.8 (CH, C-3), 83.3 (CH, C-5), 115.0 (CH_2, C-14), 126.9 (CH, C-8, 12), 127.3 (CH, C-10), 127.9 (CH, C-9, 11), 138.9 (CH, C-13), 140.7 (C-7); IR ν 3031, 2900, 1492, 1215, 1060, 1014 cm^{-1}; MS (CI-isobutane) *m/z* (%) 245 (M+H^{+}, 100), 227 (10), 145 (23), 69 (48); HRMS (CI-isobutane) *m/z* 245.1903 ($C_{17}H_{25}O$, M+H^{+}, requires 245.1900).



7aj

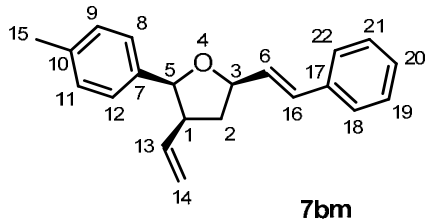
7aj was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.49, stains visualized by UV and PMA) to afford **7aj** (92%, 10:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) 1.05-1.39 (m, 6H, H-15, 16, 17, 18, 19), 1.60-1.81 (m, 5H, H-15, 6, 19), 2.05-2.15 (m, 1H, H-2), 2.13 (ddd, $^2J_{H\text{-}H}$ = 12.6, $^3J_{H\text{-}H}$ = 7.3 and 5.5 Hz, 1H, H-2), 3.10-3.19 (m, 1H, H-1), 3.72 (ddd, $^3J_{H\text{-}H}$ = 9.7, 7.8 and 5.5 Hz, 1H, H-3), 4.79 (dd, $^3J_{H\text{-}H}$ = 9.9 Hz, $^2J_{H\text{-}H}$ = 1.9 Hz, 1H, H-14), 4.89 (ddd, $^3J_{H\text{-}H}$ = 17.0 Hz, $^2J_{H\text{-}H}$ = 2.0 Hz, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H, H-14), 5.03 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-5), 5.17 (ddd, $^3J_{H\text{-}H}$ = 17.1, 10.0 and 9.1, 1H, H-13), 7.19-7.35 (m, 5H, H-8, 9, 10, 11, 12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.1 (CH_2, C-17), 26.3 (CH_2, C-16, 18), 26.7 (CH_2, C-15, 19), 43.3 (CH, C-1), 48.9 (CH, C-6), 83.0 (CH, C-3), 84.2 (CH, C-5), 114.8 (CH_2, C-14), 126.9 (CH, C-8, 12), 127.0 (CH, C-10), 127.9 (CH, C-9, 11), 139.0 (CH, C-13), 140.8 (C, C-7); IR ν 3007, 2919, 1485, 1208, 1069 cm^{-1}; MS (CI-isobutane) *m/z* (%) 257 ($M+H^+$, 100), 239 (16), 145 (18), 69 (83); HRMS (CI-isobutane) *m/z* 257.1899 ($C_{18}H_{25}O$, $M+H^+$, requires 257.1900).



7bb

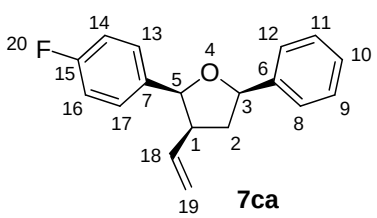
7bb was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F = 0.34, stains visualized by UV and PMA) to afford **7bb** (85%, 21:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (ddd, $^2J_{H\text{-}H}$ = 12.5, $^3J_{H\text{-}H}$ = 9.5 and 9.5 Hz, 1H, H-2), 2.33 (s, 3H, H-20), 2.37 (s, 3H, H-21), 2.51 (ddd, $^2J_{H\text{-}H}$ = 12.6 Hz, $^3J_{H\text{-}H}$ = 7.3 and 5.8 Hz, 1H, H-2), 3.27-3.37 (m, 1H, H-1), 4.78 (ddd, $^3J_{H\text{-}H}$ = 10.1 Hz, $^2J_{H\text{-}H}$ = 1.9, $^4J_{H\text{-}H}$ = 1.9 and 0.5 Hz, 1H, H-19), 4.92 (ddd, $^3J_{H\text{-}H}$ = 17.0 Hz, $^2J_{H\text{-}H}$ = 1.9, $^4J_{H\text{-}H}$ = 1.9 and 0.9 Hz, 1H, H-19), 5.05 (dd, $^3J_{H\text{-}H}$ = 9.7 and 5.8 Hz, 1H, H-3), 5.19 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 1H, H-5), 5.26 (ddd, $^3J_{H\text{-}H}$ = 17.0, 10.1, and 8.9 Hz, 1H, H-18), 7.11 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, H-14, 16), 7.14-7.25 (m, 4H, H-9, 11, 8, 12), 7.39 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, H-13, 17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3, C-20), 21.4 (CH_3, C-21), 40.8 (CH_2, C-2), 49.3

(CH, C-1), 80.5 (CH, C-3), 83.6 (CH, C-5), 115.2 (CH_2, C-19), 126.0 (CH, C-13, 17), 127.0 (CH, C-8, 12), 128.7 (CH, C-14, 16), 129.2 (CH, C-9, 11), 136.7 (C, C-15), 137.1 (C, C-10), 137.4 (C, C-7), 138.6 (CH, C-18), 139.0 (C, C-6); IR ν 3012, 2405, 2361, 1515, 1220, 1200 cm^{-1}; MS (CI-isobutane) *m/z* (%) 279 ($M+H^+$, 100), 261 (90), 159 (28), 121(22); HRMS (CI-isobutane) *m/z* 279.1746 ($C_{20}H_{23}O$, $M+H^+$, requires 279.1749).



7bm

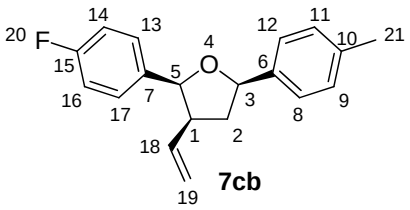
7bm was prepared by method **C.** Cinnamaldehyde (6 mg, 0.04 mmol) was added via Hamilton syringe to a solution of alcohol **2** (4 mg, 0.02 mmol) in dry THF (1 mL) at room temperature under Ar. The solution was stirred at -90 °C for 10 min, then a suspension of tin(II) triflate (7 mg, 0.02 mmol) in THF (0.5 mL) was added slowly *via cannula* on the wall of the reaction vessel. The reaction mixture was stirred at –90 °C overnight and then allowed to warm to the room temperature over 4-5 h. The solvent was then evaporated at reduced pressure and the crude product was purified by chromatography on a column of silica gel (0.4 x 5 cm) with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 95:5 mixture; R_F=0.42, stains visualised by UV and PMA) to afford **7bm** (3.5 mg, 75%, 89% de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84-2.10 (m, 2H, H-2), 2.05-2.10 (m, 1H, H-1), 2.34 (s, 3H, H-15), 4.20-4.26 (m, 1H, C-3), 4.77 (dd, $^3J_{H-H}$ = 10.1 Hz, $^2J_{H-H}$ = 1.9 Hz, 1H, H-14), 4.88-4.92 (m, 1H, H-6), 4.92-4.96 (m, 1H, H-16), 4.97 (m, 1H, H-14), 5.19 (d, $^3J_{H-H}$ = 8.3 Hz, 1H, H-5), 5.25 (ddd, $^3J_{H-H}$ = 17.4, 9.5, and 8.3 Hz, 1H, H-13), 7.10-7.34 (m, 9H, H-8, 9, 11, 12 and 18-22); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3, C-15), 32.5 (CH_2, C-2), 49.0 (CH, C-1), 78.8 (CH, C-3), 83.3 (CH, C-5), 115.0 (CH_2, C-14), 126.3 (CH, C-20), 126.8 (CH, C-8, 12), 128.5 (CH, C-9, 11), 128.6 (CH, C-18, 22), 128.8 (CH, C-6), 129.0 (CH, C-19, 21), 129.2 (CH, C-16), 138.1 (C, C-7), 138.3 (C,C-10), 138.9 (CH, C-13), 142.2 (C, C-17); MS (EI) *m/z* (%) 292 ($M+H^+$, 10), 222 (15), 172 (15), 131 (40), 130 (50), 91 (100); HRMS (EI) *m/z* 292.1831 ($C_{21}H_{24}O$, $M+H^+$, requires 292.1827).



7ca

7ca was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum

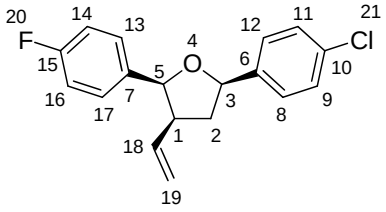
ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.23, stains visualized by UV and PMA) to afford **7ca** (92%, >25:1 de) as a colourless oil: $[\alpha]_D$ +45.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (ddd, $^2J_{H\text{-}H}$ = 12.5 Hz, $^3J_{H\text{-}H}$ = 9.6 and 9.6 Hz, 1H, H-2), 2.57 (ddd, $^2J_{H\text{-}H}$ = 12.5 Hz, $^3J_{H\text{-}H}$ = 7.3 and 6.0 Hz, 1H, H-2), 3.27-3.39 (m, 1H, H-1), 4.79 (dd, $^3J_{H\text{-}H}$ = 9.8 Hz, $^2J_{H\text{-}H}$ = 1.8, 1H, H-19), 4.93 (dd, $^3J_{H\text{-}H}$ = 16.9 Hz, $^2J_{H\text{-}H}$ = 1.8 Hz, 1H, H-19), 5.08 (dd, $^3J_{H\text{-}H}$ = 9.7 and 5.9 Hz, 1H, H-3), 5.16-5.26 (m, 1H, H-18), 5.22 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-5), 6.9-7.02 (m, 2H, H-14, 16), 7.26-7.54 (m, 7H, H-13, 17 and 8-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.6 (CH_2, C-2), 49.2 (CH, C-1), 80.6 (CH, C-3), 83.2 (CH, C-5), 114.9 (d, $^2J_{C\text{-}F}$ = 21.3 Hz, CH, C-14, 16), 116.0 (CH_2, C-19), 125.9 (CH, C-10), 126.1 (CH, C-9, 11), 127.6 (CH, C-8, 12), 128.5 (d, $^3J_{C\text{-}F}$ = 10.5 Hz, CH), C-13, 17) 136.0 (C, C-7), 138.2 (CH, C-18), 141.8 (C, C-6), 162.1 (d, $^1J_{C\text{-}F}$ = 248.1 Hz, C, C-15); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.8 (tt, $^3J_{H\text{-}F}$ = 8.8 Hz, $^4J_{H\text{-}F}$ = 5.6 Hz, 1F); IR ν 3019, 2400, 2361, 1510, 1215 cm^{-1}; MS (CI-isobutane) *m/z* (%) 269 ($M+H^+$, 100), 251 (65), 233 (15), 163 (15); HRMS (CI-isobutane) *m/z* 269.1338 ($C_{18}H_{18}FO$, $M+H^+$, requires 269.1342); (Chiralpak IA-3 column, hexane/2-propanol = 98:2, 0.5 mL/min) showed 87 % ee (t_{major} = 18.3 min, t_{minor} = 23.6 min).



7cb

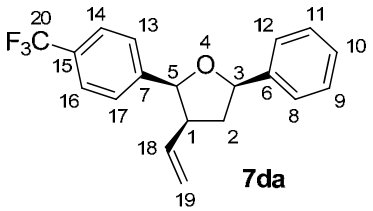
7cb was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.26, stains visualized by UV and PMA) to afford **7cb** (91%, 15:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.87 (ddd, $^2J_{H\text{-}H}$ = 12.5 Hz, $^3J_{H\text{-}H}$ = 9.6 and 9.6 Hz, 1H, H-2), 2.38 (s, 3H, H-21), 2.53 (ddd, $^2J_{H\text{-}H}$ = 12.9 Hz, $^3J_{H\text{-}H}$ = 8.6 and 5.9 Hz, 1H, H-2), 3.32 (m, 1H, H-1), 4.79 (dd, $^3J_{H\text{-}H}$ = 10.1 Hz, $^2J_{H\text{-}H}$ = 1.5, 1H, H-19), 4.92 (ddd, $^3J_{H\text{-}H}$ = 17.0 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H, H-19), 5.05 (dd, $^3J_{H\text{-}H}$ = 9.6 and 5.9 Hz, 1H, H-3), 5.15-5.30 (m, 1H, H-18), 5.19 (d, $^3J_{H\text{-}H}$= 7.4 Hz, 1H, H-5), 6.97-7.31 (m, 4H, H-9, 11, 14, 16), 7.20 (d, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, H-8, 12), 7.35-7.42 (m, 2H, H-13, 17); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3, C-21), 40.5 (CH_2, C-2), 49.2 (CH, C-1), 80.6 (CH, C-3), 83.1 (CH, C-5), 114.9 (d, $^2J_{C\text{-}F}$ = 21.4 Hz, CH, C-14, 16), 115.5 (CH_2, C-19), 126.0 (CH, C-8, 12), 128.5 (d, $^3J_{C\text{-}F}$ = 10.5 Hz, CH, C-13, 17), 129.3 (CH, C-9, 11), 136.1 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C, C-7), 137.3 (C, C-10), 138.3 (CH, C-18), 138.7 (C, C-6), 162.1 (d, $^1J_{C\text{-}F}$ = 244.6 Hz, C, C-15); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.9 (tt, $^4J_{H\text{-}F}$ = 8.7 Hz, $^3J_{H\text{-}F}$ = 5.5 Hz, 1F); IR

ν 3015, 2399, 2356, 1524, 1200, 1187 cm^{-1}; MS (CI-isobutane) *m/z* (%) 283 ($M+H^+$, 55), 265 (20), 190 (25), 79 (100); HRMS (CI-isobutane) *m/z* 283.1502 ($C_{19}H_{20}FO$, $M+H^+$, requires 283.1498).



7cg

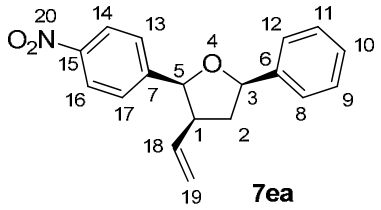
7cg was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.34, stains visualized by UV and PMA) to afford **7cg** (90%, 23:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.84 (ddd, $^2J_{H-H}$ = 12.5, $^3J_{H-H}$ = 9.5 and 8.4 Hz, 1H, H-2), 2.56 (ddd, $^2J_{H-H}$ = 12.5 Hz, $^3J_{H-H}$ = 8.3 and 6.1 Hz, 1H, H-2), 3.32 (m, 1H, H-1), 4.80 (dd, $^3J_{H-H}$ = 10.1 Hz, $^2J_{H-H}$ = 1.5, 1H, H-19), 4.92 (dd, $^3J_{H-H}$ = 17.0 Hz, $^2J_{H-H}$ = 1.5 Hz, H-19), 4.98 (dd, $^3J_{H-H}$ = 9.4 and 8.3 Hz, 1H, H-3), 5.05-5.26 (m, 1H, H-18), 5.13 (d, $^3J_{H-H}$ = 8.2 Hz, 1H, H-5), 6.91-6.97 (m, 2H, H-14, 16), 7.14-7.22 (m, 2H, H-8, 12), 7.29 (d, $^3J_{H-H}$ = 8.5 Hz, 2H, H-13, 17), 7.35 (d, $^3J_{H-H}$ = 8.5 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5 (CH_2, C-2), 49.0 (CH, C-1), 79.8 (CH, C-3), 83.2 (CH, C-5), 115.0 (d, $^2J_{C-F}$ = 21.4 Hz, CH, C-14, 16), 115.8 (CH_2, C-19), 127.3 (CH, C-8, 12), 128.4 (d, $^3J_{C-F}$ = 8.0 Hz, CH, C-13, 17), 128.7 (CH, C-9, 11), 133.2 (C, C-10), 137.7 (d, $^4J_{C-F}$ = 2.9 Hz, C, C-7), 137.9 (CH, C-18), 140.4 (C, C-6), 162.1 (d, $^1J_{C-F}$ = 244.9 Hz, C, C-15); ^{19}F NMR (377 MHz, $CDCl_3$) δ -115.6 (tt, $^4J_{H-F}$ = 8.8 Hz, $^3J_{H-F}$ = 5.4 Hz, 1F); IR ν 3020, 2390, 2361, 1590, 1518, 1219 cm^{-1}; MS (CI-isobutane) *m/z* (%) 305/303 ($M+H^+$, 31/100), 285 (27), 178 (20), 81 (72); HRMS (CI-isobutane) *m/z* 303.0939 ($C_{18}H_{17}{}^{35}ClFO$, $M+H^+$, requires 303.0952).



7da

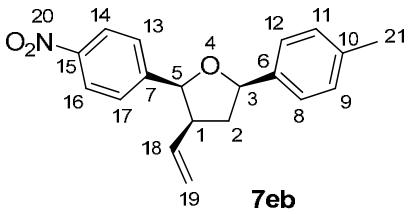
7da was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.40, stains visualized by UV and PMA) to afford **7da** (79%, >25:1 de) as a colourless oil: $[\alpha]_D$ +40.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90 (ddd, $^2J_{H-H}$ = 12.6 Hz, $^3J_{H-H}$ = 9.6 and 8.6 Hz, 1H, H-2), 2.60 (ddd, $^2J_{H-H}$ = 12.6 Hz, $^3J_{H-H}$ = 7.4 and 6.0 Hz, 1H, H-2), 3.31-

3.42 (m, 1H, H-1), 4.8 (ddd, $^{3}J_{H\text{-}H}$ = 10.1 Hz, $^{2}J_{H\text{-}H}$ = 1.8, $^{4}J_{H\text{-}H}$ = 0.4, 1H, H-19), 4.94 (ddd, $^{3}J_{H\text{-}H}$ = 16.9 Hz, $^{2}J_{H\text{-}H}$ = 1.9 Hz, $^{4}J_{H\text{-}H}$ = 0.9 Hz, 1H, H-19), 5.12 (dd, $^{3}J_{H\text{-}H}$ = 9.7 and 6.0 Hz, 1H, H-3), 5.17 (ddd, $^{3}J_{H\text{-}H}$ = 17.0, 10.0, and 9.1, 1H, H-18), 5.27 (d, $^{3}J_{H\text{-}H}$ = 8.2, 1H, H-5), 7.30-7.61 (m, 9H, H-13,14,16,17 and 8-12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5 (CH_2, C-2), 49.2 (CH, C-1), 80.7 (CH, C-3), 83.0 (CH, C-5), 116.1 (CH_2, C-19), 125.5 (q, $^{3}J_{C\text{-}F}$ = 3.6 Hz, CH, C-14, 16), 125.0 (q, $^{1}J_{C\text{-}F}$ = 269.0 Hz, CF_3, C-20), 126.0 (CH, C-13, 17), 127.2 (CH, C-10), 127.7 (CH, C-8, 12), 128.7 (CH, C-9, 11), 130.5 (q, $^{2}J_{C\text{-}F}$ = 31.6 Hz, C, C-15), 137.8 (CH, C-18), 141.6 (C, C-7), 144.4 (C, C-6); ^{19}F NMR (377 MHz, $CDCl_3$) δ -62.4 (s, 3F); IR ν 3014, 2392, 2370, 1523, 1218, 1201 cm^{-1}; MS (CI-isobutane) *m/z* (%) 319 ($M+H^+$, 29), 301 (100), 223 (34), 205 (45), 197 (78), 129 (21); HRMS (CI-isobutane) *m/z* 319.1302 ($C_{19}H_{18}F_3O$, $M+H^+$, requires 319.1310); chiral GC (Supelco γ-DEX 120 column, oven for 1 min at 130 °C, then increase to 170 °C at 0.5 deg.min^{-1}) showed 90% ee (t_{minor} = 95.5 min, t_{major} = 96.4 min).



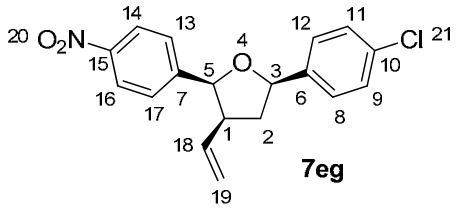
7ea

7ea was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.14, stains visualized by UV and PMA) to afford **7ea** (90%, >25:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.91 (ddd, $^{2}J_{H\text{-}H}$ = 12.6, $^{3}J_{H\text{-}H}$ = 9.5 and 8.5 Hz, 1H, H-2), 2.64 (ddd, $^{2}J_{H\text{-}H}$ = 12.7 Hz, $^{3}J_{H\text{-}H}$ = 8.0 and 6.2 Hz, 1H, H-2), 3.42 (m, 1H, H-1), 4.81 (dd, $^{3}J_{H\text{-}H}$ = 10.0 Hz, $^{2}J_{H\text{-}H}$ = 1.4, 1H, H-19), 4.95 (ddd, $^{3}J_{H\text{-}H}$ = 17.0 Hz, $^{2}J_{H\text{-}H}$ = 1.5 Hz, $^{4}J_{H\text{-}H}$ = 0.7 Hz, 1H, H-19), 5.05-5.26 (m, 2H, H-3, 18), 5.30 (d, $^{3}J_{H\text{-}H}$ = 8.2 Hz, 1H, H-5), 7.31-7.32 (m, 7H, H-13, 17 and 8-12), 8.17-8.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5 (CH_2, C-2), 49.2 (CH, C-1), 80.9 (CH, C-3), 82.8 (CH, C-5), 116.4 (CH_2, C-19), 123.4 (CH, C-13, 17), 126.0 (CH, C-8, 12), 127.7 (CH, C-10), 127.9 (CH, C-13, 17), 128.7 (CH, C-9, 11), 137.5 (CH, C-18), 141.3 (C, C-6), 147.2 (C, C-7), 147.8 (C, C-15); IR ν 3016, 2927, 1492, 1454, 1215, 1090, 1060, 1014 cm^{-1}; MS (CI-isobutane) *m/z* (%) 296 ($M+H^+$, 70), 266 (100), 173 (10), 122 (38); HRMS (CI-isobutane) *m/z* 296.1283 ($C_{18}H_{18}NO_3$, $M+H^+$, requires 296.1287).



7eb

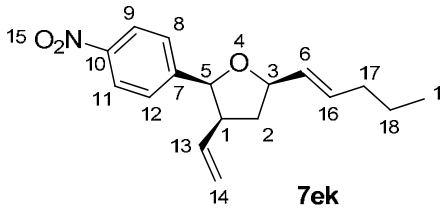
7eb was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 96:4 mixture; R_F = 0.10, stains visualized by UV and PMA) to afford **7eb** (89%, >25:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (ddd, $^2J_{H\text{-}H}$ = 12.7 Hz, $^3J_{H\text{-}H}$ = 9.7 and 8.6 Hz, 1H, H-2), 2.60 (ddd, $^2J_{H\text{-}H}$ = 12.8 Hz, $^3J_{H\text{-}H}$ = 7.6 and 6.1 Hz, 1H, H-2), 3.41 (m, 1H, H-1), 4.80 (ddd, $^3J_{H\text{-}H}$ = 9.9 Hz, $^2J_{H\text{-}H}$ = 1.7 Hz, $^4J_{H\text{-}H}$ = 0.4 Hz, 1H, H-19), 4.95 (ddd, $^3J_{H\text{-}H}$ = 17.0 Hz, $^2J_{H\text{-}H}$ = 1.7 Hz, $^4J_{H\text{-}H}$ = 0.7 Hz, 1H, H-19), 5.09 (dd, $^3J_{H\text{-}H}$ = 9.7 and 6.1 Hz, 1H, H-3), 5.15 (ddd, $^3J_{H\text{-}H}$ = 17.0, 9.8, and 8.6 Hz, 1H, H-18), 5.28 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-5), 7.23 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, H-9, 11), 7.38 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 2H, H-8, 12), 7.47 (m, 2H, H-13, 17), 8.18 (dd, $^3J_{H\text{-}H}$ = 8.8 Hz, $^4J_{H\text{-}H}$ = 2.3 Hz, 2H, H-14, 16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3 (CH_3, C-21), 40.4 (CH_2, C-2), 49.2 (CH, C-1), 80.9 (CH, C-3), 82.8 (CH, C-5), 116.4 (CH_2, C-19), 123.4 (CH, C-14, 16), 126.0 (CH, C-8, 12), 127.7 (CH, C-9, 11), 129.4 (CH, C-13, 17), 137.6 (CH, C-18), 137.7 (C, C-10), 138.2 (C, C-6), 147.2 (C, C-7), 147.9 (C, C-15); IR ν 3016, 2927, 1495, 1457, 1220, 1090, 1069 cm^{-1}; MS (CI-isobutane) *m/z* (%) 310 ($M+H^+$, 66), 292 (100), 187 (14), 122 (27); HRMS (CI-isobutane) *m/z* 310.1439 ($C_{19}H_{20}NO_3$, $M+H^+$, requires 310.1443).



7eg

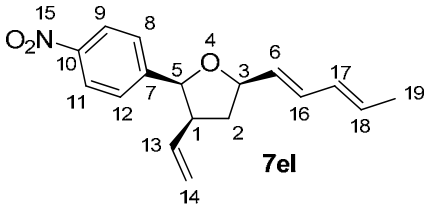
7eg was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 90:10 mixture; R_F = 0.20, stains visualized by UV and PMA) to afford **7eg** (92%, 10:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (ddd, $^2J_{H\text{-}H}$ = 12.7, $^3J_{H\text{-}H}$ = 9.4 and 8.3 Hz, 1H, H-2), 2.64 (ddd, $^2J_{H\text{-}H}$ = 12.7 Hz, $^3J_{H\text{-}H}$ = 7.5 and 6.3 Hz, 1H, H-2), 3.40 (m, 1H, H-1), 4.81 (dd, $^3J_{H\text{-}H}$ = 10.0 Hz, $^2J_{H\text{-}H}$ = 1.5, 1H, H-19), 4.94 (ddd, $^3J_{H\text{-}H}$ = 16.7 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, $^4J_{H\text{-}H}$ = 0.6 Hz, 1H, H-19), 5.06-5.18 (m, 2H, H-3, 18), 5.35 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, H-5), 7.44-7.54 (m, 6H, H-8,9,11,12,13,17), 8.24-8.28 (m, 2H, H-14, 16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 40.5 (CH_2, C-2), 49.1 (CH, C-1), 80.2 (CH, C-3), 82.9 (CH, C-5), 116.6 (CH_2, C-19), 123.4 (CH, C-14, 16), 127.3 (CH, C-8, 12), 127.6 (CH, C-9, 11), 128.9 (CH, C-13, 17), 136.6 (C, C-10), 137.2 (CH, C-18), 139.9 (C, C-6),

147.3 (C, C-7), 147.5 (C, C-15); IR ν 3014, 2965, 1494, 1454, 1215, 1058, 1013 cm^{-1}; MS (CI-isobutane) *m/z* (%) 332/330 ($M+H^+$, 12/39), 302 (40), 300 (100), 266 (10), 122 (75); HRMS (CI-isobutane) *m/z* 330.0899 ($C_{18}H_{17}{}^{35}ClNO_3$, $M+H^+$, requires 330.0897).



7ek

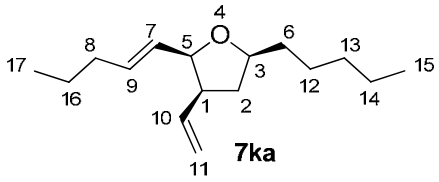
7ek was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.46, stains visualized by UV and PMA) to afford **7ek** (95%, >25:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (t, $^3J_{H-H}$ = 7.4, 3H, H-1), 1.41-1.53 (m, 2H, H-18), 1.67 (ddd, $^2J_{H-H}$ = 12.6, $^3J_{H-H}$ = 10.0 and 9.3 Hz, 1H, H-2), 2.05-2.15 (m, 2H, H-17), 2.27 (ddd, $^2J_{H-H}$ = 12.8 Hz, $^3J_{H-H}$ = 7.1 and 5.9 Hz, 1H, H-2), 3.25-3.33 (m, 1H, H-1), 4.49 (td, $^3J_{H-H}$ = 9.4 and 6.5 Hz, 1H, H-3), 4.81 (dd, $^3J_{H-H}$ = 10.0 Hz, $^2J_{H-H}$ = 1.7, 1H, H-14), 4.95 (ddd, $^3J_{H-H}$ = 16.9 Hz, $^2J_{H-H}$ = 1.8 Hz, $^4J_{H-H}$ = 0.5 Hz, 1H, H-14), 5.10 (ddd, $^3J_{H-H}$ = 17.0, 9.9 and 9.2, 1H, H-13), 5.15 (d, $^3J_{H-H}$ = 8.17 Hz, 1H, H-5), 5.68 (tdd, $^3J_{H-H}$ = 14.0 and 6.7, $^4J_{H-H}$ = 1.4, 1H, H-16), 5.84 (td, $^3J_{H-H}$ = 13.8 and 6.7, 1H, H-6), 7.35 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-9, 11), 8.11 (d, $^3J_{H-H}$ = 8.6 Hz, 2H, H-8, 12); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3, C-1), 22.4 (CH_2, C-18), 34.5 (CH_2, C-17), 38.7 (CH_2, C-2), 49.2 (CH, C-1), 80.8 (CH, C-3), 82.5 (CH, C-5), 116.4 (CH_2, C-14), 123.3 (CH, C-9, 11), 127.6 (CH, C-8, 12), 134.5 (CH, C-6), 136.9 (CH, C-16), 137.4 (CH, C-13), 147.1 (C, C-7), 148.2 (C, C-10); IR ν 3020, 2931, 1492, 1488, 1447, 1216, 1088, 1060, 1011 cm^{-1}; MS (CI-isobutane) *m/z* (%) 288 ($M+H^+$, 19), 258 (41), 240 (8), 113 (20), 97 (21), 69 (100); HRMS (CI-isobutane) *m/z* 288.1601 ($C_{17}H_{22}NO_3$, $M+H^+$, requires 288.1594).



7el

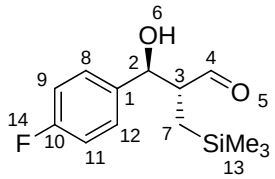
7el was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.40, stains visualized by UV and PMA) to afford **7el** (91%, 7:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (td, $^2J_{H-H}$ = 12.6, $^3J_{H-H}$ = 6.8, 1H, H-2), 1.79 (dd, $^3J_{H-H}$ = 6.7, $^4J_{H-H}$ = 1.1, 3H, H-19), 2.30 (ddd, $^2J_{H-H}$ = 12.6, $^3J_{H-H}$ = 7.1 and 6.5 Hz, 1H, H-2), 3.25-3.34 (m, 1H, H-1), 4.56 (td, $^3J_{H-H}$ = 9.1 and 6.5 Hz, 1H, H-3), 4.82 (dd, $^3J_{H-H}$ = 9.9 Hz, $^2J_{H-H}$ = 1.8, 1H, H-14), 4.95 (ddd, $^3J_{H-H}$ =

17.0 Hz, $^{2}J_{H\text{-}H}$ = 1.8 Hz, $^{4}J_{H\text{-}H}$ = 0.6 Hz, 1H, H-14), 5.09 (ddd, $^{3}J_{H\text{-}H}$ = 17.0, 9.9 and 9.2, 1H, H-13), 5.17 (d, $^{3}J_{H\text{-}H}$ = 8.3 Hz, 1H, H-7), 5.73-5.82 (m, 2H, H-6, 18), 6.13 (ddd, $^{3}J_{H\text{-}H}$ = 15.0, 10.5 and 1.4 Hz, 1H, H-16), 6.33 (dd, $^{3}J_{H\text{-}H}$ = 15.2 and 10.4, 1H, H-17), 7.41 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 2H, H-8, 12), 8.18 (d, $^{3}J_{H\text{-}H}$ = 8.1 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.3 (CH_3, C-19), 38.7 (CH_2, C-2), 49.3 (CH, C-1), 80.4 (CH, C-3), 82.6 (CH, C-5), 116.5 (CH_2, C-14), 123.3 (CH, C-9, 11), 127.6 (CH, C-18), 129.5 (CH, C-8, 12), 130.7 (CH, C-17), 131.0 (CH, C-16), 132.8 (CH, C-6), 137.3 (CH, C-13), 147.2 (C, C-7), 148.1 (C, C-10); IR ν 3010, 2920, 1490, 1472, 1095, 1049, 1024 cm^{-1}; MS (CI-isobutane) *m/z* (%) 286 ($M+H^+$, 100), 243 (8), 238 (10), 69 (80); HRMS (CI-isobutane) *m/z* 286.1432 ($C_{17}H_{20}NO_3$, $M+H^+$, requires 286.1438).



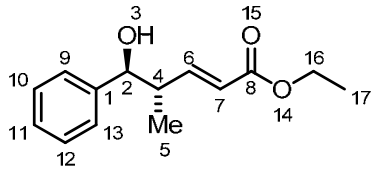
7ka

7ka was prepared by method **C.** The crude product was purified by chromatography on a column of silica gel (0.4 × 5 cm) with a mixture of petroleum ether and AcOEt (99:1) (TLC in a petroleum ether-AcOEt 9:1 mixture; R_F = 0.62, stains visualized by PMA) to afford **7ka** (70%, 9:1 de) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, $^{3}J_{H\text{-}H}$ = 7.3, 6H, H-15, 17), 1.22-1.52 (m, 10H, H-6, 12, 13, 14, 16), 1.65-1.73 (m, 1H, H-1), 1.95-2.06 (m, 2H, H-8), 2.12 (ddd, $^{2}J_{H\text{-}H}$ = 12.7, $^{3}J_{H\text{-}H}$ = 7.0 and 5.8 Hz, 1H, H-2), 2.88-2.97 (m, 1H, H-2), 3.86 (tdd, $^{3}J_{H\text{-}H}$ = 9.7, 9.4 and 6.8 Hz, 1H, H-3), 4.33 (t, $^{3}J_{H\text{-}H}$ = 7.7 Hz, 1H, H-5), 5.00 (dd, $^{3}J_{H\text{-}H}$ = 9.0 Hz, $^{2}J_{H\text{-}H}$ = 1.5 Hz, 1H, H-11), 5.37 (tdd, $^{3}J_{H\text{-}H}$ = 15.3 and 7.8 Hz, $^{4}J_{H\text{-}H}$ = 1.3 Hz, 1H, H-11), 5.62 (td, $^{3}J_{H\text{-}H}$ = 15.3 and 6.7 Hz, 1H, H-10), 5.65-5.70 (m, 1H, H-7), 5.70 (ddd, $^{3}J_{H\text{-}H}$ = 17.1, 9.4 and 8.6, 1H, H-9); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8 (CH_3, C-15), 14.2 (CH_3, C-17), 22.4 (CH_2, C-14), 22.7 (CH_2, C-16), 26.2 (CH_2, C-12), 32.1 (CH_2, C-13), 34.5 (CH_2, C-6), 36.4 (CH_2, C-2), 38.5 (CH_2, C-8), 48.1 (CH, C-1), 79.4 (CH, C-3), 82.6 (CH, C-5), 115.0 (CH_2, C-11), 128.1 (CH, C-9), 133.5 (CH, C-7), 138.6 (CH, C-10); IR ν 2998, 2941, 1450, 1210, 1090, 1001 cm^{-1}; MS (CI-isobutane) *m/z* (%) 237 ($M+H^+$, 28), 219 (22), 123 (35), 97 (23), 85 (66), 69 (100); HRMS (CI-isobutane) *m/z* 237.2213 ($C_{16}H_{29}O$, $M+H^+$, requires 237.2213); chiral GC (Supelco β-DEX 120 column, oven for 1 min at 60 ^{o}C, then increase at 0.5 deg min^{-1}) showed 98% ee (t_{minor} = 135.9 min, t_{major} = 136.5 min).



276c

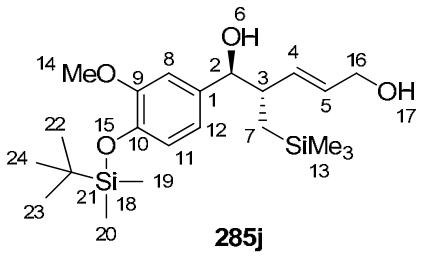
(267c). The homoallylic alcohol **4c** (20 mg, 0.079 mmol) was dissolved in dry methanol (10 mL) and cooled to -90°C. Stream of ozone was bubbled through the mixture, while stirring vigorously. Samples of the reaction mixture were then checked by the TLC frequently, until the reaction reached the full conversion (typically several minutes). The reaction was then immediately quenched with DMS (2 mL) and the mixture was left stirring for another hour at room temperature. A solution of semi-saturated potassium iodide (10 mL) was added and the mixture was extracted with diethyl ether (3×10 mL). The organic layer was washed with brine (1×30), dried (Na_2SO_4), and evaporated *in vacuo* to afford the pure product **276c** (19 mg, 95%): ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.05 (s, 9H, H-13), 0.39 (dd, $^2J_{H\text{-}H}$ = 14.9 Hz, $^3J_{H\text{-}H}$ = 3.6 Hz, 1H, H-7), 0.76 (dd, $^2J_{H\text{-}H}$ = 14.9 Hz, $^3J_{H\text{-}H}$ = 10.8 Hz, 1H, H-7), 2.45 (d, $^3J_{H\text{-}H}$ = 3.4 Hz, 1H, H-3), 2.69-2.78 (m, 1H, H-6), 4.79 (dd, $^3J_{H\text{-}H}$ = 7.8 and 3.2 Hz, 1H, H-2), 7.07 (m, 2H, H-9, 11), 7.33 (dd, $^3J_{H\text{-}F}$ = 8.7 Hz, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, H-8, 12), 9.74 (dd, $^3J_{H\text{-}H}$ = 3.0 Hz, $^4J_{H\text{-}H}$ = 0.8 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ 0.3 (CH_3, C-13), 14.5 (CH_2, C-7), 56.2 (CH, C-3), 77.2 (CH, C-2), 116.7 (d, $^2J_{C\text{-}F}$ = 22.4 Hz, CH, C-9, 11), 129.7 (d, $^3J_{C\text{-}F}$ = 7.8 Hz, CH, C-8, 12), 138.4 (d, $^4J_{C\text{-}F}$ = 2.9 Hz, C, C-1), 162.5 (d, $^1J_{C\text{-}F}$ = 245.0 Hz, C, C-10), 205.5 (CH, C-4); ^{19}F NMR (377 MHz, $CDCl_3$) δ -113.8 (tt, $^3J_{H\text{-}F}$ = 8.6 Hz, $^4J_{H\text{-}F}$ = 5.4 Hz, 1F); IR ν 3027, 2866, 2754, 1725, 1249, 1217 cm^{-1}; MS (CI-isobutane) *m/z* (%) 237 ($M+H^+$-H_2O, 12), 125 (100), 115 (52), 85 (64); HRMS (CI-isobutane) *m/z* 237.1110 ($C_{13}H_{18}FOSi$, $M+H^+$, requires 237.1105).



38a

(38a). Ethyl acrylate (1 ml, 9.2 mmol) was added in one portion to the racemic homoallylic alcohol **37a** (100 mg, 0.62 mmol, *anti:syn* = 3:1) in CH_2Cl_2 (10 mL) under Ar at room temperature. The mixture was stirred for 5 min, a solution of Grubs 2nd generation catalyst (13 mg, 15 μmol) in CH_2Cl_2 (1 mL) was added. The mixture was stirred at 40 °C for 2 days, then it was allowed to cool to room temperature, and diluted with CH_2Cl_2 (10 mL) and water (10 mL). The organic phase was separated and washed with water (2×10 mL) and brine (1×10 mL), and dried (Na_2SO_4). The drying agent was filtered off and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on a column of silica gel (2 g), using petroleum ether-AcOEt (4:1) as an eluent to afford the

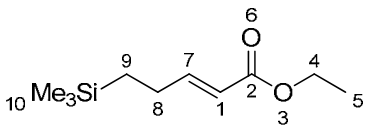
unreacted starting alcohol **37a** (26 mg, 26%) and the desired ester **38a** as a colourless oil (48 mg, 33%, *anti:syn* = 3:1). (TLC in PE:EtOAc 4:1, R_F = 0.21, visualized by PMA): **Major diastereoisomer (*anti*)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, $^3J_{H\text{-}H}$ = 6.9 Hz, 3H, H-5), 1.30 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H, H-17), 1.95 (bs, 1H, H-3), 2.61–2.71 (m, 1H, H-4), 4.19 (q, $^3J_{H\text{-}H}$ = 7.1 Hz, 2H, H-16), 4.51 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 1H, H-2), 5.91 (dd, $^3J_{H\text{-}H}$ = 15.8 Hz, $^4J_{H\text{-}H}$ = 1.0 Hz, 1H, H-7), 7.04 (dd, $^3J_{H\text{-}H}$ = 15.7 Hz, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-6), 7.27-7.38 (m, 5H, H-9,10,11,12,13). **Minor diastereoisomer (*syn*)** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (d, $^3J_{H\text{-}H}$ = 6.7 Hz, 3H, H-5), 1.26 (t, $^3J_{H\text{-}H}$ = 7.1 Hz, 3H, H-17), 1.95 (bs, 1H, H-3), 2.69–2.76 (m, 1H, H-4), 4.12 (q, $^3J_{H\text{-}H}$ = 7.2 Hz, 2H, H-16), 4.71 (d, $^3J_{H\text{-}H}$ = 5.4 Hz, 1H, H-2), 5.79 (dd, $^3J_{H\text{-}H}$ = 15.8 Hz, $^4J_{H\text{-}H}$ = 1.3 Hz, 1H, H-7), 6.95 (dd, $^3J_{H\text{-}H}$ = 15.8 Hz, $^3J_{H\text{-}H}$ = 7.4 Hz, 1H, H-6), 7.27-7.38 (m, 5H, H-9,10,11,12,13) in accordance with the literature data.[146]



285j

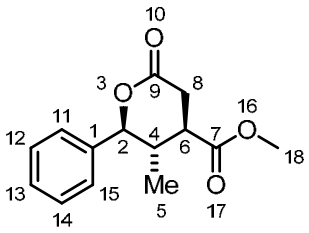
(285j). DIBAL (260 µL, 0.260 mmol, 1M solution in cyclohexane) was added to a solution of ester **273j** (12 mg, 0.026 mmol) in dry dichloromethane (1 mL) at -90°C in one portion, while stirring vigorously. The solution was then further stirred at that temperature for another hour and then left to warm to 0 °C overnight. The reaction mixture was then cooled to approx. -60 °C and quenched with water. The mixture was extracted with dichloromethane (3×10 mL) and the organic phase was dried over Na_2SO_4 and evaporated *in vacuo* to yield crude **285**, which was purified by chromatography on a column of silica gel (0.5×5cm) with diethyl ether as an eluent (TLC in diethyl ether, R_F = 0.40, stains visualized by PMA) to afford pure **285** as a viscous colourless oil (9 mg, 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.12 (s, 9H, H-13), 0.13 (s, 3H, H-19), 0.14 (s, 3H, H-20), 0.35 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 3.2 Hz, 1H, H-7), 0.41 (dd, $^2J_{H\text{-}H}$ = 14.6 Hz, $^3J_{H\text{-}H}$ = 11.0 Hz, 1H, H-7), 0.98 (s, 9H, H-22, 23, 24), 1.70 (br s, 1H, H-17), 2.02 (br s, 1H, H-6), 2.32-2.45 (m, 1H, H-3), 3.80 (s, 3H, H-14), 4.13 (d, $^3J_{H\text{-}H}$ = 5.5 Hz, 2H, H-16), 4.19 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-2), 5.51 (dd, $^3J_{H\text{-}H}$ = 15.4 and 9.4 Hz, 1H, H-4), 5.78 (dt, $^3J_{H\text{-}H}$ = 15.4 and 5.7 Hz, 1H, H-5), 6.72 (dd, $^3J_{H\text{-}H}$ = 8.0 Hz, $^4J_{H\text{-}H}$ = 1.8 Hz, 1H, H-12), 6.78-6.83 (m, 2H, H-8, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -4.5 (CH_3, C-19, 20), -0.6 (CH_3, H-13), 18.5 (C, C-21), 18.6 (CH_2, C-7), 25.9 (CH_3, C-22, 23, 24), 47.3 (CH, C-3), 55.6 (CH, C-2), 63.5 (CH_2, C-16), 79.3 (CH_3, C-14), 110.7 (CH, C-8), 120.1 (CH, C-12), 120.6 (CH, C-11), 132.1 (CH, C-5), 135.2 (CH, C-6), 136.0 (C,

C-1), 144.7 (C. C-10), 151.1 (C, C-9); IR ν 3520, 2995, 2832, 2856, 2221, 1254, 1215 cm^{-1}; MS (CI-isobutane) *m/z* (%) 407 ($M+H^+-H_2O$, 28), 391 (11), 317 (8), 267 (100); 209 (9); HRMS (CI-isobutane) *m/z* 407.2435 ($C_{22}H_{39}O_3Si_2$, $M+H^+-H_2O$, requires 407.2432).



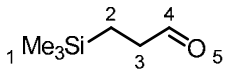
277

277 was formed as an undesired byproduct of the Wittig-Horner reaction (95 mg, 42%): ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.00 (s, 9H, H-10), 0.61-0.67 (m, 2H, H-9), 1.28 (t, $^3J_{H-H}$ = 7.1 Hz, 3H, H-5), 2.15-2.22 (m, 2H, H-8), 4.18 (q, $^3J_{H-H}$ = 7.1, 2H, H-4), 5.80 (dt, $^3J_{H-H}$ = 15.5 Hz, $^4J_{H-H}$ = 1.6 Hz, 1H, H-1), 7.02 (dt, $^3J_{H-H}$ = 15.5 Hz, $^3J_{H-H}$ = 6.6 Hz, 1H, H-7); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.6 (CH_3, C-10), 14.4 (CH_3, C-5), 15.1 (CH_2, C-9), 26.8 (CH_2, C-8), 60.2 (CH_2, C-4), 120.1 (CH, C-1), 152.0 (CH, C-7), 167.1 (CO, C-2); IR ν 3005, 2984, 2954, 1740, 1222 cm^{-1}; MS (CI-isobutane) *m/z* (%) 201 ($M+H^+$, 100), 181 (10), 121 (12), 85 (30); HRMS (CI-isobutane) *m/z* 200.1200 ($C_{10}H_{20}O_2Si$, $M+H^+$, requires 200.1233).



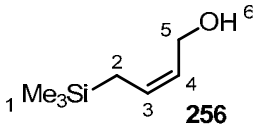
275

(275). $PdCl_2$ (1 mg, 5.6 μmol), $Cu(OAc)_2.H_2O$ (17.1 mg, 86 μmol) and MeOH (100 μL) were added to a solution of the homoallylic alcohol **37a** (6.7 mg, 29 μmol) in dry MeCN (5 mL). The reaction flask was flushed with CO for 30 min and then stirred under atmospheric pressure of CO at 60 °C for 3 days (while monitoring by TLC). The reaction mixture was allowed to cool to room temperature, AcOEt (15 mL) was added, and the mixture was washed with saturated aqueous solution of $NaHCO_3$ (1×10 mL) and brine (1×10 mL). The organic phase was separated and dried (Na_2SO_4). The solids were filtered off and solvent was evaporated *in vacuo* to afford the crude product, which was purified by chromatography on a column of silica gel (0.2 g) using petroleum ether-AcOEt (7:1) as an eluent to afford **275** as a colourless oil (3.1 mg, 34%) (TLC in PE/EtOAc = 4:1, R_F = 0.50, visualized by $KMnO_4$): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.00 (d, $^3J_{H-H}$ = 7.2 Hz, 3H, H-5), 1.95 (dd, $^2J_{H-H}$ = 17.0 Hz, $^3J_{H-H}$ = 9.1 Hz, 1H, H-8), 2.65-2.70 (m, 1H, H-8), 2.76–2.84 (m, 1H, H-4), 3.14-3.18 (m, 1H, H-6), 3.70 (s, 3H, H-18), 5.25 (d, $^3J_{H-H}$ = 2.4 Hz, 1H, H-2), 7.30-7.43 (m, 5H, H-11, 12, 13, 14, 15).



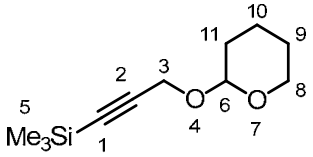
36m

(36m). A solution of DMSO (8 mL, 112.6 mmol) in CH_2Cl_2 (20 mL) was added dropwise to a solution of oxalylchloride (4.8 mL, 56.7 mmol) in CH_2Cl_2 (30 mL) at -78° C while stirring vigorously. 3-(Trimethylsilyl)-1-propanol (5g, 37.8 mmol) in CH_2Cl_2 (20 mL) was then added dropwise and the reaction mixture was stirred at -78° C for 30 min. Hünig's base (38.3 mL, 213.3 mmol) was added portionwise, the reaction mixture was stirred at -78° C for 20 minutes and then left to warm to 0° C during 1 h and then poured into an ice-cold saturated aqueous solution of NH_4Cl (200 mL). The organic layer was separated, the aqueous layer was extracted with CH_2Cl_2 (2×50 mL), the organic phases were combined, washed with water (3×50mL) and brine (1×50mL), dried (Na_2SO_4), and evaporated *in vacuo* to afford the product in a form of an yellowish oil, which was used without further purification (4.0 g, 82%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.02 (s, 9H, H-1), 0.80 (t, $^3J_{H\text{-}H}$ = 9.0 Hz, 2H, H-2), 2.43 (dt, $^3J_{H\text{-}H}$ = 8.7 Hz, $^3J_{H\text{-}H}$ = 2.0, 2H, H-3), 9.79 (t, $^3J_{H\text{-}H}$ = 1.8 Hz, 1H, H-4); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.6 (CH_3, C-1), 11.9 (CH_2, C-2), 36.2 (CH_2, C-3), 198.0 (CO, C-4) in accordance with the literature data.[147]



256

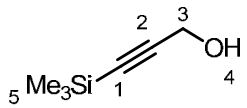
(256). A round bottom flask was charged with the Lindlar catalyst (240 mg), evacuated, and filled with Ar three times. A solution of alkyne **228** (1.200 g, 8.4 mmol) in MeOH (10 mL) was added and the reaction vessel was flushed with the hydrogen gas for 30 min and then kept under an atmospheric pressure of hydrogen overnight while stirring vigorously. Lindlar catalyst was filtered off on a short plug of Celite and the filtrate was concentrated *in vacuo* giving **256** as a viscous yellowish oil (1.144 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H, H-1), 1.52 (d, $^3J_{H\text{-}H}$= 8.6 Hz, 2H, H-2), 4.13 (d, $^3J_{H\text{-}H}$= 6.5 Hz, 2H, H-5), 5.49 (dt, $^3J_{H\text{-}H}$= 10.2 and 6.7 Hz, 1H, H-3), 5.58 (dt, $^3J_{H\text{-}H}$ = 10.0 and 8.7 Hz, 1H, H-4) in accordance with the literature data.[144]



299

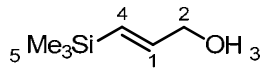
(299). *n*-BuLi (1.6M solution in hexane, 54 mL, 86.22 mmol) was added to a solution of 2-(2'-propynyl)tetrahydro-2*H*-pyran (12.09 g, 86.22 mmol) in dry THF (150 mL) at -78 °C over 1 h while stirring vigorously. The mixture was then stirred at the same temperature for an additional 15 min and then at -20 °C for another 20 min. Then the reaction mixture was cooled to -78 °C and a solution of

chlorotrimethylsilane (10.9 mL, 86.22 mmol) in dry THF (40 mL) was added slowly *via cannula* over a period of 1 h and the reaction mixture was then stirred at 0 °C for 5 h. The reaction was then quenched with a saturated solution of ammonium chloride (150 mL) and the mixture was extracted with ether (50 mL). The aqueous layer was extracted with ether (3×150 mL) and the combined organic extracts were dried ($MgSO_4$) overnight. $MgSO_4$ was filtered off and the solvents were evaporated *in vacuo* to give crude **299** as a pale yellow liquid, which was used in the next step without further purification (17.76 g, 97%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.16 (s, 9H, H-5), 1.48-1.84 (m, 6H, H-9, 10, 11), 3.51 (dddd, $^2J_{H\text{-}H}$ = 11.1 Hz, $^3J_{H\text{-}H}$ = 8.5 and 4.4 Hz, $^4J_{H\text{-}H}$ = 1.7 Hz, 1H, H-8), 3.82 (ddd, $^2J_{H\text{-}H}$ = 11.7 Hz, $^3J_{H\text{-}H}$ = 9.2 and 3.1 Hz, 1H, H-8), 4.20 (d, $^2J_{H\text{-}H}$ = 15.9 Hz, 1.7 Hz, 1H, H-2), 4.28 (d, $^2J_{H\text{-}H}$ = 15.9 Hz, 1.7 Hz, 1H, H-2), 4.80 (t, $^4J_{H\text{-}H}$ = 3.4 Hz, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (CH_3, C-5), 18.9 (CH_2, C-10), 25.3 (CH_2, C-9), 30.2 (CH_2, C-11), 54.8 (CH_2, C-8), 61.9 (CH_2, C-3), 90.8 (C, C-1), 96.7 (CH, C-6), 101.4 (C, C-2) in accordance with the literature data.[148]



300

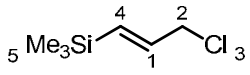
(300). A solution of PTSA (3.16 g, 16.73 mmol) and pyridine (1.34 mL, 16.73 mmol) in ethanol (120 mL) was added in one portion to a solution of the THP protected alcohol **300** (17.76 g, 83.63 mmol) in a mixture of ethanol (120 mL) and water (40 mL) and the reaction mixture was stirred at 60 °C for 24 h. Ethanol was then evaporated *in vacuo*, the residue was diluted with petroleum ether (150 mL) and washed with saturated $NaHCO_3$ (1×150 mL) and brine (3×150 mL). Combined organic layers were dried (Na_2SO_4) overnight and evaporated *in vacuo* to afford **300** (10.28 g, 95%) as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.18 (s, 9H, H-5), 1.7 (t, $^3J_{H\text{-}H}$ = 6.1 Hz , 1H, H-4), 4.27 (d, $^3J_{H\text{-}H}$ = 6.1 Hz, 2H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$) δ -0.2 (CH_3, C-5), 51.6 (CH_2, C-3), 90.6 (C, C-1), 103.8 (C, C-2) in accordance with the literature data.[149]



301

(301). A solution of alkyne **300** (10.29 g, 79.48 mmol) in dry THF (50 mL) was added dropwise to a stirred suspension of lithium aluminium hydride (6.03 g, 158.96 mmol) in THF (50 mL) at 0 °C under Ar. The resulting mixture was stirred for another 10 min and then heated at reflux for 1 h. The mixture was cooled in an ice-water bath and cold water (50 mL) was added dropwise until the gas stopped evolving, and then a 20% aqueous NaOH solution (50 mL). The mixture was filtered through a short plug of sand and Celite, the filtrate was diluted with water (50 mL) and extracted with dichloromethane (5×150 mL). Combined organic

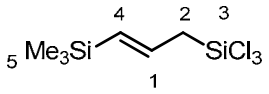
extracts were dried ($MgSO_4$) and the solvents were evaporated *in vacuo* to afford the alkene **301** in a form as a yellow liquid (9.73 g, 94%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 9H, H-5), 1.47 (t, $^3J_{H\text{-}H}$ = 6.0 Hz, 1H, H-3), 4.18 (ddd, $^3J_{H\text{-}H}$ = 6.0 and 4.5 Hz, $^4J_{H\text{-}H}$ = 1.7 Hz, 2H, H-2), 5.92 (dt, $^3J_{H\text{-}H}$ = 18.8 Hz, $^4J_{H\text{-}H}$ = 1.7 Hz, 1H, H-4), 6.18 (dt, $^3J_{H\text{-}H}$ = 18.8 and 4.5 Hz, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.4 (CH_3, C-5), 65.5 (CH_2, C-2), 129.5 (CH, C-4), 144.7 (CH, C-1), consistent with the literature data.[150]



302

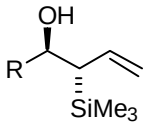
(302). DMF (13.3 mL, 171.65 mmol) was added dropwise to a stirred solution of oxalyl chloride (14.73 mL, 171.65 mmol) in dichloromethane (350 mL) at 0 °C and the resulting white suspension was allowed to warm to the room temperature and after a period of 10 min was cooled to 0 °C again. Allylic alcohol **302** (22.36 g, 171.65 mmol) was added in one portion and the resulting solution was heated at reflux for 24 h. The reaction mixture was then left to cool to room temperature, brine (150 mL) was added, and the product was extracted into dichloromethane (2 × 150 mL). Combined organic extracts were washed with water (3×100 mL) and dried ($MgSO_4$). $MgSO_4$ was filtered off and the solvents were distilled off (bath temperature 60 °C). Ethyl acetate (20 mL) was added (to form an azeotrope with the residual dichloromethane) and distilled off again (bath temperature 90 °C) and this procedure was repeated once more to afford **302** (22.97 g, 90%) as a colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 9H, H-5), 4.07 (dd, $^3J_{H\text{-}H}$ = 5.8 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 2H, H-2), 5.98 (dt, $^3J_{H\text{-}H}$ = 18.3 Hz, $^4J_{H\text{-}H}$ = 0.9 Hz, 1H, H-4), 6.09 (dt, $^3J_{H\text{-}H}$ = 18.3 and 5.8 Hz, 1H, H-1); ^{13}C NMR (100 MHz, $CDCl_3$) δ -1.7 (CH_3, C-5), 47.2 (CH_2, C-2), 134.5 (CH, C-4), 140.3 (CH, C-1) consistent with the literature data.[151]

Alternative procedure: Allylic alcohol **301** (510 mg, 3.92 mmol) was added to a solution of triphenylphosphine (1.03 g, 3.92 mmol) in CCl_4 (15 mL, 156 mmol) and heated to 85 °C under argon while stirring for 1 h and then tetrachloromethane was distilled off (bath temperature 90 °C). Ethyl acetate (10 mL) was added and distilled off twice. Dry diethyl ether (20 mL) was added and the resulting suspension was filtered through a short plug of Celite, and the solvent was distilled off to afford the chloride **302** as a colourless oil (379 mg, 65%).



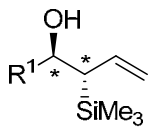
3

(3). Hünig's base (2.14 mL, 16.57 mmol) was added to a suspension of CuCl (2.63 g, 26.51 mmol) and powder 4Å molecular sieves (1 g) in dry ether (15 mL) in an oven-dried flask at 0 °C under Ar. A solution of allylic chloride **302** (982 mg, 6.63 mmol) in diethyl ether (20 mL) was added *via cannula* in one portion and the resulting mixture was stirred at 0 °C for 10 min. Trichlorosilane (3.54 g, 26.51 mmol) was added dropwise over a period of 10 min while stirring vigorously and the reaction mixture was stirred at 0 °C for another 10 min and then at the room temperature until reaching the full conversion, checked by NMR (typically 1-5 h). The reaction mixture was then filtered under Ar and the diethyl ether was distilled off under Ar. The crude product was purified by distillation under reduced pressure (120 -125 °C / 50 torr) to give the trichlorosilane **3** as a colourless liquid (1.10 g, 67%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.07 (s, 9H, H-5), 2.43 (d, $^{3}J_{H\text{-}H}$ = 6.3 Hz, 2H, H-2), 5.85 (d, $^{3}J_{H\text{-}H}$ = 18.5 Hz, 1H, H-4), 5.93 (td, $^{3}J_{H\text{-}H}$ = 18.5 and 6.3 Hz, 1H); ^{13}C MR (100 MHz, $CDCl_3$) δ -1.4 (CH_3, C-5), 33.8 (CH_2, C-2), 134.1 (CH, C-4), 137.0 (CH, C-1); MS (FAB+) *m/z* (%) 247 [$(M+H)^+$, 40], 207 (100), 193 (75), 147 (50), 133 (60).



6

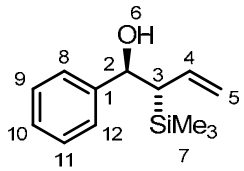
Method D: General procedure for the synthesis of racemic homoallylic alcohols 6. Hünig's base (4 mmol), DMF (4 mmol), and the corresponding aldehyde (2 mmol) were added consecutively to a solution of trimethyl[3-(trichlorosilyl)-2-propenyl]silane **3** (2 mmol) in dry acetonitrile (8 mL) at 0 °C and the resulting mixture was stirred at this temperature for 48 h. The reaction was quenched with a saturated solution of $NaHCO_3$ (10 mL), dichloromethane (20 mL) was added, and the resulting suspension was filtered through a short pad of Celite. The organic layer was separated and the aqueous layer was extracted with dichloromethane (3×40 mL). Combined organic layers were dried (Na_2SO_4) overnight, Na_2SO_4 was filtered off, and the solvent was evaporated *in vacuo* to furnish the crude product that was purified on a column of silica gel (2.0 × 25 cm) with a mixture of petroleum ether and AcOEt (98:2).



6

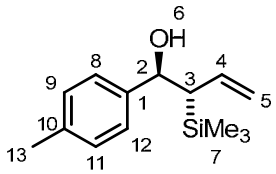
Method E: General procedure for the synthesis of enantio-enriched homoallylic alcohols 6. A solution of the chiral catalyst in an appropriate solvent (MeCN, DCM or THF depending on the catalyst, see **Table 19**), Hünig's base (300 mg, 2.4 mmol), and the

corresponding aldehyde (0.5 mmol) were added consecutively in this order to a solution of allyldisilane **3** (100 mg, 0.4 mmol) in the appropriate solvent (10 mL) at -78 °C. The reaction mixture was then transferred to a freezer (-35 °C). Upon reaching the full conversion (monitored by NMR spectroscopy), the reaction was quenched with a saturated $NaHCO_3$ solution (1 mL) and left to warm up to room temperature. The solid residue was removed by filtration, the solvent was evaporated, and the residue was dissolved in ether (30 mL) and the solution was washed with a saturated $NaHCO_3$ solution (2 × 20 mL) and brine (1 × 30 mL) and dried (Na_2SO_4) and evaporated. The crude product was purified by chromatography on a column of silica gel (2 × 25 cm) with a mixture of petroleum ether and AcOEt (98:2).



6a

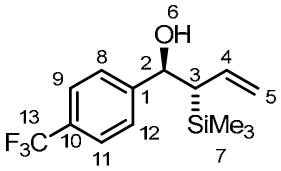
6a was prepared by method **D** / **E.** The crude product was purified by chromatography on a column of silica gel (2.0×25 cm) with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 7:1 mixture; R_F = 0.37, stains visualized by UV and PMA) to afford **6a** (51 mg, 9%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.20 (s, 9H, H-7), 2.08 (dd, $^3J_{H\text{-}H}$ = 10.1 and 8.8 Hz, 1H, H-3), 2.22 (d, $^3J_{H\text{-}H}$ = 2.2 Hz, 1H, H-6), 4.80 (dd, $^3J_{H\text{-}H}$ = 8.8 and 2.2 Hz, 1H, H-2), 5.03 (dd, $^3J_{H\text{-}H}$ = 17.1 Hz, $^2J_{H\text{-}H}$ = 1.3 Hz, 1H, H-5), 5.11 (dd, $^3J_{H\text{-}H}$ = 10.3 Hz, $^2J_{H\text{-}H}$ = 1.8 Hz, 1H, H-5), 5.86 (td, $^3J_{H\text{-}H}$ = 17.1, 10.3, and 10.1 Hz 1H, H-4), 7.27-7.34 (m, 5H, H-8, 9, 10, 11, 12); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.4 (CH_3, C-7), 45.6 (CH, C-3), 74.5 (CH, C-2), 116.0 (CH_2, C-5), 126.9 (CH, C-10), 127.8 (CH, C-9, 11), 128.4 (CH, C-8, 12), 136.6 (CH, C-4), 143.6 (C, C-1), consistent with the literature data.[152]



6b

6b was prepared by method **D** / **E.** The crude product was purified by chromatography on a column of silica gel (2.0×25 cm) with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 7:1 mixture; R_F = 0.40, stains visualized by UV and PMA) to afford **6b** (102 mg, 17%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.20 (s, 9H, H-7), 2.07 (dd, $^3J_{H\text{-}H}$ = 10.2 and 8.7 Hz, 1H, H-3), 2.19 (d, $^3J_{H\text{-}H}$ = 2.1 Hz, 1H, H-6), 2.34 (s, 3H, H-13), 4.76 (dd, $^3J_{H\text{-}H}$ = 8.7 and 2.1 Hz, 1H, H-2), 5.02 (ddd, $^3J_{H\text{-}H}$ = 17.1 Hz, $^2J_{H\text{-}H}$ = 1.9 Hz, $^4J_{H\text{-}H}$ = 0.7 Hz, 1H, H-5), 5.1 (dd, $^3J_{H\text{-}H}$ = 10.3 Hz, $^2J_{H\text{-}H}$ = 1.9 Hz, 1H, H-5), 5.86 (td, $^3J_{H\text{-}H}$ = 17.1 and 10.2 Hz, 1H, H-4), 7.14 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 2H, H-9, 11), 7.21-7.24 (m, 2H, H-8, 12); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.4

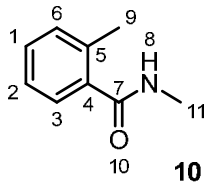
(CH_3, C-7), 21.2 (CH_3, C-13), 45.5 (CH, C-3), 74.3 (CH, C-2), 115.8 (CH_2, C-5), 126.8 (CH, C-8, 12), 129.0 (CH, C-9, 11), 136.8 (CH, C-4), 137.5 (C, C-10), 140.6 (C,C-1).



6d

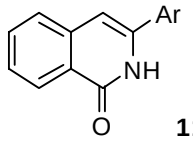
6d was prepared by method **D** / **E.** The crude product was purified by chromatography on a column of silica gel (2.0×25 cm) with a mixture of petroleum ether and AcOEt (98:2) (TLC in a petroleum ether-AcOEt 7:1 mixture; R_F = 0.46, stains visualized by UV and PMA) to afford **31** (205 mg, 29%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ -0.13 (s, 9H, H-7), 2.00 (dd, $^3J_{H\text{-}H}$ = 10.4 and 7.5 Hz, 1H, H-3), 2.34 (d, $^3J_{H\text{-}H}$ = 2.5, 1H, H-6), 4.87 (dd, $^3J_{H\text{-}H}$ = 7.5 and 2.5 Hz, 1H, H-2), 4.96 (dd, $^3J_{H\text{-}H}$ = 17.1 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, 1H, H-5), 5.08 (dd, $^3J_{H\text{-}H}$ = 10.3 Hz, $^2J_{H\text{-}H}$ = 1.5 Hz, 1H, H-5), 5.83 (td, $^3J_{H\text{-}H}$ = 17.1, 10.4, and 10.3 Hz, 1H, H-4), 7.43 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, H-8, 12), 7.58 (d, $^3J_{H\text{-}H}$ = 8.1 Hz, 2H, H-9, 11); ^{13}C NMR (100 MHz, $CDCl_3$) δ -2.4 (CH_3, C-7), 45.4 (CH, C-3), 73.9 (CH, C-2), 116.4 (CH_2, C-5), 124.3 (q, $^1J_{C\text{-}F}$ = 272 Hz, CF_3, C-13), 125.4 (q, $^3J_{C\text{-}F}$ = 3.7 Hz, CH, C-9, 11), 127.1 (CH, C-8, 12), 129.9 (q, $^2J_{C\text{-}F}$ = 32.3 Hz, C, C-10), 135.6 (CH, C-4), 148.0 (C, C-1); ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.4 (CF_3).

5.3 The N,N'-Dioxide Catalyst



10

(10). *o*-Toluoyl chloride (46.38g, 0.3 mol) was added dropwise to a 40% aqueous solution of methylamine (78 mL, 0.9 mol) in water (50 mL) at 0 °C during 30 min, while stirring vigorously. The mixture was then left to stand at room temperature for 30 min. The white precipitate was filtered off and left to dry in the air to give pure *o*-toluamide (43 g, 96%): mp = 74 - 75 °C [lit.[153] gives 74-75 °C]; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.44 (s, 3H, H-9), 2.98 (d, $^3J_{H\text{-}H}$ = 3.6 Hz, 3H, H-11), 5.76 (bs, 1H, H-8), 7.17-7.35 (m, 4H, H-1, 2, 3, 6) in accordance with the literature data.[10]



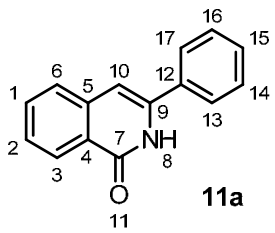
11

Method F: A 10M solution of *n*-BuLi in hexanes (0.40 mL 4.0 mmol) was added dropwise during period of 5 min to a solution of *N*-methyl-*o*-toluamide (2 mmol) in dry THF (5 mL) in an oven-dried flask under Ar at -20 °C. The reaction mixture turned red after addition of half of the *n*-BuLi solution. The mixture was stirred at -20 °C for 30 min and then it was allowed to warm up to 0 °C, and stirred for another 30 min. The reaction mixture was cooled to -50 °C and a solution of the corresponding nitrile (2.2 mmol) in dry THF (5 mL) was added in one portion. The mixture was warmed rapidly to room temperature during a period of 10 min and then added dropwise to water or to a saturated aqueous solution of NH_4Cl or to a mixture of water and THF (40 mL). The resulting suspension was diluted with CH_2Cl_2 (40 mL) and the organic phase was separated. Solid NaOH (0.4 g) was added to the aqueous phase and the aqueous phase was extracted again with CH_2Cl_2 (2×40 mL). Combined organic phases were washed with water (1×40 mL), and brine (1×40 mL), and dried ($MgSO_4$). The drying agent was filtered off and the solvent was evaporated *in vacuo*. The resulting solid was purified by chromatography on a column of silica gel (15 g), using petroleum ether-AcOEt (7:1 to 1:1) as an eluent.

Method G: A 10M solution of *n*-BuLi in hexanes (0.44 mL 4.4 mmol) was added dropwise during period of 5 min to a solution of *N*-methyl-o-toluamide (2 mmol) in dry THF (5 mL) in an oven-dried flask under Ar at -20 °C. The reaction mixture was stirred at -20 °C

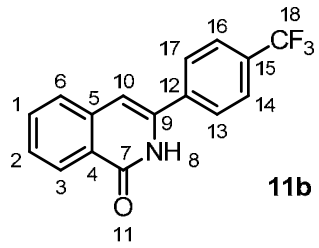
for 30 min and then it was allowed to warm up to 0 °C and stirred for another 30 min. The reaction mixture was cooled to -50 °C and a solution of the corresponding nitrile (2.2 mmol) in dry THF (1 mL) was added in one portion. The resulting mixture was warmed up rapidly to room temperature during a period of 10 min and then water (5 mL) was added. The resulting suspension was diluted with CH_2Cl_2 (40 mL) after 15 min, and the organic phase was separated. Solid NaOH (0.4 g) was added to the aqueous phase, and the aqueous phase was extracted with CH_2Cl_2 (1×40 mL). Combined organic phases were washed with water (3×40 mL) and brine (1×40 mL) and dried ($MgSO_4$). The drying agent was filtered off and the solvent was evaporated *in vacuo*. The resulting solid was purified by chromatography on a column of silica gel (15 g), using petroleum ether-AcOEt (7:1 to 1:1) as an eluent.

Method H: A 10M solution of *n*-BuLi in hexanes (0.44 mL 4.4 mmol) was added dropwise during period of 5 min to a solution of *N*-methyl-*o*-toluamide (2 mmol) in dry THF (5 mL) in an oven-dried flask under Ar at -20 °C. The reaction mixture was stirred for 30 min at -20 °C and then it was allowed to warm up to 0 °C and stirred for another 30 min. The reaction mixture was cooled to -50 °C and a solution of the nitrile (2.2 mmol) in dry THF (5 mL) was added in one portion. The resulting mixture was warmed up rapidly to room temperature during a period of 10 min. Water (5 mL) was added slowly and dropwise at room temperature (the reaction was exothermic). The resulting suspension was diluted with CH_2Cl_2 (40 mL) after 15 min and the organic phase was separated. Solid NaOH (0.4 g) was added to the aqueous phase and the aqueous phase was extracted with CH_2Cl_2 (40 mL). Combined organic phases were washed with water (1×40 mL) and brine (1×40 mL) and dried ($MgSO_4$). The drying agent was filtered off and the solvent was evaporated *in vacuo*. The resulting solid was purified by chromatography on a column of silica gel (15 g), using petroleum ether-AcOEt (7:1 to 1:1) as an eluent.



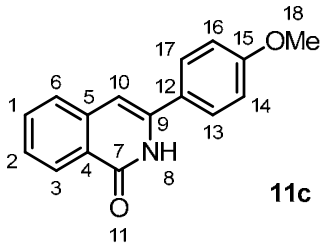
11a

(11a). Compound **11a** was synthesized from benzonitrile according to **method H** and was further purified by crystallization from EtOAc to afford of **11a** as white crystals (510 mg, 65%): mp = 203-205 °C [lit.[154] gives 205 °C]; R_F = 0.57 (PE:EtOAc 1:1, visualised by UV). ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.77 (s, 1H, H-10), 7.42-7.52 (m, 4H, H-2, 14, 15, 16), 7.60 (d, $^3J_{H\text{-}H}$ = 7.7 Hz, 1H, H-6), 7.68-7.71 (m, 3H, H-1, 13, 17), 8.41 (d, $^3J_{H\text{-}H}$ = 8.5 Hz, 1H, H-3) in accordance with the literature data.[153]



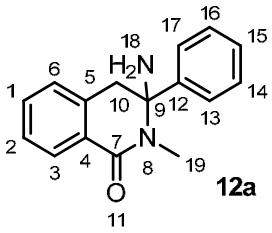
11b

(11b). Compound **11b** was synthesized from 4-trifluoromethylbenzonitrile according to **method H** and further purified by crystallization from EtOAc to afford **11b** as white crystals (980 mg, 79%): mp > 250 °C; R_F = 0.64 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 6.84 (s, 1H, H-10), 7.54 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 1H, H-2), 7.63 (d, $^3J_{H\text{-}H}$ = 7.7 Hz, 1H, H-6), 7.72 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 1H, H-1), 7.78 (d, $^3J_{H\text{-}H}$ = 8.4 Hz, 2H, H-13, 17), 7.86 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 2H, H-14, 16) , 8.42 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 1H, H-3), 10.51 (bs, 1H, H-8); ^{19}F NMR (376.4 MHz, d_6-DMSO) δ -61.1; ^{13}C NMR (100 MHz, d_6-DMSO) δ 104.7 (CH, C-10), 124.1 (q, $^1J_{C\text{-}F}$ = 269.5 Hz, CF_3, C-18), 128.1 (C, C-4), 128.9 (C, C-15), 129.8 (CH, C-14, 16), 131.0 (CH, C-13, 17), 133.5 (CH, C-3), 134.4 (CH, C-2), 134.9 (CH, C-6), 135.5 (C, C-5), 137.0 (CH, C-1), 137.8 (C, C-9), 142.1 (C, C-12), 160.9 (CO, C-12); IR ν 3169, 1638, 1620, 1325, 1112, 1072, 821 cm^{-1}; HRMS (CI, isobutane) *m/z* 290.0795 ($C_{16}H_{11}F_3NO$, M+H$^+$, requires 290.0787).

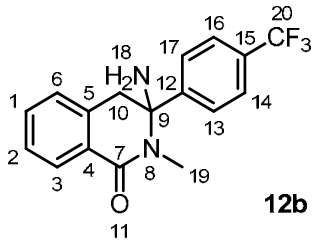


11c

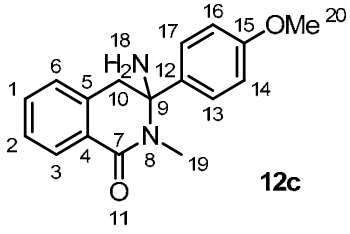
Lactam **(11c)** was synthesized from 4-methoxybenzonitrile according to **method H** and was further purified by crystallization from EtOAc to afford **11c** as white crystals (1.1g, 65%): mp = 238-241° C [lit.[153] gives 242 C]; R_F = 0.5 (PE:EtOAc 1:1, visualized by UV). ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.88 (s, 3H, H-18), 6.77 (s, 1H, H-10), 7.03 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 2H, H-14, 16), 7.45 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 1H, H-2), 7.57 (d, $^3J_{H\text{-}H}$ = 7.7 Hz, 1H, H-6), 7.62-7.68 (m, 2H, H-1, 3), 8.39 (d, $^2J_{H\text{-}H}$ = 8.6 Hz, 2H) according to the literature;[153] ^{13}C NMR (100 MHz, d_6-DMSO) δ 55.3 (CH_3, C-18), 102.0 (CH, C-10), 114.1 (CH, C-14, 16), 124.5 (C, C-12), 126.0 (CH, C-6), 126.1 (C, C-4), 126.5 (CH, C-3), 126.6 (CH, C-2), 128.0 (CH, C-13, 17), 132.5 (CH, C-1), 138.1 (C, C-9), 139.8 (C, C-5), 160.1 (C, C-15), 162.8 (CO, C-7); HRMS (CI, isobutane) *m/z* 252.1023 ($C_{16}H_{14}NO_2$, M+H$^+$, requires 252.1019).



(12a). Compound **12a** was synthesized from benzonitrile according to **method F** and further purified by crystallization from EtOH to afford **12a** in a form of white crystals (423 mg, 57%): mp = 166-168 °C; R_F = 0.20 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.12 (bs, 2H,H-18), 2.97 (s, 3H, H-19), 3.25 (d, $^2J_{H\text{-}H}$ = 16.0 Hz, 1H, H-10), 3.45 (d, $^2J_{H\text{-}H}$ = 16.0 Hz, 1H, H-10), 7.05 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 1H), 7.20-7.40 (m, 6H, H-2, 13, 14, 15, 16, 17), 7.46-7.48 (m, 2H, H-1, 3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 28.9 (CH_3, C-19), 45.4 (CH_2, C-10), 75.8 (C, C-9), 126.3 (CH, C-15), 127.3 (CH, C-3), 127.4 (CH, C-6), 128.0 (CH, C-13, 17), 128.3 (CH, C-2), 128.5 (C, C-12), 128.3 (CH, C-14, 16), 132.1 (CH, C-1), 134.5 (C, C-5), 142.6 (C, C-4), 165.6 (CO, C-11); IR ν 3395, 3316, 1636, 1491, 1443, 1375, 1325, 737 cm^{-1}; HRMS (CI, isobutane) *m/z* 253.1345 ($C_{16}H_{17}N_2O$, M+H$^+$, requires 253.1335).

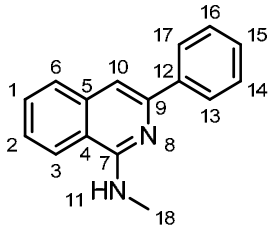


(12b). Compound **12b** was synthesized from 4-trifluoromethylbenzonitrile according to **method F** and further purified by crystallization from EtOH to afford orange crystals of **12b** (456 mg, 74%): mp = 142-145 °C; R_F = 0.23 (PE:EtOAc 1:1, visualized by UV). ^{1}H NMR (400 MHz, d_6-DMSO) δ 2.15 (bs, 2H, H-18), 2.97 (s, 3H, H-19), 3.27 (d, $^2J_{H\text{-}H}$ = 16.0 Hz, 1H, H-10), 3.41 (d, $^2J_{H\text{-}H}$ = 16.0 Hz, 1H, H-10), 7.05 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 1H, H-2), 7.35-7.42 (m, 2H, H-13, 17), 7.57-7.62 (m, 4H, H-1, 6, 14, 16), 8.14 (dd, $^3J_{H\text{-}H}$ = 7.3 Hz, $^4J_{H\text{-}H}$ = 1.9 Hz, 1H, H-3); ^{19}F NMR (376.4 MHz, d_6-DMSO) δ -61.0; ^{13}C NMR (100 MHz, d_6-DMSO) δ 28.1 (CH_3, C-19), 44.6 (CH_2, C-10), 75.7 (C-9), 125.5 (q, $^1J_{C\text{-}F}$ = 268.0 Hz, CF_3, C-20), 127.9 (C-12), 128.6 (CH, C-13, 17), 129.0 (CH, C-3), 129.1 (CH, C-6), 129.9 (CH, C-2), 130.5 (CH, C-14, 16), 132.3 (C-5), 133.0 (CH, C-1), 135.0 (C, C-4), 165.8 (CO, C-7); IR ν 3387, 3281, 1640, 1325, 1159, 1111, 1067, 839, 739 cm^{-1}; HRMS (CI, isobutane) *m/z* 321.1217 ($C_{17}H_{16}F_3N_2O$, M+H$^+$, requires 321.1209).



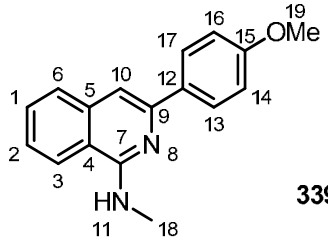
Aminal **12c** was synthesized from 4-methoxybenzonitrile according to **method A** and was further purified by crystallization from EtOH to afford **12c** as white crystals (865 mg, 71%): mp = 141-143 °C; R_F = 0.21 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400

MHz, d_6-DMSO) δ 2.10 (bs, 2H, H-18), 2.97 (s, 3H, H-19), 3.23 (d, $^2J_{H-H}$ = 15.9 Hz, 1H, H-10), 3.42 (d, $^2J_{H-H}$ = 16.0 Hz, 1H, H-10), 3.78 (s, 3H, H-20), 6.84 (d, $^3J_{H-H}$ = 8.9 Hz, 2H, H-14, 16), 7.06 (d, $^3J_{H-H}$ = 6.9 Hz, 1H, H-2), 7.32-7.41 (m, 4H, H-1, 6, 13, 17), 8.13 (dd, $^3J_{H-H}$ = 7.5 Hz, $^4J_{H-H}$ = 1.5 Hz, 1H, H-3); ^{13}C NMR (100 MHz, d_6-DMSO) δ 26.3 (CH_3, C-19), 45.1 (CH_2, C-10), 57.6 (CH_3, C-15), 75.2 (C, C-9), 126.1 (CH, C-14, 16), 126.9 (CH, C-3), 127.1 (CH, C-6), 127.8 (CH, C-2), 128.1 (CH, C-13, 17), 128.9 (C, C-12), 129.2 (CH, C-1), 132.5 (C, C-5), 133.4 (C, C-4), 159.1 (C, C-15), 166.8 (CO, C-7); IR ν 3397, 3298, 2967, 1634, 1605, 1578, 1383, 1242, 1030, 833, 733 cm^{-1}; HRMS (EI) *m/z* 282.1364 ($C_{17}H_{18}N_2O_2$, M+H$^+$, requires 282.1368).



339a

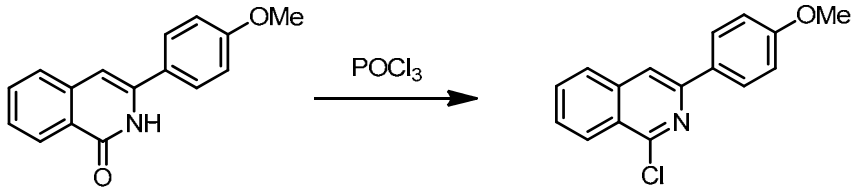
(339a). Compound **339a** was formed as a minor byproduct while utilizing **method H**. It was separated from the main products by a flash chromatography on a column of silica gel (5g) using PE/EtOAc (7:1) as an eluent to afford **339a** as a yellow solid (211 mg, 19%), which rapidly decomposes in a solution: R_F = 0.9 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.22 (d, $^3J_{H-H}$ = 4.2 Hz, 3H, H-18), 5.23 (bs, 1H, H-11), 7.26-7.42 (m, 5H, H-13, 14, 15, 16, 17), 7.50 (ddd, $^3J_{H-H}$ = 8.1 Hz, $^3J_{H-H}$ = 7.0 Hz, $^4J_{H-H}$ = 1.1 Hz, 1H, H-1), 7.64-7.69 (m, 2H, H-3, 10), 8.11-8.14 (m, 2H, H-2, 6) in accordance with the literature data.[155]



339c

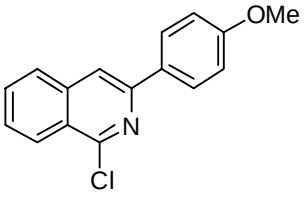
(339c). Compound **339c** was formed as a minor byproduct while utilizing **method H**. It was separated from the main products by a flash chromatography on a column of silica gel (3g) using PE/EtOAc (7:1) as an eluent to afford **339c** as a yellow solid (85 mg, 15%). It rapidly decomposes in a solution. R_F = 0.86 (PE:EtOAc 1:1, visualised by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.21 (d, $^3J_{H-H}$ = 4.8 Hz, 3H, H-18), 3.80 (s, 3H, H-19), 5.21 (bs, 1H, H-11), 6.93 (d, $^3J_{H-H}$ = 8.9 Hz, 2H, H-14, 16), 7.28 (s, 1H,

H-10), 7.32 (t, $^3J_{H\text{-}H}$ = 7.8 Hz, 1H, H-1), 7.49 (t, $^3J_{H\text{-}H}$ = 7.7 Hz, 1H, H-2), 7.75-7.79 (m, 1H, H-3), 7.80-7.85(m, 1H, H-6), 8.07 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 2H, H-13, 17).



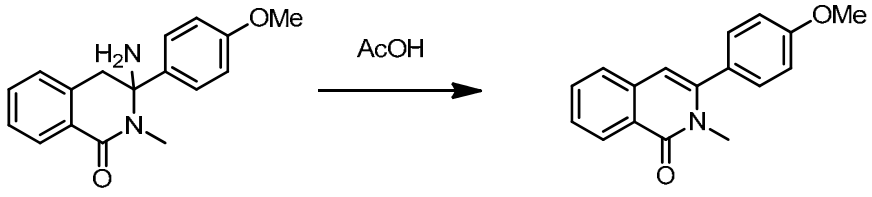
11b **311b**

From 3-(4-methoxyphenyl)isoquinolin-1(2*H*)-one (**11b**):

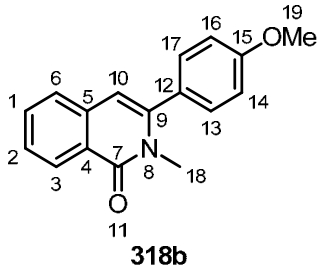


311b

(311b). Lactam **11b** (6.00 g, 23.8 mmol) was dissolved in $POCl_3$ (50 mL) and the reaction mixture was refluxed at 135 °C for 4 h. Then it was allowed to cool to room temperature and poured slowly and portion-wise to a large excess of ice. The resulting mixture was allowed to warm to the room temperature, the solid product was filtered off and washed with plenty of water (until neutral reaction to litmus). The crude product was dried in the air and was further purified by crystallization from hexane to give pure chloride **311b** (5.25 g, 82%) as white crystals. For the characterization data, *vide infra*.



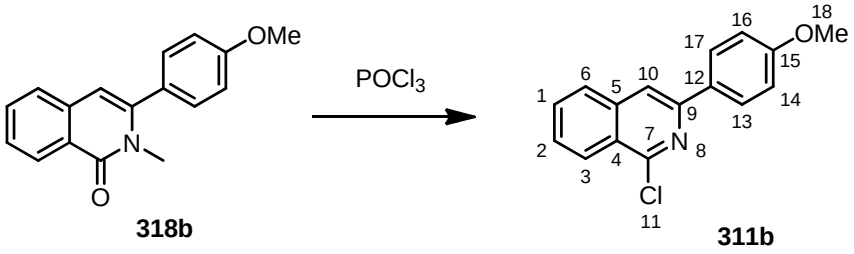
12b **311b**



318b

(318b). 3-amino-3-(4-methoxyphenyl)-2-methyl-3,4-dihydroisoquinolin-1(2H)-one (**12b**) (18.3 g, 64.8 mmol) was dissolved in glacial acetic acid (100 mL) and the solution was stirred at 80° C for 8h. The reaction mixture was allowed to cool to

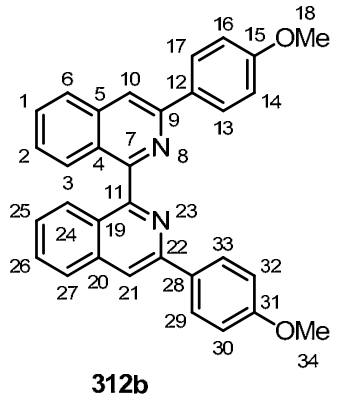
room temperature and the acetic acid was evaporated *in vacuo*. The crude product was purified by crystallization from EtOAc to afford **318b** as yellow crystals (11.8 g, 69%): mp = 133-135 °C [lit.[156] gives 136 °C]; R_F = 0.5 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.36 (s, 3H, H-18), 3.80 (s, 3H, H-19), 6.36 (s, 1H, H-10), 6.92 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 2H, H-14, 16), 7.25 (d, $^3J_{H\text{-}H}$ = 8.7 Hz, 2H, H-13, 17), 7.36-7.42 (m, 2H, H-1, 6), 7.55 (ddd, $^3J_{H\text{-}H}$ = 8.2 Hz, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{H\text{-}H}$ = 1.3 Hz, 1H, H-2), 8.36 (d, $^3J_{H\text{-}H}$ = 7.9 Hz, 1H, H-3) in accordance with the literature;[157] ^{13}C NMR (100 MHz, d_6-DMSO) δ 33.1 (CH_3, C-18), 54.4 (CH_3, C-19), 106.5 (CH, C-10), 113.0 (CH, C-14, 16), 123.8 (C, C-12), 124.7 (CH, C-13, 17), 125.4 (CH, C-6), 126.8 (CH, C-2), 127.6 (C, C-9), 129.1 (CH, C-1), 131.2 (CH, C-3), 135.4 (C, C-5), 142.7 (C, C-4), 159.0 (C, C-15), 162.4 (CO, C-7); IR ν 2999, 2967, 2936, 1637, 1609, 1510, 1246, 1179, 1032, 822, 758 cm^{-1}; HRMS (CI, isobutane) *m/z* 266.1183 ($C_{17}H_{16}NO_2$, M+H$^+$, requires 266.1176).



From 3-(4-methoxyphenyl)-2-methylisoquinolin-1(2*H*)-one (**318b**):

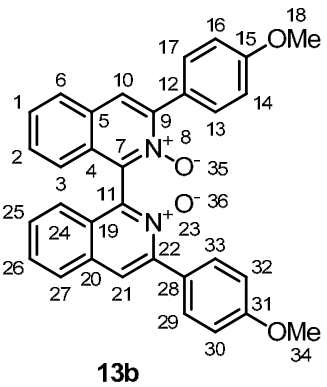
318b (11.8 g, 41.5 mmol) was dissolved in $POCl_3$ (100 mL) and then same protocol as above was used to afford **311b** as white crystals (6.10 g, 51%): mp = 84-87 °C [lit.[156] gives 88 °C]; R_F = 0.50 (PE:EtOAc 7:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.90 (s, 3H, H-18), 7.04 (d, $^3J_{H\text{-}H}$ = 8.9 Hz, 2H, H-14, 16), 7.63 (ddd, $^3J_{H\text{-}H}$ = 8.2 Hz, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz, 1H, H-2), 7.73 (ddd, $^3J_{H\text{-}H}$ = 8.2 Hz, $^3J_{H\text{-}H}$ = 6.9 Hz, $^4J_{H\text{-}H}$ = 1.2 Hz, 1H, H-1), 7.86 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-6), 7.93 (s, 1H, H-10), 8.09 (d, $^3J_{H\text{-}H}$ = 8.9 Hz, 2H, H-13, 17), 8.32 (dd, $^3J_{H\text{-}H}$ = 8.4 Hz, $^4J_{H\text{-}H}$ = 0.7 Hz, 1H, H-3) in accordance with the literature;[158] ^{13}C NMR (100 MHz, d_6-DMSO) δ 55.4 (CH_3, C-18), 114.2 (CH, C-14, 16), 115.1 (CH, C-10), 125.6 (C, C-12), 126.5 (CH, C-13, 17), 127.2 (CH, C-6), 127.8 (CH, C-3), 128.2 (CH, C-2), 130.6 (C, C-5), 131.2 (CH, C-1), 138.8 (C-4), 150.2 (C, C-9), 151.2 (C, C-7), 160.5 (C, C-15); IR ν 2936, 2836, 1606, 1560, 1516, 1249, 1173, 976, 824, 745 cm^{-1}; HRMS (CI,

isobutane) *m/z* 270.0688 ($C_{16}H_{13}{}^{35}ClNO$, $M+H^+$, requires 270.0680); 272.0658 ($C_{16}H_{13}{}^{37}ClNO$ requires 272.0651).



312b

(312b). Zinc dust (855 mg, 13.1 mmol) and $NiCl_2.6H_2O$ (3.11 g, 13.1 mmol) were added to a solution of triphenylphosphine (13.65 g, 52.1 mmol) in DMF (45 mL) and the mixture was left in an ultrasound bath for 30 min, while a steady stream of argon was bubbled through the suspension. The suspension was then heated to 65 °C and stirred for 1 h under argon while changing the colour from green to orange. A solution of chloride **311b** (2.35 g, 8.70 mmol) in DMF (10 ml) was then added in one portion, the mixture was stirred at 65 °C for 3 h and then allowed to cool to room temperature. A 30% aqueous solution of ammonia (300 mL) was then added and the mixture was allowed to stand for a few hours in the fridge, while yellow crystals of product **312b** were formed and filtered off (1.44 g, 71%): mp = 242-245 °C; R_F = 0.59 (PE:EtOAc 1:1, visualized by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.86 (s, 6H, H-18, 34), 7.00 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 4H, H-14, 16, 30, 32), 7.42 (t, $^3J_{H\text{-}H}$ = 7.5 Hz, 2H, H-1, 26), 7.68 (t, $^3J_{H\text{-}H}$ = 7.4 Hz, 2H, H-2, 25), 7.94-7.98 (m, 2H, H-6, 27), 7.95 (s, 2H, H-10, 21), 8.09 (d, $^3J_{H\text{-}H}$ = 8.0 Hz, 4H, H-13, 17, 29, 33), 8.40-8.51 (m, 2H, H-3, 24); ^{13}C NMR (100 MHz, d_6-DMSO) δ 55.4 (CH_3, C-18, 34), 114.1 (CH, C-14, 16, 30, 32), 115.8 (CH, C-10, 21), 126.7 (CH, C-2, 6, 25, 27), 126.8 (C, C-19, 4), 127.6 (CH, C-3, 24), 128.4 (CH, C-17, 13, 29, 33), 130.2 (CH, C-1, 26), 132.2 (C, C-5, 20), 138.1 (C, C-12, 28), 149.6 (C, C-9, 22), 157.8 (C, C-15, 31), 160.1 (C, C-7, 11); IR ν 3052, 2830, 1607, 1514, 1244, 1175, 1028, 835, 750 cm^{-1}; HRMS (FAB, NOBA) *m/z* 469.1919 ($C_{32}H_{25}N_2O_2$, $M+H^+$, requires 469.1911).

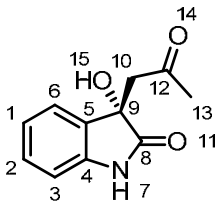


13b

(13b). *m*-CPBA (75%, 1.0 g, 4.3 mmol) was added portion-wise to a solution of 3,3'-bis(4-methoxyphenyl)-1,1'-biisoquinoline (**312b**) (200 mg, 0.43 mmol) in CH_2Cl_2 (10 mL) at the room temperature and the mixture was stirred for 5 days. The reaction mixture was then diluted with CH_2Cl_2 (40 mL) and washed with water (3×50 mL) and brine (1×50 mL). The organic phase was separated and dried ($MgSO_4$). The solids were filtered off and the solvent was evaporated *in vacuo* to

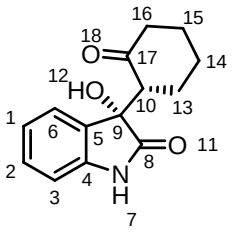
afford a colourless oil. The crude product was purified by chromatography on a column of silica gel (2 g), using first a petroleum ether-AcOEt mixture (1:1) to elute the impurities and then CH_2Cl_2-MeOH (20:1) to afford the dioxide **13b** as an orange solid (93 mg, 44%): mp > 250 °C; R_F = 0.20 (DCM:MeOH 50:1, visualised by UV); ^{1}H NMR (400 MHz, d_6-DMSO) δ 3.84 (s, 6H, H-18, 34), 6.97 (d, $^3J_{H\text{-}H}$ = 8.9 Hz, 4H, H-14, 16, 30, 32), 7.17 (dd, $^3J_{H\text{-}H}$ = 8.4 Hz, $^4J_{H\text{-}H}$ =0.7 Hz, 2H, H-6, 27), 7.41 (ddd, $^3J_{H\text{-}H}$ = 8.2 Hz, $^3J_{H\text{-}H}$ = 7.0 Hz, $^4J_{H\text{-}H}$ =1.1 Hz, 2H, H-1, 26), 7.52 (ddd, $^3J_{H\text{-}H}$ = 8.1 Hz, $^3J_{H\text{-}H}$ = 7.1 Hz, $^4J_{H\text{-}H}$ =1.0 Hz, 2H, H-2, 25), 7.85-7.93 (m, 6H, H-3, 13, 17, 24), 7.97 (s, 2H, H-10, 21); ^{13}C NMR (100 MHz, d_6-DMSO) δ 55.4 (CH_3, C-18, 34), 113.4 (CH, C-14, 16, 30, 32), 123.4 (CH, C-1, 26), 124.8 (CH, C-3, 24), 124.9 (C, C-4, 20), 127.1 (CH, C-2, 25), 128.4 (CH, C-6, 27), 129.1 (C, C-4, 19), 129.4 (CH, C-10, 21), 131.6 (CH, C-13, 17, 29, 33), 138.9 (C, C-12, 28), 147.2 (C, C-9, 22), 160.5 (C, C-7, 11), 171.2 (C, C-15, 31); IR ν 3052, 2830, 1607, 1514, 1244, 1175, 1028, 835, 750 cm^{-1}; HRMS (FAB, NOBA) *m/z* 501.1812 ($C_{32}H_{25}N_2O_4$, M+H$^+$, requires 501.1809).

5.4 Asymmetric Aldol Reactions



(S)-(-)-383

(383). Solid isatine (43 mg, 0.292 mmol) was added to (*S*)-PicAm-DNBSA (8 mg, 0.015 mmol) or (*R*)-PicAm-tart respectively (6 mg, 0.013 mmol) in brine (1.5 mL) in a 10 mL round-bottom flask. Acetone (71 μL, 0.970 mmol) was then added in one portion via a Hamilton syringe and the suspension was stirred at the room temperature for 24 h. The reaction mixture was extracted with diethylether (3 × 10 mL) and the organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by chromatography on a column of silica gel (0.5 × 7 cm) with diethyl ether as an eluent to afford **(*S*)-(-)-383** as a white solid (48 mg, 87%): $[\alpha]_D$ –25.9 (c 0.50, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO, 4:1) δ 2.09 (s, 3H, H-13), 2.95 (d, $^2J_{H\text{-}H}$ = 16.2 Hz, 1H, H-10), 3.13 (d, $^2J_{H\text{-}H}$ = 16.2 Hz, 1H, H-10), 5.55 (br s, 1H, H-15), 6.79 (d, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-1), 6.86 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-2), 7.10 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-3), 7.17 (d, $^3J_{H\text{-}H}$ = 7.8 Hz, 1H, H-6), 9.7 (s, 1H, H-7); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO, 4:1) δ 35.8 (CH_3, C-13), 54.8 (CH_2, C-10), 78.0 (C, C-9), 114.6 (CH, C-3), 126.3 (CH, C-6), 127.4 (CH, C-1), 133.9 (CH, C-2), 135.1 (C, C-5), 146.8 (C, C-4), 183.4 (CO, C-8), 210.7 (CO, C-12) consistent with the literature data;[132] chiral HPLC (Chiracel OJ-H column, hexane/2-propanol = 4:1, 1 mL/min) showed 62% ee (t_{minor} = 12.9 min, t_{major} = 16.7 min) for the (*S*)-PicAm-DNBSA catalyst. The reaction catalysed by (*R*)-PicAm-tart did not show any conversion even after a prolonged reaction time.

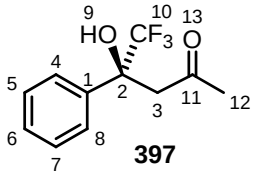


418

(**418).** Solid isatine (43 mg, 0.292 mmol) was added to (*S*)-PicAm-DNBSA (8 mg, 0.015 mmol) or (*R*)-PicAm-tart respectively (6 mg, 0.013 mmol) in brine (1.5 mL) in a 10 mL round-bottom flask. Cyclohexanone (102 μL, 0.987 mmol) was then added in one portion via a Hamilton syringe, followed by sodium dodecylbenzenesulfonate (102 mg, 0.293 mmol) as a phase-transfer catalyst and the suspension was stirred at room temperature for 24 h. The reaction mixture was extracted with ether (3 × 10 mL) and the organic phase was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by

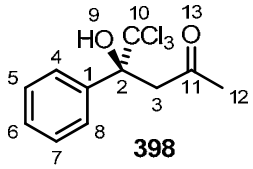
chromatography on a column of silica gel (0.5 × 7 cm) with ether as an eluent, to afford **418** as a white solid (65 mg, 90%): $[\alpha]_D$ –9.2 (c 0.50, MeOH); ^{1}H NMR (400 MHz; d_6-DMSO) δ 1.50-2.10 (m, 6H. H-13, 14, 15), 2.30-2.32 (m, 1H, H-10), 2.47-2.52 (m, 1H, H-16), 3.23 (dd, $^3J_{H\text{-}H}$ = 7.9 and 5.9 Hz, 1H, H-16), 5.70 (br s, 1H, H-12), 6.80 (d, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-3), 6.83 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-2), 7.18 (t, $^3J_{H\text{-}H}$ = 7.3 Hz, 1H, H-1), 7.25 (d, $^3J_{H\text{-}H}$ = 7.7 Hz, 1H, H-6), 9.7 (s, 1H, H-7); ^{13}C NMR (100 MHz; d_6-DMSO) δ 24.5 (CH_2, C-13), 26.8 (CH_2, C-14), 27.5 (CH_2, C-15), 41.9 (CH_2, C-16), 57.8 (CH, C-10), 73.7 (C, C-9), 110.4 (CH, C-3), 121.5 (CH, C-6), 124.3 (CH, C-1), 128.5 (CH, C-2), 130.1 (C, C-5), 143.2 (C, C-4), 178.7 (CO, C-8), 209.0 (CO, C-17) consistent with the literature data.[160] HPLC (Chiracel OJ-H column, hexane/2-propanol = 4:1, 1 mL/min) showed 44% ee (t_{minor} = 13.3 min, t_{major} = 17.4 min) for the (*S*)-PicAm-DNBSA catalyst. The reaction catalysed by (*R*)-PicAm-tart did not show any conversion even after a prolonged reaction time. The absolute configuration was determined by comparison of the specific rotation with that of the literature value.

General Method for the Aldol Reactions using (*R*)-(-)-Leucinol as a Catalyst (Method I). Acetone (4 mL) and water (0.5 mL) were added to a solution of the corresponding trifluoromethyl ketone (5 mmol) and (*R*)-(-)-leucinol (1 mmol) in CH_2Cl_2 (24 mL) and the reaction mixture was stirred at 0 °C for 24 h. The mixture was then diluted with CH_2Cl_2 (20 mL) and washed with water (3×20 mL). The organic layer was dried ($MgSO_4$) and the solvent was evaporated *in vacuo*. The crude product was purified by chromatography on a column of Al_2O_3 (30 g of alumina) pre-treated with Et_3N. Racemic standards (for HPLC) were prepared in the same way, using aminoethanol (20 mol %) as a catalyst.



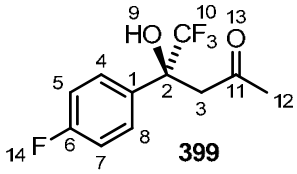
397

397 was prepared by the **Method I.** White solid (85%): mp 50-55 °C; $[\alpha]_D$ –7.7 (*c* 0.40, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3, H-12), 3.31 (d, $^2J_{H\text{-}H}$ = 17.2 Hz, 1H, H-3), 3.37 (d, $^2J_{H\text{-}H}$ = 17.2 Hz, 1H, H-3), 5.45 (s, 1H, H-9), 7.35-7.43 (m, 3H, H-5, 6, 7), 7.55-7.59 (m, 2H, H-4, 8); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.1 (CH_3, C-12), 45.1 (CH_2, C-3), 76.0 (q, $^2J_{C\text{-}F}$ = 29.2 Hz, C, C-2), 124.4 (q, $^1J_{C\text{-}F}$ = 284.9 Hz, CF_3, C-10), 126.1 (q, $^4J_{C\text{-}F}$ = 0.8 Hz, CH, C-4, 8), 128.4 (CH, C-5, 7), 128.8 (CH, C-6), 137.4 (C, C-1), 208.9 (CO, C-11); IR ν 3466, 1715, 1450, 1406, 1238, 1195, 1167, 1155, 1136, 994, 767, 710 cm^{-1}; MS (EI) *m/z* (%) 232 (M^+, 10), 175 (10), 163 (35), 105 (100); HRMS (EI) *m/z*: 232.0714 ($C_{11}H_{11}O_2F_3$, $M^{+\bullet}$, requires 232.0711); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 0.75 mL min^{-1}) showed 77% ee (t_{minor} = 17.9 min, t_{major} = 11.9 min).



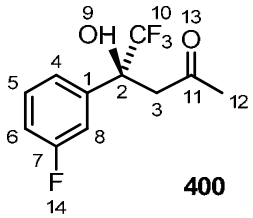
398

398 was prepared by the **Method I.** White solid (70%): mp 43-46 °C; $[\alpha]_D$ –9.8 (*c* 0.63, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.20 (s, 3H, CH_3, H-12), 3.44 (d, $^2J_{H\text{-}H}$ = 17.0 Hz, H-3), 3.94 (d, $^2J_{H\text{-}H}$ = 17.0 Hz, H-3), 5.69 (s, 1H, OH), 7.25-7.45 (m, 3H, Ar), 7.70-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.2 (CH_3, C-12), 46.9 (CH_2, C-3), 83.9 (C-O), 105.4 (CCl_3), 127.6 (CH, C-6), 128.6 (CH, C-4, 8), 128.8 (CH, C-5, 7), 138.1 (C, C-1), 209.3 (CO, C-11); IR ν 3481, 1694, 1409, 1391, 1363, 1328, 1317, 1180, 837, 802, 765, 711, 610 cm^{-1}; MS (CI/isobutane) *m/z* (%) 281 (M^+, 100), 185 (10), 163 (30), 105 (5); HRMS (EI) *m/z*: 280.9893 ($C_{11}H_{11}O_2Cl_3$, $M^{+\bullet}$, requires 280.9903); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 0.75 mL min^{-1}) showed 64% ee (t_{minor} = 44.4 min, t_{major} = 17.6 min).



399

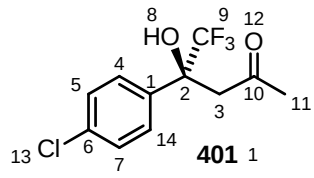
399 was prepared by the **Method I.** White solid (86%): mp 38-41 °C; $[\alpha]_D$ –11.2 (*c* 1.4, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3), 3.21 (d, $^2J_{H\text{-}H}$ = 17.2 Hz, C*H*H'), 3.31 (d, $^2J_{H\text{-}H}$ = 17.2 Hz, CH*H'*), 5.50 (s, 1H, OH), 7.05-7.11 (m, 2H, Ar), 7.52-7.57 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.1 (CH_3), 45.0 (CH_2), 75.7 (q, $^2J_{C\text{-}F}$ = 29.4 Hz, C-O), 115.4 (d, $^2J_{C\text{-}F}$ = 21.6 Hz, CH, C-5, 7), 124.3 (q, $^1J_{C\text{-}F}$ = 285.5 Hz, CF_3), 128.1 (dq, $^3J_{C,F}$ = 8.3 Hz, $^4J_{C\text{-}F}$ = 0.8 Hz, CH, C-4, 8), 133.3 (d, $^4J_{C\text{-}F}$ = 3.3 Hz, C, C-1, 8), 162.9 (d, $^1J_{C\text{-}F}$ = 248.2 Hz, CF, C-6), 208.9 (CO, C-11); IR (NaCl) ν 3475, 1714, 1511, 1420, 1365, 1337, 1238, 1195, 1166, 1134, 837, 736 cm^{-1}; MS (EI) *m/z* (%) 250 (M^+, 5), 181 (40), 123 (100); HRMS (EI) *m/z*: 250.0615 ($C_{11}H_{10}O_2F_4$, $M^{+\bullet}$, requires 250.0617); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 82% ee (t_{minor} = 16.5 min, t_{major} = 11.4 min).



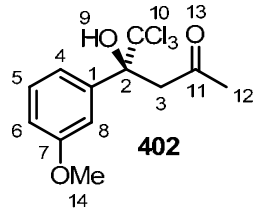
400

400 was prepared by the **Method I.** Colourless liquid (87%): $[\alpha]_D$ –6.6 (*c* 0.65, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.22 (s, 3H, CH_3), 3.21 (d, $^2J_{H\text{-}H}$ = 17.3 Hz, C*H*H'), 3.31 (d, $^2J_{H\text{-}H}$ = 17.3 Hz, CH*H'*), 5.53 (s, 1H, OH), 7.03 – 7.09 (m, 1H, Ar), 7.29 – 7.40 (m, 3H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.0 (CH_3), 45.0 (CH_2), 75.7 (qd, $^2J_{C\text{-}F}$ = 29.5 Hz, $^4J_{C\text{-}F}$ = 1.8 Hz, C-O), 113.8 (d, $^2J_{C\text{-}F}$ = 23.8 Hz, CH), 115.8 (d, $^2J_{C\text{-}F}$ = 21.1 Hz, CH), 121.5 – 121.7 (m, CH), 124.2 (q, $^1J_{C\text{-}F}$ = 285.0 Hz, CF_3, C-10), 130.0 (d, $^3J_{C\text{-}}$

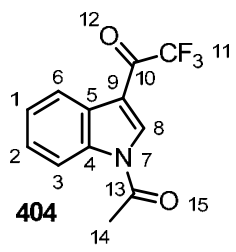
$_F$ = 8.2 Hz, CH, C-5), 140.1 (d, $^3J_{C\text{-}F}$ = 7.0 Hz, C, C-1), 162.8 (d, $^1J_{C\text{-}F}$ = 246.4 Hz, CF, C-7), 208.7 (CO, C-11); IR (NaCl) ν 3455, 1714, 1593, 1491, 1444, 1420, 1365, 1344, 1275, 1240, 1146, 1061, 865, 790, 726 cm^{-1}; MS (EI) *m/z* (%) 250 (M^+, 10), 181 (30), 123 (60); HRMS (EI) *m/z*: 250.0619 ($C_{11}H_{10}O_2F_4$, $M^{+\bullet}$, requires 250.0617); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 73% ee (t_{minor} = 12.0 min, t_{major} = 10.2 min).



401 was prepared by the **Method I.** White solid (84%): mp 42-45 ^{o}C; $[\alpha]_D$ –9.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.22 (s, 3H, CH_3), 3.20 (d, $^2J_{H\text{-}H}$ = 17.3 Hz, C*H*H'), 3.30 (d, $^2J_{H\text{-}H}$ = 17.3 Hz, CH*H'*), 5.49 (s, 1H, OH), 7.35-7.39 (m, 2H, Ar), 7.48-7.52 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.1 (CH_3), 44.9 (CH_2), 75.8 (q, $^2J_{C\text{-}F}$ = 29.5 Hz, C-O), 124.2 (q, $^1J_{C\text{-}F}$ = 284.9 Hz, CF_3), 127.6 (d, $^4J_{C\text{-}F}$ = 0.8 Hz, CH, C-4, 14), 128.7 (CH, C-5,7), 135.0 (C, C-1), 136.1 (C, C-6), 208.7 (C=O); IR ν 3478, 1713, 1494, 1410, 1363, 1336, 1240, 1192, 1169, 1138, 1112, 1095, 1057, 915, 825, 734 cm^{-1}; MS (EI) *m/z* (%) 266 (M^+, 5), 197 (35), 139 (90); HRMS (EI) *m/z*: 266.0325 ($C_{11}H_{10}O_2F_3Cl$, $M^{+\bullet}$, requires 266.0321); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 78% ee (t_{minor} = 14.7 min, t_{major} = 10.7 min).

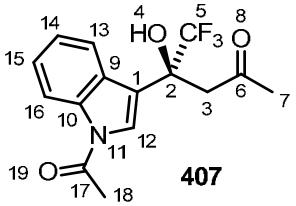


402 was prepared by the **Method I.** White solid (72%): mp 35-38 ^{o}C; $[\alpha]_D$ –7.7 (*c* 0.34, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3), 3.41 (d, $^2J_{H\text{-}H}$ = 17.1 Hz, C*H*H'), 3.82 (s, 3H, C*H*$_3$O), 3.91 (d, $^2J_{H\text{-}H}$ = 17.1 Hz, CH*H'*), 5.70 (s, 1H, OH), 6.88-6.92 (m, 1H, Ar), 7.24-7.36 (m, 3H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.2 (CH_3), 47.0 (CH_2), 55.3 (*C*H_3O), 83.8 (C-O), 105.2 (CCl_3), 113.8 (CH, C-8), 115.6 (CH, C-6), 120.8 (CH, C-4), 128.5 (CH, C-5), 139.8 (C, C-1), 159.0 (C, C-7), 209.3 (CO, C-11); IR (NaCl) ν 3448, 1697, 1489, 1464, 1426, 1363, 1264, 1234, 1172, 1033, 801, 777, 728, 702 cm^{-1}; MS (CI/isobutane) *m/z* (%): 311 (80), 259.1 (80), 207.2 (100); HRMS (CI) *m/z*: 310.9995 ($C_{12}H_{14}O_3Cl_3$, M+H$^+$, required 311.0009); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 66% ee (t_{minor} = 25.1 min, t_{major} = 21.1 min).



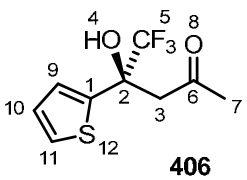
(404). 3-(Trifluoroacetyl)indole (543 mg, 2.55 mmol) was added to a solution of pyridine (0.21 mL, 2.55 mmol) and acetic anhydride (1.19 mL, 12.73 mmol) in dry THF (20 mL). The reaction

mixture was refluxed for 5 h and then stirred at room temperature overnight. The solvent was evaporated, the residue was dissolved in CH_2Cl_2 (50 mL), washed with water (3×100 mL), dried over anhydrous $MgSO_4$, and evaporated. The residue was evaporated with toluene (3×20 mL) under reduced pressure and crystallized from an ethyl acetate-hexane mixture to afford **404** (586 mg, 90%) as colourless crystals: mp 127-128 °C (ethyl acetate/hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, CH_3, 3H), 7.36-7.46 (m, 2H, H-1, 2), 8.16-8.20 (m, 1H, H-3), 8.26-8.31 (m, 1H, H-8), 8.33-8.38 (m, 1H, H-6); ^{13}C NMR (100 MHz, $CDCl_3$) δ 22.9 (CH_3), 113.2 (C), 115.5 (CF_3, q, $^1J_{C\text{-}F}$ = 295 Hz), 116.7 (C, C-9), 121.2 (CH, C-3), 125.0 (CH, C-6), 125.9 (C, C-5), 126.3 (CH, C-2), 133.0 (CH, C-8), 134.7 (C, C-4), 167.4 (CO, C-13), 175.0 (CO, C-10); IR (KBr) ν 1735, 1700, 1542, 1450, 1216, 1146 cm^{-1}; MS (EI) *m/z* (%) 255 (M^{+}, 36), 213 (41), 186 (5), 144 (100); HRMS (EI) *m/z* 255.0511 ($C_{12}H_8F_3NO_2$, $M^{+\bullet}$, requires 255.0507).



407

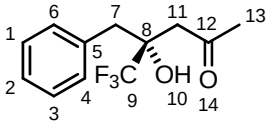
407 was prepared by the **Method I.** Purification was carried out by column chromatography on neutral alumina (8 g of Al_2O_3 pre-treated with 1% Et_3N solution in ether and washed with dichloromethane) with dichloromethane (R_F = 0.40) and the product was crystallized from a dichloromethane-hexane mixture to afford **407** (145 mg, 76%) as white crystals: mp 150-151 °C (dichloromethane/hexane); $[\alpha]_D$ -10.0 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.20 (s, 3H, H-7), 2.67 (s, 3H, H-18), 3.27 (d, $^2J_{H\text{-}H}$ = 17.0 Hz, 1H, H-3), 3.51 (d, $^2J_{H\text{-}H}$ = 17.0 Hz, 1H, H-3), 5.81 (s, 1H, H-4), 7.26-7.35 (m, 1H, H-14), 7.35-7.44 (m, 1H, H-15), 7.62 (s, 1H, H-12), 8.48 (d, $^3J_{H\text{-}H}$ = 8.2 Hz, 1H, H-13), 7.73 (d, $^3J_{H\text{-}H}$ = 7.9 Hz, 1H, H-16); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.1 (CH_3, C-7), 31.2 (CH_3, C-18), 43.1 (CH_2, C-3), 76.1 (C, q, $^2J_{C\text{-}F}$ = 51 Hz), 115.9 (CH, C-14), 118.6 (CH, C-15), 119.7 (CH, C-12), 123.0 (CH, C-13), 123.5 (CF_3, q, $^1J_{C\text{-}F}$ = 285 Hz), 124.5 (CH, C-16), 125.7 (C, C-9), 126.1 (C, C-1), 135.5 (C, C-10), 167.5 (CO, C-17), 208.1 (CO, C-6); IR (KBr) ν 3496, 3440, 3020, 1704, 1602, 1450, 1384, 1217; MS (EI) *m/z* (%) 313 (M^{+}, 43), 271 (10), 244 (11), 214 (29), 144 (100) cm^{-1}; HRMS (EI) *m/z* 313.0927 ($C_{15}H_{14}F_3NO_3$, $M^{+\bullet}$, requires 313.0926); chiral HPLC (Chiralpack, IB, hexane/2-propanol (96:4), 0.75 mL/min, t_{minor} = 35.5 min, t_{major} = 47.9 min) showed 46% ee.



406

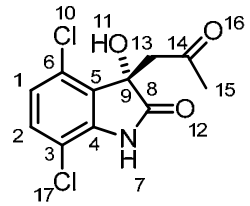
406 was prepared by the **Method I.** Purification of alcohol **406** was carried out by column chromatography on neutral alumina (13 g of

Al_2O_3 pre-treated with 1% Et_3N solution in ether and washed with dichloromethane) with a petroleum ether-dichloromethane mixture (3:7, R_F = 0.44) and the product was crystallized from a dichloromethane-hexane mixture to afford **406** (324 mg, 79%) as colourless crystals: mp 44-46 °C (dichloromethane/hexane); $[\alpha]_D$ +13.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H, H-7), 3.15 (d, $^2J_{H\text{-}H}$ = 17.1 Hz, 1H, H-3), 3.32 (d, $^2J_{H\text{-}H}$ = 17.1 Hz, 1H, H-3), 5.87 (s, 1H, OH), 7.01 (dd, $^3J_{H\text{-}H}$ = 5.1 and 3.3 Hz, 1H, H-10), 7.11 (d, $^3J_{H\text{-}H}$ = 3.3 Hz, 1H, H-9), 7.34 (d, $^3J_{H\text{-}H}$ = 5.1 Hz, 1H, H-11); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.2 (CH_3), 45.7 (CH_2), 75.6 (C, q, $^2J_{C\text{-}F}$ = 31 Hz, C-2), 123.8 (CF_3, q, $^1J_{C\text{-}F}$ = 285 Hz), 125.8 (CH, C-9), 126.6 (CH, C-10), 127.3 (CH, C-11), 141.7 (C, C-1), 209.0 (CO, C-6); IR (KBr) ν 3453 3114, 2921, 1711, 1422, 1367, 1338, 1167 cm^{-1}; MS (EI) *m/z* (%) 238 ($M^{+\bullet}$, 37), 181 (15), 169 (54), 111 (100), 84 (78); HRMS (EI) *m/z* 238.0277 ($C_9H_9F_3O_2S$ requires 238.0275, $M^{+\bullet}$,); chiral HPLC [Chiracel, OJ-H, hexane/2-propanol (96:4), 0.75 mL min^{-1} t_{minor} = 15.2 min, t_{major} = 21.8 min) showed 82% ee.



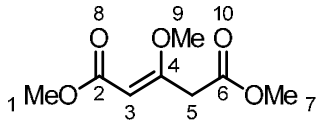
408

408 was prepared by the **Method I.** ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.67 (s, 3H, H-13), 2.22 (d, $^2J_{H\text{-}H}$ = 16.7 Hz, 1H, H-7), 2.37 (d, $^2J_{H\text{-}H}$ = 16.7 Hz, 1H, H-7), 2.68 (d, $^2J_{H\text{-}H}$ = 13.8 Hz, 1H, H-11), 3.05 (d, $^2J_{H\text{-}H}$ = 13.8 Hz, 1H, H-11), 5.60 (bs, 1H, OH), 7.21 (m, 5H, Ar). Chiral HPLC (Chiracel, OJ-H, hexane/2-propanol (96:4), 0.75 mL/min) showed 0% ee.



384

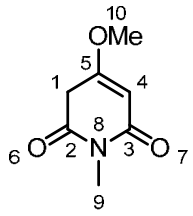
384 was prepared by the **Method I**. Crystallization from ethyl acetate-hexane afforded **384** in a form of yellow crystals: $[\alpha]_D$ +50.7 (c 0.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 3H, H-15), 3.37 (d, $^3J_{H\text{-}H}$ = 17.3 Hz, 1H, H-13), 3.68 (d, $^3J_{H\text{-}H}$ = 17.3 Hz, 1H, H-13), 5.71 (bs, 2H, H-11), 6.91 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 1H, H-1), 7.18 (d, $^3J_{H\text{-}H}$ = 8.8 Hz, 1H, H-2); chiral HPLC (Chiralpack, IB, hexane/2-propanol (90:10), 0.75 mL/min, t_{minor} = 23.9 min, t_{major} = 28.0 min) showed 95% ee.



388

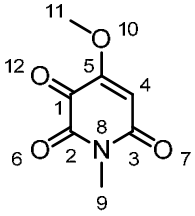
(388). Methanol (1 mL) and concentrated H_2SO_4 (1 mL) were added to a mixture of trimethyl orthoformate (30 mL, 274.2 mmol) and dimethyl 1,3-acetonedicarboxylate (29.5 mL, 199.9 mmol). The neat reaction mixture was heated at reflux for 6 h under Ar, then diluted with ether (100 mL), washed with saturated aqueous $NaHCO_3$ (3×50

mL) and dried (Na_2SO_4). The solvent was evaporated *in vacuo* to afford the product in a form of yellow oil which was used in the next step without further purification (20.6 g, 80%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.67 (s, 3H, H-1), 3.68 (s, 3H, H-7), 3.71 (s, 3H, H-9), 3.83 (s, 2H, H-5), 5.19 (s, 1H, H-3) in accordance with the literature.[159]



390

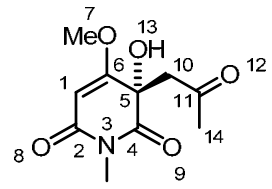
(390). A 40% aqueous solution of methylamine (26 mL, 300 mmol) was added dropwise to the diketone **390** (20.0 g, 106 mol) at 0 °C and the reaction mixture was stirred at room temperature overnight. The reaction mixture was then diluted with water (100 mL) and extracted with ethyl acetate (3×100 mL). The organic layer was dried ($MgSO_4$) and the solvent was removed *in vacuo*. The yellow crystalline residue thus obtained, was dissolved in methanol (100 mL). Sodium (5.0 g, 217 mmol) was added slowly in small pieces while stirring and the reaction mixture was heated at reflux for 2 h. The methanol was then evaporated *in vacuo*, the residue was dissolved in water and washed with diethyl ether (2×20 mL). Glacial acetic acid (20 mL) was added to the aqueous layer, which was then extracted with CH_2Cl_2 (3×50 mL). The organic extract was dried (Na_2SO_4), the solvent was evaporated *in vacuo* and the crude product was purified by crystallization as follows: CH_2Cl_2 was added in portions, until all the residue dissolved. Then diethyl ether was added dropwise until the solid product just begun to appear and then few drops of CH_2Cl_2 were added to dissolve it again. The resulting solution was then kept in the fridge overnight, crystals were filtered off and washed with a small amount of cold diethyl ether to give the pure product (9.1 g, 55%) in a form of white crystals: mp 112 – 114^o C (lit159 gives 114^{o}C); ^{1}H NMR (400 MHz; $CDCl_3$) δ3.21 (s, 3H, H-9), 3.44 (s, 2H, H-1), 3.76 (s, 3H, H-10), 5.44 (s, 1H, H-4) in accordance with the literature.[159]



386

(386). Diketone **390** (1000 mg, 6.45 mmol) and SeO_2 (1200 mg, 10.81 mmol) with one drop of concentrated hydrochloric acid were stirred at room temperature in $CHCl_3$ (50 mL) overnight. The mixture was then filtered through a short pad of Celite, the filtrate was evaporated *in vacuo* and the product was purified by chromatography on a column of silica gel (30 g) with a mixture of CH_2Cl_2 and AcOEt (90:10) (TLC in a CH_2Cl_2-AcOEt 90:10 mixture; R_F = 0.25, stains visualized by PMA) to give orange crystals (794 mg, 73%): mp 127 – 130^o C C (lit[159] gives 132 ^{o}C); ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.32 (s, 3H, H-9), 3.85 (s, 3H, H-

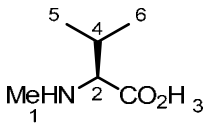
11), 6.16 (s, 1H, H-4); ^{13}C NMR (100 MHz; $CDCl_3$) δ 27.1 (CH_3, C-9), 56.8 (CH_3, C-11), 107.3 (CH, C-4), 155.3 (C, C-5), 158.1(CO, C-2), 162.8 (CO, C-3), 170.5 (CO, C-1) in accordance with the literature.[159]



385
(Speranskatine A)

(385). Speranskatine A was prepared by the **Method I**. White crystals (202 mg, 80%): mp 150-152 °C (decomp.; lit[160] gives 158-160 °C); $[\alpha]_D$ +15.0 (*c* 0.5, MeOH) [lit[160] gives $[\alpha]_D$ +14.8 (*c* 0.54, MeOH)]; ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.26 (s, 3H, H-14), 2.16 (s, 3H, H-15), 3.23 (s, 3H, H-7), 3.26 (s, 2H, H-10), 3.78 (s, 3H), 5.45 (s, 1H, H-1); ^{1}H NMR (400 MHz; C_6D_6) δ 1.49 (s, 3H, H-14), 2.74 (d, 1H, C*H*H, $^2J_{H\text{-}H}$ = 16.7 Hz, H-10), 2.76 (s, 3H, H-15), 2.86 (d, 1H, CH*H*, $^2J_{H\text{-}H}$ = 16.7 Hz, H-10), 3.05 (s, 1H, H-7), 5.18 (s, 1H, H-1); ^{13}C NMR (100 MHz; $CDCl_3$) δ 26.6 (CH_3, C-14), 30.6 (CH_3, C-15), 50.0 (CH_2, C-10), 56.7 (OCH_3, C-7), 70.8 (C, C-5), 94.7 (CH, C-1), 164.5 (C, C-6), 167.5 (CO, C-2), 172.9 (CO, C-4), 205.5 (CO, C-11); MS (CI/isobutane) *m/z* (%): 228 (M+H), 172 (80), 113 (30), 85 (80); HRMS (CI/isobutene) *m/z* (%): 228.0870 ($C_{10}H_{11}NO_5$, M+H$^+$-H_2O, requires 228.0872); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 80% ee (t_{minor} = 21.4 min, t_{major} = 23.2 min).

General Method for the Boc-Protection of α-Amino Acids (Method J): The α-amino acid (6 mmol) was added to a solution of sodium carbonate (0.5 g) in water (100 mL). To the mixture, di-tert-butyl dicarbonate was added (7.5 mmol) in *t*-butyl alcohol (20 mL), after which the mixture was stirred at room temperature overnight. The solution was washed with hexane (1×50 mL) and the aqueous phase was cooled to 0 °C. Then a 40% aqueous solution of $KHSO_4$ was added, until pH 3 was reached. The mixture was extracted with ethyl acetate (3×50 mL) and the organic phase was washed with water (3×50 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The product was used directly in the next step without further purification.



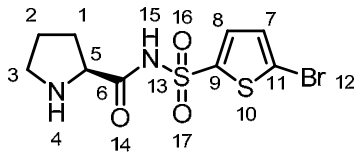
378

N-Methyl- L-valine **378.** A 250 mL flask was charged with the Boc protected *N*–methyl-L-valine (3.326 g, 15.3 mmol), dry THF (150 mL), and iodomethane (16.300 g, 114.8 mmol) and cooled to 0 °C under Ar atmosphere. Sodium hydride (5.512 g, 229.7 mmol) was then added in small portions during 2 h while stirring vigorously. The reaction mixture was then stirred at room temperature for 24 h. The reaction was quenched with water (50 mL) and THF was

evaporated under reduced pressure. The concentrate was diluted with water (50 mL) and washed with ethyl acetate (1×100 mL). The aqueous phase was acidified with 1M hydrochloric acid (10 mL) and extracted with ethyl acetate (3×100 mL). The organic phase was washed with a water (2×100 mL) and brine (1×100 mL) and dried over $MgSO_4$. The solvent was evaporated to give yellow viscous oil, which on crystallization from ethyl acetate afforded *N*-methyl-L-valine **378** (2.868 g, 81%) as white crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 3H, H-5), 1.01 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 3H, H-6), 2.13-2.36 (m, 1H, H-4), 2.85 (s, 3H, H-1), 4.22 (d, $^3J_{H\text{-}H}$ = 10.4 Hz, 1H, H-2), in agreement with literature.[161]

General Method for Coupling of Boc-Protected α-Amino Acids with *N*-Sulfonamides (Method K): The corresponding *N*-sulfonamide (1.22 mmol) was added to a solution of the Boc-protected α-amino acid (1.22 mmol) in dry dichloromethane (30 mL), followed by dry Et_3N (0.25 mL, 1.83 mmol). The reaction mixture was cooled to 0 °C and HOBT (1.58 mmol) was added, followed by EDCI (1.58 mmol). The resulting solution was stirred at 0 °C for 1h under Ar and then at room temperature for 24 h. The reaction mixture was diluted with ethyl acetate (100 mL) and washed with cold 1M hydrochloric acid (2×50 mL), cold water (2×50 mL), and brine (2×50 mL). The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The product was used directly in the next step without further purification.

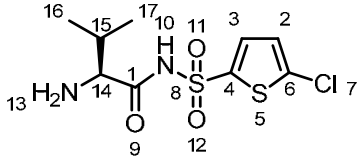
General Method for the Boc-Deprotection (Method L): TFA (5 mL) was added dropwise to a solution of proline or valine *N*-sulfonamide (1 mmol) in dichloromethane (5 mL) at 0 °C while stirring vigorously. The reaction mixture was stirred at 0 °C for 1h and then co-evaporated at reduced pressure with toluene (5×10 mL). The crude catalyst was obtained, which was further purified by column chromatography (*vide supra*).



371

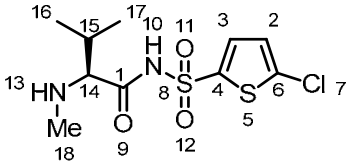
371 was prepared by **Method J** followed by **Method K** and **Method L.** Purification by column chromatography on silica gel (3 g of SiO_2) with an ethyl acetate-methanol mixture (1:1, R_F = 0.30) afforded **371** as viscous colourless oil (128 mg, 91% over 2 steps): ^{1}H NMR ($CDCl_3$ and drop of d_4-MeOH) δ 1.89-2.16 (m, 4H, H-1, 2), 2.29-2.41 (m, 2H, H-3), 4.07 (t, $^3J_{H\text{-}H}$ = 7.0 Hz, 1H, H-5), 6.97 (d, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-7), 7.48 (d, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-8);

^{13}C NMR (100 MHz, $CDCl_3$ and drop of d_4-MeOH) δ 24.8 (CH_2, C-2), 30.6 (CH_2, C-1), 47.2 (CH_2, C-3), 63.4 (CH, C-5), 127.3 (CH, C-8), 131.9 (CH, C-7), 136.2 (C, C-11), 143.5 (C, C-9), 173.9 (CO, C-6); IR (KBr) ν 3074, 1676, 1397, 1375, 1283, 1203, 1133, 968 cm^{-1}; MS (FAB/NOBA) *m/z* (%) 339/341 ($M+H^+$, 85/83), 273 (25), 142 (32), 75 (100); HRMS (FAB/NOBA) *m/z* 338.9492 ($C_9H_{12}{}^{79}BrN_2O_3S_2$, $M+H^+$, requires 338.9467).



372

372 was prepared by **Method J** followed by **Method K** and **Method L.** Purification by column chromatography on silica gel (4 g of SiO_2) with an ethyl acetate-methanol mixture (4:1, R_F = 0.30) afforded **372** (82 mg, 61% over 2 steps) as viscous colourless oil (61% over 2 steps): ^{1}H NMR (400 MHz, $CDCl_3$ and drop of d_4-MeOH) δ 0.85 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 3H, H-16), 0.91 (d, $^3J_{H\text{-}H}$ = 6.8 Hz, 3H, H-17), 2.14-2.22 (m, 1H, H-15), 3.49 (d, $^3J_{H\text{-}H}$ = 4.2 Hz, 1H, H-14), 6.83 (d, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-2), 7.44 (d, $^3J_{H\text{-}H}$ = 4.0 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$ and drop of d_4-MeOH) δ 17.9 (CH_3, C-16), 19.5 (CH_3, C-17), 31.4 (CH, C-15), 61.5 (CH, C-14), 127.5 (CH, C-2), 132.9 (C, C-6), 137.7 (CH, C-3), 141.9 (C, C-4), 173.2 (CO, C-1); IR (KBr) ν 3426, 3096, 2977, 1675, 1471, 1407, 1219, 1142, 772 cm^{-1}. MS (FAB/NOBA) *m/z* (%) 297/299 ($M+H^+$, 49/17), 231 (20), 180 (100), 69 (82); HRMS (FAB/NOBA) *m/z* 297.0152 ($C_9H_{14}{}^{35}ClN_2O_3S_2$ requires 297.0129).



373

373 was prepared by **Method J** followed by **Method K** and **Method L.** Purification by column chromatography on silica gel (7 g of SiO_2) with an ethyl acetate-methanol mixture (R_F = 0.30) afforded **373** (153 mg, 60% over 2 steps) as viscous colourless oil: ^{1}H NMR (400 MHz, $CDCl_3$ and drop of d_4-MeOH) δ 0.89 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, H-16), 0.92 (d, $^3J_{H\text{-}H}$ = 7.6 Hz, 3H, H-17), 2.08-2.17 (m, 1H, H-15), 2.52 (s, 3H, H-18), 3.40 (d, $^3J_{H\text{-}H}$ = 4.4 Hz, 1H, H-14), 6.89 (d, $^3J_{H\text{-}H}$ = 3.5 Hz, 1H, H-2), 7.51 (d, $^3J_{H\text{-}H}$ = 3.5 Hz, 1H, H-3); ^{13}C NMR (100 MHz, $CDCl_3$ and drop of d_4-MeOH) δ 18.8 (CH_3, C-16), 19.0 (CH_3, C-17), 31.5 (CH, C-15), 33.8 (CH_3, C-18), 69.9 (CH, C-14), 127.8 (CH, C-2), 133.7 (C, C-6), 138.5 (CH, C-3), 141.0 (C, C-4), 170.9 (CO, C-1); IR (KBr) ν 3429, 3107, 2977, 2882, 1681, 1472, 1206, 1091, 842 cm^{-1}; MS (FAB/NOBA) *m/z* (%) 311/313 ($M+H^+$, 53/20), 245 (29), 194 (100), 75 (79); HRMS (FAB/NOBA) *m/z* 311.0301 ($C_{10}H_{16}{}^{35}ClN_2O_3S_2$, $M+H^+$, requires 311.0285).

General Method for the Aldol Reaction, using *N*-Sulfonamide Catalysts (Method M): The corresponding non-enolizable ketone was added to the catalyst **371**, **372** or **373** (0.02 mmol) in acetone (3.2 mL) and water (39 μL, 2.16 mmol). The reaction mixture was stirred at 10 °C overnight. The reaction mixture was diluted with ethyl acetate (40 mL) and washed with water (5×20 mL). The organic layer was dried ($MgSO_4$), the solvent was evaporated *in vacuo* and the product was purified by flash chromatography on a short column of neutral Al_2O_3 (2 g of alumina, pre-treated with 1% Et_3N in ether), using ethyl acetate as an eluent.

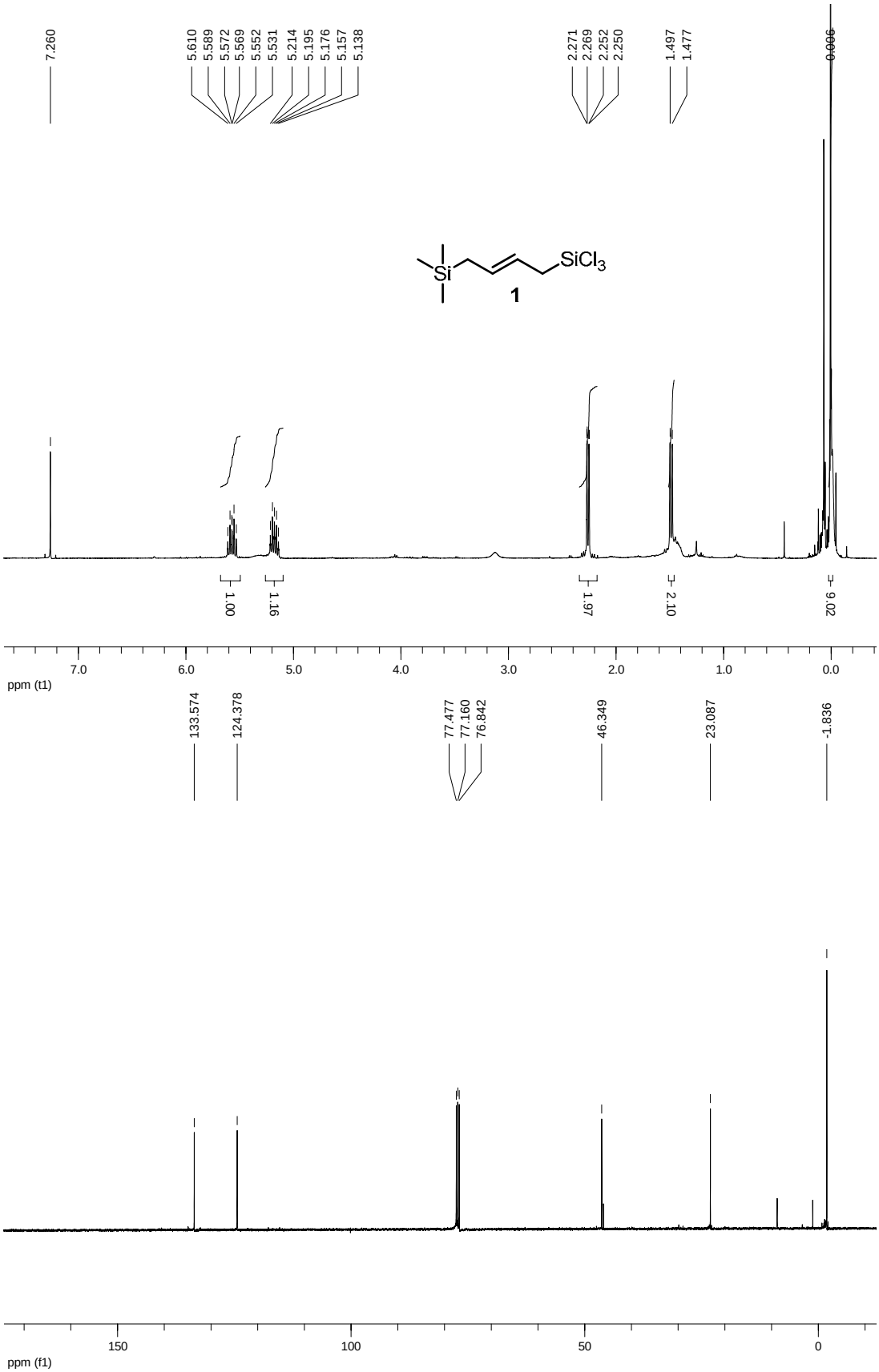
Racemic standards (for HPLC) were prepared in the same way, using 20 mol% of aminoethanol as a catalyst.

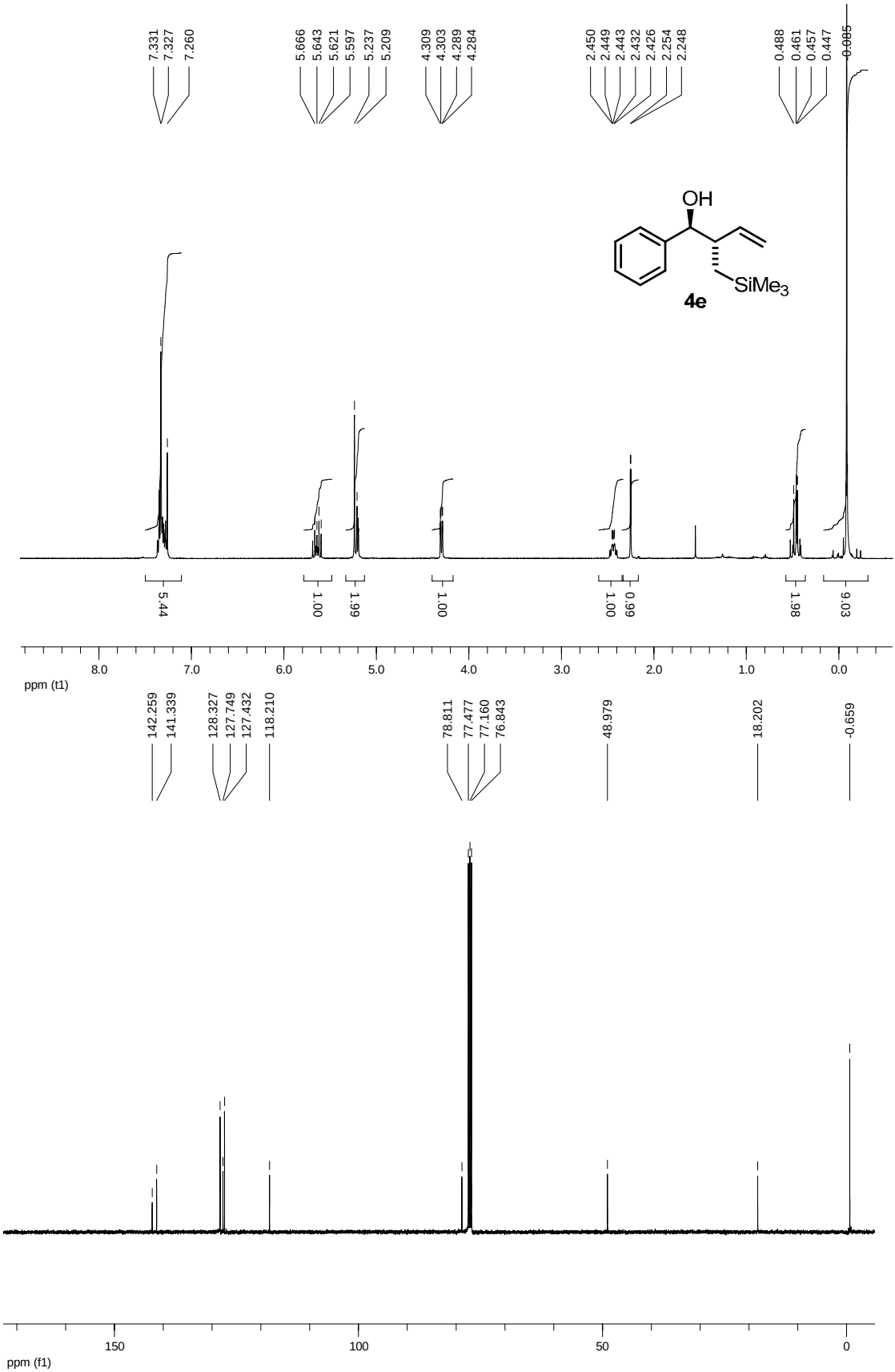
Sulfonamide catalyst regeneration: The aqueous phase from the workup above was acidified with one drop of concentrated hydrochloric acid and extracted with small portions of CH_2Cl_2 several times. The organic phase was washed with water and brine and dried ($MgSO_4$). The solvent was evaporated *in vacuo* to afford the pure catalyst.

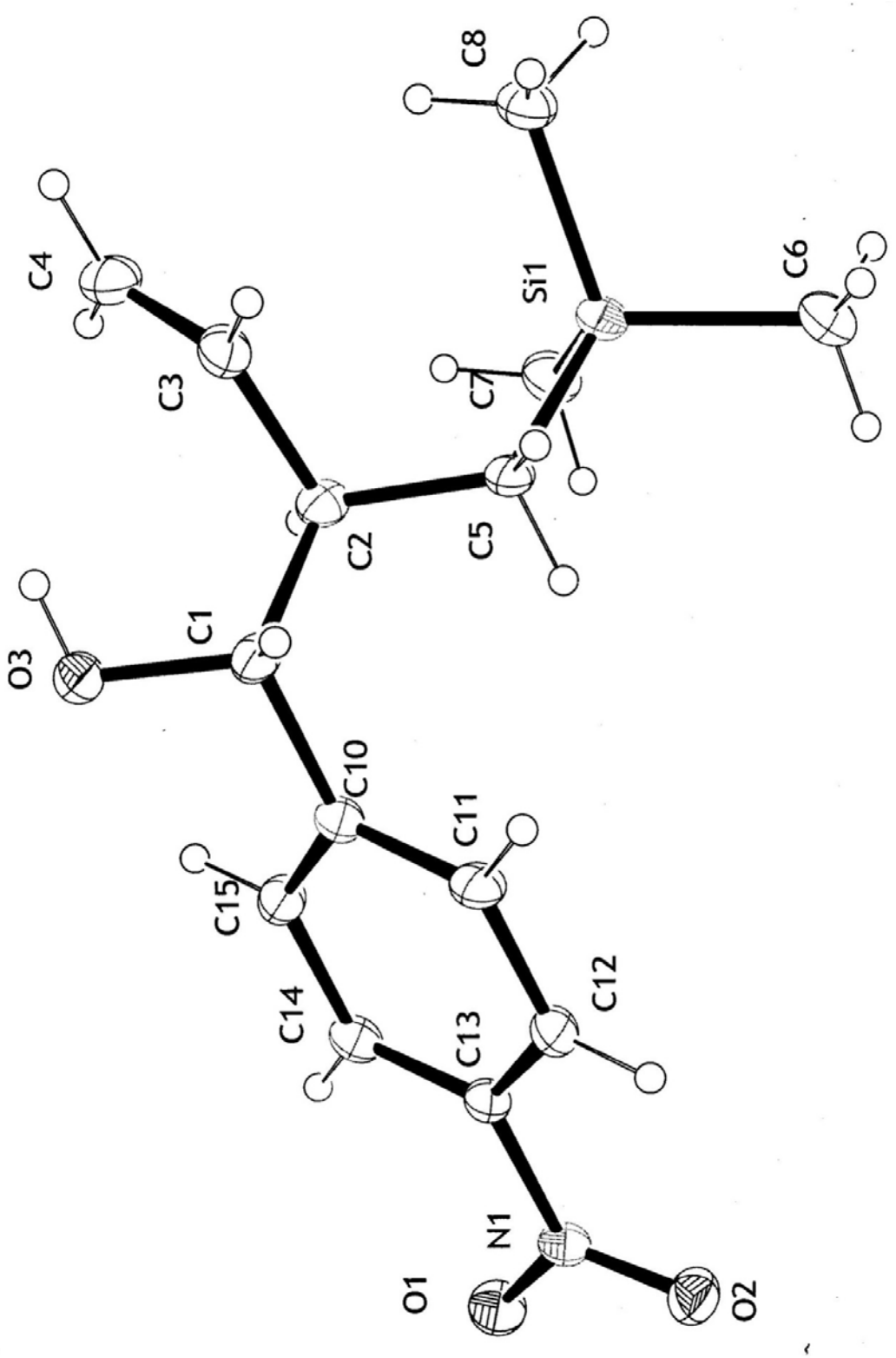
6 Appendix

Contents:

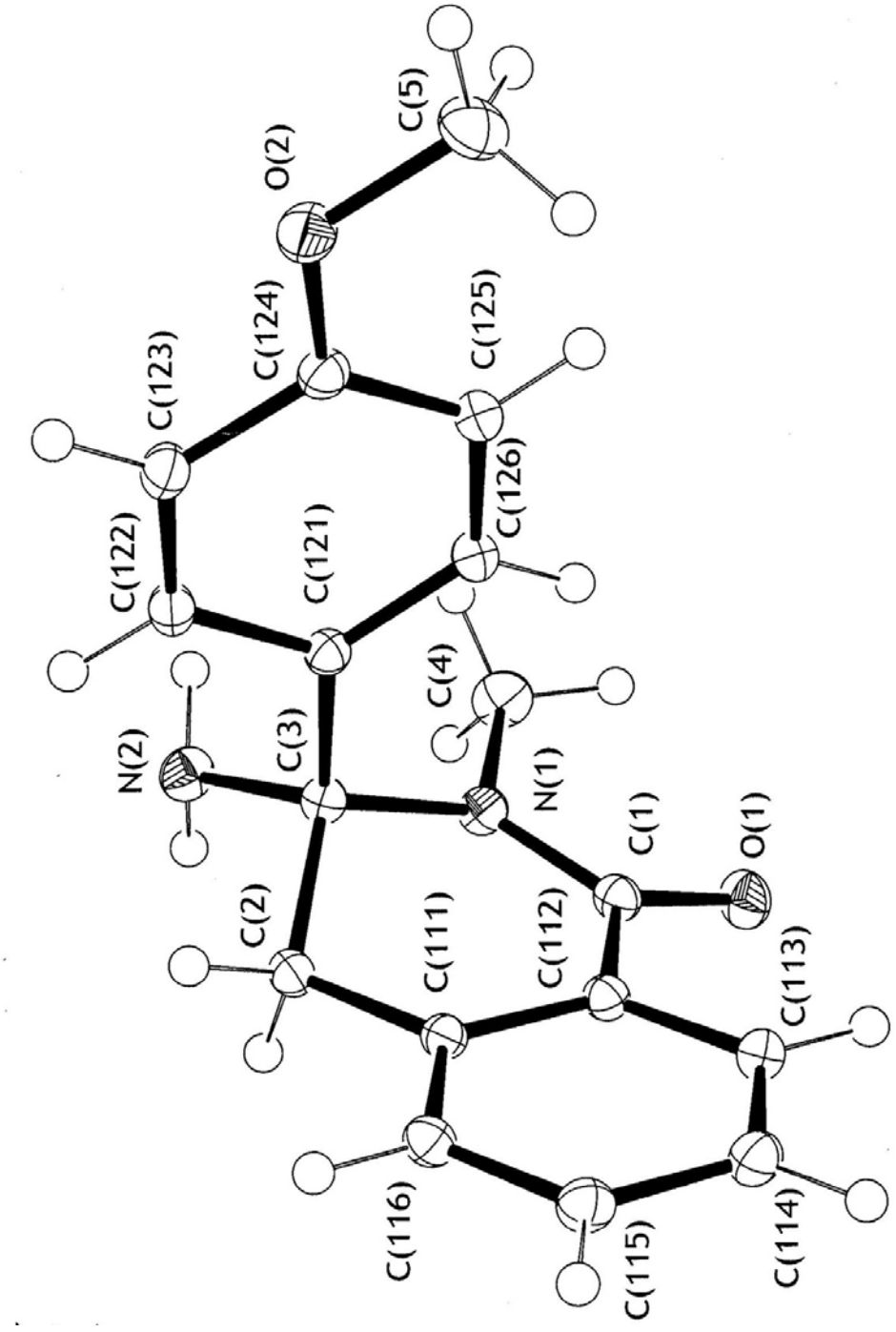
- ^{1}H and ^{13}C NMR traces of the disilane **1**
- ^{1}H and ^{13}C NMR traces of the homoallylic alcohol **4a**
- ORTEP diagram of the homoallylic alcohol **4e**
- ORTEP diagram of the aminal **12b**
- ORTEP diagram of **385** (*Speranskatine A*)


7.260
5.610
5.589
5.572
5.569
5.552
5.531
5.214
5.195
5.176
5.157
5.138
2.271
2.269
2.252
2.250
1.497
1.477
0.006
SiCl3
Si
1
1.00
1.16
1.97
2.10
9.02
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
133.574
124.378
77.477
77.160
76.842
46.349
23.087
-1.836
150
100
50
0
ppm (f1)

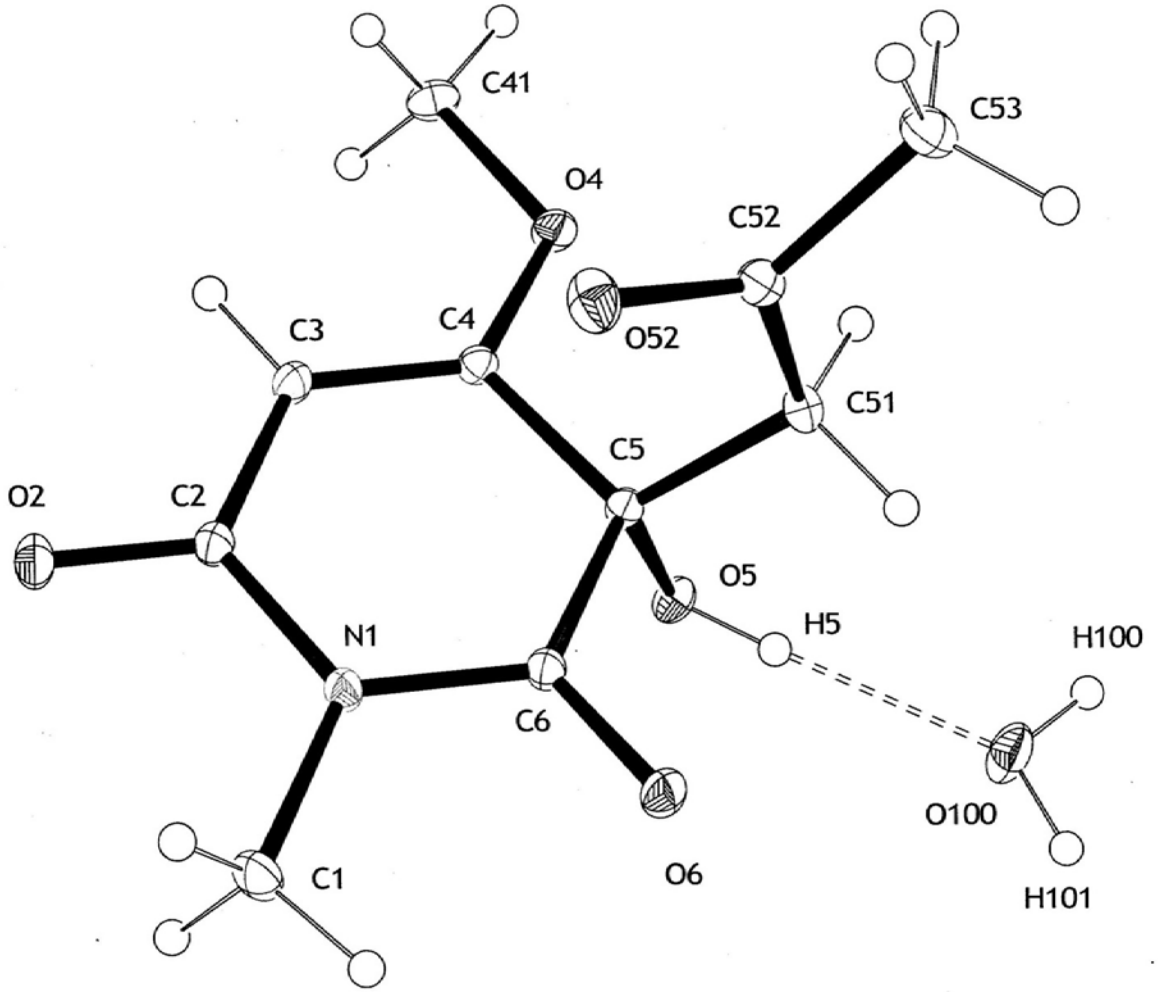

7.331
7.327
7.260
5.666
5.643
5.621
5.597
5.237
5.209
4.309
4.303
4.289
4.284
2.450
2.449
2.443
2.432
2.426
2.254
2.248
0.488
0.461
0.457
0.447
0.085
OH
SiMe3
4e
5.44
1.00
1.99
1.00
1.00
0.99
1.98
9.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)
142.259
141.339
128.327
127.749
127.432
118.210
78.811
77.477
77.160
76.843
48.979
18.202
-0.659
150
100
50
0
ppm (f1)



4e


C(5)
O(2)
C(124)
C(125)
C(123)
C(126)
C(122)
C(121)
C(4)
N(2)
C(3)
N(1)
C(1)
O(1)
C(2)
C(111)
C(112)
C(113)
C(116)
C(115)
C(114)

12b



385

(*Speranskatine A*)

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