Organocatalytic asymmetric alkenylation of carbonyl compounds

Loughborough University

Organocatalytic Asymmetric Alkenylation of Carbonyl Compounds

by

Nikolay S. Kondratyev

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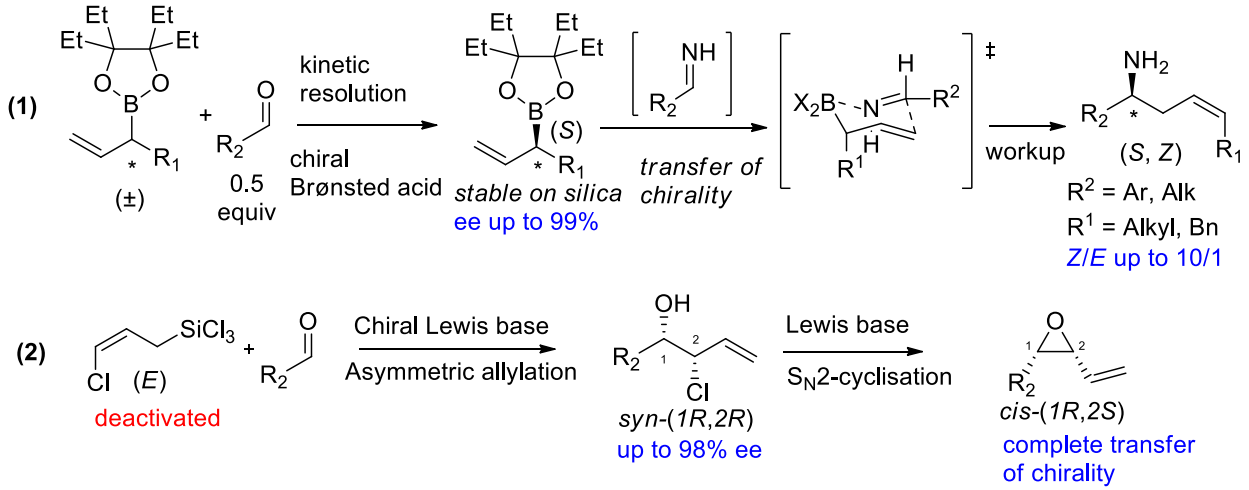
Abstract

Asymmetric alkenylation of carbonyl compounds using organocatalysed reaction with respective organoelement reagents has developed into a useful and practically important method for the synthesis of enantiomerically enriched homoallylic amines and alcohols. As Type 1 reagents, secondary allylboronates and linear γ-functionalised allyltrichlorosilanes transfer stereochemical information (chirality or *E*/*Z* configuration) into the product (Scheme, reactions 1 and 2).



Scheme

The first reaction leads to synthetically important, unprotected *Z*-homoallylic amines which were previously inaccessible by direct methods. These compounds can serve as useful synthetic building blocks for syntheses of alkaloids and other natural, medicinal and bioactive compounds. The second reaction is the key step in the preparation of chiral *cis*-vinyl epoxides, a structural motif that was employed in the total synthesis of prostaglandins and other bioactive compounds.

The first chapter of this thesis describes a novel, highly efficient kinetic resolution method of a novel class of chromatographically-stable chiral secondary crotylboronates, and their application for a practical, direct synthesis of unprotected (*S*,*Z*)-homoallylic amines. Synthesis of homoallylic amines with an internal double bond so far was hampered by the lack of efficient asymmetric synthesis of precursor boronates, which are mostly unstable during purification by chromatography or by distillation and therefore difficult to access as individual compounds.

The second part uncovers efficient activation of unreactive γ-chloroallyltrichlorosilanes by employing novel chiral bipyridine-*N,N'*-dioxides as chiral Lewis base catalysts and demonstrates their synthetic potential for the asymmetric synthesis of difficult-to-access chiral *cis*-vinylepoxides. It is important to note that direct synthesis of chiral *cis*-vinylepoxides is problematic due to difficulty in achieving chemoselective oxidation of the respective dienes.

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I want to thank Prof. Andrei Malkov for his great patience, support and everlasting belief in my chemistry future, without which it would not be possible to come to the end of my doctorate. I much acknowledge and say respectful thanks to my father Sergey Kondratyev, who provided all funding and covered all my living costs throughout all this difficult time and never seized helping me. I thank my beloved mother for raising me a compassionate person who wish to help people and to make beautiful and useful things.

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I also thank the LU gardeners for bringing fantastic beauty and peace to my heart.

Dedicated to my family

List of abbreviations

°C	degrees Celsius
Å	ångström
Ac	Acetyl
acac	Acetylacetonate
Ar	Aryl
BINOL	1,1'-Bi-2-naphthol
Bn	Benzyl
ca.	*circa*
Chloroform-d_1	$CDCl_3$
Cy	Cyclohexyl
DCM	dichloromethane
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DMF	*N,N*-dimethylformamide
DMSO-d6	$(CD_3)_2SO$
E	*trans*
EDG	electron-donating group
ee	*enantiomeric excess, (R-S)/(R+S)*
equiv	equivalents
Et	Ethyl
EWG	electron-withdrawing group

h	hours
HB	Hünig's base
Hex	*n*-Hexane
HFIP	Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
Hünig's base	*N*,*N*-Diisopropylethylamine
Hz	Hertz
i-Pr	Isopropyl
IR	Infrared
J	spin-spin coupling constant
L	ligand
L	litre, volume
LAH	Lithium aluminium hydride
LDA	Lithium diisopropylamide
M	molar concentration, Mol/liter
m-	*meta*
m.p.	melting point
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MHz	megahertz
MS	molecular sieves
n-Bu	*n*-Butyl

nm	nanometer
NMR	nuclear magnetic resonance
Nu	nucleophile
o-	*ortho*
P	Plus configuration
p-	*para*
PE	Petroleum Ether, boiling range 40-60 °C
Pempidine	1,2,2,6,6-Pentamethylpiperidine
Ph	Phenyl
R	organic radical
R	*Rectus*
R*f*	Retention factor
rt	rt
S	*Sinister*
TBS	*tert*-Butyldimethylsilyl
t-Bu	*tert*-Butyl
Tf	Triflate (trifluoromethane sulfonate)
THF	tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TRIP	*(R)*-3,3'-Bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogenphosphate
UV	ultraviolet

Z	*cis*
δ	chemical shift, NMR
µ	micro
υ	frequency, IR
ω	mass concentration

Table of Contents

General Introduction

Over the last two decades, organocatalysis has begun to play an important role in asymmetric synthesis. The vast majority of new drug candidates, natural products and bioactive compounds are synthesised via organocatalysis.[1] Moreover, in the synthesis of a successful drug candidate, it is desirable to use organocatalysis in the later stages, due to the need for minimising traces of metals in pure compounds for pharmaceutical needs.

The central part in the synthesis of any complex organic molecule, whether it is for the pharmaceutical or for any other chemical industry, such as polymers, new materials, pesticides etc., is the formation of a C-C bond.

On the other hand, in the world of natural products or bioactive compounds, the property which stands out due to its importance is Chirality. This fundamental quality of three-dimensional objects defines key chemical and biological properties of such molecules. It is very important, and also often difficult, to synthesise a chiral molecule with well-defined stereocenters. Thus, the development of chiral catalysts for the construction of stereocenters with defined topology is fundamentally important and persistent challenge of modern organic synthesis.

Since the dawn of Organic Chemistry as a distinct scientific discipline, chiral molecules have been widely used in organic synthesis. The earliest known separation of chiral compounds was achieved by Pasteur with *L*- and *D*-Tartaric acid, in which he manually separated crystals of opposite enantiomers.

Chiral molecules have since been used in asymmetric synthesis as chiral media, chiral reagents, chiral substrates or auxiliary groups, and many efficient and reliable methods have been developed over the last century. But there are still several issues including their high cost, lack of scope and reaction variability, as well as the difficulty of the introduction of chiral groups which therefore demands new and efficient approaches.

Organocatalysts are small molecules which are easier to handle than enzymes. They are cheaper and easier to produce, and their chemical diversity provides an opportunity for optimisation of catalysts for each specific process, as well as finding catalysts with a broad application scope, which would be capable of catalysing many different chemical processes.

They are often more cost-effective and also provide higher atom-economy in chemical processes then the use of chiral auxiliary groups. Also, in large scale processes, chiral catalysts can be recycled, and their synthesis can be often based on the use of available chiral pool compound.

Organocatalytic reactions are relatively clean, efficient, and leave less toxic traces in the reaction products, than methods which employ metal complex as catalysts. Under these circumstances, it is very appealing to develop an efficient, highly selective and versatile methodology for the asymmetric formation of C-C bonds.

If we consider an organocatalytic formation of a new C-C bond with a stereogenic center using allylating reagents, two different organocatalytic strategies are available.

The first is the addition of nucleophilic reagent to an electrophilic substrate, where a chiral catalyst is a Brønsted acid, which coordinates to the substrate or the reagent in the transition state, thus allowing the nucleophilic attack to proceed preferably from one enantiotopic face.

The second strategy is when Chiral Lewis base is used as a catalyst; it coordinates to the reagent in the transition state, which again directs it from one side only to the electrophilic centre.

The literature overview in this thesis will cover the two main parts of the work investigated. The background of different asymmetric C-C bond formation methods using organoboron and organosilicon reagents will be discussed from the historical and applied perspective, and the literature survey will be presented with the focus on the latest achievements in the field of organocatalysis. The critical discussion will lead to the formulation of the research goals of the current Thesis, and reasons for setting up the research tasks will emerge from the critical analysis.

Chapter 1: Literature Review. Asymmetric Allylation of C=N bond.

1.1. Introduction

Addition of allylmetals to imines can proceed through different transition states, a closed cyclic TS **1**, which is often called Zimmerman-Traxler model, or through open acyclic TS **2** (Figure 1).

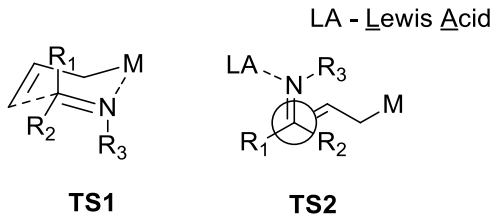


Figure 1

Transition state **TS1** is often realised when the carbon-metal bond in the reagent is highly polarised resulting in substantial partial positive charge on the metal, e.g. allylmagnesium or allylboron reagents. These can then proceed through different conformations, depending on the nature of substituents on the allylmetal and imine. Therefore, the selectivity and stereochemistry of the reaction is mainly defined by pseudoaxial and pseudoequatorial interactions in the transition state.[2] In contrast, for the reactions employing trialkylallylsilanes and tetraallylstannane in the presence of Lewis acids, the addition proceeds through an open acyclic transition state **TS2** and stereoselectivity is defined by chiral substituents on the metal, chiral auxiliary groups or stereochemical configuration of the imine itself. In some cases, it is difficult to determine, which transition state is realised, and therefore various models are suggested.[3]

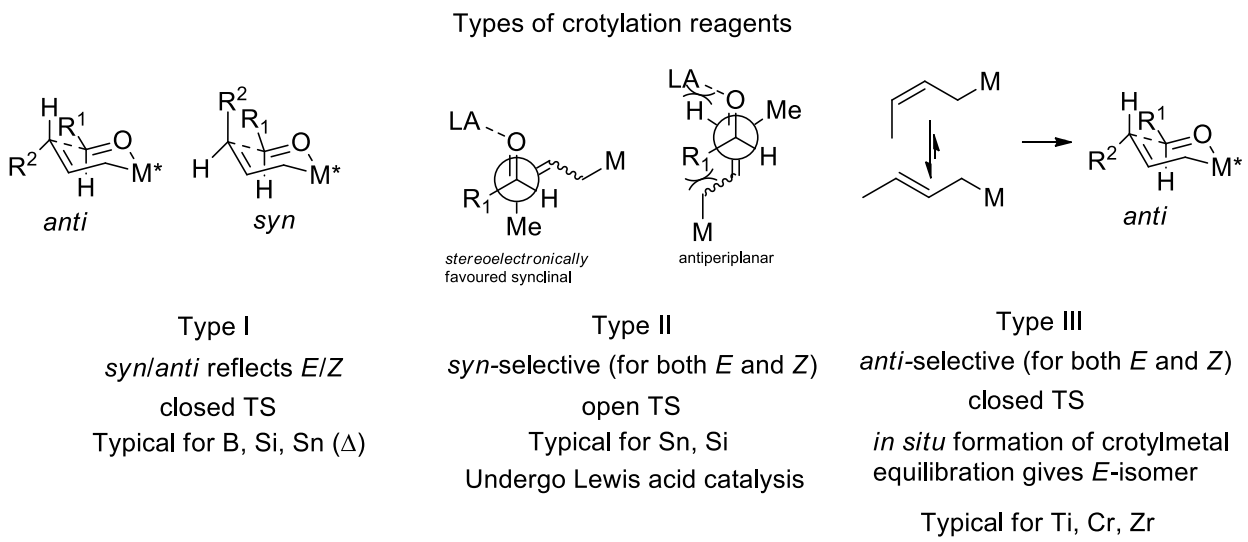


Figure 2

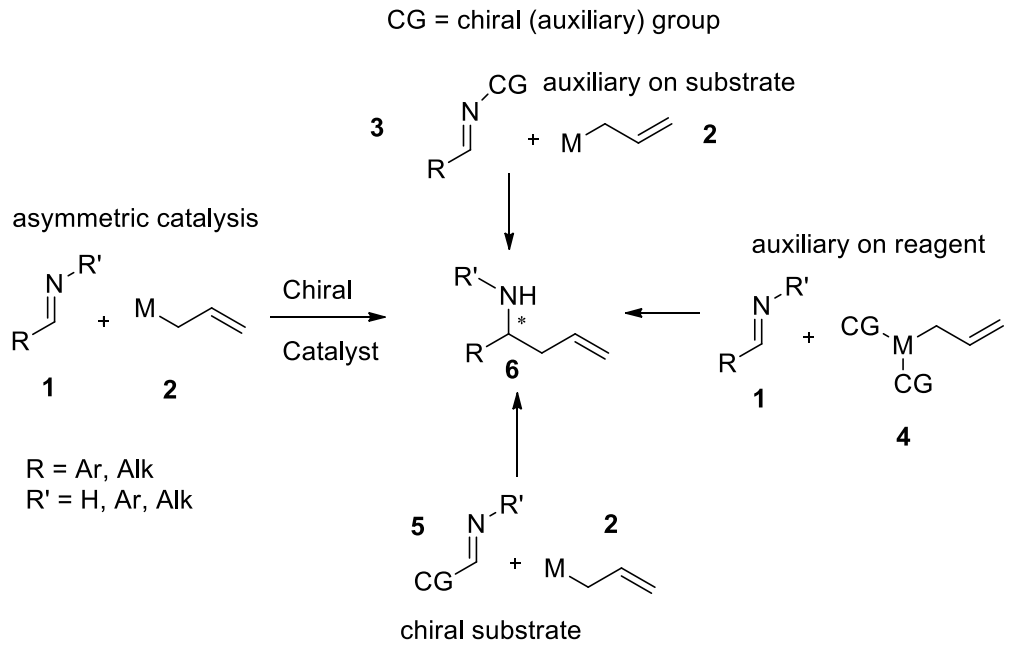
According to Denmark and Weber[4], There are 3 different types of reagents in crotylation reactions (Figure 2): Type 2 reagents react via open transition state, which is realised with crotyl metals having low Lewis acidity and stable geometry. The geometry of such a transition state is usually hard to control, and it usually provides a synthetic outcome of *ca*. 9:1 *syn/anti* relative stereochemistry. The other group is Type 3 reagents, which are usually crotyl metals having a strong Lewis acidic nature. They are usually configurationally unstable, which results in a fast equilibrium between the *E* and *Z* forms in the reaction medium. Since the *E*-form is more stable, it usually gives predominantly pure *anti* product irrespective of the precursor's double bond geometry.

Finally, Type 1 reagents react via the closed Zimmerman-Traxler transition state, which is characterised by a highly organised configuration and close contact of allylmetal with an aldehyde. In this case, the reaction outcome is completely predefined by the configuration of the crotylmetal. As a consequence, *syn*/*anti* ratios reflect the isomeric purity of the reagent, thus making this pathway synthetically most attractive and useful.

In this literature review, we will focus generally on Type 1 reagents reacting via closed transition state, which is commonly realised with boron.

1.2.Classification of approaches

For general understanding, it would be useful to classify possible ways of chirality transfer during the formation of homoallylic amine. Possible routes can be illustrated with the simplest linear homoallylic amines, such as depicted in Scheme 1.



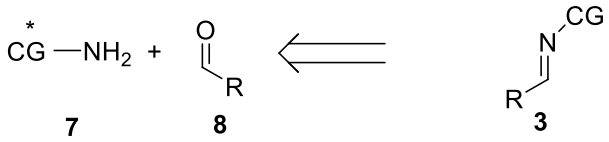
Scheme 1

There are a few different ways of chiral induction for this general type of transformation. Chirality could be introduced by employing a chiral catalyst[5], which is the most useful and desirable synthetic pathway. This approach will be described in further detail, due to the large variety of synthetic protocols and different catalytic models. The main difficulties associated with this approach are related to the need to design specific catalysts for different substrates, and the fact that additional functional groups on the nitrogen of imine **1** are sometimes necessary that then affects the overall atom-efficiency and limit the reaction scope due to specific steric and stereoelectronic requirements. In practice, enantioselectivity drops significantly for the reactants with small aliphatic or slightly for electron-deficient aromatic substituents.[6]

1.2.1. Auxiliary on substrate

A large number of examples have been reported using chiral auxiliary groups on imines **3** and closely related analogues, which include chiral hydrazones[7], valine-derived imines[8], chiral

aminoalcohols, chiral *p*-tolylsulfinyl imines, galactosamine-derived imines and chiral oxime ethers[6]. The weakest point of these methodologies is the need for stoichiometric amounts of the chiral compound during the installation of the chiral auxiliary and its further cleavage after the allylation step, which makes this methodology at least 3 step longer.[9]



7 **8** **3**

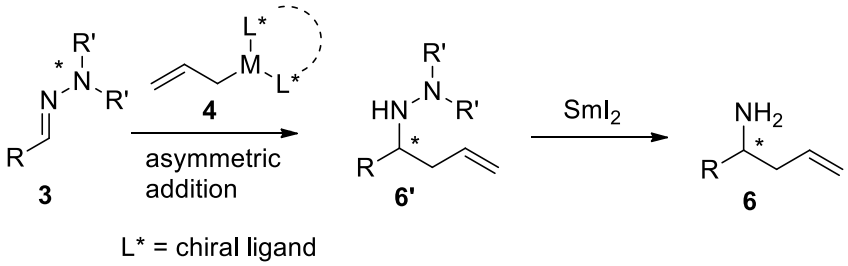
Scheme 2

Despite the fact that most chiral auxiliary precursors **7** for imines **3** (Scheme 2) are derived from available natural chiral sources and that the chiral amines used can be recovered in large-scale preparations, the practicality of this methodology depends on the overall cost and amount of time and labour required for their synthesis. Another weakness of this approach is that both imine **3** and allylmetallic reagent **2** often need activation[10], or harsher reaction conditions, mainly due to steric hindrance of the nitrogen substituents and unsatisfactory activity of the allylmetal reagent. Also, in some cases, aromatic aldehydes **8** do not form hydrazides *in situ* due to the lower reactivity of the carbonyl group.[11]

1.2.2. Auxiliary on reagent

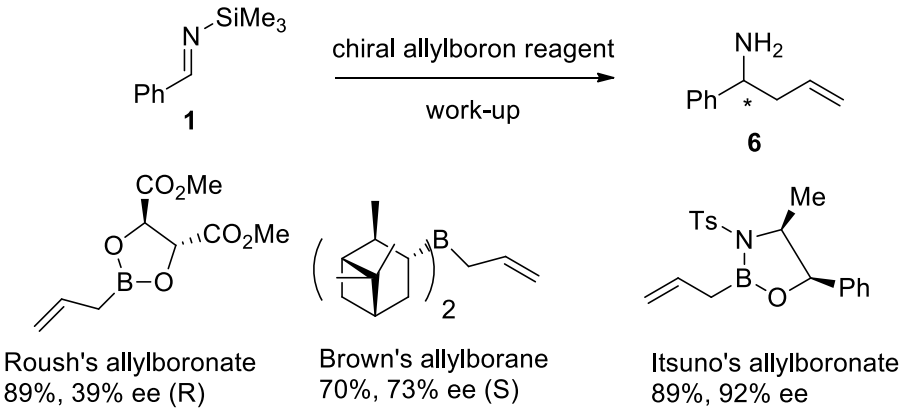
A different interesting approach using chiral auxiliaries relies on placing a chiral fragment on the metal centre (Scheme 1). Various allylmetals **4** bearing chiral chelating groups are known, mostly on silicon and boron atoms.[6] The main disadvantages of this approach are in regards to the use of stoichiometric amount of chiral compounds as was previously discussed. However, the chiral compound, in many cases can be recycled. Furthermore, the resulting primary homoallylic amines **6** are readily available after aqueous work-up, and there is no need for additional deprotection except in the case of hydrazones.[12] The scope of possible imine substrates is wider[6]; however, the most effective and universal Brown's reagents require two large auxiliary groups in one molecule[13], which significantly lowers the overall atom-economy of the process. The silicon-based reagents **4** usually show lower reactivity than the boron analogues, and therefore activation of either the reagent or the imine substrate is usually required.[6] Sometimes, synthetic protocols use stoichiometric amounts of chiral Lewis bases which can be viewed as a chiral auxiliary on silicon[14]; though, the mechanistic details are often

not clear. In general, silicon reagents give better enantioselectivities with hydrazones[14], which can be related to their greater hydrolytic stability[15] and significantly lower basicity than that of imines[16], which allows chiral base catalysis. Another advantage of hydrazones **3** is that they can be easily recrystallised, thus significantly improving the enantiopurity of the products.[12] However, the disadvantage of such a method is that the formed hydrazine derivative **6'** requires cleavage of the N-N bond by single-electron oxidation agents, e.g. SmI_2, which has to be also tolerant of other functional groups if they are present (Scheme 3).



Scheme 3

There are several examples of such allylation reagents that have been designed. The most widely known of them are Brown's isocampheyl-derived allylborane[17,18], Roush's tartrate allylboronate[19], and Itsuno's *N*-tosyl-norephedrine derived B-allyloxazaborolidine[20] (Scheme 4).

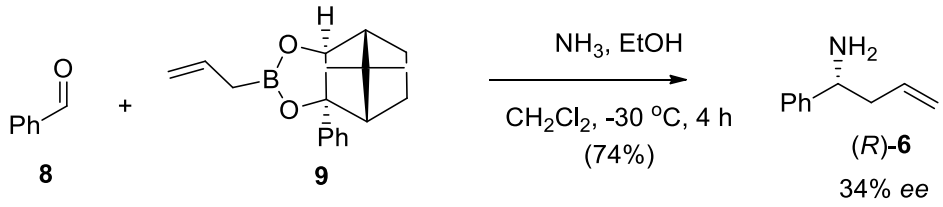


Scheme 4

The first example of modestly successful application of chiral boron reagents with trimethylsilyl-substituted aromatic imines was conducted by Itsuno and coworkers[21], with the best result shown on B-allyldiisopinocampheylboran, known as Brown's borane. Further prolonged screening of possible auxiliaries in the same group of Itsuno led to the significantly optimised method to afford homoallylic amines in excellent yields with *ee* up to 92%.[20] It was then shown by Brown, that water is a principal reagent in this process and that

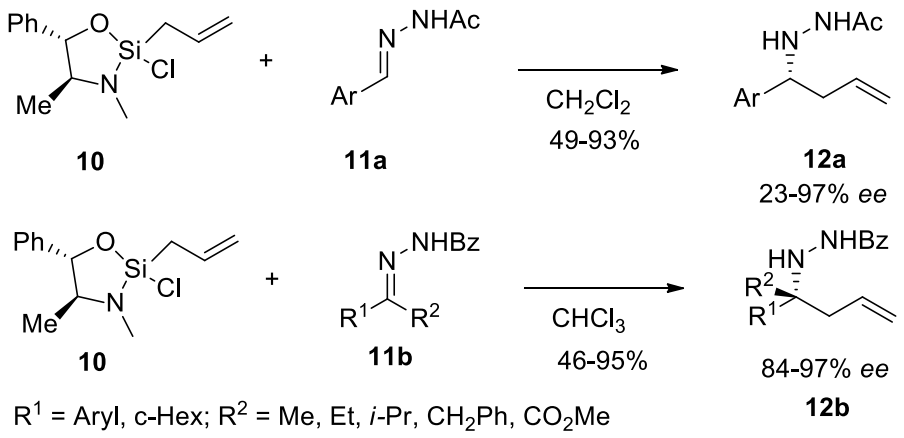
trimethylsilylimines undergo allylation by boron reagents only after being hydrolyzed to unstable primary aldimine.[22] Itsuno and coworkers also extended this approach based on Brown's allylborane to previously inaccessible aliphatic imines, by using *in situ* reduction of nitriles by Dibal-H.[13] The results were fairly good, which means such a methodology can be used for the synthesis of optically active unprotected homoallylic amines; however, aliphatic derivatives gave lower yields and selectivity. The biggest disadvantage of the use of trimethylsilyl imines is that their preparation requires distillation to purify them, and also their significant sensitivity to hydrolysis, which requires operations in a closed dry system. The need for distillation also limits the scope and makes it impossible to use larger molecular weight imines, which means that this methodology can be applied on late stages of a synthesis only in the case that the trimethylsilyl imines compound can be formed *in situ.*

The first attempt to synthesise enantioenriched homoallylic amines using ammonia as a source of nitrogen was undertaken by Kobayashi and coworkers.[23] This work was based on the use of B-allyldiisopinocampheylboronic ester **9** for the allylation of the *in situ* formed primary imine in ammonia solution in DCM. This early example provided only a modest *ee*, but showed the possibility of developing a versatile approach, which enables the synthesis of a large range of homoallylic amines in a very convenient and highly effective way by using *in situ* formation of imine from benzaldehyde (**8**) and ammonia solution (Scheme 5).



Scheme 5

Excellent enantioselectivity was also achieved by Leighton who used norephedrine-derived chiral allyltrichlorosilanes **10** in additions to acylhydrazines **11a,b** derived from aldehydes and ketones (Scheme 6).[12,24]



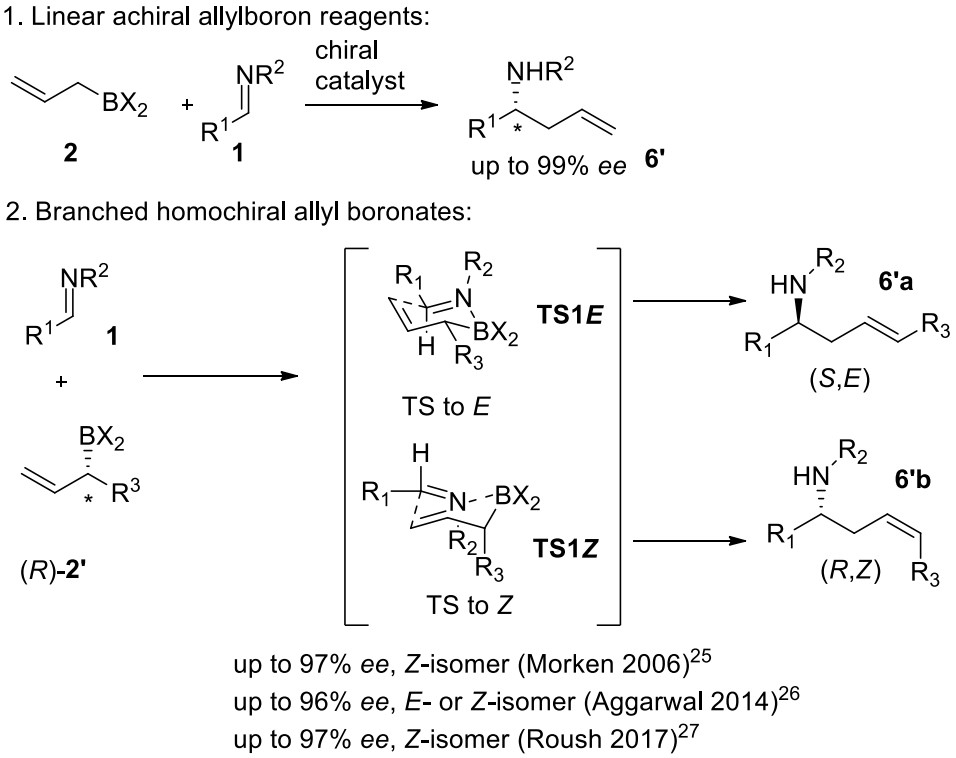
Scheme 6

It is worth noting that reagents like **10** were unreactive with simple imines. The reaction was effective with various acyl hydrazones, with high tolerance to functional groups in substrates, providing high yields and enantioselectivities. The advantage of this methodology is that the resulting products can be recrystallised to afford acylated allylhydrazines **12a,b** in exceptionally high enantiomeric purity. In contrast to acetylhydrazones, benzoylhydrazones have bigger delocalisation energy, which eases the Nucleophilic attack in case of ketone-derived substrates **11b**. Another advantage of benzoylhydrazones is easier hydrazine group reduction and their ready crystallisation which significantly eases purification process. Also, the reaction was effective on a 5-gram scale. The hydrazine can be converted to amine in a single step by single-electron reduction with 1 equiv of SmI_2 in THF solution over minutes at RT with high yields and 98% recovery of chiral auxiliary aminoalcohol without a loss of enantiopurity in 86% yield. Over the last decade, the use of chiral auxiliary-based methods has been superseded by asymmetric catalytic methods.

1.2.3. Chiral reagents

In contrast to reagents with a chiral auxiliary on the metal centre, the chiral secondary allylation regents **2'** possess chiral centre adjacent with C—M bond, where M is B or Si (Scheme 7). These chiral reagents are limited only to the Type 1 since only configurationally stable organoelement compounds can preserve chiral configuration, thus providing a high regio- and enantioselectivity in the allylation reactions. If such a reagent reacts with an imine, then, in contrast to simple allylation, a chiral homoallylic amine with an internal double bond is formed. The reaction proceeds through a chair-like transition state, in which the position of the substituent of the secondary allylation reagent (pseudoaxial or pseudoequatorial) defines the

configuration of the resulting internal double bond of the homoallylic amine. Chiral allylboronates **2'** for decades have been known as excellent asymmetric allylation tools for various electrophiles such as aldehydes **8**, imines **1** and hydrazones **3**.[25] Usually, such chiral boronates are synthesised using chiral catalytic methods[26] or stoichiometric chiral reagents,[27,28] while a kinetic resolution of such boronates was not known due to the difficulty of their isolation.[29] If such a boronate has (*R*)-configuration (**2'**), then (*S*,*E*) or (*R*,*Z*)-amines are formed. Recently, a number of highly enantioselective syntheses of *E*- and *Z*-homoallylic amines using such chiral secondary allylboronates were reported by Morken[26], Aggarwal[27] and Roush[28] (Scheme 7).



Scheme 7

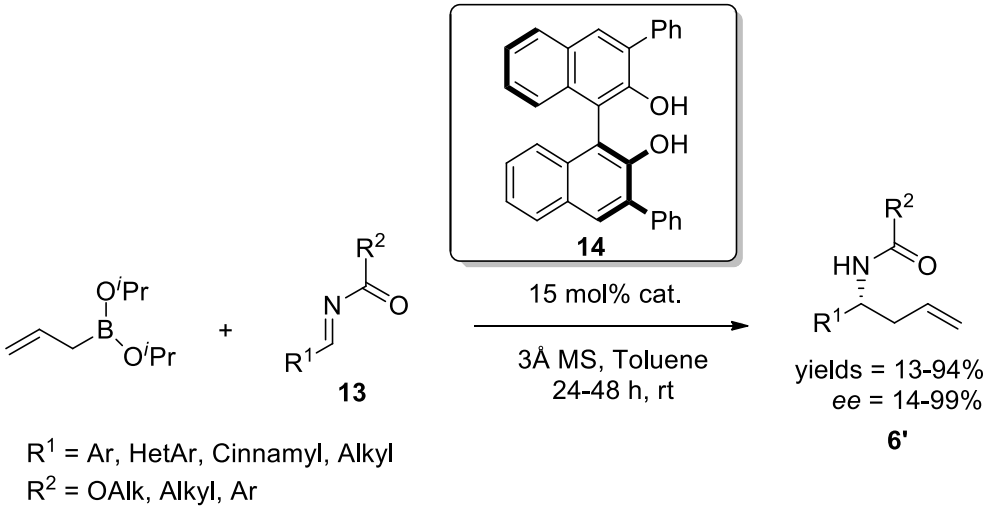
The advantage of using chiral allylation reagents is complete transfer of chirality observed with the vast majority imines (aromatic, aliphatic and α,β-unsaturated), while a disadvantage is the limitation to the Type 1 reagents, and, if the reagent is synthesised using stoichiometric reagents, usually this is associated with a high cost of the chiral auxiliary and low atom-economy of the process.

1.2.4. Chiral substrate

Another well-established method relies on the use of imines **5** derived from aldehydes or ketones having chiral substituents on the adjacent C-atom. Usually, these ketones and aldehydes are derived from aldoses or other natural compounds. It is important to note that many examples of the addition to chiral aldehydes or ketones bearing chiral centres both on α- and β-carbon atoms have been studied and several comprehensive reviews are published on this topic discussing reactions of various chiral aldimines with a full spectrum of allylmetal reagents.[30] Of particular interest in these systems, especially in case of crotylation and other high-functional allylmetals, is that they were used to study Cram's rule and related chelation models, to test the ability to predict stereochemistry in the nucleophilic addition to imino and carbonyl groups.[31]

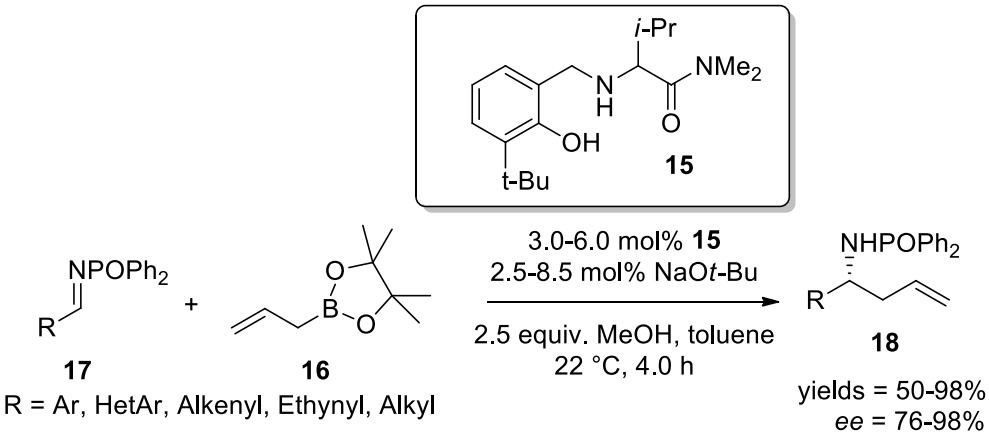
1.2.5. Asymmetric Catalysis

Pioneering research on metal-free, asymmetric organocatalytic allylation of imino compounds **13** was conducted by the group of Schaus.[32] In this elegant approach, high enantioselectivities (95:5-99.5:0.5) and good yields (75-94%) on a wide range of substrates, both aromatic and aliphatic, were achieved by facile exchange of isopropoxide substituent on boron to a chiral BINOL **14** (Scheme 8) which, as proposed by the researchers, facilitates the asymmetric reaction through activation of the acyl group on the imine with a free OH group on the BINOL.



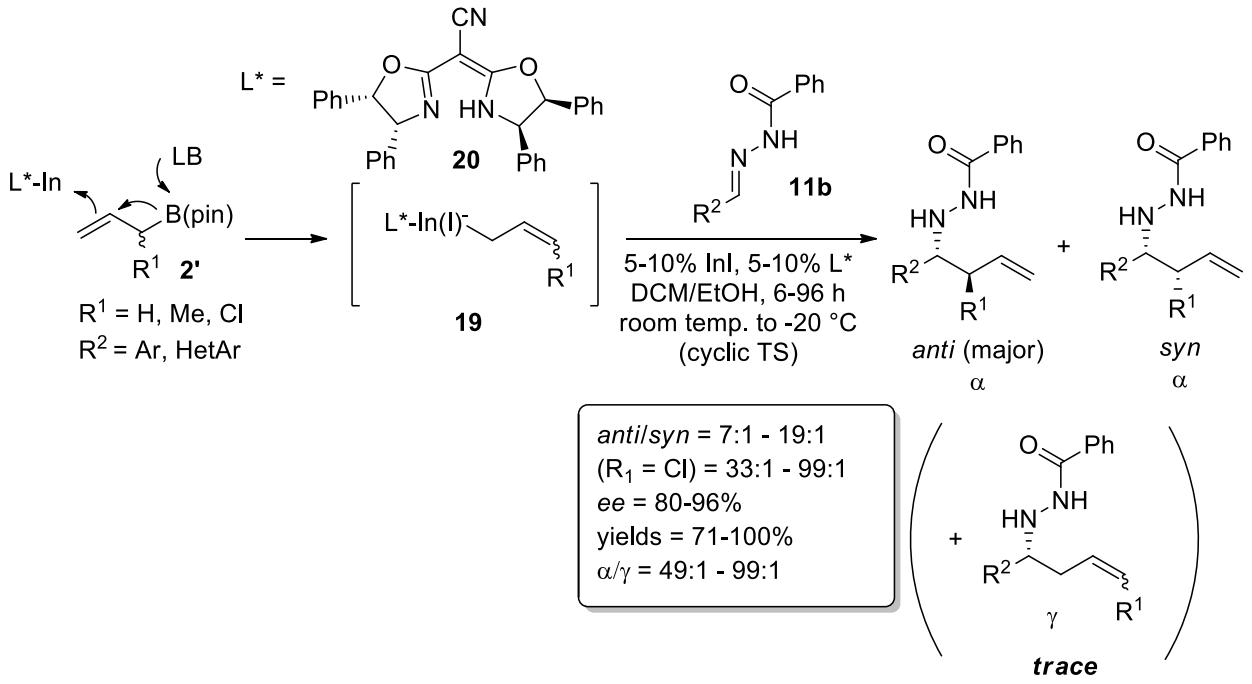
Scheme 8

Recently an important paper by Hoveyda has been published, which focuses on the potential of small organic molecules to serve as asymmetric catalysts in nucleophilic allylation reactions of various organoelement reagents, especially allylboronates.[33] The authors proposed a new approach for activation of both the substrate and the reagent by utilisation of catalyst **15**, which can bind to boronic ester **16** through its phenolic hydroxyl, and simultaneously activate *N*-phosphinoylimine **17**. As a result, remarkably high enantioselectivity (*ee* 76-98%) and yields (up to 98%) were achieved on a wide range of substrates, from aromatic and hetero aromatic to aliphatic, and unsaturated imines (Scheme 9).



Scheme 9

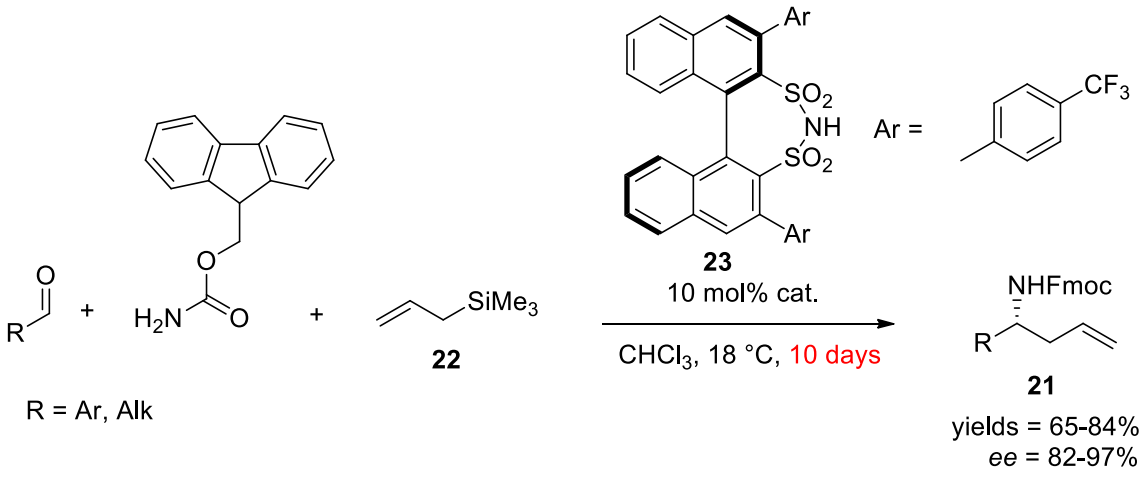
One of the first enantioselective reactions between secondary chiral allylboronates **2'** and C=N-electrophiles was the enantioselective α-crotylation of benzoylhydrazones **11b**, developed by Kobayashi's group.[34] This reaction was highly selective towards *anti* branched α-allylation products, due to catalytic transmetallation from boron to indium, during which the linear reagent **19** was formed and added to acylhydrazone (Scheme 10).



Scheme 10

The reaction scope is limited to aromatic and heteroaromatic aldimine hydrazones. While aliphatic cyclohexanal-derived hydrazone provided high yield, the reaction *ee* dropped to 30%, making it inapplicable for asymmetric synthesis. The reaction proceeds via chiral In(I)-semicorrin complex **20** which was detected by MALDI.

Another interesting and efficient method for direct synthesis of Fmoc-protected homoallylic amines **21** by three-component coupling of trimethylallylsilane **22** with *in situ* formed imines was reported by List and co-workers[35](Scheme 11).



Scheme 11

Since trialkyl crotylsilanes belong to the Type 2 reagents, the Nucleophilic addition reaction proceeds via open transition state. Analogously, reaction with Allyltrimethylsilane proceeds through an open transition state (Figure 3). The authors propose two possible mechanistic pathways, where Lewis acid Fmoc imine is activated either with Brønsted or Lewis acid. In both cases, allyl group of the silane reagent attacks from *Re*-face imine, leading to the major *R*-enantiomer. Authors tend to prefer Lewis acid pathway as the most plausible based on experimental data with preformed silylated catalyst **23** and preformed imine, which showed nearly identical selectivities to that of the three-component reaction.

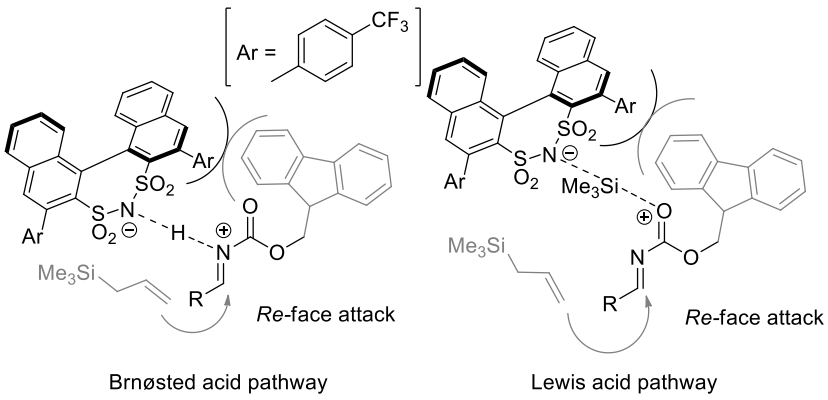


Figure 3

Interestingly, in this study, chiral phosphoric acids failed to catalyse the coupling, but chiral sulfonimide **23** achieve up to 97% ee and up to 84% yield on various aromatic and aliphatic aldehydes. However, the disadvantages of such a method include extremely low reactivity of the trimethylallylsilane which required extended reaction time of 10 days, which makes the method impractical, and relatively low activity of the expensive sulphonamide catalyst which makes it necessary to use loadings as much as 10 mol%.

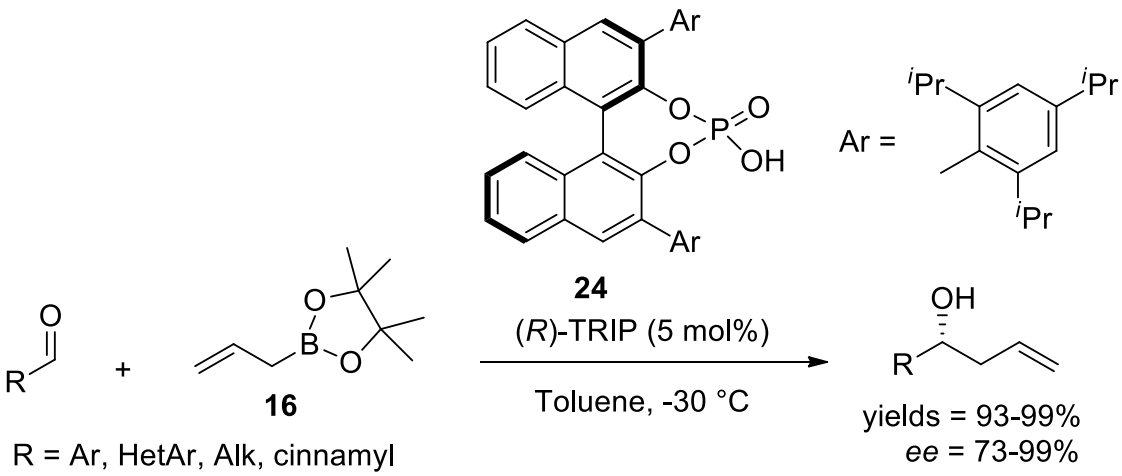
1.3.Conclusion

Many examples of highly enantioselective synthesis of homoallylic amines with internal double bonds have been reported. The most successful examples rely either on allylation of imines with boronates with chiral auxiliary on boron or on the allylation of hydrazones with chiral auxiliary-bearing allylsilanes. On the other hand, the use of secondary chiral reagents remains relatively under-explored. The methods for their synthesis are based either on chiral transition metal catalysis or the use of stoichiometric chiral reagents, while no practical kinetic resolution method is described, partially due to intricate isolation methods of such boronates.

Chapter 2: Results. Chiral Phosphorus Brønsted Acids as catalysts in Asymmetric crotylation of primary amines

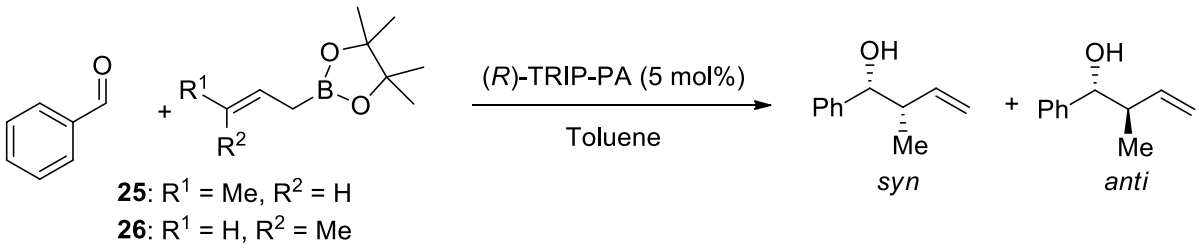
2.1.Introduction

Activation of both the substrate and the organoboron reagent that can be achieved in Type 1 allylation via a cyclic TS is a very appealing approach. This can be achieved by the use of Chiral Brønsted acid as a catalyst. Thus, an excellent study was conducted by the group of Antilla,[36] which disclosed the potential of chiral phosphoric acids (PA) such as TRIP **24** to serve as the best catalyst for allylations and γ-crotylation of aldehydes by pinacol-derived allylboronates **16** (Scheme 12).



Scheme 12

In this study, γ-crotylation of benzaldehyde was also examined. Under similar reaction conditions, the same catalyst **24** showed excellent efficiency and enantioselectivity (Scheme 13).



25: R^1 = Me, R^2 = H
26: R^1 = H, R^2 = Me

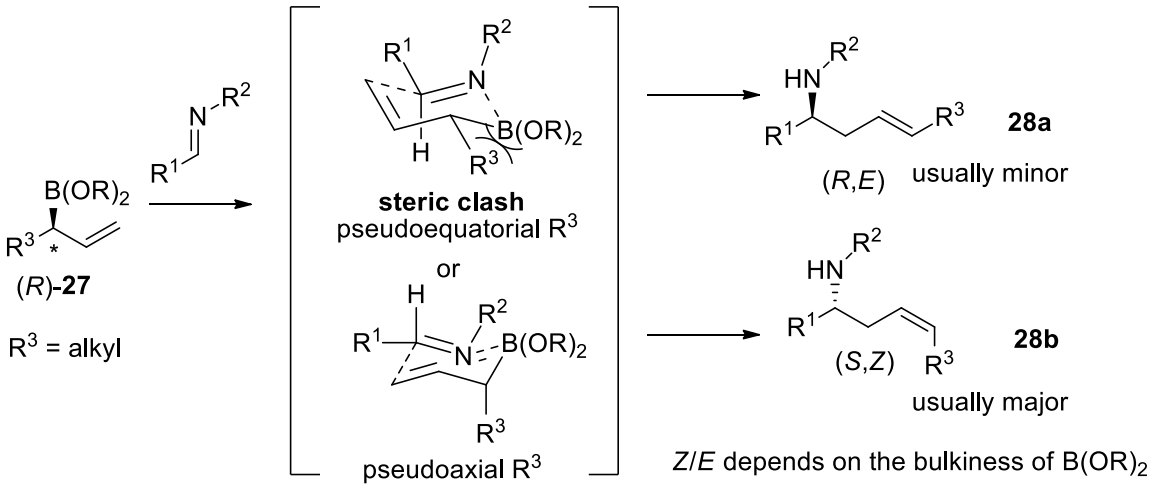
Entry	R^1	R^2	Temp, °C	*syn*/*anti*	Yield (%)	*ee* (%)
1	Me	H	rt	2:98	96	96
2	Me	H	0	2:98	96	99
3	H	Me	-30	98:2	95	94

Scheme 13

While clearly showing that (*R*)-TRIP **24** is highly effective for both allylation and γ-crotylation, there were no successful examples of highly efficient enantioselective crotylation with branched secondary boronates. However, such boronates are potentially very interesting since they could be used for the synthesis of stereodefined δ-substituted *E*- and *Z*-homoallylic amines, which haven't been reported at this time.

2.2. Aims and objectives

Homochiral homoallylic amines serve as a fundamental structural motif in the synthesis of amino acids and various nitrogen-containing bioactive compounds, which are of great pharmacological interest.[33,37] There is a limited number of catalytic approaches for their synthesis, (see Literature Review, Chapter 1, p. 21) however, most of them rely on the use of achiral linear allylboronate reagents and prevailingly give unsubstituted products with terminal C=C bond[38]. At the same time, the synthesis of chiral enantiopure secondary allylboronates **27** is highly challenging,[29] due to the absence of an efficient and practical method for the resolution of enantiomers. Such boronates are mostly unstable under even mildly acidic or basic conditions, and therefore cannot be isolated by chromatography on *silica*. Upon the reaction of this type of chiral boronates with imines, two products of opposite enantiomeric series and the configuration of the double bond can be formed with the ratio depending on the steric size of the substituents on boron (Scheme 14).



Scheme 14

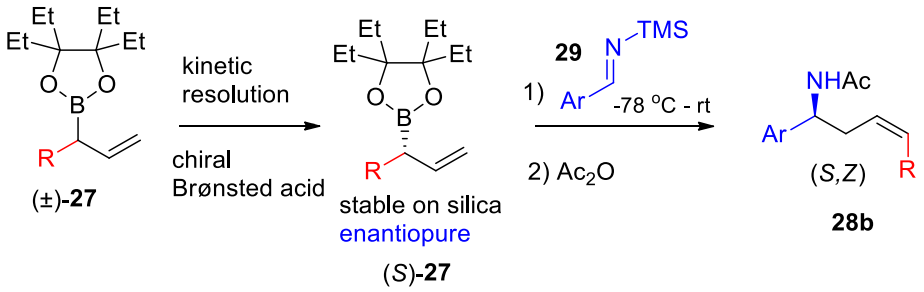
If a suitable method for synthesis of highly enantioenriched secondary boronates were designed, these reagents could be used for selective synthesis of either (*S*,*Z*)- or (*R*,*E*)-homoallylic amines. While selective synthesis of (*R*,*E*)-homoallylic amines was previously reported by Aggarwal,[27] (*S*,*Z*)-homoallylic amines still remain a challenging synthetic target.

Therefore, we aimed to develope the synthesis of enantiopure *Z*-homoallylic amines. This project can be broken into the following two main objectives:

1. *To develop kinetic resolution of chiral racemic boronates **27**.*

2. *To develop the asymmetric allylation of imines, leading to synthetically important chiral homoallylic amines **28b**.*

These objectives are summarised in Scheme 15.

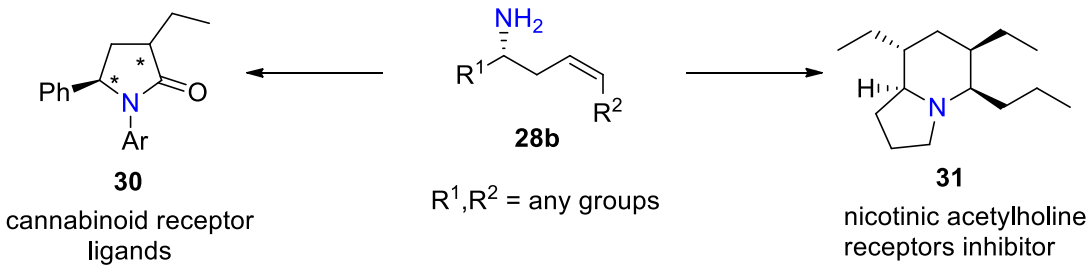


Scheme 15

2.3. Results and Discussion

2.3.1. Background

Chiral homoallylic amines **28b** are important motifs in the synthesis of natural products and various biologically active compounds and can also be used as building blocks for the synthesis of agrochemicals and pharmaceuticals.[33] One of the possible applications of chiral homoallylic amines can be in the synthesis of highly substituted and stereochemically defined heterocyclic alkaloids with pyrrolidinone **30**[39] and piperidine **31**[40] skeletons which include various medicinally important compounds (Scheme 16).

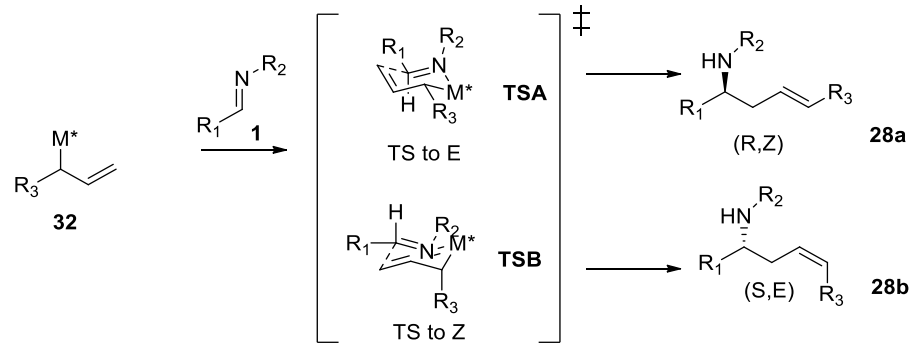


Scheme 16

Since the 80s, homoallylic amines have earned significant attention from the chemical community, and a plethora of methods for their synthesis have been developed.[6] However, most of the approaches have been based on enantioselective construction of homoallylic amines containing terminal double bond, whereas the highly enantio- and chemoselective synthesis of homoallylic amines containing internal double bonds is significantly less developed with only a limited number of studies reported.[26,41]

The most appropriate strategy for the construction of molecules with such a skeleton is the employment of chiral secondary allylmetal reagents **32**, which are known to be able to effectively transfer their chirality into the product without the need for other chiral directing groups or additives.[42,43] However, there are few challenges which make a wide application of this methodology difficult. The first challenge is that synthesis of such chiral organometallic reagents commonly relies on chiral stoichiometric agents, which significantly increase the cost

of such a method. The second challenge is that the reactions with such organometallic reagents proceed through two possible chairlike transition states (Scheme 17):

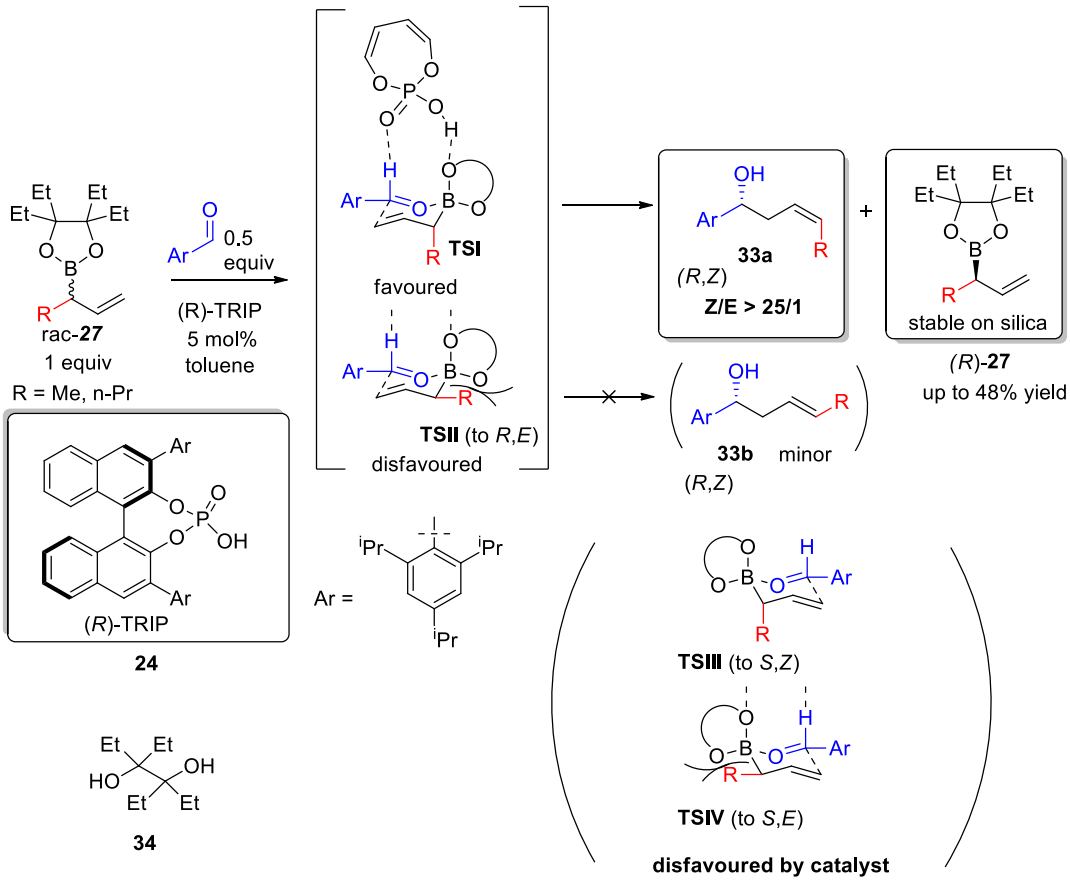


Scheme 17

Due to the pseudoaxial or pseudoequatorial position of the R_3 substituent in **TSA** or **TSB**, the *E* or *Z* alkene may form. The situation also becomes more complex due to by the fact that the *E* and *Z* isomers also contain opposite enantiomer centres, which affects the overall enantioselectivity of the process. In addition, the R_2 the substituent on imine **1** can also have an impact on the stability of the transition states, thus complicating the prediction of the reaction outcome.

Recently, a highly enantio- and stereoselective method for the synthesis of *E*-configured homoallylic amines **28a** by allylation of imines using a chiral boronate was described by Aggarwal.[27] In parallel, our group was engaged in the development of a general approach towards the selective formation of highly enantioenriched *Z*-homoallylic amines **28b**.

Our group have recently described a highly effective approach towards chiral *Z*-homoallylic alcohols **33a** (Scheme 18).[44] The method is based on the kinetic resolution of racemic secondary allyl boronates **27** in reaction with aldehydes, catalysed by chiral Broensted acid TRIP **24**.



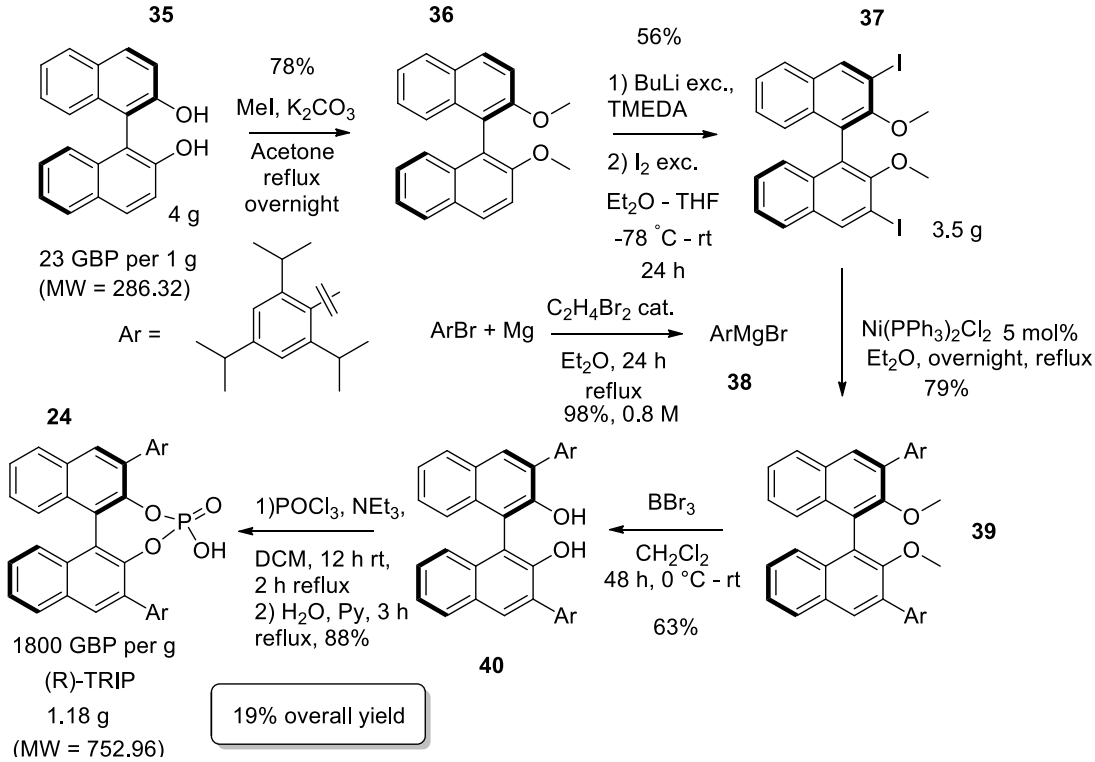
Scheme 18

The selectivity of the reaction relies on two main factors: enantiofacial selectivity in the allylation provided by the chiral catalyst (**TSI** and **TSII**) and kinetics determined by a transition state with axially-oriented substituent (**TSI** and **TSIII**) on the chiral boronate carbon. In combination this leads to the highly selective formation of (*S,Z*)-homoallylic alcohol **33a** out of four possible products (Scheme 18). Notably, due to a high enantiofacial selectivity, both *E* and *Z* homoallylic alcohols are of the same absolute configuration unlike in the case of enantiopure boronates. The tetraethylethylene glycol **34** scaffold (Epin) was designed with the aid of quantum chemical calculations to improve the observed low *E/Z* selectivity using sterically less hindered pinacolyl and 2,2-dimethylpropan-1,3-diol derived boronates. It was found that the steric bulk of the Epin is responsible for pushing the boronate alkyl substituent into an axial position. Obtained results were in excellent agreement with the computational data. Additionally, it was observed that the remaining unreacted enantioenriched boronates showed increased stability to hydrolysis to enable chromatographic purification on *silica*.

This observation led us to the idea, that this protocol might be converted to a method for the synthesis of highly enantioenriched, stable secondary allylboronic esters (*R*)-**27**, suitable for enantioselective allylation of electrophilic species, favouring the formation of *S* stereogenic centre and *Z* double bond. Indeed, the ability to synthesise *Z*-homoallylic amines appears to be very appealing, especially taking into account that this class of compounds is difficult to access by other methods. It is worth noting that due to their highly basic nature, imines cannot be involved in asymmetric catalytic processes with chiral Brønsted acids, which makes our proposed strategy even more relevant.

2.3.2. Synthesis of starting materials

Chiral phosphoric acids derived from BINOL **35** were independently introduced as chiral catalysts by Akiyama[45] and Terada[45] in 2003-2004. Since then, this new type of chiral Brønsted acid has been widely used for a broad spectrum of asymmetric transformations, including asymmetric reactions with pinacol allylboronates, developed by Antilla[36] and Hu[46]. The unprecedented efficiency and enantioselectivity, shown in these reactions defined our choice in favour of TRIP **24**.

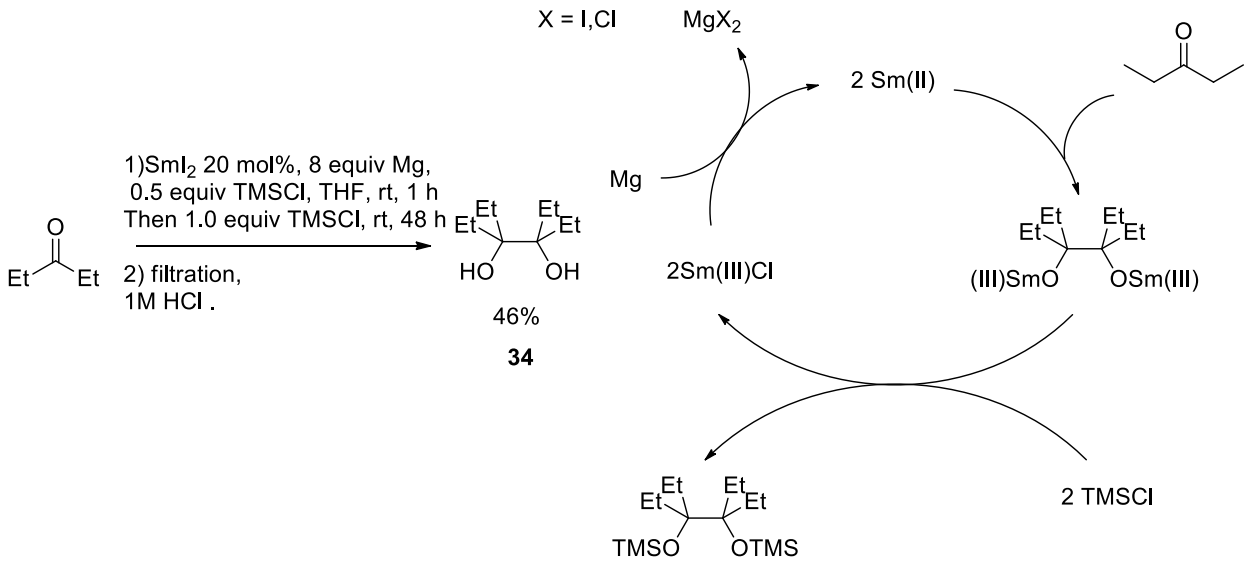


Scheme 19

This catalyst is commercially available but rather expensive (1800 GBP per gram, Sigma-Aldrich), therefore we decided to synthesise it in house. The catalyst was synthesised according to the literature procedure published by List[47] and was accomplished with a slight improvement in the second step in a 19% overall yield (Scheme 19).

The *(R)*-BINOL **35** was protected by treatment with methyl iodide and potassium carbonate in refluxing acetone, to give dimethylated derivative **36** in 78% yield. Further, chemoselective double deprotonation using butyllithium directed by the methoxy groups, followed by oxidative iodination in Et_2O/THF mixture at -78 °C with slow warming to rt furnished 3,3-diiodide **37** in 56% yield. The diiodide was then subjected to Ni-catalyzed Kumada coupling with separately prepared (2,4,6-triisopropyl)phenylmagnesium bromide **38**. The formation of Grignard reagent was checked by iodometric titration. The reaction yielded protected binaphthol **39** in 79% yield. Treatment with the strong Lewis acid BBr_3 in DCM afforded the cleaved product **40** in 63% yield. Treatment of the resulting BINOL derivative with freshly distilled phosphorus oxychloride in the presence of triethylamine in refluxing DCM overnight yielded TRIP chloroanhydride (not shown), which was then hydrolyzed by heating at reflux with pyridine in water (88% over two steps) to give *(R)*-TRIP **24** as a target compound in 19% overall yield.

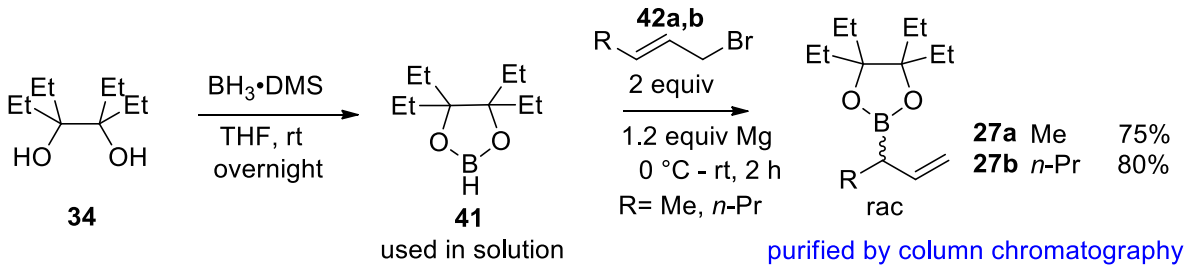
With the catalyst necessary for kinetic resolution in hand, we turned our attention to the synthesis of allylboronates **27**. The bulky boronate moiety, tetraethylethylene glycol **34,** was prepared according to the literature procedure, developed by Endo.[48] In this protocol, 3-pentanone is subjected to pinacol coupling using catalytic amounts of samarium(II) iodide, and the resulting dialkoxide is trapped with TMSCl, producing SmI_2Cl, which is reduced back by metallic magnesium powder to maintain the catalytic cycle with Sm(II) species (Scheme 20).



Scheme 20

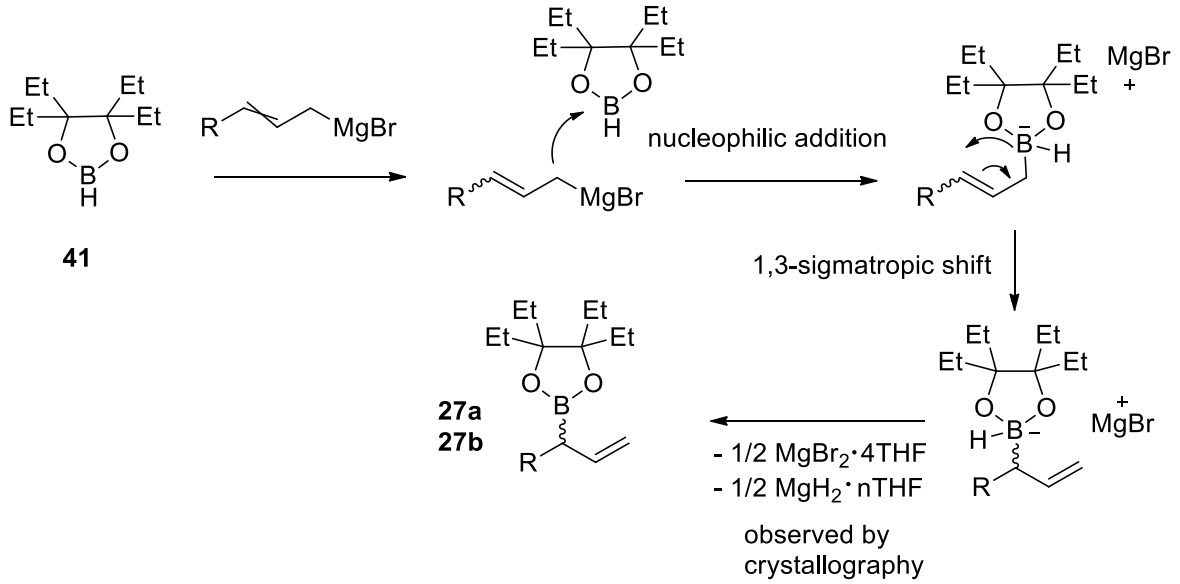
Deprotection of the resulting trimethylsilyl diol ether under acidic conditions during work-up led to the target tetraethylethylene glycol **34**. The highest yield that we managed to achieve was 46%. A lot of unreacted starting material remained even after prolonged reaction times, which was also noted in the original paper. An increased amount of samarium(II) iodide and magnesium (also in the form of powder, in contrast to turnings in the original article) was found to be necessary to maintain similar yield as was reported in the article. The diol-TMSCl mixture should be added very slowly at rt to maintain the catalytic cycle; otherwise, samarium would not recover in sufficient concentration, and the reaction rate would dramatically slow down. Another limiting factor is the magnesium surface. We have found that it must be as high as possible to reduce samarium(III) species efficiently. Thus vigorous stirring is also necessary for this reaction.

The obtained diol was then treated with $BH_3 \cdot Me_2S$ in THF overnight, to produce cyclic 4,4,5,5-tetraethyl-1,3,2-dioxaborolane **41**, which was used without further purification for the synthesis of racemic secondary allylboronate according to the procedure described by Singaram[49] (Scheme 21).



Scheme 21

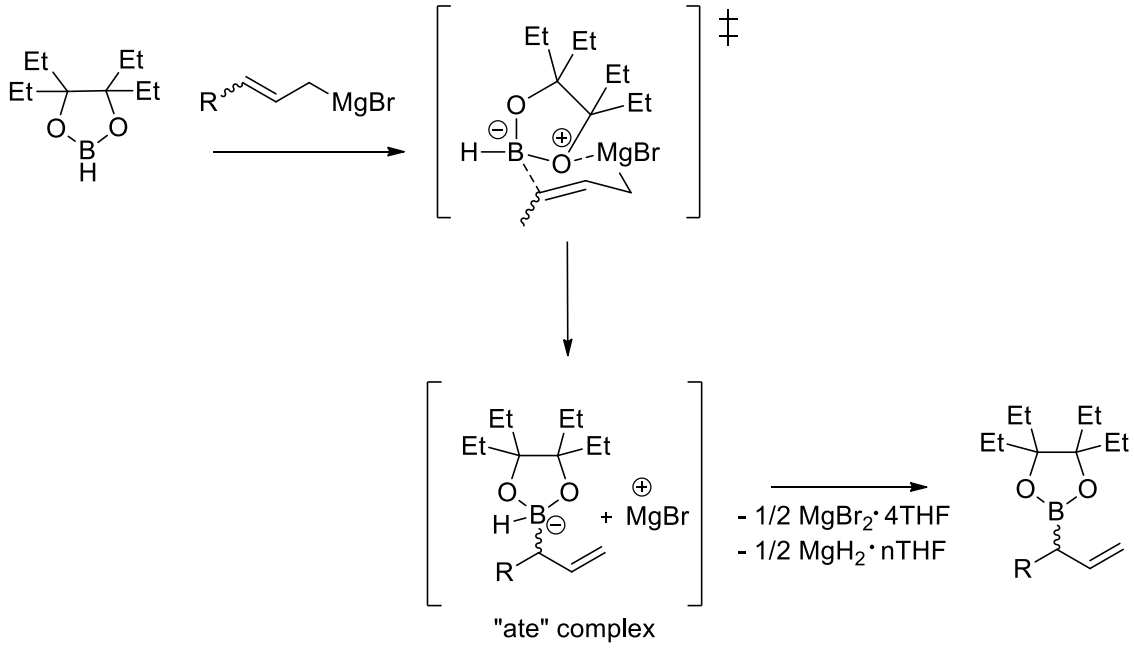
Such a reaction is often called a Barbier-type process, in which the *in situ* formed crotylmagnesium bromide adds to dioxaborolane in THF to afford racemic secondary boronates as a colourless oil in good yield after column chromatography on silica. In the original paper, it was proposed that the reaction proceeds through the formation of an "ate" complex with hydride on boron, which was not observed by ^{11}B-NMR studies of the reaction mixture[49] (Scheme 22).



Scheme 22

However, in the investigation conducted by Aggarwal and co-workers,[27] analogous species have shown no activity towards such a rearrangement. Recently, Hoveyda et al.[50] proposed, based on literature data, that borotropic rearrangements go slow when boron carries donating groups and has low Lewis acidity, but if Lewis or Broensted acid binds to one of such a group, then the energy barrier for this transformation drops.

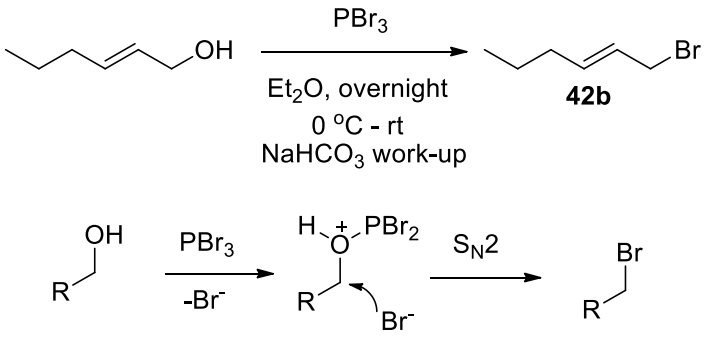
Taking this into account, it seems more likely that the reaction proceeds through a six-membered transition state, where Lewis acidic magnesium binds to one of the oxygen atoms in dioxaborolane, thus facilitating crotyl transfer to boron (Scheme 23).



Scheme 23

While crotylboronate was synthesised from a commercial technical grade crotyl bromide (90% *E*-isomer), *n*-propyl substituted boronate required synthesis of starting 2-hexenyl bromide **42b** from the corresponding allylic alcohol.

For the synthesis of 1-bromohex-2-ene, we opted for a reliable protocol based on an S_N2 reaction.[51] Hex-2-en-1-ol was treated with phosphorus tribromide in diethyl ether at 0 °C with further stirring at rt overnight, affording the target allylic bromide **42b** in 55% yield as a colourless oil (Scheme 24).

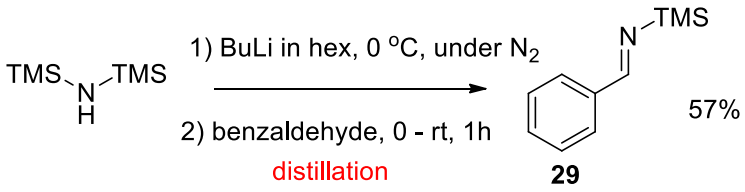


Scheme 24

2.3.3.Synthesis of racemic homoallylic amines and reaction optimisation

To determine the enantiomeric purity of homoallylic amines by HPLC on chiral stationary phase, a comparison with the corresponding racemic mixture is required, therefore it was decided first to prepare racemates and to optimise the reaction conditions employing the racemic allylboronates.

For our initial studies, we have decided to prepare *N*-TMS benzaldimine **29**. To do so, the method by Hart and co-workers was chosen,[52] adopted from the original method by Rochow.[53] LiHMDS was prepared *in situ* by addition of freshly titrated butyllithium to hexamethyldisilazane at 0 °C under an inert atmosphere. Benzaldehyde was then added to the resulted amide and subsequent fractional distillation afforded *(E)*-*N*-benzylidene-1,1,1-trimethylsilanamine **29** as yellow viscous oil in 57% yield (Scheme 25).

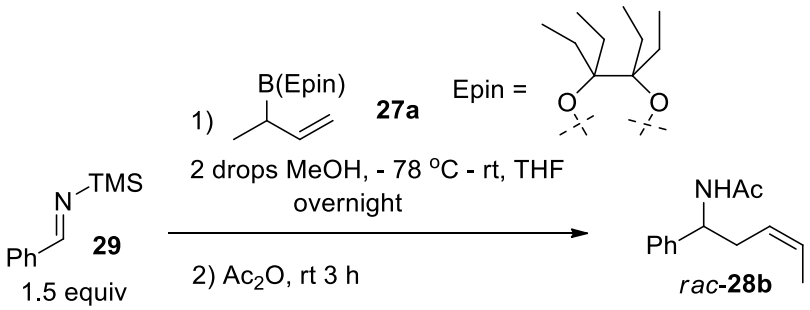


Scheme 25

There are several important points to note. First, the resulting imine is highly moisture-sensitive; it can only be isolated by distillation under reduced pressure; it immediately decomposes in contact with silica. In the high humidity of the British Isles, for successful purification, the distillation apparatus must be dried for several hours prior to use, otherwise imines decompose in contact with glass, forming white crystals on the glass walls of the apparatus.

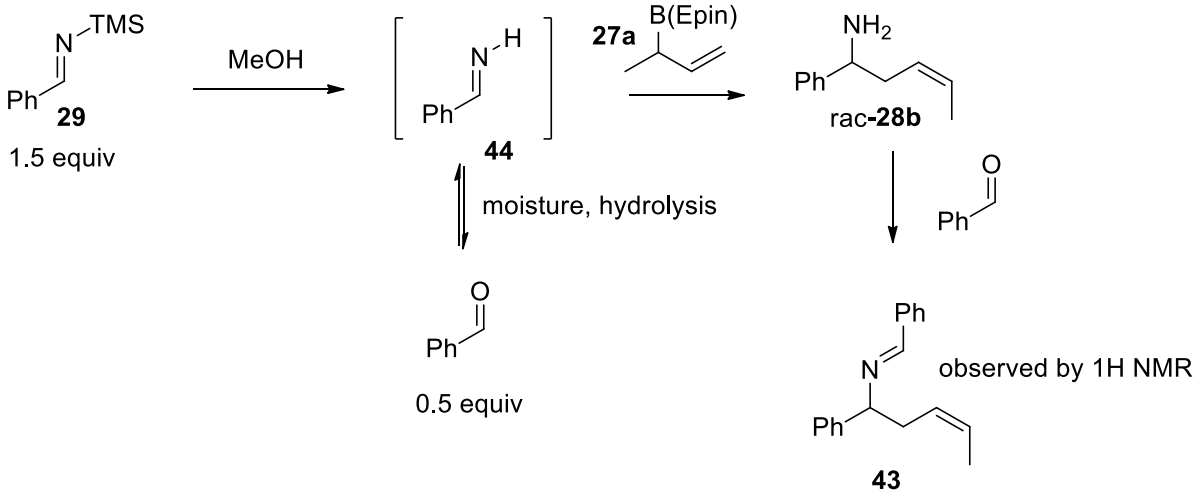
With the imine in hand, we ran our model experiment. But as soon as the experiments began, we faced new challenges.

The model experiment for the synthesis of homoallylic amine was based on the reaction between racemic crotylboronate **27a** and excess *N*-TMS benzaldimine **29** in THF with a catalytic amount of methanol to liberate the primary imine (Scheme 26).



Scheme 26

However, after stirring overnight and then protecting the amine (3 hours) with acetic anhydride (3 hours), only *ca*. 30% of the desired acylated product was formed according to the analysis of the crude reaction mixture, along with complicated mixture of inseparable byproducts, unidentifiable by ^{1}H-NMR. After thorough analysis, It was found that instead of the acylation product, an imine derivative **43** was formed. However, it was difficult to measure approximate yield due to the impurities in the NMR spectrum (Scheme 27).



Scheme 27

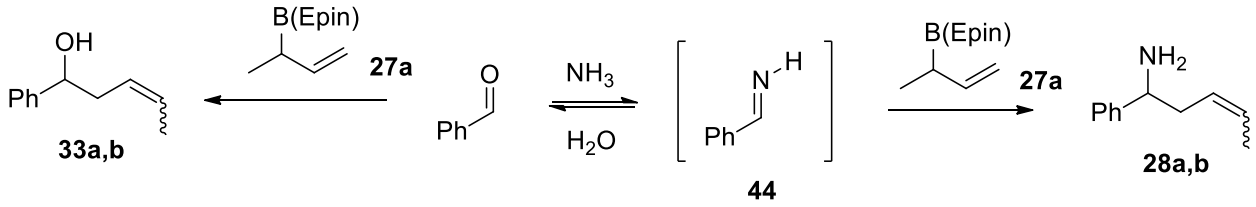
This byproduct has resulted from hydrolysis of imine **44** to release benzaldehyde, traces of which were detected in crude ^{1}H-NMR, which then possibly reacted with the homoallylic amine **28b**.

Furthermore, it soon became clear, that since *N*-TMS imines can be only isolated by distillation, it dramatically narrows the scope of this synthetic protocol. At the same time, there were literature reports on a racemic variant of the addition of allylboronates to imines formed *in situ* from aldehydes and ammonia in methanol, aqueous ammonia in ethanol[23] and even in

aqueous ammonia solution in the presence of surfactants.[54] Thus, we decided to turn our attention to this methodology.

Using ammonia as a source of nitrogen is inexpensive and a more atom-economic approach. Also, unprotected primary homoallylic amines can be isolated without chromatographic methods, by exploiting acid/base extraction.

However, this approach also has several challenges. First, aldehyde and unstable primary imine exist in equilibrium; thus both homoallylic alcohols **33a,b** and amines **28a,b** are formed. Therefore, it is crucial to shift equilibrium as far as possible towards the imine formation, since it does not seem plausible to inhibit the reaction with an aldehyde or accelerate the reaction with an imine (Scheme 28).



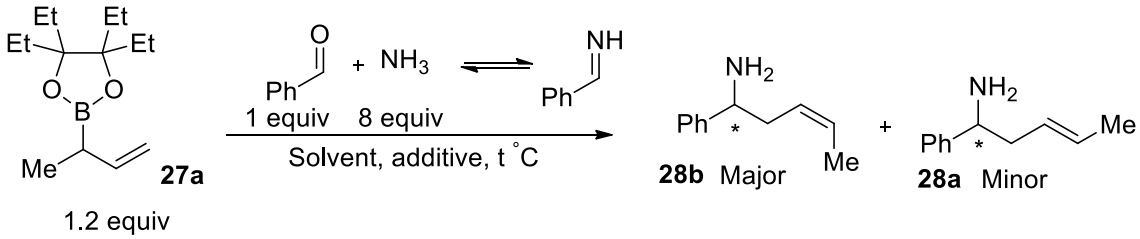
Scheme 28

We decided to use a 4M ethanol ammonia solution, proposed by Kobayashi et al., for our initial experiment.[23] Benzaldehyde was chosen as the model substrate.

Benzaldehyde was premixed for 2 hours with 8 equiv. of 4M ammonia in ethanol at -10 ℃ to allow the equilibrated imine formation, and after that boronate **27a** (1.2 equiv.) was added (Table 1, entry 1). The reaction was stirred at -10 ℃ for 96 hours. Pleasingly, the target racemic homoallylic amine **28b** was formed in 83% yield, and the *Z/E* ratio (8/1) was similar to that reported by Aggarwal.[27] During the extraction, the aqueous phase was first acidified with 1M HCl and washed three times with Et_2O, then it was basified with KOH until pH=14 and extracted three times with DCM to afford a nearly pure homoallylic amine.

One of the disadvantages of handling unprotected primary amines is the difficulty of their chromatographic purification due to their high basicity and affinity for silica gel. Nonetheless, the addition of triethylamine to a highly polar eluent enabled isolation of pure homoallylic amines through chromatographic purification.

Having achieved our first promising result, we began optimisation of the reaction conditions, which are summarised in Table 1.



Scheme 29

Table 1. Optimisation of the model reaction of 27a with *in situ* formed Benzaldimine

Entry	Solvent ([NH_3])	T ℃	Additive	Time, h	Isolated yield, %	*E/Z*
1[a]	EtOH (4 M)	-10	No	96	83	8/1
2[b]	EtOH (4 M)	-10	No	18	83	8/1
3[c]	EtOH (4 M)	-20	No	18	67	(8/1)
4	EtOH (4 M)	0	No	18	78	(8/1)
5	EtOH (4 M)	0	NEt_3 (1.5 equiv)	18	42	7/1
6	MeOH (7 M)	0	No	18	38	7/1
7	*t*BuOH (4 M)	0	No	18	30	n.d.
8	THF (2 M)	0	No	18	27	n.d.
9	*i*PrOH (2 M)	0	No	18	24	n.d.
10	EtOH (4 M)	-42	No	96	29	24/1

[a]Benzaldehyde was stirred for 2 h in the ammonia solution prior to addition of **27a**.

[b] 0.5 h of stirring before addition of **27a**. [c] 1.0 equiv of **27a** was used.

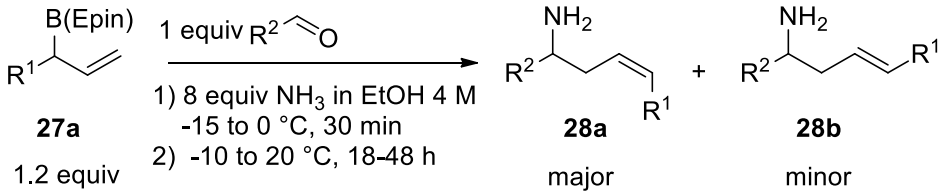
First, we showed that the initial equilibration and the reaction time can be significantly shortened without a noticeable drop in yield and selectivity (entry 2). Then we demonstrated that lowering the amount of boronate from 1.2 to 1 equivalent led to a decline in the yield (entry 3). The reaction temperature can also be increased to 0 ℃ without loss of selectivity (entry 4). To investigate an effect of reaction media basicity on the reaction outcome, we ran

an experiment in presence of 1.5 equiv of Et_3N. The addition of tertiary amine proved ineffective and led to a significant drop in yield and selectivity due to deactivation or decomposition of boronate **27a** (entry 5). By altering solvents and concentration of the reagents (each reaction includes 8 equiv of ammonia), we also showed that ethanolic ammonia solution was optimal (Entries 6-9). Finally, we performed the reaction at a lower temperature (-42 °C) (entry 10) which resulted in an excellent *Z*-selectivity, but unfortunately, the reaction rate decreased, giving poor yield, even after prolonged reaction time.

Neither basic (entry 5, table 1) nor acidic catalysis (due to highly basic reaction media) was feasible. The concentration of the reactant was already optimal: soon after the addition of boronate **27a** a white precipitate was formed, so there was no sense in a further increase in the concentration of the reactants since any increase in the concentration of ammonia resulted in the evaporation of ammonia gas from solution.

After the determination of the optimal conditions, an investigation into the reaction scope using aromatic and aliphatic aldehydes and different boronates was carried out (Table 2).

Table 2. Scope of the reaction of boronate 27a with *in situ* formed aldimines



Entry	R^1	R^2	Product	T, °C	Time	Yield	*Z/E*
1	Me	4-Cl-C_6H_4	**28ab**	-10	18 h	57%	10/1
2	Me	4-Cl-C_6H_4	**28ab**	0	18 h	75%	8/1
3	Me	Cinnamyl	**28ac**	-10	18 h	45%	10/1
4	Me	Cinnamyl	**28ac**	0	18 h	72%	10/1
5[b]	Me	C_6H_5	**28aa**	-10	18 h	83%	8/1
6	Me	$PhCH_2CH_2$-	**28ad**	0	18 h	59%	(8/1)
7	Me	2-naphtyl	**28ae**	0	18 h	62%	8/1
8	Me	1-naphtyl	**28af**	0	18 h	80%	8/1
9	*n*Pr	1-naphtyl	**28bf**	0	18 h	20%	5/1
10	*n*Pr	C_6H_5	**28ba**	0-20	48 h	69%	(10/1)

[b] Benzaldehyde was stirred in etanolic ammonia solution for 5 min prior addition of boronate.

First, we have conducted a reaction with 4-chlorobenzaldehyde in standard conditions (table 2, entry 1) at -10 °C during 18 hours. The *Z*/*E* ratio of the resulting product was enough high (10/1), however the yield was only moderate (57%). In an attempt to increase yield, we have performed the reaction at elevated temperature (0 °C) what resulted in deterioration of the *Z*/*E* ratio (entry 2). But in case of cinnamaldehyde the increase in temperature let to the improvement in the yield without the disruption in the *Z*/*E* ratio (entries 3 and 4). Repeating the reaction with model benzaldehyde at -10 °C with a shorter imine generation step (5 min) did not change the reaction outcome (entry 5). Interestingly, the reaction with enolisable aliphatic 3-phenylpropionaldehyde gave good *Z*/*E* ratio and slightly decreased yield (Entry 6). The use of bulkier substrates such as 1-naphtyl and 2-naphtyl aldehydes provided moderate and good yield respectively, while maintaining the same good level of *Z*-selectivity (8/1) (entries 7 and 8). A combination of larger less reactive *n*-propyl boronate with bulky 1-naphtyl aldehyde resulted in a much slower reaction, furnishing corresponding homoallylic amine **28bf** in poor yield (20%) and even lower *Z*/*E* ratio (5/1) (entry 9). However, using less bulky benzaldehyde, slowly increasing reaction temperature over the course of the reaction up to 20 °C and extending reaction time to 48 hours allowed the synthesis of homoallylic amine **28ba** in a reasonable yield (69%) and a high *Z*/*E* ratio (10/1).

Several important conclusions can be made.

1. The high *Z*-selectivity can be accomplished by lowering the reaction temperature but at the expense of yield.

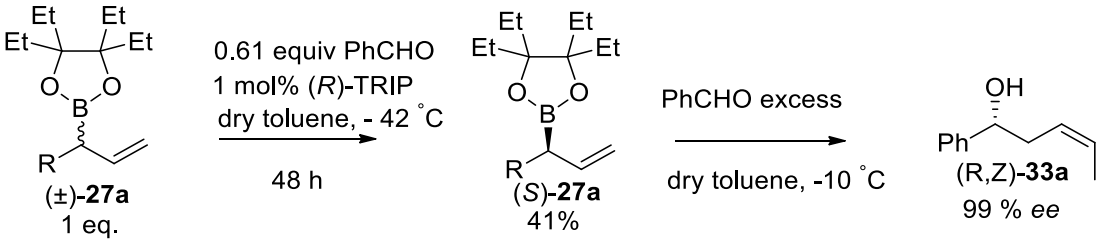
2. For enolisable 1-phenylpropionaldehyde, the yield decreased, possibly due to a low reactivity. It should be noted that Kobayashi used modified allylation method and rt for alkyl substrates.[23]

2.3.4. Kinetic resolution improvement

In the kinetic resolution protocol of racemic crotylboronate, we were able to reduce the loading of *(R)*-TRIP. It was found that at -42 °C the reaction between boronate and benzaldehyde does not proceed at an observable rate without the addition of catalyst. We

suggested that it could be possible to reduce the amount of TRIP to 1 mol%. It seems very relevant, taking into account the high commercial price of *(R)*-TRIP.[55] Also, we have found that the addition of benzoic acid was not necessary for the high yield and enantioselectivity since it is present in trace quantities in benzaldehyde itself, formed by oxidation by atmospheric oxygen.

Under our new conditions for the resolution, the enantioenriched boronate was isolated in 41% yield. The enantiopurity was established by the reaction of the resolved boronate with an excess of aldehyde at -10 ℃ to furnish homoallylic alcohol in 99% *ee* (Scheme 30).



Scheme 30

In conclusion, we have developed an efficient kinetic resolution of crotylboronate. We have designed conditions for the racemic synthesis of primary *Z*-homoallylic amines using ammonia as a source of nitrogen and screened them with various aromatic and aliphatic aldimines. We showed that *Z*-homoallylic amines are formed with high *Z*-selectivity.

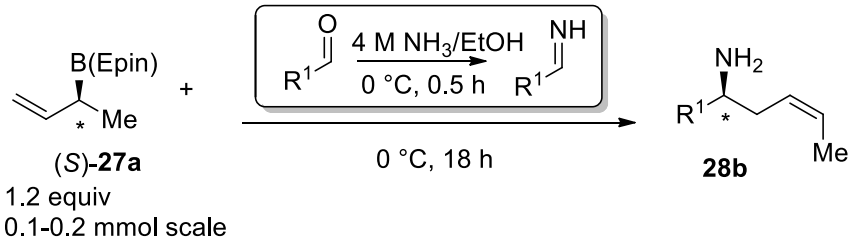
At the beginning of the studies, when we used *N*-silylated amine **29** and pinacol-derived boronate **27a**, the primary amine was formed during the reaction via removal of the TMS group by addition of substoichiometric quantities of MeOH. The reaction was started at -78 ℃ and warmed to RT after 12 hours. Acetic anhydride and triethylamine were then added, and the reaction was stirred for an additional 5 hours. ^{1}H NMR analysis showed that the target homoallylic amine **28b** was formed in dr 5:1 and 70% yield. With the change from pinacolyl to Epin (tetraethylglycol ether) the selectivity was boosted to 10/1, and the product was formed in 82% yield. Overall, such an approach is making the overall protocol much more complicated.

The subsequent studies were conducted in collaboration with our colleagues in Spain. Enantiomeric excesses were identified by the Vicario group and published in a joint recent

paper.[56] Kinetically resolved chiral boronate **27a** provided complete chirality transfer to the product (98% *ee* / 98% *ee*).

Table 3

aminoallylation of aldehydes



Entry	R^1	Yield [%]	*Z*/*E*	*ee*[1]
1	Ph	76	8:1	97
2 (-40 °C, 96h)	Ph	29	24:1	n.d
3	4-MeC_6H_4	72	10:1	99
4	4-BrC_6H_4	65	8:1	98
5	4-ClC_6H_4	75	9:1	99
6 (-10 °C)	4-ClC_6H_4	57	10:1	99
7	4-FC_6H_4	53	7:1	99
8	4-$MeOC_6H_4$	63	9:1	98
9	3-$MeOC_6H_4$	78	9:1	98
10	2-$MeOC_6H_4$	61	10:1	85
11	PhCH=CH	72	10:1	94
12	$PhCH_2CH_2$	59	8:1	93

In the allylation reaction with **27a**, the product was formed with 97% *ee* in 76% yield and 8:1 ratio. Repeating the reaction at -40 °C significantly improved the *Z*/*E* ratio (24:1) although at the expense of the reaction yield (29% after four days).

Notably, the *Z*/*E* ratio for 4-Cl-benzaldehyde might be improved by a slight decrease in the reaction temperature from 0 to -10 °C (9/1 vs 10/1). However, the yield was also slightly reduced.

Sterically-hindered *ortho*-substituted aldehyde (entry 10) required the reaction to be carried out at elevated temperatures, which negatively reflected on the *ee* of the product (85%).

[1] Enantioselectivity was measured in collaboration with Dr L. Villar. Entries 3,4 and 7-10 were also performed by Dr L.Villar and Dr N. Orlov and published in a joint paper. [56]

2.4.Conclusions

1) A highly practical method of enantioselective synthesis of secondary allyl boronates (up to 99% *ee*) by kinetic resolution of the corresponding racemic allylboronates using the chiral phosphoric acid TRIP has been developed.

2) Stability of the allyl boronates towards silica was enhanced by the use of the new Epin fragment at boron, which simplified the purification and handling of these reagents.

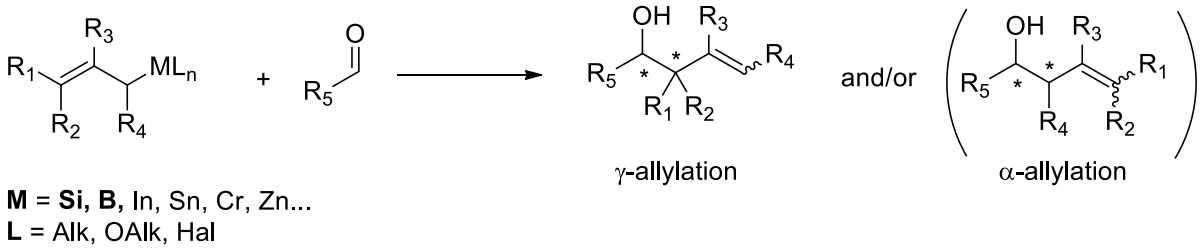
3) The resolved boronates were used for the efficient stereoselective synthesis of chiral *Z*-homoallylic amines by the reaction with *in situ* formed aldimines in ethanolic ammonia solution.

4) The advantage of the method is the excellent chirality transfer and high *Z*-selectivity arising from the steric property of the novel Epin fragment.

Chapter 3: Literature Review. Chiral Lewis Bases in Asymmetric Catalysis

3.1.Opening remarks

One of the most widely used methods for the construction of new C-C bonds is the nucleophilic addition of organometallic reagents to electrophiles such as carbonyl compounds. The product of such a reaction is alcohol, which in case of aldehyde or unsymmetrical ketone will bear a stereogenic centre. Such an addition of C-nucleophiles has been thoroughly studied since the chiral products are of great interest in the vast majority of the different branches of Chemical Science. Among many different classes, one of the most exciting types of such an addition is the reaction of aldehydes with allylmetal reagents (Scheme 31).



Scheme 31

In case of crotylation, the resulting homoallylic alcohol bears two adjacent stereocenters, and an *E* or *Z* double bond, depending on the structure of the allylation reagent. As was discussed in Chapter 1, the Type 1 allylmetal reagents are the most useful for application in synthesis, since their *Z*/*E* ratio directly influences the *syn*:*anti* ratio of the product because the cyclic chair-like transition state allows a precise control of the stereochemical outcome of the reaction. The most widely used Type 1 reagents are Boron- and Silicon-based reagents (M = B, Si). While crotylation reactions were studied for both of these types of reagents, the synthesis of the corresponding crotylboronates is less straightforward and more expensive, as well as the scalability of boron-based crotylation is much less facile than that of silanes.[57] Therefore, our literature review and subsequent studies focus on asymmetric alkenylation of aldehydes using allylsilanes.

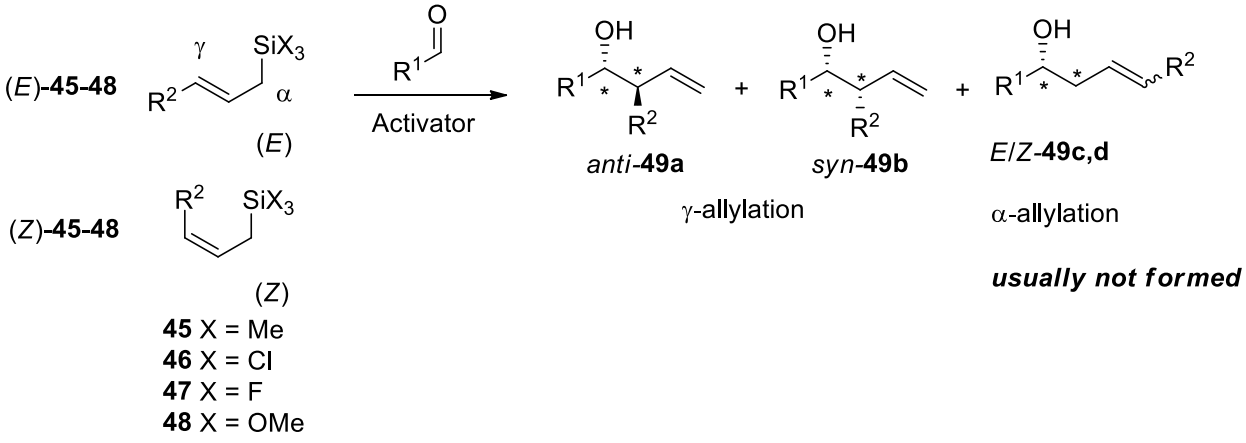
3.2.Literature Review

3.2.1. Chiral Lewis Base Asymmetric Catalysis

Allylation of aldehydes using organosilicon reagents is a useful tool for creating C-C bond in a stereoselective manner. The reaction can be divided into 4 major types with general formula allylSiX_3: allylSiMe_3, allylSiCl_3, allylSiF_3 and allylSi$(OMe)_3$ (Scheme 32).

One of the famous early examples is the Hosomi-Sakurai reaction which employs allyltrimethylsilane in the presence of strong Lewis acids such as $TiCl_4$, that coordinates to a carbonyl group, thus enhancing its electrophilicity.[9]

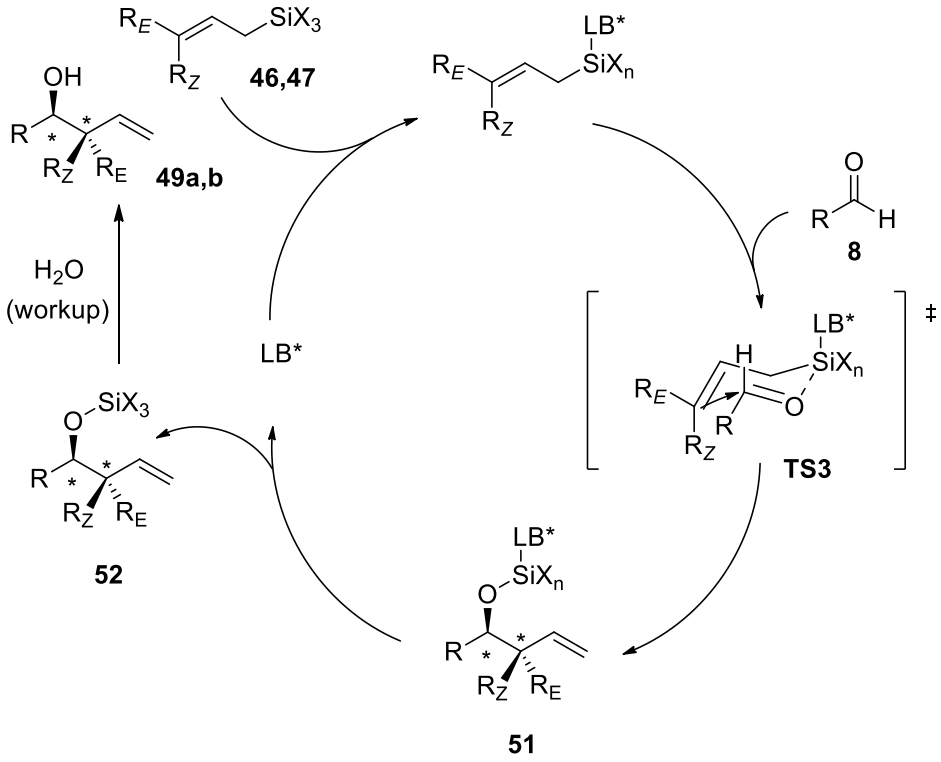
According to the classification developed by Denmark and Weber[4], allyltrimethylsilanes **45** belongs to the Type 2 reagents which react through an open-chain transition state where γ-addition occurs prevailingly and gives a *syn*-product from both the *cis*- and *trans*-isomers of the silane. Notably, α-allylation products **49c,d** are usually not observed in the reactions with silanes (Scheme 32).



Scheme 32

In contrast to allyltrimethylsilanes, allyltrihalosilanes such as **46, 47** are classified as Type 1 reagents that react with aldehydes via closed cyclic **TS3** resulting in a more precise stereocontrol of the γ-crotylation, with *Z*-isomers producing selectively *anti*-adducts and *E*-isomers giving the *syn*-isomers. Moreover, the proximity of the reaction centres in the highly-

packed transition state creates a possibility for employing a chiral Lewis base as a catalyst for the reaction, which can result in efficient transfer of chirality to the product (Scheme 33).



Scheme 33

Another interesting point is that the Lewis base itself is increasing the electrophilicity of the Si atom, thus facilitating coordination of the reagent to the carbonyl oxygen in the **TS3**. As a result, the branched γ-adducts **49a/49b** are commonly formed while the linear α-counterpart is typically not observed.

As noted above, the pioneering work by Sakurai in the late 1980s unveiled the possibility of nucleophilic activation of silanes by using CsF[58] or dilithium catheholates[59] as stoichiometric additives what resulted in a highly diastereoselective reaction of aldehydes with trihalosilanes **46** and **47** (Scheme 33).

In the early 90s, Kobayashi and coworkers[60] reported the use of DMF as both a mild Lewis base activator and the reaction medium. However, the disadvantage of such a protocol

was that DMF must be used in large excess. It was later altered by Denmark,[61] who showed that HMPA promotes the reaction as an additive, however, this compound is highly carcinogenic.[62]

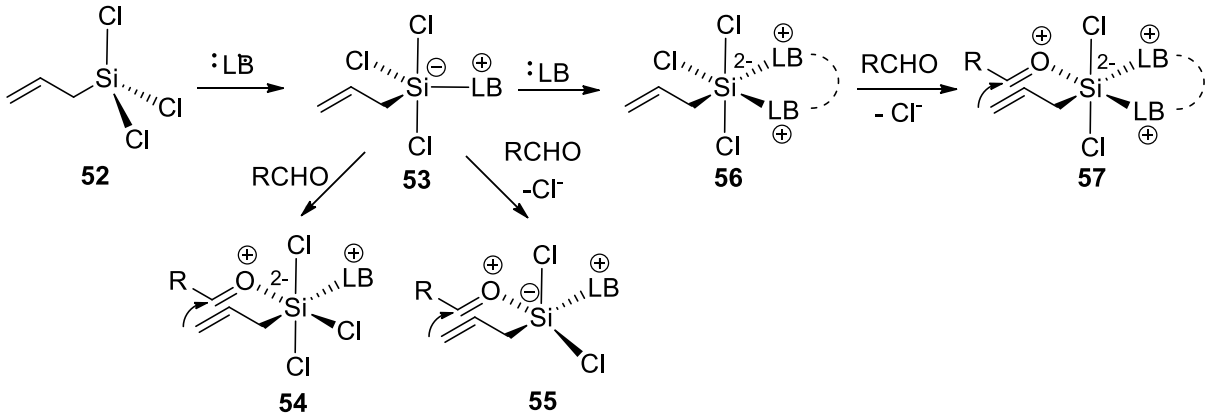
Fluoride ions F^- are commonly known to have high affinity for silicon and can be delivered as tertiary ammonium salts, such as NBu_4F. This process is used in the Hosomi-Sakurai reaction.[63] However, in the reaction of γ-substituted trimethylcrotylsilanes **45** with aldehydes, the free F^- facilitates the formation of both α- and γ-adducts, which makes this method less practical.

With allylSi$(OMe)_3$ reagents, the protocol requires the use of transition metal catalysis (e.g. AgF or CdF_2)[64] and chiral phosphine ligands such as BINAP[65] to deliver chirality. It was observed, that upon the reaction of crotylSi$(OMe)_3$ with aldehydes under such conditions, the *anti*-isomer **49a** was formed irrespective of the configuration of the starting silane, which indicates the formation of an intermediate crotylsilver species that exists in dynamic *E*/*Z* equilibrium, and behaves as Type 3 reagent, progressing through a chair-like transition state.[66]

Type 1 allyltrichlorosilane reagents **46** appear to be the most versatile reagents for asymmetric γ-allylation and crotylation of aldehydes. They react through a closed chair-like **TS3** providing high regio- and stereocontrol in the reaction. More importantly, weak Lewis acidity of the silicone atom makes them perfect candidates for designing asymmetric catalytic route using chiral Lewis bases.

Another important feature of this trichlorosilane-based methodology is the ready availability of such silanes and their homologs, which can be prepared from the corresponding commercial crotyl and allyl chlorides usually in a single synthetic step.[67,68] Furthermore, such trichlorosilanes can serve as precursors for the above mentioned trimethyl- (**45**), trifluoro- (**47**) and trimethoxysilyl (**48**) reagents.

The racemic reaction between aldehydes and allyltrichlorosilanes is usually performed at rt in a DMF solution, and its scope is very rich: aromatic, α,β-unsaturated (1,2-addition only) and even aliphatic aldehydes react swiftly react under these conditions to provide products in good to excellent yields.[60]



Scheme 34

During the allylation process, the Lewis base can occupy various positions around the silicon centre (Scheme 34). In the case of monodentate Lewis base catalysts, two different reaction pathways are possible. In the first pathway, also known as the associative mechanism (**52** → **53** → **54**), the Lewis base coordinates to silicon (**52** and **53**), then the aldehyde adds to it, and the octahedral hexacoordinate complex **54** is formed; thus the Lewis base occupies *trans*-axial position to allyl group and *cis*-equatorial position to the aldehyde molecule.[69] In the second pathway, also known as the dissociative mechanism (**52** → **53** → **55**), the aldehyde adds to the silicon centre in **53** which is followed by the loss of a Cl^- ion, and results in the formation of the pentacoordinate distorted trigonal bipyramidal charged intermediate **55**.[70]

In cases where two molecules of a Lewis base are involved or when a bidentate ligand is used, the plausible reaction path is shown by the sequence **53** → **56** → **57**. In this case, octahedral hexacoordinate species **56** is formed, where two Lewis base molecules can be linked together, followed by the simultaneous dissociation of a chloride and addition of an aldehyde molecule.[71,72] Both aldehyde and allyl group are positioned in *trans* axial geometry to the Lewis base, which enables a more efficient transfer of chiral information at the reaction centre.

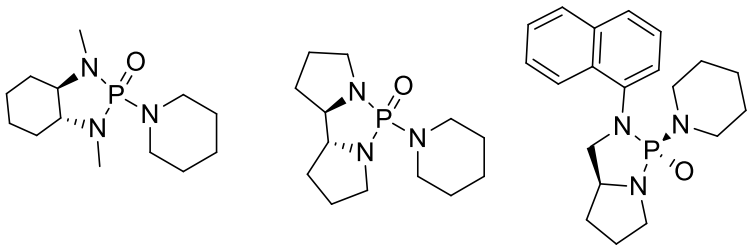
The mode of activation and configuration of the transition complex depend on the nature of both starting materials, which will be discussed in detail later in the text.

Early examples of organocatalytic asymmetric allylation of aldehydes with allyltrichlorosilanes utilised Lewis basic pyridine-oxazolines[73] and ureas[74]. However, the chiral additives required sub-stoichiometric loadings and provided only low-to-moderate enantioselectivities.

All these complications led to the idea of increasing the Lewis basicity of the catalyst. Since the oxophilic properties of the silicon atom are well-known, the researchers switched their attention to the other Lewis base classes such as chiral phosphine oxides, phosphoramides, phosphonamide, chiral formamides, chiral sulfoxides, and, more importantly, to chiral *N*-oxides.[75] A vast range of chiral catalysts have emerged; therefore, all these catalysts in the current review will be discussed according to their structural classes.

3.2.2. Phosphorus-based and other early catalysts

The first known asymmetric system to catalyse the allylation of aldehydes was a phosphorus-based catalyst introduced by Denmark[61,76] as based on structures **58** and **59**, although they provided only moderate enantioselectivities. However, these examples played an important part in elucidation and determination of the reaction mechanism and led to the development of much more effective catalysts of the 2nd generation. While the Lewis base **60**[77] showed slightly higher enantioselectivity compared to **58-59,** its use was hampered by the need of separating two diastereomers formed in the synthesis, which in the end have shown to have an effect on the sense of the enantioselection (Figure 4).



58 **59** **60**

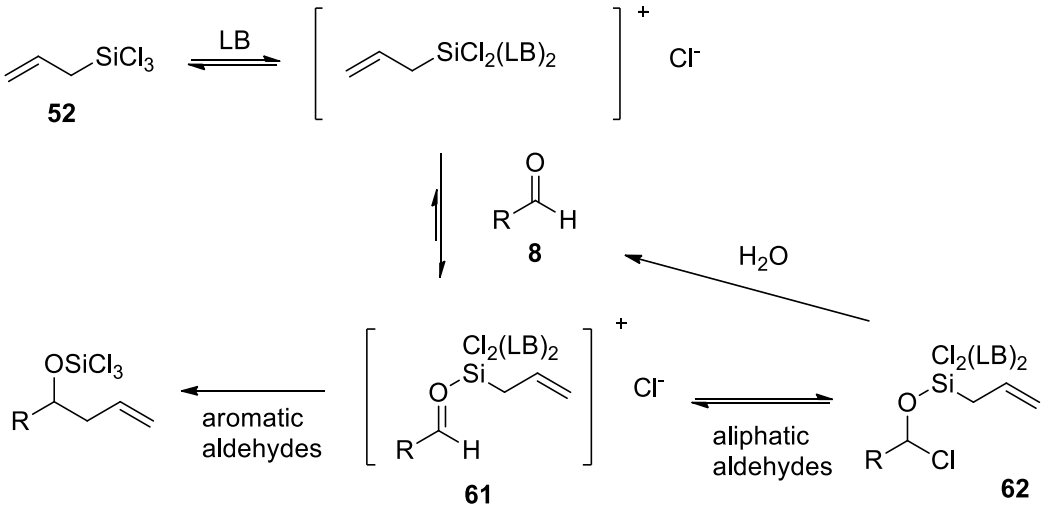
Figure 4

The positive nonlinear effect of the reaction observed with catalyst **58** suggested that more than one molecule of the catalyst is participating in the stereochemistry-determining step.[76] The reaction order was found to be 1.77, which led to the proposal of two possible mechanistic pathways, which were competing. One pathway includes two phosphoramide ligands bound to a silicon centre, and in this manifold one chloride has to dissociate to coordinate benzaldehyde, thus forming a charged hexacoordinate cyclic chair-like transition state **57**. The closed geometry of the transition state is supported by the observation that the

syn:*anti* ratio completely resembles the *Z*/*E* purity of the crotyl silanes. The other pathway suggests the formation of either neutral octahedral complex **54** or the cationic trigonal bipyramidal complex **55**.

Aliphatic aldehydes are more reactive towards Nucleophilic attack from the allyltrichlorosilanes, it was observed that with 3-phenylpropionaldehyde the conversion of the reaction at rt did not exceed 6% even in the presence of 20 mol% of HMPA as an activator.[77]

Denmark *et al.*[78] showed that such a decrease in the efficiency of the reaction could be related to the nucleophilic attack of the chloride anion, which is liberated from intermediate **61** and thus reversibly forms chloroadduct **62**, which prevents nucleophilic addition of the allyl group (Scheme 35).

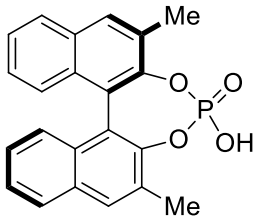


Scheme 35

It is important to note that this equilibrium, existing in both reactions involving aromatic and aliphatic aldehydes, in the latter case is strongly shifted towards adduct **62**, while the concentration of free aldehyde is significantly lowered, thus strongly decreasing the rate of the allylation. Upon aqueous workup, the chloroadduct **62** hydrolyses back to aldehyde. Previously it was thought, that aldehyde was too inert itself to react with silane, rather than being masked with reversible addition of chloroide. The equilibrium between **61** and **62** at rt is achieved much faster, therefore the allylation reaction can take place. The increase of the reaction temperature to RT improves the yield, because when free aldehyde is consumed, the equilibrium concentration is restored faster than the reaction take place, thus constantly renewing the free aldehyde concentration for the reaction to proceed. In contrast, when the

temperature is low, the equilibrium restored slower than the rate of the reaction, and after normal reaction times (12-48 hours) only a trace amount of the product could be detected.

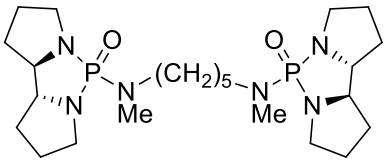
To address this issue, Denmark *et al.*[77] used transition metals such as Hg(II) to complex the chloride ions. The addition of 1 equiv. of $HgCl_2$ to the 3-phenylpropionaldehyde with 20 mol% HMPA in CH_2Cl_2 solution resulted in a 30% yield over 2 hours. However, this had a negative effect on enantioselectivity in the reaction.



63

Figure 5

Interestingly, chiral BINOL-derived phosphoric acids like **63**[79] (Figure 5) were also found to catalyse asymmetric allylation of aldehydes with allyltrichlorosilane **52**. Phosphoric acid **63** provided the best results, with up to 98% yield and 87% *ee* in toluene at -20 ℃. Overall, the use of this catalyst gave good to excellent yields and moderate to good *ee*'s. The mechanism was explained by coordination of the Lewis basic P=O bond to the silicon, while the acidic OH bond provided additional activation of the benzaldehyde by hydrogen bonding to carbonyl oxygen. Notably, aliphatic 3-phenylpropionaldehyde gave 88% yield albeit only moderate enantioselectivity (43% *ee*).

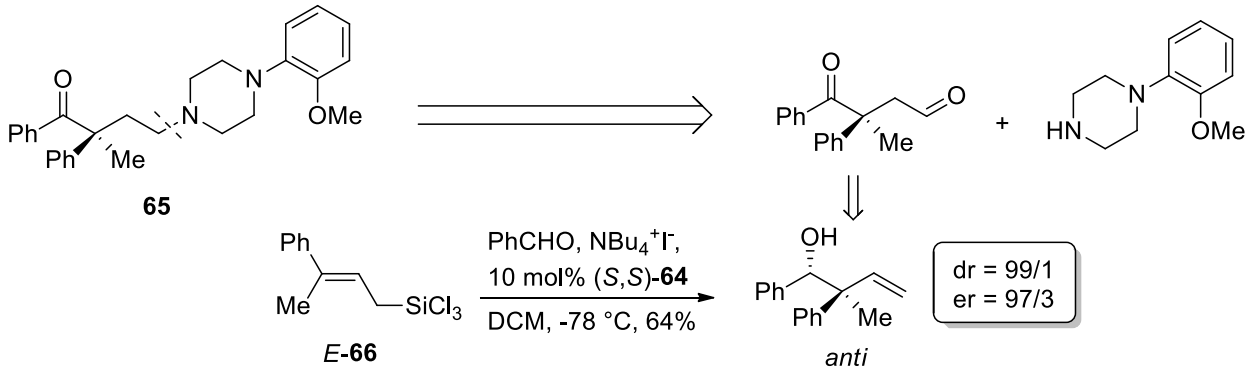


64

Figure 6

An important observation of the nonlinear effect (Scheme 34, **53** → **56** → **57**) and the second order dependance in the catalyst[76] led Denmark and coworkers to an important idea that the Lewis base molecules can be bridged together, thus bidentate ligands could give better yields and enantioselectivities. Not only did the bidentate catalyst **64**[80] prove to be effective, but it also showed higher reaction rates compared to monodentate analogues, which enabled

researchers to reduce its loading to 5 mol%. The diastereoselectivity of the reaction was also consistent with chair-like **TS3**. The designed catalyst was then applied to the synthesis of the serotonin antagonist **65**, where the chiral configuration at the quaternary centre was established in the key step by addition of *E*-trichlorosilane **66** to benzaldehyde in the presence of 10 mol% of **64**.[78] Importantly, $NBu_4^+I^-$ was found to increase the yield of the reaction without disrupting the enantioselectivity[81] (Scheme 36).



Scheme 36

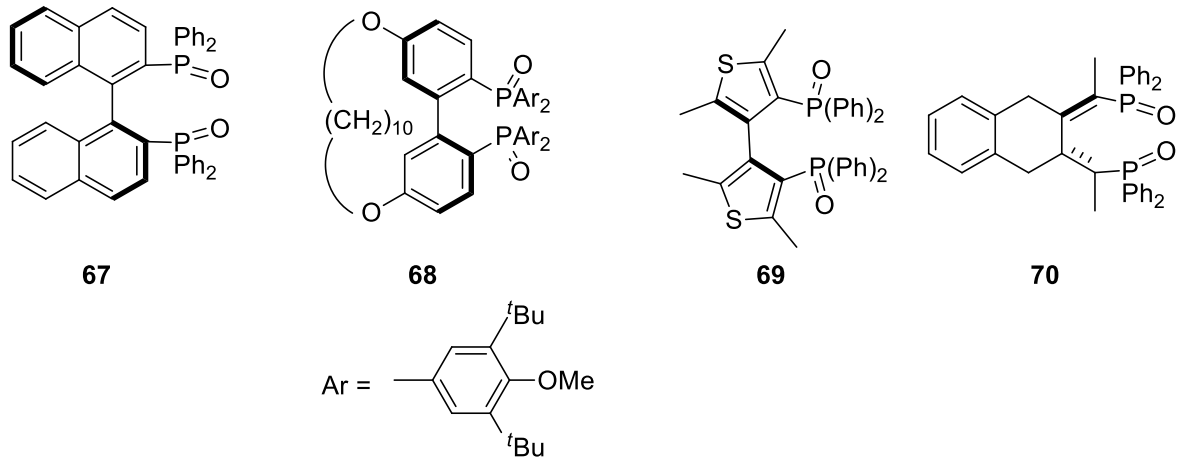


Figure 7

Another group of bidentate catalysts includes the axially chiral bis-heterocyclic diphosphine oxides **67** (BINAPO) as reported by Nakajima[82] and **68** (C_{10}-BridgePHOS) by Chen[83] (Figure 7). However, they proved to be less active than the phosphoramides. Indeed the reactions had to be carried out at rts which eventually led to only modest selectivities. Nonetheless, bithiophene diphosphine oxide **69** ((*S*)-tetraMe-BITIOPO) introduced by Benaglia[84] showed excellent *ee* at 0 ℃ and also worked on the wide range of substrates with 5 mol%

loadings. The activity of **69** was by far exceeded by Nakajima's atropoisomeric chiral diene-based catalyst **70**,[85] which proved effective with even 1 mol% loadings at temperatures as low as –90 °C. This increased activity was attributed to the unusually small dihedral angle between the phosphine-bearing diene planes of the catalyst, of 89.2° (in contrast to BINAPO's 94.2°), which can additionally enhance the nucleophilicity of the silane and Lewis acidity of the silicon centre.[86]

3.2.3. Chiral Mono-*N*-Oxides as Chiral Lewis Base Catalysts

Chiral mono-*N*-oxides presented themselves as a very successful group of chiral catalysts for asymmetric allylation of aldehydes. First introduced by Malkov and Kočovský,[87] this group includes terpene-derived chiral bipyridine mono-*N*-oxides **71-73** (PINDOX, Me_2PINDOX and *iso*-PINDOX respectively). The most successful catalyst in this family Me_2PINDOX (**72**)[88] combines center and axial chirality to deliver maximal enantioselectivity. Unfortunately, due to the low potential energy barrier of rotation, if stored in solution, this compound slowly isomerises at rt and reaches the thermodynamic equilibrium between the two atropoisomers in one week. Because the configuration of the chiral axis defines the sense of enantioselection of the allylation reaction, atropoisomerisation of the catalyst leads to a drop in enantioselectivity.

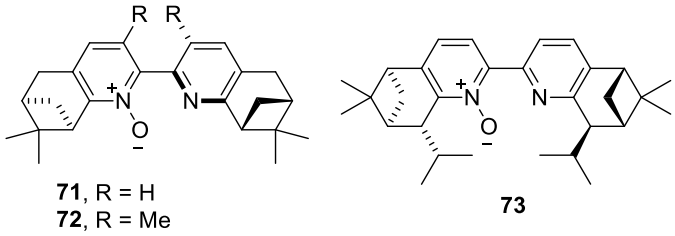
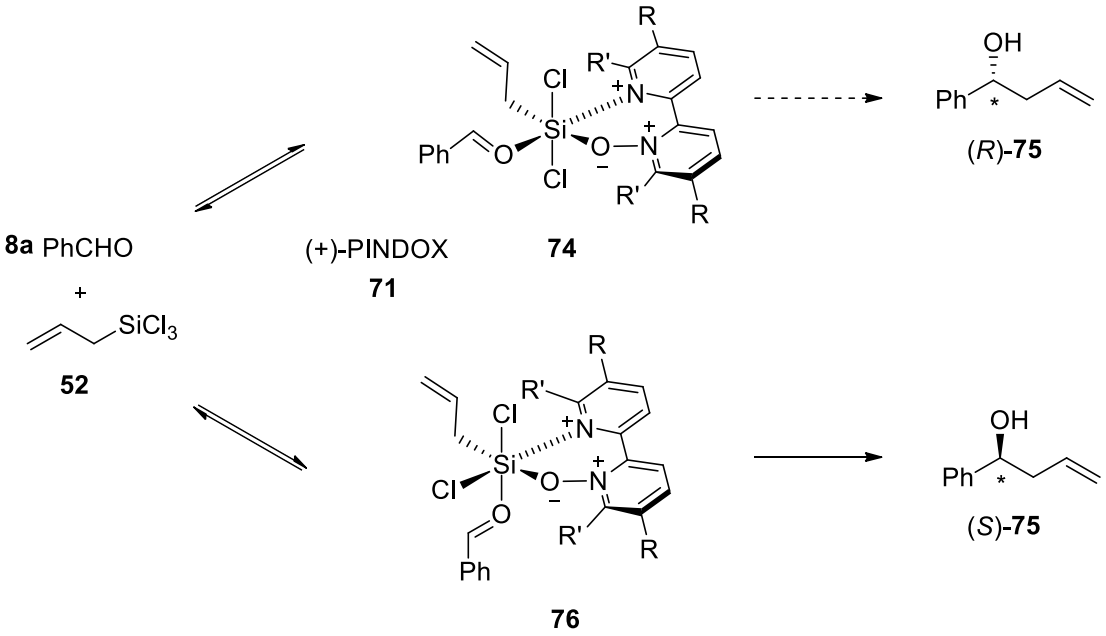


Figure 8

Due to the free rotation about the bipyridyl bond in the PINDOX **71** and *iso*-PINDOX **73**, it is assumed that enantioselectivity is solely provided by the chirality of the terpene moiety of both catalysts.

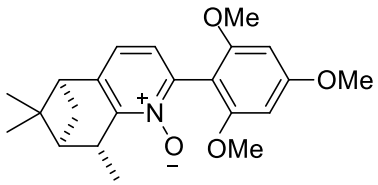
Originally, the mode of action of catalysts **71**—**73** was attributed to the same model proposed by Denmark for structure **64** which is represented by complex **74** (Scheme 37), with chlorides *trans* to each other and allyl group *trans*-positioned to the *N*-oxide oxygen atom.[88] However, subsequent computational analysis provided by Wheeler and coworkers[89] for PINDOX

71 showed that if this model was correct, the formation of the opposite enantiomer (*S*)-**75** should be favoured, which contradicted the experimental data. Computational optimisation of the transition state configuration identified structure **76**, where the ligand is positioned in such a way that a chloride swaps places with the benzaldehyde, which leads to the correct *S*-selectivity observed in the experiment, as well as it accurately predicts the observed level of enantioselectivity (98.5/1.5 predicted *vs* 95/5 measured).[89]



Scheme 37

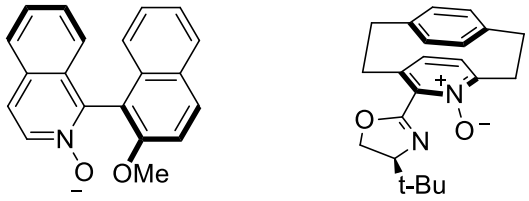
Another chiral catalyst designed by Malkov and co-workers METHOX (**77**) is a pinene-based chiral pyridine mono-*N*-oxide. Despite lacking any rigid or induced axial chirality during the coordination, the catalyst showed excellent enantioselectivity (≤96% *ee* at loadings 1-5 mol% in MeCN at –40 °C)[90,91] which may suggest that coordination of silicon to bipyridine nitrogen atom in **71**-**73** does not significantly affect the reaction outcome and is not a requirement for attaining high enantioselectivity in the allylation reactions[90,91]. Excellent enantioselectivities were also achieved with **77** in the reactions with α,β-unsaturated aldehydes, (≤96% *ee*).[92] However, the aliphatic non-conjugated aldehydes failed to show high enantioselectivity.



77

Figure 9

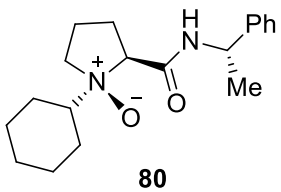
Other members of this group of successful *N*-monoxide catalysts are the isoquinoline-*N*-oxide **78** QUINOX, (≤96% *ee* at 5 mol% at –40 °C in DCM)[93–95] and an interesting paracyclophane derivative **79**[96] which deliver the same level of efficiency at 1.5 mol% loadings in MeCN at –40 °C.



78 **79**

Figure 10

An interesting "non-pyridine" *N*-oxide catalyst **80** was introduced by Hoveyda and coworkers.[97] It was synthesised in three steps from commercially available proline and gave good enantioselectivities on a wide range of aromatic and α,β-unsaturated aldehydes at rt in 1,2-dichloroethane (up to 92% *ee*). Interestingly, crotylation also was attempted; however enantioselectivities remained moderate. Also, an insignificant but notable disruption of diastereoselectivity was observed (*e.g.* the diastereoselectivity of *trans*- and *cis*-crotylation did not completely match the isomeric purity of the crotylsilanes) that may suggest that a boat-like transition state may be contributing to the reaction.



80

Figure 11

Among the advantages of the catalyst are the ease and high efficiency of its synthesis starting from the chiral pool of natural amino acid in addition to the possibility to tailor the amide substituent, easily adjusting the steric size and electronics of substituents to match the requirements of a particular substrate. However, the scope of allyltrichlorosilanes studied for this reaction was rather narrow, and enantioselectivities were generally below 90%, with the reaction only working with aromatic aldehydes.

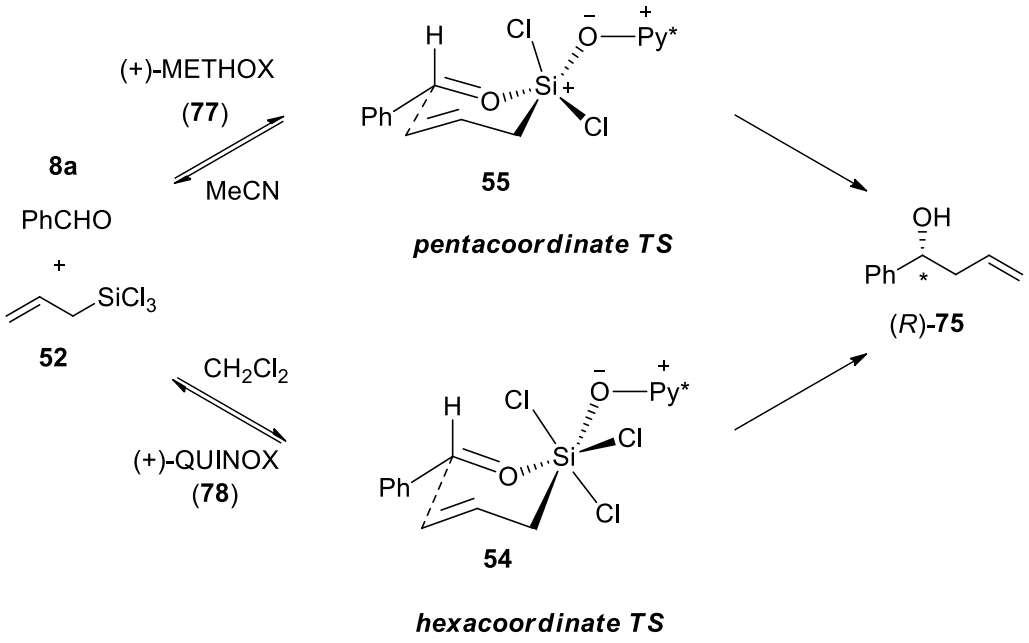
The authors later extend their study by designing piperidine-[98] and tetrahydroquinoline-based[99] analogues, but the enantioselectivities did not reach the level of the primary proline-based catalyst. Notably, with the piperidine-based catalyst a 85% *ee* and 67% yield for 3-phenylpropionaldehyde was achieved, however, at the cost of 30 mol% loading. Interestingly, the tetrahydroquinoline-based catalyst worked best in THF, while the pyridine-based catalysts were usually more effective in DCM and MeCN.[75]

Also, many pyridine-*N*-oxide based catalysts bearing different monoterpene moieties were studied[100], as well as polysaccharide-based[101] and chemoenzymatically synthesised[102] *N*-oxide catalysts, but none of them showed good enantioselectivities.

An important factor, affecting the selectivity of the allylation using pyridine mono-*N*-oxide **78** is the nature of the aromatic aldehyde.

While METHOX (**77**) has no preference for the electronic properties of the aldehydes, giving similar enantioselectivities in the range of 93-96%[90,103], a variation was observed for QUINOX (**78**).[93,95] Electron-deficient aldehydes, such as 4-$CF_3C_6H_4CHO$, showed excellent *ee* (89-96%), whereas for the electron-rich substrates (4-$MeOC_6H_4CHO$) enantioselectivity dropped to lower levels (37-81%).

This interesting reactivity pattern was explained by employing computational and kinetic studies, which are summarised in Scheme 38.

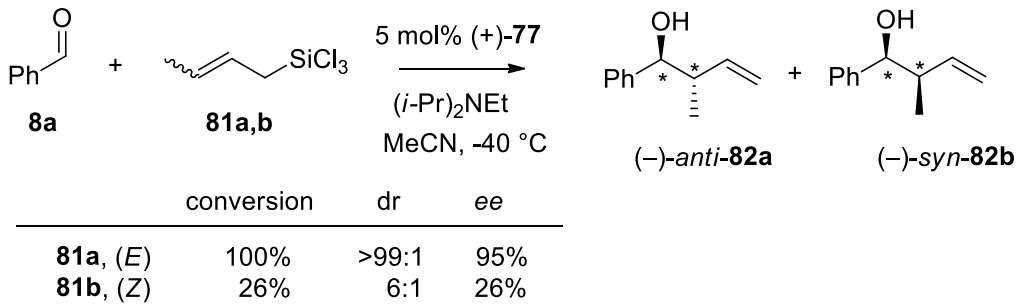


Scheme 38

The catalytic reaction with METHOX proceeds through a cationic pentacoordinate transition state **55**[90,93], which requires polar solvent such as MeCN. In a polar reaction media, the enantioselectivity arises predominantly from the steric repulsion, which distinguishes stabilisation energies of the (*R*)- and (S)-leading transition states. The energies of such states were calculated by quantum chemistry methods and were found to differ by 3.2 kcal mol^{-1}, while the differences in London Dispersion Forces (LDF), solvation and entropic effects were less significant. These results are supported by the observed insensitivity of METHOX-catalysed reaction to the nature of substituents on the aromatic aldehyde and by the lack of reactivity of highly hindered 2,6-dimethyl-benzaldehyde.[103] In contrast to METHOX, the QUINOX-catalysed reaction proceeds *via* neutral octahedral complex **54,** which is stabilised by non-polar solvents such as DCM. In this case, the (*R*)- and (*S*)-leading transition states are almost isoenergetic in terms of energy in vacuo, and the enantioselectivity originates from entropic, solvation and, more importantly, London Dispersion Forces, which are commonly observed only in non-polar media. Such a result is supported by the observed sensitivity to the electronic properties of the aldehyde, solvent nature and temperature.[95]

It is important to note, that crotylation reaction of benzaldehyde also was studied using **77**,[103] and it was found that METHOX is preferentially active towards *E*-crotyltrichlorosilane **81a**, forming the *anti*-product **82a** in more that 99:1 dr and 95% *ee* from an 87:13 *E*/*Z*-mixture of

crotylsilanes, while reaction with pure *Z*-crotylsilane **81b** was sluggish and resulted in 26% conversion, 1:6 dr and 26% *ee* (Scheme 39).



	conversion	dr	*ee*
81a, (*E*)	100%	>99:1	95%
81b, (*Z*)	26%	6:1	26%

Scheme 39

3.2.4. Chiral Bis-*N*-Oxides as Chiral Lewis Base Catalysts

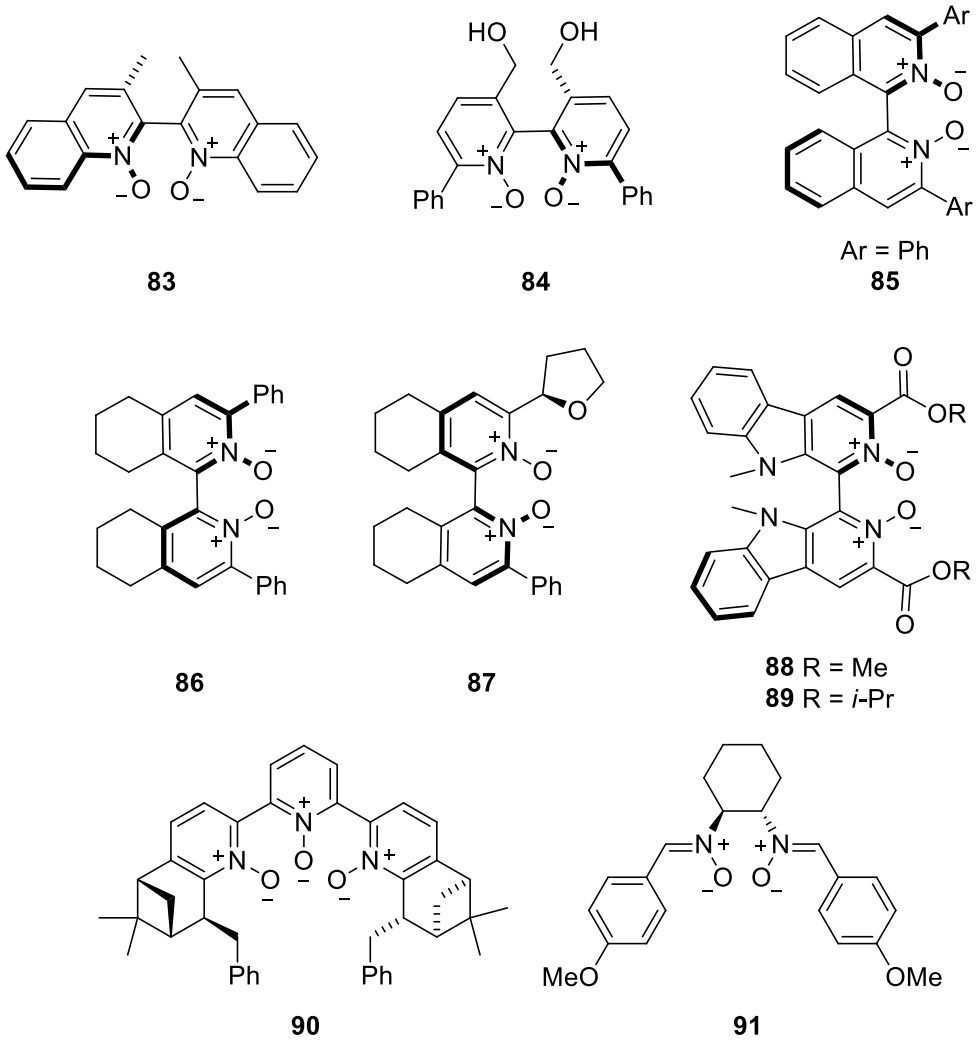


Figure 12

The first axially chiral bis-isoquinoline bis-*N*-oxide **83** was reported by Nakajima *et al.* in 1998[104]. In this seminal paper, the importance of Hünig base was unveiled, which is responsible for trapping HCl liberated from, allyltrichlorosilane upon hydrolysis, preventing deactivation of the catalyst. Allylation of benzaldehyde using **83** gave only 71% *ee* after 2 hours at 23 °C in DCM, but the addition of 5 equiv of diisopropylethylamine increased the reaction rate dramatically, to provide full conversion in just 10 minutes. It also enabled the reaction to be carried out at –78 °C, which resulted in a new higher level of selectivity of 88% ee. After screening a large number of aldehydes and substrates, the yield was found to vary between 68% and 85% and *ee* between 71% and 92% for aromatic and α, β-unsaturated aldehydes. At the same time, aliphatic aldehydes again showed low yield and *ee* due to the formation of chlorohydrine **62** as discussed earlier.

The use of *E*- and *Z*-crotylsilanes in reaction with benzaldehyde in the presence of 10 mol% (*S*)-**83** showed a complete transfer of the *Z/E* ratio of the crotylsilanes to the *syn*:*anti* ratio of the product, with *cis* giving selectively *syn*, while *trans* gave selectively the *anti*-product, which corresponds to a cyclic chair-like **TS3**. Both *syn* and *anti* diastereomers were isolated in moderate yields and good enantioselectivity. Interestingly, both γ,γ-dimethyl and β-methyl allylsilanes did not fit the into the catalyst's chiral pocket and so gave reduced *ee* and yield. The two γ-methyl groups reduce the reaction rate due to steric repulsion. β-Substituted silane possesses almost equal nucleophilicity to the crotyl counterparts, but its methyl group in the β-position disrupts the transition state geometry, thus reducing enantioselectivity.

Hayashi group[105] attempted to improve this methodology by introduction of axially chiral bipyridine bis-*N*-oxide **84**, which showed remarkable reactivity at a catalyst loading of 0.1 mol% at –45 °C and remained usable at loadings as low as 0.01 mol%. The catalyst was able to deliver the product of allylation of 4-methoxy-benzaldehyde in 96% yield and 94% *ee* with 1 mol% in just 20 minutes. Unfortunately, the catalyst turned out to be extremely sensitive to the nature of the aldehyde, and the introduction of even one electron-withdrawing group such as 4-CF_3 led to a drop in *ee* to 56%.[106]

Another example in this series is bis(isoquinoline-*N*-oxide) **85a**[94], which gave *ee* in the range 71-81% for aromatic aldehydes. Its analogue, *N'*,*N''*-dioxide **86**, showed *ee* in the range 60-82% for 4-substituted benzaldehydes.[107] An interesting effect was uncovered while

screening solvents for the reactions catalysed by **86**. It was found, that the enantiomeric selectivity and product chirality depended on the solvent polarity. Thus, allylation with **52** catalysed by (*S*)-**86** furnished (*R*)-**75** in DCM (55% *ee*), MeCN (65% *ee*), $CHCl_3$ (36% *ee*), $EtNO_2$ (53% *ee*), while the (*S*)-enantiomer was observed with the same (*S*)-catalyst in solvents such as toluene (83% *ee*), PhF (78% *ee*), PhCl (79% *ee*), THF (70% *ee*) and EtOAc (74% *ee*).[107]

Computational analysis of the reaction mechanism and transition state energies in different media revealed that in the electrophilic solvents, which are facilitating dissociation of the silane-catalyst complex by solvation of chloride ion (such as MeCN), the reaction proceeds via a cationic chelating transition state **57**, in which the bis-*N*-oxide resides on the Si-center in a bidentate manner, while in solvents, in which the solvation effects towards charged species are less pronounced (such as EtOAc), the uncharged hexacoordinate transition state **54** is realised with monodentate coordination of catalyst.[108,109]

The unsymmetrical axially chiral bis-*N*-oxide **87** and its atropoisomer also showed good to excellent *ee*'s over the wide range of aromatic and α, β-unsaturated aldehydes, varying from 14 to 96% *ee* and yields from 42 to 100% at loadings as low as 1 mol%.[110,111]

Biscarboline *N'*,*N''*-dioxide **88** is another example of a highly successful catalyst for the allylation of aromatic, heteroaromatic and α, β-unsaturated aldehydes. The selectivity was in the range 91-99% at –80 °C, while the yields were good to excellent. Remarkably, these catalysts provided excellent enantioselectivity even with cyclohexyl (92% *ee*) and hydrocinnamyl aldehydes (92% *ee*), however the yields were much lower.[112]

The dependence of the reaction outcome on the temperature and solvent was studied with the analogous catalyst **89**.[113] It was found that the reaction was facilitated by solvents such as MeCN and DCM (100% conversion), and strongly inhibited by Et_2O, THF and EtOAc (5-10% conversion). The explanation for this phenomenon might be found in the study by Kotora group[108]. As discussed earlier, the allylation reaction may proceed via neutral chloride-associated hexacoordinated transition state **54** or charged chloride-dissociated pentacoordinated transition state **55**. The course of the reaction via that or other state depends on the solvation power of the solvent, which is defined by its electrophilic property, which can be measured by ^{31}P NMR effects in solutions of charged compounds such as phosphine oxides or ylides[114]. Now, in less electrophilic EtOAc and ether solvents, which are not effectively

solvating the chloride ion, the hexacoordinated associated uncharged transition state **54** is favoured, in which the catalyst is bound to the silicon center in a monodentate manner. But the silane, bound to only one oxygen is not sufficiently activated, and Nucleophilic attack of the allyl group does not proceed effectively, which results in low yield. Apart from that, the dependence of *ee* on temperature was also examined for the reaction of benzaldehyde with **52** in DCM and dropped from 95% *ee* at -80 °C to 91% *ee* at -20 °C. Interestingly, both species **88** and **89** catalysed crotylation of benzaldehyde under the same conditions -80 °C, DCM, 1 mol% of **88** or **89**, 16 h) , and the *Z*/*E* ratio of silanes completely matched the *syn*:*anti* ratio of products **82a** and **82b**, with 94% and 95% *ee* respectively, with both **88** and **89** providing the same result. Unfortunately, the yields were only moderate (59-64%).

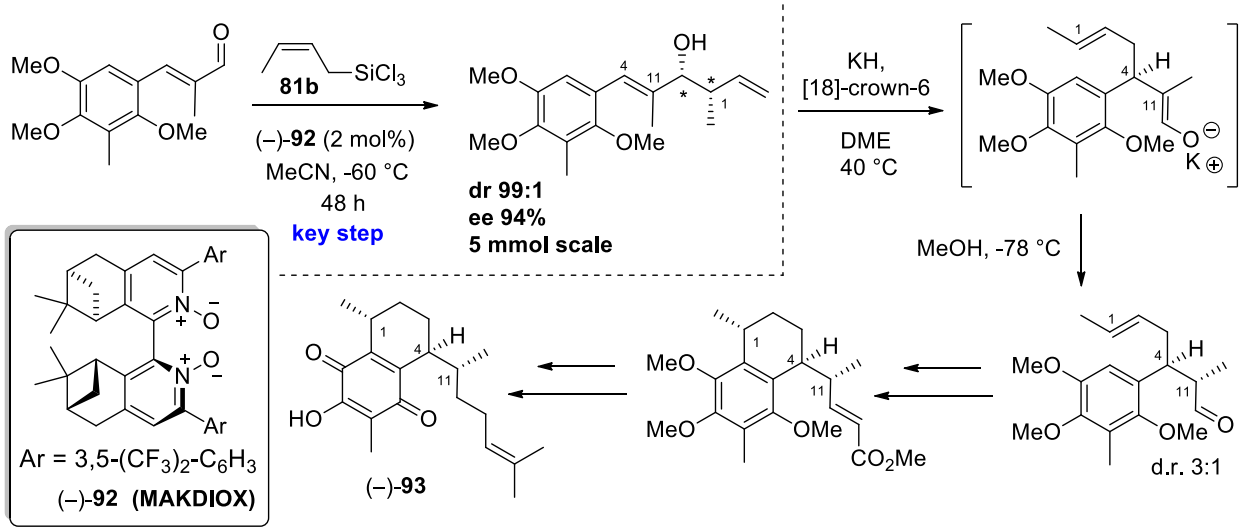
During the development of the chiral *N*-oxide catalysts for the enantioselective allylations of aldehydes, it was noted, that increasing the number of the Lewis-Basic oxygen atoms generally increases the activity of the catalyst. Thus, Kwong *et al.*[115] devised the unusual terpyridine-*N*,*N'*,*N"*-trioxide catalyst **90**, which has three Lewis Basic oxygen atoms capable of coordinating to the allyl silane. Several chiral monoterpene-derived terpyridines have been synthesised and turned into *N*,*N'*,*N"*-trioxides, and then tested in reactions with silanes. The activity of these catalysts were much lower than initially expected, being less active than the corresponding bipyridine-*N*,*N'*-dioxides **83**-**89**, and the reactions had to be conducted at 0 °C at loadings of 10 mol%, that negatively affected enantioselectivity (44-86% *ee*). The enantioselectivity could be improved by lowering the reaction temperature, albeit at the expense of the yield.

Chiral dinitrones such as **91** have also been studied as catalysts for the allylation of aldehydes by Nakajima[116], although the selectivities varied between 63-87% ee, that is even lower than in the case of terpyridine trioxide **90**. Interestingly, in the case of dinitrones, Hünig's base ((*i*-Pr)$_2$NEt) did not significantly improve the reaction efficiency, yielding (*R*)-homoallylic alcohol **75** in 13% yield and 11% ee. The optimal additive for the reaction was found to be DMPU (1.5 equiv).

The most effective catalyst MAKDIOX (**92**) was introduced by the Malkov's group in 2015.[57] It was used in the asymmetric catalytic crotylation of aldehydes. This methodology commonly relies on the use of stoichiometric reagents.[117] The catalysts excellent activity (works

at optimal loadings of 2 mol%) combined with a straightforward 6-steps synthesis from cheap and available chiral pool (–)-myrtenal, made it the catalyst of choice for asymmetric crotylation of aldehydes. All selectivities for aromatic aldehydes were above 90% *ee* with the only exception of 4-Cl-benzaldehyde.

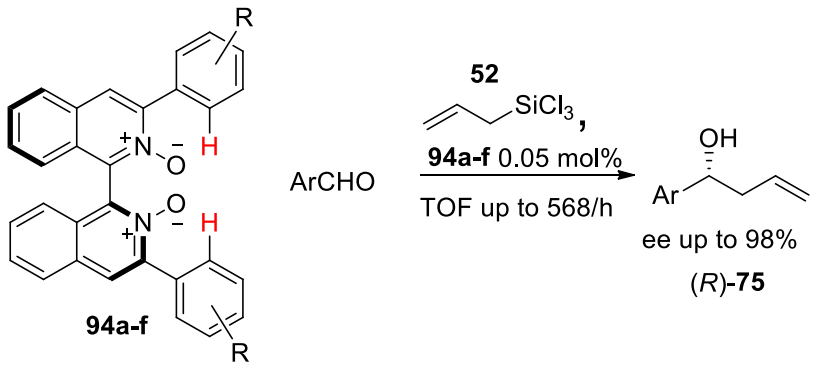
The effectiveness of the approach was demonstrated by a highly efficient enantioselective synthesis of the natural product (–)-Elisabethadione (**93**), with 99:1 diastereoselectivity and excellent *ee* (94%) in the key step, which is based on asymmetric catalytic addition of *Z*-crotylsilane **81b** to the aldehyde precursor on the 5 mmol scale (Scheme 40).



Scheme 40

Over the last 15 years, asymmetric allylation of aldehydes has received the attention of many research groups across the world.

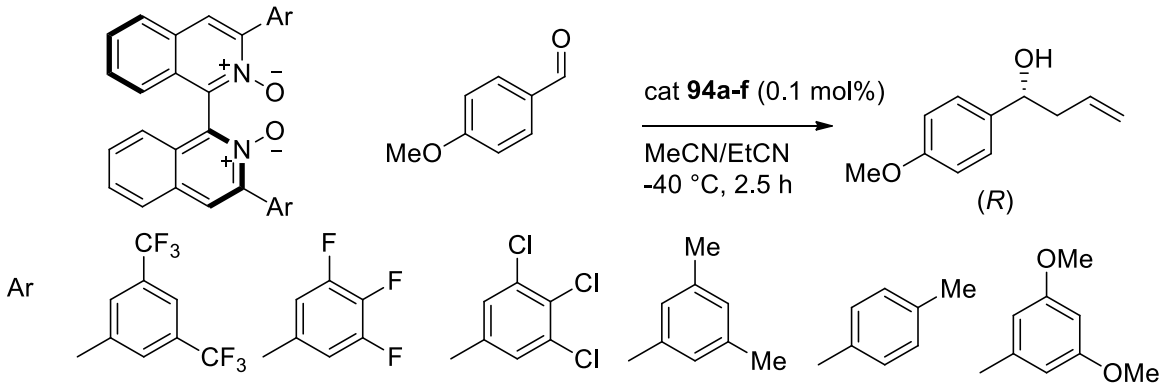
After the report on MAKDIOX (**92**), Takenaka *et al.* introduced similar axially-chiral bisquinoline *N*,*N'*-dioxide[118] catalysts **94a-f**, which turned out to be very active in allylation of aldehydes with allyltrichlorosilane **52** (Scheme 41 and 42).



Scheme 41

Notably, the paper provided a detailed discussion of the possible mechanism of action of the catalyst, supported by the DFT-calculations for the complex with $SiCl_4$, which irreversibly forms a complex with the catalyst, which makes experimental evidence easier to obtain for the results of such calculations.

The authors have synthesised 6 different catalysts and found, that catalyst with strongly electronegative groups, such as 3,4,5-trifluorophenyl (**94b**) or 3,5-bis-(CF_3)-Ph (**94a**) had the highest enantioselectivity of the allylation reactions (Scheme 42).



cat.	**94a**	**94b**	**94c**	**94d**	**94e**	**94f**
ee, %	96	96	91	95	88 (*S*)	82
yield, %	87	83	81	86	96	83

Scheme 42

Interestingly, such bisquinoline-*N*,*N*'-dioxides, in contrast to MAKDIOX, did not catalyse the reaction with aliphatic aldehydes.

The authors suggested that *ortho*-protons of the catalyst (Scheme 41, highlighted red) tend to form hydrogen bonds with the electronegative Cl atoms of the silane. It was predicted by quantum chemical calculations that the distance between the *ortho*-hydrogens and chlorine atoms should be 2.4 Å, which corresponds to H-bonding between *trans*-Cl and formyl protons of an aldehyde in the transition state complex (Figure 13).

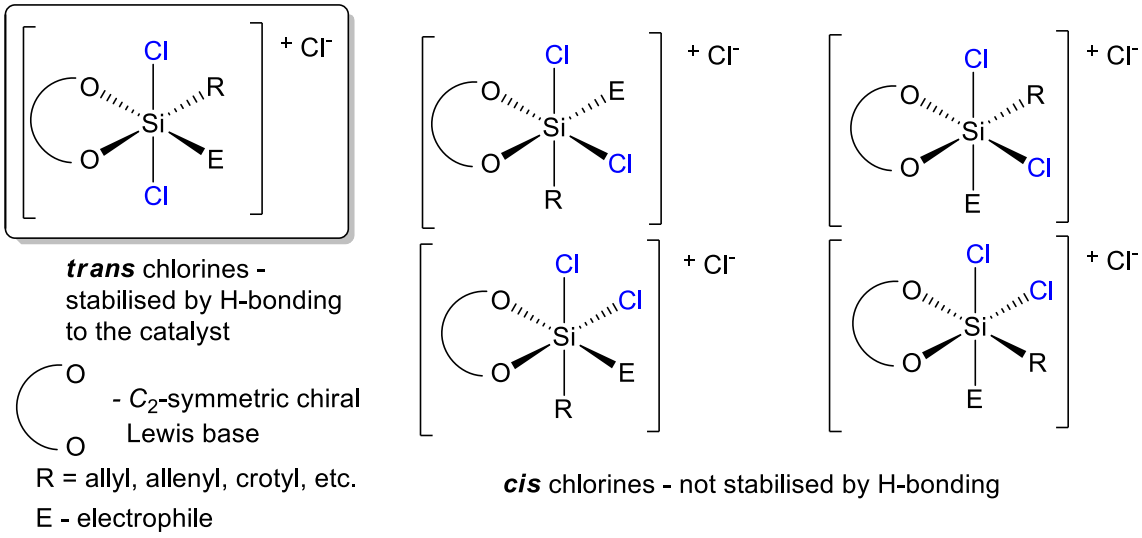


Figure 13

The authors screened the allylation of 4-anisaldehyde and *E*-cinnamaldehyde with **52** and identified, that **94a**, **94b** and **94d** had the highest selectivities and efficiencies.[118] They selected catalysts **94a** and **94b** as the structurally closest analogues to investigate the scope of the allylation with various aromatic aldehydes. The yields varied in the range 11-90% and *ee* varied in the range 56-98%. It was observed, that electron-deficient aldehydes such as *o*-, *m*- and *p*-Cl-benzaldehyde gave lower yields with **94a**. Therefore, the authors suggested that introduction of electron-donating MeO-group at the 6-isoquinoline positions of catalyst **94a** (Figure 14) should increase the activity of the catalyst due to increase of its basic properties by building up a negative charge on the N-oxide oxygen atoms. Indeed, the yields with **94g** were 10-20% higher than the average yields with the same substrates in the reactions catalysed by **94a**.

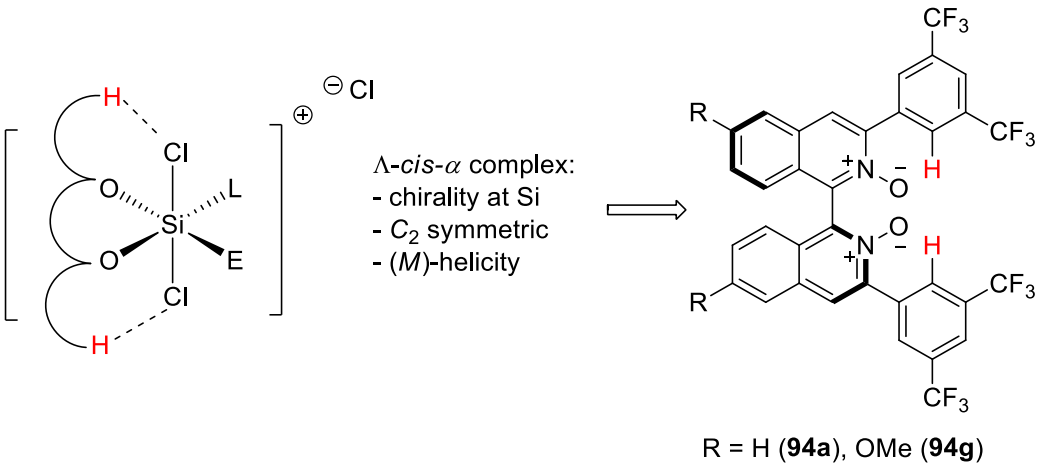
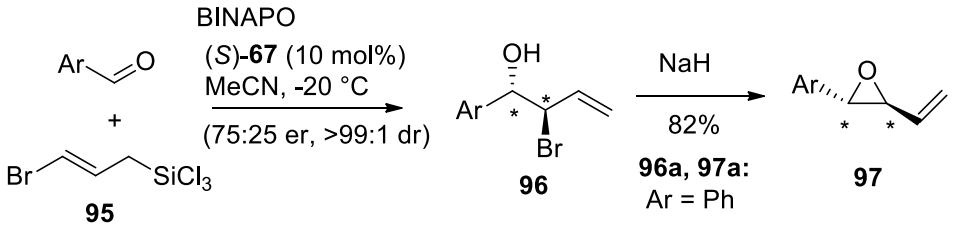


Figure 14

The limitations of the catalyst **94a** and its structural analogs include aliphatic aldehydes, halogen-substituted inactivated electron-poor aldehydes, (in contrast, MAKDIOX works well with these type of substrates). With 3-furancarboxaldehyde, the *ee* was notably lower than the average *ee* observed in the reactions with **94a** (56%). Another important fact is that only allylation reactions were studied, while crotylation and γ-functionalised allylation are of high interest as well.

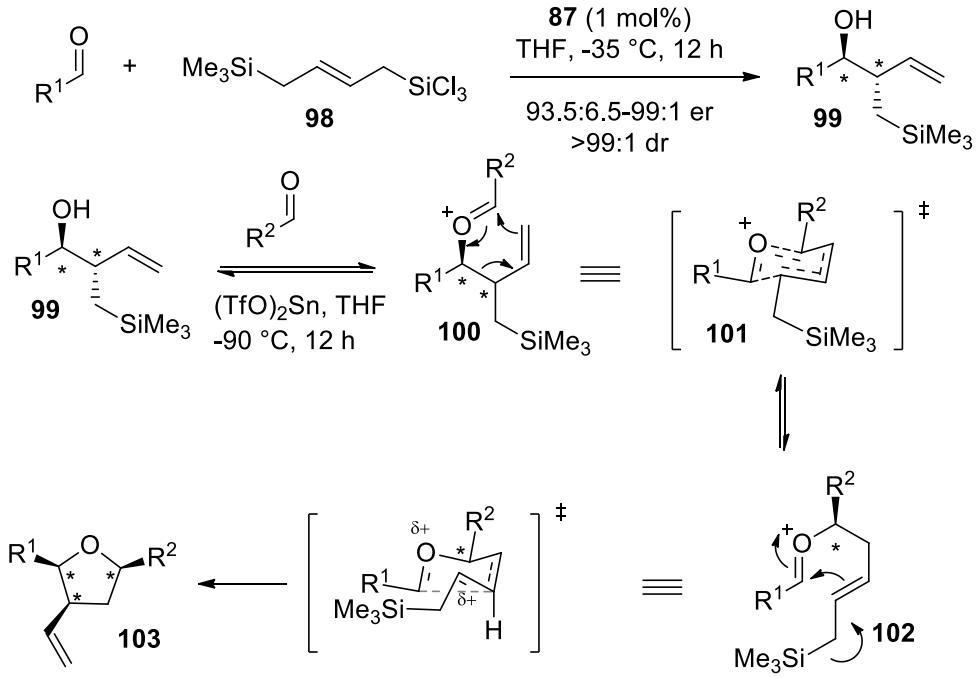
3.2.5. Organocatalytic asymmetric reactions of aldehydes with γ-functionalised allylsilanes and their applications in synthesis

Apart from asymmetric allylation and crotylation, asymmetric additions of other γ-functionalised silanes have also been studied. Thus, γ-bromosilane **95**, reported by Malkov, Kočovský and co-workers[119] was tested in the nucleophilic addition to aromatic aldehydes to produce bromohydrins such as **96** (Scheme 43). The diastereoselectivity of the racemic reactions was found to be excellent (99:1). The chiral bis-phosphine oxide BINAPO (**67**) proved to be the best available catalyst generating modest yields and enantioselectivities, while the mono-*N*-oxides METHOX (**77**) and QUINOX (**78**) failed to catalyse the reaction at all. This reflects the deactivated nature of the γ-halogenated silanes, which require stronger Lewis bases. Nonetheless, bromohydrin **96a** was efficiently cyclised upon the action of a strong base into the corresponding *trans*-epoxide **97a** (Scheme 43).



Scheme 43

The bifunctional reagent **98** can serve as a bis-allylic system and be coupled with various aromatic and α,β-unsaturated aldehydes to provide excellent enantio- and diastereoselectivities in the presence of METHOX (**77**) or QUINOX (**78**) (≤99:1 dr and 88-97% *ee)*, however, the reaction rate was slow, with the reaction being conducted over 7 days, which makes the methodology impractical. Interestingly, the use of the chiral bis-*N*,*N'*-dioxide **87**, developed by Kotora *et al.* [110,111] gave a dramatically increased rate of the reaction, achieving full conversion in 12 hours, with accompanied high level of stereoselectivity (87% *ee* and 99:1 dr) [110] (Scheme 44).



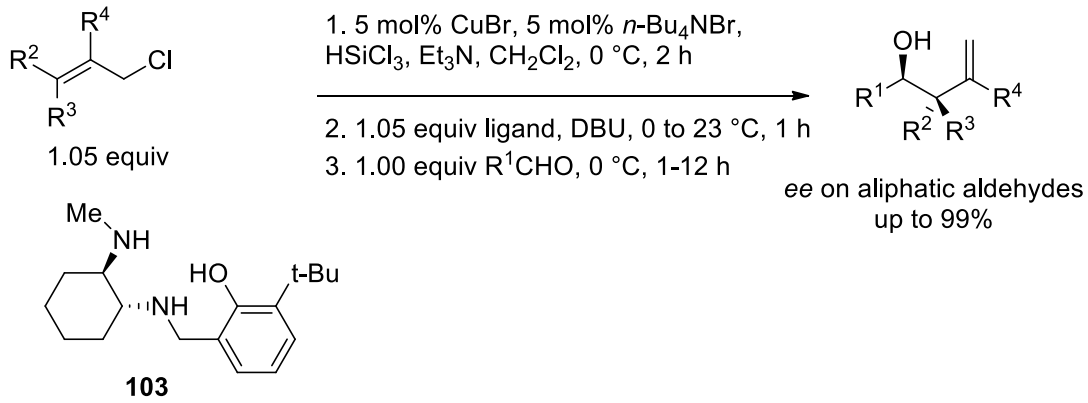
Scheme 44

Notably, the resulting chiral product **99**, bearing trimethylsilyl functionality was further subjected to $(TfO)_2Sn$-catalysed reaction at low temperature (-90 °C), which via oxonium ion **100**, underwent oxy-Cope rearrangement through cyclic transition state **101** to give another

allylsilane moiety **102**, which then was successfully involved in intramolecular cyclisation to give selectively the *cis*-trisubstituted trihydrofuran **103** with dr 7:1–25:1 and preserved enantiopurity.[110] The reaction provides good diastereoselectivities only for aromatic and α,β-unsaturated aldehydes, while with aliphatic aldehydes the diastereoselectivity was lower.

Because of the vast number of available methods, allylsilanes have attracted significant attention in total synthesis due to being much less toxic compared to allylstannanes whilst enabling a high level of stereocontrol.

Recently, Leighton's group[120] introduced a useful *in situ* method for allylation of aldehydes by various functionalised crotyltrichlorosilanes, as well as *E* and *Z* analogues of γ-crotyltrichlorosilanes, bearing the previously developed[121] chiral *trans*-1,2-diaminecyclohexane motif **103** which serves as the chiral auxiliary in their "EZ-CrotylMix" methodology.

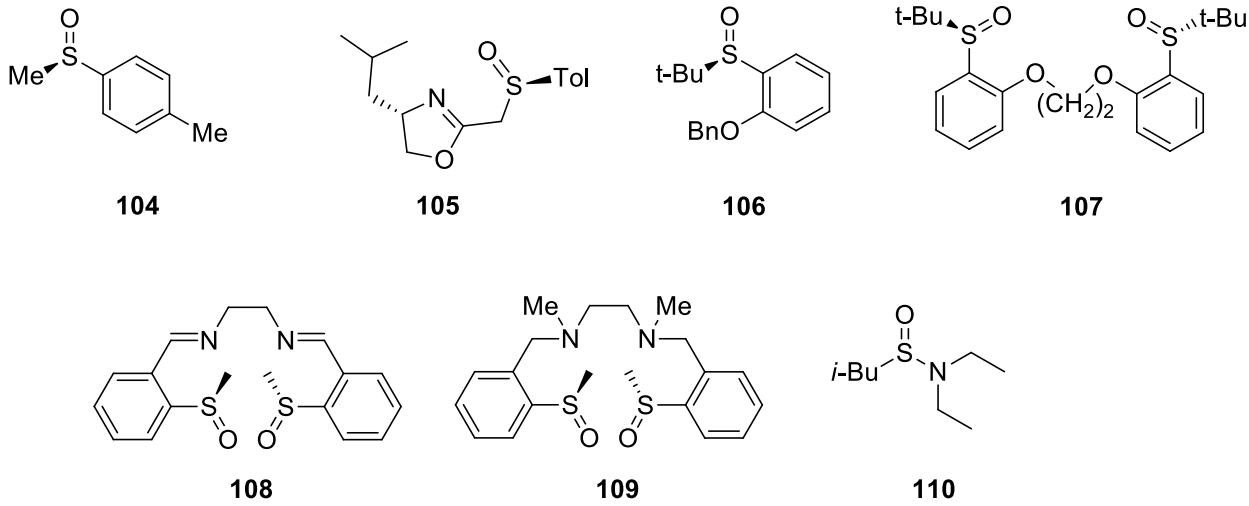


Scheme 45

The advantage of such a protocol is the silane scope, which can bear almost any functional group and does not require distillation. The reaction works with both *E* and *Z* γ-functionalised silanes. The diastereoselectivity was better than 15:1 in all cases. The challenging β-functionalised silanes showed *ee*'s up to 99%. Also, notably, the reaction reached >95% conversion in 20 minutes for nearly all cases and did not require special cooling equipment, since it can be conducted at 0 °C. The *ee* proved high even on challenging aliphatic aldehydes. Interestingly, it was suitable even for the production of chiral quaternary centres, which is of great importance for total synthesis. However, the chiral auxiliary has to be used in an equimolar amount, which may constrain scaling up the method.

3.2.6. Allylation of Aliphatic Aldehydes

Aliphatic aldehydes are challenging substrates and, as described above, give generally low yields and enantiomeric ratios with axially chiral bipyridine bis-*N*,*N'*-dioxides e.g. **87** . However, there are some literature precedents, when chiral catalysis was successfully applied with aliphatic substrates.



104 **105** **106** **107**

108 **109** **110**

Figure 15

These catalysts can be subdivided into three groups: chiral sulfoxides, chiral sulphonamides and chiral amides (Figure 15 and 16). The first two groups include catalysts **104**-**110**[122–127] which exhibit Lewis basic properties, bearing sulfoxide oxygens capable of coordination to the silicon centre of the reagent, thus promoting allylation of the aldehydes. These chiral sulfoxides are obtained in high enantiopurity by using either chemical or enzymatic oxidation methods.[123,125] They usually, however, provide only moderate yields and low to moderate enantioselectivity.

In the case of hindered γ-substituted allylsilanes, the *ee* was significantly enhanced.[128] However, such a methodology requires stoichiometric use of chiral Lewis bases, with the only exceptions being **108**[125] and **109**[126], which nonetheless work at minimal loadings of 30 mol%.

What is more, such bases are either decomposed or reduced during the reaction, which makes their recovery impossible[123]. Massa *et al.* published an extensive study, in which the dependence of the *ee* and yield on the structure of the chiral sulfoxide was investigated.[128] A positive nonlinear effect was observed for the reaction of allylsilane with benzaldehyde and an even more pronounced positive nonlinear effect was observed for the reaction with 5-nitro-2-furaldehyde. This evidence excludes the pentacoordinate TS **55**, and adds support to the hexacoordinate charged TS **57**, where two molecules of chiral sulfoxide are involved.

One of the first activators of silane to be discovered was DMF.[60,129] Based on this discovery, Iseki *et al.* introduced a C_2-symmetric chiral formamide **111**,[72] which gave high to excellent *ee*'s (68-98%) and modest to good yields (50-84%) in allylation of a wide range of aliphatic aldehydes using allyltrichlorosilane **52**. The reaction of *E*-crotylsilane with cyclohexanal and cinnamaldehyde was also tried and gave excellent enantio- and diastereoselectivities and yields. Despite all the excellent results, the method had several severe drawbacks. First, to achieve high level of *ee* it was necessary to conduct the reaction at the temperatures as low as -78 °C and use a stoichiometric amount of HMPA as a co-catalyst. Second, because at such low temperatures the catalyst activity was very low, the reaction required up to the 20 mol% loadings of **111**, and significantly prolonged reaction times of 1-2 weeks. Up to 4 weeks and 40 mol% loadings of **111** were required for sterically hindered aldehydes, such as pivaldehyde (*t*-BuCHO). Finally, the catalyst proved to be ineffective on aromatic aldehydes, giving only 8% *ee* with benzaldehyde under standard reaction conditions. All these complications make the protocol impractical.

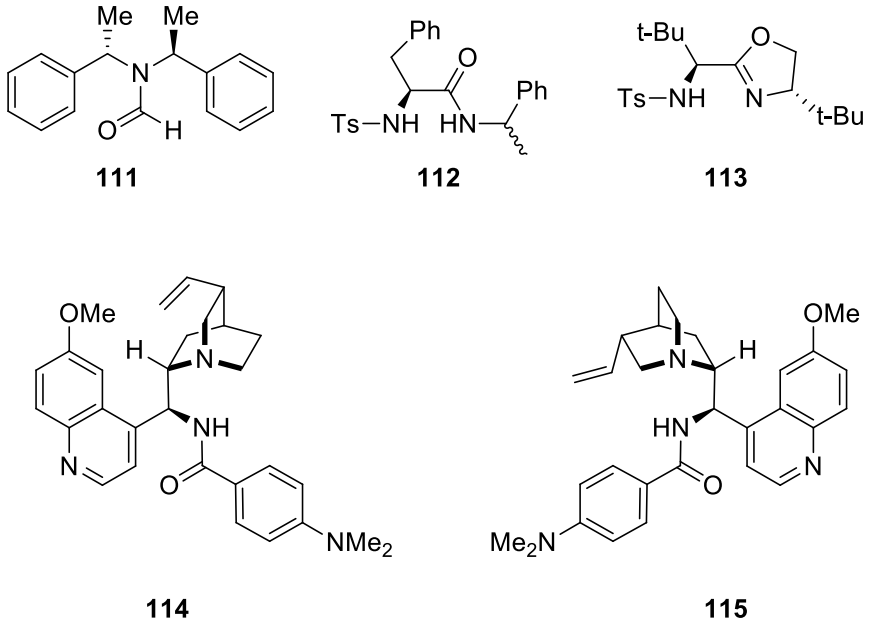
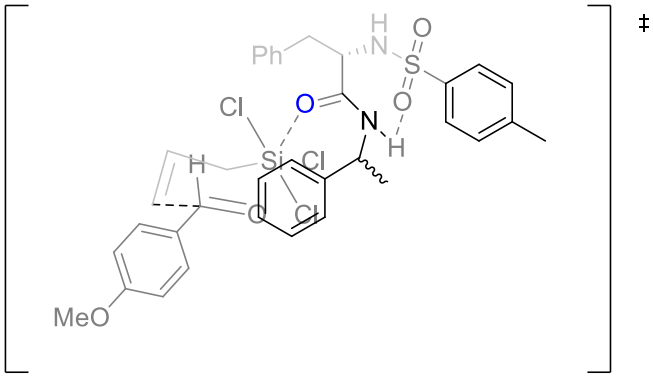


Figure 16

Unlike compound **111**, sulfonamides **112**[130] and **113**[131] (Ts = 4-Me-$C_6H_4SO_2$) (Figure 16) were more active allowing loadings of 15 mol% at 0 °C to achieve complete conversion in 24 hours on most of the aromatic and α,β-unsaturated aldehydes tested. The authors first tried to catalyse the reaction with pure amino-acids, but the *ee* did not exceed 38%. Next, these amino acids were converted to sulfonamides which brought *ee* to the level of 60%. The catalyst **112** was found to provide the highest enantioselectivity in DCM:THF mixture (7:3) at 0 °C with 2 equiv of DIPEA as an additive. In the reaction with **112**, the yields varied in a range of 55-90% and the *ee* varied in a range of 40% (4-MeO-C_6H_4CHO) and >99% (4-BnO-C_6H_4CHO). The reaction catalysed by **113** was optimal in pure DCM at 0 °C with 2 equiv of DIPEA as an additive and provided yields in a range of 52-90% and *ee* in the range of 64-99%. The selectivities followed the same general trend as with **112**.

Quantum chemical calculations of the energies of the transition states, along with ^{1}H and ^{13}C-NMR studies of the reaction mixture, led to the hypothesis that in the catalytic cycle the sulfone group of **112** increases the rigidity of the sulphonamide-silane complex, while a highly Lewis basic group of amide is coordinated to the allylsilane, thus blocking one face of the aldehyde in the closed chair-like transition state **54** (Figure 17).



TS **54**

Figure 17

The challenge of allylation of aliphatic aldehydes had a breakthrough with the introduction of cinchona-derived amides **114** and **115** by Zhao and co-workers (figure 16).[132] These catalysts set a new record for efficiency for both aromatic and aliphatic aldehydes at rt, with excellent enantioselectivity at the level of 90-98% *ee* with loadings of 10 mol%. The reaction times generally did not exceed one day, and the catalyst could be recovered almost quantitatively after the reaction completion. The catalysts also worked perfectly with isomerically enriched *E*- and *Z*-crotyltrichlorosilanes.

Variation in the catalyst structure was studied in the model allylation of benzyloxyacetaldehyde. A drop in *ee* and a significant drop in conversion (from 88 to 35%) were observed when the *para*-substituent of the phenyl group of the amide moiety of the catalyst was changed from highly electron-donating NMe_2 to a highly electron-withdrawing NO_2, which suggests, that the benzamide group is coordinating to the silicon centre rather than acting as a C-H bond donor.[132] Interestingly, the quinidine-derived isomer **114** gave the opposite isomer with the same enantiopurity of 96% *ee*.

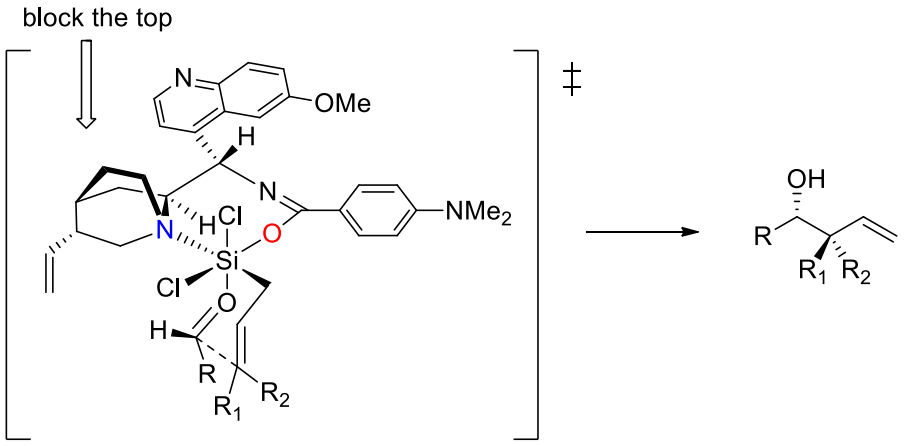


Figure 18

The proposed transition state (figure 18) structure was supported by the kinetic studies, which was revealed to be first order in respect to the catalyst. What is more, even after 12 hours, the reaction showed chloroadduct **62** only in trace amounts, in contrast to reaction with HMPA and other donating additives, which due to high basicity led to 50% conversion into **62** after 15 minutes. This difference may be attributed to the fact that the cinchona-derived catalyst is much less basic than HMPA, DMF or other amide activators, which suppresses the ionisation of the Si—Cl bond thus making the formation of aliphatic adduct possible.

In contrast to all previously reported catalysts, the cinchona-based catalyst is capable of providing high enantioselectivities even at elevated temperatures (0-20 ℃). The equilibrium between free aldehyde and α-Cl adduct **62** is reached much slower at -78 ℃. Hence, the effective concentration of the aldehyde after the beginning of the reaction stays very low, and the reaction requires weeks for completion[72]. At elevated temperatures, the equilibrium between **61** and **62** is reached much faster; thus, free aldehyde concentration is constantly replenished upon the reaction. For other catalysts, the selectivity is significantly reduced at higher temperatures.

3.2.7. Asymmetric propargylation and allenylation

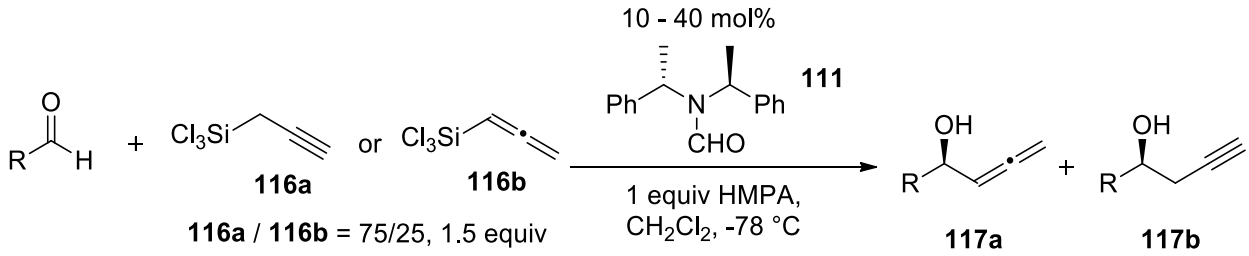
Over recent decades, catalytic asymmetric allenylation and propargylation reactions have become of great interest in organic synthesis,[133] particularly using allylmetals, which proceed through a closed 6-membered transition state **TS4** or **TS5**, where a direct transfer of allenyl or propargyl group from metal to electrophile takes place (Figure 19).

TS4 **TS5**

Figure 19

As well as several examples of chiral Lewis and Brønsted acids catalysis[133,134], chiral Lewis bases have also been investigated in the asymmetric allenylation and propargylation reactions.

One of the first attempts to catalyse propargylation through the use of a chiral Lewis base was reported by Iseki[135] in 1998 when chiral formamide **111** was used as an organocatalyst in combination with a stoichiometric amount of HMPA as an additive (Scheme 46).



Scheme 46

However, this protocol suffers from a number of disadvantages such as long reaction times, and modest *ee*'s (Table 4).

Table 4. Scope of the asymmetric allenylation, catalysed by 111

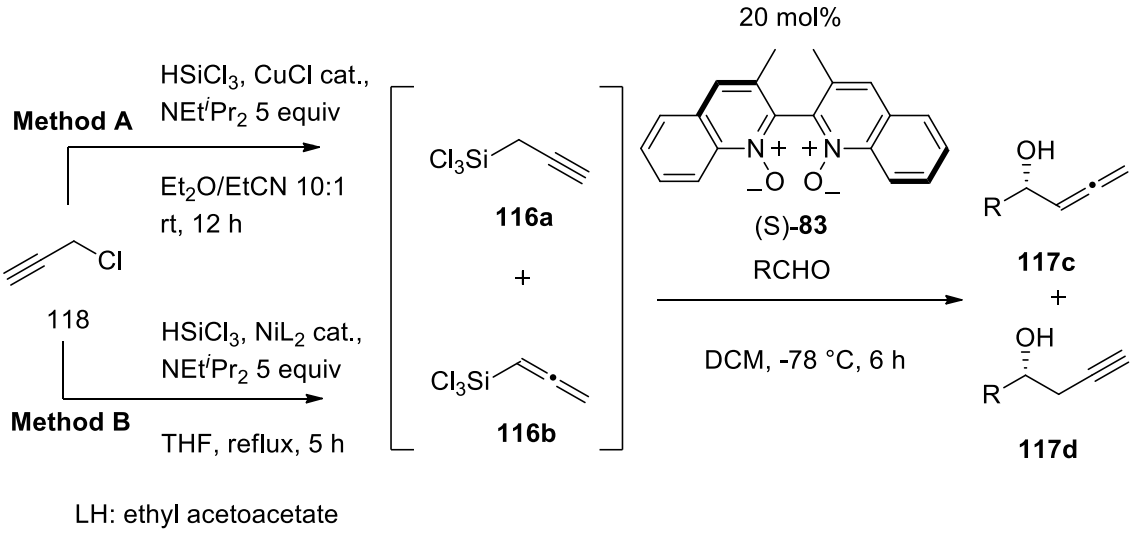
Entry	R	**111**, mol%	HMPA, mol%	Time, days	Yield (**117, a**+**b**)	**117, a**/**b**	*ee*, %
1	Cy	20	100	14	71	98/2	79 (S)
2	Cy	10	50	14	35	98/2	79 (S)
3	Cy	10	0	7	28	98/2	43 (S)
4	$PhCH_2CH_2$	20	100	14	71	99/1	79
5	Et_2CH	20	100	14	70	96/4	77
6	*t*-Bu	20	100	14	55	94/6	95
7[a]	*n*-Hexyl	20	100	14	37	93/7	56
8	Ph	40	200	4	59	96/4	0

[a] The reaction was conducted in acetone.

The reaction was found to be effective only with hindered aliphatic aldehydes such as pivaldehyde (entry 6), providing only moderate selectivities with other substrates. The higher content of allenyl alcohol **117a** compared to the propargyl product **117b** suggested that chiral formamide **111** was only efficient in the activation of propargylsilane **116a**, whereas allenyltrichlorosilane **116b** was much less reactive. The other disadvantage of this method is the use of carcinogenic additive HMPA.

After it turned out that chiral formamides of type **111** are in general ineffective in allenylation and propargylation reactions, organic chemists turned their attention to other types of Lewis base catalysts. The first catalyst to promote both propargylation and allenylation was chiral bipyridine bis-*N*-oxide **83** as reported by Nakajima.[136] This catalyst enabled the syntheses of allenic (**117a**) and homopropargylic (**117b**) alcohols with relatively high chemoselectivities from the same available source such as propargylic chloride **118** (Scheme 47).

The advantage of the utilisation of reagents **116a** and **116b** as trichlorosilane derivatives is that they can be prepared selectively from propargyl halides **118** using either copper or nickel catalysts and that such reagents can be used for subsequent highly selective propargylation and allenylation reactions.[137,138,139] However, enantioselectivities in these methods never exceeded 62% and were particularly low with the aliphatic substrates (Table 5).

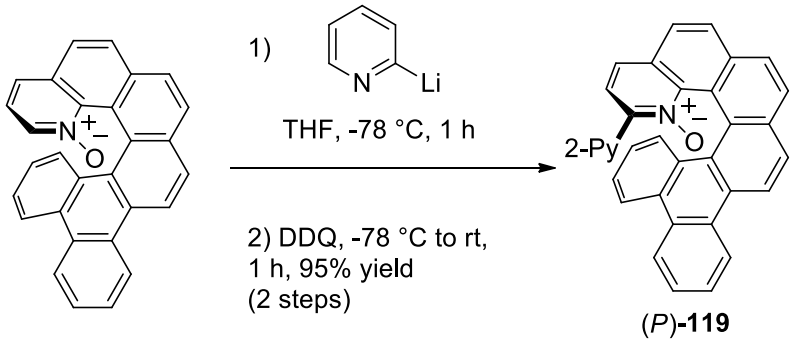


Scheme 47

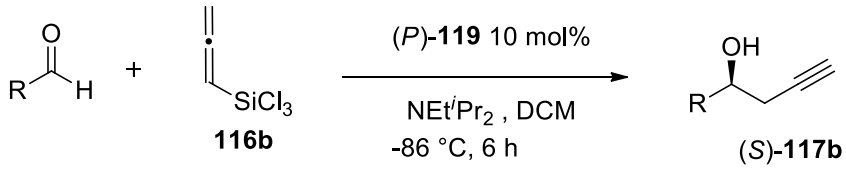
Table 5

Entry	Method	R	Yield	117, a:b	*ee*	Configuration
1	A	Ph	65	>30:1	52	*R*
2		4-MeO-Ph	62	>30:1	40	*R*
3		4-Cl-Ph	49	>30:1	46	*R*
4		$PhCH_2CH_2$	35	>30:1	23	*R*
5	B	Ph	72	1:15	54	*R*
6		4-MeO-Ph	76	1:9	62	*R*
7		4-Cl-Ph	48	1:9	49	*R*
8		$PhCH_2CH_2$	44	1:10	22	*R*

The most efficient method for enantioselective synthesis of homopropargylic alcohols developed so far was reported by Takenaka *et al*.[140] It is based on the use of a new type of chiral helical bipyridine *N*-monoxide **119** as a Lewis base catalyst (Scheme 48) and enabled selective synthesis of homopropargylic alcohols **117b** with high yields and high *ee*. Several examples are shown in Table 6.



Scheme 48



Scheme 49

Table 6. The scope of the propargylation with (*P*)-119

Entry	R	Yield (%)	*ee*
1	Ph	87	86
2	2-naphtyl	86	84
3	4-Br-Ph	95	92
4	4-MeO-Ph	80	74
5	2-MeO-Ph	78	94
6	Cy	61 (12 h) 80 (36 h)	59

A proposed mode of action is described by the stereochemical model **TS6** (Figure 20). In the cationic transition state **TS6A**, the *Si*-face attack is favoured by π-stacking interaction between the aldehyde and the helicene framework, thus leading to the major (*S*)-isomer of homopropargylic alcohol **117b**. On the other hand, the attack from *Re*-face (**TS6B**) is disfavoured by steric repulsion between the aldehyde *ortho*-substituent and anthracene tail of the helical catalyst. This proposal is supported by the fact that *ortho*-substituted substrates showed generally higher *ee*'s than the *para*-isomers, with the most significant difference between the methoxy-substituted benzaldehydes (entries 4 and 5). In addition, the fact that unbranched helicene catalyst **120** showed only a moderate selectivity compared to **119** while retaining the same catalytic activity offers further evidence (Scheme 50).

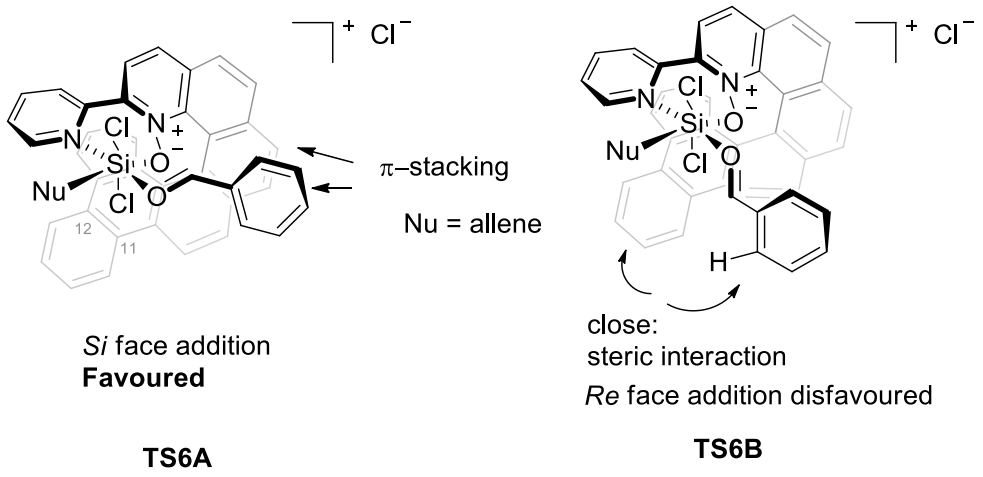
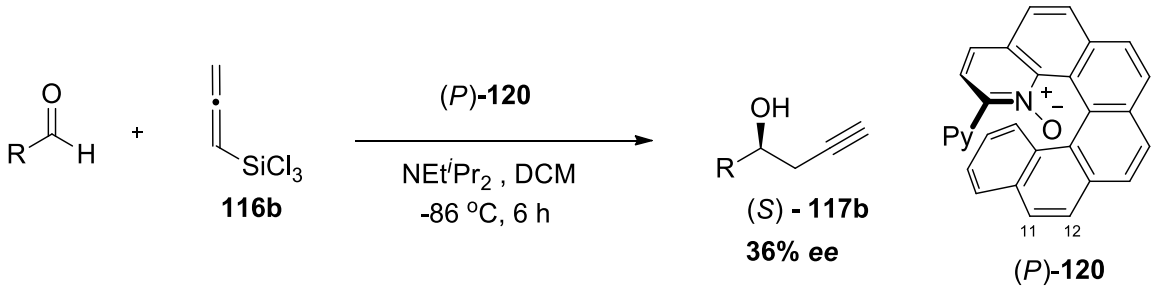


Figure 20



Scheme 50

An interesting computational insight into the reaction mechanism and *ee* prediction (Table 7) by analysis of the transition states was provided by Wheeler *et al*.[141] They screened 59 different possible catalysts with 3 different scaffolds (Figure 21) for the model reaction between allenyltichlorosilane **117b** and benzaldehyde. From their findings, several broad trends have emerged.

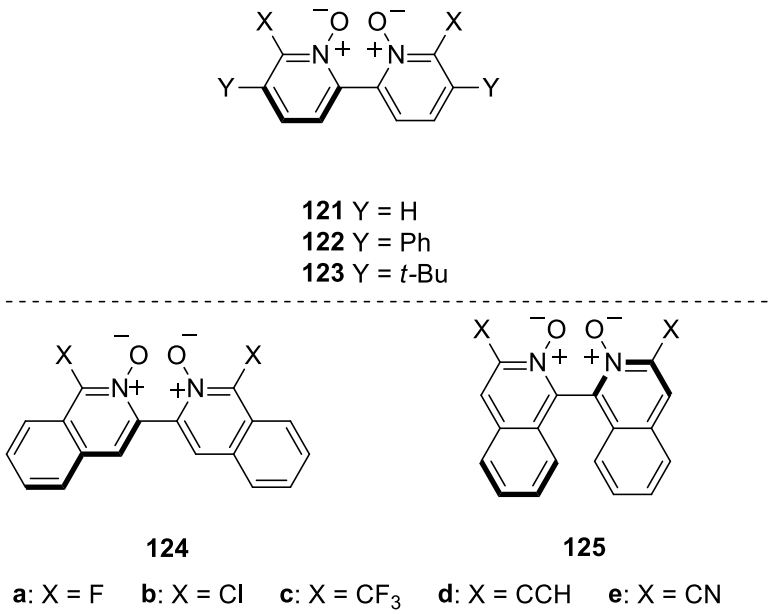


Figure 21

Table 7. Simulation of ee values.[a]

Cat.	121	122	123	124	125
a	89	94	**97**	90	89
b	91	**96**	**97**	92	91
c	94	**99**	**97**	**97**	**96**
d	86	**97**	**97**	92	91
e	93	**99**	**99**	**96**	94

[a]The number indicates the *ee* value for the catalyst. The letter indicates **X** substituent; the number indicates **Y** substituent or the type of the catalyst scaffold.

1. It was predicted that **TS7** is favoured for both *R* and *S* transition states for most catalysts (Figure 22) where electrostatic interaction between formyl proton of benzaldehyde and chlorine has a high impact on the stability of the transition states.

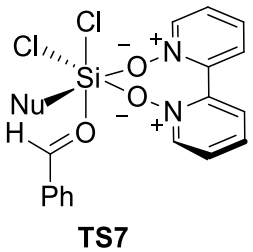


Figure 22

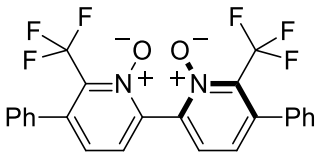
2. Bulky alkyl substituents, such as *i*-Pr and *t*-Bu destabilise both the *R* and *S* transition states, which usually leads to lower *ee*.

3. The bigger energy gap between **TS7** (*R*) and (*S*) transition states is achieved with substituents such as Cl, F, or CF_3. This is due to hydrogen bond formation between the formyl benzaldehyde proton and the electronegative group of the catalyst. The effect is much more significant in the case of a CF_3 group with the distance between F and formyl proton of just 2.83Å, compared to 3.59Å in the case of fluorine substituent. It is related to energy barrier differences of 1.8 and 1.4 kcal/mol, respectively.

4. Nitrile- and ethynyl-substituted catalyst should also have high *ee*'s, due to CH-π interaction between benzaldehyde and the catalyst's functional groups, stabilising the **TS7** (*R*).

5. Sterically hindered bipyridine-*N*,*N*'-dioxide catalysts should give generally higher enantioselectivities compared to bis-isoquinoline analogues with a variety of substituents.

Taking into account all their findings regarding the structural features which could impact the enantioselectivity, the authors rationally designed and proposed catalyst **122c**, which is likely to give *ee's* higher than 99% (Figure 23).



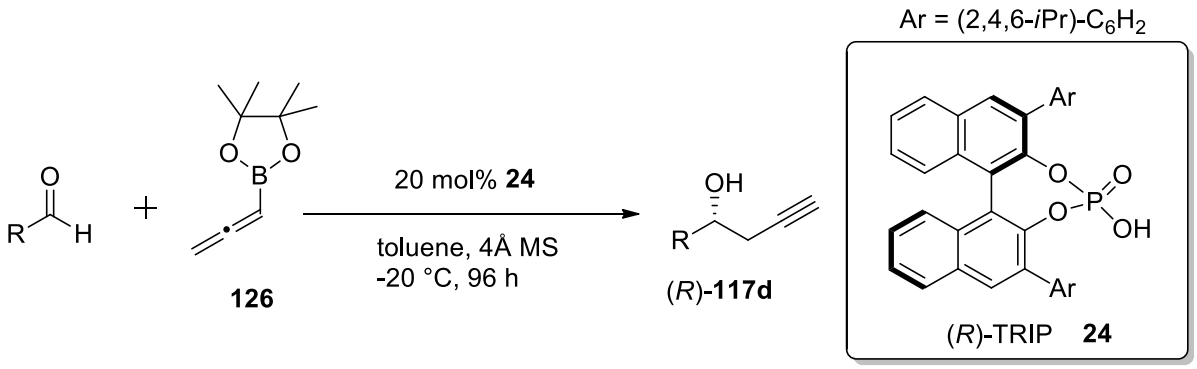
122c

Figure 23

The hypothesis being that a strong stabilising interactions in **TS7** (*R*) between the formyl H and the fluorine atom of the catalyst, and strong destabilising effect on **TS7** (*S*) due to electrostatic repulsion between the F and a Cl atom of allenyltrichlorosilane would lead to high selectivity. This effect increases the energy difference between the two TS up to 2.2 kcal/mol which corresponds to a predicted *ee* of no less than 99%.

Apart from Lewis acids, Brønsted acids can also catalyse propargylation reactions. An interesting example of an asymmetric Brønsted acid-catalysed propargylation reaction was

reported by Antilla and co-workers.[142] The reaction is based on the use of the previously mentioned hindered BINOL-derived phosphoric acid **24** ((*R*)-TRIP) (Scheme 51).



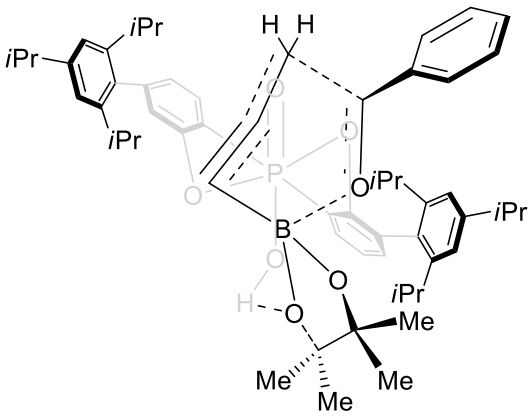
Scheme 51

It was experimentally shown that among several chiral BINOL derivatives, (*R*)-TRIP (**24**) serves as the best catalyst for this transformation. It gave excellent yields and enantioselectivities for various aromatic aldehydes and good selectivities for the aliphatic aldehydes (Table 8).

Table 8. Scope of allenylation with TRIP (24)

R	Yield, %	*ee, %*
Ph	94	91
p-Cl-Ph	95	93
p-NO_2-Ph	96	93
p-OMe-Ph	87	92
o-Me-Ph	91	92
2-Naphtyl	93	91
$PhCH_2$	90	79
$PhCH_2CH_2$	92	82
Cy	89	77

The mechanism of action for this catalyst was studied by quantum chemical calculations and relies on the enantioselective transfer of a proton to one of the oxygens of boronic ester **126**, which is supported by the prediction of calculated transition state **TS8**, which should have the lowest energy (Figure 24).



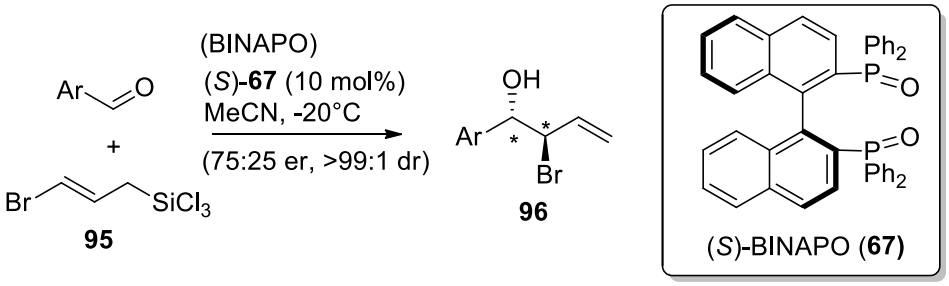
TS8

Figure 24

Despite delivering good yields and enantioselectivities, the reaction requires high loadings of the costly chiral catalyst **24** (20 mol%).

3.3.Conclusion

The asymmetric allylation of aldehydes is an important topic in Modern Synthetic Organic Chemistry. Among the many developed methods, the latest and most promising approaches are the organocatalytic methods. From the range of available catalysts, the most effective are based upon chiral bis-*N*,*N*'-dioxides, which have been shown to give excellent yields and enantioselectivities even at loadings as low as 0.1 mol%. Among the vast number of reported protocols, the most under-developed (yet synthetically important) is the allylation of aldehydes with γ-functionalised allyltrichlorosilanes such as **95**.



Scheme 52

Chiral enantioenriched halohyrines such as **96** bear two chiral centers, three functional groups (alcohol, halogen and a double bond) and can be transformed into chiral stereodefined

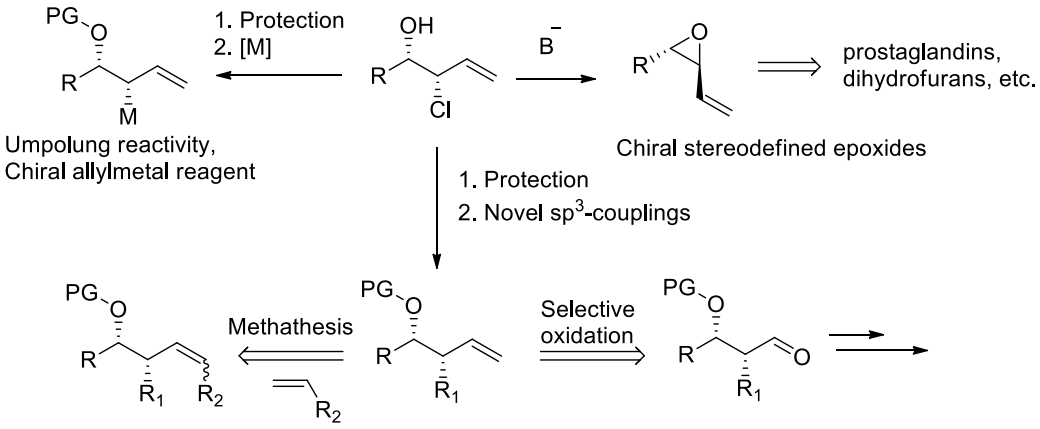
vinylepoxides[119], which can serve as versatile building blocks for the synthesis of a wide range of biologically active and practically important compounds[143]

Therefore, we have decided to turn our attention to γ-halogenated allyltrichlorosilane reagents.

Chapter 4: Results. Chiral 2,2-Bipyridine *N,N'*-dioxides as Lewis Base Catalysts for Asymmetric reactions of trichlorosilanes with aldehydes

Aims and objectives

Chiral vinyl-α-halohydrines serve as important building blocks for the asymmetric synthesis of a variety of products (Scheme 53). However, so far, only a limited number of methodologies existed to make such compounds directly from readily available starting materials.



Scheme 53

In addition, most of the existing methods, except the very recent example by Leighton group[120], were aimed at the asymmetric synthesis of *syn*-α-halohydrines (**128a**), while the synthesis of *anti*-α-halohydrines (**128b**) presently remain challenging synthetic target (figure 25).

128a

up to 99/1 *syn*:*anti*
up to 99:1 er
up to 99:1 alpha/gamma

128b

No direct methods
poor *ee*
always minor

Figure 25

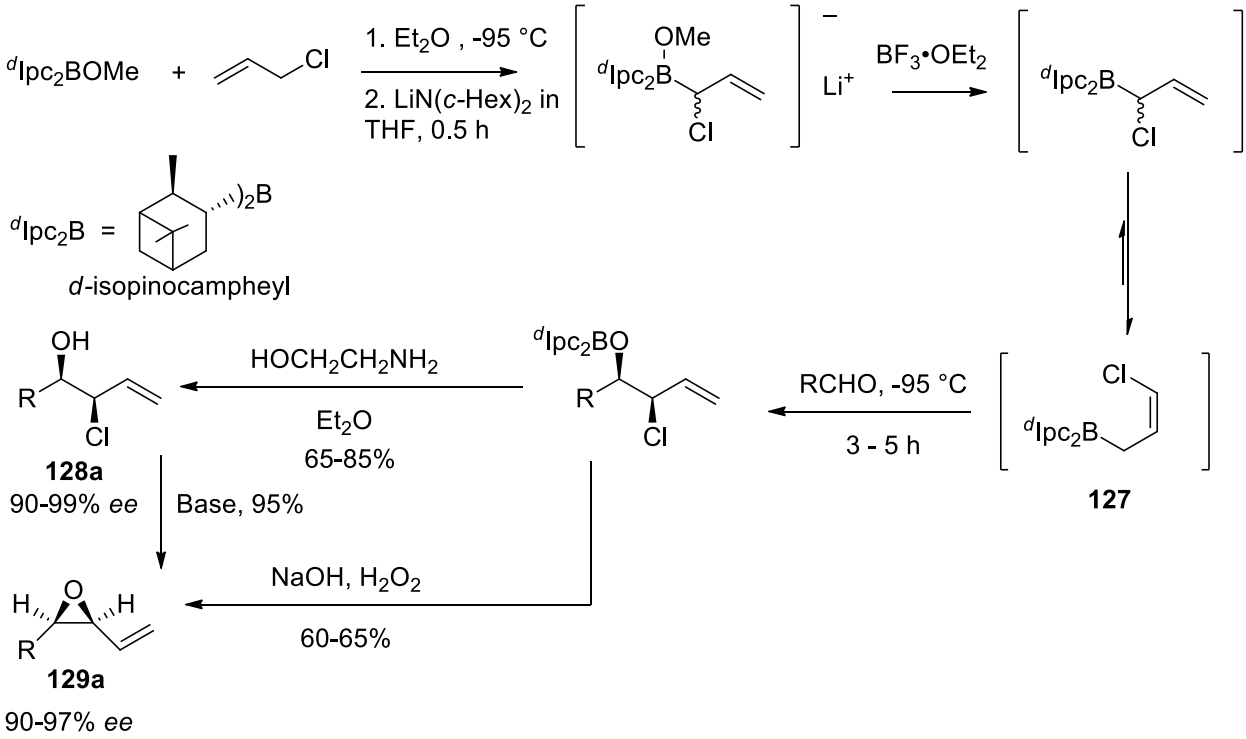
The aim of this work was to design a highly efficient and versatile method for the asymmetric synthesis of *trans*- and *cis*-vinylepoxides. It can be divided into three main objectives:

1. *Develop a highly efficient and enantioselective organocatalytic method for chloroallylation of aldehydes using trichlorosilyl reagents.*
2. *Optimise catalyst's structure to enhance effectiveness on chloroallylation of aldehydes.*
3. *Achieve stereoselective cyclisation of homochiral chlorohydrins into chiral epoxides to illustrate the practical importance of the developed method.*

4.1.Results and Discussion

4.1.1. Background

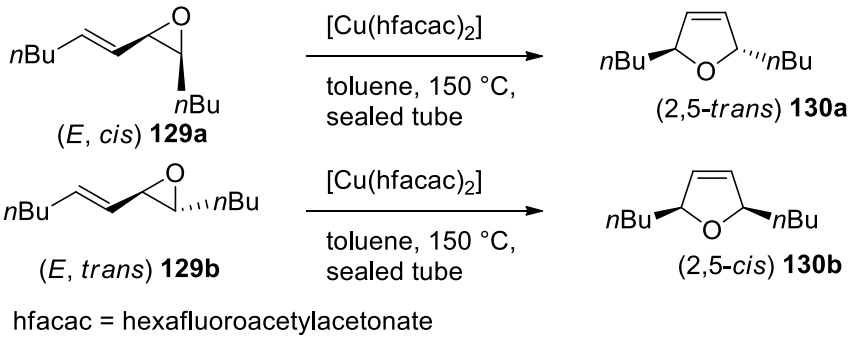
The initial attempt to prepare *syn*-chlorohydrins **128a** was undertaken by the Oehlschlager group[144] and dates back to 1995. This pioneering study evaluated chiral auxiliary-bearing Brown-type allylboranes **127** and provided excellent ee's above 90% and 68-85% yields (Scheme 54).



Scheme 54

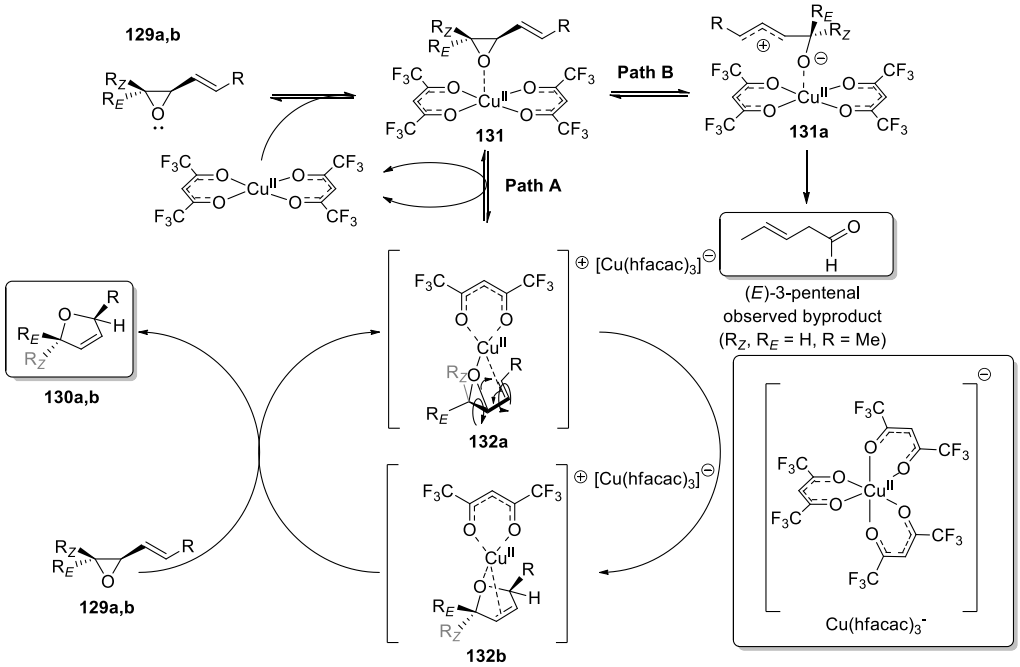
Importantly, both aromatic and aliphatic aldehydes worked equally well under the given conditions. The products were successfully converted to chiral *cis*-vinylepoxides **129a** in good yields and with complete retention of enantiopurity. However, the significant drawback of the methodology was that the crude material always contained *ca.* 5% of linear regioisomer, which had to be separated by column chromatography. Later on, the same group optimised their borane-based methodology by varying the chiral auxiliary on the boron[145] to achieve regioselectivity >99:1 in favour of the branched halohydrin **128a** while retaining 99:1 *syn*-selectivity and up to 99% *ee* of the resulting *cis*-vinyl epoxide **129a**.

The importance of such chiral chlorohydrins stems from the fact that upon treatment with a strong base, such as NaH, they undergo a cyclisation into enantiomerically enriched vinyl epoxides which themselves could serve as intermediates in total synthesis of some bioactive molecules containing 2,5-dihydrofuran scaffolds such as (-)-goniothalesdiol[146] via stereoselective ring expansion (Scheme 55).



Scheme 55

The catalytic cycle, proposed by the authors, explain observed transfer of chirality from epoxides to 2,5-dihydrofurans (Scheme 56).



Scheme 56

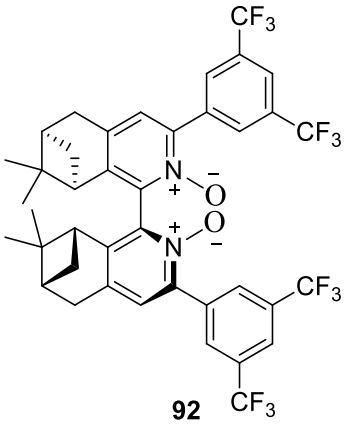
First, copper(II) hexafluoroacetylacetonate reversibly coordinates a vinylepoxide **129** by a lone pair of oxygen, which leads to the formation of neutral intermediate **131**. Resulting intermediate species have two general reactivity patterns. In the first pattern (Path B), the

vinylepoxide opens up oxiran ring, which result in an unstable allylic zwitter-ion complex **131a**, which then undergoes (if both R_E and R_Z groups are H) a hydride shift resulting in the formation of a byproduct 3-pentenal, which was observed by ^{1}H NMR. In the main reactivity pattern (Path A), the substrate-catalyst complex **131** undergoes reversible exchange with a free Cu(hfacac)$_2$ complex to form cationic reaction intermediate **132a** with increased Lewis acidity which holds transition state complex toghether, while freshly formed Cu(hfacac)$_3^-$ species acts as a non-nucleophilic counteranion. Because of increased Lewis acidity of Cu(II), the chirality of C-O bond migrates in concerted process without the inversion of neighbouring double bond configuration. As a result, *cis*-oxirane **129a** gives *trans*-dihydrofurane **130a**, while *trans*-oxirane **129b** gives *cis*-dihydrofurane **130b**. In the resulting dihydrofurane-catalyst complex **132b** the product of the reaction has a weaker chelation force then starting oxirane **129** which allows its exchange with the latter and the release of a product, which closes up the catalytic cycle.

An interesting example of the synthesis of vinylbromohydrins **96** was reported in 2010 by Malkov and Kocovsky[119]. Their approach relies on synthesis and utilisation of γ-functionalised allyltrichlorosilanes, which can be then transformed into chiral stereodefined epoxides **129b** (Scheme 52, p. 84).

However, the yields and enantioselectivities of this protocol were poor, up to 50% *ee* and 48% yield. Mono-*N*-oxides (**77** and **78**) were shown to be inactive, bis-phosphine dioxides were active but showed poor enantioselectivity. Since chiral bipyridine *N*,*N'*-dioxides are more active we suggested that a bipyridine *N*,*N'*-dioxide catalyst might provide the desired efficiency.

Previously, it has been reported by our group that axially chiral bipyridine *N,N'*-dioxide **92** can efficiently catalyse asymmetric addition of (*E*)- and (*Z*)-crotyltrichlorosilanes to aromatic aldehydes in DCM at low temperatures in high diastereo- and enantioselectivity.[57]



92

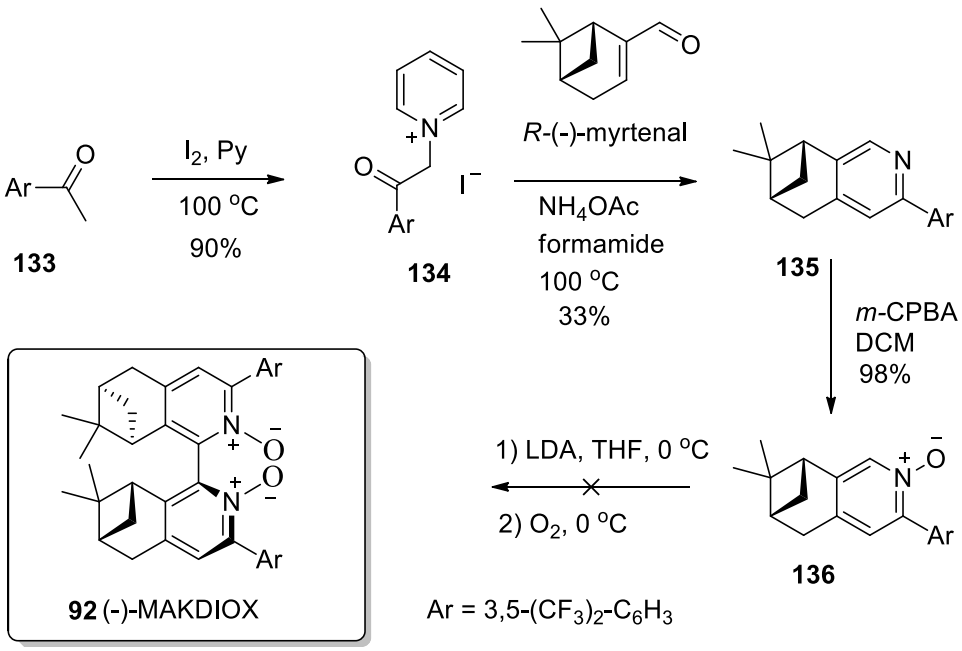
(-)-MAKDIOX

Figure 26

We decided to begin our investigation by testing the efficiency of this catalyst in the synthesis of halohydrins **128a**. Our proposal was to test this catalyst and also to develop improved catalyst structures by modifying the original catalyst structure.

4.1.2. Synthesis of Chiral Bipyridine-bis-*N*-Oxides

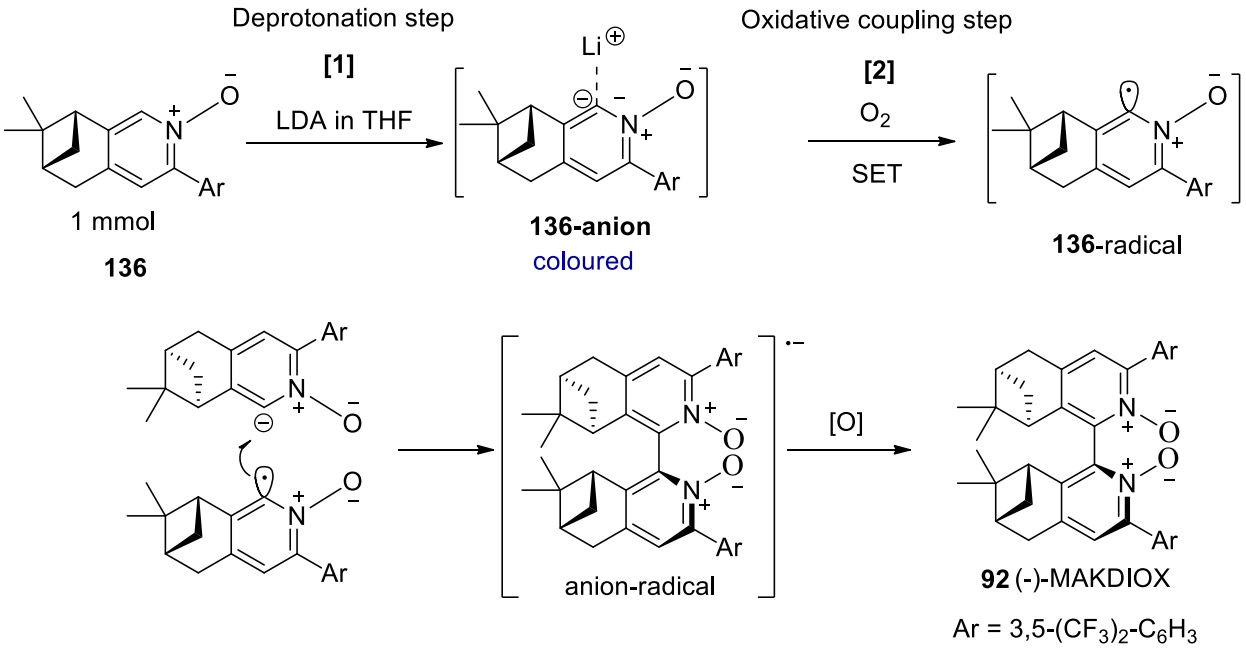
First, we undertook the synthesis of (-)-MAKDIOX from cheap commercial (-)-myrtenal as a natural source of chirality and 3,5-bis-(trifluoromethyl)acetophenone **133** in 4 steps following the originally published method (Scheme 57).[57]



Scheme 57

The first step was the preparation of the Kröhnke salt **134** from acetophenone **133** and pyridine, which was completed in 90% conversion. The resulting salt was then used in the next step without separating it from pyridine hydroiodide after its molar (and weight) ratio was determined by NMR analysis. The cyclisation step with (-)-myrtenal and ammonium acetate was performed in formamide at 100 °C, but the best yield of pyridine **135** never exceeded 33%. The next step was the oxidation of pyridine **135** with *m*-CPBA in dichloromethane, which worked perfectly, giving pyridine *N*-oxide **136** in 98% yield.

In the beginning of our studies, we proposed that the pyridine *N*-oxide coupling reaction (**136** → (-)-**92**) would proceed via 2 key steps (Scheme 58).

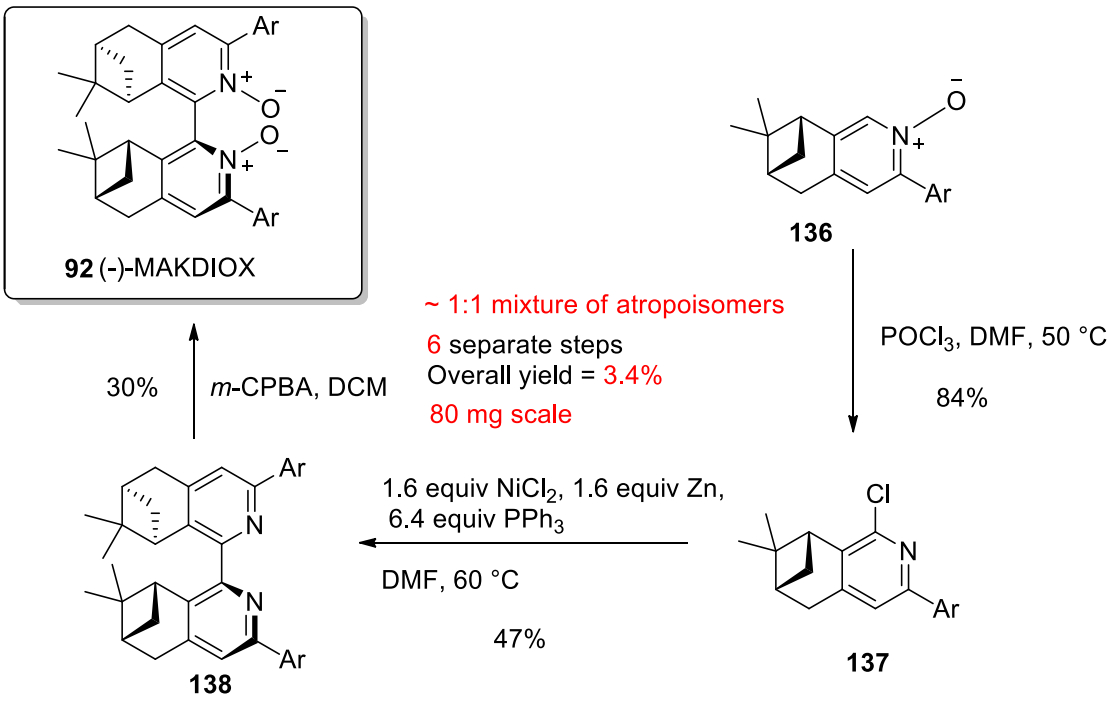


Scheme 58

The first step would be a fast deprotonation of **136** by strong hindered base (LDA), which will generate a strongly coloured 2-anion. Lithium ion may occupy a specific place between oxygen and 2-anion of **136**, but a detailed experimental work aided with the quantum chemistry calculations is needed to evaluate its position in detail. Single-electron oxidation of the **136**-anion that would occur after the addition of oxygen, would produce a radical which subsequently will react with anionic form of **136**. The reaction is likely to proceed through the oxidative coupling pathway via the formation of highly ordered organolithium aggregates,[147] which resembles the oxidative coupling of lithium enolates.[148] The resulting anion-radical is then will be oxidised to form a neutral molecule of **92**.

Unfortunately, our attempts to perform the final coupling of **136** using literature[149]-30-minute deprotonation step method to reach the target bipyridine-*N,N'*-dioxide **92** met with limited success. Even with distilled diisopropylamine and freshly titrated butyllithium, only trace quantities of the product were detected. When we tried to gradually increase the reaction temperature to enhance the rate of the reaction, it only led to complete decomposition of the starting material.

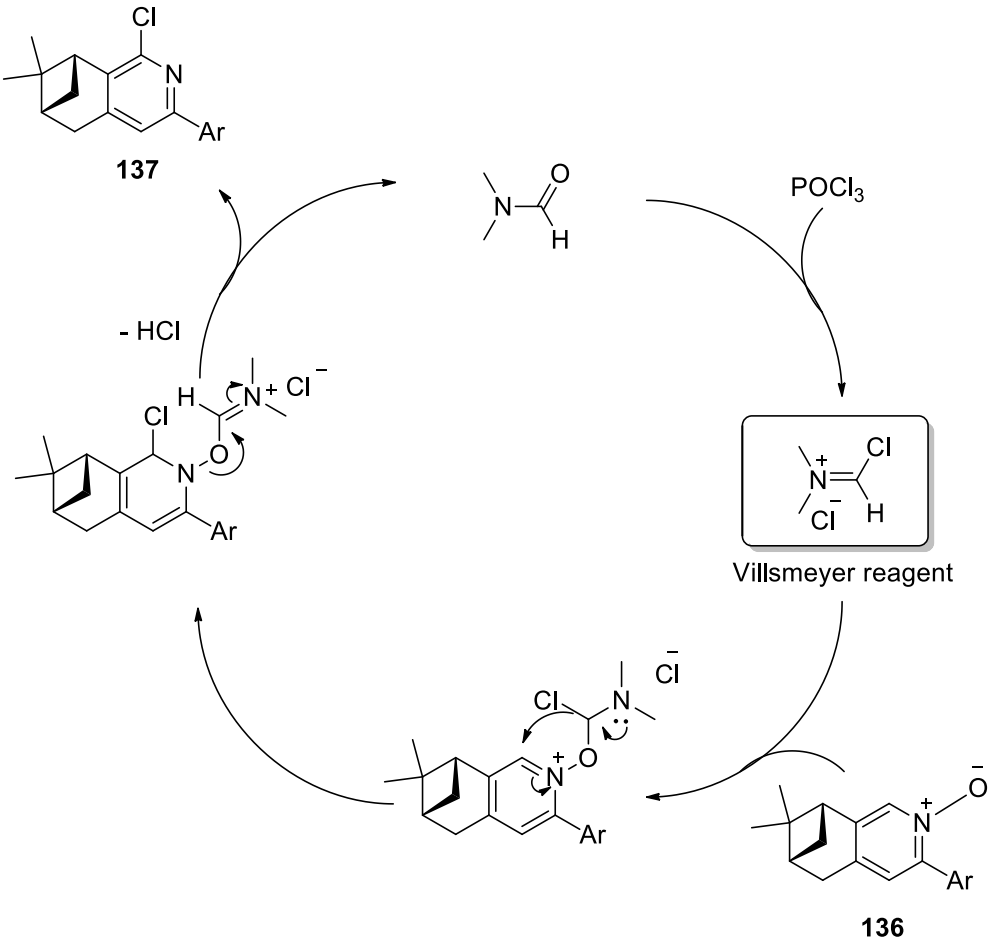
After that, it was decided to explore an alternative route, used previously in our group for the synthesis of 2,2'-Bipyridine ligands. [150]



Scheme 59

This new route is based on Ni^0-mediated coupling of the corresponding 2-chloropyridine **137** (Scheme 59). Despite being longer, this methodology seemed more reliable, especially for the future synthesis of functionalised catalysts. To perform the coupling, we decided to convert *N*-oxide **136** into the 2-chloropyridine **137**. First, we tried to run the reaction in DCM with triethylamine according to the common literature method, which was reported to be effective with unsubstituted pyridine-*N*-oxide at 40 °C.[151] Unfortunately, under these conditions, we observed an acid-catalysed opening of the highly strained bicyclic terpene unit of the molecule. We then used a previous method used in our group[150] for the conversion of pyridones into 2-chloropyridines and tried to vary the temperature. Finally, we were able to synthesise target 2-

chloropyridine **137** in 84% yield by stirring the reaction mixture in DMF at 50 °C for 18 hours. The reaction mechanism was proposed recently in the study by Wang group. [152] The method is based on the *in situ* formation of the Villsmeyer reagent, which reacts mildly with pyridine-*N*-oxides, resulting in a selective and efficient 2-chlorination.

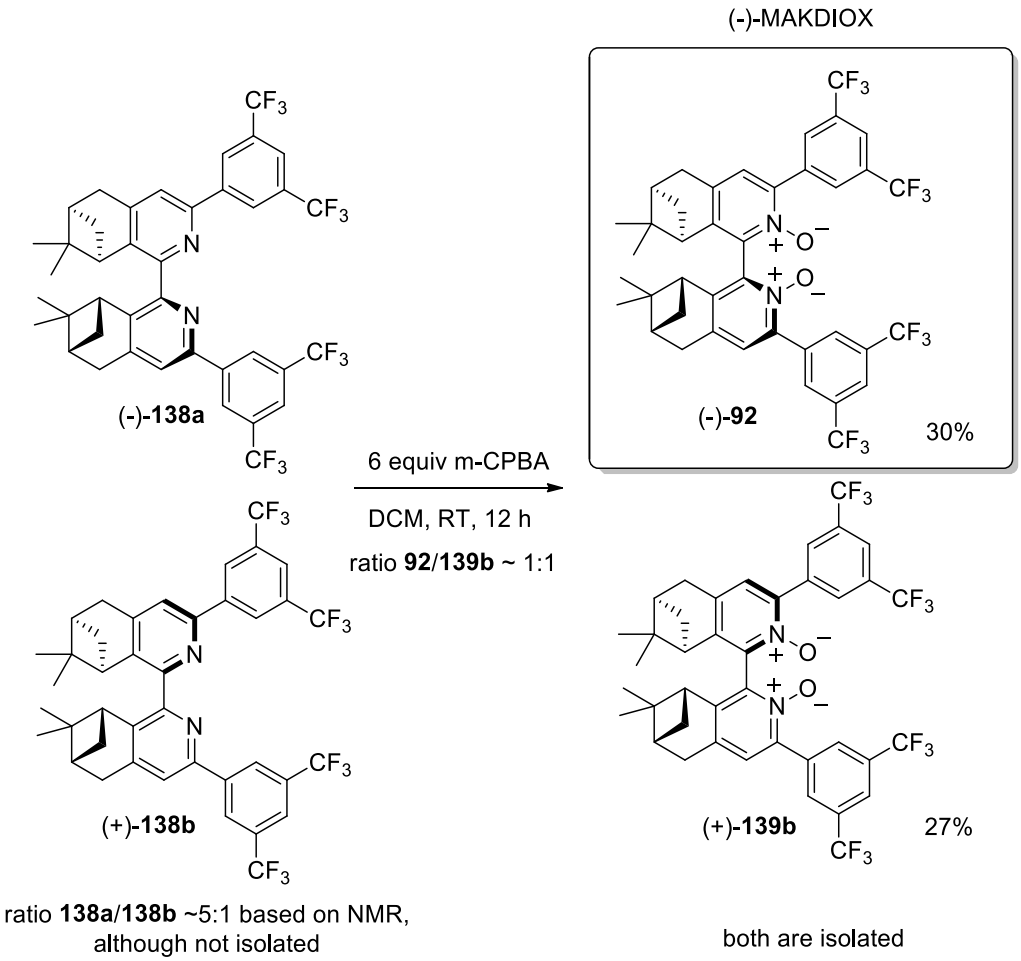


Scheme 60

First, the DMF reacts with $POCl_3$ and forms *in situ* the Villsmeyer reagent, which serves both as electrophilic activator and a chloride source for chlorination of **136**. In the next step the reaction of Villsmeyer reagent with **136** proceeds through the nucleophilic attack of N-oxide oxygen at electrophilic carbonyl carbon of the Villsmeyer reagent. The subsequent redistribution of electron density and a highly regioselective intramolecular nucleophilic attack of a chloride results in a quaternary σ-complex iminium salt, which rearomatises by elimination of HCl and generation of a DMF molecule, with the latter being returned to the catalytic cycle, forming the target 2-chloropyridine **137** exclusively (Scheme 60).

The next step was the Ni-catalyzed coupling. While this reaction is usually performed as a catalytic variant, in our case the use of catalytic amounts of Nickel resulted in a stable complex of the coupling product **138** with Ni ions, thus breaking the catalytic cycle. To avoid this problem, we used an increased amount (1.6 equiv) of Nickel(II) chloride, which was reduced *in situ* to Ni^0 species by Zn metal. The reaction was carried out in DMF at 60 °C. This protocol is not ideal, as a large excess of Ph_3P ligand is needed to stabilise Ni^0 active species, which significantly complicated purification of the product by chromatography. To separate Ph_3P, it was necessary to wash the *silica* column for a long time with a non-polar eluent such as *n*-hexane or PE.

Nonetheless, the sequence from **135** to **138** afforded the target 2,2-bipyridine **138** in 28% yield over the three steps (oxidation, deoxychlorination and coupling) without isolation of the intermediate compounds. Surprisingly, we have discovered by ^1H NMR, that the resulting 2,2-bipyridine product was formed as a mixture of axial diastereomers **138a** and **138b** in approximately 5:1 ratio, which were difficult to separate by column chromatography (Scheme 61). The reason for this ratio is that in the Ni-mediated coupling two pyridine molecules are separated by a Nickel atom, and they can readily occupy both (+) and (-) axial configurations before undergoing oxidative elimination (Figure 27).



Scheme 61

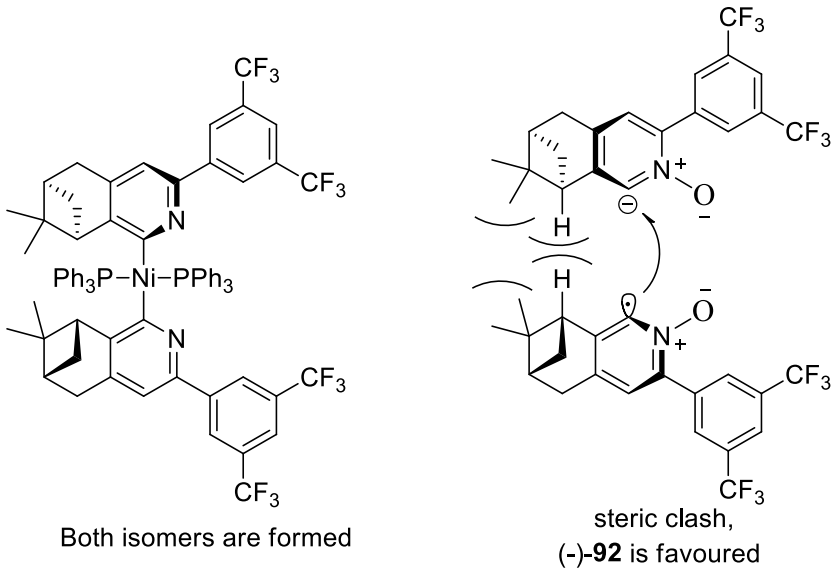


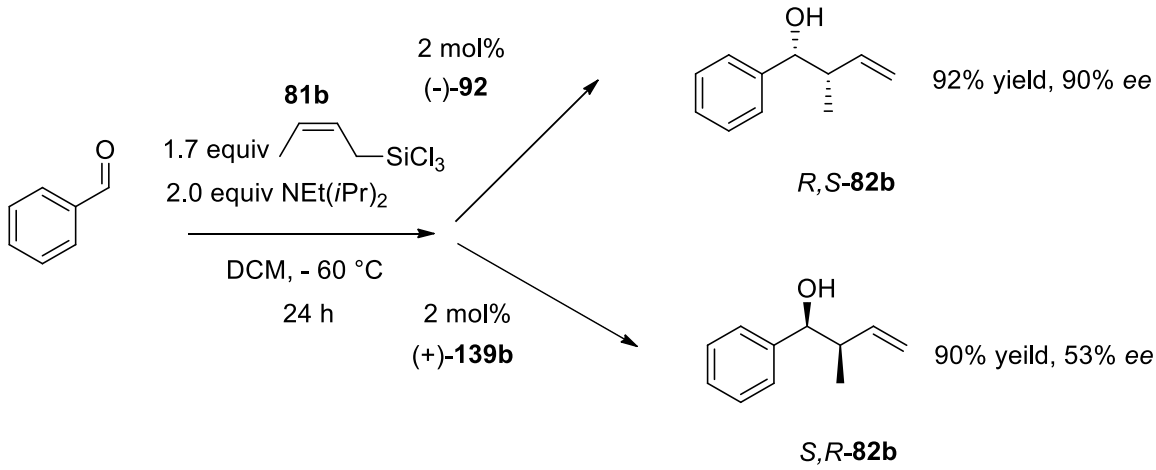
Figure 27

Nevertheless, we decided to perform oxidation of the mixture of bipyridine ligands with an excess of *m*-CPBA and then to separate the bis-*N,N'*-dioxides by column chromatography,

since they have a higher difference in retention factor (R_f). We were able to isolate the two atropoisomers in yields of 30% and 27% for (-)-**92** and (+)-**139b,** respectively. The change of the ratio of the atropoisomer is likely to take place in the acidic conditions during the oxidation by coordination of a proton. The overall yield of the target catalyst (-)-**92** was just 3.4%.

Both catalysts (-)-**92** and (+)-**139b** were tested in the reaction between benzaldehyde and (*Z*)-crotyltrichlorosilane **81b** in DCM at -60 °C. While (-)-MAKDIOX (**92**) gave an expected 90% *ee* of *syn*-alcohol **82b** (slightly reduced due to a little impurity of the axial isomer (+)-**139b** in the catalyst sample), the other diastereomer **139b** gave the opposite enantiomer of **82b** with 53% *ee* (Scheme 62).

The difference in selectivity could be due to a different bite angle for the two catalysts, where the two internal CMe_2 groups affect the structure of the transition state. The *ee* was determined by chiral HPLC and compared with the racemate.[57,153]



Scheme 62

To expand the range of catalysts, we also decided to synthesise other derivatives bearing 2-furanyl (**140**), ethyl ester (**141**) and a bulky 2,4,6-trimethyl phenyl (**142**) groups. (Figure 28) It was decided to follow Ni-mediated coupling route, since at the time the LDA-route was not well reproducible.

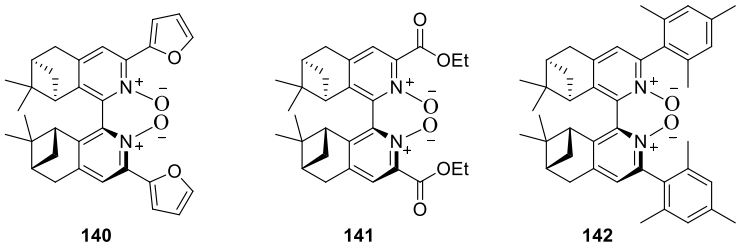
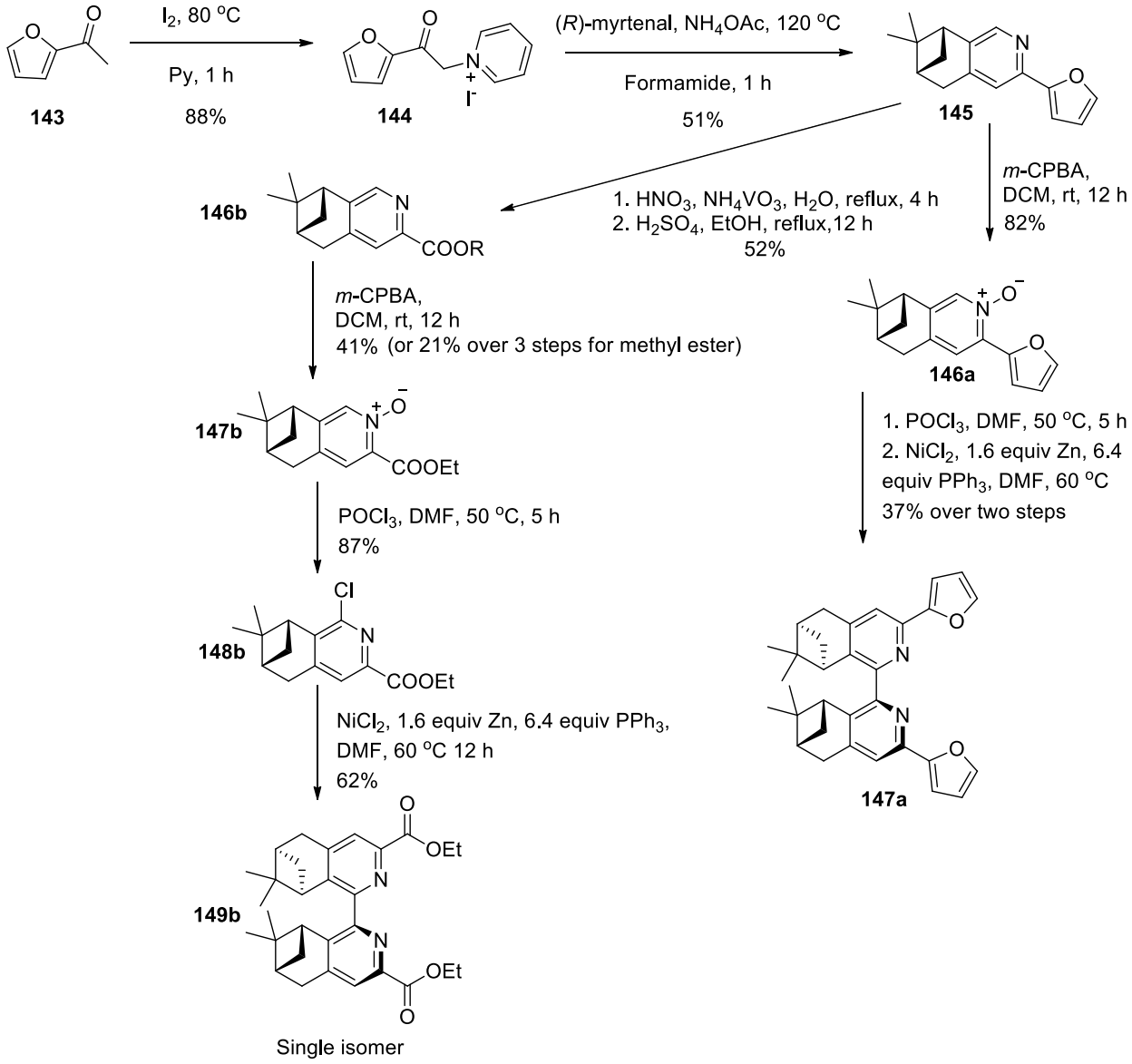


Figure 28



Scheme 63

For the synthesis of catalysts **140** and **141**, we partially adopted the methodology developed by Bernhard *et al*.[154] (Scheme 63). The key step in this procedure is the oxidative

cleavage of the furan moiety, which allows the introduction of a carboxyl function on the catalyst structure.

We began the synthesis with the preparation of the furan Kröhnke salt **144**. The first attempt to follow the procedure from the original paper[154], where the reaction was conducted in a mixture of chloroform and pyridine with bromine, was unsuccessful. Therefore, we repeated the experiment using Iodine and pyridine as a solvent, and the reaction proceeded at an increased temperature (80 ℃) for a shorter time with 88% yield. The content of the Kröhnke salt **144** in the reaction mixture was determined by NMR. The subsequent cyclisation was performed using standard conditions. The reaction proceeded better than in the case of bis-CF_3-substituted substrate **135**, but the yield was still only moderate (51%). The pyridine product **144** was divided into two parts to take forward (Scheme 63).

The first part was carried through the standard sequence of reactions to obtain furan-substituted bipyridine **147a**. *N*-Oxidation of **145** with *m*-CPBA proceeded in good yield (82%). The following deoxychlorination of **146a** provided the 2-chloropyridine derivative exclusively according to ^{1}H and ^{13}C NMR analysis, which was used in the next step without purification. The Ni-mediated coupling was conducted in DMF at 60 ℃, and the target bipyridine **147a** was isolated in 37% yield over the two steps.

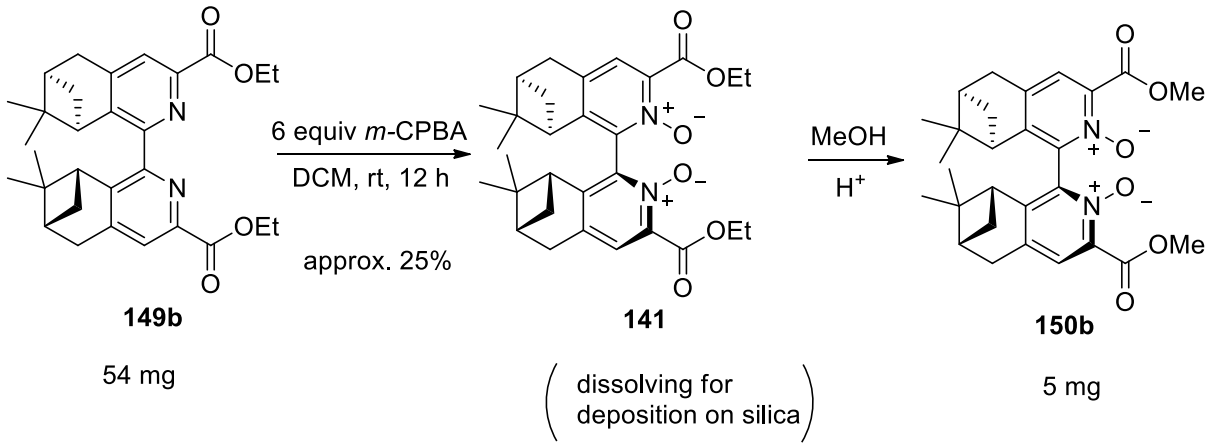
A slightly modified route was used for the preparation of the alternative ester-derived bipyridine **149b**. The oxidative cleavage of furanyl group in **145** as catalysed by NH_4VO_3 was performed under reflux in HNO_3-H_2O mixture. After the evaporation of water at high temperature under vacuum, esterification with ethanol and H_2SO_4 was conducted, and the resulting isoquinoline ethyl ester **146b** was obtained in 52% yield. This step provides an opportunity for varying of ester substituent. We decided to focus on methyl and ethyl esters (R = Me, Et).

Further *N*-oxidation of the resulting ethyl ester **146b** by *m*-CPBA in DCM afforded the corresponding pyridine-*N*-oxide **147b** in 41% yield (Scheme 63). A loss of yield might be associated with partial hydrolysis of the ester because commercial *m*-CPBA contains ~25 mass% of water. Further deoxychlorination provided pure 2-chloropyridine **148b** in 87% yield. The Isolated 2-chloropyridine was subjected to our coupling conditions and target bipyridine ligand **149b** was isolated in 62% yield as a single diastereomer.

With bipyridines **147a** and **149b** in hand, we attempted to perform the *N*-oxidation reaction. Unfortunately, our attempts to synthesise the furan bipyridine *N*,*N*'-dioxide **140** led to complete decomposition of the substrate. It might be associated with higher reactivity of furan group compared to that of pyridine **145** and the use of a large excess of the oxidant.

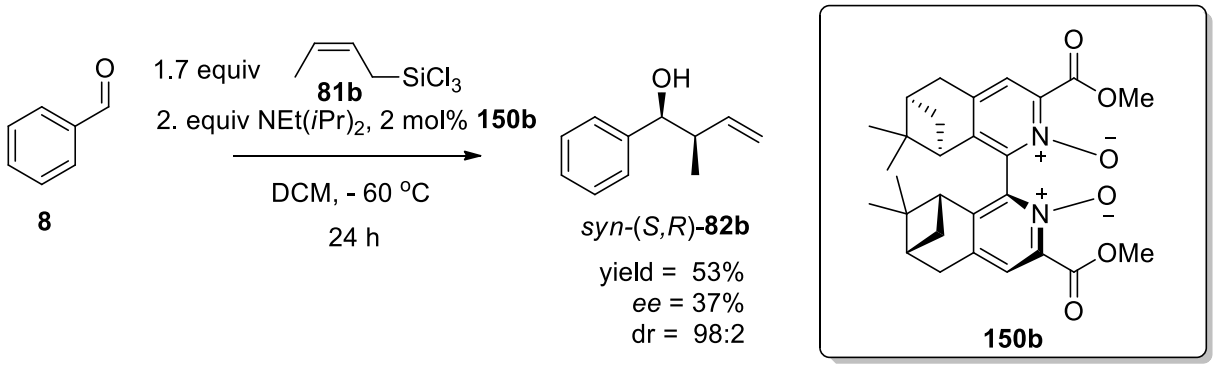
Next we focused on the oxidation of the ester **149b**. Treatment of 2,2-bipyridine **149b** with 6 equiv of *m*-CPBA in chloroform at rt led to the formation of target bipyridine bis-*N*-oxide **141**, which was confirmed by ^{1}H NMR. Unfortunately, the quantity of the starting bipyridine **149b** was so small that we were unable to synthesise the final catalyst on a usable scale.

NMR analysis of the reaction mixture showed the complete conversion to **141**. The axial diastereoisomer could not be detected by ^{1}H NMR of the crude mixture. During the purification of the crude material by chromatography using the methanol-EtOAc mixture as eluent, a complete exchange of Et to Me group took place (Scheme 64).



Scheme 64

Unfortunately, impurities could not be removed on the column, and after washing the sample with sat. $NaHCO_3$, we only obtained 5 mg of the ^{1}HNMR-pure target compound **150b** from 54 mg of the starting material. Nevertheless, this amount was sufficient to run a test crotylation reaction. Benzaldehyde was reacted with (*Z*)-crotyltrichlorosilane **81b** in the presence of catalyst **150b** and 2 equiv of Hünig's base at -60 °C in DCM for 24 hours (Scheme 65).

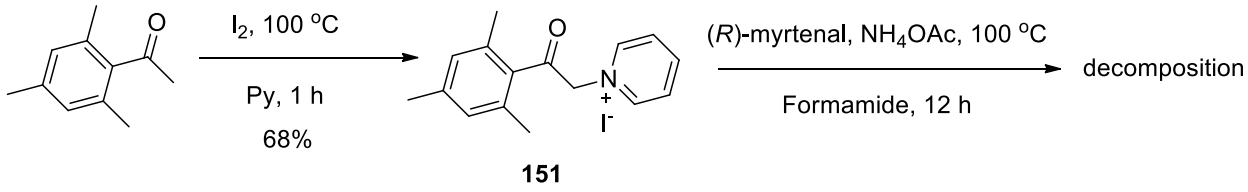


Scheme 65

The *ee* was lower than with MAKDIOX, and to our surprise, the catalysts favoured the formation of the opposite (*S*,*R*) enantiomer of the product **82b**, presumably due to coordination of the ester oxygens to the silicon centre in the transition state. The overall yield was 53%, and the major *syn*-product was obtained in 37% *ee.*

We also attempted to synthesise the bulky catalyst **142**, carrying 2,4,6-trimethyl groups (Figure 28, p. 98).

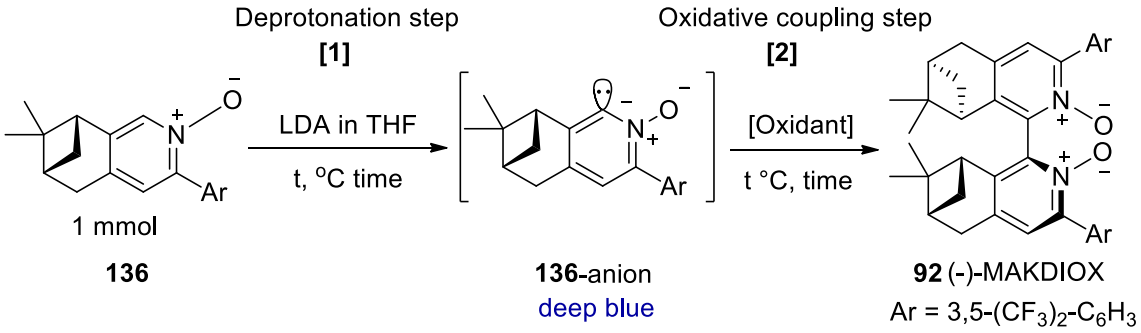
However, despite the Kröhnke salt **151** formation proceeding successfully, further attempts to cyclise it failed to give the desired product. Only the decomposition of starting salt occurred with no detectable traces of the product (Scheme 66).



Scheme 66

Summarising all gained data on Ni-catalysed pyridine coupling reaction, it became obvious that the scope is limited, the practicality and the yields of such protocol are low, the procedures are laborous and long. All this results turned us to the reinvestigation of the original poorly reproducible, but very appealing reaction which was used for the synthesis of MAKDIOX catalyst (-)-**92**.

Whilst in the original report the oxidant (O_2) was added after 30 mins of stirring the deprotonated *N*-monoxide **136**, we initially stirred it for 15-30 minutes, and the results were barely reproducible; thus we decided to optimise the protocol (Scheme 67, Table 9).



Scheme 67

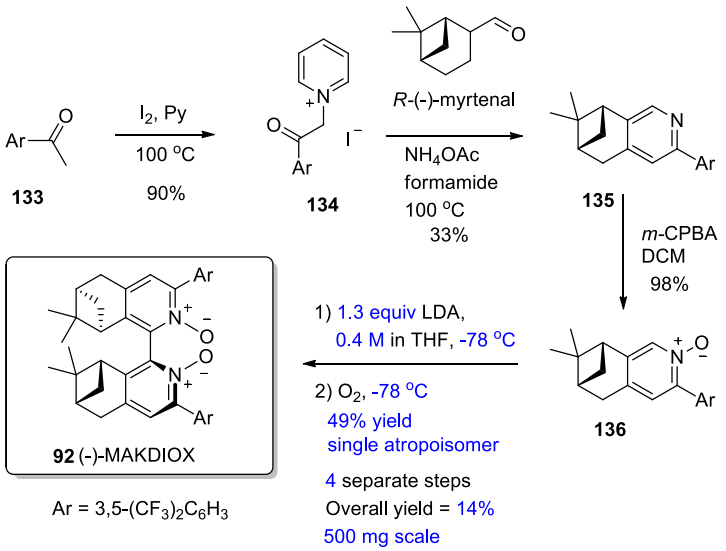
	Deprotonation step				Oxidative coupling step				
Entry	Equiv LDA	Temp, °C	T, hours	THF, mL	Oxidant	Temp, °C	T, hours	Additive	Yield, %
1	1	0 to RT	2.5	20	O_2	RT	24	None	n.r., SM
2	5	RT to 50[a]	18	18	O_2	50	3	None	Decomp.
3	10	0	18	20	O_2	0	12	None	Decomp.
4	1	0	3	20	O_2	0	72	None	Traces, SM
5	1	0	3 min	5	O_2	0	12	CuCl(0.1)	30[b]
6	1	0	3 min	5	O_2	0	12	CuI(0.1)	n.r.
7	1	0	3 min	5	O_2	0	12	$CuCl_2$(0.1)	n.r.
8	1	0	3 min	7.5	O_2	0	12	None	39[b]
9	1	0	1 min	5	O_2	-78	12	None	40[c]
10	1.3	-78	1 min	2.5	O_2	-78	12	None	49[d]

[a]LDA was added dropwise to **136** over 18 hours. [b]*ca.* 5-8% of the corresponding bipyridine mono-*N*-oxide observed.[c]No mono-*N*-oxide observed.[d] 1 gram scale; No bipyridine mono-*N*-oxide observed; 195 mg of SM recovered (68% yield brsm)

Table 9

First, we tried to reproduce the initial conditions (entry 1). A blue colour in the solution (possibly due to bipyridine anion formation) was observed upon addition of starting *N*-monoxide **136** to an LDA solution, but after the reaction was quenched, no product was detected, and the starting material was recovered. Assuming that the problem might be a deprotonation step, we tried to increase the amount of base, the reaction temperature and time (entry 2), but this time the solution turned brown, and a black precipitate was observed in the deprotonation step **[1]**, and after streaming oxygen gas through the mixture, neither product nor starting material were observed. Based on this observation, we decided to lower

the temperature for both steps, and further increase the concentration of LDA (entry 3). Again, complete decomposition of the reactant was observed. Realising that prolonged deprotonation is not necessary, we turned back to the original conditions but increased the reaction time 6-fold (entry 4). This time, a trace of the product was observed by ^{1}H NMR, suggesting that the reaction was progressing very slowly. We also realised that the intense blue colour, which may correspond to the 2-pyridine anion, is developed almost instantly, and there is no need to extend the deprotonation step any further. Therefore, we decided to shorten the deprotonation step to 3 minutes. Another observation was that the concentration of oxygen in the solution might be low, and therefore, reaction the should be performed at a higher concentration. To increase the efficiency of anion oxidation, we decided to use catalytic amounts of CuCl, in the hope that it will react fast with oxygen in the solution and then oxidise the 2-pyridine anion. To our delight, the product was formed in 30% yield, containing a small amount of bipyridine *N*-monoxide as a byproduct (entry 5). Interestingly, both CuI and $CuCl_2$ failed to catalyse the reaction (entries 6 and 7). We decided to run a control experiment without CuCl, but with an instant addition of oxygen, and to our surprise, the reaction worked even better, producing (-)-**92** in 39% yield and a small amount of bipyridine *N*-monoxide as a side product (entry 8). Proposing that bipyridine *N*-monoxide formation may be a result of oxygen atom loss in the process of oxidative coupling, we tackled this problem by lowering the reaction temperature to -78 °C (entry 9). Despite the almost identical yield, this time (-)-**92** was formed exclusively, thus simplifying the isolation process. Trying to maximise the efficiency of the new method, we optimised the amount of deprotonating agent and further concentrated the reaction, which led to the highest achieved yield of 49% (entry 10). The advantage of the newly established method is not only the exclusive formation of single atropoisomer (-)-**92** but also the possibility to recover the starting material, which corresponds to a 68% yield based on the recovered starting material and corresponds to 14% overall yield.



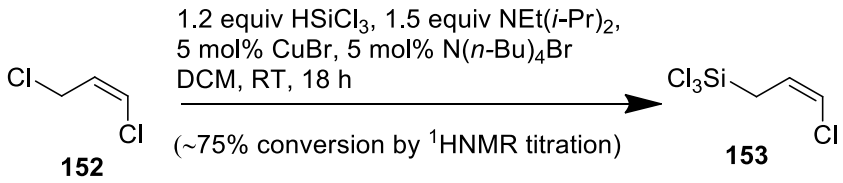
Scheme 68

It is worth noting, that recently a versatile method, for the atroposelective synthesis of axially chiral bipyridine *N,N'*-dioxides was designed in our group, which is based on these original contributions and in which the mechanistic aspects of the reaction were investigated.[155]

4.1.3. Synthesis of *E*- and *Z*-γ-chloroallyl trichlorosilanes

With the effective method for the catalysts synthesis in hand, we decided to focus on asymmetric chloroallylation of aldehydes. This topic is particularly interesting since the products of the reaction can be converted to chiral vinylepoxides that are difficult to synthesise by other methods.

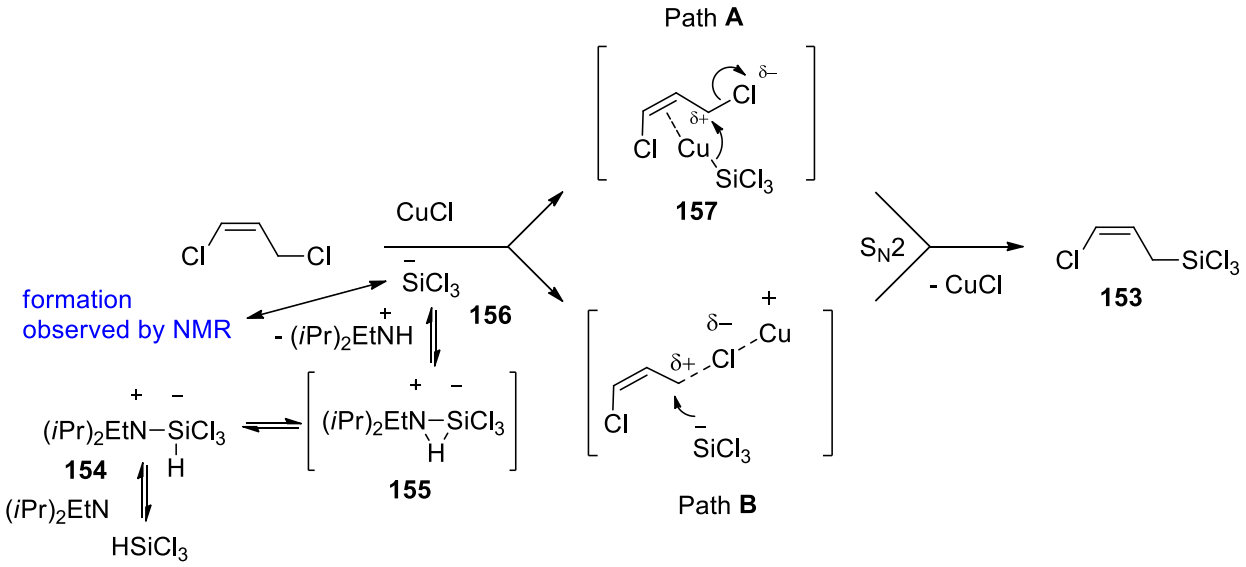
We started preparation of *cis*-γ-chloroallyltrichlorosilane **153** according to the original literature method (Scheme 69).[120]



Scheme 69

The *Z*-1,3-dichloropropene **152** was treated with trichlorosilane under copper-catalysed Benkeser[156]-Furuya[157] hydrosilylation protocol[120] in DCM at rt to furnish a diluted solution of the target *Z*-3-chloroallyltrichlorosilane **153**. The reaction needs a base for activation of

trichlorosilane and proceeds through a polar[158] transition state, which is stabilised by the addition of tetrabutylammonium salt, thus increasing the medium polarity and the rate of the reaction. The resulting silane tolerates trace amounts of moisture that eases the process of its handling (Scheme 69).

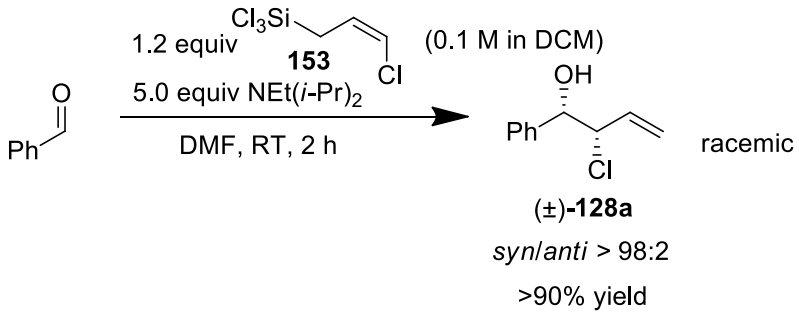


Scheme 70

The reaction mechanism was extensively studied in 1970-1990s. First, according to Bernstein[159], trichlorosilane reacts reversibly with the amine base to produce complex **154**. The ^{1}H NMR kinetic studies showed that at the initial concentration of 1 M of the tertiary amine and trichlorosilane, the equilibrium, where half of trichlorosilane is dissociated, is reached in 5-6 hours. The observed absence of kinetic isotope effect suggests that a hydrogen loss proceeds through a concerted mechanism, while the fact, that the formation of $SiCl_3^-$ ion occurs even at concentrations of 0.01 M suggests that only one molecule of the tertiary amine is involved. All these observations correspond to 1,2-migration of the proton from the silicon to the nitrogen atom in the charged transition state **155**. Next, the protonated amine leaves and the key intermediate **156** is formed, which was evidenced by ^{1}H NMR.[160] Next, the copper-catalysed addition occurs. It may proceed via two different mechanistic pathways.[158] In Path **A**, the transient organocuprate reagent **157** coordinates to the double bond of *Z*-1,3-dichloropropene, and simultaneously a chlorine atom undergoes bimolecular nucleophilic substitution which leads to the formation of target silane **153**. Alternatively (Path **B**), the copper ion polarises allylic C-Cl bond in the *Z*-1,3-dichloropropene and facilitates the substitution by trichlorosilyl anion (**156**), which also gives the target *Z*-γ-chloroallyltrichlorosilane **153**.

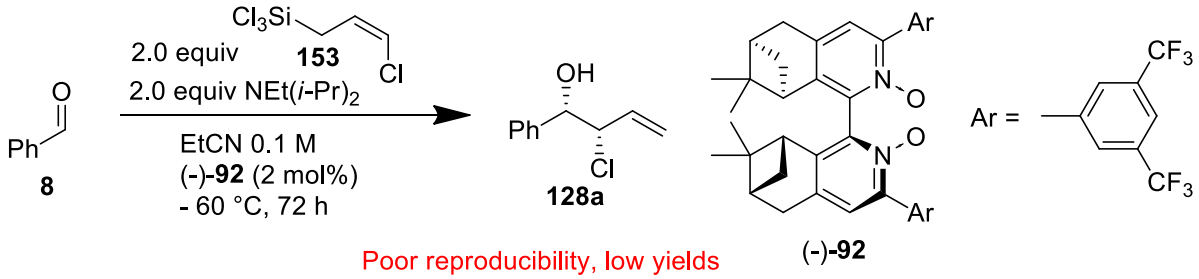
To our delight, the reaction worked well, affording the silane in approximately 75% conversion. The conversion was determined by NMR using internal standard: an exact amount of the resulting reaction solution in DCM was dissolved in 500 µL of $CDCl_3$, and an exact amount of naphthalene was added, and then δ=6.0 ppm double bond signal of the silane was integrated against δ=8.0 ppm signal of the proton in the 2-position of naphthalene. By this technique, the concentration (0.1 M) was determined, and the yield was calculated by measuring the total volume of the *Z*-γ-chloroallyltrichlorosilane solution.

Once the silane reagent **153** was synthesised, we performed the racemic addition of *Z*-silane to benzaldehyde in DMF according to the Kobayashi method[67].



Scheme 71

While the racemic variant of the reaction was successful (Scheme 71), our attempts to perform a catalytic reaction to achieve high yields and enantioselectivities failed (Scheme 72).

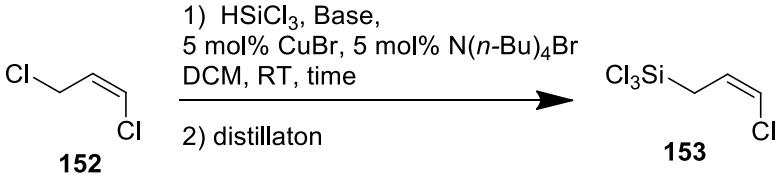


Poor reproducibility, low yields

Scheme 72

The presence of the copper salts in the solution of the reagent may deactivate MAKDIOX (**92**) due to chelation by the highly Lewis basic oxygens of the bis-*N*-oxide. It became clear that the reagent, synthesised by the original methodology, is ineffective in the asymmetric catalytic reaction, and we decided to reoptimise the protocol (Table 10).

Table 10



152 **153**

Entry	Base	Equiv Base	equiv $HSiCl_3$	DCM, mL/mmol	Reaction time, h	Conversion,%	Yield, %	*c* after dist.
1	$N(iPr)_2Et$	1.2	1.4	10	18	100	75(NMR)	0.2M[a]
2	NEt_3	1.2	1.4	10	18	100	0	-[b]
3	NEt_3	1.0	1.1	0.5(Et_2O)	18	0	-	-[c]
4	PS-bound-DIPA	1.4	1.2	2.5	18	50	-	-
5	PS-bound-DEA	1.25	2.8	5	72	95	4	0.05M[d]
6	$N(iPr)_2Et$	1.2	1.4	1	18	20	-	-
7	$N(iPr)_2Et$	1.4	1.8	1	18	70	-	-
8	$N(iPr)_2Et$	2.4	2.8	1	12	100	92	1.2M[e]
9	$N(iPr)_2Et$	2.0	2.4	1	12	100	80	7.35M[f,g]

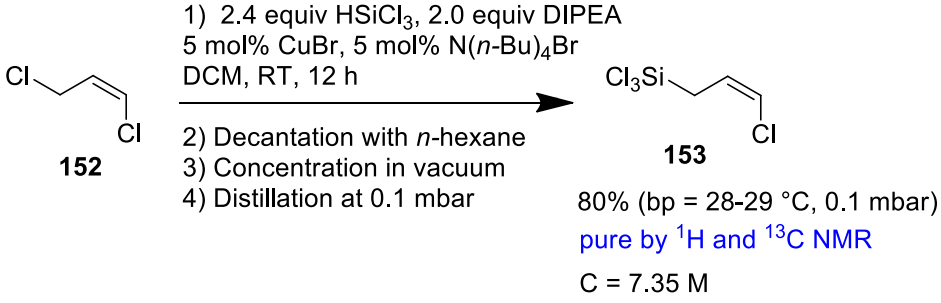
[a] The distillate contained large amounts of *N*,*N*-diisopropylethylamine hydrochloride and the free amine. [b] The silane decomposed during distillation. [c] Allenyl conditions: Et_2O, 5 mol% of CuCl and no $N(n\text{-}Bu)_4Br$. [d] 10 mol% CuBr and 10 mol% $N(n\text{-}Bu)_4Br$. [e] The distillate contained large amounts of free amine and the corresponding hydrochloride. [f] DCM was partially evaporated under vacuum, and the residue was extracted with *n*-hexane and concentrated under vacuum, then distilled two times under 0.1 mbar. ^1H and ^{13}C NMR showed pure **153** (bp = 28-29 °C at 0.1 mbar). [g] Trichlorosilane was added dropwise under -78 °C, and the mixture was allowed to reach RT over the next hour.

First, we tried solvent evaporation and direct fractional distillation of **153**. Unfortunately, due to the very low concentration and partial hydrolysis of the silane, after distillation even at the atmospheric pressure, neither residue nor distillate contained any practically useful amount of **153**. Direct bulb-to-bulb distillation under high vacuum (0.1 mbar) was then tried, using liquid nitrogen to cool the receiving flask. This time all solids (CuBr, TBABr) were separated, but the resulting solution contained a significant amount of distilled base, and the allylation reactions again failed, while the conversion was slightly higher (entry 1). Since the *N*,*N*-diisopropylethylamine has a too close boiling point to that of the target silane **153**, we decided to use triethylamine as a base and achieved full conversion of the starting halide **152** under standard conditions (entry 2). Unfortunately, when we tried to distil the reaction mixture using fractional distillation, the target silane completely decomposed. Next, we attempted to apply method for the synthesis of trichloroallenylsilane,[138] which relies on a similar protocol and uses diethyl ether (which has a lower boiling point) as a solvent, but this reaction also did not work (entry 3). We then come up with an idea to use a commercially available polymer-bound tertiary amine base, since after the reaction the DCM solution of the target silane could be decanted from the reaction mixture (entry 4). Our original proposal was that the best polymer-

bound base should be analogous to DIPEA, which gave the best results at the beginning of this study, and that the reaction should be as concentrated as possible to ease the distillation process and limit environmentally-harmful halogenated solvent waste. Also, we proposed that there should be a slight excess of the base in relation to $HSiCl_3$, to prevent the excess HCl from catalysing the decomposition of **153**. The reaction worked, however, the conversion was only 50%, and we decided to optimise the reaction further. During the tests, several drawbacks of such a methodology were noted. First, a polystyrene-bound diisopropylamine base is significantly (by order of magnitude) more expensive than DIPEA. Second, it is a solid and is insoluble in organic solvents. Third, its amino group content is approximately twice lower than that of Hünig's base based on mass concentration (3.2 mmol/g vs 7.7 mmol/g). Despite these drawbacks, we pushed forward and achieved nearly complete conversion with less expensive solid polystyrene-bound diethylamine base (entry 5). Despite the promising achievement, the reaction required a significantly larger excess of trichlorosilane and extended reaction times. Disappointingly, after decantation and direct bulb-to-bulb distillation of the resulting solution, only 4% of target silane was detected in the solution, and thus the concentration was too low to begin enantioselective tests.

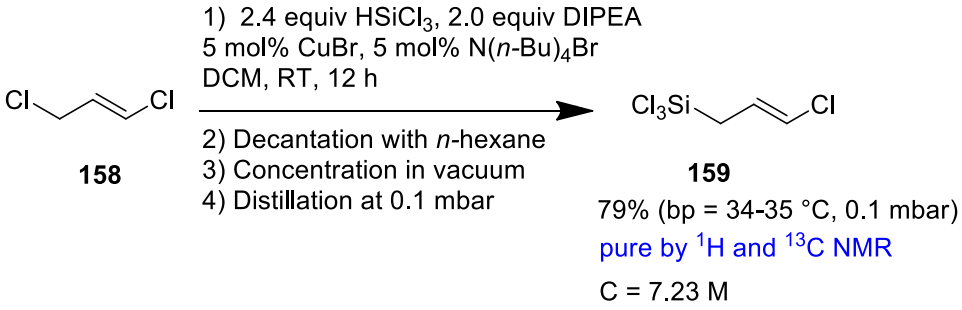
It became clear that a more practical and direct method was required. Hence, we decided to focus on the refinement of the original Leighton's methodology.[120] We took the originally reported conditions and increased the concentration ten times in an attempt to avoid the use of an excessive amount of solvent which complicated the isolation of the target silane, but an 80% drop in conversion was observed (entry 6). We then started to gradually increase concentration the of trichlorosilane, which resulted in a lower (30%) drop of conversion compared to the original conditions (entry 7). Next, we further increased the excess of both Hünig's base and trichlorosilane (entry 8). Delightfully, the target silane **153** was formed in 12 times higher concentration (1.2 M) and was purified by the direct bulb-to-bulb distillation to a liquid nitrogen-cooled receiving flask. This time, the distillate contained significant amounts of target *Z*-γ-chloroallyltrichlorosilane and was highly effective in the asymmetric γ-chlroallylation of benzaldehyde, providing 90% yield and 94% *ee* of *syn*-chlorohydrin **128a** in MeCN-DCM solution at -60 °C in 72 hours. Despite this inspiring result, the silane reagent still contained a significant amount of DIPEA salt, and it could not be used for the optimisation of the solvent since the solvent exchange by evacuation led to the loss in the silane and was impractical. To

tackle this problem and achieve reproducibility, it seemed necessary to isolate the target silane. To do so, we further optimised the conditions and conducted the reaction again at a higher scale (56 mmol) (entry 8). It is important to note that, due to a high concentration and a large amount of trichlorosilane, this highly exothermic reaction has to be initiated at -78 °C, and the silane has to be added dropwise. Another important note is that the loading of $HSiCl_3$ should only slightly exceed the load of the amine base, which should be high enough to precipitate all amine, but low enough not to produce a high excess of free HCl, which negatively affects the yield of the reaction (entry 5). After dropwise addition of the trichlorosilane, the reaction has to be kept at 0 °C for another hour and then can be allowed to warm up to RT. After 12 hours full conversion is achieved. We decided to separate the excess of DIPEA hydrochloride, which complicates the distillation and inhibits the reaction of the target reagent with an aldehyde. In order to achieve this, a larger part of DCM was evaporated under reduced pressure, and the residue was diluted with excess of anhydrous *n*-hexane. A large amount of white precipitate, presumably DIPEA hydrochloride, was formed. After careful decantation, the colourless hexane solution was collected, followed by two additional hexane washes of the precipitate, the combined *n*-hexane solutions were transferred to another flask via a syringe and were concentrated. The resulting concentrate still contained a minor amount of the white precipitate and was transferred into a smaller distillation kit and carefully distilled at 20-70 °C under the pressure of 0.1 mbar. Unfortunately, no stable boiling point was observed, and the ^{1}H NMR analysis of the mixture showed that the distillate contains almost pure silane and DIPEA chloride in a ~1:1 ratio, as well as traces of *n*-hexane. This mixture was distilled again to afford pure **153** as a colourless clear liquid in 80% yield (bp = 28-29 °C, 0.1 mbar). For the ease of use, the concentration of target silane was measured by ^{1}H NMR analysis using naphthalene as an internal standard. These final conditions are shown in Scheme 73.



Scheme 73

Importantly, this particular type of organosilicon reagent has never been reported previously in pure form. By application of the newly established method to *E*-1,3-dichloropropene, we were able to achieve similar satisfactory results (Scheme 74).



Scheme 74

E-γ-chloroallyltrichlorosilane was isolated in 79% yield as a colourless clear liquid (bp = 34-35 ℃ at 0.1 mbar), and also it has not been reported previously in pure form.

With the isolated reagents in hand, we turned our attention to the optimisation of the catalyst.

4.1.4. Optimisation of the catalyst

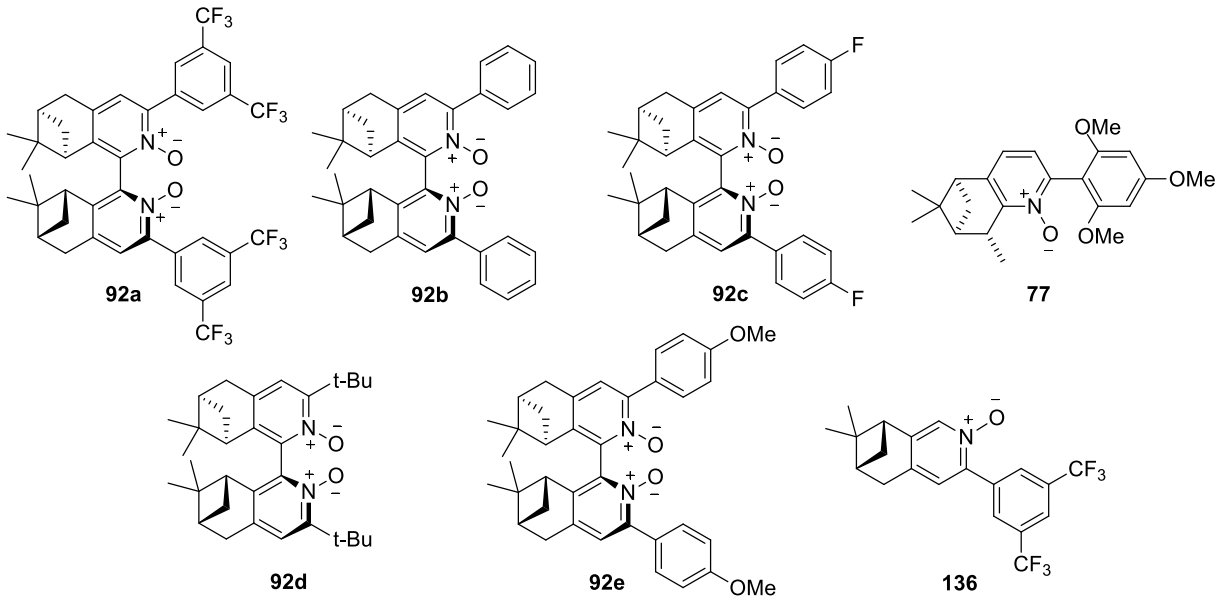


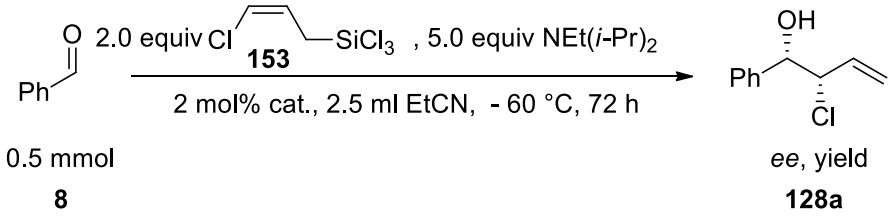
Figure 29

As was mentioned previously, based on the groups developed pyridine-*N*-oxide coupling protocol, the preparation of various catalysts was enabled (Figure 29).[155] Because our laboratory is actively involved in the search for new applications of such catalysts, batch

samples were available to us, which we applied to the optimisation of *syn*-γ-chloroallylation reaction.

MAKDIOX (**92a**) was selected as a reference catalyst, and the following compounds were selected, based on their steric and electronic properties: *N*,*N'*-dioxide **92b** served as a reference; **92c** was selected to study the electron-withdrawing effect without significant steric hindrance; catalyst **92e** was used to study the electron-donating effect of OMe group; and **92d** was selected to study the steric effect of the bulky *t*-Bu group. Catalysts **77** and **136** known to catalyse allylation and crotylation of aldehydes[70] were selected as references for better demonstration of the catalyst activity requirements, posed by the chloroallylation reaction.

The chloroallylation reactions were carried out under standard conditions on a 0.5 mmol scale, using benzaldehyde **8** as a model substrate. The standard conditions included a two-fold excess of *Z*-silane, 5-fold excess of the Hünig's base and 2 mol% of the catalyst in EtCN at -60 ℃ for 72 hours (Scheme 75).



Scheme 75

The results of this optimisation are summarised in Table 11. The conversion was determined by ^{1}H NMR analysis with naphthalene as an internal standard. Enantiomeric excess was determined by chiral HPLC with comparison to the corresponding racemic chlorohydrin.

Table 11

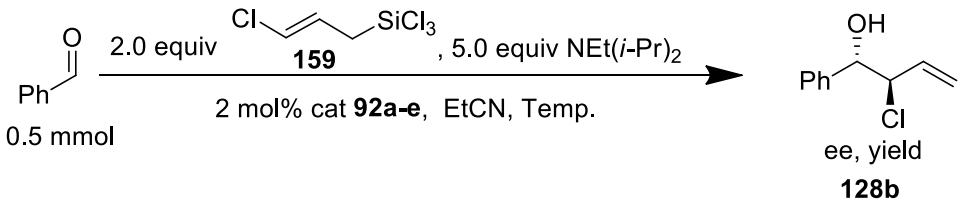
Entry	Catalyst	Conversion (by internal standard), %	% ee
1	92a	99 (90% isolated yield)	95
2	**92b**	99	90
3	**92c**	99	89
4	**92d**	0	-
5	**92e**	29	78
6	**77**	0	-
7	**136**	0	-

Analysis of the enantioselectivities by chiral GC revealed several trends, emerging from the catalyst structure.

The reaction with MAKDIOX (**92a**) provided excellent *ee* and full conversion. The target *syn*-chlorohydrin **128a** was isolated in excellent yield (90%) (entry 1). The experiment with catalyst **92b** also gave full conversion, but the enantioselectivity was slightly lower (entry 2). 4-Fluorophenyl-substituted catalyst **92c** worked analogously to **92b** indicating that the electron-withdrawing group in the 4-position of the catalyst phenyl ring has no significant effect on the reaction outcome (entry 3). Unfortunately, **92d** failed to catalyse the reaction (entry 4). This may be related to the bulky *t*-Bu groups that are shielding the basic oxygen atoms of the catalyst, thus preventing its coordination to silane **153**. Interestingly, 4-methoxyphenyl-derived catalyst **92e** showed significantly lowered conversion and enantioselectivity (entry 5). This might be attributed to the increased stability of the transient complex, due to the increased basicity of the catalyst, thus reducing the effective concentration of the catalyst and lowering the reaction rate and enantioselectivity.[161] Interestingly, an effective catalyst for asymmetric allylation **77** (METHOX) failed to catalyse the reaction. So, while catalyst **77** had limited activity with *Z*-crotyltrichlorosilane,[103] it was unable to catalyse the reaction of γ-bromoallylsilanes[119] or silane **153**, due to the highly deactivated nature of these γ-halogenated reagents (entry 6). Additionally, it was revealed that the last intermediate in the MAKDIOX synthesis, pyridine *N*-oxide **136**, is also ineffective as a catalyst in this reaction (entry 7). These results might be attributed to lower basicity of the pyridine *N*-monoxides in comparison to chelating bypiridine-*N*,*N'*-dioxides.

It can be concluded, that the reaction is facilitated, when the basicity of the catalyst is high enough to activate the silane, (entries 1-3 vs 6-7) but not too high to prevent the transient complex from dissociating effectively after the new C-C bond is formed (entry 5). At the same time, the steric hindrance of the pyridine 2-substituent should provide sufficient steric bias to maximise the *ee* of the product (entry 1) but not too bulky to prevent the reaction (entry 4).

After gaining these results, we focused on the reaction with *E*-γ-chloroallyltrichlorosilane **159**. The same set of catalysts **92a-e** were used (Scheme 76). The results are summarised in Table 12. The conversions were determined by ^{1}H NMR analysis using naphthalene as an internal standard, and enantioselectivities were measured by chiral HPLC.



Scheme 76

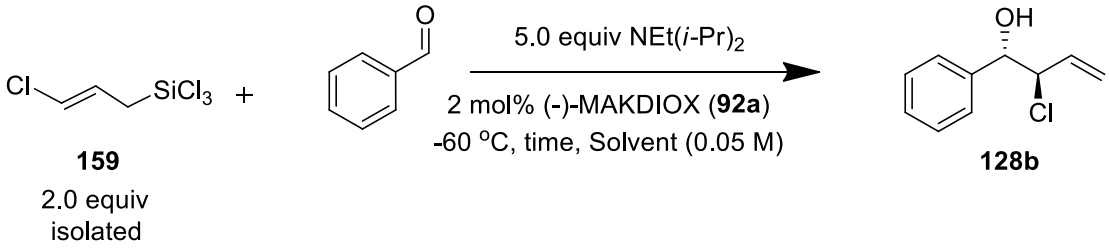
Table 12

Entry	Catalyst	Volume of EtCN	Temp., ℃	Conversion, %	% *ee*
1	**92a**	2.5 mL	-60	40	-
2	**92a**	**10 mL**	**-60**	**83 (78% isolated yield)**	**61**
3	**92b**	10 mL	-60	61	60
4	**92c**	10 mL	-60	58	62
5	**92d**	10 mL	-60	0	-
6	**92e**	10 mL	-60	20	33
7	**92a**	2.5 mL	-90	0	-

E-γ-chloroallyltrichlorosilane **159**, in general, was found to be less reactive and more sensitive to moisture and impurities, than the *Z*-isomer. Thus, in contrast to **153**, which worked even without complete isolation (Table 10, entry 8), silane **159** never gave conversions higher than 10% until it was isolated free from any traces of the DIPEA salt. Based on our experience with *Z*-silane **153**, the initial experiment was performed with MAKDIOX (**92a**), which was expected to provide a good result. However, in contrast to *Z*-γ-chloroallyltrichlorosilane, the reaction with *E*-isomer was not as effective at higher concentration (entry 1). It was then decided to dilute the reaction to 0.05 M. Conversion this time was satisfactory, but the enantioselectivity was only moderate (entry 2). Phenyl substituted catalyst **92b** and 4-fluorophenyl-substituted catalyst **92c** gave slightly lower conversions (58-61%) and *ee*'s (60-62%), following the general pattern observed in the reaction with *Z*-silane **153** (entries 3-4). It shows that the electron-withdrawing group in the *para*-position of the 2-phenyl substituent of the catalyst does not affect the enantioselectivity of the reaction. As expected, the catalyst **92d** did not catalyse the reaction, due to the bulky *t*-Bu groups (entry 5). Catalyst **92e** also followed a similar trend as with the *Z*-silane, but this time both *ee* and conversion were lower (entry 6). The effect of a lower temperature was also investigated (entry 7), however, unfortunately, the reaction did not proceed at all, possibly due to the low solubility of the catalyst.

4.1.5. Optimisation of the solvent

In the attempt to improve the yield and enantioselectivity of the reaction with *E*-γ-chloroallyltrichlorosilane **159**, we took the most effective catalyst **92a** and varied the solvent (Table 13). EtCN, DCM and $CHCl_3$ were selected as the most common solvents used for allylation reactions with chiral bipyridine *N,N'*-dioxides (see Literature Review). The reactions were carried out under standard conditions, as depicted in Scheme 77.



Scheme 77

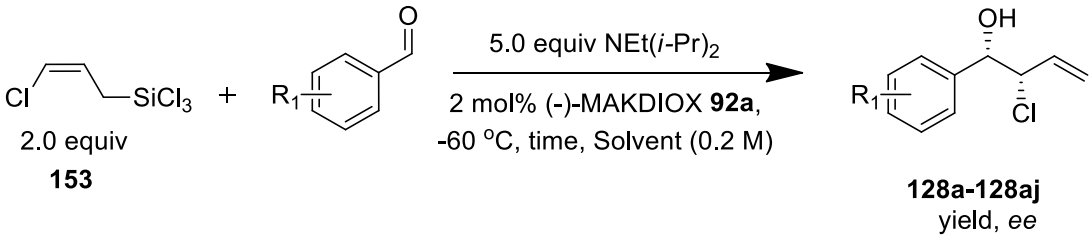
Table 13

Entry	Solvent	Time	Conversion, %	% *ee*
1	**EtCN**	**72 h**	**81**	**61**
2	DCM	72 h	80%	33
3	$CHCl_3$	72 h	40%	n.d.

The reaction in DCM gave good conversion, but enantioselectivity dropped significantly (entry 2). When the reaction was conducted in $CHCl_3$, the conversion dropped (entry 3). Since only EtCN gave satisfactory enantioselectivity and yield, further experiments were conducted in this solvent.

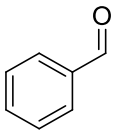
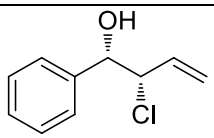
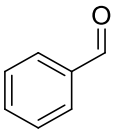
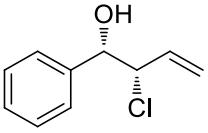
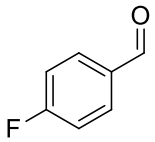
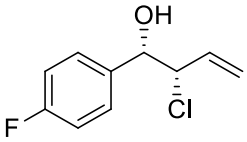
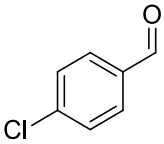
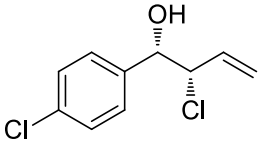
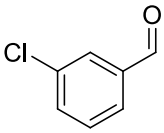
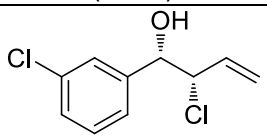
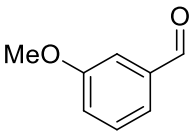
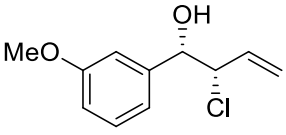
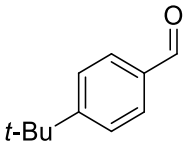
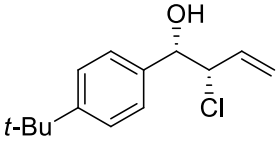
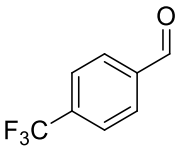
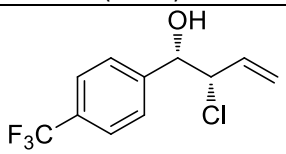
4.1.6. Scope of the asymmetric γ-chloroallylation

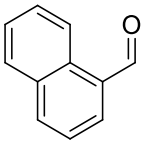
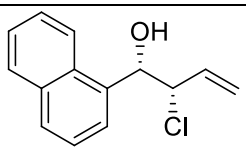
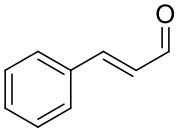
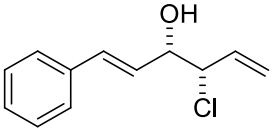
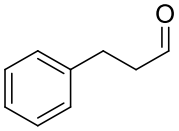
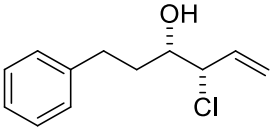
With the optimal conditions in hands, we began to investigate the scope. *Z*-γ-chloroallyltrichlorosilane was tested first because it was expected to better results. The reactions were carried out under standard conditions on a 0.5 mmol scale, with a two-fold excess of silane **153** in 2.5 mL of EtCN or DCM, with 5.0 equiv. of the Hünig's base and 2 mol% of ligand **92a**, at -60 °C for 72 hours. Various aromatic, α,β-unsaturated, and aliphatic aldehydes were used (Scheme 78). The results of the screening are summarised in Table 15.



Scheme 78

Table 14

Entry (product)	Aldehyde	Product **128**	Solvent	Time	Yield, %	ee, %
1		 (**128a**)	EtCN	72 h	90	95
2		 (**128a**)	DCM	72 h	89	88
3		 (**128ab**)	EtCN	72 h	91	93
4		 (**128ac**)	EtCN	72 h	85	91
5		 (**128ad**)	EtCN	72 h	93	78
6		 (**128ae**)	EtCN	72 h	90	91
7		 (**128af**)	EtCN	72 h	76	82
8		 (**128ag**)	EtCN	72 h	90	81

9		 (**128ah**)	EtCN	72 h	66	90
10		 (**128ai**)	EtCN	72 h	50	71
11		 (**128aj**)	EtCN	72 h	30	20

Benzaldehyde afforded the target *syn*-product **128a** in excellent yield and *ee* (entry 1). The use of a less polar solvent DCM led to an insignificant drop in the yield, while *ee* dropped notably, possibly due to a slight decomposition of the silane reagent (entry 2). An electronegative fluorine atom at the *para*-position was well-tolerated, with no notable drop in enantioselectivity and yield being observed (entry 3). An increase in the size of the halogen led to some reduction in yield, but the enantioselectivity remained high (entry 4). The shift of the chlorine substituent to the *meta*-position significantly lowered the enantioselectivity (entry 5). Replacing the *meta*-substituent from an electron-withdrawing to a strongly electron-donating returned the enantioselectivity back to the higher level (entry 6). The introduction of a bulky 4-*t*-Bu group negatively affected both yield and enantioselectivity (entry 7). The strongly electron-withdrawing 4-CF_3 group led to a mild drop in enantioselectivity, while the yield remained high (entry 8). A larger 1-naphthyl aldehyde still provided excellent ee, while the yield dropped to a moderate level (entry 9). The use of α,β-unsaturated *E*-cinnamaldehyde gave a fair yield and moderate *ee,* (entry 10), while the reaction with aliphatic 3-phenylpropionaldehyde was sluggish due to the aldehyde chloroadduct formation (entry 11).

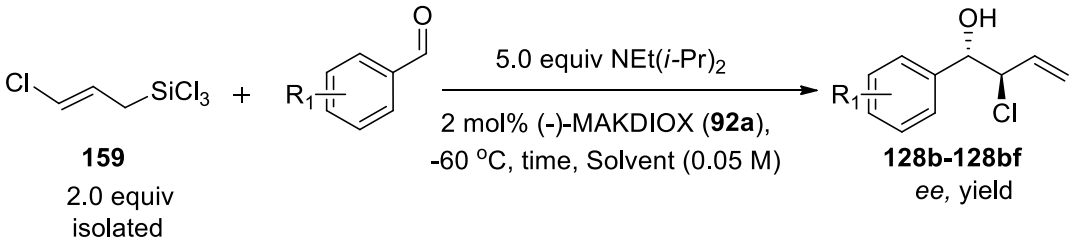
Several general trends can be highlighted. Electron-withdrawing groups on the benzaldehyde slightly reduce enantioselectivity (entries 3-5 and 8). The increase in the size of the substituent in the *para*-position reduces the enantioselectivity and the yield (entries 3-4, 8 and 7), with the largest *tert*-butyl group having the most negative effect on the yield and enantioselectivity (entry 7). On the other hand, a larger but flat molecule such as 1-

naphtaldehyde, shows high *ee* but lowered yield (entry 9). The reaction efficiency and enantioselectivity significantly decreased with an α,β-unsaturated aldehyde (entry 10) and reached its minimum with an aliphatic aldehyde (entry 11).

After these results were obtained and analysed, we focused on the reactions with *E*-γ-chloroallyltrichlorosilane (**159**). The reactions were carried out using the optimal conditions, and the only difference to *syn*-allylation with **153** was a lower concentration of the reactants (Scheme 79).

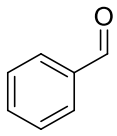
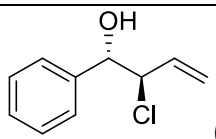
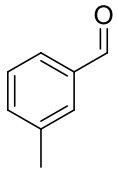
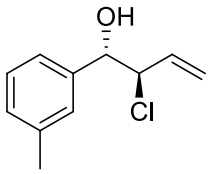
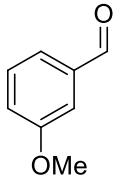
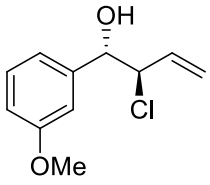
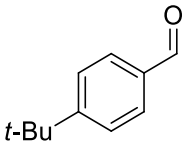
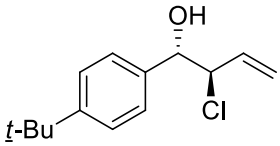
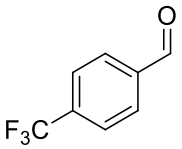
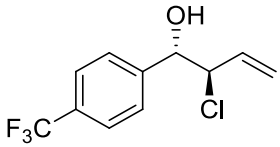
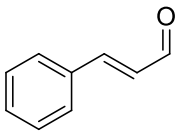
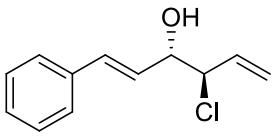
The reaction with benzaldehyde **8** provided the target *anti*-halohydrin **128b** in good yield and moderate selectivity (entry 1). A methyl group in *meta*-position of the aldehyde led to a 20% drop in yield, while enantioselectivity remained unchanged (entry 2). Changing the *meta*-substituent to a donating methoxy group increased the yield, while the enantioselectivity dropped (entry 3). A bulky *tert*-butyl group in *para*-position led to a slight drop in enantioselectivity and yield (entry 4) compared to the reaction with benzaldehyde, while introduction of a strongly electron-withdrawing *para*-trifluoromethyl group led to an even further drop in yield and enantioselectivity (entry 5). Following the similar trend observed with the *Z*-γ-chloroallyltrichlorosilane, α,β-unsaturated *E*-cinnamaldehyde gave fair yield and poor enantioselectivity, which were the lowest in the whole set.

Based on these results, we tried to rationalise the observed reactivity.

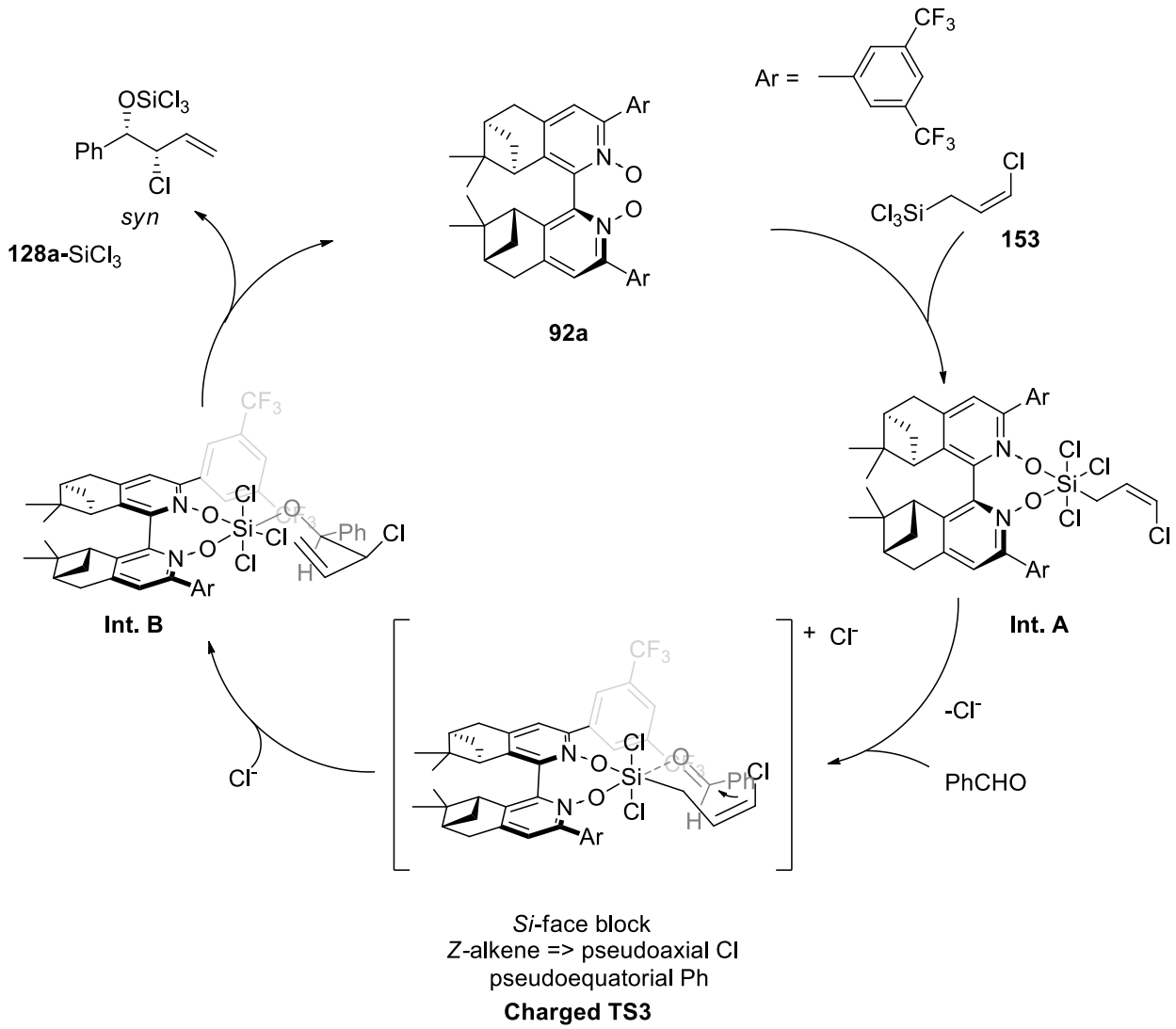


Scheme 79

Table 15

Entry (product)	Aldehyde	Product	Solvent	Time	Yield, %	% *ee*
1		 (**128b**)	EtCN	72 h	80	61
2		 (**128bb**)	EtCN	72 h	60	60
3		 (**128bc**)	EtCN	72 h	83	50
4		 (**128bd**)	EtCN	72 h	70	52
5		 (**128be**)	EtCN	72 h	64	45
6		 (**128bf**)	EtCN	72 h	51	40

The reaction proceeds through a cyclic Zimmerman-Traxler transition state **TS3** (Scheme 80). The aldehyde is coordinated to a Lewis acidic silicon atom of the γ-chloroallyltrichlorosilane **153** (Intermediate **A**). The enantioselectivity of the reaction is likely to be controlled through the bidentate coordination by the catalyst (**TS8**). The bulky aromatic substituent on the bipyridine-*N*,*N'*-dioxide moiety blocks one enantiotopic face of the aldehyde, and the *Z*-γ-chloroallyl group attacks the electrophilic carbon atom of the carbonyl group (**TS3**). In this arrangement, the *cis*-chlorine atom of the attacking allyl group is occupying a pseudoaxial position. After the addition is complete, the complex (Intermediate **B**) is broken down, and the catalyst **92a** is liberated.

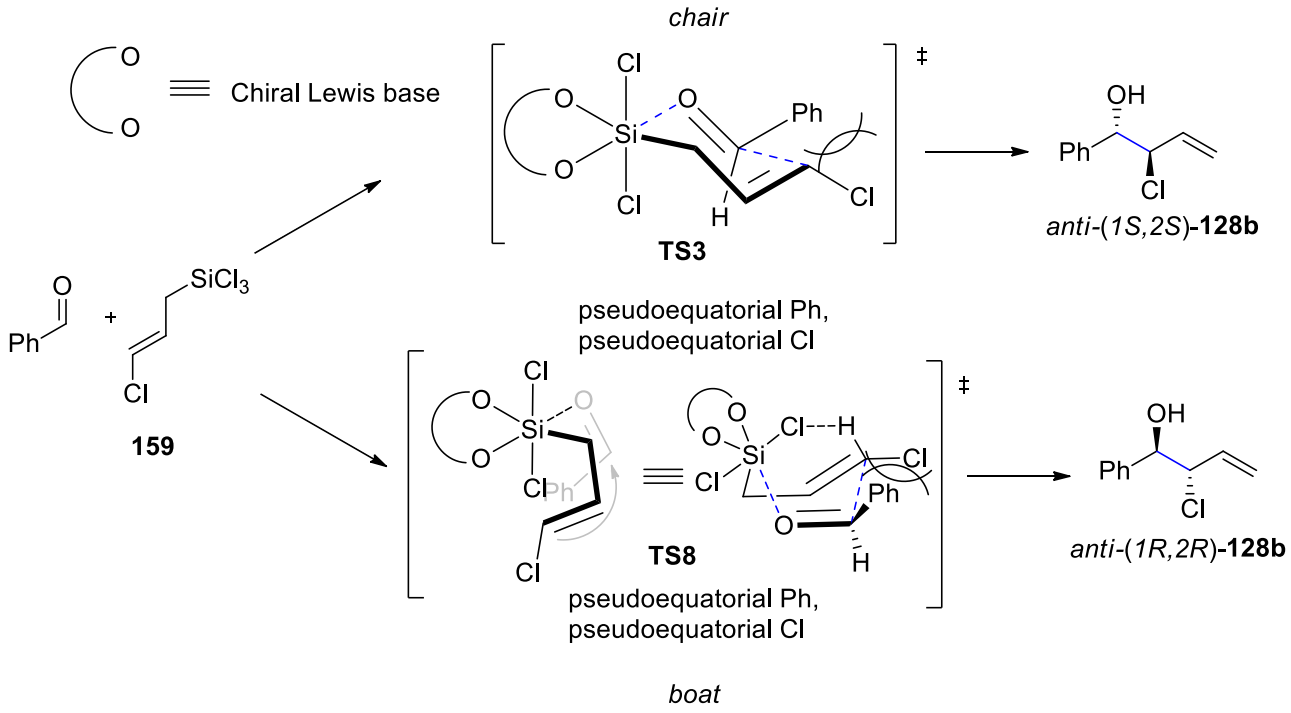


Scheme 80

In contrast to the reaction of aldehydes with *Z*-γ-chloroallyltrichlorosilane (**153**), the reaction with *E*-γ-chloroallyltrichlorosilane (**159**) may proceed through two different competing transition states.

The first transition state fits in the classical chair-like Zimmerman-Traxler transition state **TS3**, which leads to major (*1S*,*2S*)-product (Scheme 81). The second competing transition state might be a boat-like transition state **TS8** (Scheme 81), which is less common but might be more favoured due to the steric arrangement of the chiral pockets and possible stabilising interaction of vinylic proton with chloride atom on silicon. This transition state leads to the formation of the opposite enantiomer of **128b**. In both, chair- and boat-like transition states,

Ph-group of the aldehyde and Cl atom of the reagent occupy more favourable pseudoequatorial position.

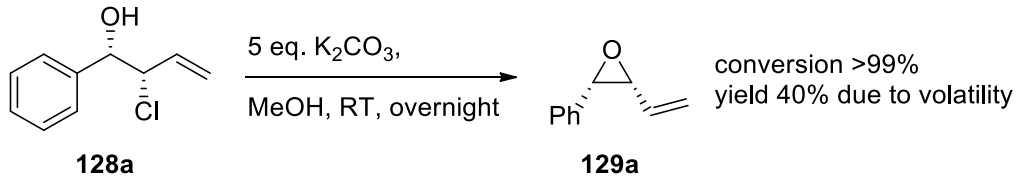


Scheme 81

As a result, *ee* in the case of *E*-γ-chloroallyltrichlorosilane (**159**) is significantly lowered in comparison to the reaction with *Z*-γ-chloroallyltrichlorosilane (**153**).

4.1.7. Formation of vinylepoxide

To illustrate the practical value of our method, we performed cyclisation of the *syn*-chlorohydrin **128a** by treating it with anhydrous potassium carbonate in methanol at rt (Scheme 82).



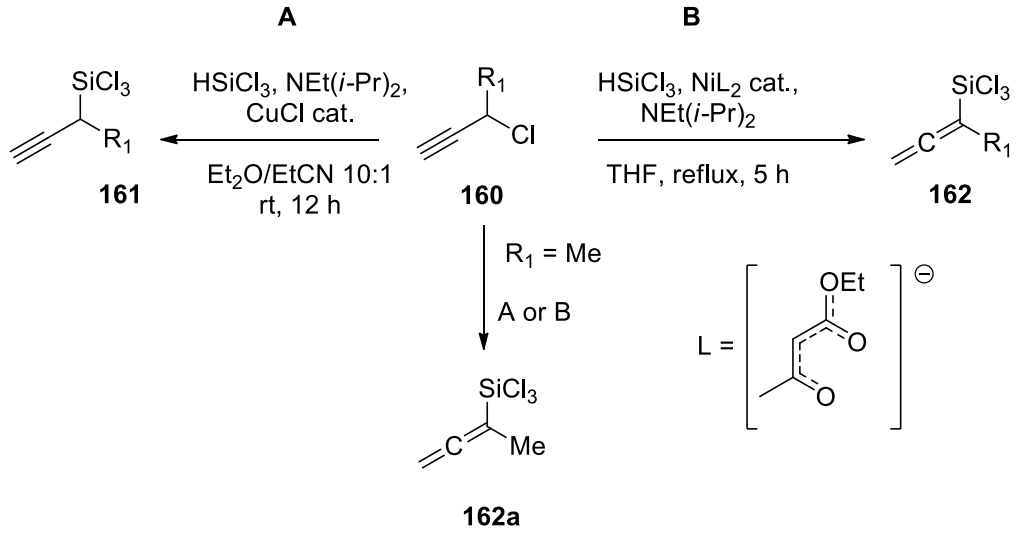
Scheme 82

The reaction proceeds smoothly furnishing the corresponding *cis*-vinylepoxide with complete conversion. However, due to the high volatility of the product, the isolated yield was decreased.

4.1.8. Synthesis of allenyl- and propargyltrichlorosilanes and their reactions with benzaldehyde

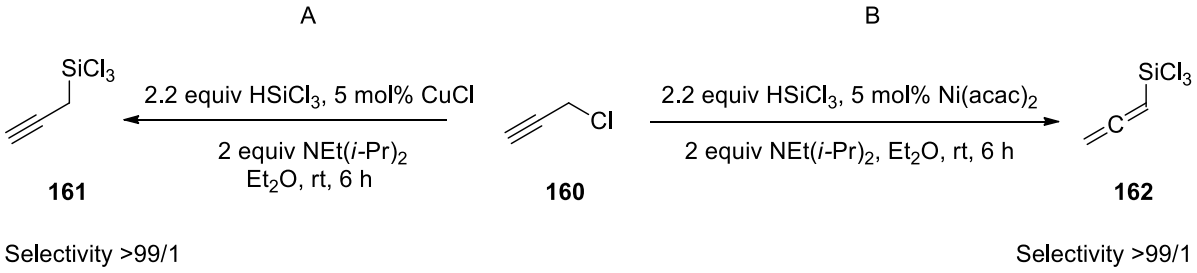
The original method for the selective preparation of allenyl- and propargyltrichlorosilanes was described by Kobayashi back in 1995.[139]

The method is based on selective reactions between trichlorosilane and propargyl chloride **160**, catalyzed either by CuCl in Et_2O/EtCN with NEt(*i*-Pr)$_2$ as a base at rt, leading to selective formation of propargyltrichlorosilane **161**, or by refluxing the reagent in THF with Ni(II) salts and NEt(*i*-Pr)$_2$ resulting in the formation of allenyltrichlorosilane **162**. Both methods gave high chemoselectivity over 30/1. It was noted, that if a propargylic proton is substituted by an alkyl group, then, regardless of the catalyst and the conditions used, the reaction proceeds towards the substituted allene **162a** (Scheme 83).

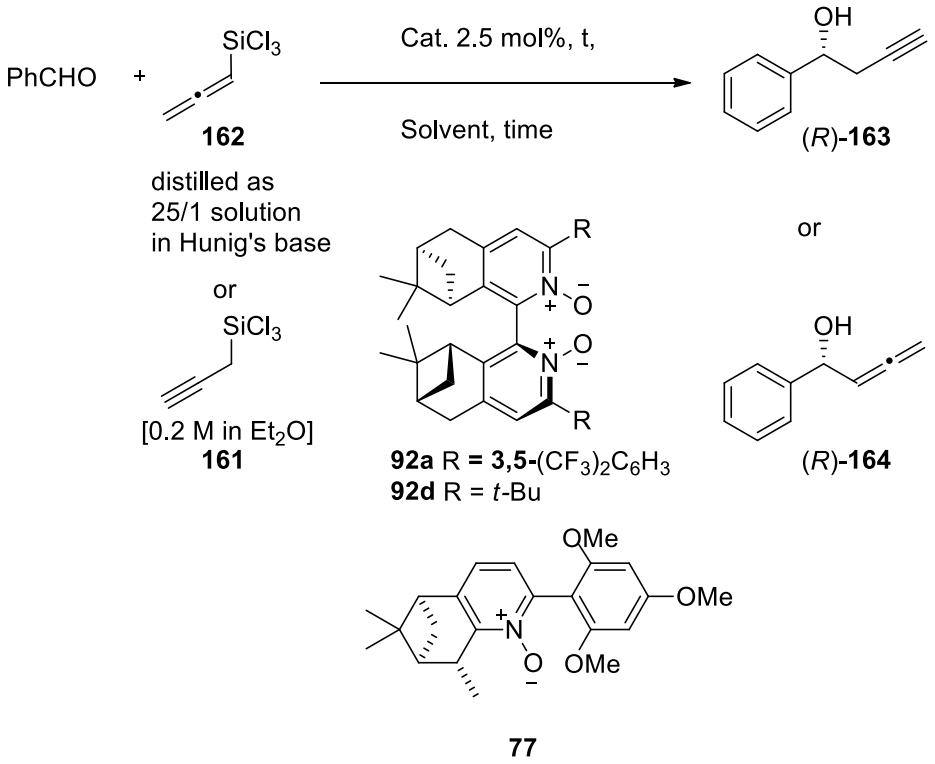


Scheme 83

Later, this method was simplified and improved by the same group.[137] The new method (Scheme 84) seemed much more appealing since it was more practical and more efficient. In contrast to the original method, which used a mixture of solvents and different conditions and bases for the selective preparation of **161** and **162**, the improved method unified conditions and improved selectivity, which was adopted by us for the synthesis of the reagents.



Scheme 84



Scheme 85

Table 16

Entry	Silane	Equiv	Cat.	mol%	T, °C	Solv.	Time	Conv.	**164**	**163**	Yield	*% ee* **163**	*% ee* **164**
1	**161**	1.7	(-)-**92a**	2	-40	DCM	48h	30%	72	28	-	70	26
2	**161**	1.7	(-)-**92a**	2	-40	DCM	18h	>90%	71.4	18.6	-	78	1
3	**162**	1.7	(-)-**92a**	2.5	-60	DCM	18h	75%	<1	>99	-	91	-
4	**162**	1.7	(+)-**77**	10	-60	DCM	18h	0	0	0	-	-	-
5	**161**[a]	1.5	(-)-**92a**	2.5	-45	DCM	18h	75%	>99	<1	66%	-	-[b]
6	**161**[a]	1.5	(-)-**92d**	2.5	-60	DCM	16h	<1%	-	-	-	-	-
7	**162**	1.5	(-)-**92d**	5	-60	DCM	18h	<1%	-	-	-	-	-
8[c]	**162**	1.5	(-)-**92a**	12.5[c]	-40[c]	DCM	24h[c]	90%[c]	<1	>99	-	78	-

[a] The reagent was distilled. [b] HPLC Chromatogram was too complicated to analyse. [c] Initial conditions: 2.5 mol% cat., -60 °C, 16 h; conversion = 0. After observation of zero conversion, another 10 mol% of **92a** was added, and the reaction temperature raised to -40 °C, and the reaction was stirred for additional 8 h.

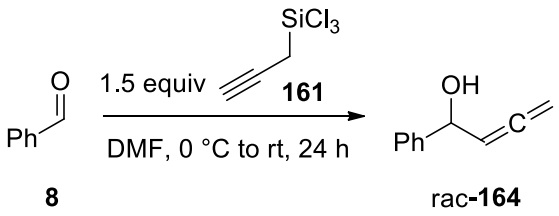
Although this methodology seemed very simple, we faced a number of difficulties during the preparation of reagents. First, it was realised that the resulting allenyl- and

propargyltrichlorosilane are extremely sensitive to moisture. Our initial attempts using commercial dry metal catalysts and solvents failed. We found that the Et_2O must be distilled directly prior to its use and kept in a sealed flask over MS 4Å. Also, commercial CuCl must be redissolved in HCl and precipitated, and subsequently separated from $CuCl_2$, and then dried and stored in a greased Schlenk tube under argon. It must be white or bluish colour, with no traces of green-coloured $CuCl_2$. We also noticed that it was not enough to store Hünig's base over MS 4Å to dry it, instead it must be distilled from solid KOH and then stored in a sealed container over oven-dried MS 4Å. Additionally, all glassware must be dried before use, and it should not be exposed to prolonged contact with humid air after it was removed from the oven.

When we finally managed to synthesise propargyltrichlorosilane (**161**) under these conditions, we used dry $CDCl_3$ and naphthalene as an internal standard for concentration determination by ^{1}H NMR analysis. It was necessary to dilute the resulting trichlorosilanes **161** and **162** with the deuterated solvent to obtain informative spectra since impurities of *d*-metals significantly reduced the quality of the spectra. However, the more the sample was diluted, the less accurate were the measurements, because trichlorosilanes partially decomposed in contact with traces of water from $CDCl_3$. Nonetheless, the NMR yield of propargyltrichlorosilane **161** was measured to be 56%.

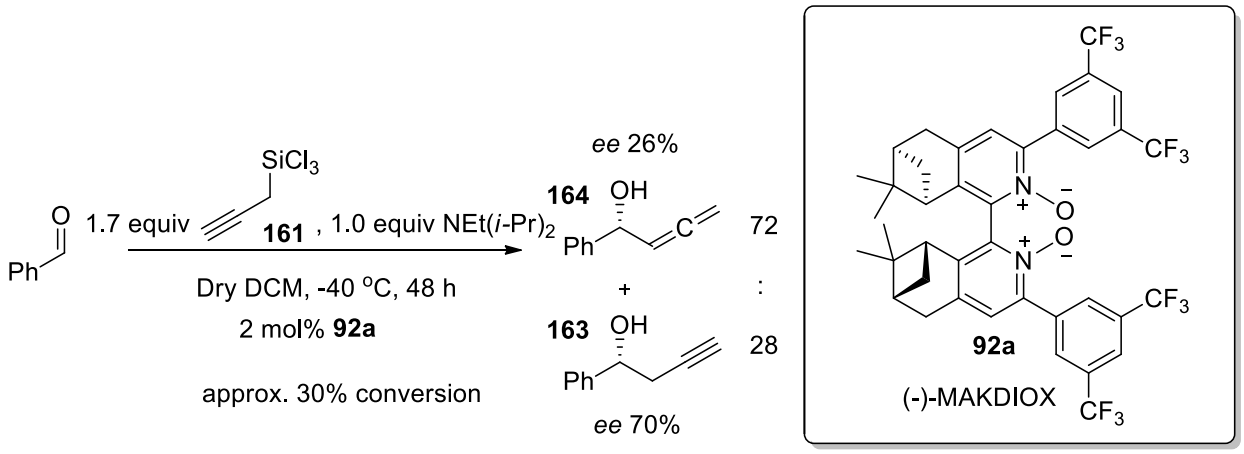
Since propargyltrichlorosilane **161** is known to isomerise to a more thermodynamically stable allenyl isomer **162** upon distillation[139], it was decided not to distil it, but to decant and concentrate it. We hoped that since CuCl is insoluble in Et_2O, it would settle at the bottom of the flask, and thus the silane solution could be collected. Hünig's base is needed for binding HCl in the addition of trichlorosilanes **161** and **162** to aldehydes, so there was no need to separate it from the other reagents. Based on our experience with γ-chloroallyltrichlorosilanes, where allylation did not proceed until a suitable concentration of reagent was used, we decided to concentrate the decanted reagent by evaporation of the solvent under slightly reduced pressure. The concentration of the propargyltrichlorosilane **161** was then determined to be 1.87 M by ^{1}H NMR analysis with naphthalene as an internal standard.

With propargyltrichlorosilane reagent **161** in hand, we turned our attention to a racemic reaction with benzaldehyde in DMF at rt (Scheme 86). The reaction proceeded smoothly in agreement with the literature. The product was used as a reference for chiral HPLC analysis.



Scheme 86

Next, we began our investigation on the asymmetric variant of the reaction using (-)-MAKDIOX (**92a**) as a catalyst. The reaction conditions used were similar to those reported for crotylation (Scheme 87).



Scheme 87

Unfortunately, the conversion was low even after 48 hours. Nonetheless, the resulting allenic alcohol **164** showed some enantioselectivity. However, the product was significantly contaminated by its homopropargylic isomer **163**, which was formed in higher *ee* (70%). We assumed, that these factors (low conversion, low selectivity and presence of the isomer) are mostly due to partial isomerisation of propargyltrichlorosilane **161** and deactivation of the catalyst **92a** by the traces of copper(I) chloride, which strongly binds to bipyridine *N,N'*-dioxide ligand, thus significantly reducing the effective concentration of the catalyst.

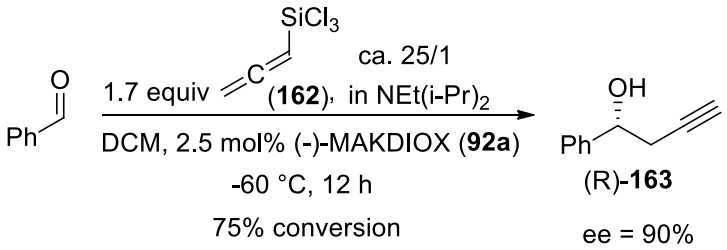
Another important observation was that despite the isomerised allenyltrichlorosilane **162** being in lower quantity, it reacted faster, producing a significant amount of the homopropargylic alcohol **163** in higher *ee*. This led us to the suggestion, that while propargyltrichlorosilane **161** cannot be distilled, its allenyl isomer **162** can be, so we should distil it and run the reaction under salt-free conditions at low temperatures.

Allenyltrichlorosilane **162** was prepared selectively by a similar procedure using $Ni(acac)_2$ as a catalyst. Formation of the target silane was confirmed by ^1H NMR analysis with naphthalene as an internal standard. Although the conversion was always complete, the concentration of the synthesised allenyltrichlorosilane **162** remained low. The best NMR yield was only 17%, possibly due to residual moisture in nickel catalyst and hydrolysis of the target silane.

We adopted the procedure that was used for isolation of **153**. First, we separated the ether solution of allenyltrichlorosilane **162** from its solids by filtration using a special hermetic glass filter operated under an inert atmosphere. It must be noted that because of the high sensitivity to water, the filtration cannot be performed on silica or cellulose, since these absorbents contain a significant amount of moisture. Next the ether was evaporated at a slightly reduced pressure and distilled under high vacuum using a dry-ice-cooled receiving flask.

The resulting pure colourless distillate contained a solution of allenyltrichlorosilane **162** and Hünig's base, *ca.* 1/25. The molar concentration was determined to be 0.44 M by ^1H NMR using naphthalene as an internal standard.

Since Hünig's base is needed in the reaction to bind HCl, which can deactivate Lewis base catalyst, there is no need to separate it from the distillate.



Scheme 88

Benzaldehyde was reacted with a slight excess of silane **162** in a DCM-NEt(*i*-Pr)$_2$ mixture, which corresponds to approximately a 40-fold excess of Hunig's base, in the presence of 2.5 mol% of (-)-MAKDIOX (Scheme 88). To our delight, the reaction proceeded with excellent enantioselectivity (90% *ee)*. We believe this result can be further improved because the catalyst contained some impurity of atropoisomeric compound (+)-**139b**. It can be avoided by using the oxidative coupling 4-step protocol for catalyst preparation.

This result indicates that the new catalyst could potentially promote asymmetric addition of allenyltrichlorosilane **162** to aromatic aldehydes with excellent selectivities and yields.

4.2.Conclusion

A highly chemo- and stereo- selective method for oxidative dimerisation of monomeric chiral pyridine *N*-oxides enabling gram-scale synthesis of atropisomeric *N,N'*-dioxide **92a** was developed. The method is significantly more effective and practical compared to the classical methodology based on Ni-catalysed coupling. The novel catalyst showed high activity and good to excellent enantioselectivity for a wide range of aromatic aldehydes in the reaction with deactivated γ-chloroallyltrichlorosilanes and challenging allenyltrichlorosilane reagent.

A new efficient method for the stereoselective syntheses of homoallylic *syn*-chlorohydrins was developed. The scope of the reaction was studied in detail; the effect of the catalyst structure on the reaction yield and enantioselectivity was investigated, as well as the effects of solvent and temperature. The purity of silane was found to be crucial for the reaction enantioselectivity and efficiency. A new protocol for practical isolation of γ-chloroallyltrichlorosilanes in pure form was designed, and the corresponding *E*- and *Z*-silanes were characterised by ^{1}H and ^{13}C NMR. The synthetic utility of the method was demonstrated by successful synthesis of *anti*-chlorohydrin **128a** followed by cyclisation into corresponding chiral *cis*-vinylepoxide.

Additionally, an efficient reaction of unstable and moisture-sensitive allenyltrichlorosilane **162** with benzaldehyde was described. The reaction yielded highly enantioenriched homopropargyl alcohol **163**, which highlights the synthetic potential of the reaction and shows the broad applicability of catalyst **92a**.

Chapter 5: Experimental part

General Procedures

Unless otherwise noted all reactions were performed under inert atmosphere (vacuumed flushed with nitrogen 3 times or flushed with argon). Analytical grade solvents were used without additional purification. All reagents were purchased from commercial sources, were of reagent grade, and were used as received. Liquid ammonia was condensed from gas using dry ice-filled condenser. For reactions carried out under inert conditions, the argon was previously dried through a column of P_2O_5 and a column of KOH and $CaCl_2$. All the glassware was dried for 12 hours prior to use in an oven at 140 ℃, and allowed to cool under a dehumidified atmosphere. For flash and column chromatography Silicycle 40-63, 230-400 mesh silica gel was used. Yields are given for isolated products showing one spot on a TLC plate and no impurities according to the NMR spectrum.

TLC: All reactions were monitored by TLC on aluminium plates with Merck Kiesel 60 F254 silica gel as the stationary phase. TLCs were visualised by UV radiation at a wavelength of 254 nm, and stained by exposure to a saturated potassium permanganate aqueous solution.

NMR: ^{1}H, ^{13}C and ^{19}F NMR spectra were acquired at 25 ℃ at 400 or 500 MHz for ^{1}H, 100.6 or 75.5 MHz for ^{13}C with $CDCl_3$(7.26 ppm for ^{1}H NMR, 77.0 ppm for ^{13}C NMR) as an internal standard. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals.

IR: Infrared spectra (IR) were measured in a Jasco FT/IR 4100, a Perkin-Elmer 1600 and a Perkin-Elmer Spectrum BX apparatus, in the interval between 4000 and 400 $cm^{-1}$with a 4 cm^{-1} resolution in the KBr discs unless otherwise stated.

HRMS: High-resolution mass spectra (HRMS) on an Acquity UPLC coupled to a QTOF mass spectrometer (SYNAPT G2 HDMS) using electrospray ionisation (ESI^+or ESI^-).

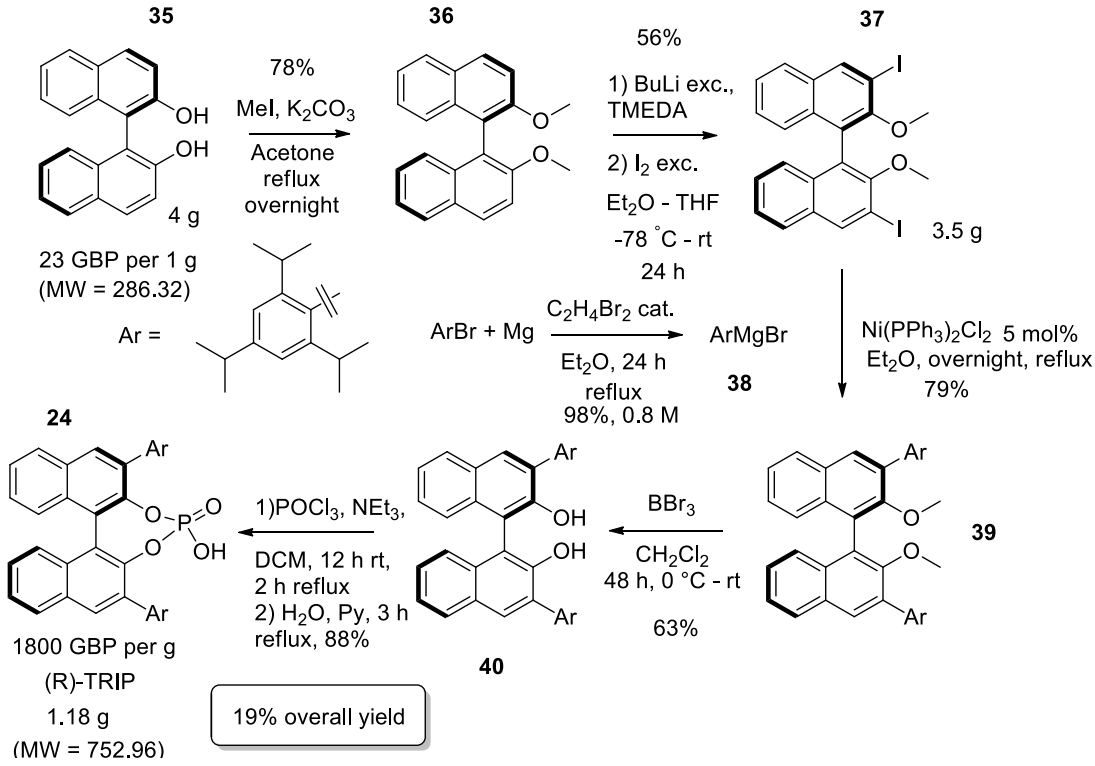
HPLC: High-performance liquid chromatography on a chiral stationary phase was performed using Daicel *Chiralpak IA-3, IB-3* and *IC-3* (0.46 cm x 25 cm); specific conditions are indicated for each case.

Chiral GC: Chiral GC analysis was performed using HP 6890 Series GC System with helium as a carrier gas and hydrogen flame ionisation detector on Supelco α-DEX 120, Supelco β-DEX 120 or Supelco γ-DEX 120 columns.

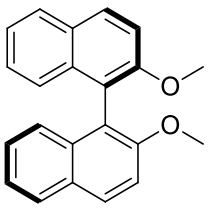
Anhydrous solvents and reagents: Anhydrous solvents were purified and dried with activated molecular sieves prior to use. Toluene and DCM were distilled from calcium hydride. THF and diethyl ether were distilled under argon atmosphere from the sodium/benzophenone and used directly after that. Petroleum ether and *n*-hexane were distilled from anhydrous molecular sieves. DMF was distilled from P_2O_5 under high vacuum and stored over oven-dried molecular sieves. Hunig's base was distilled from dry KOH under atmospheric pressure and stored over oven-dried molecular sieves.

Chiral Phosphorus Brønsted Acids as catalysts in Asymmetric crotylation of primary amines

5.1.Synthesis of (*R*)-TRIP (24)



*(R)-2,2'-dimethoxy-1,1'-binaphthyl (**36**)*



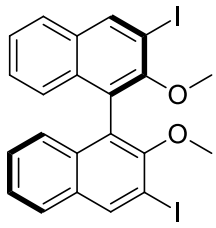
36

A 250 mL three-necked flask was charged with *R*-BINOL **35** (1 equiv, 4g, 14 mmol), sealed, evacuated and filled with nitrogen. The procedure was repeated three times. A reflux condenser was placed on a top of the flask and sealed; a nitrogen balloon was attached using a needle. Then acetone (100 mL) dried over MS 4Å was introduced by syringe into the flask and K_2CO_3 (3.3 equiv, 6.37g, 46.2 mmol) was added after BINOL completely dissolved. Then MeI (4 equiv, 56 mmol, 3.5 mL) was added dropwise over 2 minutes by syringe. The mixture was

heated at reflux overnight. The colour changed to light-yellow, and a white precipitate formed. The mixture was transferred to a round-bottom 250 mL flask and evaporated on a rotary evaporator. The resulting white-yellow precipitate was washed with water (3×15 mL) and separated on a glass filter, and dried under high vacuum, furnishing the target compound as a light-yellow powder (3.45 g, 11 mmol, 78%).

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 3.76 (s, 6H), 7.11 (d, *J* = 8.6 Hz, 2H), 7.21 (ddd, *J* = 8.4 Hz, 6.8 Hz, 1.5 Hz, 2H), 7.31 (ddd, *J* = 8.1 Hz, 6.8 Hz, 1.3 Hz, 2H), 7.46 (d, *J* = 9.0 Hz, 2H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.98 (d, *J* = 8.9 Hz, 2H), In agreement with the literature.[47]

*(R)-3,3'-diiodo-2,2'-dimethoxy-1,1'-binaphthyl (**37**)*

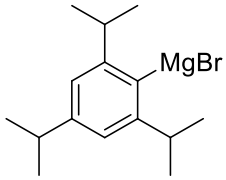


37

A 250 mL three-necked flask was loaded with protected BINOL **36** (1 equiv, 11 mmol, 3.45 g) and evacuated, and then filled with nitrogen. The procedure was repeated twice. Then 100 mL of Et_2O was added, and a light-yellow suspension was formed. Then dry TMEDA (3.2 equiv, 35.2 mmol, 5.25 mL), freshly distilled from KOH, was added via syringe at rt followed by a dropwise addition of freshly titrated BuLi in hexanes (3.6 equiv, 39.7 mmol, 2.28 M, 17.4 mL). The mixture turned dark. It was stirred for additional 4 hours at rt. Iodine (4 equiv, 44 mmol, 11.2 g) was dissolved in 50 mL of Et_2O and transferred to a dropping funnel. It was poorly soluble in Et_2O. Then the dropping funnel was attached to the reaction vessel, and the I_2 - solution was added dropwise at -78 °C. Upon addition, the solution started to freeze on the glass walls above the bulk solution. The mixture was stirred overnight. Next day, it was quenched with 150 mL of saturated $Na_2S_2O_3$ solution and extracted with Et_2O (3×50 mL). The combined organic layers were dried over anhydrous Na_2SO_4, vacuum-filtered through cotton wool and evaporated. The resulting solid was recrystallised three times from EtOAc/hexanes, and the residue was purified by column chromatography (insertion on silica) in Hex/EtOAc 95:5 eluent to yield target compound **37** as a light-yellow solid (3.5 g, 6.2 mmol, 56%)

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 3.40 (s, 6H), 7.06 (d, *J* = 8.51 Hz, 2H), 7.25 (ddd, *J* = 8.4 Hz, 6.9 Hz, 1.3 Hz, 2H), 7.39 (t, *J* = 7.56 Hz, 2H), 7.78 (d, *J* = 8.2 Hz, 2H), 8.52 (s, 2H), In agreement with the literature.[162]

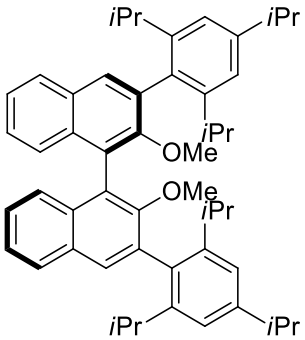
*(2,4,6-triisopropylphenyl)magnesium bromide (**38**)*



38

A 250 mL round-bottomed flask with a stirrer was charged with magnesium turnings (2 equiv, 128 mmol, 3.1 g), evacuated and filled with nitrogen, then evacuated again and heated up to 200 ℃ with a heat gun whilst being maintained under vacuum. Then, dry Et_2O (70 mL) was added via syringe, and few crystals of I_2 were added to activate the Mg surface. Next, 2-bromo-1,3,5-triisopropylbenzene (1 equiv, 64 mmol, 16.21 mL) was added dropwise at rt, and the mixture was heated at reflux overnight. The next day, an aliquot was taken for iodometric titration, and no product was observed. 200 µL of TMSCl and 100 µL of 1,2-dibromoethane was added, and the flask was submerged in an ultrasound bath for 15 minutes, then heated at reflux overnight. The next day the Mg turnings were partially dissolved and titration of resulting mixture showed 0.78 M of the corresponding Grignard reagent solution **38** (80 mL, 62.4 mmol, 98% conversion). For the titration; 300 µL solution of I_2 (59 mg, 233 µmol) was used. The solution was used directly in the next step.

*(1R,3R)-2,2'-dimethoxy-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl (**39**)*

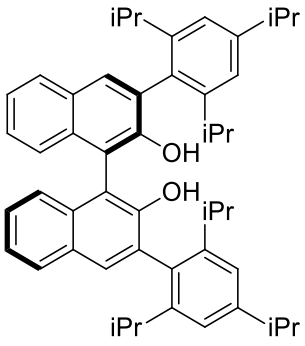


39

A 250 mL heat gun-dried flask was charged with protected BINOL diiodide **37** (1 equiv, 6.27 mmol, 3.55 g), $[Ni(PPh_3)_2Cl_2]$ powder (12 mol%, 0.75 mmol, 493 mg), and a stirring bar. The flask was evacuated and filled with nitrogen three times. Distilled Et_2O (50 mL) was added to the powders, and a grey suspension was formed. Then the Grignard reagent (10 equiv, 62.7 mmol, 80 mL) was added dropwise to the mixture via syringe, and the suspension turned into a brown solution. Then the flask was filled with an oven-dried reflux condenser, and the mixture was refluxed for 12 hours. The mixture was cooled and slowly poured into 1 M HCl ice-cooled solution, and the resulting slurry extracted with Et_2O (3×40 mL), the combined organic layers were dried over Na_2SO_4, filtered through a cotton wool, concentrated in vacuum and purified by column chromatography on silica using gradient Hex:EtOAc (50/1 → EtOAc) elution to afford the target compound as a pale yellow oil. (3.44 g, 5.0 mmol, 79%)

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 1.08 (d, *J* = 6.8 Hz, 6H), 1.13 (d, *J* = 6.8 Hz, 6H), 1.18 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.8 Hz, 6H), 1.33 (d, *J* = 6.9 Hz, 12H), 2.75-2.91 (m, 4H), 2.97 (sept, *J* = 6.9 Hz, 2H), 3.10 (s, 3H), 7.10 (dd, *J* = 6.9 Hz, 1.7 Hz, 4H), 7.28-7.35 (m, 4H), 7.41 (ddd, *J* = 8.10 Hz, 6.43 Hz, 1.64 Hz, 2H), 7.75 (s, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), In agreement with the literature.[47]

*(1R,3R)-3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diol (**40**)*



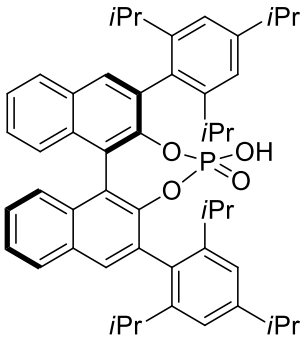
40

A 250 mL flask was evacuated and filled with nitrogen three times and charged with hindered protected dimethoxy BINOL **39** (1 equiv, 5.0 mmol, 3.44 g), and dry, freshly distilled DCM (50 mL) was added by syringe. The resulting solution was cooled to 0 °C, and then BBr_3 (1 M in DCM, 7.0 equiv, 35 mmol, 35 mL) was added dropwise, the mixture was allowed to reach rt and was stirred for 48 h. After that, 100 mL of water was added and the mixture was extracted with DCM (3×60 mL), washed with brine, and the solvent was removed in vacuum.

The crude material was dissolved in PE and purified by column chromatography using 20/1 Hex:EtOAc as an eluent to afford the target compound as a light-yellow powder (2.19 g, 3.1 mmol, 63%)

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 1.03 (d, *J* = 6.9 Hz, 6H), 1.08 (d, *J* = 6.9 Hz, 6H), 1.11 (d, *J* = 6.9 Hz, 6H), 1.19 (d, *J* = 6.8 Hz, 6H), 1.31 (d, *J* = 6.9 Hz, 12H), 2.68 (sept, *J* = 6.9 Hz, 2H), 2.84 (sept, *J* = 6.9 Hz, 2H), 2.96 (sept, *J* = 6.9 Hz, 2H), 4.91 (s, 2H), 7.13 (dd, *J* = 7.80 Hz, 1.7 Hz, 4H), 7.35-7.27 (m, 4H), 7.38 (ddd, *J* = 8.0 Hz, 6.3 Hz, 1.8 Hz, 2H), 7.76 (s, 2H), 7.86 (d, *J* = 7.9 Hz, 2H), In agreement with the literature.[47]

*(R)-TRIP (**24**)*



24

A joint two-neck Schlenk flask, equipped with a reflux condenser was evacuated and filled with nitrogen three times. Then $CaCl_2$-tube was placed on top, **40** (1 equiv, 1.78 mmol, 1.23 g) and 6.5 mL of dry CH_2Cl_2 were added to the flask. Freshly distilled $POCl_3$ (2.0 equiv, 3.56 mmol, 333 µL) was added subsequently in one portion at rt, followed by a dropwise addition of triethylamine (3.0 equiv, 5.34 mmol, 750 µL). The mixture was stirred for 12 hours at rt. TLC analysis showed that some starting material remained. Another 150 µL of $POCl_3$ (0.8 equiv, 1.6 mmol) and Et_3N (1.8 equiv, 3.2 mmol, 450 µL) were added, and the reaction mixture was refluxed for additional 2 hours. After that, the reaction mixture was cooled to rt, quenched with distilled water and transferred into a separating funnel. It was washed twice with 10 mL of distilled water, and the separated organic layer was dried over Na_2SO_4, filtered through cotton wool under vacuum suction, and then the solvent was removed in vacuum. Resulting solid was purified by flash chromatography in DCM-hexanes with gradient (Hex→DCM) and refluxed in 1:1 mixture of Py/H_2O for 3 hours. Then 20 mL of distilled DCM was added, and the mixture was transferred to a separating funnel. It was washed with 1 M HCl until the aqueous layer reached

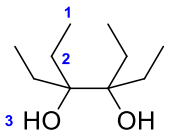
pH=1, detected by indicator paper. The organic layer was separated, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The resulting light yellow solid was dissolved in hot acetonitrile and recrystallised while slowly cooling to 0 °C overnight. The resulting yellow crystals were dried under 1 mbar for 10 hours to afford *(R)*-TRIP as a half-hydrate ((*R*)-TRIP × 0.5 H_2O). (1.18 g, 1.57 mmol, 88%)

^{1}H NMR (400 MHz; $CDCl_3$): δ_H 0.64 (d, *J* = 6.5 Hz, 6H), 0.87 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 6.8 Hz, 6H), 0.98 (d, *J* = 6.7 Hz, 6H) 1.19 (d, *J* = 6.9 Hz, 6H), 1.20 (d, *J* = 6.9 Hz, 6H), 2.47 (sept, *J* = 6.5 Hz, 2H), 2.55 (sept, *J* = 6.5 Hz, 2H), 2.80 (sept, *J* = 6.9 Hz, 2H), 5.42 (s, 3H), 6.90 (d, *J* = 12.0 Hz, 4H), 7.33-7.27 (m, 4H), 7.48 (ddd, *J* = 8.1, 6.1, 2.0 Hz, 2H), 7.78 (s, 2H), 7.86 (d, *J* = 8.2 Hz, 1H), In agreement with the literature.[47]

5.2.Synthesis of allylboronates

5.2.1. Synthesis of the precursors

*3,4-diethylhexane-3,4-diol (**34**)*

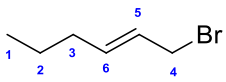


34

A 250 mL round bottom flask was charged with magnesium powder (9.7g, 400 mmol, 8 eq), evacuated and filled with Ar. After that, SmI_2 solution in THF (0.1M, 50 mL, 5 mmol, 10 mol%) and TMSCl (3.15 mL, 25 mmol, 0.5 equiv) were added at rt. A mixture of 3-pentanone (5.4 mL, 50 mmol, 1 equiv) and TMSCl (6.3 mL, 50 mmol, 1 equiv) was added dropwise maintaining the blue colour of the solution. After 48h of stirring, the reaction turned grey, and aqueous HCl (1M) was added dropwise until all magnesium metal was dissolved (caution! H_2 emission). The mixture was extracted with Et_2O (3×20 mL), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by flash chromatography using gradient (PE → PE/EtOAc 8:2) to afford target diol **34** as a colourless oil (4 g, 22.9 mmol, 46%)

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.90 (t, *J* = 7.5 Hz, 12 H, 1), 1.64-1.50 (m, 8 H, 2), 2.02 (d, *J* = 1.0 Hz, 2 H, 3), In agreement with the literature.[163]

*(E)-1-bromohex-2-ene (**42b**)*

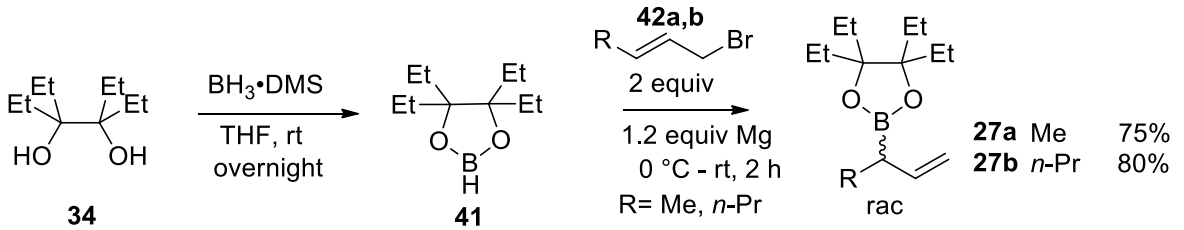


42b

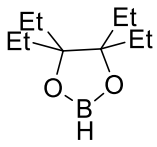
PBr_3 (0.5 equiv, 12.9 mmol, 1.21 mL) was added at 0 °C to (*E*)-3-hex-2-en-1-ol (1 equiv, 25.7 mmol, 1.00 mL) in freshly distilled THF (30 mL). The reaction mixture was stirred for 12 hours at rt. After full conversion of starting alcohol was evidenced by TLC analysis, the mixture was cooled to 0 °C using an ice bath and quenched by a dropwise addition of water (4 mL), washed with $NaHCO_3$ until CO_2 formation stopped and extracted with Et_2O (3×10 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. Flash chromatography using 100% petroleum ether as an eluent afforded the target bromide **42b** as a colourless oil (2.3 g, 14 mmol, 55%).

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.90 (t, *J* = 7.2 Hz, 3 H, 1); 1.41 (sept, *J* = 7.6 Hz, 2 H, 2); 2.04 (q, *J* = 7.2 Hz, 2 H, 3); 3.95 (d, *J* = 7.4 Hz, 2 H, 4); 5.65-5.81 (m, 2 H, 5+6); In agreement with the literature.[51]

5.2.2. General procedure for the synthesis of racemic allylboronates



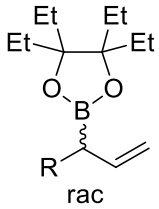
*4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**41**)*



41

(±)-**27a and** (±)-**27b** were synthesised following a procedure described in the literature with slight modifications.[44] A dried round bottom flask was charged with diol **34** (1 equiv, 7.06

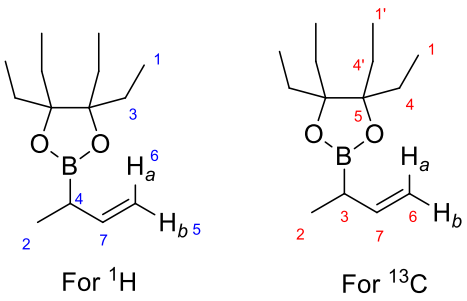
mmol, 1.23 g) in dry THF (5.2 mL, 3.7 M). The solution was cooled to 0 °C and BH_3·DMS in THF (2.0 M, 0.9 equiv, 6.3 mmol, 3.2 mL) was added dropwise to the mixture. Then the reaction was stirred at 0 °C for 30 min and then at rt for 5 hours. The resulting borane **41** (1.3 M in THF) was used in the next step without purification.



27a Me 75%
27b *n*-Pr 80%

A 50 mL two-neck round bottom flask was equipped with a condenser and charged with magnesium powder (1.2 equiv). Dry THF (1.6 mL per 1 mmol of **41**) was added by syringe, followed by dropwise addition of borane adduct **41** (1.3 M in THF, 1 equiv) via cannula during vigorous stirring. The corresponding allyl bromide **42** (1 equiv) was added dropwise at rt (exothermic!) and was stirred for 30 minutes. A second equiv of the allyl bromide was added to the reaction and the mixture was stirred for 90 minutes (for **27a**) or 12 hours (for **27b**). The reaction was quenched carefully with aqueous HCl 0.1 M (15 mL per 1 mmol of **41**) until the excess of magnesium was fully consumed. The reaction mixture was extracted with *n*-hexane (3×15 mL), dried over Na_2SO_4 and filtered. The solvent was removed in vacuum, and the crude material was purified by flash chromatography using PE/EtOAc (gradient 10:0 to 5:5) to afford the target boronate as a colourless oil.

*(±)-2-(But-3-en-2-yl)-4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**27a**)*



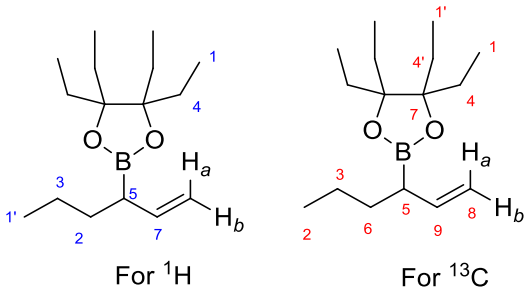
27a

Colourless oil (3.4 g, 19.3 mmol, 1 equiv. of diol **34** was used as starting material). 75% yield (3.3 g, 14.0 mmol).

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96 (ddd, *J* = 17.3, 10.3, 7.1 Hz, 1 H, 7), 5.00- 4.86 (m, 2 H, 5+6), 1.90 (t, *J* = 7.3 Hz, 1 H, 4), 1.71-1.58 (m, 8 H, 3), 1.10 (d, *J* = 7.3 Hz, 3 H, 2), 0.90 (t, *J* = 7.4 Hz, 12 H, 1).

^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3 (7), 111.2 (6), 88.5 (5), 26.9 (4'), 26.2 (4), 14.1 (2,3), 8.7 (1'), 8.6 (1). In agreement with the literature.[44]

*(±)-2-(Hex-1-en-3-yl)- 4,4,5,5-tetraethyl-1,3,2-dioxaborolane (**27b**)*



27b

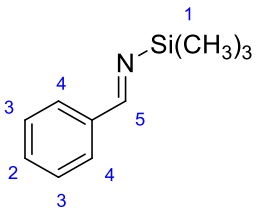
Obtained as a light-yellow oil (1.6 g, 9.3 mmol, 1 equiv. of diol **34** was used as starting material). 80% yield (1.8 g, 6.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.74-5.83 (m, 1 H, 7), 4.95 (ddd, *J* = 17.2, 2.0, 1.2 Hz, 1 H, ***H$_a$***), 4.89 (ddd, *J* = 10.0, 2.0, 0.8 Hz, 1 H, ***H$_b$***), 1.84 (q, *J* = 7.6 Hz, 1 H, 5), 1.60-1.66 (m, 8 H, 4), 1.25-1.42 (m, 4 H, 2+3), 0.89 (m, 15 H, 1+1').

^{13}C NMR (100 MHz, $CDCl_3$): δ 140.2 (9), 112.9 (8), 88.1 (7), 32.5 (6), 26.2 (5+4'), 26.1 (4), 22.0 (3), 14.1 (2), 8.8 (1'), 8.7 (1). In agreement with the literature.[44]

5.3.Synthesis of substrates

*(E)-N-benzylidene-1,1,1-trimethylsilanamine (**29**)*



29

An oven-dried 50 mL round-bottomed flask was equipped with a magnetic stirring bar, then evacuated and filled with nitrogen three times. The vessel was flame dried. Then hexamethyldisilazane (1.1 equiv, 37.9 mmol, 7.95 mL) was added and the mixture was cooled to 0 °C. Freshly titrated BuLi in hexanes (2.37 M, 1.05 equiv, 36.2 mmol, 15.3 mL) was slowly added dropwise. A white precipitate formed, and the mixture was allowed to reach ambient temperature. After 5 minutes of stirring, the precipitate dissolved, and the mixture was cooled back to 0 °C, and benzaldehyde (1 equiv, 34.4 mmol, 3.5 mL) was added dropwise by syringe. After 5 minutes, the mixture was warmed up to rt and stirred for 1 hour. Hexane was removed in vacuum and the resulting concentrate was dried under reduced pressure (50 mbar) without being exposed to air and was transferred via syringe to an oven-dried, dry nitrogen-filled distillation kit and distilled under high vacuum (0.8 mbar, bp 73-75 °C) to afford target *N*-TMS benzaldimine **29** as a yellow oil (3.5 g, 19.8 mmol, 57%).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 0.27 (s, 9 H, 1), 7.43 (m, 3 H, 2+3), 7.82-7.80 (m, 2 H, 4), 9.00-8.97 (m, 1 H, 5). In agreement with the literature.[164]

5.3.1. Ammonia solutions preparation

Ammonia gas was liquefied as depicted in the figure below.

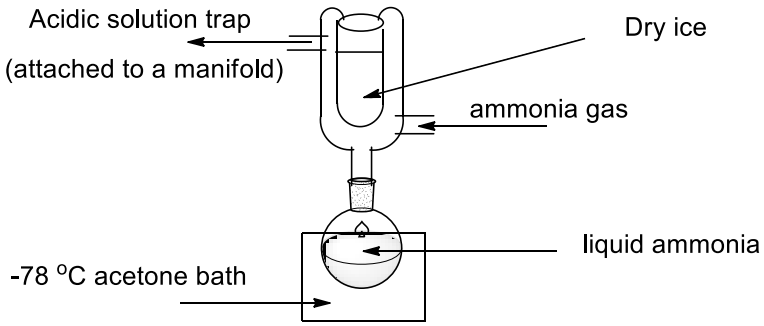


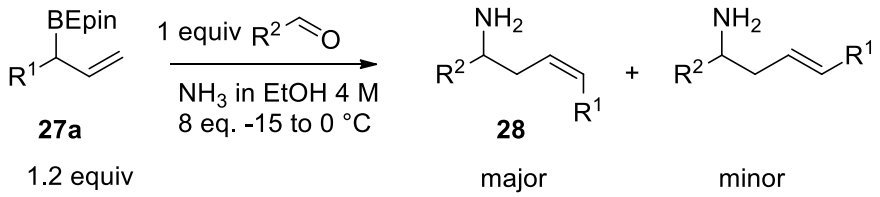
Figure 30

Liquid NH_3 (20 mL, 800 mmol) was dissolved in 200 mL of corresponding alcohol (EtOH, *i*-PrOH or *t*-BuOH), or THF, which were cooled to -35 °C before the addition of NH_3. The resulting solution was sealed, stored at -30 °C and used *ca.* 4M (the concentration drop is due to evaporation of ammonia). In the case of *t*BuOH the solution was stored at 0 °C to prevent crystallisation of the solvent.

5.4.General procedure for the synthesis of homoallylic amines

An oven-dried test tube was sealed and evacuated-backfilled with nitrogen. An aldehyde (1.0 equiv, 0.5 mmol) was added through a syringe by weght measured on scales and cooled to -15 ℃ using an acetone bath. Then ammonia solution (4 M in EtOH, 8 equiv, 4 mmol, 1 mL) was added through seal, and the mixture was stirred at -15 ℃ for 15 minutes. Then allylboronate (1.2 equiv, 0.6 mmol) was added by syringe, and the mixture was stirred at -10 ℃ or 0 ℃ as specified in the table below for the time specified.

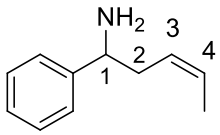
The mixture was next quenched with 1 M HCl and the pH was checked to be 1 using universal indicator paper. Then the reaction was washed three times with 5 mL of Et_2O, and basified again with 4 M KOH solution and pH was rechecked to be higher than 12. A white precipitate of homoallylic amine was formed and the water layer was extracted three times with hexane (5 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, and the solvent was removed under reduced pressure to afford almost pure homoallylic amine as a single spot on TLC. The *Z/E* ratio was determined by ^{1}H NMR. The crude mixture was purified by flash column chromatography in 1:1 Hex:EtOAc + 5 vol% of Et_3N. The resulting compound was analysed by ^{13}C NMR.



Entry	Product	R_1	R_2	T ℃	Time	Yield	*E/Z*
1	**28ab**	Me	4-Cl-Ph	-10	18 h	57%	10/1
2	**28ab**	Me	4-Cl-Ph	0	18 h	75%	8/1
3	**28ac**	Me	Cinnamyl	-10	18 h	45%	10/1
4	**28ac**	Me	Cinnamyl	0	18 h	72%	10/1
5	**28aa**	Me	Ph	-10	18 h	83%	8/1
6	**28ad**	Me	$PhCH_2CH_2$-	0	18 h	59%	(8/1)

7	**28ae**	Me	2-naphtyl	0	18 h	62%	8/1
8	**28af**	Me	1-naphtyl	0	18 h	80%	8/1
9	**28bf**	*n*-Pr	1-naphtyl	0	18 h	20%	5/1
10	**28ba**	*n*-Pr	Ph	0-20	48h	69%	(9/1)
11	**28aa**	Me	Ph	-42	96h	29%	24/1

*(±)-(Z)-1-phenylpent-3-en-1-amine (**28aa**)*



28aa

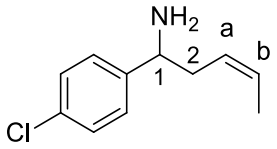
Colourless oil, 77 mg (83%) *Z/E* = 8/1 (at -10 °C).

^{1}H-NMR (400 MHz; $CDCl_3$): δ 1.54 (s, 2 H, N***H*$_2$**), 1.59 (dd, *J* = 6.8, 0.8 Hz, 3 H, C***H*$_3$**), 2.47-2.34 (m, 2 H, 2-***H***), 3.96 (dd, *J* = 7.5, 6.1 Hz, 1 H, 1-***H***), 5.40-5.33 (m, 1 H, 4-***H***), 5.60-5.53 (m, 1 H, 3-***H***), 7.25-7.21 (m, 1 H, *p*-Ph-***H***), 7.36-7.30 (m, 4 H, *o*-, *m*-Ph-***H***).

^{13}C NMR (100 MHz; $CDCl_3$): δ 13.3 (***C***H_3), 37.4 (***C***H_2), 56.2 (***C***HNH_2), 126.6 (=***C***HCH_3), 126.9 (2,6-***C*** in Ph), 127.1 (4-***C*** in Ph), 128.1 (***C***=CHMe), 128.6 (3,5-***C*** in Ph), 146.4 (*ipso*-***C*** in Ph).

IR (CH_2Cl_2, cm^{-1}): 3019, 2922, 2780, 1597. HRMS: Calculated for $[C_{11}H_{16}N]^+$: 162.1283 $[M+H]^+$; found: 162.1280.

*(±)-(Z)-1-(4-chlorophenyl)pent-3-en-1-amine (**28ab**)*



28ab

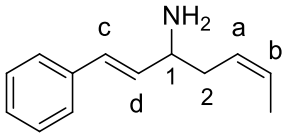
Yellowish oil, 73mg, 75%, *Z/E* = 8/1 (at 0 °C).

^{1}H NMR (400 MHz; $CDCl_3$): δ 1.56 (dt, *J* = 6.8, 0.8 Hz, 3 H, C***H***$_3$),1.79 (s, 2 H, N***H***$_2$), 2.43-2.29 (m, 2 H, 2-***H***), 3.94 (dd, *J* = 7.6, 6.0 Hz, 1 H, 1-***H***), 5.35-5.28 (m, 1 H, C***H***$_a$), 5.60-5.52 (m, 1 H, C***H***$_b$), 7.24-7.28 (m, 4 H, ***Ph***).

^{13}C NMR (100 MHz; $CDCl_3$): δ 13.1 (***C***H_3), 37.1 (***C***H_2), 55.5 (***C***HNH_2), 126.4 (=***C***HCH_3), 127.1 (3,5-***C*** in Ph), 127.9 (***C***=CHMe), 128.5 (2,6-***C*** in Ph), 132.5 (***C***-Cl), 144.3 (*ipso*-***C*** in Ph).

IR (CH_2Cl_2, cm^{-1}): 3012, 2926, 2851, 1591, 1088. HRMS: Calculated for $[C_{11}H_{15}NCl]^+$: 196.0893 $[M+H]^+$; found: 196.0895.

*(±)-(1E,5Z)-1-phenylhepta-1,5-dien-3-amine (**28ac**)*



28ac

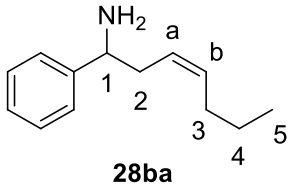
Yellowish oil, 86 mg, 72%, *Z/E* = 10/1

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 2 H, N***H***$_2$), 1.64 (d, *J* = 6.9 Hz, 3 H, C***H***$_3$), 2.28 (t, *J* = 6.9 Hz, 2 H, 2-***H***), 3.54 (q, *J* = 6.4 Hz, 1 H, 1-***H***), 5.46-5.40 (m, 1 H, C***H***$_b$), 5.63-5.58 (m, 1 H, C***H***$_a$), 6.20 (dd, *J* = 15.9, 6.8 Hz, 1 H, C***H***$_d$), 6.49 (d, *J* = 15.9 Hz, 1 H, C***H***$_c$), 7.22-7.18 (m, 1 H, *p*-***Ph***), 7.31-7.27 (m, 2 H, *m*-***Ph***), 7.37-7.35 (m, 2 H, *o*-***Ph***).

^{13}C NMR (100 MHz, $CDCl_3$): δ 137.30 (*ipso*-***C*** in Ph), 134.6 (Ph***C***=C), 128.9 (PhC=***C***), 128.65 (3,5-***C*** in Ph), 127.4 (4-***C*** in Ph), 126.9 (***C***=$CHCH_3$), 126.6 (2,6-***C*** in Ph), 126.4 (C=***C***HCH_3), 54.0 (***C***HNH_2), 35.5 (***C***H_2), 13.2 (***C***H_3).

IR (CH_2Cl_2, cm^{-1}): 3019, 2915, 2830, 1490. HRMS: Calculated for $[C_{13}H_{18}N]^+$:188.1439 $[M+H]^+$; found: 188.1444.

*(±)-(Z)-1-phenylhept-3-en-1-amine (**28ba**)*



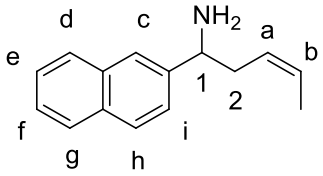
28ba

Colourless oil, 72 mg, 69%, *Z/E* ≈ 9/1

^{1}H NMR (400 MHz; $CDCl_3$): δ 0.88-0.93 (m, 3 H, C***H***$_3$), 1.29-1.39 (m, 2 H, 4-***H***), 1.52 (s, 2 H, N***H***$_2$), 2.00-2.05 (m, 2 H, 3-***H***), 2.41-2.45 (m, 2 H, 2-***H***), 3.99 (t, *J* = 6.8 Hz, 1 H, 1-***H***), 5.35-5.41 (m, 1 H, C***H***$_b$), 5.49-5.55 (m, 1 H, C***H***$_a$), 7.24-7.30 (m, 1 H, *p*-***Ph***), 7.32-7.42 (m, 4 H, *o*-***Ph***+*m*-***Ph***).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*denotes minor isomer) 146.0, 133.8*, 132.6, 128.3, 126.9, 126.6*, 126.3, 126.0, 125.5, 56.0, 55.7*, 43.0*, 37.5, 30.3*, 29.4, 22.7, 22.5*, 13.7, 13.6*. IR (CH_2Cl_2, cm^{-1}): 3055, 2987, 2840, 1422, 1266. HRMS: Calculated for $[C_{13}H_{20}N]^+$: 190.1590 $[M+H]^+$; found: 190.1593.

*(±)-(Z)-1-(naphthalen-2-yl)hept-3-en-1-amine (**28ae**)*

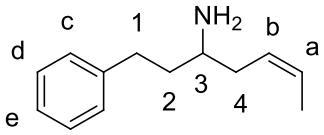


28ae

Colourless oil. 66 mg, 62% yield, *E/Z* = 8/1

^{1}H NMR (400 MHz; $CDCl_3$): δ 1.65 (ddt, *J* = 6.8, 1.7, 0.8 Hz, 5 H, (C***H***$_3$ + N***H***$_2$), 2.48-2.60 (m, 2 H, 2-***H***), 4.18 (t, *J* = 6.8 Hz, 1 H, 1-***H***), 5.40-5.48 (m, 1 H, C***H***$_b$), 5.58-5.66 (m, 1 H, C***H***$_a$), 7.45-7.54 (m, 3 H, **c+h+i**), 7.82-7.86 (m, 4 H, **d+e+f+g**).

*(±)-(Z)-1-phenylhept-5-en-3-amine (**28ad**)*



28ad

Colourless oil, 47 mg, 59%, *Z/E* = 8/1

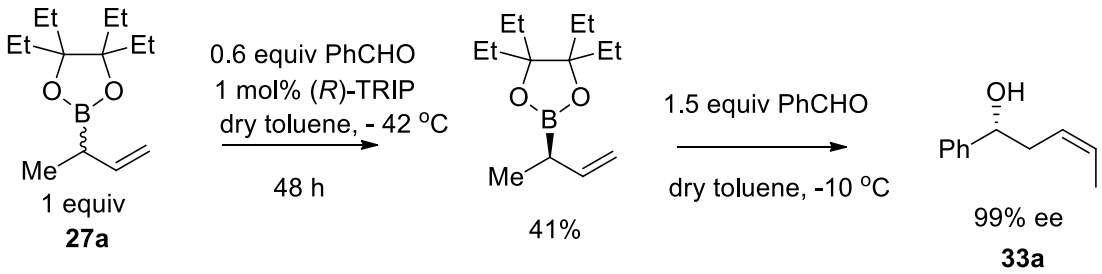
^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.29 (s, 2 H, N***H***$_2$), 1.67 (d, *J* = 5.9 Hz, 3 H, C***H***$_3$), 1.71-1.86 (m, 2 H, 2-***H***), 2.10-2.26 (m, 2 H, 4-***H***), 2.63-2.71 (m, 1 H, 3-***H***) 2.74 -2.87 (m, 2 H, 1-***H***), 5.41-5.47 (m, 1 H, C***H***$_a$), 5.61-5.66 (m, 1 H, C***H***$_b$), 7.19-7.27 (m, 3 H, **e**+**d**), 7.29-7.33 (m, 2 H, **c**).

^{13}C NMR (100 MHz, CD_3OD): δ (*denotes minor isomer) 143.5, 129.39, 129.35,

129.2*, 128.8*, 127.9, 127.4, 126.8, 51.9, 51.5*, 41.2*, 39.8*, 35.3, 33.5, 33.4*, 18.2*, 13.2.

IR (CH_2Cl_2, cm^{-1}): 3026, 2919, 2857, 1605, 1583. HRMS: Calculated for $[C_{13}H_{20}N]^+$: 190.1596 $[M+H]^+$; found: 190.1599.

5.5.Kinetic resolution of crotyl boronate improvement



5.5.1. Step 1: Kinetic resolution

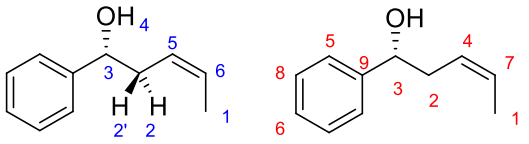
An oven-dried reaction test tube was evacuated and filled with nitrogen. Benzaldehyde (0.6 equiv, 1.2 mmol, 127.4 mg) was added via syringe. The mixture was cooled to -42 °C using cryostat and *(R)*-TRIP (1 mol%, 0.02 mmol, 15 mg) was added as a solution in toluene (8 mL)

through a syringe. The mixture was stirred for 10 minutes, and racemic crotyl boronate (1 equiv, 2.0 mmol, 476 mg) was added. The mixture was stirred at -42 °C for 48 hours, and TLC analysis showed complete consumption of the aldehyde. The reaction was quenched with saturated $NaHCO_3$ and extracted with *n*-hexane (3×7 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The crude material was purified by flash chromatography with *n*-hexane elution to afford enantioenriched crotyl boronate **27a** as a colourless oil (173 mg, 0.73 mmol, 41%).

5.5.2. Step 2: *ee* determination

Resulting enantioenriched (*R*)-boronate **27a** (1 equiv, 0.73 mmol, 173 mg) was dissolved in 2.6 mL of dry toluene in the same flask. It was then cooled to -10 °C using cryostat, and subsequently, an excess of benzaldehyde (1.5 equiv, 1.10 mmol, 116 mg) was added. The mixture was then stirred at – 10 °C overnight. After the reaction was complete, saturated $NaHCO_3$ aqueous solution was added. The water layer was extracted with (3×5 mL) of EtOAc, and the combined organic layers were dried over anhydrous Na_2SO_4 and filtered using cotton wool. The extract was concentrated in vacuum furnishing a colourless oil, which was purified by flash chromatography in 10/1 Hex:EtOAc system to afford homoallylic alcohol **33a**. The product was analysed by chiral HPLC (Chiralpak IB-3 column, in hexane/2-propanol = 98:2 eluent system, flow rate 0.75 mL/min, UV detection at 225 nm) and showed 99% *ee*.

*(R,Z)-1-phenylpent-3-en-1-ol (**33a**)*



For ^{1}H **33a** For ^{13}C

Colourless oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.60 (dt, *J* = 6.8, 0.9 Hz, 3 H, 1), 2.06 (s, 1 H, 4), 2.40-2.50 (m, 1 H, 2), 2.53-2.61 (m, 1 H, 2'), 4.70 (t, *J* = 13.3 Hz, 1 H, 4), 5.38-5.46 (m, 1 H, 5), 5.57-5.68 (m, 1 H, 6), 7.25-7.29 (m, 1 H, *o*-***Ph***), 7.32-7.38 (m, 4 H, *m*- + *p*-***Ph***).

^{13}C NMR (100 MHz, $CDCl_3$): δ (*denotes minor isomer) 144.2 (9), 129.6* (8), 128.5(8), 127.8 (7), 127.6 (6), 127.6* (7), 126.9* (6), 126.0 (5), 125.9* (4), 125.8 (4), 74.0 (3), 73.6* (3), 43.0* (2), 37.1 (2), 18.2* (1), 13.1 (1).

(Chiralpak IB-3, hexane/2-propanol = 98:2, 0.75 mL/min, UV detection at 225 nm) 99% *ee* (t_R = 27.5 min (major), t_S = 28.6 min (minor).

Chiral 2,2-Bipyridine Bis-*N*-oxides as Lewis Base Catalysts for Asymmetric reactions of trichlorosilyl reagents with aldehydes

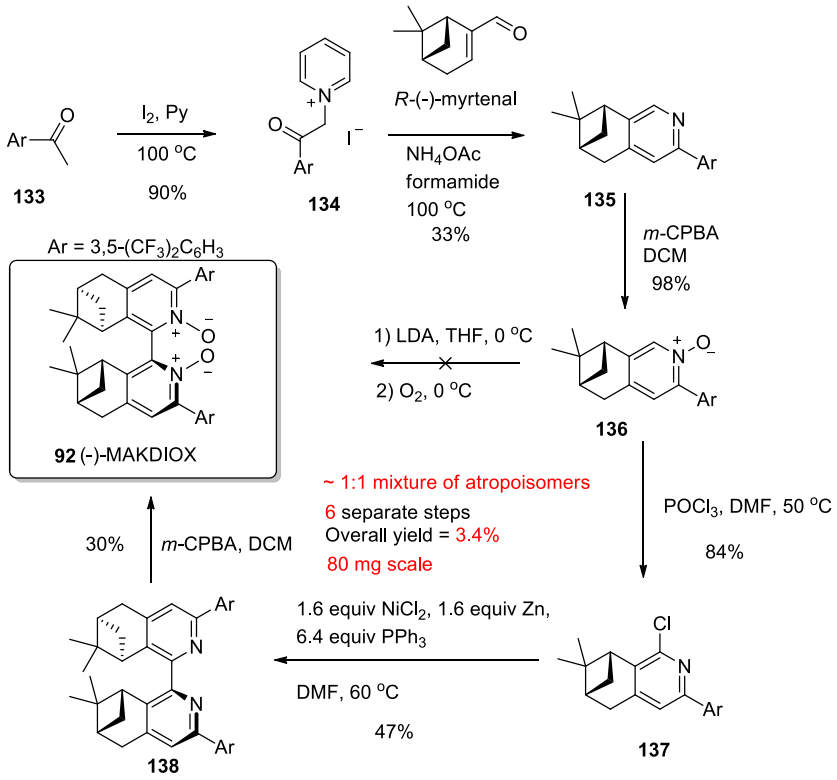
General procedures

All NMR spectra were recorded in $CDCl_3$ solution, ^{1}H at 400 MHz and ^{13}C at 100.6 MHz with chloroform-d_1 (δ 7.26 ppm, ^{1}H; δ 77.0 ppm, ^{13}C) as an internal standard. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen or Argon using oven-dried glassware. Yields are given for isolated products showing one spot on a TLC plate and no impurities according to the NMR spectrum. Column chromatography was completed using mesh 60 silica gel as the absorbent. All reactions were monitored by thin-layer chromatography on aluminium plates with Merck Kiesel 60 F254 silica gel as the stationary phase. TLCs were visualised by UV radiation at a wavelength of 254 nm, and stained by exposure to a saturated potassium permanganate aqueous solution. Chromatography was carried out using Merck Kiesel 60 H silica adsorbent. Benzaldehyde was used without purification from Sigma Aldrich 98+% pure. THF was distilled under argon atmosphere from the sodium/benzophenone and used directly after that. Petroleum ether is the 40-60 ℃ boiling range fraction. Chiral HPLC was performed on Chiralpak IB-3 or IC-3 columns, in *n*-hexane/2-propanol = 98:2 eluent system, flow rate 0.75-1.00 mL/min, UV detection at 220 nm.

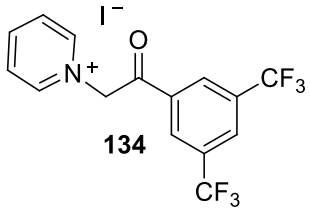
All research experiments was performed in an atmosphere of dry nitrogen. Commercial solvents were used as purchased. Anhydrous formamide and stored above dry MS 4Å and used as purchased. Et_2O was distilled from $LiAlH_4$ and stored under nitrogen above MS 4Å. $NEt(i\text{-}Pr)_2$ was distilled from anhydrous KOH. Diisopropylamine was distilled directly prior to use from sodium hydride. Commercial *n*-butyllithium in hexanes was titrated prior to use and stored in a fridge. Dry DMF was stored under MS 4Å. Molecular Sieves were activated by heating under 0.1 mbar at 300 ℃ for 4 hours.

5.6.Syntheses of chiral Bipyridine-bis-*N*-Oxides

5.6.1. Synthesis of (+)-MAKDIOX (Route A)



*1-{2-[3',5'-bis(trifluoromethyl)phenyl]-2-oxoethyl}pyridinium iodide (**134**)*

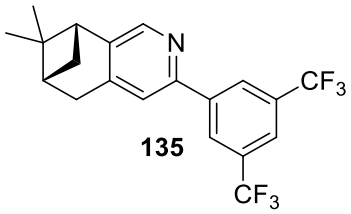


A 50 mL round-bottomed flask was equipped with stirring bar and flushed with Argon. 3,5-bis-(trifluoromethyl)acetophenone (3.5 mL, 5.0 g, 19.5 mmol, 1.0 equiv) was added via syringe, and the flask was equipped with a reflux condenser. An excess of pyridine (8.2 mL, 105.6 mmol, 5.4 equiv) was added via syringe, and the mixture was stirred at 80 °C. A pale yellow colour occurred, and crystalline Iodine (5.89 g, 23.2 mmol, 1.19 equiv) was added in small portions. The mixture was refluxed for an hour, then cooled and diluted with PE (35 mL). A dark brown precipitate was observed. After cooling to rt, the precipitate was transferred to a filter and washed with *n*-hexane (3×30 mL) and dried using vacuum suction. The obtained solid was dried under vacuum and to afford the target salt **134** as a mixture (1/1.50 by molar ratio)

with pyridinium iodide (13.0 g, 17.5 mmol, ω=62.1%, 90% NMR yield). The crude product was used directly in the next step.

^{1}H NMR (400 MHz, DMSO-d_6): δ_H 6.56 (s, 2 H, C***H*****$_2$**), 8.28 (dd, 2 H, *J* = 7.83 Hz; 6.75 Hz; 2,6-Py***H***), 8.58 (s, 1 H, 4-***H Ph***), 8.74 (tt, 1 H, *J* = 7.85 Hz; 1.30 Hz, 4-***H Py***), 8.86 (s, 2 H) 8.93 (dd, 2 H, *J* = 6.77 Hz; 1.30 Hz; 3,5-***H Py***), In agreement with the literature. [90]

*(6S,8S)-3-(3,5-bis(trifluoromethyl)phenyl)-7,7-dimethyl-5,6,7,8-tetrahydro-6-methanoisoquinoline (*135*)*

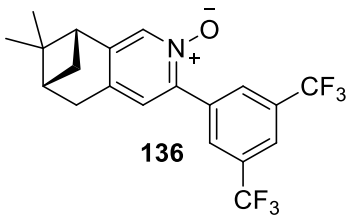


135

The product **134** (1.0 equiv, 17.5 mmol, 13.00 g, ω = 62%) was placed in an Argon-flushed 100 mL round-bottomed flask and dissolved in dry formamide (40 mL). Then ammonium acetate (2.0 equiv, 35 mmol, 2.70 g) was added, and the mixture was heated to 50 ℃ and stirred for approx. 20 minutes until all solids dissolved to form a dark-brown solution. After that, (*R*)-(-)-myrtenal (1.1 equiv, 19.25 mmol, 2.93 g) was added dropwise via a syringe, and the mixture was heated to 100 ℃ and stirred for 12 hours. The mixture became darker and was cooled to rt. Then the mixture was diluted with hexanes (50 mL) and transferred to a 500 mL separation funnel, where it was quenched with 100 mL of saturated Na_2CO_3 solution and extracted with *n*-hexane (3×30 mL). The combined hexane layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The resulting crude material was purified by column chromatography (Hex:EtOAc, gradient 20:1 → 10:1, R_f=0.59 (10:1)) to afford pure **135** as brown-red oil (2.21 g, 5.7 mmol, 33% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.67 (s, 3 H, C***H*****$_3$**), 1.25 (d, 1 H, *J* = 9.7Hz; Bn-***H***), 1.44 (s, 3 H, C***H*****$_3$**); 2.36 (tt, 1 H, *J* = 5.77 Hz; 2.87 Hz; C***H*** lower); 2.75 (dt, 1 H, *J* = 9.7 Hz, 5.8 Hz; C***H***-bridge), 2.90 (t, 1 H, *J* = 5.5 Hz, C***H*** Bn), 3.07 (d, 2 H, *J* = 2.7 Hz, C***H*****$_2$** Bn), 7.60 (s, 1 H, 2-***H*** Py), 7.88 (s, 1 H), 8.27 (s, 1 H), 8.45 (s, 2 H, 2,6-***H*** Ph).

*(6S,8S)-3-(3,5-bis(trifluoromethyl)phenyl)-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-methanoisoquinoline 2-oxide (**136**)*



136

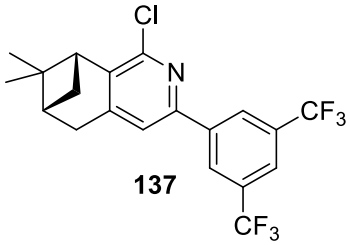
Isoquinoline **135** (450 mg, 1.17 mmol, 1 equiv) was dissolved in CH_2Cl_2 (14 mL) to give a brown solution and was cooled to 0 °C. *m*-Chloroperoxybenzoic acid (3.0 equiv, 3.5 mmol, 605 mg,) was added in portions, and the mixture colour changed to bright yellow. The reaction mixture was stirred for 12 hours at rt and then diluted with Et_2O and washed with saturated solution of $NaHCO_3$ (3×10 mL) and brine (50 mL). After separation organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The material was purified by flash chromatography using EtOAc/MeOH (30:1, R_f=0.50) to afford **136** as a white solid (460 mg, 1.15 mmol, 98%), m.p. 150-155 °C.[149]

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.74 (s, 3 H, C***H*****$_3$**), 1.29 (d, 1 H, *J* = 10.0 Hz; C***H***-terpene), 1.43 (s, 3 H, C***H*****$_3$**); 2.36 (tt, 1 H, *J* = 5.7 Hz; 2.9 Hz; C***H*** terpene); 2.76 (dt, 1 H, *J* = 10.0 Hz, 5.8 Hz; C***H***-terpene), 2.83 (t, 1 H, *J* = 5.4 Hz, benzylic C***H***) 3.02 (d, 2 H, *J* = 2.3 Hz, benzylic C***H*****$_2$**), 7.25 (s, 1 H), 7.92 (s, 1 H), 8.10 (s, 1 H, 2-***H Py***), 8.32 (s, 2 H, 2,6-***H Ph***)

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 21.5, 25.9, 31.4, 32.3, 39.5, 40.0, 44.8, 122.0, 123.2 (q $^1J_{C\text{-}F}$ = 272 Hz), 126.3, 129.9, 131.7 (q $^2J_{C\text{-}F}$ = 33 Hz), 134.8, 137.0, 143.8, 146.4.

In agreement with the literature.[149]

*(1R,9R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-chloro-10,10-dimethyl-4-azatricyclo[7.1.1.0^{2,7}]undeca-2,4,6-triene (**137**)*



137

A 100 mL round-bottomed flask was charged with *N*-Oxide **136** (1.0 equiv, 3.13 mmol, 1.25 g) dissolved in dry DMF (15.7 mL). $POCl_3$ (5.0 equiv, 15.7 mmol, 2.40 g, 1.46 mL) was added

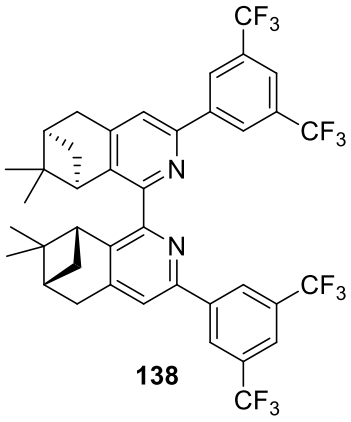
dropwise via syringe at rt. The reaction was heated to 50 °C using thermostate, and stirred for 18 hours. Then the reaction was quenched with saturated $NaHCO_3$ until CO_2 emission has stopped (approx. 50 mL), and the mixture was transferred to a 100 mL separation funnel and extracted with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4 and filtered through cotton wool, and then evaporated under reduced pressure. The resulting brownish oil was purified by flash chromatography using Hex:EtOAc mixture as an eluent (1:1, R_f= 0.80) to afford **137** as light brown oil (1.11 g, 2.65 mmol, 84% yield).

^{1}H NMR (400 MHz, $CDCl_3$): δ_H 0.68 (s, 3 H, C***H*****$_3$**), 1.23 (d, 1 H, *J* = 9.9 Hz; Bn-***H***), 1.46 (s, 3 H, C***H*****$_3$**); 2.35 (tt, 1 H, *J* = 5.7 Hz; 2.8 Hz; C***H*** lower); 2.75 (dt, 1 H, *J* = 10.0 Hz, 5.8 Hz; C***H***-bridge), 3.07 (d, 2 H, *J* = 2.7 Hz, C***H*****$_2$ *Bn***), 3.33 (t, 1 H, *J* = 5.5 Hz, C***H Bn***) 7.55 (d, 1 H, *J* = 0.6 Hz, 2-***H Py***), 7.89 (s, 1 H), 8.44 (s, 2 H, 2,6-***H Ph***)

^{13}C NMR ($CDCl_3$, 101 MHz): δ_C 21.2, 25.8, 31.0, 33.3, 39.0, 39.8, 43.4, 119.2, 122.3 (q, $^3J_{C-F}$ = 4 Hz), 123.3 (q, $^1J_{C-F}$ = 273 Hz), 126.7 (d, *J* = 2.5 Hz), 132.0 (q, $^2J_{C-F}$ = 33 Hz), 140.2, 141.0, 148.4, 149.0, 151.5.

IR: υ 2933, 1728, 1621, 1591, 1541, 1467, 1438, 1426, 1387, 1356, 1275, 1247, 1222, 1171, 1129, 1107, 1034, 961, 899, 881, 867, 842, 779, 735, 723, 701, 681, 665, 650, 605, 545, 498, 450, 420, 413, 404 cm^{-1};

*(1R,9R)-5-[3,5-bis(trifluoromethyl)phenyl]-3-[(1R,9R)-5-[3,5-bis(trifluoromethyl)phenyl]-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2,4,6-trien-3-yl]-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2,4,6-triene (**138**)*



138

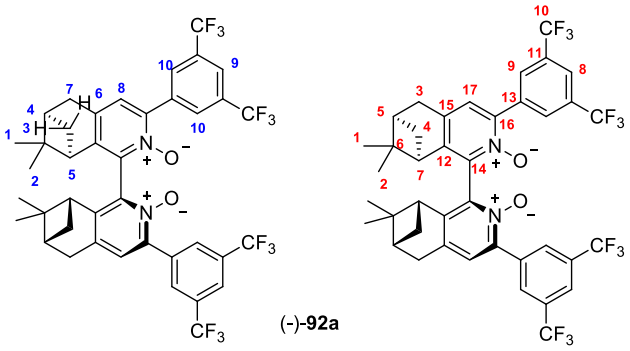
A dry 50 mL test tube equipped with a stirring bar, dry Zinc powder 60 mesh (1.6 equiv, 2.14 mmol, 140 mg), was sealed and dry DMF (24.2 mL) was added with a syringe. The mixture

was evacuated and backfilled with nitrogen on a Schlenk line (×3). Two drops of TMSCl were added to the stirred suspension of Zn powder, and the mixture was heated by a heat gun to approx. 60 ℃ until the TMSCl started to boil. When Zn dust condensed to the bottom of the flask, nickel(II) chloride (1.6 equiv, 2.14 mmol, 227 mg) was added in one portion, followed by addition of Ph_3P (6.4 equiv, 8.58 mmol, 2.25 g). The mixture was heated to 60 ℃ and stirred for 1 hour until a dark red colour was observed. Next, the solution of 2-chloropyridine **137** (1.34 mmol, 1 equiv, 563 mg) in DMF (2 mL) was added dropwise via syringe. The mixture became darker and was stirred overnight (12 hours) at 60 ℃. Then the excess of aqueous ammonia was added (30 mL) and the mixture was transferred to a separation funnel and extracted with EtOAc (3×20 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid. The solid was dissolved in hexanes/Et_2O mixture (*ca*. 1:2) and purified on a long silica column (500 g, 50×7.5 cm), washed first with 500 mL of hexanes until all Ph_3P was separated, and then with Hex:EtOAc gradient (10:1→EtOAc) to afford 5:1 inseparable mixture of **138a** and **138b** as a colourless oil (290 mg, 0.38 mmol, 57% overall yield) which was used in the next step without further purification.

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H 0.68 (s, 6 H), 1.25 (d, *J* = 5.9 Hz, 2 H), 1.45 (s, 6 H), 2.75 (dt, *J* = 9.7, 5.8 Hz, 2 H), 2.91 (t, *J* = 5.5 Hz, 2 H), 3.08 (d, *J* = 2.7 Hz, 4 H), 7.61 (s, 2 H), 8.29 (s, 2 H) 8.47 (s, 4 H).

*(-)-MAKDIOX-**92a** and (+)-**139b***

A mixture of bipyridine axial isomers **138a** and **138b** from the previous step (290 mg, 0.377 mmol, 1.0 equiv) were dissolved in DCM (4.4 mL) in a reaction tube, and *m*-CPBA (6.0 equiv, 390 mg, 2.26 mmol) was added at rt. The mixture was stirred for 12 hours at rt, quenched with saturated $NaHCO_3$ (20 mL), transferred to a separation funnel and extracted with EtOAc (20 mL). The lower aqueous layer was separated, and the organic layer was washed with sat. $NaHCO_3$ (3×20 mL) and dried over anhydrous $MgSO_4$ filtered, and then concentrated under reduced pressure. Resulting solid was dissolved in DCM-*n*-Hexane mixture (1:1) and purified by column chromatography on *silica*, eluting with Hexane:EtOAc mixture (4/1). Isomers (+)-**139b** (R_f = 0.38, 82 mg, 0.102 mmol, 27% yield) and (-)-**92a** (R_f = 0.28, 91 mg, 0.113 mmol, 30% yield) were obtained as yellow amorphous solids.



(-)-**92a**

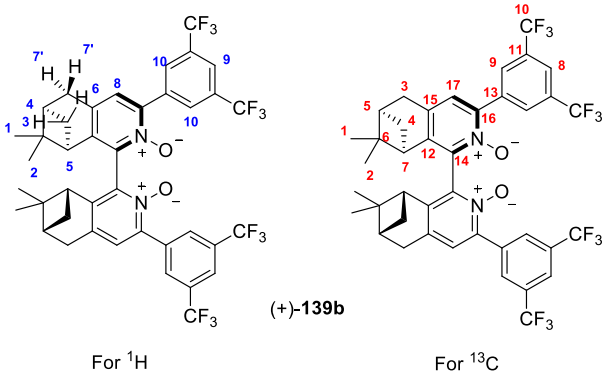
For ^{1}H For ^{13}C

m.p. 190-191 °C, in agreement with the literature.[149]

Note: The colour code highlights the corresponding protons in **92a** and **139b**.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (s, 6 H, ***1***), 1.25 (d, *J* = 9.9 Hz, 2 H, ***3***), 1.33 (s, 6 H, ***2***), 2.31-2.38 (m, 4 H, ***7+7'***), 2.64 (dt, *J* = 10.3, 5.4 Hz, 2 H, ***6***), 3.02-3.14 (m, 4 H, ***4+5***), 7.34 (s, 2 H, ***8***), 7.89 (s, 2 H, ***9***) 8.39 (s, 4 H, ***10***).

^{13}C NMR (101 MHz, $CDCl_3$): δ_C 21.5 (1), 25.9 (2), 31.4 (3), 32.3 (4), 39.5 (5), 40.0 (6), 44.8 (7), 122.0 (8), 123.9 (q, $^{1}J_{C\text{-}F}$ = 273 Hz, 10), 126.6 (9), 129.9 (17), 131.7 **(**q, $^{2}J_{C\text{-}F}$ = 33.5 Hz, 11**)**, 134.8 (13), 139.2 (14), 143.8 (15), 146.4 (16). In agreement with the literature[57]



(+)-**139b**

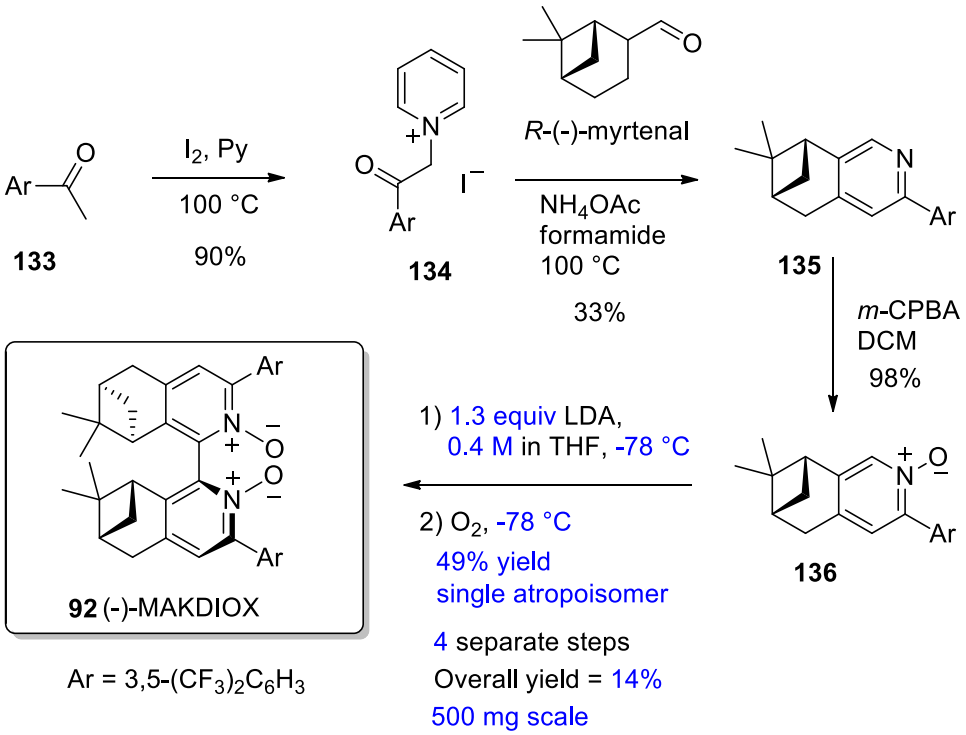
For ^{1}H For ^{13}C

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.84 (s, 6 H, ***1***), 1.34 (s, 6 H, ***2***), 1.45 (d, *J* = 10.2 Hz, 3 H, ***3***), 2.33 (tt, *J* = 5.5, 2.6 Hz, 2 H, ***7'***), 2.42 (t, *J* = 5.4 Hz, 2 H, ***7***), 2.70 (dt, *J* = 10.6, 5.5 Hz, 2 H, ***6***), 3.08 (s, 4 H, ***4+5***), 7.36 (s, 2 H, ***8***), 7.89 (s, 2 H, ***9***) 8.41 (s, 4 H, ***10***).

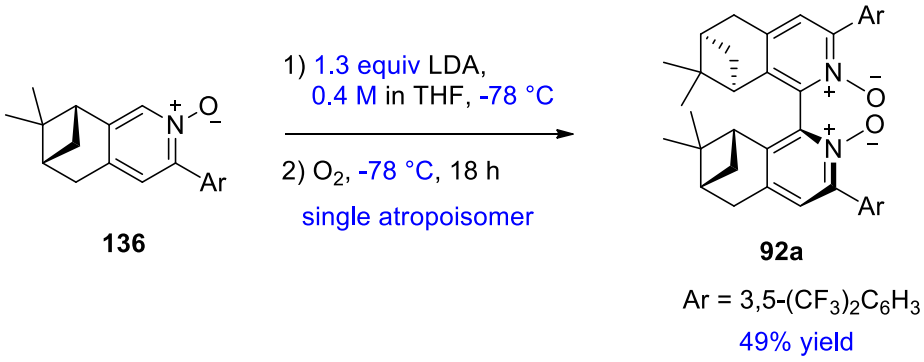
^{13}C NMR ($CDCl_3$, 101 MHz): δ 21.5 (1), 25.9 (2), 31.5 (3), 32.4 (4), 39.0 (5), 39.7 (6), 44.0 (7), 122.8 (9), 123.2 (q, $^1J_{C\text{-}F}$ = 273 Hz, 10), 126.5 (8), 129.8 (17), 131.4 (q, $^2J_{C\text{-}F}$ = 33.5 Hz, (11)), 134.4 (13), 135.0 (12), 139.1 (14), 143.3 (15), 146.4 (16).

5.6.1. MAKDIOX Direct Coupling Reaction (Route B)

5.6.1.1. General Scheme of Synthesis



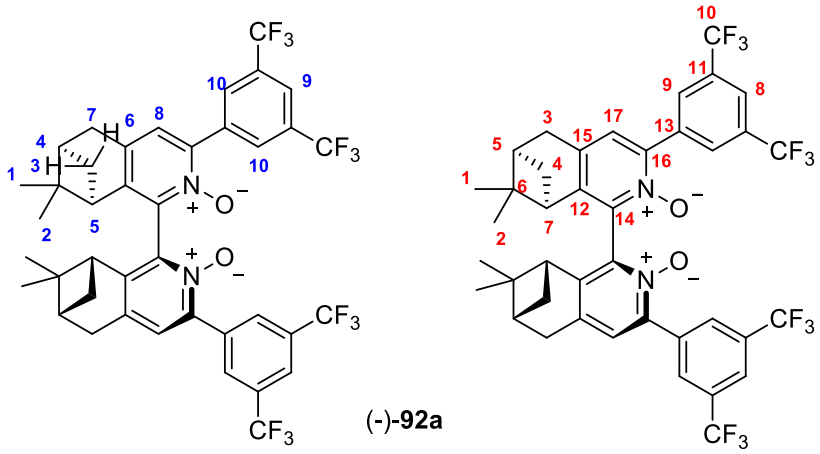
5.6.1.1.1. Pyridine *N*-Oxide Oxidative Coupling



A flame dried nitrogen-flushed 50 mL round-bottomed flask was charged with a magnetic stirrer and sealed. Diisopropylamine (1.3 equiv, 3.23 mmol, 0.454 mL) was added via syringe, followed by dilution in dry THF (2.5 mL). The resulting solution was cooled to 0 ℃ and *n*-BuLi in hexanes was slowly added dropwise via syringe (1.3 equiv, 3.23 mmol, 1.32 mL) and the mixture was stirred for 30 minutes, then allowed to warm up to ambient temperature. Next,

the mixture was cooled to −78 °C, using a dry ice bath and a solution of monoxide **136** (1.00 g, 2.49 mmol, 1.0 equiv) in THF (2.5 mL) was added dropwise via syringe. The mixture turned dark blue immediately, and after addition, a balloon with dry oxygen was inserted, with the needle submerged into the solution. The needle was changed a few times to assure that the stream of oxygen was maintained. The mixture was then stirred for 12 hours at -78 °C. The next day the mixture was warmed to rt (the colour of the solution changed to a greenish-black and then to dark brown) and quenched with 30 mL of saturated $NaHCO_3$, and extracted with DCM (3×20 mL). The combined organic extracts were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The reddish-brown residue was purified by column chromatography in 5:1 hexanes/EtOAc (R_f = 0.5) to afford **92a** as yellow crystals (486 mg, 0.606 mmol, 49% yield), m.p. 190-191 °C.

The eluent polarity was increased to EtOAc:MeOH (20/1) and elution continued to recover unreacted starting material **136** (196 mg, 0.486 mmol, 20%, 69% brsm yield of **92a**).



(-)-**92a**

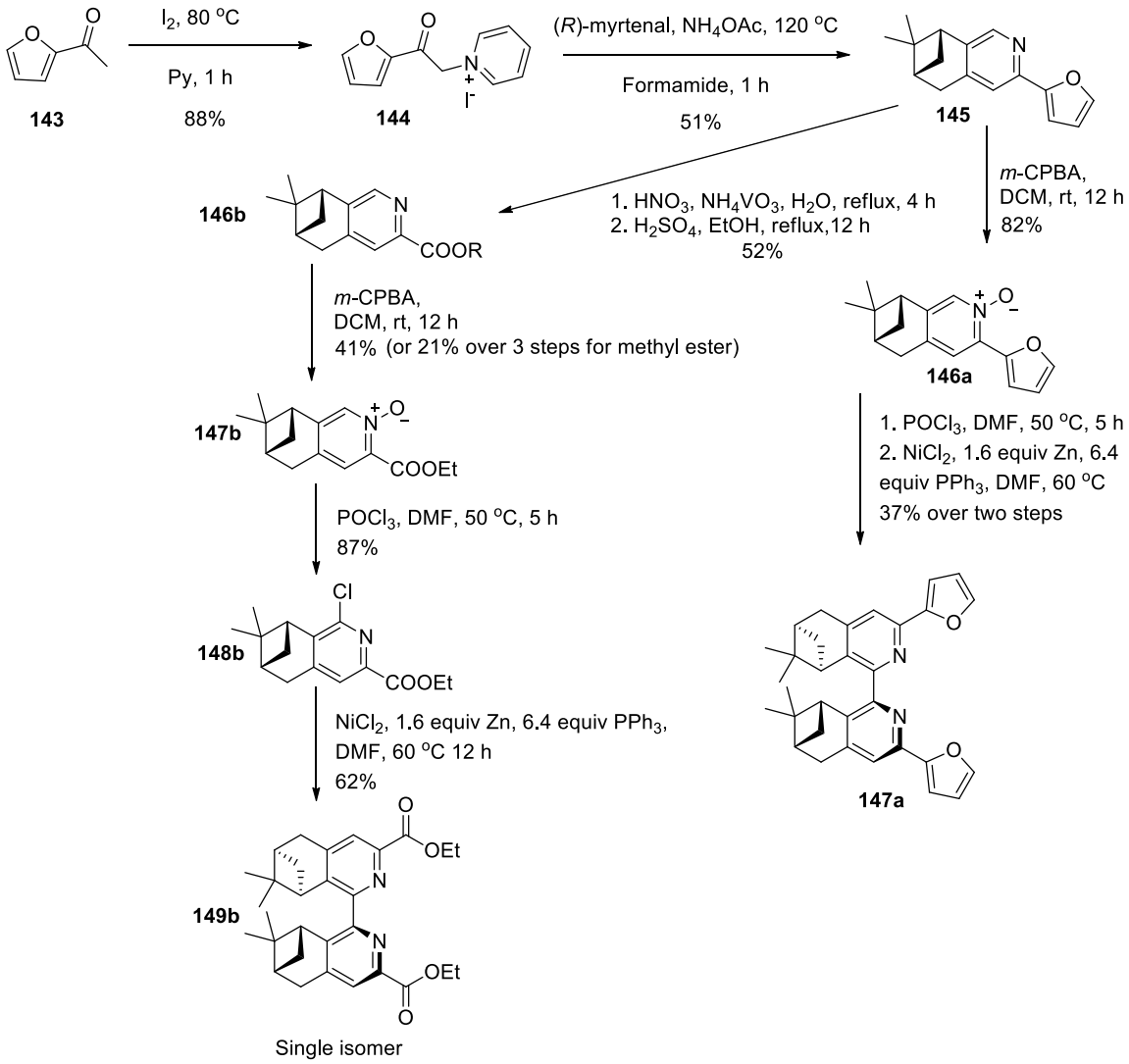
For ^{1}H For ^{13}C

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (s, 6 H, 1), 1.25 (d, *J* = 9.8 Hz, 2 H, 3), 1.33 (s, 6 H, 2), 2.39-2.30 (m, 4 H, 7), 2.66-2.62 (m, 2 H, 6), 3.14-3.02 (m, 4 H, 4+5), 7.33 (s, 2 H, 8), 7.89 (s, 2 H, 9), 8.39 (s, 4 H, 10).

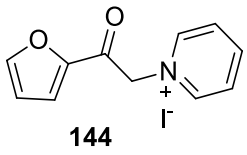
For ^{13}C see p. 152.

In agreement with the literature.[57]

5.6.2. Synthesis of Other bipyridine *N',N''*-dioxides.



*1-[2-(furan-2-yl)-2-oxoethyl]pyridin-1-ium iodide (**144**)*

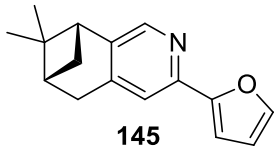


A 250 mL round-bottomed flask was equipped with stirring bar, flushed with Argon and charged with 2-acetylfuran **143** (5 g, 45.4 mmol, 1.0 equiv). A reflux condenser was attached, and an excess of pyridine (22.9 mL, 284 mmol, 6.26 equiv) was added via syringe to dissolve **143**. Crystalline Iodine (13.83 g, 54.5 mmol, 1.2 equiv) was added in one portion. The resulting mixture was refluxed for an hour and turned dark brown. The mixture was allowed to cool and crystallise, the resulting crystals were washed on a filter with EtOAc (3×50 mL). The obtained

solid was dried under vacuum affording solvent-free target salt **144** as a 1/1.39 mixture with pyridinium iodide (24.2 g, 40.14 mmol, ω=52.3%, 88% yield). The crude product was used directly in the next step.

^{1}H NMR (DMSO-d_6, 400 MHz): δ 6.28 (s, 2 H), 6.89 (dd, *J* = 3.6, 1.7 Hz, 1 H), 7.71 (d, *J* = 3.6 Hz, 1 H), 8.22 (d, *J* = 1.5 Hz, 1 H), 8.28 (t, *J* = 7.1 Hz, 2 H), 8.74 (t, *J* = 7.8 Hz, 1 H) 9.01 (d, *J* = 5.5 Hz, 2 H). In agreement with the literature.[165]

*(1R,9R)-5-(furan-2-yl)-10,10-dimethyl-4-azatricyclo[7.1.1.0^{2,7}]undeca-2(7),3,5-triene (**145**)*

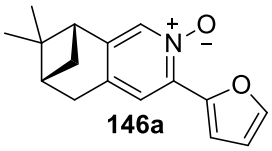


145

Unrecrystallised Kröhnke salt **144** (1.0 equiv, 9.63 mmol, 5.81 g, $\omega = 52.3\%$) was placed in an argon-flushed 100 mL round-bottomed flask and dissolved in dry formamide (25.7 mL). Ammonium acetate (2.0 equiv, 19.3 mmol, 932 mg) was added, and the mixture was heated to 50 ℃ and stirred 20 minutes until all solids dissolved and the dark-brown solution was formed. (-)-Myrtenal (1.1 equiv, 10.6 mmol, 1.59 g) was added dropwise via syringe, and the mixture was heated to 100 ℃ and stirred for 18 hours. The mixture became dark and was cooled to rt, diluted with hexanes (50 mL), and precipitated solid was transferred to a 250 mL separation funnel, quenched with 100 mL of saturated Na_2CO_3 solution and extracted with *n*-hexane (3×30 mL). The combined extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The resulting crude material was purified by column chromatography, using Hex:EtOAc with gradient elution (10:1 → 5:1, R_f=0.16) to afford the target isoquinoline **145** as a brown oil (1.16 g, 4.87 mmol, 51% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.64 (s, 3 H), 1.22 (d, *J* = 9.6 Hz, 1 H), 1.41 (s, 3 H), 2.30 (tt, *J* = 5.8, 2.9 Hz, 1 H), 2.70 (dt, *J* = 9.6, 5.8 Hz, 1 H), 2.83 (t, *J* = 5.5 Hz, 1 H), 3.01 (d, *J* = 2.8 Hz, 2 H), 6.51 (dd, *J* = 3.4, 1.8 Hz, 1 H), 7.00 (s, 1 H), 7.50 (dd, *J* = 1.7, 0.8 Hz, 2 H) 8.13 (s, 1 H). In agreement with the literature.[154]

*(1R,9R)-5-(furan-2-yl)-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-trien-4-ium-4-olate (**146a**)*



146a

Isoquinoline **145** (400 mg, 1.67 mmol, 1 equiv) was dissolved in DCM (20 mL) to give a brown solution and cooled to 0 °C. *m*-CPBA (3.0 equiv, 5.02 mmol, 867 mg,) was added in portions, and mixtures colour changed to a bright yellow. The reaction mixture was stirred for 5 h at rt, quenched with a saturated solution of $NaHCO_3$ (10 mL) and then extracted with Et_2O (3×10 mL). The combined ethereal layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford **146a** as a pale yellow oil (350 mg, 1.37 mmol, 98%).

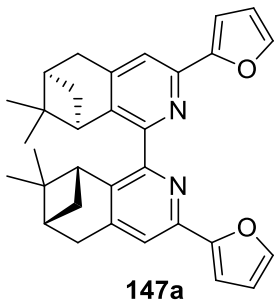
^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.66 (s, 3 H), 1.24 (d, *J* = 9.0 Hz, 1 H), 1.37 (s, 3 H), 2.29 (tt, *J* = 5.7, 2.8 Hz, 1 H), 2.69 (dq, *J* = 9.7, 5.1 Hz, 2 H), 2.97 (d, *J* = 2.3 Hz, 2 H), 6.56 (dd, *J* = 3.4, 1.7 Hz, 1 H), 7.52 (d, *J* = 1.1 Hz, 1 H), 7.66 (s, 1 H), 7.88 (s, 1 H) 7.94 (d, *J* = 3.4 Hz, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 21.5, 26.0, 31.6, 32.2, 39.6, 40.1, 44.6, 112.6, 115.7, 121.4, 134.9, 136.5, 138.0, 142.9, 143.3, 145.8.

$[\alpha]_D^{20}$ = -81° (*c* 0.333, CH_2Cl_2).

In agreement with the literature.[166]

*(1R,9R)-5-(furan-2-yl)-3-[(1R,9R)-5-(furan-2-yl)-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5trien-3-yl]-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-triene (**147a**)*



147a

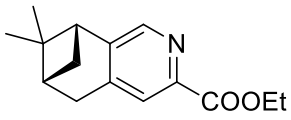
N-Oxide **146a** (1.0 equiv, 350 mg, 1.37 mmol) was dissolved in dry DMF (6.85 mL) in 25 mL round-bottomed flask, and $POCl_3$ (5.0 eq, 6.85mmol, 638 µl) was added dropwise via syringe at rt. The reaction was immediately heated to 50 °C using a thermostat, and stirred for 18 hours. The reaction was quenched with saturated $NaHCO_3$ until CO_2 emission stopped (approx. 20 mL),

and the mixture was transferred to a 100 mL separating funnel and extracted with Et_2O (3×15 mL). The combined ethereal extracts were dried over anhydrous Na_2SO_4, filtered, and then concentrated in vacuum. The resulting brown 2-chloropyridine DMF solution was used directly in the next step.

A dry 50 mL test tube was equipped with a stirring bar, dry Zinc powder 60 mesh (1.6 equiv, 2.19 mmol, 143 mg), was sealed and dry DMF (24.6 mL) was added via a syringe. The flask was evacuated and backfilled with nitrogen on a Schlenk line (×3). Two drops of TMSCl were added to the stirred suspension of Zn powder and mixture was heated using a heat gun to approx. 60 ℃ until TMSCl started to boil. When Zn dust precipitated at the bottom of the flask, nickel(II) chloride (1.6 equiv 2.19 mmol, 284 mg) was added in one portion, followed by addition of Ph_3P (6.4 equiv, 8.77 mmol, 2.30 g). The mixture was heated to 60 ℃ and stirred for 1 hour until a dark red colour was observed. Then a DMF solution of the furanyl-2-chloropyridine (*ca*. 1.37 mmol, 1 equiv) in DMF (2 mL) was added dropwise via syringe. The mixture became darker and was stirred for 12 hours at 60 ℃. Next, an excess of aqueous ammonia was added (30 mL) and the mixture was transferred to a separating funnel and extracted with EtOAc (3×20 mL). The combined organic extracts were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid. The solid was dissolved in hexanes/Et_2O mixture (*ca*. 1:2) and subjected to a long *silica* column (500 g, 50×7.5 cm), washed first with 500 mL of hexanes until all Ph_3P was removed, and then eluted using Hex:EtOAc (10:1 to EtOAc) gradient to afford **147a** as a colourless oil (122 mg, 0.256 mmol, 37% yield over two steps).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.63 (s, 6 H), 1.20 (d, *J* = 8.8 Hz, 2 H), 1.40 (s, 6 H), 2.29 (tt, *J* = 5.8, 2.9 Hz, 2 H), 2.69 (dt, *J* = 9.6, 5.7 Hz, 2 H), 2.81 (t, *J* = 5.5 Hz, 2 H), 2.99 (d, *J* = 2.6 Hz, 4 H), 6.50 (dd, *J* = 3.4, 1.8 Hz, 2 H), 6.98 (d, *J* = 3.3 Hz, 2 H), 7.49 (s, 4 H) 8.11 (s, 2 H).

*Ethyl (1R,9R)-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-triene-5-carboxylate (**35b**)*



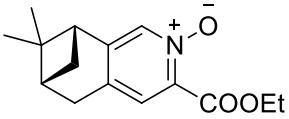
146b

Isoquinoline **144** (1.0 equiv, 0.82 mmol, 197 mg) was dissolved in 5 mL of *n*-hexane and transferred to an Ar-filled test tube. Then a pinch of crystalline NH_4VO_3 (1-2 mol%, 8.2µmol, 1-2 mg) was dissolved in water (0.5 mL) and added via syringe followed by addition of 260 µl of concentrated HNO_3. The mixture was heated under reflux for 4 hours and evaporated until dry at 180 °C. Then resulting brown mass was dissolved in 5 mL of EtOH and 200 µl of concentrated H_2SO_4 was added. The mixture was refluxed for 12 hours and then diluted with 10 mL of hexane, neutralised with 5 mL of sat. $NaHCO_3$ and extracted with *n*-hexane (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum. The resulting brown oil was purified by column chromatography using Hex:EtOAc gradient (3/1 → 2/1, R_f= 0.15 (3/1)) to afford **146b** as a colourless oil (105 mg, 0.43 mmol, 52% yield).

^{1}H NMR (400 MHz): δ 0.60 (s, 3 H), 1.19 (d, *J* = 9.6 Hz, 1 H), 1.41 (s, 3 H), 1.43 (t, *J* = 7.2 Hz, 3H), 2.33 (tt, *J* = 5.8, 2.9 Hz, 1 H), 2.71 (dt, *J* = 9.8, 5.7 Hz, 1 H), 2.89 (t, *J* = 5.5 Hz, 1 H), 3.03 (d, *J* = 2.6 Hz, 2 H), 4.46 (q, *J* = 7.2 Hz, 2 H), 7.93 (s, 1 H), 8.28 (s, 1 H).

In agreement with the literature.[154]

*(1R,9R)-5-(ethoxycarbonyl)-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-trien-4-ium-4-olate (**147b**)*



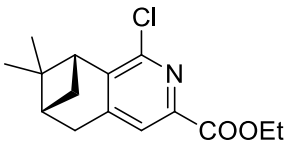
147b

Isoquinoline **146b** (700 mg, 2.85 mmol) was dissolved in DCM (34 mL) to give a yellow solution and cooled to 0 °C. *m*-CPBA (3.0 equiv, 8.5 mmol, 1.47 g) was added in portions and reaction mixture was stirred for 12 hours at rt and then diluted with Et_2O and quenched with a saturated solution of $NaHCO_3$ (10 mL). Then aqueous layer was extracted with ether (3×15 mL), and the combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The material was purified by column chromatography on *silica* using

Hex/EtOAc/MeOH eluent (10/10/1, R_f=0.14) to afford **147b** as a colourless oil (305 mg, 1.17 mmol, 41% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.67 (s, 3 H), 1.22 (d, *J* = 9.3 Hz, 1 H), 1.39 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H) 2.31 (tt, *J* = 5.8, 2.9 Hz, 1 H), 2.67-2.74 (m, 2 H), 2.93 (d, *J* = 2.7 Hz, 2 H), 4.44 (q, *J* = 7.1 Hz, 2 H), 7.35 (s, 1 H) 7.88 (s, 1 H).

*Ethyl (1R,9R)-3-chloro-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-triene-5-carboxylate (**148b**)*



148b

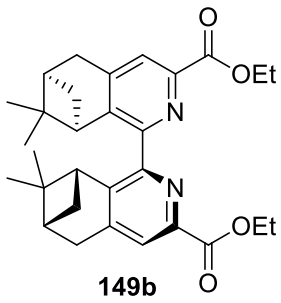
N-Oxide **147b** (1.0 equiv, 305 mg, 1.17 mmol) was dissolved in dry DMF (5.85 mL) in 25 mL round-bottomed flask and $POCl_3$ (5.0 equiv, 5.84 mmol, 2.40 g, 544 µl) was added dropwise via syringe at rt. The reaction was immediately heated to 50 °C using a thermostat, and stirred for 15 hours. The reaction was quenched with saturated $NaHCO_3$ until CO_2 emission stopped (approx. 50 mL), and then the mixture was transferred to a 100 mL separation funnel and extracted with Et_2O (3×20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting brown oil was purified by flash chromatography using Hex:EtOAc eluent (1:1, R_f = 0.70) to afford **148b** as a pale yellow oil (285 mg, 1.02 mmol, 87% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.54 (s, 3 H), 1.10 (d, *J* = 9.9 Hz, 1 H), 1.36 (dt, *J* = 8.3 Hz, 0.9 Hz) 1.37 (s, 3 H), 2.26 (tt, *J* = 5.7, 2.8 Hz, 1 H), 2.65 (dt, *J* = 10.0, 6.0 Hz, 1 H), 2.91-3.01 (m, 2 H), 3.26 (t, *J* = 5.5 Hz, 1 H), 4.38 (dd, *J* = 7.1, 1.0 Hz, 2 H) 7.78 (s, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 14.4, 21.3, 26.0, 30.8, 33.3, 38.8, 39.8, 43.8, 62.1, 124.0, 145.1, 145.8, 148.3, 148.8, 164.6.

IR: υ 2973, 2933, 2871, 2130, 1974, 1740, 1715, 1585, 1541, 1465, 1442, 1422, 1384, 1364, 1336, 1301, 1251, 1221, 1200, 1176, 1137, 1104, 1028, 962, 928, 910, 883, 855, 840, 789, 747, 698, 652, 608, 544, 499 cm^{-1}.

*Ethyl (1R,9R)-3-[(1R,9R)-5-(ethoxycarbonyl)-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-trien-3-yl]-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-triene-5-carboxylate (**149b**)*

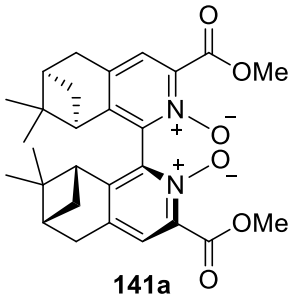


149b

A dry 25 mL test tube was equipped with a stirring bar, dry Zinc powder (60 mesh) (1.6 equiv, 0.57 mmol, 37 mg), sealed, and dry DMF (6.4 mL) was added through a syringe. The flask was evacuated and backfilled with nitrogen on a Schlenk line (×3). A drop of TMSCl was added to the stirring suspension of Zn powder and the mixture was heated with a heat gun to approx. 60 °C until TMSCl started to boil. When Zn dust precipitated to the bottom of the flask, nickel(II) chloride (1.6 equiv, 0.57 mmol, 74 mg) was added in one portion, followed by addition of Ph_3P (6.4 equiv, 2.29 mmol, 600 mg). The mixture was heated to 60 °C and stirred for 1 hour, until a dark red colour was observed. Next, the solution of 2-chloropyridine **148b** (0.357 mmol, 1 equiv, 160 mg) in DMF (1 mL) was added dropwise via syringe. The mixture became darker and was stirred for 23 hours at 60 °C. Then an excess of aqueous ammonia was added (10 mL) and the mixture was extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford a white solid. The solid was dissolved in hexanes/Et_2O mixture (*ca*. 1:2) and subjected to a long *silica* column (250 g, 50×3.5 cm), washed first with hexanes:Et_2O mixture (20/1) until all Ph_3P was removed, and then with pure EtOAc to afford **149b** as a colourless oil (54 mg, 0.11 mmol, 62% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.71 (s, 6 H), 1.28 (d, *J* = 3.1 Hz, 2 H), 1.31 (s, 6 H), 1.38 (t, *J* = 7.1 Hz, 6 H), 2.29 (tt, *J* = 5.5, 2.5 Hz, 2 H), 2.59 (dt, *J* = 9.8, 5.5 Hz, 2 H), 2.76 (t, *J* = 5.5 Hz, 2 H), 3.08 (dd, *J* = 3.1, 0.6 Hz, 2H), 4.42 (q, *J* = 7.1 Hz, 4 H) 7.91 (d, *J* = 0.6 Hz, 2 H).

*(1R,9R)-5-(ethoxycarbonyl)-3-[(1R,9R)-5-(ethoxycarbonyl)-10,10-dimethyl-4-oxido-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-trien-4-ium-3-yl]-10,10-dimethyl-4-azatricyclo[7.1.1.0²,⁷]undeca-2(7),3,5-trien-4-ium-4-olate (**141a**)*

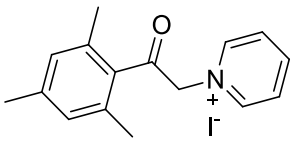


141a

Bipyridine **149b** from the previous step (54 mg, 0.11 mmol, 1.0 equiv) was dissolved in DCM (1.2 mL) in a reaction tube, and *m*-CPBA (6.0 equiv, 107 mg, 0.624 mmol) was added at rt. The mixture was stirred for 12 hours at rt, quenched with saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting solid was dissolved in methanol-EtOAc and purified by flash chromatography, eluting with Hexane:EtOAc:MeOH mixture (10/10/2). ^1H NMR analysis showed 53% yield of **141a** (34 mg impure fraction, 90 mass% of **141a**), and impurity of *m*-CPBA. The solids were dissolved in DCM and washed with $NaHCO_3$ saturated solution (3×5 mL), dried over anhydrous $MgSO_4$ and concentrated in vacuum to afford pure **141a** as a colourless oil (5 mg, 0.01 mmol, 8% yield)

^1H NMR ($CDCl_3$, 400 MHz): δ 0.72 (s, 6 H), 1.27 (s, 6 H), 1.42 (d, *J* = 10.2 Hz, 2 H), 2.26 (tt, *J* = 5.5, 2.7 Hz, 2 H), 2.33 (t, *J* = 5.4 Hz, 2 H), 2.63 (dt, *J* = 10.6, 5.5 Hz, 2 H), 2.99 (s, 4 H), 3.92 (s, 6 H) 7.53 (s, 2 H).

*1-[2-oxo-2-(2,4,6-trimethylphenyl)ethyl]pyridin-1-ium iodide (**142**)*



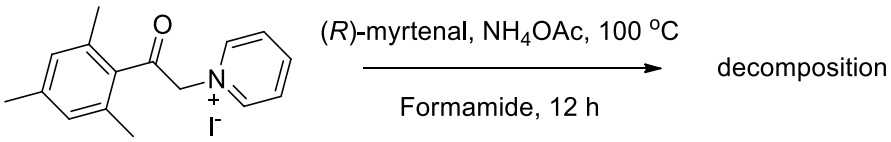
142

A 50 mL round-bottomed flask was equipped with a stirring bar and flushed with argon. 2,4,6-trimethylacetophenone (5.0 g, 30.8 mmol, 1.0 eqiuv.) was added via syringe, and the flask was equipped with a reflux condenser. An excess of pyridine (13 mL, 161 mmol, 5.2 equiv) was

added via syringe. Iodine (9.39 g, 37.0 mmol, 1.2 equiv) was added in small portions at rt under vigorous stirring. The mixture was refluxed for 1 hour, then cooled and diluted with hexanes (35 mL). The dark brown viscous slurry was formed. 20 mL of absolute ethanol was added, and the slurry was at first dissolved and then beige crystals were precipitated. The mixture was cooled to rt, transferred to a filter and washed with absolute ethanol (3×30 mL) under vacuum suction and the solid residue was dried. ^{1}H NMR analysis showed target Kröhnke salt **142** as a mixture with pyridinium iodide (ω=85%, 9.1 g, 21.10 mmol, 68% yield).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 2.48 (s, 3 H), 2.69 (s, 6 H), 6.41 (s, 2 H), 7.20 (s, 2 H), 8.50 (t, *J* = 6.9 Hz, 2 H), 8.97 (t, *J* = 7.8 Hz, 1 H) 9.25 (d, *J* = 5.6 Hz, 2 H).

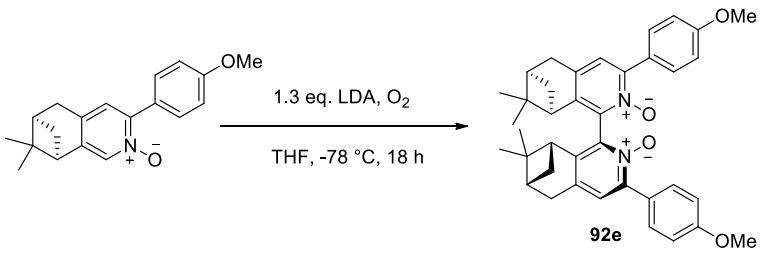
*Attempted Kröhnke cyclisation of **142***



142

Crude Kröhnke salt **142** (1.0 equiv, 1.57 mmol, 575 mg, ω = 85%) was placed in an Argon-flushed 25 mL round-bottomed flask and dissolved in dry formamide (4 mL). Then ammonium acetate (2.0 equiv, 3.13 mmol, 151 mg) was added, and the mixture was heated to 50 °C and stirred approx. 20 minutes until all solids had dissolved to form a dark-brown solution. Next, (*R*)-(-)-myrtenal (1.1 equiv, 1.72 mmol, 259 mg) was added dropwise via a syringe, and the mixture was heated to 100 °C and stirred for 15 hours. The mixture became darker and was cooled to rt. The mixture was diluted with hexanes (50 mL) and transferred to a 100 mL separating funnel, where it was quenched with 20 mL of saturated Na_2CO_3 solution and extracted with *n*-hexane (3×10 mL). The combined hexane layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The resulting brown oil showed no target pyridine signals in the ^{1}H NMR spectrum.

Synthesis of ***92e***



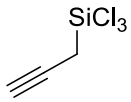
A 50 mL oven-dried round-bottomed flask was equipped with stirring bar, flushed with dry argon and sealed. Diisopropylamine (465 µL, 3.3 mmol, 1.3 equiv) was added dropwise via syringe, and 2.8 mL of MS 4Å-dried THF was added to form a colourless solution. The mixture was then cooled to 0 ℃ using an ice bath and *n*BuLi in hexanes (2.5 M) was added cautiously dropwise via syringe (1.35 mL, 3.3 mmol, 1.3 equiv) After the addition, the water ice bath was removed, and, after 10 minutes of stirring, the mixture was cooled to -78 ℃ using a dry ice bath. The solution of mono-*N*-oxide (718 mg, 2.54 mmol, 1.0 equiv) in 4 mL of dry THF was added dropwise with vigorous stirring, and the mixture turned dark-blue. A dry O_2 balloon was attached instantly, with a needle dipped into the stirring solution. After stirring overnight at –78 ℃, the mixture turned brown and was quenched with sat. $NaHCO_3$ solution (20 mL). The aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were separated and dried over $MgSO_4$, concentrated under reduced pressure, and the crude material was purified by column chromatography in gradient (5/1 PE:EtOAc→20/1 EtOAc:MeOH) to afford **92e** as a pale yellow solid (224 mg, 0.38 mmol, 30% yield), m.p. 237-239 ℃

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.82 (s, 6 H), 1.24 (d, J = 9.8 Hz, 2 H), 1.28 (s, 6 H), 2.29 (d, J = 5.5 Hz, 4 H), 2.58 (dt, J = 9.8, 5.7 Hz, 2 H), 3.07—2.96 (m, 4 H), 3.83 (s, 6 H), 6.95—6.91 (m, 4 H), 7.26 (m, 2 H), 7.92—7.88 (m, 4 H).

In agreement with the literature.[166]

5.7.Synthesis of Allenyl- and Propargyltrichlorosilanes

*Propargyltrichlorosilane (**161**)*



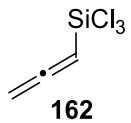
161

An oven-dried test tube was charged with dry CuCl (5 mol%, 0.5 mmol, 50 mg), sealed, evacuated under high vacuum at 100 ℃ and filled with dry nitrogen. Freshly distilled Et_2O (20 mL) was added via syringe and a suspension formed. Hünig's base (2.0 equiv, 20 mmol, 3.48 mL) was added dropwise via syringe at rt. The mixture was stirred for 5 minutes, and propargyl chloride (1.0 equiv 10 mmol, 723 µL) was added via syringe dropwise. The mixture changed colour to yellow, and an orange precipitate was formed. $HSiCl_3$ (2.2 eq, 22 mmol, 2.22 mL) was added slowly dropwise via syringe at rt. A white precipitate was formed, and the mixture began to heat, and the reaction vessel was immersed in a cold bath. After 6 hours of stirring, the mixture changed its colour to light brown and was analysed by ^{1}H NMR using naphthalene as an internal standard. NMR analysis showed the solution of target silane **161** (0.28 M, 23 mL, 6.44 mmol, 64%).

The silane solution was used directly in racemic reaction with benzaldehyde.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.11 (t, *J* = 2.9 Hz, 1 H, ≡C***H***) 2.42 (d, *J* = 2.9 Hz, 2 H, C***H***$_2$Si), in agreement with the literature. [139]

*Allenyltrichlorosilane (**162**)*



162

An oven-dried sealed tube was charged with dry $Ni(acac)_2$ (5 mol% 1.0 mmol, 260 mg), evacuated under high vacuum at 100 ℃ and filled with dry nitrogen. Freshly distilled Et_2O (40 mL) was added via syringe and a light-green suspension was formed. Hünig's base (2.0 equiv, 40 mmol, 6.96 mL) was added dropwise via syringe at rt. The mixture was stirred for 5 minutes, and propargyl chloride (1.0 equiv 20 mmol, 1.44 mL) was slowly added via syringe. Then $HSiCl_3$ (2.2 equiv, 44 mmol, 4.44 mL) was added by syringe at rt. The colour immediately changed to light-cyan, and the reaction started to heat, following by formation of a cyan precipitate. The

tube was placed in an ice bath and stirred for 6 hours slowly warming to rt, and, after 6 hours of stirring, changed its colour to dark green. NMR analysis using naphthalene as an internal standard showed the target silane **162** in Et_2O solution (0.11 M, 46 mL, 4.4 mmol, 22 %). The silane solution was used directly in racemic reaction with benzaldehyde.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.90 (d, *J* = 7.0 Hz, 2 H, =•=C***H***$_2$) 5.31 (t, *J* = 7.0 Hz, 1 H, =C***H***Si). In agreement with the literature. [139]

5.7.1. Distillation of Allenyltrichlorosilane

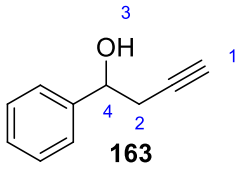
The resulting reagent reaction mixture was filtered using an oven-dried glass filter under a dry nitrogen atmosphere into a 100 mL round-bottomed oven-dried flask. A distillation apparatus, connected to dry nitrogen manifold, was attached, and the ether was distilled off at the atmospheric pressure. The resulting brown concentrate was transferred via syringe to a smaller oven-dried distillation apparatus and distilled bulb-to-bulb under 1 mbar at rt into a dry ice-cooled receiving flask.

NMR analysis with naphthalene as an internal standard showed the target silane **162** as a solution in Hünig's base (1/25 by molar ratio), and its concentration (0.44 M) was determined, (0.75 mmol, 1.7 mL, 2% yield). The solution was used directly in asymmetric reaction with benzaldehyde.

5.8. General Procedure for the preparation of racemic allenyl and homopropargyl alcohols

A dry reaction tube was equipped with a stirring bar and sealed. Benzaldehyde (1.0 equiv, 0.5 mmol, 53 mg) was dissolved in DMF (5 mL) and silane **161** or **162** (1.5 equiv, 0.75 mmol, 0.1 M, 7.5 mL) was added at 0 ℃ via syringe. The reaction was stirred 18 hours, quenched with saturated $NaHCO_3$, and extracted with Et_2O (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure (50 mbar), and the resulting colourless oil was purified by flash chromatography using Hex:EtOAc mixture with gradient (20/1 → 5/1) to afford pure **163** or **164** as racemates.

*(±)-1-phenylbut-3-yn-1-ol (**163**)*



163

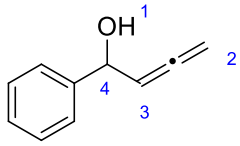
Colourless oil, 61 mg, 0.42 mmol, 85% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.08 (t, *J* = 2.6 Hz, 1 H, 1), 2.36-2.37 (m, 1 H, 3), 2.65 (dd, *J* = 6.3, 2.5 Hz, 2 H, 2), 4.89 (td, *J* = 6.3, 3.4 Hz, 1 H, 4) 7.29-7.41 (m, 5 H, *Ph*)

In agreement with the literature.[139]

HPLC (Chiralcel IB-3, hexane/2-propanol = 98:2, 1 mL/min, UV detection at 220 nm) showed 0% *ee*: t_R = 16.07 min, t_S = 20.21 min.

*(±)-1-phenylbuta-2,3-dien-1-ol (**164**)*



164

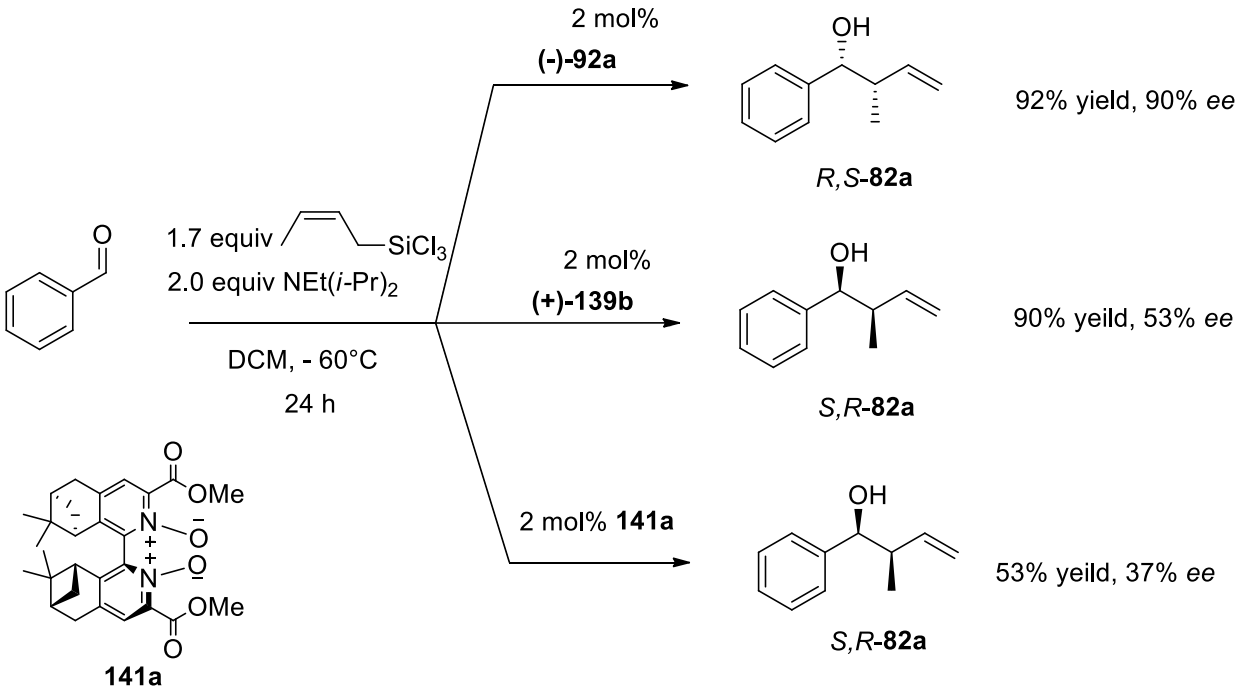
Colourless oil. 58 mg, 0.40 mmol, 80% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.12 (s, 1 H, 1), 4.94 (dt, *J* = 6.6, 2.3 Hz, 2 H, 2), 5.29 (ddt, *J* = 6.5, 3.9, 2.3 Hz, 1 H, 4), 5.46 (q, *J* = 6.5 Hz, 1 H, 3) 7.36-7.42 (m, 5 H, ***Ph***), in agrement with the literature.[139]

HPLC (Chiralcel IB-3, hexane/2-propanol = 98:2, 1 mL/min, UV detection at 220 nm) racemate: t_R = 13.19 min, t_S = 16.92 min.

5.9.Asymmetric reactions between benzaldehydes and trichlorosilyl reagents

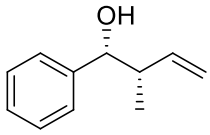
5.9.1. Crotylation of Benzaldehyde with (+)-139b, (-)-92a and 141a



General procedure

Benzaldehyde (1 equiv, 0.5 mmol, 53 mg) and NEt(*i*-Pr)$_2$ (2.0 equiv, 1.0 mmol, 174 µL) were added to a dry, sealed nitrogen-filled test tube, equipped with a magnetic stirring bar, and dissolved in a solution of the organocatalyst **(+)-139b**, **(-)-92a**, or **141a** (2 mol%, 0.01 mmol) in dry DCM (2 mL). Then the mixture was immersed in an ethanol bath and cooled to -60 ℃ using a cryostat. Next, (*Z*)-crotyltrichlorosilane (*Z*/*E* 98:2) (1.7 equiv, 0.85 mmol, 161 mg) was added dropwise over 5 minutes, and the mixture was stirred for 18 hours at -60 ℃. The mixture was quenched with $NaHCO_3$ (5 mL), filtered using vacuum suction and extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude material was purified using flash chromatography with Hex/EtOAc eluent mixture (10:1) to afford an enantioenriched *syn*-crotylated alcohol **82a**, which was analysed by chiral HPLC. [57]

*(+)-(1R,2S)-2-Methyl-1-phenylbut-3-en-1-ol ((R,S)-**82a**)*



R,S-**82a**

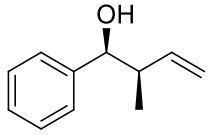
Using 8 mg of (-)-**92a** as catalyst. Colourless oil, 75 mg, (90% yield).

^{1}H NMR ($CDCl_3$, 400 MHz): δ_H , 1.01 (t, *J* = 6.6 Hz, 3 H, C***H***$_3$), 2.00 (d, *J* = 3.2 Hz, 1 H, O***H***), 2.56-2.61 (m, 1H, C***H***Me) 4.62 (dd, *J* = 5.0, 3.5 Hz, 1 H, C***H***OH) 5.09-5.11 (m, 2 H, =C***H***$_2$), 5.73-5.82 (m, 1 H, C***H***=CH_2), 7.27-7.35 (m, 5 H, ***Ph***).

HPLC (Chiralcel IC-3, hexane/2-propanol = 98:2, 0.7 mL/min, UV detection at 220 nm) showed 90% ee: $t_{R,S}$ = 8.46 min (major), $t_{S,R}$ = 9.30 min (minor).

In agreement with the literature.[57]

*(+)-(1S,2R)-2-Methyl-1-phenylbut-3-en-1-ol ((S,R)-**82a**)*



S,R-**82a**

1. Using 8 mg of (+)-**139b** as catalyst. Colourless oil, 73 mg, (90% yield).

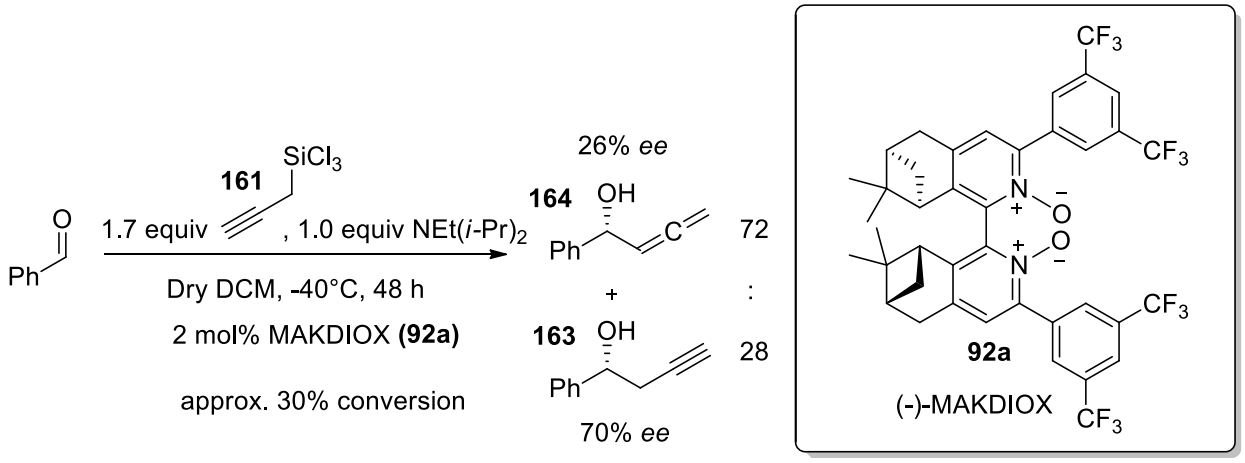
The ^{1}H NMR is equal to the enantiomer. Identified by HPLC.

HPLC (Chiralcel IC-3, hexane/2-propanol = 98:2, 0.7 mL/min, UV detection at 220 nm) showed 53% ee: $t_{R,S}$ = 8.45 min (minor), $t_{S,R}$ = 9.29 min (major).

2. Using 4.7 mg of **141a** as catalyst. Colourless oil, 44 mg (53% yield).

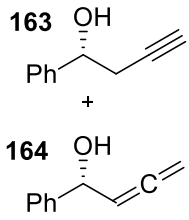
HPLC (Chiralcel IC-3, hexane/2-propanol = 98:2, 0.7 mL/min, UV detection at 220 nm) showed 37% ee: $t_{R,S}$ = 8.45 min (minor), $t_{S,R}$ = 9.29 min (major).

5.9.2. Reaction of Benzaldehyde with Propargyltrichlorosilane in presence of (-)-92a



Benzaldehyde (1 equiv, 0.5 mmol, 53 mg) and $NEt(^{i}Pr)_2$ (1.0 equiv, 0.5 mmol, 87 µL) was added to a dry, sealed and nitogen-filled test tube, equipped with a magnetic stirring bar, and dissolved with a solution of (-)-MAKDIOX (2 mol%, 0.01 mmol, 8 mg) (**92a**) in dry DCM (2 mL). Then, the mixture was immersed in an absolute ethanol bath and cooled to -40 ℃ using a cryostat. Next, undistilled concentrated propargyltrichlorosilane solution **161** (1.7 equiv, 0.85 mmol, 455 µl, C = 1.87 M) was added dropwise, and the mixture was stirred for 48 hours at -40 ℃. Then, the mixture was quenched with $NaHCO_3$ (5 mL), filtered under vacuum suction, and extracted with EtOAc (3×5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography using Hex:EtOAc gradient (10/1 → 5/1) to afford **82a** as a colourless oil, which was analysed by chiral HPLC.

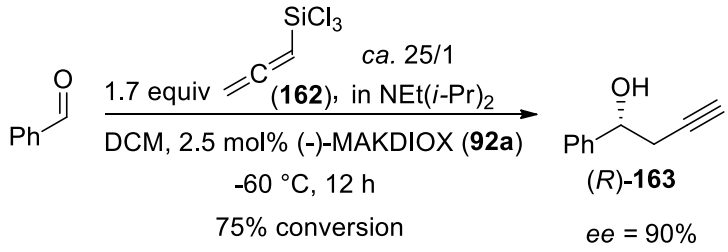
*(R)-1-phenylbut-3-yn-1-ol (**163**) and (R)-1-phenylbuta-2,3-dien-1-ol (**164**) mixture*



Colourless oil, 18 mg, (25% overall yield). NMR is equal to a homochiral product (see p. 167).

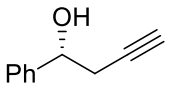
HPLC (Chiralcel IB-3, hexane/2-propanol = 98:2, 1 mL/min, UV detection at 220 nm) showed: 26% *ee* of **164**: t_R = 13.19 min (major), t_S= 16.92 min (minor), and 70% *ee* of **163**: t_R = 15.60 min (major), t_S= 19.62 min (minor). **164/163** = ∫ [t_R = 13.19 min (major)] / ∫ [t_R = 15.60 min (major)] = 72:28

5.9.3. The reaction of Benzaldehyde with Allenyltrichlorosilane in the presence of (-)-92a



Benzaldehyde (1 equiv, 0.26 mmol, 27.5 mg) was added to a dry, sealed and nitrogen-filled test tube, equipped with a magnetic stirring bar and dissolved by a stock solution of (-)-MAKDIOX (2.5 mol%, 6.5 µmol, 5 mg) (**92a**) in dry DCM (1.3 mL). The mixture was immersed in absolute ethanol bath and cooled to -60 °C using a cryostat. A distilled solution of propargyltrichlorosilane in Hünig base (1.7 equiv, 0.44 mmol, 1 mL, C = 0.44 M) was added dropwise, and the mixture was stirred for 12 hours at -60 °C. The mixture was then quenched with sat. $NaHCO_3$ (5 mL), filtered under vacuum suction washing filter with Et_2O (10 mL), and the liquid aqueous filtrate was extracted with Et_2O (3×5 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The resulting colourless oil was purified by flash chromatography using Hex:EtOAc gradient (10/1 → 5/1) to afford (*R*)-**163** as a colourless oil, which was analysed by chiral HPLC.

*(R)-1-phenylbut-3-yn-1-ol (**163**)*



163

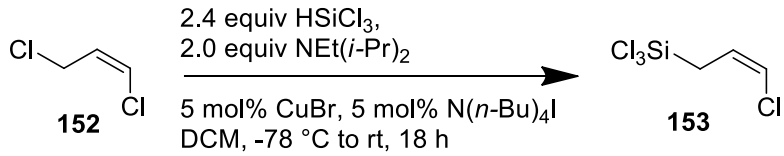
Colourless oil, 27 mg, 73% yield.

^{1}H NMR matches the racemate (see p. 167).

HPLC (Chiralcel IB-3, hexane/2-propanol = 98:2, 1 mL/min, UV detection at 220 nm) showed 90% *ee*: t_R = 16.07 min (major), t_S = 20.21 min. (minor)

5.10. Syntheses of γ-chloroallyltrichlorosilanes

5.10.1. *Z*-γ-chloroallyltrichlorosilane.

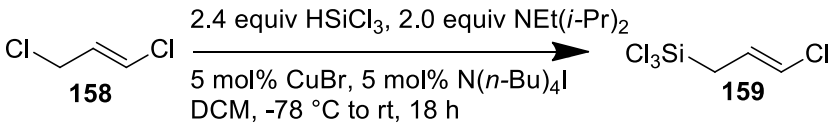


An oven-dried round-bottomed flask was charged with a stirring bar, (5 mol%, 1.15 mmol, 165 mg), and anhydrous NBu_4I (5 mol%, 1.15 mmol, 425 mg), flushed with dry nitrogen and sealed. Anhydrous distilled DCM was added via syringe (23 mL, 1 M in respect to **152**). Subsequently, $NEt(i\text{-}Pr)_2$ (2.0 equiv, 46.14 mmol, 8.04 mL) and *cis*-1,3-dichloropropene (1.0 equiv 23.07 mmol, 2 mL) were added by syringe. The mixture was then cooled to -78 ℃ by immersion into an ethanol bath with dry ice. After 5 minutes of stirring, trichlorosilane (2.4 equiv, 55.3 mmol, 5.6 mL) was added via syringe dropwise, very slowly with intensive stirring. The mixture was stirred for 15 minutes at -78 ℃, and then the dry ice bath was removed, and the mixture was stirred overnight for 18 hours. Next day, the seal was rapidly removed and direct bulb-to-bulb distillation kit was attached. The receiving flask was immersed into liquid nitrogen, and the mixture was distilled under 0.1 mbar first at rt and then using 200 ℃ hot plate until a solid in the mother flask and a colourless solution in the receiving flask were obtained. After that, 200 mL of dry distilled *n*-hexane was added in portions by syringe and the mixture was stirred vigorously. Two layers formed, and the upper layer was separated by syringe and transferred to an oven-dried 250 mL round-bottomed flask, equipped with a stirring bar. The remaining DCM layer was washed with 30 mL of dry *n*-hexane and the white precipitate was observed. The combined solution was concentrated in vacuum to approx. 20-25 mL, and the resulting cloudy brown liquid was distilled bulb-to-bulb in high vacuum (0.1 mbar) into a liquid nitrogen-cooled receiving flask, and the resulting colourless liquid was distilled again in the same way. The obtained distillate was analysed by NMR with naphthalene as an internal standard to reveal the pure *cis*-γ-chloroallyltrichlorosilane **153** as a colourless liquid (7.35 M, 2.5 mL, 18.5 mmol, 80% yield), bp = 28-29 ℃ at 0.1 mbar.

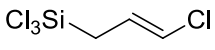
^{1}H NMR (400 MHz, $CDCl_3$): δ 2.57 (dd, *J* = 8.2, 1.3 Hz, 2 H, C***H***$_2$), 5.82 (t, *J* = 7.3 Hz, 1 H, =C***H***Cl), 6.27 (dt, *J* = 7.3, 1.3 Hz, 1 H, C***H***=CHCl).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 25.3 (***C***H_2), 121.3 (=***C***HCl), 122.03 (***C***=CHCl).

5.10.2. *E*-γ-chloroallyltrichlorosilane.



The *E*-isomer was obtained by analogous procedure from **158** (1.0 equiv, 25.20 mmol, 2.796 g), using anhydrous CuBr (5 mol%, 1.26 mmol, 180 mg) and anhydrous nBu$_4$NI (5 mol%, 1.26 mmol, 465 mg), dry distilled NEt(*i*-Pr)$_2$ (2.0 equiv, 50.4 mmol, 8.78 mL) and trichlorosilane (2.4. equiv, 60.47 mmol, 6.11 mL). 79% yield, colourless oil, b.p. 34-35 ℃ at 0.1 mbar (7.23 M, 2.7 mL, 19.9 mmol)

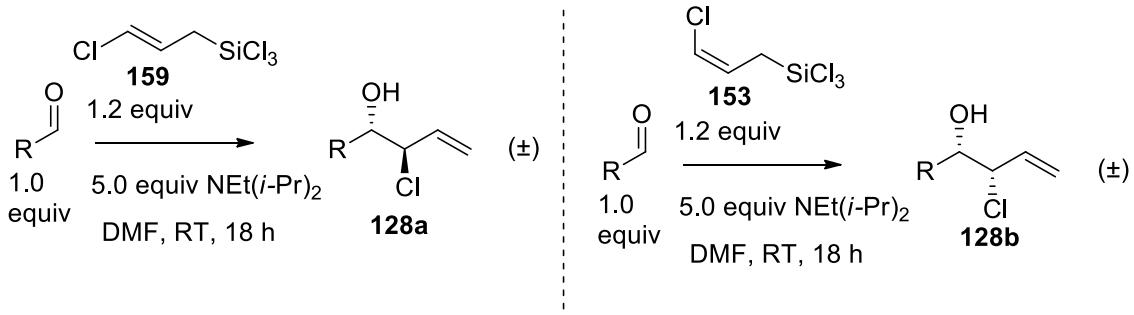


159

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.33 (dd, *J* = 8.2, 1.3 Hz, 2 H, C***H***$_2$), 5.88 (dt, *J* = 13.3, 8.2 Hz, 1 H, C***H***=CHCl), 6.09 (dt, *J* = 13.3, 1.3 Hz, 1 H, =C***H***Cl).

^{13}C NMR (101 MHz; $CDCl_3$): δ 27.7 (***C***H$_2$), 120.9 (***C***HCl), 122.9 (***C***H=CHCl).

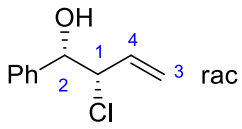
5.11. General procedure for racemic reactions of aldehydes with *Z*- or *E*-γ-chloroallyltrichlorosilane:



A dry test tube, equipped with a stirring bar, was charged with an aldehyde (1.0 equiv, 0.5 mmol) and sealed. Hünig's base (5.0 equiv, 2.5 mmol, 435 µL) and dry distilled DMF (2 mL) were added via syringe. The mixture was stirred for 2 minutes at rt, and the γ-chloroallyltrichlorosilane (1.2 equiv, 0.6 mmol) was added dropwise via syringe at rt, then the mixture was stirred for additional 12 hours. The mixture was extracted with diethyl ether (3×5 mL), and combined organic layers were dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. Flash chromatography using PE:EtOAc mixture with the gradient (10/1 →

5/1) afforded the desired chlorohydrin **128**. The chlorohydrin was used as a reference for chiral HPLC traces.

*(±)-2-chloro-1-phenyl-1-buten-1-ol ((±)-**128aa**)*



128aa

82% yield (75 mg, 0.41 mmol).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.61 (s, 1 H, broad, O*H*), 4.60-4.56 (m, 1 H, 1), 4.94 (d, *J* = 4.6 Hz, 1 H, 2), 5.28-5.22 (m, 2 H, 3), 5.93 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1 H, 4), 7.37-7.32 (m, 5 H, *Ph*).

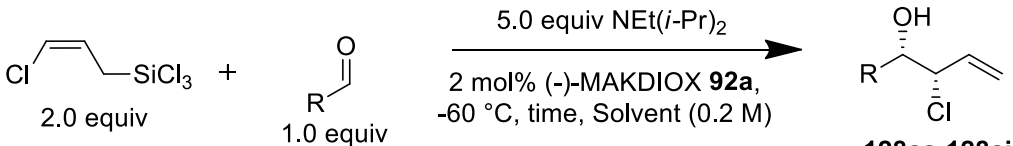
^{13}C NMR ($CDCl_3$, 101 MHz): δ 67.57 (***C***HCl), 77.13 (***C***HOH), 120.30 (=***C***H_2), 127.01 (*o*-***C***H), 128.50 (*m*-***C***H), 128.55 (*p*-***C***H), 133.60 (***C***H=CH_2), 139.45 (ipso-***C***).

NMR signals are in agreement with the literature.[167]

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 0% ee: $t_{R,R}$ = 13.62 min $t_{S,S}$ = 14.43 min.

Spectra of all obtained racemic chlorohydrins were identical to homochiral products **128** (Described in 5.11.1 and 5.11.2).

5.11.1. General procedure for the asymmetric reaction of aldehydes with *Z*-γ-chloroallyltrichlorosilane



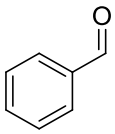
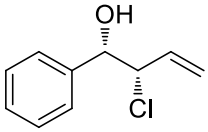
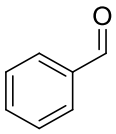
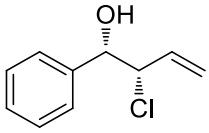
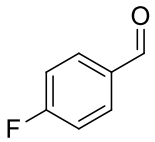
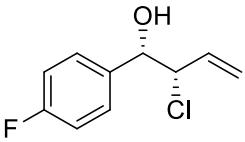
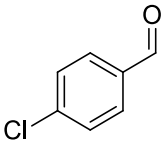
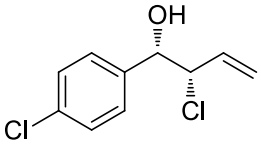
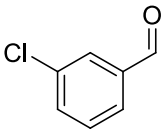
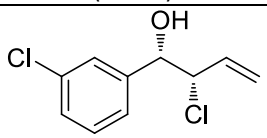
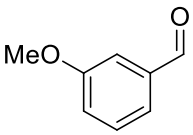
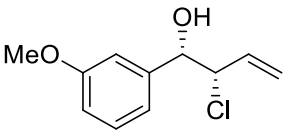
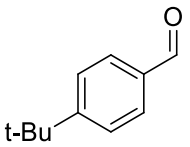
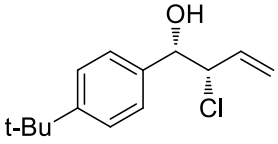
2.0 equiv **153**

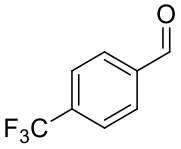
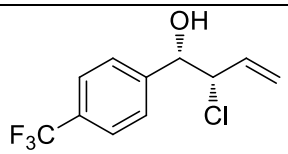
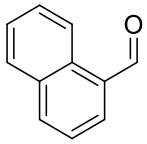
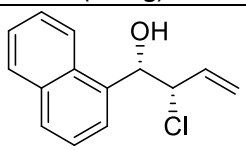
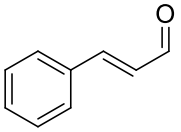
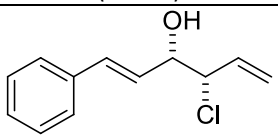
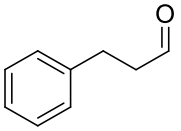
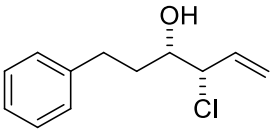
1.0 equiv

128aa-128aj

An oven-dried test tube, equipped with a magnetic stirring bar, was charged with dry crystals of (-)-MAKDIOX (2 mol%, 0.01 mmol, 8 mg) (**92a**), flushed with dry nitrogen and sealed. Hünig's base (5.0 equiv, 2.5 mmol, 435 µL) and an aldehyde (1.0 equiv, 0.5 mmol) were added

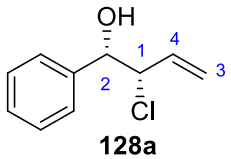
via syringe in dry solvent (1mL). The distilled solvent (DCM or EtCN) (2.5 mL) was added via syringe, and the mixture was stirred for 10 minutes until turned homogenous, and then was cooled to -60 ℃ using a cryostat. Pure ^{1}HNMR-titrated *Z*-γ-chloroallyltrichlorosilane (2.0 equiv, 1.0 mmol, 7.12 M, 140 μL) was added by volume dropwise via syringe, and the mixture was stirred for 72 hours at -60 ℃. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with Et_2O (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The resulting crude material was purified by column chromatography on *silica* eluting with hexane-ethyl acetate mixture in gradient (10/1→5/1) to afford the target *syn*-chlorohydrin **128a**-**128aj**.

Entry (product)	Aldehyde	Product **128**	Solvent	Time	Yield, %	% *ee*
1		 (**128a**)	EtCN	72 h	90	95
2		 (**128aa**)	DCM	72 h	89	88
3		 (**128ab**)	EtCN	72 h	91	93
4		 (**128ac**)	EtCN	72 h	85	91
5		 (**128ad**)	EtCN	72 h	93	78
6		 (**128ae**) lit	EtCN	72 h	90	91
7		 (**128af**)	EtCN	72 h	76	82

8		 **(128ag)**	EtCN	72 h	90	81
9		 **(128ah)**	EtCN	72 h	66	90
10		 **(128ai)**	EtCN	72 h	50	71
11		 **(128aj)**	EtCN	72 h	30	20

*(1S,2S)-2-chloro-1-phenylbut-3-en-1-ol (**128aa**)*

Colourless oil. (82 mg, 0.45 mmol, 90% yield). $[\alpha]_D^{25} = -49.0°$ (*c* 0.58, $CHCl_3$)

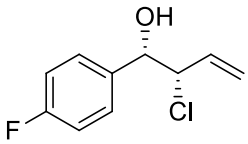


128a

^{1}H and ^{13}C NMR data is equal to that of the racemate (see p. 174). Identified by the same HPLC trace.

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 95% ee: $t_{R,R}$ = 13.63 min (minor), $t_{S,S}$ = 14.44 min (major).

*(1S,2S)-2-Chloro-1-(4-fluorophenyl)but-3-en-1-ol (**128ab**)*



128ab

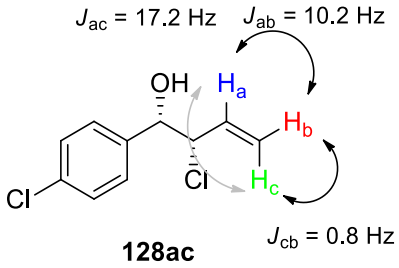
Colourless oil. 91 mg, 0.46 mmol, 91% yield.

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.58 (s, 1 H, O***H***), 4.58 (dd, *J* = 8.5, 4.5 Hz, 1 H, C***H***-Cl), 4.94 (dd, *J* = 4.5, 2.6 Hz, 1 H, C***H***-OH), 5.27—5.22 (m, 2 H, =C***H***$_2$), 5.93 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1 H, C***H***=CH_2), 7.37—7.31 (m, 4 H).

Chiral **GC** (Supelco β-CD 120 column, oven: 110 °C for 2 min, then 1.5 °C/min to 200 °C) showed 93% *ee*: $t_{R,R}$ = 51.15 min (minor) $t_{S,S}$ = 51.23 min (major).

In agreement with the literature.[168]

*(1S,2S)-2-Chloro-1-(4-chlorophenyl)but-3-en-1-ol (**128ac**)*



128ac

Colourless oil. 92 mg, 0.43 mmol, 85% yield.

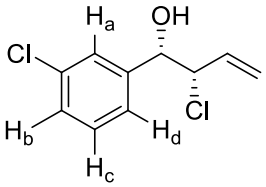
^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.91 (s, 1 H, O***H***) 4.45 (t, *J* = 7.6 Hz, 1 H, C***H***Cl), 4.68 (d, *J* = 6.8 Hz, 1 H, C***H***OH), 5.09 (dd, *J* = 10.2, 0.8 Hz, 1 H, H_b), 5.16 (dd, *J* = 17.1, 0.8 Hz, 1 H, H_c), 5.75 (ddd, *J* = 17.1, 10.2, 8.2 Hz, 2 H, H_a), 7.48—7.31 (m, 2 H, 2,6-***H*** in Ph), 7.95—7.76 (m, 2 H, 3,5-***H*** in Ph).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 69.43 (1 C, ***C***-Cl), 76.51 (***C***-OH), 120.15 (=***C***H$_2$), 128.64 (2 C, 2,6-***C*** in Ph), 128.87 (2 C, 3,5-***C*** in Ph), 134.21 (1 C, *ipso*-***C***-Cl), 134.52 (1 C, ***C***H=CH_2), 137.84 (1 C, ipso-***C***-CH(OH) in Ph).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 91 % ee: $t_{R,R}$ = 35.73 min $t_{S,S}$ = 40.08 min.

In agreement with the literature.[169]

*(1S,2S)-2-Chloro-1-(3-chlorophenyl)but-3-en-1-ol (**128ad**)*



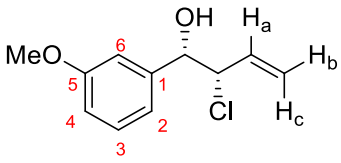
128ad

Colourless oil. 101 mg, 0.46 mmol, 93% yield

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97 (s, O***H***) 4.56 (dd, *J* = 7.5, 7.5 Hz, 1 H, C***H***Cl), 4.76 (d, *J* = 6.8 Hz, 1 H, C***H***OH), 5.19-5.31 (m, 2 H, =CH_2), 5.86 (ddd, *J* = 16.9, 10.1, 8.2 Hz, 2 H, C***H***=CH_2), 7.33—7.25 (m, 3 H, $H_{b,c,d}$), 7.40 (s, 1 H, H_a).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 78% ee: $t_{R,R}$ = 12.46 min $t_{S,S}$ = 13.43 min.

*(1S,2S)-2-Chloro-1-(3-methoxyphenyl)but-3-en-1-ol (**128ae**)*



128ae

Colourless oil. 96 mg, 0.45 mmol, 90% yield.

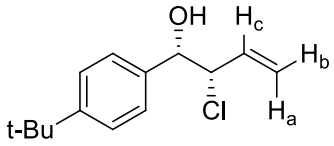
^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.14 (s, 1 H, O***H***) 3.77 (s, 3 H, CH_3), 4.52 (dd, *J* = 7.8, 7.4 Hz, 1 H, C***H***-Cl), 4.67 (d, *J* = 7.1 Hz, 1 H, C***H***-OH), 5.10 (d, *J* = 10.3 Hz, 1 H, H_b), 5.19 (d, *J* = 16.9 Hz, 1 H, H_c), 5.78 (ddd, *J* = 16.9, 10.3, 7.1 Hz, 1 H, H_a), 6.89—6.80 (m, 2 H), 7.25—7.20 (m, 1 H).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 55.36 (1 C, O***Me***), 69.37 (1 C, ***C***-Cl), 77.11 (1 C, ***C***-OH), 112.60 (1 C, 6-***C***), 113.94 (1 C, 4-***C***), 119.40 (1 C, =***C***H_2), 119.51 (1 C, 2-***C***), 129.53 (1 C, 3-***C***), 134.33 (1 C, ***C***H=CH_2), 140.80 (1 C, 1-***C***), 159.72 (1 C, 5-***C***-OMe).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 91% ee: $t_{R,R}$ = 36.16 min $t_{S,S}$ = 45.62 min.

In agreement with the literature.[167]

*(1S,2S)-2-chloro-1-(4-tert-butylphenyl)-2-but-3-en-1-ol (**128af**)*



128af

Colourless oil. 91 mg, 0.38 mmol, 76% yield.

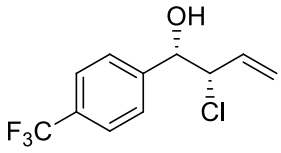
^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.29 (s, 9 H, *t*Bu-***H***), 2.73 (s, 1 H, O***H***), 4.57 (t, *J* = 7.8 Hz, 1 H, C***H***-Cl), 4.69 (d, *J* = 7.2 Hz, 1 H, C***H***-OH), 5.14 (dd, *J* = 10.2, 1.0 Hz, 1 H, $\boldsymbol{H_b}$), 5.24 (dd, *J* = 16.9, 1.0 Hz, 1 H, $\boldsymbol{H_a}$), 5.80 (ddd, *J* = 16.9, 10.2, 7.8 Hz, 1 H, $\boldsymbol{H_c}$), 7.27—7.25 (m, 2 H, 3,5-C***H*** in Ph), 7.37—7.34 (m, 2 H, 2,6-C***H*** in Ph).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 31.39 (3 C, C($\boldsymbol{C}H_3)_3$), 34.69 (1 C, $\boldsymbol{C}(CH_3)_3$), 69.31 (1 C, ***C***-Cl), 77.27 (1 C, ***C***-OH), 119.40 (1 =$\boldsymbol{C}H_2$), 125.44 (2 C, 3,5-***C*** in Ph), 126.72 (2 C, 2,6-***C*** in Ph), 134.46 (1 C, ***C***=CH_2), 136.19 (1 C, *ipso*-***C***-CHOH), 151.55 (1 C, *ipso*-***C***-*t*Bu).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 82% ee: $t_{R,R}$ = 14.24 min $t_{S,S}$ = 16.64 min.

In agreement with the literature.[168]

*(1S,2S)-2-chloro-1-(4-(trifluoromethyl)phenyl)-2-but-3-en-1-ol (**128ag**)*



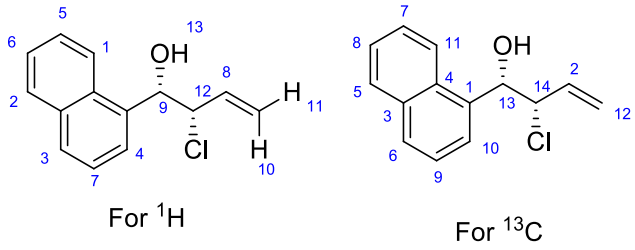
128ag

Colourless oil. 112 mg, 0.45 mmol, 90% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.57 (s, 1 H, O***H***), 4.57 (dd, *J* = 8.5, 4.5 Hz, 1 H, C***H***Cl), 4.93 (dd, *J* = 4.2, 2.6 Hz, 1 H, C***H***OH), 5.26—5.21 (m, 2 H, C$\boldsymbol{H}_2$), 5.92 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1 H, C***H***=CH_2), 7.36—7.29 (m, 4 H, *Ph*).

Chiral **GC** (Supelco β-CD 120 column, oven: 110 °C for 2 min, then 1.5 °C/min to 200 °C) showed 81% *ee*: $t_{S,S}$ = 49.05 min (major) $t_{R,R}$ = 50.51 min (minor)

(1S,2S)-2-Chloro-1-(naphthalen-1-yl)but-3-en-1-ol ***(128ah)***



128ah

Colourless oil. 77 mg, 0.33 mmol, 66% yield.

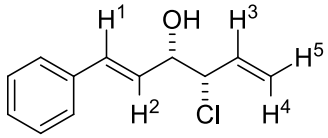
^{1}H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 1 H, *13*), 4.89 (t, *J* = 7.4 Hz, 1 H, *12*), 5.05 (d, *J* = 10.2 Hz, 1 H, *11*), 5.22 (dd, *J* = 16.9, 0.9 Hz, 1 H, *10*), 5.52 (d, *J* = 6.7 Hz, 1 H, *9*), 5.89 (ddd, *J* = 16.8, 10.2, 8.1 Hz, 1 H, *8*), 7.56-7.47 (m, 3 H, *5+6+7*), 7.64 (d, *J* = 7.1 Hz, 1 H, *4*), 7.83 (d, *J* = 8.2 Hz, 1 H, *3*), 7.89 (dd, *J* = 7.2, 2.1 Hz, 1 H, *4*), 8.08 (d, *J* = 8.0 Hz, 1 H, *1*).

^{13}C NMR (101 MHz, $CDCl_3$): δ 69.27 (1 C, *14*), 74.43 (1 C, *13*), 119.17 (1 C, *12*), 123.29 (1 C, *11*), 125.43 (2 C, *8+9*), 125.86 (1 C, *10*), 126.54 (1 C, *7*), 129.21 (1 C, *6*), 129.32 (1 C, *5*), 130.87 (1 C, *4*), 134.05 (1 C, *3*), 134.81 (1 C, *2*), 135.30 (1 C, *1*).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 90% *ee*: $t_{R,R}$ = 22.64 min $t_{S,S}$ = 32.50 min.

In agreement with the literature.[167]

(3S,4S,E)-4-Chloro-1-phenylhexa-1,5-dien-3-ol ***(128ai)***



128ai

Colourless oil. 52 mg, 0.25 mmol, 50% yield.

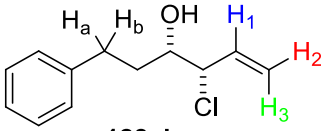
^{1}H NMR ($CDCl_3$, 400 MHz): *δ* 2.42 (s, 1 H, O***H***), 4.46—4.37 (m, 2 H, C***H***OH + C***H***Cl), 5.29 (d, *J* = 10.2 Hz, 1 H, ***H*^{5}**), 5.40 (d, *J* = 16.9 Hz, 1 H, ***H*^{4}**), 5.97 (ddd, *J* = 16.9, 10.2, 8.1 Hz, 1 H, ***H*^{3}**), 6.21 (dd, *J* = 15.8, 5.8 Hz, 1 H, ***H*^{2}**), 6.71 (d, *J* = 15.8 Hz, 1 H, ***H*^{1}**), 7.27—7.23 (m, 1 H, 4-***H*** in Ph), 7.34—7.29 (m, 2 H, 3,5-***H***), 7.39—7.36 (m, 2 H, 2,6-***H*** in Ph).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 67.87 (1 C, ***C***-Cl), 75.26 (1 C, C***H***OH), 119.70 (1 C, =C$\boldsymbol{H_2}$), 126.75 (2 C, 2,6-***C*** in Ph), 126.94 (1 C, 4-***C*** in Ph), 128.15 (1 C, PhCH=***C***H), 128.71 (2 C, 3,5-***C*** in Ph), 133.17 (1 C, Ph***C***H=CH), 134.64 (1 C, ***C***H=CH_2), 136.29 (1 C, *ipso*-***C*** in Ph).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 71% ee: $t_{S,S}$ = 20.86 min $t_{R,R}$ = 21.79 min.

In agreement with the literature.[170]

(3S,4S)-4-Chloro-1-phenylhex-5-en-3-ol ***(128aj)***



128aj

Colourless oil. 32 mg, 0.15 mmol, 30% yield.

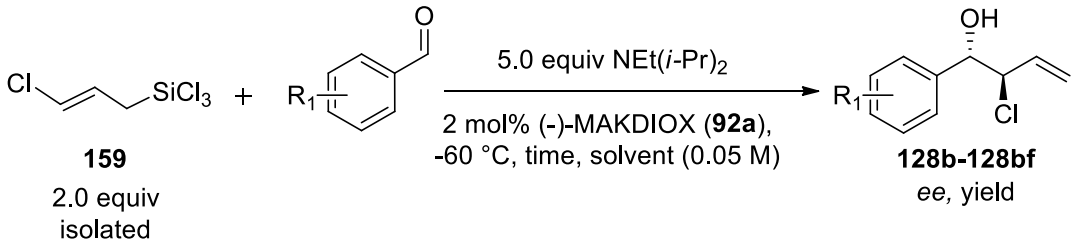
^{1}H NMR (400 MHz, $CDCl_3$): *δ* 1.89—1.78 (m, 2 H, C$\boldsymbol{H_2}$-CHOH), 2.26 (d, *J* = 4.5 Hz, 1 H, O***H***), 2.76—2.66 (m, 1 H, Ph-C$\boldsymbol{H_a}$), 2.92—2.82 (m, 1 H, Ph-C$\boldsymbol{H_b}$), 3.71—3.63 (m, 1 H, C***H***-OH), 4.34 (dd, *J* = 8.7, 6.1 Hz, 1 H, C***H***-Cl), 5.25 (d, *J* = 10.1 Hz, 1 H, $\boldsymbol{H_2}$), 5.35 (d, *J* = 16.9 Hz, 1 H, $\boldsymbol{H_3}$), 5.90 (ddd, *J* = 16.9, 10.1, 8.8 Hz, 1 H, $\boldsymbol{H_1}$), 7.31—7.20 (m, 5 H, ***Ph***).

^{13}C NMR ($CDCl_3$, 101 MHz): δ 31.86 (1 C, Ph-***C***H_2), 35.53 (1 C, ***C***H_2-CHOH), 69.14 (1 C, ***C***H-Cl), 73.49 (1 C, ***C***H-OH), 119.34 (1 C, =***C***H_2), 126.10 (1 C, 4-***C*** in Ph), 128.57 (4 C, 2,3,5,6-***C*** in Ph), 135.16 (1 C, ***C***H=CH_2), 141.61 (1 C, *ipso*-***C*** in Ph).

HPLC (Chiralpak IB-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 20% *ee*: $t_{R,R}$ = 21.86 min $t_{S,S}$ = 35.00 min.

In agreement with the literature.[170]

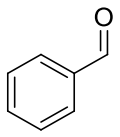
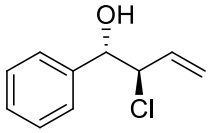
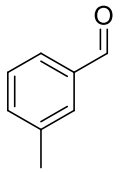
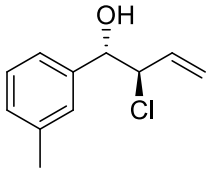
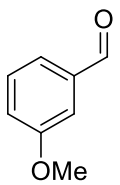
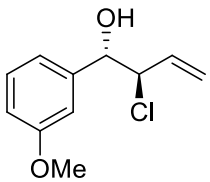
5.11.2. General procedure for the asymmetric reaction of aldehydes with *E*-γ-chloroallyltrichlorosilane

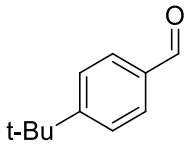
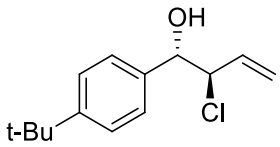
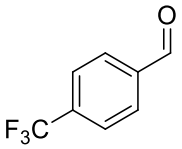
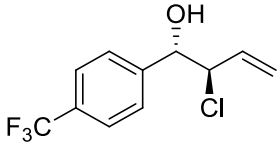
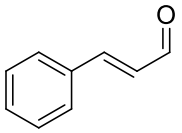
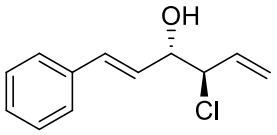


159
2.0 equiv
isolated

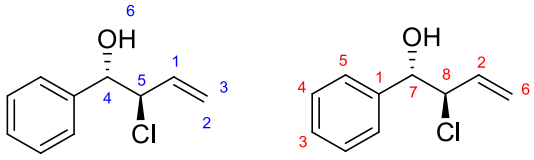
128b-128bf
ee, yield

An oven-dried test tube, equipped with a magnetic stirring bar, was charged with dry crystals of (-)-MAKDIOX (2 mol%, 0.01 mmol, 8 mg) (**92a**), flushed with dry nitrogen and sealed. Hünig's base (5.0 equiv, 2.5 mmol, 435 µL) and an aldehyde (1.0 equiv, 0.5 mmol) were added via syringe or in dry solvent (1mL). The distilled Distilled EtCN (10 mL) was added via syringe, and the mixture was stirred for 10 minutes until turned homogenous, and then was cooled to −60 ℃ using a cryostat. *E*-γ-chloroallyltrichlorosilane (2.0 equiv, 1.0 mmol, 7.23 M, 138 µL) was added dropwise via syringe, and the mixture was stirred for 72 hours at −60 ℃. The reaction was quenched with sat. $NaHCO_3$ solution and extracted with Et_2O (3×5 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuum. The resulting crude material was purified by column chromatography on *silica* eluting with hexane-ethyl acetate mixture in gradient (10/1→5/1) to afford the target *syn*-chlorohydrin **128b**-**128bf**.

Entry (product)	Aldehyde	Product	Solvent	Time	Yield, %	% *ee*
1		 (**128b**)	EtCN	72 h	80	61
2		 (**128bb**)	EtCN	72 h	60	60
3		 (**128bc**)	EtCN	72 h	83	50

4		 **(128bd)**	EtCN	72 h	70	52
5		 **(128be)**	EtCN	72 h	64	45
6		 **(128bf)**	EtCN	72 h	51	40

*(1S,2R)-2-chloro-1-phenylbut-3-en-1-ol (**128ba**)*



For ^{1}H **128ba** For ^{13}C

Colourless oil. 73 mg, 0.40 mmol, 80% yield.

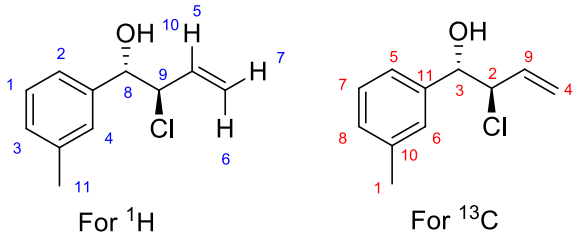
^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.90-2.20 (s (broad), 1 H, 6), 4.56 (dd, *J* = 8.5, 4.7 Hz, 1 H, 5), 4.92 (d, *J* = 4.6 Hz, 1 H, 4), 5.25-5.21 (m, 2 H, 2+3), 5.91 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1 H, 1), 7.36-7.28 (m, 5 H, ***Ph***).

^{13}C NMR (r-ded on 400 MHz spectrometer) ($CDCl_3$, 101 MHz): δ 67.57 (1 C, 8), 77.13 (1 C, 7), 120.29 (2 C, 6), 127.01 (2 C, 5), 128.49 (2 C, 4), 128.55 (1 C, 3), 133.61 (1 C, 2), 139.46 (1 C, 1).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 61% *ee*: $t_{R,S}$ = 12.22 min $t_{S,R}$ = 14.02 min.

In agreement with the literature. [120,171]

(1S,2R)-2-Chloro-1-(3-methylphenyl)but-3-en-1-ol ***(128bb)***



128bb

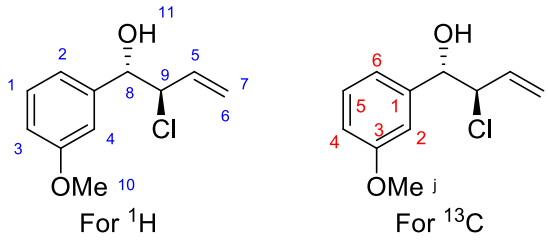
Colourless oil. 59 mg, 0.30 mmol, 60% yield.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.35 (s, 3 H, 11), 2.65-2.39 (s (broad), 1 H, 10), 4.56 (dd, *J* = 8.4, 4.7 Hz, 1 H, 9), 4.89 (d, *J* = 4.7 Hz, 1 H, 8), 5.27-5.21 (m, 2 H, 6+7), 5.92 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1 H, 5), 7.25-7.10 (m, 4 H, 1+2+3+4).

^{13}C NMR (101 MHz, $CDCl_3$): *δ* 21.57 (1), 67.35 (2), 76.99 (3), 120.11 (4), 123.92 (5), 127.41 (6), 128.27 (7), 129.09 (8), 133.48 (9), 138.09 (10), 139.22 (11)

HPLC (Chiralpak IA-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 60% *ee*: $t_{S,R}$ = 23.70 min $t_{R,S}$ = 29.60 min.

(1S,2R)-2-Chloro-1-(3-methoxyphenyl)but-3-en-1-ol ***(128bc)***



128bc

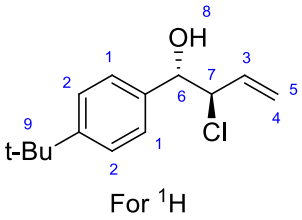
Colourless oil. 88 mg, 0.415 mmol, 83% yield.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.90-2.35 (s, 1 H, 11), 3.79 (s, 3 H, 10), 4.55 (dd, *J* = 8.5, 4.6 Hz, 1 H, 9), 4.90 (d, *J* = 4.6 Hz, 1 H, 8), 5.26-5.18 (m, 2 H, 6+7), 5.91 (ddd, *J* = 17.0, 10.2, 8.5 Hz, 1 H, 5), 6.82 (ddd, *J* = 8.3, 2.5, 1.0 Hz, 1 H, 4), 6.92-6.91 (m, 2 H, 2+3), 7.25 (dd, *J* = 8.1, 8.1 Hz, 1 H, 1).

^{13}C NMR (r-ded on 400 MHz spectrometer) ($CDCl_3$, 101 MHz): δ 55.3 (***C***H_3), 67.3 (***C***-Cl), 77.3 (***C***-OH), 112.4 (2-***C***), 113.72 (4-***C***), 119.1 (=***C***H_2), 120.1 (6-***C***), 129.4 (5-***C***), 133.3 (***C***=CH_2), 140.9 (1-***C***), 159.6 (3-***C***).

HPLC (Chiralpak IB-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 50% *ee*: $t_{R,S}$ = 37.70 min $t_{S,R}$ = 61.54 min

*(1S,2R)-2-chloro-1-(4-tert-butylphenyl)-2-but-3-en-1-ol (**128bd**)*



For ^{1}H

128bd

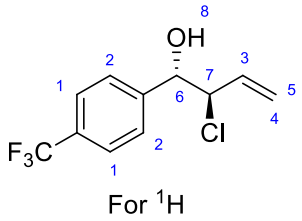
Colourless oil. 83 mg, 0.35 mmol, 70% yield.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.30 (s, 9 H, 9), 2.44 (d, *J* = 2.5 Hz, 1 H, 8), 4.57 (dd, *J* = 8.4, 4.8 Hz, 1 H, 7), 4.89 (dd, *J* = 4.3, 3.1 Hz, 1 H, 6), 5.30-5.23 (m, 2 H, 4+5), 5.93 (ddd, *J* = 17.0, 10.2, 8.4 Hz, 1 H, 3), 7.30—7.27 (m, 2 H, 2), 7.38—7.35 (m, 2 H, 1).

HPLC (Chiralpak IC-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 52% *ee*: $t_{R,S}$ = 11.54 min $t_{S,R}$ = 13.53 min.

In agreement with the literature.[168]

*(1S,2R)-2-chloro-1-(4-(trifluoromethyl)phenyl)-2-but-3-en-1-ol (**128be**)*



For ^{1}H

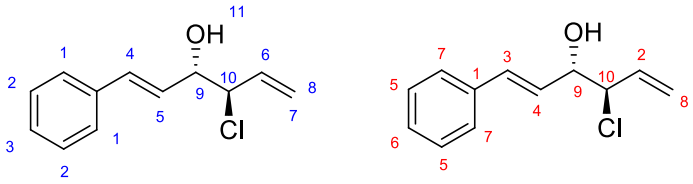
128be

Colourless oil. 80 mg, 0.32 mmol, 64% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.62 (s, 1H, 8), 4.56 (dd, *J* = 8.6, 4.5 Hz, 1H, 7), 5.00 (d, *J* = 4.3 Hz, 1H, 6), 5.26-5.22 (m, 2H, 4+5), 5.92-5.85 (m, 1H, 3), 7.50 (d, *J* = 8.3 Hz, 2H, 2), 7.62 (d, *J* = 8.3 Hz, 2H, 1).

Chiral **GC** (Supelco β-CD 120 column, oven: 110 °C for 2 min, then 1.5 °C/min to 200 °C) showed 45% *ee*: $t_{S,R}$ = 65.12 min (major) $t_{R,S}$ = 66.12 min (minor)

*(3S,4R,E)-4-Chloro-1-phenylhexa-1,5-dien-3-ol (**128bf**)*



For ^{1}H For ^{13}C

128bf

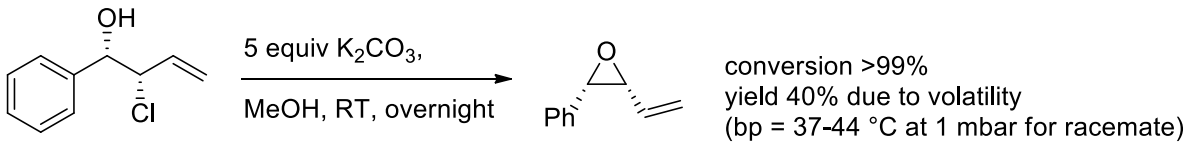
Colourless oil. 53 mg, 0.26 mmol, 51% yield.

^{1}H NMR (500 MHz, $CDCl_3$): δ 2.30 (s, 1 H, 11), 4.50-4.45 (m, 1 H, 10), 4.53 (dd, *J* = 8.3, 4.1 Hz, 1 H, 9), 5.31 (d, *J* = 10.3 Hz, 1 H, 8), 5.40 (d, *J* = 16.9 Hz, 1 H, 7), 6.00-5.93 (m, 1 H, 6), 6.21 (dd, *J* = 16.1, 6.6 Hz, 1 H, 5), 6.69 (d, *J* = 16.1 Hz, 1 H, 4), 7.27-7.25 (m, 1 H, 3), 7.32 (dd, *J* = 7.6, 7.6 Hz, 2 H, 2), 7.38 (d, *J* = 7.4 Hz, 2 H, 1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 67.43 (1 C, 10), 75.64 (1 C, 9), 120.18 (1 C, 8), 126.65 (2 C, 7), 126.97 (1 C, 6), 128.41 (2 C, 5), 128.92 (1 C, 4), 133.85 (1 C, 3), 134.14 (1 C, 2), 136.46 (1 C, 1).

Chiral HPLC: HPLC (Chiralpak IB-3, hexane/2-propanol = 99:1, 1 mL/min, UV detection at 225 nm) showed 40% *ee*: $t_{S,R}$ = 37.95 min $t_{R,S}$ = 48.35 min

5.12. Cyclisation into vinylepoxide

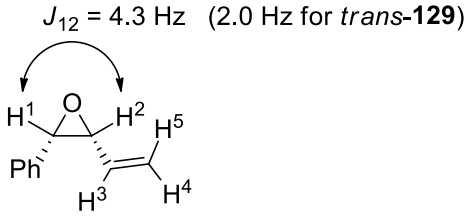


(*1S,2S*)-**128aa** (*1S,2R*)-*cis*-**129aa**

Chlorohydrin **128aa** (95% *ee*, 47.6 mg, 0.26 mmol, 1.0 equiv) was dissolved in methanol (2.5 mL). Anhydrous potassium carbonate (72 mg, 0.52 mmol, 2.0 equiv) was added in one portion. The mixture was stirred for 12 hours at rt. After the consumption of **128aa** was evidenced by TLC, methanol was removed by evaporation via a flow of nitrogen under

atmospheric pressure. Water (5 mL) was added, and the compound was extracted with Et_2O (3×3 mL). The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated by evaporation under a flow of nitrogen. The residue was purified by flash chromatography using Hex-EtOAc mixture (20:1) and evaporated overnight at atmospheric pressure under air at 40 ℃ to afford **129aa** as a colourless oil (17 mg, 0.12 mmol, 45% yield). Lowered yield might be attributed to an accidental evaporation and oxidation by air.[172]

*Cis-(1S,2R)-1,2-Epoxy-1-phenyl-3-butene (**129aa**)*



129aa

$[\alpha]_D^{25}$ = – 6.1° (*c* 0.93, $CHCl_3$)

^{1}H NMR (400 MHz): δ 3.66 (dd, *J* = 8.1, 4.3 Hz, 1 H, ***H*^{2}**), 4.24 (d, *J* = 4.3 Hz, 1 H, ***H*^{1}**), 5.26 (dd, *J* = 10.3, 1.7 Hz, 1 H, ***H*^{4}**), 5.38 (ddd, *J* = 17.1, 10.3, 8.1 Hz, 1 H, ***H*^{3}**), 5.54 (dd, *J* = 17.1, 1.7 Hz, 1 H, ***H*^{5}**), 7.37—7.27 (m, 5 H, ***Ph***). In agreement with the literature.[168]

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