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

Development of Novel Enantioselective Catalytic Reactions

Mikhail A. Kabeshov

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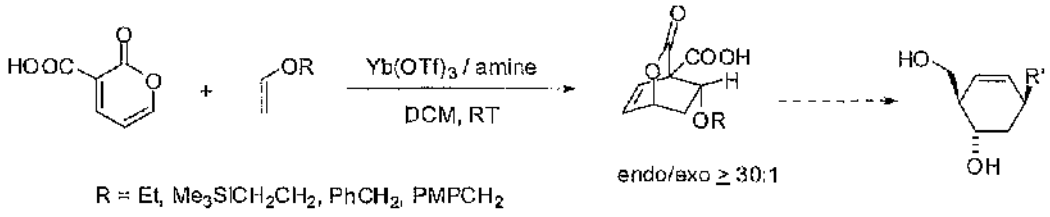
To my first chemistry lesson in September 1995

Contents

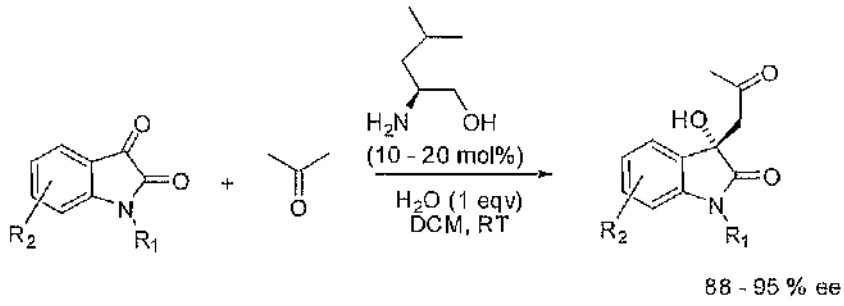
Abstract

The inverse electron demand Diels-Alder reaction between 2-pyrone-3-carboxylic acid and various vinyl ethers has been performed to attain the respective products with very high diastereoselectivity, which can be used for the synthesis of cyclohexenyl nucleosides (Scheme 1).



Scheme 1. Highly diastereoselective Inverse Electron Demand Diels-Alder reaction

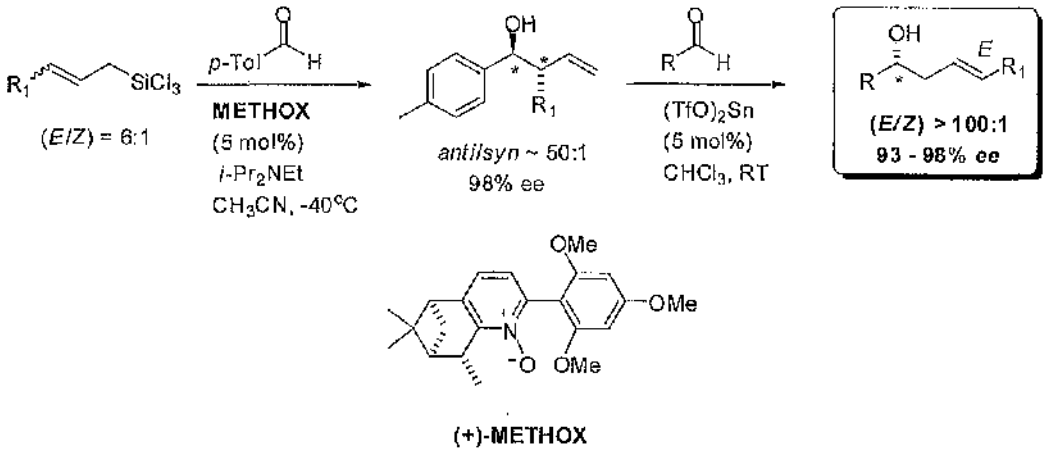
Primary amino alcohols derived from natural amino acids have been found to be efficient organocatalysts for the cross-aldol reaction between acetone and activated ketones, affording the respective products with high enantioselectivity (Scheme 2).



Scheme 2. The enantioselective cross-aldol reaction catalysed by leucinol

A practical, highly stereoselective, two-step protocol for the α-allylation of aldehydes, starting from allyltrichlorosilanes, has been developed. As a result of the kinetic resolution in each step, virtually enantio- and geometrically pure linear

homoallylic alcohols were obtained in high yield from the technical grade allyltrichlorosilanes by using only 5 mol% of a chiral catalyst (Scheme 3).



Scheme 3. The highly enantioselective α-allylation of aldehydes.

Abbreviations

Å	Ångström
Aq	Aqueous
BINOL	1,1'-Binaphthol
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
bs	broad singlet (NMR spectroscopy)
t-Bu	Tertiary butyl
°C	Degrees centigrade
cat	Catalytic
CI	Chemical ionisation
Cy	Cyclohexyl
d	Doublet (NMR spectroscopy)
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DEAD	Diethylazodicarboxylate
DIPEA	*N,N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDAC/EDCI*HCl	*N*-Ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride
ee	Enatiomeric excess
EI	Electron impact
Eq/Equiv	Equivalents
FAB	Fast atom bombardment
GC	Gas chromatography
h	Hour(s)
HMPA	Hexamethylphosphoramide
HOBT	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
Hz	Hertz
IR	Infrared
LR	Lawesson's reagent
M	Molarity
m	Multiplet (NMR spectroscopy)
Ms/mesyl	Methanesulfonate
min(s)	Minute(s)
MS	Mass Spectroscopy
Naphth	Naphthyl
NMM	*N*-Methylmorpholine
NMR	Nuclear Magnetic Resonance
Phth	Phthalimide
PMA	Polymolybdic acid
PMP	4-Methoxyphenyl

q	Quartet (NMR spectroscopy)
rt	Room temperature
t	Triplet (NMR spectroscopy)
TBDMS	*tert*-Butyldimethylsilane
TLC	Thin Layer Chromatography
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	Tetramethylenediamine
Ts/Tosyl	4-Toluenesulfonate
UV	Ultraviolet

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I want to write at this point the name of Dr Andy Parkin, a great person and researcher, who recently passed away. We are preparing a paper with him as a co-author and it will be published soon.

It is difficult to mention all the people I have met in the Chemistry Department at Glasgow and in the UK during conferences and meetings. It is hard to put all the names here but it is very easy to keep them in memory.

I cannot forget my old friend Denis Malyshev and the Erasmus student from Moscow Antonina Symakova, who were with me here for short periods. Many thanks to them for a bit of spirit from my Motherland. Also, my special gratitude goes to Dr Dalia Malkova for her warm welcome during the last month of my work in Glasgow.

I always remember my first chemistry teacher Olga Tulyakova. She made me love chemistry by her attitude and passion. This love was grown up later with the help of

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This work and my whole life would not have any meaning without my closest people. I was brought to this world and raised by my mother Elena Kabeshova, my father Andrei Kabeshov, my grandmothers Nadezhda Vasina, Innesa Kabeshova and my grandfathers Aleksei Vasin and Valentin Kabeshov. My special feelings are always with my fiancée Julia Kovalenko. We feel that we are together every day even if separated by many kilometres.

Preface

Chirality is the most specific and startling feature of living matter. It accompanies Nature from the earliest days, being at the central place of evolution, functioning and reproduction of living species. It is due to chirality that all these processes are extremely specific, resulting in many years of our civilization development. Without chiral objects it would be impossible to imagine the world we live in now, with all its diversity, perfection, complexity and beauty. It is not surprising that science and industry introduce more and more chiral compounds and systems into our everyday life. By doing that the human mind does not create anything new but tries to mimic the nature, tries to use its best approach which is as mature as the planet Earth. Without any doubt new chiral molecules and enantioselective methods of synthesis will help to solve many intriguing problems we are facing.

Introduced in 1835 by the Swedish chemist I. Berzellius, the term "catalysis" was to explain another fundamental process in nature. Rough estimation says that 90% of all commercially produced chemicals involve catalysts at least at one stage of their manufacturing. The importance of catalysis increases every day as our civilization is continuously expanding its size, consumption and demand. More and more familiar to every person are phrases "green chemistry", "alternative sources of energy", "efficient use of natural resources", and "sustainability", etc. For any chemist it would be impossible to imagine modern chemical industry or science being efficient and compatible with healthy environment without everyday use of catalysis. It is catalysis, which allows making a lot of product of high quality and purity from usually simple and available starting materials employing just a bit of an essential activator. By means of catalysis, many issues in chemistry, technology and industry were elegantly solved. It is also clear that importance of catalysis may only increase in the future.

In this work we address three independent topics in the large field of asymmetric catalysis.

In *Chapter I* we discuss the results we obtained in the development of the new enantioselective method of synthesis of cyclohexenyl nucleosides. We also explain why

these compounds attract much attention of medicinal and biological chemists and review the known methodologies used to synthesize cyclohexenyl nucleosides.

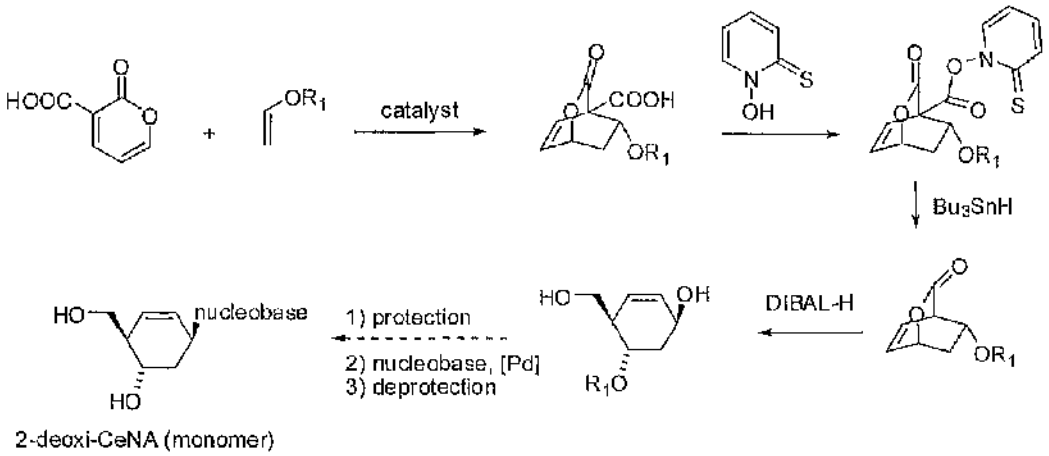
In *Chapter II* we introduce the new catalytic system based on amino alcohols derived from natural amino acids as catalysts for the aldol condensation between acetone and activated ketones. We describe syntheses of two natural products – Convolutamydine A and Speranskatine A – using the methodology developed. We also discuss the mechanism of the aldol reaction.

In *Chapter III* we present a highly diastereo- and enantio-selective two-step method for the α-allylation of aldehydes employing the Lewis base- catalysed enantioselective allylation with trichlorosilane and the Sn-catalysed allyl transfer reactions. This methodology allows the use of technical grade crotyl chlorides as starting materials to produce enantio- and geometrically pure homoallylic alcohols.

Chapter I. Cyclohexenyl Nucleosides

Introduction

We propose the synthesis of cyclohexenyl nucleosides based on regio-, diastereo- and, potentially, enantioselective inverse electron demand Diels-Alder reaction (IEDDA) as a key step (Scheme 4).



Scheme 4. The synthesis of 2-deoxi-CeNA

An each step of the proposed synthesis is reviewed below.

1. Cyclohexenyl nucleosides and nucleic acids: properties and potential

It is well known that ribonucleic acids (RNA) are among the most versatile, intriguing and widespread natural polymers. They carry out a lot of different functions in the living nature as they are messengers to transfer genetic information, catalysts at the ribosome level, and primers in DNA replication. RNA also plays a key role in the processing of precursor mRNA during splicing and editing, and it assists in the RNA processing events, in the replication of viral genomes and in the control of translation.[1] This is possible because RNA, in contrast to DNA, has a broad structural and functional versatility: it folds in a variety of tertiary structures and can catalyze a broad range of reactions, of which dephosphorylation and peptide formation are the best known types. This versatility is ascribed to the presence of the ribose moiety in the backbone of RNA.

The increased catalytic potential of RNA versus DNA is due to the presence of the 2'-OH group and the flexibility of the sugar moiety. Investigations of synthetic nucleosides that can mimic the properties of RNA have, for a long time, been mainly focused on the synthesis of conformationally restricted *N*-type nucleoside analogues. Considerations about the dynamics of the ribonucleotide structures have led to the synthesis of cyclohexenyl nucleic acids (CeNAs) (Chart 1). Since cyclohexene is one of the basic structures often utilized as a scaffold in organic chemistry, molecular geometry and conformational characteristics of cyclohexene were extensively investigated using various experimental and theoretical methods.[2]

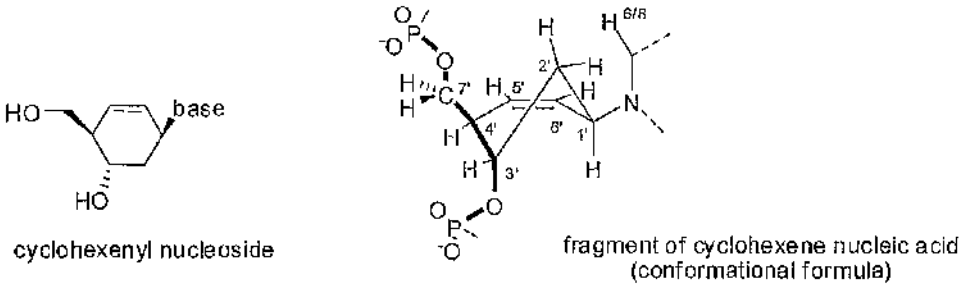
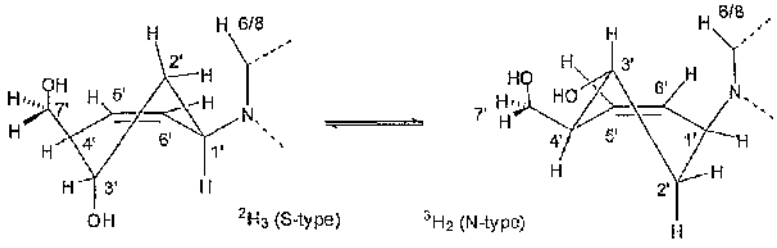


Chart 1. Cyclohexenyl nucleoside and CeNA.

At present, the pseudorotation model introduced originally for ribonucleosides by Sundaraligam[3] is used to describe the conformational equilibrium for cyclohexene nucleosides. The idea is that to describe the conformation of the nucleoside with a cyclohexene ring, we need the same number of parameters (namely, two – phase angle and puckering amplitude) as to describe the conformation of the five-membered carbohydrate ring. In other words, the carbon-carbon double bond plays the role of a pseudo atom. Two stable conformations have been identified for the cyclohexene ring in nucleosides and nucleic acids (Scheme 5).



Scheme 5. S-type and N-type conformations of cyclohexene nucleosides.

Here, 'H' stands for a half-chair conformation of a six-membered ring, superscript and subscript digits (2 or 3) show which carbon atom is above the carbon-carbon double bond plane and which is below. Herdewijn has recently shown[4] that if a 2'-OH function is introduced into the cyclohexenyl nucleoside in ribo-position, a shift is observed from the $^3H_2$ (N-Type) to the $^2H_3$ (S-Type) state. This shift can be explained by the 2'-OH and the nucleobase that are placed in an energetically favourable equatorial position (despite the fact that the other two substituents become pseudo-axially oriented) and the gauche effect that exists between the nucleobase and 2'-OH and between the 2'-OH and 3'-OH when the molecule adopts the $^2H_3$ conformation. The cyclohexenyl nucleoside derivative, where the 2'-OH nucleoside is placed in the arabino position, was characterized by a larger energy difference between the $^2H_3$ and $^3H_2$ conformers (4.8 kJ/mol) with $^3H_2$ being the energetically most preferred conformation and the energy barrier comparable with the deoxy compound (8.1 kJ/mol). This behaviour can be explained by stabilization of the N-type state, where both hydroxyl groups occupy an equatorial position and are situated in gauche form relative to each other and to the base moiety. However, $\Delta_r G^o_{298}$ for S-type – N-type interconversion is no more than 1 kJ/mol[4] both for 2'-deoxy and 2'-oxy (ribo-type) cyclohexene nucleosides, e.g., these compounds are conformationally flexible. Thus, at 27 °C monomer of cyclohexene nucleoside (2'-deoxy with adenine as a base) exists in a fast equilibrium between two low energy states ($^3H_2$ and $^2H_3$ with populations of 56 and 44%, respectively). Various DNA sequences (cyclohexene analogues), where the cyclohexene nucleosides adopt either N-type or S-type conformation, have also been synthesised.[4]

2. Cyclohexenyl nucleosides and nucleic acids. Biological properties.

Herdewijn[5] investigated antiviral activities of cyclohexene nucleosides (2'-deoxy analogues) and showed that D- and L-isomers of cyclohexenyl-G show very similar activity against herpes viruses. Using molecular modelling, it was shown that the energy of interaction between the nucleoside and the active centre of HSV-1 thymidine kinase is approximately the same for both enantiomers of cyclohexenyl-G. It is pertinent to note that the conformation of the cyclohexene ring in the nucleoside bound to the active centre of the virus enzyme is $^2H_3$, different from the most stable conformation of the free

nucleoside in solution. The antiviral activity data is summarised in the Table 1, while cytotoxicity (IC_{50}, μg/mL) data is shown in the Table 2.

Table 1. Antiviral activities (IC_{50}, μg/mL) of cyclohexene nucleosides and other compounds.

Virus	D-cyclohexenyl-G		L-cyclohexenyl-G		Brivudin	Acyclovir	ganeyclovir	Cidofovir
	Activity	Selectivity index	Activity	Selectivity index				
HSV-1 (KOS)	0.002	$>2\times10^5$	0.003	$>5\times10^3$	0.001	0.01	0.001	
HSV-1 (F)	0.002	$>2\times10^5$	0.003	$>5\times10^3$	0.001	0.003	0.001	
HSV-1 (McIntyre)	0.004	$>1\times10^5$	0.004	$>4\times10^3$	0.001	0.005	0.001	
HSV-2 (G)	0.05	$>8\times10^3$	0.07	$>2.2\times10^2$	>80	0.02	0.002	
HSV-2 (196)	0.07	$>5\times10^3$	0.1	$>1.6\times10^2$	>80	0.02	0.001	
HSV-2 (Lyons)	0.07	$>5\times10^3$	0.07	$>2.2\times10^2$	>80	0.02	0.001	
HSV-1 (TK^- KOS ACV)	0.38	$>1\times10^3$	1.28	>12	>80	9.6	0.48	
HSV-1 (TK^-/TK^+ VMW1837)	0.01	$>4\times10^4$	0.01	$>1.6\times10^3$	>80	0.07	0.01	
VZV (YS)	0.49	>40	1.2	>16	0.03	1.1		
VZV (OKA)	0.64	>30	1.9	>10	0.003	0.8		
VZV (TK^- 07/1)	2.1	>10	5.8	>3	>20	13		
VZV (TK^- YS/R)	2.8	>7	6.8	>3	>50	28		
CMV (AD 169)	0.6	>30	1.5	>13			0.6	0.08
CMV (Davis)	0.8	>25	1.7	>12			0.8	0.2

Table 2. Cytotoxicity of cyclohexene nucleosides and antiviral compounds (IC_{50}, μg/mL).

Cell line	D-cyclohexenyl-G	L-cyclohexenyl-G	Brivudin	Acyclovir	ganeyclovir	Cidofovir
HeLa	400	400	>400			
Vero	400	400	>400			
E_6SM	>400	>16	>400	>400	>100	
HEL	11	>20	>200	>200	>50	>50

The potential of utilising cyclohexene oligonucleotides (2'-deoxy analogues) in molecular biology to stabilize natural DNA duplex and activate RNase-H has been demonstrated.[6] The influence of the cyclohexene nucleosides incorporation on melting points of DNA-DNA and DNA-RNA duplexes was investigated (Table 3).

Table 3. T_m studies of DNA-DNA and DNA-RNA duplexes with incorporated cyclohexene nucleosides.

DNA-sequence	DNA complement		RNA complement	
	T_m	ΔT_m/mod	T_m	ΔT_m/mod
5'-CCAGTGATATGC-3'	49.8		44.0	
5'-CCAGTGA$_1$TATGC-3'	49.4	-0.4	45.1	1.1
5'-CCAGTGA$_1$TA$_1$TGC-3'	48.5	-0.6	45.6	0.8
5'-CCA$_1$GTGA$_1$TA$_1$TGC-3'	48.1	-0.6	49.2	1.7
5'-(dA)$_{13}$-3'	33.1		15.2	
6'-(A$_1$)$_{13}$-4'	33.5	0.0	34.2	1.4
RNA sequence				
5'-CCAGUGAUAUGC-3'	49.1		58.3	
5'-CCA$_1$GUGA$_1$UA$_1$UGC-3'	47.6	-0.5	58.9	0.2

For cyclohexene nucleosides, the $^3H_2$ conformation is the most stable one and it is identical to the conformation of nucleosides in natural RNA. As a result, incorporation of cyclohexenyl nucleosides in dsRNA leads to a reasonable increase of duplex stability. On the other hand, Herdewijn[6] carried out molecular dynamics simulation and observed another conformation of cyclohexenyl nucleosides in dsDNA, namely $^2H_3$, which is marginally less stable. This fact explains why incorporation of cyclohexenyl nucleosides into dsDNA slightly decreases the melting point.

It is important to mention that, according to Herdewijn's observation,[6] the pure strand of cyclohexene nucleotides (with adenine as a base, 2'-deoxy analogue) form triplex with oligothymidylate with the structure $(dT)_n$-$(A_1)_n$-$(dT)_n$. These authors[6] performed the experiment where they exposed DNA-RNA duplex to RNAse (Figure 1).

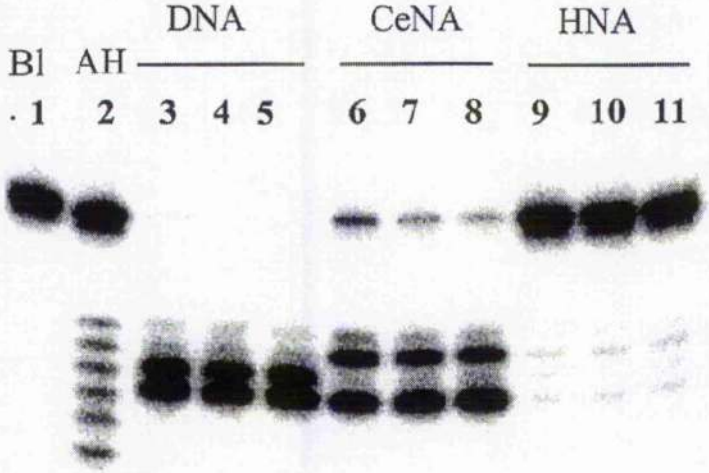


Figure 1. RNAse hydrolysis experiment: RNA strand: 5'-m(CGGCG)r(U)$_6$m(CAGGA)-3'. DNA strand (complementary): 5'-d(TCCTG)(X)$_6$d(CGCCG). Line 1 – starting RNA, line 2 – partial alkaline hydrolysis of starting RNA, line 3 – 5 RNase H activity toward DNA/RNA duplex (X = dA, incubation times 1, 3 and 6 hours), lines 6 – 8 RNase H activity toward CeNA/RNA strand (X = A_1, incubation times 1h, 3h, 6h), lines 9 – 11 RNase H activity toward HNA/RNA duplex (X – anhydrohexitol, incubation times 1h, 3h, 6h). From Figure 1 we can know, that DNA/RNA duplex is easily degraded under RNase catalysis, HNA/RNA is stable and CeNA/RNA is also easily degraded. Also, this degradation occurs only in two places of the oligonucleotide – between U_7 and U_8, and between U_9 and U_{10}. This experiment shows that CeNA potentially is very efficient as an activator of RNase H.

More accurate measurements of RNase H activation by CeNA compared to DNA were later reported by the same group.[7] They used the same RNA strand with the corresponding DNA or CeNA strands for the disintegration experiment (Figure 1). The determined kinetic parameters are shown in the Table 4.

Table 4. Kinetic parameters for CeNA- or DNA-accelerated RNA degradation.

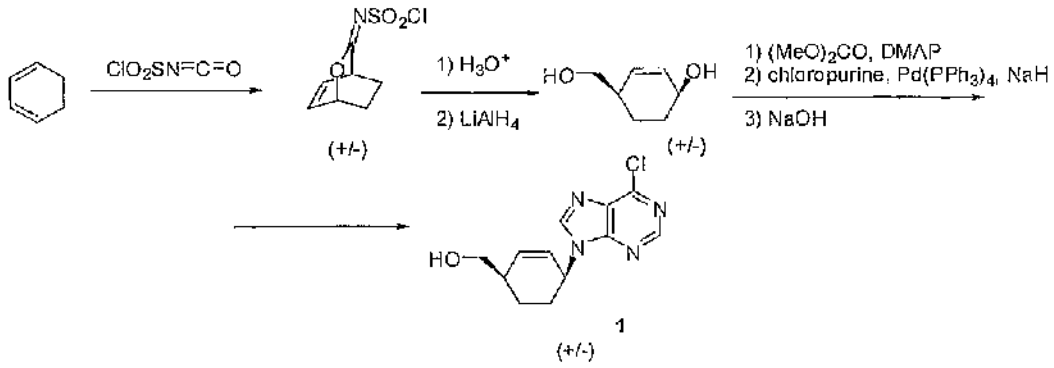
	K_M (nM)	V_{max} (nM/min)	k_{cat} (nmol/min.U)
CeNA	300±100	16±2 ($E_0 = 1\times10^6$ U/l)	$(6\pm2)\times10^{-6}$
DNA	110±40	17±1 ($E_0 = 5\times10^3$ U/l)	$(3.5\pm0.2)\times10^{-6}$

So far, there is a reasonable promise that cyclohexenyl nucleosides may have applications in biology, where the flexibility of the sugar moiety of the nucleoside is important for its function.

3. Cyclohexenyl nucleosides and nucleic acids: synthesis

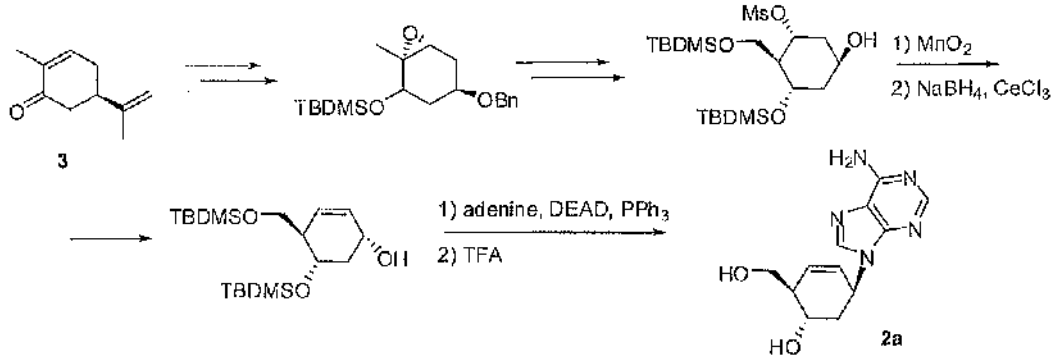
As valuable objects for biochemistry and molecular biology, cyclohexenyl nucleosides have attracted most interest of synthetic chemists. A few approaches have been developed to date.

Konkel published one of the early practical syntheses of cyclohexene nucleosides in 1996.[8] In a few steps they obtained racemic 2',3'-bisdeoxy cyclohexenyl nucleoside **1** (Scheme 6).



Scheme 6. Konkel's synthesis of the 2',3'-bisdeoxycyclohexenyl nucleoside **1**

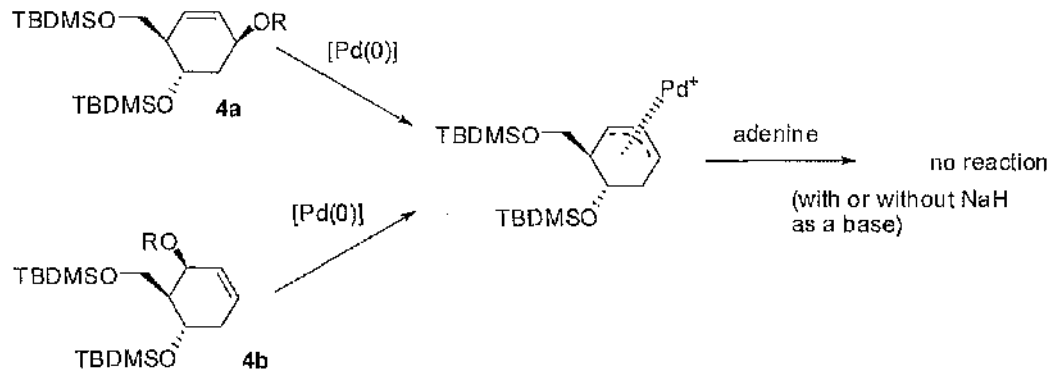
Herdewijn performed the first enantioselective synthesis of 2'-deoxy cyclohexenyl nucleosides **2** in 1999 (Scheme 7).[9] Carvone **3** was used as the chiral presursor. The main disadvantage of the synthesis was its length (more than 10 steps from carvone) and complexity.



Scheme 7. The enantioselective synthesis of cyclohexenyl nucleosides

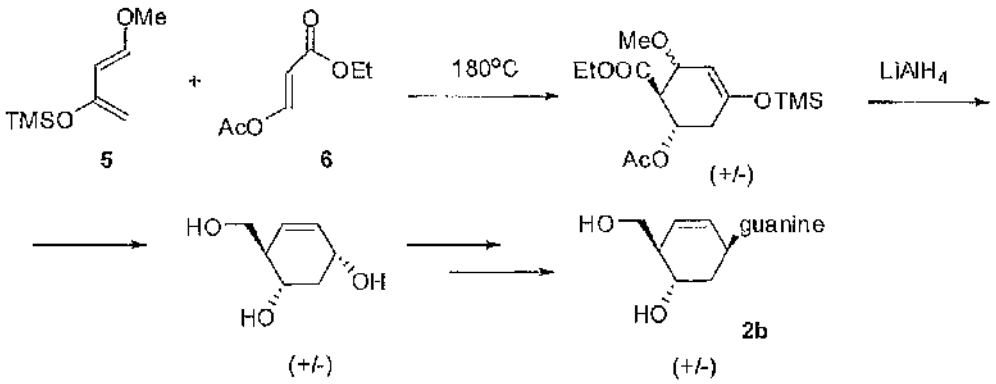
Furthermore, in the last step before the final deprotection, Mitsunobu reaction gave only fair regioselectivity (a mixture of 5- and 7-substituted adenines with a 1:6 ratio). Using this methodology the guanine analogue of **2** has also been synthesised[9].

In the same work[9] Herdewijn and Wang attempted to use the Pd-catalysed amination of the respective allylic ester **4** with adenine (Scheme 8), but this approach failed and the starting material was fully recovered.

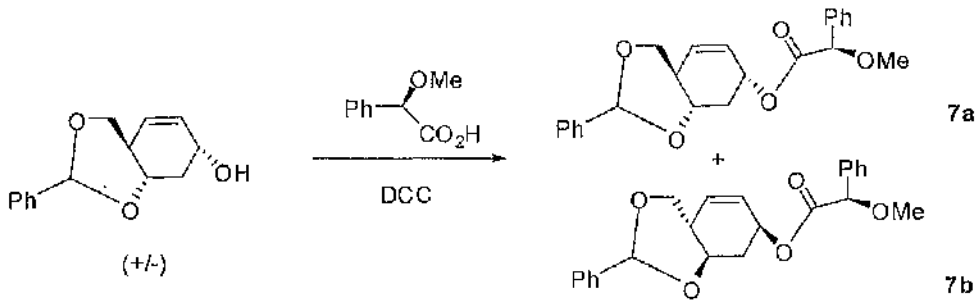


Scheme 8. Attempted Pd-catalysed allylic amination.

More recently, the same authors reported a short diastereoselective synthesis of 2-deoxy-cyclohexylnucleosides (Scheme 9).[10] They used Diels-Alder reaction between Danishefsky diene **5** and the dienophile **6** to build up the six-membered skeleton of the molecule, followed by a few steps to produce the enantiopure nucleoside. Resolution was carried out by chromatographic separation of the diastereomeric esters **7** (Scheme 10).

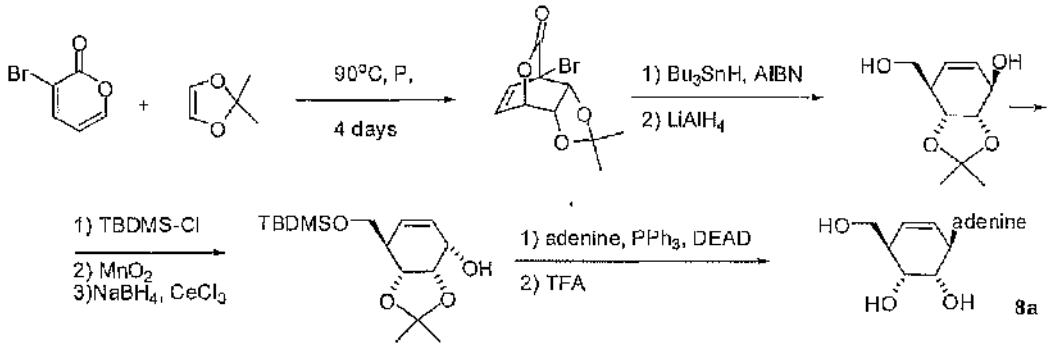


Scheme 9. Short diastereoselective synthesis of the cyclohexenyl nucleoside.



Scheme 10. Resolution of the nucleosides' precursors.

Herdewijn *et al.*[4a] later proposed another diastereoselective synthesis of the ribo-analogue of the cyclohexene nucleosides **8** based on Diels-Alder reaction. The deamination with adenosine deaminase was used to obtain a single enantiomer of **8a** (Scheme 11).



Scheme 11. Diastereoselective synthesis of the racemic ribo-analogue of the cyclohexenyl nucleoside.

It is important to note that the challenge to develop an enantioselective catalytic method of synthesis of cyclohexenyl nucleosides remains vital.

4. Inverse electron demand catalytic Diels-Alder reaction (IEDDA)

We chose the inverse electron demand Diels-Alder reaction as a key step of the synthesis of cyclohexenyl nucleosides.

Diels-Alder reaction is a powerful and very efficient synthetic method, which allows the creation of up to 4 stereogenic centres.[11] However, most of the examples rely on the normal electron demand Diels-Alder reaction, e.g., between an electron-rich diene and an electron-deficient dienophile (Figure 2)

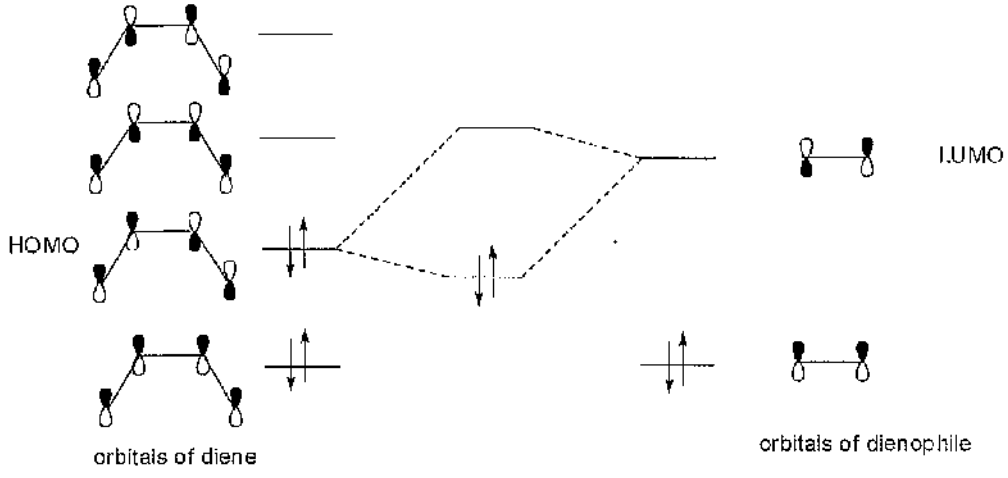


Figure 2. Normal electron demand Diels-Alder reaction.

The usual role of the catalyst (commonly Lewis acid) in the normal electron demand Diels-Alder reaction, apart from bringing reacting molecules together and decreasing $\Delta S^{\neq}$ of the reaction, is to decrease the energy of the LUMO of the dienophile, thus closing the gap between the interacting orbitals and decreasing the E_a of the reaction (Figure 2). In the case of inverse electron demand, a rather different picture of overlapping orbitals can be observed (Figure 3).

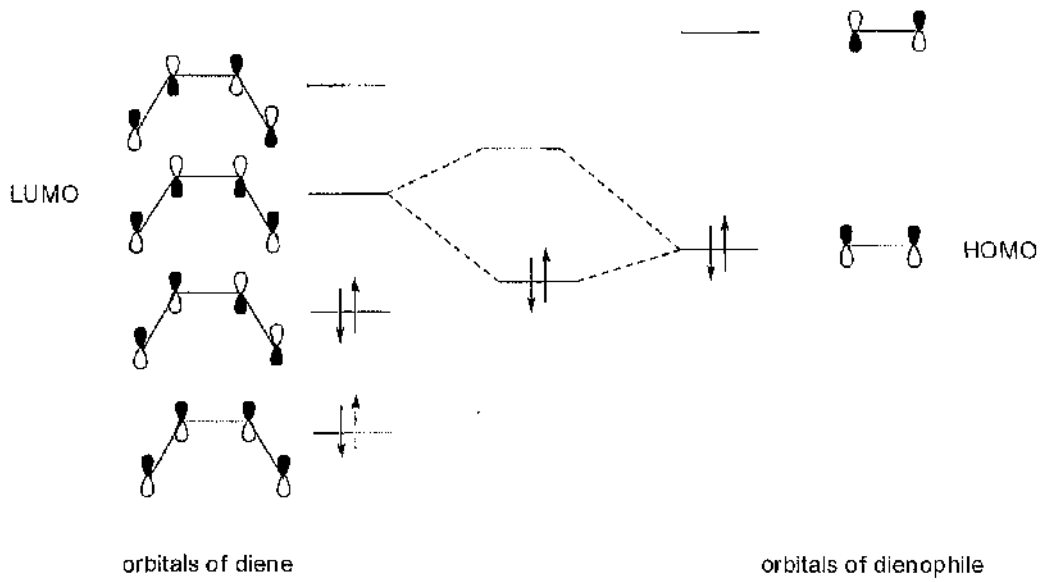
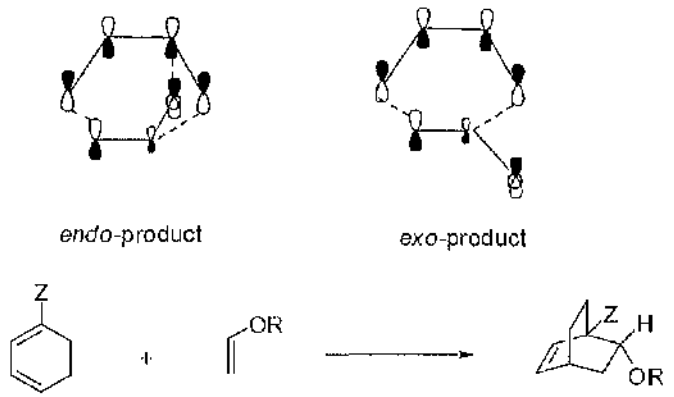


Figure 3. Inverse electron demand in the Diels-Alder reaction

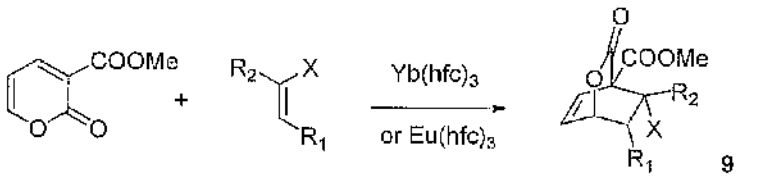
IEDDA reactions proceed usually with high diastereoselectivity providing corresponding *endo*-products due to the secondary orbital effect (Scheme 12).



Scheme 12. Secondary orbital effect in IEDDA reaction.

The transition state which leads to the endo-product is stabilized by an extra overlap between orbitals of reactants (Scheme 12).

In analogy to the well-known normal electron demand Diels-Alder reaction, Lewis acid catalysts can be employed to activate diene by decreasing energy of its LUMO, rather than dienophile. This idea was explored by Markó *et al.*[12] who developed catalytic systems to perform IEDDA, however the number of papers in this field is rather limited. Markó *et al.* developed the most universal method in 1996.[13] They used ytterbium or europium as a main component of the catalytic systems. First, they developed a catalytic stereoselective reaction leading to racemic products **9** (Scheme 13).

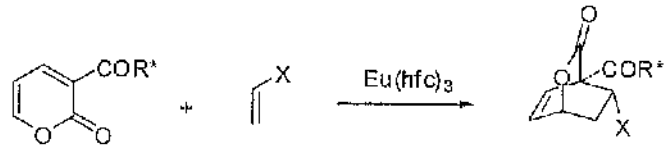


X = OBu, SPh, OTMS
R_1 = H, Me
R_2 = H, Me, $-CH_2CH_2CH=CH_2$

Yield = 80 - 98%

Scheme 13. The Yb-catalysed Diels-Alder reaction.

Then they[13] introduced a chiral auxiliary into the diene **10** and performed Diels-Alder reaction in a diastereoselective manner (Scheme 14).

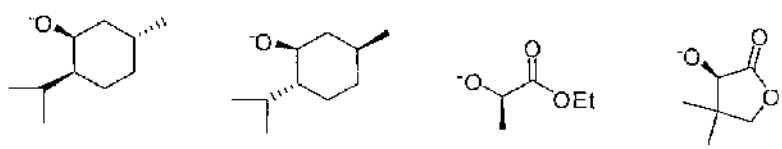


10

X = OBu, SBu, SPh (low d.e. in this case)

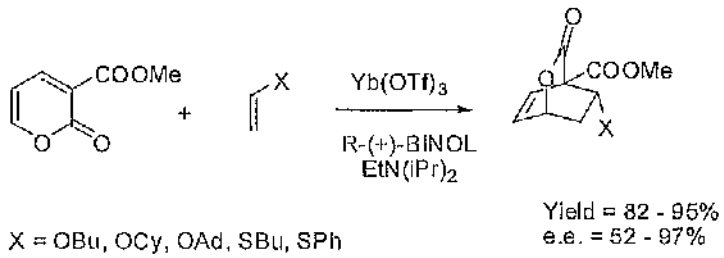
Yield = 84 - 97%
d.e. > 95%

R* =



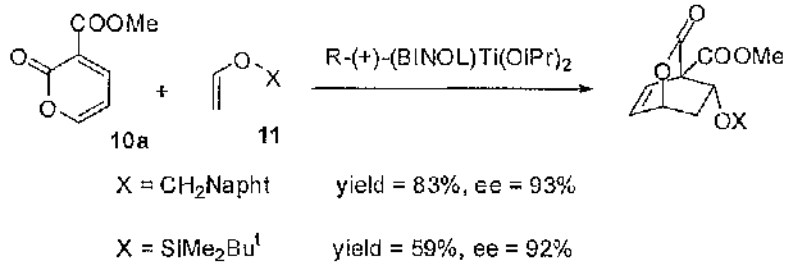
Scheme 14. The diastereoselective Diels-Alder reaction with chiral auxiliary.

More recently, they developed[13] an enantioselective version of the Diels-Alder reaction using the catalytic system based on Yb(OTf)$_3$ – BINOL – EtN(*i*Pr)$_2$ (Scheme 15). They have shown that the solvent purity and the absence of traces of alcohols (e.g., ethanol) are crucial to attain high enantioselectivities.



Scheme 15. The catalytic enantioselective DA reaction.

In 1996 Posner *et al.*[14] reported on the IEDDA reaction promoted by stoichiometric (BINOL)Ti(OiPr)$_2$. First, the latter complex was allowed to react with 3-carbomethoxypyrone **10a** at elevated temperature (50 °C) to form a complex which subsequently was treated with excess of the respective vinyl ether **11** at –30 °C. The products were obtained in high enantioselectivity (Scheme 16).



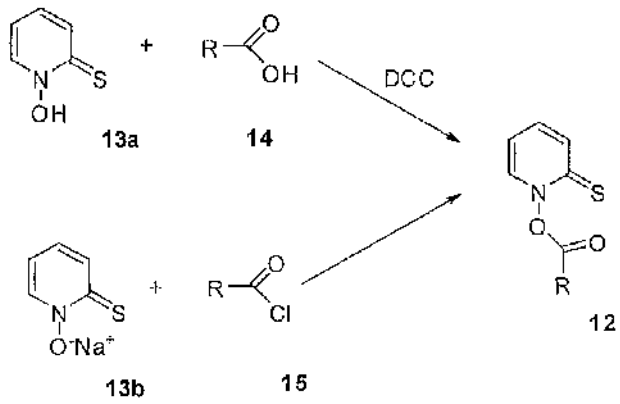
Scheme 16. The stoichiometric enantioselective IEDDA reaction.

However, there has been no report on IEDDA reaction employing unprotected pyrone carboxylic acid as a diene.

5. Barton ester formation: problem of sterically hindered carboxylic acids and ways to initiate radical decomposition

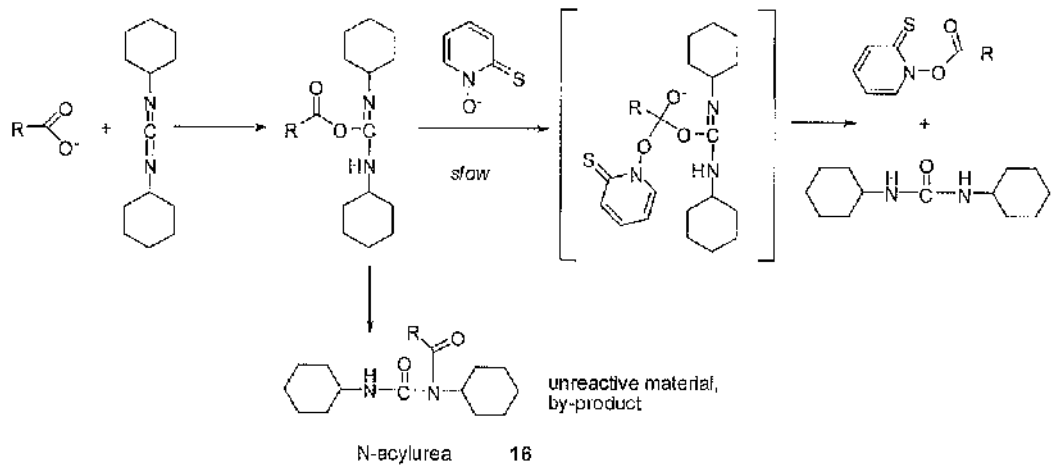
On the next step of the proposed synthesis of cyclohexenyl nucleosides we used selective reductive decarboxylation employing Barton-type esters.

Discovered and developed by Barton, radical reactions of *N*-hydroxy-2-thiopyridone derivatives **12** have found a variety of applications in organic synthesis.[15] The most common and widely used approach towards esters of *N*-hydroxy-2-thiopyridone (Barton esters) **12** relies either on coupling between the respective carboxylic acid **14** and *N*-hydroxy-2-thiopyridone **13a** in the presence of a coupling agent (DCC or EDCI)[16] or the reaction between acyl chloride **15** (generated from the respective carboxylic acid) and sodium salt of *N*-hydroxy-2-thiopyridone **13b** (Scheme 17).[17]



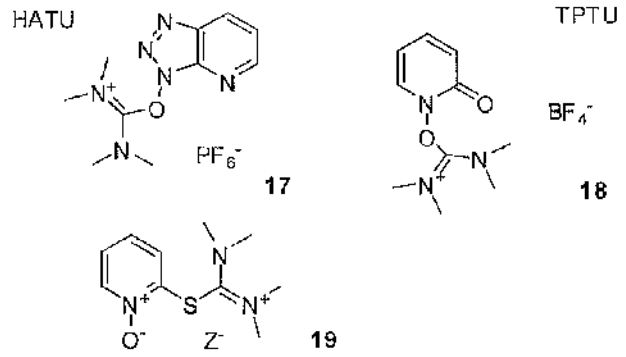
Scheme 17. Usual synthetic pathways towards Barton esters.

However, in a number of cases this simple approach fails. Problems may arise from instability of acyl chloride **15** or, what is more serious and difficult to overcome, from inactivity of the carboxylic acid **14** due to steric hindrance. A recent review[18] discussed the mechanism of the coupling reaction between a carboxylic acid and *N*-hydroxy compounds (such as *N*-hydroxy-2-thiopyridone or hydroxybenzotriazole), suggesting *N*-acylurea **16** formation in the case of slow substitution reaction (Scheme 18).



Scheme 18. The mechanism of the DCC coupling. Formation of *N*-acylurea.

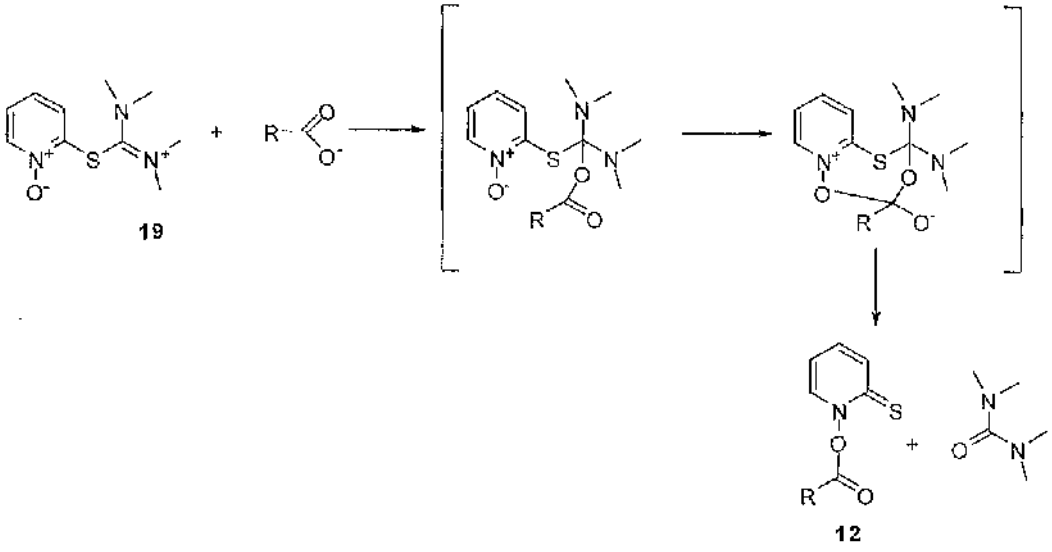
As a solution to the problem, new coupling agents were developed, such as HATU (**17**)[19] and TPTU (**18**) (Chart 2).[20] *N*-Hydroxy-2-thiopyridone derivatives, HOTT (**19a**) and TOTT (**19b**), deserve our special attention.



Z^- = BF_4^- TOTT (S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate)
Z^- = PF_6^- HOTT (S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium hexafluorophosphate)
HATU O-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
TPTU O-(1,2-dihydro-2-oxo-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate

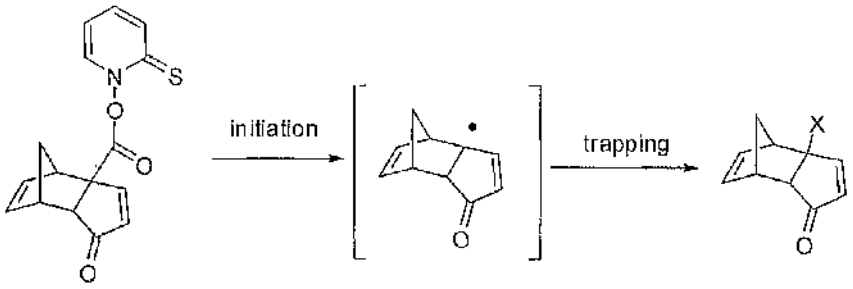
Chart 2. HATU, TPTU, TOTT and HOTT.

These compounds were successfully used for peptide couplings[21] and Barton esters **12** syntheses.[22] The mechanism of the coupling with TOTT or HOTT includes an intramolecular reaction, which occurs much easier than its intermolecular counterpart (Scheme 19).



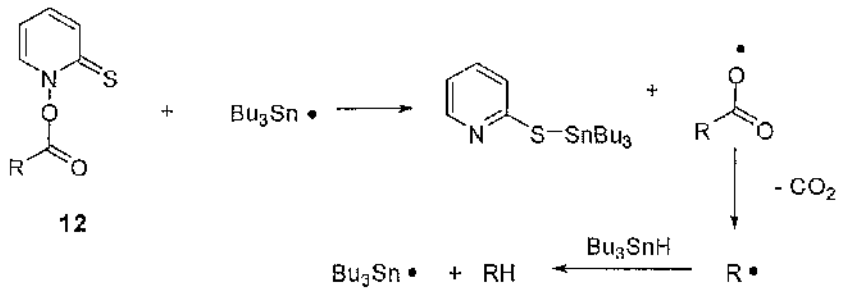
Scheme 19. The mechanism of HOTT/TOTT coupling.

Barton esters **12** thus obtained can be used without further purification in a number of radical transformations. Thus, Zhu *et al.*[23] described a series of radical reactions with various trapping agents (Scheme 20).



Scheme 20. Barton ester transformations.

Until recently, the most usual way to trigger the radical chain reaction of Barton ester **12** was irradiation or heating (the influence of temperature was discussed in the paper[24]). In addition, Barton esters can be reduced using Et_3B as an initiator in the presence of oxygen. These conditions are milder and usually give better results in terms of yields and selectivity.[25] The whole mechanism of the radical reduction of Barton esters **12** is shown in Scheme 21.



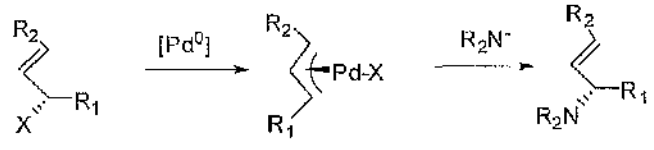
12

Scheme 21. Mechanism of the radical reduction of Barton esters.

6. Palladium-catalysed allylic amination

The last key step in the proposed synthesis of cyclohexenyl nucleosides is a palladium-catalysed stereoselective allylic amination.

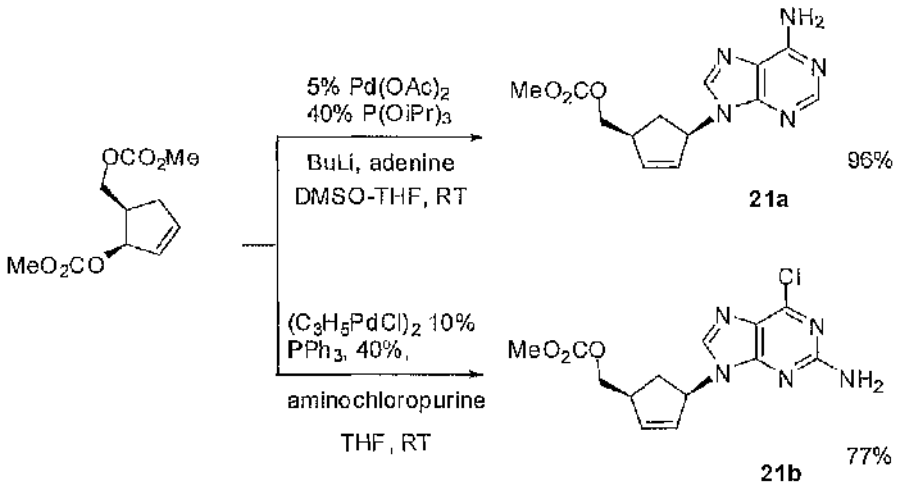
Transition metal-catalysed allylic amination is a well-developed area in modern organic synthesis (catalysis by complexes of iridium,[26] ruthenium,[27] molybdenum,[28] iron,[29] copper[30] is routinely used) however the central part is occupied by palladium-catalysed reactions.[31] Generally, amines react smoothly with allylic substrates under Pd catalysis via π-complex **20**.[32] Usually the stereochemical result of the amination is retention of the configuration of the carbon where the substitution occurred (Scheme 22).



20

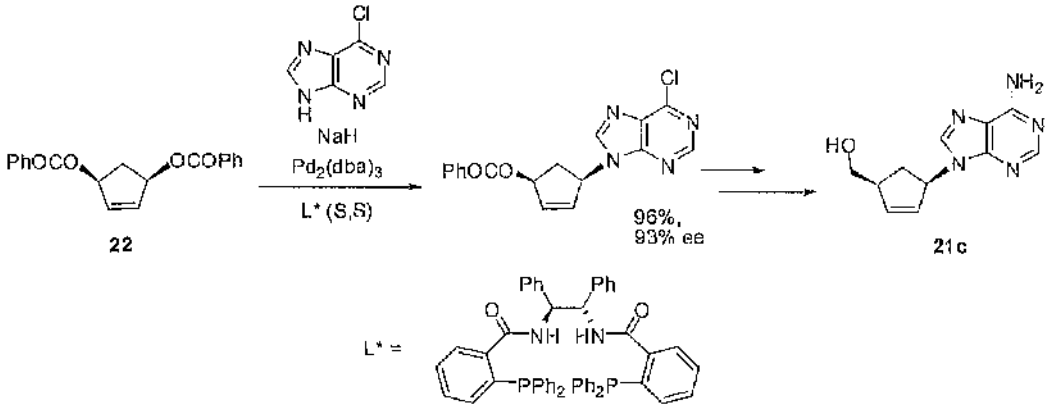
Scheme 22. Pd-catalysed allylic amination.

Pd-Catalysed substitution using nitrogen nucleophiles is well developed for simple amines.[31] In contrast to that, our area of interests – nucleoside chemistry – is less explored and deserves special attention. Nitrogen atoms of nucleosides are far less nucleophilic than those of alkyl and many aryl amines as their lone pair is involved in aromatic conjugation. In 1985 Bäckvall *et al.* reported on the first example of use of electron-deficient nitrogen nucleophiles, namely amides, in allylic amination.[33] The substitution reaction works well with both acyclic and cyclic allylic substrates, using sodium sulfoimide as a nucleophile and $Pd(PPh_3)_4$ or $Pd(dppe)_2$ as a catalyst. Trost pioneered the area of the allylic substitution with a nucleobase. In 1992, a new approach to carbanucleosides **21** was developed,[34] employing $Pd(OAc)_2$ or allylpalladium chloride as Pd precursors and phosphorus-based ligands (Scheme 23).



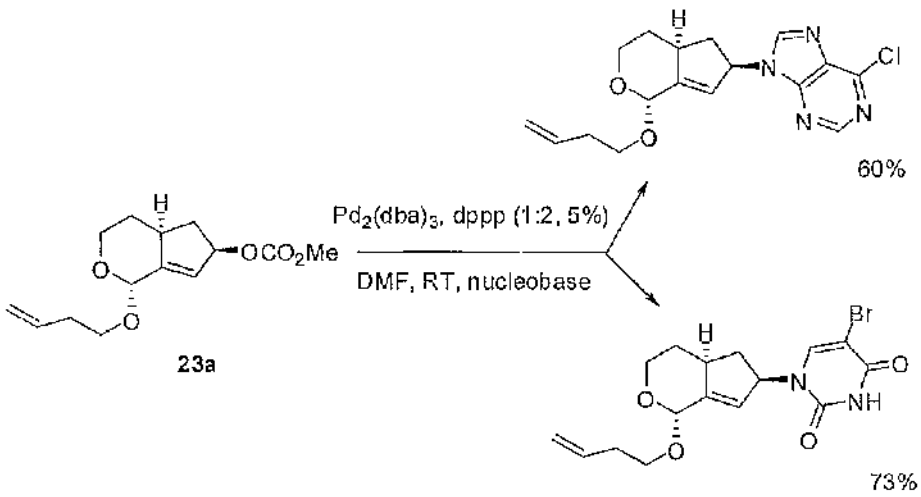
Scheme 23. The Pd-catalysed amination.

In 1996 Trost *et al.* published an enantioselective version of the amination with nucleobases,[35] based on desymmetrisation of allylic diacetate **22** (Scheme 24).



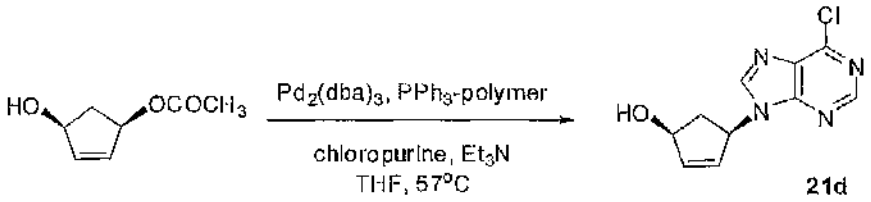
Scheme 24. Enantioselective allylic amination with a nucleobase.

There were a few recent publications where allylic cyclopentenes **23** were successfully used in the syntheses of various biomimetic molecules by employing Pd-catalysed amination with nucleobases under relatively mild conditions. Thus, Lanver and Shmaltz[36] were able to carry out amination of the allylic carbonate **23a** at room temperature without additional base for both purine and pyrimidine nucleobases (Scheme 25).



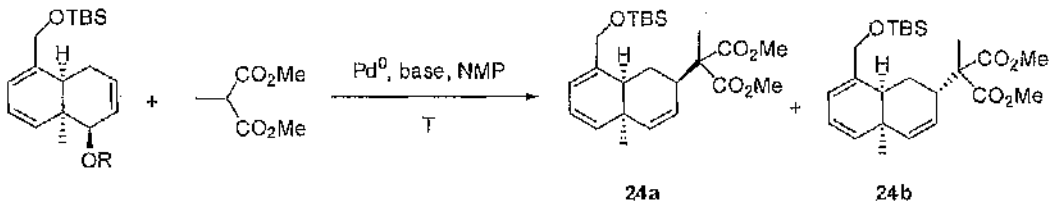
Scheme 25. Pd-catalysed allylic amination.

Weigl *et al.*[37] managed to perform amination reaction with polymer-bonded phosphine as a ligand and allylic acetate in THF at elevated temperature, affording the respective nucleoside **21d** (Scheme 26).



Scheme 26. The allylic amination with a nucleobase and solid-supported catalyst.

Recently, Kündig *et al.*[38] reported on allylic alkylation, where they investigated the factors which influenced stereoselectivity of the Pd-catalysed substitution reaction (Scheme 27). This investigation is summarised in the Table 5.



Scheme 27. Studies on the allylic substitution.

Table 5. Studies on the allylic substitution. (Scheme 27).

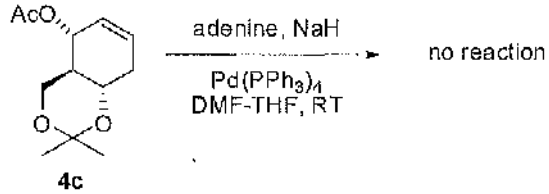
Entry	R	T, °C	Base	Pd^0	**24a**:**24b** ratio	yield
1	Ac	60	NaH	$Pd(PPh_3)_4$	75:25	60
2	OCO_2Me	25	NaH	$Pd(PPh_3)_4$	75:25	67
3	OCO_2Me	60	None	$Pd(PPh_3)_4$	15:85	61
4	OCO_2Me	25	NaH	$Pd(dppe)_2$	>98:2	99
5	OCO_2Me	50	None	$Pd(dppe)_2$	92:8	75

According to the Table 5, acetates are less reactive in the Pd-catalysed substitution reaction than the corresponding allylic carbonates (compare entries 1 and 2, Table 5). At the same time, addition of a base facilitates the reaction, changing or improving its stereoselectivity (compare entries 4 and 5; 2 and 3). However, the influence of the ligand is even more substantial than that of the base. Thus, the chelating donor dppe reasonably accelerates the substitution reaction, making it very stereoselective (retention of stereochemistry, entry 4, Table 5). It was suggested[38] that there is equilibrium between allylic palladium complex **20a** and Pd^0-phosphine complex. It spoils stereoselectivity of the reaction as leads to isomerisation (Scheme 28). Donor and bidentate phosphine ligands suppress the equilibrium.

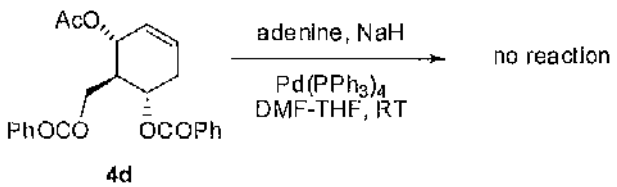
20a

Scheme 28. Pd-Allylic complex isomerisation.

Cyclohexene derivatives appeared to be generally slower in the allylic amination. It was noticed by Trost[34] and then Herdewijn also faced a problem attempting Pd-catalysed amination to prepare cyclohexene nucleosides.[9] He showed that $Pd(PPh_3)_4$ was not efficient as a catalyst for the amination of allylic acetate **4c** or **4d** by adenine in the presence of sodium hydride at room temperature (Scheme 29).



4c

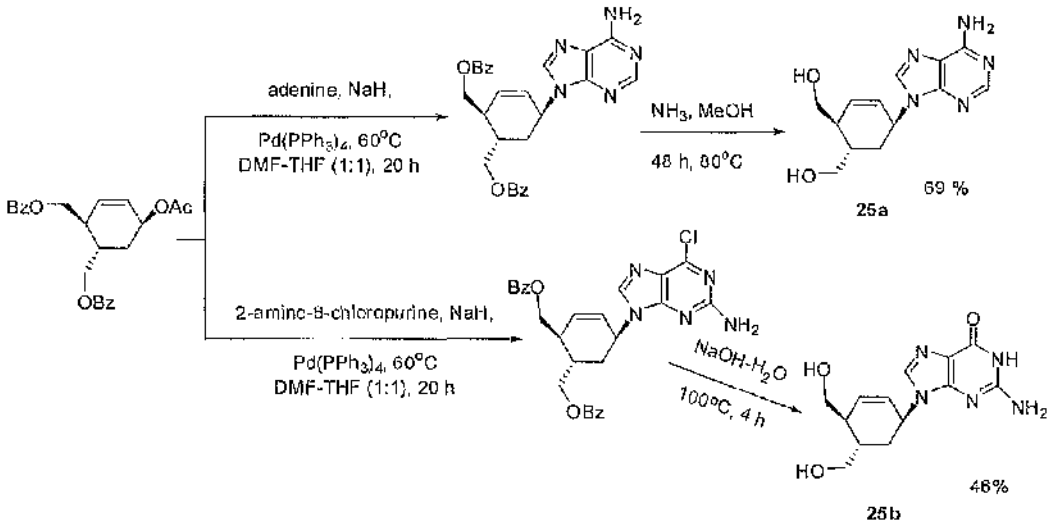


4d

Scheme 29. Unsuccessful attempts to perform Pd-catalysed allylic amination.

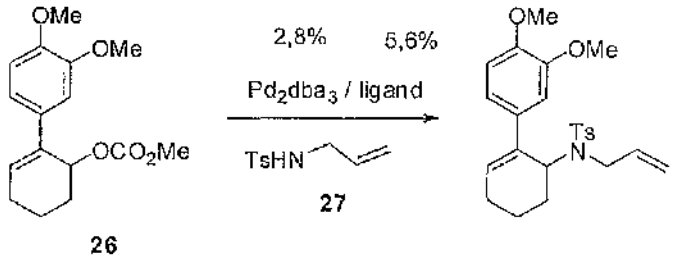
However, Konkel and Vince[8] earlier presented the synthesis of 2',3'-bis-deoxy analogue **1** of cyclohexene nucleoside by Pd-catalysed allylic amination (see Scheme 6).

Kvarnström and Samuelson[39] described synthesis of cyclohexene nucleosides derivatives **25**, which were found to be inactive against HIV virus, however. In their sequence, Pd-catalysed allylic amination was used in the last step (Scheme 30).



Scheme 30. Pd-catalysed allylic amination.

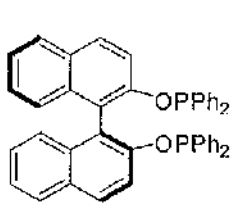
Recently Mori[40] reported on the investigation of palladium catalysed allylic amination of cyclohexene derivatives **26** by tosylamide **27** (Scheme 31). First, they focused on the influence of the ligand, solvent, and temperature on the reaction efficiency (Table 6; Chart 3)



Scheme 31. Pd-catalysed allylic amidation.

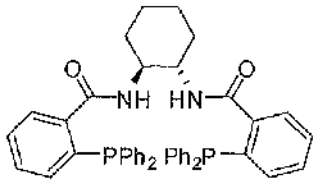
Table 6. Ligands used in the Pd-catalysed allylic amination (Scheme 31)

Entry	Ligand	Solvent	T, °C	Time, h	Yield, %	ee, %
1	Dppb	DMSO	50	13	36	-
2	S-BINAP	DMSO	75	50	12	9
3	(+)-Trost **28** [34]	THF	50	98	0	-
4	S-BINAPO **29**	DMSO	RT	3	51	70
5	S-BINAPO **29**	DMF	RT	3	70	71
6	S-BINAPO **29**	Toluene	RT	31	76	80
7	S-BINAPO **29**	CH_3CN	RT	4	68	66
8	S-BINAPO **29**	CH_2Cl_2	RT	2	75	73
9	S-BINAPO **29**	THF	RT	19	80	86
10	S-BINAPO **29**	THF	0	216	53	87



29

(S)-BINAPO

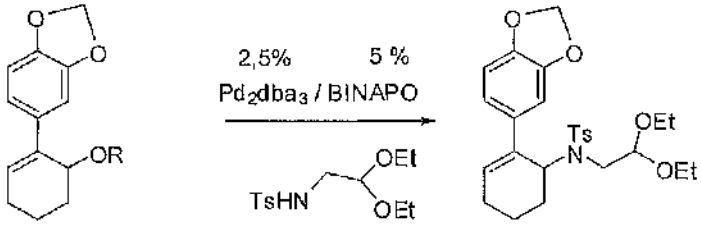


28

(+)-Trost

Chart 3. Trost ligand and BINAPO.

BINAPO (**29**) performed the best (entries 1 – 4, Table 6). The reaction proved to run faster in more polar solvents, while room temperature was found to be optimal for the reaction with BINAPO (**29**) as a ligand. Optimisation of the leaving group in the amination reaction was carried out next (Scheme 32 and Table 7).

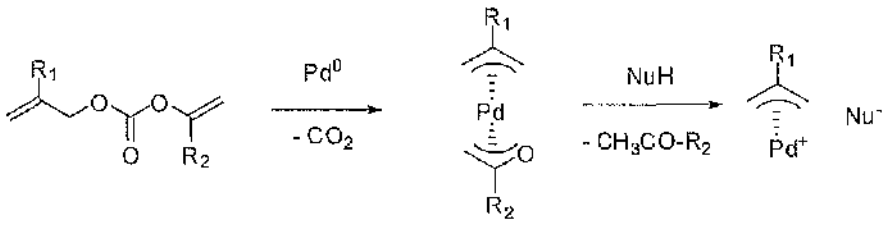


Scheme 32. Optimisation of the amination reaction.

Table 7. Leaving group screening in the palladium catalysed allylic amination (Scheme 32).

Entry	R	T, °C	Time, h	Yield, %	ee, %
1	CO_2Me	0	106	31	68
2	$PO(OEt)_2$	0	4	73	69
3	$PO(OEt)_2$	-20	48	80	74
4	$C(O)OCH–CH_2$	0	2.5	69	68
5	$C(O)OCH=CH_2$	-20	53	82	74
6	$C(O)OC(Me)=CH_2$	-20	245	39	74

This study (Table 7) revealed a strong dependence of the reaction rate on the leaving group and it was suggested that an extra stabilisation by vinyl alkoxide can accelerate the reaction (Scheme 33).

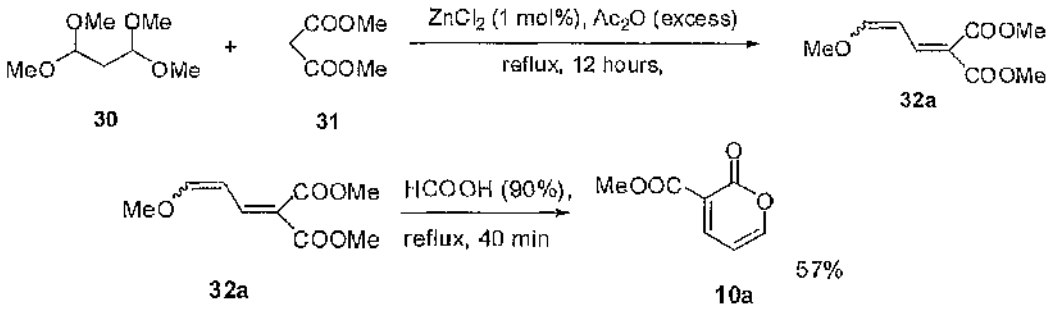


Scheme 33. A possible mechanism for the substitution reaction involving vinyl carbonate.

Results and discussion

1. Synthesis of 2-pyrone derivatives

3-carbomethoxy-2-pyrone **10a** (commercially available, but relatively expensive) can be prepared in two steps from simple starting materials – tetramethoxypropane **30** and dimethyl malonate **31** – using literature protocols[41,42] in a good yield and purity (Scheme 34).

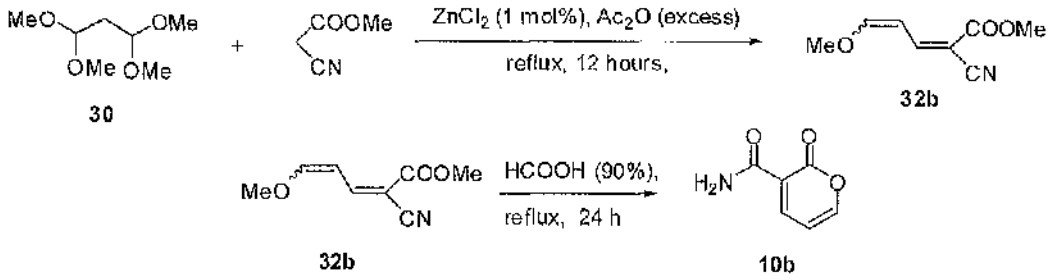


Scheme 34. Synthesis of 3-carbomethoxy-2-pyrone.

According to Corey and Watt,[41] malonate **31** should be added slowly (for 30 min) to the reaction mixture in the first step. However, in our hands, the rate of malonate addition did not have any influence on the yield. We found that either mixing the starting materials prior to the reaction or slow addition of malonate **31** over 30 min or 2 h resulted in almost identical isolated yields of the product **32a**. Increasing catalyst loading led to decrease in the yield (from 85% with 1 mol% of $ZnCl_2$ to 65% with 5 mol% of $ZnCl_2$) due to polymerization of the reaction components. Importantly, excess of acetic anhydride (10:1 to tetramethoxypropane) was found to be essential providing 85% of pure product **32a** after distillation, whereas with 1.2 eq[41] of acetic anhydride only 17% of **32a** was isolated.

The second step was performed without any significant modification. We believe the cyclisation is a fast process but the product **10a** is not thermally stable, so that the reaction time should be kept to a minimum. Thus, refluxing for 1.5 h[41] resulted in 47% yield of **10a**, whereas 40 min reflux afforded 57%.

An analogous sequence of the two reactions in attempt to synthesise 3-cyano-2-pyrone failed. Instead, we isolated 2-pyrone-3-carboxyamide **10b** (Scheme 35; synthesised previously a different way[43]).



Scheme 35. Synthesis of amide of 2-pyrone-3-carboxylic acid.

It is pertinent to note that cyclisation of **32b** was much slower than of **32a** and required 24 hours reflux in 90% formic acid (compared with 40 minutes for **32a**). The resulting amide **10b** (65% yield over two steps) was insoluble in all common organic solvents except DMSO.

2. Selective hydrolysis of the methyl ester.

Scheme 36. Synthesis of 2-pyrone-3-carboxylic acid **10c**

A few methods for the hydrolysis of 3-carbomethoxy-2-pyrone **10a** into 2-pyrone-3-carboxylic acid **10c** were published (Scheme 36). Firstly, we monitored the hydrolysis of **10a** employing concentrated HCl solution[12] as a reagent at 45 °C (Table 8).

Table 8. Hydrolysis reaction.

Entry	Time, min	Conversion (NMR) of starting ester **10a**, %
1	15	18
2	45	42
3	90	62
4	150	75
5	330	85

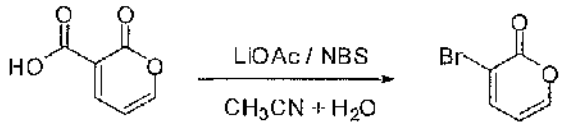
Table 8 shows that it was difficult to reach a complete conversion of the starting material **10a** (presumably, owing to the reverse reaction). The best result was only 20% yield of the product **10c** (85% purity by NMR), due to the instability and water solubility of **10a** and **10c**. Attempted alkaline hydrolysis was also unsuccessful. Thus, NaOH in MeOH at room temperature gave an intractable complex mixture, while $NaHCO_3$ in water failed to react.

Using Me_3SiI as a reagent for hydrolysis,[44] the conversion of the ester **10a** into the acid **10c** after 24 h heating at reflux in chloroform was only 30%. However, when the reaction was carried out overnight at 75 °C without any solvent, acid **10c** was isolated in almost quantitative yield and high purity (by ^1H and ^{13}C NMR) so that it could be used for further transformations without an extra purification. We have to emphasise that it is the workup should be carried out with special care because acid **10c** is fairly soluble in water and unstable to any base.

3. Conversion of 2-pyrone-3-carboxylic acid (10c) into 3-bromo-2-pyrone (33) via Hunsdiecker-type bromination

3-bromo-2-pyrone **33** was the next step in our proposed synthesis of cyclohexenyl nucleosides.[1,a)] Previously, 3-bromo-2-pyrone **33** was prepared by the bromo-

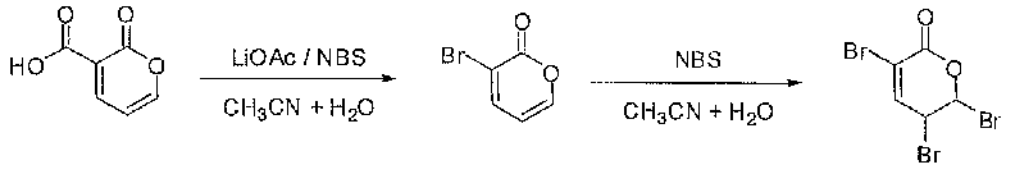
decarboxylation reaction from the respective carboxylic acid **10c**[45] (Scheme 37). However, the reaction details were not given.



10c **33**

Scheme 37. Bromo-decarboxylation reaction.

Monitoring the reaction (by CO_2 evolution) we have found that it was fairly fast. Indeed, the crude mixture after 1.5 h contained no starting acid **10c** (by ^{1}H-NMR). Moreover, after 3 h, the crude mixture contained about 30% percent of tribromo derivative **33b** in addition to the desired 3-bromo-2-pyrone **33**.[46] (Scheme 38).



10c **33** **33b**

Scheme 38. The side reaction in the bromination reaction.

We found that a large excess (6 eq) of NBS is essential. With 1 equivalent, the reaction gives a complex mixture because of polymerisation. With 2 equivalents of NBS, we still could detect polymers in the ^{1}H-NMR spectrum and the isolated yield was only half of that obtained by using 6 equivalents of NBS (15% vs. 33%).

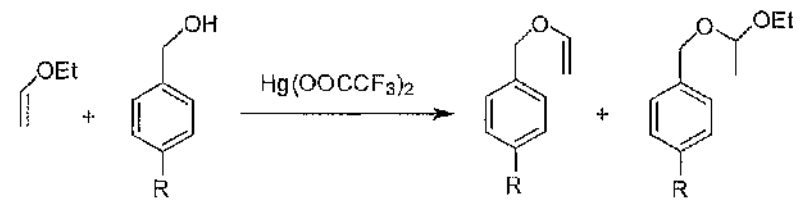
The best ratio between LiOAc and the starting acid **10c** is 1:1. When the catalytic amount of LiOAc was used, only traces of the desired product **33** were isolated. At the same time, increasing the amount of LiOAc up to two equivalents resulted in polymerization of **10c**. Hence, it can be concluded that the reaction requires 1 equivalent

of a weak base to produce the carboxylic anion, which should be quickly trapped to avoid polymerization.

Optimal ratio of water and acetonitrile for the reaction is 1:5. More water causes NBS hydrolysis and higher concentration of free Br_2 which fuels the side reaction leading to the tribromo-compound **33b** (Scheme 38). On the other hand, LiOAc does not dissolve in CH_3CN without water which blocks the reaction. We only managed to obtain a moderate yield of the desired compound **33** because the product was not stable during chromatography. Flash chromatography on neutral alumina afforded 33% of pure **33** as white crystals.

4. Synthesis of vinyl ethers

For the synthesis of benzyl vinyl ethers **11**, modification of the known procedure was used (the reaction time was increased from 20 min to 12 h; Scheme 39).[47]



11a

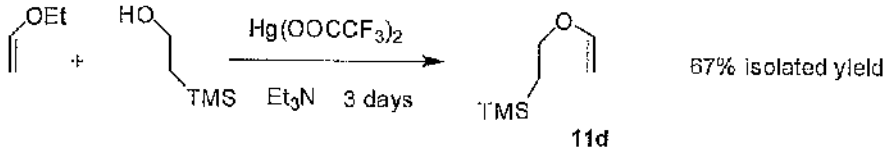
11 **34**

11b R = H
11c R = OMe

Scheme 39. Synthesis of vinyl ethers.

After an overnight stirring at room temperature, two products were detected in the reaction mixture by ^1H NMR – the respective **11b** or **11c** and the acetal **34** (ratio 2:1). However, the desired products **11b** and **11c** were isolated by distillation in good purity, presumably, due to thermal decomposition of the acetal **34** into the respective vinyl ether **11b** or **11c**.

2-(trimethylsilyl)ethyl vinyl ether **11d** was synthesised using published protocol without any optimisation (Scheme 40).[48]



Scheme 40. Preparation of SEM-protected vinyl ether.

5. Diels-Alder reaction.

Initially, we planned to develop an enantioselective protocol for the Diels-Alder reaction between 3-bromo-2-pyrone **33** and various vinyl ethers (the racemic version employing high pressure and temperature has been described[4,a]). Catalytic systems **A-D** were investigated[49,50] (Chart 4), however 3-bromo-2-pyrone **33** proved to be unreactive (Scheme 41).

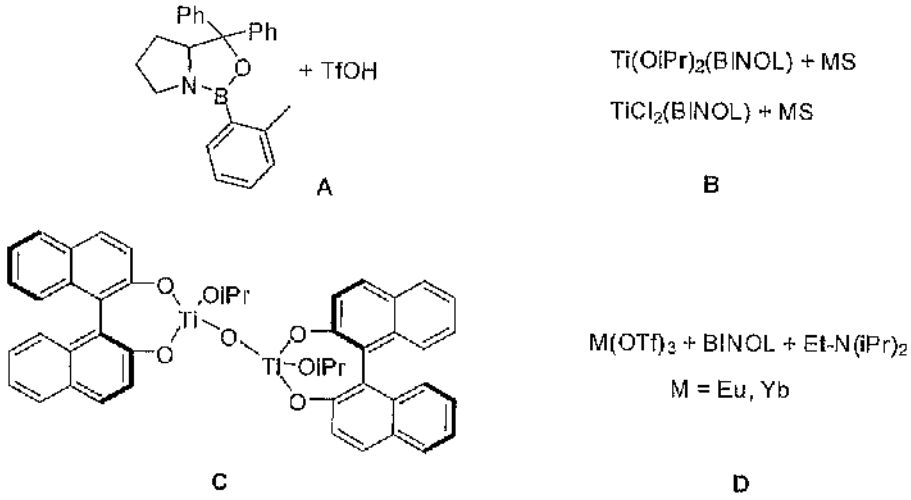
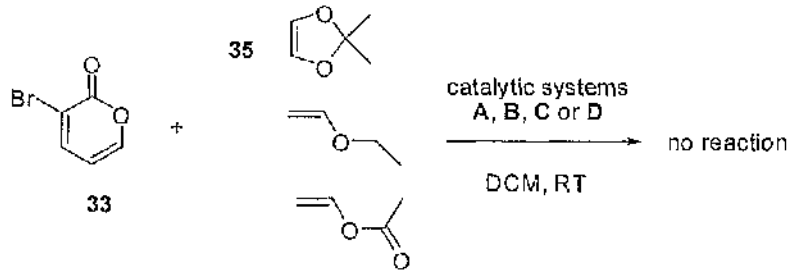
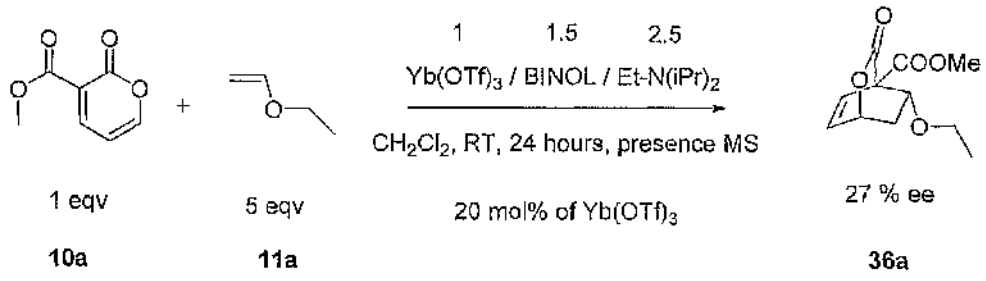


Chart 4. Catalytic systems explored in Diels-Alder reactions



Scheme 41. Attempts with 3-bromo-2-pyrone.

Later, we successfully reproduced the procedure published by Markó[13] by reacting 3-carbomethoxy-2-pyrone **10a** with ethyl vinyl ether **11a** to afford the respective product **36a** in high yield, regio- and stereoselectivity (only *endo* isomer was detected in the crude mixture by ^{1}H NMR) and rather low enantioselectivity (Scheme 42).



Scheme 42. Diels-Alder reaction of 3-carbomethoxy-2-pyrone.

We have shown that $Eu(OTf)_3$ catalyses the reaction with the same efficiency as $Yb(OTf)_3$, whereas a number of other metal complexes were inactive (Ti, Ru, Ir).

We propose that the chelate-type complex **37** between pyrone **10a** and the respective metal catalyst is the key intermediate taking part in the Diels-Alder reaction (Chart 5). Pyrone **33** cannot form the same type of chelate which might be a reason for its poor reactivity.

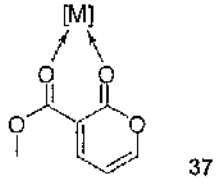


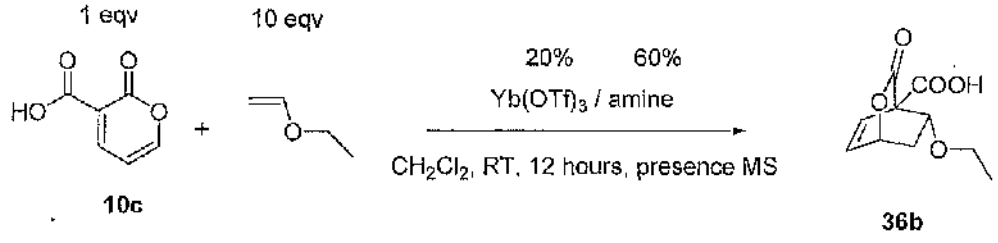
Chart 5. The chelate complex as the proposed key intermediate in the Diels-Alder reaction.

Carboxymethyl group cannot be selectively cleaved from the ester **36a** thus making the compound **36a** not synthetically valuable. Looking for a more promising alternative and assuming an important role of chelation, we tested 2-pyrone-3-carboxylic acid **10c** in the Diels-Alder reaction with ethyl vinyl ether **11a**. To our delight, it reacted readily to furnish the respective *endo*-**36b** as a single regioisomer (racemate; conditions as specified in the Scheme 42) with full conversion of the starting **10c**.

Excluding BINOL from the catalytic system did not influence conversion, regio- or stereoselectivity. By varying the amine in the catalytic system, we have found that tertiary mono- or diamines performed equally well (Table 9, Scheme 43).

Table 9. Amine variation in the DA reaction of 2-pyrone-3-carboxylic acid with ethyl vinyl ether

Entry	Amine	Conversion of **10c**, %
1	$EtN(iPr)_2$	99
2	$HN(iPr)_2$	90
3	Naphth-$CH(CH_3)$-NH_2	25
4	TMEDA	99
5	L-proline	no reaction
6	$(CH_3)_2N$-CH_2-$N(CH_3)_2$	no reaction



Scheme 43. Amine variation in the DA reaction of 2-pyrone-3-carboxylic acid with ethyl vinyl ether.

Then, we carried out the DA reaction (DCM, RT, 12 h, 10-fold excess of the vinyl ether, 20% of $Yb(OTf)_3$) employing lithium acetate or lithium prolinate as bases instead of amines. Interestingly, none of these systems was efficient (up to 5% of a mixture of *endo*/*exo* isomers **36b** and polymers of vinyl ether were recovered). Based on this result, we concluded that amine played a role of ligand for Yb in the catalytic system.

A number of different chiral amines were tested as catalysts with or without Yb^{3+}, however only one catalytic system induced modest enantioselectivity (Table 10, entry **1**; Chart 6, Scheme 44).

Table 10. Studies on the enantioselective DA reaction with 2-pyrone-3-carboxylic acid

Entry	Catalyst	ee of **36b**, %
1	$Yb(OTf)_3$ (20 mol%)/ **38** (40 mol%)	33
2	**38** (40 mol%)	0
3	$Yb(OTf)_3$ (20 mol%)/ **39a** (40 mol%)	0
4	**39a** (40 mol%)	0
5	$Yb(OTf)_3$ (20 mol%)/ **39b** (40 mol%)	0
6	**39b** (40 mol%)	0
7	$Yb(OTf)_3$ (20 mol%)/ **40** (40 mol%)	0
8	**40** (40 mol%)	0
9	$Yb(OTf)_3$ (20 mol%)/ **41** (40 mol%)	0
10	**41** (40 mol%)	0
11	$Yb(OTf)_3$ (20 mol%)/ **42a** (40 mol%)	0
12	**42a** (40 mol%)	0

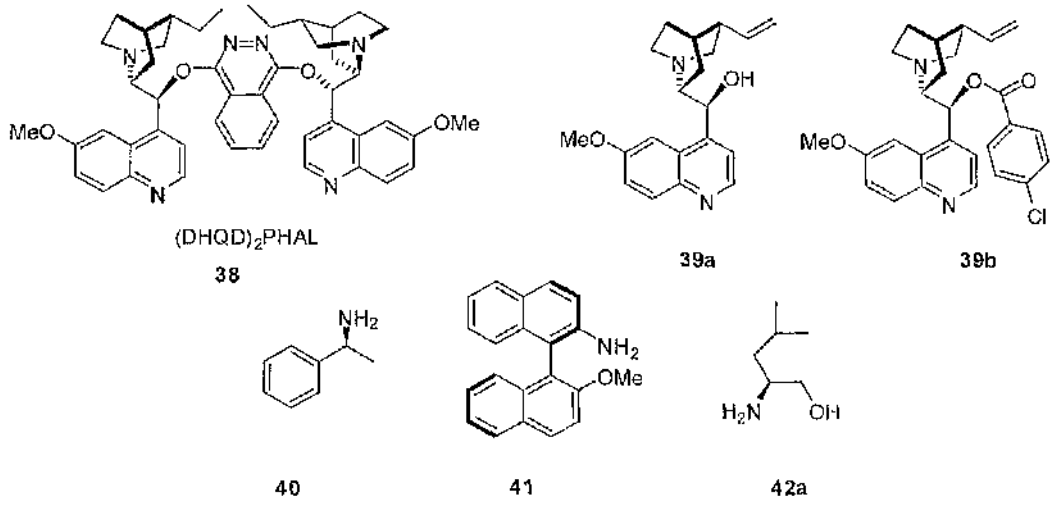
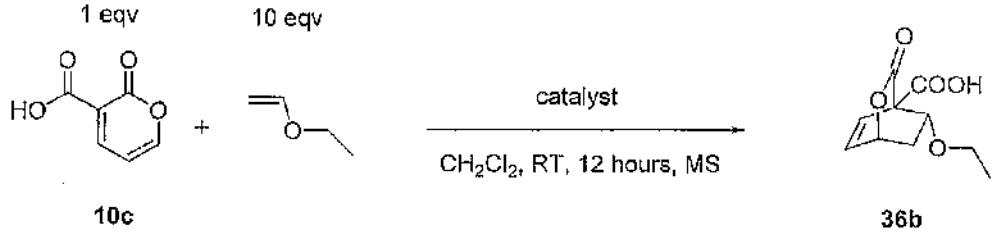


Chart 6. Chiral amines for the optimisation of the enantioselective DA reaction



Scheme 44. Studies on the enantioselective DA reaction with 2-pyrone-3-carboxylic acid.

Using the optimised procedure (racemic version; 20% of $Yb(OTf)_3$, 50% of TMEDA, 10 equivalents of vinyl ether, 21 °C, DCM, molecular sieves (4Å), 12 h with stirring) we explored the reactivity of vinyl ethers **11a-d** in the Diels-Alder reaction (Chart 7). All of them reacted readily, providing the respective products with excellent regio- (single isomer by ^1H NMR) and stereoselectivity (*endo*/*exo* ≥ 30:1). However, **11b-11d** reacted with **10c** slower than **11a**.

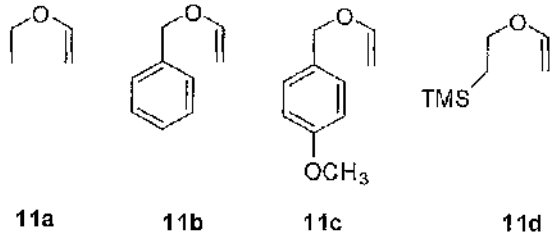
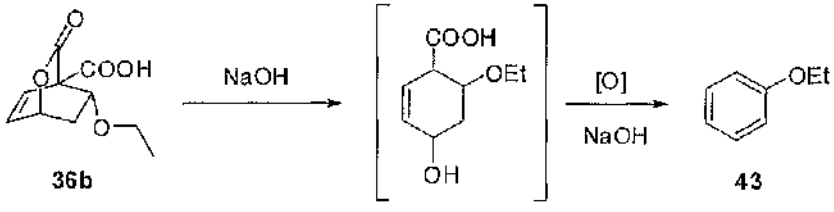


Chart 7. Vinyl ethers tested in the DA reaction.

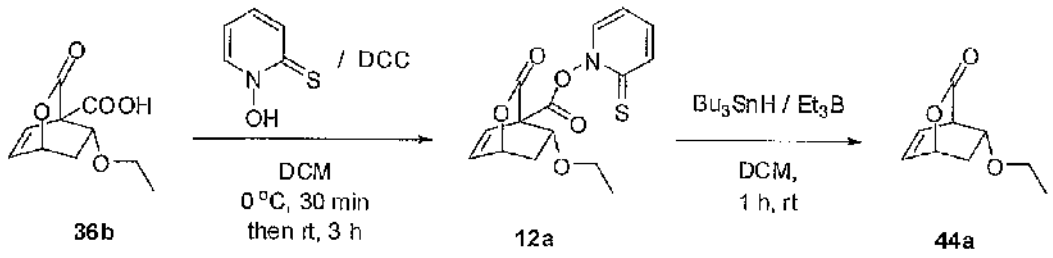
6. Decarboxylation

Decarboxylation of **36b** was the next step of the proposed approach towards cyclohexenyl nucleosides. In our first attempts we used basic conditions for the decarboxylation reaction, but unsuccessfully. Bases, such as $NaHCO_3$ or Na_2CO_3, were unreactive, whereas sodium hydroxide in aqueous methanol promoted a non-selective reaction, resulting in the formation of ethoxybenzene **43** (20-30% yield; Scheme 45).



Scheme 45. Decarboxylation under strong basic conditions. Side reaction.

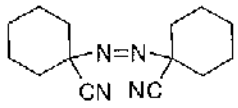
Next, we turned to decarboxylation employing the method developed by Barton[16,23] (Scheme 46).



Scheme 46. Decarboxylation using Barton reaction.

We were unable to isolate a pure product **12a** after the first step. It was unstable on column (SiO_2 or Al_2O_3) and could not be crystallised from the reaction mixture. However, the crude material was sufficiently pure (80% purity by ^1H NMR) to be used in the next step without an extra purification.

We tested different activators for the radical reaction but the most common methods (irradiation and VAZO **45**) failed.

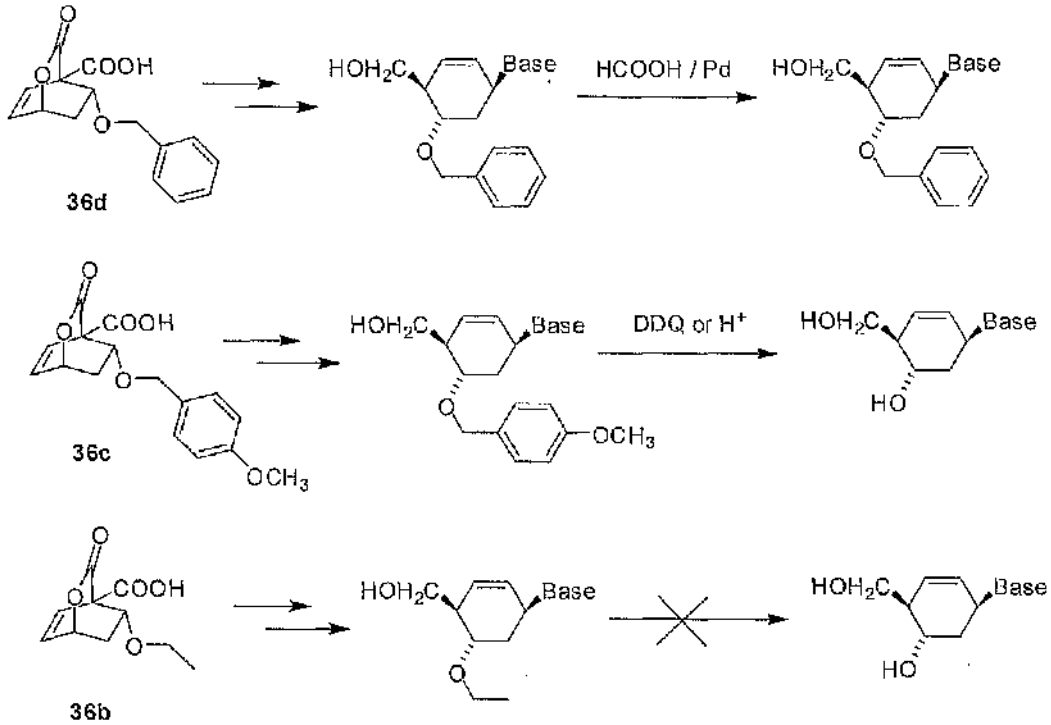


45

Chart 8. The structure of VAZO (radical initiator).

However, the mild activator Et_3B (20 mol%, 1 h in DCM, RT, 5 equivalents of Bu_3SnH) induced a clean radical reduction providing full conversion of the starting ester **12a** to the desired product **44a** (23% isolated yield over 3 steps).

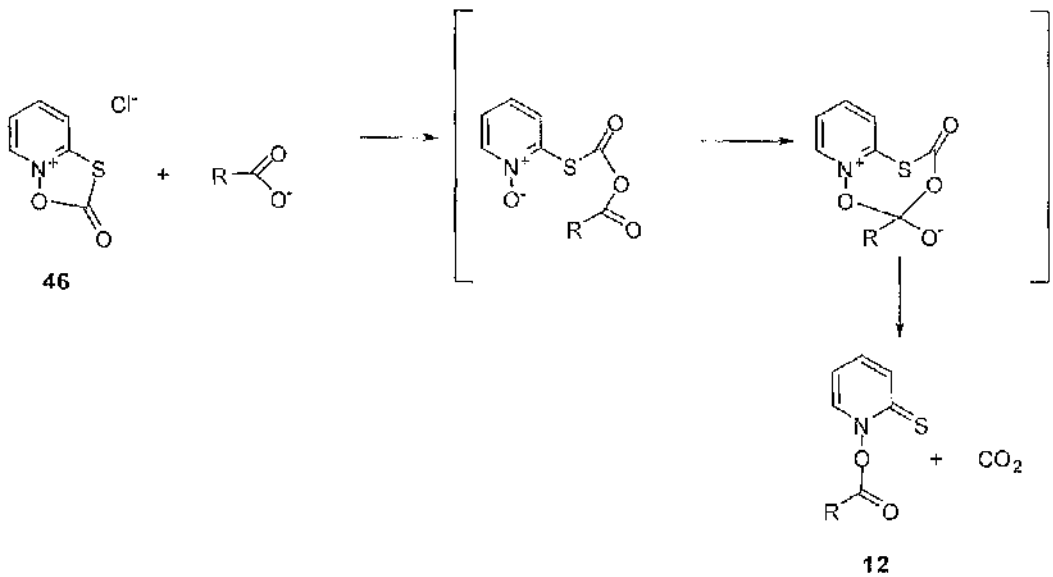
To be able to continue the synthesis of the target cyclohexenyl nucleosides, we had to enlarge the scope of the decarboxylation reaction employing synthetically more useful adducts of 2-pyrone-3-carboxylic acid **10c** with p-methoxybenzyl vinyl ether **11c** or benzyl vinyl ether **11b** (Scheme 47).



Scheme 47. Options for the final nucleoside deprotection.

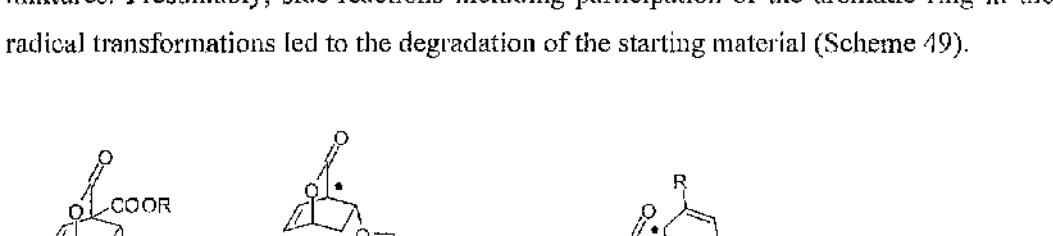
First, to obtain the respective Barton-type esters of the adducts **36c** and **36d**, we employed the previously optimised procedure (*N*-hydroxy-2-thiopyridone **13a**, DCC, DCM, RT, 3 h; Scheme 46) but it failed. The only product we could isolate after the coupling reaction (or after the following reduction with Bu_3SnH), was the corresponding *N*-acyl urea **16** (its formation was described as one of the most probable side-reactions which occur in the case of sterically hindered carboxylic acids; see Scheme 18).[18] Other methods which failed to give the desired products include EDCI (in the presence or absence of Et_3N), its modifications, and the mixed anhydride protocol using methylchloroformate. On the other hand, HOTT and TOTT **19**[22] reacted with acid **36** smoothly with complete conversion (1 equivalent of the acid, 1.25 equivalents of HOTT or TOTT, 3 equivalents of $EtN(iPr)_2$, 10% of DMAP, THF-CH_3CN (3:1), RT, 1 h) to afford the respective Barton esters **12** as the only products. Additionally, we found that another coupling agent **46**, formed from *N*-hydroxy-2-thiopyridone **17** and phosgene, can be successfully used in this reaction: products **12b** and **12c** were obtained from the

respective starting acid **36** within 2 hours in good purity and complete conversion. We suggest that the coupling in the presence of **46** proceeds via the same intramolecular mechanism as in the case of HOTT or TOTT (Scheme 48).



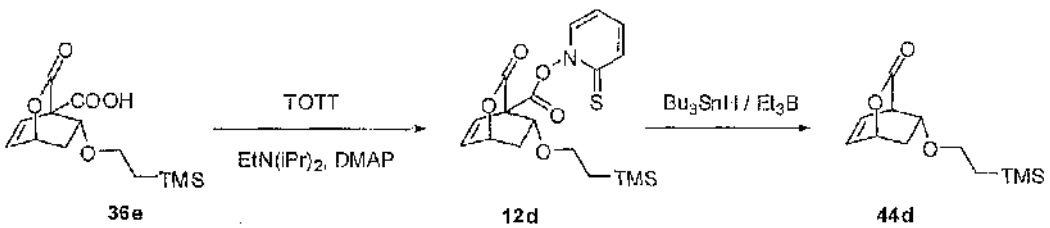
Scheme 48. Proposed mechanism of the reaction between carbonylated *N*-hydroxy-2-thiopyridone **46** and carboxylate.

Barton esters **12b,c** thus obtained were tested in the radical reduction (Bu_3SnH, Et_3B, air), but neither **44b** nor **44c** could be isolated from the respective reaction mixtures. Presumably, side-reactions including participation of the aromatic ring in the radical transformations led to the degradation of the starting material (Scheme 49).



Scheme 49. Possible degradation pathway.

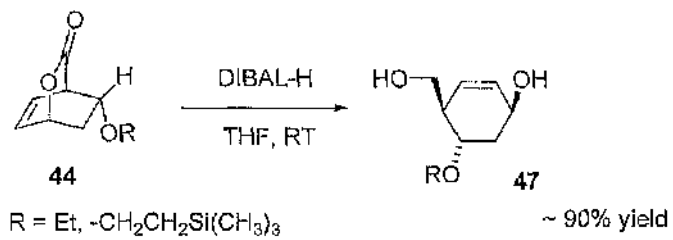
Next, we investigated 2-(trimethylsilyl)-ethyl (SEM) group as a prospective protecting group. It should not take part in the radical side-reactions and it can be cleaved by Py*HF or KHF_2. Indeed, the coupling and the following reduction (5 equivalents of Bu_3SnH, 40% of Et_3B, room temperature, 2 h) proceeded smoothly to provide the product **44d** from **36c** in 43% isolated yield (over two steps; Scheme 50).



Scheme 50. The selective decarboxylation method

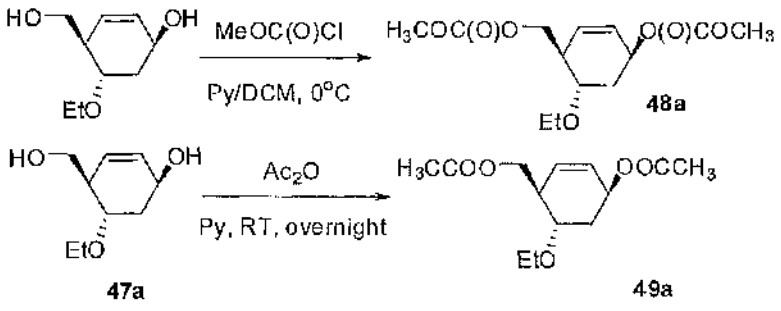
7. Precursor for amination. Determination of its relative stereochemistry by X-ray analysis.

Both lactones **44a** and **44d** were successfully reduced to the corresponding diols **47** with DIBAL-H (Scheme 51).



Scheme 51. DIBAL-H reduction.

Diols **47** can be converted to the respective acetates and methyl carbonates (Scheme 52).



Scheme 52. Derivatisation of the diol **47a**.

High quality crystals of the acetate **49a** were analysed by X-Ray crystallography. It confirmed the relative stereochemistry of the substituents in the ring and showed that in the solid state acetate **49a** adopts the $^{3}H_{2}$-conformation (Figure 4).

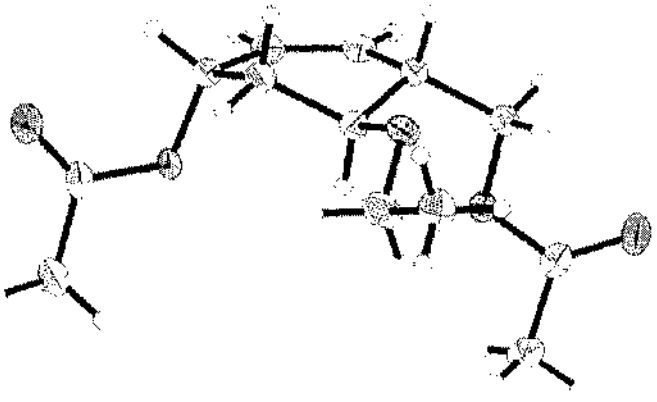


Figure 4. The structure of the acetate **49a** determined by X-Ray analysis

Conclusions

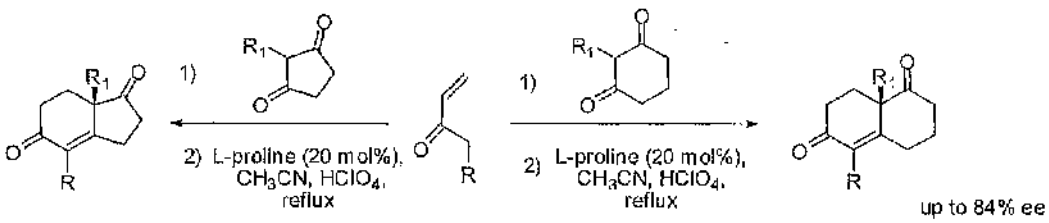
The inverse electron demand Diels-Alder reaction between 2-pyrone-3-carboxylic acid and different vinyl ethers has been performed to attain the respective products **36** with very high diastereoselectivity, which could potentially be used for the synthesis of cyclohexenyl nucleosides. It has been shown that Yb complexes can catalyse the reaction with low enantioselectivity.

Chapter II. The organocatalytic aldol reaction

Introduction

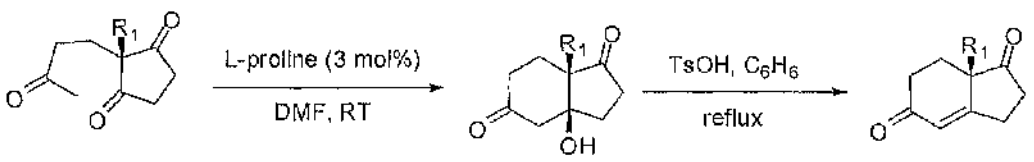
1. Introduction to aminocatalysis. Proline as the catalyst of choice

The first examples of asymmetric aminocatalysis go back to the early 1970s. Wiechert[51] reported on an asymmetric aldol reaction catalysed by various amino acids (Scheme 53). Proline provided the best enantioselectivity for this reaction.



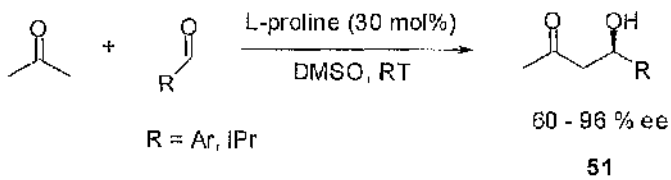
Scheme 53. The proline-catalysed asymmetric aldol reaction.

Later the intermediate **50** was isolated by Hajos[52] and its absolute configuration was determined by X-Ray crystallography (Scheme 54). Under milder conditions higher enantioselectivities were achieved for a family of the aldol reactions employing lower catalyst loading.



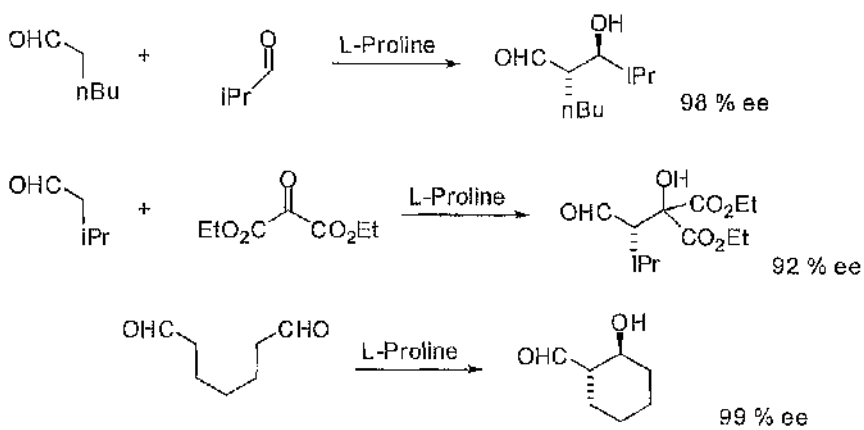
Scheme 54. The proline-catalysed asymmetric aldol reaction.

Surprisingly, after these two publications, enantioselective aminocataysis remained untouched for nearly 30 years until 2000 when Barbas reported on discovery of the proline-catalysed direct asymmetric intermolecular aldol reaction.[53] Using 30 mol% of L-proline, a series of aldol products **51** were obtained from acetone and aldehydes with enantiopurity ranging from moderate to high (Scheme 55).



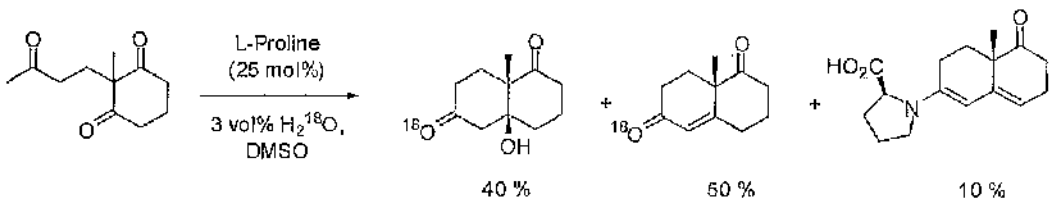
Scheme 55. Proline catalysed ketone – aldehyde condensation.

Since then, an explosive growth has been witnessed in the area of organocatalysis and particularly in asymmetric amine catalysis (Scheme 56).[54]



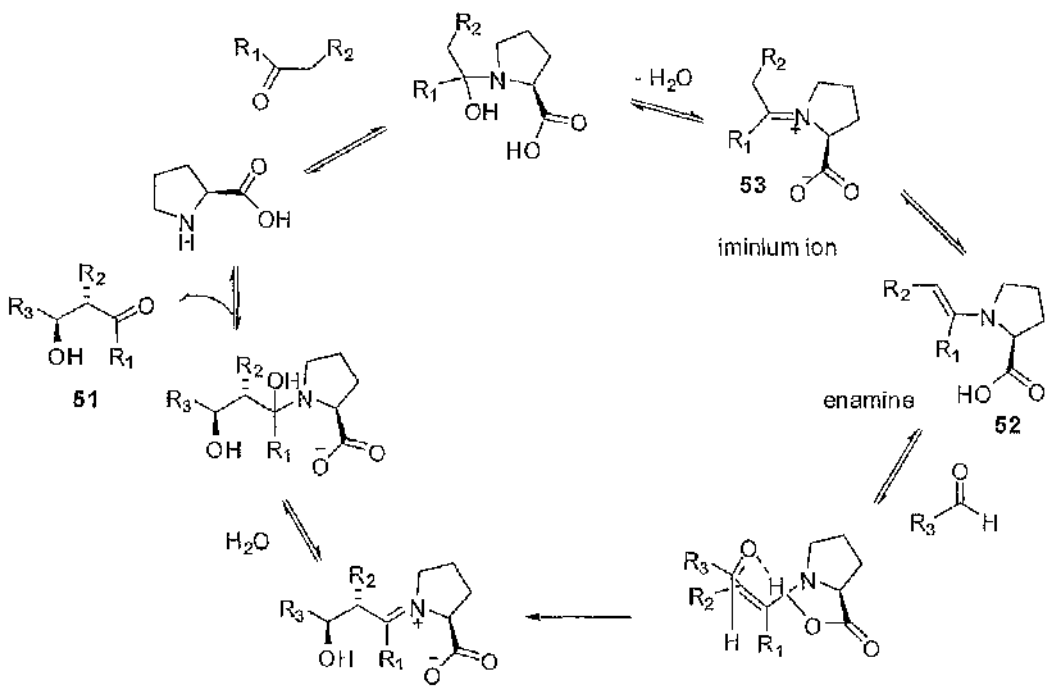
Scheme 56. Proline-catalysed enantioselective reactions.

Both experimental and theoretical studies contributed significantly to the elucidation of the reaction mechanism. List[55] showed that in the presence of $H_2{}^{18}O$ much of ^{18}O incorporates into the aldol products (Scheme 57).



Scheme 57. The O-18-incorporation experiment.

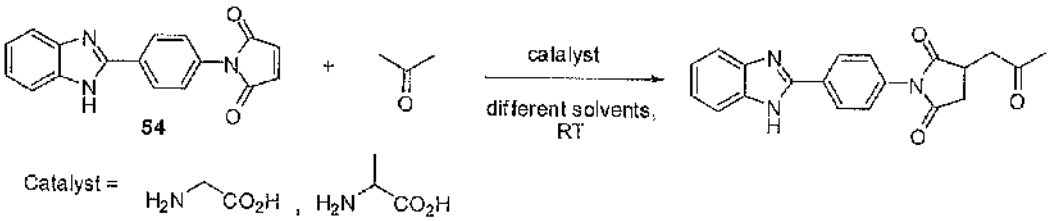
According to List,[55] proline-catalysed aldol reactions do not show any non-linear effects in the asymmetric catalysis. DFT calculations by Houk[56] also support the single enamine mechanism for the proline-catalysed aldol reactions. On the basis of these results, the mechanism shown in Scheme 58 was proposed. The key intermediate in the aldol reaction is the enamine **52** which is in equilibrium with the respective iminium ion **53**. The enamine reacts with an aldehyde giving, after hydrolysis, the desired aldol product **51**.



Scheme 58. The proposed mechanism of the proline-catalysed aldol reaction.

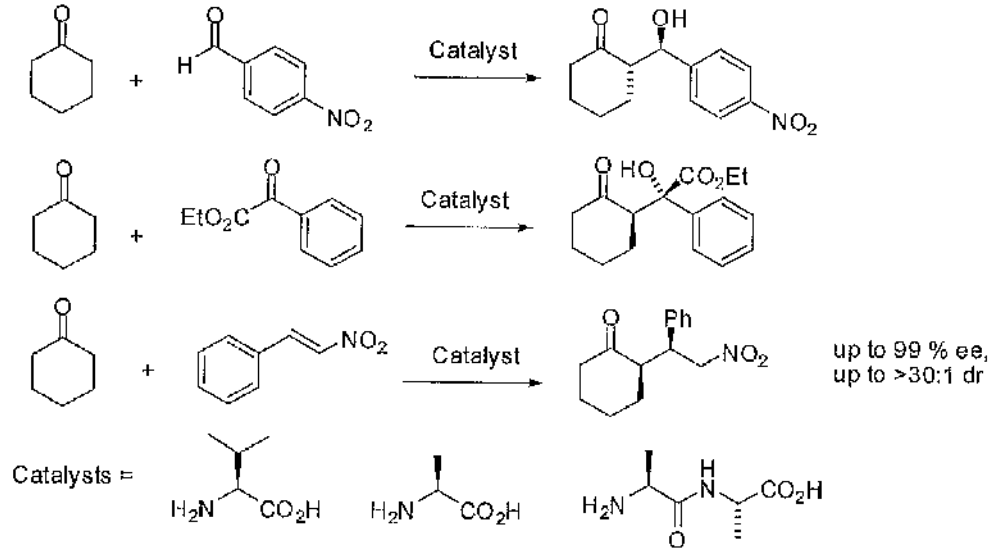
2. The use of primary amines as catalysts in aminocatalysis

While secondary amines are usually employed to mediate aldol-type reactions, the use of primary amines is less common, presumably owing to their tendency to form stable imines rather than enamines. However, there are a few examples of compounds with primary amino group used in aminocatalysis. Thus, Michael addition between acetone and the substituted maleimid **54** was studied by Barbas[57] (Scheme 59).



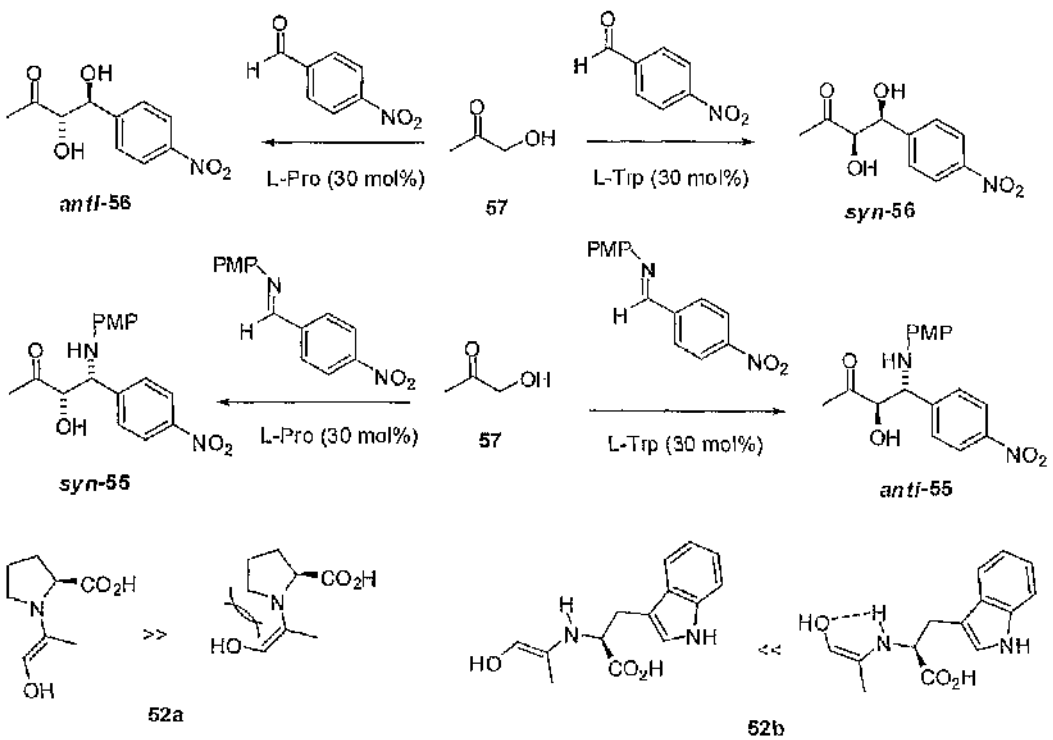
Scheme 59. Catalytic Michael addition.

The key intermediate in the reaction (Scheme 59) is the enamine formed from acetone and the corresponding amino acid. Córdova[58] showed that various primary amino acids and small peptides can be used as efficient catalysts for different aldol-type reactions (Scheme 60).



Scheme 60. Aldol reactions catalysed by primary amino acids and small peptides.

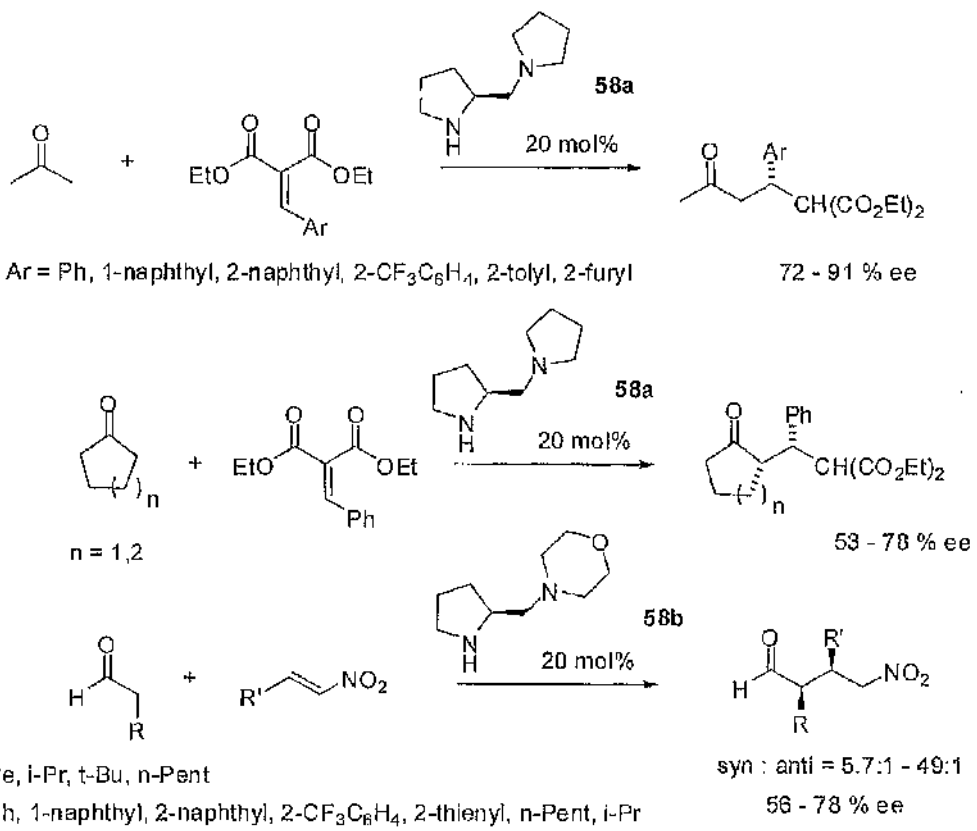
Primary amino acids and their derivatives give different major diastereomers (**55** and **56**, Scheme 61) compared to proline in aldol and Mannich reactions with 2-hydroxyketones **57** (Scheme 61).[59] This can be explained if the geometry of the enol carbon-carbon double bond changes because of hydrogen bonding leading to the formation of an opposite diastereoisomer in the subsequent aldol reaction (compare **52a** and **52b**, Scheme 61).



Scheme 61. Aldol and Mannich reactions catalysed by primary amino acids

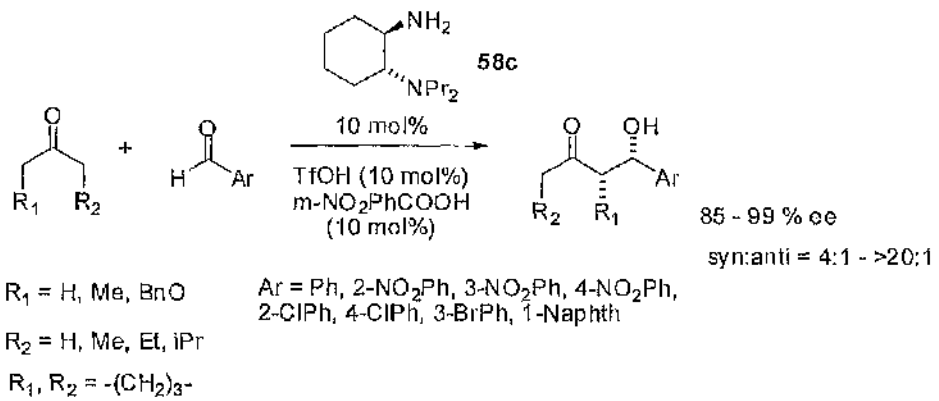
3. Hydrogen bond as an important feature in aminocatalysis. Amino alcohols as catalysts

The dominant position of proline (a secondary amine) is partly related to the key function of its carboxyl group in steering the reactants, whereas amines lacking the carboxyl or its equivalent operate mainly on steric grounds. DFT calculations support this postulate showing the great importance of the carboxylic group of proline in the catalytic aldol reactions.[56] However, other amines bearing groups capable of forming hydrogen bonds have been shown to catalyze aldol reactions equally well. The aldol-type reactions catalysed by chiral diamines were reviewed by Barbas (Scheme 62).[60]



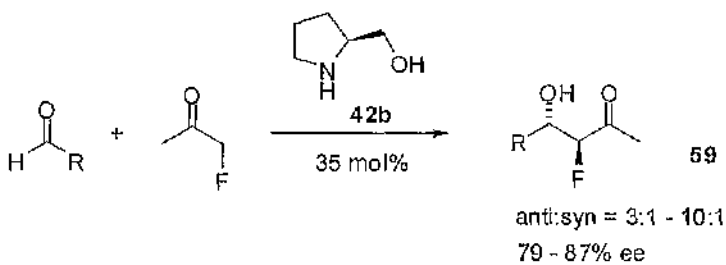
Scheme 62. Reactions catalysed by chiral diamines.

A catalytic pair of chiral diamine **58c** and a Brønsted acid can be used to promote aldol reactions with high diastereo- and enantioselectivity (Scheme 63).[61]



Scheme 63. The aldol reaction catalysed by chiral diamine and Brønsted acid.

Chiral amino alcohols **42** are sparsely precedented to be effective catalysts for enantioselective aldol reactions to compare with amino acids. Prolinol **42b** was found to be an efficient catalyst for the enantioselective synthesis of anti-α-fluoro-β-hydroxy ketones **59** (Scheme 64).[62]



Scheme 64. The prolinol catalysed aldol reaction.

The transition state for the reaction with a crucial role of hydrogen bonding was proposed (Figure 5).

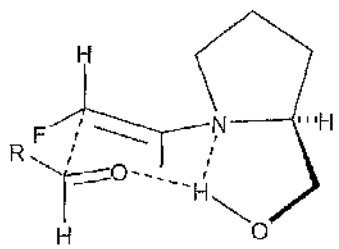
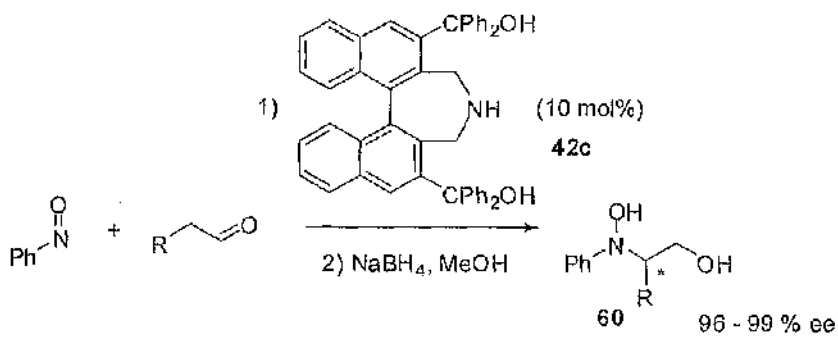


Figure 5. The transition state for the prolinol catalysed aldol reaction.

The highly enantioselective direct asymmetric hydroxyamination reaction catalysed by the axially chiral amino alcohol **42c** can be used to attain chiral hydroxylamines **60** (Scheme 65).[63]

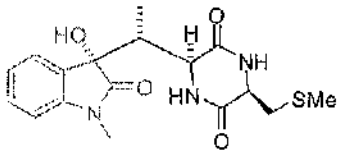


Scheme 65. The hydroxyamination reaction catalysed by the amino alcohol **42c**.

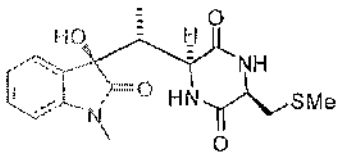
4. The ketone-ketone aldol condensation issue. The 3-Hydroxyindol-2-one motif as an important structural block in nature

In contrast to the aldol reactions involving aldehydes, intermolecular ketone-ketone cross-aldol reactions are rare and represent a significant challenge.[64] Among all possible ketone-ketone condensations, the reactions with isatins **61** attract most interest. This is due to the fact that 3-hydroxyindol-2-one motif (shown in the Chart 9 in red)

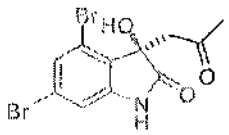
constitutes a core structural feature of a number of natural products. A series of compounds **62 – 63** with promising pharmacological properties were isolated and studied by Aimi (Chart 9).[65]



Maremycin A **62a**

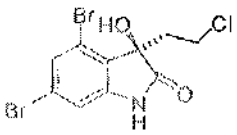


Maremycin B **62b**



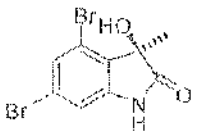
Convolutamydine A

63a



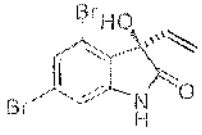
Convolutamydine B

63b



Convolutamydine C

63c

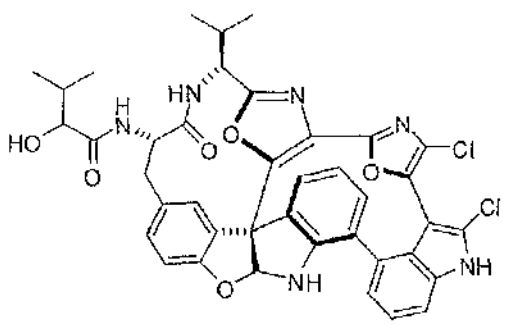


Convolutamydine D

63d

Chart 9. Natural products containing 3-hydroxyindol-2-one motif.

Significant synthetic efforts have been directed towards diazonamide A **64** (Chart 10) by a number of laboratories around the world because of the unique challenges posed by this structural framework, its impressive in vitro cytotoxicity, and the inability to harvest additional material from the original source.[66]

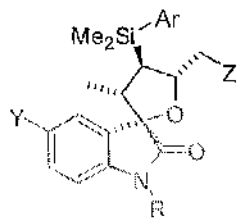


Diazonamide A

64

Chart 10. The revised[66,c)] structure of Diazonamide A **64.**

The synthesis of the group of organosilicon small molecules **65** bearing 3-hydroxyindol-2-one motif and showing promising cytotoxic and antitumor activities was suggested by Schreiber[67] (Chart 11).

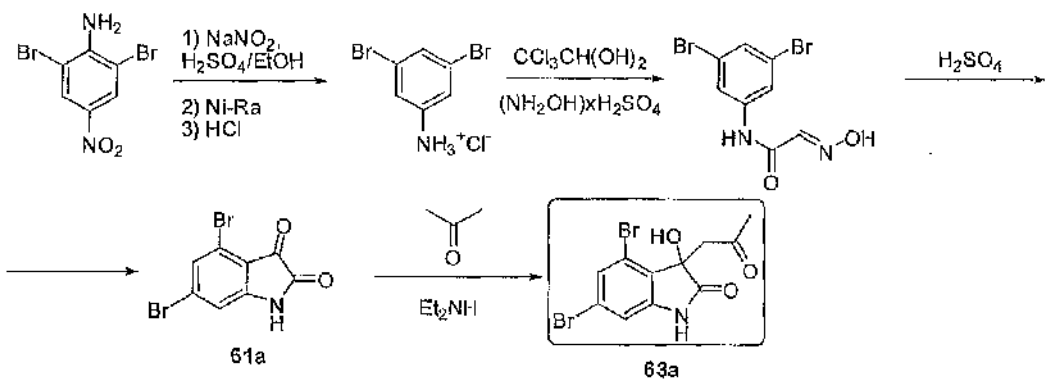


65

Chart 11. A group of organosilicon biologically active compounds.

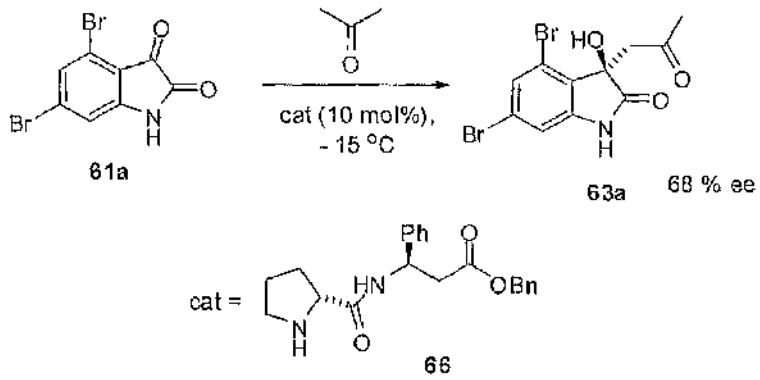
5. Convolutamydine A as a target for synthetic chemists.

Among all the Convolutamydines, Convolutamydine A **63a** attracted most attention of synthetic organic chemists. First isolated by Kamano[68] from the Floridian marine bryozoan *Amathia Convoluta*, it was synthesised shortly after that in a racemic form by Garden using a modified Sandmeyer methodology (Scheme 66).[69]



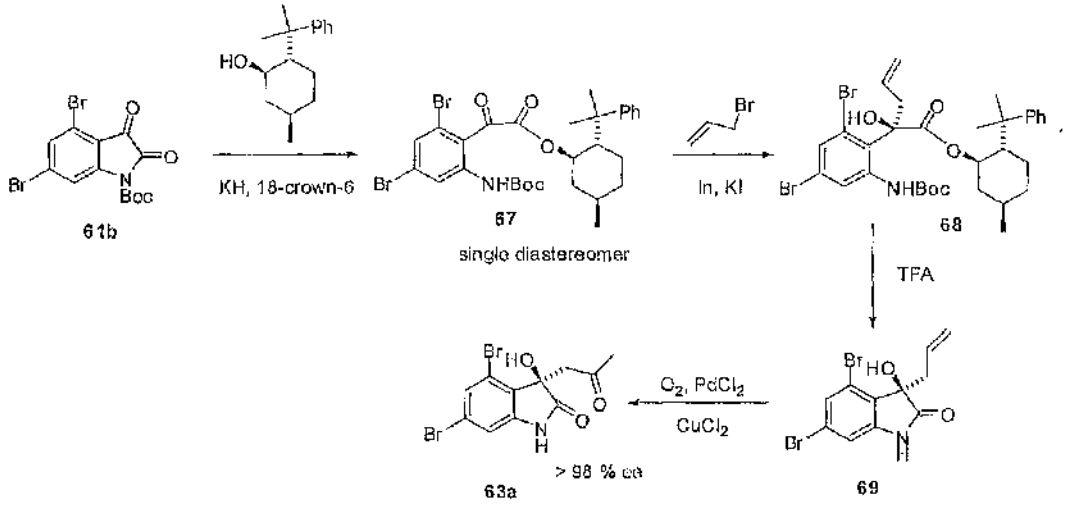
Scheme 66. The Synthesis of racemic Convolutamydine A.

The first enantioselective synthesis of (*R*)-Convolutamydine A **63a** was published by Tomasini.[70] In the key step they used the prolinamide derivative **66** as a catalyst (Scheme 67).



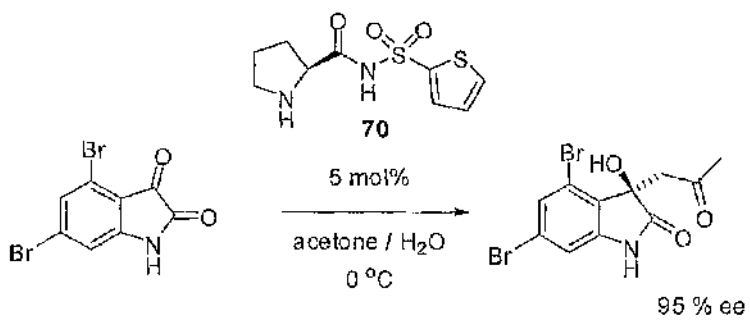
Scheme 67. The first enantioselective synthesis of (*R*)-Convolutamydine A.

Shortly after that a longer but more selective synthesis of enantiopure Convolutamydine A **63a** was reported by Palmisano.[71] The key steps of the synthesis were the In-catalysed diastereoselective allylation of **67** and Wacker oxidation of **69** (Scheme 68). The absolute configuration of Convolutamydine A **63a** was determined by X-Ray crystallography.[71]



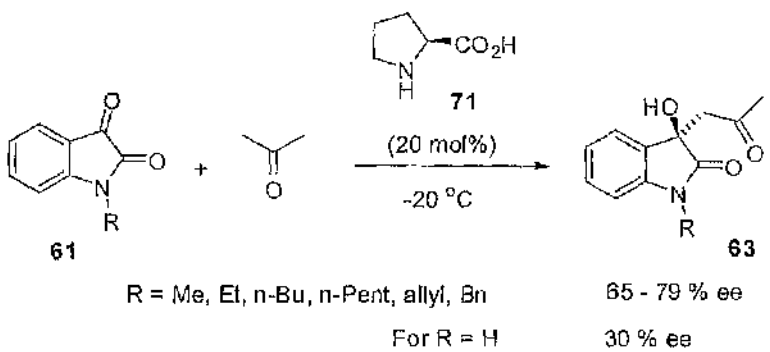
Scheme 68. The enantioselective synthesis of Convolutamydine A **63a** via Wacker oxidation.

Later, a short and efficient synthesis of Convolutamydine A **63a** was reported by our group (see Results and Discussion and Experimental part for details). During our work and after we had published our preliminary communication, another enantioselective synthesis of Convolutamydine A **63a** was reported by Nakamura.[72] As the key step they used the enantioselective reaction catalysed by the proline derivative **70** (Scheme 69).



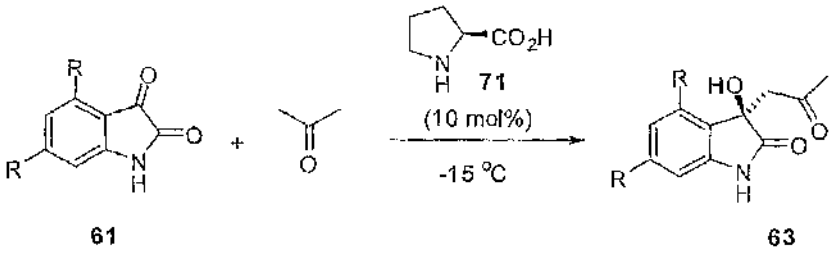
Scheme 69. Enantioselective synthesis of Convolutamydine A.

Hao[73] showed simple proline **71** to be a fairly effective catalyst for the asymmetric aldol reaction of *N*-substituted isatins **61** with acetone at low temperature (Scheme 70). However, his method was poor for unsubstituted isatin.



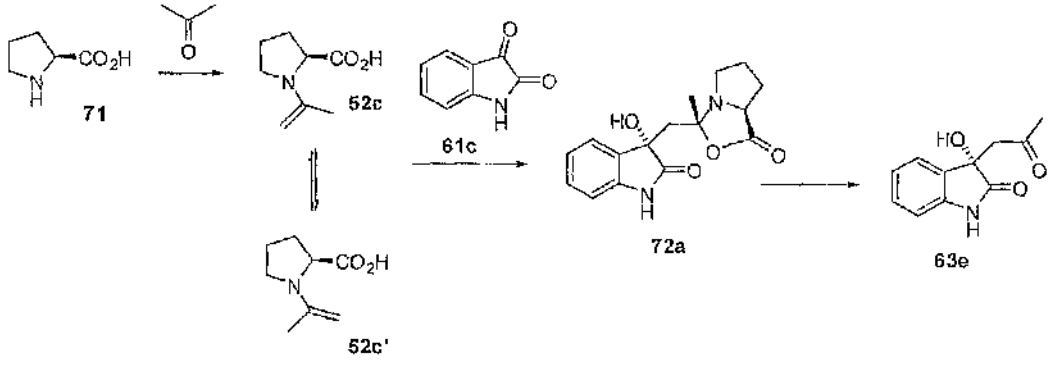
Scheme 70. The asymmetric aldol condensation of isatins with acetone catalysed by L-proline.

Studies of the aldol reaction between isatins and acetone revealed that the introduction of a substituent to the position 4 of the isatin molecule **61** reverses the absolute configuration of the product **63** (Scheme 71).[74]



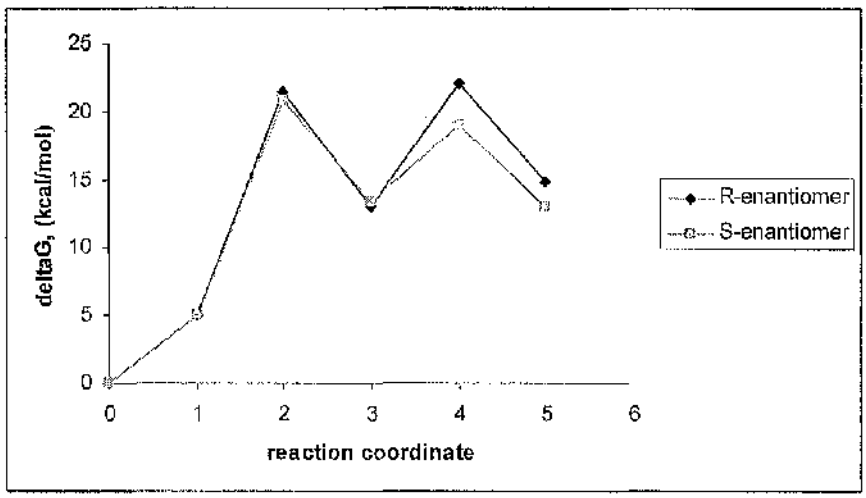
Scheme 71. The proline-catalysed aldol reaction between isatins **61** and acetone.

The mechanism of the aldol reaction between various isatins **61** and acetone catalysed by proline **71** was investigated by Tomasini and Garden by using DFT calculations.[70,74] They claim that the reaction of the unsubstituted isatin **61c** with the enamine **52c** is controlled by stereoelectronic effects (the key step is protonation of the keto-group by the enamine hydroxyl) while the reaction of the 4-substituted isatin is mainly governed by steric interactions. Oxazolidinone **72a** has been proposed as an important intermediate in the proline catalysed aldol reaction (Scheme 72).[74]



Scheme 72. The proposed mechanism for the proline catalysed aldol reaction between isatin and acetone.

Different stability of diastereoisomeric oxazolidinones **72a** which give two enantiomers of the aldol product may influence the overall enantioselectivity of the aldol reaction. The reaction coordinates leading to (*R*)- and (*S*)-enantiomer of the product **63e** differ mainly in the energies of the corresponding transition states of hydrolysis of oxazolidinone **72a** (Figure 6).[71]



0 – isatin **61c** + *anti*-enamine **52c**; 1 – H-bond complex;

2 – aldol TS; 3 – oxazolidinone **72a**; 4 – oxazolidinone TS;

5 – zwitterion intermediate

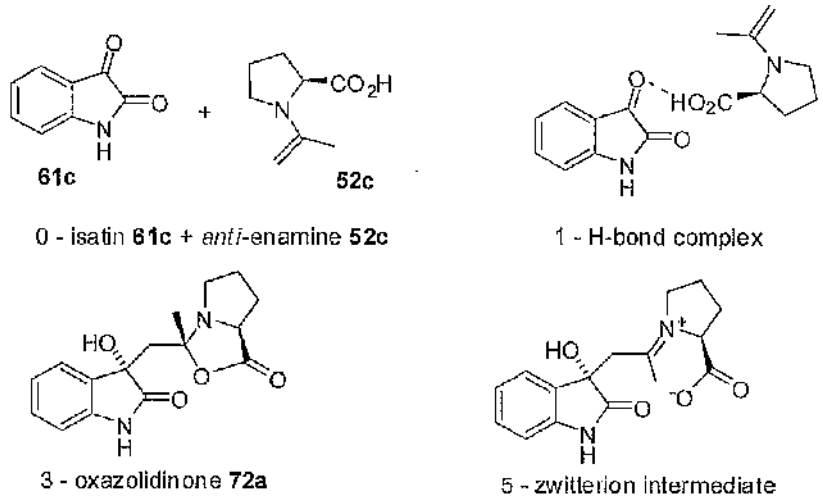
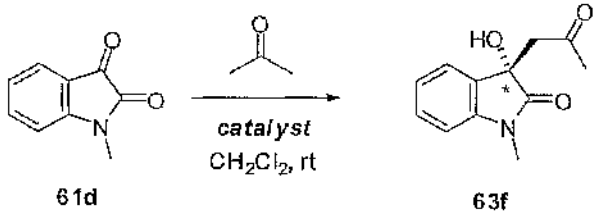


Figure 6. The reaction coordinates for the formation of two enantiomers of **63e**.

Results and discussion

1. Cross-aldol condensation of isatins with acetone. Optimisation

In our search for expedient construction of chiral synthetic building blocks,[65,66,67] we became interested in the cross-aldol reaction of two ketone molecules, in particular, isatins with acetone. Tomasini has recently reported that in the case of condensation of isatin with acetone, proline **71** gave inferior results, whereas dipeptides, having proline at the *N*-terminus, catalysed the reaction effectively with up to 73% ee.[70,74] Using *N*-methylisatin (**61d**) and acetone as a model pair of ketones (Scheme 73), we embarked on the development of a more efficient catalyst, hoping to expand its scope and improve the turnovers. To this end, we first screened several amino acids and amino alcohols as potential catalysts (Table 11).



Scheme 73. Aldol condensation of the isatin **61d** with acetone. For catalysts, see Table 11.

Consistent with the Tomasini report[70], proline **71a** exhibited rather low enantioselectivity at room temperature (Table 11, entry 1) and inferior results were also obtained with its methyl ester and prolinol (entries 2 and 3); diphenylprolinol **42d** and valine **71c** failed to catalyze the reaction (entries 4 and 5). By contrast, amino alcohols with a primary amino group, namely valinol and its homologues **42a,e-i**, turned out to catalyze the reaction very efficiently, exhibiting 88-95% ee (entries 6-12).

Table 11. Aldol condensation of *N*-methylisatin **(61d)** with acetone catalysed by selected amino acids and amino alcohols.[a]

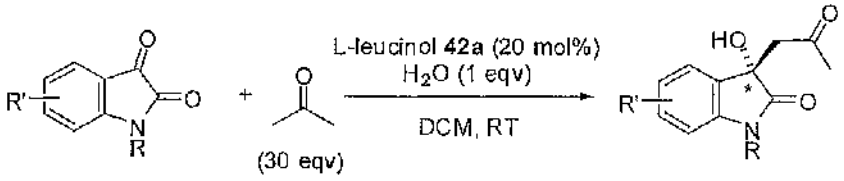
entry	catalyst	solvent	conversion in %[b]	**63f**, % ee[c] (configuration)[d]
1	L-proline **71a**	CH_2Cl_2	18	40 (*S*)
2	L-proline methyl ester **71b**	CH_2Cl_2	12	25 (*R*)
3	L-prolinol **42b**	CH_2Cl_2	20	20 (*S*)
4	L-α,α-diphenylprolinol **42d**[e]	CH_2Cl_2	traces	–
5	L-Valine **71c**	CH_2Cl_2	traces	–
6	L-Valinol **42e**	CH_2Cl_2	84	95 (*S*)
7	D-cyclohexylglycinol **42f**	CH_2Cl_2	50	95 (*R*)
8	L-Phenylglycinol **42g**	CH_2Cl_2	70	88 (*S*)
9	L-Phenylalaninol **42h**	CH_2Cl_2	50	94 (*S*)
10	L-*tert*-leucinol **42i**	CH_2Cl_2	50	95 (*S*)
11	L-leucinol **42a**	CH_2Cl_2	98	95 (*S*)
12	L-leucinol[f]	CH_2Cl_2	88	94 (*S*)
13	L-leucinol	Me_2CO	98	72 (*S*)
14	L-leucinol	MeOH	98	racemic
15	L-leucinol[g]	CH_2Cl_2	50	95 (*S*)

[a]The reaction was carried out at 0.6 mol scale (**61d**) with 30 equiv of acetone in the presence of 20 mol% of the catalyst and H_2O (1 equiv) in CH_2Cl_2 (unless stated otherwise) for 36 hours at room temperature. The crude product was purified by chromatography on aluminium oxide pre-treated with Et_3N to suppress racemisation. [b]Determined by NMR. [c]Determined by chiral HPLC (see the Experimental for details). [d]The absolute configuration was inferred from the Tomasini assignment[70] and from our own results discussed below. [e]The corresponding TMS ether also failed to catalyze the reaction. [f]At 40 °C in 8 h. [g] No water added

Leucinol **42a** was identified as the most effective catalyst, both in terms of the reaction rate (which was considerably higher than that observed with other amino alcohols) and in the enantioselectivity (entry 11). The solvent effect was identified as another feature of importance. The highest enantioselectivities were obtained in CH_2Cl_2; in pure acetone, the reaction was faster but at the expense of the level of asymmetric induction (entry 13), whereas in methanol, further acceleration was observed but the product turned out to be practically racemic (entry 14). Importantly, addition of H_2O (1 equivalent) to the system resulted in significant acceleration of the reaction (compare entries 11 and 15).

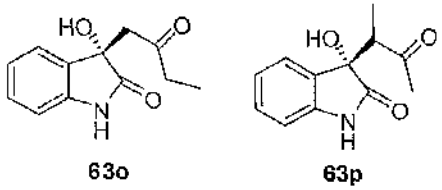
2. Cross-aldol reaction of isatins with acetone. Scope of the reaction.

The optimised catalytic system has been successfully employed for the aldol reaction between acetone and various isatins **61** to obtain the respective products **63** in high yields and enantiopurity (Scheme 74 and Table 12).



61d, R = Me, R' = H
61e, R = Allyl, R' = H
61c, R = H, R' = H
61f, R = H, R' = 5-Me
61g, R = H, R' = 5-F
61h, R = H, R' = 5-Cl
61i, R = H, R' = 5-Br
61j, R = H, R' = 5-NO_2
61k, R = H, R' = 4,7-di-Cl
61l, R = H, R' = 5,7-di-Br
61a, R = H, R' = 4,6-di-Br

63f, R = Me, R' = H
63g, R = Allyl, R' = H
63e, R = H, R' = H
63h, R = H, R' = 5-Me
63i, R = H, R' = 5-F
63j, R = H, R' = 5-Cl
63k, R = H, R' = 5-Br
63l, R = H, R' = 5-NO_2
63m, R = H, R' = 4,7-di-Cl
63n, R = H, R' = 5,7-di-Br
63a, R = H, R' = 4,6-di-Br



63o **63p**

Scheme 74. The aldol condensation reaction between isatins **61** and acetone and 2-butanone.

Table 12. Aldol condensation of isatins **61** with selected ketones catalysed by L-leucinol **42a**.[a]

entry	isatin **61**	ketone	**63** (% ee)[b]
1	**61e**	Me_2CO	(*S*)-(–)-**63g** (94)[c]
2	**61c**	Me_2CO	(*S*)-(–)-**63c** (94)[c,d]
3	**61f**	Me_2CO	(*S*)-(–)-**63h** (92)[c]
4	**61g**	Me_2CO	(*S*)-(–)-**63i** (90)[c,d]
5	**61h**	Me_2CO	(*S*)-(–)-**63j** (92)[c]
6	**61i**	Me_2CO	(*S*)-(–)-**63k** (95)[d,e]
7	**61j**	Me_2CO	(*S*)-(–)-**63l** (92)[c]
8	**61k**	Me_2CO	(*S*)-(–)-**63m** (86)[c]
9	**61l**	Me_2CO	(*S*)-(–)-**63n** (93)[c]
10	**61a**	Me_2CO	(*S*)-(–)-**63a** (93)[c]
11	**61c**	MeEtCO	(*S*)-(–)-**63o** (88)[c,f]

[a]The reaction was carried out with 30 equiv of ketone in the presence of L-leucinol (20 mol%) as catalyst in CH_2Cl_2 at room temperature for 36 h. In all cases the conversion was ≥93%, according to the ^{1}H NMR spectrum of the crude product. The crude product was purified by chromatography on aluminium oxide pre-treated with Et_3N. [b]Determined by chiral HPLC (see the Experimental for details). [c]The absolute configuration was deduced from the configuration of **63a** and **63k**, which was determined by X-ray crystallography. [d]The product was obtained as a pure enantiomer (>99% ee) on a single crystallization from a mixture of hexane, CH_2Cl_2, and MeOH. [e]The absolute configuration was determined by X-ray crystallography. [f]Two regioisomers were obtained in a 5:1 ratio in favour of R-CH_2COCH_3 (**63o**).

As shown in the Table 12, the method is robust and general for isatins. Either *N*-alkylated or free isatins **61** with different substituents in the benzene ring perform equally well in the aldol reaction with acetone to form the aldol products **63** with high enantioselectivity (entries 1-10, Table 12). However, sterically more demanding ketones turned to be unreactive under our optimised aldol condensation conditions with isatins (except for 2-butanone). The reaction between 2-butanone and **61c** resulted in the formation of the two respective regioisomers **63o** : **63p** = 5 : 1.

3. The enantioselective synthesis of Convolutamydine A.

The high-yielding condensation of isatins with acetone opened a straightforward route to Convolutamydine A (**63a**), whose (+)-enantiomer was isolated from the marine bryozoan species *Amathia convoluta* and identified as a promising antitumor agent.[65] The L-leucinol-catalysed condensation afforded its unnatural (–)-enantiomer (Table 12, entry 10), whose absolute configuration was determined as (*S*)-(–)-**63a** by single crystal X-ray analysis (Figure 7).

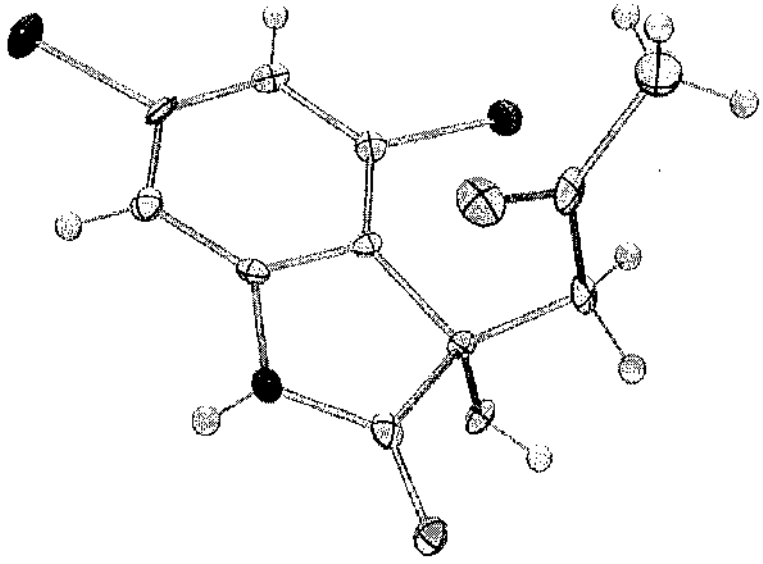
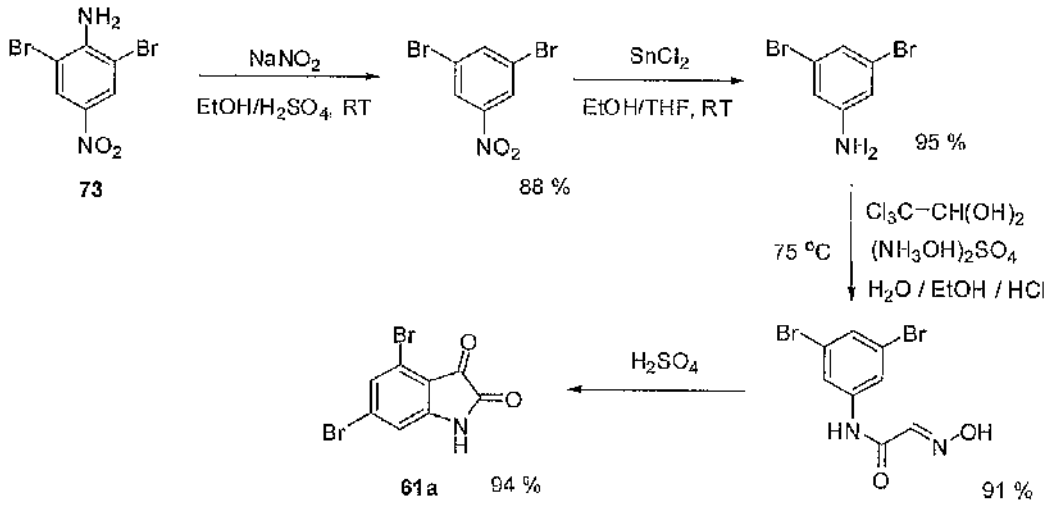


Figure 7. (S)-(-)-Convolutamydine A

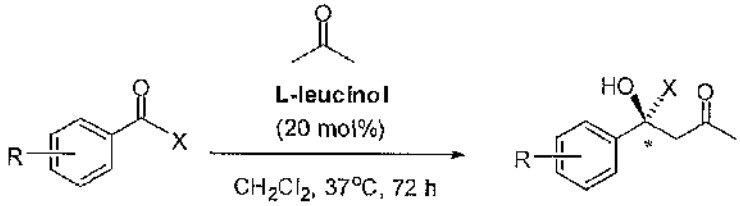
Therefore, the natural (+)-convolutamydine A must be (*R*)-(+)-**63a**, which is consistent with the assignment based on the CD spectroscopy.[65] The X-ray crystallography also revealed the absolute configuration of (*S*)-(–)-**63k**; hence, by analogy, the same configuration can be assumed for the remaining derivatives **63**. The natural convolutamydine A (*R*)-(+)-**63a** was then prepared on a gram scale by the aldol reaction using D-leucinol as catalyst and found identical with the natural product. The respective isatin **61a** was synthesised according to the published procedure[69] starting from the commercially available dibromide **73** (Scheme 75).



Scheme 75. The synthesis of 4,6-dibromoisatin **61a**.

4. Cross-aldol reaction of activated ketones with acetone catalysed by leucinol. Scope of the reaction.

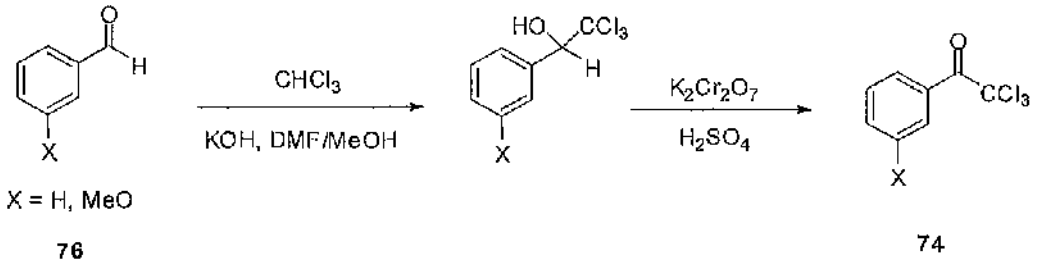
As the next step, we briefly screened the reactivity of acetone to a set of other ketones with L-leucinol as catalyst. While enolisable aromatic ketones ArCOMe (R = Ph, and 4-$NO_2C_6H_4$) proved inert, non-enolisable activated ketones **74a-f** exhibited good reactivity at slightly elevated temperature and modest enantioselectivity (Scheme 76).



74a, R = H, X = CF_3	**75a**, R = H, X = CF_3	(85%, 77% ee)
74b, R = H, X = CCl_3	**75b**, R = H, X = CCl_3	(70%, 64% ee)
74c, R = 4-F, X = CF_3	**75c**, R = 4-F, X = CF_3	(86%, 82% ee)
74d, R = 3-F, X = CF_3	**75d**, R = 3-F, X = CF_3	(86%, 73% ee)
74e, R = 4-Cl, X = CF_3	**75e**, R = 4-Cl, X = CF_3	(84%, 78% ee)
74f, R = 3-MeO, X = CCl_3	**75f**, R = 3-MeO, X = CCl_3	(72%, 66% ee)

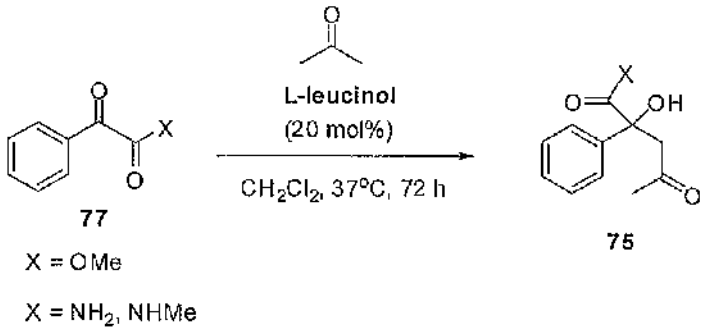
Scheme 76. Aldol condensation of activated ketones with acetone.

The starting ketones **74b,f** were made by a two-step procedure from the respective commercially available aldehydes **76b,f** (Scheme 77).[75]



Scheme 77. Synthesis of trichloroacetophenones **74**.

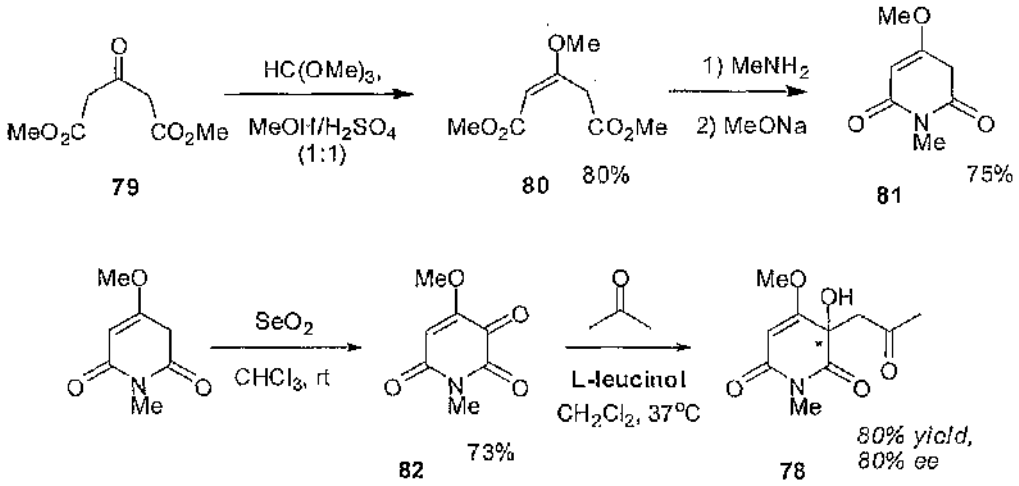
The aldol reaction of the α-ketoester and α–ketoamides 77 with acetone catalysed by L-leucinol resulted in the formation of the respective products **75**, but exhibits no enantioselectivity (Scheme 78).



Scheme 78. Aldol condensation reaction of the α-ketoester and α–ketoamides 77 with acetone

5. The synthesis of (+)-Speranskatine A (78)

Speranskatine A **78** is an alkaloid from *Speranskia tuberculata*, the plant which is used in traditional medicine to obtain antibacterial extracts. Speranskatine A was isolated for the first time in 1995[76] and since then no synthesis of it has been proposed. We have now developed a four-step approach attaining (+)-Speranskatine A **78** with 80% ee (Scheme 79).



Scheme 79. The synthesis of Speranskatine A.

The cyclic amide **81** was prepared in two steps from oxoglutarate **79** according to the published procedure[77] with good yield. Further oxidation of **81** to the dicarbonyl compound **82** was unsuccessful when the published procedure was used (a two-step oxidation with potassium persulfate followed by nitric acid at low temperature). The various oxidizing agents (potassium permanganate, nitric acid, $PhI(OAc)_2$, and Dess-Martin periodate) failed. However, we have subsequently found that selenium dioxide, SeO_2, reacts smoothly with the amide **81** in acidic chloroform at room temperature, and the product **82** was isolated in 50 % yield after column chromatography purification. Surprisingly, simple sulfuric acid catalyses the reaction efficiently, giving the best yield of the desired tricarbonyl compound **82**.

6. Mechanistic studies on the aldol reaction between isatins and acetone catalysed by leucinol

The aldol reaction of **61c** with Me_2CO in the presence of leucinol **42a** (20 mol %) proved to be the first-order in **61b**. The reaction can also be catalysed by $BuNH_2$ or Et_2NH, whereas Et_3N was found to be inert, suggesting an enamine intermediate **52**. Accordingly, *N*-methylleucinol failed to catalyze the reaction at an appreciable rate,

showing the key importance of the primary amino group. On the other hand, the methyl ether of leucinol and *O*-trimethylsilylleucinol turned out to catalyze the reaction but more slowly and far less selectively than leucinol (both reached ~50% conversion over 36 h at rt, with 50% ee). A linear correlation was found between the enantiopurity of leucinol and that of the product **63e** (Figure 8), which indicates that only one molecule of the catalyst is likely to be involved in the stereo-discriminating step.

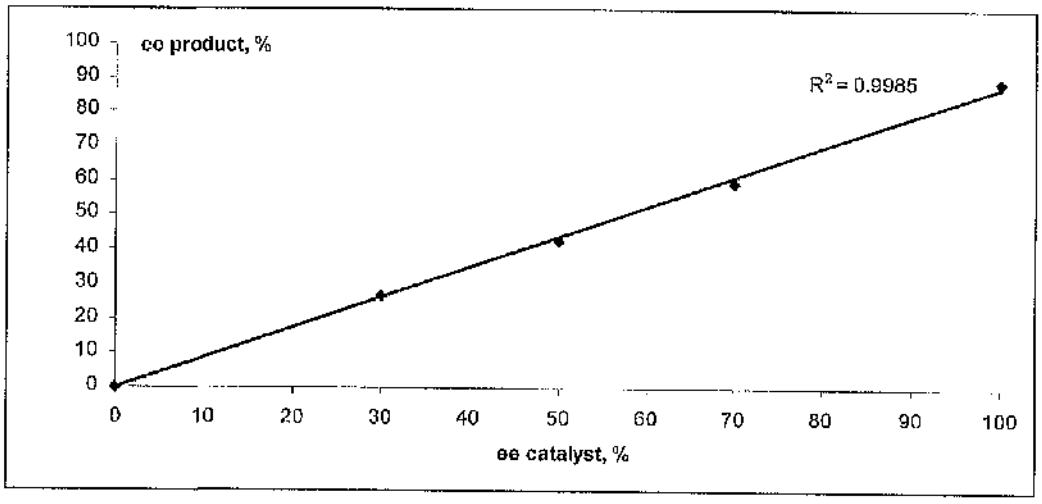
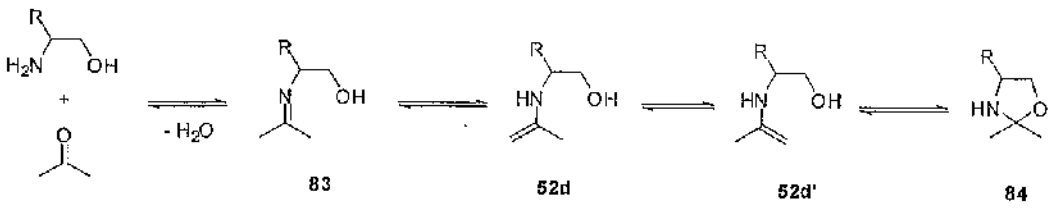


Figure 8. A linear correlation between the enantiopurity of leucinol and the product **63e**.

On mixing acetone and leucinol, formation of species **83, 52d, 52d', 84** can be a priori expected (Scheme 80).



Scheme 80. Equilibrium in the acetone-leucinol mixture.

Monitoring of a 30:1 acetone-leucinol mixture in $CDCl_3$ by ^1H NMR at 37 °C revealed a gradual disappearance of leucinol with a concomitant build-up of oxazolidine **84**. The reaction was complete within 2 h, and no other species could be detected during this process. The presence of water (1 equiv with respect to leucinol) did not have any noticeable effect on the formation of **84**. On the other hand, when isatin (**61c**) (5-fold excess to leucinol) was added to a 150:1 acetone-leucinol mixture (this ratio mimics the concentrations in the catalytic reaction) in $CDCl_3$ at room temperature, a quantitative conversion of leucinol into **84** was observed within several minutes, demonstrating the catalytic effect of isatin on this transformation. On the other hand, the isolated oxazolidine **84** proved to be unstable in the absence of an excess of acetone, as its solution in wet $CDCl_3$ slowly decomposed back to acetone and leucinol, presumably via enamine **52d**. The aldol reaction of **61c** with acetone in $CHCl_3$ at 37 °C was found to be catalysed by oxazolidine **84** as effectively as by leucinol, with the same rate constant (at 20 mol % catalyst loading; Figure 9).

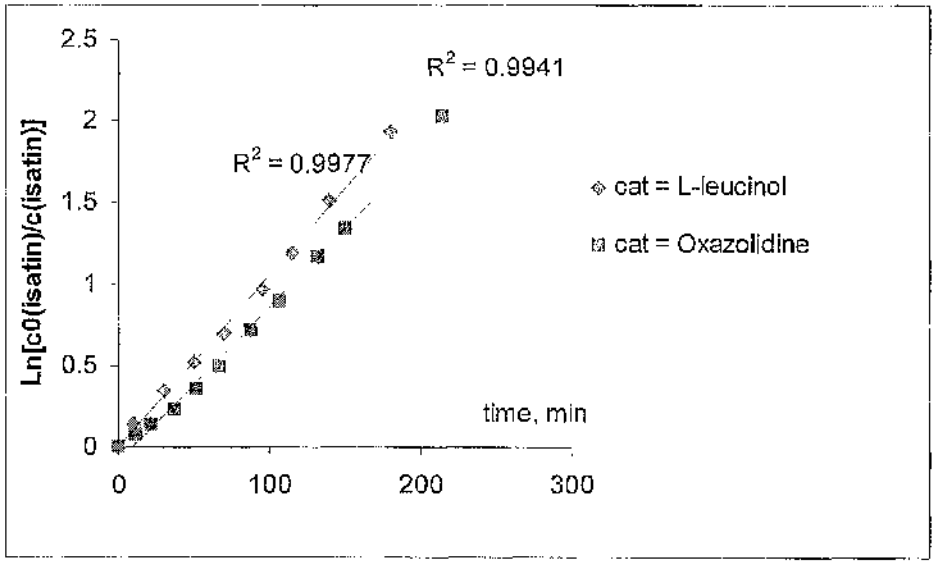


Figure 9. The aldol reaction of **61c** with acetone in $CDCl_3$.

By contrast, in CH_2Cl_2, the reaction catalysed by leucinol was 3 times slower than that in $CHCl_3$, and 10 times slower with **84** (Figure 10).[18]

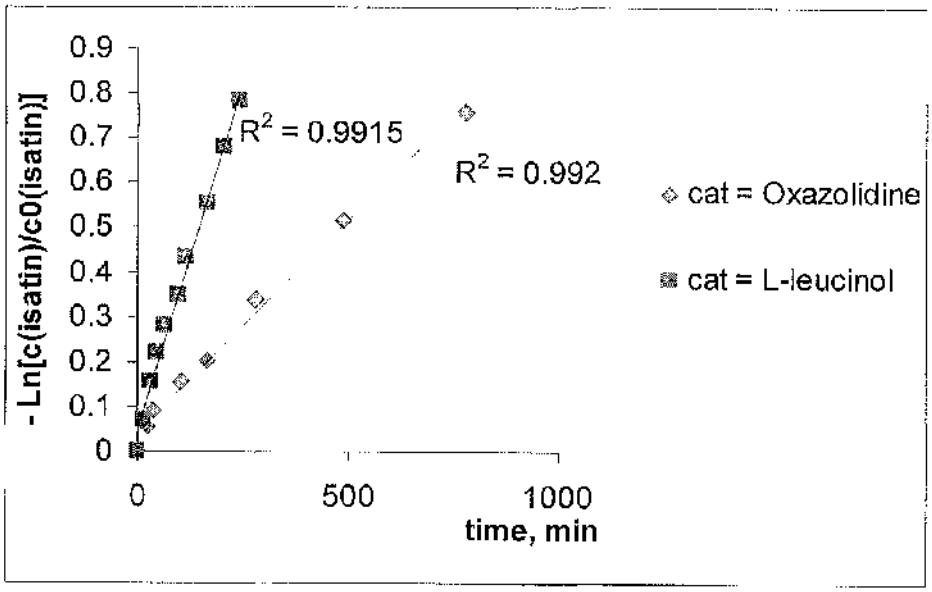


Figure 10. The aldol reaction of **61c** with acetone in CH_2Cl_2

Only marginal differences in the enantioselectivity were observed for $CHCl_3$ (86% vs. 90% ee), whereas in CH_2Cl_2 both reactions gave the same result (90% ee).

Monitoring the enantiomeric ratio while the reaction was in progress (at 37 °C) revealed little enantioselectivity in the initial stages, whereas after ca. 20-30 min, one enantiomer began to dominate (Figure 11).

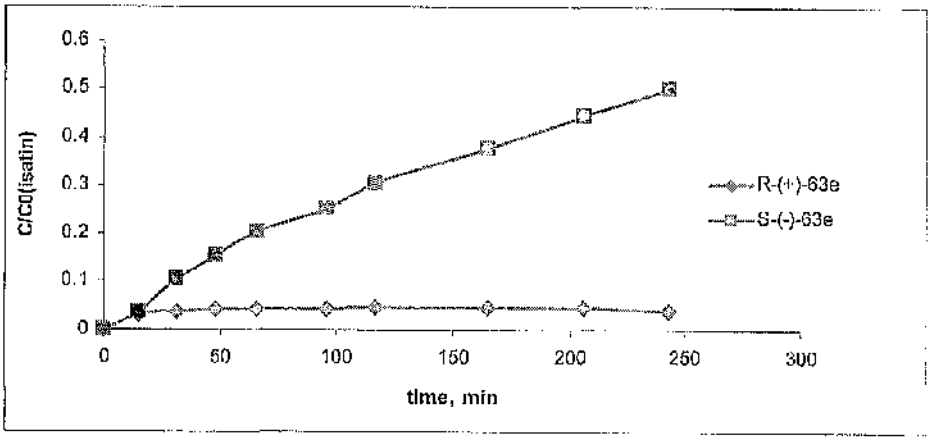
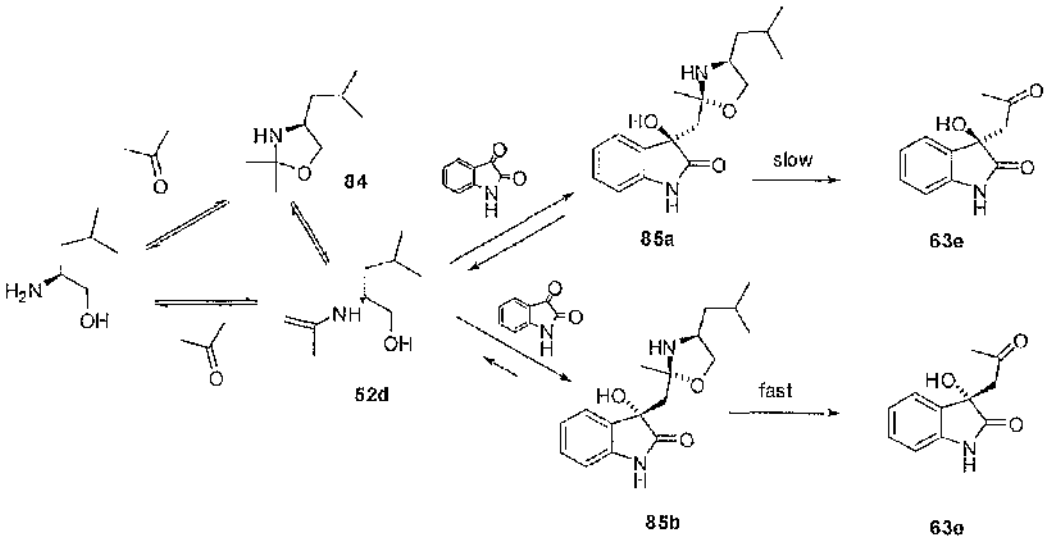


Figure 11. Monitoring of the aldol reaction between isatin **61c** and acetone.

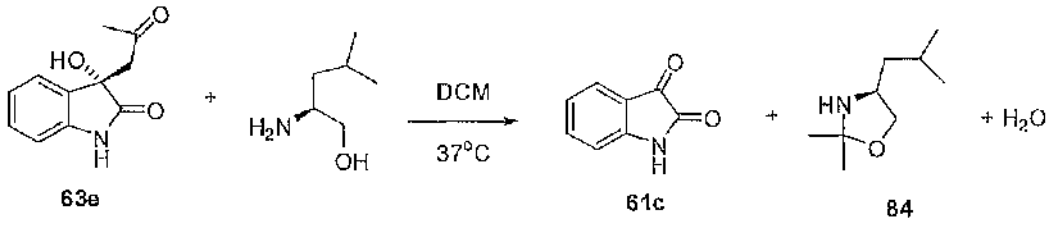
This intriguing behaviour may seem to suggest an autocatalysis by the product (**63e**), but this mechanism was ruled out by a control experiment, carried out in the presence of (*S*)-(-)-**63e** (20 mol %), added at the onset of the reaction. The latter additive neither catalysed the reaction nor altered the enantiomeric ratio of the gradually produced **63e** when L-leucinol was also added to the mixture. Therefore, it can be alternatively suggested that the catalytic aldol reaction proceeds via oxazolidine **85** formation as an intermediate. According to the recent mechanistic studies,[74] different stability of two diastereoisomeric oxazolidinones **72** may greatly affect the overall enantioselectivity of the aldol reaction catalysed by proline, causing the respective kinetic resolution effect. Assuming that the reaction between isatin and the enamine **52d** is reversible, we can propose the following mechanism for the aldol reaction between isatin **61c** and acetone catalysed by leucinol (Scheme 81).



Scheme 81. The proposed mechanism for the aldol condensation reaction between isatin and acetone catalysed by leucinol.

Intermediates **85** cannot be isolated from the reaction mixture, however their presence has been confirmed by ^{1}H NMR spectroscopy during the kinetic measurements of the aldol reaction in $CDCl_3$ [C*H*$_2$-O and C*H*-N signals (similar to the analogous ones

of **84**) with the respective signals of aromatic protons]. To prove that the reaction between isatins and the enamine **52d** is reversible, the aldol product **63e** was stirred with 2 equivalents of leucinol in DCM at 37 °C for 12 h. As a result 50% of the starting **63e** reacted to produce nearly equal amounts of isatin **61c** and oxazolidine **84** (Scheme 82).



Scheme 82. The reverse aldol reaction.

In conclusion, it is clear that oxazolidine **84** plays a role of a resting state of the catalyst. The reaction between isatin **61** and enamine **52d** is reversible. We also assume that the unusual changing of enantiomeric ratio of the products **63** can be associated with different stability of the diastereoisomers of the intermediate oxazolidines **85**.

Conclusions

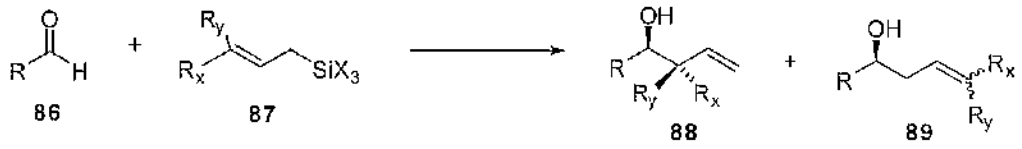
Primary amino alcohols derived from natural amino acids have been found to be efficient organocatalysts for the cross-aldol condensation reaction between acetone and activated ketones affording the respective products with high enantioselectivity. Two natural products – Convolutamydine A (**63a**) and Speranskatine A (**78**) – have been synthesised in high yields and enantiopurity using the method developed. The mechanism of the aldol condensation between isatins and acetone, catalysed by leucinol, has been studied and the corresponding oxazolidine **84** has been identified as the resting state.

Chapter III. The allyl transfer reaction

Introduction

1. Allylsilanes as well-known and efficient allylating agents

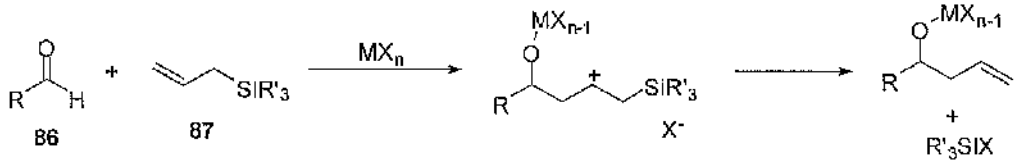
Asymmetric allylation of carbonyl compounds with allylsilanes has evolved into a valuable synthetic tool for the construction of C-C bonds. As a rule, allylation of aldehydes **86** with organosilicon **87** and other organometallic reagents affords γ-adducts **88**, resulting from the attack at carbonyl by the distal carbon of the allylic system (Scheme 83). In the case of crotylsilanes, this reaction gives rise to the branched products; high enantio- and diastereo-selectivities have been attained here by application of various chiral catalysts.



Scheme 83. Allylation of aldehydes

2. The Lewis acid-catalysed allylation reaction with allylsilanes

The majority of catalytic enantioselective allylation reactions involve the chiral Lewis acid-catalysed additions of allyltrimethylsilane **87a** or allyltributylstannane to aldehydes **86.**[78] In this process, the Lewis acid that activates the aldehyde toward nucleophilic attack directs the course of addition (Scheme 84).

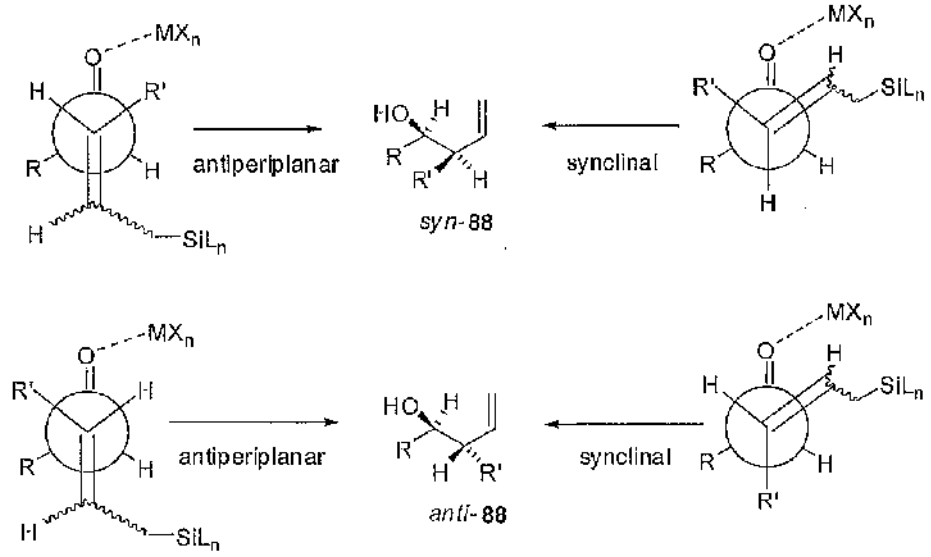


Scheme 84. Lewis Acid-catalysed allylation reaction.

Although many Lewis acids have been reported to promote the addition of allylic silanes to aldehydes, the reactions using only a catalytic amount of a Lewis acid were initially scarce. Moreover, in some of these reactions, the Lewis acid was actually found not to be responsible for the reaction.[79] Often the trimethylsilyl cation Me_3Si^+, generated in the system as a side product, plays the role of a powerful catalyst.[78]

The Lewis acid-promoted addition of allylic silanes to aldehydes proceeds through an open transition structure with an *anti* S_E' arrangement of the metal with respect to the aldehyde regardless of the Lewis acid employed

With regard to the diastereoselectivity in Lewis acid-catalysed additions of 2-butenylsilanes **87**, the *syn* homoallylic alcohol **88** is the major product, independent of the geometry of the starting silane. The transition structures were proposed to explain the selectivities observed in the allylation reaction (Scheme 85). Also, the dihedral angle between the two reacting double bonds has been identified as an important parameter (Scheme 85).

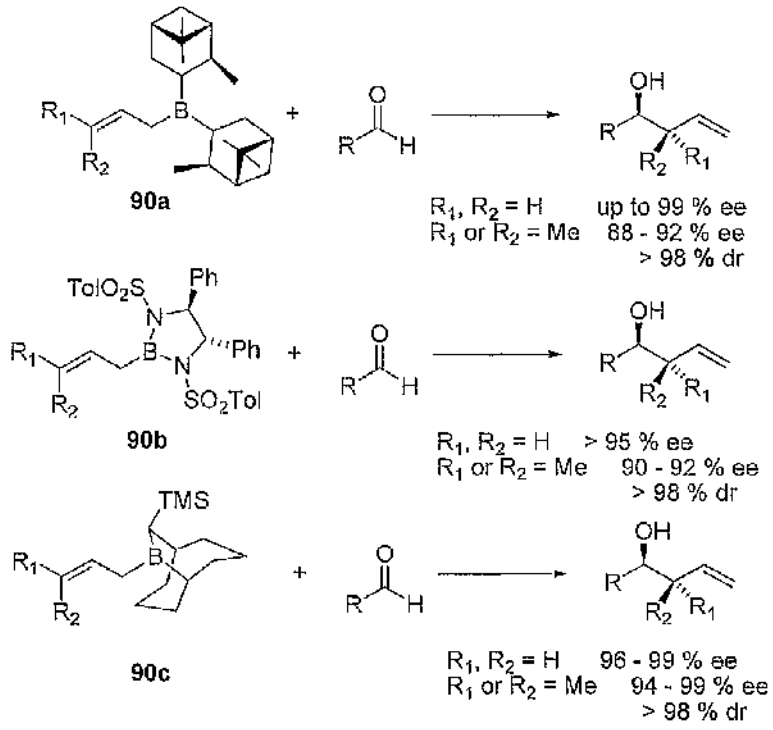


Scheme 85. Transition structures in the Lewis acid-catalysed allylation reaction.

Denmark has shown that the synclinal orientation of the double bonds is favoured from a combination of steric and stereoelectronic contributions, although to varying extents.[80]

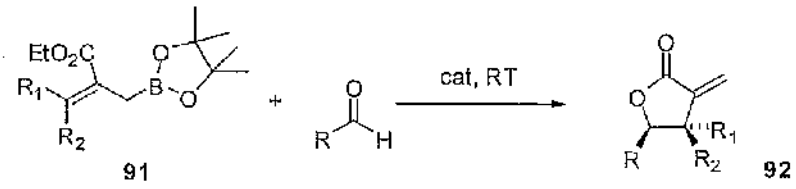
3. Enantioselective allylation. Chiral allylic boranes

Chirally modified allylic boranes **90** are among the most successful reagents for the allylation reactions.[78,81] The Lewis acidity of the boron atom, the ease of modification with chiral ligands, and organized transition structures lead to high yields and selectivities. Allylic boron reagents **91** react with aldehydes via closed cyclic, six-membered chair-like transition states characterized by internal activation of the carbonyl by the boron atom, unlike with allylic trialkylsilanes and allylic trialkylstannanes, which generally react with aldehydes under the activation by an external Lewis acid, and react via open transition structures. Since the 1980s a number of highly efficient methods have been developed to control the absolute stereoselectivity by using chiral allylic boranes reagents **90a-c** (Scheme 86).[81]



Scheme 86. Application of the chiral allylborane reagents.

Although the carbonyl oxygen atom of the aldehyde is already activated by boron, external Lewis or Brønsted acids can be used as catalysts for the allylation of aldehydes with boron reagents **91**. The tandem allylation – lactone **92** formation reaction catalysed by various Lewis acids was reported by Hall (Scheme 87).[82]

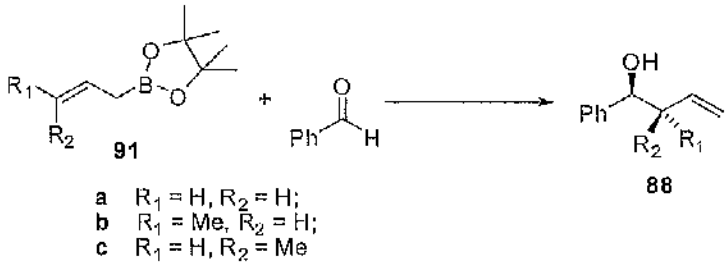


Scheme 87. The diastereoselective allylation reaction.

According to Ishiyama, the rate difference between the catalysed and non-catalysed addition of allylic boronates **91** to aldehydes is significant at -78 °C (Scheme 88, Table 13) as non-catalytic reaction produces only traces of the desired product.[83]

Table 13. The catalytic allylation reaction with allyl boranes.

Boronate	Lewis acid	Yield, %	*anti*/*syn* **88**	er
a	$AlCl_3$	88	-	-
a	$Sc(OTf)_3$	80	-	-
b	$AlCl_3$	92	99/1	-
c	$AlCl_3$	87	2/98	-
b	Et_2AlCl/BINOL	40	99/1	75.5/24.5
c	Et_2AlCl/BINOL	19	2/98	54/46

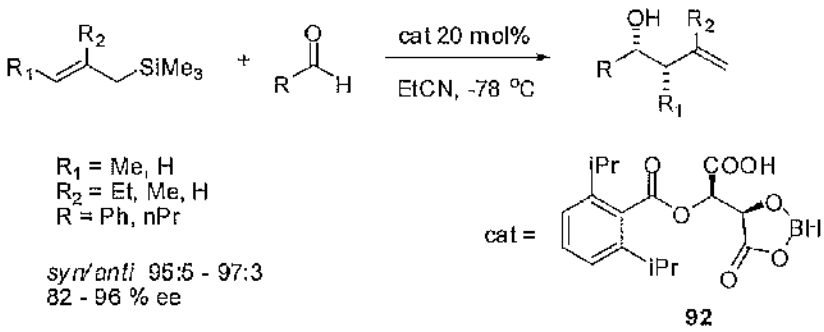


Scheme 88. The catalytic allylation reaction with allyl boranes.

Overall, the enantioselectivities of the allylation reactions with allyl boranes **91** and chiral catalysts are not yet competitive with other methods and the field is dominated by stoichiometric chiral auxiliaries.[78,81]

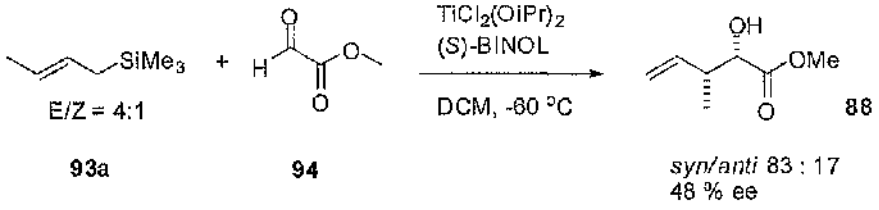
4. Lewis acid catalysed enantioselective allylation

In view of the importance of chiral Lewis acids in asymmetric catalysis, especially in the enantioselective addition of nucleophiles to carbonyl groups, it is not surprising that many chiral Lewis acids have been employed in the allylation reaction. The first examples of chiral Lewis acid-catalysed enantioselective allylation of aldehydes were reported by Yamamoto in 1991, who used chiral acyloxy borane (CAB) **92** catalysts (Scheme 89).[84]



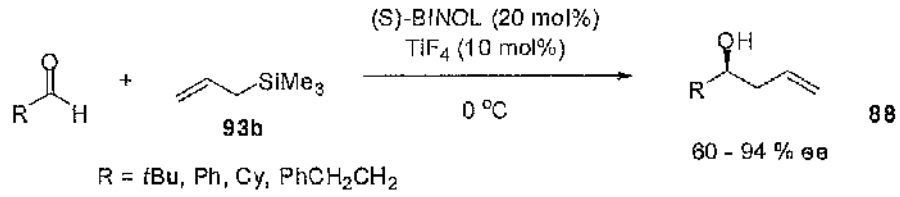
Scheme 89. Diastereo- and enantioselective allylation of aldehydes.

The titanium(IV) – BINOL complexes proved to be efficient catalysts for allylation of aldehydes with allylstannanes but not with allylsilanes.[78] This is due to the fact that titanium complexes are relatively weak Lewis acids. The application of BINOL/Ti(IV) complexes in enantioselective allylation with allyl trialkylsilanes **93** was first documented by Mikami in the addition of allylic silanes and stannanes to glyoxylates **94** (Scheme 90).[85]



Scheme 90. Ti-catalysed allylation by crotyltrimethylsilane **93a**.

An elegant solution to the problem of weak Lewis acidity of Ti(IV) was devised by Carreira[86], who found that enhanced reactivity could be secured by the use of TiF_4 in place of Ti(O*i*Pr)$_4$ (Scheme 91).

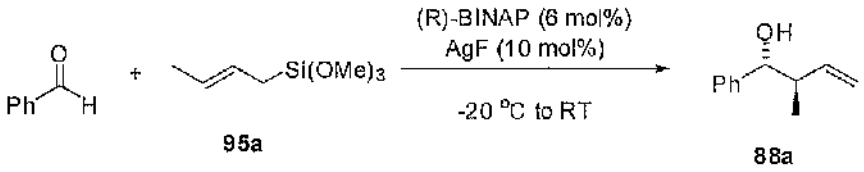


Scheme 91. TiF_4-BINOL catalysed allylation of aldehydes.

Allyltrimethoxysilanes **95** display sufficient reactivity to function as effective nucleophiles in allylation reactions catalysed by the BINAP/silver salt complexes.[87] Interestingly, whereas the BINAP/AgOTf complex is ineffective here, the use of AgF in place of AgOTf produces satisfactory results (Scheme 92, Table 14).

Table 14. Silver-catalysed crotylation of benzaldehyde.

E/Z of **95a**	yield, %	*anti* (er) : *syn* (er) **88°**
83:17	77	92 (98/2) : 8 (81/19)
< 1:99	82	94 (97/3) : 6 (80/20)
45:55	99	93 (97/3) : 7 (80/20)



95a **88a**

Scheme 92. Silver-catalysed crotylation of benzaldehyde.

It is pertinent to highlight the reversed diastereoselectivity in the reaction compared to other examples of Lewis acid-catalysed allylation with allylsilanes. A transmetallation mechanism has been proposed,[87] which involves a fast isomerisation of the 2-butenylsilver reagent prior to the addition to aldehyde that occurs through a closed, chair-like transition structure (Figure 12).

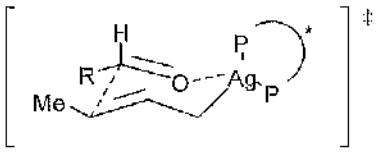


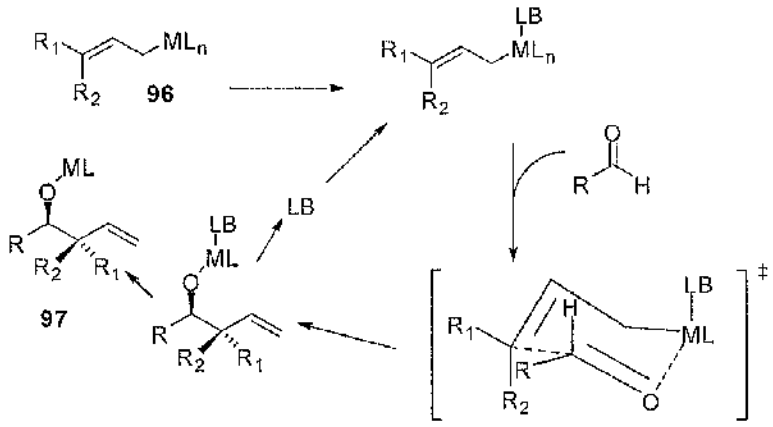
Figure 12. The proposed transition state for the Ag-catalysed crotylation of aldehydes.

5. Lewis base-catalysed enantioselective allylation

Although high enantioselectivities have been achieved in the allylation catalysed by chiral Lewis acids, the advantages of catalysis are significantly offset by the lack, in

general, of diastereocontrol because of the non-rigid nature of the transition structure for most additions. A mechanistically different process that addresses the problem of diastereoselectivity is the Lewis base-catalysed addition of allylic trichlorosilanes **96** to aldehydes. The demonstration that Lewis bases promote this addition in a fundamentally different way compared to the Lewis acid activated addition of allylic trialkylsilanes **93** and stannanes, has led to the invention of a new enantioselective process that would have greater stereochemical control and generality.

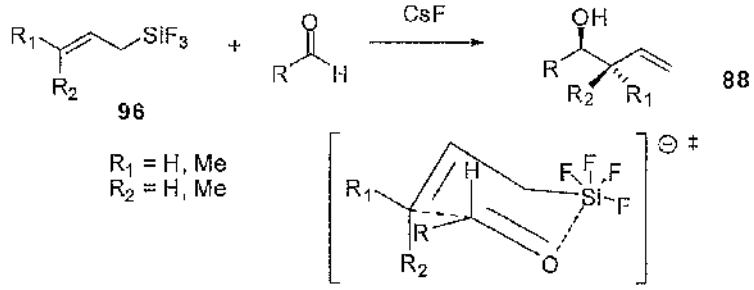
The general scheme by which Lewis bases activate allyltrihalometal reagents **96** starts with coordination of the base to the central, electrophilic element (Scheme 93).[78] The resulting complex retains sufficient Lewis acidity to coordinate the aldehyde, and the ternary complex of allylmetal, aldehyde, and chiral Lewis base reacts through a closed transition structure. This reactive intermediate could provide an opportunity to control diastereoselectivity as well as to allow the chirality of the chiral Lewis base to be transferred to the product **88**. Finally, dissociation of the Lewis base from the product trichlorosilyl ether **97** is required for catalyst turnover so that it can re-enter the cycle.



Scheme 93. The mechanism of the Lewis base catalysed allylation reaction.

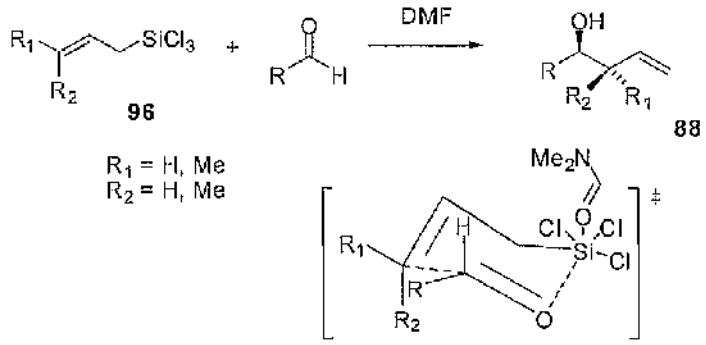
The use of anionic activators or strong donor solvents in the allylation of aldehydes has been pioneered by Sakurai and Kobayashi. Sakurai reported[88] that the

addition of allylic trifluorosilanes **96** to aldehydes could be promoted by fluoride ion to provide homoallylic alcohols **88** with high regioselectivities (Scheme 94).



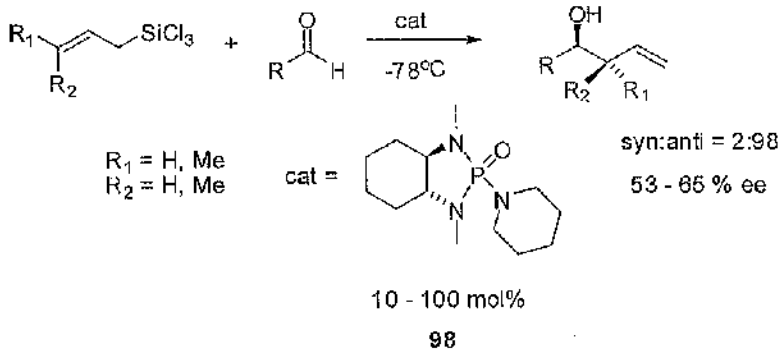
Scheme 94. CsF catalysed allylation of aldehydes with triflourosilanes.

Later, Kobayashi and co-workers described the stereoselective allylation of aldehydes with allylic trichlorosilanes **96** in dimethylformamide (Scheme 95).[89]



Scheme 95. DMF catalysed allylation of aldehydes with trichlorosilanes.

The use of chiral Lewis bases as promoters of the asymmetric allylation and crotylation was first demonstrated by Denmark in 1994 (Scheme 96). With chiral phosphoramide as a stoichiometric activator or a catalyst the allylation reaction proceeded with excellent diastereoselectivity and modest enantioselectivity.



Scheme 96. The first enantioselective allylation reaction catalysed by Lewis base.

In further mechanistic studies[90] it was proposed that the phosphoramide-catalysed allylation reaction proceeds via the cationic transition state with the hexa-coordinate silicon atom and two molecules of phosphoramide coordinated to it (Chart 12).

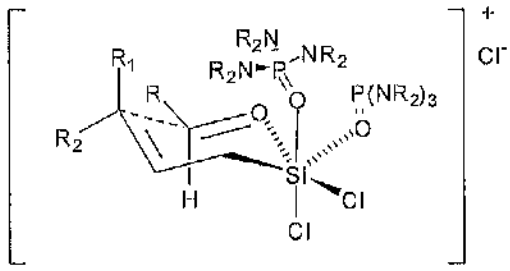
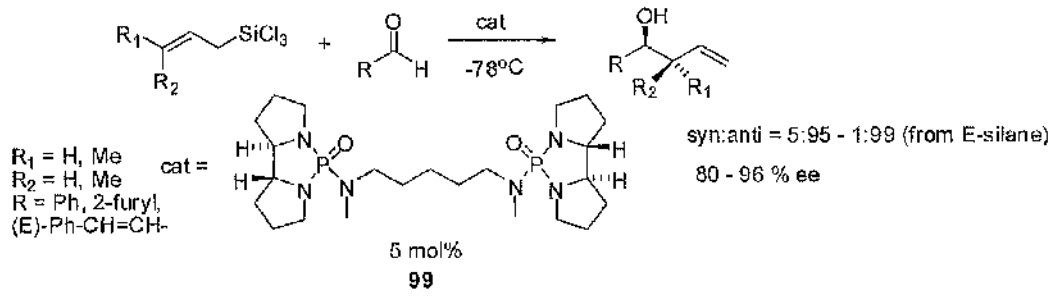


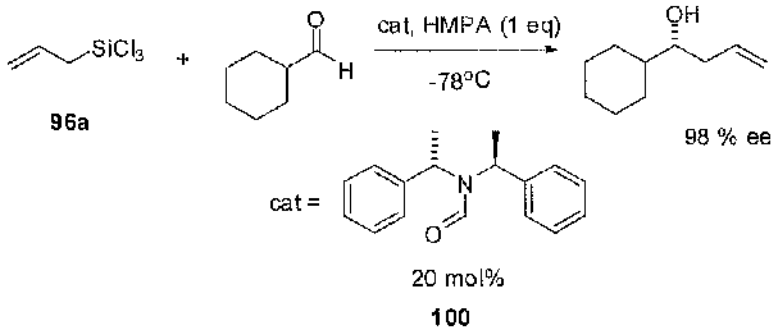
Chart 12. The proposed transition state for the phosphoramide catalysed allylation reaction.

The latter mechanistic insight led Denmark to the development of new highly enantioselective allylation reaction catalysed by the chiral bisphosphoramide **99** (Scheme 97).[91]



Scheme 97. The enantioselective allylation reaction catalysed by the chiral bisphosphoramide **99**.

Following on the original observation by Kobayashi that DMF (as solvent) promoted the allylation of aldehydes with trichlorosilanes **96**, Iseki developed chiral DMF analogues **100** for enantioselective additions (Scheme 98).[92]

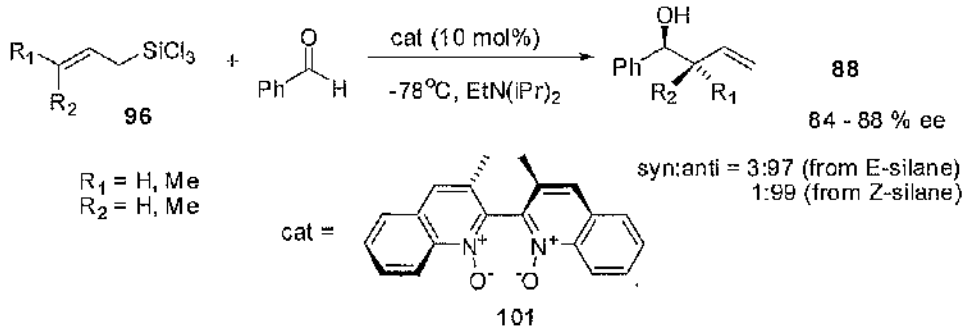


Scheme 98. The chiral amide catalysed allylation reaction

6. Chiral *N*-oxides as highly selective catalysts for the addition of allyl trichlorosilanes to aldehydes

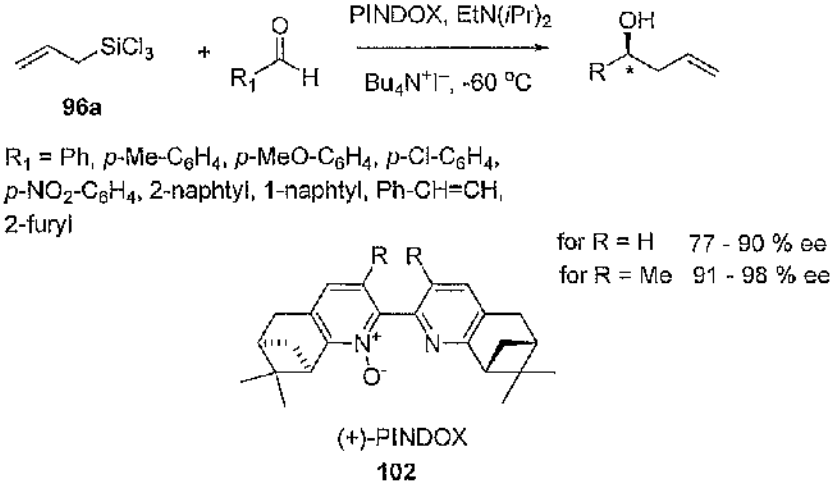
Chiral *N*-oxides have emerged as another class of highly selective catalysts for the addition of allylic trichlorosilanes **96**.[78] The first example was published by Nakajima, who used axially chiral biquinoline *N,N*-dioxide **101** as a catalyst to promote diastereo-

and enantioselective allylation of benzaldehyde (Scheme 99).[93] The reaction was dramatically accelerated by addition of $EtN(iPr)_2$ to the system.



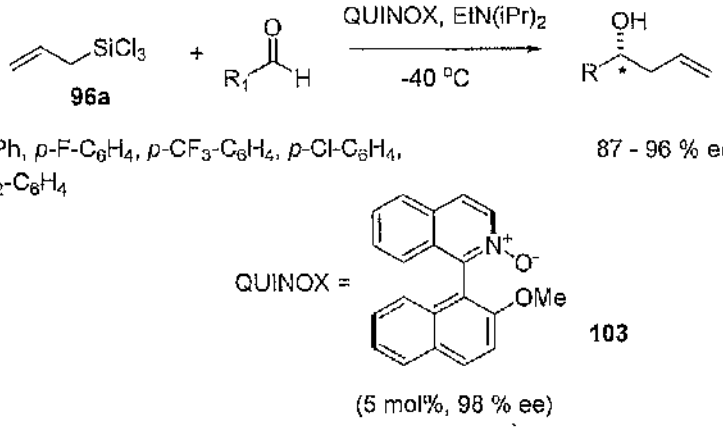
Scheme 99. The first chiral *N*-oxide catalysed allylation of benzaldehyde.

A number of highly prominent catalytic systems for the stereoselective allylation of aldehydes have been developed recently by our group. The pioneering work introduced in 2002 monoxide PINDOX **102a** and its dimethyl derivative **102b** as efficient catalysts for the allylation of aromatic aldehydes with allyl trichlorosilane **96** (Scheme 100).[94]



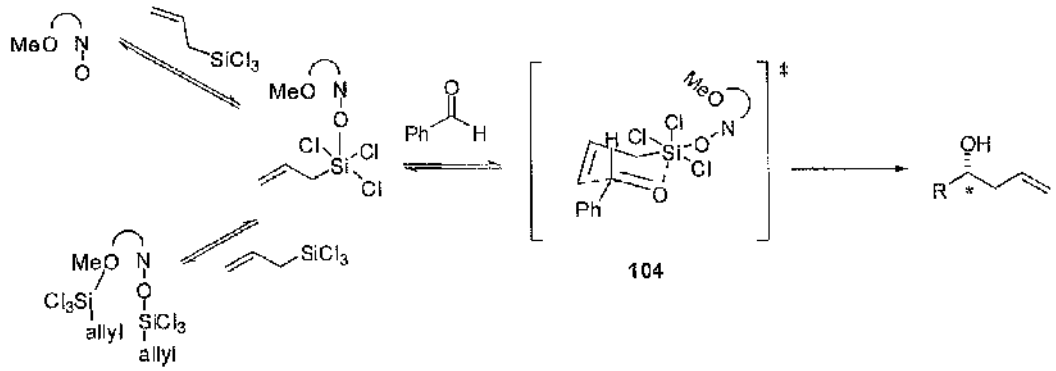
Scheme 100. Allylation of aromatic aldehydes catalysed by PINDOX..

QUINOX **103** expanded the family of chiral *N*-monoxide catalysts, promoting the enantioselective allylation reaction of aromatic aldehydes (Scheme 101).[95]



Scheme 101. The allylation of aromatic aldehydes catalysed by QUINOX.

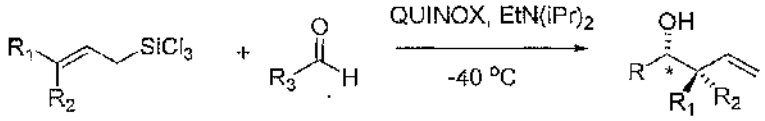
The recent mechanistic studies[96] resulted in the formulation of a mechanism of the allylation reaction catalysed by QUINOX (Scheme 102). The rate limiting step was elucidated by using Hammett correlation. The reaction catalysed by QUINOX proceeds faster and more selectively in non-polar solvents. Based on this fact and on the low ρ value the tightly packed transition state with octahedral configuration of the silicon atom for the rate limiting step was proposed by Malkov and Kočovský (Scheme 102).



Scheme 102. The mechanism of QUINOX catalysed allylation reaction.

Quantum chemical calculations[96] supported the previously suggested underlying role of π-π interactions in the QUINOX catalysed reaction.

The crotylation reaction catalysed by QUINOX was found to be highly diastereoselective (Scheme 103), which is consistent with the cyclic chair-like transition state (Scheme 102).



96b R_1 = Me, R_2 = H *syn*:*anti* = 17:83 - 4:96

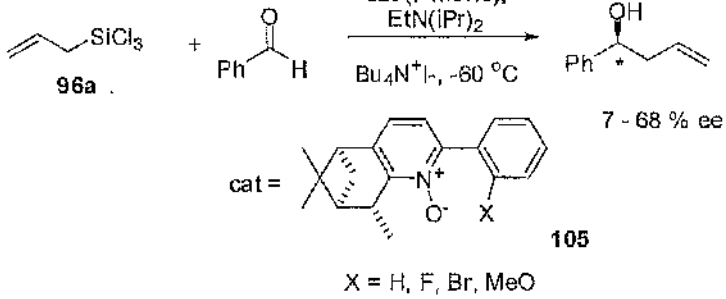
96c R_1 = H, R_2 = Me *syn*:*anti* = 96:4 - 99:1

R_3 = Ph, *p*-$CF_3C_6H_4$, *p*-$MeOC_6H_4$

Scheme 103. The crotylation of aldehydes catalysed by QUINOX.

Interestingly, *cis*-crotylsilane **96c** exhibited a higher rate of allylation compared to the *trans*-isomer **96b**, which represents a reversal of the trend commonly observed with other *N*-oxide catalysts.[96]

Another set of new promising catalysts has been synthesised by employing Kröhnke annulation as the key transformation and tested for the allylation of benzaldehyde (Scheme 104).[97]

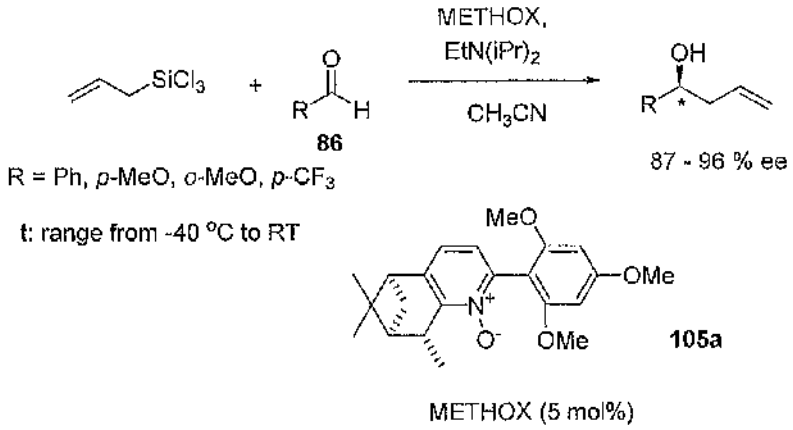


96a

105

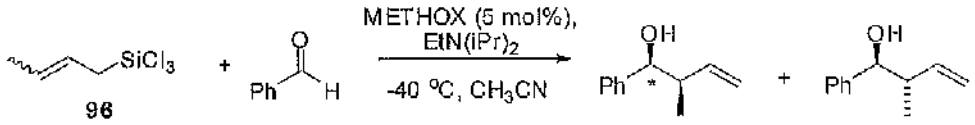
Scheme 104. The enantioselective allylation of benzaldehyde catalysed by a family of N-monoxides.

Subsequent tuning of the catalyst structure revealed the superior one, METHOX **105a**.[98] High enantioselectivities were attained for a variety of aromatic aldehydes **86** at different temperatures (Scheme 105).



Scheme 105. The allylation of aldehydes catalysed by METHOX

METHOX-catalysed allylation of benzaldehyde has been carried out with crotyltrichlorosilanes **96** (*E*/*Z* 6:1) (Scheme 106).[98] The (*E*)-isomer **96b** (1.2 mol excess) reacted uneventfully, affording pure *anti* product **88a** (anti/syn 99:1) of high enantiopurity (95% ee), which indicates a kinetic preference for the (*E*)-isomer. Accordingly, the reaction with pure (*Z*)-isomer **96c** proved to be sluggish (26% conversion).

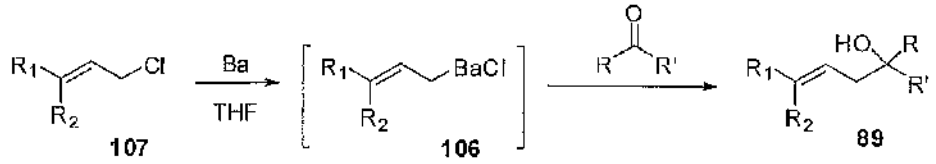


E/Z	conversion of PhCHO, %	syn (ee, %) / anti (ee, %)	88a
87:13	95	1 : 99 (95)	
1:99	26	6 (26) : 1	

Scheme 106. The crotylation of benzaldehyde catalysed by METHOX.

7. The α-allylation issue. Known examples of the regioselective α-allylation

Unlike with γ-allylation, the regio- and stereoselective α-allylation is unusual and far less known. Yamamoto introduced allylic barium reagents **106** generated *in situ* from allylic chlorides **107** for the α-selective allylation of aldehydes or ketones (Scheme 107).[99] The respective racemic homoallylic alcohols **89** were obtained with virtually full retention of the carbon-carbon double bond configuration.



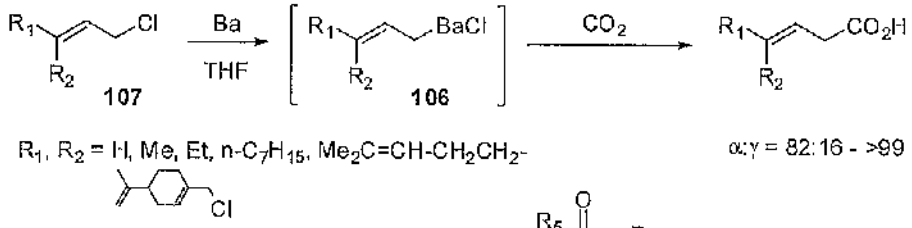
R_1, R_2 = H, Me, Et, n-C_7H_{15}, Me_2C=CH-CH_2CH_2-

α:γ = 75 :25 - >99 :1

carbonyl compounds: PhCH=O, n-C_5H_{11}CH=O, (E)-PhCH=CHCH=O, acetophenone, cyclohexanone

Scheme 107. α-Allylation of carbonyl compounds with allylbarium reagents.

Later the scope of the allylation reaction using allylbarium species **106** has been greatly expanded by Yamamoto (Scheme 108).[100] As substrates, beside simple aldehydes and ketones, he successfully employed CO_2 and α,β-unsaturated ketones **108**.



R_1, R_2 = H, Me, Et, n-C_7H_{15}, Me_2C=CH-CH_2CH_2-

α:γ = 82:16 - >99 :1

R_1, R_2 = H, Me, Et, n-C_7H_{15}

R_3, R_4, R_5, R_6 = H or Me

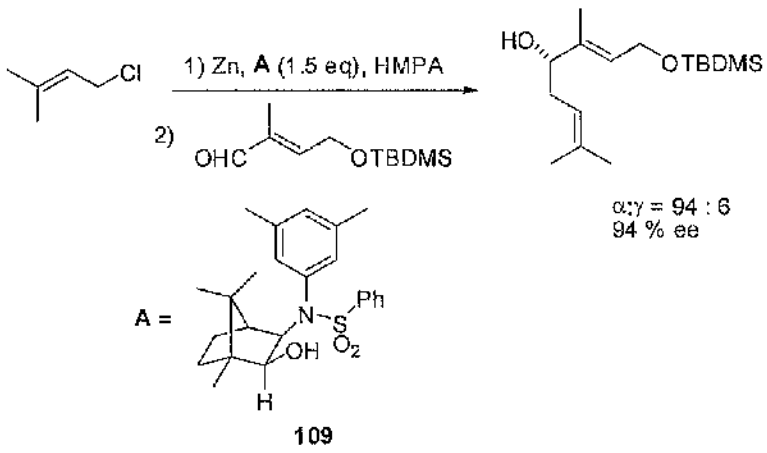
α:γ up to >99 :1

1,4 : 1,2 up to >99:1

Scheme 108. The use of allylbarium reagents for the regio- and stereoselective allylation of CO_2 and 1,4-addition to α,β-unsaturated ketones.

The reason why an allylbarium compound reacts selectively at the α-carbon with a carbonyl compound is not clear; however, the unusually long barium-carbon bond (2.76-2.88 Å) might prevent the formation of the six-membered cyclic transition structure leading to the γ-product. The four-membered cyclic structure including Ba-C and C=O bonds is one of the possible transition-states for the α-selective allylation.[100]

Hong reported on one example of regio- and enantioselective α-allylation using allylzinc reagent with a stoichiometric amount of the chiral amido alcohol **109** (Scheme 109).[101]



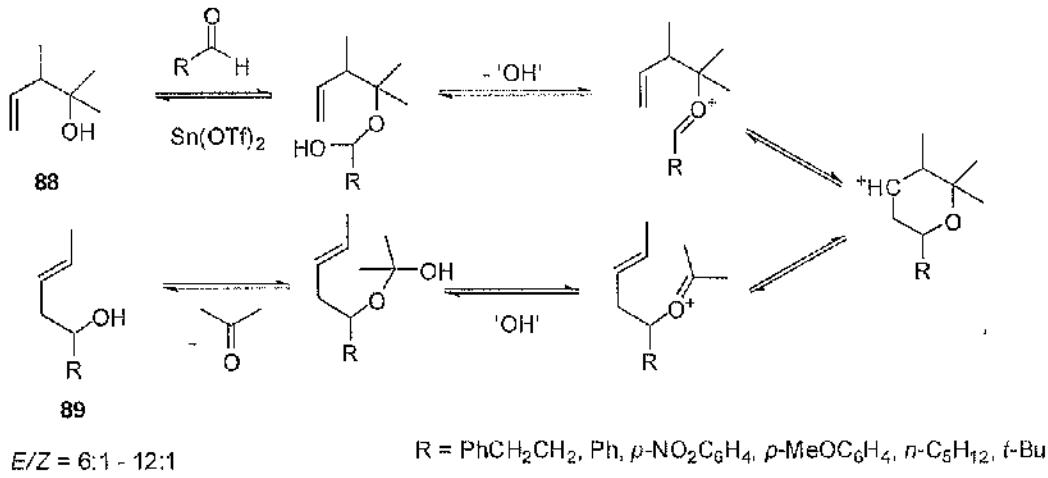
109

Scheme 109. The regio- and enantioselective allylation reaction.

8. Allyl transfer as a new method to synthesize linear homoallylic alcohols

A break through new concept in the α-allylation of aldehydes was introduced by Nokami in 1998.[102] In the presence of $Sn(OTf)_2$, an allylic functionality can be stereoselectively transferred from γ–homoallylic alcohol **88** to an aldehyde to obtain the respective α-homoallylic alcohol **89**. Together with the corresponding regioselective γ-allylation towards the initial alcohol, this allyl transfer may serve as a two step α-allylation method. Nokami assumed that the allyl transfer reaction proceeds in the

direction to give: 1) a more stable cation, 2) a sterically less hindered homoallylic alcohol, and 3) thermodynamically more stable olefin (Scheme 110).



Scheme 110. The $Sn(OTf)_2$ catalysed allyl transfer reaction.

A six-membered transition state was suggested for the key transformation in the allyl transfer reaction to account for the formation of mainly (*E*)-isomer of the homoallylic alcohol. CH_3 group occupies preferentially an equatorial position resulting in trans-configuration of the forming carbon-carbon double bond (Chart 13).[102]

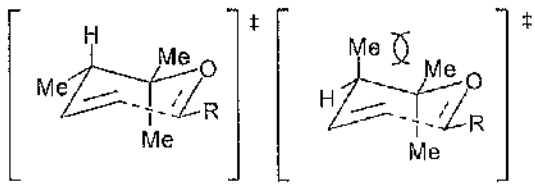
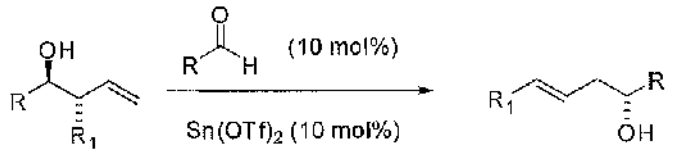


Chart 13. Proposed transition states for the allyl transfer reaction

The highly stereoselective catalytic conversion of γ-adducts **88** to α-adducts **89** using 10 mol% of the respective aldehyde and $Sn(OTf)_2$ was reported (Scheme 111).[103]

The *E/Z* ratio of the products isolated was virtually equal to the *anti/syn* ratio of the respective starting alcohols.



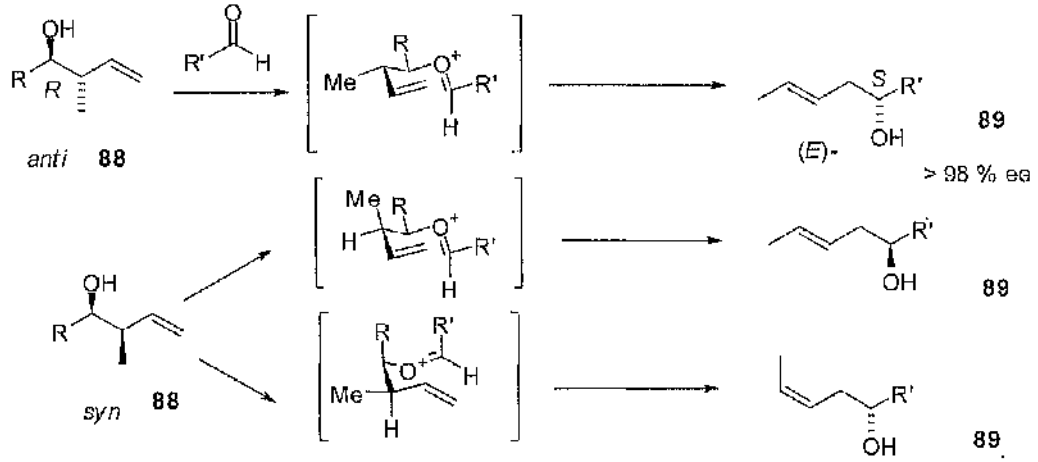
88 **89**

R = Ph, $PhCH_2CH_2$, $CH_3(CH_2)_8$ E/Z = 11:1 - 49:1

R_1 = Me, Ph, CO_2Et

Scheme 111. The catalytic conversion of γ-adducts to α-adducts.

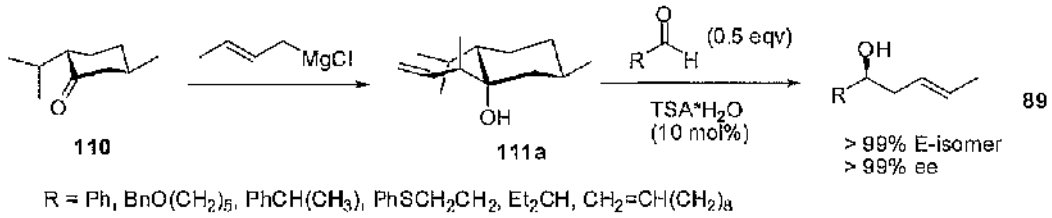
Further studies on the concept revealed that the allyl transfer can be used as a method for the enantioselective synthesis of homoallylic alcohols.[103] Nokami showed one example of α-selective allylation of aldehydes via allyl-transfer reactions with *anti* homoallylic alcohols **88**, derived from aldehydes, which proceeds with virtually full inversion of the alcohol configuration (Scheme 112). Their *syn* isomers react less selectively.



R' = $PhCH_2CH_2$
R = Ph

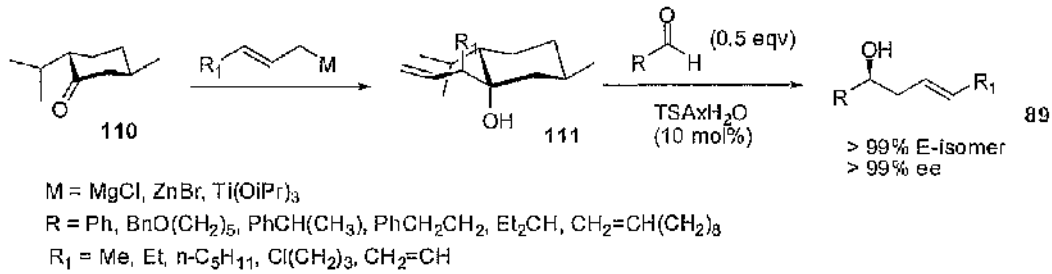
Scheme 112. The enantioselective allyl-transfer reaction.

The first general method for the enantioselective crotylation of aldehydes via an allyl transfer reaction from a chiral crotyl donor was developed by Nokami in 2001.[104] As the initial source of chirality, he used (-)-menthone **110** which was subjected to the crotylation reaction with the respective Grignard reagent (Scheme 113). After column chromatography purification, the pure diastereoisomer of the product **111a** was used as a crotyl donor for a number of aldehydes under acid-catalysed conditions to obtain the enantiomerically pure homoallylic alcohols **89**.



Scheme 113. The enantioselective crotylation of aldehydes.

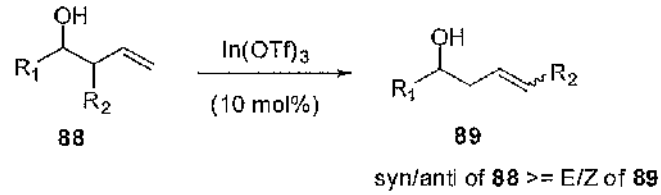
Later this method was further generalized, allowing employment of various allylation reagents **111**.[105] All the linear homoallylic alcohols **89** obtained by this method were stereochemically and enantiomerically pure (Scheme 114).



Scheme 114. The enantioselective allylation of aldehydes.

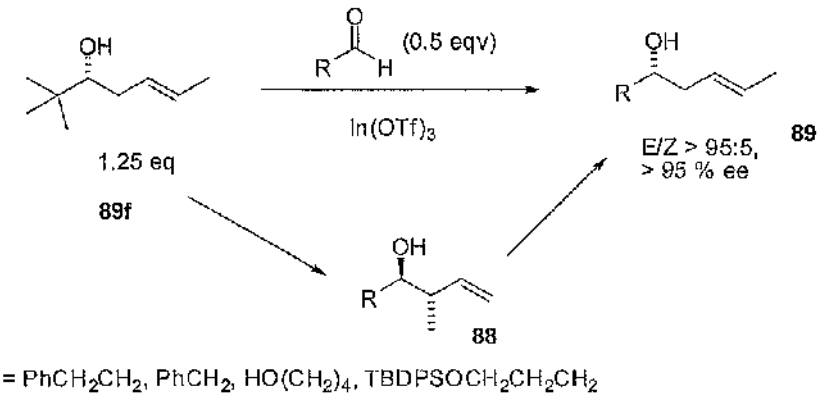
Loh showed that addition of an aldehyde to a γ-homoallylic alcohol **88** is not essential for its rearrangement into the α-isomer **89** to take place.[106] Thus, in the presence of $In(OTf)_3$ (10 mol%), the respective α-homoallylic alcohols **89** were obtained from

their γ-isomers (Scheme 115). However, he proposed the same mechanism for rearrangement as the mechanism of the allyl transfer published by Nokami.[102] Loh suggested that the catalytic amount of the respective aldehyde formed in situ from the starting alcohol **88**.



Scheme 115. In-catalysed rearrangement reaction

In accordance with the prediction of Nokami[102], the sterically strained linear homoallylic alcohol **89f** was found to be an efficient crotyl donor for a number of aldehydes.[107] Based on the fact that the configurations of the respective product and the starting alcohol were the same, Nokami suggested two subsequent reactions to take place in the system (Scheme 116)

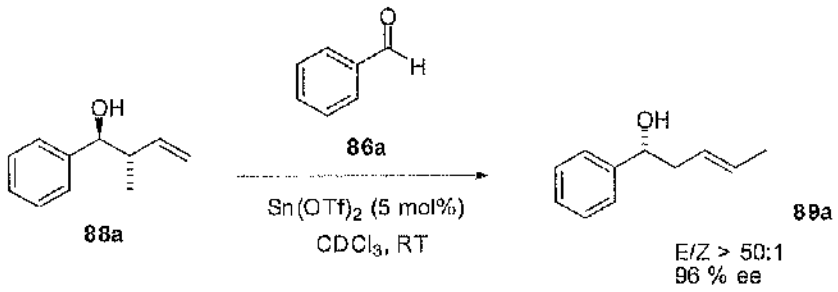


Scheme 116. The enantioselective crotyl transfer from the linear homoallylic alcohol **89f**.

Results and discussion.

1. The enantioselective allyl-transfer reaction. Optimisation

To probe the potential of alcohols **88** for the enantioselective allyl-transfer reaction, we first carried out the rearrangement of γ– to α-product (Scheme 117). A 1:1 mixture of benzaldehyde **86a** and (1*S*,2*R*)-**88a** (*anti*/*syn* 50:1, 97% ee), was treated with $(TfO)_2Sn$ (5 mol%) in $CDCl_3$. Monitoring the reaction by ^1H NMR showed a complete conversion in just 20 min; the product (*R*)-**89a** was obtained with 96% ee and (*E*/*Z*) > 50:1 (Scheme 117), indicating a virtually complete preservation of the stereochemical information.

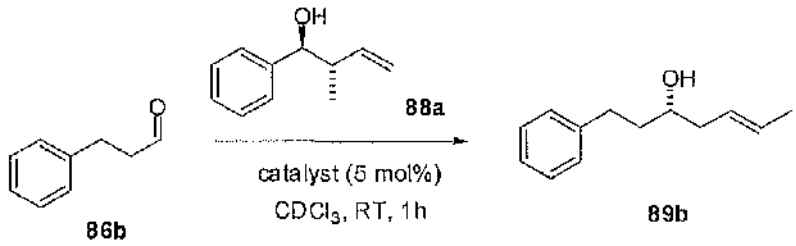


Scheme 117. The enantioselective γ-α rearrangement of the homoallylic alcohol.

Next, we focused on cross-crotylation, employing hydro-cinnamaldehyde (**86b**) as a model receptor aldehyde (Scheme 118, Table 15). A brief screening led to the identification of $(TfO)_2Sn$ as an optimal Lewis-acidic catalyst, ensuring fast and clean conversion of **88a** into **89b** (Table 15, entry 3).

Table 15. Catalyst optimisation for the enantioselective allyl-transfer reaction.

Catalyst	Conversion to **89b**, %
TsOH	10
$Yb(OTf)_3 \times 3H_2O$	5
$Sn(OTf)_2$	50

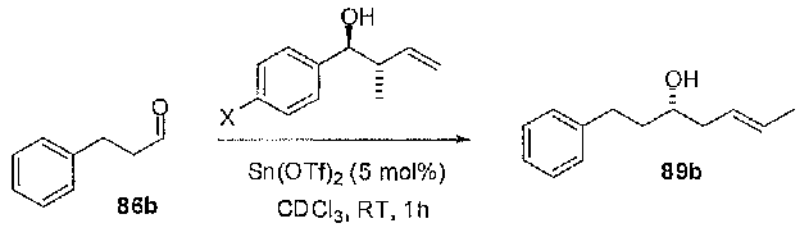


Scheme 118. The enantioselective allyl-transfer reaction.

In earlier reports,[103] **88a** proved to be a poor allyl-transfer reagent as the benzaldehyde released became involved in the reaction giving **89a** as an undesired by-product. We found that using a 3-fold excess of the receptor aldehyde **86b** completely suppressed the side reaction. However, we felt that the substitution pattern in the donor alcohol **88** may affect the reactivity and consequently improve the efficiency of the cross-crotylation. Therefore, we examined alcohols **88b-d** (ee ≥96%, *anti/syn* ≥ 25:1; Table 16, Scheme 119)

Table 16. The enantioselective allyl-transfer reaction

Entry	X	Conversion to **89b**, %
1	NO_2	Traces
2	MeO	10
3	Me	95



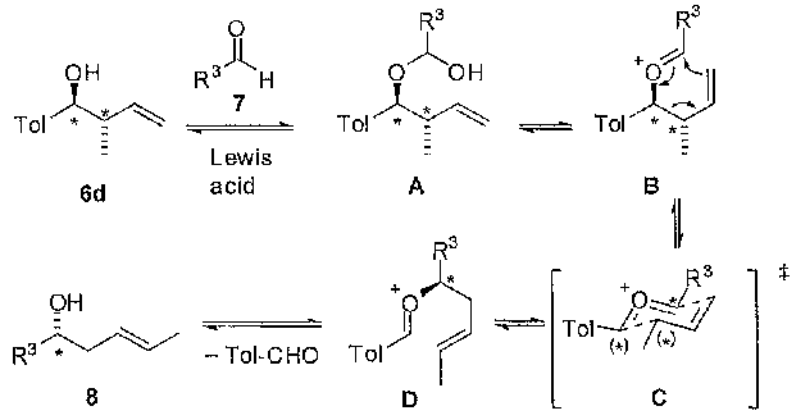
X = NO_2 **88b**

X = MeO **88c**

X = Me **88d**

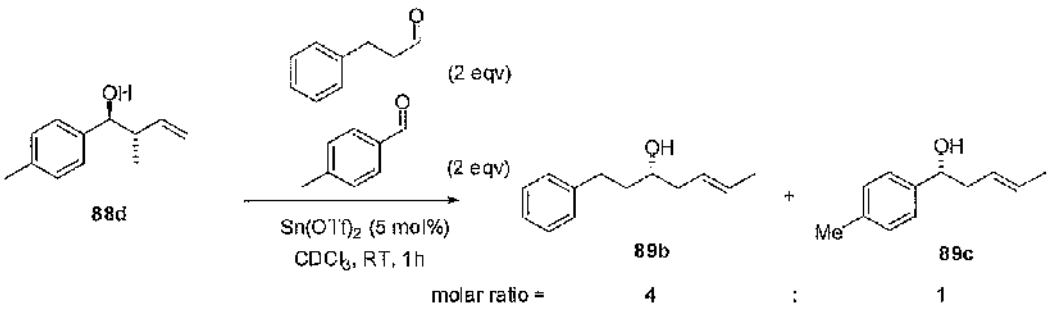
Scheme 119. The enantioselective allyl-transfer reaction.

According to the mechanism formulated by Nokami (Scheme 120),[103] the driving force for the key oxonia-Cope rearrangement (**B** → **D** via the transition state **C**) is the formation of the more stable cation **D**, complemented by the shift of the terminal double bond to an internal position and by the release of the steric constrains existing in **A**/**B**.



Scheme 120. The proposed mechanism for the enantioselective allyl-transfer reaction.

Indeed, the more electron-rich *p*-tolyl derivative **88d** (entry 3, Table 16) emerged as a clear winner, presumably owing to its enhanced capability to stabilize the positive charge in **D**, compared to the phenyl in **88a** (entry 3, Table 15). On the other hand, the even more electron-rich *p*-methoxy analogue **88c** (entry 2, Table 16) was found to be unstable under the reaction conditions, resulting mainly in the formation of degradation products, whereas the electron-poor *p*-nitro derivative **88b** (entry 1, Table 16) was virtually inactive. As an additional benefit of **88d**, the reduced electrophilic character of *p*-tolualdehyde **86c** released during the reaction makes it less competitive with the receptor aldehyde **86** in the allyl-transfer process, thereby avoiding the formation of the corresponding alcohol (**89c**). Indeed, a competition experiment (Scheme 121), employing a 1:1 mixture of **86b** and **86c**, showed that the crotyl transfer from **88d** to **86c** proceeded at least 4 times slower than that to **86b**.



Scheme 121. The competition experiment of the enantioselective allyl-transfer reaction.

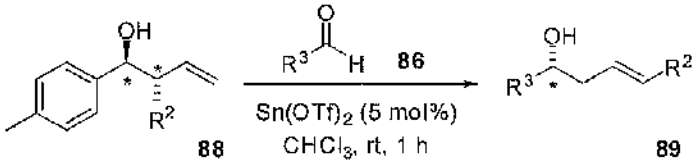
2. The enantioselective allyl-transfer reaction. Scope of the method

Alcohol **88d** was employed in crotylation of a range of recipient aldehydes (Scheme 122, Table 17). The reaction proved to be very efficient in every instance, with the enantioselectivity varying in the range of 93-98% ee, essentially irrespective of the nature of aldehyde **86**.

Table 17. The scope of the enantioselective allyl-transfer reaction.

Entry	**88**	R^2	**86**	R^3	**89**	Yield, %[b,c]	ee, %[d]
1	**88d**	Me	**86d**	4-$NO_2C_6H_4$	**89d**	75	98
2	**88d**	Me	**86e**	$PhCH_2$	**89e**	82	96
3	**88d**	Me	**86f**	*t*Bu	**89f**	60	93
4	**88d**	Me	**86g**	*c*C_6H_{11}	**89g**	80	97
5	**88d**	Me	**86h**	Et_2CH	**89h**	83	≥95
6	**88d**	Me	**86i**	*n*C_6H_{11}	**89i**	85	≥97
7	**88d**	Me	**86j**	$MeS(CH_2)_2$	**89j**	72[e]	≥97
8	**88e**	*n*Pr	**86b**	$Ph(CH_2)_2$	**89k**	83	97
9	**88f**	Bn	**86b**	$Ph(CH_2)_2$	**89l**	85	96
10	**88g**	CH_2OBn	**86b**	$Ph(CH_2)_2$	**89m**	85[e]	95

[a] The reactions were carried out with 1 mmol of **88** and 3 mmol of **86** in $CHCl_3$ (15 mL). [b] Isolated yield. [c] In all cases the (*E*/*Z*) ratio was >100:1. [d] Determined by HPLC for **89d**, **89e**, **89k**, **89l**, **89m**; determined by ^{19}F NMR of the corresponding Mosher ester for **89f**, **89i**, **89j**; determined by GC for **89g**, **89h**. [e] After 12 h.



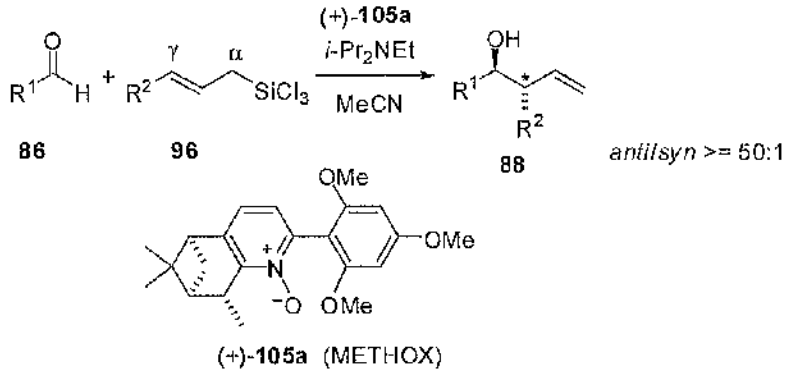
Scheme 122. The general scheme for the enantioselective allyl-transfer reaction.

The respective homoallylic alcohols **88** were prepared by the diastereo- and enantioselective allylation reaction using METHOX **105a** as a chiral catalyst (Table 18, Scheme 123).

Table 18. The diastereo- and enantioselective allylation of aromatic aldehydes with allyltrichlorosilanes (Scheme 123).

Entry	R_1	R_2	Temperature, °C	ee, %
1	Ph	Me	-40	97[c]
2	p-Tol	Me	-40	98[a]
3	p-Tol	n-Pr	-40	97[b]
4	p-Tol	CH_2Ph	-20	97[c]
5	p-Tol	CH_2OCH_2Ph	-20	97[c]

[a] Using 5 mol% of METHOX [b] Using 20 mol% of METHOX; [c] Using 50 mol% of METHOX

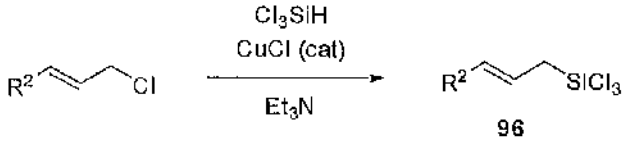


(+)-**105a** (METHOX)

Scheme 123. The diastereo- and enantioselective allylation of aromatic aldehydes with allyltrichlorosilanes.

Significantly, this allyl-transfer is not restricted to the products of crotylation (**88a-d**). Thus, a set of γ-derivatives **88e-g**, obtained from (*E*)-3-alkyl allyltrichlorosilanes **96d-f** (Table 17), were converted into the corresponding linear homoallylic alcohols **89k-m** in high yields and enantioselectivities (Table 17, entries 8-10).

The respective trichlorosilanes **96** were obtained from the allylic chlorides **107** (commercial or easily accessible by published procedures[108]) using copper-catalysed silylation reaction (Scheme 124)



107a, R = Me (*E*/*Z* = 6:1)
107b, R = *n*Pr (pure E)
107c, R = Bn (pure E)
107d, R = $BnOCH_2$ (pure E)

Scheme 124. The synthesis of allyltrichlorosilanes

The pinene-derived *N*-oxide METHOX **105a** exhibits a strong kinetic preference towards the *trans*-isomer **96b**, leaving the *cis*-isomer **96c** unreacted. As an important consequence, the latter catalyst **105a** allows the use of crotyl silane **96** (*E*/*Z* = 6:1), obtained from the technical grade crotyl chloride **107a** (*E*/*Z* = 6:1), without additional purification, giving the homoallylic alcohols **88a-d** in excellent diastereo- and enantiopurity (≥ 50:1 anti/syn, ≥ 96 % ee).

Conclusions.

A practical, highly stereoselective, two-step protocol for the α-allylation of aldehydes, starting from allyltrichlorosilanes, has been developed. Due to kinetic resolution in each step, virtually enantiomerically and geometrically pure linear homoallylic alcohols were obtained in high yield from technical grade allyltrichlorosilanes by using only 5 mol% of the chiral catalyst METHOX.

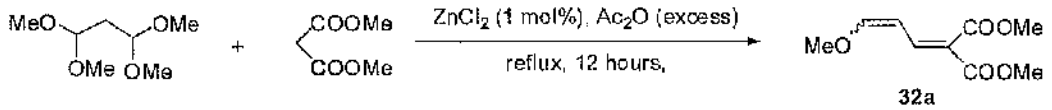
Future work.

1. Optimization of the enantioselective IEDDA reaction employing pyrone-carboxylic acid as a diene. Search for a new efficient ligand for the Yb-based catalytic system.
2. Optimization of the palladium-catalysed allylic amination to obtain cyclohexenyl nucleosides. Variation of leaving groups.
3. Determination of the absolute configuration of Speranskatine A.

Experimental.

General methods. The NMR spectra were recorded at room temperature in $CDCl_3$ (δ 7.26, ^1H; δ 77.16, ^{13}C) or DMSO-d6 (δ 2.50, ^1H; δ 39.52, ^{13}C), ^1H at 400 MHz and ^{13}C at 100.6 MHz. Various 2D-techniques and DEPT experiments were used to establish the structures and to assign the signals. The IR spectra were recorded for a thin film between KBr plates or for $CHCl_3$ solutions or in a solid by the Golden Gate technique. The mass spectra (EI and/or CI) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. All reactions were performed under an atmosphere of dry, oxygen-free nitrogen (or argon where specified) in oven-dried glassware twice evacuated and filled with the nitrogen. Solvents and solutions were transferred by syringe-septum and cannula techniques. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use as follows: diethyl ether from lithium aluminium hydride; tetrahydrofuran (THF) from sodium/benzophenone; dichloromethane from calcium hydride. Petroleum ether refers to the fraction boiling in the range of 40-60 ^{0}C. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. The identity of the products prepared by different methods was checked by comparison of their NMR, IR, and MS data and by the TLC behaviour.

Dimethyl 3-Methoxyallylidenemalonate (32a).[41]

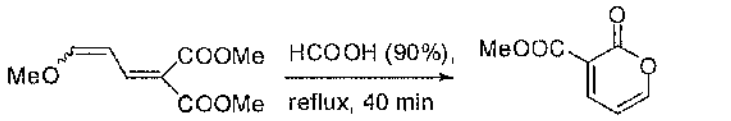


32a

1,1,3,3-tetramethoxypropane (24.7 mL, 0.15 mol), dimethyl malonate (11.4 mL, 0.10 mol), anhydrous $ZnCl_2$ (0.204 g, 1.5 mmol) and acetic anhydride (135 mL, 1.4 mol) were mixed quickly in a 500 mL round bottom flask and the mixture was refluxed with stirring overnight (12 h). Solvents were distilled off using water pump (careful heating up

to 70 °C by oil bath) and the dark oily residue was immediately distilled (135-150 °C, 1 mmHg) to afford **32a** (*trans/cis* = 6:1) as a bright yellow oil (16.76 g, 85% yield): ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.73 (s, 3H, *trans*), 3.75 (s, 3H, *trans+cis*), 3.82 (s, 3H, *cis*), 3.83 (s, 3H, *trans*), 5.67 (dd, J = 6.1 and 12.4 Hz, 1H, *cis*), 6.22 (t, J = 12.1 Hz, 1H, *trans*), 6.40 (dd, J = 6.1 and 1.0 Hz, 1H, *cis*), 7.10 (d, J = 12.1 Hz, 1H, *trans*), 7.42 (d, J = 12.1 Hz, 1H, *trans*), 7.87 (dd, J = 12.4 and 1.0 Hz, 1H, *cis*) in accordance with the literature.[41]

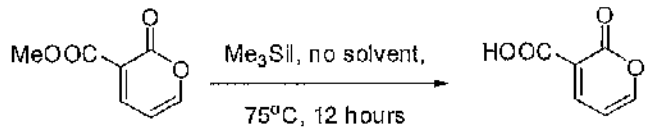
3-Carbomethoxy-2-pyrone (10a).



32a **10a** 57%

The substance was prepared by modification of the literature procedure.[41] A solution of dimethyl 3-methoxyallylidenemalonate (45.5 g, 0.23 mol) in 90% formic acid (120 mL) was refluxed for 40 minutes in a 250 mL round bottom flask while stirring. When the reaction was complete, solvents were distilled off using a water pump (careful heating up to 80 °C by oil bath) and the oily residue was immediately distilled, using a long air condenser (cooled on its end by paper/dichloromethane) to furnish **10a** as a yellow solid (18.9 g, 57%): mp 74-76 °C [lit.[41] 75-77 °C]; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 3.93 (s, 3H), 6.42 (dd, J = 6.8 and 5.0 Hz, 1H), 7.73 (dd, J = 5.0 and 2.0 Hz, 1H), 8.25 (dd, J = 6.8 and 2.2 Hz, 1H) in accordance with the literature.[41]

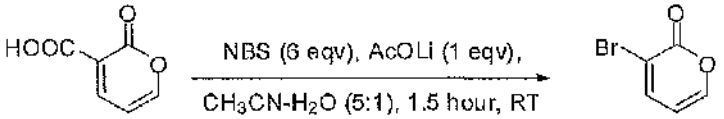
2-Pyrone-3-carboxylic Acid (10c).[44]



10a **10c**

Hexamethyldisilane (30.4 g, 0.208 mol) and iodine (26.4 g, 0.104 mol) were stirred for half an hour at 35 °C in a 1 L round bottom flask (equipped with a long condenser and 3 balloons) resulted in dark violet solution. Then the temperature was carefully increased up to 38 °C and a vigorous exothermic reaction occurred. At this point the colour of the solution almost disappeared. The mixture was heated at 120 °C for 2 h to complete the reaction. As a result, a colourless solution formed, which was then cooled to room temperature and 3-carbomethoxy-2-pyrone (11.2 g, 0.073 mol) was added and the mixture was stirred at 75 °C for overnight. After the reaction was complete the mixture was diluted with 200 mL of dichloromethane, quenched with H_2O (10 mL) and stirred for 10 min. Then the mixture was shaken with saturated aqueous solution of $Na_2S_2O_3$, acidified to pH = 1, the organic layer was separated, and the aqueous layer was extracted by EtOAc for 3 times. The combined organic fractions were dried over sodium sulfate and evaporated to furnish **10c** (10.0 g, 98%), as a light brown solid pure by ^{1}H-NMR: mp 117–119 °C [lit[44] 121-123]; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 6.52 (d, J = 6.8 and 5.0 Hz, 1H), 7.97 (dd, J = 5.0 and 2.2, 1H), 8.16 (dd, J = 6.8 and 2.2, 1H); ^{13}C-NMR (100 MHz; DMSO-d_6) δ 106.3, 117.4, 148.8, 157.4, 157.8, 164.1 in accordance with literature[44].

3-Bromo-2-pyrone.[45,109]



10c **33**

2-Pyrone-3-carboxylic acid (2.50 g, 0.017 mol), *N*-bromosuccinoimide (15.1 g, 0.085 mol) and LiOAc (1.122 g, 0.017 mol) were placed to a flat bottom flask (250 mL) followed by the mixture of CH_3CN (125 mL) and H_2O (25 mL) and the reaction mixture was stirred at room temperature for 1.5 h. After the reaction was complete, the mixture was diluted with EtOAc (250 mL) and shaken with $Na_2S_2O_3$ saturated aqueous solution till the colour disappeared. The aqueous layer was extracted with EtOAc 2 times and the

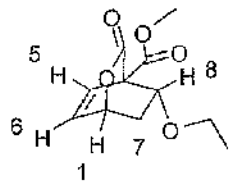
combined organic fractions were dried over sodium sulfate and evaporated. The crude product was purified by flash chromatography on neutral alumina (2.5 cm × 20 cm; Petroleum ether - EtOAc gradient from 100:0 to 50:50). The desired product **33** was obtained as a white solid (1.1 g, 33%): mp 56-59°C; ^{1}H-NMR (400 MHz; DMSO-d_6) δ 6.40 (dd, J = 6.8 and 5.0 Hz, 1H), 7.88 (dd, J = 5.0 and 2.2 Hz, 1H), 8.05 (dd, J = 6.8 and 2.2 Hz, 1H); MS (EI), *m/e* (%): 176 (M^{+1}, 5), 174 (M^{+1}, 5), 148 (10), 146 (10), 83 (100), 47 (20). Anal. Calcd for $C_5H_3O_2Br$: C, 34.28; H, 1.71. Found: C, 34.44; H, 1.69.

General Procedure for Diels-Alder Reactions. All reactions were performed in the atmosphere of dry argon. Oven-dried (250 °C, for at least 24 h) molecular sieves (4 Å) were placed in an oven-dried 25 mL round bottom flask, followed by $Yb(OTf)_3$ (229 mg, 0.43 mmol), BINOL (183 mg, 0.64 mmol), Et-N(iPr)$_2$ (0.28 mL, 1.6 mmol) and distilled DCM (5 mL). Under an atmosphere of dry argon the flask was closed with a suba seal and the reaction mixture was stirred for 1 h at room temperature. After that the diene (2.1 mmol) and the dienophile (21 mmol) were added by syringe as solutions in distilled DCM (10 mL). The reaction mixture was stirred at room temperature (20 °C) for 24 h. When complete, the mixture was poured into 70 mL of EtOAc and shaken with 20 mL of $NaHCO_3$ saturated aqueous solution for 5 minutes. Then the mixture was carefully acidified by concentrated aqueous HCl (till pH is equal to 1) and the organic layer was separated. The aqueous layer was extracted with EtOAc (2 × 50 mL), the combined organic fractions were dried over Na_2SO_4 and dried on a Büchi rotavap with addition of toluene (2 × 50 mL) and finally with DCM (2 × 10 mL), furnishing the product as a light brown oil.

For acid preparation a different work-up procedure can be used. When the reaction was finished, the reaction mixture was poured into EtOAc (150 mL) and the resulting solution was extracted with saturated aqueous $NaHCO_3$ (3 × 50 mL). Combined aqueous layers were washed with ether (200 mL) and carefully neutralized with concentrated HCl to pH = 3. Acidified aqueous layer was extracted with EtOAc (3 × 150 mL each), the combined organic fractions were dried over sodium sulfate and then the solvents were removed in vacuo.

Methyl *endo*-8-Ethoxy-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-carboxylate (36a).[12]

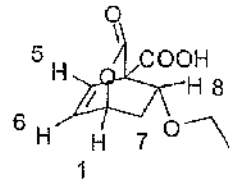
The compound was purified using column chromatography on silica (1.5 cm × 15 cm; petroleum ether – ethyl acetate gradient from 100:0 to 50:50). Isolated yield – 200 mg (68%) as a yellow oil.



36a

^{1}H-NMR (400 MHz; $CDCl_3$) δ 1.07 (t, J = 7.0 Hz, CH_3CH_2), 1.65 (dt, J = 13.9 and 1.5 Hz, *endo*-H-7), 2.57 (ddd, J = 13.9, 7.6 and 3.8 Hz, *exo*-H-7), 3.50 and 3.40 (dq, J_i = 9.6 and 7.0 Hz, CH_2CH_3), 3.88 (s, CH_3O), 4.34 (dd, J = 7.6 and 3.8 Hz, 8-H), 5.23 (m, 1-H), 6.58 (dd, J = 8.0 and 5.3 Hz, 6-H), 6.75 (d, J = 8.0 Hz, 5-H); ^{13}C-NMR (100 Hz; $CDCl_3$) δ 15.1 (CH_3CH_2), 35.4 (C-7), 52.8 (CH_3O), 62.0 (C-4), 65.6 (OCH_2), 72.4 (C-8), 74.3 (C-1), 129.7 (C-6), 130.7 (C-5), 172.2 (*C*=O), 174.5 (*C*=O) in accordance with the literature.[12]

***Endo*-8-ethoxy-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-carboxylic Acid (36b).**

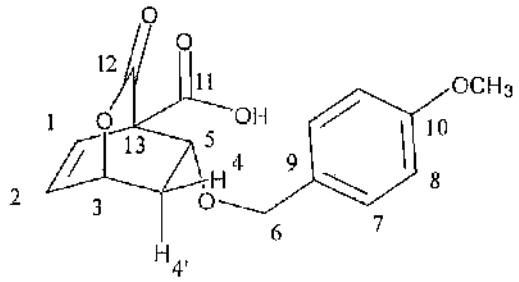


36b

The compound was not purified as it is unstable on column and does not crystallize. The crude mixture obtained (complete conversion of the starting acid, one product by NMR) was used directly in the radical reduction sequence. Brown oil.

^{1}H-NMR (400 MHz; DMSO-d_6) δ 6.67 (1H, dd, J = 7.8 and 5.0 Hz), 6.60 (1H, d, J = 7.8 Hz), 5.36 (1H, m), 4.26 (1H, m), 3.46 and 3.34 (1H each, dq, J = 9.8 and 6.8 Hz), 2.54 (1H, ddd, J = 13.9, 7.1 and 3.8 Hz), 1.56 (1H, J = 13.9 Hz), 1.17 (3H, t, J = 6.82 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ 15.3 (CH_3CH_2), 35.6 (C-7), 63.2 (C-4), 65.8 (OCH_2), 72.9 (C-8), 74.5 (C-1), 129.9 (C-6), 131.3 (C-5), 172.8 (C=O), 174.9 (C=O); IR (NaCl) ν 3550, 3035, 2968, 2950, 2934, 1764, 1755, 1612, 1362 cm^{-1}.

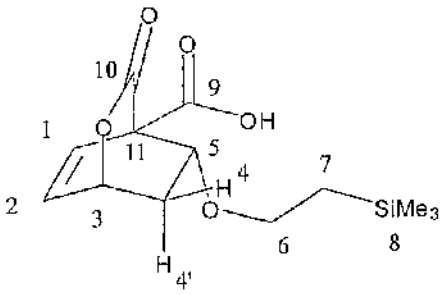
***Endo*-8-[(4-methoxybenzyl)oxy]-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-carboxylic Acid (36c).**



36c

^{1}H NMR (400 MHz; DMSO-d_6): 1.62 (dt, $J_{4\text{-H},4'\text{-H}}$ = 14.2 Hz, $J_{4'\text{-H},5\text{-H}}$ = $J_{4'\text{-H},3\text{-H}}$ = 1.7 Hz, 1H, 4'-H), 2.50 (ddd, $J_{4\text{-H},4'\text{-H}}$ = 14.2 Hz, $J_{4\text{-H},5\text{-H}}$ = 7.6 Hz, $J_{4\text{-H},3\text{-H}}$ = 3.8 Hz, 1H, 4-H), 3.73 (s, 3H, CH_3O), 4.31 (d, $J_{6\text{-H},6'\text{-H}}$ = 11.1 Hz, 1H, 6-H), 4.40 (dd, $J_{4\text{-H},5\text{-H}}$ = 7.6 Hz, $J_{4'\text{-H},5\text{-H}}$ = 1.7 Hz, 1H, 5-H), 4.42 (d, $J_{6\text{-H},6'\text{-H}}$ = 11.1 Hz, 1H, 6'-H), 5.37 (ddd, $J_{2\text{-H},3\text{-H}}$ = 5.0 Hz, $J_{4\text{-H},3\text{-H}}$ = 3.8 Hz, $J_{4'\text{-H},3\text{-H}}$ = 1.7 Hz, 1H, 3-H), 6.65 (br.d, $J_{1\text{-H},2\text{-H}}$ = 7.8 Hz, 1H, 1-H), 6.69 (dd, $J_{1\text{-H},2\text{-H}}$ = 7.8 Hz, $J_{2\text{-H},3\text{-H}}$ = 5.0 Hz, 1H, 2-H), 6.87 (d, $J_{7\text{-H},8\text{-H}}$ = 8.6 Hz, 1H, 8-H), 7.16 (d, $J_{7\text{-H},8\text{-H}}$ = 8.6 Hz, 1H, 7-H), 13.5 (br.s, 1H, OH); ^{13}C NMR (100 MHz; DMSO-d_6) δ 34.4 (4-C), 56.0 (CH_3O), 60.9 (13-C), 70.6 (6-C), 72.0 (5-C), 74.2 (3-C), 113.5 (8-C), 129.3 (9-C), 129.4 (1-C), 129.6 (7-C), 131.6 (2-C), 158.8 (10-C), 168.5 (12-C), 170.3 (11-C); (NaCl) ν 3590, 3032, 2972, 2951, 2932, 1763, 1758, 1612, 1503, 1381, 1362, 1260, 1121 cm^{-1}.

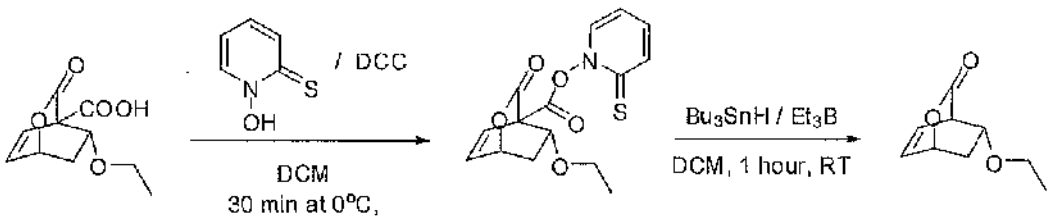
***Endo*-8-[(2-trimethylsilyl)ethoxy]-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-carboxylic Acid (36e)**



36e

^{1}H NMR (400 MHz, $CDCl_3$): -0.02 (s, 9H, 8-H), 0.78 – 0.92 (m, 2H, 7-H), 1.71 (dt, $J_{4\text{-}H,4'\text{-}H}$ = 13.9 Hz, $J_{4'\text{-}H,5\text{-}H}$ = $J_{4'\text{-}H,3\text{-}H}$ = 1.5 Hz, 1H, 4'-H), 2.62 (ddd, $J_{4\text{-}H,4'\text{-}H}$ = 13.9 Hz, $J_{4\text{-}H,5\text{-}H}$ = 7.6 Hz, $J_{4\text{-}H,3\text{-}H}$ = 3.7 Hz, 1H, 4-H), 3.61 – 3.48 (m, 2H, 6-H), 4.36 (dt, $J_{4\text{-}H,5\text{-}H}$ = 7.3 Hz, $J_{4'\text{-}H,5\text{-}H}$ = $J_{1\text{-}H,5\text{-}H}$ = 1.5 Hz, 1H, 5-H), 5.29 (ddt, $J_{2\text{-}H,3\text{-}H}$ = 5.1 Hz, $J_{4\text{-}H,3\text{-}H}$ = 3.7 Hz, $J_{4'\text{-}H,3\text{-}H}$ = $J_{1\text{-}H,3\text{-}H}$ = 1.5 Hz, 1H, 3-H), 6.63 (dd, $J_{1\text{-}H,2\text{-}H}$ = 7.8 Hz, $J_{2\text{-}H,3\text{-}H}$ = 5.1 Hz, 1H, 1-H), 6.79 (dt, $J_{1\text{-}H,2\text{-}H}$ = 7.8 Hz, $J_{1\text{-}H,5\text{-}H}$ = $J_{1\text{-}H,3\text{-}H}$ =1.5 Hz, 1H, 2-H); ^{13}C NMR (100 MHz; DMSO-d^6) δ 0.2 (8-C), 19.7 (7-C), 31.1 (4-C), 62.4 (11-C), 69.1 (6-C), 72.1 (5-C), 76.4 (3-C), 128.9 (*C*=C), 129.3 (C=*C*), 169.1 (10-C), 171.2 (9-C); (NaCl) ν 3520, 3033, 2963, 2952, 1762, 1751, 1610, 1362, 1105, 1008 cm^{-1}.

8-Ethoxy-2-oxabicyclo[2.2.2]oct-5-en-3-one (44a).[16,25]

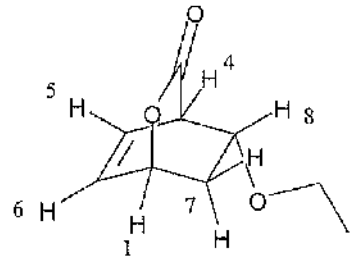


36b **12a** **44a**

The reaction was performed in a flask under argon, sealed with suba seal and wrapped with foil. To the crude endo-8-ethoxy-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-

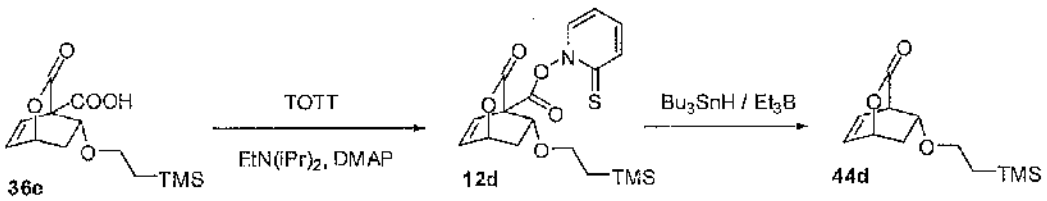
carboxylic acid **36b** (prepared as described above, 2.1 mmol) 1-hydroxypyridin-2(1*H*)-thione (2.4 mmol, 0.3 g) and distilled DCM (3 mL) was added. The reaction mixture was cooled to 0 °C and the solution of dicyclohexylcarbodiimide (3 mmol, 0.619 g) in distilled DCM (1 mL) was added to it in one portion by syringe. The reaction mixture was stirred at 0 °C for 30 min and then at room temperature for 3 h. Afterwards the suspension was filtered; the solid was washed by DCM (2 × 1.5 mL). The combined organic fractions were dried and the crude product was used in the next step.

The crude ester **12a** obtained above (2 mmol) was put in a 25 mL round-bottom flask followed by Bu_3SnH (10 mmol, 2.65 mL), DCM (7 mL), and Et_3B (1M solution in THF, 0.4 mmol, 0.4 mL) and the mixture was stirred at room temperature for 1 h. After the reaction was complete, the solution was poured into EtOAc (30 mL) and the resulting solution was washed with brine (2 × 10 mL) and dried over Na_2SO_4. Chromatography on silica (1.5 cm × 10 cm; Petroleum ether - EtOAc gradient from 100:0 to 50:50) gave the desired product as colourless oil (80 mg, 24% yield for 3 steps). The assignment was made by using HSQC, COSY NMR and according to the spin-spin interaction constants analysis published.[110]

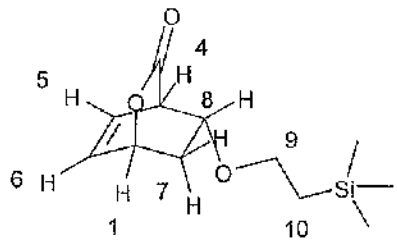


^{1}H-NMR (400 MHz; DMSO-d_6) δ 1.16 (t, J = 7.1 Hz, CH_3CH_2), 1.54 (m, *endo*-7-H), 2.53 (ddd, J = 13.9, 7.8 Hz and 3.8 Hz, *exo*-7-H), 3.54 and 3.43 (dq, J = 9.1 and 7.1 Hz, OCH_2), 3.92 (m, 4-H), 3.98 (m, 8-H), 5.20 (m, 1-H), 6.37 (m, 5-H), 6.59 (ddd, J_1 = 7.83, 5.0 and 1.5 Hz, 6-H); ^{13}C-NMR (100 Hz; $CDCl_3$) δ 15.2 (CH_3CH_2), 35.1 (7-C), 46.6 (4-C), 64.6 (OCH_2), 70.5 (8-C), 73.9 (1-C), 128.9 (5-C), 131.6 (6-C), 172.3 (*C*=O); IR (NaCl) ν 3033, 2965, 2952, 2932, 1761, 1614, 1363 cm^{-1}.

8-(2-Trimethylsilanyl-ethoxy)-2-oxabicyclo[2.2.2]oct-5-en-3-one



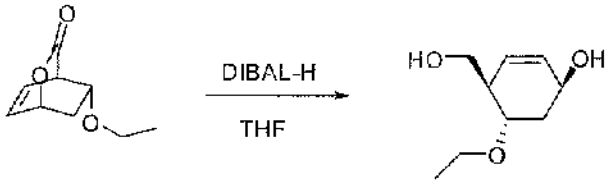
Endo-8-[(2-trimethylsilyl)ethoxy]-3-oxo-2-oxabicyclo[2.2.2]oct-5-ene-4-carboxylic acid **36e** (600 mg, 2.1 mmol), TOTT (S-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiouronium tetrafluoroborate; 940 mg, 3.0 mmol), Hünig base (1.1 mL, 6.3 mmol) and DMAP (25.6 mg, 0.21 mmol) were subsequently dissolved in the mixture of THF (100 mL) and CH_3CN (30 mL) and stirred at room temperature. Bu_3SnH (2.65 mL, 10 mmol) was added to the reaction mixture followed by Et_3B (1M solution in THF, 0.4 mmol, 0.4 mL) and it was kept stirring ar room temperature for another 2 h. Once **12d** was consumed (checked by ^1H NMR of an aliquote) the reaction mixture was diluted with EtOAc (400 mL) and the resulting solution was subsequently washed with 1M NH_4Cl solution (2×150 mL) and brine (2×200 mL) and dried over Na_2SO_4. The product **44d** was purified using colomn chromatography on silica (2 cm × 15 cm; gradient petroleum ether – EtOAc from 100:0 to 70:30) to afford yellowish oil (216 mg, 43 % yield).



^1H-NMR (400 MHz; DMSO-d_6) δ 0.21 (s, 9H, TMS), 0.32 – 0.46 (2H, m, 10-H), 1.47 – 1.55 (1H, m, *endo*-7-H), 2.50 (1H, ddd, J = 13.9, 7.9 Hz and 3.8 Hz, *exo*-7-H), 3.52 and 3.41 (2H, dq, J = 9.1 and 7.1 Hz, 9-H), 3.87 – 3.95 (1H, m, 4-H), 3.92 – 4.01 (1H, m, 8-H), 5.12 – 5.20 (1H, m, 1-H), 6.30 – 6.39 (1H, m, 5-H), 6.59 (1H, ddd, J_1 = 7.9, 5.1 and 1.4 Hz, 6-H); ^{13}C-NMR (100 Hz; $CDCl_3$) δ 1.2 (TMS), 5.0 (10-C), 34.7 (7-C), 46.2 (4-C),

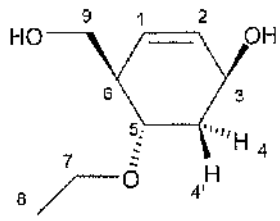
64.0 (9-C), 70.1 (8-C), 73.6 (1-C), 128.5 (5-C), 131.0 (6-C), 171.8 (*C*=O); IR (NaCl) ν 3031, 2962, 2955, 2934, 1760, 1611, 1361, 1230, 1002 cm^{-1}.

(1*S,4*R**,5*R**)-(±)-5-Ethoxy-4-(hydroxymethyl)-2-cyclohexen-1-ol (47a)**



44a **47a**

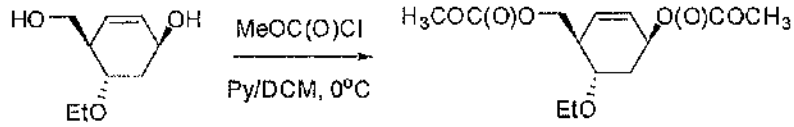
A solution of DIBAL-H (2.4 mL of 1.5M solution in toluene, 3.6 mmol) was carefully added to a solution of lactone **44a** (150 mg, 0.9 mmol) in THF (20 mL) at 0 °C (ice bath). When the addition was finished, the cooling bath was removed and the reaction mixture was allowed to stir at room temperature for 3 h. The excess of DIBAL-H was quenched by addition of EtOAc at 0 °C; the m ixture was stirred for an additional 15 min and then diluted with EtOAc (150 mL) and stirred with a saturated aqueous solution of sodium-potassium tartrate at room temperature for 12 h. Afterwards the organic layer was separated and the aqueous layer was extracted with EtOAc (3×100 mL). Combined organic fractions were dried over Na_2SO_4 and evaporated in vacuo giving the desired product **47a** as slightly yellowish oil (140 mg, 92%).



^{1}H NMR (400 MHz; $CDCl_3$): 1.22 (t, $J_{7\text{-H,8-H}}$ = 7.1 Hz, 3H, 8-H), 1.80 (ddd, $J_{4\text{-H,4'-H}}$ = 13.2 Hz, $J_{4\text{-H,5-H}}$ = 11.3 Hz, $J_{4\text{-H,3-H}}$ = 4.5 Hz, 1H, 4-H), 2.21 (dtd, $J_{4\text{-H,4'-H}}$ = 13.2 Hz, $J_{4'\text{-H,5-H}}$ = $J_{4'\text{-H,3-H}}$ = 3.3 Hz, $J_{4'\text{-H,2-H}}$ = 1.0 Hz, 1H, 4'-H), 2.32 – 2.38 (m, 1H, 6-H), 3.47 (dq,

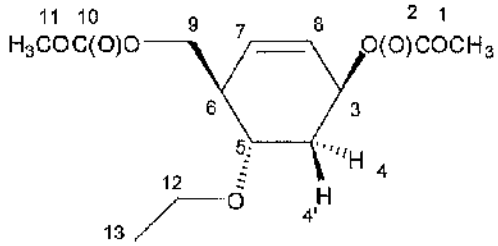
$J_{7\text{-H},7'\text{-H}}$ = 9.1 Hz, $J_{7\text{-H},8\text{-H}}$ = 7.1 Hz, 1H, 7-H), 3.64 – 3.78 (m, 4H, 7'-H, 5-H, 9-H), 4.32 – 4.37 (m, 1H, 3-H), 5.58 (dd, $J_{1\text{-H},2\text{-H}}$ = 9.8 Hz, $J_{1\text{-H},3\text{-H}}$ = 2.3 Hz,1H, 1-H), 5.88 (dddd, $J_{1\text{-H},2\text{-H}}$ = 9.8 Hz, $J_{2\text{-H},3\text{-H}}$ = 4.5 Hz, $J_{2\text{-H},6\text{-H}}$ = 2.3 Hz, $J_{4'\text{-H},2\text{-H}}$ = 1.0 Hz, 1H, 2-H); ^{13}C NMR (100 MHz): 15.7 (8-C), 35.4 (4-C), 44.8 (6-C), 64.6 (7-C), 65.1 (3-C), 66.0 (9-C), 75.3 (5-C), 129.7 (1-C), 128.8 (2-C); IR (NaCl) ν 3410, 3340, 3032, 2962, 2950, 2931, 1609, 1363, 1240 cm^{-1}; MS (CI) *m/z* (%) 173 (40, M^++H), 93 (100); HRMS (CI) *m/z* 173.1180 ($C_9H_{17}O_3$ requires 173.1178).

{(1*R**,4*S**,6*R**)-(±)-6-Ethoxy-4-[(methoxycarbonyl)oxy]-2-cyclohexen-1-yl}methyl Methyl Carbonate (48a).



47a **48a**

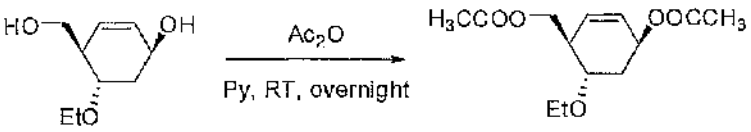
Methylchloroformate (1.15 mL, 17 mmol) was added to a solution of **47a** (crude, 480 mg, 2.8 mmol) in dry DCM (30 mL) and pyridine (2.5 mL) upon stirring at 0 °C. After a few minutes evolution of CO_2 was observed. The reaction mixture was stirred at 0 °C for 1.5 h, then diluted with EtOAc (150 mL) and the resulting solution was washed with saturated $NaHCO_3$ solution (2×30 mL) and brine (2×30 mL). The organic layer was dried over Na_2SO_4, the organic solvents were evaporated under reduced pressure, and the crude product was purified by using column chromatography on neutral Al_2O_3 (2 cm × 15 cm; pertroleum ether – EtOAc gradient from 100:0 to 50:50) to afford the pure product **48a** as colourless oil (300 mg, 36%).



^{1}H NMR (400 MHz; $CDCl_3$): 1.19 (t, $J_{13\text{-H},12\text{-H}}$ = 7.1 Hz, 3H, 13-H), 1.82 (ddd, $J_{4\text{-H},4'\text{-H}}$ = 13.9 Hz, $J_{4\text{-H},5\text{-H}}$ = 10.6 Hz, $J_{4\text{-H},3\text{-H}}$ = 4.8 Hz, 1H, 4-H), 2.24 (dtd, $J_{4\text{-H},4'\text{-H}}$ = 13.9 Hz, $J_{4'\text{-}}$

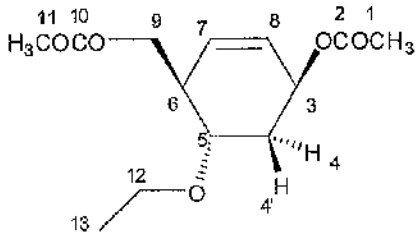
$_{H,5\text{-}H}$ = $J_{4'\text{-}H,3\text{-}H}$ = 3.3 Hz, $J_{4'\text{-}H,8\text{-}H}$ = 0.8 Hz, 1H, 4'-H), 2.41 – 2.48 (m, 1H, 6-H), 3.42 (dq, $J_{12\text{-}H,12'\text{-}H}$ = 9.4 Hz, $J_{12\text{-}H,13\text{-}H}$ = 7.1 Hz, 1H, 12-H), 3.53 (ddd, $J_{5\text{-}H,4\text{-}H}$ = 10.6 Hz, $J_{5\text{-}H,6\text{-}H}$ = 8.1 Hz, $J_{4'\text{-}H,5\text{-}H}$ = 3.3 Hz, 1H, 5-H), 3.66 (dq, $J_{12\text{-}H,12'\text{-}H}$ = 9.4 Hz, $J_{12\text{-}H,13\text{-}H}$ = 7.1 Hz, 1H, 12'-H), 3.78 (s, 6H, 11-H and 1-H), 4.19 (dd, $J_{9\text{-}H,9'\text{-}H}$ = 10.6 Hz, $J_{9\text{-}H,6\text{-}H}$ = 6.3 Hz, 1H, 9-H), 4.34 (dd, $J_{9\text{-}H,9'\text{-}H}$ = 10.6 Hz, $J_{9'\text{-}H,6\text{-}H}$ = 4.8 Hz, 1H, 9'-H), 5.22 – 5.25 (m, 1H, 3-H), 5.85 (dd, $J_{7\text{-}H,8\text{-}H}$ = 10.1 Hz, $J_{7\text{-}H,3\text{-}H}$ = 2.0 Hz, 1H, 7-H), 5.88 – 5.93 (m, 1H, 8-H); ^{13}C NMR (100 MHz; $CDCl_3$) 15.6 (13-C), 32.5 (4-C), 42.3 (6-C), 54.8 (OCH_3), 55.0 (OCH_3), 64.5 (12-C), 67.8 (9-C), 71.5 (3-C), 71.6 (5-C), 125.8 (8-C), 131.8 (7-C), 155.4 (2-C), 155.9 (10-C); IR (NaCl) ν 3030, 2963, 2952, 2933, 1737, 1610, 1361, 1234 cm^{-1}; MS (CI) *m/z* (%) 289 (M+H, 20), 93 (100); HRMS (CI) *m/z* 289.1289 ($C_{13}H_{21}O_7$ requires 289.1287).

[(1*R,4*S**,6*R**)-(±)-4-(Acetyloxy)-6-ethoxycyclohex-2-en-1-yl]methyl Acetate (49a)**



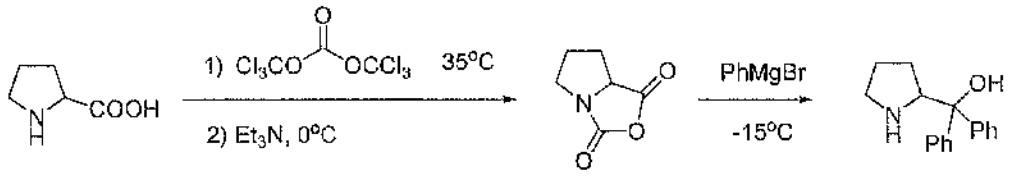
47a **49a**

Acetic anhydride (567 µl, 6 mmol) was added to a solution of **47a** (crude, 345 mg, 2 mmol) in dry pyridine (20 mL) at 0 °C (ice bath) upon stirring. After 1 h the cooling bath was removed and the reaction mixture was allowed to stir overnight at room temperature. Afterwards the reaction mixture was diluted with EtOAc (300 mL) and the resulting solution was washed with saturated solution of $NaHCO_3$ (100 mL). The aqueous layer was extracted with EtOAc (2×100 mL), the combined organic layers were dried over Na_2SO_4, and the solvents were evaporated under reduced pressure (to remove pyridine, evaporation with toluene was used). The crude product was purified by column chromatography on silica (2 cm ×15 cm) (petroleum ether – EtOAc gradient from 100:0 to 50:50) to afford pure **49a** (300 mg, 59%) as a colourless oil, crystallising upon standing.



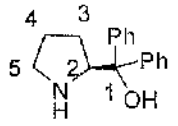
Mp 33 – 35 °C; ^{1}H NMR (400 MHz; $CDCl_3$): 1.19 (t, $J_{13\text{-H},12\text{-H}}$ = 6.8 Hz, 3H, 13-H), 1.80 (ddd, $J_{4\text{-H},4'\text{-H}}$ = 13.6 Hz, $J_{4\text{-H},5\text{-H}}$ = 10.4 Hz, $J_{4\text{-H},3\text{-H}}$ = 4.8 Hz, 1H, 4-H), 2.05 (s, 3H, CH_3CO), 2.07 (s, 3H, CH_3CO), 2.12 (dt, $J_{4\text{-H},4'\text{-H}}$ = 13.6 Hz, $J_{4'\text{-H},5\text{-H}}$ = $J_{4'\text{-H},3\text{-H}}$ = 3.5 Hz, 1H, 4'-H), 2.39 – 2.45 (m, 1H, 6-H), 3.40 (dq, $J_{12\text{-H},12'\text{-H}}$ = 9.1 Hz, $J_{12\text{-H},13\text{-H}}$ = 6.8 Hz, 1H, 12-H), 3.48 (ddd, $J_{5\text{-H},4\text{-H}}$ = 10.4 Hz, $J_{5\text{-H},6\text{-H}}$ = 8.0 Hz, $J_{4'\text{-H},5\text{-H}}$ = 3.5 Hz, 1H, 5-H), 3.66 (dq, $J_{12\text{-H},12'\text{-H}}$ = 9.1 Hz, $J_{12\text{-H},13\text{-H}}$ = 6.8 Hz, 1H, 12'-H), 4.09 (dd, $J_{9\text{-H},9'\text{-H}}$ = 10.9 Hz, $J_{9\text{-H},6\text{-H}}$ = 6.3 Hz, 1H, 9-H), 4.28 (dd, $J_{9\text{-H},9'\text{-H}}$ = 10.9 Hz, $J_{9'\text{-H},6\text{-H}}$ = 4.8 Hz, 1H, 9'-H), 5.34 – 5.39 (m, 1H, 3-H), 5.77 – 5.85 (m, 2H, 7-H and 8-H); ^{13}C NMR (100 MHz; $CDCl_3$): 15.6 (13-C), 21.0 (1-C), 21.4 (11-C), 32.4 (4-C), 42.1 (6-C), 64.4 (12-C), 64.6 (9-C), 67.8 (3-C), 72.2 (5-C), 126.3 (8-C), 131.4 (7-C), 170.6 (2-C), 171.2 (10-C); IR (NaCl) ν 3031, 2964, 2954, 2931, 1752, 1612, 1382, 1225 cm^{-1}; MS (FAB) *m/z* (%) 257 (M+H, 10), 198 (80), 93 (100); HRMS (FAB) *m/z* 257.1385 ($C_{13}H_{21}O_5$ requires 257.1389).

Diphenyl(2-pyrrolidinyl)methanol (42d).[111]



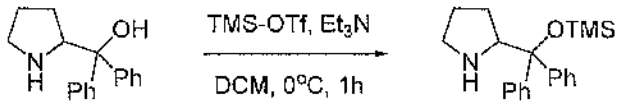
A solution of triphosgene (900 mg, 3 mmol) in THF (10 mL) was added to a suspension of (*S*)-proline (805 mg, 7 mmol) in dry THF (15 mL) at 0 °C (ice bath) over a 30 min period. The reaction was stirred at 35 °C for 1.5 h, which resulted in a homogeneous yellowish solution. The latter solution was evaporated carefully in vacuo (phosgene!) and after diluted with 10 mL of dry THF. Et_3N (1.1 mL, 7.5 mmol) was

added to the latter solution over a period of 15 min, which resulted in the precipitation of $Et_3N{\times}HCl$. The mixture was stirred for 30 min at 0 °C and the precipitate was filtered off. The filtrate was slowly added to a pre-cooled (to –15 °C) solution of PhMgBr in THF (21 mL of 1M solution, 21 mmol) for a period of 1 h and the reaction mixture was stirred for an additional 3 h. The solution thus obtained was carefully quenched by 2M H_2SO_4 (100 mL) and washed with ether (3×100 mL). NaOH solution was carefully added until pH reached 12 and the desired aminoalcohol was extracted by EtOAc (3×200 mL). Combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The crude product (1.7 g) isolated was not very pure according to ^1H or ^{13}C NMR spectra and was purified as an oxalate by crystallization (from THF) to give the pure product **42d** (600 mg, 35%) as a white crystalline solid.



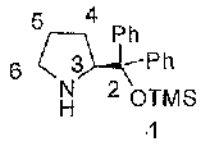
^1H NMR (400 MHz; $CDCl_3$): 1.52 – 1.77 (m, 4H, 3-H and 4-H), 2.90 – 3.05 (m, 2H, 5-H), 4.26 (t, $J_{2\text{-}H,3\text{-}H}$ = 7.8 Hz, 1H, 2-H), 7.13 – 7.19 (m, 2H, Ph), 7.25 – 7.32 (m, 4H, Ph), 7.48 – 7.51 (m, 2H, Ph), 7.55 – 7.59 (m, 2H, Ph); ^{13}C NMR (100 MHz; $CDCl_3$): 25.6 (3-C), 26.4 (4-C), 46.9 (5-C), 64.6 (2-C), 77.2 (1-C), 125.7 (Ph), 126.0 (Ph), 126.5 (Ph), 126.6 (Ph), 128.1 (Ph), 128.4 (Ph), 145.5 (Ph, ipso-*C*), 148.2 (Ph, ipso-*C*) in accordance with the literature.[111]

Diphenyl(2-pyrrolidinyl)methyl trimethylsilyl ether (42j).[112]



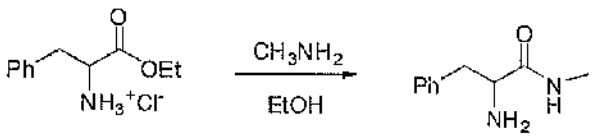
Trimethylsilyl triflate (580 μL, 3 mmol) was added carefully to a solution of aminoalcohol **42d** (590 mg, 2.3 mmol) and Et_3N (350 μl, 2.5 mmol) in dry DCM (20 mL)

at 0 °C (ice bath) upon stirring. The cooling bath was then removed and the mixture was stirred at room temperature for an additional 1 h. The reaction mixture was then diluted with DCM (200 mL) and water (100 mL). The organic layer was saperated, and the aqueous layer was extracted with DCM (2×100 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure to afford **42j** (700 mg, 93%) as yellowish oil that did not require further purification.

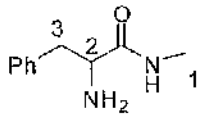


^{1}H NMR (400 MHz; $CDCl_3$): -0.09 (s, 9H, 1-H), 1.46 – 1.38 (m, 1H, 4-H), 1.81 – 1.67 (m, 3H, 4'-H and 5-H), 2.76 (dt, $J_{6\text{-H},6'\text{-H}}$ = 10.4 Hz, $J_{6\text{-H},5\text{-H}}$ = 7.3 Hz, 1H, 6-H), 2.96 (dt, $J_{6\text{-H},6'\text{-H}}$ = 10.4 Hz, $J_{6'\text{-H},5\text{-H}}$ = 7.1 Hz, 1H, 6'-H), 4.26 (t, $J_{3\text{-H},4\text{-H}}$ = 7.3 Hz, 1H, 3-H), 7.26 – 7.37 (m, 8H, Ph), 7.41 – 7.45 (m, 2H, Ph); ^{13}C NMR (100 MHz; $CDCl_3$): 2.33 (1-C), 24.9 (4-C), 27.5 (5-C), 47.2 (6-C), 66.1 (3-C), 82.9 (2-C), 127.4 (Ph), 127.6 (Ph), 127.9 (Ph), 128.0 (Ph), 128.0 (Ph), 128.5 (Ph), 144.7 (Ph, ipso-*C*), 145.1 (Ph, ipso-*C*) in agreement with the literature.[112]

2-Amino-*N*-methyl-3-phenylpropanamide (42k).[113]

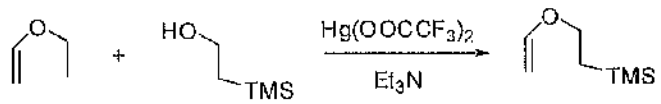


Ethyl ester of phenylalanine hydrochloride (2.00 g, 9.3 mmol) was dissolved in ethanolic CH_3NH_2 (10 mL of 33% solution, 80 mmol) and stirred at room temperature for 2 days. The reaction mixture was then diluted with EtOAc (200 mL) and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and evaporated in vacuo, giving the desired compound amide **42k** (1.54 g, 93%) as a white solid.



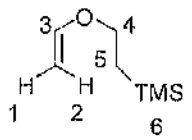
^{1}H NMR (400 MHz; DMSO-d_6): 2.56 (d, $J_{1\text{-H},NH}$ = 4.7 Hz, 3H, 1-H), 2.65 (dd, $J_{3\text{-H},3'\text{-H}}$ = 13.3 Hz, $J_{3\text{-H},2\text{-H}}$ = 8.0 Hz, 1H, 3-H), 2.92 (dd, $J_{3\text{-H},3'\text{-H}}$ = 13.3 Hz, $J_{3'\text{-H},2\text{-H}}$ = 5.3 Hz, 1H, 3'-H), 7.16 – 7.22 (m, 3H, Ph), 7.25 – 7.30 (m, 2H, Ph), 8.00 (q, $J_{NH,1\text{-H}}$ = 4.7 Hz, 1H, N*H*); ^{13}C NMR (100 MHz; DMSO-d_6): 25.3 (1-C), 40.5 (3-C), 55.9 (2-C), 126.1 (Ph), 128.1 (Ph), 129.2 (Ph), 138.3 (ipso-*C*, Ph), 173.7 (*C*=O)

2-(Trimethylsilyl)ethyl vinyl ether (11d).[48]



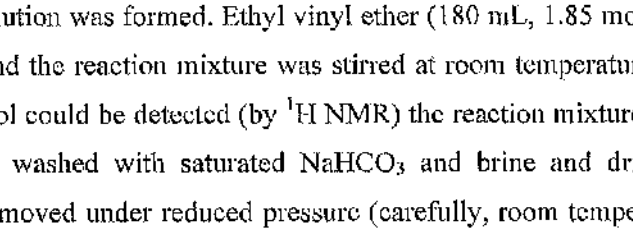
11d

2-Trimethylsilyl alcohol (40 mmol, 5.74 mL), $Hg(OOCCF_3)_2$ (0.85 g, 2 mmol) and Et_3N (0.56 mL, 4 mmol) were mixed together at 0 °C forming a homogeneous solution. Ethyl vinyl ether (200 mL) was added to the latter solution and the reaction mixture was stirred at room temperature for 3 days. When no starting alcohol could be detected (by ^{1}H NMR), the reaction mixture was diluted with ether (200 mL), washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Solvents were removed under reduced pressure (carefully, room temperature, 300 mbar) and the crude product **11d** was distilled (61–63 °C/60 mmHg) giving the desired compound **11d** (5.77 g, 64%) as colourless oil with specific smell.



^{1}H NMR (400 MHz; $CDCl_3$): 0.04 (s, 9H, 6-H), 1.01 (m, 2H, 5-H), 3.77 (m, 2H, 4-H), 3.97 (dd, $J_{1\text{-H},3\text{-H}}$ = 6.8 Hz, $J_{1\text{-H},2\text{-H}}$ = 1.8 Hz, 1H, 1-H), 4.16 (dd, $J_{2\text{-H},3\text{-H}}$ = 14.4 Hz, $J_{1\text{-H},2\text{-H}}$ = 1.8 Hz, 1H, 2-H), 6.45 (dd, $J_{1\text{-H},3\text{-H}}$ = 6.8 Hz, $J_{3\text{-H},2\text{-H}}$ = 14.4 Hz, 1H, 3-H); ^{13}C NMR (100 MHz; $CDCl_3$): -1.3 (6-C), 17.6 (5-C), 65.7 (4-C), 86.4 ((1+2)-C), 151.9 (3-C) in acc.ordance with the literature.[4]

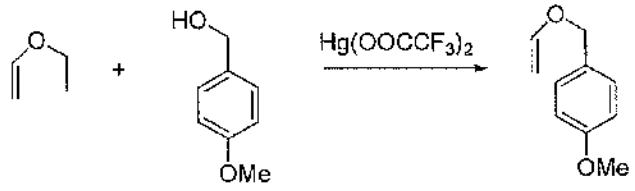
Benzyl vinyl ether (11b).[47,a]



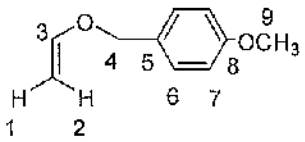
Benzyl alcohol (38.3 mL, 0.37 mol) was stirred with $Hg(OOCCF_3)_2$ at 0°C until a homogeneous solution was formed. Ethyl vinyl ether (180 mL, 1.85 mol) was then added to the solution and the reaction mixture was stirred at room temperature for 12 h. When no starting alcohol could be detected (by ^{1}H NMR) the reaction mixture was diluted with ether (500 mL), washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Solvents were removed under reduced pressure (carefully, room temperature, 100 mbar) and the final product was distilled using a water pump and column (bp 50–53 °C / 15 mmHg) giving the desired compound **11b** (24.3 g, 50%) as colourless oil with specific smell.

^{1}H NMR (400 MHz; $CDCl_3$): 4.14 (dd, $J_{1\text{-H},3\text{-H}}$ = 6.8 Hz, $J_{1\text{-H},2\text{-H}}$ = 2.0 Hz, 1H, 1-H), 4.36 (dd, $J_{2\text{-H},3\text{-H}}$ = 14.3 Hz, $J_{1\text{-H},2\text{-H}}$ = 2.0 Hz, 1H, 2-H), 4.80 (s, 2H, 4-H), 6.63 (dd, $J_{1\text{-H},3\text{-H}}$ = 6.8 Hz, $J_{3\text{-H},2\text{-H}}$ = 14.3 Hz, 1H, 3-H), 7.34 – 7.45 (m, 5H, Ph); ^{13}C NMR (100 MHz; $CDCl_3$): 70.1 (4-C), 87.4 ((1+2)-C), 127.6 (Ph), 128.0 (Ph), 128.6 (Ph), 137.0 (Ph, *ipso-C*), 151.7 (3-C).

1-Methoxy-4-[(vinyloxy)methyl]benzene (11c).[47,a]

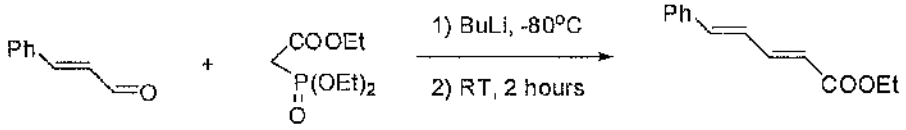


p-Methoxybenzyl alcohol (40 g, 0.29 mol) was stirred with $Hg(OOCCF_3)_2$ at 0 °C until a homogeneous solution formed. Ethyl vinyl ether (140 mL, 1.45 mol) was then added to the solution and the reaction mixture was stirred at room temperature for 12 h. When no starting alcohol could be detected (by ^1H NMR) the reaction mixture was diluted with ether (500 mL), washed with saturated $NaHCO_3$ and brine and dried over Na_2SO_4. Solvents were removed under reduced pressure (carefully, room temperature, 100 mbar) and the crude product was distilled using a membrane pump and column (53–62 °C/0.4 mmHg) giving the desired compound **11c** (36.4 g, 77%) as colourless oil with specific smell.

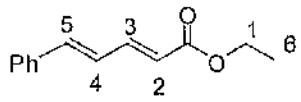


^1H NMR (400 MHz; $CDCl_3$): 3.81 (s, 3H, 9-H), 4.08 (dd, $J_{1\text{-}H,3\text{-}H}$ = 6.8 Hz, $J_{1\text{-}H,2\text{-}H}$ = 2.1 Hz, 1H, 1-H), 4.30 (dd, $J_{2\text{-}H,3\text{-}H}$ = 14.3 Hz, $J_{1\text{-}H,2\text{-}H}$ = 2.1 Hz, 1H, 2-H), 4.69 (s, 2H, 4-H), 6.90 (dd, $J_{1\text{-}H,3\text{-}H}$ = 6.8 Hz, $J_{3\text{-}H,2\text{-}H}$ = 14.3 Hz, 1H, 3-H), 6.90 (d, $J_{6\text{-}H,7\text{-}H}$ = 8.7 Hz, 2H, 7-H), 7.29 (d, $J_{6\text{-}H,7\text{-}H}$ = 8.7 Hz, 2H, 6-H); ^{13}C NMR (100 MHz; $CDCl_3$): 55.5 (9-C), 70.1 (4-C), 87.1 ((1+2)-C), 114.1 (7-C), 129.1 (5-C), 129.4 (6-C), 151.9 (3-C), 159.6 (8-C) in accordance with the literature.[47a]

Ethyl (2*E*,4*E*)-5-Phenyl-2,4-pentadienoate (112).[114]

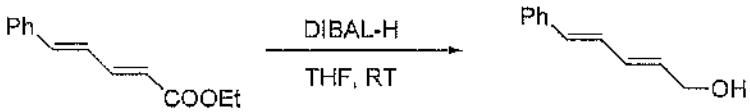


n-Butyllithium solution (40 mL of 2M solution in pentane, 80 mmol) was slowly added to a solution of triethylphosphonoacetate (15.1 mL, 76 mmol) in dry THF (100 mL) at –80 °C (ethyl acetate – liquid nitrogen) to produce an orange suspension. The mixture was stirred at –80 °C for 1 h and then cinnamic aldehyde (10.0 g; 76 mmol, in 20 mL of THF) was added, followed by removing of the cooling bath and the mixture was allowed to stir at room temperature for 2 h. The mixture was then diluted with EtOAc (1 L) and washed with brine (3×300 mL). The organic layer was dried over Na_2SO_4 and the solvents were removed under reduced pressure. The product **112** was obtained as yellow oil (13 g, 85%), reasonably pure by ^{1}H NMR (about 96%), and suitable for the following step without further purification.

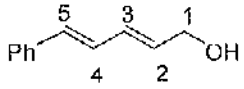


^{1}H NMR (400 MHz; $CDCl_3$): 1.32 (t, $J_{1\text{-H},6\text{-H}}$ = 7.1 Hz, 3H, 6-H), 4.23 (q, $J_{1\text{-H},6\text{-H}}$ = 7.1 Hz, 2H, 1-H), 5.99 (d, $J_{2\text{-H},3\text{-H}}$ = 15.2 Hz, 1H, 2-H), 6.83 – 6.93 (m, 2H, 3-H and 4-H), 7.28 – 7.39 (m, 3H, Ph and 5-H), 7.41 – 7.49 (m, 3H, Ph); ^{13}C NMR (100 MHz; $CDCl_3$): 14.4 (6-C), 60.4 (1-C), 121.4 (2-C), 126.3 (3-C), 127.3 (Ph), 128.9 (Ph), 129.2 (Ph), 136.1 (Ph, ipso-*C*), 140.5 (4-C), 144.6 (5-C), 167.2 (*C*=O).

(2*E*,4*E*)-5-Phenyl-2,4-pentadien-1-ol (113).[115]

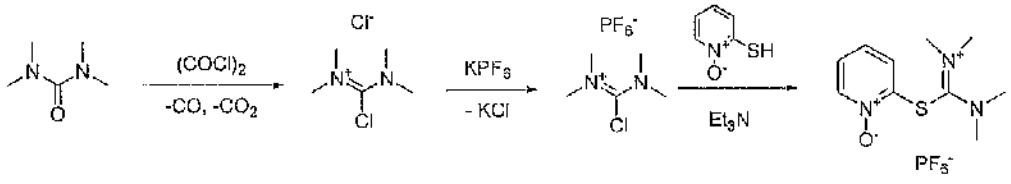


DIBAL-H (27 mL of 1.5M solution in toluene, 40 mmol) was slowly added to a solution of ethyl (2*E*,4*E*)-5-phenyl-2,4-pentadienoate (3.29 g, 16 mmol) was in dry THF (150 mL) at 0 °C (ice bath). When the addition was complete, the cooling bath was removed and the reaction was allowed to stir at room temperature for 2 h. The excess of DIBAL-H was quenched by EtOAc (50 mL) at 0 °C and the mixture was stirred for an additional 15 minutes, then diluted with EtOAc (600 mL) and stirred with a saturated aqueous solution of sodium-potassium tartrate (300 mL) at room temperature overnight. The organic layer was separated and the aqueous layer was extracted with EtOAc (3×300 mL). Combined organic fractions were dried over Na_2SO_4 and evaporated in vacuo to give **113** (2.3 g, 90%) as a slightly yellowish oil.

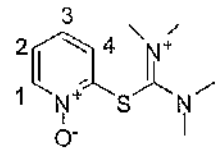


^{1}H NMR (400 MHz; $CDCl_3$): 1.40 (t, $J_{OH,1\text{-}H}$ = 5.8 Hz, 1H, O*H*), 4.26 (t, $J_{OH,1\text{-}H} = J_{1\text{-}H,2\text{-}H}$ = 5.8 Hz, 2H, 1-H), 5.97 (dt, $J_{2\text{-}H,3\text{-}H}$ = 15.2 Hz, $J_{1\text{-}H,2\text{-}H}$ = 5.8 Hz, 1H, 2-H), 6.43 (dd, $J_{2\text{-}H,3\text{-}H}$ = 15.2 Hz, $J_{3\text{-}H,4\text{-}H}$ = 10.6 Hz, 1H, 3-H), 6.56 (d, $J_{4\text{-}H,5\text{-}H}$ = 15.7 Hz, 1H, 5-H), 6.79 (dd, $J_{4\text{-}H,5\text{-}H}$ = 15.7 Hz, $J_{3\text{-}H,4\text{-}H}$ = 10.6 Hz, 1H, 4-H), 7.20 – 7.42 (m, 5H, Ph); ^{13}C NMR (100 MHz; $CDCl_3$): 63.6 (1-C), 126.5 (Ph), 127.8 (Ph), 128.2 (4-C), 128.8 (Ph), 131.8 (3-C), 132.6 (2-C), 132.9 (5-C), 137.2 (Ph, ipso-*C*).

_N_-{(Dimethylamino)[(1-oxido-2-pyridinyl)sulfanyl]methylene}-_N_-methylmethanaminium Hexafluorophosphate (19a).[21]



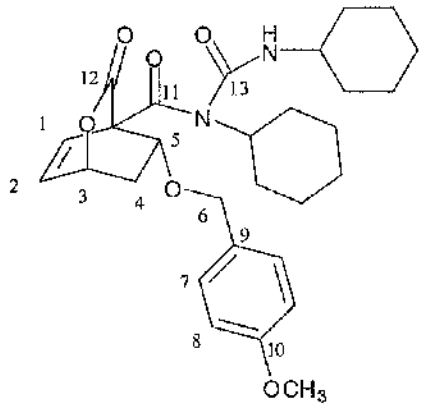
Tetramethylurea (4.8 mL, 40 mmol), DMF (0.3 mL) and dry DCM (40 mL) were mixed together and cooled down to 0 °C. Oxalyl chloride was added dropwise to the mixture while not allowing the temperature of the reaction to reach 15 °C. When the addition was complete, the reaction mixture was stirred at room temperature for 1 h and then refluxed for 4 h. The solvents were then evaporated under the reduced pressure (two times after the first evaporation with DCM) and the solid thus obtained was added to a solution of KPF_6 (8.8 g, 48 mmol) in dry CH_3CN (40 mL) and the mixture was stirred at room temperature for 24 h. *N*-Hydroxythiopyridone (5.1 g, 40 mmol) was then added to the mixture, followed by Et_3N (6.7 mL, 48 mmol) at 0 °C and the resulting mixture was stirred at room temperature for 5 h and then at 45 °C for 1 h. The mixture was filtered through celite, the solvents were removed under reduced pressure, and the residue was crystallized by addition of a mixture of MeOH and *i*-PrOH (1:3) to the oil. The precipitate was isolated by filtration and washed with *i*-PrOH and dried in vacuo to afford **19a** (10 g, 67% as yellow crystals).



PF_6^-

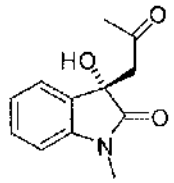
^{1}H NMR (400 MHz; DMSO-d^6): 3.20 (s, 12H, C*H*$_3$), 7.51 (td, $J_{3\text{-H},4\text{-H}} = J_{3\text{-H},2\text{-H}} = 7.8$ Hz, $J_{1\text{-H},3\text{-H}} = 1.5$ Hz, 1H, 3-H), 7.57 (ddd, $J_{3\text{-H},2\text{-H}} = 7.8$ Hz, $J_{1\text{-H},2\text{-H}} = 6.4$ Hz, $J_{2\text{-H},4\text{-H}} = 2.0$ Hz, 1H, 2-H), 7.86 (dd, $J_{3\text{-H},4\text{-H}} = 7.8$ Hz, $J_{2\text{-H},4\text{-H}} = 2.0$ Hz, 1H, 4-H), 8.50 (dd, $J_{1\text{-H},2\text{-H}} = 6.4$ Hz, $J_{1\text{-H},3\text{-H}} = 1.5$ Hz, 1H, 1-H); ^{13}C NMR (100 MHz; DMSO-d^6): 43.5 (*C*H$_3$), 126.6 (2-C), 126.9 (3-C), 129.7 (4-C), 139.7 (1-C), 140.7 (ipso-C), 168.4 (*C*=N$^+$).

N,*N*'-Dicyclohexyl-*N*-({8-[(4-methoxybenzyl)oxy]-3-oxo-2-oxabicyclo[2.2.2]oct-5-en-4-yl}carbonyl)urea (113)



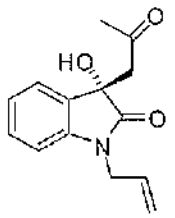
^{1}H NMR (400 MHz; $CDCl_3$): 1.0 – 1.9 (m, 21H, Cy (only C*H*$_2$-groups) and 4-H (endo)), 2.41 (m, 1H, 4-H (exo)), 3.50 (m, 1H, C*H*-N), 3.79 (s, 3H, C*H*$_3$O), 4.40 (m, 1H, C*H*-N), 4.40 (d, $J_{6\text{-H},6'\text{-H}}$ = 11.6 Hz, 1H, 6-H), 4.54 (d, $J_{6\text{-H},6'\text{-H}}$ = 11.6 Hz, 1H, 6'-H), 4,78 (m, 1H, 5-H), 5.24 (m, 1H, 3-H), 6.45 (br.t, $J_{1\text{-H},2\text{-H}} = J_{2\text{-H},3\text{-H}}$ = 6.3 Hz, 1H, 2-H), 6.65 (m, 1H, N*H*), 6.73 (br.d, $J_{1\text{-H},2\text{-H}}$ = 6.3 Hz, 1H, 1-H), 6.82 (d, $J_{7\text{-H},8\text{-H}}$= 7.8 Hz, 1H, 8-H), 7.18 (d, $J_{7\text{-H},8\text{-H}}$= 7.8 Hz, 1H, 7-H); ^{13}C NMR (100 MHz; $CDCl_3$): 24.6 (*C*H$_2$(Cy)), 24.6 (CH$_2$(Cy)), 25.3 (*C*H$_2$(Cy)), 25.4 (*C*H$_2$(Cy)), 26.0 (*C*H$_2$(Cy)), 26.1 (*C*H$_2$(Cy)), 36.2 (4-C), 50.1 (*C*H-N), 55.3 (*C*H$_3$O), 56.0 (*C*H-N), 72.8 (6-C), 73.5 (5-C), 74.7 (3-C), 113.7 (8-C), 128.9 (2-C), 129.8 (7-C), 129.9 (9-C), 130.5 (1-C), 153.0 (13-C), 159.3 (10-C), 172.6 (12-C), 175.1 (11-C).

General Procedure for the Catalytic Aldol Condensation of Acetone with Isatins. The carbonyl compound **61** (0.65 mmol) was added in one portion to a solution of L-leucinol (15 mg, 0.13 mmol), H_2O (23 mg, 1.3 mmol), and acetone (1.5 mL) in dichloromethane (6 mL) at room temperature and the reaction mixture was stirred at 24 °C for 1.5 d and monitored by NMR. The solvents were then carefully evaporated (without heating) and the product **63** obtained was purified by flash chromatography on a column of neutral Al_2O_3 pre-treated with Et_3N (1.5 cm × 15 cm), using a gradient of petroleum ether, ethyl acetate, and methanol (from 100:0:0 to 0:90:10 vv) as an eluent.



(*S*)-(–)-3-Hydroxy-1-methyl-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63f).

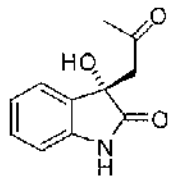
Yellow solid (92%): mp 140-145 °C (decomp); $[\alpha]_D$ –35.6 (*c* 0.81, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.10 (s, 3H, CH_3), 3.03 (d, J_{gem} = 16.7 Hz, 1H, C*H*H'), 3.14 (s, 3H, NMe), 3.22 (d, J_{gem} = 16.7 Hz, 1H, CH*H*'), 4.79 (br s, 1H, OH), 6.81 (dd, $J_{6\text{-H},7\text{-H}}$ = 7.8 Hz, $J_{5\text{-H},7\text{-H}}$ = 1.0 Hz, 1H, 7-H), 7.04 (td, $J_{5\text{-H},6\text{-H}} = J_{4\text{-H},5\text{-H}}$ = 7.8 Hz, $J_{5\text{-H},7\text{-H}}$ = 1.0 Hz, 1H, 5-H), 7.29 (td, $J_{5\text{-H},6\text{-H}} = J_{6\text{-H},7\text{-H}}$ = 7.8 Hz, $J_{6\text{-H},4\text{-H}}$ = 1.3 Hz, 1H, 6-H), 7.33 (dd, $J_{4\text{-H},5\text{-H}}$ = 7.8 Hz, $J_{4\text{-H},6\text{-H}}$ = 1.3 Hz, 1H, 4-H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 26.3 (CH_3), 31.5 (CH_3N), 48.5 (CH_2), 74.3 (C-3), 108.5 (C-7), 123.1 (C-5), 123.9 (C-4), 130.0 (C-6, C-3a), 143.5 (C-7a), 176.0 (C-2), 207.8 (CO); IR (KBr) ν 3393, 1718, 1698, 1616, 1497, 1432, 1420, 1205, 1173, 1134, 1023, 775, 701 cm^{-1}; MS (EI) *m/z* (%) 219 (M^+, 30), 162 (50); HRMS (EI) *m/z* 219.0892 ($C_{12}H_{13}NO_3$ requires 219.0895); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 1 mL min^{-1}) showed 94.5% ee (t_R = 11.4 min, t_S = 13.8 min).



(*S*)-(–)-1-Allyl-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63g).

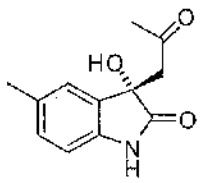
Yellow oil (80%): $[\alpha]_D$ –1.0 (*c* 1.0, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.16 (s, 3H, CH_3), 3.03 (d, J_{gem} = 17.2 Hz, 1H, C*H*H'), 3.24 (d, J_{gem} = 17.2 Hz, 1H, CH*H*'), 4.25 (ddt, *J* = 16.4, 5.3, and 1.8 Hz, 1H, C*H*H'N), 4.36 (br s, 1H, OH), 4.39 (ddt, *J* = 16.4, 5.3, and 1.8 Hz, 1H, CH*H*'N), 5.24 (dq, *J* = 10.4, 1.8, and 1.8 Hz, 1H, CH=C*H*H'),

5.31 (dq, J = 17.2, 1.8, and 1.8 Hz, 1H, CH=CH*H'*), 5.85 (ddt, J = 17.2, 10.4, and 5.3 Hz, 1H, C*H*=CHH'), 6.84 (dd, $J_{7\text{-H},6\text{-H}}$ = 7.8 Hz, $J_{5\text{-H},7\text{-H}}$ = 1.0 Hz, 1H, 7-H), 7.06 (td, $J_{5\text{-H},6\text{-H}}$ = $J_{4\text{-H},5\text{-H}}$ = 7.8 Hz, $J_{5\text{-H},7\text{-H}}$ = 1.0 Hz, 1H, 5-H), 7.29 (td, $J_{5\text{-H},6\text{-H}}$ = $J_{6\text{-H},7\text{-H}}$ = 7.8 Hz, $J_{6\text{-H},4\text{-H}}$ = 1.3 Hz, 1H, 6-H), 7.37 (dd, $J_{4\text{-H},5\text{-H}}$ = 7.8 Hz, $J_{4\text{-H},6\text{-H}}$ = 1.3 Hz, 1H, 4-H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 31.3 (CH_3), 42.4 (CH_2N), 49.1 (CH_2), 74.0 (C-3), 109.5 (C-7), 117.8 (CH_2=CH), 123.0 (C-5), 123.8 (C-4), 129.7 (C-6), 129.9 (C-3a), 131.0 (CH_2=CH), 142.7 (C-7a), 176.0 (C-2), 207.1 (CO); IR (NaCl) ν 3392, 1713, 1645, 1614, 1491, 1468, 1432, 1364, 1338, 1181, 778, 754 cm^{-1}; MS (EI) *m/z* (%) 245 (M^+, 100), 188 (80), 160 (80), 146 (90), 130 (80); HRMS (EI) *m/z* 245.1053 ($C_{14}H_{15}NO_3$ requires 245.1052); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 1 mL min^{-1}) showed 94% ee (t_R = 8.3 min, t_S = 9.1 min).



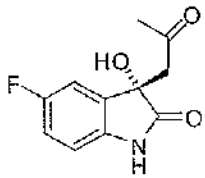
(*S*)-(–)-3-Hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63e).

White solid (87%), which on recrystallisation from a mixture of hexane, CH_2Cl_2, and MeOH afforded an enantiopure form: mp 160-165 °C (decomp); $[\alpha]_D$ –37.3 (*c* 0.33, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.05 (s, 3H, CH_3), 2.98 (d, J_{gem} = 16.2 Hz, 1H, C*H*H'), 3.15 (d, J_{gem} = 16.2 Hz, 1H, CH*H'*), 5.60 (br s, 1H, OH), 6.76 (d, $J_{7\text{-H},6\text{-H}}$ = 7.3 Hz, 1H, 7-H), 6.86 (t, $J_{5\text{-H},6\text{-H}}$ = $J_{4\text{-H},5\text{-H}}$ = 7.3 Hz, 1H, 5-H), 7.10 (t, $J_{5\text{-H},6\text{-H}}$ = $J_{6\text{-H},7\text{-H}}$ = 7.3 Hz, 1H, 6-H), 7.19 (d, $J_{4\text{-H},5\text{-H}}$ = 7.8 Hz, 1H, 4-H), 9.8 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 35.9 (CH_3), 55.0 (CH_2), 78.5 (C-3), 115.0 (C-7), 126.7 (C-5), 128.5 (C-4), 134.2 (C-6), 135.6 (C-3a), 146.8 (C-7a), 183.4 (C-2), 210.7 (CO); IR (KBr) ν 3357, 3299, 1716, 1620, 1484, 1470, 1428, 1402, 1389, 1362, 1332, 1298, 1264, 1116, 1088, 1014, 781, 677, 647, 623 cm^{-1}; MS (EI) *m/z* (%) 205 (M^+, 5), 129 (10), 120 (10); HRMS (EI) *m/z* 205.0741 ($C_{11}H_{11}NO_3$ requires 205.0739); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 1 mL min^{-1}) showed 93.5% ee (t_R = 13.9 min, t_S = 16.7 min).



(*S*)-(–)-3-Hydroxy-5-methyl-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63h).

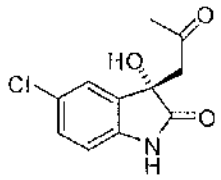
White solid (82%), which on recrystallisation from a mixture of hexane, CH_2Cl_2, and MeOH afforded an enantiopure form: mp 160-165 °C (decomp); $[\alpha]_D$ –26.5 (*c* 0.44, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.08 (s, 3H, CH_3), 2.22 (s, 3H, *Me*Ar), 2.96 (d, J_{gem} = 16.7 Hz, 1H, CH_2), 3.12 (d, J_{gem} = 16.7 Hz, 1H, CH_2), 5.23 (br s, 1H, OH), 6.68 (d, $J_{7\text{-H},6\text{-H}}$ = 7.8 Hz, 1H, 7-H), 6.94 (br d, $J_{6\text{-H},7\text{-H}}$ = 7.8 Hz, 1H, 6-H), 7.04 (br s,1H, 4-H), 9.24 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 21.0 (CH_3Ar), 31.2 (CH_3), 49.6 (CH_2), 74.0 (C-3), 110.0 (C-7), 124.6 (C-5), 129.9 (C-6), 130.6 (C-4), 131.7 (C-3a), 139.1 (C-7a), 178.4 (C-2), 206.8 (CO); IR (KBr) ν 3362, 3252, 1728, 1701, 1492, 1359, 1310, 1202, 1178, 1153, 1063, 827, 601 cm^{-1}; chiral HPLC (Chiracel AD hexane/2-propanol 4:1, 0.75 mL min^{-1}) showed 92% ee (t_R = 15.0 min, t_S = 19.1 min).



(*S*)-(–)-5-Fluoro-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63i).

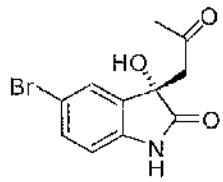
White solid (82%), which on recrystallisation from a mixture of hexane, CH_2Cl_2, and MeOH afforded an enantiopure form: mp 150-155 °C (decomp); $[\alpha]_D$ –34.6 (*c* 0.41, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.04 (s, 3H, CH_3), 3.01 (d, J_{gem} = 16.7 Hz, 1H, C*H*H'), 3.16 (d, J_{gem} = 16.7 Hz, 1H, CH*H*'), 5.88 (br s, 1H, OH), 6.72 (dd, $J_{7\text{-H},6\text{-H}}$ = 8.3 Hz, $J_{7\text{-H},F}$ = 4.3 Hz, 1H, 7-H), 6.81 (td, $J_{7\text{-H},6\text{-H}} = J_{6\text{-H},F}$ = 8.3 Hz, $J_{6\text{-H},4\text{-H}}$ = 2.5 Hz, 1H, 6-H), 7.05 (dd, $J_{4\text{-H},F}$ = 8.3 Hz, $J_{6\text{-H},4\text{-H}}$ = 2.5 Hz, 1H, 4-H) 10.0 (s, 1H, NH); ^{13}C

NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.4 (CH_3), 49.8 (CH_2), 73.2 (C-3), 110.2 (d, $J_{C\text{-}7,F}$ = 8 Hz, C-7), 111.3 (d, $J_{C\text{-}4,F}$ = 24 Hz, C-4), 114.9 (d, $J_{C\text{-}6,F}$ = 23 Hz, C-6), 132.1 (d, $J_{C\text{-}3a,F}$ = 7 Hz, C-3a), 137.8 (d, $J_{C\text{-}7a,F}$ = 2 Hz, C-7a), 158.1 (d, $J_{C\text{-}5,F}$ = 240 Hz, C-5), 178.1 (C-2), 204.9 (CO); MS (EI) *m/z* (%) 223 (M^+, 30), 180 (50), 138 (40); IR (KBr) ν 3361, 3295, 1722, 1491, 1364, 1341, 1265, 1185, 825, 604 cm^{-1}; HRMS (EI) *m/z* 223.0648 ($C_{11}H_{10}FNO_3$ requires 223.0645); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 1.0 mL min^{-1}) showed 90% ee (t_R = 19.2 min, t_S = 13.4 min).



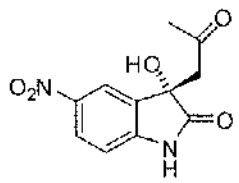
(*S*)-(–)-5-Chloro-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63j).

White solid (85%): mp 160-165 °C (decomp); $[\alpha]_D$ –22.6 (*c* 0.67, MeOH); ^1H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.04 (s, 3H, CH_3), 3.04 (d, J_{gem} = 16.9 Hz, 1H, C*H*H'), 3.16 (d, J_{gem} = 16.9 Hz, 1H, CH*H*'), 5.80 (br s, 1H, OH), 6.72 (d, $J_{7\text{-}H,6\text{-}H}$ = 8.3 Hz, 1H, 7-H), 7.06 (dd, $J_{6\text{-}H,7\text{-}H}$ = 8.3 Hz, $J_{4\text{-}H,6\text{-}H}$ = 2.0 Hz, 1H, 6-H), 7.16 (d, $J_{4\text{-}H,6\text{-}H}$ = 2.0 Hz, 1H, 4-H), 9.90 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.8 (CH_3), 50.1 (CH_2), 73.4 (C-3), 111.1 (C-7), 124.1 (C-4), 126.8 (C-3a), 129.0 (C-6), 132.7 (C-5), 140.8 (C-7a), 178.2 (C-2), 205.4 (CO); MS (EI) *m/z* (%) 239 (M^+, 80), 196 (100), 154 (80); IR (KBr) ν 3393, 3269, 1720, 1703, 1619, 1482, 1416, 1362, 1180, 1075, 820, 655 cm^{-1}; HRMS (EI) *m/z* 239.0343 ($C_{11}H_{10}{}^{35}ClNO_3$ requires 239.0349), 241.0316 ($C_{11}H_{10}{}^{37}ClNO_3$ requires 241.0320; chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1; 1 mL min^{-1}) showed 92% ee (t_R = 26.6 min, t_S = 12.8 min).



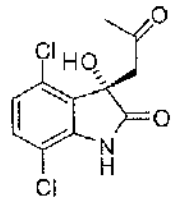
(*S*)-(–)-5-Bromo-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63k).

White solid (80%), which on recrystallisation from a mixture of hexane, CH_2Cl_2, and MeOH afforded an enantiopure form: mp 180-185 °C (decomp); $[\alpha]_D$ –17.6 (*c* 0.60, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.02 (s, 3H, CH_3), 3.06 (d, J_{gem} = 16.9 Hz, 1H, C*H*H'), 3.19 (d, J_{gem} = 16.9 Hz, 1H, CH*H*'), 6.02 (br s, 1H, OH), 6.70 (d, $J_{7\text{-}H,6\text{-}H}$ = 8.1 Hz, 1H, 7-H), 7.22 (dd, $J_{6\text{-}H,7\text{-}H}$ = 8.1 Hz, $J_{4\text{-}H,6\text{-}H}$ = 1.8 Hz, 1H, 6-H), 7.30 (d, $J_{4\text{-}H,6\text{-}H}$ = 1.8 Hz, 1H, 4-H), 10.15 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.3 (CH_3), 50.0 (CH_2), 72.8 (C-3), 111.2 (C-7), 113.5 (C-5), 126.4 (C-4), 131.4 (C-6), 133.1 (C-3a), 141.3 (C-7a), 177.8 (C-2), 204.6 (CO); IR (KBr) ν 3391, 3300, 1722, 1615, 1480, 1414, 1363, 1323, 1179, 1072, 818, 651 cm^{-1}; chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 1 mL/min) showed 95% ee (t_R = 38.1 min, t_S = 12.8 min). The absolute configuration has been confirmed by X-Ray analysis. The crystals for X-ray analysis were grown from CH_2Cl_2–hexane (1:3) with 5% of MeOH.



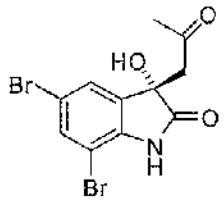
(*S*)-(–)-3-Hydroxy-5-nitro-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63l).

Yellow solid (85%): mp >160 °C (decomp); $[\alpha]_D$ –34.0 (*c* 0.35, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.02 (s, 3H, CH_3), 3.16 (d, J_{gem} = 17.7 Hz, 1H, C*H*H'), 3.45 (d, J_{gem} = 17.7 Hz, 1H, CH*H*'), 6.27 (br s, 1H, OH), 6.93-6.97 (m, 1H, 7-H), 8.14-8.09 (m, 2H, 6-H and 4-H), 10.7 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.0 (CH_3), 50.0 (CH_2), 72.1 (C-3), 109.3 (C-7), 119.2 (C-4), 126.0 (C-6), 132.3 (C-3a), 142.0 (C-5), 149.1 (C-7a), 178.4 (C-2), 204.6 (CO); MS (EI) *m/z* (%) 250 (M^+, 60), 207 (90), 165 (60); IR (KBr) ν 3254, 1709, 1626, 1608, 1525, 1482, 1460, 1402, 1365, 1337, 1261, 1246, 1223, 1189, 1172, 1128, 1078, 843, 651 cm^{-1}; HRMS (EI) *m/z* 250.0591 ($C_{11}H_{10}N_2O_5$ requires 250.0590); chiral HPLC (Chiracel OJ-H hexane/2-propanol 3:2, 0.8 mL min^{-1}) showed 92% ee (t_R = 18.8 min, t_S = 14.6 min).



(*S*)-(–)-4,7-Dichloro-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63m).

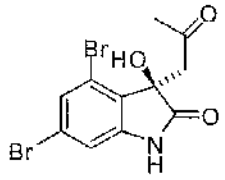
Yellow solid (87%): mp >160 °C (decomp); $[\alpha]_D$ –57.3 (*c* 1.47, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.00 (s, 3H, CH_3), 3.22 (d, J_{gem} = 17.7 Hz, 1H, C*H*H'), 3.72 (d, J_{gem} = 17.7 Hz, 1H, CH*H*'), 6.15 (br s, 1H, OH), 6.76 (d, $J_{6\text{-}H,5\text{-}H}$ = 8.8 Hz, 1H, 5-H), 7.07 (d, $J_{6\text{-}H,5\text{-}H}$ = 8.8 Hz, 1H, 6-H), 10.5 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 35.0 (CH_3), 53.5 (CH_2), 79.4 (C-3), 118.4 (C-7), 128.2 (C-5), 133.6 (C-4), 133.7 (C-3a), 135.2 (C-6), 147.2 (C-7a), 182.6 (C-2), 209.8 (CO); MS (EI) *m/z* (%) 275 (M^+, 30), 273 (M^+, 45), 230 (45), 216 (60); IR (KBr) ν 3324, 3273, 1725, 1703, 1618, 1468, 1380, 1370, 1161, 796, 626 cm^{-1}; HRMS (EI) *m/z* 272.9961 ($C_{11}H_9{}^{35}Cl_2NO_3$ requires 272.9959), 274.9929 ($C_{11}H_{10}{}^{37}C^{35}ClNO_3$ requires 274.9930); chiral HPLC (Chiracel OD-H hexane/2-propanol 9:1, 0.75 mL min^{-1}) showed 86% ee (t_R = 24.9 min, t_S = 19.9 min).



(*S*)-(–)-5,7-Dibromo-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63n).

White solid (85%): mp 150-155 °C (decomp); $[\alpha]_D$ –34.4 (*c* 0.39, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.07 (s, 3H, CH_3), 3.06 (d, J_{gem} = 17.4 Hz, 1H, C*H*H'), 3.16 (d, J_{gem} = 17.4 Hz, 1H, CH*H*'), 5.50 (br s, 1H, OH), 7.29 (d, $J_{6\text{-}H,4\text{-}H}$ = 1.5 Hz, 1H, 6-H), 7.43 (d, $J_{4\text{-}H,6\text{-}H}$ = 1.5 Hz, 1H, 4-H), 8.75 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.8 (CH_3), 49.9 (CH_2), 74.8 (C-3), 103.6 (C-7), 115.1 (C-5), 126.1 (C-6), 133.7 (C-4), 134.4 (C-3a), 140.3 (C-7a), 177.0 (C-2), 205.8 (CO); MS (EI)

m/z (%): 363 (M^+, 40), 318 (80), 306 (30); HRMS (EI) *m/z*: 362.8931 ($C_{11}H_9NO_3Br_2$ requires 362.8929); IR (KBr) ν 3320, 3264, 1732, 1616, 1460, 1363, 1332, 1305, 1223, 1159, 1076, 1065, 862 cm^{-1}; chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 0.75 mL. min^{-1}) showed 93% ee (t_R = 19.1 min, t_S = 14.9 min).



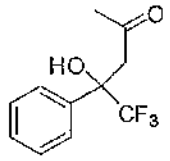
(*R*)-(+)-4,6-Dibromo-3-hydroxy-3-(2-oxo-propyl)-1,3-dihydro-indol-2-one (63a).

White solid (80%), which on recrystallisation from a mixture of hexane, CH_2Cl_2, and MeOH afforded an enantiopure form: mp 160-165 °C (decomp) [literature[65,68] gives 190-195 °C (MeOH), presumably for the partially racemised product]; $[\alpha]_D$ +48.9 (*c* 0.33, MeOH) [literature[65,68] gives +27.4 (*c* 0.06, MeOH)]; ^1H NMR (400 MHz; $CDCl_3$ and d_6-DMSO) δ 2.02 (s, 3H, CH_3), 3.22 (d, J_{gem} = 17.4 Hz, 1H, C*H*H'), 3.72 (d, J_{gem} = 17.4 Hz, 1H, CH*H'*), 5.16 (br s, 1H, OH), 6.90 (d, $J_{7\text{-}H,5\text{-}H}$ = 1.5 Hz, 1H, 7-H), 7.14 (d, $J_{7\text{-}H,5\text{-}H}$ = 1.5 Hz, 1H, 5-H), 9.74 (s, 1H, NH); ^{13}C NMR (100 MHz; $CDCl_3$ and d_6-DMSO) δ 30.5 (CH_3), 48.1 (CH_2), 74.7 (C-3), 113.0 (C-7), 119.3 (C-4), 123.5 (C-6), 127.6 (C-3a), 128.1 (C-5), 145.6 (C-7a), 177.9 (C-2), 205.5 (CO); IR (KBr) ν 3316, 1706, 1609, 1579, 1433, 1359, 1316, 1168, 1078, 847, 681 cm^{-1}; chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 0.75 mL min^{-1}) showed 93% ee (t_R = 19.1 min, t_S = 14.9 min). The crystals for X-ray analysis were grown from CH_2Cl_2–hexane (1:3) with 5% of MeOH.

(*S*)-(–)-63a. Obtained in the same manner, employing D-leucinol: $[\alpha]_D$ -48.3 (*c* 0.80, MeOH).

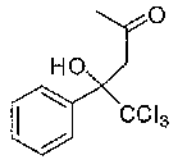
General Procedure for the Catalytic Aldol Condensation of Acetone with activated ketones. The carbonyl compound **74** (0.65 mmol) was added in one portion to a solution of L-leucinol (15 mg, 0.13 mmol), H_2O (23 mg, 1.3 mmol), and acetone (1.5 mL) in dichloromethane (6 mL) at room temperature and the reaction mixture was stirred

at 24 °C for 1.5 d and monitored by NMR. The solvents were then carefully evaporated (without heating) and the product **75** obtained was purified by flash chromatography on a column of neutral Al_2O_3 pre-treated with Et_3N (1 cm ×10 cm), using a gradient of petroleum ether, ethyl acetate, and methanol (from 100:0:0 to 0:90:10) as eluent.



(–)-5,5,5-Trifluoro-4-hydroxy-4-phenyl-pentan-2-one (75a).

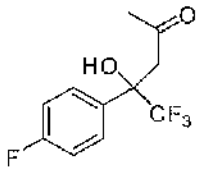
White solid (85%): mp 50-55 °C; $[\alpha]_D$ –7.7 (*c* 0.40, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3), 3.31 (d, J_{gem} = 17.2 Hz, 1H, C*H*H'), 3.37 (d, J_{gem} = 17.2 Hz, 1H, CH*H'*), 5.45 (s, 1H, OH), 7.35-7.43 (m, 3H, Ar), 7.55-7.59 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.1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



(–)-5,5,5-Trichloro-4-hydroxy-4-phenyl-pentan-2-one (75b).

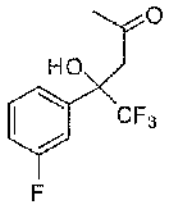
White solid (70%): mp 43-46 °C; $[\alpha]_D$ –9.8 (*c* 0.63, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.20 (s, 3H, CH_3), 3.44 (d, J_{gem} = 17.0 Hz, C*H*H'), 3.94 (d, J_{gem} = 17.0 Hz, CH*H'*), 5.69 (s, 1H, OH), 7.25-7.45 (m, 3H, Ar), 7.70-7.80 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.2 (CH_3), 46.9 (CH_2), 83.9 (C-O), 105.4 (CCl_3), 127.6 (CH), 128.6 (CH), 128.8 (CH), 138.1 (C), 209.3 (C=O); IR (NaCl) ν 3481, 1694, 1409, 1391, 1363,

1328, 1317, 1180, 837, 802, 765, 711, 610 cm^{-1}; MS (CI/isobutane) *m/z* (%) 281 (M^+, 100), 185 (10), 163 (30), 105 (5); HRMS (EI) *m/z*: 280.9893 ($C_{11}H_{11}O_2Cl_3$ requires 280.9903); chiral HPLC (Chiracel OJ-H hexane/2-propanol 4:1, 0.75 mL min^{-1}) showed 64% ee (t_{minor} = 44.4 min, t_{major} = 17.6 min).



(–)-5,5,5-Trifluoro-4-(4-fluoro-phenyl)-4-hydroxy-pentan-2-one (75c).

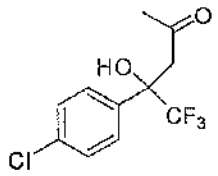
White solid (86%): mp 38-41 °C; $[\alpha]_D$ –11.2 (*c* 1.4, MeOH); ^1H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3), 3.21 (d, J_{gem} = 17.2 Hz, C*H*H'), 3.31 (d, J_{gem} = 17.2 Hz, CH*H'*), 5.50 (s, 1H, OH), 7.05-7.11 (m, 2H, Ar), 7.52-7.57 (m, 2H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.1 (CH_3),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



(–)-5,5,5-Trifluoro-4-(3-fluoro-phenyl)-4-hydroxy-pentan-2-one (75d).

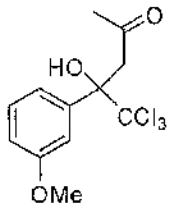
Colourless liquid (87%): $[\alpha]_D$ –6.6 (*c* 0.65, MeOH); ^1H NMR (400 MHz; $CDCl_3$) δ 2.22 (s, 3H, CH_3), 3.21 (d, J_{gem} = 17.3 Hz, C*H*H'), 3.31 (d, J_{gem} = 17.3 Hz, CH*H'*), 5.53 (s, 1H, OH), 7.03 – 7.09 (m, 1H, Ar), 7.29 – 7.40 (m, 3H, Ar); ^{13}C NMR (100 MHz;

$CDCl_3$) δ 32.0 (CH_3), 45.0 (CH_2), 75.7 (qd, $^2J_{C,F}$ = 29.5 Hz, $^4J_{C,F}$ = 1.8 Hz, C-O), 113.8 (d, $^2J_{C,F}$ = 23.8 Hz, CH), 115.8 (d, $^2J_{C,F}$ = 21.1 Hz, CH), 121.5 – 121.7 (m, CH), 124.2 (q, $^1J_{C,F}$ = 285.0 Hz, CF_3), 130.0 (d, $^3J_{C,F}$ = 8.2 Hz, CH), 140.1 (d, $^3J_{C,F}$ = 7.0 Hz, C), 162.8 (d, $^1J_{C,F}$ = 246.4 Hz, CF), 208.7 (C=O); IR (NaCl) ν 3455, 1714, 1593, 1491, 1444, 1420, 1365, 1344, 1275, 1240, 1146, 1061, 865, 790, 726 cm^{-1}; MS (EI) *m/z* (%) 250 (M^+, 10), 181 (30), 123 (60); HRMS (EI) *m/z*: 250.0619 ($C_{11}H_{10}O_2F_4$ requires 250.0617); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 73% ee (t_{minor} = 12.0 min, t_{major} = 10.2 min).



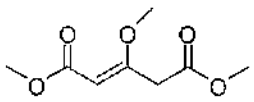
(–)-4-(4-Chloro-phenyl)-5,5,5-trifluoro-4-hydroxy-pentan-2-one (75e).

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



(–)-5,5,5-Trichloro-4-hydroxy-4-(3-methoxy-phenyl)-pentan-2-one (75f).

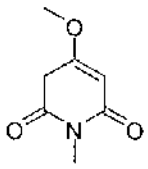
White solid (72%): mp 35-38 °C; $[\alpha]_D$ –7.7 (*c* 0.34, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.21 (s, 3H, CH_3), 3.41 (d, J_{gem} = 17.1 Hz, C*H*H'), 3.82 (s, 3H, CH_3O), 3.91 (d, J_{gem} = 17.1 Hz, CH*H'*), 5.70 (s, 1H, OH), 6.88-6.92 (m, 1H, Ar), 7.24-7.36 (m, 3H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 32.2 (CH_3), 47.0 (CH_2), 55.3 (CH_3O), 83.8 (C-O), 105.2 (CCl_3), 113.8 (CH), 115.6 (CH), 120.8 (CH), 128.5 (CH), 139.8 (C), 159.0 (C_{ar}-O), 209.3 (C=O); IR (NaCl) ν 3448, 1697, 1489, 1464, 1426, 1363, 1264, 1234, 1172, 1033, 801, 777, 728, 702 cm^{-1}; MS (CI/isobutane) *m/z* (%): 311 (80), 259.1 (80), 207.2 (100); HRMS (CI) *m/z*: 310.9995 ($C_{12}H_{14}O_3Cl_3$ required 311.0009); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 66% ee (t_{minor} = 25.1 min, t_{major} = 21.1 min).



80

(Z)-3-Methoxy-pent-2-enedioic acid dimethyl ester (80).

To a mixture of trimethyl orthoformate (30mL, 274.22 mmol) and dimethyl 1,3-acetondicarboxylate (29.5 mL, 199.88 mmol), 1 mL of MeOH and 1 mL of concentrated sulphuric acid were added. Solution was refluxed for 6h under Ar, diluted with ether, washed with aqueous sodium hydrogen carbonate, dried with Na_2SO_4. After evaporation of solvents the product was obtained as yellow oil (30 g, 80%): ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.67 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 3.71 (s, 3H, OCH_3), 3.83 (s, 2H, CH_2), 5.19 (s, 1H, CH).

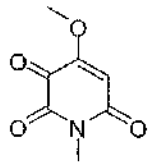


81

4-Methoxy-1-methyl-3*H*-pyridine-2,6-dione (81).

(Z)-3-Methoxy-pent-2-enedioic acid dimethyl ester **80** (38.6 g, 205.12 mmol) was cooled in ice-water bath and 40% solution of methylamine (25 mL, 721.99 mmol) was added dropwise while stirring. Mixture was then allowed to warm to room temperature, extracted with ethylacetate (3x100mL) and evaporated. Methanol (270 mL) and sodium (5g, 217.49) were added and solution was refluxed for 2 h. Methanol was then evaporated, the residue was dissolved in water and extracted with diethyl ether (3x50 mL). Acetic acid (35 mL) was added to the water layer which was then extracted with CH_2Cl_2. The extract was dried with Na_2SO_4, evaporated and then chromatographed (silica gel, 5 cm × 20 cm, CH_2Cl_2/ethyl acetate 5:1)

White crystals (23.8 g, 75%): mp 112 – 114°C; ^{1}H NMR (400 MHz; $CDCl_3$) δ 3.21 (*s*, 3H, NCH_3), 3.44 (*s*, 2H, CH_2), 3.76 (*s*, 3H, OCH_3), 5.44 (*s*, 1H, CH).

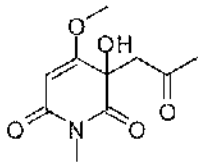


82

4-Methoxy-1-methyl-pyridine-2,3,6-trione (82).

4-Methoxy-1-methylpyridine-2,6-(1H,3H)-dione **81** (800 mg, 5.16 mmol) and SeO_2 (800 mg, 7.21 mmol) with one drop of sulfuric acid were stirred at room temperature in $CHCl_3$ overnight. Mixture was then dried with Na_2SO_4, filtrated a chromatographed (silica gel, 1.5 cm × 20 cm, CH_2Cl_2).

Orange crystals (635 mg, 73%): mp 174 – 177°C; ^{1}H NMR (400 MHz; $CDCl_3$) δ3.32 (*s*, 3H, NCH_3), 3.85 (*s*, 3H, OCH_3), 6.16 (*s*, 1H, CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 27.1 (NCH_3), 56.8 (OCH_3), 107.3 (C-3), 155.3 (C-4), 158.1(C-6), 162.8 (C-2), 170.5 (C-5).



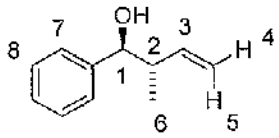
78

3-Hydroxy-4-methoxy-1-methyl-3-(2-oxo-propyl)-3*H*-pyridine-2,6-dione (Speranskatine A; 78).

The compound was prepared using standard procedure for the catalytic aldol condensation of acetone with activated ketones (see above).

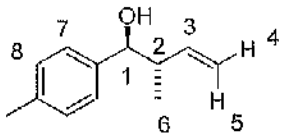
White crystals (80%): mp 150°C (decomp); $[\alpha]_D$ 15.0 (*c* 0.5, MeOH); ^{1}H NMR (400 MHz; $CDCl_3$) δ1.26 (s, 1H, OH), 2.16 (s, 3H CH_3), 3.23 (s, 3H, NCH_3), 3.26 (s, 2H, CH_2), 3.78 (s, 3H, CH_3), 5.45 (s, 1H, CH); ^{13}C NMR (100 MHz; $CDCl_3$) δ 26.6 (NCH_3), 30.6 (CH_3), 50.0 (CH_2), 56.7 (OCH_3), 70.8 (C-5), 94.7 (C-3), 164.5 (C-4), 167.5 (C-1), 172.9 (C-6), 205.5 (C=O); MS (CI/isobutane) *m/z* (%): 228 (M+H), 172 (80), 113 (30), 85 (80); HRMS (CI/isobutene) *m/z* (%): 228.0870 ($C_{10}H_{11}NO_5$ requires 228.0872); chiral HPLC (Chiracel OJ-H hexane/2-propanol 9:1, 1 mL min^{-1}) showed 80% ee (t_{minor} = 21.4 min, t_{major} = 23.2 min)..

General Procedure for the Allylation of Aldehydes Catalysed by METHOX. The respective trichlorosilane **96** (3 mmol) was added to a solution of the respective aldehyde **86** (1.5 mmol), Hünig base (1.57 mL, 9 mmol) and METHOX **105a** (28 mg, 0.075 mmol) in freshly distilled CH_3CN (10 mL) under argon at -40 °C. The reaction mixture was stirred at the corresponding temperature for 24 h and monitored by TLC. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ and diluted with ethyl acetate (150 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2×100 mL). The combined organic fractions were dried over Na_2SO_4 and the solvents were removed in vacuum. The product was purified on a column of silica gel (2.5 × 25 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 80:20).



(1*S*,2*S*)-(-)-2-Methyl-1-phenyl-but-3-en-1-ol (88a).[116]

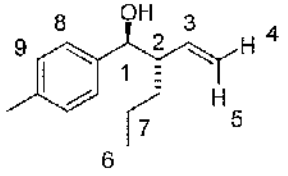
The reaction was carried at -40 °C to produce **88a** as a yellowish liquid (90%). $[\alpha]_D$ -120.3 (*c* 0.9, $CHCl_3$; literature[117] gives $[\alpha]_D$ -115.4 (*c* 1.5, $CHCl_3$)); ^1H NMR (400 MHz; $CDCl_3$) δ 0.79 (d, $^3J_{6\text{-}H,2\text{-}H}$ = 6.8 Hz, 3H 6-H), 2.15 (br.s., 1H, O*H*), 2.35-2.45 (m, 1H, 2-H), 4.26 (d, $^3J_{1\text{-}H,2\text{-}H}$ = 7.8 Hz, 1H, 1-H), 5.07-5.14 (m, 2H, 4-H and 5-H), 5.72 (ddd, $^3J_{2\text{-}H,3\text{-}H}$ = 8.2 Hz, $^3J_{3\text{-}H,4\text{-}H}$ = 10.3 Hz, $^3J_{3\text{-}H,5\text{-}H}$ = 17.2 Hz, 1H, 3-H), 7.16-7.29 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.5 (CH_3), 46.2 (CH), 77.8 (CH-O), 116.7 ($CH{=}CH_2$), 126.8 (CH), 127.6 (CH), 128.2 (CH), 140.6 ($CH{=}CH_2$), 142.4 (C); IR (NaCl) ν 3684, 3422, 2975, 2875, 1455, 1260, 1019, 914, 799, 761, 701 cm^{-1}; chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 100 °C, then 0.5 deg.min^{-1}) showed 97% ee (t_{SS} = 37.3 min, t_{RR} = 37.0 min).



(1*S*,2*S*)-(-)-2-Methyl-1-*p*-tolyl-but-3-en-1-ol (88d).[118]

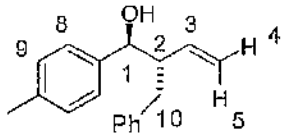
The reaction was carried at -40 °C to produce **88d** as a colourless liquid (90%): $[\alpha]_D$ -99.5 (*c* 0.6, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 0.86 (d, $^3J_{6\text{-}H,2\text{-}H}$ = 6.8 Hz, 3H, 6-H), 2.11 (d, $^3J_{OH,1\text{-}H}$ = 2.6 Hz, 1H, O*H*), 2.35 (s, 3H, C*H*$_3$-Ar), 2.42-2.52 (m, 1H, 2-H), 4.32 (dd, $^3J_{2\text{-}H,1\text{-}H}$ = 8.0 Hz, $^3J_{OH,1\text{-}H}$ = 2.6 Hz, 1H, 1-H), 5.16-5.24 (m, 2H, 4-H and 5-H), 5.81 (ddd, $^3J_{2\text{-}H,3\text{-}H}$ = 8.2, $^3J_{4\text{-}H,3\text{-}H}$ = 10.3 Hz, $^3J_{5\text{-}H,3\text{-}H}$ = 17.2 Hz, 1H, 3-H), 7.16 (d, $^3J_{8\text{-}H,9\text{-}H}$ = 8.0 Hz, 1H, 8-H), 7.22 (d, $^3J_{8\text{-}H,9\text{-}H}$ = 8.0 Hz, 1H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.6 (CH_3), 21.1 (CH_3), 46.2 (CH), 77.7 (CH-O), 116.7 ($CH{=}CH_2$), 126.7 (CH), 128.9 (CH), 137.3 (C), 139.4 (C), 140.8 ($CH{=}CH_2$); IR (NaCl) ν 3652, 3420, 2976, 2927, 2870, 1637, 1514, 1456, 1417, 1374, 1261, 1179, 1103, 1017, 914, 813, 760, 722, 677 cm^{-1}; MS (CI) *m/z* (%) 159 (100, M^+-OH), 121 (40); HRMS (CI) 159.1172 ($C_{12}H_{15}$ requires

159.1174); chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 100 °C, then 0.5 deg.min^{-1}) showed 98% ee (t_{RR} = 49.5 min, t_{SS} = 50.0 min).



(1*S*,2*S*)-(-)-1-*p*-Tolyl-2-vinyl-pentan-1-ol (88e).

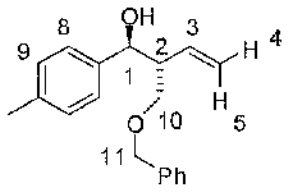
The reaction was carried at -40 °C using 20 mol% of METHOX as a catalyst to produce **88e** as a colourless liquid (80%): $[\alpha]_D$ -66.0 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.78 (t, $^3J_{6\text{-H},7\text{-H}}$ = 7.0 Hz, 3H, 6-H), 1.10-1.20 (m, 3H, C*H*$_2$), 1.25-1.37 (m, 1H, CH$_2$), 2.13 (d, $^3J_{OH,1\text{-H}}$ = 2.0 Hz, 1H, O*H*), 2.25-2.35 (m, 1H, 2-H), 2.36 (s, 3H, C*H*$_3$-Ar), 4.30-4.40 (m, 1H, 1-H), 5.20 (dd, $^3J_{5\text{-H},3\text{-H}}$ = 17.2 Hz, $^2J_{5\text{-H},4\text{-H}}$ = 1.8 Hz, 1H, 5-H), 5.25 (dd, $^3J_{4\text{-H},3\text{-H}}$ = 10.3 Hz, $^2J_{5\text{-H},4\text{-H}}$ = 1.8 Hz, 1H, 4-H), 5.67 (dt, $^3J_{4\text{-H},3\text{-H}}$ = $^3J_{2\text{-H},3\text{-H}}$ = 10.3 Hz, $^3J_{5\text{-H},3\text{-H}}$ = 17.2 Hz, 1H, 3-H), 7.15 (d, $^3J_{8\text{-H},9\text{-H}}$ = 8.0 Hz, 1H, 9-H), 7.22 (d, $^3J_{8\text{-H},9\text{-H}}$ = 8.0 Hz, 1H, 8-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9 (CH_3), 20.7 (CH_3), 21.7 (CH_2), 32.6 (CH_2), 52.5 (CH), 76.5 (CH-O), 118.5 (CH=*C*H$_2$), 126.9 (CH), 128.9 (CH), 137.2 (C), 139.5 (C), 139.6 (*C*H=CH$_2$); IR (NaCl) ν 3710, 3421, 3074, 2957, 2930, 2871, 1638, 1514, 1456, 1419, 1378, 1317, 1193, 1179, 1108, 1032, 1000, 912, 816, 75, 682 cm^{-1}; MS (CI) *m/z* (%) 187 (100, M$^+$-OH), 121 (55); HRMS (CI) 187.1484 ($C_{14}H_{19}$ requires 187.1487); chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 115 °C, then 0.5 deg.min^{-1}) showed 97% ee (t_{RR} = 48.3 min, t_{SS} = 48.7 min).



(1*S*,2*S*)-(-)-2-Benzyl-1-*p*-tolyl-but-3-en-1-ol (88f).

The reaction was carried at -20 °C using 50 mol% of METHOX as a catalyst to furnish **88f** as a colourless liquid (85%): $[\alpha]_D$ -73.0 (*c* 1.8, $CHCl_3$); ^{1}H NMR (400 MHz;

$CDCl_3$) δ 2.06 (d, $^3J_{OH,1\text{-}H}$ = 3.2 Hz, 1H, O*H*), 2.34 (s, 3H, C*H*$_3$-Ar), 2.50 (dd, $^2J_{10\text{-}H,10\text{-}H'}$ = 12.9 Hz, $^3J_{10\text{-}H,2\text{-}H}$ = 8.8 Hz, 1H, 10-H), 2.60-2.72 (m, 2H, 10-H' and 2-H), 4.80 (dd, $^3J_{2\text{-}H,1\text{-}H}$ = 6.4 Hz, $^3J_{OH,1\text{-}H}$ = 3.2 Hz, 1H, 1-H), 4.97 (br d, $^3J_{5\text{-}H,3\text{-}H}$ = 17.2 Hz, 1H, 5-H), 5.12 (dd, $^3J_{4\text{-}H,3\text{-}H}$ = 10.3 Hz, $^2J_{5\text{-}H,4\text{-}H}$ = 1.7 Hz, 1H, 4-H), 5.71 (ddd, $^3J_{4\text{-}H,3\text{-}H}$ = 10.3 Hz, $^3J_{2\text{-}H,3\text{-}H}$ = 8.5, $^3J_{5\text{-}H,3\text{-}H}$ = 17.2 Hz, 1H, 3-H), 6.98-7.19 (m, 9H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.1 (CH_3), 37.2 (CH_2), 53.8 (CH), 75.4 (CH-O), 118.8 (CH=*C*H$_2$), 125.8 (CH), 126.6 (CH), 128.1 (CH), 129.0 (CH), 129.1 (CH), 137.2 (C), 137.9 (*C*H=CH$_2$), 139.4 (C), 140.0 (C); IR (NaCl) ν 3724, 3432, 3061, 3025, 2977, 2920, 1638, 1603, 1513, 1495, 1454, 1419, 1380, 1317, 1196, 1179, 1111, 1031, 997, 915, 817, 749, 699, 678 cm^{-1}; MS (CI) *m/z* (%) 235 (100, M$^+$-OH), 143 (80), 121 (40); HRMS (CI) 235.1488 ($C_{18}H_{19}$ requires 235.1487); chiral HPLC (Chiracel IB column, hexane/2-propanol = 99:1, 0.75 mL min^{-1}) showed 97% ee (t_{RR} = 20.8 min, t_{SS} = 23.1 min).

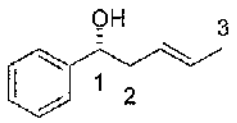


(1*S*,2*R*)-(-)-2-Benzyloxymethyl-1-*p*-tolyl-but-3-en-1-ol (88g).

The reaction was carried at -20 °C using 50 mol% of METHOX as a catalyst to produce **88g** as a yellowish liquid (85%): $[\alpha]_D$ -43.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.33 (s, 3H, C*H*$_3$-Ar), 2.64-2.72 (m, 1H, 2-H), 2.84 (d, $^3J_{OH,1\text{-}H}$ = 3.2 Hz, 1H, O*H*), 3.48 (dd, $^2J_{10\text{-}H,10\text{-}H'}$ = 9.2 Hz, $^3J_{10\text{-}H,2\text{-}H}$ = 4.9 Hz, 1H, 10-H), 3.53 (dd, $^2J_{10\text{-}H,10\text{-}H'}$ = 9.2 Hz, $^3J_{10\text{-}H,2\text{-}H}$ = 5.8 Hz, 1H, 10-H'), 4.46 (d, $^2J_{11\text{-}H,11\text{-}H'}$ = 12.0 Hz, 1H, 11-H), 4.51 (d, $^2J_{11\text{-}H,11\text{-}H'}$ = 12.0 Hz, 1H, 11-H'), 4.84-4.88 (m, 1H, 1-H), 5.11 (br d, $^3J_{5\text{-}H,3\text{-}H}$ = 17.3 Hz, 1H, 5-H), 5.19 (br, $^3J_{4\text{-}H,3\text{-}H}$ = 10.4 Hz, 1H, 4-H), 5.86 (ddd, $^3J_{4\text{-}H,3\text{-}H}$ = 10.4 Hz, $^3J_{2\text{-}H,3\text{-}H}$ = 8.5, $^3J_{5\text{-}H,3\text{-}H}$ = 17.3 Hz, 1H, 3-H), 7.11-7.37 (m, 9H, Ar); ^{13}C NMR (100 MHz; $CDCl_3$) δ 21.1 (CH_3), 51.4 (CH), 71.6 (CH_2-O), 73.4 (CH_2-O), 74.5 (CH-O), 118.5 (CH=CH_2), 126.3 (CH), 127.6 (CH), 127.7 (CH), 128.4 (CH), 128.8 (CH), 135.5 (C), 136.9 (C), 137.9 (*C*H=CH$_2$), 139.2 (C); IR (NaCl) ν 3445, 3064, 3027, 2918, 2860, 1611, 1513, 1495, 1454, 1420, 1361, 1203, 1178, 1098, 1026, 916, 816, 736, 698 cm^{-1}; MS (CI) *m/z*

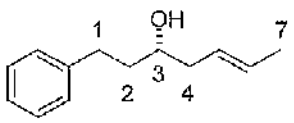
(%) 265 (100, M^+-OH), 235 (40), 159 (60), 121 (20); HRMS (CI) 265.1589 ($C_{19}H_{21}O$ requires 265.1592); chiral HPLC (Chiracel AD column, hexane/2-propanol = 98:2, 0.75 mL min^{-1}) showed 97% ee (t_{RS} = 26.9 min, t_{SR} = 32.3 min).

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



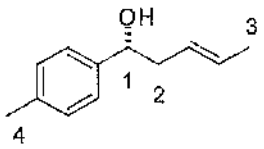
***R*-(+)-(E)-1-Phenyl-pent-3-en-1-ol (89a).**[104]

Yellowish liquid (85% yield): $[\alpha]_D$ +67.5 (*c* 1.2, $CHCl_3$; literature[104] gives $[\alpha]_D$ -66.4 (*c* 1.0, $CHCl_3$) for the (*S*)-(-)-enantiomer); ^1H NMR (400 MHz; $CDCl_3$) δ 1.56-1.59 (br d, $^3J_{3\text{-}H,CH=CH}$ = 6.4 Hz,, 3H, 3-H), 2.23-2.37 (m, 3H, 2-H and O*H*), 4.52 (dd, $^3J_{1\text{-}H,2\text{-}H}$ = 5.1 Hz, $^3J_{1\text{-}H,2\text{-}H'}$ = 7.8 Hz, 1H, 1-H), 5.25-5.35 (m, 1H, C*H*=CH), 5.41-5.52 (m, 1H, C*H*=CH), 7.12-7.26 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 42.6 (CH_2), 73.4 (CH-O), 125.7 (CH), 126.7 (CH), 127.2 (CH), 128.2 (CH), 129.1 (CH), 144.0 (C); IR (NaCl) ν 3650, 3360, 3027, 2963, 2916, 1493, 1453, 1270, 1026, 912, 872, 799, 758, 700 cm^{-1}; ^{19}F NMR of the corresponding Mosher ester showed 96% ee (δ_R = -71.31 ppm and δ_S = -71.45 ppm).



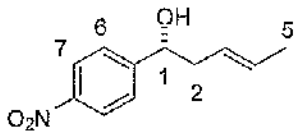
***S*-(-)-(E)-1-Phenyl-hept-5-en-3-ol (89b).**[104]

Colourless liquid (85% yield): $[\alpha]_D$ -15.7 (*c* 0.7, $CHCl_3$; literature[104] gives $[\alpha]_D$ -14.0 (*c* 1.0, $CHCl_3$)); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.57 (br s, 1H, O*H*), 1.62 (br d, $^3J_{7\text{-}H,C\mathit{H}=CH}$ = 6.3 Hz, 3H, C*H*$_3$), 1.66-1.74 (m, 2H, 2-H), 2.01-2.04 (m, 1H, 4-H), 2.13-2.22 (m, 1H, 4-H'), 2.61 (dt, $^2J_{1\text{-}H,1\text{-}H'}$ = 13.8 Hz, $^3J_{1\text{-}H,2\text{-}H}$ = 8.0 Hz, 1H, 1-H), 2.74 (dt, $^2J_{1\text{-}H,1\text{-}H'}$ = 13.8 Hz, $^3J_{1\text{-}H',2\text{-}H}$ = 7.5 Hz, 1H, 1-H'), 3.50-3.60 (m, 1H, 3-H), 5.30-5.40 (m, 1H, C*H*=CH), 5.45-5.55 (m, 1H, C*H*=CH), 7.08-7.25 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 32.1 (CH_2), 38.4 (CH_2), 40.8 (CH_2), 70.1 (CH-O), 125.7 (CH), 126.8 (CH), 128.3 (CH), 128.4 (CH), 129.3 (CH), 142.1 (C); IR (NaCl) ν 3654, 3374, 3062, 3025, 2929, 2856, 1603, 1495, 1454, 1377, 1261, 1045, 968, 746, 699 cm^{-1}; MS (CI) *m/z* (%) 191 (M+H, 5), 173 (100), 134 (30), 117 (40); HRMS (CI) 191.1426 ($C_{13}H_{19}O$ requires 191.1436); chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 120 °C, then 0.5 deg.min^{-1}) showed 97% ee (t_R = 40.9 min, t_S = 41.3 min).



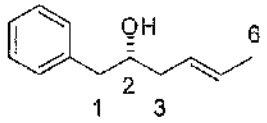
***R*-(+)-(E)-1-*p*-Tolyl-pent-3-en-1-ol (89c).**[119]

Yellowish liquid (60% yield): $[\alpha]_D$ +25.5 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.68-1.72 (br d, $^3J_{3\text{-}H,C\mathit{H}-CH}$ = 6.5 Hz,, 3H, 3-H), 2.06 (d, $^3J_{OH,1\text{-}H}$ = 3.1 Hz, 1H, O*H*), 2.35 (s, 3H, 4-H), 2.36-2.49 (m, 2H, 2-H), 4.61-4.67 (m, 1H, 1-H), 5.38-5.48 (m, 1H, C*H*=CH), 5.55-5.65 (m, 1H, C*H*=CH), 7.14-7.18 (m, 2H, Ar), 7.23-7.27 (m, 2H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 21.1 (CH_3), 42.7 (CH_2), 73.3 (CH-O), 125.7 (CH), 126.9 (CH), 129.0 (CH), 129.2 (CH), 137.0 (C), 141.1 (C); IR (NaCl) ν 3645, 3353, 3029, 2961, 2915, 1491, 1455, 1269, 1023, 918, 817, 734, 693 cm^{-1}; MS (CI) *m/z* (%) 159 (M^+-OH, 100), 104 (40); HRMS (CI) 159.1172 ($C_{12}H_{15}$ requires 159.1174); ^{19}F NMR of the corresponding Mosher ester showed 55% ee (δ_R = -71.36 ppm and δ_S = -71.50 ppm).



***R*-(+)-(E)-1-(4-Nitro-phenyl)-pent-3-en-1-ol (89d).**

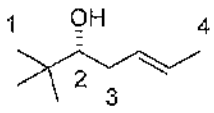
Yellowish liquid (75%): $[\alpha]_D$ +61.5 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 1.68-1.72 (br d, $^3J_{5\text{-}H,CH\text{-}CH}$ = 6.3 Hz,, 3H, 5-H), 2.25 (d, $^3J_{OH,1\text{-}H}$ = 3.2 Hz, 1H, OH), 2.30-2.40 (m, 2H, 2-H), 2.45-2.54 (m, 1H, 2-H'), 4.76-4.82 (m, 1H, 1-H), 5.35-5.45 (m, 1H, C*H*=CH), 5.57-5.67 (m, 1H, C*H*=CH), 7.50-7.54 (m, 2H, 6-H), 8.18 – 8.22 (m, 2H, 7-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3), 42.9 (CH_2), 72.3 (CH-O), 123.6 (CH), 125.5 (CH), 126.5 (CH), 130.9 (CH), 147.2 (C), 151.3 (C); IR (NaCl) ν 3565, 2940, 2357, 1715, 1605, 1520, 1437, 1347, 1107, 1050, 1013, 969, 854, 751, 701 cm^{-1}; MS (CI) *m/z* (%) 208 (100, $M+H^+$), 190 (10), 152 (10); HRMS (CI) 208.0972 ($C_{11}H_{14}NO_3$ requires 208.0974); chiral HPLC (Chiracel OJH column, hexane/2-propanol = 96:4, 0.75 mL min^{-1}) showed 98% ee (t_R = 39.7 min, t_S = 36.9 min).



***R*-(-)-(E)-1-Phenyl-hex-4-en-2-ol (89e).**[107]

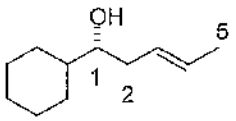
Colourless liquid (82% yield): $[\alpha]_D$ -4.5 (*c* 1.0, MeOH; literature[107] gives $[\alpha]_D$ +5.25 (*c* 1.56, MeOH) for the enantiomer); ^1H NMR (400 MHz; $CDCl_3$) δ 1.60-1.67 (m, 4H, O*H* and C*H*$_3$), 2.07 (dt, $^2J_{3\text{-}H,3\text{-}H'}$ = 14.7 Hz, $^3J_{3\text{-}H,2\text{-}H}$ = $^3J_{3\text{-}H,4\text{-}H}$ = 7.6 Hz, 1H, 3-H), 2.15-2.25 (m, 1H, 3-H'), 2.65 (dd, $^2J_{1\text{-}H,1\text{-}H'}$ = 13.6 Hz, $^3J_{1\text{-}H,2\text{-}H}$ = 7.8 Hz, 1H, 1-H), 2.72 (dt, $^2J_{1\text{-}H,1\text{-}H'}$ = 13.6 Hz, $^3J_{1\text{-}H',2\text{-}H}$ = 5.0 Hz, 1H, 1-H'), 3.72-3.82 (m, 1H, 2-H), 5.35-5.45 (m, 1H, C*H*=CH), 5.48-5.58 (m, 1H, C*H*=CH), 7.12-7.27 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 40.0 (CH_2), 43.2 (CH_2), 72.0 (CH-O), 126.4 (CH), 126.9 (CH), 128.5 (CH), 129.1 (CH), 129.4 (CH), 138.5 (C); MS (EI) *m/z* (%) 176 (M^+, 7), 121 (80), 92 (100); HRMS (EI) 176.1199 ($C_{12}H_{16}O$ requires 176.1201); chiral HPLC

(Chiracel IB column, hexane/2-propanol = 98:2, 0.75 mL min^{-1}) showed 96% ee (t_R = 11.9 min, t_S = 10.3 min).



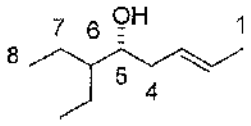
***R*-(+)-(E)-2,2-Dimethyl-hept-5-en-3-ol (89f).**[107]

Yellowish liquid (60%): $[\alpha]_D$ +12.0 (*c* 5.0, MeOH; literature[107] gives $[\alpha]_D$ +11.4 (*c* 5.19, MeOH)); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.90 (s, 9H, 1-H), 1.67-1.71 (br d, $^3J_{4-H,CH=CH}$ = 6.5 Hz,, 3H, 4-H), 1.85-1.95 (m, 1H, 3-H), 2.24-2.32 (m, 1H, 3-H'), 3.17-3.21 (m, 1H, 2-H), 5.39-5.62 (m, 2H, C*H*=C*H*); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (CH_3) , 25.7 (CH_3), 34.5 (C), 35.2 (CH_2), 78.3 (CH-O), 128.6 (CH), 128.7 (CH); ^{19}F NMR of the corresponding Mosher ester showed 93% ee (δ_R = -71.51 ppm and δ_S = -71.15 ppm).



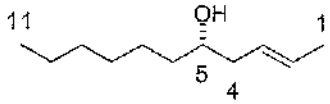
***R*-(+)-(E)-1-Cyclohexyl-pent-3-en-1-ol (89g).**[120]

Colourless liquid (80% yield): $[\alpha]_D$ +7.6 (*c* 2.5, $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 0.80-1.35 (m, 6H, Cy and O*H*), 1.55-1.70 (m, 7H, Cy and CH_3), 1.75-1.82 (m, 1H, Cy), 1.92-2.02 (m, 1H, 2-H), 2.15-2.25 (m, 1H, 2-H'), 3.22-3.28 (m, 1H, 1-H), 5.32-5.42 (m, 1H, C*H*=CH), 5.45-5.55 (m, 1H, C*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.1 (CH_3), 26.2 (CH_2), 26.3 (CH_2), 26.5 (CH_2), 28.2 (CH_2), 29.1 (CH_2), 37.5 (CH), 42.3 (CH_2), 74.9 (CH-O), 127.6 (CH), 128.9 (CH); IR (NaCl) ν 3362, 2925, 2857, 1449, 1261, 1027, 969 cm^{-1}; MS (CI) *m/z* (%) 151 (M^+-OH, 100), 113 (15), 95 (25); HRMS (CI) 151.1485 ($C_{11}H_{19}$ requires 151.1487); chiral GC (Supelco α-DEX 120 column, oven for 30 min at 105 °C, then 0.5 deg.min^{-1}) showed 97% ee (t_R = 30.1 min, t_S = 31.0 min).



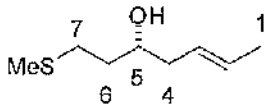
***R*-(+)-(E)-3-Ethyl-oct-6-en-4-ol (89h).**[104]

Colourless liquid (83% yield): $[\alpha]_D$ +4.0 (*c* 1.0, $CHCl_3$; literature[104] gives $[\alpha]_D$ -3.1 (*c* 1.0, $CHCl_3$)); ^1H NMR (400 MHz; $CDCl_3$) δ 0.90 (t, $^3J_{7\text{-}H,8\text{-}H}$ = 7.4 Hz, 6H, 8-H), 1.22-1.50 (m, 6H, 6-H and 7-H), 1.65-1.72 (br d, $^3J_{1\text{-}H,CH=CH}$ = 6.6 Hz, 3H, 1-H), 2.01-2.11 (m, 1H, 4-H), 2.18-2.26 (m, 1H, 4-H'), 3.52-3.60 (m, 1H, 5-H), 5.38-5.48 (m, 1H, C*H*=CH), 5.51-5.61 (m, 1H, C*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.6 (CH_3), 11.7 (CH_3), 18.1 (CH_3), 21.3 (CH_2), 21.9 (CH_2), 37.5 (CH), 46.0 (CH_2), 72.1 (CH-O), 127.9 (CH), 128.8 (CH); chiral GC (Supelco α-DEX 120 column, oven for 2 min at 65 ^{0}C, then 0.5 deg.min^{-1}) showed 95% ee (t_R = 36.0 min, t_S = 36.6 min).



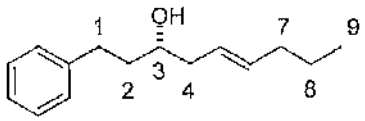
***S*-(-)-(E)-Undec-2-en-5-ol (89i).**[121]

Colourless liquid (85% yield): $[\alpha]_D$ -1.5 (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 0.87 (t, $^3J_{11\text{-}H,10\text{-}H}$ = 7.0 Hz, 3H, 11-H), 1.22-1.45 (m, 10H, CH_2CH_2), 1.52 (d, $^3J_{OH,5\text{-}H}$ = 3.9 Hz, 1H, O*H*), 1.65-1.72 (br d, $^3J_{1\text{-}H,CH\text{-}CH}$ = 6.4 Hz,, 3H, 1-H), 1.97-2.07 (m, 1H, 4-H), 2.15-2.25 (m, 1H, 4-H'), 3.52-3.60 (m, 1H, 5-H), 5.37-5.47 (m, 1H, C*H*=CH), 5.50-5.60 (m, 1H, C*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1 (CH_3), 18.1 (CH_3), 22.6 (CH_2), 25.7 (CH_2), 29.4 (CH_2), 31.8 (CH_2), 36.8 (CH_2), 40.7 (CH_2), 71.0 (CH-O), 127.2 (CH), 128.9 (CH); IR (NaCl) ν 3360, 3021, 2957, 2928, 2857, 1456, 1378, 1260, 1034, 967, 800 cm^{-1}; MS (CI) *m/z* (%) 153 (M^+-OH, 100), 97 (50), 71 (60); HRMS (CI) 153.1642 ($C_{11}H_{21}$ required 153.1643); ^{19}F NMR of the corresponding Mosher ester showed 97% ee (δ_R = -71.31 ppm and δ_S = -71.35 ppm).



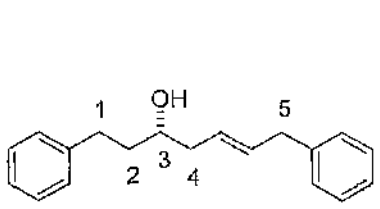
***R*-(-)-(E)-1-Methylsulfanyl-hept-5-en-3-ol (89j).**

Colourless liquid (72% yield): $[\alpha]_D$ -14.5 (*c* 0.5, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 1.67-1.77 (m, 5H, 6-H and 1-H), 1.92 (d, $^3J_{OH,5\text{-}H}$ = 3.9 Hz, 1H, O*H*), 2.05-2.15 (m, 4H, 4-H and CH_3S), 2.17-2.27 (m, 1H, 4-H'), 2.57-2.67 (m, 2H, 7-H), 3.67-3.77 (m, 1H, 5-H), 5.37-5.47 (m, 1H, C*H*=CH), 5.52-5.62 (m, 1H, C*H*=CH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.5 (CH_3), 18.1 (CH_3), 30.8 (CH_2), 35.6 (CH_2), 40.7 (CH_2), 70.1 (CH-O), 126.7 (CH), 129.2 (CH); IR (NaCl) ν 3734, 3375, 3025, 2915, 1437, 1260, 1016, 968, 800 cm^{-1}; MS (CI) *m/z* (%) 143 (M^+-OH, 100), 102 (40); HRMS (CI) 143.0892 ($C_8H_{15}S$ requires 143.0894); ^{19}F NMR of the corresponding Mosher ester showed 97% ee (δ_R = -71.24 ppm and δ_S = -71.22 ppm).



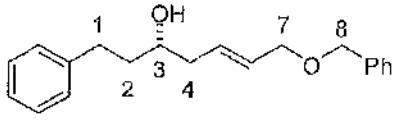
***S*-(-)-(E)-1-Phenyl-hept-5-en-3-ol (89k).**

Yellowish liquid (83%): $[\alpha]_D$ -11.2 (*c* 1.7, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 0.90 (t, $^3J_{9\text{-}H,8\text{-}H}$ = 7.3 Hz, 3H, 9-H), 1.40 (sex, $^3J_{9\text{-}H,8\text{-}H}$ = 7.3 Hz, 2H, 8-H), 1.68 (br s, 1H, O*H*), 1.74-1.82 (m, 2H, 2-H), 2.01 (q, $^3J_{7\text{-}H,8\text{-}H} = {}^3J_{7\text{-}H,HC=C}$ = 7.3 Hz, 2H, 7-H), 2.08-2.16 (m, 1H, 4-H), 2.24-2.30 (m, 1H, 4-H'), 2.64-2.74 (m, 1H, 1-H), 2.78-2.86 (m, 1H, 1-H'), 3.58-3.66 (m, 1H, 3-H), 5.36-5.46 (m, 1H, C*H*=CH), 5.52-5.60 (m, 1H, C*H*=CH), 7.18-7.32 (m, 5H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6 (CH_3), 22.5 (CH_2), 32.1 (CH_2), 34.7 (CH_2), 38.4 (CH_2), 40.8 (CH_2), 70.1 (CH-O), 125.6 (CH), 125.7 (CH), 128.3 (CH), 128.4 (CH), 134.8 (CH), 142.2 (C); IR (NaCl) ν 3690, 3391, 3062, 3027, 2957, 2928, 2870, 1495, 1455, 1260, 1050, 970, 799, 745, 698 cm^{-1}; MS (CI) *m/z* (%) 201 (100, M^+-OH), 134 (40); HRMS (CI) 201.1644 ($C_{15}H_{21}$ requires 201.1643); chiral HPLC (Chiracel IB column, hexane/2-propanol = 98:2, 0.75 mL min^{-1}) showed 97% ee (t_R = 32.6 min, t_S = 19.6 min).



***S*-(-)-(E)-1,7-Diphenyl-hept-5-en-3-ol (89l).**

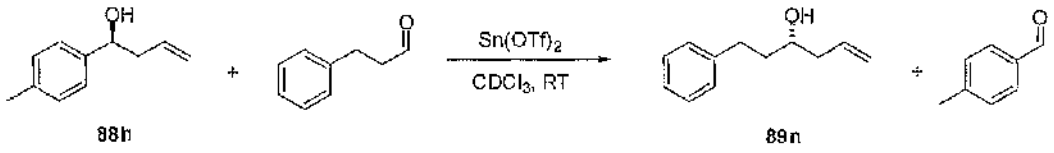
Yellowish liquid (85%): $[\alpha]_D$ -6.6 (*c* 0.8, $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$) δ 1.59 (br s, 1H, OH), 1.64-1.74 (m, 2H, 2-H), 2.04-2.12 (m, 1H, 4-H), 2.16-2.24 (m, 1H, 4-H'), 2.54-2.63 (m, 1H, 1-H), 2.67-2.76 (m, 1H, 1-H'), 3.28 (d, $^3J_{5\text{-}H,CH=CH}$ = 6.7 Hz, 2H, 5-H), 3.52-3.60 (m, 1H, 3-H), 5.37-5.47 (m, 1H, C*H*=CH), 5.58-5.67 (m, 1H, C*H*=CH), 7.06-7.13 (m, 6H, Ph), 7.16-7.23 (m, 4H, Ph); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0 (CH_2), 38.4 (CH_2), 39.1 (CH_2), 40.7 (CH_2), 70.2 (CH-O), 125.8 (CH), 126.0 (CH), 127.2 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 133.1 (CH), 140.4 (C), 142.1 (C); IR (NaCl) ν 3567, 3397, 3061, 3026, 2926, 1520, 1495, 1454, 1346, 1260, 1178, 1030, 971, 802, 746, 698 cm^{-1}; MS (CI) *m/z* (%) 249 (100, M^+-OH), 171 (40), 132 (60), 117 (30); HRMS (CI) 249.1641 ($C_{19}H_{21}$ requires 249.1643); chiral HPLC (Chiracel IB column, hexane/2-propanol = 93:7, 0.75 mL min^{-1}) showed 96% ee (t_R = 14.8 min, t_S = 16.6 min).



***S*-(-)-(E)-7-Benzyloxy-1-phenyl-hept-5-en-3-ol (89m).**[122]

Yellowish liquid (86%): $[\alpha]_D$ -9.7 (*c* 1.0, $CHCl_3$) (literature[122] gives $[\alpha]_D$ -9.30 (*c* 1.0, $CHCl_3$)); ^1H NMR (400 MHz; $CDCl_3$) δ 1.72-1.84 (m, 3H, 2-H and O*H*), 2.18-2.26 (m, 1H, 4-H), 2.29-2.36 (m, 1H, 4-H'), 2.66-2.74 (m, 1H, 1-H), 2.78-2.86 (m, 1H, 1-H'), 3.64-3.72 (m, 1H, 3-H), 3.96-4.08 (m, 2H, 7-H), 4.52 (s, 2H 8-H), 5.68-5.80 (m, 2H, C*H*=C*H*), 7.19-7.38 (m, 10H, Ar); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.0 (CH_2), 38.5 (CH_2), 40.6 (CH_2), 70.1 (CH-O), 70.6 (CH_2-O), 72.1 (CH_2-O), 125.8 (CH), 127.6 (CH), 127.7 (CH), 128.3 (CH), 128.4 (CH), 128.4 (CH), 129.8 (CH), 130.1 (CH), 138.2 (C), 142.0 (C); chiral HPLC (Chiracel IB column, hexane/2-propanol = 9:1, 0.75 mL min^{-1}) showed 95% ee (t_R = 46.3 min, t_S = 21.4 min).

***S*-(-)-1-*p*-tolyl-but-3-en-1-ol (88h).**[123,124] Allyltrichlorosilane (1.3 mL, 8.9 mmol) was added to a solution of *p*-tolylaldehyde (1.00 g, 8.3 mmol), METHOX (**105a**) (100 mg, 0.26 mmol) and Hünig base (6 mL, 30 mmol) in freshly distilled CH_3CN (50 mL) at -40 °C and the resulting mixture was stirred at that temperature for 18 h. A chilled saturated aqueous solution of $NaHCO_3$ (20 mL) was then added to the mixture and the organic layer was separated. The aqueous layer was extracted with AcOEt (2 × 100 mL), the combined organic layers were dried with Na_2SO_4, and the solvents were removed in vacuo. The crude product was purified by chromatography on a column of silica gel (2.5 × 25 cm) using a gradient of petroleum ether and ethyl acetate as eluent (100:0 to 80:20) to afford **88h** (1.30 g, 90%) as a yellowish oil: $[\alpha]_D$ -41.0 (*c* 0.8, C_6H_6; literature[124] gives $[\alpha]_D$ -47.1 (*c* 1.5, C_6H_6)); ^{1}H NMR (400 MHz; $CDCl_3$) δ 2.05 (br s, 1H, O*H*), 2.35 (s, 3H, C*H*$_3$), 2.48-2.54 (m, 2H, C*H*$_2$), 4.68-4.73 (m, 1H, C*H*-O), 5.12-5.20 (m, 2H, C*H*$_2$=CH), 5.76-5.88 (m, 1H, C*H*=CH$_2$), 7.15-7.19 (m, 2H, Ar), 7.24-7.27 (m, 2H, Ar); chiral GC (Supelco β-DEX 120 column, oven for 2 min at 100°C, then 1 deg.min^{-1}) showed 91% ee (t_R = 32.2 min, t_S = 32.7 min).

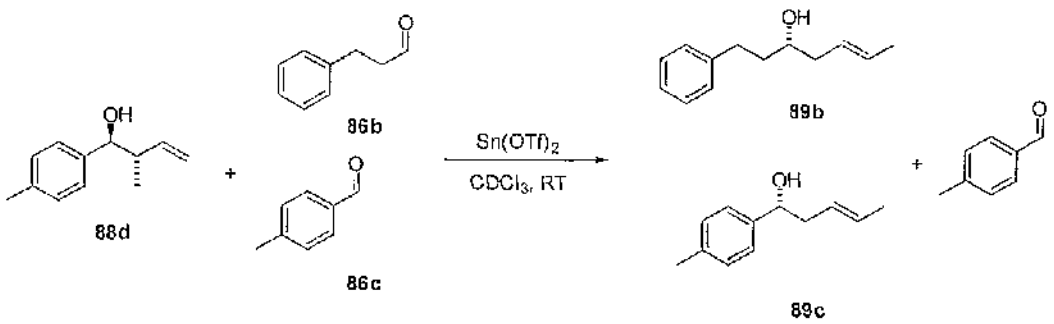


Tin(II) Triflate–Catalysed Reaction between 88h and 86b. $(TfO)_2Sn$ (6.5 mg, 0.015 mmol) was added to a solution of *S*-(-)-**88h** (50 mg, 0.31 mmol) and **86b** (134 mg, 1 mmol) in dry $CDCl_3$ (2 mL) and the reaction mixture was stirred at room temperature, while monitoring by NMR and GC (50 μL aliquots were taken at the specified time).

Time, h	Conversion of **88h**, %	ee of **89n**, %
0.3	20	72
2	38	54
24	83	14

***S*-(-)-1-Phenyl-hex-5-en-3-ol 89n.**[125]

Colourless liquid (60%). ^{1}H NMR (400 MHz; $CDCl_3$) δ 1.68-1.77 (m, 2H, CH_2), 2.07-2.16 (m, 1H, CH_2), 2.22-2.31 (m, 1H, CH_2), 2.57-2.67 (m, 1H, CH_2), 2.70-2.79 (m, 1H, CH_2), 3.57-3.65 (m, 1H, C*H*-O), 5.04-5.11 (m, 2H, CH_2=CH), 5.69-5.81 (m, 1H, C*H*=CH_2), 7.09-7.25 (m, 5H, Ph); chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 110 °C, then 0.5 deg.min^{-1}) showed t_S = 41.5 min, t_R = 41.0 min



Tin(II) Triflate–Catalysed Crotyl Transfer from 88d; a Competition experiment. $(TfO)_2Sn$ (6.5 mg, 0.015 mmol) was added to a solution of **88d** (55 mg, 0.31 mmol), **86c** (74 mg, 0.62 mmol), and **86b** (83 mg, 0.62 mmol) in $CDCl_3$ (4 mL) and the reaction mixture was stirred at room temperature and monitored by NMR. After 20 min the ^{1}H NMR spectrum showed the following ratio of the compounds in the mixture: **88d** : **89c** : **89b** = 0.115 : 0.161 : 0.724

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