**CHARLES UNIVERSITY IN PRAGUE**

FACULTY OF SCIENCE

DEPARTMENT OF ORGANIC AND NUCLEAR CHEMISTRY


# DIPLOMA THESIS

Enantioselective α-allylation of aldehydes
as a two-step catalytic process

Enantioselektivní α-allylace aldehydů jako dvoustupňový
katalytický proces

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Praha 2009

I thereby declare that this work was elaborated by myself personally under the supervision of Prof. Kočovský and all the sources are properly cited.

In Prague, 21st July 2009 Vojtěch Kapras

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# List of abbreviations:

| | |
|---|---|
| 4Å MS | Molecular sieves, pore size 4 Å |
| APT | Attached proton test |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| BINOL | 1,1‘-Bi-2-naphthol |
| CI | Chemical ionization |
| CSA | 10-Camphorsulfonic acid |
| DIPEA | *N*,*N*-Diisopropyl-ethylamine |
| DMAP | 4-(Dimethylamino)-pyridine |
| DMF | *N*,*N*-Dimethylformamide |
| DMSO | Dimethylsulfoxide |
| DRIFT | Diffuse Reflectance Infrared Fourrier transform |
| EI | Electron impact |
| $Et_2O$ | Diethyl ether |
| Fmoc | 9-Fluorenylmethoxycarbonyl |
| GC | Gas chromatography |
| H,H-COSY | Hydrogen-hydrogen correlation spectroscopy |
| H,C-HSQC | Hydrogen-carbon heteronuclear single quantum coherence |
| HMPA | Hexamethylphosporamide |
| HPLC | High performance liquid chromatography |
| HRMS | High resolution mass spectrum |
| $H_2TPP$ | 5,10,15,20-Tetraphenyl-21*H*,23*H*-porphine |
| IR | Infrared spectroscopy |
| MCPBA | 3-Chloroperoxybenzoic acid |
| METHOX | 5-(2’,4’,6’-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.02,7]undeca-2,4,6-triene 6-Oxide |
| MS | Mass spectrometry |
| MTPA | 2-Methoxy-2-(trifluoromethyl)-phenylacetic acid |
| NMR | Nuclear magnetic resonance |
| PCC | Pyridinium chlorochromate |
| PINDOX | (6*R*, 6’*R*, 8*R*, 8‘*R*)-(+)-5, 5‘, 6, 6‘, 7, 7‘, 8, 8‘- Octahydro-6,6‘,7,7‘-tetramethyl bis(6,8-methanoquinoline) *N*-Monoxide |
| *p*-Tol | *p*-Tolyl |
| QUINOX | 1-(2-Methoxy-1-naphthyl)-isoquinoline-*N*-oxide |

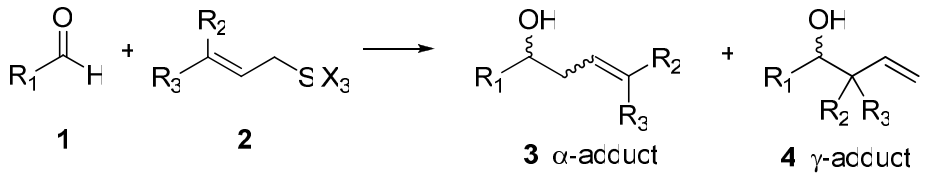
| | |
|---|---|
| TBABr | Tetrabutylammonium bromide |
| TBAF | Tetrabutylammonium fluoride |
| TfOH | Trifluoromethanesulfonic acid |
| THF | Tetrahydrofuran |
| TLC | Thin layer chromatography |
| TMSOTf | Trimethylsilyl trifluoromethanesulfonate |
| TsOH | *p*-Toluenesulfonic acid |
| UV | Ultraviolet |

# Contents

# 1. Introduction

## *1.1. Allylation of aldehydes mediated by organosilicon compounds*

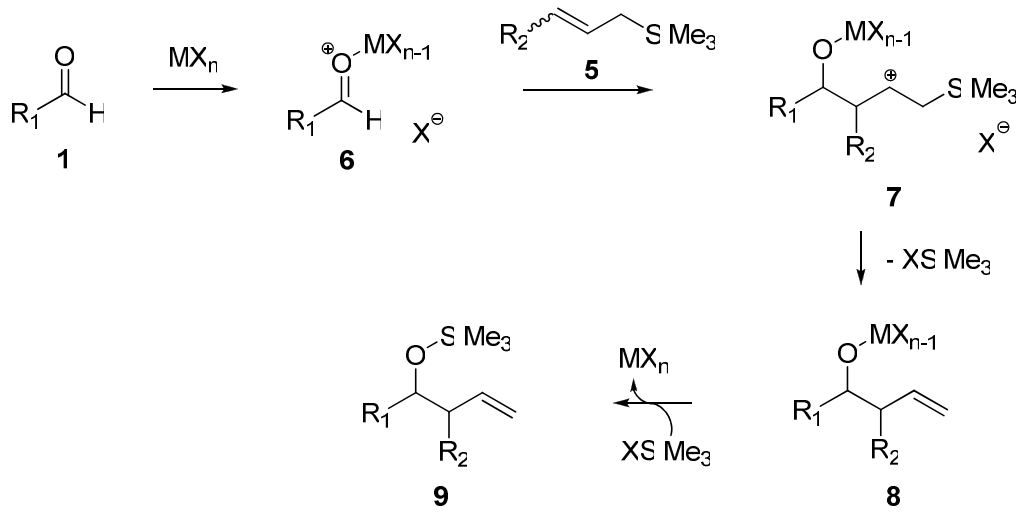
C-C bond forming reactions have always been the backbone of synthetic organic chemistry. Amongst them stands the allylation of aldehydes **1** mediated by organosilicon species **2** - a reliable and efficient synthetic method. The common feature of organosilicon and organometallic allylations in general are two distinct courses of reaction: α-allylation forming the linear product **3**, or with formal allylic rearrangement forming branched product **1** of γ-allylation. Of these two, the latter alternative almost exclusively predominates (**Scheme 1**). Intensive research in this area during the past few decades has brought its catalytic and asymmetric variant[1]. Our aim was to probe the α-allylation issue and develop it into a widely applicable synthetic method.




**Scheme 1** Alyllation of aldehydes with organosilicon species

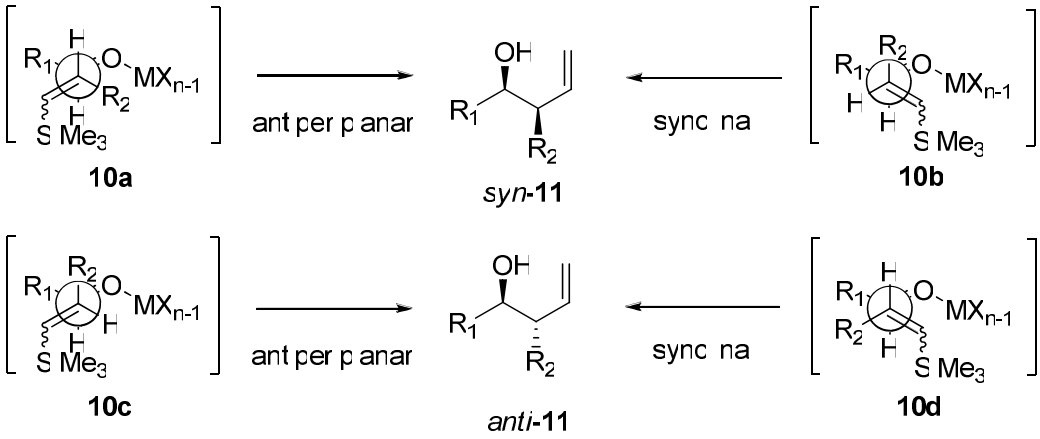
## *1.2. Lewis acid-catalyzed enantioselective allylation*

Allylations mediated by organosilicon compounds constitute an important part of this group of reactions (also called Hosomi-Sakurai reaction), organostannanes being also widely used. The majority of enantioselective addition of organosilicons to aldehydes involve trimethylsilanes **5**[1]. Here, a Lewis acid activates the carbonyl group towards the nucleophilic attack of the allylic double bond. The whole process is stepwise, addition is followed by elimination of the trimethylsilyl cation from intermediate **7** (**Scheme 2**) [2]. Several catalytic variants were described, employing various Lewis acids. However, the *in situ* released trimethylsilyl cation was found to be significantly competing with some of the catalysts or even substituting them[3]. This fact complicates the enantioselective reaction by forming a hardly avoidable achiral side-path in the mechanism.

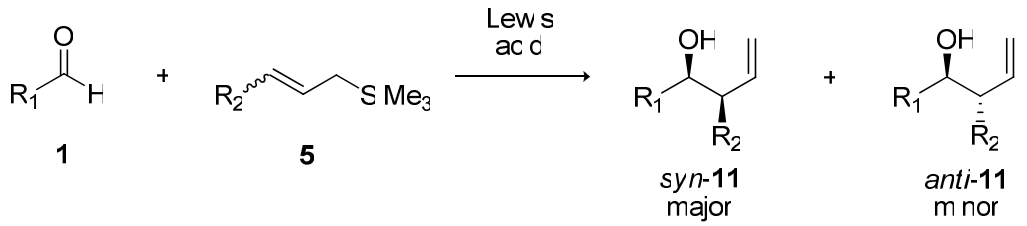



**Scheme 2** Mechanism of Lewis acid catalyzed allylation with allylic trimethylsilanes

The Lewis acid-promoted addition of allylic silanes **5** to aldehydes typically proceeds through an open-state transition structure **10**, characterized by an *anti* $S_E$' arrangement of the silyl electrofuge with respect to the aldehyde, regardless of the Lewis acid employed. The stereochemical outcome of the reaction is directed by the conformational preference of this transition structure **10** (**Scheme 3**). The ratio of synclinal and antiperiplanar orientation has been found to be dependent on the Lewis acid applied[4]. Generally, in the case of 3-substituted allylic silanes **5**, the *syn*- product **11** is formed independently on E/Z geometry of the starting compound (**Scheme 4**)[5].

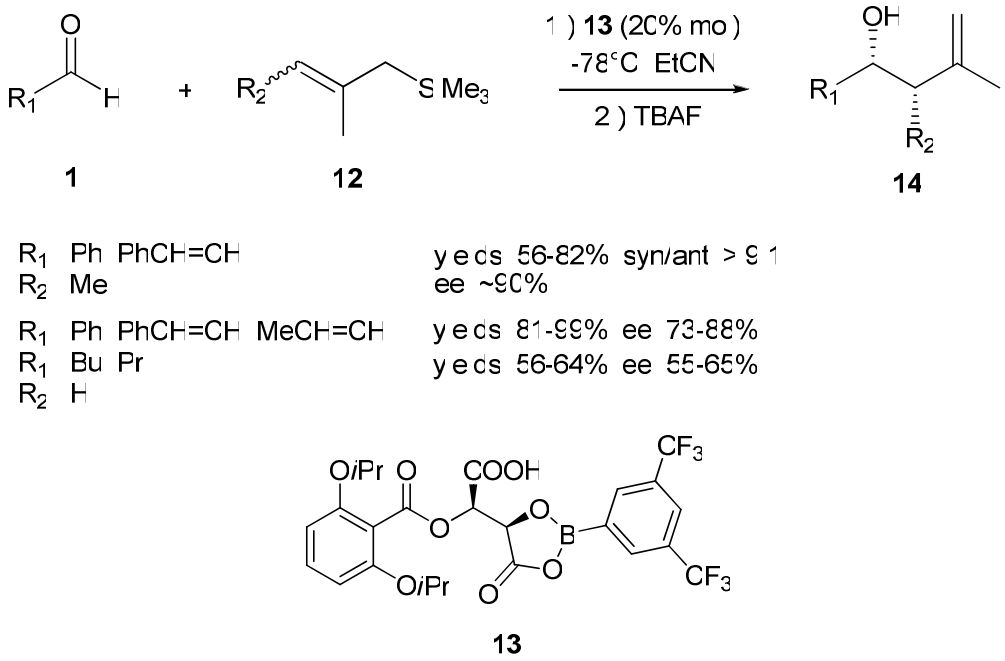



**Scheme 3.** The effect of the transition state conformations on the stereochemical outcome of the allylation of aldehydes with allylsilanes.



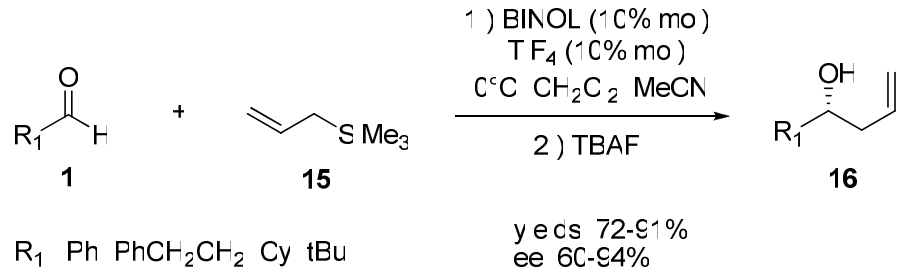

**Scheme 4** General outcome of the Lewis acid-catalyzed allylations

With the boom of asymmetric synthesis, it is not surprising that the field of chiral Lewis acids has received considerable attention by many chemists and that vast array of chiral Lewis acids have been employed to date. The first enantioselective addition of allylic silanes **12** to aldehyde **1** was reported by Yamamoto in 1991, who used the chiral acyloxyborane catalysts **13** (**Scheme 5**) [6,7]. The *syn*- diastereoisomer **14** was formed with excellent selectivity and the enantiomeric excess was good for 2-alkyl allylic silanes; however, a rather high catalyst loading was required (10-20 mol %) and selectivities dropped for linear allylic silanes **5**.



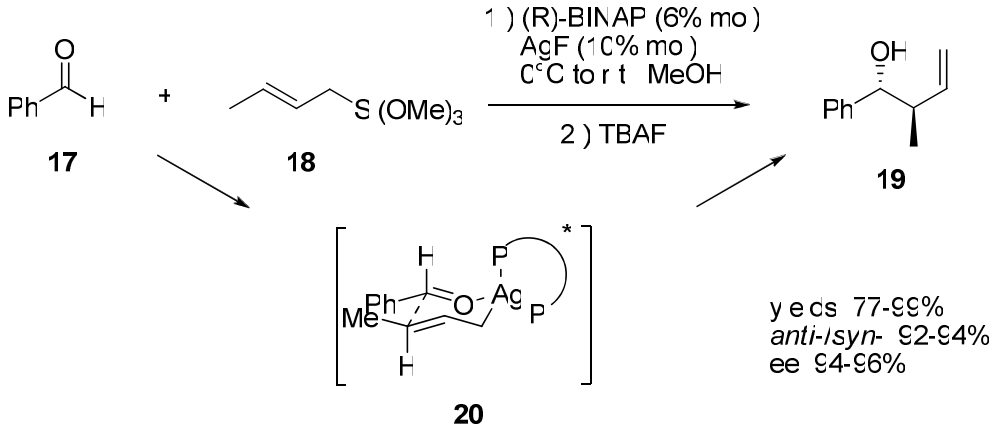

**Scheme 5** Asymmetric Lewis acid catalyzed allylation

One of the most extensively studied catalysts were Ti(IV)-BINOL complexes. The first use of this system was described by Mikami, who used glyoxylates as model substrates[8]. This system was later extended to less reactive aliphatic and aromatic aldehydes **1**, although only for allylic stannanes[1]. The Lewis acidity of Ti(IV)-BINOL type complexes is not sufficient for convenient reactions with allylic silanes. An elegant solution to this problem was devised by Carreira, who found that enhanced reactivity could be secured by the use of $TiF_4$ in place of $Ti(O\textit{i}\text{-}Pr)_4$[9].




**Scheme 6** Asymmetric Lewis acid catalyzed allylation

Yamamoto has developed the complex BINAP-AgF as catalyst for allylic trimethoxysilanes **18**, a new class of reactants [10]. Interestingly, the diastereoselectivity of this reaction is reversed, which led in consent with the spectral data to the formulation of a mechanism different from typical Lewis acid catalyzed additions. A fast transmetallation precedes the addition process, which involves the closed chair-like transition state **20**. Surprisingly, the configuration of product **19** is virtually independent of the starting (*E/Z*)-geometry (**Scheme 7**).

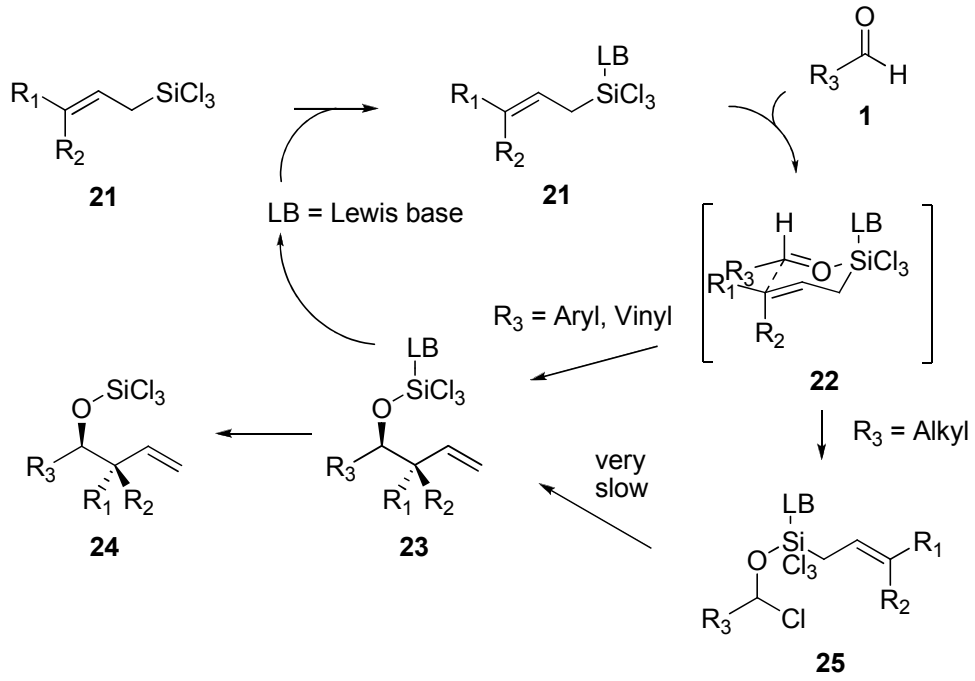



**Scheme 7** BINAP-AgF catalyzed allylation

## *1.3. Lewis base-catalyzed enantioselective allylation*

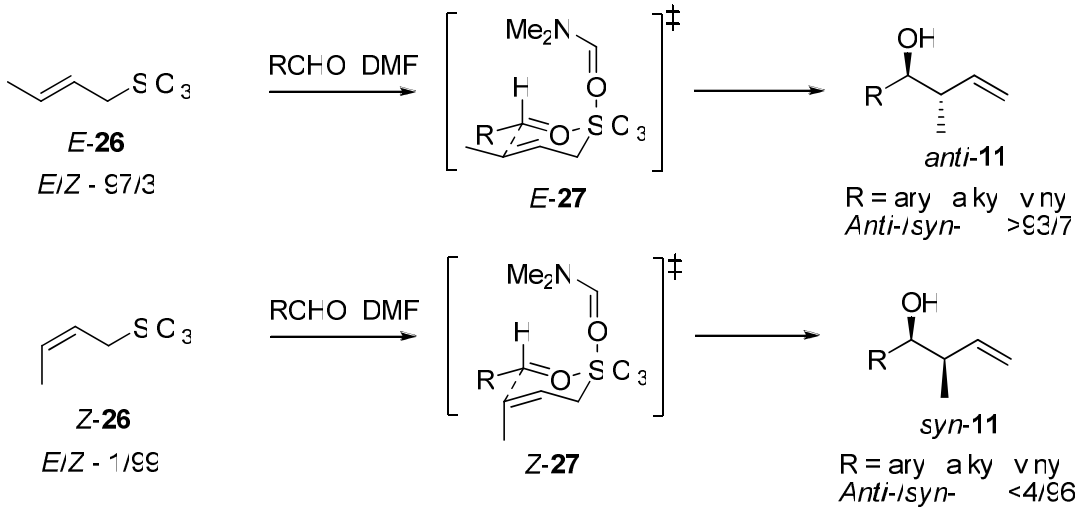
The Lewis base-catalyzed enantioselective allylation mediated by organosilicon compounds **21** was pioneered by Sakurai[11] and Kobayashi[12] in the end of the 1980. In contrast to the previously discussed Lewis acid-catalyzed reactions, excellent diastereoselectivity was observed in all experiments. This lead to the formulation of a cyclic trasition state mechanism, significantly different from the acid catalyzed variant[12,13]. The new mechanism relies on reversible coordination of a Lewis base to the central silicon atom of the trihalogenosilyl group, thus making the silicon atom of intermediate **21** more Lewis acidic. The allylation itself is then faciliated by coordination of the silicon atom to the carbonyl oxygen and formation of the six-membered cyclic transition state **22**. This arrangement 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. Dissociation of the Lewis base

from complex **23** is then a prerequisite for completing the whole catalytic circle. Notable side reaction takes place in the case of aliphatic aldehydes, where reaction of trichlorosilane **21** leads to the formation of α-chlorosilyl ether **25**, which is unreactive in the sense of cyclic process (**Scheme 8**)[14]. Eficient protocol for such reaction still remains elusive.




**Scheme 8** Mechanism of Lewis base catalyzed allylations

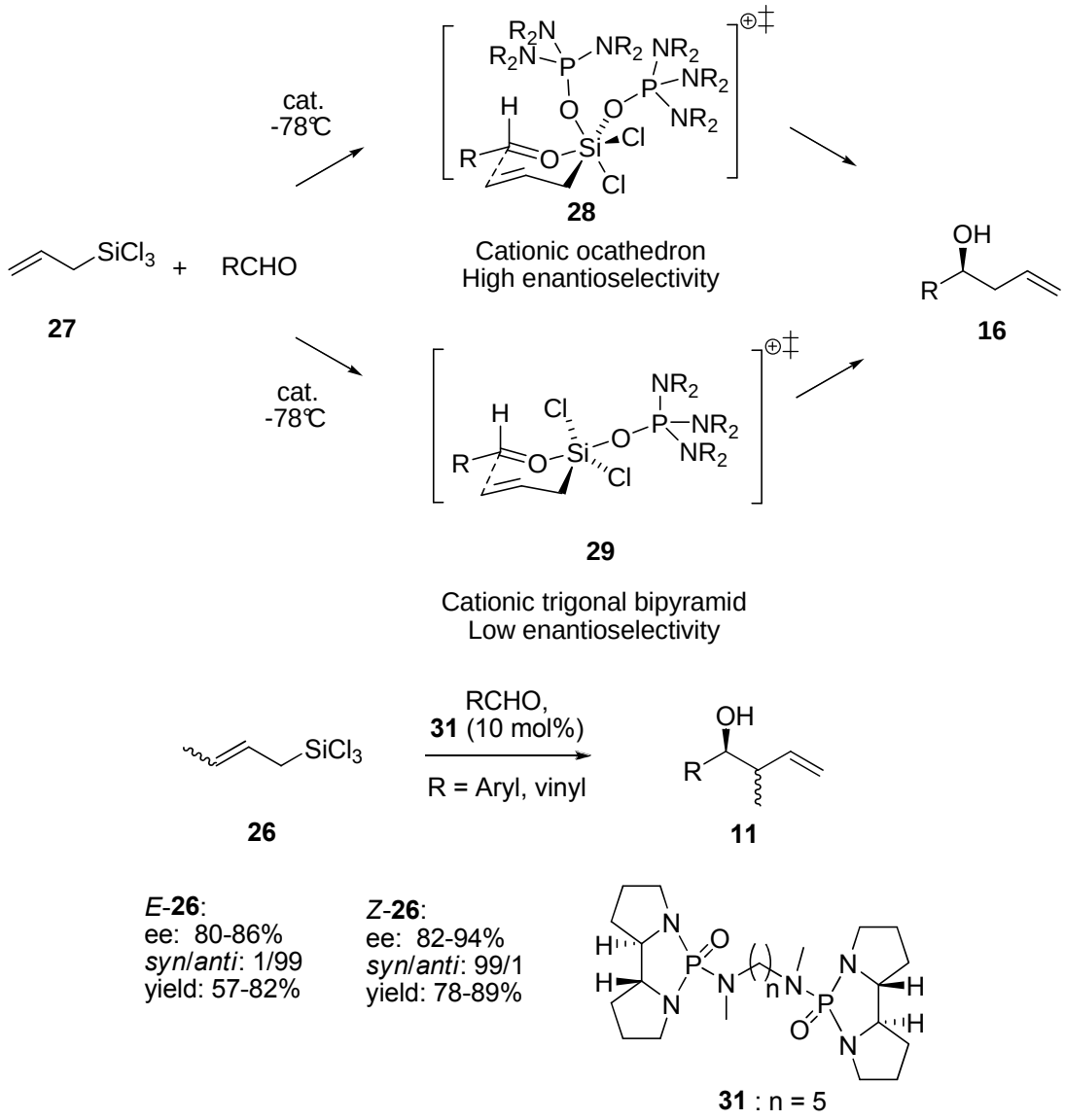
The first example of this type of reaction was reported by Sakurai, who utilized allylic trifluorosilanes and the source of fluoride anions[11]. Anionic six-membered cyclic transition state was proposed on the basis of excellent diastereoselectivity. Thus, reaction of (*E*)-2-butenyl-trifluorosilane gave rise specifically to the *anti*-homoallylic alcohol, whereas (*Z*)-2-butenyl-trifluorosilane formed exclusively the *syn* isomer.




**Scheme 9** DMF catalyzed allylation

In 1993, Kobayashi and coworkers described the reaction of allylic trichlorosilanes **26** with aldehydes in the presence of the Lewis basic solvent DMF[12]. Again, the selectivities observed were supporting the idea of the closed rigid transition state **27** (**Scheme 9**).

The latter observation was soon followed by the first asymmetric variant, reported by Denmark, employing chiral phosphoramides as stoichiometric activators of trichlorosilanes[15]. Lower promotor loading (0.1 eqiv.) showed the possibility of catalytic arrangement of this reaction, in spite of a rather low yield and enantioselectivity of the reaction. Similar phosphoramides derived from proline were reported by Iseki[16,17]. Kinetic studies and the observation of a nonlinear effect of the chiral phosphoramide catalysis enabled Denmark to suggest a corrected reaction mechanism (**Scheme 10**)[18]. According to the new model, the highly enantioselective transition state consisted of two molecules of phosphoramide coordinated to the silicon atom. This insight led to the application of chiral bisphosphoramides, displaying both high yields and enantioselectivity[18,19].

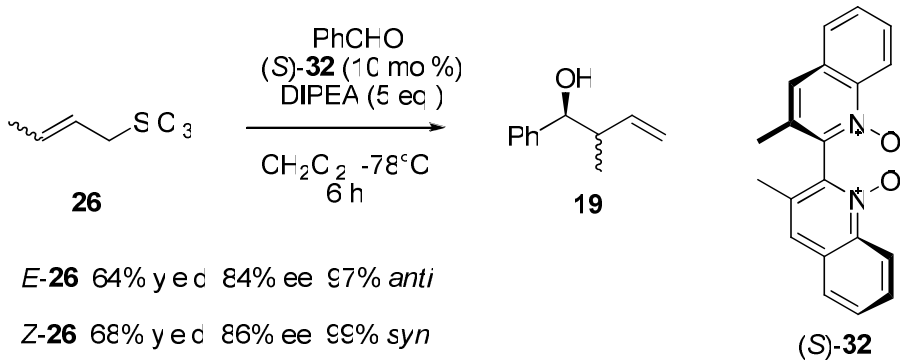



**Scheme 10** Phosphoramide catalyzed allylation of aldehydes

Turning his attention back to DMF, Iseki developed chiral formamide promoters showing modest yields and enantioselectivity in the reaction with aliphatic aldehydes; however, the reaction times were measured in weeks[20,21]. Further addition of 1 equivalent of HMPA allowed a catalytical arrangement of the reaction and much improved the yields and enantioselectivity up to 95% ee.

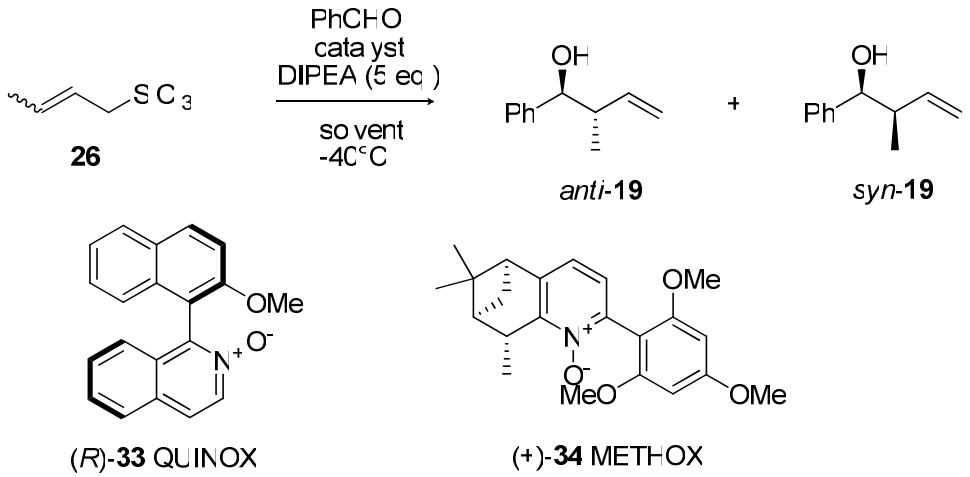
Amongst other chiral catalysts, developed over the time, are the urea[22], diamine[23], phosphineoxide[24,25] and phosphonamide[26] analogues, all exhibiting only modest enantioselectivities.

Chiral *N*-oxides have emerged as another class of highly selective catalysts for the addition of allylic trichlorosilanes. The first example was published by Nakajima, who used axially chiral biquinoline *N*,*N*-dioxide **32** as a catalyst to promote diastereo- and enantioselective allylation of benzaldehyde (**Scheme 11**)[27]. The reaction was dramatically accelerated by addition of DIPEA to the system.




**Scheme 11** Catalysis by chiral N-oxides

Very efficient catalysts were synthesised by the group of Kočovský as a result of intensive research in this field. Extension of the bipyridyl motiff led to PINDOX catalyst and its conformationaly locked derivative, displaying high diastereoselectivities and modest yields[28,29]. Further investigation brought the monodentate pyridine-N-oxides QUINOX **33** [30,31] and notably METHOX **34** [32], acting as a remarkably efficient catalysts in the allylation reaction with up to 98% ee. Although the two latter compounds promote the reaction with excellent diastereoselectivity in respect to configuration of allylic bond in crotyltrichlorosilanes **26**, different kinetic preference is observed in each of them. Whereas METHOX **34** shows a strong kinetic preference toward the *E*-isomer of **26**, QUINOX **33** exhibits a kinetic preference toward *Z*-isomer of **26**, which is an uncommon phenomenon in this field (**Scheme 12**). In contrast to METHOX, which is tolerant to a wide range of electronic effect on the aldehyde (ee 89-96%), QUINOX's asymmetric induction is highly dependent on the electron density of the carbonyl group.

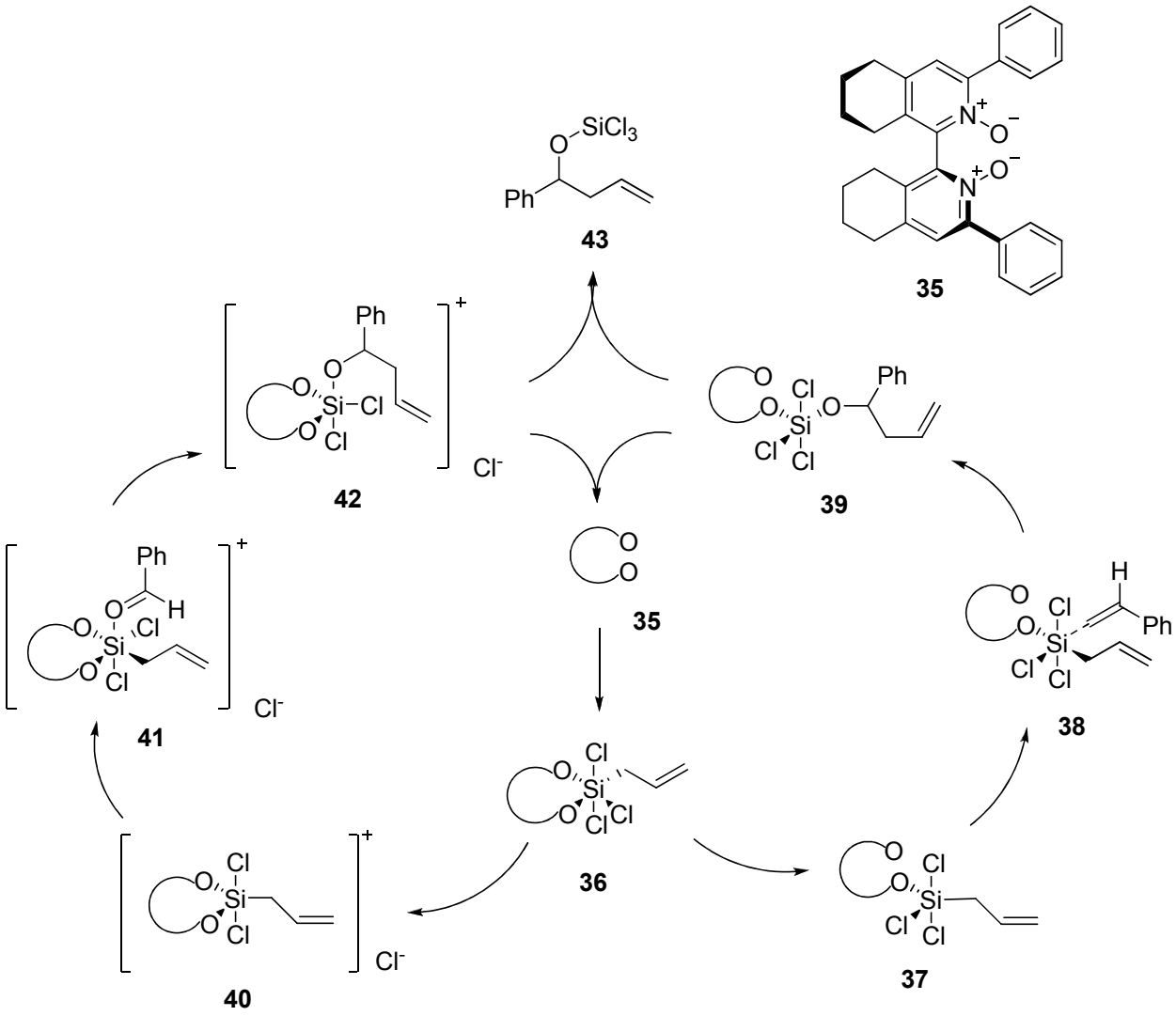



| Composition of **7** *E* / *Z* ratio | Catalyst (5 mol % ) | Solvent | Conversion (%) | anti / *syn* ratio | ee (%) |
|---|---|---|---|---|---|
| 87 / 13 | (*R*)-**33** | $CH_2Cl_2$ | 70 | 68 / 32 | 65 / 78 |
| 87 / 13 | (+)-**34** | MeCN | 95 | > 99 / 1 | 95 / x |
| < 1 / 99 | (+)-**34** | MeCN | 26 | 14 / 86 | x / 26 |

**Scheme 12** Catalysis by METHOX[32] and QUINOX[31]

Thus, QUINOX exhibits 96% ee with 4-$CF_3C_6H_4CHO$ and only 16% ee for 4-$MeOC_6H_4CHO$. Recent mechanistic studies together with computational methods led to proposition of reaction mechanism of QUINOX catalyzed allylation[33]. Noteworthy advances in the field of pyridine-*N*-oxide catalysis were also reached by the groups of Hayashi[34], Andrus[35] and Kotora[36], giving comparable yields and enantioselectivities of aromatic homoallylic alcohols **11** and **16**.

Quite recently, an interesting feature was observed and described by Kotora[37] on *N*,*N*'-dioxide catalysis. Depending on the solvent used, allylation of benzaldehyde with catalyst **35** gave opposite enantioselectivities. The conductivity experiments together with computational analysis led to proposal of two distinct mechanisms. In less polar solvents such as toluene, THF and EtOAc the reaction proceeds via neutral intermediates **37**-**39** forming (*S*) isomer of **43**, whereas in polar solvents, more capable of stabilising ionic compounds, the reaction proceeds via charged intermediates **40**-**42**, resulting into opposite enantiomer of **43** (**Scheme 13**

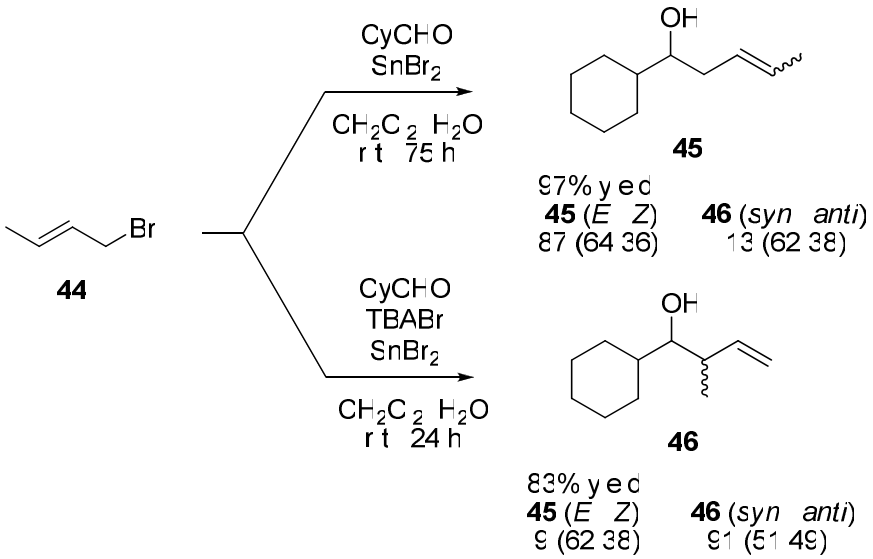



**Scheme 13** Mechanistic rationale for solvent effect in Lewis-base catalyzed allylations[37]

## *1.4. α-Allylation of carbonyl compounds*

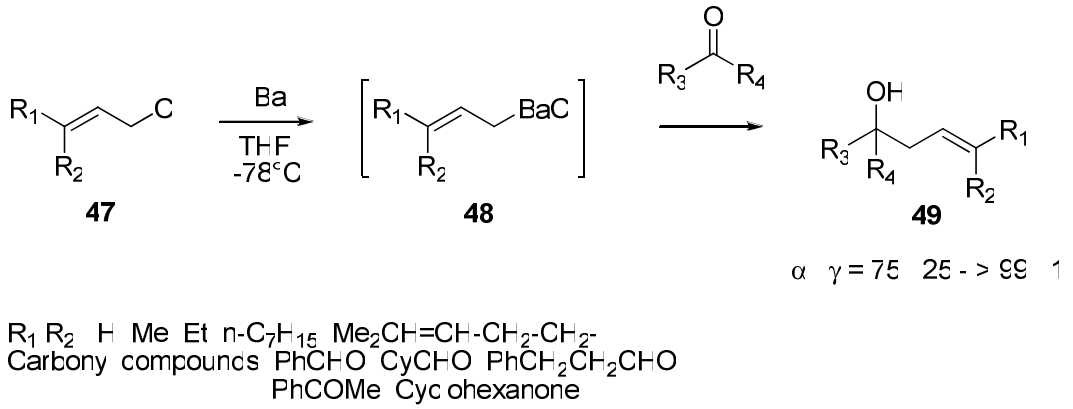
In contrast to allylation reactions with formal allylic rearrangement, the reports of regioselective and stereoselective α-allylation are scarce up to present date. The first example of regioselective α-allylation was reported by Y. Yamamoto in 1983, who utilized a mixture of allylic Grignard reagents with $AlCl_3$[38]. The respective homoallylic alcohols were obtained in high yields with 83-94% regio- and 80-90% (*E/Z*)-stereoselectivity. Higher regioselectivities were achieved by Masuyama in Barbier-type reaction of allylic bromides such as **44** with tin(II) bromide in water:DCM biphasic system[39]. However, the range of (*E/Z*) stereoselectivities was broader (**Scheme 14**).

Yamamoto described the use of allylic organobarium compounds **48** generated *in situ* for addition to various aldehydes and ketones (**Scheme 15**)[40]. The reaction occured with complete retention of the the allylic double bond configuration. The scope of the reaction was later greatly expanded, encompassing reaction with conjugated ketones or carbon dioxide[41]. α,β-Unsaturated ketones gave




**Scheme 14** Direct α-allylation of aldehydes

almost exclusively the product of 1,4-addition. The mechanistic rationale for the unusual reactivity of allylic organobarium compounds **48** is not clear. The authors proposed a possible four-membered cyclic transition state between C=O and C-Ba bonds, while competitive six-membered transition state leading to γ-adduct is disfavored by unusually long C-Ba bond (2.76-2.88 Ĺ).



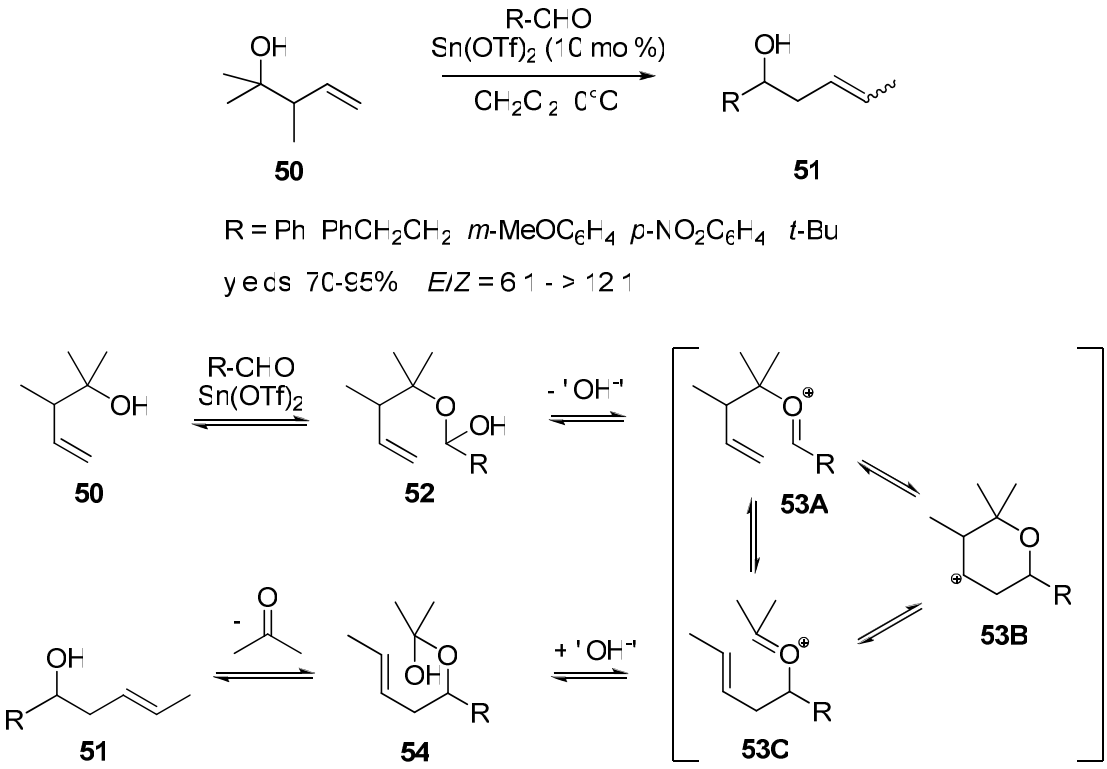

**Scheme 15** α-Allylation via allylbarium species

One example of stereoselective α-prenylation was used by Hong, in his synthesis of rosiridol[42]. The exact mechanism of this reaction remains unknown.

## *1.5. Allylic transfer*

Entirely new approach to the α-allylation issue was introduced by Nokami in 1998[43]. With a catalytic amount of $Sn(OTf)_2$, allylic group was stereoselectively transferred from homoallylic alcohols to aldehydes. Thus, the product of γ-allylation **50** can be easily and stereoselectively transformed to the formal product of α-allylation **51**, making it a promising method for syntesis of linear chains bearing chiral centers. Notably, other Lewis acids and even *N*-

hydroxybenzenesulfonamide, a mild Brønsted acid, were able to promote this reaction[44]. This fact, together with the stereochemical outcome of the reaction led Nokami to the formulation of a reaction mechanism (**Scheme 16**). At first, with the catalysis by $Sn(OTf)_2$, the hemiacetal **52** is formed, followed by elimination of a hydroxyl and formation of the oxycarbenium ion **53A**. The latter species undergoes an oxonia-[3.3]-sigmatropic rearrangement to generate the oxycarbenium ion **53C**, which is attacked by the hydroxyl equivalent, present in the reaction mixture, thus forming hemiacetal **54**. Cleavage of the latter hemiacetal **54** gives the final product **51** and acetone. The key step of the whole process is the oxonia-Cope rearrangement. Formation of the third type of carbocation **53B** was also described, which gives rise to side product of Prins cyclization reaction. The driving force of the reaction is the formation of (1) more stable cations, (2) sterically less

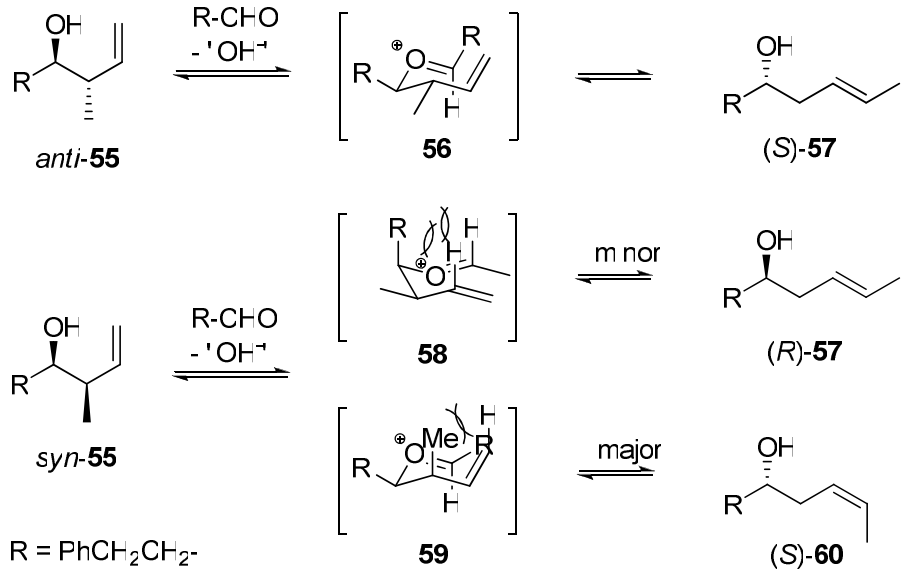



**Scheme 16** Lewis acid catalyzed allylic transfer

hindered homoallylic alcohols and/or (3) thermodynamically more stable olefins. This reaction was later modified by Yanagisawa, who employed acetophenone instead of acetone as leaving stable ketone and dibutyltin oxide, affording the rearranged product **51** in slightly higher yields[45].

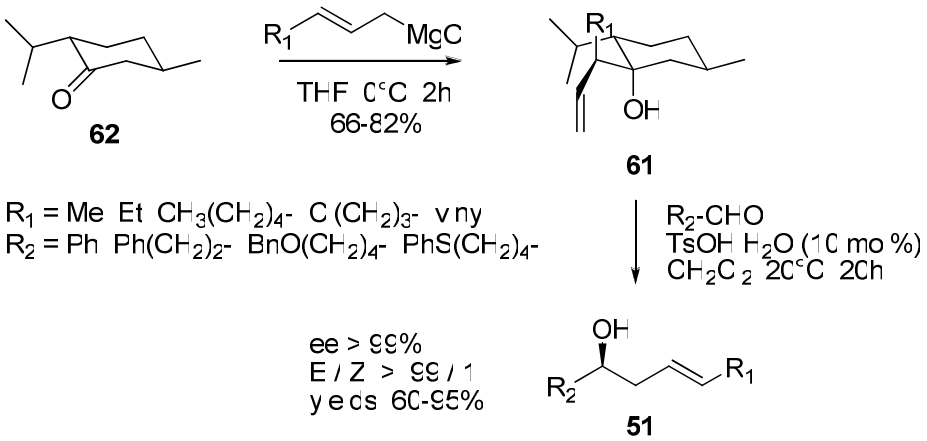
The six-membered cyclic transition state **53** was supported by a following study of allyl transfer from *syn*- or *anti*- homoallylic alcohols **55**. The use of *anti*-isomer of **55** gave specifically the (*E*)-olefin (*S*)-**57** with 85% yield and >98% ee, whereas the *syn*-isomer of **55** gave predominantly the (*Z*)-olefin (*S*)-**60** (80% yield of *E*/*Z*-1:18) with ee >98% and minor amount of (*E*)-isomer of the enantiomeric (*R*)-**57** (**Scheme 17**). Loh later showed that the allylic transfer can succesfully proceed even without addition of aldehyde under $In(OTf)_3$ catalysis[46]. A catalytic amount of the respective

aldehyde was supposed to be formed in situ by retro-allylation reaction.



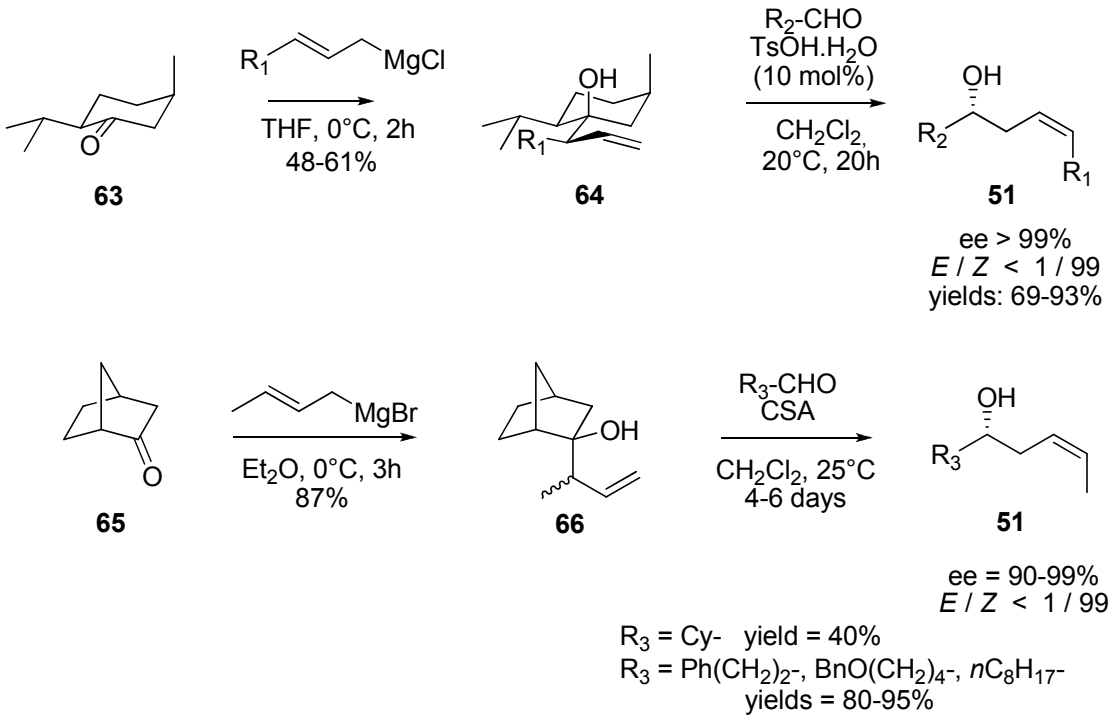

**Scheme 17** Stereoselectivity of allylic transfer

The first general method for the enantioselective crotylation of aldehydes via an allyl transfer reaction from a chiral crotyl donor **61** was developed by Nokami in 2001[47]. The enantiopure homoallylic alcohol **61** was prepared in 77% from (-)-menthone (**62**), by addition of crotylmagnesium chloride. Analogous linear allylic chlorides can also be employed in this reaction[48]. The chirality was then stereospecifically transferred in an acid catalyzed rearrangement to various aldehydes, giving enantiomerically pure (*E*)- homoallylic alcohols **51** (**Scheme 18**). Further exploration of this reaction towards branched products by Lee showed limitations in case of stericaly hindered or stabilized aldehydes, such as aromatic or conjugated systems[49].




**Scheme 18** Chiral auxiliary mediated allylic transfer towards *E*-isomers

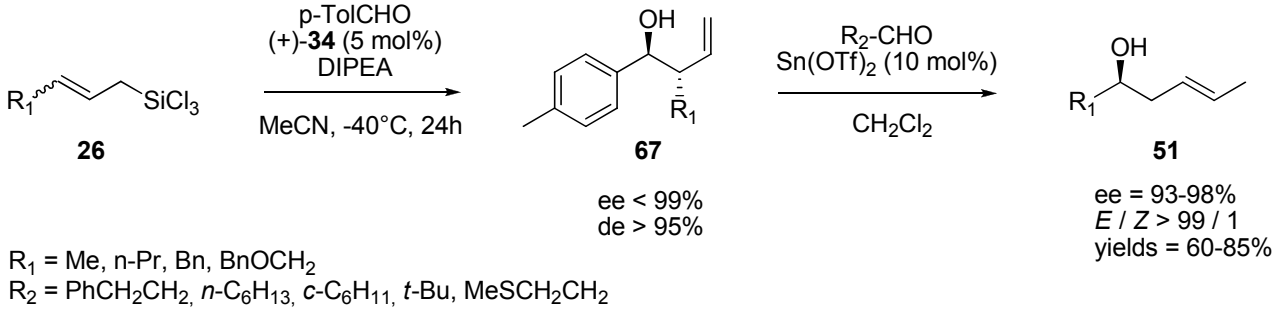
A complementary synthetic method was later devised by Nokami, employing (+)-isomenthone (**63**) as the source of chirality[50]. Addition of crotylmagnesium chloride provides the desired




**Scheme 19** Chiral auxiliary mediated allylic transfer towards *Z*-isomers

diastereoisomer **64** in moderate yield and the acid catalyzed allylic transfer proceeds stereospecifically to afford the enantiopure linear (*Z*)-allylic alcohols **51** in good yields (**Scheme 19**). A similar method was devised by Loh, who employed (+)-camphor (**65**) as the chiral auxiliary and CSA as the catalyst of choice for the subsequent rearrangement. This approach gave excellent results for linear aldehydes but the yields were lower for branched substrates and negligible in aromatic series (**Scheme 19**)[51].

Most recently, a catalytic method avoiding the use of chiral auxiliaries was developed by Kočovský[52]. The chiral crotyl donor **67** was prepared by asymmetric crotylation of tolualdehyde, catalyzed by METHOX **(+)-34**. From the resulting *anti*-alcohol **67**, the crotyl group was transferred to various aldehydes employing $Sn(OTf)_2$ as catalyst. Notably, the desired stereochemistry of both products **67** and **51** is kinetically favored, allowing the use of mixture of (*E/Z*)-isomers of starting trichlorosilanes **26**. The choice of substituent on the aromatic ring of the crotyl donor **67** was a result of tuning of electronic properties. Whereas electron withdrawing substituent, such as nitro group, inhibits the allyl transfer reaction, *p*-methoxy group render the alcohol **67** too unstable under the reaction conditions. Hence, the tolyl derivative represents a healthy compromise. Various linear homoallylic alcohols **51** were prepared by this method in very good yields and with high enatio- and regio- selectivity (**Scheme 20**).




**Scheme 20** Catalytic approach towards enantioselective allylic transfer.

# 2. Aims of the Thesis

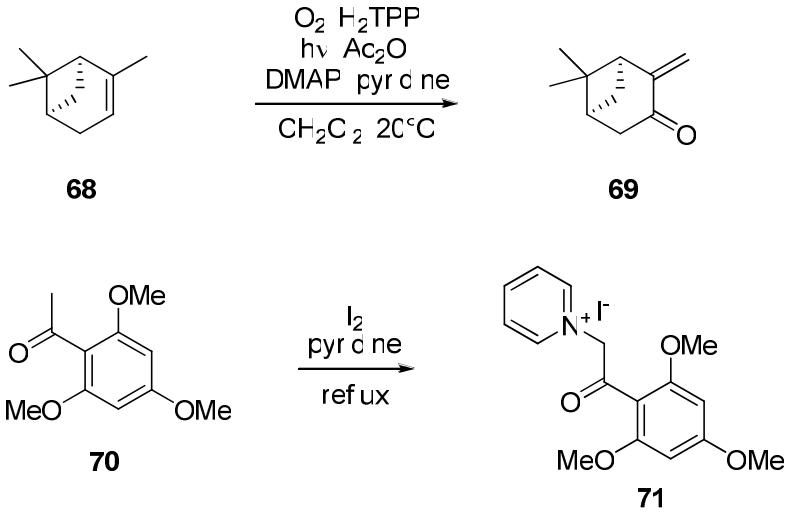
The aims of this thesis are to develop a metal-free methodology for catalytic enantioselective allyl transfer reaction. Inseparable part of the thesis is the synthesis of METHOX as the key organocatalyst and the preparation of starting chiral material, employing the METHOX catalyzed addition of crotyltrichlorosilane to *p*-tolualdehyde. The procedure could be concluded into few following points:

1. Preparation of METHOX catalyst **(+)-34** following the known procedures.
2. Organocatalytic syntesis of chiral and racemic 1-(4-methyl-phenyl)-2-methyl-but-3-en-1-ol (**67**) as a starting material for allyl transfer reaction.
3. Screening for optimal metal-free acidic catalyst for allyl transfer and optimization of the reaction conditions.
4. Scope and limitations of the allyl transfer reaction under the optimized conditions.

# 3. Results and Discussion

## *3.1. Synthesis of METHOX catalyst*

Synthesis of the catalyst (+)-**34** was carried out according to the literature[32,53]. Commercially available enantiopure (+)-α-pinene (**68**) was converted almost quantitatively into (-)-pinocarvone (**69**) via the ene-reaction with singlet oxygen, followed by elimination of the intermediate acetate. Iodination of trimethoxyacetophenone **70** in dry pyridine afforded directly the Kröhnke salt **71** in 98% yield (**Scheme 21**). The METHOX precursor **72** was then synthetised in 85% yield from the two building blocks **69** and **71** via Kröhnke annulation. The chelation-assisted deprotonation of benzylic position of the pyridine core with lithium diisopropylamide, followed by methylation, afforded the tricyclic pyridine derivative **73**. The diastereoisomeric product of *endo*-methylation was not observed due to the steric hindrance excercised by the *endo*-methyl group at the bridgehead. Final oxidation with substechiometric amount (0.92 eq.) of MCPBA proceeded smoothly to give METHOX (+)-**34** in 81% yield along with 10% of isolated starting material (**Scheme 22**). Use of excess of peroxyacid had to be avoided due to easy overoxidation of the substrate, which would result a non-separable mixture of product.



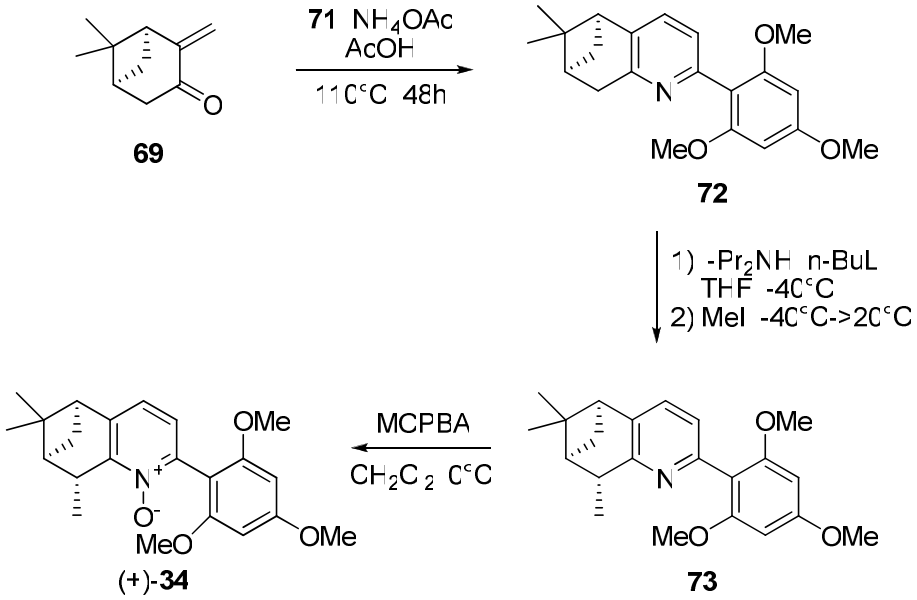

**Scheme 21** Synthesis of METHOX

## *3.2. Synthesis of crotyl donor*

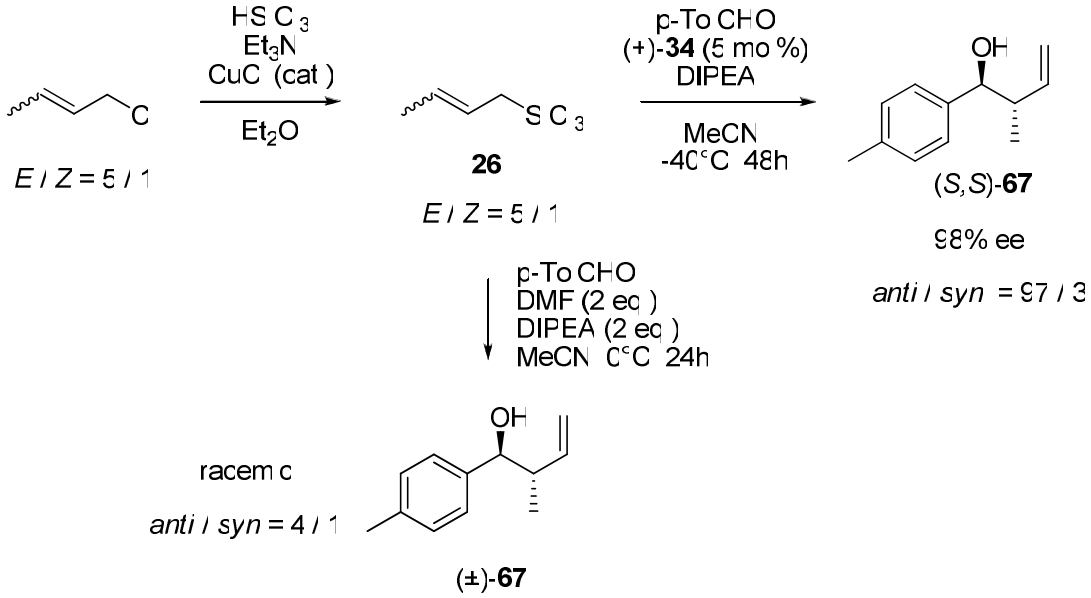
Copper(I)-catalyzed trichlorosilylation of crotyl chloride (technical grade, 70%) in the presence of triethylamine afforded crotyl trichlorosilane (**26**) in 71% yield. The ratio of *E/Z* isomers remained untouched (*E/Z* - 5:1 ).

Racemic homoallylic alcohol (±)-**67** was prepared by allylation of *p*-tolualdehyde with **26** in the

presence of DIPEA as a bulky base and DMF as a Lewis base in 67% yield. In the asymmetric variant, using METHOX (+)-**34** as Lewis-basic catalyst, the enantioenriched (*S,S*)-**67** (98% ee) was obtained. (**Scheme23**).




**Scheme 22** Synthesis of METHOX, continue

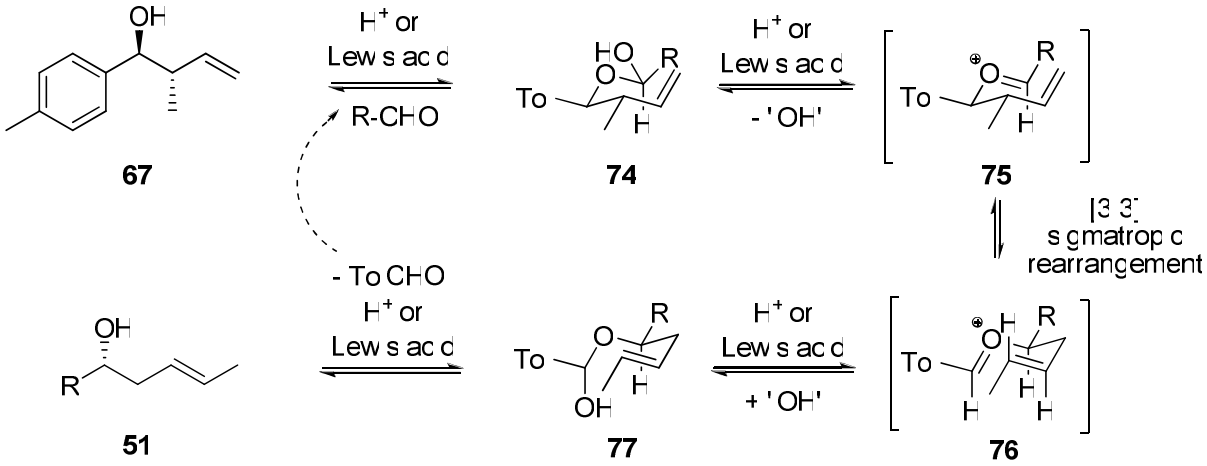



**Scheme 23** Synthesis of crotyl donor

Kinetic preference for the (*E*)-isomer of **26** to form the six membered chair-like transition state (**Scheme 8**) allowed the use of mixture of both isomers **26**, still forming the *anti*-homoallylic alcohol (S,S)-**67** in 97% yield and high purity (94% de). Trichlorosilane (*Z*)-**26** thus remained in the reaction mixture unreacted and was easily disposed off during workup.

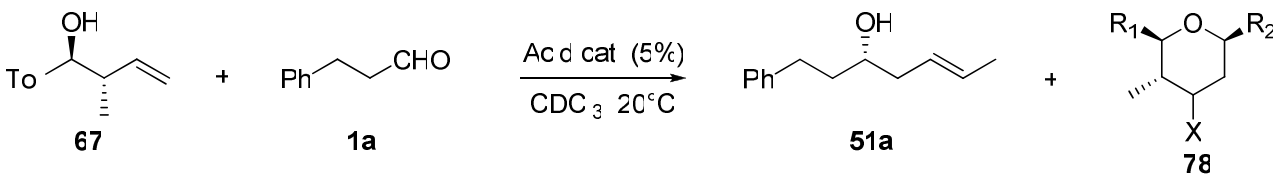
## *3.3. Allyl transfer optimization*

As mentioned in the introduction, *p*-tolyl alcohol **67** was chosen as the crotyl donor on the basis of its electronic properties[52]. Stabilization of the reactive intermediate **67** due to the I+ effect of the methyl group on the aromatic ring results in the shifting of the equilibrium towards **77** and **51** (**Scheme 24**). On the other hand, the M- effect of the nitro group slows down the allylic transfer by stabilising the reactive intermediate **75** (in contrast to **76**). The more strongly electron donating methoxy group could not be used as this leads to decomposition of the starting material, presumably due to elimination of hydroxyl under acidic catalysis. Another issue arises with the release of tolualdehyde at the end of the allyl transfer. Here, the aldehyde thus released can compete with the aliphatic aldehyde, thereby forming an undesired side product. However, it was found that this scenario could be circumvented by use of a 3-fold excess of the starting aldehyde, supressing this side product almost completely[52].




**Scheme 24** Mechanism of allyl transfer

Our primary goal was to probe different catalysts promoting the allyl transfer reaction and conditions of their use. Hitherto, a broad scale of catalysts was tested with different amount of success in the previous works[43,47,51,52]. For our purpose, we have tested a range of catalysts on a small scale (0.1 mmol) in an NMR tube, monitoring the course of the reaction by $^{1}$H NMR spectroscopy; dihydrocinnamaldehyde (**1a**) was chosen as a model substrate (**Scheme 25**). The results are shown in **Table 1**.




**Scheme 25**

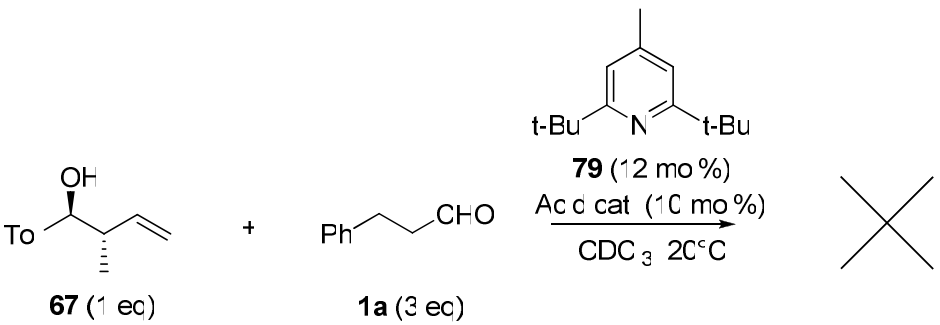
**TABLE 1. Allylic transfer from homoallylic alcohol 67 to aldehyde 1a, catalyzed by various acidic catalysts.**[a]

| Entry | Catalyst (mol%) | Reaction time | Conversion | Yield[b] of **51a** (%) | Prins' products[b] **78** (%) |
|---|---|---|---|---|---|
| 1 | CSA (10%) | 3h | 77 | 78 | 16 |
| 2 | CSA (10%) | 24h | 95 | 87 | 13 |
| 3 | TfOH (5%) | 20 min | > 95 | > 95 | < 5 |
| 4 | $BF_3.Et_2O$ (5%) | 20 min | > 95 | > 95 | < 5 |
| 5 | TMSOTf (5%) | 20 min | > 95 | > 95 | < 5 |
| 6 | $Sn(OTf)_2$ (5%) | 20 min | > 95 | > 95 | < 5 |

[a]The reactions were carried out with 0.1 mmol of **67** and 0.3 mmol of **1a** in $CDCl_3$ (0.6 mL) at 20°C. [b]Determined from $^1H$ NMR spectrum.

From this screening, several catalysts emerged as potentially efficient. Trifluoromethane sulfonic acid, together with boron trifluoride, trimethylsilyl trifluoromethanesulfonate and tin(II) trifluoromethanesulfonate gave almost identical results, all of them giving fast, clean and virtually complete conversion to linear homoallylic alcohol **51a**. By contrast, CSA afforded a significant amount of side product **78** and the reaction proved to be considerably slower.

However, we wished to gain a deeper insight into the nature of the catalyst. Most Lewis acids, including all the tested ones, are known to be prone to hydrolysis. Therefore, the question arose, whether the formation of the reactive intermediate **75** is truly catalyzed by Lewis acid or by a product of its decomposition. To address this question, we employed the sterically hindered base 2,6-di-*tert*-butyl-4-methylpyridine (**79**). The basic electron pair of this molecule is concealed by two bulky groups, thus allowing only proton to form a complex succesfully. On the other hand, the action of other Lewis acids remains unaffected[54]. Therefore, **79** is commonly employed, for example, as a proton trap in living carbocationic polymerization[55]. For our purpose we have




**Scheme 26**

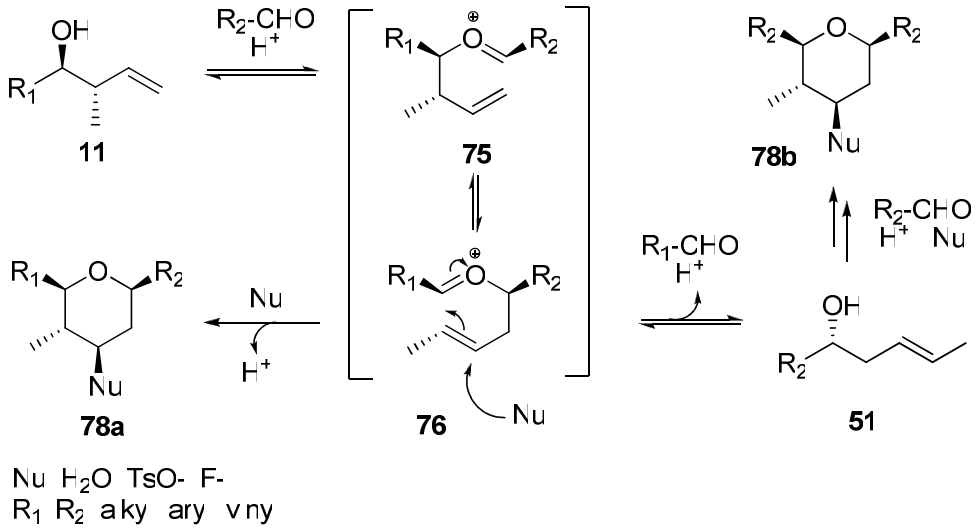
**TABLE 2. Effect of proton scavenger 79 on course of allyl transfer from 67 to aldehyde 1a.**[a]

| | | With base **79** (12 mol%) | | Without base **79** | |
|---|---|---|---|---|---|
| Entry | Catalyst (mol%) | Reaction time | Conversion[b] | Reaction time | Conversion[b] |
| 1 | TfOH (10%) | 48h | no reaction | 15 min | >95 |
| 2 | $Sn(OTf)_2$ (10%) | 48h | no reaction | 15 min | >95 |
| 3 | TMSOTf (10%) | 48h | decomposition | 15 min | >95 |
| 4 | $BF_3.Et_2O$ (10%) | 48h | no reaction | 15 min | >95 |
| 5 | $Yb(OTf)_3$ (10%) | 48h | no reaction | 15 min | 5 |

[a]The reactions were carried out with 0.1 mmol of **67** and 0.3 mmol of **1a** in $CDCl_3$ (0.6 mL) at 20°C. [b]Determined from $^1H$ NMR spectrum.

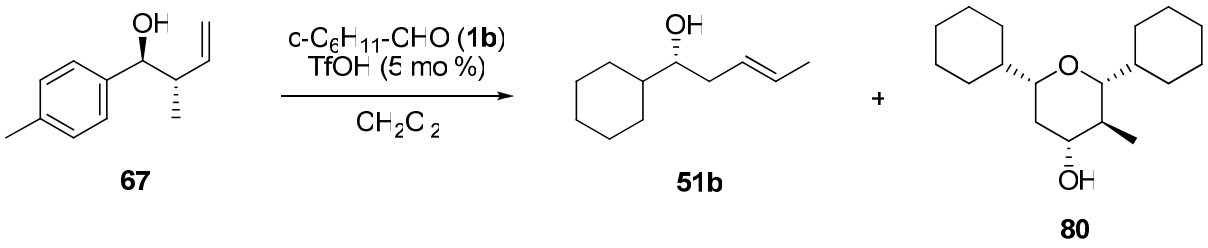
compared the reaction carried out in the presence of the hindered base **79** (12 mol%) and acidic catalysts (10 mol%) with the reaction performed in the absence of the base (**Table 2, Scheme 26**). According to our observation, none of the acids used were able to promote the reaction in the slight excess of the hindered base **79**. In all cases, with a notable exception of TMSOTf catalysis, no product formation was observed in the $^1H$ NMR spectrum, even after 2 days. On the other hand, combination of TMSOTf with base **79** caused slow decomposition of the starting material without formation of the desired product **51a**. In the control experiment, carried out in the absence of the base, reactions in entries 1 - 4 proceeded cleanly with virtually full conversion prior to first NMR measurement. Reaction with $Yb(OTf)_3$ was sluggish, resulting in only 5% conversion in 15 minutes. These results strongly suggest that the actual catalyst is a Brønsted acid, either added directly into the reaction mixture or formed by decomposition of the Lewis acid. This conclusion is supported by the behavior of ytterbium(III) trifluoromethanesulfonate, a hydrolysis resistant Lewis acid, which proved to be only a poor catalyst for the allyl transfer.

Another issue connected with the oxonia-Cope rearrangement is the possibility of forming the six-membered cyclic side product **78** via Prins cyclisation. This phenomenon was observed by both Nokami[43] and Loh[56] in their early work dealing with this topic. The supposed mechanism for this side reaction is depicted in **Scheme 27**. Further research on this reaction was conducted by Nokami[57], who elaborated a feasible protocol for the synthesis of substituted tetrahydropyrans of type **78b**, employing various nucleophiles. Notably, the acid catalyst was also used as the source of nucleophile, competing with water, which is inevitably formed *in situ*. Thus, $BF_3.Et_2O$ was used as a source of fluoride and TsOH afforded tosyloxyderivatives **78b** in modest yields. Since the trifluoromethanesulfonate anion is completely non-nucleophilic, we resolved to use triflic acid as catalyst in all our allyl transfer reactions, to minimize the Prins cyclization.




**Scheme 27:** Prins reaction

Branched aldehydes, such as **1b**, were found to be most sensitive to Prins cyclisation. Interestingly, the cyclic product **80** was absent in the $^{1}$H NMR spectrum of the reaction mixture, even after a prolonged period. Despite this, a considerable amount of **80** (32%) was found in the reaction mixture after quenching with saturated aqueous solution of sodium hydrogencarbonate and drying with magnesium sulfate. Switching to less acidic sodium sulfate brought only minor improvement, decreasing the portion of tricyclic product **80** to 25%. The explanation of this effect could be the nucleophilic attack of intermediates **75** and **76** by carbonate anion or water. We have therefore



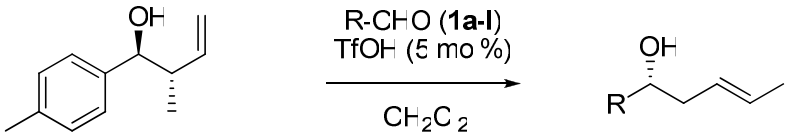

**Scheme 27** Allyl transfer with cyclohexyl carbaldehyde

employed neutralization of the catalyst by non-nucleophilic Hünig's base, which has indeed prevented the formation of **80**. However, the Prins product was formed even during chromatography on silica gel, albeit in smaller amount (20%). Using basic alumina prevented the formation of byproduct **80** but the separation was complicated by the products of aldol reaction, decreasing the isolated yield of **51b** to 60%. Pre-washing of the silica gel column with 1% solution of triethylamine in petroleum ether negatively affected the separation to an unacceptable level. Despite all our efforts, the formation of **80** was unavoidable and the best results were reached with standard column chromatography on silica gel.

## *3.4. Scope and Limitations*

To test the optimized reaction, a number of substrates were subjected to the allyl transfer from branched homoallylic alcohol **67** (**Scheme 28**). The results are summarized in **Table 3**; all reactions were carried out with both racemic and enantioenriched alcohol **67** for the purpose of explicit determination of enantio- and regioselectivity. In the first series, simple alkyl aldehydes were tested in the conditions of the reaction. While the enantioselectivity and regioselectivity were excellent in all three cases, varying only marginally, a significant difference was observed in the respective yields. Interestingly, the reaction with linear aldehyde **54a** gave only the expected product **51a**, whereas α-branched aldehydes **1b** and **1c** and their respective products **51b** and **51c** were reacting further via Prins cyclization during the separation on silica gel. The yield of **51c** was further decreased by the volatility of that compound.

We then turned our attention to aromatic aldehydes. To observe the effect of substitution on the aromatic ring, different electron withdrawing or donating groups in *para*- position to the aldehyde were employed. The presence of the *p*-methoxy group, as in **1d**, had a detrimental effect on the course of the reaction, resulting in the formation of the desired homoallylic alcohol **51d** only in trace amounts. Instead, elimination took place and 1-(*p*-methoxyphenyl)-penta-1,3-diene was observed in the NMR spectrum as the major product. Replacement of triflic acid with boron trifluoride etherate as catalyst showed no improvement. Analysis of the NMR spectrum of the reaction mixture showed the presence of *p*-tolylaldehyde

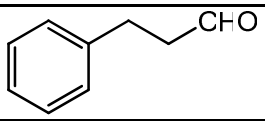
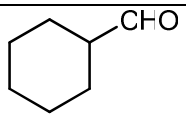
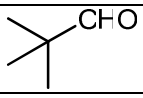
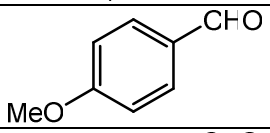
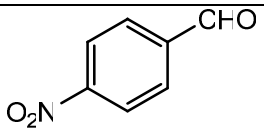
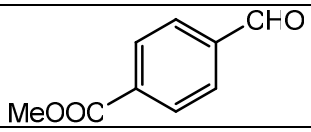
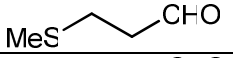
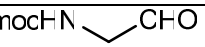
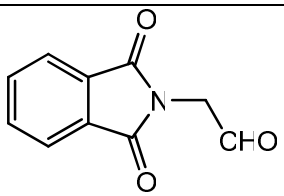
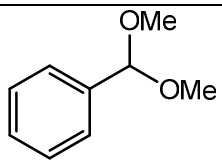
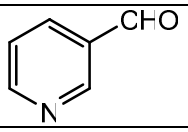
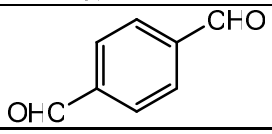



**67** **51a-l**

**Scheme 28** Allyl transfer: Scope and Limitations

and unreacted *syn*-**67**, which indicates that the elimination follows the oxonia-Cope rearrangement. On the other hand, the electron poor substrates **1e** and **1f** afforded the respective linear alcohols **1e** and **1f** in good yields and excellent selectivity. No product of Prins cyclisation was observed in either case. The observed electronic demands are in consent with the propoposed mechanism of allylic transfer (**Scheme 23**). Conjugated electron-withdrawing groups are shifting the equilibrium of sigmatropic rearrangement towards products, favoring intermediate **76** over **75** by destabilisation of the positive charge of the latter.

**TABLE 3. Crotyl transfer from alcohol 67 to aldehydes 1a-*l*.[a]**

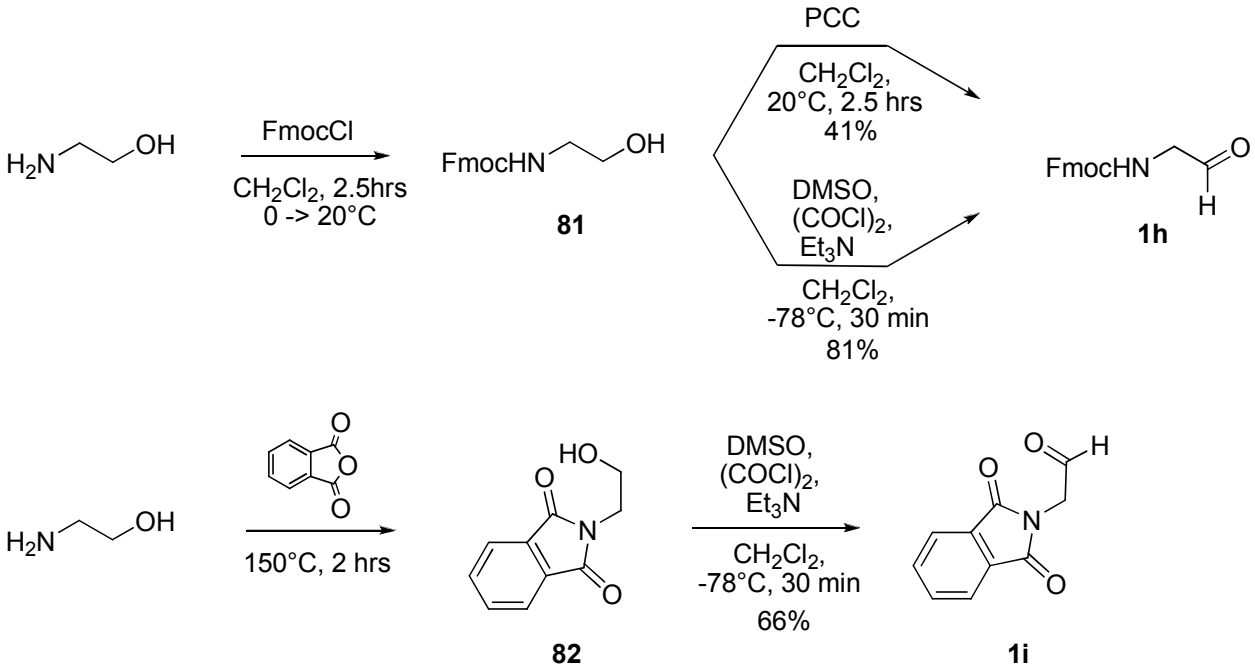
| Entry | 1 | R-CHO | 51 | Yield (%)[b] | ee (%)[d] | E / Z[d] |
|---|---|---|---|---|---|---|
| 1 | **1a** |  | **51a** | 94 | 99 | > 99 : 1 |
| 2 | **1b** |  | **51b** | 78 | 97 | 94 : 6 |
| 3 | **1c** |  | **51c** | 56 | 96 | 96 : 4 |
| 4 | **1d** |  | **51d** | traces | - | - |
| 5 | **1e** |  | **51e** | 72 | 96 | 97 : 3 |
| 6 | **1f** |  | **51f** | 72 | 98 | 96 : 4 |
| 7 | **1g** |  | **51g** | 64 | > 95 | > 95 : 5 |
| 8[e] | **1h** |  | **51h** | 0 | 0 | 0 |
| 9[e] | **1i** |  | **51i** | 0 | 0 | 0 |
| 10 | **1j** |  | **51j** | 37 | 96 | > 95 : 5 |
| 11 | **1k** |  | **51k** | 0 | 0 | 0 |
| 12 | **1l** |  | **51l** | 54 (17[c]) | 93 | > 99 : 1 |

[a]The reactions were carried out with 1 mmol of **67** and 3 mmol of **1** in $CH_2Cl_2$ (5 mL) at 20°C with 0.05 mmol of TfOH [b]Isolated yield. [c]Product of double allyl transfer. [d]Determined by HPLC for **51e**, **51l**; determined by $^{19}F$ NMR of the corresponding Mosher ester for **51f**, **51g**, **51j**; determined by GC for **51a**, **51b, 51c**. [e]0.15 mmol of TfOH was used instead of usual 0.05 mmol.

The final set of experiments was focused on the presence of various functional groups in the molecule of substrate. The general conditions were found to be tolerant to thioethers, such as **1g**,

although the yield was lower (64%) than that in the case of simple linear alkyl. However, is likely to be due to the volatility of **51g**, since no significant amount of byproduct was observed and the conversion was complete.

Our attention was then paid to molecules containing electron pair on nitrogen. For this purpose we have synthetised aldehydes **1h** and **1i**, both from the readily available 2-ethanolamine (**Scheme 29**). The Fmoc-protected alcohol **81**was prepared from 9-fluorenyl-methoxycarbonyl chloride in excess of 2-ethanolamine[58]. Mild oxidation of the alcohol **81** resulted in the formation of aldehyde **1h**. For this purpose PCC was our first choice reagent, but the yield was unexpectedly low (41%). We have therefore employed the Swern oxidation which gave more satisfactory results, affording **1h** in 81% yield. Phthalimide derivative **82** was prepared directly by heating phthalic anhydride with ethanolamine followed by recrystallisation from methanol[59]. Swern oxidation of **82** gave then **1i** in 66% yield. Both aldehydes **1h** and **1i** reacted only slowly with alcohol **67** in the presence of 5 mol% of the triflic acid. Raising the catalyst loading to 15 mol% helped to drive the reaction to completion, but led to the formation of a complex mixture of products; no alcohol **51h** or **51i** was detected amongst the products, although *p*-tolualdehyde was present in both cases. Substitution of triflic acid with $BF_3.Et_2O$ as a milder acid gave similar results.



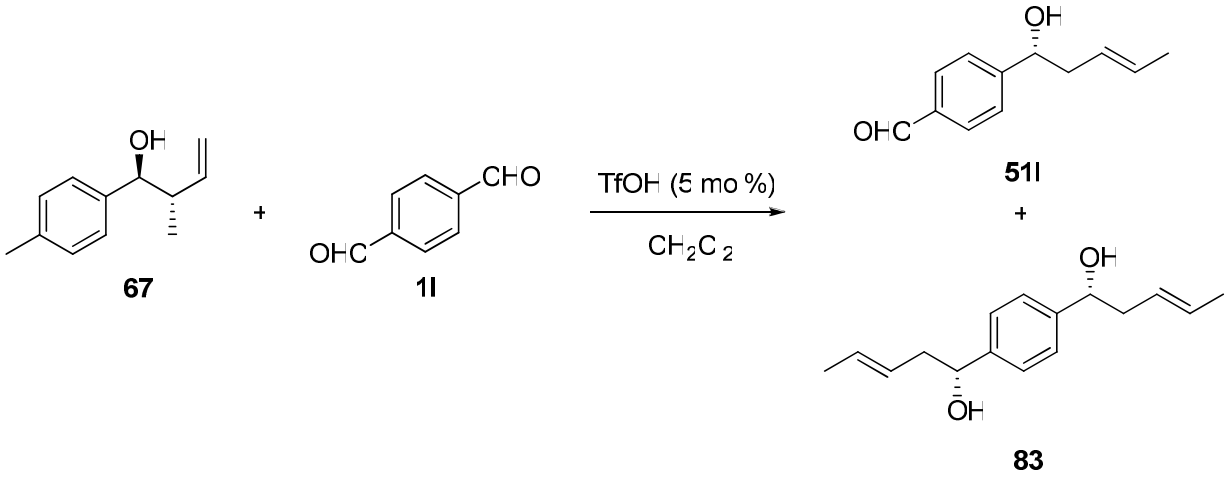

**Scheme 29** Synthesis of protected glycinaldehydes

Dimethylacetal **1j** was subjected to the allyl transfer from alcohol **67** with essentially the same selectivity as other substrates, despite the lower yield (37%). Nicotinaldehyde (**1k**) proved to be unreactive under the reaction conditions, due to precipitation of the salt from the dichloromethane solution. In our opinion, the protection of the basic nitrogen, which would prevent the formation of

insoluble salt, could enable the allyl transfer on this type of substrates. These options are now examined closely in our Laboratory.

Finally, we were interested in the selectivity of allyl transfers on the dialdehydes. For this purpose, terephthalaldehyde (**1*l***) was employed. The resulting alcohol **51*l*** was isolated in 54% yield and 93% ee. The product of double allylic transfer was isolated in 17% yield in respect to starting alcohol **67** (**Scheme 30)**.

Overall, all the yields and selectivities were found to be similar to the previously described catalysis with $Sn(OTf)_2$, most importantly the enantioselectivity was essentialy the same. However the main advantage of triflic acid catalysis is the lower possible catalyst loading and more accurate dosing. According to our results, TfOH indeed is the true catalyst rather than the trifluoromethanesulfonate salts and TMSOTf, being formed *in situ* by their hydrolysis. Also, TfOH is cheaper, easier to handle and more environmentally friendly.




**Scheme 30** Crotyl transfer onto aromatic dialdehyde **1l**.

# 4. Experimental section

## *4.1 General methods*

Proton, $^{13}C$ and $^{19}F$ NMR spectra were measured on a FT NMR spectrometer Bruker AVANCE-400 (at 400 MHz, 100.6 MHz, and 376.3 MHz respectively) in $CDCl_3$ with tetramethylsilane (δ 0.00, $^{1}H$) as the internal standard. $^{13}C$ NMR spectra were recorded using APT technique, using solvent signal as standard ($CDCl_3$ δ 77.00). H,H-COSY and H,C-HSQC spectra were used to establish the structures and to assign the signals where necessary. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) are given in Hz.

The IR spectra were recorded on FTIR - 8400S spectrometer (Shimadzu, Japan) by the DRIFT technique or on Jasco 410 FTIR spectrometer in a thin film of the sample in chloroform between NaCl plates. The mass spectra (EI and/or CI using isobutane) were measured on a dual sector mass spectrometer using direct inlet and the lowest temperature enabling evaporation. Optical rotations were recorded on Autopol V (Rudolph Research Analytical) in $CHCl_3$ at 25 °C unless otherwise indicated, with an error of ≤±0.1. The $[\alpha]_D$ values are given in $10^{-1}$ deg.cm$^3$.g.$^{-1}$. Analytical HPLC was performed on Agilent 1100 Series instrument in the mode of constant pressure and solvent system composition.

Gas chromatography was run on Hewlett Packard HP6890 Series device, using Supelco γ-DEX column and temperature gradient unless stated otherwise. Melting points were determined on a Kofler block (Reichert, Austria) and are uncorrected. Thin layer chromatography was performed on comercial TLC plates (Merck, Silica gel 60 $F_{254}$), visualisation was faciliated by UV quenching (254 nm) or dipping into an ethanolic solution of phosphomolybdic acid and subsequent heating to approximately 150°C. For column chromatography, silica gel 60–120μm was used.

Inert conditions stands for reactions which were performed under an atmosphere of dry argon in oven-dried glassware three-times evacuated and refilled with the argon. Solvents and solutions were transferred by syringe-septum and cannula techniques. Reactions employing trichlorosilanes were performed in Schlenk apparatus.

All solvents for the reactions under inert conditions were of reagent grade and were dried and distilled immediately before use as follows: THF from sodium/benzophenone; dichloromethane, acetonitrile, $Et_3N$ and DIPEA from calcium hydride. Petroleum ether refers to the fraction boiling in the range of 40-60 $^{o}$C. DMSO was distilled under reduced pressure from calcium hydride and stored over 4Å MS, DMF was distilled from $P_2O_5$ and stored over 4Å MS.

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 with the literature data and by the TLC behaviour. Enantiopurity was determined by comparison of the spectra or chromatograms of racemates and enantioenriched products.

## *4.2. General procedures*

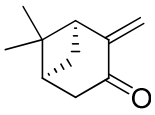
**Allyl Transfer Reaction.**

Under inert conditions, tolyl alcohol **67** (176 mg, 1 mmol) and the respective aldehyde (3 mmol) were dissolved in dichloromethane (5 mL). From a stock solution of TfOH in dichloromethane (100 μL of acid in 1 mL of solvent), 100 μL was added dropwise into the reaction mixture while stirring, turning the solution orange-brown. The reaction mixture was stirred at room temperature and monitored by TLC. When no further change was observable in composition of the reaction (usually 2 h), a drop of DIPEA (5 μL, 0.05 mmol) was added, turning the reaction colourless. Solvents were removed in vacuo and the product was purified by chromatography on a column of silica gel (15 g) in gradient of petroleum ether-EtOAc (100:0 to 90:10).

**Preparation of Mosher's Esters**

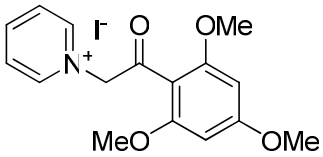
Under inert conditions, oxalyl chloride (90 μL, 1 mmol) was added to a solution of (*R*)-MTPA (24 mg, 0.1 mmol) and DMF (16 μL, 0.2 mmol) in hexane (5 ml) at room temperature. A white precipitate formed immediately. After stirring for 2 h, the reaction mixture was filtered through a cotton plug in syringe and the solvent was evaporated *in vacuo* to give a residue of chiral acyl chloride. Solid DMAP (24 mg, 0.2 mmol) was added to the reaction flask and again, it was evacuated and refilled with argon. A solution of the alcohol (0.04 mmol) in dichloromethane (2 mL) was then transferred to the mixture, which was then stirred until no starting alcohol was observed on TLC. Typically, the conversion was complete in 2-3 h. The reaction was quenched with saturated aq. $NH_4Cl$ (5 mL) and the product was extracted into $Et_2O$ (20 mL). The organic phase was washed consecutively with saturated aq. $NaHCO_3$ (5 mL) and brine (5 mL) and dried over $MgSO_4$ and solvent was removed under reduced pressure to give the desired Mosher's ester in quantitative yield (the absence of the starting alcohol was checked by $^1H$ NMR).

## *4.3. Procedures*



**(-)-7,7-Dimethyl-4-methylidenebicyclo[3.1.1]heptan-3-one (pinocarvone) (69).**

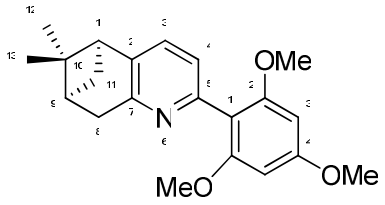
Compound **69** was prepared according to the literature[53]. A reaction flask was filled with a solution of (+)-pinene (**68**, 40.00 g, 0.293 mol, 97% ee), acetic anhydride (29.1 mL, 0.303 mol), pyridine (11.9 mL, 0.147 mol), $H_2TPP$ (0.021 g, 0.034 mmol), and DMAP (0.716 g, 0.006 mol) in dichloromethane (270 mL). Oxygen was bubbled through the mixture while cooling with water and the source of light (400W sodium lamp) was turned on. After 1.5 h, no spot of starting material was observed by TLC. The solution was diluted with dichloromethane (270 mL) and washed subsequently with saturated $NaHCO_3$ (2 × 200 mL), 1 N HCl (2 × 100 mL), saturated $CuSO_4$ (100 mL), and finally with brine (200 mL). The organic phase was dried with $MgSO_4$ and concentrated *in vacuo to* give crude (-)-pinocarvone (**69**) (43.52 g, 99%) as a colorless oil: $^1$H NMR ($CDCl_3$) δ 5.97 (d, *J* = 1.6, 1H, CH-vinylic), 5.00 (d, *J* = 1.6, 1H, CH-vinylic), 2.78–2.55 (m, 4H), 2.21–2.19 (m, 1H), 1.36 (s, 3H, $CH_3$), 1.31–1.28 (d, *J* = 10.2, 1H), 0.81 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) δ 200.04 (CO), 149.04 (vinylic - $CH_2$), 117.42 (vinylic - C), 48.22 (CH), 42.47 ($CH_2$), 40.77 (CH), 38.52 (C), 32.40 ($CH_2$), 25.96 ($CH_3$), 21.53 ($CH_3$).




**1-[2-(2',4',6'-Trimethoxyphenyl)-2-oxo-ethyl]-pyridinium Iodide (71)**

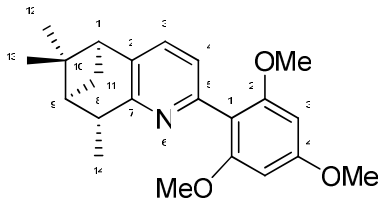
Compound **71** was prepared according to the literature[32]. 2',4',6'-Trimethoxyacetophenone (**70**,10.1 g, 48.0 mmol) was heated in pyridine (20 mL) until a clear solution was obtained. Crystalline iodine (17.4 g, 57.0 mmol) was then added portionwise and the resulting solution was refluxed for 1 h and then cooled to room temperature. The brownish precipitate was filtered off and successively washed with absolute pyridine (3 × 15 mL) to give the Kröhnke salt **71** (19.5 g, 98%) as a pale yellow solid, which could be used directly in the Kröhnke annulation. (19.5 g, 98%): mp 201-204 ºC (MeOH-toluene) (Lit[32] gives 202-206 ºC); $^1$H NMR ($d_6$-DMSO) δ 8.74, (t, *J* = 5.8, 2H, Py), 8.69 (t, *J* = 7.6, 1H, Py), 8.24 (t, *J* = 7.2, 2H, Py), 6.37 (s, 2H), 6.01 (s, 2H), 3.88 (s, 3H, OMe), 3.85 (s, 6 H, OMe);$^{13}$C NMR ($d_6$-DMSO) δ 190.7 (CO), 164.8 (C-Ar), 160.8 (C-Ar), 146.6 (CH-Py), 146.4 (CH-Py), 128.2 (CH-Py), 91.6 (CH-Ar), 69.7 ($CH_2$), 56.6 ($CH_3O$), 56.2 ($CH_3O$); MS (FAB) *m/z* (%)

288.3 ($M^+$-I, 69); HRMS (FAB) 288.1233 ($C_{16}H_{18}NO_4$ requires 288.1236).




**(+)-5-(2',4',6'-Trimethoxyphenyl)-10,10-dimethyl-6-aza-tricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene (72)**

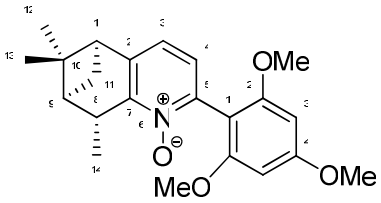
Compound **72** was prepared according to the literature[32]. Anhydrous ammonium acetate (110.0 g) was heated in acetic acid (100 mL) at 110 °C until it dissolved. Kröhnke salt **62** (19,5 g, 47.0 mmol) was then dissolved in the mixture at 110 °C. Finally, pinocarvone **70** (6.46 g, 43.0 mmol) was added and the solution was stirred at 110 °C for 48 h. The reaction mixture was then diluted with water (20 mL) and extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with water (3 × 50 mL) and brine (30 mL), and dried with $MgSO_4$. The solvent was removed *in vacuo* to afford an oil that was purified via flash chromatography on silica gel (50 g) using petroleum ether, followed by a 9:1 mixture of petroleum ether and ethyl acetate to give pure **72** (12.41 g, 85%) as an off-white solid: mp 97-99 ºC (toluene-EtOAc) (Lit[32] gives 98-100 ºC); $[\alpha]_D$ +54.4 (*c* 1.1, $CH_2Cl_2$; literature[32] gives $[\alpha]_D$ +49.5 (*c* 1.0, $CH_2Cl_2$)); $^1$H NMR ($CDCl_3$): δ 7.14 (d, *J* = 7.6, 1H, CH-Py), 6.88 (d, *J* = 7.6, 1H, CH-Py), 6.12 (s, 2H, CH-Ar), 3.77 (s, 3H, OMe), 3.63 (s, 6H, OMe), 3.09 (d, *J* = 2.8, 2H, $CH_2$-8), 2.69 (t, *J* = 5.6, 1H, CH-1), 2.61 (dt, *J* = 9.6, J = 5.6, 1H, $CH_2$-11a), 2.30 (m, 1H, CH-9), 1.34 (s, 3H, $CH_3$), 1.31 (d, *J* = 9.4, 1H, $CH_2$-11b), 0.63 (s, 3H, $CH_3$); $^{13}$C NMR δ 161.3 (C), 159.3 (C), 156.3 (C), 151.6 (C), 139.5 (C), 133.1 (CH-Py), 123.1 (CH-Py), 113.3 (C), 91.2 (CH-Ar), 56.3 (OCH3), 55.7 (OCH3), 46.7 (CH-1), 40.6 (CH-9), 39.9 (C-10), 37.0 ($CH_2$-8), 32.1 ($CH_2$-11), 26.5 ($CH_3$), 21.8 ($CH_3$); MS (EI) *m*/*z* (%) 339 ($M^{\bullet+}$, 95), 324 ($M^{\bullet+}$-Me, 53); HRMS (EI) 339.1835 ($C_{21}H_{25}NO_3$ requires 339.1834).




**(+)-5-(2',4',6'-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.$0^{2,7}$]undeca-2(7),3,5-triene (73).**

Compound **73** was prepared according to the literature[32]. Under inert conditions, a solution of *n*-

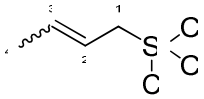
butyllithium (1.6 M in hexane, 4.44 mL, 7.11 mmol) was added dropwise to a solution of diisopropylamine (1.10 mL, 7.82 mmol) in THF (10 mL) at -40 °C, the mixture was brought to 0 °C, stirred for 30 min, and cooled to -40 °C. A solution of the pyridine derivative **72** (1.609 g, 4.74 mmol) in THF (5 mL) was added at -40 °C, immediately turning the solution dark red. The mixture was stirred at that temperature for 2 h. Methyl iodide (0.44 mL, 7.82 mmol) was then added dropwise (changing the colour of solution to green), the reaction flask was moved to ice bath and during overnight stirring left to warm up to room temperature. The reaction mixture was quenched with water (30 mL) and extracted with $CH_2Cl_2$ (3 × 30 mL). The organic layers were combined, washed with brine (30 mL) and dried with $MgSO_4$ and the solvent was removed under reduced pressure. Chromatography on a column of silica gel (50 g) with a mixture of petroleum ether and ethyl acetate (9:1) gave **73** as a white solid. (1.057 g, 63%): mp 109-111 °C (toluene-EtOAc; Lit[32] gives mp 110-112 °C); $[\alpha]_D$ +16.4 (*c* 1.1, $CH_2Cl_2$; literature[32] gives $[\alpha]_D$ +14.9 (*c* 1.0, $CH_2Cl_2$)); $^1$H NMR ($CDCl_3$) δ 7.12 (d, *J* = 7.2, 1H, CH-Py), 6.88 (d, *J* = 7.2, 1H, CH-Py), 6.14 (s, 2H, CH-Ar), 3.77 (s, 3H, OMe), 3.64 (s, 6H, OMe), 3.17 (qd, *J* = 7.1, *J* = 2.5, 1H, CH-8), 2.68 (t, *J* = 5.7, 1H, CH-1), 2.47 (dt, *J* = 9.7, *J* = 5.6, 1H, $CH_2$-11a), 2.07 (td, J = 6.0, J = 2.7, 1H, CH-9), 1.35 (s, 3H, $CH_3$), 1.34 (d, 1H, $CH_2$-11b), 1.31 (d, *J* = 7.0, 3H, $CH_3$-14), 0.63 (s, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) δ 161.0 (C), 159.8 (C), 159.1 (C), 151.1 (C), 138.8 (C), 132.5 (CH-Py), 122.7 (CH-Py), 113.4 (C), 91.5 (CH-3‘), 56.2 ($OCH_3$), 55.4 ($OCH_3$), 47.1 (CH-1), 47.0 (CH-9), 41.5 (C-10), 38.8 (CH-8), 28.6 ($CH_2$-11), 26.4 ($CH_3$), 21.0 ($CH_3$), 18.6 ($CH_3$-14); MS (EI) *m*/*z* (%) 353 ($M^{\bullet+}$, 36), 338 ($M^{\bullet+}$-Me, 100); HRMS (EI) 353.1991 ($C_{22}H_{27}NO_3$ requires 353.1991).




**(+)-5-(2’,4’,6’-Trimethoxyphenyl)-8,10,10-trimethyl-6-azatricyclo[7.1.1.02,7]undeca-2,4,6-triene 6-Oxide (+)-(34).**

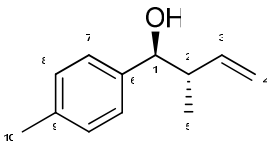
Compound **(+)-34** was prepared according to literature[32]. MCPBA (660 mg, 77%, 2.93 mmol) was added portionwise while stirring vigorously to a solution of the pyridine derivative **73** (1130 mg, 3.18 mmol) in dichloromethane (30 ml) at 0 $^oC$ (ice bath) and the mixture was stirred at that temperature for 2 h, after which time no further change was observable by TLC. The reaction mixture was then diluted with ether (60 mL) and washed successively with satd. $NaHCO_3$ (2 × 30 mL) and brine (30 mL). The ethereal solution was dried over $Na_2SO_4$ and the solvent was evaporated in vacuo. The resulting crude product was purified by column chromatography on silica

gel (40 g) with ethyl acetate (10:1) to elute the unreacted starting material, followed by an ethyl acetate-methanol mixture (1:9). The solid product thus obtained was crystallized from a $CH_2Cl_2$-petroleum ether mixture to afford the enantiopure **(+)-34** (952 mg, 81%) as white crystals: mp 141-143 °C ($CH_2Cl_2$-petroleum ether; Lit[32] gives mp 110-112 °C from Petroleum ether-EtOAc); $[\alpha]_D$ +9.5 (*c* 1.0, $CH_2Cl_2$; literature[32] gives $[\alpha]_D$ +8.6 (*c* 1.0, $CH_2Cl_2$)); $^1$H NMR ($CDCl_3$) δ 6.94 (d, *J* = 7.7, 1H, CH-Py), 6.75 (d, *J* = 7.7, 1H, CH-Py), 6.14-6.13 (m, 2H, CH-Ar), 3.78 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.32 (qd, *J* = 6.6, *J* = 2.8, 1H, CH-8), 2.70 (t, *J* = 5.7, 1H, CH-1), 2.47 (dt, *J* = 9.9, *J* = 5.7, 1H, $CH_2$-11a), 2.08 (td, *J* = 6.0, *J* = 2.9, 1H, CH-9), 1.42 (d, *J* = 6.5, 3H, $CH_3$-14), 1.42 (d, *J* = 10.0, 1H, $CH_2$-11b), 1.35 (s, 3H, $CH_3$), 0.59 (s, 3H, $CH_3$); $^{13}$C NMR δ 162.1 (C), 159.5 (C), 158.8 (C), 149.5 (C), 143.6 (C), 143.3(C), 125.9 (CH-Py), 121.8 (CH-Py), 105.0 (C), 90.83 (CH-Ar), 90.82 (CH-Ar), 56.1 ($OCH_3$), 55.8 ($OCH_3$), 55.4 ($OCH_3$), 47.5 (CH-9), 46.9 (CH-1), 41.6 (C-10), 34.9 (CH-8), 28.1 ($CH_2$-11), 26.0 ($CH_3$), 20.6 ($CH_3$), 14.7 ($CH_3$-14); MS (EI) *m/z* (%) 369 ($M^{\bullet+}$, 10), 338 ($M^{\bullet+}$-Me,-O, 100); HRMS (EI) 369.1940 ($C_{22}H_{27}NO_4$ requires 369.1940).




**(*E*)-Crotyltrichlorosilane (26).**

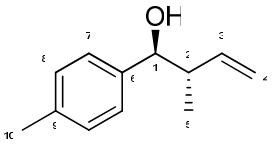
Compound **26** was prepared according to literature[60]. In a Schlenk-type apparatus consisted of a three-necked reaction flask with magnetic stir bar, fritted glass filter and distillation flask with another stir bar, dry $Et_2O$ (150 mL) was transferred, followed subsequently by CuCl (750 mg, 7.58 mmol), dry $Et_3N$ (27.5 mL, 197.3 mmol) and crotylchloride (technical, 70%, 1:5-*Z:E* ratio; 17.75 mL, 126.7 mmol). The flask was immersed in an ice bath and trichlorosilane (22.0 ml, 217.8 mmol) was added slowly during 10 min. The mixture was stirred for 30 min, the ice bath was then removed and the mixture was stirred for another 30 min, during which time the color of the suspension turned brown. The resulting mixture was filtered in the apparatus into the distillation flask and the solid residue was washed with a small volume of dry $Et_2O$. The fltrate was then fractionally distilled under argon, the high boiling fraction at 142-145° C was collected to afford (*E/Z*)-crotyltrichlorosilane (**26**) (17.01 g, 89.74 mmol, 70.8%, (*E/Z*) 5:1 ratio, as determined by NMR; Lit[60] gives bp 142-144 °C): $^1$H NMR ($CDCl_3$), * denotes minor (Z) isomer: δ 5.69-5.61 (m, 1H, CH-3,)*, 5.57-5.49 (m, 1H, CH-3), 5.38-5.26 (m, 1H* + 1H, CH-2 + CH-2*), 2.28 (d, *J* = 8.1, 2H, $CH_2$-1)*, 2.18 (d, *J* = 7.5, 2H, $CH_2$-1), 1.64 (d, *J* = 6.4, 3H, $CH_2$-4), 1.59 (d, *J* = 6.8, 3H, $CH_2$-4)*.



**(1*S*,2*S*)-(-)-2-Methyl-1-*p*-tolyl-but-3-en-1-ol (67).**

*p*-Tolualdehyde (2.06 mL, 17.47 mmol) was added to a solution of METHOX (+)-**34** (324 mg, 0.87 mmol, 5 mol% with respect to the aldehyde) and DIPEA (11.5 mL, 66.0 mmol) in acetonitrile (45 mL) under inert atmosphere and the mixture was cooled to -40°C. Crotyltrichlorosilane **26** (4.25 g, 22.40 mmol) was then added dropwise while stirring vigorously and the reaction mixture was stirred at -40 $^{o}$C for 48 h and monitored by TLC. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (90 mL) and the mixture extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine (90 mL) and dried over $MgSO_4$. Solvents were evaporated *in vacuo* and the product was purified on a column of silica gel (100 g) using a gradient of petroleum ether and ethyl acetate as eluent (97.5:2.5 to 80:20). As previously described, this procedure gave the enantioenriched alcohol **67** (3.00 g, 97% with respect to the aldehyde) as a yellowish oil: $[\alpha]_D$ -166.0 (*c* 1.0, $CHCl_3$; literature[52] gives $[\alpha]_D$ -99.5 (*c* 0.6, $CHCl_3$)); $^1$H NMR ($CDCl_3$) δ 7.22 (d, $^3J_{CH\text{-}7,CH\text{-}8}$ = 8.0, 1H, CH-7), 7.16 (d, $^3J_{CH\text{-}7,CH\text{-}8}$ = 8.0, 1H, CH-8), 5.81 (ddd, $^3J_{CH\text{-}2,CH\text{-}3}$ = 8.2, $^3J_{CH\text{-}3,\,cis\ CH\text{-}4}$ = 10.3, $^3J_{CH\text{-}3,\,trans\ CH\text{-}4}$ = 17.2, 1H, CH-3), 5.24-5.16 (m, 2H, $CH_2$-4), 4.32 (dd, $^3J_{CH\text{-}1,CH\text{-}2}$ = 8.0, $^3J_{OH,CH\text{-}1}$ = 2.6, 1H, CH-1), 2.52-2.42 (m, 1H, CH-2), 2.35 (s, 3H, $CH_3$-10), 2.11 (d, $^3J_{OH,CH\text{-}1}$ = 2.6, 1H, OH), 0.86 (d, $^3J_{CH\text{-}2,CH\text{-}5}$ = 6.8, 3H, $CH_3$-5); $^{13}$C NMR ($CDCl_3$) δ 140.8 (CH-3), 139.4 (C-Ar), 137.3 (C-Ar), 128.9 (CH-8), 126.7 (CH-7), 116.7 ($CH_2$-4), 77.7 (CH-1), 46.2 (CH-2), 21.1 ($CH_3$-10), 16.6 ($CH_3$-5); 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 $^{o}$C, then 0.5 deg.min$^{-1}$) showed 98% ee ($t_{RR}$ = 49.5 min, $t_{SS}$ = 50.0 min) and 94% de ($t_{syn1}$ = 51.0 min, $t_{syn2}$ = 51.8 min).

METHOX **(+)-34** was eluted from the column with a methanol-ethyl acetate mixture (20:80) and could be reused after recrystallisation from dichloromethane-petroleum ether (310 mg, 95%).



**racemic, syn-/anti 1:4**

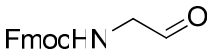
**(±)-2-Methyl-1-*p*-tolyl-but-3-en-1-ol (±)-(67)**

*p*-Tolualdehyde (2.17 mL, 18.5 mmol) was added to a solution DMF (2.85 mL, 36.9 mmol) and DIPEA (6.43 mL, 36.9 mmol) in dichloromethane (5 mL) under inert atmosphere and the mixture was cooled to 0°C. Crotyltrichlorosilane **26** (3.5 g, 18.5 mmol) was then added dropwise while stirring vigorously. The reaction temperature was maintained at 0 °C for 4 h, let to warm up slowly to room temperature and the mixture was stirred overnight. The reaction was quenched with a saturated aqueous solution of $NaHCO_3$ (50 mL) and extracted with ethyl acetate (3 × 40 mL). The combined organic phase was washed with brine (50 mL) and dried over $MgSO_4$. Solvents were evaporated *in vacuo* and the product was purified on a column of silica gel (100 g) using a gradient of petroleum ether and ethyl acetate as eluent (97:3 to 80:10) to afford a racemic mixture of *syn*- and *anti*-alcohol (±)-**67** (2.17 g, 67% in respect to crotyltrichlorosilane **26**, *syn* : *anti* = 1:4 according to $^1$H NMR) as pale yellow oil: $^1$H NMR ($CDCl_3$) (signals of the minor *syn*-isomer are marked with * where possible) δ 7.23-7.14 (m, 2H + 2H*, CH-7, CH-7*, CH-8, CH-8*), 5.86-5.70 (m, 1H + 1H*, CH-3, CH-3*), 5.22-5.16 (m, 2H, $CH_2$-4), 5.06-5.02 (m, 2H, $CH_2$-4*), 4.57 (d, $^3J_{CH\text{-}1^*,CH\text{-}2^*}$ = 5.1, 1H*, CH-1*) 4.32 (d, $^3J_{CH\text{-}1,CH\text{-}2}$ = 8.1, 1H, CH-1), 2.59-2.54 (m, 1H*, CH-2*), 2.52--2.42 (m, 1H, CH-2), 2.34 (s, 3H + 3H*, $CH_3$-10, $CH_3$-10*), 1.01 (d, $^3J_{CH\text{-}2^*,CH\text{-}5^*}$ = 6.7, 3H*, $CH_3$-5*), 0.86 (d, $^3J_{CH\text{-}2,CH\text{-}5}$ = 6.8, 3H, $CH_3$-5); $^{13}$C NMR ($CDCl_3$) δ 140.8 (CH-3, CH-3*), 140.4 (C-Ar*), 139.4 (C-Ar), 137.3 (C-Ar), 128.9 (CH-8*), 128.8 (CH-8), 126.7 (CH-7), 126.4 (CH-7*), 116.7 (*C*$H_2$-4), 115.3 (*C*$H_2$-4*), 77.7 (CH-1), 77.2 (CH-1*), 46.2 (CH-2), 44.5 (CH-2*), 21.1 ($CH_3$-10, $CH_3$-10*), 16.6 ($CH_3$-5), 14.2 ($CH_3$-5*); 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 $^o$C, then 0.5 deg.min$^{-1}$) showed 4 isomers at: $t_{anti1}$ = 49.5 min, $t_{anti2}$ = 50.0 min, $t_{syn1}$ = 51.0 min, $t_{syn2}$ = 51.8 min.


**(9H-Fluoren-9-yl)methyl 2-hydroxyethylcarbamate (81).**

Ethanolamine (1.00 mL, 20 mmol) was dissolved in dry dichloromethane (50 ml) and the reaction flask was immersed in ice bath. Fmoc chloride (2.10 g, 8.11 mmol) was dissolved in another portion of dichloromethane and added to reaction mixture via dropping funnel over period of 30 min while stirring vigorously. The mixture was then let to heat up to room temperature and stirred for another 2 hrs. The reaction was then quenched with 0.5M aq. HCl (100 mL), organic phase was again washed with 0.5M aq. HCl (2 x 100 mL) and extracted with dichloromethane (2x50 ml). Combined organic fractions were dried by $MgSO_4$ and the solvents were evaporated under diminished pressure to give protected aminoalcohol **81** as slightly yellow solid which was recrystallized from hot MeOH-petroleum ether to give white crystals (2.07 g, 90%). M.p. = 127°C; (Lit[61] gives 144-

145°C); $^{1}$H NMR ($CDCl_3$) δ 7.69 (d, *J* = 7.5, 2H, Ar), 7.52 (d, *J* = 7.5, 2H, Ar), 7.33 (t, *J* = 7.4, 2H, Ar), 7.24 (t, *J* = 7.4, 2H, Ar), 5.08 (s, 1H, NH), 4.36 (d, *J* = 6.7, 2H, Fmoc-$CH_2$), 4.15 (t, *J* = 6.8, 1H, Fmoc-CH), 3.65 (q, *J* = 4.8, 2H, C*H*$_2$-OH), 3.28 (q, *J* = 4.9, 2H, C*H*$_2$-NH), 2.00 (t, J = 4.9, 1H, OH). $^{13}$C NMR ($CDCl_3$) δ 143.9 (C), 141.3 (C), 127.7 (CH-Ar), 127.0 (CH-Ar), 125.0 (CH-Ar), 120.0 (CH-Ar), 66.7 ($CH_2$-OH), 62.3 ($CH_2$-NH-), 47.22 (-*CH*-Fmoc), 43.4 (*CH*$_2$-Fmoc);



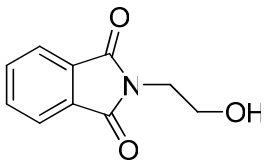

**(9H-fluoren-9-yl)methyl 2-oxoethylcarbamate (1h).**

*Method I:*

Fmoc-protected ethanolamine **81** (1.00 g, 3.53 mmol) was dissolved in dichloromethane (60 mL) and PCC (3.04 g, 14.12 mmol) was added portionwise while stirring. Reaction mixture was stirred for 2.5 hr, precipitated by addition of $Et_2O$ (60 mL) and filtered through pad of silica gel (3 x 5 cm). Solvents were evaporated in vacuo and product **1h** was purified by chromatography on silica gel (30 g) in gradient of petroleum ether-EtOAc (3:2 to 1:1). Aldehyde **1h** was obtained as white solid (412 mg, 41%).

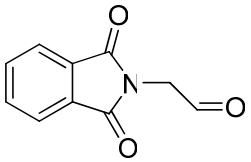
*Method II:*

Under inert conditions, oxalyl chloride (420 μL, 4.96 mmol) was dissolved in dichloromethane (15 mL) and the solution was cooled down to -78°C. DMSO (690 μL, 9.71 mmol) was then added dropwise to cold reaction mixture, which was then stirred for 30 min at the same temperature. After the formation of reactive intermediate, a solution of fmoc-protected ethanolamine **81** (911 mg, 3.22 mmol) in THF (7 mL) was added slowly and the reaction mixture was stirred for another 15 min. Finally triethylamine (1.80 mL, 12.91 mmol) was added dropwise, followed by another 15 min of stirring. Reaction flask was then brought to the ice bath, reaction mixture was quenched with saturated aq. $NH_4Cl$ (40 mL), extracted with EtOAc (3 x 25 mL), washed with brine (2 x 25 mL) and dried over $MgSO_4$. Product was purified by chromatography as described in Method I to obtain identical compound **1h** (735 mg, 81%). M.p. = 103-107°C (dichloromethane-petroleum ether, Lit[62] give M.p. = 124-126°C); $^{1}$H NMR ($CDCl_3$) δ 9.59 (s, 1H, CHO), 7.70 (d, *J* = 7.5, 2H, Ar), 7.53 (d, *J* = 7.5, 2H, Ar), 7.34 (bt, *J* = 7.5, 2H, Ar), 7.25 (td, *J* = 7.5, *J* = 1.2, 2H, Ar), 5.39 (bs, 1H, NH), 4.36 (d, *J* = 7.0, 2H, $CH_2$-Fmoc), 4.16 (t, *J* = 6.9, 1H, CH-Fmoc), 4.09 (d, *J* = 5.0, C*H*$_2$-N); $^{1}$13 NMR (CDCl3) δ 196.3 (CHO), 143.7 (C), 141.3 (C), 127.8 (CH-Ar), 127.1 (CH-Ar), 125.0 (CH-Ar), 120.0 (CH-Ar), 67.2 (*C*$H_2$-N), 51.7 ($CH_2$-Fmoc), 47.1 (CH-Fmoc);



***N*-(1-Hydroxy-2-ethyl)-phthalimide (82).**

Phthalic anhydride (3.70 g, 25 mmol) and ethanolamine (1.51 mL, 25 mmol) were heated to 150 °C and stirred at this temperature for 2 hrs. After that, the source of heat was turned off and product crystallized spontaneously. Recrystallization from hot MeOH gave white crystals of phtalimide **82** (3.71 g, 78%); M.p. = 127-128 °C (Lit[63] gives 130-131 °C ); $^{1}$H NMR (CDCl3) δ 7.85-7.82 (m, 1H, Ar), 7.72-7.69 (m, 1H, Ar), 3.90-3.84 (m, 4H, N-$CH_2$-$CH_2$-O), 2.39 (bs, 1H, OH); $^{13}$C NMR (CDCl3) δ 168.8 (CO), 134.1 (CH-Ar), 131.9 (C-Ar), 123.3 (CH-Ar), 60.97 ($CH_2$-OH), 40.77 ($CH_2$-N);



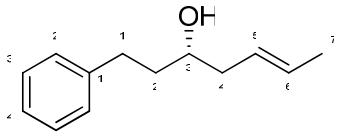
***N*-(1-Oxo-2-ethyl)-phthalimide (1i).**

Under inert conditions, oxalyl chloride (2.53 μL, 29.9 mmol) was dissolved in dichloromethane (90 mL) and the solution was cooled down to -78°C. DMSO (4.17 mL, 58.7 mmol) was then added dropwise to cold reaction mixture, which was then stirred for 30 min at the same temperature. After the formation of reactive intermediate, a solution of phtalimide derivative **82** (3.70 g, 19.35 mmol) in THF (35 mL) was added slowly and the reaction mixture was stirred for another 15 min. Finally triethylamine (10.9 mL, 78.0 mmol) was added dropwise, followed by another 15 min of stirring. Reaction flask was then brought to the ice bath, reaction mixture was quenched with saturated aq. $NH_4Cl$ (240 mL), extracted with EtOAc (3 x 75 mL), washed with brine (2 x 150 mL) and dried over $MgSO_4$. Product was purified by chromatography on silica gel (100 g) in petroleum ether-EtOAc(1:1) to obtain aldehyde **1i** (2.41 g, 66%). M.p. = 106-108°C ($CHCl_3$-Petroleum ether, Lit[64] gives 110-112 °C), $^{1}$H NMR ($CDCl_3$) δ 9.59 (s, 1H, CHO), 7.83 (dd, *J* = 3.0, 5.5, 2H, Ar), 7.70 (dd, *J* = 3.0, 5.5, 2H, Ar), 4.50 (s, 2H, $CH_2$-N); $^{13}$C NMR (CDCl3) δ 193.5 (CHO), 167.5 (CO), 134.3 (CH-Ar),131.9 (C-Ar), 123.7 (CH-Ar), 47.3 ($CH_2$-N);

**Mechanistic Experiment for the Allyl Transfer Reaction**

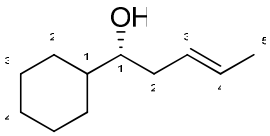
Tolyl alcohol **67** (20.0 mg, 114 μmol) and 3-phenyl-propionaldehyde (**1a**, 44.7 μL, 340 μmol) were

added consecutively to a solution of 2,6-di-*tert*-butyl-4-methyl-pyridine (**79**) (2.8 mg, 13.6 μmol, 12 mol%) and a catalytic amount of acid (11.3 μmol, 10 mol%) in dry $CDCl_3$ (0.6 mL). The $^1H$ NMR spectra were recorded immediately and after 1 day and 2 days. For comparison, each experiment was run in parallel with the acid catalyst (5 mol%) in the absence of 2,6-di-*tert*-butyl-4-methyl-pyridine (**79**).




**(*S*,*E*)-(-)-1-Phenyl-hept-5-en-3-ol (-)-(51a).**

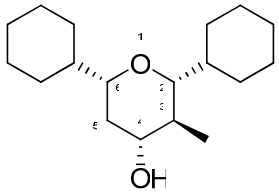
Prepared from 3-phenyl-propionaldehyde (**1a**) following general procedure. Product **51a** was obtained as a colorless oil (94%): $[\alpha]_D$ -15.7 (*c* 0.7, $CHCl_3$; literature[47] gives $[\alpha]_D$ -14.0 (*c* 1.0, $CHCl_3$)); $^1H$ NMR ($CDCl_3$) δ 7.23-7.10 (m, 5H, Ph); 5.54-5.55 (m, 1H, CH-6), 5.39-5.31 (m, 1H, CH-5), 3.57-3.51 (bm, 1H, CH-3), 2.74 (dt, $J_{CH1a\text{-}CH1b}$ = 13.8, $J_{CH1a\text{-}CH\text{-}2}$ = 7.7, 1H, $CH_2$-1a), 2.61 (dt, $J_{CH1a\text{-}CH1b}$ = 13.8, $J_{CH1b\text{-}CH\text{-}2}$ = 8.3, 1H, $CH_2$-1b), 2.21-2.13 (m, 1H, $CH_2$-4a), 2.03 (dt, $J_{CH4a\text{-}CH4b}$ = 13.9, $J_{CH4b\text{-}CH5}$ = $J_{CH4b\text{-}CH3}$ = 7.8, 1H, $CH_2$-4b), 1.72-1.67 (m, 2H, $CH_2$-2), 1.62 (d, $^3J_{CH3\text{-}7,CH3\text{-}6}$ = 6.4, 3H, $CH_3$-7), 1.57 (br s, 1H, OH); $^{13}C$ NMR ($CDCl_3$) δ 142.1 (C-Ar), 129.3 (CH-6), 128.4 (CH-Ar), 128.3 (CH-Ar), 126.8 (CH-5), 125.7 (CH-Ar), 70.1 (CH-3), 40.8 ($CH_2$-4), 38.4 ($CH_2$-2), 32.1 ($CH_2$-1), 18.1 ($CH_3$-7); 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 $^oC$, then 0.5 deg.$min^1$) showed 99% ee ($t_R$ = 44.2 min, $t_S$ = 44.6 min) and less than 1% of (*Z*)-isomer ($t_{Z1}$ = 46.7 min, $t_{Z2}$ = 47.2 min).



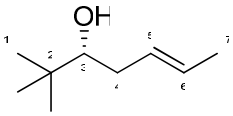

**(*R*,*E*)-(+)-1-Cyclohexyl-pent-3-en-1-ol (+)-(51b).**

Prepared from cyclohexyl-carbaldehyde (**1b**) following general procedure. Product **51b** was obtained as colourless oil (78%): $[\alpha]_D$ +3.0 (*c* 1.0, $CHCl_3$, ; literature[52] gives $[\alpha]_D$ +7.6 (*c* 2.5, $CHCl_3$)); $^1H$ NMR ($CDCl_3$) δ 5.55-5.45 (m, 1H, CH-4), 5.42-5.32 (m, 1H, CH-3), 3.28-3.23 (m, 1H, CH-1), 2.25-2.15 (m, 1H, CH-2a), 1.97 (dt, $J_{CH2a\text{-}CH2b}$ = 13.9, $J_{CH2b\text{-}CH1}$ = $J_{CH2b\text{-}CH3}$ = 8.4, 1H, CH-

2b), 1.82-1.75 (m, 1H, CH-1'), 1.71-1.65 (m, 2H, Cy), 1.62 (d, $J_{CH5\text{-}CH4}$ = 6.2, 3H, C*H*$_3$-5), 1.62-1.57 (bm, 2H, Cy), 1.32-0.88 (m, 7H, Cy and O*H*); $^{13}$C NMR ($CDCl_3$) δ 128.9 (CH-4), 127.6 (CH-3), 74.9 (CH-1), 42.3 (CH-1'), 37.5 ($CH_2$-2), 29.1 ($CH_2$-Cy), 28.2 ($CH_2$-Cy), 26.5 ($CH_2$-Cy), 26.3 ($CH_2$-Cy), 26.2 ($CH_2$-Cy), 18.1 ($CH_3$-5); 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 γ-DEX 120 column, oven for 30 min at 105 $^o$C, then 0.5 deg.min$^{-1}$) showed 97% ee ($t_R$ = 33.2 min, $t_S$ = 34.3 min) and 6.5% of (*Z*)-isomer ($t_Z$ = 36.9 min).

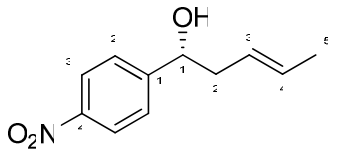



Along with chiral alcohol **51b**, a byproduct **80** was isolated as white solid (20%).$^1$H NMR ($CDCl_3$) δ 3.23 (td, *J* = 10.3, 4.7, 1H, CH-4), 2.88 (dd, *J* = 11.7, 6.7, 1H, CH-6), 2.62 (d, *J* = 9.8, 1H, CH-2), 1.88-1.84 (m, 2H, CH-5eq + CH), 1.69-0.87 (m, 24H): 1.32-1.25 (m, CH-3), 1.16-1.03 (m, CH-5ax) 0.84 (d, J = 6.5, 3H, $CH_3$); $^{13}$C NMR ($CDCl_3$) δ 84.4 (CH-2), 79.6 (CH-6), 74.8 (CH-4), 42.9 (CH-3), 40.4 (CH), 38.7 (CH), 38.4 ($CH_2$-5), 31.1 ($CH_2$), 28.9 ($CH_2$), 26.9 ($CH_2$), 26.64 ($CH_2$), 26.61 ($CH_2$), 26.2 ($CH_2$), 26.1 ($CH_2$), 24.9 ($CH_2$), 12.3 ($CH_3$); MS (CI) *m/z* (%) 281 ($M+H^+$, 17), 263 ($M^+$-OH, 30), 151 (100), 136 (25); HRMS (CI) 281.2477 ($C_{18}H_{33}O_2$ requires 281.2481).



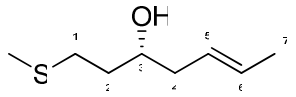

**(*R*,*E*)-(+)-2,2-Dimethyl-hept-5-en-3-ol (+)-(51c).**

Prepared from pivalaldehyde (**1c**) following general procedure. Product **51c** was obtained as colourless oil (56%): $[\alpha]_D$ +12.0 (*c* 5.0, MeOH; literature[56] gives $[\alpha]_D$ +11.4 (*c* 5.19, MeOH)); $^1$H NMR ($CDCl_3$) δ 5.54-5.45 (m, 1H, CH-6); 5.43-5.35 (m, 1H, CH-5), 3.12 (dd, $J_{CH\text{-}3,CH\text{-}4b}$ = 10.7, $J_{CH\text{-}3,CH\text{-}4a}$ = 1.4, 1H, CH-3), 2.25-2.19 (m, 1H, CH-4a), 1.83 (ddd, $J_{CH\text{-}4a,CH\text{-}4b}$ = 13.9, $J_{CH\text{-}4b,CH\text{-}3}$ = 10.7, $J_{CH\text{-}4b,CH\text{-}5}$ = 8.5,1H, CH-4b), 1.63 (bd, $J_{CH\text{-}7,\ CH\text{-}6}$ = 6.3, 3H, CH-7), 0.84 (s, 9H, 1-H); $^{13}$C NMR ($CDCl_3$) δ 128.7 (CH-6); 128.6 (CH-5), 78.3 (CH-3), 35.2 ($CH_2$-4), 34.5 (C-2), 25.7 ($CH_3$-1), 18.0 ($CH_3$-7); Chiral GC (Supelco γ-DEX 120 column, oven for 2 min at 50 $^o$C, then 0.5 deg.min$^{-1}$) showed 96% ee ($t_R$ = 31.4 min, $t_S$ = 31.9 min) and 4% of (*Z*)-isomers ($t_{Z1}$ = 32.5 min, $t_{Z2}$ = 33.2 min).



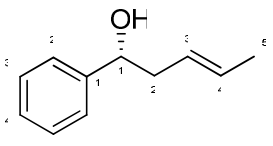
**(*R*,*E*)-(+)-1-(4'-Nitrophenyl)pent-3-en-1-ol (+)-(51e).**

Prepared from *p*-nitrobenzaldehyde (**1e**) following general procedure. Product **51e** was obtained as a pale yellow oil (72%): $[\alpha]_D$ +123.5 (*c* 1.0, $CHCl_3$, literature[52] gives $[\alpha]_D$ +61.5 (*c* 0.5, $CHCl_3$)); $^1H$ NMR ($CDCl_3$) δ 8.13 (d, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.6, 2H, CH-3'); 7.45 (d, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.6, 2H, CH-2'), 5.60-5.51 (m, 1H, CH-4), 5.36-5.29 (m, 1H, CH-3), 4.72 (dd, $J_{CH\text{-}1,CH\text{-}2b}$ = 8.0, $J_{CH\text{-}1,CH\text{-}2a}$ = 4.4, 1H, CH-1), 2.46-2.40 (m, 1H, CH-2a), 2.28 (dt, $J_{CH\text{-}2a,CH\text{-}2b}$= 14.0, $J_{CH\text{-}2b,CH\text{-}1}$ = $J_{CH\text{-}2b,CH\text{-}3}$ = 8.0, 1H, CH-2b), 2.20 (bs, 1H, OH), 1.63 (d, $J_{CH\text{-}5,CH\text{-}4}$ = 6.4, 3H, CH-5); $^{13}C$ NMR ($CDCl_3$) δ 151.3 (C-Ar), 147.2 (C-Ar), 130.9 (CH-4), 126.5 (CH-2'), 125.5 (CH-3), 123.6 (CH-3'), 72.3 (CH-1), 42.9 ($CH_2$-2), 18.0 ($CH_3$-5); 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 IB column, hexane/2-propanol = 98:2, 0.75 mL $min^{-1}$) showed 96% ee ($t_R$ = 38.5 min, $t_S$ = 40.6 min) and 3.5% of (*Z*)-isomers ($t_Z$ = 44.5 min).



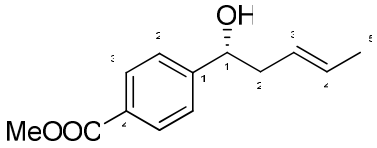
**(*R*,*E*)-(-)-1-(Methylthio)-hept-5-en-3-ol (-)-(51g)**

Prepared from 3-(methylthio)-propionaldehyde (**1g**) following general procedure. Product **51g** was obtained as a colorless oil (64% yield): $[\alpha]_D$ -14.5 (*c* 0.5, $CHCl_3$, literature[52] gives $[\alpha]_D$ -28.5 (*c* 1.0, $CHCl_3$)); $^1H$ NMR ($CDCl_3$) δ 5.54-5.46 (m, 1H, CH-6), 5.40-5.32 (m, 1H, CH-5), 3.70-3.63 (m, 1H, CH-3), 2.62-2.51 (m, 2H, CH-1), 2.19-2.13 (m, 1H, CH-4a), 2.07-2.00 (m, 1H, CH-4b), 2.05 (s, 3H, C*H*$_3$S), 1.85 (d, $J_{OH,5\text{-}H}$ = 4.0, 1H, O*H*), 1.70-1.62 (m, 2H, CH-2), 1.63 (d, $J_{CH\text{-}7,CH\text{-}6}$ = 6.3, 3H, $CH_3$-7); $^{13}C$ NMR ($CDCl_3$) δ 15.5 ($CH_3$-7), 18.1 (S*C*$H_3$), 30.8 ($CH_2$), 35.6 ($CH_2$), 40.7 ($CH_2$), 70.1 (CH-3), 126.7 (CH-5), 129.2 (CH-6); 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 >95% ee ($\delta_R$ = -71.24 ppm and $\delta_S$ = -71.22 ppm).



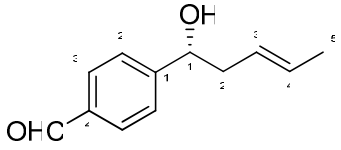
**(*R*,*E*)-(+)-1-Phenylpent-3-en-1-ol (+)-(51j)**

Prepared from benzaldehyde dimethylacetal (**1j**) following the general procedure. Product **51j** was obtained as colorless oil (37% yield): $[\alpha]_D$ +67.5 (*c* 1.2, $CHCl_3$; literature[47] gives $[\alpha]_D$ -66.4 (*c* 1.0, $CHCl_3$) for the (*S*)-enantiomer); $^1$H NMR ($CDCl_3$) δ 7.49-7.46 (m, 4H, CH-2' + CH-3'); 7.43-7.37 (m, 1H, CH-4'); 5.78-5.69 (m, 1H, CH-4), 5.60-5.52 (m, 1H, CH-3), 4.80 (dd, $J_{CH\text{-}1,CH\text{-}2a}$ = 4.9, $J_{CH\text{-}1,CH\text{-}2b}$ = 8.2, 1H, CH-1), 2.63-2.49 (m, 2H, *CH-2*), 2.20 (bs, 1H, *CH-2*), 1.61 (bd, $J_{CH\text{-}5,CH\text{-}4}$ = 6.4,3H, *CH-5*); $^{13}$C NMR ($CDCl_3$) δ 144.0 (C-1'), 129.1 (CH), 128.2 (CH), 127.2 (CH), 126.7 (CH), 125.7 (CH), 73.4 (CH-1), 42.6 ($CH_2$-2), 18.0 ($CH_3$-5); 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 ($\delta_R$ = -71.31 ppm and $\delta_S$ = -71.45 ppm).



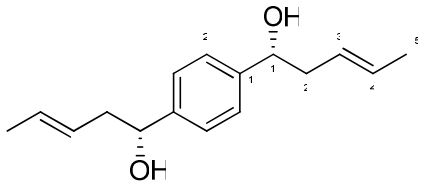

**Methyl (*R*,*E*)-(+)-4-(1-hydroxypent-3-enyl)benzoate (+)-(51f)**

Prepared from methyl 4-formylbenzoate (**1f**) following general procedure. Product **51f** was obtained as white crystals (72% yield): m.p = 51-53°C (petroleum ether-acetone); $[\alpha]_D$ +53.5 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 7.95 (d, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.2, 2H, CH-2'); 7.35 (d, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.2, 2H, CH-3'); 5.58-5.50 (m, 1H, CH-4), 5.37-5.29 (m, 1H, CH-3), 4.67 (dd, $J_{CH\text{-}1,CH\text{-}2a}$ = 4.4, $J_{CH\text{-}1,CH\text{-}2b}$ = 7.8, 1H, CH-1), 3.84 (s, 3H, $OCH_3$), 2.44-2.37 (m, 1H, CH-2a), 2.30 (dt, $J_{CH\text{-}2a,CH\text{-}2b}$ = 13.9, $J_{CH\text{-}1,CH\text{-}2b}$ = $J_{CH\text{-}3,CH\text{-}2b}$ = 7.9, 1H, CH-2b), 2.07 (bs, 1H, OH), 1.62 (d, $J_{CH\text{-}5,CH\text{-}4}$ = 6.3, 3H, CH-5); $^{13}$C NMR ($CDCl_3$) δ 149.1 (C-Ar); 130.2 (CH-4), 129.7 (CH-2'), 126.1 (CH-3), 125.7 (CH-3'), 72.9 (CH-1), 52.1 ($OCH_3$), 42.8 ($CH_2$-2), 18.1 ($CH_3$-5); IR (NaCl) ν 3294, 2940, 2914, 1712, 1434, 1281, 1020, 1001, 877, 855, 707 $cm^{-1}$; MS (CI) *m/z* (%) 221 ($M+H^+$, 100), 203 ($M^+$-OH, 40); HRMS (CI) 221.1178 ($C_{13}H_{17}O_3$ requires 221.1179); $^{19}$F NMR of the corresponding Mosher ester showed 98% ee ($\delta_R$ = -71.23 ppm and $\delta_S$ = -71.38 ppm) and 4% of (*Z*)-isomers ($\delta_{Z1}$ = -71.28 ppm and $\delta_{Z2}$ = -71.41 ppm).



**(*R*,*E*)-(+)-4-(1-hydroxypent-3-enyl)benzaldehyde (51l) and bis[(1S,3E)-1-hydroxy-pent-3-enyl]benzene (+)-(83).**

Prepared from terephthalaldehyde (**1l**) following general procedure. After separation, **51l** was obtained as colourless oil (54% yield) and last fraction gave diol **83** as colourless oil (17%). **51l**: $[\alpha]_D$ +61.0 (*c* 1.0, $CHCl_3$); $^1$H NMR ($CDCl_3$) δ 9.93 (s, 1H, CHO), 7.79 (bd, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.3, 2H, CH-2'), 7.45 (bd, $J_{CH\text{-}2',CH\text{-}3'}$ = 8.3, 2H, CH-3'), 5.59-5.50 (m, 1H, CH-4), 5.38-5.29 (m, 1H, CH-3), 4.71-4.68 (m, 1H, CH-1), 2.46-2.39 (m, 1H, CH-2a), 2.30 (dt, $J_{CH\text{-}2a,CH\text{-}2b}$ = 14.0, $J_{CH\text{-}1,CH\text{-}2b}$ = $J_{CH\text{-}3,CH\text{-}2b}$ = 8.1, 1H, CH-2b), 2.15 (d, $J_{CH\text{-}1,OH}$ = 2.7, 1H, OH), 1.63 (d, $J_{CH\text{-}5,CH\text{-}4}$ = 6.4, 3H, CH-5); $^{13}$C NMR ($CDCl_3$) δ 192.0 (CHO), 150.9 (C-Ar), 135.6 (C-Ar), 130.4 (CH-2'), 129.9 (CH-2), 126.3 (CH-3), 125.9 (CH-3'), 72.8 (CH-1), 42.9 ($CH_2$-2), 18.1 ($CH_3$-5); IR (DRIFT) ν 3423, 2916, 1697, 1606, 1425, 1305, 1209, 1166, 1047, 966, 829, 798 cm$^{-1}$; MS (EI) *m/z* (%) 221 ($M^{\bullet+}$, 100), 161 ($M^{\bullet+}$-CHO, 7); HRMS (EI) 190.0997 ($C_{12}H_{14}O_2$ requires 190.0994); Chiral HPLC (Chiracel IB column, hexane/2-propanol = 96:4, 0.75 mL min$^{-1}$) showed 93% ee ($t_S$ = 24.9 min, $t_R$ = 26.3 min) and 0.5% of (*Z*)-isomers ($t_Z$ = 28.8 min).




**83**:

$^1$H NMR ($CDCl_3$) δ 7.25 (s, 4H, CH-2'), 5.58-5.47 (m, 1H, CH-4), 5.39-5.31 (m, 1H, CH-3), 4.60 (dd, $J_{CH\text{-}1,CH\text{-}2a}$ = 8.0, $J_{CH\text{-}1,CH\text{-}2b}$ = 4.8, 1H, CH-1), 2.42-2.30 (m, 2H, CH-2), 2.02 (d, $J_{CH\text{-}1,OH}$ = 2.7, 1H, OH), 1.62 (d, $J_{CH\text{-}5,CH\text{-}4}$ = 6.3, 3H, CH-5); $^{13}$C NMR ($CDCl_3$) δ 143.2 (C-1'), 129.4 (CH-2), 126.7 (CH-3), 125.8 (CH-2'), 73.27 (CH-1a), 73.24 (CH-1b), 42.8 ($CH_2$-2), 18.0 ($CH_3$-5); MS (EI) *m/z* (%) 191 ($M^{\bullet+}$-$C_4H_8$, 100), 136 ($M^{\bullet+}$-$C_8H_{14}$, 85), 135 (55), 79 (49); IR (DRIFT) ν 3370, 2918, 2854, 1421, 1377, 1259, 1038, 966, 831, 813 cm$^{-1}$;

# 5. Conclusion

We have developed a practical two-step protocol for a catalytic enantioselective α-allylation of aldehydes. Due to the kinetic preference in each step, high regioselectivity could be achieved using mere technical grade allylic chloride. The elaborated reaction sequence consists of asymmetric organocatalytic γ-allylation of tolualdehyde, faciliated by 2-5 mol% of the Lewis base METHOX (**34**), followed by an allyl transfer to recipient aldehyde, catalyzed by trifluoromethanesulfonic acid. In this work, crotyl residue was used as a model substrate for the transfer reaction. Since other linear allylic substrates are known from literature to behave equally well under similar conditions, the potential of the reaction can be regarded as quite broad. Most attention was paid to the second step, the allylic transfer. We have proved that the actual promotor of the reaction is a Brønsted acid, either used directly or generated *in situ* by decomposition of the hydrolysis-sensitive Lewis acids. We have then optimised the conditions for the allyl transfer employing trifluormethanesulfonic acid as the catalyst of choice. The allyl transfer, based on the oxonia-Cope rearrangement, was shown to proceed well with aliphatic aldehydes, giving slightly lower yields for α-branched aldehydes. Reactivity of aromatic aldehydes is dependent on the electron density of the aromatic ring. Electron-poor aldehydes afforded good results, whereas allyl transfer with electron-rich aromatic aldehydes proved troublesome. Several functional groups, including thioethers and esters, were found to be compatible with the reaction conditions, with a notable exception of compounds containing nitrogen as a basic site. It is pertinent to note that our method offers a metal-free, fully catalytic protocol for the preparation of homoallylic linear alcohols with excellent stereocontrol.

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