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DIPLOMOVÁ PRÁCE

Enantioselective synthesis of homoallylic alcohols using chiral *N*-oxide organocatalysts

Hradec Králové, 2011 **Jiří Mikušek**

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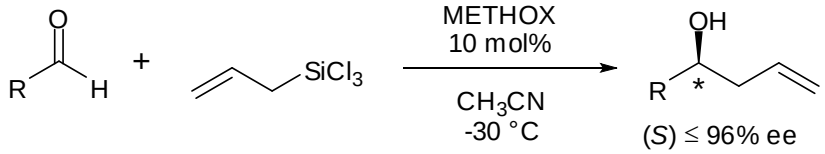
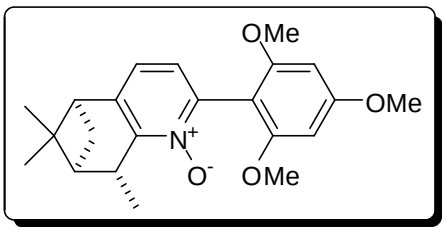
I declare that this thesis is my original work. All the literature and other sources which I was drawing from are quoted in the list of references and properly cited throughout my work.

Prohlašuji, že tato práce je mým původním autorským dílem. Veškerá literatura a další zdroje, z nichž jsem při zpracování čerpal, jsou uvedeny v seznamu použité literatury a v práci řádně citovány.

ABSTRACT

In order to extend the earlier work in the group,[1] we endeavored to explore the ability of the terpene-derived pyridine *N*-oxide organocatalyst (+)-METHOX to catalyze allylations of non-aromatic, α,β-conjugated aldehydes with allyltrichlorosilane in CH_3CN. This thesis describes the synthesis of 5 novel homoallylic alcohols of high enantioselectivities (≤ 96% ee).



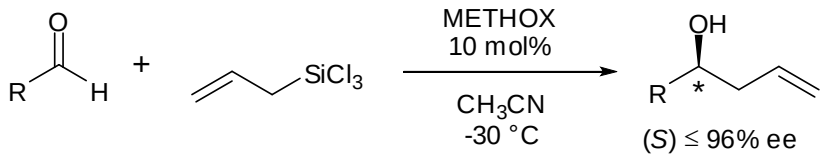


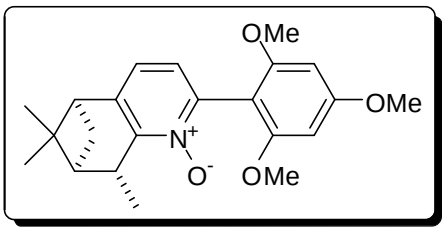
(+)-METHOX

[1] Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219

ABSTRAKT

Abychom rozšířili dřívější výzkum,[1] rozhodli jsme se dále prozkoumat schopnosti organokatalyzátoru (+)-METHOX katalyzovat allylace nearomatických, α,β-konjugovaných aldehydů pomocí allyltrichlorosilanu v prostředí CH_3CN. Tato práce se zabývá syntézou pěti nových homoallylických alkoholů s vysokou enantioselektivitou (≤ 96% ee).





(+)-METHOX

[1] Malkov, A. V.; Bell, M.; Castelluzzo, F.; Kočovský, P. *Org. Lett.* **2005**, *7*, 3219

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ABBREVIATIONS AND ACRONYMS

API	Active pharmaceutical ingredient
CI	Chemical ionisation
DCM	Dichloromethane
de	Diastereoisomeric excess
dr	Diastereoisomeric ratio
DMF	Dimethylformamide
ee	Enantiomeric excess
EI	Electron impact
FAB	Fast atom bombardment
GC	Gas chromatography
h	Hour
HPLC	High-pressure liquid chromatography
HRMS	High resolution mass spectrometry
IR	Infrared
LB	Lewis base
LB*	Chiral Lewis base
MS	Mass spectrometry
NMR	Nuclear magnetic resonance
Ph	Phenyl
PMA	Phosphomolybdic acid
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultraviolet

1 INTRODUCTION

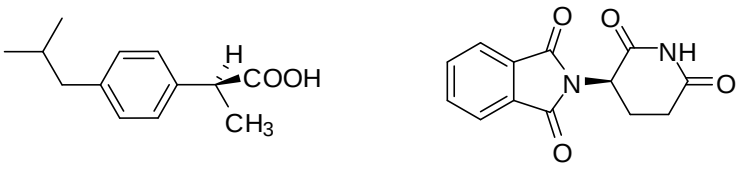
1.1 Chiral molecules as API

Chiral organic molecules that surround us are playing an essential role in our lives. Human organism itself is in general composed of basic chiral molecules such as amino acids and sugars that occur in one enantiopure form only. Also nature that surrounds us synthesizes a large library of homochiral compounds every day. The reason of Earth's homochirality is still a subject of a scientific debate.[1]

With the knowledge of these basic facts it is not a big surprise to us then, that chirality of compounds that have to interact with our organ systems is absolutely crucial. The main theory that pushes chirality to the fore of interest of pharmacologists, molecular biologists, biochemists and many others was called the "lock and key" model.[2] The same as it is impossible to fit the left foot into the right shoe it is also impossible to force one enantiomer to fit into a "keyhole" in enzyme that matches the other one. When generalizing the fact that we are talking about chiral molecules as active pharmaceutical substances we have to emphasize the fact that the non-fitting enantiomer can behave in many different ways but in principle these effects are usually undesired or, so much the worse, harmful.

As a horrifying example stands the thalidomide case. In the years 1957 – 1961 thalidomide was being sold without a prescription as a safe sedative and mild hypnotic drug that alleviates the morning sickness of pregnant women. After a series of heavy malformations among babies that were born to women that had taken thalidomide during their pregnancy, thalidomide was pulled off the market. Further investigation revealed that the sedative and hypnotic effect of thalidomide was caused by only one of its enantiomers (*S*). On the other side the (*R*) enantiomer was causing serious malformations.[3] On the other hand, not all of the side effects caused by non-matching enantiomers have to be so drastic. Ibuprofen, a widely used non-steroidal anti-inflammatory drug, also comes in a form of racemate and only one of its enantiomers is pharmacologically active (*S*). The opposite (*R*) enantiomer does not cause any harm but it is totally ineffective. It has been proven that if we take ibuprofen as a racemate, the pain relieving effect appears in approx. 38 minutes. The effect of the enantiopure (*S*) ibuprofen comes in about 12 minutes.[4] The difference is significant.

Better pharmacokinetic and pharmacodynamic properties and elimination of undesired side effects are just two of many reasons why pharmaceutical companies are targeted on a synthesis of enantiopure drugs nowadays.



(*S*)-ibuprofen (*R*)-thalidomide

Figure 1. (*S*)-ibuprofen – enantiomer that is responsible for anti-inflammatory effect and (*R*)-thalidomide – enantiomer responsible for serious fetal malformations

1.2 Organocatalysis

Molecules of a single enantiomer can be prepared in different ways, e.g., by chiral resolution, chiral pool synthesis, by using chiral auxiliaries and asymmetric catalysis. Chiral resolution separates the desired isomer from the racemate using various types of chiral chromatography.[5] There is no need to say that these methods are highly wasteful and cannot have better yields than 50 % because the unwanted isomer is usually disposed. Chiral pool synthesis starts with a chiral compound that is commercially available and relatively cheap (amino acids, sugars, terpenes). The built-in chirality of these compounds is preserved for the series of subsequent reactions. Disadvantage of this method is a limited structure variation of starting material, usually long and many-step synthesis with low yield and a need to find a starting material that has structural and chiral resemblance with our final product not mentioning the fact that usually only one (natural) enantiomer is readily available. Chiral auxiliaries are chiral molecules that bond covalently to the achiral starting material in order to introduce a temporary chiral center that forces asymmetric formation of the other stereocenters. A drawback of this method is that it is a stoichiometric process and also it increases the number of steps involved in synthesis.

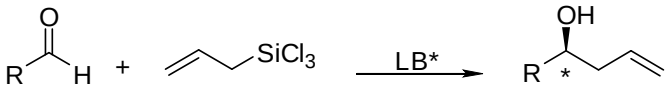
On the other hand, asymmetric catalysis presents advantageous process that allows achiral molecules to enter reaction. Only catalytic and recoverable amount of chiral catalyst is used in reaction which ends with chiral product usually in good yield and good enantiomeric

excess. Transition metal complexes were previously used as a major catalyst in asymmetric catalysis but nowadays they are being replaced by organocatalysts.

Organocatalysts are small organic molecules composed predominantly from C, H, O, N, S and P that have several significant advantages over conventional metal catalysts. They are less toxic, reactions are usually more tolerant to the moisture and air and because of that are easier to perform.[6]

1.3 Asymmetric allylation of aldehydes using trichlorosilanes

This project is focused on the synthesis of optically active secondary alcohols. These are playing an important role in the synthesis of many natural products.[7] Many research groups so far have been trying to activate allyltrichlorosilane (**2a**) and related reagents by chiral Lewis-based catalysts to develop asymmetric allylation of aromatic and heteroaromatic aldehydes (Scheme 1).[8-15] Researchers have focused on the chiral Lewis base catalysts with different functional groups such as Denmark's phosphoramides[8], Nakajima's[9] and Hayashi's[10] bipyridine *N*,*N*-bisoxides and pyridine-type *N*-monoxide organocatalysts PINDOX (**4**),[11] *iso*-PINDOX (**5**),[14] QUINOX (**6**)[13] and the latest METHOX (**7**)[15] developed recently by Malkov and Kočovský.



1 **2a** **3a**

Scheme 1. The asymmetric allylation of aldehydes using allyltrichlorosilane

Detailed reaction mechanism (Scheme 2) suggests cyclic transition state (**8**) that is formed because of high Lewis basicity of oxygen in *N*-oxides that goes together with high affinity of silicon to oxygen.[16] The mechanism is commonly explained as a result of coordination of Lewis base catalyst to the silicon atom of allyltrichlorosilane thus making the allyl ligand more nucleophilic and in the same time makes the silicon atom more Lewis acidic. This allows silicon atom to bind to the aldehyde while increasing its electron density on the α-carbon that is being attacked by the nucleophilic allyl ligand.[8]

Transition state **8** plays a crucial role in the stereocontrol of the reaction. It is especially evident in the case of *trans*- and *cis*-crotyltrichlorosilanes (**2b**, **2c**). Reaction with *trans*-crotyltrichlorosilane **2b** gives exclusively the *anti* isomer **3b** whereas the reaction with *cis*-crotyltrichlorosilane **2c** leads mostly to the *syn* isomer **3c** (although the reaction rate is slower). In this case we can also see a vast difference between the *N*-oxide catalysts **6** and **7** to which I will be referring in my thesis. METHOX (**7**) reacts well only with **2b** to give **3b** with excellent diastereocontrol (>99:1) and enantioselectivity (95 % ee).[15] QUINOX reacts well with both **2b** and **2c**. It showed higher affinity to **2c** when product from the starting material (*trans*/*cis* ratio 87:13) showed ~70:30 mixture of **2b** and **2c**.[17]

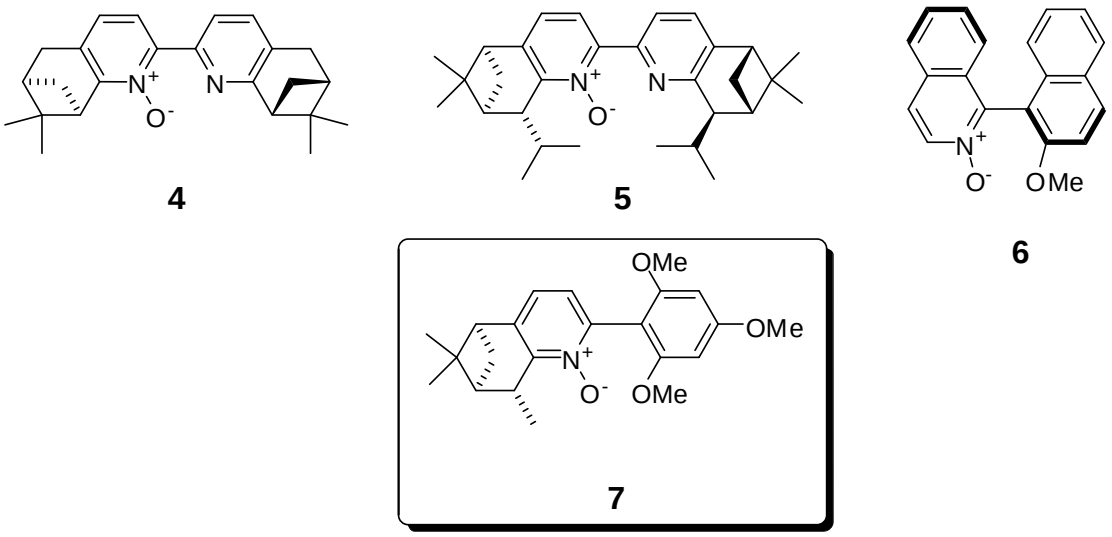
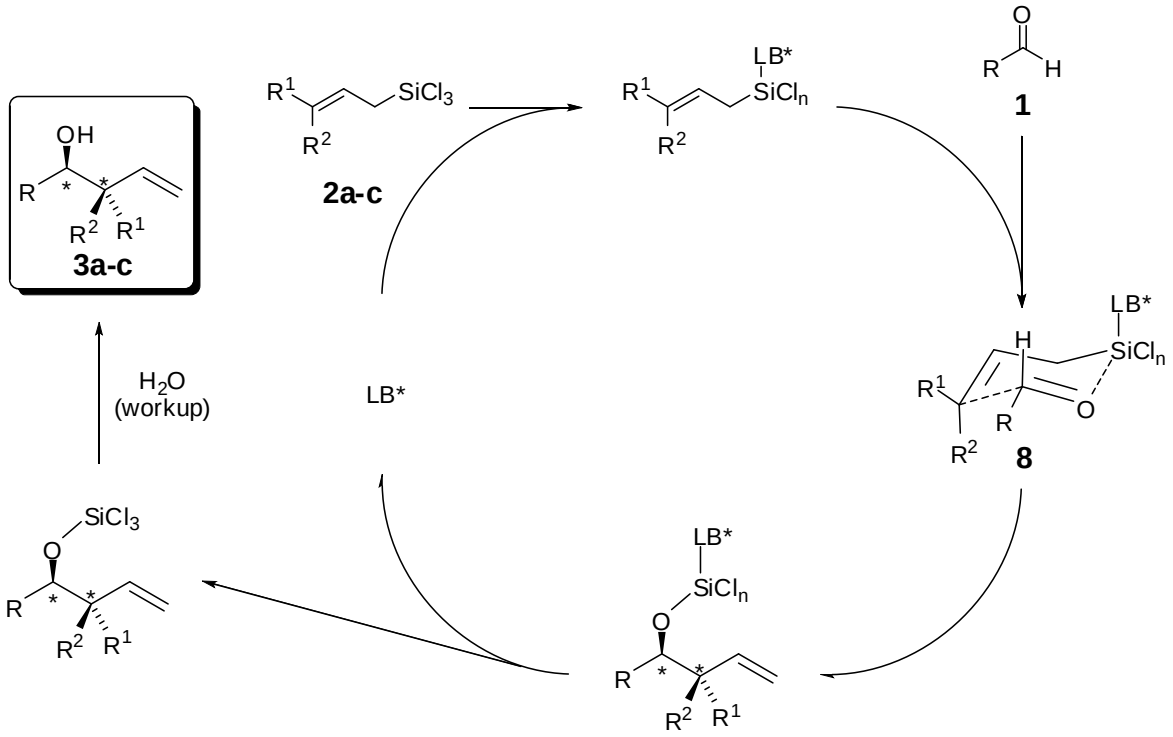


Figure 2. Chiral pyridine-type *N*-monoxide catalysts developed by Malkov and Kočovský



2a, R^1 = H, R^2 = H
2b, R^1 = Me, R^2 = H
2c, R^1 = H, R^2 = Me

3a, R^1 = H, R^2 = H
3b, R^1 = Me, R^2 = H
3c, R^1 = H, R^2 = Me

Scheme 2. Detailed mechanism of the asymmetric allylation

Unfortunately the attempts to use aliphatic aldehydes (**1**) as an allyl-accepting group have been unsuccessful, showing only low stereoselectivities. We decided to carry out the allylation reaction with a series of conjugated, α,β-unsaturared aliphatic aldehydes. Thanks to conjugated π-π system of the double bond and the carbonyl group of the aldehyde should these react in a similar way to aromatic and heteroaromatic aldehydes where the π-π stacking interactions between the catalyst and the aldehyde play a significant role. METHOX (**7**) was chosen as a chiral LB catalyst in these types of reactions because of its successful track record in the catalytic activation of organosilicon reagents.[15]

2 PROJECT AIM

The aim of this project was to investigate the ability of METHOX to catalyze the allylations and crotylations of α,β-unsaturated aliphatic aldehydes. These experiments have never been done before and we were expecting to synthesize a library of novel homoallylic alcohols with attractive functionalities that could be used as interesting starting materials for e. g. Grubbs cyclisation or Sharpless epoxidation.[18]

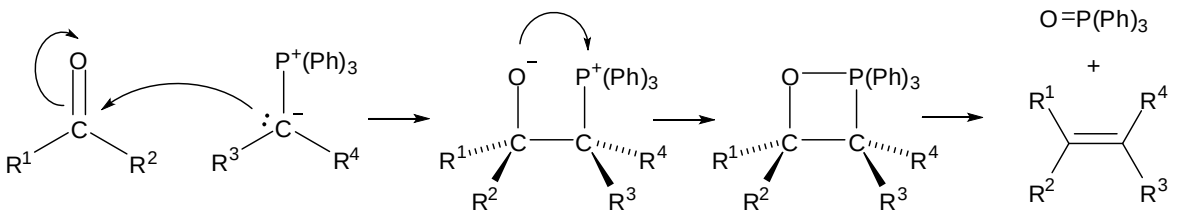
3 RESULTS AND DISCUSSION

3.1 Synthesis of α,β-unsaturated aldehydes

The first synthetic task was to prepare the conjugated aldehydes that were not commercially available. We came up with two possibilities. The first one was to extend saturated aliphatic aldehydes by reaction with stabilized phosphonium ylides (3.1.1) to obtain unsaturated aldehydes that are two carbons longer.[19] The other possibility was the methylenation of the α-carbon on saturated aldehydes (3.1.2).[20]

3.1.1 Reaction of aldehydes with stabilized phosphonium ylides

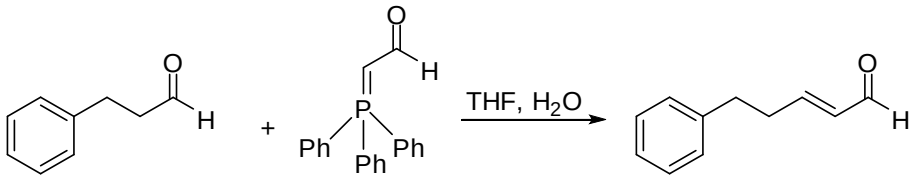
History of this reaction started in early 50s when G. Wittig first described reaction between methylenetriphenylphosphorane ($Ph_3P=CH_2$) and benzophenone to give 1,1-diphenylethene and triphenylphosphineoxide ($Ph_3P=O$) in quantitative yield.[21] The reaction mechanism is explained in Scheme 3.[22] Wittig reaction gave us an elegant opportunity to synthesize α,β-unsaturated aldehydes from almost any aldehyde available by simple reaction with (triphenylphosphoranylidene)-acetaldehyde (**10**).



Scheme 3. The mechanism of the Wittig reaction

3.1.1.1 Synthesis of (*E*)-5-Phenylpent-2-enal

In the first reaction of this series we decided to treat dihydrocinnamaldehyde (**9**) with (triphenylphosphoranylidene)-acetaldehyde (**10**) to produce (*E*)-5-phenylpent-2-enal (**11**).



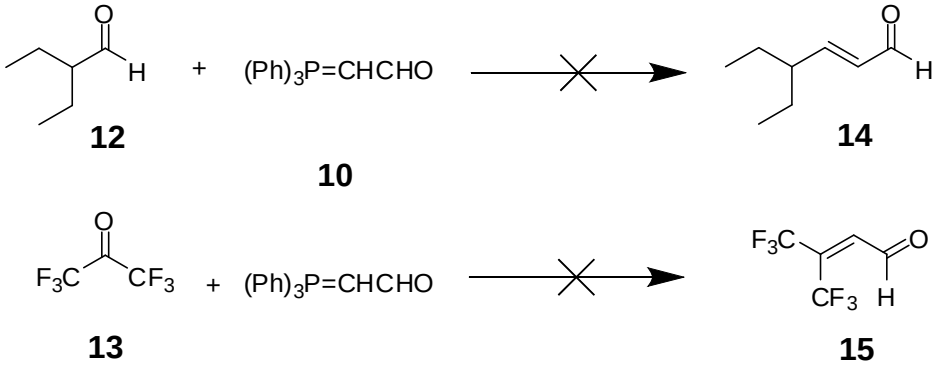
9 **10** **11**

Scheme 4.

Following a published procedure[19] we were expecting to obtain **11** as a pure *E* stereoisomer with full conversion and excellent yield. The authors carried out the reaction in a mixture of THF and D_2O (8:1) as they were focusing on a preparation of α-deuterated-α,β-unsaturated carbonyl compounds. Hence there was no need for us to add D_2O into the reaction because we needed just ordinary α,β-unsaturated compounds. Surprisingly when we followed the synthetic procedure without water, there was no sign of the product at all (checked by TLC, stained with $KMnO_4$). After a subsequent addition of water, **11** started to form and we isolated pure *E* isomer in 64 % yield.

3.1.1.2 Unsuccessful syntheses with stabilized phosphonium ylides

Not all the aldehydes that we chose for Wittig reaction turned out to undergo this reaction well. In spite of our great effort we were not able isolate **14** as a product of Wittig reaction with 2-ethylbutyraldehyde (**12**). We have tried three different reaction conditions[19,23,24] using various solvents, temperature and reaction times. Although we were able to see traces of the product on a TLC plate (stained with $KMnO_4$) and in the ^1H NMR spectrum of the crude mixture, our attempts to isolate and purify **14** from the reaction mixture failed. That was probably caused by the low conversion of **12** that went together with a high volatility of **14** that was practically impossible to concentrate under vacuum without major losses.

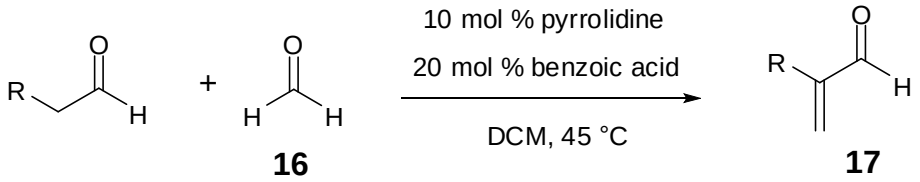


Scheme 5. Unsuccessful attempts to synthesize conjugated aldehydes

Another dead end in our synthetic attempts were experiments with hexafluoroacetone (**13**). In the commercially available aqueous solution, **13** is practically fully hydrated ($K \sim 10^6$).[25] Knowing this fact it was not a surprise that even after long reaction times we saw no product formed neither by the TLC analysis or by the ^{19}F NMR.

3.1.2 α-methylenation of aldehydes

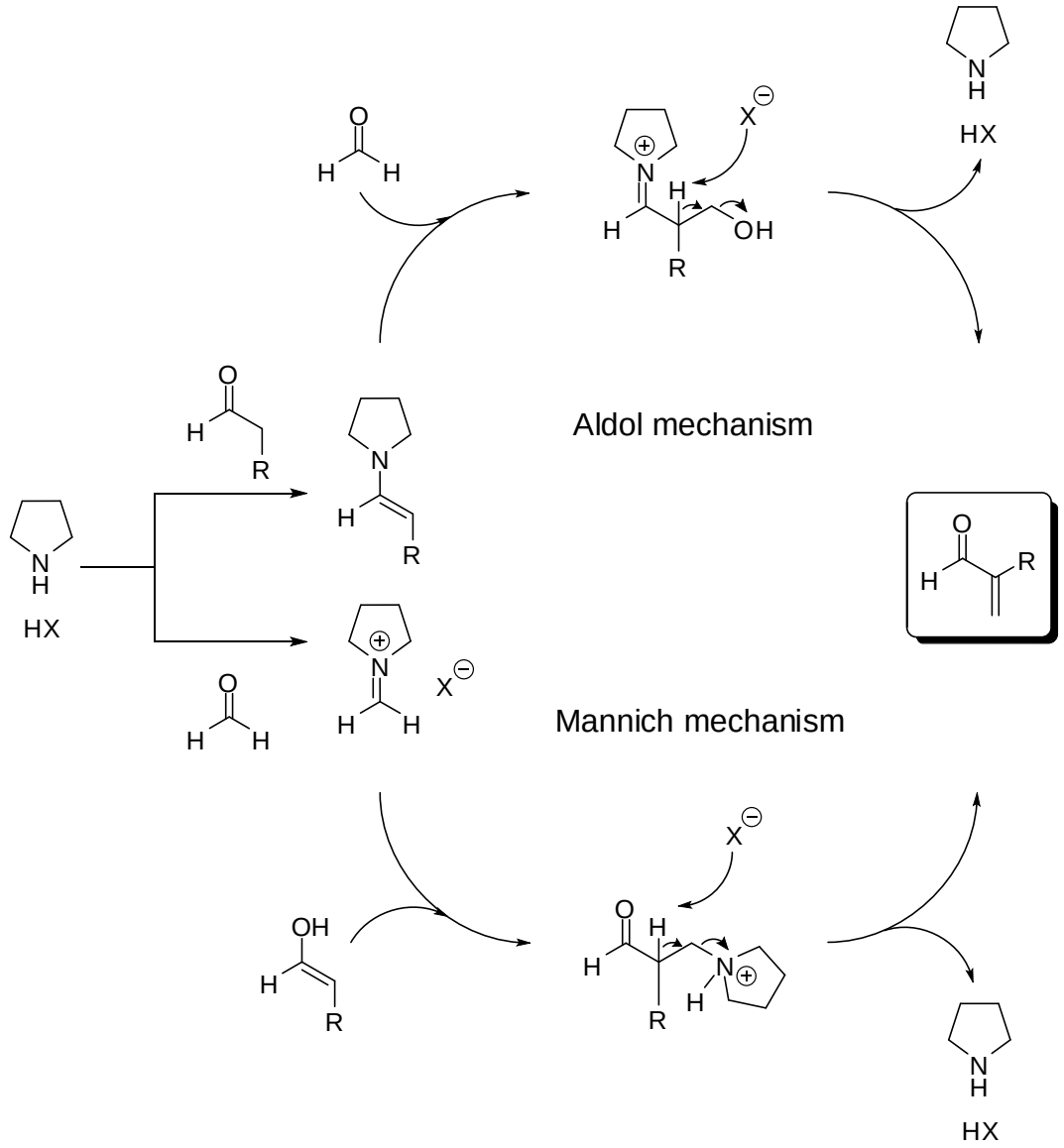
Recently Erkkilä and Pihko have optimized the α-methylenation of aldehydes using aqueous formaldehyde (**16**) with a simple combination of a secondary amine catalyst and a weak Brønsted acid co-catalyst. This method allows to synthesize a wide range of α-substituted aldehydes (**17**) in a matter of minutes (Scheme 6).[20]



Scheme 6

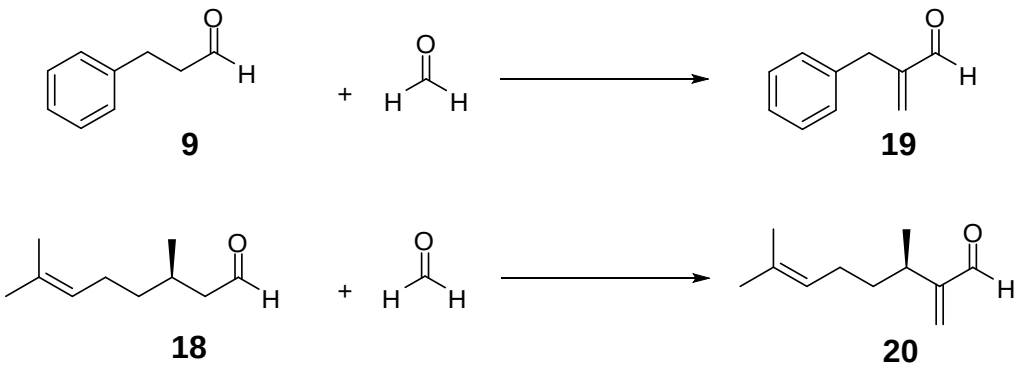
Reaction in Scheme 6 worked very well and very fast. According to the published procedure[20] we chose a secondary amine catalyst that had the best results amongst the others - pyrrolidine. By contrast we made a minor change in the weak acid co-catalyst. We employed the benzoic acid instead of 4-(dimethylamino)benzoic acid because of its better availability and lower

price. The differences between these two co-catalysts were not essential (91 % vs 100 % of conversion). For detailed reaction mechanism see Scheme 7.



Scheme 7. Two possible ways of methylenation[20]

From dihydrocinnamaldehyde (**9**) and (*R*)-citronellal (**18**) we synthesized α-methylenated aldehydes **19** and **20** shown in the Scheme 8.



Scheme 8

We obtained the aldehyde **19** in 91 % yield that exactly corresponds to the previously published results.[20] Aldehyde **20** was gained in a quite lower 55 % yield due to losses during the workup and purification. As mentioned above, reactions of this type are very fast and achieve the full conversion in a few minutes – however purely for the sake of attaining as high conversion as possible we kept reactions running for 2 hours. The conversion was perceptible immediately after adding **9** or **10** into the reaction flask (monitored by TLC, stained with $KMnO_4$).

With methods described in 3.1.1 and 3.1.2 we synthesized three known but commercially unavailable α,β-unsaturated aldehydes (**11**, **19**, **20**) that served as substrates for homoallylation (Figure 3).

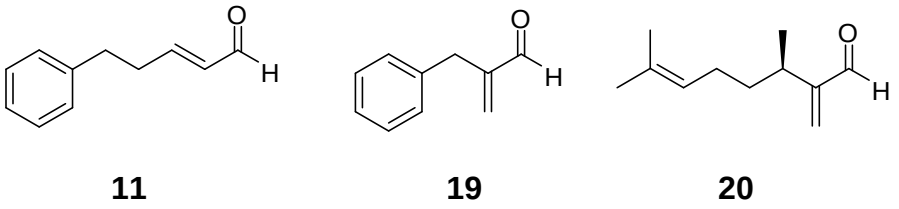
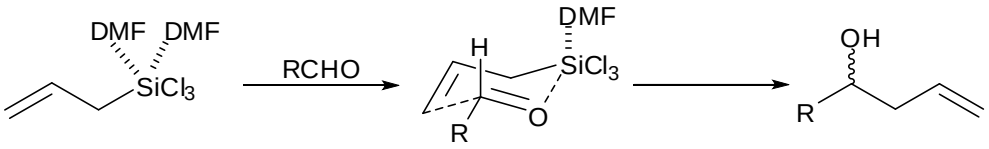


Figure 3

3.2 Synthesis of racemic homoallylic alcohols

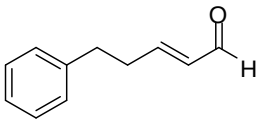
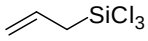
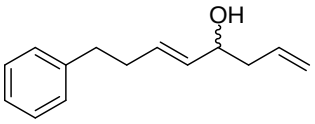
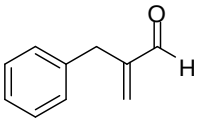
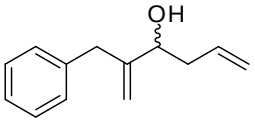
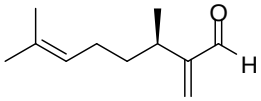
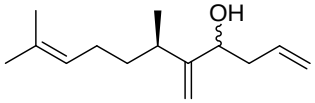
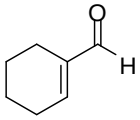
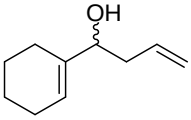
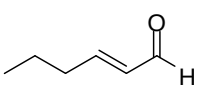
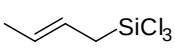
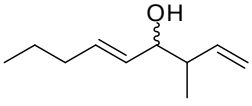
With the view of determining the best chiral separating method for each of the homoallylic alcohols, racemic samples were required. We followed the procedure developed by Kobayashi[26] who used DMF as an achiral LB catalyst (Scheme 9).



Scheme 9

For the first time, Kobayashi used DMF as a solvent but in his later work he studied the effects of the co-solvent systems on the yield of allylations and came up with the solvent system CH_3CN – DMF (5:1) that gave the best yields. We followed his procedure and synthesized a library of racemic homoallylic alcohols **23 - 27** (Table 1).

Table 1. Racemic homoallylic alcohols synthesized using DMF as a Lewis base

aldehyde	trichlorosilane	product	yield (%)
 **11**	 **2a**	 **23**	48
 **19**	**2a**	 **24**	45
 **20**	**2a**	 **25**	79
 **21**	**2a**	 **26**	80
 **22**	 *E/Z* 87:13 **2b**	 **27**	94

Although isolated yields of **23** and **24** are not that good we did not try to optimize the reaction since all the racemic alcohols were needed just in μg amounts for the calibration of the HPLC/GC methods.

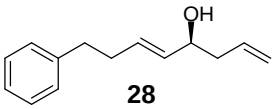
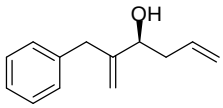
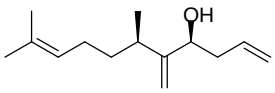
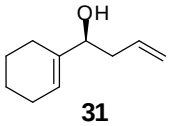
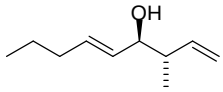
3.3 Enantioselective synthesis of homoallylic alcohols

Chiral homoallylic alcohols were the main object of interest. We followed the synthetic procedure developed by Malkov and Kočovský[15]. In this procedure allyltrichlorosilane/crotyltrichlorosilane is added to a solution of METHOX, the aldehyde and diisopropylethylamine in CH_3CN. The presence of diisopropylethylamine is mainly to neutralize the HCl that is released during the Lewis acid-base interaction of METHOX and trichlorosilane. METHOX as a Lewis base is deactivated under these conditions so the amine was used to antagonize this unwanted event.

The temperature of the reaction plays also an important role in order to gain as good ee as possible. The melting point of CH_3CN is -48 °C and is slightly lowered with the presence of diisopropylethylamine (mp < -50 °C). The temperature has to be as low as possible but not that much that it will cause congealment of the solvent. Reaction temperature was -45 °C during the dropwise addition of trichlorosilane and then we maintained on to this temperature usually for 5 hours. The reaction flask was then put into a freezer at -30 °C for several days (for detailed times see Table 2). The reason why we were proceeding this way was to get best yield possible corresponding with high enantiomeric excess. The outcome of enantioselective synthesis of homoallylic alcohols is summarized in Table 2.

Standard loading of METHOX is 10 mol%.[15] It is very easy to recover the catalyst after the reaction while METHOX as an *N*-oxide is polar and stays on silica gel during the column chromatography while eluting the product, usually with mobile phases less polar than 95:5 (petroleum ether/ethyl acetate).

Table 2. Summary of the enantioselective synthesis of homoallylic alcohols

entry	aldehyde	trichlorosilane	catalyst (mol %)	temp. (°C)	time (h)	product	yield (%)	ee (%)
1	**11**	**2a**	**7** (10)	1) -45 2) -30	1) 4 2) 120	 **28**	41	88
2	**19**	**2a**	**7** (10)	1) -45 2) -30	1) 4 2) 120	 **29**	38	70
3	**19**	**2a**	**7** (10)	-45	6	**29**	23	88
4	**19**	**2a**	**6** (5)	1) -45 2) -30	1) 5 2) 168	**29**	20	80
5	**20**	**2a**	**7** (10)	1) -45 2) -30	1) 5.5 2) 192	 **30**	50	56*
6	**21**	**2a**	**7** (10)	1) -45 2) -30	1) 4 2) 264	 **31**	31	83
7	**22**	**2b** *E*/*Z* 87:13	**7** (10)	1) -45 2) -30	1) 5 2) 168	 **32**	56	96

* refers to diastereoisomeric excess since **30** is a mixture of two diastereoisomers

As can be seen from Table 2 chiral homoallylic alcohols have been successfully synthesized in very good enantiomeric excess (over 83%).

The only exception was alcohol **30** (entry 5) that differs from other alcohols that the allyl-chain was attacking aldehyde **20** on which was one chiral center already present. Hence the question here was the diastereoisomeric excess (de). The poor result was caused by the fact that we chose the non-matching aldehyde (*R*-citronellal, **18**) and because of that the steric arrangement of the chiral centre on aldehyde **20** was not favourable by METHOX. The mismatched (*R*) enantiomer (**20**) afforded mainly the *syn*-configured **30** as a ~2:1 mixture of diastereoisomers. In further experiments it was found out that (*S*) enantiomer furnished the *anti*-diastereoisomer (6:1 dr), as revealed by the ^{1}H NMR spectra of the crude product.[27]

Another outcome that we had improved was the rather low ee of alcohol **29** prepared by the standard procedure[15] (entry 2). In order to improve the ee we decided to repeat the

reaction and to quench it immediately after 6 hours when the temperature was still -45 °C instead of keeping it in a freezer for several days at -30 °C (entry 3). The result was excellent as we improved the ee from 70% to 88%. However the yield dropped to 23%.

The next possibility of improving the ee of **29** was to try out the reaction with another catalyst – QUINOX (**6**, entry 4). QUINOX, loaded in 5 mol%, gave under the same conditions as in the entry 2 better ee (80%) but the yield dropped to mere 20% from previous 38% although the reaction was allowed to proceed longer.

Quite efficacious were the results of crotylation (entry 7). Crotyltrichlorosilane was prepared from the technical grade crotylchloride[28] that had the *E*/*Z* ratio of 87:13. In spite of this fact the reaction with METHOX led just to product **32** with unexceptionable ee of 96%. This was caused by METHOX's preference to react only with the *E*-isomer of crotyltrichlorosilane while the *Z*-isomer is left totally intact.

4 DETERMINATION OF ENANTIOMERIC EXCESS

Enantiomeric excess is defined as the absolute difference between the mole fractions of each enantiomer $|F_{(+)} - F_{(-)}|$ where $F_{(+)} + F_{(-)} = 1$. It is usually given in %.[29] In order to define the enantiomeric excess of **28 - 32** we were using three methods. Chiral GC, chiral HPLC and synthesis of Mosher's ester followed by ^{19}F NMR analysis.

4.1 Chiral GC

Basic principle of all the alternatives of chiral chromatography is that the molecules with appropriate spatial arrangement will interact with the chiral stationary phase while molecules of the opposite arrangement will be left intact thus will be eluted more rapidly. Most important stationary phases used in GC are derivatised cyclodextrines that are cyclic oligosacharides composed of α-D-glucose linked through the 1,4 position. The three most common cyclodextrines are α-, β- and γ-cyclodextrine that differ from each other by the number of glucose units: α contains 6, β 7 and γ 8 glucose units. The standard procedure of determining ee was that the racemic alcohol was injected to series of these columns in order to find out which one offers the best separation. The starting temperature and its increase rate was also set up for gaining the best result. As soon as we were able to distinguish between two enantiomers of the racemic alcohol we injected the enantiomerically enriched sample and

determine the ee by integration of the corresponding peaks. GC was used for determining the enantiomeric excess of **29**, **30** and **32**.

4.2 Chiral HPLC

The principle of the separation on chiral HPLC is the same as described in 4.1. We used chiral HPLC to determine the ee of **28**. In this case was used the Chiralcel OJ-H column that has the packing composition of cellulose tris(4-methylbenzoate) coated on 5 μm silica gel.[30]

4.3 Synthesis of Mosher's ester

In the case of alcohol **31** we were not able to find adequate conditions to separate enantiomers from each other. Therefore we came up with the synthesis of Mosher's ester.[31] The principle is that Mosher's acid (3,3,3-trifluoro-2-methoxy-2-phenyl-propanoic acid) contains a chiral centre of only one configuration, so that the synthesis of Mosher's ester with **31** led to a pair of diastereoisomers which can be distinguished in the ^{19}F NMR spectrum by their different chemical shift of the $-CF_3$ groups and the enantiomeric excess is then calculated from the integration of these peaks.[32]

5 CONCLUSION

METHOX as a chiral *N*-oxide organocatalyst showed good results in catalyzing syntheses of non-aromatic homoallylic alcohols **28**, **29**, **30**, **31** and **32**. All the alcohols we made showed very good ee, typically over 83%. Minor failure was the synthesis of **30** where the product was obtained mainly in *syn*-configuration (dr ~2:1). On the other hand METHOX showed excellent results in the reaction of **22** with crotyltrichlorosilane which gave rise to alcohol **32** with an excellent ee of 96%. In this case it has been proven that METHOX as a catalyst reacts exclusively with *E*-crotyltrichlorosilane to give pure *anti* product with excellent enantioselectivity. The task for the future is improving the yields of the reactions.

In summary, we have made 5 new alcohols that have interesting moieties and are likely to be used for synthetic purposes. Also an ecological benefit is involved in this thesis as it prefers “greener” chemistry of organocatalysts instead of transition metal catalysis.

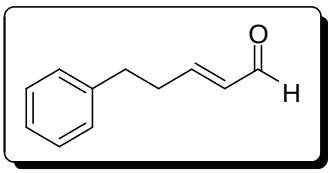
6 EXPERIMENTAL

6.1 General methods

All reactions were carried out in oven-dried glassware. Reactions were monitored by Thin Layer Chromatography using aluminium backed silica gel 60 (F254) plates, visualized using UV254/286 nm and PMA and potassium permanganate dips as appropriate. Flash chromatography was carried out using 60 Å silica gel as the stationary phase. Optical rotations were recorded 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}. The NMR spectra were recorded in $CDCl_3$, ^{1}H-NMR at 400.2 MHz and ^{13}C-NMR at 100.6 MHz on a Bruker Spectrospin 400 spectrometer. Chemical shifts are reported in δ units, parts per million with chloroform-d_1 (δ 7.26, ^{1}H; δ 77.16, ^{13}C) as internal standard, coupling constants (*J*) are measured in Hz. The IR spectra were recorded by the Golden Gate technique. The mass spectra (EI, CI and/or FAB) were measured on a Joel JMS700 spectrometer. Enantiomeric excess was determined by chiral GC analysis (using a Hewlett Packard 6890 Series GC system, Hewlett Packard 3395 integrator and Supelco α-DexTM or Supelco β-DexTM column) or by chiral HPLC analysis (using a Hewlett Packard Agilent 1100 Series quaternary pump, vacuum degasser, diode array detector, manual injector and Hewlett Packard ChemStation). The chiral GC and HPLC methods were calibrated with the corresponding racemic mixtures. All solvents for the reactions were of reagent grade and were dried and distilled immediately before use. Yields are given for isolated products showing no detectable impurities in the NMR spectrum.

6.2 Synthesis of α,β-unsaturated aldehydes

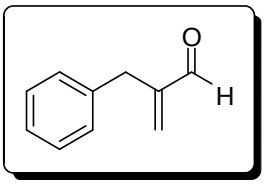
6.2.1 (*E*)-5-Phenylpent-2-enal (11)



Water (2 mL) was added to a solution of (triphenylphosphoranylidene)-acetaldehyde (1.33 g, 4.37 mmol) in THF (15 mL). The solution was stirred at the room temperature for 40 min and then dihydrocinnamaldehyde (neat; 418 mg, 3.12 mmol) was added dropwise. The solution was heated to 42 ºC and stirred for 18 h, quenched with aqueous $NaHCO_3$, the product was

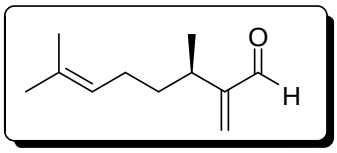
extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel (15 × 2 cm) with a mixture of petroleum ether and ethyl acetate (97:3) to give **11** as a yellowish oil (325.5 mg, 64%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.56-2.62 (m, 2H), 2.75 (t, *J* = 7.6 Hz, 2H), 6.06 (ddt, *J* = 15.6, 7.9, 1.5 Hz, 1H), 6.77 (dt, *J* = 15.6, 6.7 Hz, 1H), 7.10-7.25 (m, 5H), 9.41 (d, *J* = 7.9 Hz, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.1 (CH_2), 34.2 (CH_2), 126.4 (CH), 128.4 (CH), 128.6 (CH), 133.4 (CH), 140.3 (C), 157.3 (CH), 194.0 (CH); **IR** ν 2975, 2366, 2323, 1843, 1641, 1113, 747 cm^{-1}; **MS** (EI) *m/z* (%) 161 ($M^{\bullet+}$, 22), 130 (17), 117 (87), 105 (18), 91 (100), 83 (55), 65 (52); **HRMS** (EI) 160.0887 ($C_{11}H_{12}O^+$ requires 160.0888).

6.2.2 2-Benzylacrolein (19)



A 37% aqueous solution of formaldehyde in water (443.9 mg, 5.47 mmol) and dihydrocinnamaldehyde (neat; 807.8 mg, 6.02 mmol) were added to a solution of pyrrolidine (38.6 mg, 0.55 mmol) and benzoic acid (133.1 mg, 1.1 mmol) in CH_2Cl_2 (4 mL) at the room temperature. The reaction was then heated rapidly to 45 ºC and stirred for 2 h at this temperature. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel (15 × 2 cm) with a mixture of petroleum ether and ethyl acetate (99:1) to give **19** as a colorless oil (722.5 mg, 91%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.49 (s, 2H), 5.99 (s, 1H), 6.03 (s, 1H), 7.10-7.24 (m, 5H), 9.53 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 34.2 (CH_2), 126.5 (CH), 128.6 (CH), 129.2 (CH), 135.2 (CH_2), 138.2 (C), 149.8 (C), 194.0 (CH); **IR** ν 3055, 1689, 1427, 1265, 956, 705 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 147 ($[M+H]^+$, 10), 113 (5), 89 (100), 85 (21), 69 (27); **HRMS** (CI/isobutane) 147.0807 ($C_{10}H_{11}O^+$ requires 147.0810).

6.2.3 (*R*)-(-)-3,7-Dimethyl-2-methyleneoct-6-enal (20)



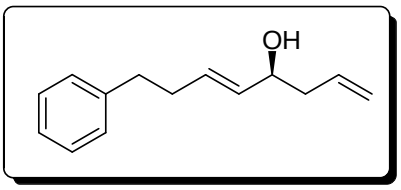
A 37% aqueous solution of formaldehyde in water (146.1 mg, 1.8 mmol) and (*R*)-citronellal (neat; 305.4 mg, 1.98 mmol) were added to a solution of pyrrolidine (12.6 mg, 0.18 mmol) and benzoic acid (43.9 mg, 0.36 mmol) in CH_2Cl_2 (2.5 mL) at the room temperature. The reaction mixture was then heated rapidly to 45 ºC and stirred for 2 h at this temperature. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel (15 × 2 cm) with a mixture of petroleum ether and ethyl acetate (99:1) to give **20** as a colorless oil (164 mg, 55%): **$[\alpha]_D$** -5.9 (*c* 2.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.99 (d, *J* = 6.9 Hz, 3H), 1.31 (tdd, *J* = 13.5, 9.2, 6.9 Hz, 1H), 1.41-1.50 (m, 1H), 1.49 (s, 3H), 1.59 (s, 3H), 1.76-1.93 (m, 2H), 2.63 (sext, *J* = 6.9 Hz, 1H), 5.01 (t, *J* = 7.1 Hz, 1H), 5.91 (s, 1H), 6.15 (s, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 17.7 (CH_3), 19.6 (CH_3), 25.7 (CH_2), 25.8 (CH_3), 31.0 (CH), 35.6 (CH_2), 124.2 (CH), 131.7 (C), 133.1 (CH_2), 155.5 (C), 194.7 (CH); **IR** ν 2337, 2052, 1265, 1087, 1018, 754 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 167 ($[M+H]^+$, 100), 149 (30), 123 (26), 109 (42), 81 (39), 69 (59); **HRMS** (CI/isobutane) 167.1440 ($C_{11}H_{19}O^+$ requires 167.1436).

6.3 Synthesis of racemic homoallylic alcohols

Racemic alcohols **23** – **27** were needed as reference samples for HPLC/GC analysis. Reactions took place in dry sealed flasks under the atmosphere of argon. Allyltrichlorosilane (0.55 mmol) was added dropwise to the solution of aldehyde (0.5 mmol) in CH_2Cl_2 (0.8 mL) and CH_3CN (3.2 mL) at the room temperature. The reaction mixture was stirred for 12 h at the room temperature, quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel. For mobile phases see enantioselective version.

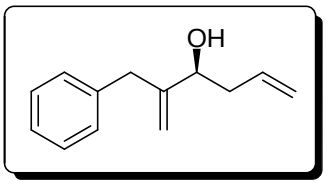
6.4 Enantioselective synthesis of homoallylic alcohols

6.4.1 (*S*,*E*)-(-)-8-Phenylocta-1,5-dien-4-ol (28)



An oven-dried flask was filled with argon and charged with Methox (27.3 mg, 0.074 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (478.3 mg, 3.7 mmol) and (*E*)-5-phenylpent-2-enal (118.6 mg, 0.74 mmol). The reaction flask was then cooled to -45 ºC and allyltrichlorosilane (194.8 mg, 1.11 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 4 h and then it was kept in a freezer at -30 ºC for 5 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with $MgSO_4$. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5) to give **28** as a light yellow oil (65 mg, 41.2%): **$[\alpha]_D$** -12.5 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 2.13-2.25 (m, 2H), 2.28 (q, *J* = 7.6 Hz, 2H), 2.62 (dd, *J* = 8.1, 7.4 Hz, 2H), 4.03 (q, *J* = 6.3 Hz, 1H), 5.02-5.07 (m, 2H), 5.42 (tdd, *J* = 15.4, 6.7, 1.3 Hz, 1H), 5.63 (dtd, *J* = 15.4, 6.7, 0.9 Hz, 1H), 5.70 (dddd, *J* = 17.9, 14.2, 7.3, 7.2 Hz, 1H), 7.09-7.13 (m, 3H), 7.17-7.22 (m, 2H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 32.9 (CH_2), 34.6 (CH_2), 40.9 (CH_2), 70.6 (CH), 117.0 (CH_2), 124.8 (CH), 127.3 (CH), 127.4 (CH), 130.1 (CH), 131.8 (CH), 133.3 (CH), 140.7 (C); **IR** ν 3315, 3055, 2932, 1435, 1265, 972, 918, 708 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 185 (M-OH, 100), 161 (43), 143 (81), 117 (19), 91 (16), 81 (9); **HRMS** (CI/isobutane) 185, 1327 ($C_{14}H_{17}^+$ requires 185.1330); **HPLC** analysis (chiralcel OJ-H, hexane/isopropanol 95:5, 0.75 mL min^{-1}) showed 88% ee (t_R = 14.64 min, t_S = 16.21 min).

6.4.2 (*S*)-(+)-2-Benzylhexa-1,5-dien-3-ol (29)



6.4.2.1 Methox catalyzed reaction at -30 ºC

An oven-dried flask was filled with argon and charged with Methox (29.2 mg, 0.079 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (510.6 mg, 3.95 mmol) and 2-benzylacrylaldehyde (115.5 mg, 0.79 mmol). The reaction flask was then cooled to -45 ºC and allyltrichlorosilane (208.9 mg, 1.19 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 4 h and then it was kept in a freezer at -30 ºC for 5 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with $MgSO_4$. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5) to give **29** as a colorless oil (56.5 mg, 37.8%): **GC** analysis (Supelco β-DEX 120 column, oven: 100ºC then 1º/min) showed 70% ee (t_R = 50.14 min, t_S = 50.49 min).

6.4.2.2 Methox catalyzed reaction at -45 ºC

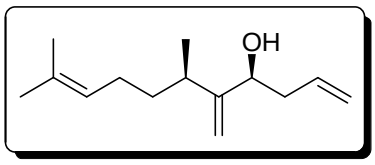
An oven-dried flask was filled with argon and charged with Methox (11.1 mg, 0.03 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (193.9 mg, 1.5 mmol) and 2-benzylacrylaldehyde (50 mg, 0.3 mmol). The reaction flask was then cooled to -45 ºC and allyltrichlorosilane (79.2 mg, 0.45 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 6 h and then quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5) to give **29** as a colorless oil (28 mg, 23%): **GC** analysis (Supelco β-DEX 120 column, oven: 100ºC then 1º/min) showed 88% ee (t_R = 50.14 min, t_S = 50.48 min).

6.4.2.3 Quinox catalyzed reaction at -30 ºC

An oven-dried flask was filled with argon and charged with Quinox (16.0 mg, 0.053 mmol), followed by DCM (5 mL), diisopropylethylamine (685.1 mg, 5.3 mmol) and 2-benzylacrylaldehyde (155 mg, 1.06 mmol). The reaction flask was then cooled to -45 ºC

and allyltrichlorosilane (279 mg, 1.59 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 5 h and then it was kept in a freezer at -30 ºC for 7 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with Na_2SO_4. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (95:5) to give **29** as a colorless oil (39.9 mg, 20.4%): **$[\alpha]_D$** 3.2 (*c* 0.5, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 1.63 (d, *J* = 3.8 Hz, 1H), 2.23 (ddd, *J* = 14.2, 7.7, 7.6 Hz, 1H), 2.31-2.38 (m, 1H), 3.27 (d, *J* = 15.6 Hz, 1H), 3.40 (d, *J* = 15.6 Hz, 1H), 4.04-4.08 (m, 1H), 4.73 (d, *J* = 1.2 Hz, 1H), 5.05 (d, *J* = 1.2 Hz, 1H), 5.07-5.10 (m, 2H), 5.72 (ddt, *J* = 14.3, 9.5, 7.2 Hz, 1H), 7.12-7.25 (m, 5H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 39.2 (CH_2), 40.4 (CH_2), 73.2 (CH), 112.4 (CH_2), 118.4 (CH_2), 126.4 (CH), 128.5 (CH), 129.3 (CH), 134.6 (CH), 139.3 (C), 150.6 (C); **IR** ν 3321, 3055, 2924, 2360, 1435, 1265, 910, 740 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 171 (M-OH, 47), 147 (8), 129 (20), 113 (21), 97 (27), 85 (81), 69 (100); **HRMS** (CI/isobutane) 171.1177 ($C_{13}H_{15}^+$ requires 171.1174); **GC** analysis (Supelco β-DEX 120 column, oven: 100ºC then 1º/min) showed 80% ee (t_R = 50.13 min, t_S = 50.48 min).

6.4.3 (4*S*,6*R*)-6,10-Dimethyl-5-methyleneundeca-1,9-dien-4-ol (30)*

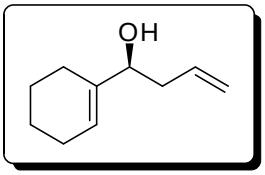


An oven-dried flask was filled with argon and charged with Methox (11.1 mg, 0.03 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (193.9 mg, 1.5 mmol) and (R)-3,7-dimethyl-2-methyleneoct-6-enal (61 mg, 0.37 mmol). The reaction flask was then cooled to -45 ºC and allyltrichlorosilane (79.2 mg, 0.45 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 5.5 h and then it was kept in a freezer at -30 ºC for 8 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with $MgSO_4$. The crude product was purified by chromatography on a column of silica gel (15 × 1,5 cm) with a mixture of petroleum ether and ethyl acetate (97:3) to give **30** as a yellowish oil (38.3 mg, 50%): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.98 (d, *J* = 6.8 Hz, 3H, diastereoisomer I), 1.01 (d, *J* = 6.8 Hz, 3H, diastereoisomer II), 1.24-1.38 (m, 1H), 1.39-1.50 (m, 1H), 1.52 (s, 3H), 1.56 (d, *J* = 3.8

* is the main expected diastereoisomer

Hz, 1H), 1.61 (s, 3H) 1.87-1.93 (m, 2H), 1.99-2.10 (m, 1H), 2.14-2.23 (m, 1H), 2.30-2.38 (m, 1H), 4.01-4.05 (m, 1H), 4.84 (s, 1H), 5.00-5.10 (m, 4H), 5.71-5.82 (m, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 17.8 (CH_3), 20.8 (CH_3), 25.8 (CH_3), 26.1 (CH_2), 35.6 (CH), 36.6 (CH_2), 41.0 (CH_2), 73.3 (CH), 108.0 (CH_2), 118.1 (CH_2), 124.6 (CH), 131.7 (C), 135.0 (CH), 157.2 (C); **IR** ν 3335, 3055, 2924, 1442, 1381, 1265, 1049, 995, 733 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 191 (M-OH, 80), 167 (17), 149 (20), 135 (39), 109 (29), 81 (69), 69 (100); **HRMS** (CI/isobutane) 191.1797 ($C_{14}H_{23}^+$ requires 191.1800); **GC** analysis (Supelco β-DEX 120 column, oven: 100ºC then 2º/min) showed 56% de (t_{minor} = 22.64 min, t_{major} = 22.90 min).

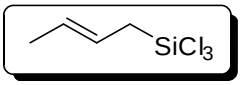
6.4.4 (*S*)-(-)-1-Cyclohexenylbut-3-en-1-ol (31)



An oven-dried flask was filled with argon and charged with Methox (16.7 mg, 0.045 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (294.1 mg, 2.28 mmol) and cyclohex-1-enecarbaldehyde (52.5 mg, 0.48 mmol). The reaction flask was then cooled to -45 ºC and allyltrichlorosilane (120.3 mg, 0.69 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 4 h and then it was kept in a freezer at -30 ºC for 11 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with $MgSO_4$. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (97:3) to give **31** as a colorless oil (22.6 mg, 31%): **$[\alpha]_D$** - 17.47 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz; $CDCl_3$) δ 1.44-1.63 (m, 4H), 1.80-2.05 (m, 4H), 2.10 (s, 1H), 2.18-2.31 (m, 2H), 3.94 (t, *J* = 6.5 Hz, 1H), 5.02-5.08 (m, 2H), 5.61 (bs, 1H), 5.72 (dddd, J = 17.0, 10.1, 7.1, 7.0 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 22.6 (CH_2), 22.6 (CH_2), 23.9 (CH_2), 25.0 (CH_2), 39.9 (CH_2), 75.2 (CH), 117.7 (CH_2), 123.1 (CH), 135.0 (C), 139.2 (CH); **MS** (CI/isobutane) *m/z* (%) 135 (M-OH, 35), 113 (57), 107 (90), 97 (40); **HRMS** (CI/isobutane) 135.1177 ($C_{10}H_{15}^+$ requires 135.1174); **^{19}F NMR** of the corresponding Mosher's ester showed 83 % ee (δ_R = -71.32 ppm and δ_S = -71.57 ppm).

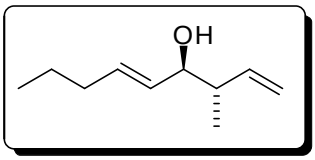
6.5 Reactions with crotyltrichlorosilane

6.5.1 Synthesis of crotyltrichlorosilane



An oven-dried flask with argon atmosphere was filled with a solution of technical grade crotylchloride – *E*/*Z* 87:13 (5 g, 55.2 mmol), CuCl (273 mg, 2.76 mmol) and diisopropylethylamine (7.134 g, 55.2 mmol) in dry diethyl ether (27 mL). Then trichlorosilane (8.225 g, 60.72 mL) was added dropwise while cooling at 0 ºC. The reaction mixture was stirred for 2 h at the room temperature. The liquid phase was then transferred with a syringe to a dry distillation flask and crotyltrichlorosilane was distilled at 142 ºC at ambient atmosphere. No other characteristics were made because the product was used straightaway for further reactions. For detailed characteristics see paper by Furuya and Sukawa.[27]

6.5.2 (3*S*,4*R*,*E*)-3-Methylnona-1,5-dien-4-ol (32)



An oven-dried flask was filled with argon and charged with Methox (35.8 mg, 0.097 mmol), followed by acetonitrile (5 mL), diisopropylethylamine (626.8 mg, 4.85 mmol) and (E)-hex-2-enal (108.8 mg, 0.97 mmol). The reaction flask was then cooled to -45 ºC and crotyltrichlorosilane (276.5 mg, 1.46 mmol) was added dropwise. The reaction mixture was stirred at -45 ºC for 5 h and then it was kept in a freezer at -30 ºC for 7 days. The reaction was quenched with aqueous $NaHCO_3$, the product was extracted with ethyl acetate (3 × 50 mL) and the organic phase was dried with $MgSO_4$. The crude product was purified by chromatography on a column of silica gel (15 × 1.5 cm) with a mixture of petroleum ether and ethyl acetate (97:3) to give **32** as a colorless oil (85.5 mg, 55.5%): $[\alpha]_D$ -3.3 (*c* 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 0.84 (t, *J* = 7.37 Hz, 3H), 0.91 (d, *J* = 6.83 Hz, 3H), 1.29-1.39 (m, 2H), 1.66 (bs, 1H), 1.93-2.00 (m, 2H), 2.11-2.20 (m, 1H), 3.73 (t, *J* = 7.3 Hz, 1H), 5.05-5.10 (m, 2H), 5.36 (tdd, *J* = 15.5, 7.7, 1.7 Hz, 1H), 5.58 (td, *J* = 15.0, 6.7 Hz, 1H), 5.70 (ddd, *J* = 17.1, 10.8, 8.2 Hz, 1H); **^{13}C NMR** (100MHz, $CDCl_3$) δ 13.8 (CH_3), 16.3 (CH_3), 22.4 (CH_2), 34.5 (CH_2), 44.7 (CH), 76.5 (CH), 116.5 (CH_2), 130.8 (CH), 133.8 (CH), 140.8 (CH);

IR ν 3734, 2962, 2360, 1265, 1095, 1018, 740 cm^{-1}; **MS** (CI/isobutane) *m/z* (%) 137 (M-OH, 35), 91 (49), 69 (100); **HRMS** (CI/isobutane) 137.1307 ($C_{10}H_{17}^{+}$ requires 137.1330); **GC** analysis (Supelco α-DEX 120 column, oven: 50ºC, then 1º/min) showed 96% ee ($t_{3S,4R}$ = 43.21 min, $t_{3S,4S}$ = 43.62 min).

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