Palladium-catalyzed Enantioselective Allylic Substitutions on Bifunctional Substrates

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Basel, den 26. Juni 2012

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Introduction

1. Introduction

1.1 General introduction

Metal catalyzed allylic substitution has been demonstrated to be a versatile and important tool in organic synthesis[1-8]. Through this reaction, the formation of many types of bonds such as C-C, C-N, C-O, C-S and C-P is possible. Furthermore, depending on the conditions, different chemo-, regio- and stereoselectivities can be achieved. Palladium has been widely used and is a well-studied metal in allylic substitution. Moreover, palladium complexes have proven to be useful compounds with a broad range of applications.

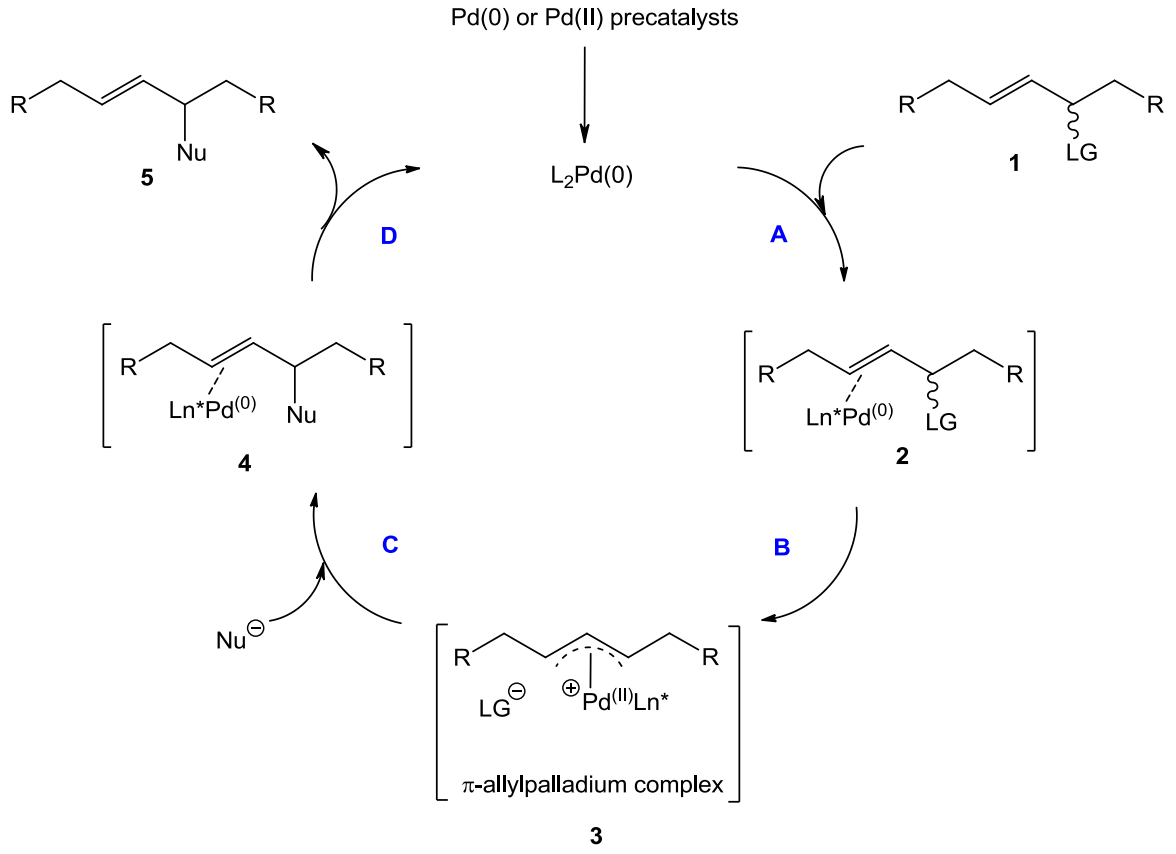
The first π-allyl-palladium complex was reported by Smidt and Hafner[9] in 1959 when they described the discovery of a $[Pd(allyl)Cl]_2$ complex. Less than 10 years after this article, in 1965, Tsuji et al.[10] presented the first C-C bond formation using the same π-allylpalladium complex in stoichiometric amount. In 1970, the discovery that zero-valent palladium complexes are active catalysts in catalytic amount was found by chemists from Toray Industries in Japan and from the Union Carbide Corporation Chemicals and Plastics[11,12]. Three years later, Trost et al. started to investigate the field and were the first group to achieve stoichiometric enantioselective allylic substitutions[13] and, in 1977, catalytic enantioselective allylic substitutions[14]. Nowadays, this field is still an interesting research area where the search for new chiral ligands and new applications for the reaction has raised an increased interest.

1.2 Palladium catalyzed enantioselective allylic substitution

Performing a palladium catalyzed enantioselective allylic substitution involves taking different factors into account, such as catalyst, ligand, nucleophile etc. Depending on the substrate, several changes are needed to optimize the reaction conditions and to get the desired product in high enantioselectivity.

1.2.1 Catalytic cycle

The generally accepted mechanism for palladium-catalyzed allylic substitutions with "soft" nucleophiles imply as the first step, the coordination of the low valent palladium(0) catalyst to the double bond of substrate **1** into a η^2-complex **2** (step A scheme 1). An oxidative addition follows which affords the η^3-π-allylpalladium complex **3** (step B)[15]. This activated substrate is then attacked by a nucleophile to form a η^2-complex **4** (step C). Decomplexation of the Pd complex releases the palladium and the desired product **5** (step D)

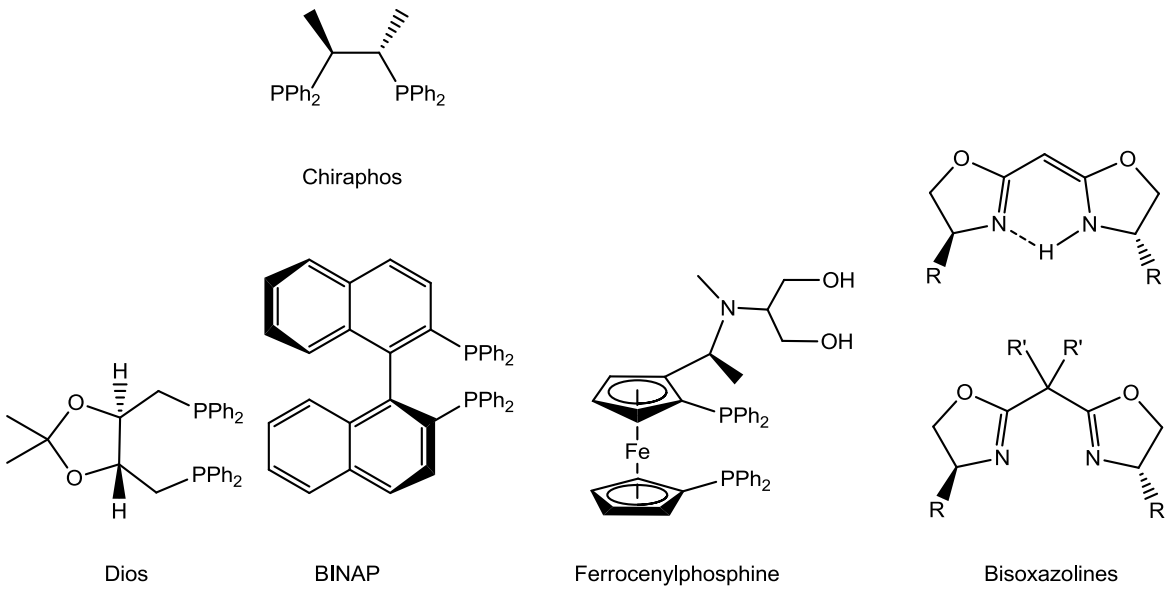


Scheme 1: Catalytic cycle

1.2.2 Catalysts and Ligands

Different sources of palladium catalysts are known, $Pd_2(dba)_3$[16] (dba = dibenzylidene acetone) and $[Pd(allyl)Cl]_2$ being the most frequently employed. With these catalysts, complexes are generated in situ by combination with the desired ligand. $[Pd(allyl)Cl]_2$ is in oxidation sate +2 but is reduced to the activated Pd(0) by nucleophilic attack on the allyl group[17].

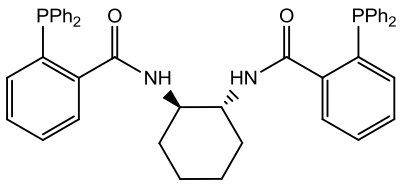
In the 1970's, a broad range of different ligands have been developed to improve the enantioselectivity of palladium catalyzed reactions. In 1972, the first C_2-symmetric chiral ligand was introduced by Kagan[18] with the DIOP ligand. Since then, several C_2-symmetric ligands[19] were developed and excellent results were obtained in hydrogenation with chelating diphosphines, i.e. Chiraphos[20,21] and Binap[22,23] (scheme 2). Unfortunately transferring these ligands into allylic substitution resulted into deceiving results probably due to the fact that in the allylic substitution the nucleophilic attack is taking place outside the coordination sphere of the complex which is not the case in hydrogenations[3,24]. Consequently, in 1986, Hayashi[25,26] developed optically active ferrocenylphosphine ligands containing a side chain capable of interacting with the nucleophile and allowing the direction of the attack on a specific allylic terminus. Nevertheless, in the early 1990, two groups demonstrated that high enantioselectivites could also be achieved with a C_2-symmetric ligand: The Pfaltz group with bisoxazolidines[27-29] and the Trost group[30] with new types of diphosphines.



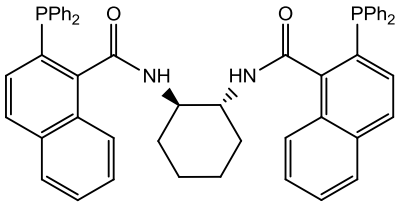
Scheme 2: First ligands used in allylic substitution

Since then, the Trost ligands based on 2-(diphenylphosphino)benzoic acid (DPPBA), scheme 3, have been applied in several allylic alkylation reactions and were involved in a number of

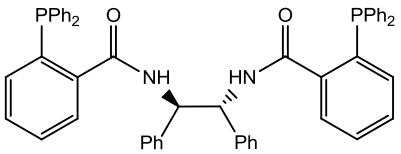
applications[31-32]. The configuration of these ligands generates Pd fragments with large bite angles which allow the palladium-ligand complex to embrace the allyl function of the substrate forming a chiral pocket (scheme 4). With this concept, Trost developed a model which allows predicting the product stereochemistry depending on the DPPBA chiral ligand used[33]. In this model, the asymmetric induction is established on steric interactions between the "wall" (phenyl substitutents of the chiral ligand) and the incoming nucleophile. Depending on how the ligand "sits" on the allyl substrate, one terminus should be favored for nucleophilic attack. However, in recent research it has been demonstrated that these ligands are forming oligomers making the reaction mechanism difficult to elucidate[34-36]. In 2009, Lloyd-Jones et al.[37] elucidated the monomeric forms of the cationic Pd-η^3-allyl complexes bearing the *trans*-cyclohexylenediamine-based Trost ligand ((*R*,*R*)-standard, scheme 3) through NMR, isotopic labeling and computation. They identified that hydrogen-bond interaction of one N-H unit in Pd-ligand complex allowed to accelerate ionization and nucleophile attack. This new model may be helpful in the interpretation of the selectivity in allylic subsitution reactions catalyzed by Pd complexes of Trost ligands.



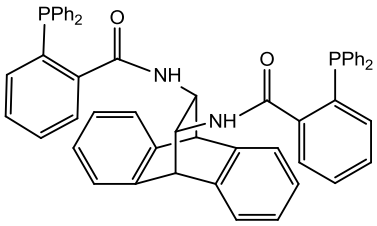
(*R*,*R*)-standard



(*R*,*R*)-naphtyl

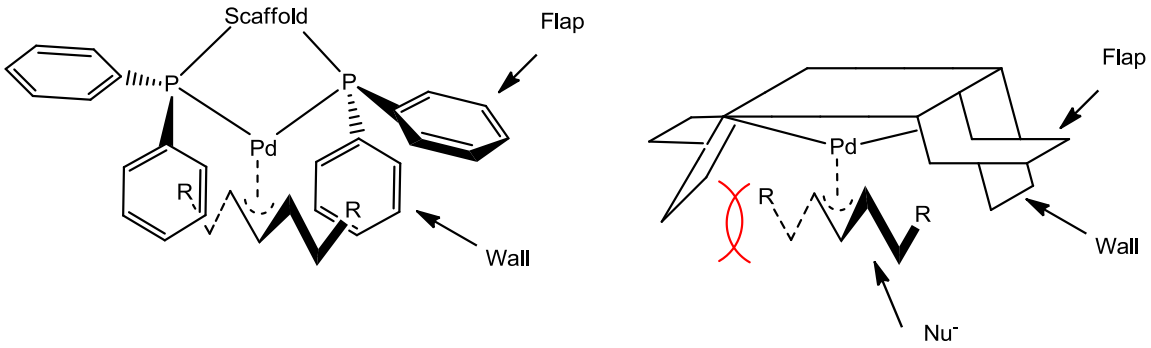


(*R*,*R*)-stillbene



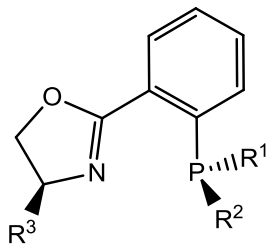
(*R*,*R*)-anthracenyl

Scheme 3: Different DPPBA Trost ligands



Scheme 4: Model developed by Trost

In 1993, non-C_2 symmetric P,N-phosphinooxazoline ligands, so called PHOX ligands (scheme 5), were developed independently by three different groups, Pfaltz[38], Helmchen[39] and Williams[40]. These ligands adopt the concept of electronic differentiation with the combination of hard, N, and soft P donor. Electronic as well as steric properties created useful ligands for allylic substitutions enabling high enantioselectivity. These ligands were particularly appropriate for substrates such as 1,3-diarylallylacetate and 1,3-diisopropylacetate and illustrated high enantioselectivity, a result which was not demonstrated with the Trost ligands. The use of an appropriate ligand for a specific substrate is not straightforward and is reflected by the vast number of ligands developed.



PHOX

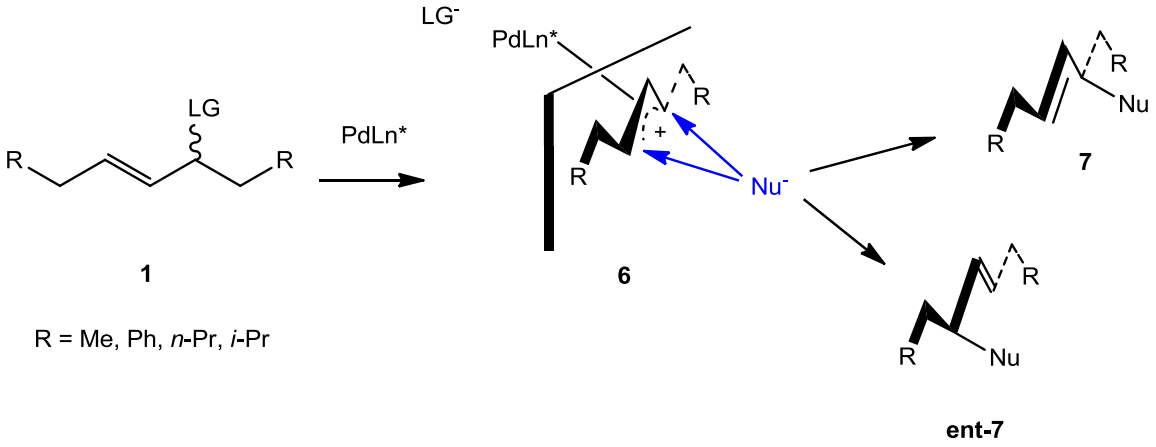
R_1 = Ph, 1-naphtyl aryl etc.
R^2 = Ph, 1-naphtyl aryl etc.
R_3 = *i*-Pr, Ph, *t*-Bu, Me, CH_2Ph etc.

Scheme 5: PHOX ligands

1.2.3 Substrates

1.2.3.1 Symmetrically substituted allyl systems

Non-functionalized substrates such as **1** which go through a symmetrical complex **6** are frequently used as test substrates for the design of new ligands.



Scheme 6: Allylic substitution through a symmetrically substituted allyl system

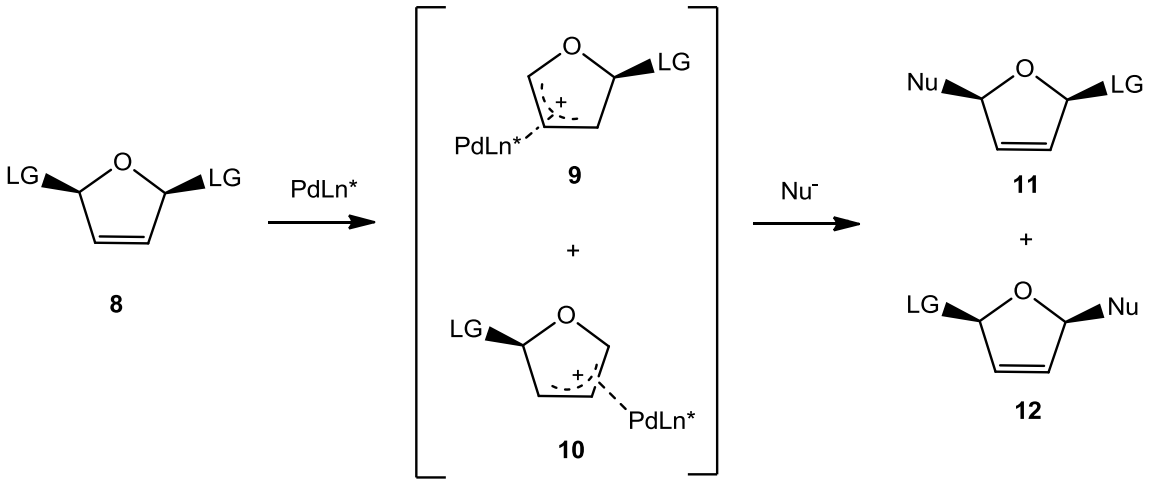
In such a system, the substitution proceeds via a symmetrical palladium-allylic-complex **6**[3,7] (scheme 6). Therefore, coordination and oxidative addition leads to the same intermediate resulting in no stereoselective differenciation on the substrate. The regioselectivity of the nucleophilic attack determines the enantioselectivity of the reaction. To exemplify the concept: if an achiral ligand is used, the allyl complex is achiral and the allylic termini enantiotopic providing a racemic product. On the other hand, the termini are diastereoisotropic with the use of a chiral ligand and a differentiated nucleophilic attack enables obtaining either enantiomer **7** or ***ent*-7**.

These substrates present the advantage of achieving a theoretic quantitative yield which is not always the case for asymmetric substrates especially if no dynamic kinetic asymmetric transformation (DYKAT) can be achieved from the reaction[41-43].

1.2.3.2 Meso-substrates

Meso-substrates are another class of compounds in which the chirality is introduced in the oxidative addition step[3,44]. Meso-cycloalkene substrates exemplify this concept (scheme 7). In that case, the Pd complex coordinates to the allyl function opposite to the leaving group and differentiation between the two leaving groups leads to control of the stereochemistry. The regioselectivity of the nucleophile attack on the chiral allyl intermediate is determined by the less hindered position.

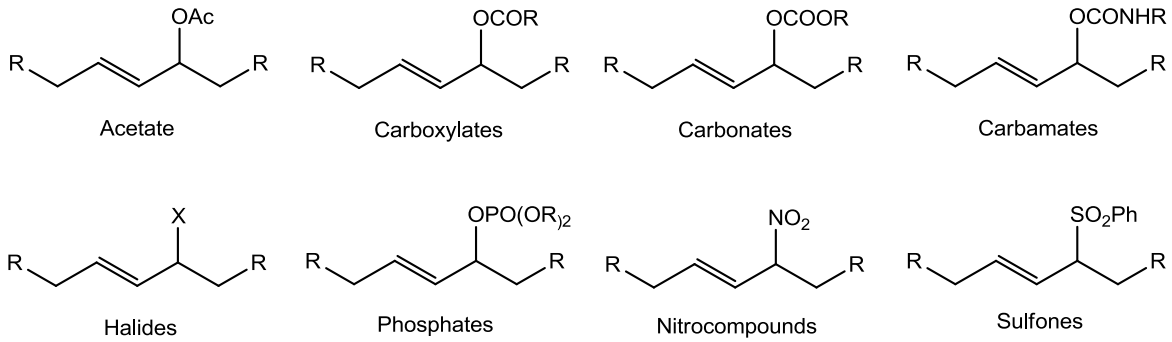
Kinetic resolution applied to the desymmetrization of meso-compounds provides high yield and high enantiomeric enrichement of a single product.



Scheme 7: Allylic substitution on meso-substrate

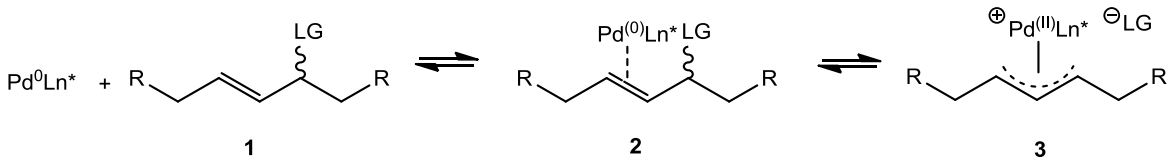
1.2.4 Leaving groups

Besides the standard acetate, alternative leaving groups such as halides, carbonates, sulfonates or phosphates have been used in enantioselective allylic substitutions (scheme 8)[45].



Scheme 8: Different leaving groups used in allylic subsitutions

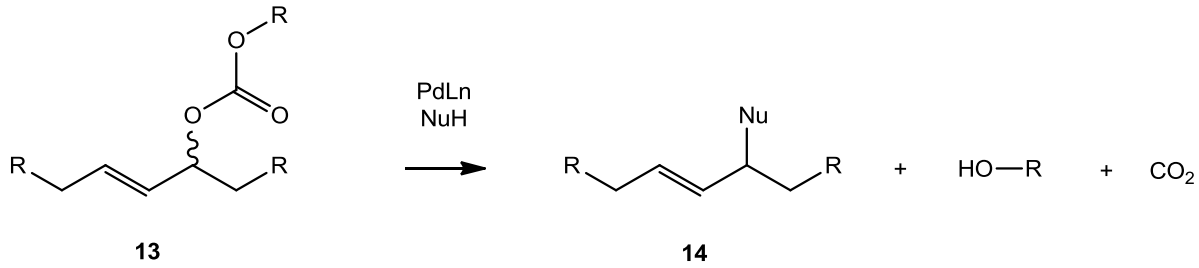
The nature of the leaving group can play an important role in the enantioselectivity of the reaction if the enantioselective step is the oxidative addition of the allylic substrate into the Pd(0) complex[46].



Scheme 9: First step of the palladium catalyzed allylic substitution

The complexation and the oxidative addition are both reversible steps as demonstrated by Amatore et al.[47-49] (scheme 9). In the course of the reaction, the concentration of leaving group anion increases. If the nucleophilic attack is slow, the ionized leaving group may itself behave as a nucleophile whic may result in a rearrangement of the allyl substrate. Therefore, a good leaving group should be a poor nucleophile and should favor the complexation and oxidative addition steps.

Carbonate leaving groups offer the advantage of decarboxylation during the process rendering the formation of the Pd-allyl-complex irreversible (scheme 10)[50-51]. The formed alkoxide can also act as a base and deprotonate the nucleophile, another benefit of such a leaving group. Tsuji et al.[52] also presented this method with allylic carbamates which could be employed under neutral conditions, without addition of a base.

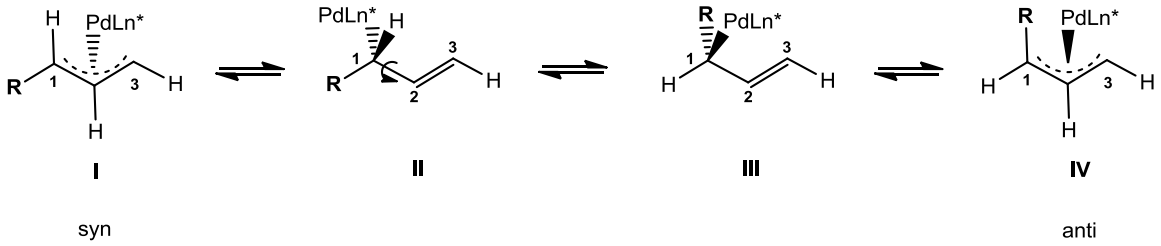


13 14

Scheme 10: Decarboxylation with the carbonate leaving group

1.2.5 π-σ-π isomerization

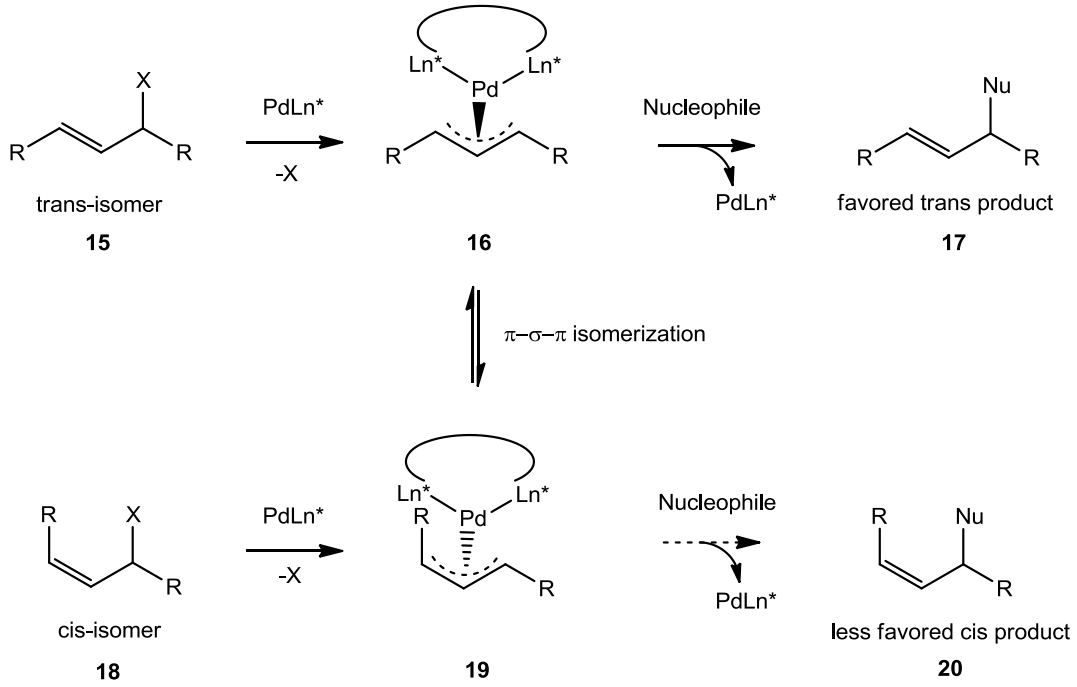
During the reaction, a well-known mechanism of isomerism along the allyl complexes is possible which involves a π-σ-π isomerization[1,3,7]. The mechanism involves the rotation around the σ-(C-C) bond which leads to a syn-anti interconversion. The syn and anti dispositions are relative to the central hydrogen (subsitutent at C_2 as shown in scheme 11). The mechanism is explained in scheme 11: starting from the syn-isomer η^3-π-allyl-complex **I** the palladium complex react to a η^1-intermediate **II** which allows rotation around the σ-(C-C) bond affording **III**. At that point, the substituent R has switched from the syn to the anti position, after a change of coordination from a η^1-σ to a η^3-π-complex, anti-isomer **IV** is obtained.



Scheme 11: Mechanism of π-σ-π isomerization

The syn-isomer is sterically favored and therefore more stable then the anti isomer. Depending on the steric hindrance applied by a ligand, the anti-isomer can be preferentially formed[53-55]. Since the σ-complex is coordinatively unsaturated, the presence of halides or the nature of nucleophile and solvent can influence the π-σ-π isomerization[56-57].

The syn-anti isomerization happens before the nucleophile attack and is dependent on the reaction conditions. If the rate of the isomerization is fast compared to the nucleophilic attack, an equilibrium can be formed where both syn and anti isomer are present. Scheme 12 illustrates an example where starting from a pure trans- or cis-isomer, the same ratio of trans- and cis-product is obtained due to the π-σ-π isomerization occuring before the nucleophilic attack.



Scheme 12: π-σ-π isomerization leading to cis/trans isomerization

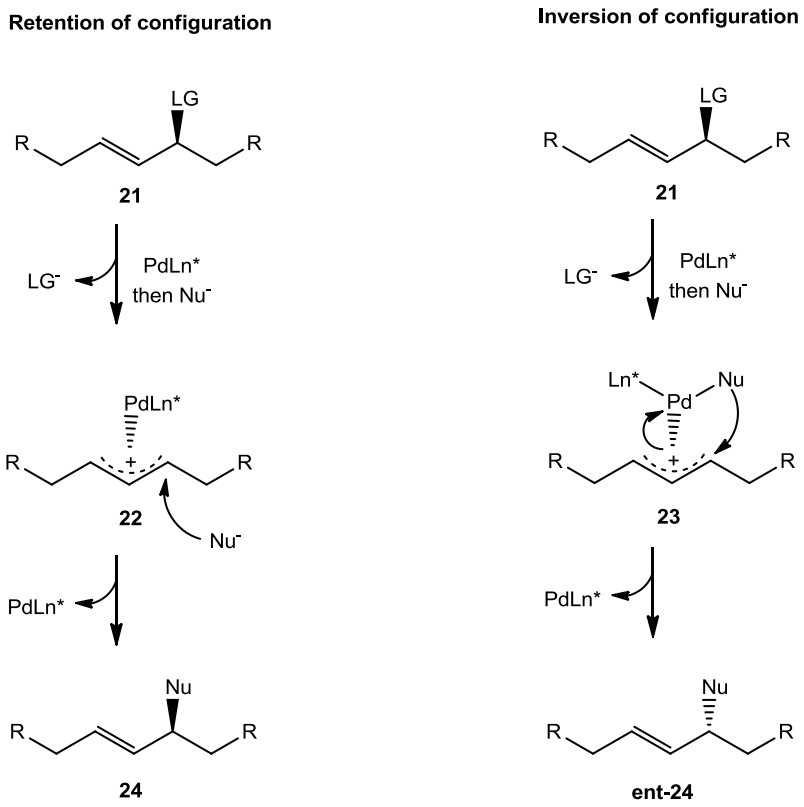
The emergence of π-σ-π isomerization is dependant on the type of substrate used and on the reaction conditions.

1.2.6 Nucleophile

In Pd-catalyzed allylic substitutions, a differentiation between two classes of nucleophiles is done: "Soft" and "hard" nucleophiles. It is an empirical classification which allows distinguishing between a reaction with retention of configuration and a reaction with inversion of configuration[3,58]. The so-called "soft" nucleophiles are stabilized carbanions and most heteroatom nucleophiles with a pK_a below 25. "Hard" nucleophiles are nonstabilized carbanions and some heteroatom nucleophiles with pK_a above 25[31].

Scheme 13 illustrates the differentiation between the two groups. For both classes, during the oxidative addition, the leaving group is ionized with inversion of configuration i.e. the Pd complex approaches from the opposite side of the leaving group. With "soft" nucleophiles,

the nucleophile attacks outside the coordination sphere of the Pd complex to give overall substitution with retention of configuration. On the other hand, "hard" nucleophiles bind at the metal and attack the allylic moiety from the same side of the Pd complex to give overall substitution with inversion of configuration.

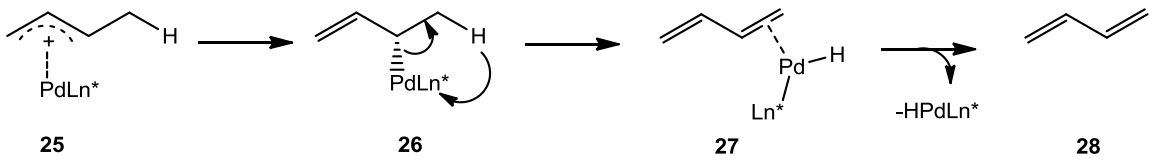


Scheme 13: Mechanism for retention and inversion of configuration

A wide range of nucleophiles are known to react under retention of configuration such as dimethyl malonate, benzylamine, phthalimides, phenols or *p*-TolSO_2Na[59-61]. In contrast, reactions with hard nucelophiles have seen much less success and a few examples with organozinc or Grignard reagents are known[44]. Most reports on allylic substitutions with hard nucleophiles employ Ni[62-63] or Cu[64-65] complexes as the catalyst.

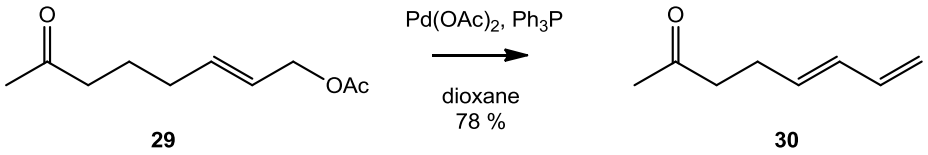
1.2.7 *β*-hydride elimination

β-hydride elimination describes the transfer of a hydride from the beta-position on a substrate to the metal center. In the case of an allylic substitution, the absence of nucleophile or the poor character of a nucleophile as well as the type of substrate can create an environment favorable for *β*-hydride elimination[66]. Scheme 14 illustrates the loss of hydrogen to form a diene.



Scheme 14: Mechanism of β-hydride elimination

In 1978, Tsuji et al.[67] published an article where he reported the formation of diene products by elimination with a palladium catalyst (scheme 15). The reaction proceeds under mild reaction conditions but temperature and addition of a base can favor the elimination product.



Scheme 15: Diene formation[67]

Chapter 2

Purpose of this work

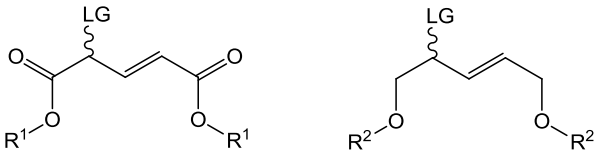
2. Purpose of this work

Enantioselective palladium catalyzed allylic substitutions reactions have been subject to numerous improvements since 1977. Nowadays, they are an important tool in organic synthesis.

Various substrates have been used in this reaction, most of them having two different substituents at each end. However, racemic allylic derivatives with two identical substituents have been widely used especially for the design of new ligands and the understanding of the mechanism specific to each ligand. The advantage of substrates proceeding via symmetrical allyl systems is that quantitative yield and true enantioselective conversion can be obtained from the reaction. Until now, these symmetrical substrates were all synthesized with unfunctionalized substitutents such as aryl- or alkyl-groups. For that reason, the synthetic application after the enantioselective substitution was rather limited.

Therefore the purpose of this thesis was:

1) To synthesize new kind of substrates with a symmetrical allyl system possessing functionalized substituents (scheme 16). The idea was to use functional groups such as esters or ethers which after substitution can easily be transformed into useful and interesting compounds.



Ester substrates

31

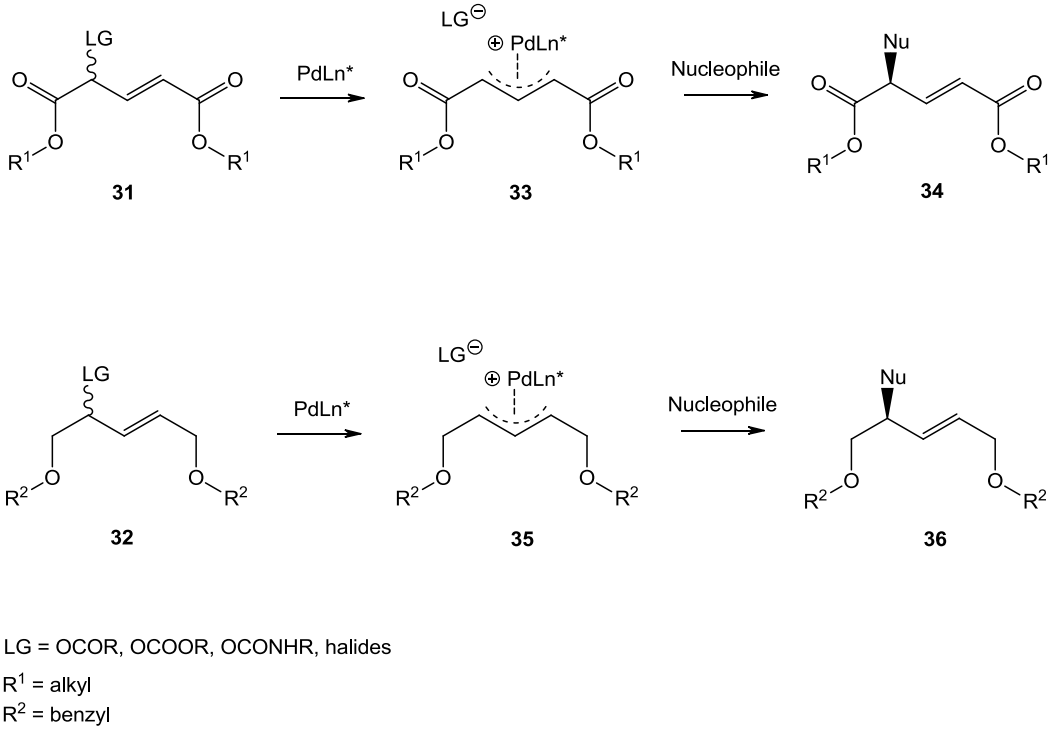
Ether substrates

32

LG = OCOR, OCOOR, OCONHR, halides
R^1 = alkyl
R^2 = benzyl

Scheme 16: Ester and ether substrates

2) To perform an enantioselective allylic substitution and improve the yield and enantioselectivity of the reaction through different screenings, for instance leaving groups, catalysts, ligands, bases, nucleophiles, temperature or solvents. In addition, these experiments could lead to a better understanding of the reaction (scheme 17).

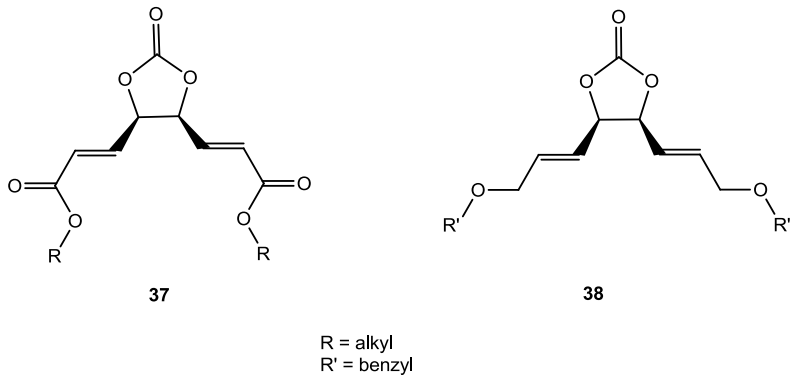


Scheme 17: Allylic substitution on symmetrically substituted allyl ester- and ether systems

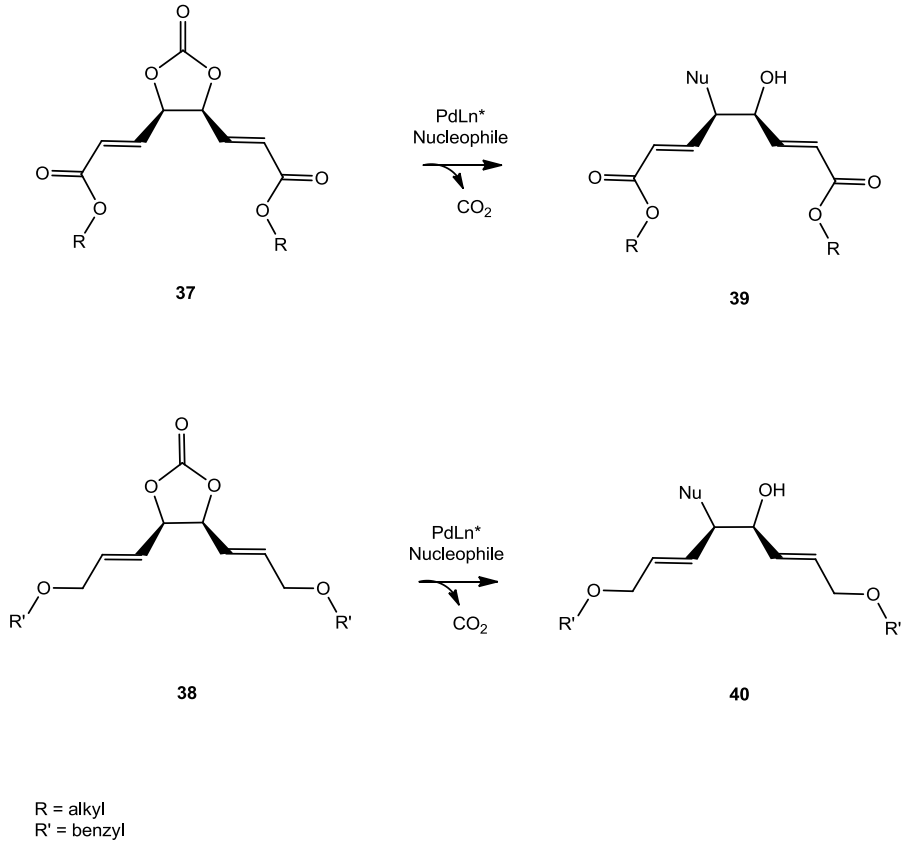
3) To synthesize new useful and interesting compounds from the enantio-enriched products obtained after allylic substitution.

If successful, this strategy with bifunctional substrates should be extended to dimeric meso-substrate where the particularity of the substrate resides in the ionization of the enantiotopic leaving group. For this purpose, compounds **37** and **38** (scheme 18) should be synthesized and used as substrates for enantioselective allylic substitutions. Coordination of the Pd complex would induce the decarboxylation of the leaving group and a presumably regioselective

nucleophilic attack on the less hindered position (scheme 19). The functionalized substituents form a particularly attractive substrate which after allylic substitution would allow the synthesis of interesting compounds.



Scheme 18: Dimeric meso ester- and ether substrates



Scheme 19: Allylic substitutions on dimeric meso ester- and ether substrates

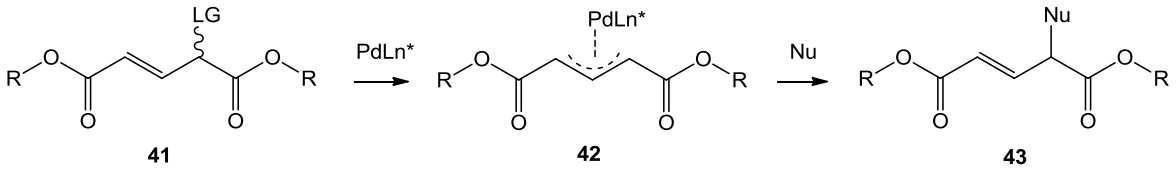
Chapter 3

Results and Discussions

3. Results and Discussions

3.1 Di-Ester substrates

Di-ester compounds such as **41** would be interesting systems to study in an enantioselective allylic substitution. The symmetry of the transition state theoretically would allow a full conversion to product with potentially high enantioselectivity (scheme 20). The obtained product **43** could be used as a valuable chiral substrate which could further be transformed into different interesting compounds through hydrolysis, epoxidation, dihydroxylation etc.



Scheme 20: Nucleophilic allylic substitution on di-ester compound **41**

Even though the synthesis of such di-ester molecules looks easy on paper, the preparation poses a challenging task.

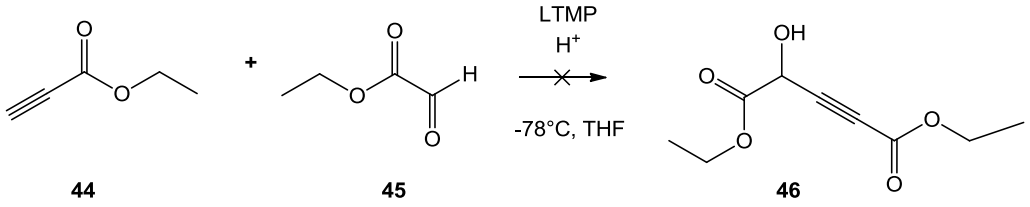
3.1.1 Substrate synthesis

3.1.1.1 Coupling of ethyl propiolate to ethyl glyoxalate

Several synthetic routes can be imagined to obtain diester compounds **41**. One of them, is the formation of compound **46** through the coupling of commercially available ethyl propiolate (**44**) to glyoxylic acid ethyl ester (**45**) using *n*BuLi and 2,2,6,6-tetramethylpiperidine (LTMP)[68] to activate the triple bond (scheme 21). Ethyl glyoxalate is commercially available as a solution in a concentration of ~50 % in toluene, partly in polymerized form. The reaction proved to be difficult due to the polymerization of the aldehyde at lower temperature, which

was problematic due to the fact that the reaction was conducted at -78 °C. The ratio of monomer and polymer in the ethyl glyoxalate solution was analyzed by NMR before adding it to the solution of activated propiolate. The amount of monomer was found to be approximately 6 % at 0 °C. Therefore, different attempts to avoid the polymerization and to obtain a reasonable amount of monomer were tried, such as refluxing the ethyl glyoxalate solution, working under dilute conditions or applying an excess of the aldehyde. After refluxing in toluene during 1h under diluted conditions, 58 % of (**45**) was present in its monomeric form, calculated from the NMR spectra (other byproducts were observed after 2h under reflux). Nevertheless, no satisfactory results were obtained from the reaction and a mixture of products was observed.

Another strategy was to perform the reaction at 0 °C but in that case the deprotonated ethyl propiolate (**44**) turned out to be unstable.



44 **45** **46**

Scheme 21: Addition of ethyl propiolate (**44**) to ethyl glyoxalate (**45**)

Due to these issues, encountered in the synthesis of alkyne compound **46**, other synthetic approaches were needed.

3.1.1.2 Reduction of dimethyl 2-oxoglutaconate

After the unsuccessful coupling attempts, ketone reduction to alcohol **48** was envisaged starting from commercially available dimethyl 2-oxoglutaconate (**47**) (scheme 22). Different reducing agents were tested such as L-Selectride[69], Luche reduction reagent[70] and also a metal-catalyzed transfer reduction with Ru catalyst[71]. Unfortunately, decomposition was observed in a reduction attempt with L-Selectride and also under Luche reduction conditions. No reaction occurred with Ru(p-cymen)(TsDPEN) in a transfer hydrogenation. After the

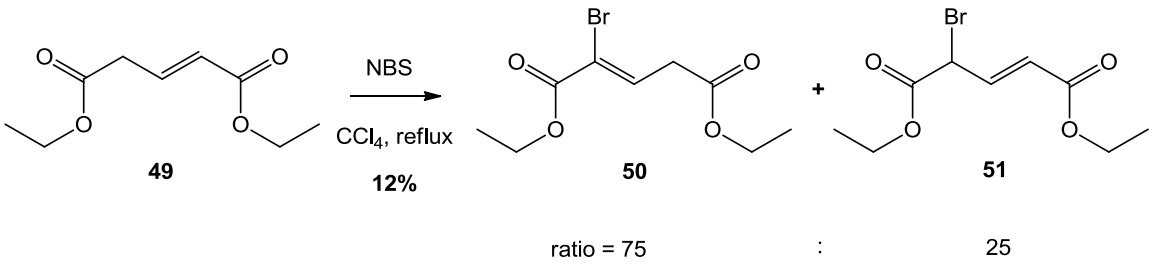
failed reduction attempts and taking into account that compound (**47**) is highly sensitive to moisture and undergoes acetal formation with MeOH, the molecule was to be found unsuitable and another synthesis strategy had to be found.

Scheme 22: Reduction of dimethyl 2-oxoglutaconate (**47**)

3.1.1.3 Bromination

Reduction of (**47**) being troublesome, another approach was followed starting with an allylic bromination of commercially available diethylglutaconate (**49**) to give compound **51** (scheme 23). The first attempt was the allylic bromination using NBS as reagent[72]. Besides monobrominated product, different dibromo products were also observed on LC-MS. After running a chromatography column, a mixture of 75:25 of vinyl **50** to allyl **51** monobrom was isolated in 12% yield.

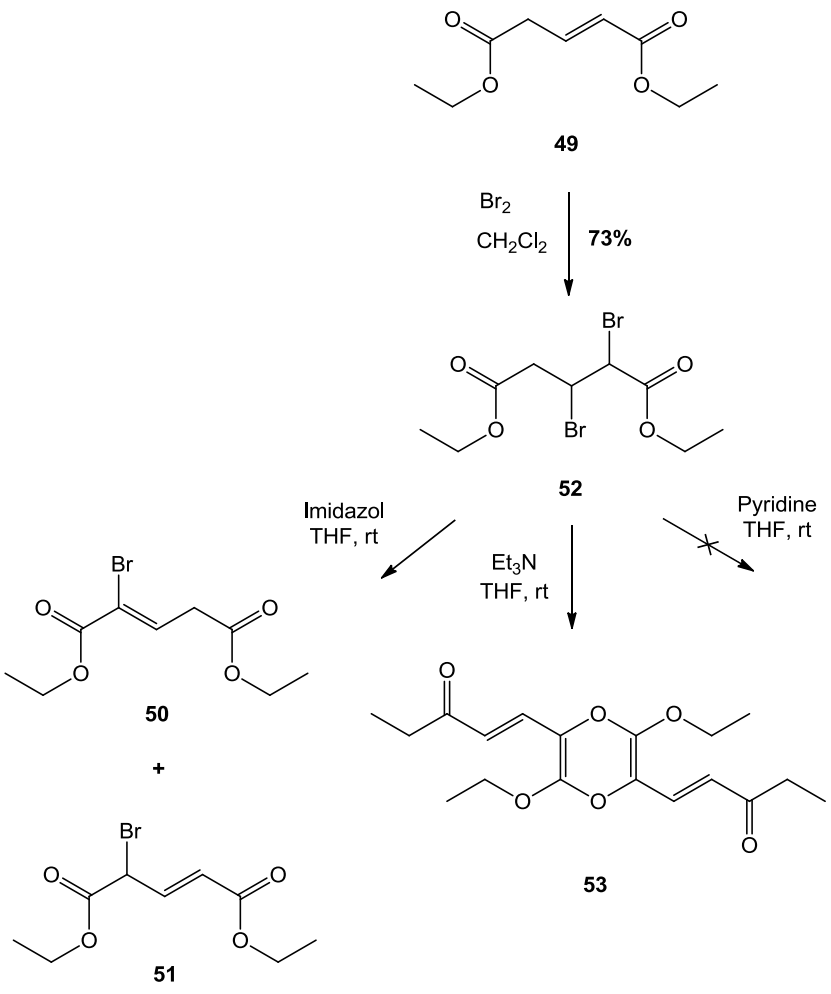
An attempt to push the equilibrium to the allyl product with the help of a base (5% cat NaOMe) was unsuccessful, the vinyl product being thermodynamically more favorable.



Scheme 23: Allylic bromination of diethylglutaconate (**49**)

Instead of an allylic bromination, a dibromination of the double bond and subsequent elimination to obtain the allylic compound **51** was tested (scheme 24). Compound **52** was

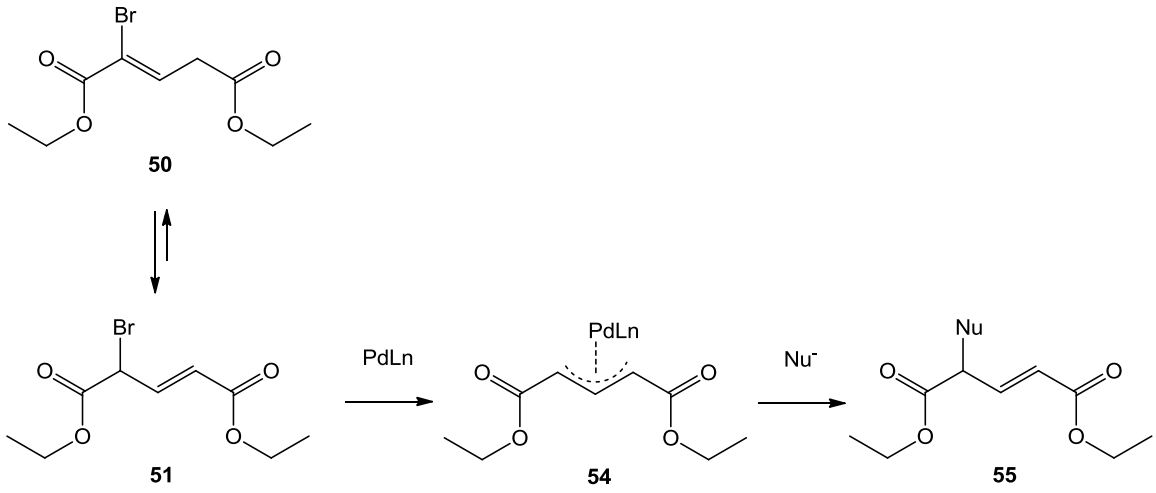
readily synthesized from (**49**) with Br_2 in 73% yield[73]. For the following reaction, different bases such as Et_3N, imidazol, pyridine were tried. Starting with the weakest base pyridine, no reaction was observed. Reaction with the strongest base, triethylamine, showed different byproducts, one of them being the dimerization to a cyclic compound **53** but the desired product was not isolated. Imidazole turned out to be a relatively good base, favouring elimination and yielding the vinyl/allyl **50**/**51** mixture in the same ratio (75:25) as for the NBS reaction. Attempts to obtain the desired di-ester compound being difficult, even though different pathways were tested; a change in the molecule was required.



Scheme 24: Dibromination of diethylglutaconate (**49**) followed by elimination with 3 different bases pyridine, Et_3N and imidazol

3.1.1.4 Allylic substitution on vinyl/allyl monobromide

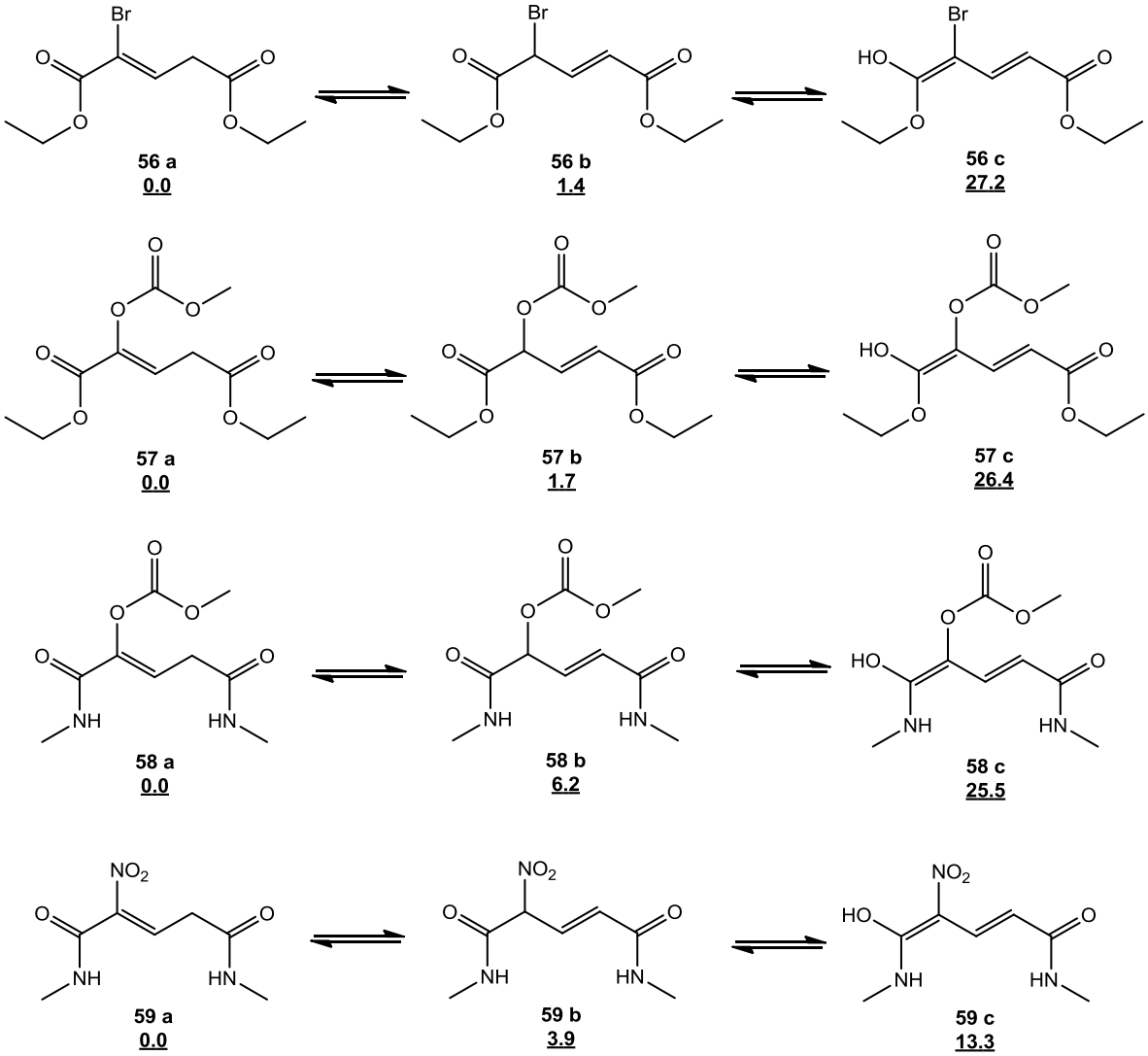
From the previous results using mixtures of vinyl/allyl isomers **50** and **51**, it seems that a dynamic equilibrium between the two isomers is taking place. If the dynamic equilibrium between vinyl and allyl bromide is fast enough compared to the nucleophile attack, then an allylic substitution could be envisaged (scheme 25). Therefore, an allylic substitution was performed on the mixture of 75:25 vinyl/allyl bromide with $Pd_2(dba)_3{\cdot}CHCl_3$ (0.03eq) as catalyst, PPh_3 (0.12eq) as ligand, $BnNH_2$ (2.2 eq) as nucleophile and toluol as solvent at rt. The reaction provided a mixture of products. Unfortunately, the desired product could not be identified nor isolated from the product mixture.



Scheme 25: Dynamic equilibrium between **50** and **51** with subsequent allylic substitution

3.1.1.5 Quantum Mechanic Study

To understand why such relatively simple compounds could not be isolated, a quantum mechanics calculation of the different isomer energies was performed. The calculation was completed with Turbomole DFT/BP86 and the in vacuo calculated energies (in kcal/mol) are given relative to the lowest form. The results are shown in scheme 26.



Scheme 26: QM calculated energies (underlined and in kcal/mol)

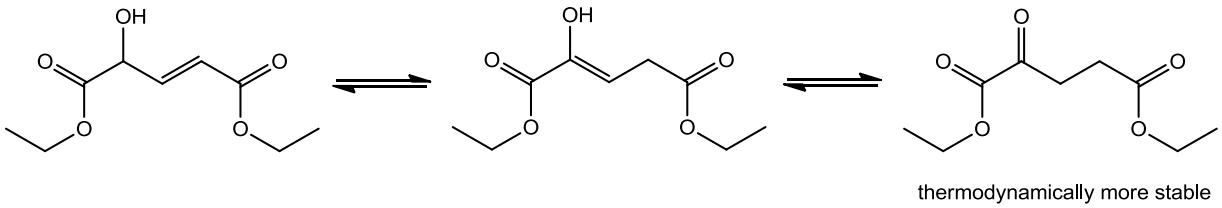
In general, the data shows that the vinyl forms **56a**, **57a**, **58a** and **59a** are thermodynamically more favorable then the allyl forms **56b**, **57b**, **58b** and **59b**. The enol-forms **c** have a significantly higher energy than the other forms, thus the probability to observe this form is low and should not be considerate.

This calculation is in accordance with the previously observed experimental data for the bromination products where the equilibrium is in favor of the vinyl form.

The calculations of series **57** take into account a substrate bearing a methyl carbonate as a leaving group. In that case as well, the calculation shows the vinyl form to be thermodynamically more favorable.

The energies of amide compounds **58** and **59** bearing a methyl carbonate- and a nitro leaving group respectively, were calculated in order to predict if the same effect would be observed as for the other substrates. It turned out that again the vinyl forms **58a** and **59a** are thermodynamically more stable than the allyl isomers **58b** and **59b**.

According to the calculations, the vinyl form seems to be the preferred configuration. A possible, keto-enol tautomerization of the alcohol to the ketone as shown in scheme 27 could then be imagined. The thermodynamically more stable vinyl form could isomerize to the keto form which would annihilate the prospect of an allylic substitution.



60 a **60 b** **60 c**

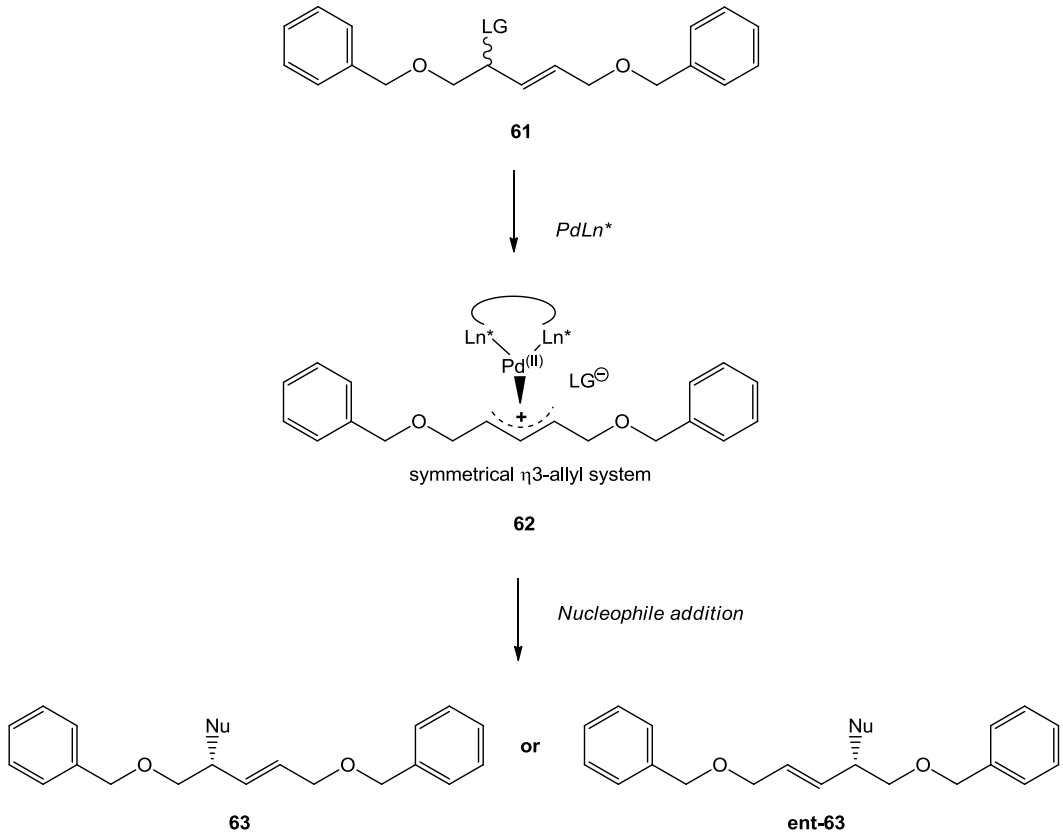
Scheme 27: Keto-enol tautomerization

These calculations combined with the theoretical considerations prompted us to skip the di-ester substrates and to concentrate on di-ether substrates.

3.2 Dibenzylether substrates

Dibenzylether substrates represent a more stable system and their synthesis is straightforward. In such a system, keto-enol tautomerization does not take place and the chiral product after substitution bears an allylic ether which allows differentiation between both ether functions. Provided good yield and enantioselectivity can be achieved with these substrates, subsequent selective functionalization of the products should be possible and would allow the synthesis of interesting compounds.

In the literature, alkoxy substituents are not commonly used in palladium catalyzed substitution since it could theoretically play the role of a leaving group[74]. Nevertheless, some studies on regioselectivity using asymmetric substrates with an alkoxy group were already reported[75] but none of them passing a symmetrical transition state as shown in scheme 28.

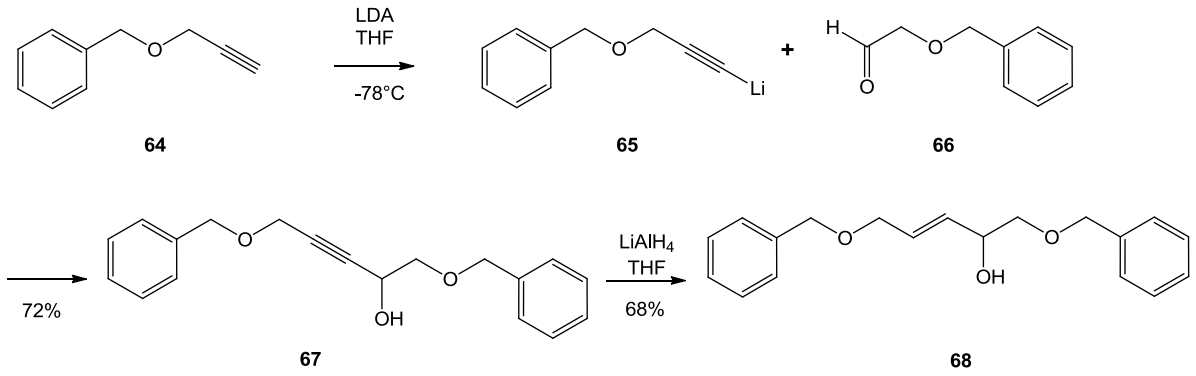


Scheme 28: Allylic substitution on dibenzylether substrates

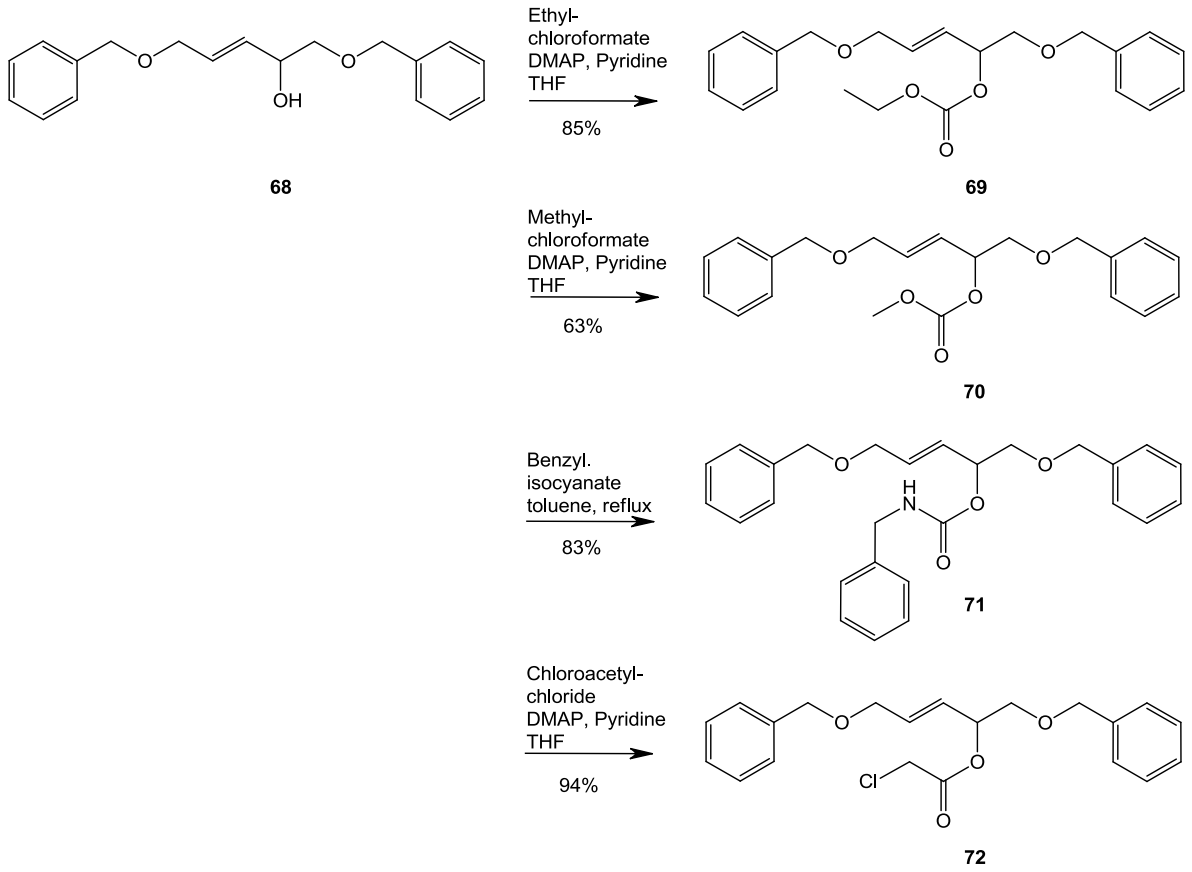
3.2.1 Substrate synthesis

3.2.1.1 (E)-Dibenzylether substrates

The (*E*)-Dibenzylether substrates (compounds **69**-**72**) were prepared as following (scheme 29): The reaction between the lithium salt of commercially available 2-propyn-1-ol (**64)** and 2-benzyloxy-acetaldehyde (**66**) gave **67** (72% yield). **67** was reduced with $LiAlH_4$[76] to obtain the (*E*) allylic alcohol **68** (68% yield) as a common intermediate. Compound **67** has a new structure not described in the literature, whereas the (*S*)-enantiomer of compound **68** is already known[77]. The introduction of the different leaving groups for the preparation of compounds **69**-**72** was achieved as follows: the carbonate derivatives **69** and **70** were prepared by treatment of **68** with ethyl-chloroformate[78] (85% yield) and methyl-chloroformate[78] (63% yield) respectively (scheme 30). Alternatively, **68** was treated with benzylisocyanate[79] to obtain the benzylcarbamate derivative, **71** (83% yield). Finally, the chloroacetate derivative **72** was prepared by reaction of **68** with chloroacetylchloride[78] (94% yield).



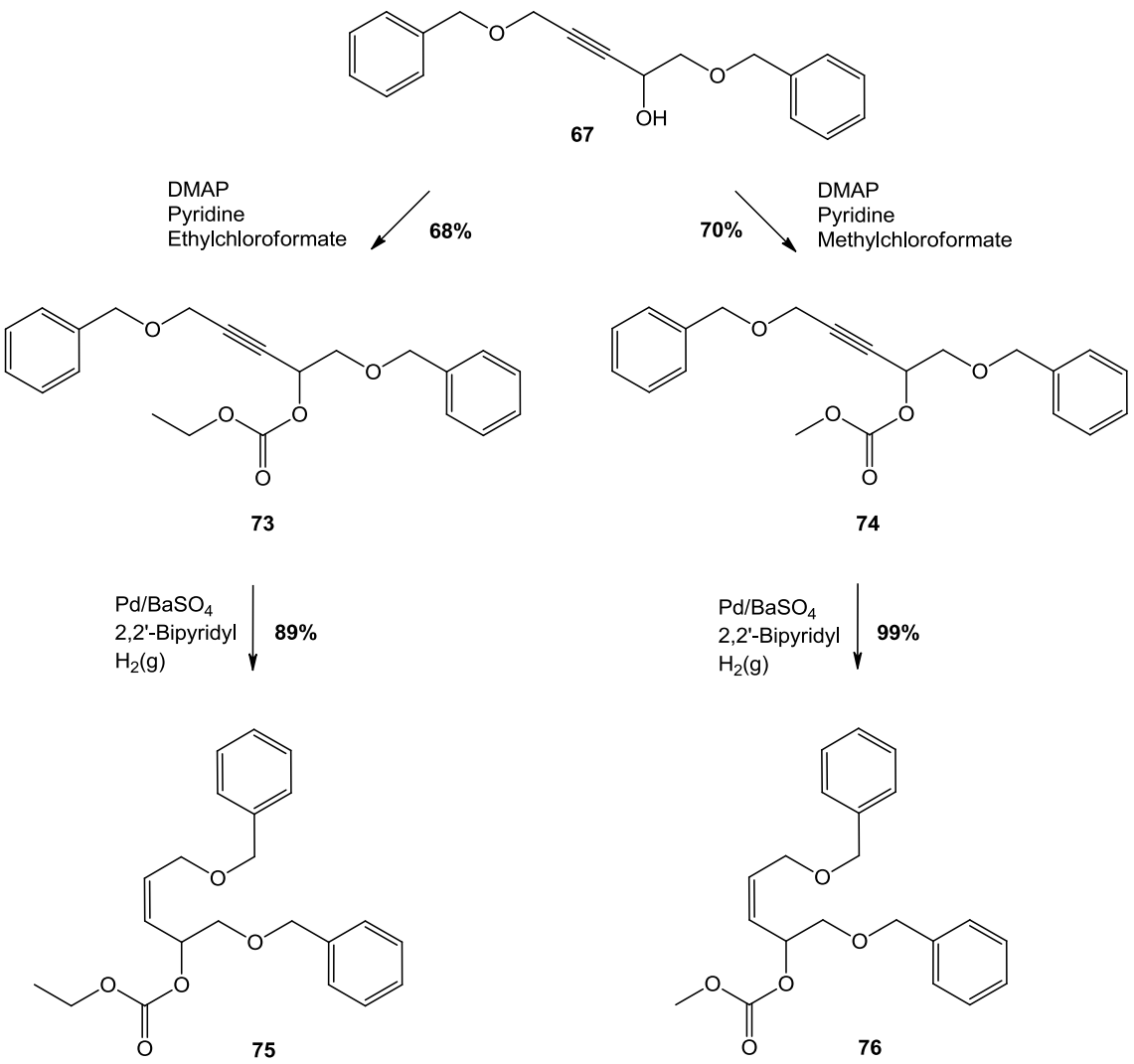
Scheme 29: Synthesis of compound **68**



Scheme 30: Synthesis of the (*E*)-Dibenzylether substrates from compound **68**

3.2.1.2 (Z)-Dibenzylether substrates

The (*Z*)-Dibenzylether substrates were synthesized according to scheme 31. First the leaving groups were introduced to compound **67** affording ethylcarbonate compound **73** (68% yield) and methylcarbonate compound **74** (70% yield)[78]. The introduction of the leaving group before hydrogenation was important to this heterogeneous reaction. Hydrogenation of **67** was not selective and mixture of the desired alkene and the fully hydrogenated product was obtained which were difficult to separate. The steric hindrance of the leaving group combined with the use of a poisoned catalyst (Pd on barium sulfate) with 2,2'-Bipyridyl allowed selective hydrogenation to obtain the (*Z*)-alkene in good yields. As reported by Hirota et al.[80], the use of 2,2'-Bipyridyl suppresses the hydrogenolysis of the benzyl ethers. Hydrogenation of **73** and **74** with $Pd/BaSO_4$, 2,2'-Bipyridyl, H_2 afforded **75** (89% yield) respectively **76** (99% yield).

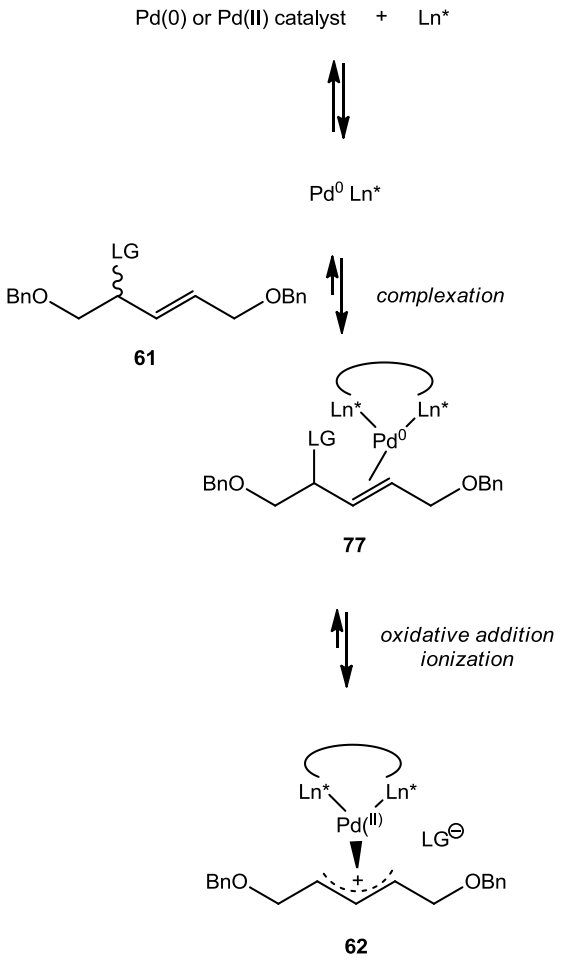


Scheme 31: Synthesis of (*Z*)-Dibenzylehter substrates

3.3 Allylic substitutions on dibenzylether substrates

3.3.1 Leaving group screening

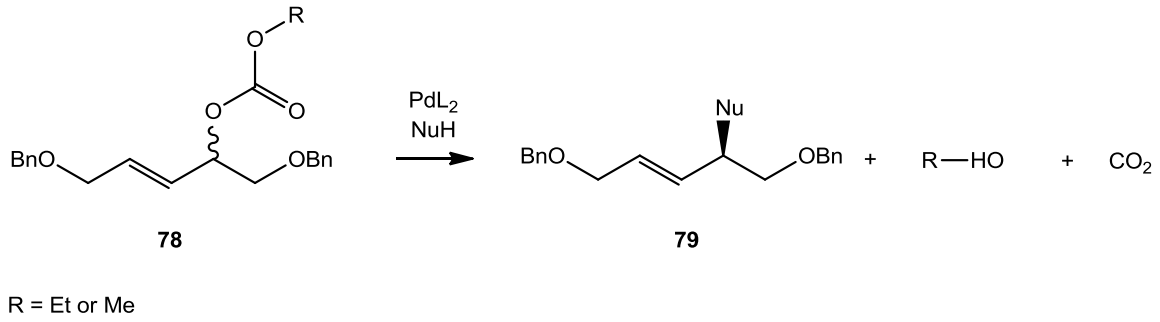
The first step of the Tsuji-Trost reaction involves the coordination of the Pd(0)-catalyst to the allylic system of the substrate **61** (scheme 32) which forms a η^2-allyl complex **77** (complexation step). An oxidative addition follows during which the leaving group is expelled (also called ionization step) leading to a η^3-allyl complex **62**. The choice of a good leaving group is an important factor in the reaction and can play a non negligible role in inducing enantioselectivity. Therein the effect of different leaving groups was studied to choose the best suited one for this system.



Scheme 32: First step of the Tsuji-Trost reaction: complexation and ionization to η^3-allyl

3.3.1.1 Ethyl carbonate substrates

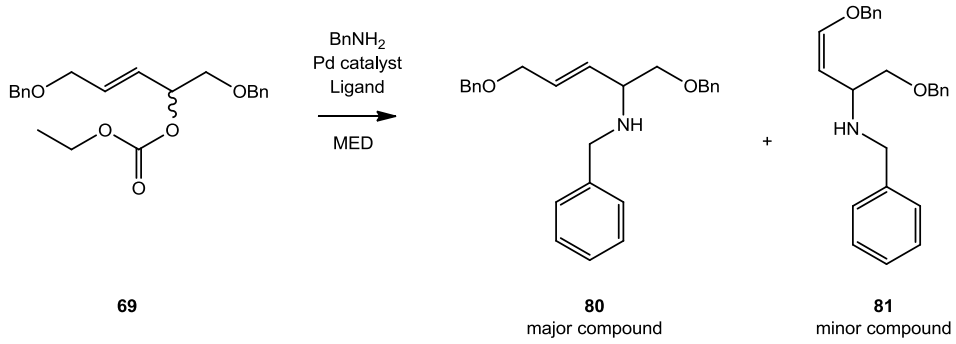
In allylic substitution, carbonate leaving groups are well known and frequently used. In a general way, allylic carbonates have the advantage of decarboxylating after the oxidative addition forming alkoxides which are able to deprotonate the nucleophile (scheme 33)[45]. Furthermore, according to a kinetic study of Amatore[47], the carbonates are good leaving groups since the ionization step is faster than the complexation step. Therefore our first experiments were performed using ethyl carbonate as leaving groups. Using these substrates, allylic substitutions of both the (*E*)- and (*Z*)-allyl carbonates were studied.



Scheme 33: Allylic carbonates decarboxylation and nucleophile deprotonation

3.3.1.1.1 (*E*)-Ethyl carbonate substrate (compound **69**)

Allylic substitutions using the (*E*)-substrate with the ethylcarbonate leaving group (compound **69**) were performed under standard reaction conditions using $BnNH_2$ as the nucleophile, at rt in dichloromethane (scheme 34).



Scheme 34: Allylic subsitution on (*E*)-Ethyl carbonate-substrate **69** with benzylamine

The results are summarized in table 1. The first reaction was a non-enantioselective substitution with PPh_3 as a ligand and $[Pd_2(dba)_3]\cdot CHCl_3$ as a catalyst (entry 1, table 1). The racemic product showed an *Z*:*E* ratio of 25:75, even though the starting material comprised >97% of the *E*-isomer. Approximately the same proportion of *E*/*Z* isomers was obtained as product in the case of the enantioselective substitution with (*R*,*R*)-Trost DACH Phenyl as ligand (entry 2 and 3, table 1), indicating that an equilibration is established either during the complex formation (catalyst/ligand coordination to the allyl system) and/or during the substitution reaction (nucleophilic attack). Entry 2 and entry 3 (table 1) show a comparison of the two different catalysts frequently used in allylic substitution: Pd(0) = $[Pd_2(dba)_3]\cdot CHCl_3$ and the in situ generated Pd(0) from Pd(II) = $[Pd(allyl)Cl]_2$. Both are almost equivalent in terms of yield and Z/E isomerization with a better ee for Pd(0). Unfortunately, both reactions were not complete leading to poor yield and moderate ee.

Table 1: Allylic substitutions on (*E*)-Ethylcarbonate substrate (compound **69**)

Entry	Catalyst	Ligand	Time	Yield[4]	Z/E ratio	ee[6]
1	Pd(0)[1]	PPh_3	5h30	48%	25 : 75[5]	-
2	Pd(0)[1]	Trost(1)[3]	4 days	34%	14 : 86[6]	80% (Z) 70% (E)
3	Pd(II)[2]	Trost(1)[3]	6 days	40%	20 : 80[6]	50% (Z) 26% (E)

Reaction conditions: Pd catalyst (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.), rt; [1] $[Pd_2(dba)_3]CHCl_3$; [2] $[Pd(allyl)Cl]_2$; [3] (*R*,*R*)-Trost DACH Phenyl; [4] isolated yield after chromatography; [5] calculated on ^1H NMR; [6] determined by HPLC (Chiralpak AD-H)

Entry 3 (table 1) was followed by HPLC on a chiral stationary phase to get an insight into the reaction. The evolution of the reaction was monitored with a chiral column (Chiralpak AD-H, eluent: 6% iPrOH 94% n-hexane). Before each injection on the column, a probe of the reaction mixture was filtered over a short pad of silica and the solvent evaporated under reduced pressure. The sample was then diluted in a mixture of 6% iPrOH and 94% n-hexane to work under isocratic conditions. The results are summarized in table 2. The *Z*/*E* ratio was constant over time. The enantioselectivity decreased with time which could be the effect of a competing side reaction or due to the (*Z*)-(*E*) isomerization and the π-σ-π interconversion as explained in section 3.3.2.

Table 2: Reaction followed by Chiral HPLC

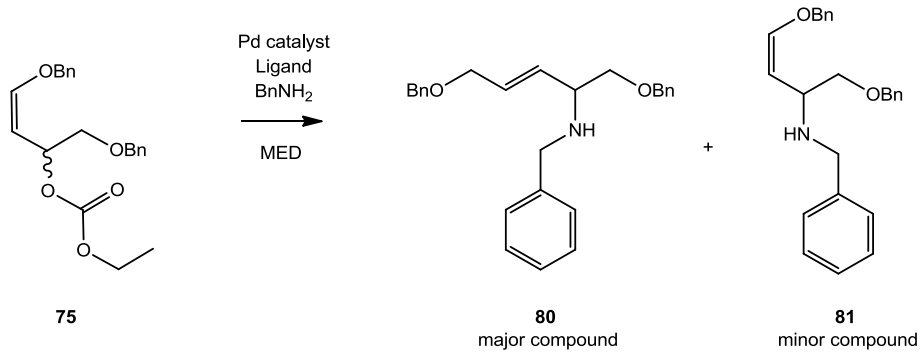
Time	Conversion	Yield[1]	Z/E ratio[2]	ee[2]
1h	89% SM 11% Product		18:82	49% (E)
2h	82% SM 18% Product		18:82	45% (E)
4h	71% SM 29% Product		20:80	67% (Z) 47% (E)
6h	69% SM 31% Product		20:80	64% (Z) 45% (E)
1 day	57% SM 43% Product		25:75	59% (Z) 37% (E)
5 days	46% SM 54% Product		24:76	50% (Z) 27% (E)
6 days	47% SM 53% Product		25:75	48% (Z) 28% (E)
6 days		40%	20:80	50% (Z) 26% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R*,*R*)-Trost DACH Phenyl (0.24 eq.), $BnNH_2$ (2 eq.), rt; [1] isolated yield after chromatography; [2] determined by HPLC (Chiralpak AD-H)

3.3.1.1.2 (*Z*)-Ethyl carbonate substrate (compound **75**)

Since isomerization to the (*Z*)-product was observed when the reaction was conducted with the (*E*)-substrate, the application of the (*Z*) substrate could help to get information about the influence the configuration has on the reaction and to better understand the reaction mechanism.

Therefore, allylic substitution on (*Z*)-Ethyl carbonate substrate (compound **75**) was investigated under the reaction conditions of benzylamine as nucleophile, dichloromethane as solvent and at room temperature (scheme 35). The results are summarized in table 3.



Scheme 35: Allylic substitution on (*Z*)-Ethylcarbonate-substrate **75** with benzylamine

Table 3: Allylic substitutions on (*Z*)-Ethylcarbonate substrate (compound **75**)

Entry	Catalyst	Ligand	Time	Yield[3]	Z/E ratio[4]	ee[5]
1	Pd(0)[1]	PPh_3	4h	64%	30:70	-
2	Pd(0)[1]	Trost(1)[2]	24h	36%	10:90	76% (Z) 64% (E)

Reaction conditions: Ligand (0.24 eq.), $BnNH_2$ (2 eq.), rt; [1] $[Pd_2(dba)_3]\cdot CHCl_3$ (0.08 eq.); [2] (*R*,*R*)-Trost DACH Phenyl; [3] isolated yield after chromatography; [4] calculated on ^1H NMR; [5] determined by HPLC (Chiralpak AD-H)

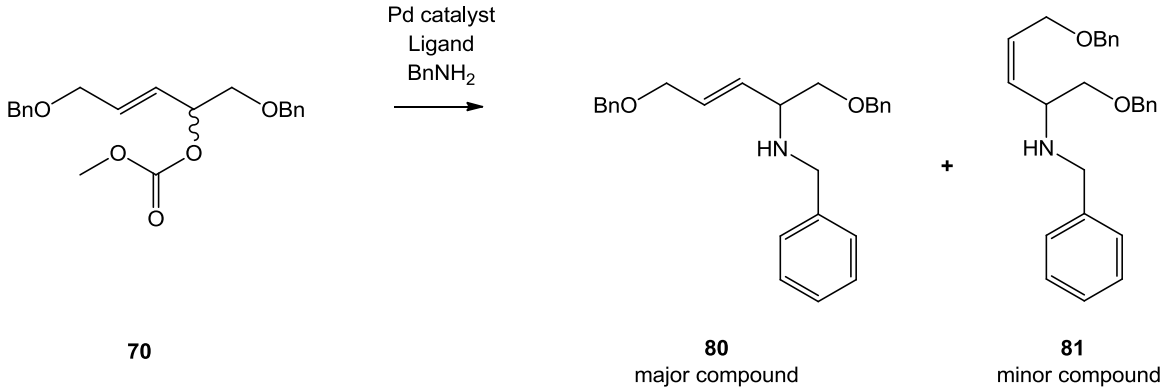
Approximately the same *Z*/*E* ratio was surprisingly observed with (*E*)-product as major compound as in the previous results starting from the (*E*)-substrate. This result again indicated the presence of an equilibrium where the (*E*)-isomer of the product is preferably formed as compared to the (*Z*)-product. The enantioselectivity is better for the (*Z*)-product than for the (*E*)-product. The *E*/*Z* isomerization is disscussed in more detail in section 3.3.2.

3.3.1.2 Methyl carbonate substrates

At the same time, since the yield and the ee of the ethyl carbonate substrates were not satisfactory, another somehow similar but more labile leaving group was tested. Methyl carbonate was introduced and evaluated in allylic substitutions.

3.3.1.2.1 (*E*)-Methyl carbonate substrate (compound **70**)

Different reaction conditions were tested with the (*E*)-Methyl carbonate substrate (scheme 36) and the results are summarized in table 4. Concerning the *Z*/*E* isomerization, the same observation was noticed as for the ethyl carbonate with approximately 20:80 *Z*:*E* isomerization. Further explanation and experiments are given in section 3.3.2.



Scheme 36: Allylic substitution on (*E*)-Methyl carbonate substrate **70** with benzylamine

Entry 2 and 3 (table 4) shows the same reaction with different catalyst: $[Pd_2(dba)_3]\cdot CHCl_3$ respectively $[Pd(allyl)Cl]_2$. In terms of ee, similar results were found but reactions with $[Pd(allyl)Cl]_2$ were completed leading to a better yield and in a shorter reaction time. Therefore, this catalyst was further used in this reaction with this substrate.

The temperature was lowered to see if the ee could be improved and a slight amelioration was observed but it was not significant (entry 4, table 4).

Since promising results were observed with this substrate, a solvent screening was performed: toluene (entry 5, table 4) showed similar results as CH_2Cl_2 but with a lower ee for the (*E*)-product. Reaction in THF was not completed and afforded only low enantioselectivity (entry 6, table 4). Reaction in more polar solvent such as CH_3CN was rapid with good yield but unfortunately the ee was low (entry 7, table 4). Dioxane (entry 8, table 4) proved to be an unsuitable solvent for this system. In summary, dichloromethane showed the best results when combining yield and enantioselectivity.

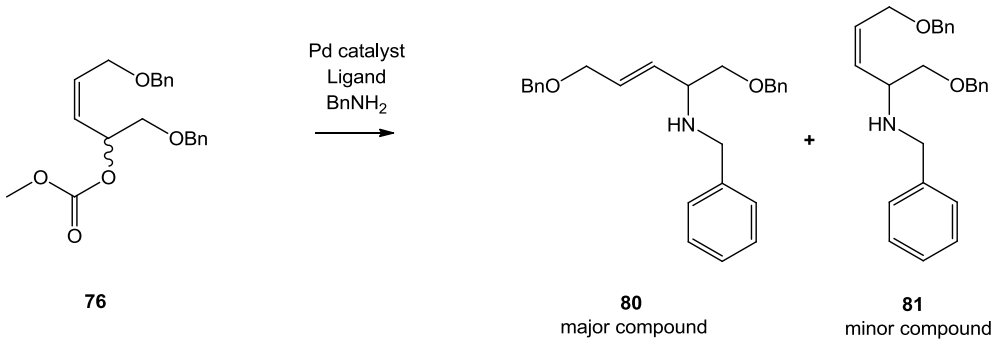
Table 4: Allylic substitutions on (*E*)-Methyl carbonate substrate (compound **70**)

Entry	Catalyst	Ligand	Solvent	T	Time	Yield[4]	Z/E ratio[5,6]	ee[6]
1	Pd(0)[1]	PPh_3	CH_2Cl_2	rt	24h	55%	18:82[5]	-
2	Pd(0)[1]	Trost(1)[3]	CH_2Cl_2	rt	24h	56%	23:77[5]	81% (Z)
							18:82[6]	59% (E)
3	Pd(II)[2]	Trost(1)[3]	CH_2Cl_2	rt	4h	90%	16:84[6]	79% (Z)
								51% (E)
4	Pd(II)[2]	Trost(1)[3]	CH_2Cl_2	0°C	5h	75%	17:83[5,6]	75% (Z)
								45% (E)
5	Pd(II)[2]	Trost(1)[3]	Toluene	rt	2h30	89%	22:78[6]	76% (Z)
								22% (E)
6	Pd(II)[2]	Trost(1)[3]	THF	rt	24h	50%	15:85[5,6]	53% (Z)
								11% (E)
7	Pd(II)[2]	Trost(1)[3]	CH_3CN	rt	1h	91%	16:84[6]	60% (Z)
								20% (E)
8	Pd(II)[2]	Trost(1)[3]	Dioxane	rt	72h	64%	22:78[56]	35% (Z)
								7% (E)

Reaction conditions: Pd catalyst (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.); [1] $[Pd_2(dba)_3]CHCl_3$; [2] $[Pd(allyl)Cl]_2$; [3] (*R*,*R*)-Trost DACH Phenyl; [4] isolated yield after chromatography; [5] calculated on ^1H NMR; [6] determined by HPLC (Chiralpak AD-H)

3.3.1.2.2 (*Z*)-Methyl carbonate substrate (compound **76**)

Allylic substitutions were performed with (*Z*)-Methyl carbonate substrate (compound **76**) to observe and confirm if the same trend could be noticed than for the (*Z*)-Ethyl carbonate (scheme 37). The results of the (*Z*)-substrate (table 5) in terms of yield and enantioselectivity were poor and isomerization to the (*E*) product occurred the same way as for (*Z*)-Ethyl carbonate indicating that substitutions on the (*Z*)-species are not very promising. Therefore, the (*Z*)-forms of the other substrates were not synthesized.



76 **80** major compound **81** minor compound

Scheme 37: Allylic substitution on (*Z*)-Methylcarbonate substrate **76** with benzylamine

Table 5: Allylic substitutions on (*Z*)-Methylcarbonate substrate (compound **76**)

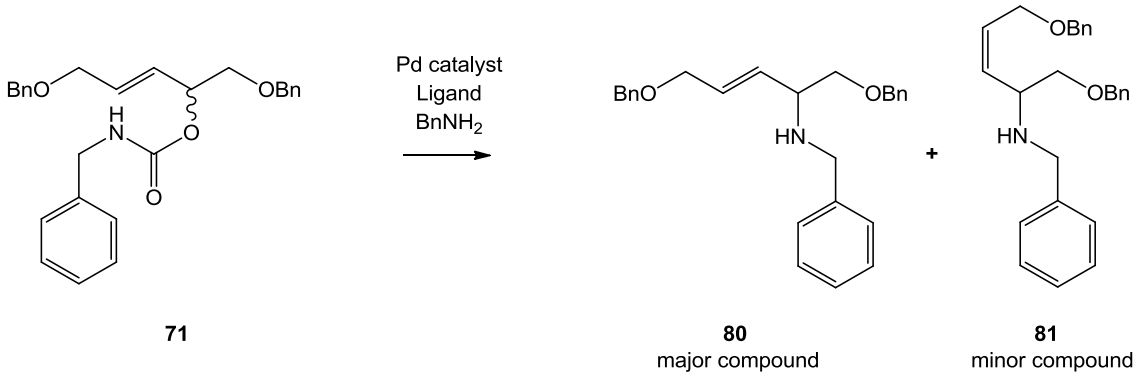
Entry	Ligand	Solvent	Time	yield[2]	Z/E ratio[3]	ee[3]
1	PPh_3	CH_2Cl_2	24h	75%	33:67	-
2	Trost(1)[1]	CH_2Cl_2	24h	33%	17:83	66% (Z) 32% (E)
3	Trost(1)[1]	Toluene	72h	13%	21:79	77% (Z) 34% (E)
4	Trost(1)[1]	THF	72h	13%	22:78	57% (Z) 9% (E)
5	Trost(1)[1]	ACNL	72h	57%	22:78	31% (Z) 2% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.), rt ; [1] (*R*,*R*)-Trost DACH Phenyl; [2] isolated yield after chromatography; [3] determined by HPLC (Chiralpak AD-H)

3.3.1.3 Benzylcarbamate substrate

As reported by Tsuji, benzylcarbamates were found to be good leaving groups with C-nucleophile under neutral reaction conditions (without addition of a base)[51,81]. In 2005, Tunge et al.[82], described reactions with carbamate leaving groups where decarboxylation lead to the formation of amine reactive intermediate. In his thesis, Claude Schärer[83] observed high enantioselectivity using benzylcarbamate as leaving group in an asymmetric allylic substitution. The advantage of such leaving groups is the catalytic decarboxylative allylic amination which represents an interesting reaction due to its good atom economy and mild reaction conditions. Therefore, reactions with this leaving group were performed.

As a first attempt, allylic substitutions with benzylamine as the nucleophile were carried out to see which influence it would have on the reaction (scheme 38). The results are summarized in table 6. The major isomer being the (*E*) form, only the ee's of the (*E*)-isomers were compared. The best ee's are correlated to CH_2Cl_2 as solvent but toluene gave the best yield. A dramatic drop of ee was observed with toluene at 40°C. Poor results were obtained with dioxane (entry 3, table 6) and DMF (entry 6, table 6) as solvents. Furthermore, the reaction was never completed leading to poor yields and recovery of starting material. The decarboxylation preceding the substitution could not be observed making the substrate unsuitable for reaction such as described by Tunge et al. From the poor results summarized in table 6 and compared to the carbonate leaving group, benzylcarbamate was found an unsuitable leaving group for our system.



Scheme 38: Allylic substitution on (*E*)-Benzylcarbamate substrate **71** with benzylamine

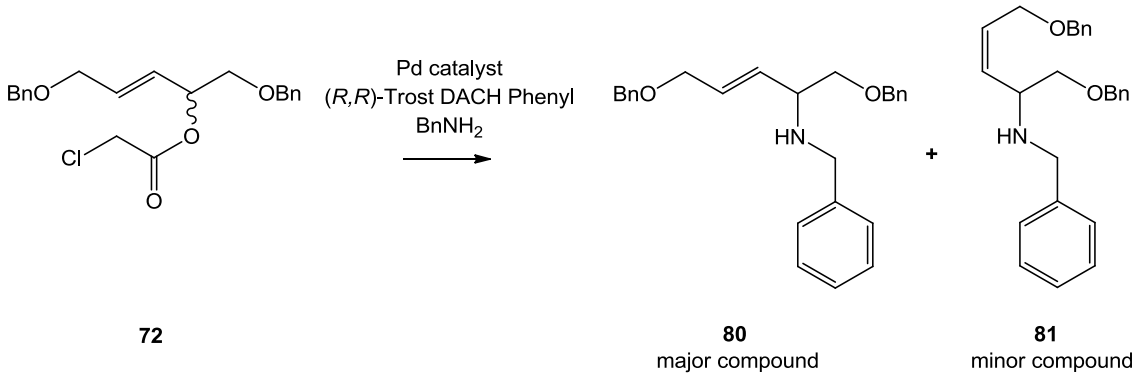
Table 6: Allylic substitutions on (*E*)-Benzylcarbamate substrate (compound **71**)

Entry	Ligand	Solvent	T	Yield[2]	Z/E ratio[3]	ee[3]
1	PPh_3	CH_2Cl_2	rt	31%	29:71	-
2	Trost(1)[1]	CH_2Cl_2	rt	29%	17:83	77% (Z) 49% (E)
3	Trost(1)[1]	Dioxane	rt	16%	11:89	44% (Z) 8% (E)
4	Trost(1)[1]	Toluene	rt	54%	22:78	79% (Z) 32% (E)
5	Trost(1)[1]	Toluene	40 °C	38%	27:73	41% (Z) 7% (E)
6	Trost(1)[1]	DMF	rt	33%	12:88	42% (Z) 32% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (3 eq.) ; [1] (*R,R*)-Trost DACH Phenyl; [1] isolated yield after chromatography; [2] determined by HPLC (Chiralpak AD-H)

3.3.1.4 Chloracetate substrate

In general, allylic carbonates are more reactive than acetates due to decarboxylation of carbonate (see section 3.3.1.1). Nevertheless, from the previous results, allyl carbonates seemed to be less suitable leaving groups in our system. In the literature, chloracetate is a known leaving group for allylic substitutions[78] and therefore, it was also tested as leaving group in this thesis (scheme 39). The results are summarized in table 7.



72 **80** major compound **81** minor compound

Scheme 39: Allylic substitution on (*E*)-Chloracetate-substrate **72** with benzylamine

Table 7: Allylic substitutions on (*E*)-Chloracetate substrate (compound **72**)

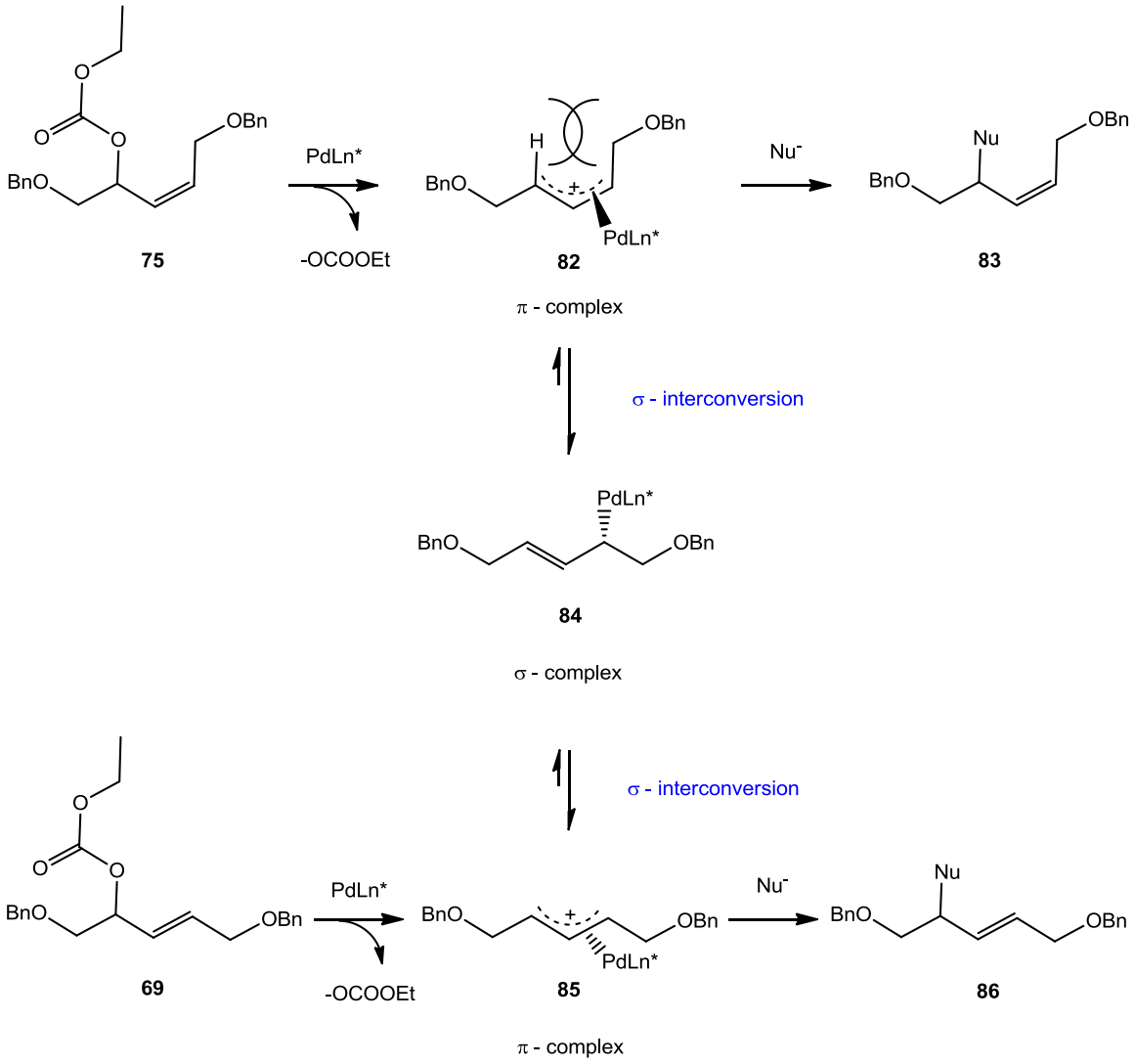
Entry	Catalyst	Solvent	T	Time	Yield[3]	Z/E ratio[4,5]	ee [5]
1	Pd(0)[1]	CH_2Cl_2	rt	36h	48%	20:80[5] 17:83[4]	76% (Z) 52% (E)
2	Pd(II)[2]	CH_2Cl_2	rt	3h30	84%	16:84[5]	78% (Z) 47% (E)
3	Pd(II)[2]	CH_2Cl_2	0°C	24h	80%	19:81[5] 16:84[4]	78% (Z) 50% (E)
4	Pd(II)[2]	Toluene	rt	36h	69%	25:75[5] 24:76[4]	78% (Z) 41% (E)

Reaction conditions: Pd catalyst (0.08 eq.), (*R,R*)-Trost DACH Phenyl (0.24 eq.), $BnNH_2$ (2 eq.) ; [1] $[Pd_2(dba)_3]\cdot CHCl_3$; [2] $[Pd(allyl)Cl]_2$; [3] isolated yield after chromatography; [4] calculated on ^1H NMR; [5] determined by HPLC (Chiralpak AD-H)

Since the choice of the catalyst seems to depend on the substrate and the leaving group, the same reaction with $[Pd_2(dba)_3]\cdot CHCl_3$ or $[Pd(allyl)Cl]_2$ (entry 1 and 2, table 7) was performed. With a better yield and similar ee, $[Pd(allyl)Cl]_2$ was chosen as the catalyst and was used as a standard for the next reaction. Lowering the temperature, slightly improved the ee. Reaction in toluene (entry 4, table 7) gave moderate results. With a short reaction time and good yields, chloracetate was identified to be a promising leaving group for further improvement of the reaction conditions.

3.3.2 *E*/*Z* isomerization

E/*Z* isomerization is frequently observed in palladium catalyzed allylic substitution. One explanation for this effect is given by the π-σ-π isomerization which results from *syn-anti* interconversion around the σ-(C-C) bond. In our system, *E*/*Z* isomerization leads to the same ratio, either starting from (*Z*) or (*E*)-substrate. A possible explanation for this effect is the σ-interconversion during complexation of the palladium-ligand[84-85]. Scheme 40 illustrates a possible mechanism involving our substrate. The oxidative addition, where Pd-ligand complex coordinates to the substrate and the leaving group is released, leads to a steric hindrance in case of the (*Z*)-compound **82** bringing the palladium to interconvert in a σ-bond which allows the molecule to rotate into a more stable (*E*)-conformation **84**. The Pd-ligand then interconvert again into the more stable π-complex **85**, which allows the nucleophilic attack. Starting either from the (*Z*) or the (*E*) substrate, the equilibrium arising during the coordination of Pd complex to the substrate affords the same (*E*)/(*Z*) ratio of product.



Scheme 40: π-σ-π isomerization

3.3.3 Ligand screening with (*E*)-Chloracetate substrate (compound 72)

Chiral ligands play a crucial role in allylic subsitutions since the ligand-substrate interactions induce enantioselectivity on the substrate. Several ligands have been designed for this reaction including different concepts. The C_2-symmetric diphosphine ligands developed by Trost, are ligands which create a chiral space enveloping the allyl substrate. The increase of the bite angle, which corresponds to the P-Pd-P angle, improves the chiral cavity which embraces the allyl moiety by extending the chiral environnment toward the allyl fragments. Chiral phosphinooxazoline (PHOX) ligands were developed independently at the same time by Pfaltz, Helmchen and Williams and compared to the C_2-symmetrical ligands control the selectivity based on electronic effects[86].

In our system, the starting substrate is a racemic mixture of compound **72** containing two identical substituents at the allylic termini, which are converted to the same symmetrical intermediate. In that case, the enantioselectivity is determined during the nucleophilic addition to the allyl system. Controlling which terminus of the allyl group is attacked would determine which enantiomer is formed[87]. Using Trost ligands would induce enantioselectivity from sterical hindrance of the phenyl group attached to the ligand. In addition, hydrogen-bond interactions of one N-H unit in the Pd-coordinated Trost complex may help the ionization and nucleophile attack[37]. On the other hand, PHOX ligands discriminates the allylic terminus by electronic effects of the P, N heteroatoms located on the ligand but also by sterical effects of the substitutents attached to the ligand.

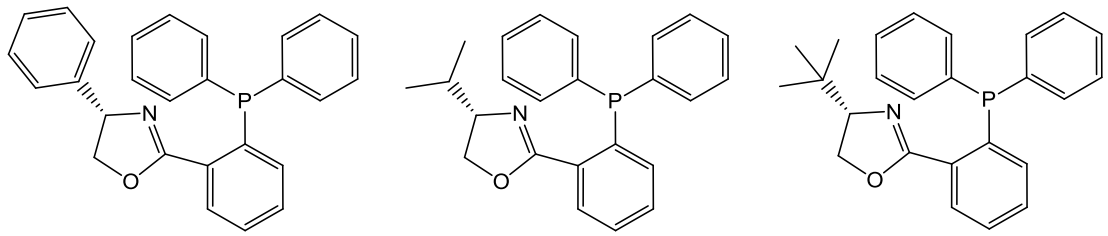
These two chiral ligand concepts have been investigated in our system. Three different PHOX ligands (scheme 41) were tested as well as four different Trost ligands (scheme 42). Table 8 summarizes the results.

Good yields were obtained with all three PHOX ligands (entry 1-3, table 8) but unfortunately the ee's were poor and long reaction times were needed to complete the reaction. It is interesting to note that PHOX ligands only showed little isomerization to the (*Z*)-product probably due to a stronger binding to the allyl system. In general, PHOX ligands are known to be good ligands for larger substrates. On the other hand, the results obtained for the Trost ligands showed moderate to good yields and in the case of Trost (1) and Trost (2) moderate ee's (entry 4 and 5, table 8). No reaction to the desired product could be observed with Trost

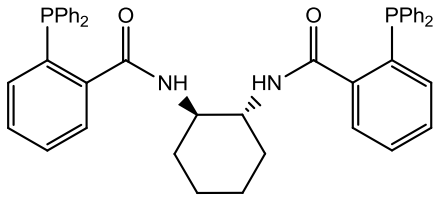
(3) (entry 6, table 8). Fortunately, promising results were obtained with Trost (4) chiral ligand (entry 7, table 8) where isomerization was reduced so that less than 5 % (*Z*)-product was observed. This was probably due to the larger bite angle of this ligand allowing a better "envelopment" or control of the substrate with good yield and a high ee.

From a general observation, the *Z*/*E* isomerization is dependent on the ligand and probably on the way the Pd-ligand complex binds to the substrate. PHOX ligands are sterically less demanding than Trost ligands and probably have a stronger binding access to the substrate, minimizing isomerization to the less stable (*Z*)-isomer. If however, Trost (1) and Trost (4) are compared, a closer look has to be taken on the bite angle (scheme 43). Trost (1) has a small bite angle compared to Trost (4). As consequence, the phenyl groups of Trost (1) ligand could be the cause of sterical hindrance with the substrate forcing it to change conformation. On the other hand, Trost (4) has a larger bite angle which could allow the substrate to fit into the "cavity" of the ligand and therefore minimizing isomerization to the (*Z*)-isomer (scheme 43)

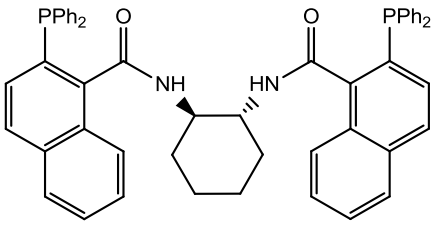
With the enantioselectivity being improved as well as the *Z*/*E* isomerization being substantially minimized, chiral ligand (*R*,*R*)-Trost ANDEN was chosen as the ligand of choice for further screenings.



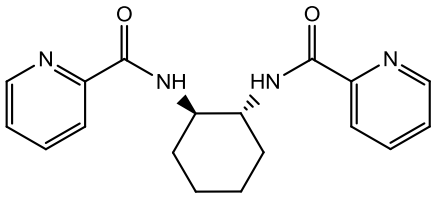
Scheme 41: PHOX ligands: PHOX (1) = (*S*)-(+)-2-[2-(Diphenylphosphino)phenyl]-4-phenyl-2-oxazoline; PHOX (2) = (*S*)-(-)-2-[2-(Diphenylphosphino)phenyl]-4-isopropyl-2-oxazoline; PHOX (3) = (*S*)-4-*tert*-butyl-2-[2-(Diphenylphosphino)phenyl]-2-oxazoline



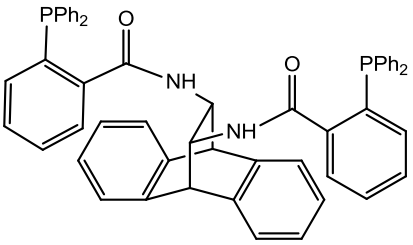
Trost (1) = (*R,R*)-DACH-phenyl Trost



Trost (2) = (*R,R*)-DACH-naphtyl Trost



Trost (3) = (*R,R*)-DACH pyridyl



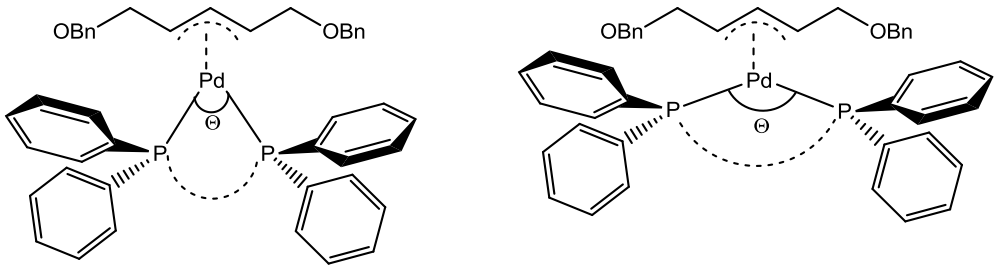
Trost (4) = (*R,R*)-ANDEN-phenyl Trost

Scheme 42: Trost ligands: Trost (1) = (*R,R*)- Trost DACH Phenyl; Trost (2) = (*R,R*)- Trost DACH Naphtyl; Trost (3) = (*R,R*)-Trost Pyridyl; Trost (4) = (*R,R*)-Trost ANDEN

Table 8: Ligands screening with (*E*)-Chloracetate substrate (compound **72**)

Entry	Ligand	Time	Yield[1]	Z/E ratio[2]	ee[3]	
1	(*S*)-PHOX(1)	7 days	84%	6:94	11% (Z)	40% (E)
2	(*S*)-PHOX(2)	7 days	84%	7:93	4% (Z)	33% (E)
3	(*S*)-PHOX(3)	7 days	88%	6:94	3% (Z)	66% (E)
4	(*R,R*)-Trost (1)	3h	84%	15:85	78% (Z)	47% (E)
5	(*R,R*)-Trost (2)	2 days	63%	14:86	30% (Z)	4% (E)
6	(*R,R*)-Trost (3)	-	-	-	-	
7	(*R,R*)-Trost (4)	4h	71%	< 5% (*Z*)	78% (E)	

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.), rt; [1] isolated yield after chromatography; [2] calculated on ^1H NMR; [3] determined by HPLC (Chiralpak AD-H)



Scheme 43: Bite angle comparison[6]

3.3.4 Solvent screening with (*E*)-Chloracetate substrate (compound 72)

The choice of solvent is another parameter which has to be taken into account[88], when performing an allylic substitution since it sometimes strongly influences the rate of the reaction and the ee. The typical solvents used in this reaction are toluene, dichloromethane or more polar solvents such as THF and DMF.

Using the (*E*)-Chloracetate substrate (compound **72**), a solvent screening from non-polar solvents such as toluene to more polar ones like DMF was conducted. Six different solvents were screened: toluene, THF, α,α,α-trifluorotoluene, dichloromethane, DMF, acetonitrile. The results are summarized in table 9.

Table 9: Solvent screening on (*E*)-Chloracetate substrate (compound **72**)

Entry	Solvent	Time	Yield[1]	Z/E ratio[2]	ee[2]
1	Toluene	2h30	63%	3:97	90% (E)
2	THF	7 days	32%	6:94	35% (E)
3	$PhCF_3$	1 day	55%	2 :98	89% (E)
4	CH_2Cl_2	4h	71%	< 5% (Z)	78% (E)
5	DMF	6 days	49%	8:92	53% (E)
6	CH_3CN	2 days	52%	5:95	66% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R*,*R*)-Trost ANDEN (0.24 eq.), $BnNH_2$ (2 eq.), rt; [1] isolated yield after chromatography; [2] determined by HPLC (Chiralpak AD-H)

Results obtained from the polar solvents, CH_3CN and DMF (entry 5 and 6, table 9), were moderate with moderate yield and moderate to low ee's, demonstrating that these solvent are not suitable to our system. Low yield and low ee was observed with THF as solvent (entry 2, table 9). $PhCF_3$ is a relatively new class of solvent used in allylic substitution. It is slightly more polar than THF and slightly less polar then dichloromethane[89]. Improvements of the ee were obtained with $PhCF_3$ (entry 3, table 9) and toluene (entry 1, table 9) but the yields were moderate, probably due to some solubility issues. The solubility in dichloromethane was better than in toluene and the yield was slightly increased compared to toluene with a good ee (entry 4, table 9). Because of solubility issues, dichloromethane was chosen as a standard solvent even though toluene and $PhCF_3$ showed good results. It is noteworthy that the solvent has only a low influence in the *Z*/*E* isomerization keeping it below 10%.

3.3.5 Base screening with (*E*)-Chloracetate substrate (compound 72)

Different bases with different basicity (DMAP, Et_3N, EDIPA, DBU, BSA) were compared under standard reaction conditions and results are summarized in table 10. BSA is frequently used in allylic substitutions. In our case, results (entry 1, table 10) showed moderate yield, moderate ee but low isomerization. Tertiary, non-nucleophilic bases such as *N*-Ethyldiisopropylamine (entry 2, table 10) improved the reaction with shorter reaction time, good yield, high ee and low isomerization. Since the reaction was fast, an experiment at 0°C (entry 3, table 10) was performed to improve the ee and succeeded giving 92% ee. Good results were also obtained with 4-DMAP (entry 4, table 10) but the yield was slightly lower. Similar to EDIPA but slightly less hindered and slightly less basic, results from Et_3N (entry 5, table 10) were as good as those from EDIPA. DBU is a stronger base with a pKa of 12.7 [90]. The results with DBU (entry 6, table 10) showed a low yield with moderate ee probably due to its higher basicity.

Table 10: Base screening on (*E*)-Chloracetate substrate (compound **72**)

Entry	Base	Time	T	Yield[3]	Z/E ratio	ee[5]
1	BSA/NaOAc[1]	36h	rt	67%	2 :98[4,5]	74% (E)
2	EDIPA[2]	1h30	rt	75%	2 :98[5]	85% (E)
3	EDIPA[2]	2h	0°C	70%	1 :99[4,5]	92% (E)
4	4-DMAP[2]	1 day	0°C	59%	only (E)[4,5]	89% (E)
5	Et_3N[2]	3h	0°C	93%	only (E)[4,5]	89% (E)
6	DBU[2]	4 days	0°C to rt	32%	5 :95[4] 6 :94[5]	74% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R,R*)-Trost ANDEN (0.24 eq.), $BnNH_2$ (2 eq.), CH_2Cl_2; [1] BSA (2 eq.), NaOAc (0.032 eq.); [2] base (1 eq.); [3] isolated yield after chromatography; [4] calculated on ^1H NMR; [5] determined by HPLC (Chiralpak AD-H)

From the results summarized in table 10, EDIPA was chosen as the best base for our allylic substitution. To find the best condition for our system and to understand which role the base plays, a screening with different amount of base was performed and is summarized in table 11. With 0.2 eq. of EDIPA, the reaction needs more time and the ee is as good as without the base. Addition of 2 eq. of base, gave results similar to addition of 1 eq. of EDIPA. Therefore 1 eq. of EDIPA was chosen as standard for our system.

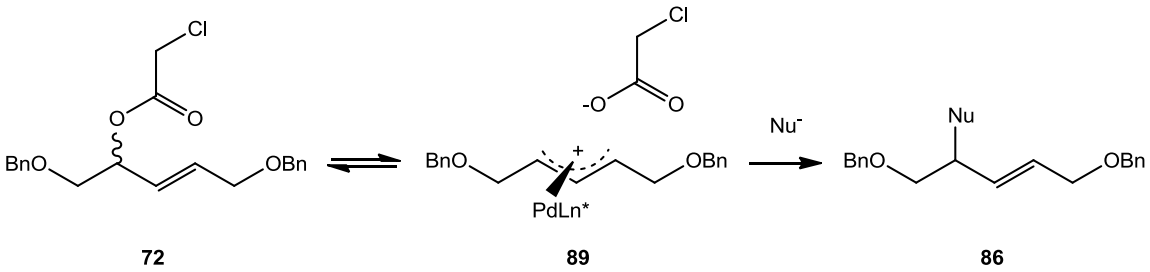
Table 11: Base amount screening on (*E*)-Chloracetate substrate (compound **72**)

Entry	Base	Time	Yield[1]	Z/E ratio[2]	ee[2]
1	EDIPA (0.2 eq.)	4h	75%	1 :99	74% (E)
2	EDIPA (1 eq.)	1h30	75%	2 :98	85% (E)
3	EDIPA (2 eq.)	1h30	82%	2 :98	80% (E)

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R,R*)-Trost ANDEN (0.24 eq.), $BnNH_2$ (2 eq.), CH_2Cl_2, rt; [1] isolated yield after chromatography; [2] determined by HPLC (Chiralpak AD-H)

As seen in the results obtained above, base addition plays an important role in the allylic substitution, shortening the reaction time, improving yield and ee. In the literature, the use of BSA and its role in allylic substitution to generate anionic nucleophile from the conjugated acid in situ with dimethyl malonate is well known[91-92]. This method was invented by Trost[22] and improved the selectivity of the reaction as well as the rate of reaction.

One possible effect the leaving group could have on the reaction is that the acetate ion may play an active role in the catalytic process acting as nucleophile and therefore competing with the poor or stabilized nucleophile (scheme 44)[47]. The low yield without the base could be explained by the fact that the chloracetate ion reacts faster with the cationic palladium system than the nucleophile. Addition of the base would quench the reversibility of the reaction avoiding the leaving group to attack before the nucleophile.



Scheme 44: Reversibility during ionization process

3.3.6 Catalyst

To get an insight into our system, stoichiometric allylic substitutions experiments were performed and followed by NMR measurements which allow the observation of the system in situ. Each step of the reaction was analyzed to get an outline of the mechanism.

For this NMR study, ^{1}H NMR spectra were recorded and the region belonging to the allylic system of the molecule was analyzed (figure 1). Before starting the experiment, spectra of $[Pd(allyl)Cl]_2$ (blue line) and (*R,R*)-Trost ANDEN (dark green line, figure 1) and (*E*)-

Chloracetate substrate (pink line, figure 1) were recorded separately. Addition of the catalyst to the ligand, showed the formation of the Pd complex with disappearance of characteristic peak belonging to ligand and catalyst and with formation of a new set of peaks (grey line, figure 1). Addition of the substrate to the Pd complex after 15min, showed no significant binding of the Pd complex to the allyl system. The allyl system of the substrate and the additional peak belonging to the Pd complex stayed unchanged (light yellow line, figure 1). After addition of EDIPA, the same was observed and no significant change of the substrate could be noticed (light blue line, figure 1). A modification occurred only when $BnNH_2$ was added to the system. A new set of peaks appeared between 5 and 5.25 ppm and new peaks in the allylic region corresponding to product (red line, figure 1). As described in the literature, activation of the palladium-ligand system and coordination of the complex to the substrate occurred only after addition of the nucleophile.

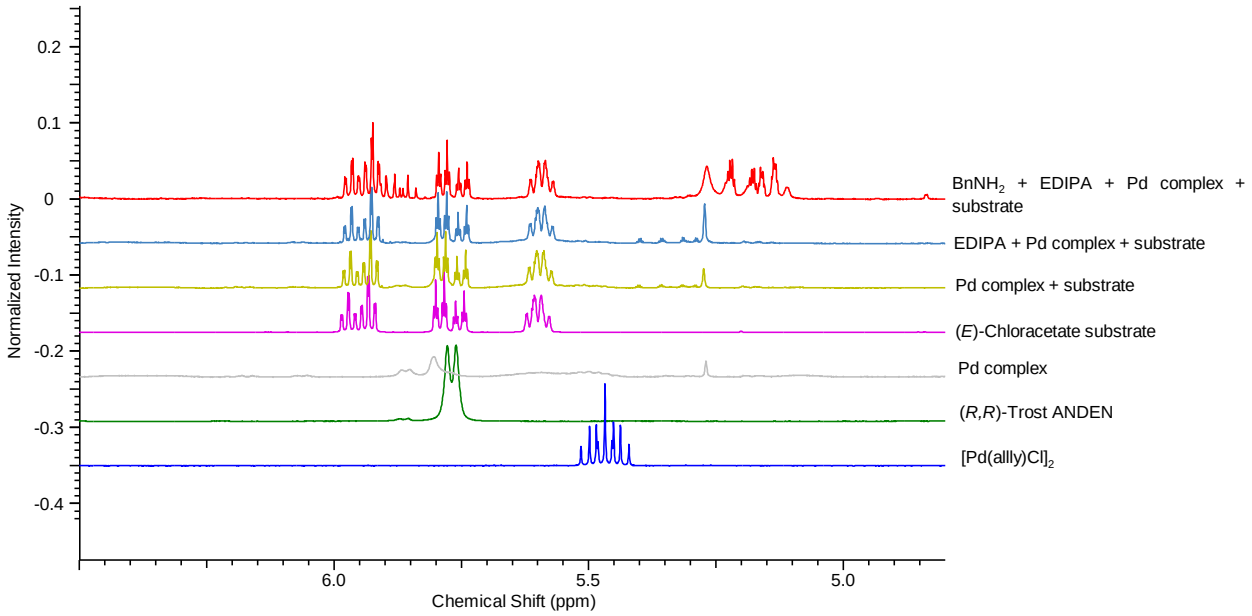
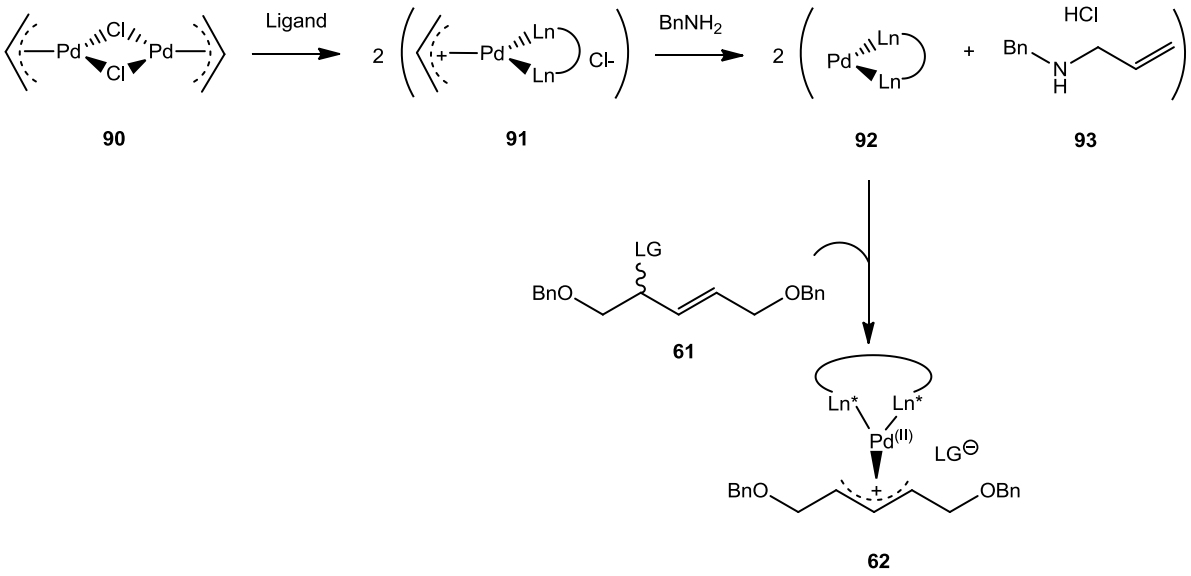


Figure 1: ^1H NMR experiments in $CDCl_3$, at rt and with $BnNH_2$ (2 eq.), $[Pd(allyl)Cl]_2$ (0.5 eq.), (*R*,*R*)-Trost ANDEN (0.72 eq.)

It is known from the literature that $[Pd(allyl)Cl]_2$ in oxidation state +2 is reduced, in situ, to the active catalyst with oxidation state 0 by addition of ligand and nucleophile. Scheme 45 illustrates the mechanism. The halogen-bridged dimer is relatively non-electrophilic[93] and

palladium-ligand complex has first to be formed to increase the electrophilic character of the allyl system. Nucelophile attack allows the formation of the active Pd(0) which is then able to coordinate with the substrate. In our reaction, after formation of the palladium-ligand complex the nucleophile reacts with the allyl group and forms the *N*-Allylbenzylamine hydrochloride. The reactive palladium-ligand is then able to react and form the η^3-allyl complex with the substrate which allows the substitution to occur.



Scheme 45: Activation of the Pd complex through the nucleophile

To prove this mechanism, other NMR (^{1}H and ^{13}C) experiments were performed where $BnNH_2$ was first added to $[Pd(allyl)Cl]_2$ in stoichiometric amount. After 1h, the ligand was added to this mixture and an NMR spectrum was measured (figure 2 and 3).

No significant change on the NMR pattern only a shift of the peaks was observed when benzylamine was added to the catalyst indicating no reaction. This was to expect due to the non-electrophilic character of the halogen-bridged dimer. After addition of (*R*,*R*)-Trost DACH Phenyl ligand, the complex was formed as well as the same set of peaks between 5-5.5 ppm which probably correspond to the allyl system of *N*-allylbenzylamine. Furthermore, 3h

after addition of the ligand, the NMR tube turned black indicating the presence of elemental palladium. Scheme 46 illustrates a possible mechanism.

To confirm our hypothesis, comparison between our reaction mixture after addition of $BnNH_2$ and commercially available *N*-Allylbenzylamine was performed on ^1H NMR (figure 4). The similarity between the spectra comfirms our assumption and *N*-Allylbenzylamine can be listed as a byproduct in our reaction.

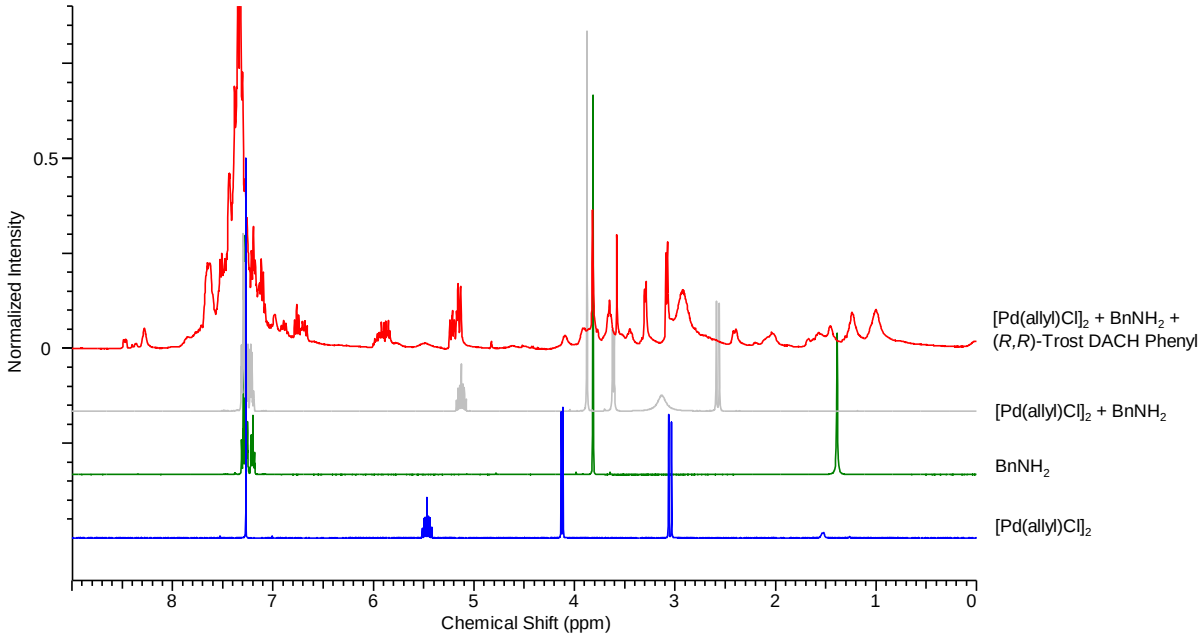


Figure 2: ^1H NMR with $BnNH_2$ (2 eq.) and $[Pd(allyl)Cl]_2$ (0.5 eq.) then addition of (*R*,*R*)-Trost DACH Phenyl (1 eq.)

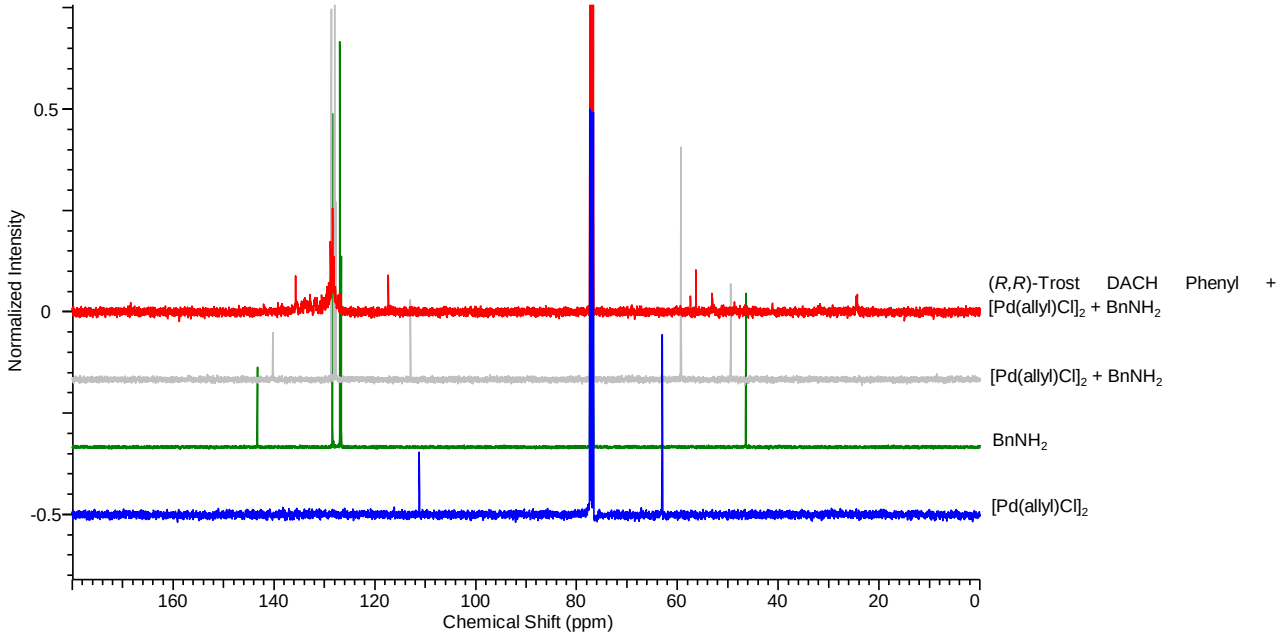
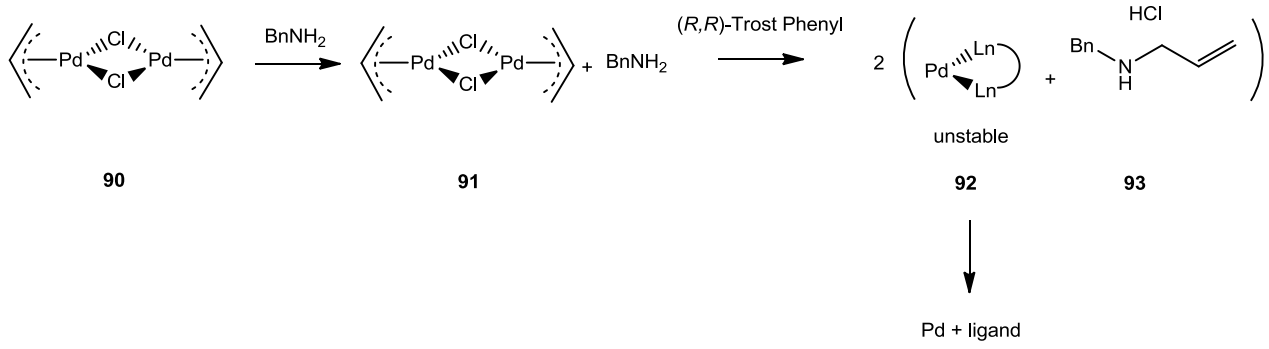


Figure 3: ^{13}C NMR with $BnNH_2$ (2 eq.) and $[Pd(allyl)Cl]_2$ (0.5 eq.) then addition of (*R*,*R*)-Trost DACH Phenyl (1 eq.)



Scheme 46: Formation of *N*-Allyl-Benzylamine hydrochloride after formation of Pd complex

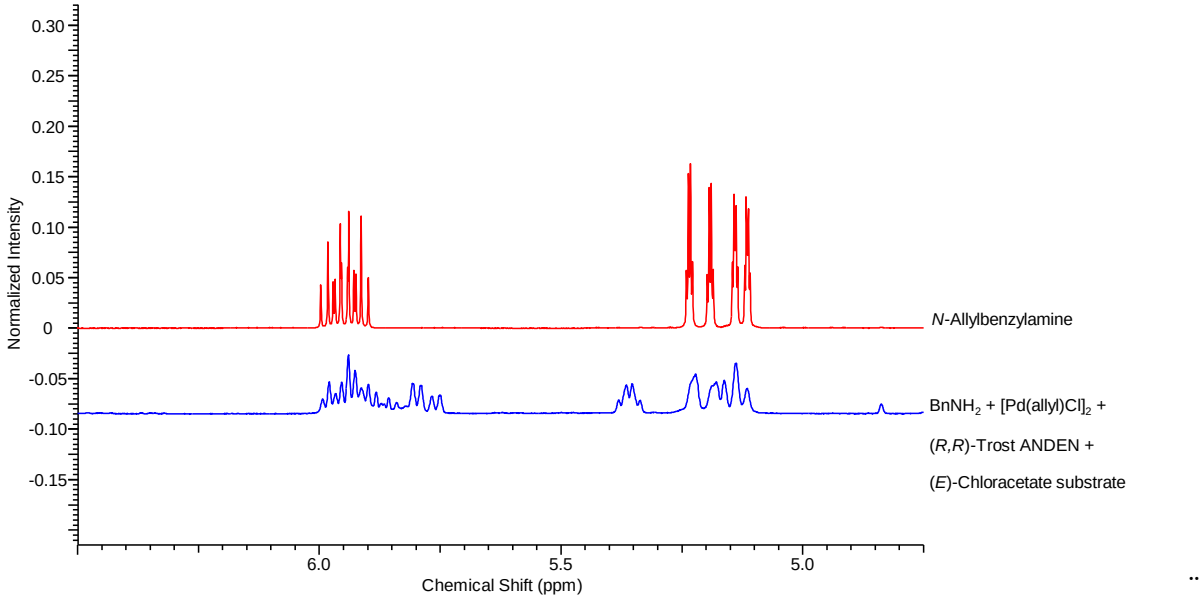


Figure 4: Comparison between reaction mixture and *N*-Allylbenzylamine

3.3.7 Catalyst Loading screening with (*E*)-Chloracetate substrate (compound 72)

On industrial level, a low catalyst loading reduces waste and cost[84]. Nevertheless, even though initial cost of palladium is high, recovery and recycling is possible and easily made. Several experiments on catalyst loading were performed on our system using different conditions (solvent screening and base addition). Toluene, $PhCF_3$ and CH_2Cl_2, our three best solvents, were tested under different catalyst loadings starting from 1 mol% up to 8 mol% with 3 times the amount of ligand respectively. The results are summarized in table 12. In toluene, comparable ee's were observed for 8, 4 and 1 mol % catalyst loading but the yield dropped when 1 mol% was used (entry 1, 2 and 4, table 12). As comparison, Pd(0) was also tested with 4 mol% in toluene and almost exactly the same results were obtained (entry 3, table 12). The screening gave similar results for $PhCF_3$ regarding ee and yield (entry 5, 6 and 7, table 12). At 1.25 mol% and with addition of EDIPA, a drop in the yield was observed. In CH_2Cl_2, the same tendency is observed with a drop of yield but also of ee with 1.25 mol%. The threshold appears to be reached below 2.5 mol%. In our case, the optimal reaction condition in terms of time, yield and ee was given with CH_2Cl_2 and 8 mol% catalyst.

Table 12: Catalyst loading screening with (*E*)-Chloracetate substrate (compound **72**)

Entry	Catalyst[1]	Base	Solvent	T [°C] /Time	Yield[3]	Z/E ratio[4]	ee[4]
1	Pd(II) 8 mol%	-	Toluol	rt/2h30	63%	3:97	90% (E)
2	Pd(II) 4 mol%	-	Toluol	rt/24h	53%	3:97	85% (E)
3	Pd(0) 4 mol%	-	Toluol	rt/24h	55%	4:96	84% (E)
4	Pd(II) 1 mol%	-	Toluol	rt/6 days	35%	2:98	89% (E)
5	Pd(II) 8 mol%	-	$PhCF_3$	rt/24h	55%	2 :98	89% (E)
6	Pd(II) 4 mol%	-	$PhCF_3$	rt/24h	59%	1:99	91% (E)
7	Pd(II) 2.5mol%	-	$PhCF_3$	rt/48h	60%	2:98	91% (E)
8	Pd(II) 1.25 mol%	EDIPA[2]	$PhCF_3$	rt/72h	40%	2 :98	88% (E)
9	Pd(II) 8 mol%	EDIPA[2]	CH_2Cl_2	0/4h30	92%	no (Z)	89% (E)
10	Pd(II) 1.25 mol%	EDIPA[2]	CH_2Cl_2	0/72h	26%	no (Z)	69% (E)

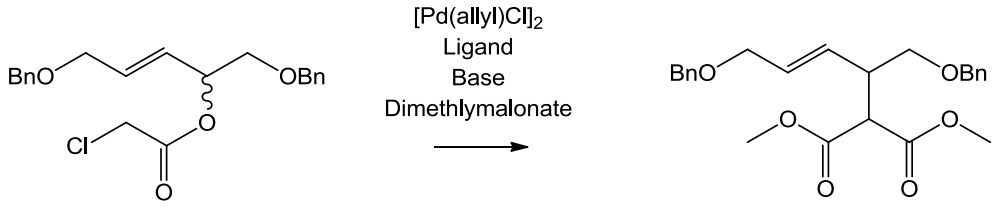
Reaction conditions:, (*R*,*R*)-Trost ANDEN (0.08 eq.), $BnNH_2$ (2 eq.); [1] Pd(II) = $[Pd(allyl)Cl]_2$ and Pd(0) = $[Pd_2(dba)_3]\cdot CHCl_3$; [2] (1 eq.); [3] isolated yield; [4] determined by HPLC (Chiralpak AD-H)

3.3.8 Nucleophile scope with (*E*)-Chloracetate substrate (compound 72)

A broad scope of different nucleophiles can be used in allylic substitutions depending on the desired product. Nevertheless, the nucleophiles are often divided into two different classes of nucleophiles, the soft ("stabilized") - and hard ("unstabilized") nucelophile. The former are derived from conjugate acids with pKa < 25 and the latter from pKa > 25[31]. Normally, overall retention of stereochemistry is observed with soft nucleophiles which add to the allyl system at the opposite side of the metal. On the other hand, inversion of stereochemistry is observed with hard nucleophiles since they undergo a transmetallation where the nucleophile attacks the metal center. In our case, we performed experiments using soft nucleophiles of three different classes: nitrogen, oxygen and carbon (*N*-, *O*-and *C*-nucleophiles).

3.3.8.1 C-nucleophiles

C-nucleophiles were the first to be tested for C-C bond forming substitution reactions. Dimethylmalonate is a standard nucleophile and our first *C*-nucleophile tried on our system (scheme 47). Results are summarized in table 13. With dimethylmalonate as nucleophile, C_2-symmetrical Trost ligands were found to be unsuitable ligands since no reaction was observed with Trost (1) and only traces of product with Trost (4) (entry 2 and 3, table 13). The reaction worked only in the presence of PHOX ligands. The PHOX (2) ligand worked with the best yield and ee when heating at 40°C in CH_2Cl_2 and toluene (entry 5 and 6, table 13). Otherwise the reaction was too slow and incomplete (entry 4, table 13). The reactions with PHOX (1) were faster with good yield but moderate ee's. To improve the ee, the temperature was lowered to 0°C but no significant change could be observed. Different solvents like CF_3Ph and THF were tried but only a drop of the yield could be detected (entry 9 and 10, table 13). Finally, PHOX (3) was tested and the reaction was fast with excellent yield but again moderate ee. Standard reaction conditions with dimethylcarbonate use BSA/NaOAc as base. Reaction with EDIPA (entry 12, table 13) was performed but no reaction could be observed. It is interesting to note that in all cases, no *Z*/*E* isomerization could be observed.



72 **94**

Scheme 47: Allylic subsitution with dimethylmalonate affording compound **94**

Other *C*-nucleophiles such as Meldrum's acid, 1,3-Cyclopentanedione, Dimethyl methylmalonate were tested but no reaction was observed under racemic reaction conditions.

Table 13: Screening with dimethylmalonate

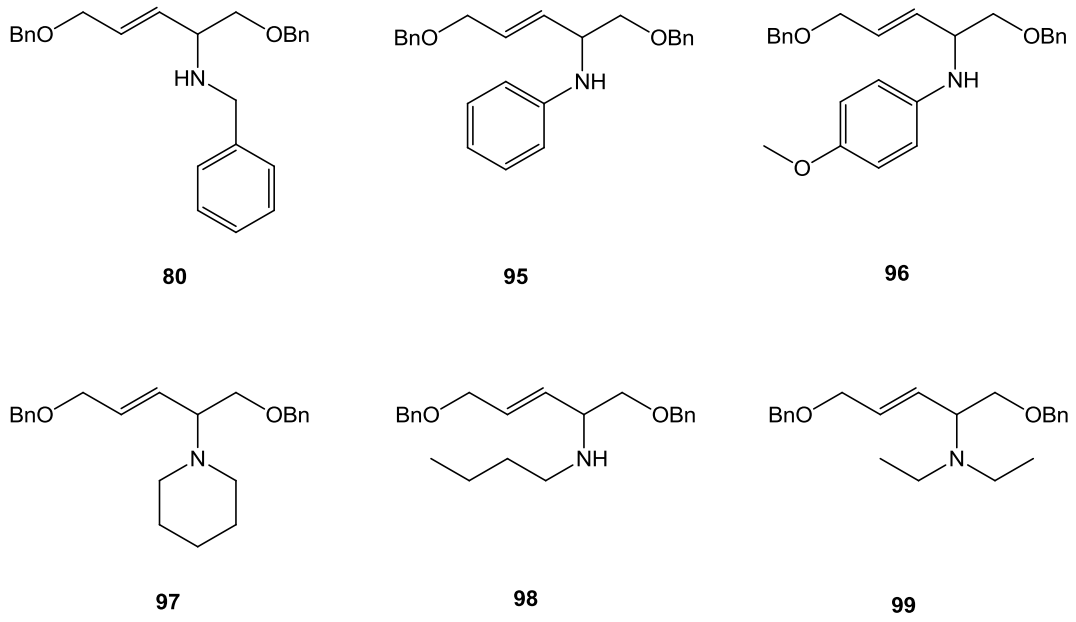
Entry	Ligand	Base	Solvent	T / Time	Yield[3]	Z/E ratio[5]	ee[5]
1	PPh_3	BSA/NaOAc[1]	MED	rt/6h	90%	onyl (E)	-
2	Trost (4)	BSA/NaOAc[1]	MED	rt/24h	-	-	-
3	Trost (1)	BSA/NaOAc[1]	MED	rt/24h	-	-	-
4	PHOX(2)	BSA/NaOAc[1]	MED	rt/6 days	32% [4]	-	-
5	PHOX(2)	BSA/NaOAc[1]	MED	40°C/24h	91%	onyl (E)	71%
6	PHOX(2)	BSA/NaOAc[1]	Toluene	40°C/48h	81% [4]	onyl (E)	77%
7	PHOX(1)	BSA/NaOAc[1]	MED	rt/5h30	88%	onyl (E)	64%
8	PHOX(1)	BSA/NaOAc[1]	MED	0 °C/ 24h	92%	onyl (E)	65%
9	PHOX(1)	BSA/NaOAc[1]	$PhCF_3$	0°C to rt/48h	61% [4]	onyl (E)	65%
10	PHOX(1)	BSA/NaOAc[1]	THF	0°C/72h	46% [4]	onyl (E)	66%
11	PHOX(3)	BSA/NaOAc[1]	MED	rt/3h30	95%	onyl (E)	61%
12	PHOX(3)	EDIPA[2]	MED	rt /24h	-	-	-

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), compound **72** (1 eq.); [1] BSA (2 eq.), NaOAc (0.032 eq.); [2] EDIPA (1 eq.); [3] isolated yield; [4] HPLC conversion; [5] determined by HPLC on a chiral stationary phase

3.3.8.2 N-nucleophiles

The enantioselective allylic amination is a well-established process and several examples using primary and secondary amines are well-known[94]. The obtained allylic amine and derivatives are interesting compounds for further functionalization and are key steps for amino sugars, pyrroles etc. A wide range of different *N*-nucleophiles was used in our system: primary and secondary aryl amines, primary and secondary alkyl amines etc. leading to a vast library of different allylic amine products in good yield and acceptable ee.

A first range of six different *N*-nucleophiles, $BnNH_2$, aniline, m-anisidine, piperidine, diethylamine and butylamine, was screened under different conditions with the three best solvents CH_2Cl_2, toluene and $PhCF_3$ to afford the desired products (scheme 48). The results are summarized in table 14.



Scheme 48: Products from allylic substitutions with different *N*-nucleophiles

Table 14: First *N*-nucleophiles screening

Entry	Nucleophile	Solvent	Time	Yield[2]	Z/E ratio[4]	ee[4]
1	$BnNH_2$	CH_2Cl_2	4h30	92%	only (E)	89% (E)
2	$BnNH_2$[1]	CH_2Cl_2	72h	72%	2:98	82% (E)
3	$BnNH_2$	Toluene	3h	88%	3 :97	86% (E)
4	$BnNH_2$	CF_3Ph	20min	93%	1:99	91% (E)
5	Aniline	CH_2Cl_2	45min	95%	only (E)	89% (E)
6	Aniline[1]	CH_2Cl_2	24h	84%	3:97	40% (E)
7	Aniline	Toluene	20min	92%	only (E)	86% (E)
8	Aniline	CF_3Ph	15min	quant	only (E)	93% (E)
9	p-Anisidin	CH_2Cl_2	20min	97%	only (E)	88% (E)
10	p-Anisidin[1]	CH_2Cl_2	1h	90%	4:96	26% (E)
11	p-Anisidin	Toluene	10min	99%	6:94	87% (E)
12	p-Anisidin	CF_3Ph	10min	quant	1:99	92% (E)
13	Piperidine	CH_2Cl_2	1h	82%	<2% (Z)	47% (E)
14	Piperidine	Toluene	7h	65%	only (E)	81%(E)
15	Piperidine	CF_3Ph	29h	51% [3]	only (E)	28% (E)
16	Butylamine	CH_2Cl_2	24h	21%	only (E)	74% (E)
17	Butylamine	Toluene	1h30	90%	3:97	88% (E)
18	Butylamine	CF_3Ph	20min	86%	only (E)	88%(E)
19	Diethylamine	CH_2Cl_2	3h	86%	2:98	19% (E)
20	Diethylamine	Toluene	6h30	64%	4:96	88% (E)
21	Diethylamine	CF_3Ph	20min	69%	2:98	41% (E)

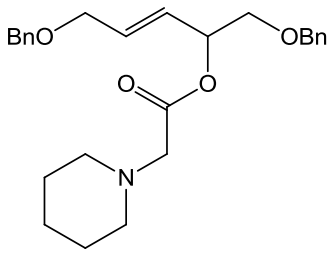
Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R*,*R*)-Trost ANDEN (0.24 eq.), compound **72** (1 eq.), EDIPA (1 eq.), 0°C;
[1]without base and at rt; [3] 25% yield of byproduct **100**; [4] determined by HPLC on a chiral stationary phase

Excellent results were obtained with primary aryl amines such as benzylamine, aniline, p-anisidine with excellent yields and good to excellent ee (entry 1-12, table 14). Noteworthy, in reactions without a base (entry 2, 6 and 10, table 14) the conversion was complete but the ee dropped dramatically underlining the role of the base in the enantioselective process. Reactions with piperidine gave moderate ee in CH_2Cl_2 and $PhCF_3$ (entry 13 and 15, table 14)

but good ee in toluene (entry 14, table 14). Good results were obtained from alkyl amines such as butylamine in toluene and CF_3Ph (entry 17 and 18, table 14) but the yield decreased when the reaction was performed in CH_2Cl_2 (entry 16, table 14). Diethylamine worked best in toluene (entry 20, table 14) while CH_2Cl_2 and $PhCF_3$ showed a decrease in ee (entry 19 and 21, table 14).

The substitution with benzylamine as a nucleophile in dichloromethane as solvent was repeated on a 2g scale resulting in the same result in terms of ee and yield as on a small scale.

During the allylic substitution with piperidine, chloracetate reacted with piperidine to afford byproduct **100** (scheme 49 and entry 15, table 14) which was isolated and characterized.

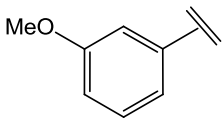


100

Scheme 49: Byproduct **100**

Results from the initial *N*-nucleophile screening showed that the primary aryl amines are good nucleophiles for our system. Therefore a second set of screening was performed with different aryl nucleophiles bearing electron withdrawing groups or electron donating groups and with an increased sterical demand. Results are summarized in scheme 50.

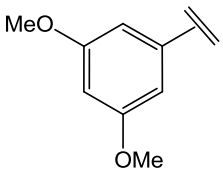
3-methoxyphenyl



2h, only (E)
yield = 83%, ee = 91%

101

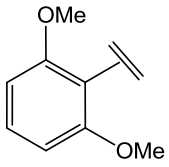
3,5-dimethoxyphenyl



2h, only (E)
yield = 67%, ee = 94%

102

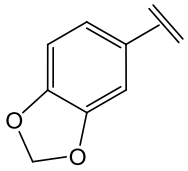
2,6-dimethoxyphenyl



3h30, only (E)
yield = 89%, ee = 97%

103

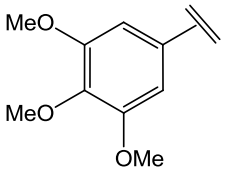
3,4-(methylendioxy)phenyl



1h, Z:E = 1:99
yield = 84%, ee = 90%

104

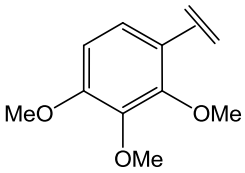
3,4,5-trimethoxyphenyl



3h, only (E)
yield = 93%, ee = 97%

105

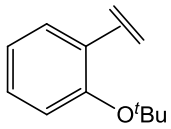
2,3,4-trimethoxyphenyl



1h30, only (E)
yield = 95%, ee = 96%

106

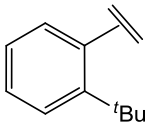
2-(*tert*-butoxy)phenyl



4 days, Z:E = 1:99
yield = 60%, ee = 89%

107

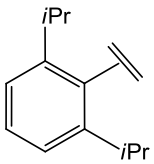
2-*tert*-butylphenyl



5h, only (E)
yield = 92%, ee = 97%

108

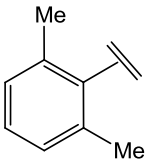
2,6-diisopropylphenyl



5 days, only (E)
yield = 47%, ee = 92%

109

2,6-dimethylphenyl



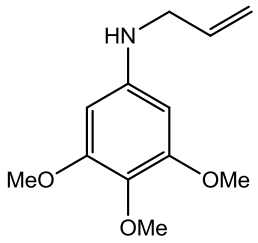
5h, only (E)
yield = 89%, ee = 97%

110

Scheme 50: Secondary aryl amine screening with the reaction conditions of $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R*,*R*)-Trost ANDEN (0.24 eq.), compound **72** (1 eq.), EDIPA (1 eq.), 0°C, CH_2Cl_2

For all these *N*-nucleophiles, excellent ee's and yields were obtained except for (2,6-diisopropylphenyl)amine which is probably due to the steric hindrance caused by the isopropyl group next to the amine.

During allylic substitution with 3,4,5-trimethoxyaniline, byproduct **111** was isolated (scheme 51). Depending on the nucleophile, the corresponding *N*-allyl products were then identified on LC-MS during allylic substitutions.

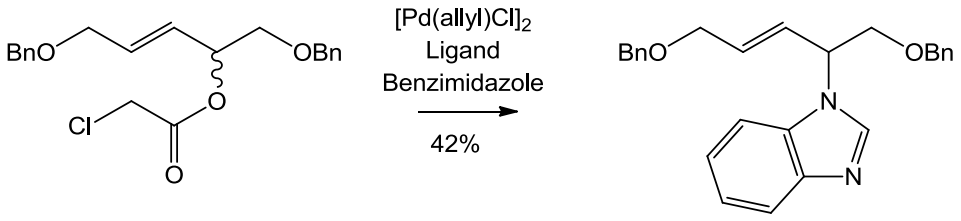


111

Scheme 51: Byproduct **111**

3.3.8.2.1 Benzimidazole, Indole and Me-indole as *N*-Nucleophiles

Allylic substitutions with a new class of *N*-nucleophiles were performed: benzimidazole, indole and Me-indole (scheme 52). The results are summarized in table 15. Reactions with such aromatic hetereocycles worked only with benzimidazole (entry 1-3, table 15) but with poor yield and ee (entry 2 and 3, table 15). Reaction of entry 3 was performed in CF_3Ph and side product **113** (scheme 53) was isolated in 11% yield. It is noteworthy that *Z*/*E* isomerization was minimized when (*R*,*R*)-Trost ANDEN was used compared to PPh_3 as ligand. Unfortunately, no reactions were observed with indole and Me-indole (entry 3 and 4, table 15) and the starting materials were recovered. Nevertheless, such products are interesting compounds and improvement of the reaction might be possible in future.



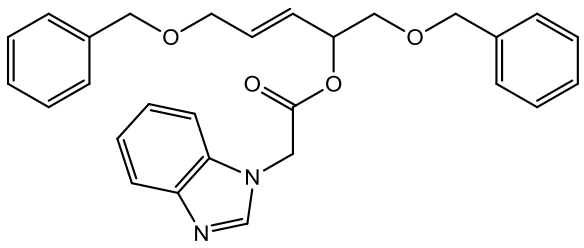
72 **112**

Scheme 52: Allylic substitution on compound **72** with benzimidazole as nucleophile.

Table 15: Screening with benzimidazole, indole and 2-methylindole as nucleophile and (*E*)-Chloracetate substrate (compound **72**)

Entry	Nucleophile	Ligand	Time	Yield[3]	Z/E ratio[4]	ee[4]
1	Benzimidazole	PPh_3	24h	88%	26:74	-
2	Benzimidazole	Trost(4)	5 days	42%	4:96	32%
3[1]	Benzimidazole	Trost(4)	5 days	36%	5:95	10%
4[2]	Indole	PPh_3	72h	-	-	-
5[2]	2-methylindole	PPh_3	72h	-	-	-

Reaction conditions: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), EDIPA (1 eq.), CH_2Cl_2, rt; [1] reaction conducted in CF_3Ph; [2] recovery of starting material; [3] yield after chromatography columns; [4] determined by HPLC (Chiralpak AD-H)



113

Scheme 53: Byproduct **113**

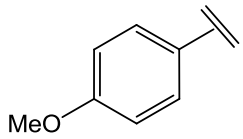
3.3.8.3 O-Nucleophiles

Oxygen nucleophiles are not commonly used in allylic substitutions since they are poor nucleophiles. However, aryloxides have been used as nucleophiles for the Tsuji-Trost reaction. Methods for the asymmetric installation of C-O bonds and the allylic ether products which are obtained are therefore very interesting. We investigated the allylic subsitution of several aryloxides on our system and the results are summarized in scheme 54.

In terms of yield and ee, nice results were obtained with 3,4-dimethoxyphenol and its "homologues" 3,4-(methylendioxy)phenol and 4-methoxyphenol. Yields for 3,5-dimethoxyphenol, 2,5-dimethoxphenol, 2-*t*ert-butyl-4-hydroxyanisole, and 2,6-dimethoxyphenol were moderate but good ee's were obtained. Steric hindrance, combined

with poor nucleophilicity may be the cause of these results. Reactions with 3,4,5-trimethoxyphenol and 2,6-di-*tert*-butyl-4-methoxyphenol were unsuccessful probably due to steric hindrance and low nucleophilicity. Nevertheless, these results show that in general phenolic *O*-nucleophiles are suitable on this system.

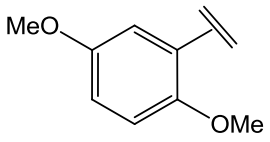
4-methoxyphenyl



2h, only (E)
yield = 78%, ee = 86%

114

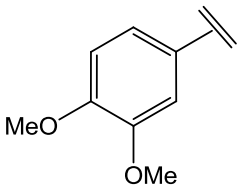
2,5-dimethoxyphenyl



24h, only (E)
yield = 45%, ee = 90%

115

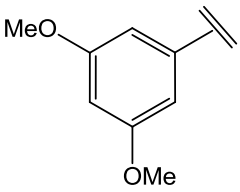
3,4-dimethoxyphenyl



6h, only (E)
yield = 77%, ee = 87%

116

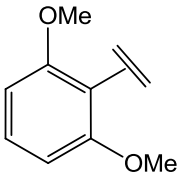
3,5-dimethoxyphenyl



3h30, only (E)
yield = 49%, ee = 81%

117

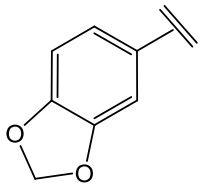
2,6-dimethoxyphenyl



48h, only (E)
yield = 32%, ee = 92%

118

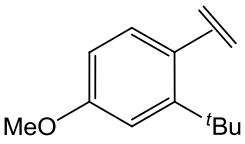
3,4-(methylendioxy)phenyl



6h30, Z:E = 3:97
yield = 83%, ee = 79%

119

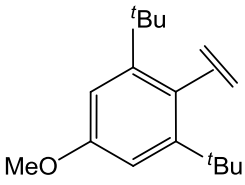
2-^{t}Bu-4-hydroxyanisole



4 days, only (E)
yield = 11%, ee = 82%

120

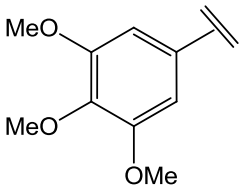
2,6-di-^{t}Bu-4-methoxyphenyl



SM recovery

121

3,4,5-trimethoxyphenyl

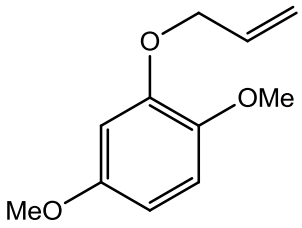


SM recovery

122

Scheme 54: *O*-nucleophile screening with the reaction conditions of $[Pd(allyl)Cl]_2$ (0.08 eq.), (*R*,*R*)-Trost ANDEN (0.24 eq.), compound **72** (1 eq.), EDIPA (1 eq.), 0°C, CH_2Cl_2

During allylic substitutions with 2,5-dimethoxyphenole, byproduct **123** was isolated (scheme 55). Depending on the nucleophile, the corresponding *O*-allyl products were then identified on LC-MS during allylic substitutions.

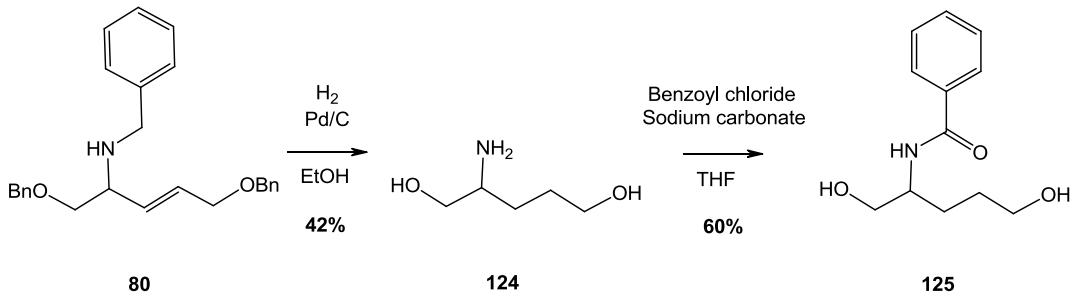


123

Scheme 55: Byproduct **123**

3.4 Determination of the absolute configuration

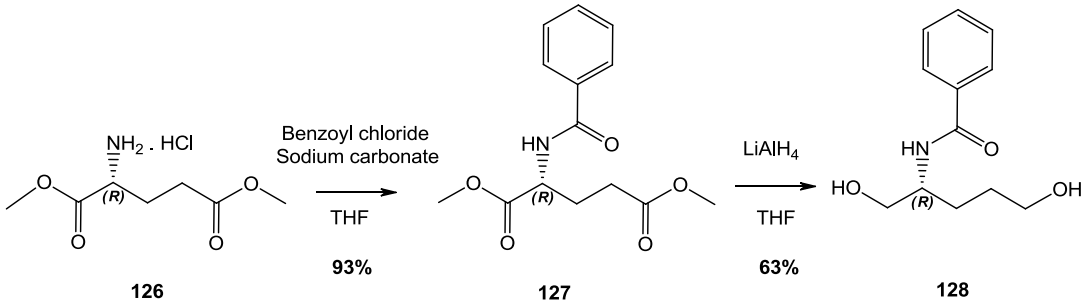
To determine the absolute configuration of our allylic amine products, derivatization to a known compound was necessary. For each obtained allylic amine, the oily-liquid consistency was troublesome and several crystallization attempts were unsuccessful. Fortunately, a way was found to overcome this problem. In the literature, *N*-(1,5-dihydroxypenta-2-yl)benzamide is known and has been characterized[95-96]. Therefore, our substitution product was derivatized into compound **125** (scheme 56). The synthesis started from the hydrogenation of benzylamine substitution product **80** with H_2, Pd(C) in EtOH to afford **124** (42% yield) which was followed by coupling with benzoyl chloride to afford the crystalline compound **125** (60% yield)



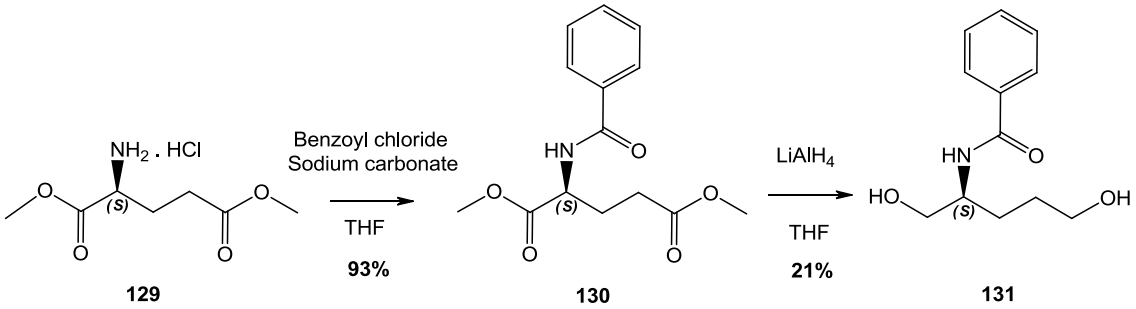
Scheme 56: Substitution product derivatization to compound **125**

At the same time, optically pure compounds were synthesized according to scheme 57 and 58 Starting from commercially available H-*D*-glu(OMe)-OMe·HCl (**126**) (scheme 57) respectively H-*L*-glu(OMe)-OMe·HCl (**129**) (scheme 58), coupling with benzoyl chloride afforded the carbamate compounds **127** (93% yield) and **130** (93% yield) respectively. Desired products **128** and **131** were obtained by reduction with $LiAlH_4$ in 63% yield respectively 21% yield. Optical rotation as well as assignment of the HPLC peaks of the enantiomers was made possible with the optically pure compounds. The comparison of the results allowed us to determine the absolute configuration of our major enantiomer from the allylic substitution which was defined as (*R*), see table 16 and figure 5. The absolute

configurations of the other allylic amines were not determined experimentally. However, supposing an analoguous mechanism of the reaction they were assumed to be (*R*).



Scheme 57: Synthesis of optically pure (*R*)-*N*-(1,5-dihydroxypenta-2-yl)benzamide **128**



Scheme 58: Synthesis of optically pure (*S*)-*N*-(1,5-dihydroxypenta-2-yl)benzamide **131**

Table 16: Optical activity and melting point of *N*-benzoyl-Glu-(OCH_3)

	Compound 125	***N*-Benzoyl-D-Glu-(OCH_3)**	***N*-Benzoyl-L-Glu-(OCH_3)**
$[\alpha]^{20}_D$ (c=0.01,MeOH)	+27	+33	-34.5
m_p [°C]	104.4 - 106.2	106.4 – 109.4	106.5 – 107.4

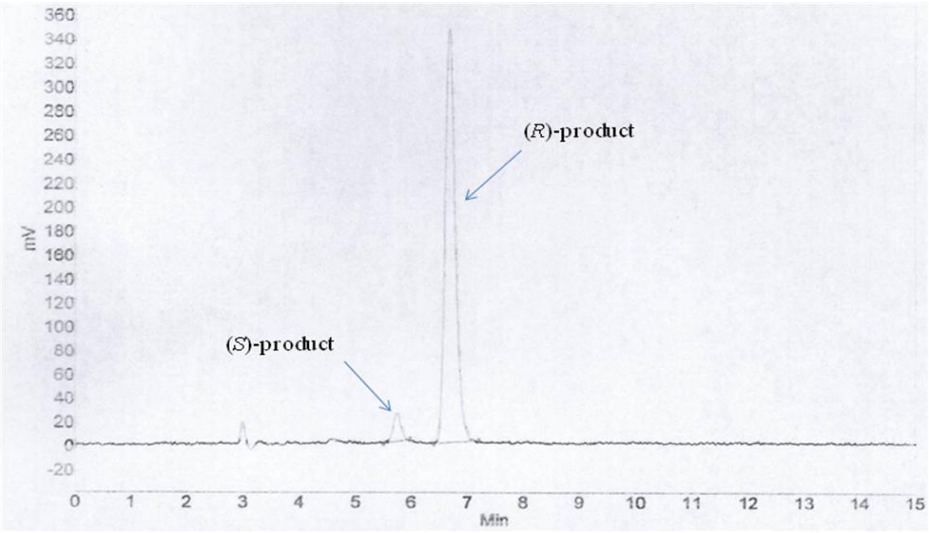


Figure 5: Chromatogram of compound **125**

A comparison of the reaction with different ligands is summarized in table 17. All products with the different (*S*)-PHOX ligands were determined as (*R*). Absolute configurations from products with (*R*,*R*)-Trost (1) and (*R*,*R*)-Trost (2) were established as (*S*). Products from (*R*,*R*)-Trost (4) were of the (*R*)-configuration.

Table 17: Comparison of the absolute configurations with different ligands

Ligand	**Yield**[2]	**ee**[3]	**Abs. conf.**[4]
(*S*)-PHOX(1)	84%	40% (E)	(*R*)
(*S*)-PHOX(2)	84%	33% (E)	(*R*)
(*S*)-PHOX(3)	88%	66% (E)	(*R*)
(*R*,*R*)-Trost(1)	84%	47% (E)	(*S*)
(*R*,*R*)-Trost(2)	63%	4% (E)	(*S*)
(*R*,*R*)-Trost(4)[1]	92%	89% (E)	(*R*)

Reaction condition: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.), CH_2Cl_2, rt; [1] with EDIPA (1 eq.), 0°C; [2] isolated yield; [3] determined by HPLC on chiral stationary phase; [4] determined by derivatization

To see if *O*-nucleophiles react in an analogous manner as *N*- and *C*-nucleophiles, an experiment was performed with the (*R,R*)-Trost DACH Phenyl and compared with (*R,R*)-Trost ANDEN experiment. Results are summarized in table 18. HPLC analyses showed that the major enantiomers from (*R,R*)-DACH Phenyl and (*R,R*)-Trost ANDEN, are of opposite configuration. The same result was obtained with $BnNH_2$ as nucleophile. Therefore, the reaction behavior being similar between *N*- and *O*-nucleophiles and based on the mechanism of the reaction, an analogy could be envisaged for the absolute configuration.

Table 18: Absolute configuration comparison between *N*- and *O*-nucleophile

Entry	Ligand	Nucleophile	Yield[4]	ee[5]	Abs. conf.[6]	Comment
1[1]	(*R,R*)-Trost(1)	$BnNH_2$	58%	52% (E)	(*S*)	major enantiomer opposite to entry 2
2[1]	(*R,R*)-Trost(4)	$BnNH_2$	92%	89% (E)	(*R*)	major enantiomer opposite to entry 1
3[2]	(*R,R*)-Trost(1)	*p*-methoxy -phenol	33%	18%	-	major enantiomer opposite to entry 4
4[3]	(*R,R*)-Trost(4)	*p*-methoxy-phenol	86%	89%	-	major enantiomer opposite to entry 3

Reaction condition: $[Pd(allyl)Cl]_2$ (0.08 eq.), ligand (0.24 eq.), $BnNH_2$ (2 eq.), EDIPA (1 eq.), CH_2Cl_2; [1] at 0°C; [2]at rt; [3]0°C to rt; [4] isolated yield; [5] determined by HPLC on chiral stationary phase; [6] determined by derivatization

3.4.2 Reaction of (*E*)-Chloracetate compound 72 with (*S,S*)-Trost ANDEN and $BnNH_2$ as *N*-nucleophile

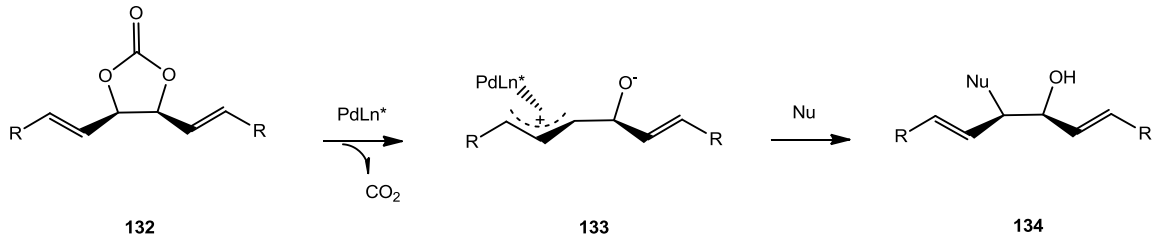
The advantage of the Trost ligands is that the (*R,R*)- and (*S,S*)-forms are commercially available. Therefore, (*R,R*) or (*S,S*) Trost ligands can be used leading to the synthesis of corresponding enantiomers. A reaction with (*S,S*)-Trost ANDEN as ligand was performed under the same reaction conditions as with (*R,R*)-Trost ANDEN as ligand to synthesize the opposite enantiomere. The following reaction conditions were used: $BnNH_2$ (2 eq.) as

nucleophile, $[Pd(allyl)Cl]_2$ (0.08 eq.) as catalyst, (*S*,*S*)-Trost ANDEN (0.24 eq.) as ligand, EDIPA (1 eq.) as base, CH_2Cl_2 as solvent and at 0°C. The product was isolated in 97% yield with 86 % ee (*E*) with (*S*)-product as major enantiomere. This results confirms that under the same reaction conditions as with (*R*,*R*)-Trost ANDEN (entry 3, table 18) the opposite enantiomere was isolated with similar yield and ee.

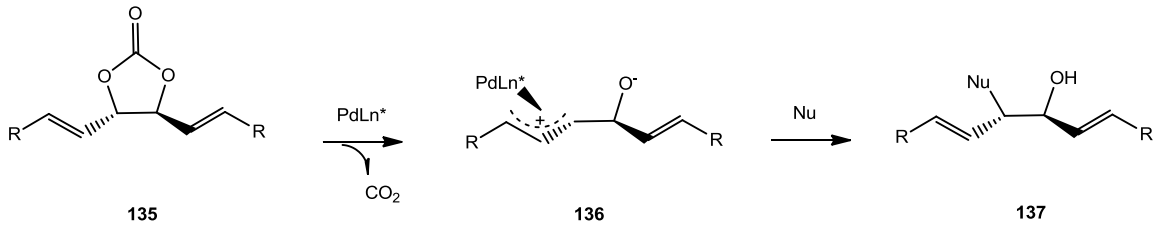
3.5 Allylic substitutions on dimeric substrates

Palladium catalyzed asymmetric allylic substitution on meso or racemo compounds such as **132** (scheme 59) and **135** (scheme 60) enable to obtain products such as **134** and **137** which offer the possibility to be derivatized into a broad range of different target compounds. The idea was to perform a palladium catalyzed allylic substitution on a symmetric system where the leaving group enables to differentiate the double bonds and where the chirality of the Pd-ligand complexe induces the enantioselective nucleophilic substitution. As illustrated in scheme 59 and 60, the coordination of palladium to the allylic system, opens the cyclic carbonate (leaving group), inducing decarboxylation. The regioselectivity of the nucleophilic attack would be determined by the palladium-ligand complex.

In 2006, Trost et al.[97] published the asymmetric allylic alkylation of meso and dl-1,2-divinylethylene carbonate and observed a palladium catalyzed DYKAT (dynamic catalytic asymmetric transformation) yielding one stereoisomer product in excellent ee[98-99]. These good results encouraged us to deepen the study on allylic substitution to our compound bearing functionalized groups on each end of the molecule. In our study, four different substrates were synthesized: A meso compound bearing ester- and benzylether functional groups and racemo compounds bearing ester- and benzylether functional groups.



Scheme 59: Allylic substitution on meso compounds

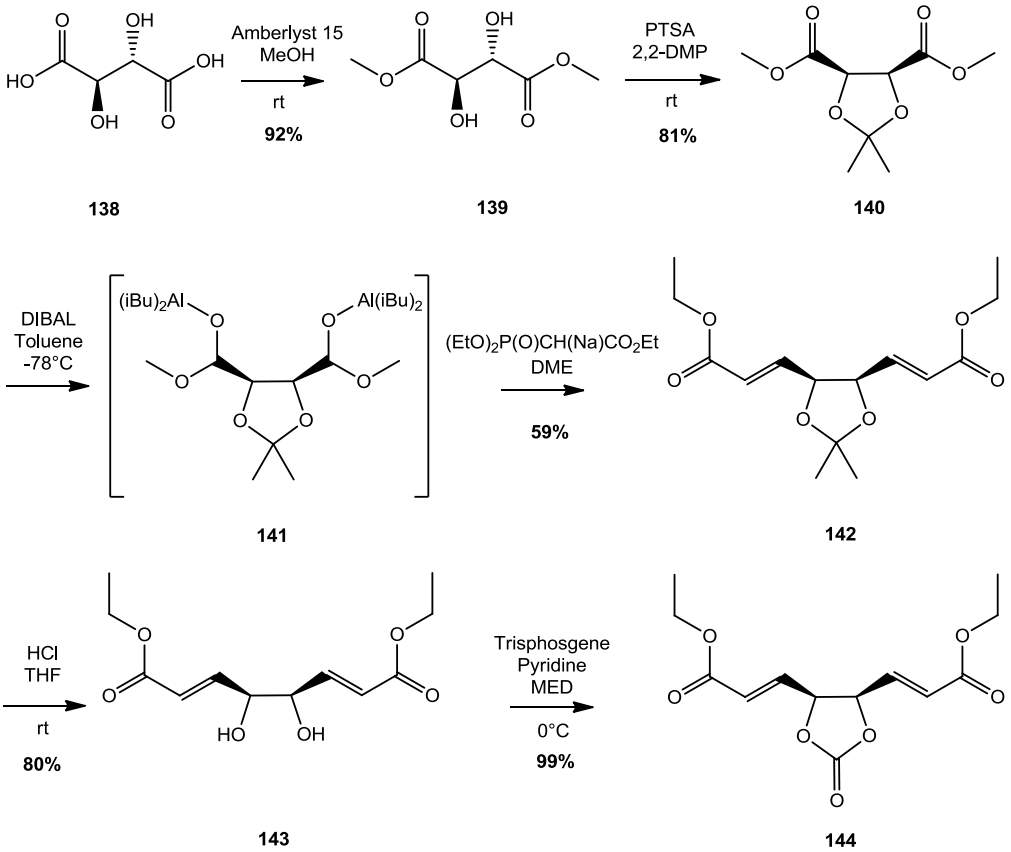


Scheme 60: Allylic substitution on racemo compounds

3.5.1 Meso diester compound

3.5.1.1 Substrate synthesis

The meso diester compound **144** was synthesized according to scheme 61. Commercially available meso-tartaric acid monohydrate (**138**) was converted into dimethyl ester with Amberlyst 15[100] in MeOH to obtain compound **139** in 92% yield. Diol **139** was protected with 2,2-Dimethoxypropane and *p*-toluensulfonic acid monohydrate[101] to afford compound **140** in 81% yield. Compound **142** was obtained from compound **140** by reduction with DIBAL followed by a Horner-Wardsworth-Emmons reaction in one pot reaction[102] and in 59% yield. **142** was deprotected with HCl[103] to afford **143** in 80% yield. The cyclic carbonate product **144** was obtained in 99% yield from reaction of compound **143** with trisphosgene[104] in MED.

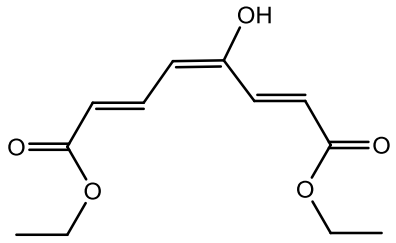


Scheme 61: Synthesis of meso diester compound **144**

*3.5.1.2 Allylic substitutions on meso diester (compound **144**)*

Allylic substitutions with substrate **144** were performed under different reaction conditions (table 19) with different ligands, nucleophiles and bases. In almost all cases, elimination product **145** (scheme 62) was observed. This product is not stable and decomposes after a while. In one case, with (*R,R*)-Trost naphtyl ligand (entry 4, table 19), no reaction and recovery of starting material was observed. In entry 5 and 7 (table 19), the reaction was performed without nucleophile, with and without base, and elimination product was detected indicating that *β*-hydride elimination occurred without participation of the nucleophile. On the other hand, no elimination was observed without palladium-ligand complex and with nucleophile (entry 12, table 19), some carbamate was also formed, indicating that the substrate is not very stable. Some byproducts were detected on HR-MS which were oligomers such as shown in scheme 63.

The ester functionality could be the reason for the instability of the substrate but *β*-hydride elimination product probably occurs due to the meso conformation of the cyclic carbonate unit and due to the presence of the palladium catalyst. Scheme 64 shows a possible mechanism of the elimination reaction. Kang et al.[105] noticed a similar behavior of palladium(0) on cyclic carbonates which undergo elimination to form dienols. These results could explain why in our system, *β*-hydride elimination is observed.



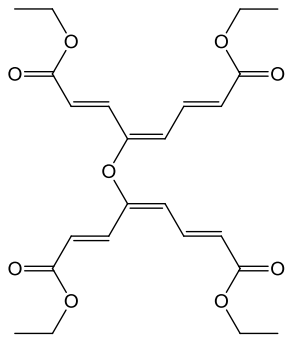
145

Scheme 62: Elimination product **145**

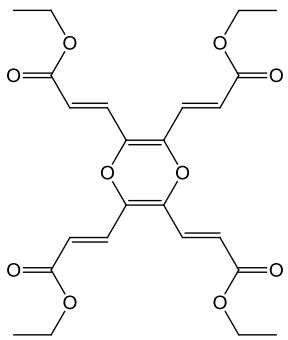
Table 19: Allylic substitutions on meso diester substrate (compound **144**)

Entry	Ligand	Pd source	Nucleophile	Base	Comment
1	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	Dimethylmalonate	BSA/NaOAc	elimination
2	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	*p*-Methoxyphenol	Na_2CO_3	elimination
3	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	Phthalimide	Cs_2CO_3	elimination
4	(*R*,*R*)-Trost(2)	$[Pd(allyl)Cl]_2$	Phthalimide	Na_2CO_3	no reaction
5	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	-	Cs_2CO_3	elimination
6	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	$BnNH_2$	-	elimination
7	(*R*,*R*)-Trost(1)	$[Pd(allyl)Cl]_2$	-	-	elimination
8[1]	PHOX(2)	$[Pd(allyl)Cl]_2$	$BnNH_2$	-	elimination
9	PPh_3	$[Pd(allyl)Cl]_2$	Phthalimide	Na_2CO_3	elimination
10	PPh_3	$[Pd(allyl)Cl]_2$	Aniline	-	elimination
11	PPh_3	$[Pd(allyl)Cl]_2$	$BnNH_2$	-	elimination
12	-	-	$BnNH_2$	-	recovery SM + some carbamate

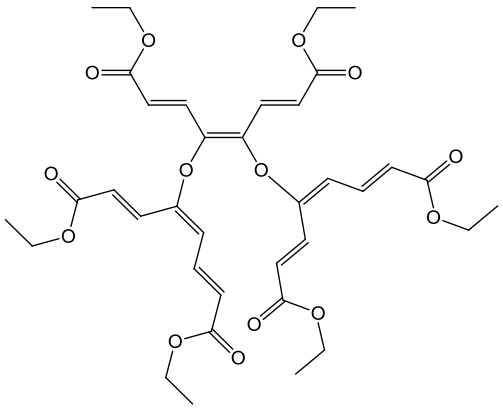
Reaction conditions: Pd catalyst (0.08 eq.), ligand (0.24 eq.), nucleophile (2 eq.), base (1 eq.), CH_2Cl_2, rt



146



147



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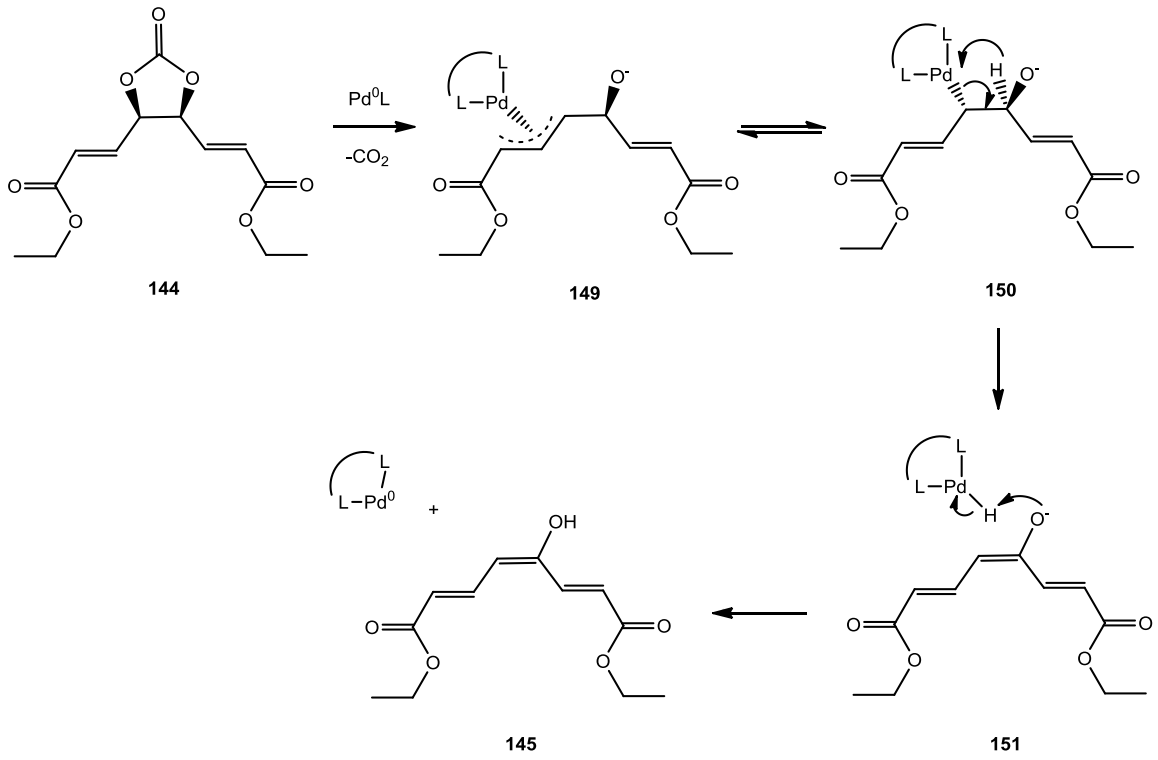
Scheme 63: Oligomers detected by HR-MS and possible structures

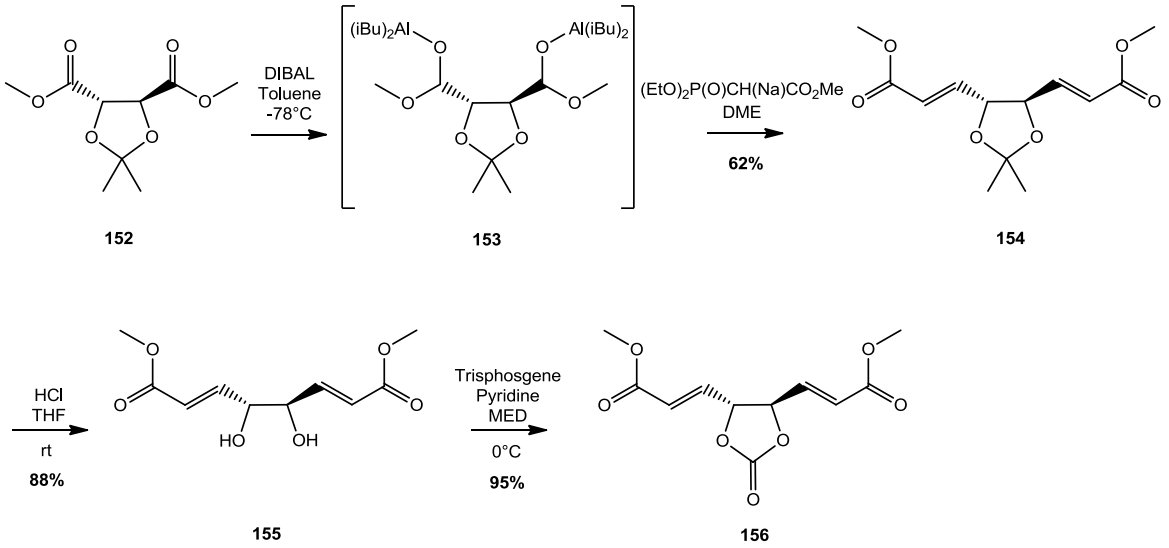


Scheme 64: *β*-hydride elimination on the meso diester substrate (compound **144**)

3.5.2 Racemo diester compound

3.5.2.1 Substrate synthesis

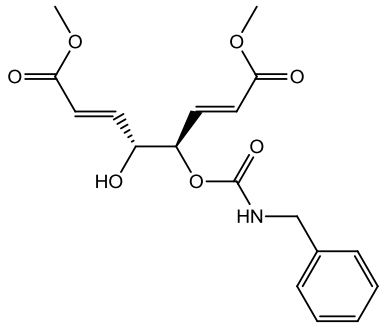
To overcome the *β*-hydride elimination, racemo dimeric ester substrate **156** was synthesized (scheme 65). The procedure was the same as for the meso diester compound **144** except that (+)-dimethyl 2,3-O-isopropylidene-*D*-tartrate (**152**) is commercially available. Reduction with DIBAL followed by Horner-Wardsworth-Emmons reaction afforded compound **154** in 62%. Diol deprotection afforded compound **155** in 88% yield. Protection with trisphosgene gave compound **156** in 95% yield.



Scheme 65: Synthesis of racemo diester substrate (compound **156**)

*3.5.2.2 Allylic substitutions on racemo diester (compound **156**)*

Allylic substitutions under various reaction conditions were performed and the results are summarized in table 20. By LC-MS, product formation could be detected, but isolation of the product was difficult and decomposition was observed (entry 1-3, table 20). The carbamate product **157** (scheme 66) was isolated with only $BnNH_2$ (entry 4, table 20) in 59% yield. The formation of the carbamate **157** was also detected with Trost (4) as ligand and $Pd_2(dba)_3 \cdot CHCl_3$ as catalyst (entry 5, table 20) but the formation was slow. The ester groups probably have a destabilizing effect but no elimination product could be detected (scheme 67).



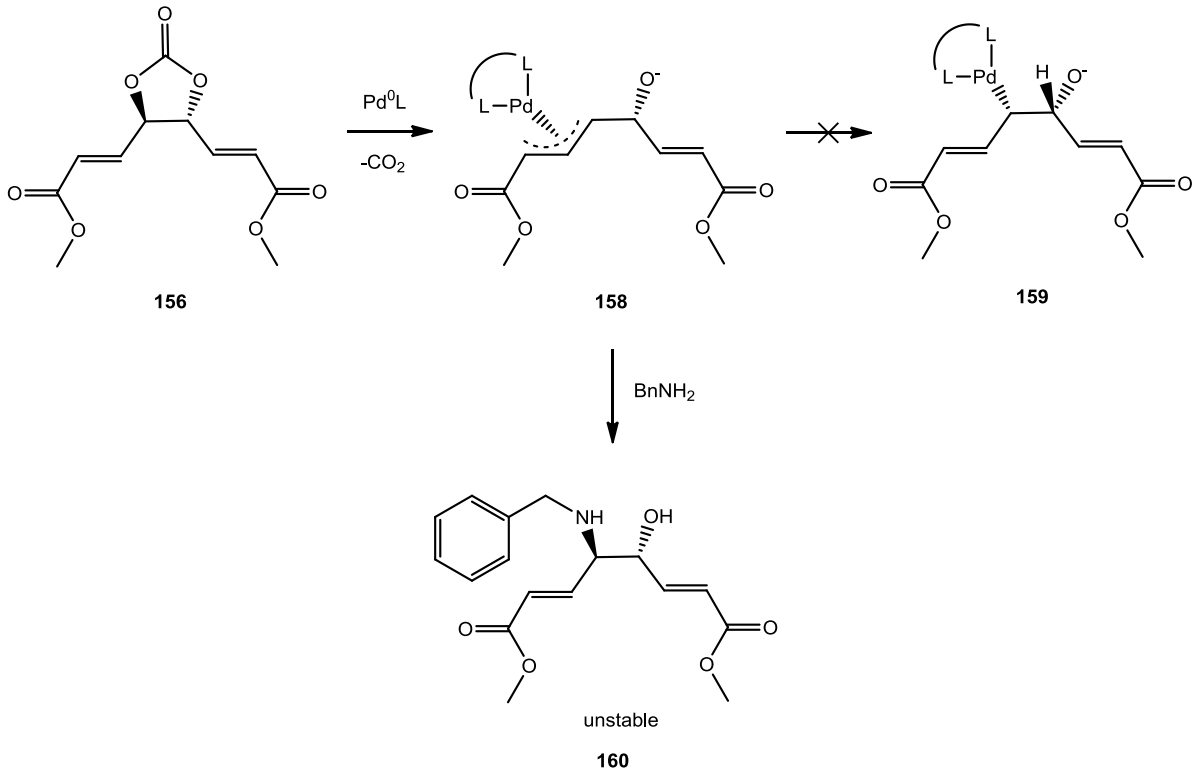
157

Scheme 66: Byproduct **157**

Table 20: Allylic substitutions on racemo-ester (compound **156**)

Entry	Ligand	Pd source	Nucleophile	Base	Comment
1	PPh_3	$[Pd(allyl)Cl]_2$	$BnNH_2$	-	Product but decomposition
2	PPh_3	$[Pd(allyl)Cl]_2$	$BnNH_2$	EDIPA[2]	Product but decomposition
3[1]	PPh_3	$[Pd_2(dba)_3]\cdot CHCl_3$	$BnNH_2$	-	Product but decomposition
4	-	-	$BnNH_2$	-	Carbamate
5[1]	(*R*,*R*)-Trost(4)	$[Pd_2(dba)_3]\cdot CHCl_3$	$BnNH_2$	-	Carbamate

Reaction condition: Pd catalyst (0.08 eq.), ligand (0.24 eq.), nucleophile (2 eq.), CH_2Cl_2, rt; [1] in toluene; [2] (1 eq.)



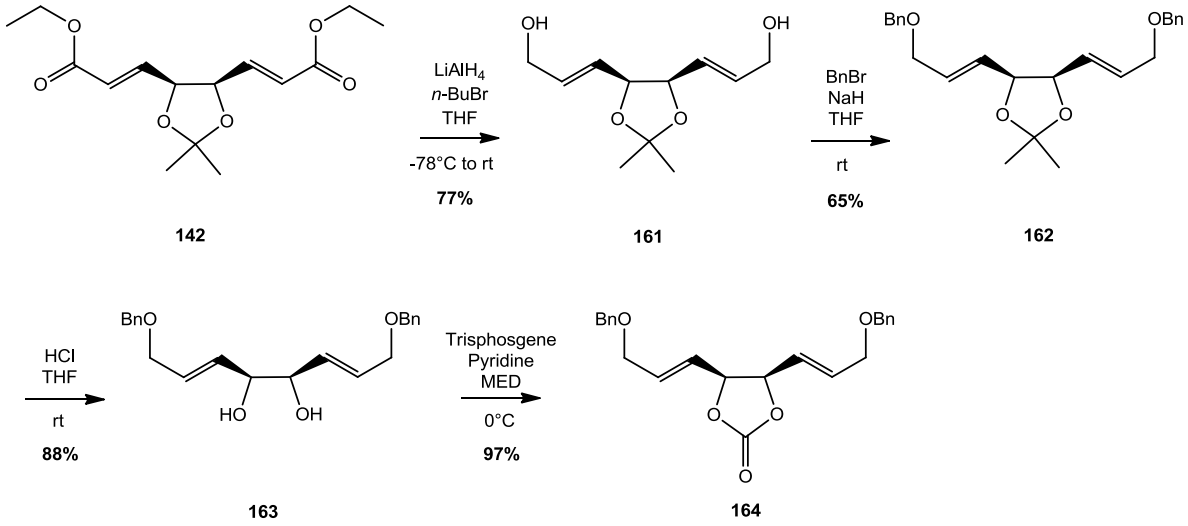
Scheme 67: Allylic substitution on racemo-ester (compound **156**)

3.5.3 Meso dibenzylether compound

The ester functionality on the system could have an undesired effect due to acidity of γ-protons inducing elimination or destabilizing the product otherwise. To overcome this effect, benzylethers were introduced as a functional group instead of the ester moiety, as it was already done in previous experiments (see Chapter 3.1 and 3.2).

3.5.3.1 Substrate synthesis

The desired compound was synthesized starting from **142** as common intermediate (scheme 68). Reduction with $LiAlH_4$[106] to the alcohol product **161** was achieved in 77% yield. The benzylation[107] of **161** afforded compound **162** in 65% yield. The obtained benzylated product **162** was deprotected with HCl to afford **163** in 88% yield. Protection of **163** with trisphogene afforded the cyclic carbonate compound **164** in 97% yield.



Scheme 68: Synthesis of meso dibenzylether substrate (compound **164**)

*3.5.3.2 Allylic subsitutions on meso dibenzylether (compound **164**)*

Compound **164** turned out to be a more stable substrate. Allylic substitutions under different reaction conditions (table 21) mostly led to recovery of starting material but also to some side products which decomposed during chromatography.

Table 21: Allylic substitutions on meso dibenzylether (compound **164**)

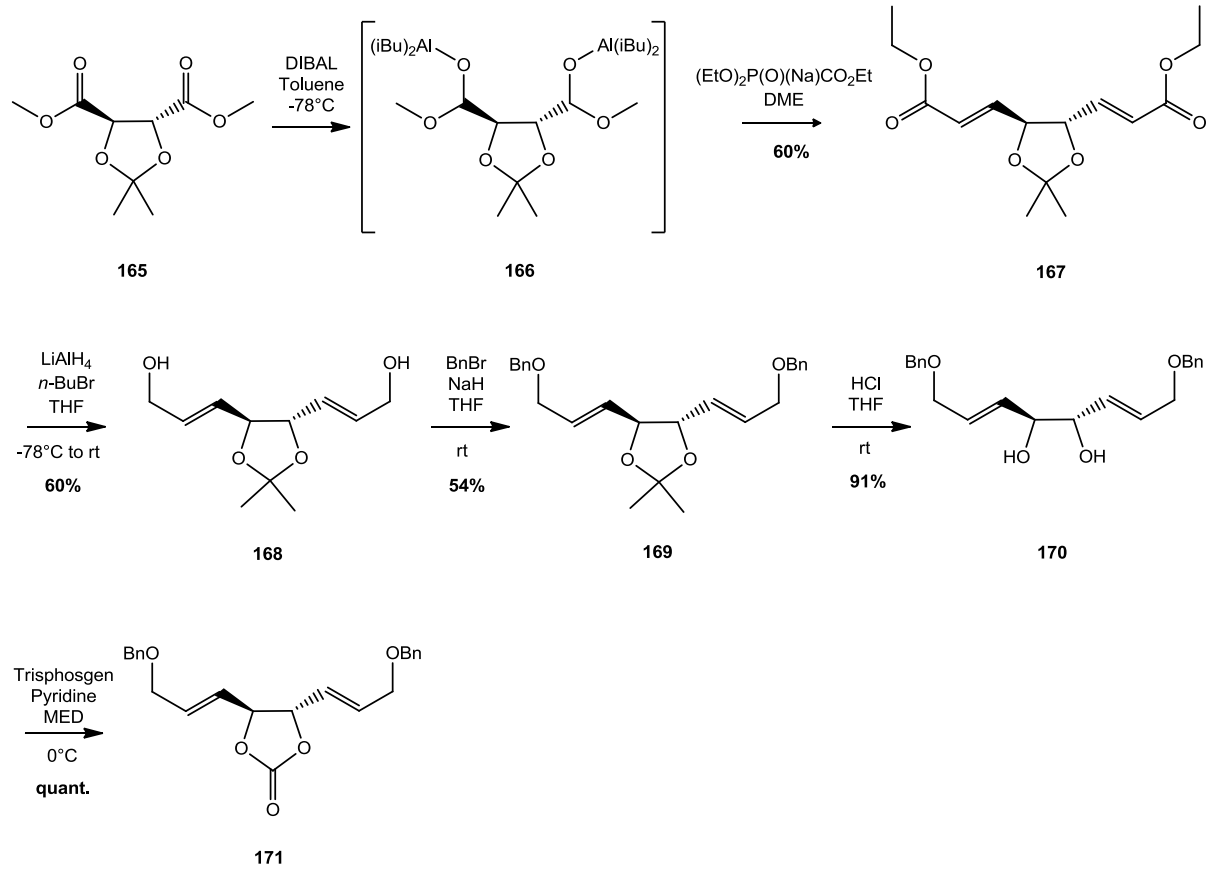
Entry	Ligand	Pd source	Nucleophile	Base	Solvent	Comments
1	-	-	$BnNH_2$	EDIPA[1]	THF	SM recovery Some carbamate
2	PPh_3	$[Pd(allyl)Cl]_2$	$BnNH_2$	EDIPA[1]	MED	SM recovery Some product but not stable
3	PPh_3	$[Pd(allyl)Cl]_2$	$BnNH_2$	-	MED	Some product but not stable
4	Trost(4)	$[Pd(allyl)Cl]_2$	$BnNH_2$	EDIPA[1]	THF	rt→60°C SM recovery
5	Trost(2)	$[Pd(allyl)Cl]_2$	potassium phtalimide	-	MED	SM recovery

Reaction condition: Pd catalyst (0.08 eq.), ligand (0.24 eq.), nucleophile (2 eq.), rt; [1] 1 eq.

3.5.4 Racemo dibenzyl ether compound

3.5.4.1 Substrate synthesis

The racemo benzyl ether compound **171** was synthesized from commercially available (-)-dimethyl 2,3-*O*-isopropylidene-*L*-tartrate (**165**) (scheme 69). Reduction with DIBAL followed by Horner-Wardsworth-Emmons reaction afforded compound **167** in 60% yield. Reduction with $LiAlH_4$ to the alcohol product **168** was achieved in 60% yield. The benzylation of **168** afforded **169** in 54% yield. **169** was deprotected with HCl to obtain **170** in 91% yield. Protection of **170** with trisphogene afforded the cyclic carbonate compound **171** in quantitative yield.

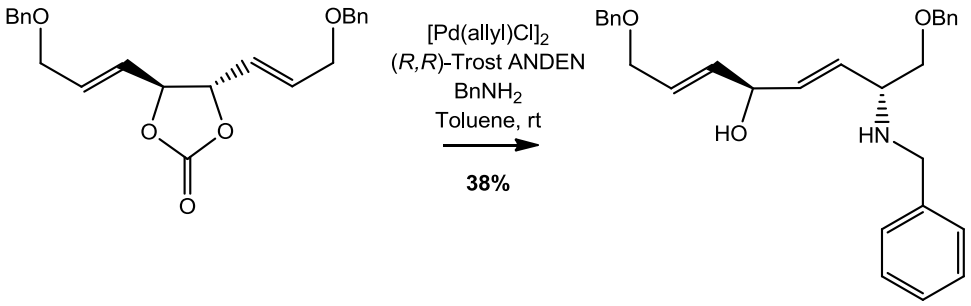


Scheme 69: Synthesis of racemo dibenzylether substrate (compound **171**)

*3.5.4.2 Allylic substitution on racemo dibenzylether (compound **171**)*

Reactions of enantiomerically pure compound **171** (>95% ee) with (*R*,*R*)-Trost ANDEN (0.24 eq.), $[Pd(allyl)Cl]_2$ (0.08 eq.), $BnNH_2$ (2 eq.), EDIPA (1 eq.), toluene and at rt afforded the product **172** in 38% yield with recovery of starting material (scheme 70). In this case, the nucleophilic attack did not occur at the position of the leaving group but on the other termini of the η^3-allyl palladium complex. Nevertheless, this result confirmed our previous hypothesis that a stabilized structure without the possibility to undergo β-hydride elimination could indeed afford the product from the allylic substitution. The low yields are not satisfactory but further improvement may be feasible. One way to prevent β-hydride elimination would be to add an additive which would coordinate to palladium such as a hydride ion as described by Keinan and Roth[108]. It is notewothy to mention that although a

chiral ligand is not necassary in this case, the chiral ligand was used to ensure comparability of the reaction conditions between the racemo and meso-substrates. The absolute configuration at the center of the substitution in compound **172** was presumed based on the common mechanism of the allylic substitution. The configuration was not determined by spectroscopical methods.

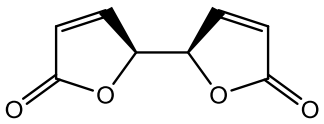


171 **172**

Scheme 70: Allylic substitution on racemo dibenzylether substrate (compound **171**)

3.5.5 Cyclic bi-lactone substrate

From the synthesis described above, we came up with the idea of another interesting substrate for allylic substitution: Cyclic bilactone substrate **173** (scheme 71).

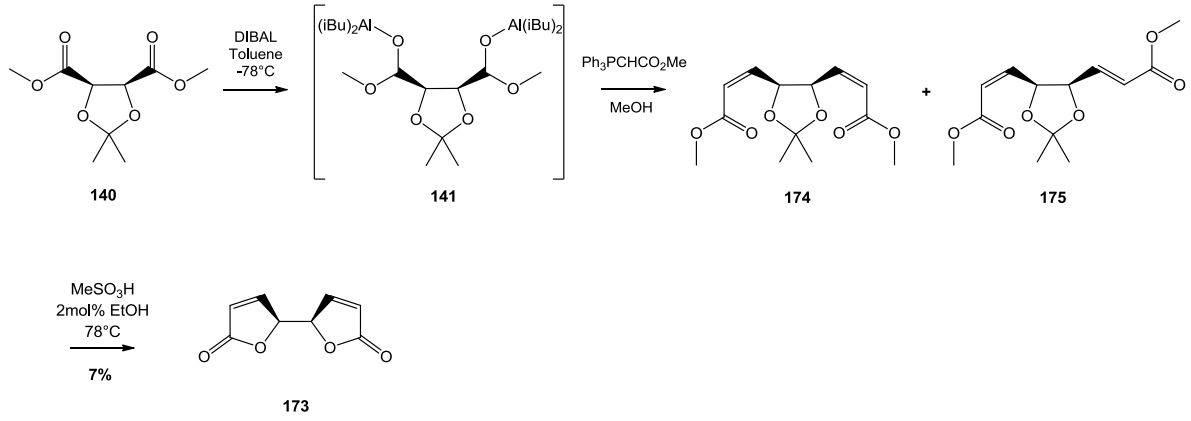


173

Scheme 71: Cyclic bilactone substrate (compound **173**)

3.5.5.1 Substrate synthesis

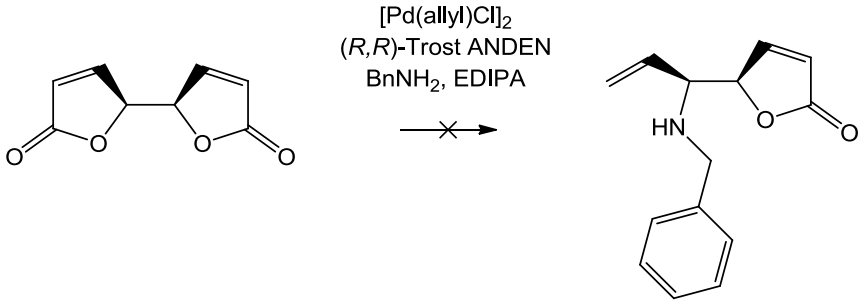
The synthesis included the same pathway starting from meso-dimethyl 2,3-*O*-isopropylidene-tartrate **140** with DIBAL reduction and Wittig olefination with methyl triphenylphosphonoanylidene acetate[102], affording a mixture of cis/cis **174** and cis/trans **175** product (scheme 72). Without purification of the crude, $MeSO_3H$ was added to the crude affording the cyclisation[109] of the cis/cis **174** product into the bilactone **173** in 7% yield.



Scheme 72: Synthesis of meso bislactone (compound **173**)

3.5.5.2 Allylic substitution on bi-lactone compound

An allylic substitution on **173** with $Pd(allyl)Cl]_2$ (0.08 eq.), (*R,R*)-Trost ANDEN (0.24 eq.), EDIPA (1 eq.), $BnNH_2$ (2 eq.), THF at rt was performed but instead of the reaction to the desired product (scheme 73), only decomposition was observed. Poor yield in the synthesis of the substrate as well as decomposition during allylic substitution made this substrate unsuitable.



173 **176**

Scheme 73: Allylic substitution on cyclic bilactone substrate (compound **173**)

3.6 Derivatization and application of chiral allylic amines and ethers

The synthesis of a wide range of interesting compounds is possible with our chiral products since all centers are chemoselectively different. Amino sugars or phenol-sugars are of interest and important compounds in many syntheses. Phenol sugars are particularly interesting due to their difficult synthesis[110].

Herein, different compounds were synthesized showing the use of our substitution product.

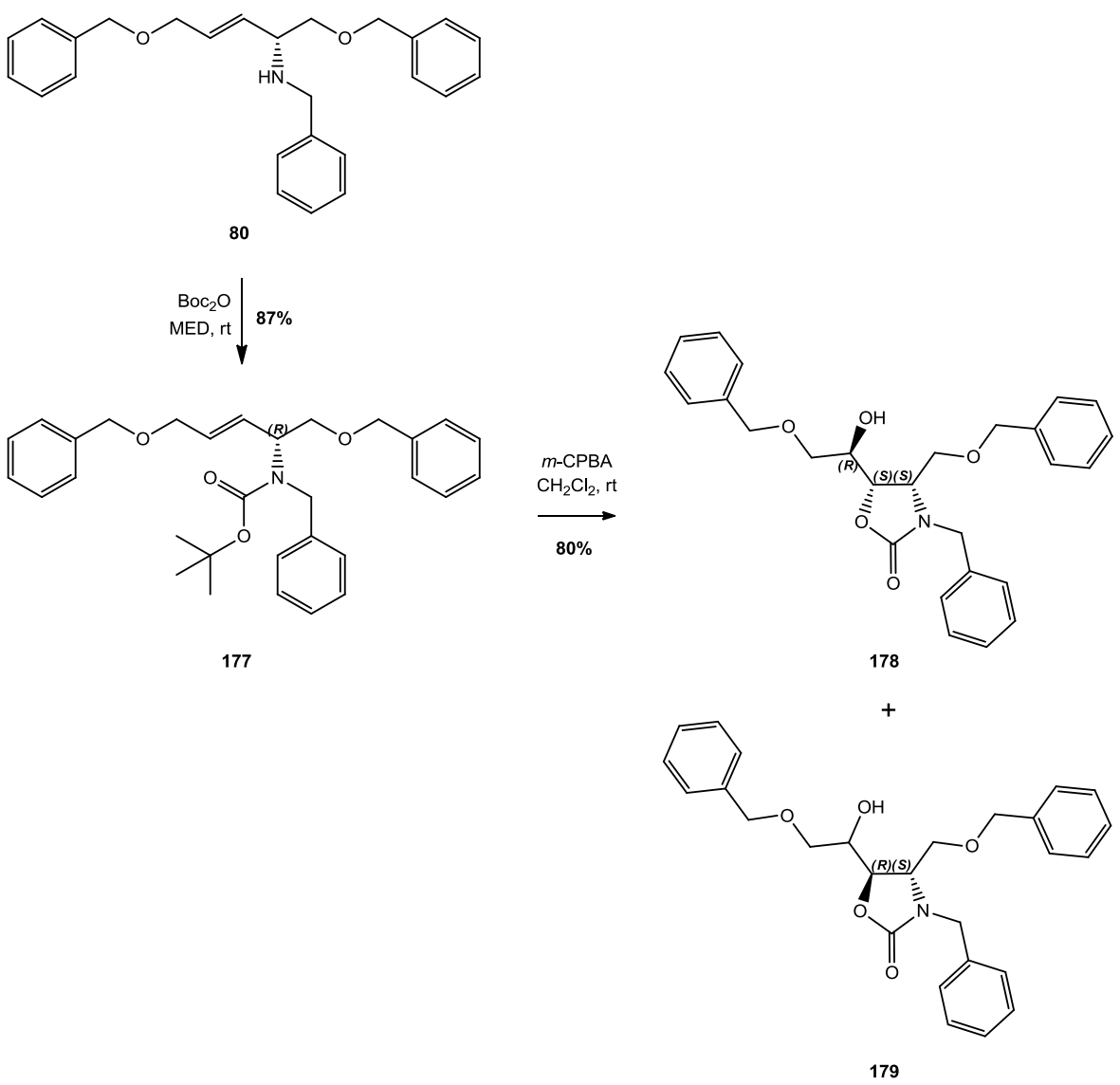
3.6.1 Synthesis of oxazolidinone derivatives

Starting from our chiral substitution product **80** (88% ee), the amine was protected with a Boc group[111] in 87% yield to obtain compound **177** (scheme 74). Interesting transformations are possible with *N*-Boc protecting groups as it was shown in 2002 by Agami[112] who published a review highlighting the different observed reactions. In our case, reaction of our product with *m*-CPBA resulted in an intramolecular cyclization affording oxazolidinone **178** and **179** in 80% yield (scheme 74). The two diastereoisomers could be separated on column chromatography in a 1:1 ratio. Their configuration was determined by NMR experiments. Diastereoisomer **178** displays a cis configuration in the 5-ring and an anti configuration relative to the exocyclic stereogenic center. Diastereoisomer **179** exhibit a trans configuration in the 5-ring. In that case, the exocyclic stereogenic center could not be determined by NMR. **178** and **179** are separable by HPLC on a chiral stationary phase and both diastereoisomers display the same ee (88% ee) as the starting compound **80** (figure 6).

In the literature several examples of *N*-alkylated *N*-Boc groups are known where the carboxyl oxygen reacts as a nucleophile with a neighbouring group, an effect related to the Thorpe-Ingold effect. For example, Ueda et al.[113] reported the synthesis of *N*-methyl-2-oxazolidinones in a stereo- and regioselective fashion proceeding through a 6-(*N*-tert-butoxycarbonyl)amino-3-oxo-4-hexenoates. Some calculations were performed by the Agami group[114] and showed the difference between HN-Boc and MeN-Boc group where a compression of the internal C-N=C angle (122.0 and 117.7° for N-H and N-Me moiety, respectively) was observed, in

agreement with a Thorpe-Ingold effect. This effect could explain our results and could imply a concerted mechanism such as shown in scheme 75.

Furthermore, the same reaction with an excess of *m*-CPBA was made with an *N*-Acetyl protected amine **183** (scheme 76). **183** was synthesized from **80** with acetylchloride, DMAP and Et_3N[115] in 71% yield. The goal of the reaction with *m*-CPBA was to observe the formation of an epoxide since cyclization with *N*-Acetyl compounds is not possible. However, no reaction was observed and the starting material was recovered. Other epoxidation reagents were tried such as urea-hydrogen peroxide (with Na_2HPO_4, TFA) or Oxone/$NaHCO_3$ but none of them were successful and starting material was recovered. This indicates a surprisingly unreactive double bond and could be seen as an indication of the concerted mechanism with the *N*-Boc compound. However, we still do not have a satisfactory explanation for the lack of reactivity of the acetyl protected compound **183** towards epoxidation.



Scheme 74: Boc protection of amine product and cyclization to oxazolidinones

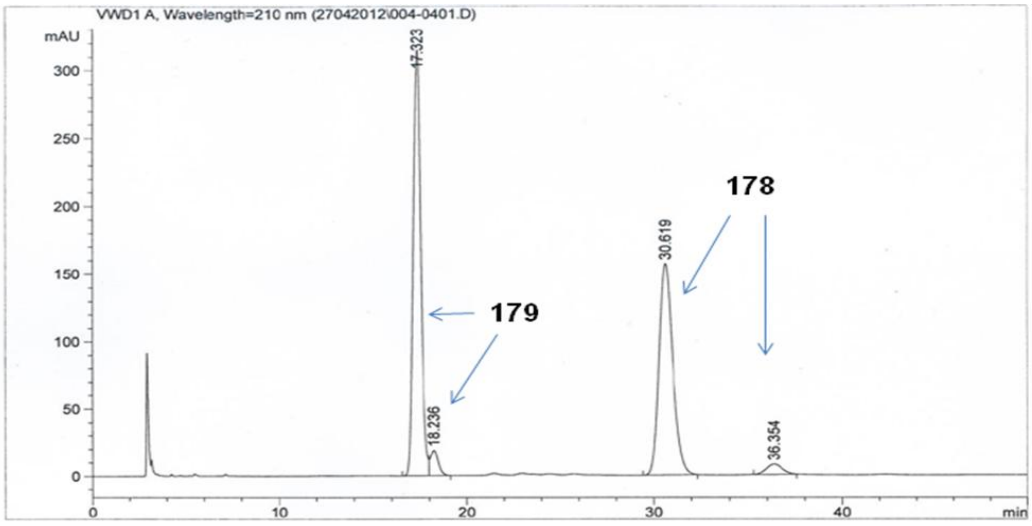
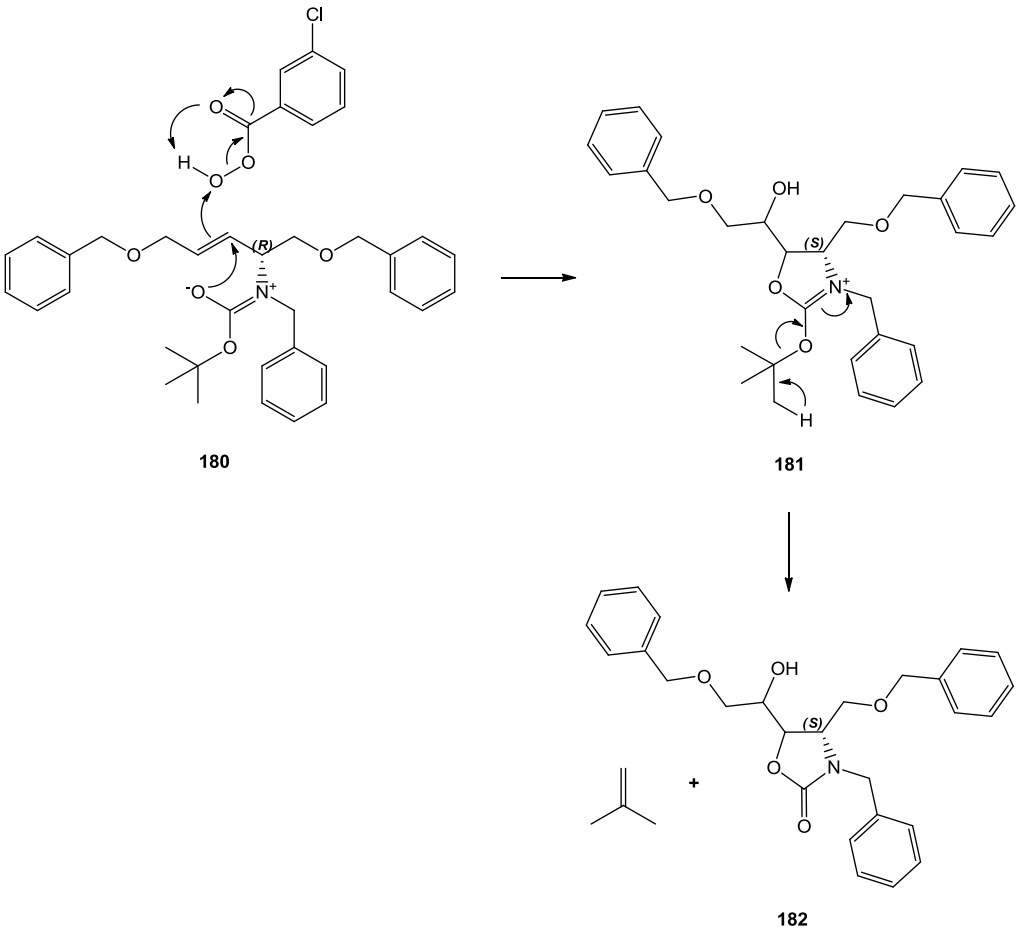
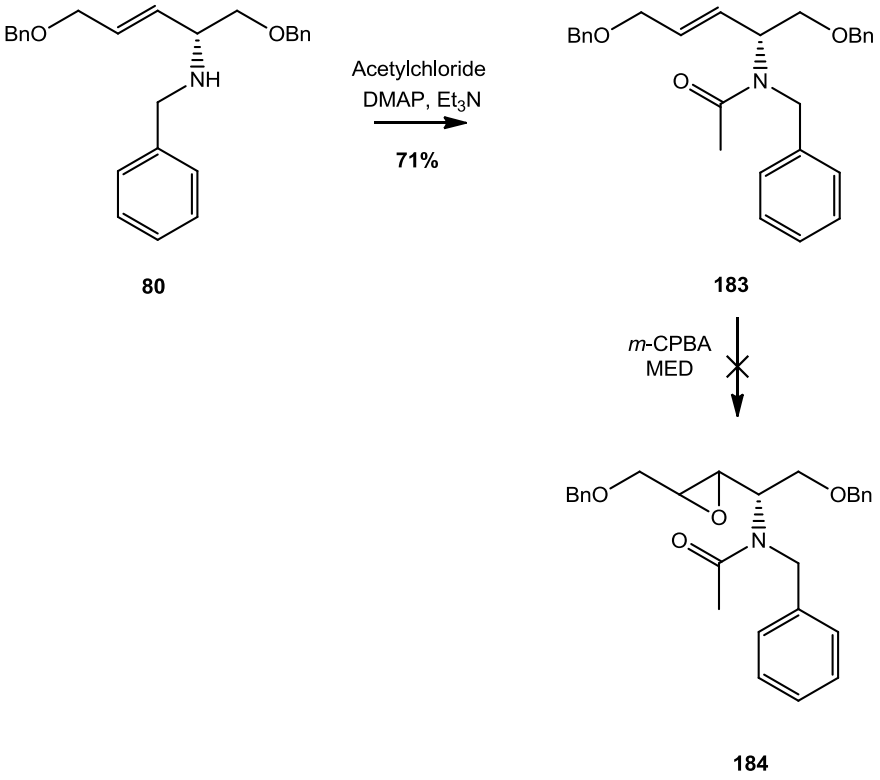


Figure 6: Chromatogram of a 1:1 (w/w) mixture of **178** and **179**



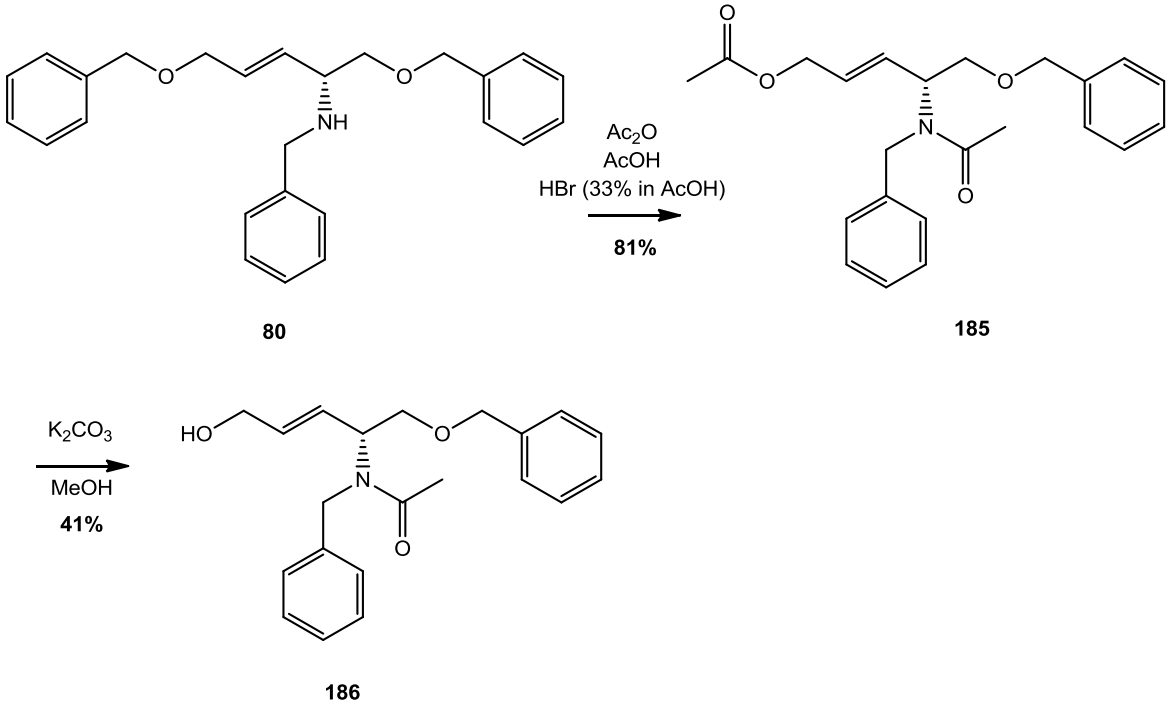
Scheme 75: Concerted reaction mechanism for cyclization to oxazolidinone derivative



Scheme 76: Acetyl protection of amine followed by attempt on epoxidation

3.6.2 Selective benzyl deprotection and functionalization

Another interesting set of compounds could be synthesized starting from our benzylamine product **80** (scheme 77) with selective deprotection of one benzylether using Ac_2O, AcOH, HBr (33% in AcOH)[116] followed by in situ protection of the alcohol as well as the amine affording compound **185** in 81% yield. Hydrolysis of the ether group was performed with K_2CO_3[117] affording compound **186** in 41% yield. Such compounds could be further functionalized by epoxidation or dihydroxylation of the double bond. A possible application of our substrate would be the synthesis of different amino-riboses.

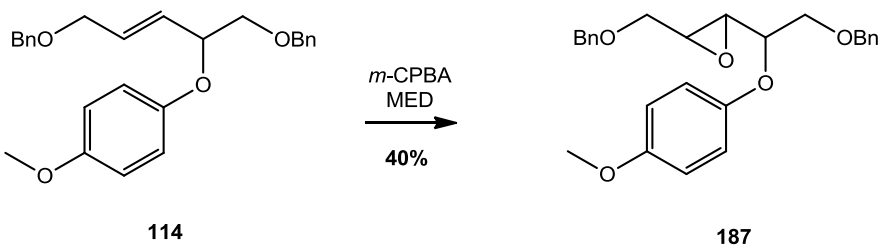


Scheme 77: Selective benzyl ether deprotection and functionalization starting from compound **80**

3.6.3 Epoxidation of phenol product 114

Functionalization of phenol compound **114** to afford phenol sugars is of interest since such compounds are difficult to obtain.

Epoxidation of compound **114** with *m*-CPBA afforded **187** in 40% yield (scheme 78). *m*-CPBA is a strong epoxidation reagent and the use of another reagent could possibly improve the yield by suppressing side reactions. The diastereoisomeric ratio was established by HPLC on chiral stationary phase and was determined to be 64:36.



114 **187**

Scheme 78: Epoxidation of phenol product (compound **114**)

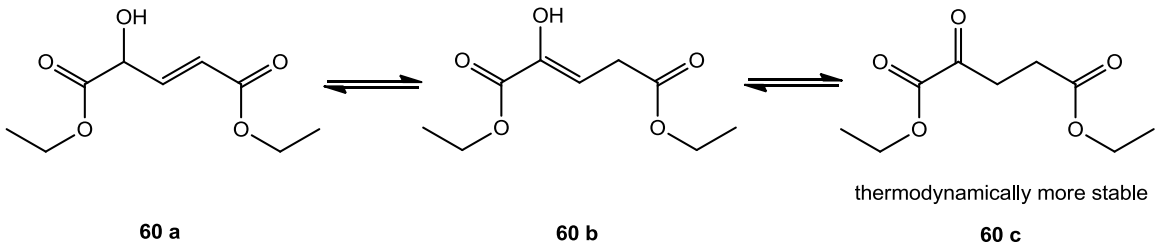
Chapter 4

Summary and Conclusion

4. Summary and Conclusion

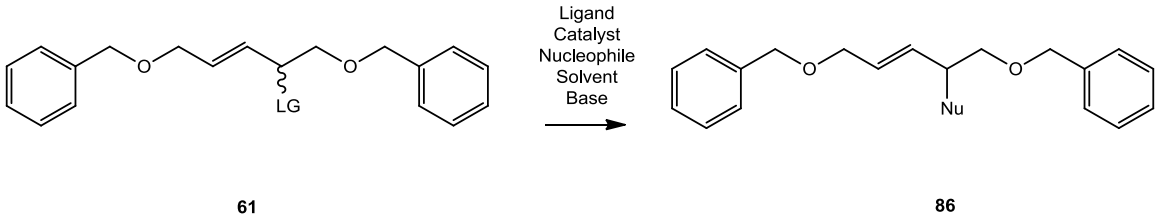
In the first part of the thesis, enantioselective palladium catalyzed allylic substitutions were developed on substrates which proceed via symmetrical η^3-allyl complexes. These substrates were designed with two identical functional groups on each end of the allyl system which allowed the derivatization of the resulting chiral products into attractive compounds. Furthermore, the advantage of a symmetrical substrate-palladium complex enabled an enantioselective attack of the nucleophile, resulting in a true enantioselective conversion.

The synthesis of di-ester substrates of this type encountered several issues. The coupling of ethyl propiolate to ethyl glyoxalate did not succeed due to the polymerization of ethyl glyoxalate at low tempereature. Several attempts to reduce dimethyl 2-oxoglutaconate remained unsuccessful. Allylic bromination on diethylglutaconate with NBS provided a mixture of 75:25 vinyl:allyl monobromide. The same vinyl/allyl ratio was observed after the elimination reaction of diethyl 2,3-dibromopentanedioate indicating a possible dynamic equilibrium. Therefore an allylic substitution on the vinyl/allyl monobromide mixture was performed but unfortunately a mixture of byproducts was observed. A quantum mechanic study was performed to determine the energies of the isomers. In all cases, the vinyl form was found thermodynamically more favorable than the allyl form. Furthermore, a keto-enol tautomerization could be imagined where the more thermodynamically stable keto form would be formed, preventing a possible allylic substitution (scheme 27).



Scheme 27: Keto-enol tautomerization

In contrast, the synthesis of di-benzylether substrates was straightforward and enabled the study of these substrates in allylic substitutions (scheme 79).



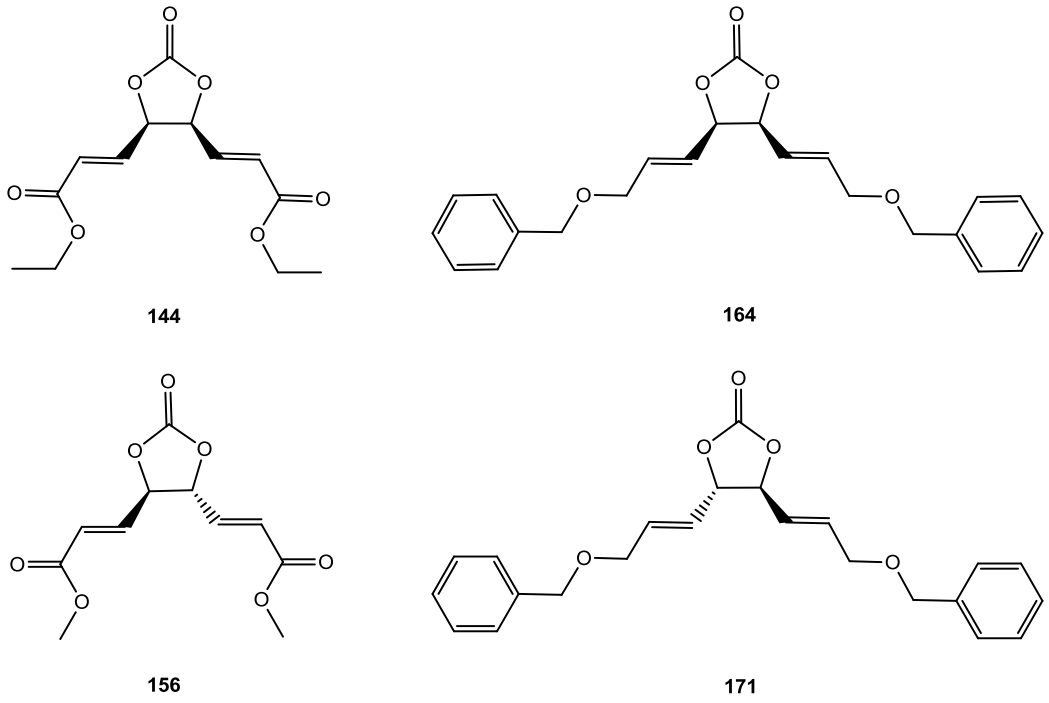
61 86

Scheme 79: Enantioselective allylic substitutions study on compound **61**

Different parameters can influence the reaction such as the leaving group, ligand, solvent, base, catalyst and nucleophile. Therefore several screenings were performed to optimize the reaction. Ethylcarbonate-, methylcarbonate, benzylcarbamate and chloracetates were chosen as leaving groups. The (*E*)-chloracetate substrate was found to give the best results and was chosen as a standard. It was observed that *E*/*Z* isomerization occurred, producing the same *E*/*Z* ratio, either starting from (*Z*) or (*E*)-ethylcarbonate substrates and (*Z*) or (*E*)-methylcarbonate substrates. An explanation for these results was given by the π-σ-π isomerization. Two classes of ligands were selected and compared on our substrate: PHOX and Trost ligands. From the results obtained, (*R*,*R*)-Trost ANDEN showed minimized *E*/*Z* isomerization as well as a good yield and ee. The choice of a good solvent is important and the screening showed three reliable solvents for our substrate: CH_2Cl_2, toluene, CF_3Ph. The addition of a base improved the ee and the yield. When different bases were screened, the best results were obtained from the addition of 1eq. EDIPA. With (*E*)-chloracetate, $[Pd(allyl)Cl]_2$ was the best suited catalyst. The catalyst loading was lowered down to 1 mol% but unfortunately lowering the catalyst loading also decreased the yield. Therefore 8 mol% of catalyst was chosen as a standard. With these optimized reaction conditions, a broad range of nucleophiles was tested on our substrate. Primary aryl amine nucleophiles were found to be excellent nucleophiles in our system with ee's up to 97% and yields up to 93%. Good results were also obtained from not commonly used phenol nucleophiles with ee's up to 92% and yields up to 83%. The absolute configuration was determined by derivatization of the substitution product (*E*)-*N*-benzyl-1,5-bis(benzyloxy)pent-3-en-2-amine into *N*-(1,5-

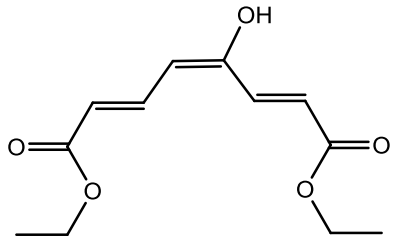
dihydroxypenta-2-yl)benzamide. Optical activity as well as the assignment of the HPLC peaks on chiral stationary phase of the enantiomers allowed determination of the absolute configuration to be (*R*).

The second part of the thesis was focused on the study of dimeric substrates possessing a cyclic carbonate as leaving group (scheme 80). The following substrates were synthesized: meso diethylester (compound **144**), meso dibenzylether (compound **164**), racemo dimethylester (compound **156**) and racemo dibenzylether (compound **171**).



Scheme 80: Meso diethylester- and dibenzylether substrates and racemo dimethylester- and dibenzylether substrates

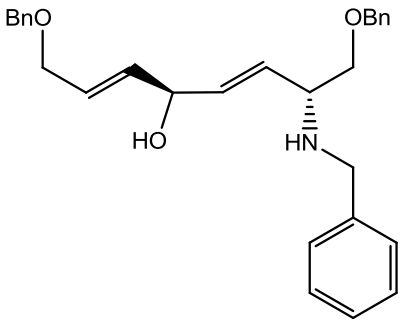
Allylic substitutions on the meso-diethylester substrate (compound **144**) were performed using different reaction conditions. The desired substitution could not be obtained and instead the elimination product **145** (scheme 62) was isolated which appeared to be unstable over time. This product showed that *β*-hydride elimination took place during the reaction.



145

Scheme 62: Elimination product **145**

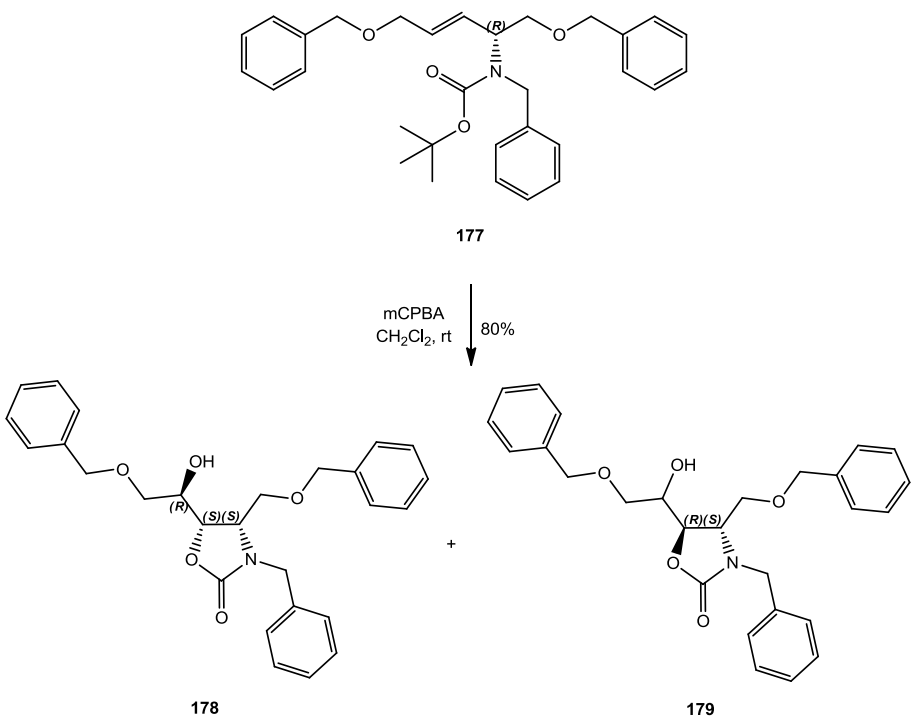
From racemo-dimethylester substrate (compound **156**), no product could be isolated and decomposition was observed. The more stable dibenzylether substrates provided better results. No reaction but also no *β*-hydride elimination was observed from meso-dibenzylether substrate (compound **164**). On the other hand, the product **172** (scheme 81) could be isolated from the racemo-dibenzylether substrate (compound **171**). Even though the yield was low (38%), the reaction was proven to be feasible and further improvements may be possible.



172

Scheme 81: Product **172** from the allylic substitution on racemo dibenzylether substrate **171**

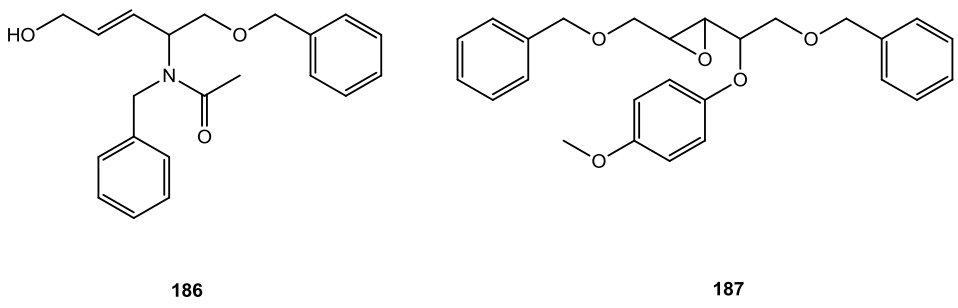
The third part of the thesis focused on the derivatization of the chiral products to give potentially useful compounds. Oxazolidinone products **178** and **179** were synthesized from **177** in a 1:1 diastereoisomeric ratio separable by column chromatography (scheme 82). From these products, the synthesis of various compounds could be imagined such as 2-aminopentoses.



Scheme 82: Oxazolidinone products **178** and **179**

Another polyfunctionalized compound **186** was synthesized from (*E*)-*N*-benzyl-1,5-bis(benzyloxy)pent-3-en-2-amine (scheme 83). This compound offers many possibilities for further transformations such as selective epoxidation or dihydroxylation.

At last, epoxidation of chiral phenol ether succeeded to afford **187** (scheme 83). Further derivatization to afford uncommon phenol sugars can be envisaged.



Scheme 83: Derivatized products **186** and **187**

Chapter 5

Experimental part

5. Experimental part

5.1 General Informations

Work conditions: All reactions were performed under an argon (all allylic substitutions) or nitrogen atmosphere with oven-dried glassware using standard Schlenk or vacuum line techniques. The following mixture were used for cooled bath: ice/water (0°C), ice/MeOH (-20°C), Dry ice/*i*-PrOH (-78°C). Silicon oil was used for heating reactions.

Chemicals: The cellflock was produced from the production site in Novartis. Commercially available reagents were purchased from Acros, Aldrich, Alfa-Aesar or Fluka unless otherwise described and used without further purification.

Solvents: Solvents were purchased from Aldrich of Fluka in septum-sealed bottles over molecular sieves.

Chromatography: Flash column chromatography was performed using silica gel 60 (0.040-0.063 mm) von Merck (Art. Nr. 1.09385.1000). The eluents employed are reported as volume : volume percentages.

Thin-layer chromatography (TLC): HPTLC Silica gel 60 F_{254} or TLC Silica gel 60 F_{254} were used to monitor reaction progress. Iodine or potassium permanganate was used to visualize the spots.

Melting points: Metling points were determined on Büchi 535 apparatus.

Optical rotations ($[\alpha]^{20}_{D}$): Optical rotations were measured on a Perkin Elmer Polarimeter 341 (serie nr. 7322) in a cuvette (l = 1 dm) at 20°C. The concentration (c) is given in g/100 mL.

NMR: The NMR sample was prepared by dissolving X in ca 40 µl DMSO-d_6. Most NMR spectra (^{1}H, ^{13}C, 2D) were measured at 300 K on a Bruker AVANCE I spectrometer (600 MHz proton frequency) equipped with a 1.7 mm $^{1}H\{^{13}C,^{15}N\}$ CryoProbe™ or on a Bruker BioSpin spectrometer (150 MHz proton frequency). ^{1}H and ^{13}C shifts were referenced to the solvent signals at 2.49 ppm and 39.5 ppm, respectively. Data for ^{1}H NMR are recorded as

follows: chemical shift (δ, ppm), multiplicity [s (singlet), br. s (broad singlet), d (doublet), t (triplet), q (quartet), and m (multiplet)], coupling constant [Hz], integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Some NMR spectra (1H, 13C, 2D) were measured on a Bruker AVANCE II spectrometer (400 MHz proton frequency). These NMR had ^{1}H and ^{13}C shifts referenced to the solvent signals at 7.27 ppm and 77.00 ppm ($CDCl_3$).

IR: The infrared spectrum was acquired as a solid film on a Vertex 70 or Tensor 27 FT-IR spectrometer (Bruker Optics, Fällanden, Switzerland) coupled with a Bruker FT-IR microscope Hyperion 2000 over a wave number range of 4000-600 cm^{-1} with a resolution of 2 cm^{-1}.

The FT Raman spectrum was recorded with a RFS 100 FT Raman spectrometer (Bruker Optics, Fällanden, Switzerland) equipped with liquid nitrogen cooled germanium detector. The resolution was 4 cm^{-1} and 150 scans were accumulated using a laser output of 700 mW. The spectrum was corrected for instrumental response.

MS: Mass spectral determination was made on high resolution mass spectrometer (HR-MS) LTQ Orbitrap XL (Thermo Scientific, USA). UPLC-MS was made on a Waters Acquity UPLC (colum: Acquity HSS T3 2.1x50mm 1.7µ) and a Waters SQD mass spectrometer.

HPLC: Agilent technologies 1200 Series HPLC (columns: Merck, Chromolith Performance RP18, 100 x 4.6 mm or Ascentis® Express C18, 5 cm x 2.1 mm, 2.7 µm; eluent: 0.1% (V/V) H_3PO_4/MeCN; 5mL/min; 40°C) was used to monitor reaction progress.

HPLC-Method for the enantiomeric excess determination: Analysis of enantiomeric excess was performed using a Hewlett Packard Series 1050 HPLC and Chiralpak AD-H chiral stationary phase column (0.46cm ø x 25cm), Chiracel OD-H chiral stationary phase column (0.46cm ø x 25cm), Chiralpak AD-RH chiral stationary phase column (150 x 4.6 mm). The temperature was set at 30°C, the flow at 1.0 mL min^{-1} and the wavelength at 210 nm for all measurements unless otherwise described. For all enantioselective allylic substitution products, a comparison with the retention time of the racemic product was performed.

C-HPLC 1 Chiralpak AD-H, *n*-Hexan : *i*PrOH = 99.5 : 0.5 (w/w)

C-HPLC 2 Chiralpak AD-H, *n*-Hexan : *i*PrOH = 99 : 1 (w/w)

C-HPLC 3 Chiralpak AD-H, *n*-Hexan : *i*PrOH = 94 : 6 (w/w)

C-HPLC 4 Chiralpak AD-H, *n*-Hexan : *i*PrOH = 90 : 10 (w/w)

C-HPLC 5 Chiralpak AD-H, *n*-Hexan : *i*PrOH = 85 : 15 (w/w)

C-HPLC 6 Chiracel OD-H, *n*-Hexan : *i*PrOH = 98 : 2 (w/w)

C-HPLC 7 Chiracel OD-H, *n*-Hexan : *i*PrOH = 85 : 15 (w/w)

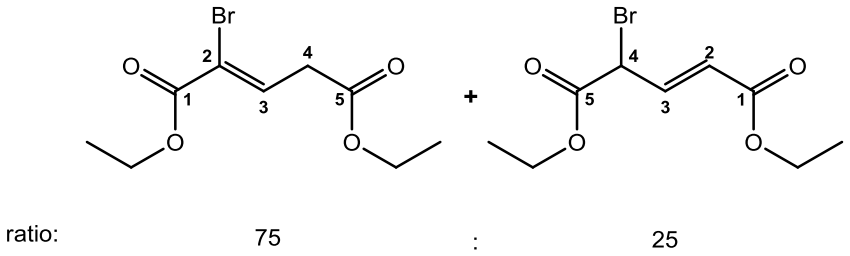
C-HPLC 8 Chiralpak AD-RH, 0.01N Na_2HPO_4 in CH_3CN

C-HPLC 9 Chiralpak AD-H, heptan : ethanol = 75 : 25 (w/w)

***Z*/*E* determination:** *Z*/*E* isomerisms were determined by ^{1}H NMR as well as with a Hewlett Packard Series 1050 HPLC and Chiralpak AD-H chiral stationary phase column (0.46cm ø x 25cm) or Chiracel OD-H chiral stationary phase column (0.46cm ø x 25cm) or Chiralpak AD-RH chiral stationary phase column (150 x 4.6 mm).

5.2 Synthesis of the compounds

(*Z*)-diethyl 2-bromopent-2-enedioate and (*E*)-diethyl 4-bromopent-2-enedioate (50 and 51)



ratio: 75 : 25

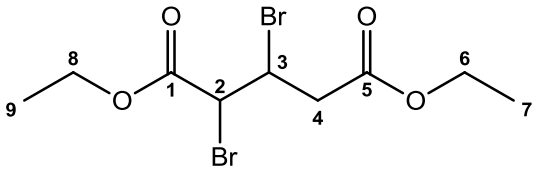
Diethylglutaconate (1.86g, 10mmol, 1 eq.) was put in solution in CCl_4 at rt. *N*-Bromsuccinimide (1.78g, 10mmol, 1 eq.) was then added to the solution at rt. The reaction mixture was put at reflux. Afer 48h, the reaction mixture was cooled down at rt, filtered through Büchner and washed with CH_2Cl_2. The filtrate was evaporated under reduced pressure. The crude was purified by flash chromatography (2:8 ESTP : HPTF) to afford the mixture of products (0.3084g, 12% yield).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.28 - 1.32 (m, 4 H) 1.33 - 1.38 (m, 4 H) 3.39 (d, *J*=6.53 Hz, 2 H vinyl) 4.18 - 4.26 (m, 3 H) 4.26 - 4.35 (m, 3 H) 4.87 (dd, *J*=9.54, 0.75 Hz, 1 H allyl) 6.08 (dd, *J*=15.56, 0.75 Hz, 1 H allyl) 7.10 (dd, *J*=15.56, 9.29 Hz, 1 H allyl) 7.54 (t, *J*=6.53 Hz, 1 H vinyl)

HR-MS: calculated: 265.00700 $[M+H]^+$; 282.03355 $[M+NH_4]^+$; found: 265.00696 $[M+H]^+$; 282.03354 $[M+NH_4]^+$, Δm =0.1ppm (the isomers are not separable on LC-MS)

FTIR: 2984 (υ(CH) aliph. CH), 2940 (υ(CH) aliph. CH), 1737 (υ(C=O) ester), 1635 (υ(C=C)), 1254 (υ(C-O ester)), 1182 (υ(C-O ester)), 1042 (υ(C-O ester)), 1028 (υ(C-O ester)) cm^{-1}

Diethyl 2,3-dibromopentanedioate (52)



Diethylglutaconate (3.72g, 20mmol, 1 eq.) was put in solution in 20mL CH_2Cl_2 and the solution was cooled down at 0°C. Br_2 (3.19g, 20mmol, 1 eq.) diluted in 10mL CH_2Cl_2 was slowly added to the solution. After end of addition, the reaction mixture was allowed to come at rt and left to stir during 17h. The reaction was extracted with $Na_2S_2O_3$ and the organic phase was dried over Na2SO4. The solvent was evaporated under reduced pressure. The crude was purified with flash chromatography (95:5 toluene:ethyl acetate) to afford the desired product (5.05g, 73% yield)

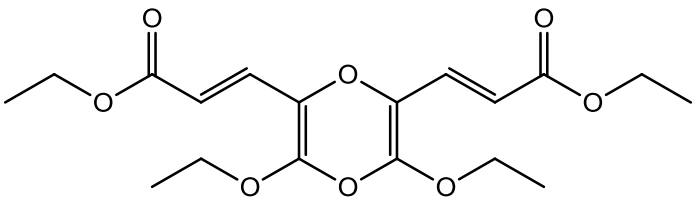
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.23 - 1.34 (m, 6 H) 2.88 - 2.98 (m, 1 H) 3.33 - 3.41 (m, 1 H) 4.15 - 4.23 (m, 2 H) 4.23 - 4.31 (m, 2 H) 4.57 - 4.62 (m, 1 H) 4.63 - 4.71 (m, 1 H)

^{13}C NMR (500 MHz, DMSO-d_6) δ ppm 13.71 (C_7 or C_9) 14.05 (C_7 or C_9) 40.41 (C_4) 46.63 (C_2 or C_3) 46.90 (C_2 or C_3) 60.74 (C_6 or C_8) 62.22 (C_6 or C_8) 167.29 (C=O) 169.23 (C=O)

HR-MS: calculated: 344.93316 $[M+H]^+$; 361.95971 $[M+NH_4]^+$; found: 344.93318 $[M+H]^+$; 361.95979 $[M+NH_4]^+$, Δm =0.1-0.2 ppm

FTIR: 2984 (υ(CH) aliph. CH), 1744 (υ(C=O) ester), 1466 (δ(C-H)), 1377 (δ(C-H)), 1266 (υ(C-O) ester), 1153 (υ(C-O) ester), 1024 (υ(C-O) ester) cm^{-1}

(2*E*,2'*E*)-diethyl 3,3'-(3,5-diethoxy-1,4-dioxine-2,6-diyl)diacrylate (53)



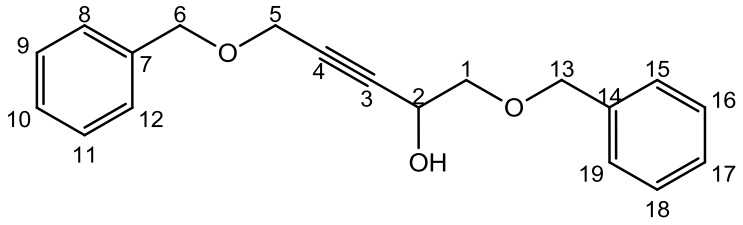
Diethyl 2,3-dibromopentanedioate **52** (0.559g, 1.615mmol, 1 eq.) was put in solution in 10mL THF at rt. Triethylamine (0.16g, 1.615mmol, 1 eq.) was added to the solution and a precipiate was formed. After 1h30, the reaction mixutre was filtered through Büchner and washed with THF. Solvent of the filtrate was evaporated under reduced pressure and the crude was purified with flash chromatography (95:5 toluene: ethyl acetate) to afford the product (0.0155g, 3% yield)

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.34 (q, *J*=7.19 Hz, 12 H) 4.24 - 4.29 (m, 4 H) 4.29 - 4.35 (m, 4 H) 6.27 (d, *J*=15.81 Hz, 2 H) 7.65 (d, *J*=15.81 Hz, 2 H)

HR-MS: calculated: 369.15727 $[M+H]^+$; 386.18788 $[M+NH_4]^+$, 391.13921 $[M+Na]^+$; found: 369.15426 $[M+H]^+$; 386.18093 $[M+NH_4]^+$, 391.13581 $[M+Na]^+$

FTIR: 2983 (υ(CH) aliph. CH), 2937 (υ(C-H) aliph. CH), 1722 (υ(C=O) ester), 1620 (υ(C=C)), 1261 (υ(C-O)), 1185 (υ(C-O)), 1027 (υ(C-O)), 971 (δ(CH) trans C=C) cm^{-1}

1,5-bis(benzyloxy)pent-3-yn-2-ol (67)



Benzyl propagyl ether (18.5g, 126.52 mmol, 1 eq.) was put in solution in 430mL THF and the solution was cooled down at -78°C. Commercially available LDA 2M (76 mL, 151.82 mmol, 1.2 eq.) was slowly added to the solution. Then benzyloxyacetaldehyde (19g, 126.52 mmol, 1 eq.) diluted in 50mL THF was added at -78°C. 3h later the yellow milky solution was quenched with a dropwise addition of HCl 2N (126.5 mL, 253.04 mmol) at -70°C then the solution was warmed up at room temperature. The aqueous phase was extracted with 2x 250mL TBME. The collected organic phases were washed with 2x 250mL H_2O and 2x 250mL NaCl sat. The organic phase was dried over anhydrous magnesium sulfate and filtered. The solution was concentrated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the corresponding product: light orange oil (27g, 72% yield).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.49 (br. s., 1 H) 3.54 - 3.69 (m, 2 H) 4.20 (d, *J*=1.76 Hz, 2 H) 4.58 (s, 2 H) 4.59 - 4.65 (m, 3 H) 7.23 - 7.39 (m, 10 H)

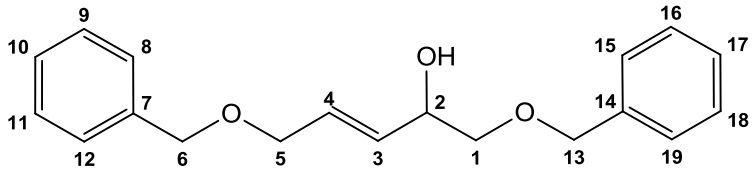
^{13}C NMR (500 MHz, DMSO-d_6) δ ppm 57.0268 (C_5) 60.2417 (C_2) 70.6141 (C_6 or C_{13}) 72.1829 (C_6 or C_{13}) 73.7778 (C_1) 80.1519 (C_3 or C_4) 86.9432 (C_3 or C_4) 128.2944-127.4290 (aromatic *C*H) 137.6761 (C_7 or C_{14}) 138.3129 (C_7 or C_{14})

HR-MS: calculated: 314.17507 $[M+NH_4]^+$; found: 314.17514 $[M+NH_4]^+$, Δm = 0.2ppm

FTIR: 3419 (υ(OH)), 3088 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2903 (υ(CH) aliph. CH), 2862 (υ(CH) aliph. CH), 1605 (benzene ring stretch), 1587 (benzene ring stretch), 1496 (benzene ring stretch), 1454 (benzene ring stretch), 1074 (υ(C-O)), 1028 (υ(C-O)), 738 (monosub. benzene), 698 (monosub. benzene) cm^{-1}

RAMAN: 2276 (C≡C), 2236 (C≡C), 1003 (monosubst. benzene)

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-ol (68)



$LiAlH_4$ in pellet form (4.16g, 109.66 mmol, 5 eq.) was put in solution in 150mL THF under argon. After the pellets were dissolved, the grey solution was cooled down at -15°C. Dropwise addition of 1,5-bis(benzyloxy)pent-3-yn-2-ol **67** (6.5g, 21.93 mmol, 1 eq.) diluted in 50mL THF at -10°C. After the end of addition, the solution was allowed to come at rt. After 30min, the reaction was finished and cooled down at 0°C. To quench, 20mL of a 10% $MgSO_4$ solution was carefully added during 20min. After the end of addition, the grey slurry was left to stir during 30min and then filtered through a fine layer of cellflok (washed with 400mL EtOAc). The solution was concentrated under reduced pressure. Flash column chromatography (7:3 hexane:EtOAc) of the crude gave the desired product: colorless oil (4.43g, 68% yield).

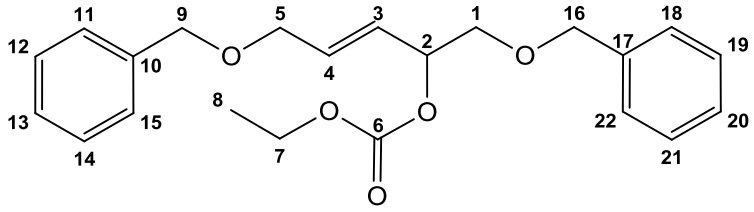
^{1}H-NMR (500 MHz, DMSO-d_6): δ ppm 3.34 (dd, *J*=5.87, 2.21 Hz, 2H) 3.97 (d, *J*=4.12 Hz, 2H) 4.18 (t, *J*=5.26 Hz, 1H) 4.44 (s, 2H) 4.49 (s, 2H) 4.98 (d, *J*=5.04 Hz, 1H) 5.54 (dd, *J*=5.57, 4.50 Hz, 2H) 7.21-7.40 (m, 10H)

^{13}C NMR (500MHz, DMSO-d_6): δ ppm 69.3323 (C_2), 69.6113 (C_5), 71.0664 (C_6 or C_{13}), 72.1552 (C_6 or C_{13}), 74.3319 (C_1), 126.6576 (C_3 or C_4), 128.2413 - 127.3527 (aromatic *C*H), 133.5996 (C_3 or C_4), 138.4864 (C_7 or C_{14}), 138.5284 (C_7 or C_{14})

HR-MS: calculated: 316.19072 $[M+NH_4]^+$, 321.14612 $[M+Na]^+$; found: 316.19076 $[M+NH_4]^+$, 321.14586 $[M+Na]^+$, Δm = 0.1-0.8 ppm

IR: 3430 (υ(OH)), 3087 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2856 (υ(CH) aliph. CH), 1604 (υ(phenyl)), 1586 (υ(phenyl)), 1496 (υ(phenyl)), 1454 (υ(phenyl)), 1102 (υ(C-O)), 1072 (υ(C-O)), 971 (δ(CH) C=C trans), 736 (δ(CH) arom. CH), 697 (monosub. benzene ring), 609 cm^{-1}

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl ethyl carbonate (69)



(*E*)-1,5-bis(benzyloxy)pent-3-en-2-ol **68** (0.52g, 1.743mmol, 1 eq.) was put in solution in 30mL THF at rt. DMAP (0.426g, 3.485mmol, 2 eq.) and pyridine (0.414g, 5.228mmol, 3 eq.) were added. The solution was cooled down at 0°C and ethylchloroformate (0.567g, 5.228mmol, 3 eq.) diluted in 5mL THF was drop wisely added at +1°C. A white suspension was formed and the solution was allowed to come at rt. Because of incomplete reaction, addition of pyridine and ethylchloroformate were added 4 more times as followed: pyridine (0.414g, 5.228mmol, 3 eq.) was added, the solution cooled down and ethylchloroformate (0.567g, 5.228mmol, 3 eq.) diluted in 5mL THF was drop wisely added at +1°C. After each portion, the reaction was allowed to come at rt and stirred for 2-16h. After reaction was complete, the mixture was poured on a cooled solution (0°C) of 40mL HCl 2N. Extraction with 100mL TMBE followed. The organic phase was extracted with 30mL HCl 2N, 100mL $NaHCO_3$ sat and 80mL NaCl sat. The organic phase was dried over anhydrous sodium sulfate and filtered. The solution was concentrated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the corresponding product: colorless oil (0.551g, 85% yield).

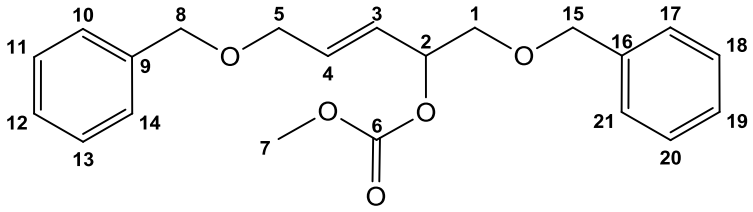
^{1}H-NMR: (500 MHz, DMSO-d_6) δ ppm 1.19 (t, *J*=7.10 Hz, 3H) 3.47-3.63 (m, 2H) 3.99 (d, *J*=5.19 Hz, 2H) 4.10 (q, *J*=7.02 Hz, 2H), 4.44 (s, 2H) 4.45-4.56 (m, 2H) 5.27 (q, *J*=5.80 Hz, 1H) 5.68-5.78 (m, 1H) 5.85 (t, *J*=5.11 Hz, 1H) 7.23-7.39 (m, 10H); $^3J_{H,H}$ = 15.69 Hz

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 14.01 (C_8), 63.52 (C_7), 68.96 (C_5), 70.84 (C_1), 71.32 (C_9 or C_{16}), 72.09 (C_9 or C_{16}), 75.98 (C_2), 126.41 (C_3 or C_4), 127.38 - 128.19 (aromatic *C*H), 130.77(C_3 or C_4), 138.04 (C_{10} or C_{17}), 138.24 (C_{10} or C_{17}), 153.95 (C_6)

HR-MS: calculated: 388.21185 $[M+NH_4]^+$, 393.16725 $[M+Na]^+$; found: 388.21206 $[M+NH_4]^+$, 393.16718 $[M+Na]^+$, Δm = 0.2 – 0.6 ppm

IR: 3088 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2859 (υ(CH) aliph. CH)), 1745 (υ(C=O)) 1604 (υ(Ph)), 1586 (υ(Ph)) 1496 (υ(Ph)), 1454 (υ(Ph)), 1258 (υ(C-O)), 1100 (υ(C-O)), 970 (δ(CH) C=C trans) 737 (monosub. C-H), 698 (monosub. Ph) cm^{-1}

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl methyl carbonate (70)



(*E*)-1,5-bis(benzyloxy)pent-3-en-2-ol **68** (2g, 6.703mmol, 1 eq.) was diluted in THF (70mL). DMAP (1.64g, 13.41mmol, 2 eq.) and pyridine (1.6mL, 20.108mmol, 3 eq.) were added to the solution at room temperature. The solution was cooled down at 0°C and methylchloroformate (1.6mL, 20.180mmol, 3 eq.) diluted in 7mL THF was added drop wise (formation of a white precipitate). After the addition, the solution was allowed to come at room temperature. Four more addition of pyridine (1.6mL, 20.108mmol, 3 eq.) and methylchloroformate (1.6mL, 20.180mmol, 3 eq.) at 0°C in an interval of 20h, 22h30, 27h30, 48h were made to complete the reaction. To quench the reaction, the mixture was poured to a cooled solution (0°C) of HCl 2N (150mL). An extraction followed with TBME (250mL). The organic phase was extracted with HCl 2N (80mL), $NaHCO_3$ sat (100mL), NaCl sat (100mL). The solution was concentrated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the corresponding product: colorless oil (1.509g, 4.23mmol, 63% yield) .

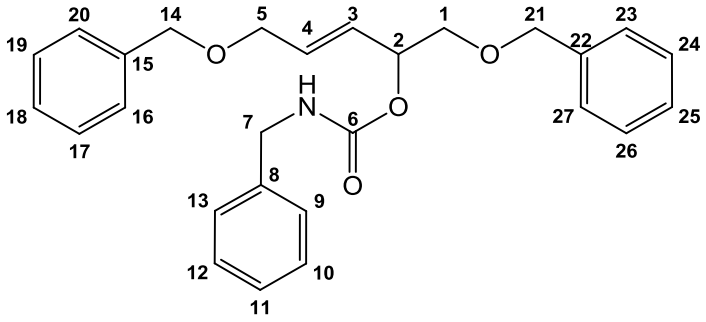
^{1}H-NMR: (500 MHz, DMSO-d_6) δ ppm 3.51 - 3.59 (m, 2 H) 3.68 (s, 3 H) 3.98 (d, *J*=5.04 Hz, 2 H) 4.44 (s, 2 H) 4.46 - 4.54 (m, 2 H) 5.24 - 5.30 (m, 1 H) 5.70 - 5.77 (m, 1 H) 5.83 - 5.90 (m, 1 H) 7.24 - 7.36 (m, 10 H)

^{13}C-NMR: (125 MHz, DMSO-d_6) δ ppm 54.66 (C_7), 68.96 (C_5), 70.78 (C_1), 71.35 (C_8 or C_{15}), 72.09 (C_8 or C_{15}), 76.30 (C_2), 126.30 (C_3 or C_4), 127.43-128.36 (aromatics *C*H), 130.88 (C_3 or C_4), 137.99 (C_9 or C_{16}), 138.32 (C_9 or C_{16}), 154.61 (C_6)

HR-MS: calculated: 374.19620 $[M+NH_4]^+$; found: 374.19602 $[M+NH_4]^+$, Δm = 0.5ppm

IR: 3088 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2955 (υ(CH) aliphatic CH), 2857 (υ(CH) aliphatic CH), 1749 (υ(C=O)), 1605 (υ(phenyl)), 1586 (υ(phenyl)), 1496 (υ(phenyl)), 1453 (υ(phenyl)), 1442 (δ(CH) aliphatic), 1308 (υ(C-O) carbonate), 1267 (υ(C-O) carbonate), 1116 (υ(C-O-C)), 738 (δ(C-H monosub.)), 698 (δ(phenyl)) cm^{-1}

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl benzylcarbamate (71)



(*E*)-1,5-bis(benzyloxy)pent-3-en-2-ol **68** (0.5g, 1.676 mmol, 1 eq.) was put in solution in 5mL toluene at rt. Benzylisocyanate (0.29g, 2.178mmol, 1.3 eq.) was added at rt then the reaction was allowed to reflux ($T_{oil\ bath}$ = 123°C). After 1h, the reaction was finished. The solution was cooled down at rt and the solvent evaporated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the desired product: white viscous oil (0.6g, 83% yield).

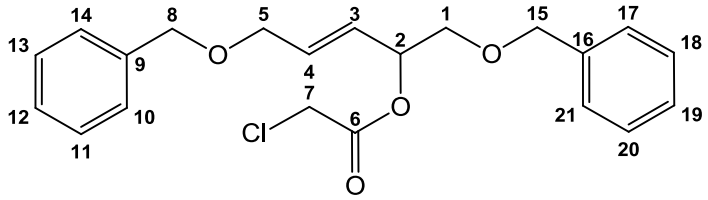
^{1}H-NMR: (500 MHz, DMSO-d_6) δ ppm 3.54 (d, *J*=3.51 Hz, 2H) 3.98 (d, *J*=4.73 Hz, 2H) 4.18 (d, *J*=5.80 Hz, 2H) 4.44 (s, 2H) 4.45-4.56 (m, 2H) 5.32 (d, *J*=5.04 Hz, 1H) 5.72-5.87 (m, 2H) 7.17-7.36 (m, 15H) 7.8 (t, *J*=6.03 Hz, 1H); $^3J_{HH}$ = 16.76 Hz

^{13}C-NMR: (500 MHz, DMSO-d_6) δ ppm 43.7455 (C_7), 69.1951 (C_5), 71.2267 (C_1), 71.3280 (C_{14} or C_{21}), 71.9862 (C_2), 72.0923 (C_{14} or C_{21}), 126.7323 - 128.3848 (aromatic *C*H), 129.1552 (C_3 or C_4), 138.2103 (C_8 or C_{15} or C_{22}), 138.3434 (C_8 or C_{15} or C_{22}), 139.8016 (C_8 or C_{15} or C_{22}), 155.8950 (C_6)

HR-MS: calculated: 432.21693 $[M+H]^+$ 454.19888 $[M+Na]^+$; found: 432.21680 $[M+H]^+$ 454.19866 $[M+Na]^+$, Δm = 0.3ppm

IR: 3334 (υ(N-H)), 1721 (υ(C=O)), 1519 (amide) 1497 (υ(Ph)), 1454 (υ(Ph)), 1245 (υ(C-O)), 1116 (υ(C-O)), 1028 (δ_{ip}(CH) arom. CH), 970 (δ(CH) C=C trans), 738 (δ(CH) arom. CH), 698 (δ(Ph)) cm^{-1}

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl 2-chloroacetate (72)



(*E*)-1,5-bis(benzyloxy)pent-3-en-2-ol **68** (4,428g, 14.84 mmol, 1 eq.) was put in solution in 94mL toluene and 31mL THF (75:25). DMAP (0.363g, 2.968 mmol, 0.2 eq.) and pyridine (2.347g, 29.68 mmol, 2 eq.) were added at room temperature. The solution was cooled down at 0°C. Chloracetylchloride (3.352g, 29.68mmol, 2 eq.) diluted in 15mL toluene was slowly added at +1-2°C. A white precipitate was formed. After 1h, the reaction mixture was poured to 150mL H_2O and 300mL TBME was added. The organic phase was extracted with 1x 150mL $NaHCO_3$ sat, 1x 150mL HCl 2N, 2x 150ml H_2O, 1x 150mL NaCl sat. and 1x 150mL H_2O. The organic phase was dried over anhydrous magnesium sulfate and filtered. The solution was concentrated under reduced pressure. Flash column chromatography (9:1

hexane:EtOAC) of the crude gave the corresponding product: colorless oil (5.228g, 13.919 mmol, 94% yield).

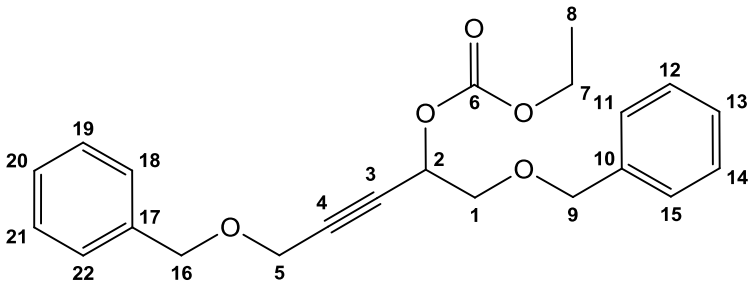
^{1}H-NMR: (600 MHz, DMSO-d_6) δppm 3.38 (br. s., 1H) 3.55 - 3.62 (m, 2 H) 4.00 (d, *J*=5.12 Hz, 2 H) 4.41 (d, 1 H) 4.46 (d, 2 H) 4.50 (d, 1 H) 4.55 (d, *J*=12.30 Hz, 1 H) 5.53 (dt, *J*=6.22, 5.73 Hz, 1 H) 5.77 (dd, *J*=15.73, 6.22 Hz, 1 H) 5.91 (dt, *J*=15.73, 5.12 Hz, 1 H) 7.13 - 7.47 (m, 10 H)

^{13}C-NMR: (150 MHz, DMSO-d_6) δ ppm 41.15 (C_7), 68.99 (C_5), 70.66 (C_1) 71.36 (C_8 or C_{15}), 72.12 (C_8 or C_{15}), 74.00 (C_2), 126.19 (C_3 or C_4), 127.33 – 128.29 (aromatic *C*H), 130.64 (C_3 or C_4), 138.02 (C_9 or C_{16}), 138.22 (C_9 or C_{16}), 166.61 (C_6)

HR-MS: calculated: 392.16638 $[M+NH_4]^+$; found: 392.16248 $[M+NH_4]^+$, Δm = 0.4ppm

IR: 3088 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2859 (υ(CH) aliph. CH), 1759 (υ(C=O) ester), 1605 (υ(phenyl)), 1586 (υ(phenyl)), 1496 (υ(phenyl)), 1454 (υ(phenyl)), 1183 (υ(C-O-C)), 1114 (υ(C-O-C)), 969 (δ(CH) C=C trans) cm^{-1}

1,5-bis(benzyloxy)pent-3-yn-2-yl ethyl carbonate (73)



Benzyl propagyl ether (2g, 13.68 mmol, 1 eq.) was put in solution in 20mL THF. The light yellow solution was cooled down at -78°C. Commercially available LDA 2M (6.84mL, 13.68 mmol, 1 eq.) was slowly added to the solution during 15min at -75°C. Benzyloxyactaldehyde (2.05g, 13.68mmol, 1 eq.) was slowly added at -75°C. After 1h, ethylchloroformate (2.97g,

27.36mmol, 2 eq.) was added at -75°C then the solution was allowed to come at rt. Extraction followed with 100mL $NaHCO_3$ sat, 100mL ammonium chlorid sat, the aqueous phase was washed with 2x 50mL CH_2Cl_2. The collected organic phases were dried over sodium sulfate and filtered. The solution was concentrated under reduced pressure. Flash column chromatography (6:1 HXF:ESTP) of the crude gave the desired product (3.432g, 68% yield).

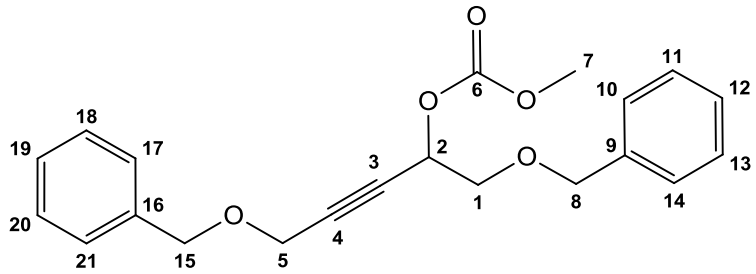
^{1}H-NMR: (500 MHz, DMSO-d_6) δ ppm 1.21 (t, *J*=7.10 Hz, 3H) 3.69 (d, *J*=5.49 Hz, 2H) 4.14 (q, *J*=7.02 Hz, 2H) 4.23 (d, *J*=1.68 Hz, 2H) 4.49 (s, 2H) 4.51-4.59 (m, 2H) 5.48 (tt, *J*=1.60 Hz, 1H) 7.22-7.40 (m, 3H) 7.22-7.40 (m, *J*=8.26, 8.26, 8.05, 1.68 Hz, 7H)

^{13}C-NMR: (500 MHz, DMSO-d_6) δ ppm 14.0393 (C_8), 56.8081 (C_5), 64.1613 (C_7), 66.4455 (C_2), 70.4967 (C_1), 70.8324 (C_9 or C_{16}), 72.2059 (C_9 or C_{16}), 81.0137 (C_3 or C_4), 83.4652 (C_3 or C_4), 127.5596 - 128.3077 (aromatic *C*H), 137.4861 (C_{10} or C_{17}), 137.8506 (C_{10} or C_{17}), 153.7194 (C_6)

HR-MS: calculated: 386.20027 $[M+NH_4]^+$; found: 386.19629 $[M+NH_4]^+$, Δm = 0.2 ppm

IR: 3088 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2865 (υ(CH) aliph. CH), 1749 (υ(C=O)), 1497 (benzene rings stretching), 1455 (benzene rings stretching), 1255 (υ(C-O)), 1093 (υ(C-O)), 1074 (υ(C-O)), 1027 (υ(C-O)), 1008 (υ(C-O)), 738 (monosubs. benzene), 698 (monosubs. benzene) cm^{-1}

1,5-bis(benzyloxy)pent-3-yn-2-yl methyl carbonate (74)



1,5-bis(benzyloxy)pent-3-yn-2-ol **67** (4g, 13.497mmol, 1 eq.) was put in solution in 300mL THF at rt. DMAP (3.298g, 26.994mmol, 2 eq.) and pyridine (3.203g, 40.491mmol, 3 eq.) were added at rt and the solution cooled down at 0°C. Methylchloroformate (3.826g, 40.491, 3 eq.) diluted in 5mL THF was slowly added. A white precipitate was formed. The solution was allowed to come at rt. Because of incomplete reaction, addition of pyridine and ethylchloroformate followed 5 more times as followed: pyridine (3.203g, 40.491mmol, 3 eq.) was added, the solution cooled down and methylchloroformate (3.826g, 40.491, 3 eq.) diluted in 5mL THF was drop wisely added at +1°C. After each portion, the reaction was allowed to come at rt and stirred for 2-15h. To quench the reaction, the mixture was poured on a cooled solution (0°C) of 300mL HCl 2N. Extraction with 150mL TMBE followed. The organic phase was extracted with 200mL $NaHCO_3$ sat and 200mL NaCl sat. The organic phase was dried over anhydrous magnesium sulfate and filtered. The solution was concentrated under reduced pressure. Flash column chromatography (7:3 hexane:EtOAC) of the crude gave the corresponding product: colorless oil (3.325g, 70% yield).

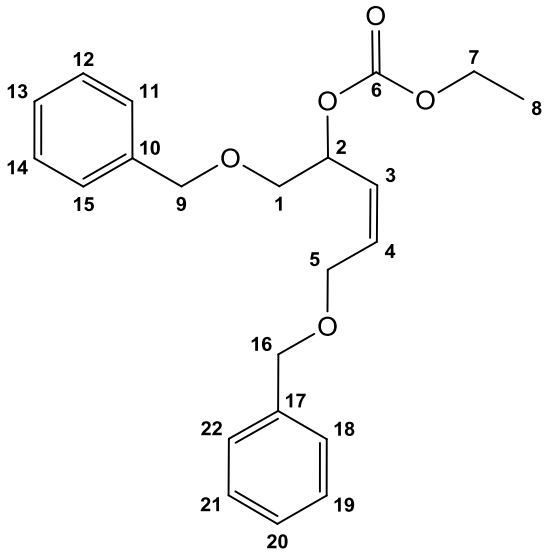
^{1}H NMR: (400 MHz, DMSO-d_6) δ ppm 3.34 (br. s., 1 H) 3.70 (d, *J*=5.52 Hz, 2 H) 3.73 (s, 3 H) 4.24 (d, *J*=1.00 Hz, 2 H) 4.50 (s, 2 H) 4.52 - 4.61 (m, 2 H) 5.48 (t, *J*=5.40 Hz, 1 H) 7.25 - 7.38 (m, *J*=6.90, 6.90, 6.90, 6.65, 6.53 Hz, 10 H)

^{13}C-NMR: (500 MHz, DMSO-d_6) δ ppm 55.1005 (C_7), 56.8167 (C_5), 66.3900 (C_2), 70.4490 (C_8 or C_{15}), 70.8624 (C_1), 72.2130 (C_8 or C_{15}), 80.9329 (C_3 or C_4), 83.5515 (C_3 or C_4), 126.6494 - 129.1706 (aromatic *C*H), 137.4887 (C_9 or C_{16}), 137.8420 (C_9 or C_{16}), 154.3641 (C_6)

HR-MS: calculated: 372.18055 $[M+NH_4]^+$, 377.13595 $[M+Na]^+$; found: 372.18074 $[M+NH_4]^+$, 377.13590 $[M+Na]^+$, Δm = 0.1-0.5 ppm

IR: 3089 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3032 (υ(CH) arom. CH), 2956 (υ(CH) aliph. CH), 2865 (υ(CH) aliph. CH), 2203 (υ(C≡C)), 1754 (υ(C=O)), 1605 (υ(Ph)), 1586 (υ(Ph)), 1497 (υ(Ph)), 1454 (υ(Ph)), 1443 (δ(C-H)), 1266 (υ(C-O)), 1098 (υ(C-O)), 1074 (υ(C-O)), 742 (monosub. C-H), 699 (monosub. Ph) cm^{-1}

(*Z*)-1,5-bis(benzyloxy)pent-3-en-2-yl ethyl carbonate (75)



1,5-bis(benzyloxy)pent-3-yn-2-yl ethyl carbonate **73** (1g, 2.714mmol, 1 eq.) was put in solution in 20mL ethanol (ALI) at room temperature and 2,2'-Bipyridyl (0.212g, 1.357mmol, 0.5 eq.) was added. The air contained in the flask was replaced with argon and Pd on $BaSO_4$ (0.1g, 10% m/m) was added. The argon was replaced with a balloon of H_2(g) at atmospheric pressure. After 3h, the suspension was filtered through cellflok and washed with ethanol (ALI). The solvent was evaporated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the corresponding product: (0.898g, 2.424mmol, 89% yield).

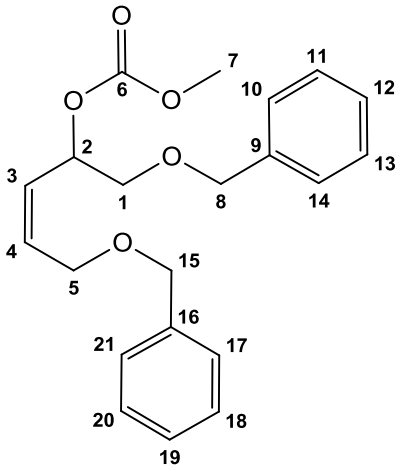
^{1}H-NMR: (500 MHz, DMSO-d_6) δ 1H NMR (500 MHz, DMSO-d_6) δ ppm 1.18 (t, *J*=7.10 Hz, 3 H) 3.46 - 3.59 (m, 2 H) 4.08 (d, *J*=7.02 Hz, 2 H) 4.12 (td, *J*=3.05, 1.37 Hz, 2 H) 4.45 (s, 2 H) 4.45 - 4.52 (m, 2 H) 5.46 - 5.55 (m, 2 H) 5.78 (ddd, *J*=10.19, 6.18, 6.07 Hz, 1 H) 7.24 - 7.36 (m, 10 H); $^{3}J_{HH}$ (cis) = 10 Hz

^{13}C-NMR: (100 MHz, DMSO-d_6) δ ppm 14.0672 (C_8), 63.6160 (C_7), 65.6984 (C_5), 70.6972 (C_1), 71.5097 (C_9 or C_{16}), 72.1017 C_9 or C_{16}), 72.7366 (C_2), 126.7877 (C_3 or C_4), 127.4363 - 128.2638 (aromatic *C*H), 131.7887 (C_3 or C_4), 138.0393 (C_{10} or C_{17}), 138.2329 (C_{10} or C_{17}), 153.9841 (C_6)

HR-MS: calculated: 388.21185 $[M+NH_4]^+$, 393.16725 $[M+Na]^+$ 409.14118 $[M+K]^+$; found: 388.21214 $[M+NH_4]^+$, 393.16709 $[M+Na]^+$, 409.14112 $[M+K]^+$, Δm = 0.1-0.7 ppm

IR: 3088(υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2983 (υ(CH) aliph. CH), 2861 (υ(CH) aliph. CH), 1744 (υ(C=O)), 1586 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1260 (υ(C-O) carbonate), 737 (monosub. C-H), 698 (monosub. Ph) cm^{-1}

(*Z*)-1,5-bis(benzyloxy)pent-3-en-2-yl methyl carbonate (76)



1,5-bis(benzyloxy)pent-3-yn-2-yl methyl carbonate **74** (500mg, 1.411mmol, 1 eq.) was put in solution in ethanol (20mL) ALI at room temperature. 2,2'-Bipyridyl (110mg, 0.705mmol, 0.5 eq.) was added and air was replaced with argon. Lindlar catalyst (0.075g, 15% w/w) was added and argon was replaced with H_2(g) (atmospheric pressure). After 15min, the reaction was stopped in replacing the H_2(g) with argon, filtered through a spritzenfilter and washed with ethanol (25mL). The solution was concentrated under reduced pressure. Flash column chromatography (4:2 hexane:EtOAC) of the crude gave the corresponding product: colorless oil (502mg, 1.408mmol, 99% yield).

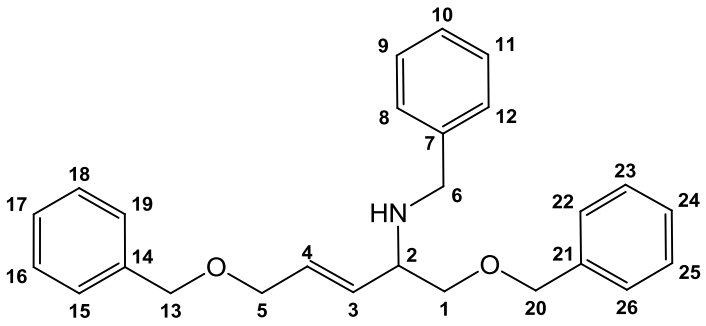
^{1}H-NMR: ^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.49 - 3.64 (m, 2 H) 3.76 (s, 3 H) 4.17 - 4.21 (m, 2 H) 4.50 (d, *J*=1.26 Hz, 2 H) 4.53 (d, *J*=3.26 Hz, 2 H) 5.49 - 5.61 (m, 2 H) 5.85 (ddd, *J*=10.16, 6.15, 6.02 Hz, 1 H) 7.24 - 7.37 (m, 10 H); $^{3}J_{HH}$ = 10.1 Hz

^{13}C-NMR: (125 MHz, DMSO-d_6) δ ppm 54.66 (C_7), 65.67 (C_5), 70.62 (C_1), 71.49 (C_8 or C_{15}), 72.08 (C_8 or C_{15}), 73.00 (C_2), 126.68 (C_3 or C_4), 127.41 - 128.24 (aromatic *C*H), 131.84 (C_3 or C_4), 137.98 (C_9 or C_{16}), 138.00 (C_9 or C_{16}), 154.60 (C_6)

HR-MS: calculated 357.16966 $[M+H]^+$, 374.20027 $[M+NH_4]^+$, 379.15159 $[M+Na]^+$, 395.12553 $[M+K]^+$, found: 357.16986 $[M+H]^+$, 374.19635 $[M+NH_4]^+$, 379.15158 $[M+Na]^+$, 395.12558 $[M+K]^+$, Δm = 0.1-0.6 ppm

IR: 3088 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2955 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1748 (υ(C=O)), 1605 (arom. rings stretch), 1586 (arom. rings stretch), 1496 (arom. rings stretch), 1269 (υ(C-O) carbonate), 1093 (υ(C-O)), 939 (υ(C-O)), 738 (monosub. benzolring), 699 (monosub. benzolring) cm^{-1}

(*E*)-*N*-benyzl-1,5-bis(benzyloxy)pent-3-en-2-amine (80)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.89 (br. s., 1 H) 3.39 - 3.54 (m, 3 H) 3.60 - 3.90 (m, 2 H) 4.03 (dd, *J*=5.90, 1.38 Hz, 2 H) 4.49 (d, *J*=2.01 Hz, 2 H) 4.51 (s, 2 H) 5.55 - 5.65 (m, 1 H) 5.83 (dt, *J*=15.50, 5.68 Hz, 1 H) 7.20 - 7.40 (m, 15 H)

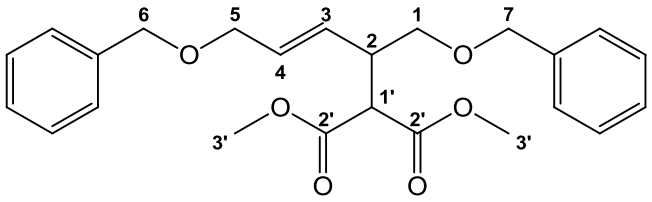
^{13}C-NMR: (100MHz, DMSO-d_6): δ ppm 50.16 (C_6), 58.30 (C_2), 69.62 (C_5), 70.93 (C_{13} or C_{20}), 71.99 (C_{13} or C_{20}), 72.94 (C_1), 126.44-128.18 (aromatic *C*H), 128.73 (C_3 or C_4), 132.89 (C_3 or C_4), 138.37 (C_7 or C_{14} or C_{21}), 138.44 (C_7 or C_{14} or C_{21}), 140.92 (C_7 or C_{14} or C_{21})

HR-MS: calculated: 388.22711 $[M+H]^+$; found: 388.22733 $[M+H]^+$, Δm = 0.6 ppm

IR: 3327 (υ(N-H)), 3086 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3029 (υ(CH) arom. CH), 2854 (υ(CH) aliph. CH), 1604 (arom. rings stretch), 1586 (arom. rings stretch), 1496 (arom. rings stretch), 1094 (υ(C-O) ether), 974 (δ(CH) C=C trans) 736 (monosub. C-H), 698 (monosub. Ph) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 7.5 min ((*Z*)-**80**), t_R = 8.4 min ((*E*)-**80**), t_R = 8.9 min ((*Z*)-***ent*-80**), t_R = 10.5 min ((*E*)-***ent*-80**)

(*E*)-dimethyl 2-(1,5-bis(benzyloxy)pent-3-en-2-yl)malonate (94)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H NMR: (600 MHz, DMSO-d_6) δ ppm 3.06 - 3.12 (m, 1 H) 3.51 (d, *J*=6.22 Hz, 2 H) 3.61 (d, *J*=2.20 Hz, 6 H) 3.70 (d, *J*=8.42 Hz, 1 H) 3.94 (d, *J*=4.02 Hz, 2 H) 4.44 (d, *J*=11.71 Hz, 4 H) 5.68 - 5.72 (m, 2 H) 7.26 - 7.38 (m, 10 H)

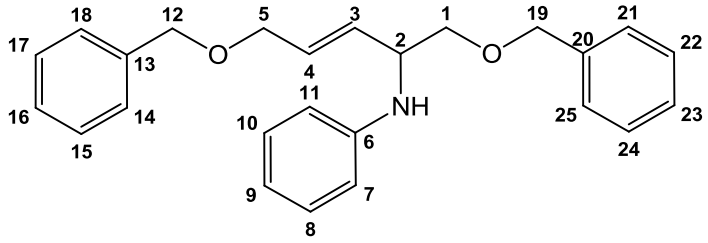
^{13}C NMR: (151 MHz, DMSO-d_6) δ ppm 42.00 (C_2), 51.91 ($C_{3'}$), 52.04 ($C_{3'}$), 52.75 ($C_{1'}$), 69.40 (C_5), 70.58 (C_1), 70.71 (C_6 or C_7), 72.04 (C_6 or C_7), 126.88-128.27 (aromatic *C*H), 129.61 (C_3 or C_4), 129.83 (C_3 or C_4), 138.04 (quaternary C), 138.31 (quaternary C), 167.90 (C=O), 168.01 (C=O)

HR-MS: calculated: $[M+H]^+$ = 413.19587; found: $[M+H]^+$ = 413.19577

IR: 3088 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 3006 (υ(CH) arom. CH), 2952 (υ(CH) aliph. C-H), 2857 (υ(CH) aliph. C-H), 1736 (υ(C=O)), 1605 (arom. rings stretching), 1586 (arom. rings stretching), 1496 (arom. rings stretching), 1454 (arom. rings stretching), 1246 (υ(C-O)), 1099 (υ(C-O-C)), 1027 (υ(C-O)), 975 (δ(CH) C=C trans), 738 (δ(C-H) monosubst.), 698 (δ(Ph) monosubst.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 14.8 min ((*E*)-**94**), t_R = 17.1 min ((*E*)-***ent*-94**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)aniline (95)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 3.45 - 3.55 (m, 2 H) 3.94 (d, *J*=5.18 Hz, 2 H) 4.06 - 4.14 (m, *J*=6.38, 6.38, 6.25, 6.00 Hz, 1 H) 4.37 (s, 2 H) 4.50 (d, *J*=1.14 Hz, 2 H) 5.53 (d, *J*=7.71 Hz, 1 H) 5.62 - 5.70 (m, 1 H) 5.72 - 5.81 (m, 1 H) 6.48 (t, *J*=7.20 Hz, 1 H) 6.58 (d, *J*=8.46 Hz, 2 H) 7.01 (t, *J*=7.52 Hz, 2 H) 7.19 - 7.37 (m, 10 H)

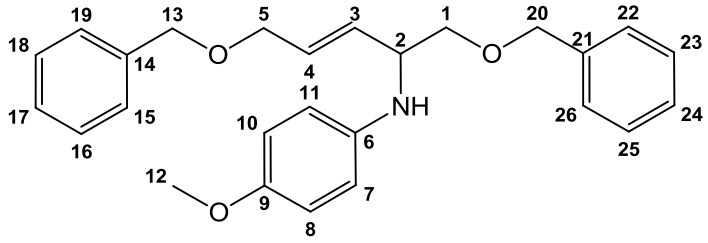
^{13}C-NMR: (100 MHz, DMSO-d_6) δ ppm 53.50 (C_2), 69.37 (C_5), 70.74 (C_1 or C_{12} or C_{19}), 71.93 (C_1 or C_{12} or C_{19}), 72.07 (C_1 or C_{12} or C_{19}), 112.45 (aromatic *C*H aniline), 115.50 (aromatic *C*H aniline), 127.06 - 127.86 (aromatic *C*H), 128.41 (aromatic *C*H aniline), 131.80 (C_3 or C_4), 138.00 (C_{13} or C_{20}), 174.52 (C_6)

HR-MS: calculated: 374.21146 $[M+H]^+$; found: 374.21137 $[M+H]^+$, Δm = 0.2 ppm

IR: 3395 (υ(N-H)), 3087(υ(CH) arom. CH), 3029(υ(CH) arom. CH), 2856 (υ(CH) aliph. CH), 1602 (benzene rings stretch), 1504 (benzene rings stretch), 1100 (υ(C-O)), 1074 (υ(C-O)), 972 (δ(CH) C=C trans), 748 (monosubst. benzene), 695 (monosubst. benzene), 605 cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 10.1 min ((*E*)-**95**), t_R = 10.7 min ((*E*)-***ent*-95**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-4-methoxyaniline (96)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 3.43 - 3.53 (m, 2 H) 3.60 (s, 3 H) 3.94 (d, *J*=5.43 Hz, 2 H) 3.97 - 4.05 (m, 1 H) 4.36 (s, 2 H) 4.50 (d, *J*=2.27 Hz, 2 H) 5.09 (d, *J*=7.83 Hz, 1 H) 5.60 - 5.69 (m, 1 H) 5.70 - 5.79 (m, 1 H) 6.50 - 6.58 (m, 2 H) 6.61 - 6.68 (m, 2 H) 7.20 - 7.34 (m, 10 H)

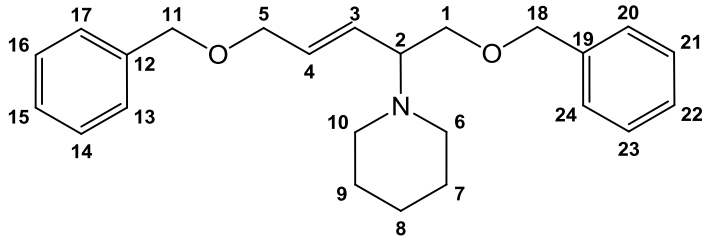
^{13}C-NMR: (100 MHz, DMSO-d_6) δ ppm 54.33 (C_2), 55.19 (C_{12}), 69.40 (C_5), 70.67 (C_{13} or C_{20}), 71.93 (C_{13} or C_{20}), 72.19 (C_1), 113.72 (aromatic *C*H methoxyphenyl), 114.17 (aromatic *C*H methoxyphenyl), 127.85 - 127.05 (aromatic *C*H and C_3 or C_4), 132.28 (C_3 or C_4), 137.99 (C_{14} or C_{21}), 141.66 (C_6), 150.36 (C_9)

HR-MS: calculated: 404.22202 $[M+H]^+$; found: 404.22223 $[M+H]^+$, Δm = 0.5 ppm

IR: 3382 (υ(N-H)), 3087 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2856 (υ(CH) aliph. CH), 1618 (υ(Ph)), 1512 (υ(Ph)), 1454 (υ(Ph)), 1100 (υ(C-O)), 1074 (υ(C-O)), 1039 (υ(C-O)), 973 (δ(CH) C=C trans), 820 (paradisub. C-H), 737 (monosub. C-H), 698 (monosub. Ph) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 17.1 min ((*Z*)-**96**), t_R = 18.6 min ((*E*)-**96**), t_R = 23.1 min ((*E*)-***ent*-96**), t_R = 25.3 min ((*Z*)-***ent*-96**)

(*E*)-1-(1,5-bis(benzyloxy)pent-3-en-2-yl)piperidine (97)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 1.29 - 1.36 (m, 2 H) 1.41 - 1.48 (m, 4 H) 2.38 - 2.48 (m, 4 H) 3.11 (t, *J*=5.85 Hz, 1 H) 3.48 (dd, *J*=9.51, 6.59 Hz, 1 H) 3.58 (dd, *J*=9.88, 5.85 Hz, 1 H) 3.99 (d, *J*=4.03 Hz, 2 H) 4.45 (s, 2 H) 4.46 (s, 2 H) 5.63 - 5.73 (m, 2 H) 7.22 - 7.38 (m, 10 H)

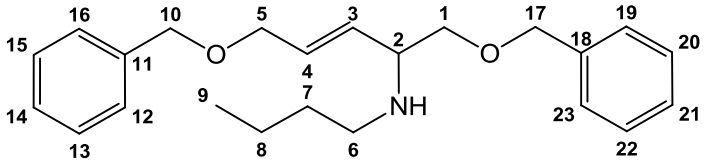
^{13}C-NMR: (150 MHz, DMSO-d_6) δ ppm 24.37 (C_8), 26.03 (C_6 and C_{10} or C_7 and C_9), 50.49 (C_6 and C_{10} or C_7 and C_9), 65.58 (C_2), 69.76 (C_5), 70.95 (C_{11} or C_{18}), 72.04 (C_{11} or C_{18}), 126.98-128.42 (aromatic *C*H), 129.29 (C_3 or C_4), 130.53 (C_3 or C_4), 138.45 (C_{12} or C_{19}), 138.52 (C_{12} or C_{19})

HR-MS: calculated: 366.24276 $[M+H]^+$; found: 366.24297 $[M+H]^+$, Δm = 0.6 ppm

IR: 3087 (υ(C-H) arom. CH), 3063 (υ(C-H) arom. CH), 3030 (υ(C-H) arom. CH), 2932 ($\upsilon_{as}(CH_2)$), 2853 ($\upsilon_{s}(CH_2)$), 2798 (N-CH), 2751 (N-CH), 1605 (υ(Ph)), 1586 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1102 (υ(C-O-C)), 1028 (δ(C-H) monosub.), 975 (δ (C-H) C=C trans), 736 (δ(C-H) monosub.), 698 (δ(C-H) monosub.) cm^{-1}

HPLC: C-HPLC 8 (1 mL/min, 40°C), t_R = 14.5 min ((*E*)-**97**), t_R = 14.8 min ((*E*)-***ent*-97**)

(*E*)-1,5-bis(benzyloxy)-*N*-butylpent-3-en-2-amine (98)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 0.82 - 0.89 (m, 3 H) 1.21 - 1.32 (m, 2 H) 1.32 - 1.42 (m, 2 H) 2.36 - 2.57 (m, 2 H) 3.29 (dd, *J*=7.50, 6.59 Hz, 1 H) 3.33 - 3.41 (m, 2 H) 3.98 (d, *J*=5.85 Hz, 2 H) 4.45 (s, 2 H) 4.49 (s, 2 H) 5.52 (dd, *J*=15.55, 7.50 Hz, 1 H) 5.74 (dd, *J*=15.55, 5.85 Hz, 1 H) 7.24 - 7.39 (m, 10 H)

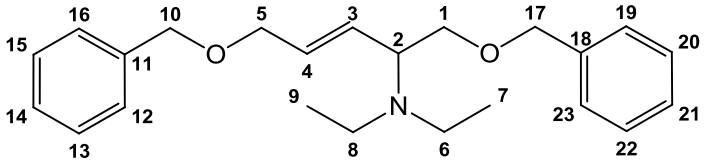
^{13}C-NMR: (150 MHz, DMSO-d_6) δ ppm 13.83 (C_9), 19.96 (C_6 or C_7 or C_8), 31.90 (C_6 or C_7 or C_8), 46.44 (C_6 or C_7 or C_8), 59.43 (C_2), 69.67(C_5), 70.95 (C_{10} or C_{17}), 72.09 (C_{10} or C_{17}), 73.04 (C_1), 127.32-128.26 (aromatic *C*H), 128.34 (C_3 or C_4), 133.30 (C_3 or C_4), 138.40 (C_{11} and C_{18})

HR-MS: calculated: 354.24276 $[M+H]^+$; found: 354.24297 $[M+H]^+$, Δm = 0.6 ppm

IR: 3326 (υ(N-H)), 3088 (υ(C-H) arom. CH), 3064 (υ(C-H) arom. CH), 3030 (υ(C-H) arom. CH), 2956 (υ(C-H) aliph. CH), 2928 (υ(C-H) aliph. CH), 2857 (υ(C-H) aliph. CH), 1605 (υ(Ph)), 1496 (υ(Ph)), 1455 (υ(Ph)), 1097 (υ(C-O-C), 1028 (δ_{ip}(C-H) monosub.), 974 (δ_{oop}(C-H) C=C), 736 (δ(C-H) monosub.) 698 (δ(Ph) monosub.) cm^{-1}

HPLC: C-HPLC 8 (1 mL/min, 40°C), t_R = 13.6 min ((*Z*)-**98**), t_R = 13.8 min ((*Z*)-***ent*-98**), t_R = 14.4 min ((*E*)-**98**), t_R = 14.6 min ((*E*)-***ent*-98**)

(*E*)-1,5-bis(benzyloxy)-*N*,*N*-diethylpent-3-en-2-amine (99)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 0.90 - 0.99 (m, 6 H) 2.34 - 2.46 (m, 2 H) 2.49 - 2.61 (m, 2 H) 3.37 - 3.42 (m, 1 H) 3.46 - 3.60 (m, 2 H) 3.99 (d, *J*=4.39 Hz, 2 H) 4.45 (s, 2 H) 4.48 (s, 2 H) 5.68 - 5.72 (m, 2 H) 7.24 - 7.37 (m, 10 H)

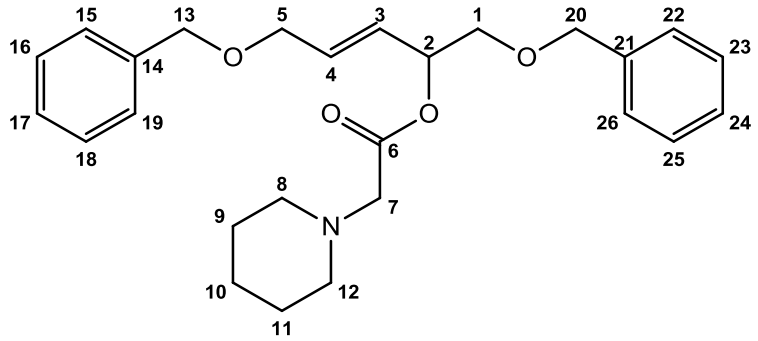
^{13}C-NMR: (150 MHz, DMSO-d_6) δ ppm 13.89 (C_7 and C_9), 43.69 (C_6 and C_8), 60.63 (C_2), 69.84 (C_5), 70.89 (C_{10} or C_{17}), 71.31 (C_1), 72.10 (C_{10} or C_{17}), 127.24-128.11 (aromatic *C*H), 129.00 (C_3 or C_4), 130.99 (C_3 or C_4), 138.46 (C_{11} or C_{18})

HR-MS: calculated: 354.24276 $[M+H]^+$; found: 354.24301 $[M+H]^+$, Δm = 0.7 ppm

IR: 3088 (υ(CH) arom. CH), 3064 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2968 (υ(C-H) aliph. CH), 2930 (υ(C-H) aliph. CH), 2854 (υ(C-H) aliph. CH), 1605 (υ(phenyl)), 1587 (υ(phenyl)), 1496 (υ(phenyl)), 1454 (υ(phenyl)), 1100 (υ(C-O-C)), 1075 (υ(C-O-C)), 1028 (δ_{ip}(C-H) monosub.) 974 (δ(CH) C=C trans), 736 (δ(C-H) monosub.), 698 (δ(Ph) monosub.) cm^{-1}

HPLC: C-HPLC 6 (1 mL/min, 30°C), t_R = 9.7 min ((*Z*)-**99**), t_R = 13.6 min ((*E*)-**99**), t_R = 14.9 min ((*Z*)-***ent*-99**), t_R = 16.1 min ((*E*)-***ent*-99**)

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl 2-(piperidin-1-yl)acetate (100)



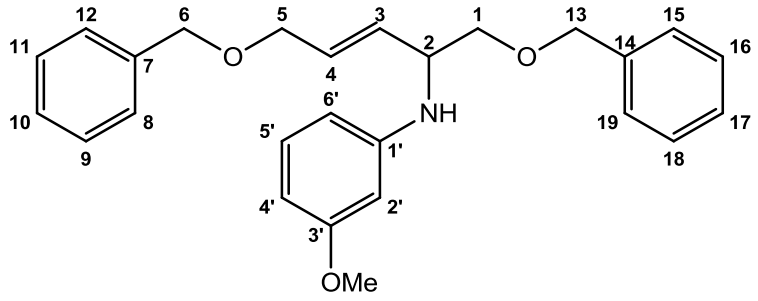
^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.29 - 1.38 (m, 2 H) 1.46 (quin, *J*=5.40 Hz, 4 H) 2.44 (br. s., 4 H) 3.21 (br. s., 2 H) 3.50 - 3.60 (m, 2 H) 3.99 (d, *J*=5.02 Hz, 2 H) 4.44 (s, 2 H) 4.46 - 4.56 (m, 2 H) 5.48 (q, *J*=5.35 Hz, 1 H) 5.70 - 5.78 (m, 1 H) 5.80 - 5.89 (m, 1 H) 7.25 - 7.38 (m, 10 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 23.46 (C_{10}) 25.37 (C_9 + C_{11}) 53.14 (C_8 + C_{12}) 59.51 (C_7) 69.05 (C_5) 70.91 (C_1) 71.26 (C_{13}) 72.04 (C_2 + C_{20}) 127.01 (C_3) 127.43 - 128.24 (aromatic *C*H) 130.09 (C_4) 138.11 (quaternary C) 138.28 (quaternary C)

HR-MS: calculated 424.24824 $[M+H]^+$, 446.23018 $[M+Na]^+$, found: 424.24805 $[M+H]^+$, 446.23007 $[M+Na]^+$, Δm = 0.2-0.4 ppm

IR:3087 (υ(CH) arom. CH + olefinic CH), 3063 (υ(CH) arom. CH + olefinic CH), 3030 (υ(CH) arom. CH + olefinic CH), 2934 (υ(CH) aliph. CH), 2854 (υ(CH) aliph. CH), 1747 (υ(C=O) ester), 1650 (υ(C=C)), 1606 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1113 (υ(C-O)), 1028 (δ_{ip}(CH) mono-sub.), 968 (δ_{oop}(CH) olefinic CH), 738 (δ_{oop}(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-ene-2-yl)-3'-methoxyaniline (101)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.53 - 3.66 (m, 2 H) 3.75 (s, 3 H) 4.03 (d, *J*=5.77 Hz, 2 H) 4.08 (q, *J*=5.27 Hz, 1 H) 4.21 (br. s., 1 H) 4.48 (d, *J*=1.51 Hz, 2 H) 4.52 - 4.61 (m, 2 H) 5.75 (dt, *J*=15.60 Hz, 1 H) 5.85 - 5.94 (m, 1 H) 6.20 - 6.23 (m, 1 H) 6.24 - 6.31 (m, 2 H) 7.06 (t, *J*=8.16 Hz, 1 H) 7.28 - 7.39 (m, 10 H)

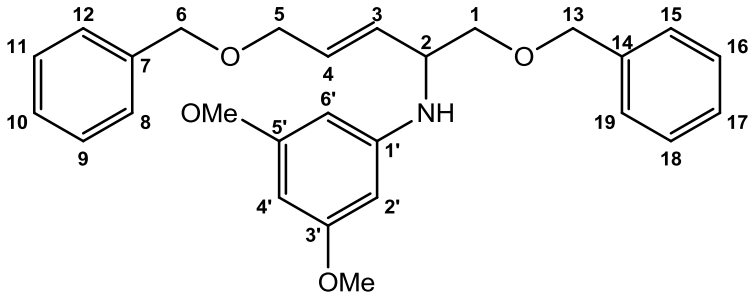
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 54.81 (C_2) 55.04 (Me) 70.11 (C_1 or C_5) 71.93 (C_6 or C_{13}) 72.47 (C_1 or C_5) 73.13 (C_6 or C_{13}) 99.79 ($C_{2'}$ or $C_{4'}$ or $C_{5'}$ or $C_{6'}$) 102.83 ($C_{2'}$ or $C_{4'}$ or $C_{5'}$ or $C_{6'}$) 106.86 ($C_{2'}$ or $C_{4'}$ or $C_{5'}$ or $C_{6'}$) 127.56-128.46 (aromatic *C*H) 128.78 (C_3 or C_4) 129.82 ($C_{2'}$ or $C_{4'}$ or $C_{5'}$ or $C_{6'}$) 132.23 (C_3 or C_4) 137.86 (quaternary C) 138.24 (quaternary C) 148.88 (quaternary C) 160.68 (quaternary C)

HR-MS: calculated: 404.22202 $[M+H]^+$; found: 404.22202 $[M+H]^+$, $\Delta m < 0.1$ ppm

IR: 3395 (υ(NH)), 3062 (υ(CH) arom. CH), 3029 (υ(CH) arom. CH), 2902 (υ(CH) aliph. CH), 2856 (υ(CH) aliph. CH), 1614 (aromatic rings stretching), 1508 (aromatic rings stretching), 1496 (aromatic rings stretching), 1454 (aromatic rings stretching), 1210 (various C-O), 1163 (various C-O), 1101 (various C-O), 972 (δ(CH) C=C trans), 739 (δ(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 20.2 min ((*Z*)-**101**), t_R = 24.8 min ((*E*)-**101**), t_R = 27.8 min ((*Z*)-***ent*-101**), t_R = 30.4 min ((*E*)-***ent*-101**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-3',5'-dimethoxyaniline (102)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.53 - 3.66 (m, 2 H) 3.73 (s, 6 H) 4.04 (d, *J*=6.27 Hz, 2 H) 4.05 - 4.10 (m, 1 H) 4.21 (br. s., 1 H) 4.44 - 4.51 (m, 2 H) 4.52 - 4.61 (m, 2 H) 5.74 (dt, *J*=15.60 Hz, 1 H) 5.84 (d, *J*=2.01 Hz, 2 H) 5.85 - 5.93 (m, 1 H) 5.88 - 5.89 (m, 1 H) 7.27 - 7.40 (m, 10 H)

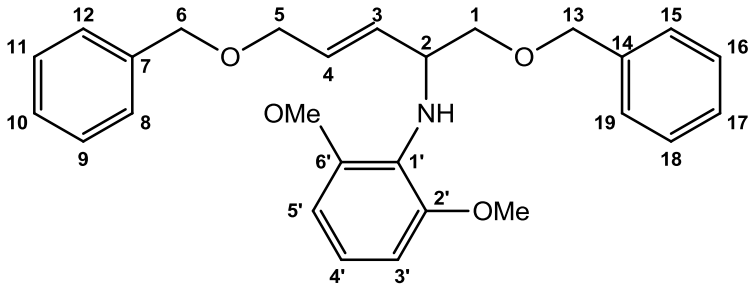
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 54.82 (C_2) 55.12 (2x Me) 70.12 (C_1 or C_5) 71.94 (C_6 or C_{13}) 72.46 (C_1 or C_5) 73.14 (C_6 or C_{13}) 90.07 ($C_{4'}$) 92.62 ($C_{2'}$ and $C_{6'}$) 127.56 (quaternary C) 127.74-128.46 (aromatic *C*H) 128.79 (C_3 or C_4) 132.25 (C_3 or C_4) 137.86 (quaternary C) 138.25 (quaternary C) 149.41 (quaternary C) 161.58 (quaternary C)

HR-MS: calculated: 434.23259 $[M+H]^+$; found: 434.23254 $[M+H]^+$, Δm = 0.1 ppm

IR: 3394 (υ(NH)), 3062 (υ(CH)), 3030 (υ(CH)), 2934 (υ(CH) aliph. CH), 2904 (υ(CH) aliph. CH), 2855 (υ(CH) aliph. CH), 1616 (aromatic rings stretching), 1512 (aromatic rings stretching), 1454 (aromatic rings stretching), 1205 (various C-O), 1152 (various C-O), 1101 (various C-O), 1069 (various C-O), 973 (δ(CH) C=C trans), 738 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 4 (1 mL/min, 30°C), t_R = 21.6 min ((*Z*)-**102**), t_R = 25.7 min ((*E*)-**102**), t_R = 29.7 min ((*Z*)-***ent*-102**), t_R = 36.1 min ((*E*)-***ent*-102**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-2',6'-dimethoxyaniline (103)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.61 - 3.73 (m, 2 H) 3.82 (s, 6 H) 3.86 - 4.03 (m, 2 H) 4.26 (d, *J*=7.78 Hz, 2 H) 4.44 - 4.50 (m, 1 H) 4.58 (d, *J*=2.26 Hz, 2 H) 5.68 (dt, *J*=15.60 Hz, 1 H) 5.80 (dt, *J*=15.30 Hz, 1 H) 6.53 (d, *J*=8.53 Hz, 2 H) 6.82 (t, *J*=8.28 Hz, 1 H) 7.21 - 7.39 (m, 10 H)

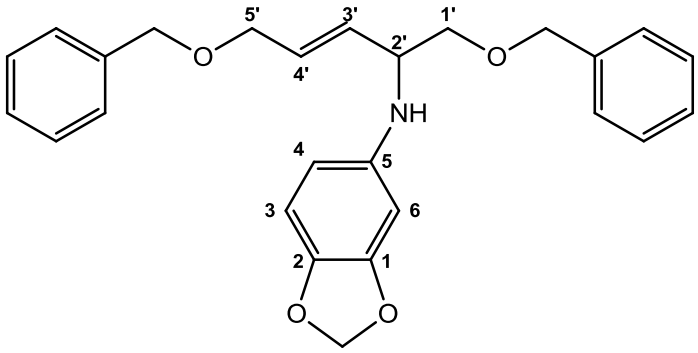
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.84 (Me) 70.18 (C_1 or C_5) 70.95 (C_6 or C_{13}) 73.11 (C_1 or C_5) 73.24 (C_6 or C_{13}) 104.57 ($C_{3'}$ and $C_{5'}$) 127.42 (C_3 or C_4) 127.44 (C_3 or C_4) 127.76 - 128.40 (aromatic *C*H) 138.41 (quaternary C) 138.48 (quaternary C) 151.29 (quaternary C)

HR-MS: calculated: 434.23259 $[M+H]^+$; found: 434.23264 $[M+H]^+$, Δm = 0.1 ppm

IR: 3362 (υ(NH)), 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 3000 (υ(CH) arom. CH), 2837 (υ_s(OCH3)), 1599 (υ(Ph)), 1492 (υ(Ph)), 1464 (υ(Ph)), 1430 (υ(Ph)), 1248 (Ph-O), 1229 (Ph-O), 1109 (υ(C-O-C)), 972 (δ(CH) C=C trans), 735 (δ(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 18.7 min ((*E*)-**103**), t_R = 20.1 min ((*Z*)-**103**), t_R = 23.8 min ((*Z*)-***ent*-103**), t_R = 26.2 min ((*E*)-***ent*-103**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)benzo[*d*][1,3]dioxol-5-amine (104)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.51 - 3.66 (m, 2 H) 3.95 - 4.01 (m, 1 H) 4.03 (d, *J*=5.52 Hz, 2 H) 4.47 (s, 2 H) 4.56 (d, *J*=2.26 Hz, 2 H) 5.73 (dt, *J*=15.60 Hz, 1 H) 5.83 - 5.85 (m, 2 H) 5.85 - 5.92 (m, 1 H) 6.11 (dd, *J*=8.28, 2.26 Hz, 1 H) 6.30 (d, *J*=2.26 Hz, 1 H) 6.64 (d, *J*=8.53 Hz, 1 H) 7.27 - 7.39 (m, 10 H)

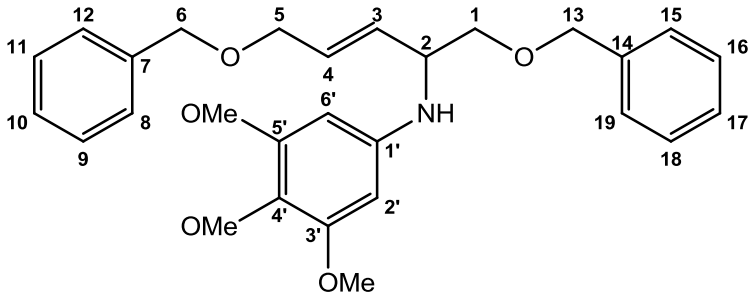
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 56.08 ($C_{2'}$) 70.08 ($C_{1'}$ or $C_{5'}$) 71.94 (CH_2 ether) 72.41 ($C_{1'}$ or $C_{5'}$) 73.16 (CH_2 ether) 97.21 (C_3 or C_4 or C_6) 100.56 (CH_2 dioxo) 106.06 (C_3 or C_4 or C_6) 108.47 (C_3 or C_4 or C_6) 127.58-128.41 (aromatic *C*H) 129.04 ($C_{3'}$ or $C_{4'}$) 132.16 ($C_{3'}$ or $C_{4'}$) 137.83 (quaternary C) 138.21 (quaternary C) 139.95 (quaternary C) 142.88 (quaternary C) 148.16 (quaternary C)

HR-MS: calculated: 418.20129 $[M+H]^+$; found: 418.20132 $[M+H]^+$, Δm = 0.1 ppm

IR: 3387 (υ(NH)), 3030 (υ(CH) arom. CH), 2858 (υ(CH) aliph. CH), 1634 (υ(Ph)), 1503 (υ(Ph)), 1490 (υ(Ph)), 1453 (υ(Ph)), 1202 (υ(C-O)), 1095 (υ(C-O)), 1039 (υ(C-O)), 972 (δ(CH) C=C (trans)), 738 (δ(CH) arom. CH), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 24.6 min ((*Z*)-**104**), t_R = 29.0 min ((*E*)-**104**), t_R = 39.5 min ((*Z*)-***ent*-104**), t_R = 42.8 min ((*E*)-***ent*-104**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2yl)-3',4',5'-trimethoxyaniline (105)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.55 - 3.67 (m, 2 H) 3.76 (s, 3 H) 3.78 (s, 6 H) 4.02 - 4.07 (m, 3 H) 4.48 (s, 2 H) 4.57 (d, *J*=2.01 Hz, 2 H) 5.76 (dt, *J*=15.60 Hz, 1 H) 5.87 - 5.93 (m, 1 H) 5.93 (s, 2 H) 7.28 - 7.40 (m, 10 H)

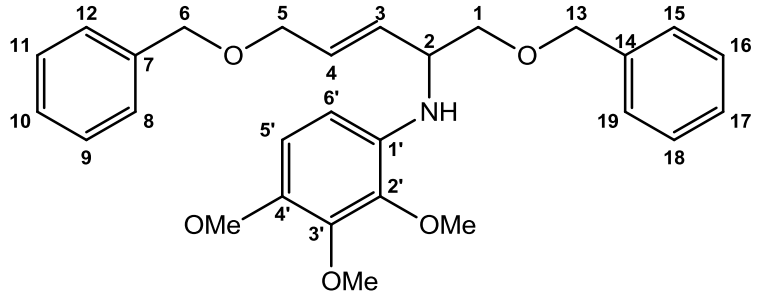
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.49 (C_2) 55.89 (CH_3O-$C_{3'}$ and -$C_{5'}$) 61.05 (CH_3O-$C_{4'}$) 70.10 (C_5) 72.07 (C_6 or C_{13}) 72.56 (C_1) 73.19 (C_6 or C_{13}) 91.51 ($C_{2'}$ and $C_{6'}$) 127.61 - 128.46 (aromatic *C*H) 128.95 (C_3 or C_4) 130.29 (quaternay C) 132.49 (C_3 or C_4) 137.82 (quaternay C) 138.15 (quaternay C) 144.27 (quaternay C) 153.77 (quaternay C)

HR-MS: calculated: 464.24315 $[M+H]^+$; found: 434.24316 $[M+H]^+$, $\Delta m < 0.1$ ppm

IR: 3382 (υ(NH)), 3062 (υ(CH) arom. CH), 3029 (υ(CH) arom. CH), 2995 (υ(CH) aliph. CH), 2933 (υ(CH) aliph. CH), 2855 (υ(CH) aliph. CH), 1610 (aromatic rings stretching), 1509 (aromatic rings stretching), 1453 (aromatic rings stretching), 1412 (aromatic rings stretching), 1237 (various C-O), 1127 (various C-O), 1014 (various C-O), 974 (δ(CH) C=C trans), 739 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 25.5 min ((*E*)-**105**), t_R = 27.2 min ((*E*)-***ent*-105**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-2',3',4'-trimethoxyaniline (106)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.55 - 3.66 (m, 2 H) 3.78 (s, 3 H) 3.86 (s, 3 H) 3.89 (s, 3 H) 3.96 - 4.01 (m, 1 H) 4.03 (dd, *J*=5.65, 0.88 Hz, 2 H) 4.47 (s, 2 H) 4.52 (s, 1 H) 4.53 - 4.62 (m, 2 H) 5.75 (m, 1 H) 5.89 (ddt, *J*=15.80 Hz, 1 H) 6.34 (d, *J*=9.03 Hz, 1 H) 6.53 (d, *J*=8.78 Hz, 1 H) 7.28 - 7.38 (m, 10 H)

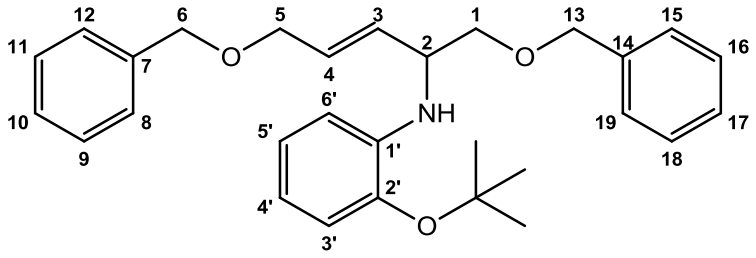
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.56 (C_2) 56.63 (CH_3) 60.42 (CH_3) 60.85 (CH_3) 70.16 (C_5) 71.90 (C_6 or C_{13}) 72.58 (C_1) 73.06 (C_6 or C_{13}) 106.42 ($C_{5'}$ or $C_{6'}$) 107.98 ($C_{5'}$ or $C_{6'}$) 127.58 - 128.40 (aromatic *C*H) 128.53 (C_4) 132.74 (C_3) 136.04 (quaternary C) 137.72 - 138.28 (quaternary C) 138.28 - 138.66 (quaternary C) 141.38 (quaternary C) 142.82 (quaternary C) 145.32 (quaternary C)

HR-MS: calculated: 464.24315 $[M+H]^+$; found: 464.24319 $[M+H]^+$, Δm = 0.1 ppm

IR: 3387 (υ(NH)), 3062 (υ(CH) arom.), 3030 (υ(CH) arom.), 2935 (υ(CH) aliph. CH), 2855 ($\upsilon_s(OCH_3)$, 1644 (υ(C=C)), 1500 (υ(Ph)), 1453 (υ(Ph)), 1268 (Ph-O), 1095 (υ(C-O)), 971 (δ(CH) C=C (trans)), 788 (δ(CH) arom. CH), 737 (δ(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 19.6 min ((*E*)-**106**), t_R = 41.1 min ((*E*)-***ent*-106**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2yl)-2'-(*tert*-butoxy)aniline (107)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.38 (s, 9 H) 3.57 - 3.68 (m, 2 H) 4.03 (dd, *J*=5.65, 0.88 Hz, 2 H) 4.04 - 4.09 (m, 1 H) 4.46 (s, 2 H) 4.53 - 4.62 (m, 2 H) 4.90 (br. s., 1 H) 5.72 - 5.80 (m, 1 H) 5.88 (dtt, *J*=15.30 Hz, 1 H) 6.59 (td, *J*=7.59, 1.63 Hz, 1 H) 6.63 (dd, *J*=8.03, 1.51 Hz, 1 H) 6.91 (td, *J*=7.72, 1.38 Hz, 1 H) 6.95 (dd, *J*=7.78, 1.51 Hz, 1 H) 7.27 - 7.39 (m, 10 H)

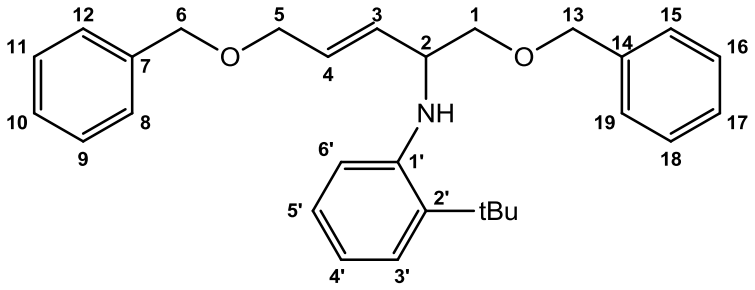
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 28.97 (CH_3-^{t}Bu) 54.73 (C_2) 70.11 (C_1) 71.78 (C_6 or C_{13}) 72.80 (C_5) 73.15 (C_6 or C_{13}) 79.51 (quaternary C of ^{t}Bu) 111.83 ($C_{3'}$ or $C_{6'}$) 116.16 ($C_{4'}$ or $C_{5'}$) 121.88 ($C_{3'}$ or $C_{6'}$) 123.60 ($C_{4'}$ or $C_{5'}$) 127.40 - 128.70 (aromatic *C*H and C_3 or C_4) 132.66 (C_3 or C_4) 137.96 (quaternary C) 138.25 (quaternary C) 142.14 (quaternary C) 142.86 (quaternary C)

HR-MS: calculated: 446.26897 $[M+H]^+$; 468.25092 $[M+Na]^+$; found: 446.26895 $[M+H]^+$, 468.25073 $[M+Na]^+$

IR: 3425 (υ(NH)), 3063 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2977 (υ(CH) aliph. CH), 2929 (υ(CH) aliph. CH), 2856 (υ(CH) aliph. CH), 1599 (υ(Ph)), 1508 (υ(Ph)), 1454 (υ(Ph)), 1366 (δ(CH3)3), 1256 (Ph-O), 1161 (υ(C-O) t-butoxy), 1100 (υ(C-O-C)), 740 (δ(CH) ortho-disub. + mono-sub.) 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 7.4 min ((*E*)-**107**), t_R = 8.1 min ((*E*)-***ent*-107**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-2'(*tert*-butyl)aniline (108)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.43 (s, 9 H) 3.60 - 3.76 (m, 2 H) 4.02 (d, *J*=6.02 Hz, 2 H) 4.12 - 4.19 (m, 1 H) 4.42 - 4.51 (m, 2 H) 4.54 - 4.63 (m, 2 H) 4.68 (d, *J*=4.77 Hz, 1 H) 5.72 - 5.80 (m, 1 H) 5.89 (ddt, *J*=15.60 Hz, 1 H) 6.63 - 6.72 (m, 2 H) 7.05 - 7.11 (m, 1 H) 7.23 - 7.26 (m, 1 H) 7.27 - 7.38 (m, 10 H)

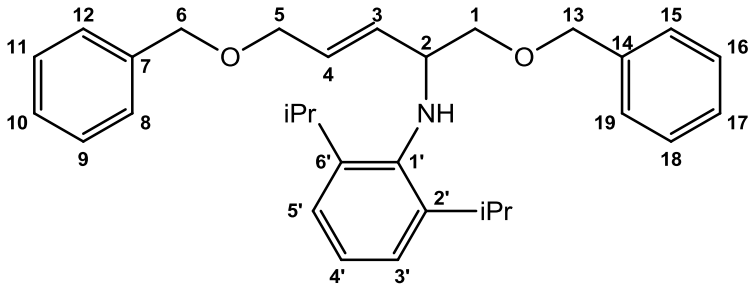
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 29.88 (^{t}Bu) 34.19 (quaternary C of ^{t}Bu) 55.00 (C_2) 70.10 (C_5) 71.85 (C_6 or C_{13}) 72.83 (C_1) 73.13 (C_6 or C_{13}) 112.89 (aromatic *C*H of amine) 117.07 (aromatic *C*H of amine) 126.16 (aromatic *C*H of amine) 126.86 (aromatic *C*H of amine) 127.56 - 128.39 (aromatic *C*H) 128.82 (C_4) 132.55 (C_3) 133.63 (quaternary C) 137.78 (quaternary C) 138.24 (quaternary C) 145.45 (quaternary C)

HR-MS: calculated: 430.27406 $[M+H]^+$; found: 430.27411 $[M+H]^+$, Δm = 0.1 ppm

IR: 3454 (υ(NH)), 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2956 (υ(CH) aliph. CH), 2858 (υ(CH) aliph. CH), 1671 (υ(C=C)), 1600 (υ(Ph)), 1578 (υ(Ph)), 1507 (υ(Ph)), 1450 (υ(Ph)), 1396 ($\delta(CH_3)_3$), 1100 (υ(C-O-C)), 1028 (δ_{ip}(CH) mono-sub.), 972 (δ(CH) C=C (trans)), 743 (δ(CH) arom. CH), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 2 (1 mL/min, 30°C), t_R = 14.4 min ((*E*)-**108**), t_R = 17.3 min ((*E*)-***ent*-108**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-2',6'-diisopropylaniline (109)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.16 - 1.22 (m, 12 H) 3.32 (quin, *J*=6.84 Hz, 2 H) 3.57 - 3.68 (m, 3 H) 3.96 - 4.01 (m, 2 H) 4.37 (s, 2 H) 4.57 (q, *J*=11.96 Hz, 2 H) 5.70 (dt, *J*=16.06, 15.31 Hz, 1 H) 5.82 - 5.92 (m, 1 H) 6.99 - 7.10 (m, 3 H) 7.28 - 7.37 (m, 10 H)

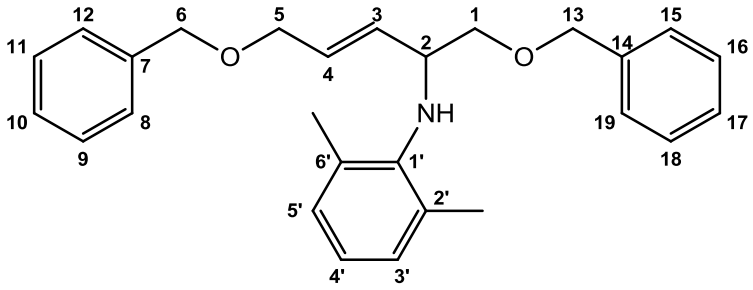
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 24.09 (CH_3-*i*Pr) 24.23 (CH_3-*i*Pr) 27.48 (*C*H-*i*Pr) 61.61 (C_2) 70.34 (C_5) 71.74 (C_6 or C_{13}) 72.63 (C_1) 73.34 (C_6 or C_{13}) 123.37 ($C_{3'}$ and $C_{5'}$) 123.41 ($C_{4'}$) 127.41 - 127.89 (aromatic *C*H) 128.12 (C_4) 128.33 (aromatic *C*H) 132.93 (C_3) 138.21 (quaternary C) 138.32 (quaternary C) 141.30 (quaternary C) 142.46 (quaternary C)

HR-MS: calculated: 458.30536 $[M+H]^+$; found: 458.30521 $[M+H]^+$, Δm = 0.3 ppm

IR: 3387 (υ(NH)), 3063 (υ(CH) aom. CH), 3030 (υ(CH) aom. CH), 2960 (υ(CH) aliph. CH), 2926 (υ(CH) aliph. CH), 2864 (υ(CH) aliph. CH), 1588 (υ(Ph)), 1495 (υ(Ph)), 1454 (υ(Ph)), 1113 (υ(C-O)), 1075 (υ(C-O)), 973 (δ(CH) C=C (trans)), 800 (δ(CH) arom. CH), 735 (δ(CH) arom. CH), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 1 (1 mL/min, 30°C), t_R = 11.1 min ((*E*)-**109**), t_R = 12.1 min ((*E*)-***ent*-109**)

(*E*)-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)-2',6'-dimethylaniline (110)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 2.27 (s, 6 H) 3.57 - 3.68 (m, 2 H) 3.87 (dt, *J*=6.71, 3.54 Hz, 1 H) 3.91 - 4.06 (m, 2 H) 4.31 - 4.40 (m, 2 H) 4.51 - 4.62 (m, 2 H) 5.74 (dt, *J*=15.81, 1 H) 5.82 - 5.89 (m, 1 H) 6.78 - 6.84 (m, 1 H) 6.97 (d, *J*=7.53 Hz, 2 H) 7.27 - 7.39 (m, 10 H)

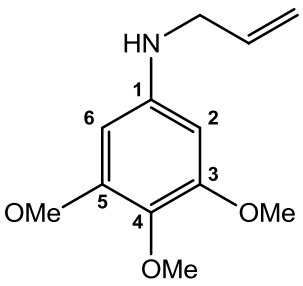
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 18.83 (CH_3) 58.51 (C_2) 70.13 (C_1 or C_5) 71.45 (C_6 or C_{13}) 72.83 (C_1 or C_5) 73.41 (C_6 or C_{13}) 121.73 ($C_{4'}$) 127.50 (quaternary C) 127.59-128.37 (aromatic *C*H) 127.64 (quaternary C) 128.77 (C_3 or C_4) 129.48 ($C_{3'}$ and $C_{5'}$) 133.06 (C_3 or C_4) 138.08 (quaternary C) 138.34 (quaternary C)

HR-MS: calculated: 402.24276 $[M+H]^+$; found: 402.24258 $[M+H]^+$, Δm = 0.4 ppm

IR: 3380(υ(NH)), 3062 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2924 (υ(CH) aliph. CH), 2855 (υ(CH) aliph. CH), 1594 (υ(Ph)), 1495 (υ(Ph)), 1474 (υ(Ph)), 1453 (υ(Ph)), 1097 (υ(C-O)), 972 (δ(CH) C=C (trans)), 765 (δ(CH) arom. CH), 736 (δ(CH) arom. CH), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 7 (1 mL/min, 30°C), t_R = 8.5 min ((*E*)-**110**), t_R = 9.8 min ((*E*)-***ent*-110**)

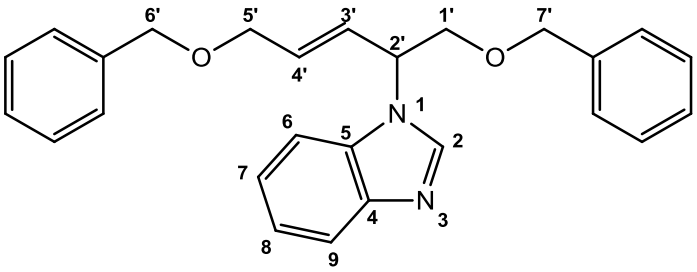
_N_-allyl-3,4,5-trimethoxyaniline (111)



^{1}H NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.76 (t, *J*=1.63 Hz, 2 H) 3.77 - 3.79 (m, 3 H) 3.83 (s, 6 H) 5.17 - 5.35 (m, 2 H) 5.90 (s, 2 H) 5.92 - 6.03 (m, 1 H)

LC-MS: M = 223

(*E*)-1-(1‘,5‘-bis(benzyloxy)pent-3‘-en-2‘-yl)-1*H*-benzo[*d*]imidazole (112)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 3.92 (dd, *J*=10.43, 4.57 Hz, 1 H) 3.98 (d, *J*=5.12 Hz, 2 H) 4.05 (dd, *J*=10.43, 8.23 Hz, 1 H) 4.42 (s, 2 H) 4.46 - 4.54 (m, 2 H) 5.44 (dd, *J*=11.89, 6.04 Hz, 1 H) 5.73 - 5.79 (m, 1 H) 6.06 (dd, *J*=15.37, 6.59 Hz, 1 H) 7.17 (d, *J*=6.59 Hz, 1 H) 7.21 (dd, *J*=8.23, 6.40 Hz, 1 H) 7.23 - 7.35 (m, 10 H) 7.60 (d, *J*=8.05 Hz, 1 H) 7.66 (d, *J*=7.32 Hz, 1 H) 8.31 (s, 1 H)

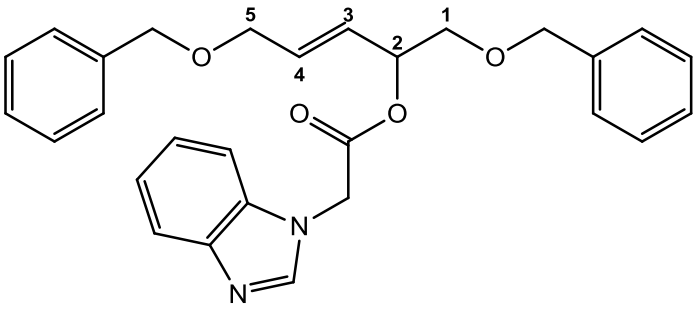
^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 56.31 ($C_{2'}$) 69.01 ($C_{5'}$) 70.21 ($C_{1'}$) 71.30 ($C_{6'}$) 71.98 ($C_{7'}$) 111.07 (C_6) 119.48 (C_9) 122.19 (C_7) 127.41 - 128.23 (aromatic *C*H + C_8 + $C_{3'}$) 130.68 ($C_{4'}$) 133.47 (quaternary C) 137.85 (quaternary C) 138.22 (quaternary C) 142.74 (C_2) 143.36 (quaternary C)

HR-MS: calculated: 399.2073 $[M+H]^+$;found: 399.2066 $[M+H]^+$

IR: 3087 (υ(CH) arom. CH), 3061 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 1613 (aromatic rings stretching), 1493 (aromatic rings stretching), 1455 (aromatic rings stretching), 1110 (υ(C-O-C)), 972 (δ(CH) C=C trans), 743 (δ(CH) arom. CH), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 19.9 min ((*Z*)-**112**), t_R = 23.6 min ((*Z*)-***ent*-112**), t_R = 27.2 min ((*E*)-**112**), t_R = 30.1 min ((*E*)-***ent*-112**)

(*E*)-1,5-bis(benzyloxy)pent-3-en-2-yl 2-(1*H*-benzo[*d*]imidazol-1-yl)acetate (113)

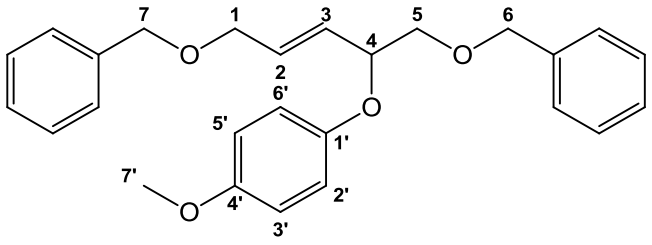


^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 3.53 - 3.62 (m, 2 H) 3.99 (d, *J*=5.12 Hz, 2 H) 4.45 (s, 2 H) 4.46 - 4.52 (m, 2 H) 5.27 - 5.39 (m, 2 H) 5.51 - 5.55 (m, 1 H) 5.76 (dd, *J*=15.92, 6.04 Hz, 1 H) 5.85 - 5.90 (m, 1 H) 7.16 - 7.23 (m, 2 H) 7.24 - 7.38 (m, 10 H) 7.45 (d, *J*=7.32 Hz, 1 H) 7.66 (d, *J*=8.05 Hz, 1 H) 8.20 (s, 1 H)

HR-MS: calculated 457.21218 $[M+H]^+$, 479.19413 $[M+Na]^+$, found: 457.21231 $[M+H]^+$, 479.19413 $[M+Na]^+$, Δm = 0.1-0.3 ppm

IR: 3061 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 1753 (υ(C=O) ester), 1616 (aromatic rings stretching), 1497 (aromatic rings stretching), 1458 (aromatic rings stretching), 1205 (υ(C-O) ester), 1114 (υ(C-O-C)), 971 (δ(C-H) C=C (trans)), 744 (δ(CH) arom. CH), 699 (δ(Ph) mono-sub.) cm^{-1}

(*E*)-(((4-(4-methoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (114)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H NMR: (600 MHz, DMSO-d_6) δ ppm 3.59 - 3.67 (m, 2 H) 3.68 (s, 3 H) 3.94 - 4.01 (m, 2 H) 4.39 (s, 2 H) 4.56 (s, 2 H) 4.89 - 4.94 (m, 1 H) 5.75 (dd, *J*=15.73, 6.22 Hz, 1 H) 5.85 - 5.91 (m, 1 H) 6.83 (d, *J*=9.15 Hz, 2 H) 6.90 (d, *J*=9.15 Hz, 2 H) 7.25 - 7.31 (m, 4 H) 7.31 - 7.36 (m, 6 H)

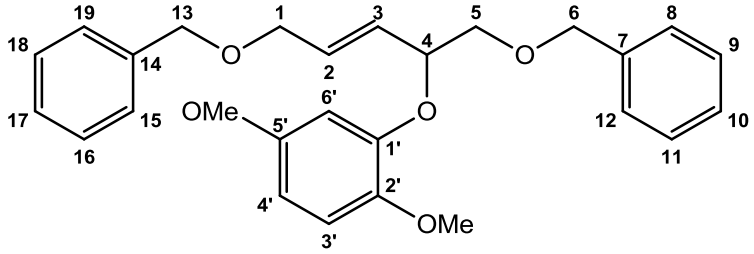
^{13}C NMR: (151 MHz, DMSO-d_6) δ ppm 55.36 ($C_{7'}$) 69.23 (C_1) 71.10 (C_7) 72.21 (C_5) 72.31 (C_6) 77.30 (C_4) 114.53 ($C_{3'}$ and $C_{5'}$) 117.14 ($C_{2'}$ and $C_{6'}$) 127.47 - 128.27 (aromatic *C*H) 129.14 (C_3) 130.15 (C_2) 138.33 (quaternary C) 151.64 (quaternary C) 153.57 (quaternary C)

HR-MS: calculated: $[M+NH4]^+$ = 422.23259, $[M+Na]^+$ = 427.18798; found: $[M+NH4]^+$ = 422.23291; $[M+Na]^+$ = 427.18785; Δm = 0.3-0.8 ppm

IR: 3087 (υ(C-H) arom. CH), 3063 (υ(C-H) arom. CH), 3030 (υ(C-H) arom. CH),3003 (υ(C-H) arom. CH), 2906 (υ(C-H) aliph. CH), 2856 (υ(C-H) aliph. CH), 1605 (υ(Ph)), 1590 (υ(Ph)), 1506 (υ(Ph)), 1454 (υ(Ph)), 1105 (C-O-C), 1037 (H_3C-O), 971 (δ(CH) C=C trans), 911, 825 (δ(CH) paradisubst.), 737 (δ(CH) monosubst.) 698 (δ(CH) monosubst.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 13.4 min ((*E*)-**114**), t_R = 14.9 min ((*E*)-***ent*-114**)

(*E*)-(((4-(2',5'-dimethoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (115)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.67 - 3.84 (m, 2 H) 3.71 (s, 3 H) 3.81 (s, 3 H) 4.03 (dd, *J*=5.40, 1.13 Hz, 2 H) 4.44 (s, 2 H) 4.60 - 4.70 (m, 2 H) 4.86 - 4.92 (m, 1 H) 5.80 - 5.88 (m, 1 H) 5.93 (dt, *J*=15.60 Hz, 1 H) 6.44 (dd, *J*=8.78, 2.76 Hz, 1 H) 6.60 (d, *J*=3.01 Hz, 1 H) 6.81 (d, *J*=9.03 Hz, 1 H) 7.27 - 7.38 (m, 10 H)

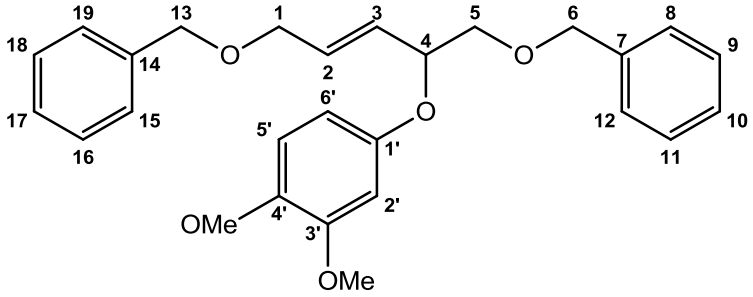
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.62 (CH_3) 56.88 (Me) 69.81 (C_1 or C_5) 71.86 (C_6 or C_{13}) 72.49 (C_1 or C_5) 73.43 (C_6 or C_{13}) 79.07 (C_4) 104.92 ($C_{3'}$ or $C_{4'}$ or $C_{6'}$) 105.04 ($C_{3'}$ or $C_{4'}$ or $C_{6'}$) 113.34 ($C_{3'}$ or $C_{4'}$ or $C_{6'}$) 127.43 - 127.97 (aromatic *C*H) 128.34 (aromatic *C*H) 129.40 (C_2 or C_3) 130.49 (C_2 or C_3) 138.19 (quaternary C) 144.73 (quaternary C) 148.36 (quaternary C) 154.09 (quaternary C)

HR-MS: calculated: 452.24315 $[M+NH4]^+$; 457.19855 $[M+Na]^+$; found: 452.24326 $[M+NH4]^+$, 457.19839 $[M+Na]^+$; Δm = 0.2-0.3 ppm

IR: 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 3001 (υ(CH) arom. CH), 2857 (υ_s (OCH_3)), 1609 (υ(Ph)), 1509 (υ(Ph)), 1454 (υ(Ph)), 1228 (Ph-O), 1118 (υ(C-O-C)), 1046 (υ(C-O)), 971 (δ(CH) C=C trans), 738 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 14.4 min ((*E*)-**115**), t_R = 17.1 min ((*E*)-***ent*-115**)

(*E*)-(((4-(3',4'-dimethoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (116)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.63 - 3.75 (m, 2 H) 3.82 (d, *J*=1.00 Hz, 6 H) 4.03 (d, *J*=5.52 Hz, 2 H) 4.47 (s, 2 H) 4.63 (d, *J*=5.77 Hz, 2 H) 4.77 - 4.83 (m, 1 H) 5.81 (dt, *J*=16.10 Hz, 1 H) 5.92 (dtt, *J*=15.60 Hz, 1 H) 6.45 (dd, *J*=8.78, 2.76 Hz, 1 H) 6.60 (d, *J*=2.76 Hz, 1 H) 6.74 (d, *J*=8.53 Hz, 1 H) 7.28 - 7.38 (m, 10 H)

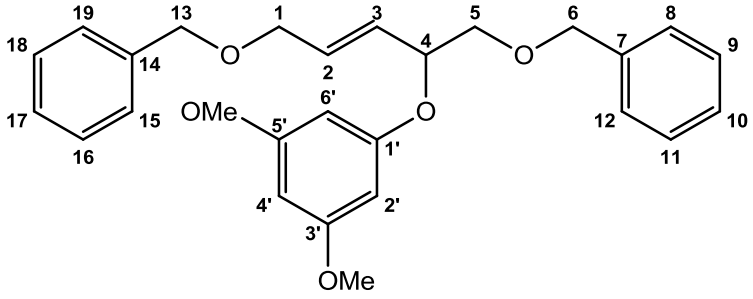
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.80 (CH_3) 56.36 (CH_3) 69.84 (C_1) 72.05 (C_6 or C_{13}) 72.63 (C_5) 73.49 (C_6 or C_{13}) 78.36 (C_4) 102.47 ($C_{2'}$ or $C_{5'}$ or $C_{6'}$) 106.42 ($C_{2'}$ or $C_{5'}$ or $C_{6'}$) 111.61 ($C_{2'}$ or $C_{5'}$ or $C_{6'}$) 127.57 - 127.83 (aromatic *C*H) 128.37 (aromatic *C*H) 129.51 (C_3) 130.15 (C_2) 138.08 (quaternary C) 143.74 (quaternary C) 149.67 (quaternary C) 152.55 (quaternary C)

HR-MS: calculated: 435.21660 $[M+H]^+$, 452.24315 $[M+NH4]^+$, 457.19855 $[M+Na]^+$; found: 435.21671 $[M+H]^+$, 452.24319 $[M+NH4]^+$, 457.19843 $[M+Na]^+$; Δm = 0.1-0.3 ppm

IR: 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 3002 (υ(CH) arom. CH), 2932 (υ(CH) aliph. CH), 2856 (υ(CH) aliph. CH), 1596 (υ(Ph)), 1510 (υ(Ph)), 1453 (υ(Ph)), 1229 (various C-O), 1198 (various C-O), 1121 (various C-O), 1028 (various C-O), 970 (δ(CH) C=C trans), 835 (δ(CH) arom. CH), 738 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 15.2 min ((*E*)-**116**), t_R = 18.8 min ((*E*)-***ent*-116**)

(*E*)-(((4-(3',5'-dimethoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (117)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.63 - 3.74 (m, 2 H) 3.75 (s, 6 H) 4.04 (d, *J*=5.52 Hz, 2 H) 4.47 (s, 2 H) 4.63 (d, *J*=4.52 Hz, 2 H) 4.87 (qd, *J*=5.48, 0.88 Hz, 1 H) 5.80 (dt, *J*=15.80 Hz, 1 H) 5.92 (dtt, *J*=15.80 Hz, 1 H) 6.07 - 6.11 (m, 1 H) 6.15 (d, *J*=2.26 Hz, 2 H) 7.27 - 7.38 (m, 10 H)

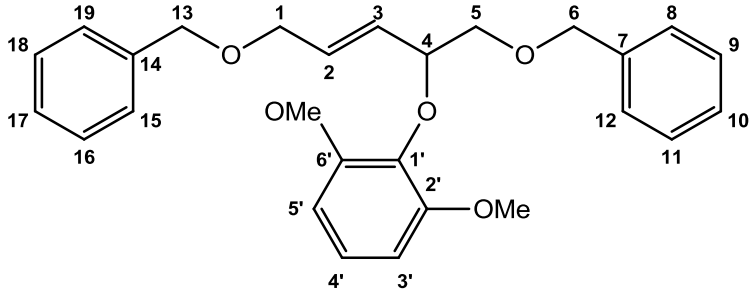
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 55.30 (Me) 69.81 (C_1) 72.01 (C_6 or C_{13}) 72.48 (C_5) 73.44 (C_6 or C_{13}) 77.38 (C_4) 93.38 ($C_{4'}$) 94.96 ($C_{2'}$ and $C_{6'}$) 127.60-128.36 (aromatic *C*H) 129.16 (C_2 or C_3) 130.15 (C_2 or C_3) 138.05 (quaternary C) 138.12 (quaternary C) 159.88 (quaternary C) 161.36 (quaternary C)

HR-MS: calculated: 435.21660 $[M+H]^+$, 452.24315 $[M+NH4]^+$; 457.19855 $[M+Na]^+$; found: 435.21667 $[M+H]^+$, 452.24307 $[M+NH4]^+$; 457.19827 $[M+Na]^+$, Δm = 0.2-0.6 ppm

IR: 3030 (υ(CH) arom. CH), 3003 (υ(CH) arom. CH), 2936 (υ(CH) aliph. CH), 2856 (υ(CH) aliph. CH), 1600 (aromatic rings stretching), 1474 (aromatic rings stretching), 1455 (aromatic rings stretching), 1362 (δ(CH_3)), 1205 (various C-O), 1153 (various C-O), 1119 (various C-O), 1068 (various C-O), 971 (δ(CH) C=C trans), 738 (δ(CH) monosub.), 698 (δ(Ph) monosub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 18.5 min ((*E*)-**117**), t_R = 20.2 min ((*E*)-***ent*-117**)

(*E*)-(((4-(2',6'-dimethoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (118)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.70 - 3.89 (m, 2 H) 3.79 - 3.82 (m, 6 H) 3.99 (ddd, *J*=12.17, 5.77, 1.13 Hz, 2 H) 4.33 (s, 2 H) 4.64 (s, 2 H) 4.84 (dt, *J*=7.72, 5.55 Hz, 1 H) 5.76 (dt, *J*=16.10 Hz, 1 H) 5.93 (ddt, *J*=16.10 Hz, 1 H) 6.55 (d, *J*=8.28 Hz, 2 H) 6.97 (t, *J*=8.41 Hz, 1 H) 7.27 - 7.39 (m, 10 H)

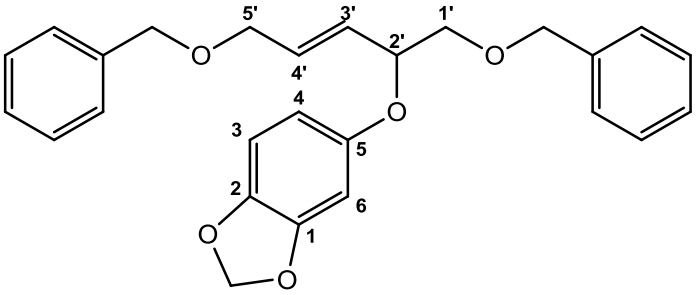
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 56.01 (*C*H_3) 69.95 (C_1) 71.36 (C_6 or C_{13}) 72.66 (C_5) 73.32 (C_6 or C_{13}) 81.08 (C_4) 105.23 ($C_{3'}$ and $C_{5'}$) 123.61 ($C_{4'}$) 127.43 – 128.45 (aromatic *C*H) 130.85 (C_2 and C_3) 135.60 (quaternary C) 138.35 (quaternary C) 138.48 (quaternary C) 153.83 (quaternary C)

HR-MS: calculated: 452.24315 $[M+NH4]^+$, 457.19855 $[M+Na]^+$; found: 452.24329 $[M+NH4]^+$, 457.19843 $[M+Na]^+$; Δm = 0.3 ppm

IR: 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 3003 (υ(CH) arom. CH), 2935 (υ(CH) aliph. CH), 2855 (υ(CH) aliph. CH), 1596 (υ(Ph)), 1493 (υ(Ph)), 1477 (υ(Ph)), 1454 (υ(Ph)), 1253 (Ph-O), 1112 (υ(C-O-C)), 971 (δ(CH) C=C (trans)), 772 (δ(CH) arom. CH), 736 (δ(CH) arom. CH), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 7 (1 mL/min, 30°C), t_R = 14.5 min ((*E*)-**118**), t_R = 18.6 min ((*E*)-***ent*-118**)

(*E*)-5-((1',5'-bis(benzyloxy)pent-3'-en-2'-yl)oxy)benzo[*d*][1,3]dioxole (119)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.61 - 3.74 (m, 2 H) 4.01 - 4.06 (m, 2 H) 4.47 (s, 2 H) 4.59 - 4.67 (m, 2 H) 4.71 - 4.78 (m, 1 H) 5.79 (dt, *J*=15.80 Hz, 1 H) 5.85 - 5.94 (m, 1 H) 5.90 - 5.91 (m, 2 H) 6.40 (dd, *J*=8.53, 2.51 Hz, 1 H) 6.55 (d, *J*=2.51 Hz, 1 H) 6.68 (d, *J*=8.53 Hz, 1 H) 7.27 - 7.38 (m, 10 H)

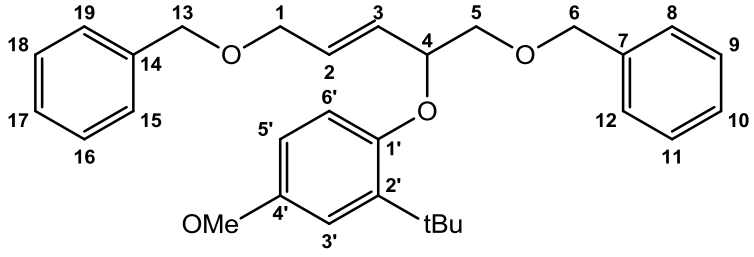
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 69.79 ($C_{1'}$ or $C_{5'}$) 72.04 (*C*H_2 ether) 72.56 ($C_{1'}$ or $C_{5'}$) 73.46 (*C*H_2 ether) 78.99 ($C_{2'}$) 99.86 (C_3 or C_4 or C_6) 101.10 (*C*H_2 dioxo) 107.87 (C_3 or C_4 or C_6) 108.36 (C_3 or C_4 or C_6) 127.29 - 128.78 (aromatic *C*H) 129.28 ($C_{3'}$ or $C_{4'}$) 130.26 ($C_{3'}$ or $C_{4'}$) 138.08 (quaternary C) 141.94 (quaternary C) 148.05 (quaternary C) 153.44 (quaternary C)

HR-MS: calculated: 436.21185 $[M+NH4]^+$; 441.16725 $[M+Na]^+$;found: 436.21198 $[M+NH4]^+$; 441.16718 $[M+Na]^+$, Δm =0.3 ppm

IR: 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2858 (υ(CH) aliph. CH), 1631 (υ(Ph)), 1501 (υ(Ph)), 1484 (υ(Ph)), 1453 (υ(Ph)), 1242 (υ(C-O)), 1185 (υ(C-O)), 1099 (υ(C-O)), 1038 (υ(C-O)), 970 (δ(CH) C=C (trans)), 816 (δ(CH) arom. CH), 737 (δ(CH) arom. CH), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 8.6 min ((*Z*)-**119**), t_R = 9.4 min ((*Z*)-***ent*-119**), t_R = 11.6 min ((*E*)-**119**), t_R = 12.3 min ((*E*)-***ent*-119**)

(*E*)-(((4-(2‘-(*tert*-butyl)-4‘-methoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene (120)



For the procedures on racemic and enantioselective substitutions see section 5.3.

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.42 (s, 9 H) 3.65 - 3.83 (m, 2 H) 3.73 - 3.76 (m, 3 H) 4.00 - 4.04 (m, 2 H) 4.45 (s, 2 H) 4.60 (d, *J*=1.51 Hz, 2 H) 4.92 (q, *J*=5.52 Hz, 1 H) 5.81 (dt, *J*=15.60 Hz, 1 H) 5.89 (td, *J*=16.56, 15.56 Hz, 1 H) 6.59 - 6.64 (m, 1 H) 6.74 (d, *J*=9.03 Hz, 1 H) 6.90 (d, *J*=3.01 Hz, 1 H) 7.28 - 7.37 (m, 10 H)

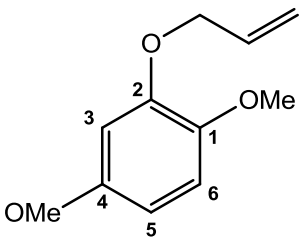
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 29.80 (^{t}Bu) 35.03 (quaternary C of ^{t}Bu) 55.58 (CH_3O) 69.83 (C_1) 71.93 (C_6 or C_{13}) 73.08 (C_5) 73.39 (C_6 or C_{13}) 76.40 (C_4) 109.57 ($C_{3'}$ or $C_{5'}$ or $C_{6'}$) 113.47 ($C_{3'}$ or $C_{5'}$ or $C_{6'}$) 114.37 ($C_{3'}$ or $C_{5'}$ or $C_{6'}$) 127.68 - 128.36 (aromatic *C*H) 129.87 (C_2 or C_3) 130.07 (C_2 or C_3)

HR-MS: calculated: 478.29519 $[M+NH4]^+$; 483.25058 $[M+Na]^+$; found: 478.29514 $[M+NH4]^+$; 483.25037 $[M+Na]^+$, Δm = 0.1-0.4 ppm

IR: 3063 (υ(NH)), 2952 (υ(CH) aliph. CH), 2861 (υ(CH) aliph. CH), 1583 (aromatic rings strechting), 1485 (aromatic rings strechting), 1454 (aromatic rings strechting), 1362 ($\delta(CH_3)_3$), 1216 (Ph-O), 1107 (υ(C-O)), 1054 (υ(C-O)), 971 (δ(CH) C=C (trans)), 800 (δ(CH) arom. CH), 737 (δ(CH) arom. CH), 698 (δ(Ph) mono-sub.) cm^{-1}

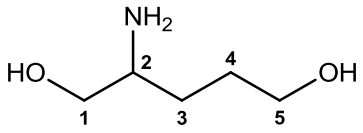
HPLC: C-HPLC 3 (1 mL/min, 30°C), t_R = 7.8 min ((*E*)-**120**), t_R = 10.7 min ((*E*)-***ent*-120**)

2-(allyloxy)-1,4-dimethoxybenzene (123)



^{1}H NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 3.77 (s, 3 H) 3.84 (s, 3 H) 4.60 (dt, *J*=5.52, 1.51 Hz, 2 H) 5.27 - 5.45 (m, 2 H) 6.09 (ddt, *J*=17.32, 10.60, 5.36, 5.36 Hz, 1 H) 6.42 (dd, *J*=8.78, 2.76 Hz, 1 H) 6.54 (d, *J*=2.76 Hz, 1 H) 6.81 (d, *J*=8.78 Hz, 1 H)

2-aminopentane-1,5-diol (124)



(*E*)-*N*-benyzl-1,5-bis(benzyloxy)pent-3-en-2-amine **80** (product from enantioselective allylic substitution with (*R,R*)-Trost ANDEN ligand) (0.95g, 2.451 mmol, 1 eq.) was put in solution in 200mL EtOH (98%) at rt. The flask was put under a flush of argon and Pd/C 10% (0.19g, 20% m/m) was added. Argon was then replaced by H_2(g) (atmospheric pressure) at rt. After 48h, the Pd/C was filtered through a spritzenfilter and washed with 30mL EtOH (98%). The flask was put under a flush of argon and Pd/C 10% (0.19g, 20% m/m) was added. After 4 days, the Pd/C was filtered through a spritzenfilter and washed with 30mL ALI. The solvent was evaporated under reduced pressure. Flash chromatography column (15% MeOH, 2% ammonia sol (25%) in MED) of the crude gave the corresponding product (oil, 0.1222g, 42%).

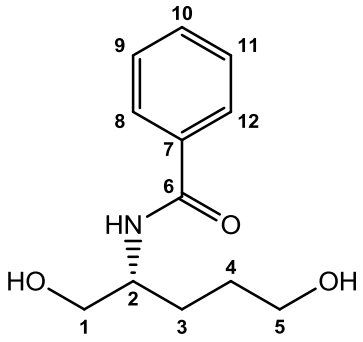
^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 1.25 - 1.38 (m, 1 H) 1.62 - 1.79 (m, 3 H) 1.96 (br. s., 2 H) 2.79 - 2.88 (m, 1 H) 3.37 (dd, *J*=10.54, 7.78 Hz, 1 H) 3.58 - 3.72 (m, 3 H)

^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 30.27 (C_3 or C_4) 32.09 (C_3 or C_4) 52.94 (C_2) 62.79 (C_1 or C_5) 67.80 (C_1 or C_5)

HR-MS: calculated 120.10191 $[M+H]^+$; found: 120.10202 $[M+H]^+$, Δm = 1 ppm

IR: 3355 (υ(OH)), 2943 (υ(CH)), 2877 (υ(CH)), 1058 (υ(C-OH)) cm^{-1}

(*R*)-*N*-(1,5-dihydroxypentan-2-yl)benzamide (125)



2-aminopentane-1,5-diol **124** (0.04g, 0.336mmol, 1 eq.) was put in solution in 4mL THF and cooled down at 0°C with an ice/water bath. 2mL of a solution of saturated aqueous sodium carbonate was slowly added at 0°C (white suspension). 0.99mL of a solution of 0.524g benzoyl chlorid in 10mL THF (0.052g, 0.369mmol, 1.1 eq.) was slowly added at 0°C during 10min. After 1h, the solution was allowed to come at rt and the solvents were evaporated under reduced pressure (the benzoyl product is soluble in water). 6mL of a solution of 20% MeOH in MED was added to the crude (white solid) and left to stir during 1h. The white precipitate was filtered and the filtrate was evaporated under reduced pressure. Flash chromatography of the evaporated filtrate (10% MeOH in MED) gave the corresponding product (0.045g, 60%, white crystals)

^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.36 - 1.55 (m, 3 H) 1.59 - 1.73 (m, 1 H) 3.33 - 3.49 (m, 4 H) 3.89 - 4.00 (m, 1 H) 4.36 (t, *J*=5.14 Hz, 1 H) 4.66 (t, *J*=5.77 Hz, 1 H) 7.41 - 7.55 (m, 3 H) 7.80 - 7.89 (m, 2 H) 8.00 (d, *J*=8.53 Hz, 1 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 27.30 (C_3 or C_4) 29.28 (C_3 or C_4) 51.34 (C_2) 60.78 (C_1 or C_5) 63.48 (C_1 or C_5) 127.24 (aromatic *C*H) 128.10 (aromatic *C*H) 130.91 (C_{10}) 134.86 (C_7) 166.09 (C_6)

HR-MS: calculated 224.12812 $[M+H]^+$, 246.11007 $[M+Na]^+$, found: 224.12801 $[M+H]^+$, 246.10985 $[M+Na]^+$, Δm = 0.5 - 0.9 ppm

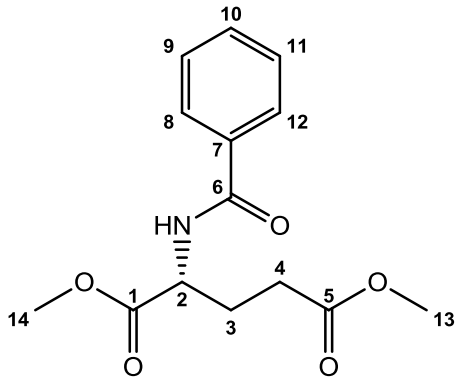
IR: 3355 (υ(NH) + υ(OH)), 3284 (υ(NH) + υ(OH)), 3082 (υ(CH) arom. CH), 2954 (υ(CH) aliph. CH), 2923 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1638 (υ(C=O) amide), 1605 (υ(Ph)), 1579 (υ(Ph)), 1541 (amide II), 1488 (υ(Ph)), 1451 (υ(Ph)), 1099 (υ(C-OH)), 1072 (υ(C-OH)), 1031 (υ(C-OH)), 704 (δ(Ph) mono-sub.) cm^{-1}

Optical activity: $[\alpha]^{20}_{D}$ = +27 (c = 0.01, MeOH)

m_p: 104.4 - 106.2 °C

HPLC: C-HPLC 9 (1 mL/min, 30°C), ee = 90%, t_R = 5.7 min ((*S*)-**125**), t_R = 6.6 min ((*R*)-**125**). Major enantiomer is the (*R*)-enantiomer.

(*R*)-dimethyl 2-benzamidopentanedioate (127)



H-*D*-glu(OMe)-OMe·HCl (5g, 23.624mmol, 1 eq.) was put in solution in 100mL THF at rt. The white suspension was then cooled down at 0°C with an ice/water bath. A solution of saturated sodium carbonate (90mL) was slowly added at 0°C. At 0°C, Benzoyl chloride (4.317g, 30.711mmol, 1.3 eq.) was slowly added with adjustment of the pH with a solution of saturated sodium carbonate (pH=9.6). After 30min, the reaction was allowed to come at rt. After 1h30, the solvents were evaporated under reduced pressure. To dissolve the salt, 100mL water were added, then 250mL ethyl acetate were added and the phase separated. The organic

phase was extracted with 3x 50mL $NaHCO_3$ sat, 3x 50mL $KHSO_4$ sat and 3x 50mL NaCl sat and then dried over $MgSO_4$. The solvents were evaporated under reduced pressure. Flash chromatography column (1:1 Hexane:Ethyl acetate) of the crude gave the corresponding product (6.16g, 93% yield, white crystals)

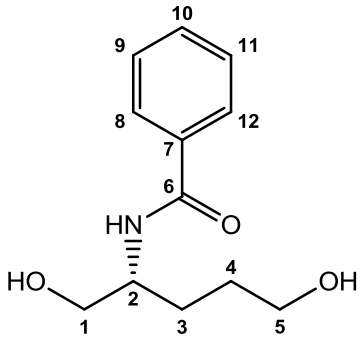
^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.96 - 2.20 (m, 2 H) 2.42 - 2.49 (m, 2 H) 3.59 (s, 3 H) 3.65 (s, 3 H) 4.48 (ddd, *J*=9.54, 7.53, 5.27 Hz, 1 H) 7.44 - 7.52 (m, 2 H) 7.52 - 7.59 (m, 1 H) 7.84 - 7.93 (m, 2 H) 8.76 (d, *J*=7.53 Hz, 1 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 25.70 (C_3 or C_4) 29.94 (C_3 or C_4) 51.36 (C_{13} or C_{14}) 51.92 (C_{13} or C_{14} or C_2) 51.93 (C_{13} or C_{14} or C_2) 127.46 (aromatic *C*H) 128.28 (aromatic *C*H) 131.52 (C_{10}) 133.61 (C_7) 166.66 (C_6) 172.23 (C_1 or C_5) 172.68 (C_1 or C_5)

HR-MS: calculated 280.11795 $[M+H]^+$, 302.09990 $[M+Na]^+$, found: 280.11798 $[M+H]^+$, 302.09973 $[M+Na]^+$, Δm = 0.1-0.5 ppm

IR: 3285 (υ(NH)), 3072 (υ(CH) arom. CH), 3029 (υ(CH) arom. CH), 3001 (υ(CH) arom. CH), 2955 (υ(CH) aliph. CH), 2852 (υ(CH) aliph. CH), 1748 (υ(C=O) ester), 1733 (υ(C=O) ester), 1638 (υ(C=O) amide), 1602 (υ(Ph)), 1578 (υ(Ph)), 1542 (amide II), 1491 (υ(Ph)), 1274 (υ(C-O) ester), 1197 (υ(C-O) ester), 1174 (υ(C-O) ester), 781 (δ(CH) mono-sub.), 702 (δ(Ph) mono-sub.) cm^{-1}

(*R*)-*N*-(1,5-dihydroxypentan-2-yl)benzamide (128)



Pellet of $LiAlH_4$ (0.815g, 21.483 mmol, 3 eq.) were dissolved in 40mL THF at rt. The grey suspension was then cooled down at 0°C with an ice/water bath. (*R*)-dimethyl 2-benzamidopentanedioate **127** (2g, 7.161 mmol, 1 eq.) was dissolved in 20mL THF and slowly added at 0°C to the suspension of $LiAlH_4$. After the end of the addition, the solution was allowed to come at rt. After 20min, the reaction was finished, cooled down at 0°C and 20mL of water were slowly added .The reaction mixture was then allowed to come at rt. The grey gel was filtered though a short pad of cellflock and washed with 250mL THF. The solvent (filtrate) was evaporated under reduced pressure. A white solid crystallized from the crude. 8mL of TBME was added to the crystals, cooled down at 0°C and stirred during 30min. The obtained white powder was filtered, washed with a minimum of TBME and dried in the oven. Then a recrystallisation was done. Ethyl acetate (40mL) was added to the crystals and heated until a clear solution was obtained. A hot filtration was done and then slowly cooled to rt. Crystals were formed in the filtrate which were filtered, washed with a minimum of TBME and dried in the oven to give the corresponding desired product (1.0086g, 63% yield, white crystals)

^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.36 - 1.55 (m, 3 H) 1.59 - 1.72 (m, 1 H) 3.33 - 3.42 (m, 3 H) 3.42 - 3.49 (m, 1 H) 3.89 - 4.00 (m, 1 H) 4.36 (t, *J*=5.14 Hz, 1 H) 4.65 (t, *J*=5.77 Hz, 1 H) 7.41 - 7.48 (m, 2 H) 7.48 - 7.54 (m, 1 H) 7.83 - 7.87 (m, 2 H) 8.00 (d, *J*=8.53 Hz, 1 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 27.32 (C_3 or C_4) 29.30 (C_3 or C_4) 51.36 (C_2) 60.80 (C_1 or C_5) 63.51 (C_1 or C_5) 127.27 (aromatic *C*H) 128.11 (aromatic *C*H) 130.93 (C_{10}) 134.88 (C_7) 166.13 (C_6)

HR-MS: calculated 224.12812 $[M+H]^+$, 246.11007 $[M+Na]^+$, found: 224.12816 $[M+H]^+$, 246.10991 $[M+Na]^+$, Δm = 0.1-0.2 ppm

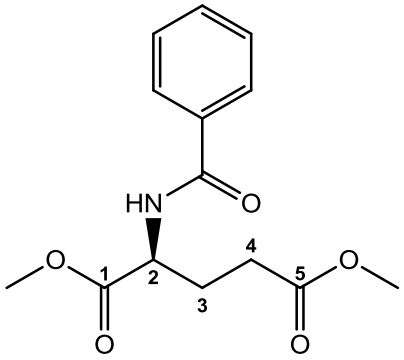
IR: 3356 (υ(NH) + υ(OH)), 3284 (υ(NH) + υ(OH)), 3084 (υ(CH) arom. CH), 3033 (υ(CH) arom. CH), 2954 (υ(CH) aliph. CH), 2923 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1637 (υ(C=O) amide), 1605 (υ(Ph)), 1579 (υ(Ph)), 1540 (amide II), 1490 (υ(Ph)), 1452 (υ(Ph)), 1098 (υ(C-OH)), 1072 (υ(C-OH)), 1031 (υ(C-OH)), 704 (δ(Ph) mono-sub.) cm^{-1}

Optical activity: (recrystallized) $[\alpha]^{20}_D$ = +33 (c = 0.01, MeOH)

m_p: 106.4 – 109.4 °C

HPLC: C-HPLC 9 (1 mL/min, 30°C), t_R = 6.6 min ((*R*)-**128**)

(*S*)-dimethyl 2-benzamidopentanedioate (130)



Same procedure as for (*R*)-dimethyl 2-benzamidopentanedioate **127** (yield of **130** = 93%, white crystals)

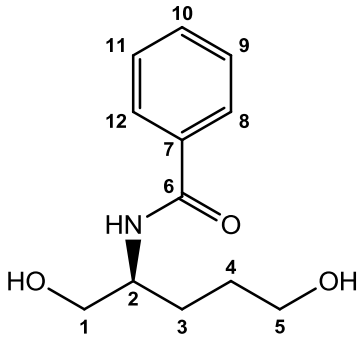
^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 2.11 - 2.22 (m, 1 H) 2.34 (dtd, *J*=14.24, 7.06, 7.06, 5.02 Hz, 1 H) 2.41 - 2.59 (m, 2 H) 3.66 (s, 3 H) 3.79 (s, 3 H) 4.80 - 4.88 (m, 1 H) 7.02 (d, *J*=7.53 Hz, 1 H) 7.42 - 7.49 (m, 2 H) 7.50 - 7.56 (m, 1 H) 7.80 - 7.86 (m, 2 H)

^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 27.20 (C_3) 30.19 (C_4) 51.89 (CH_3) 52.25 (C_2) 52.60 (CH_3) 127.08 (aromatic *C*H, 2C) 128.59 (aromatic *C*H, 2C) 131.83 (aromatic *C*H, 1C) 133.57 (quaternary C) 167.08 (quaternary C) 172.39 (quaternary C) 173.64 (quaternary C)

HR-MS: calculated 280.11795 $[M+H]^+$, 302.09990 $[M+Na]^+$, found: 280.11807 $[M+H]^+$, 302.09976 $[M+Na]^+$, Δm = 0.4 ppm

IR: 3285 (υ(NH)), 3072 (υ(CH) arom. CH), 2955 (υ(CH) aliph. CH), 1750 (υ(C=O) ester), 1733 (υ(C=O) ester), 1577 (υ(Ph)), 1542 (amide II), 1491 (υ(Ph)), 1273 (υ(C-O) ester), 701 (δ(Ph) mono-sub.) cm^{-1}

(*S*)-*N*-(1,5-dihydroxypentan-2-yl)benzamide (131)



Pellet of $LiAlH_4$ (1.08g, 28.465 mmol, 3 eq.) were dissolved in 40mL THF at rt. The grey suspension was then cooled down at 0°C with an ice/water bath. (*S*)-dimethyl 2-benzamidopentanedioate (2.65g, 9.488 mmol, 1 eq.) was dissolved in 20mL THF and slowly added at 0°C to the suspension of $LiAlH_4$. After the end of the addition, the solution was allowed to come at rt. After 15h, the solution was heated to 40°C with an oil bath during 6h. Then, the solution was cooled down at rt and 60mL of diethyl ether were added. After 18h, the reaction mixture was cooled down at 0°C and 20mL of water were slowly added .The reaction mixture was then allowed to come at rt and left to stir during 30min. The grey gel was filtered though a short pad of cellflock and washed with 300mL THF. The solvent was evaporated under reduced pressure. A white solid crystallized from the crude and was filtered with a minimum of TBME. The crystals were dried in the oven (m=0.7424g). Then a recrystallisation was done. Ethyl acetate (40mL) was added to the crystals and heated until a clear solution was obtained. A hot filtration was done and then slowly cooled to rt. Crystals were formed in the filtrate which were filtered, washed with a minimum of TBME and dried in the oven to give the corresponding desired product (0.443g, 21% yield, white crystals)

^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.35 - 1.55 (m, 3 H) 1.59 - 1.72 (m, 1 H) 3.34 - 3.50 (m, 4 H) 3.89 - 4.00 (m, 1 H) 4.36 (t, *J*=5.14 Hz, 1 H) 4.66 (t, *J*=5.77 Hz, 1 H) 7.41 - 7.54 (m, 3 H) 7.82 - 7.88 (m, 2 H) 8.00 (d, *J*=8.53 Hz, 1 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 27.30 (C_3 or C_4) 29.28 (C_3 or C_4) 51.34 (C_2) 60.78 (C_5) 63.48 (C_1) 127.24 (C_{12} and C_8) 128.09 (C_9 and C_{11}) 130.91 (C_{10}) 134.86 (C_7) 166.10 (C_6)

HR-MS: calculated 224.12812 $[M+H]^+$, 246.11007 $[M+Na]^+$, found: 224.12804 $[M+H]^+$, 246.10991 $[M+Na]^+$, Δm = 0.4-0.6 ppm

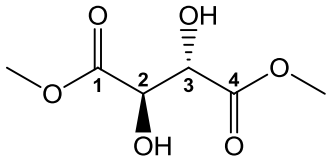
IR: 3359 (υ(NH) + υ(OH)), 3301 (υ(NH) + υ(OH)), 3284 (υ(NH) + υ(OH)), 3085 (υ(CH) arom. CH), 2953 (υ(CH) aliph. CH), 2924 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1637 (υ(C=O) amide), 1537(amide II), 1072 (υ(C-OH)), 702 (δ(Ph) mono-sub.) cm^{-1}

Optical activity: (recrystallized) $[\alpha]^{20}_D$ = -34.5 (c = 0.01, MeOH)

m_p: 106.5 – 107.4 °C

HPLC: C-HPLC 9 (1 mL/min, 30°C), t_R = 5.7 min

(2*R*,3*S*)-dimethyl 2,3-dihydroxysuccinate (139)



Meso-tartaric acid monohydrate (10g, 66.63mmol, 1 eq.) was put in solution in 270mL MeOH. Amberlyst 15 (H^+-form 20-50 mesh, 120g) was added portion wise (addition of Amberlyst heat up the solution) and left under soft shaking (no stirring) for 96h. The reaction mixture was filtered through Büchner and washed with 400mL MeOH. The solvent was evaporated under reduced pressure and the product crystallized during the process. The brawn crystals were dissolved in MED/ESTP and 1g of activated charcoal was added. After 30min, the mixture was filtered through a disposable bottle-top filter (Zapcap®-CR) and the solvent was evaporated under reduced pressure to afford white crystals (10.95g, 92% yield).

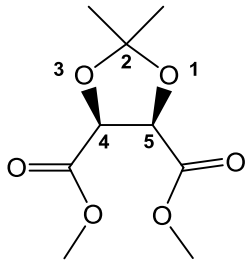
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.62 (s, 6 H) 4.28 (s, 2 H) 5.80 (br. s., 2 H)

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 51.60 (CH_3) 72.87 (C_2 and C_3) 171.51 (C=O)

HR-MS: calculated 179.05502 $[M+H]^+$, 196.08157 $[M+NH_4]^+$; found 179.05506 $[M+H]^+$, 196.08162 $[M+NH_4]^+$; Δm =0.3 ppm

IR: 3427 (υ(OH)), 2960 (υ(CH)), 1743 (υ(C=O)), 1444 (δ(CH)), 1229 (υ(C-O)), 1125 (υ(C-O)) cm^{-1}

(4*S*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic (140)



(2*R*,3*S*)-dimethyl 2,3-dihydroxysuccinate **139** (6g, 33.68mmol, 1 eq.) was put in solution in 4mL CH_2Cl_2 at rt. *p*-toluenesulfonic acid monohydrate (3.2g, 16.84mmol, 0.5 eq.) was added to the solution followed by addition of 2,2-dimethoxypropane (27mL, 6.5 eq.). Molecular sieves (3Å) were added to the mixture. After 24h, the reaction was filtered through Büchner and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure. 200mL H_2O was added to the crude and extracted with 2x 200mL ESTP. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Flash chromatography of the crude (9:1 HXF:ESTP) afforded the desired product (yellow oil, 5.941g, 81% yield)

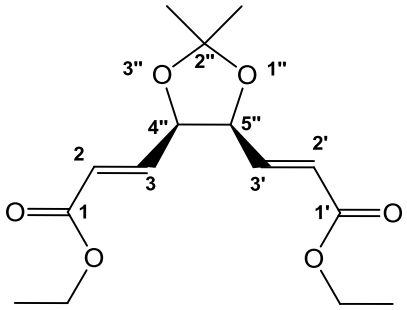
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.43 (s, 3 H) 1.67 (s, 3 H) 3.77 (s, 6 H) 4.85 (s, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 25.78 (CH_3-C_2) 26.61 (CH_3-C_2) 52.47 (CH_3 ester) 113.12 (C_4 and C_5) 168.66 (C=O)

HR-MS: calculated 219.08632 $[M+H]^+$, 236.11287 $[M+NH_4]^+$, 241.06826 $[M+Na]^+$; found 219.08626 $[M+H]^+$, 236.11275 $[M+NH_4]^+$, 241.06806 $[M+Na]^+$; Δm = 0.2-0.8 ppm

FTIR: 2991 (υ(CH)), 2956 (υ(CH)), 2853 (υ(CH)), 1768 (υ(C=O) ester), 1439 (δ(CH)), 1385 (δ (CH)), 1213 (C-O ester), 1108 (C-O) cm^{-1}

(2*E*,2'*E*)-diethyl 3,3'-[(4''*R*,5''*S*)-2'',2''-dimethyl-1'',3''-dioxolane-4'',5''-diyl]diacrylate (142)



(4*S*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic **140** (4g, 18.33mmol, 1 eq.) was put in solution in 120mL toluene and the solution was cooled down at -78°C. DIBAL (1M in toluene, 37mL, 36.66mmol, 2 eq.) was slowly added to the solution at -78°C during 30min and left to react during 2h30. Meanwhile, a solution of sodio triethyl phosphonoacetate was prepared by dissolving sodium hydrid (55-65% in mineral oil, 2g, 45.83mmol, 2.5 eq.) in 20mL DME at 0°C and adding triethyl phosphonoacetate diluted in 10mL DME at 0°C. After end of addition, the white suspension was allowed to come at rt and the mixture was stirred to react during 20min at rt. The solution of sodio triethyl phosphonoacetate was added to the reaction mixture at -70°C during 15min. After the end of addition, the solution was allowed to come at rt. After 4h, the reaction mixture was cooled at 0°C and 50mL H_2O was slowly added. A grey gel was formed which was filtered through a small pad of cellflock and washed with TBME. The filtrate was transferred into a separatory funnel and extracted with 3x 50mL H_2O. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (8:2 HXF:ESTP) afforded the desired product (yellow oil, 3.22g, 59% yield)

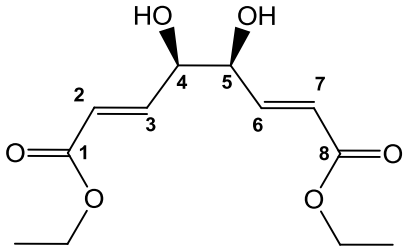
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.28 (t, *J*=7.15 Hz, 6 H) 1.42 (s, 3 H) 1.57 (s, 3 H) 4.19 (q, *J*=7.03 Hz, 4 H) 4.85 (dt, *J*=2.45, 1.16 Hz, 2 H) 6.04 - 6.12 (m, 2 H) 6.67 - 6.76 (m, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 14.16 (*C*H_3 ethyl) 25.35 (*C*H_3-$C_{2''}$) 27.67 (*C*H_3-$C_{2''}$) 60.57 (*C*H_2 ethyl) 77.42 ($C_{4''}$ and $C_{5''}$) 110.25 ($C_{2''}$) 123.72 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 141.86 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 165.55 (C_1 and $C_{1'}$)

HR-MS: calculated 299.14892 $[M+H]^+$, 316.17547 $[M+NH_4]^+$; found 299.14881 $[M+H]^+$, 316.17531 $[M+NH_4]^+$; Δm = 0.3-05 ppm

FTIR: 2987 (υ(CH) aliph. CH), 2940 (υ(CH) aliph. CH), 2907 (υ(CH) aliph. CH), 1723 (υ(C=O) ester), 1663 (υ (C=C)), 1465, 1372, 1308, 1262 (C-O), 1180 (C-O), 1123 (C-O), 1042 (C-O), 981 (δ(CH) CH=CH trans), 859cm^{-1}

(2*E*,4*R*,5*S*,6*E*)-diethyl 4,5-dihydroxyocta-2,6-dienedioate (143)



(2*E*,2'*E*)-diethyl 3,3'-((4*R*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)diacrylate **142** (3g, 10.056mmol, 1 eq.) was put in solution in 60mL THF and 60mL H_2O at rt. HCl (fuming 37%, 24mL) was slowly added to the solution. After 4h, the reaction was quenched with a dropwise addition of 40mL K_2CO_3 10N. 40mL NaCl sat was then added and followed by extraction with 3x 60ml TBME. The organic layer was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Flash chromatography of the crude (1:1 HXF:ESTP) afforded the desired product (white crystals, 2.073g, 80% yield)

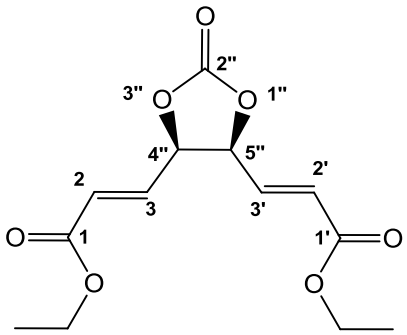
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.30 (t, *J*=7.15 Hz, 6 H) 2.42 (br. s., 2 H) 4.22 (q, *J*=7.03 Hz, 4 H) 4.45 - 4.52 (m, 2 H) 6.15 (dt, *J*=15.69, 0.69 Hz, 2 H) 6.88 - 6.97 (m, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 14.18 (*C*H_3-ethyl) 60.69 (*C*H_2-ethyl) 73.50 (C_4 or C_5) 123.47 (C_2 and C_7) 144.06 (C_3 and C_6) 165.90 (C_1 and C_8)

HR-MS: calculated 259.11762 $[M+H]^+$, 276.14417 $[M+NH_4]^+$, 281.09956 $[M+Na]^+$; found 259.11749 $[M+H]^+$, 276.14404 $[M+NH_4]^+$, 281.09940 $[M+Na]^+$

FTIR: 3439 (υ(OH)), 2991 (υ(CH) aliph. CH), 2942 (υ(CH) aliph. CH), 2914 (υ(CH) aliph. CH), 1694 (υ(C=O) ester), 1660 (υ(C=C)), 1480 (δ(CH)), 1458 (δ(CH)), 1445 (δ(CH)), 1398 (δ(CH)), 1310, 1283 (υ(C-O)), 1273 (υ(C-O)), 1189 (υ(C-O)), 1096 (υ(C-O)), 1033 (υ(C-O)), 987 (δ(CH) CH=CH trans) cm^{-1}

(2*E*,2'*E*)-diethyl 3,3'-[(4*R*'',5*S*'')-2''-oxo-1'',3''-dioxolane-4'',5''-diyl]diacrylate (144)



(2*E*,4*R*,5*S*,6*E*)-diethyl 4,5-dihydroxyocta-2,6-dienedioate **143** (1.95g, 7.55mmol, 1 eq.) was put in solution in 75mL CH_2Cl_2 at rt. Pyridine (3.062g, 38.72mmol, 5.1 eq.) was added at rt and then the reaction was cooled down at 0°C. Trisphosgen (3.447g, 11.616mmol, 1.5 eq.) diluted in 35mL CH_2Cl_2 was slowly added to the reaction mixture at 0°C during 15min. After 15min, the reaction was finished and 100mL NH_4Cl sat was added at 0°C to quench the reaction. The solution was then allowed to come at rt. The organic phase was separated and the aqueous phase was extracted with 2x 70mL TBME. The organic phases were put together and extracted with 1x 100mL $NaHCO_3$ sat, 1x 100mL NaCl sat and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (6:4 HXF:ESTP) afforded the desired product (2.123g, 99% yield).

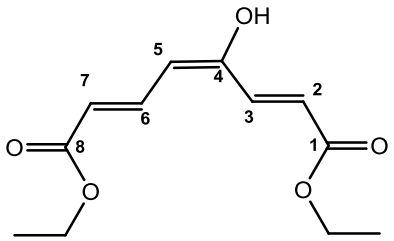
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.31 (t, *J*=7.03 Hz, 6 H) 4.24 (q, *J*=7.03 Hz, 4 H) 5.37 - 5.43 (m, 2 H) 6.19 - 6.25 (m, 2 H) 6.66 - 6.75 (m, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 14.10 (*C*H_3 ethyl) 61.21 (*C*H_2 ethyl) 126.47 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 136.28 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 152.65 ($C_{2''}$) 164.43 (C_1 and $C_{1'}$)

HR-MS: calculated 285.09688 $[M+H]^+$, 302.12343 $[M+NH_4]^+$, 307.07883 $[M+Na]^+$; found 285.09665 $[M+H]^+$, 302.12317 $[M+NH_4]^+$, 307.07858 $[M+Na]^+$; Δm = 0.8-0.9 ppm

FTIR: 3072 (υ(CH) arom.), 3042 (υ(CH) arom.), 2984 ((υ(CH) aliph.), 2936 (υ(CH) aliph.), 1818 (υ(C=O) carbonate), 1718 (υ(C=O) ester), 1662 (υ(C=C)), 1370, 1309, 1262, 1177 (υ(C-O)), 1051 (υ(C-O)) cm^{-1}

(2*E*,4*E*,6*E*)-diethyl 4-hxdroxyocta-2,4,6-trienedioate (145)

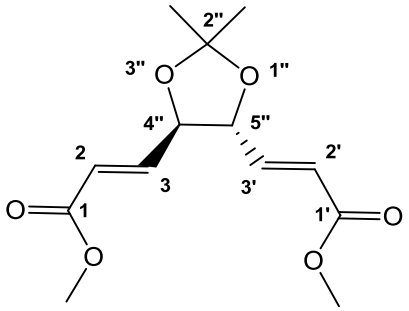


^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 1.22 (q, *J*=6.95 Hz, 6 H) 4.14 (dq, *J*=17.93, 7.20 Hz, 4 H) 5.88 - 5.93 (m, 2 H) 6.31 (d, *J*=15.73 Hz, 1 H) 7.04 (d, *J*=15.37 Hz, 1 H) 7.78 (dd, *J*=15.00, 12.07 Hz, 1 H) 10.07 (s, 1 H)

HR-MS: found 195.06511 $[M-HOC_2H_5]^+$, 241.10692 $[M+H]^+$, 263.08880 $[M+Na]^+$

HSQC, COSY, ROESY and HMBC spectras available.

(2*E*,2'*E*)-dimethyl 3,3'-[(4*R*'',5*R*'')-2'',2''-dimethyl-1'',3''-dioxolane 4'',5''diyl]diacrylate (154)



Dimethyl (4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (3g, 13.75mmol, 1 eq.) was put in solution in 60mL toluene and the solution was cooled down at -78°C. DIBAL (1M in toluene, 3.91g, 27.5mmol, 2 eq.) was slowly added to the solution during 30min and left to react during 2h (inner temperature went up to-70°C during addition). In the meantime, a solution of sodio methyl diethylphosphonate was prepared by dissolving NaH (55-65% in mineral oil, 1.5g, 34.37mmol, 2.5 eq.) in 20mL DME. The mixture was cooled down at 0°C and methyl diethylphosphonoacetate (7.22g, 34.37mmol, 2.5 eq.) diluted in 15mL DME was slowly added to the NaH mixture at 0°C. After the end of addition, the white suspension was allowed to come at rt and was stirred to react during 20min at rt. Sodio methyl diethylphosphonate was added to the DIBAL solution during 20min (inner temperature went up to -65°C during reaction). After the end of addition, the clear solution was allowed to come at rt. After 4h, the reaction mixture was slowly quenched with 50mL H_2O. The formed gel was filtered through a thin pad of cellflock then poured to 150mL TBME and extracted. The organic phase was washed 3x 50mL H_2O and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (9:1 HXF:ESTP) afforded the desired product (colorless oil, 2.317g, 62%).

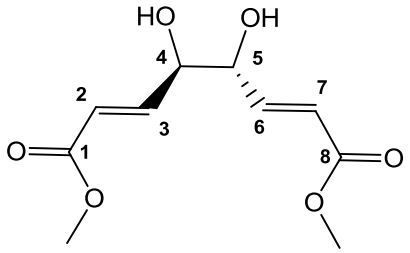
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.48 (s, 6 H) 3.78 (s, 6 H) 4.30 (ddd, *J*=2.95, 1.32, 1.00 Hz, 2 H) 6.16 (d, *J*=15.81 Hz, 2 H) 6.85 - 6.92 (m, 2 H)

^{13}C NMR (400 MHz, $CDCl_3$-*d*) δ ppm 26.78(*C*H_3-$C_{2''}$) 51.82 (*C*H_3 ester) 79.72 ($C_{4''}$ and $C_{5''}$) 110.94 ($C_{2''}$) 123.27 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 142.15 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 166.06 (C_1 and $C_{1'}$)

HR-MS: calculated 271.11762 $[M+H]^+$, 288.14417 $[M+NH_4]^+$; found: 271.11750 $[M+H]^+$, 288.14402 $[M+NH_4]^+$, Δm = 0.4-0.5 ppm

FTIR: 2990 (γ(CH), aliph. CH), 2954 (γ(CH), aliph. CH), 2883 ($\gamma_s(OCH_3)$), 1729 (γ(C=O) ester), 1666 (γ(C=C)), 1438 (δ(C-H)), 1375 (δ(C-H)), 1307 (C-O), 1279 (C-O), 1167 (C-O), 979 (δ(CH) trans C=C) cm^{-1}

(2*E*,4*R*,5*R*,6*E*)-dimethyl 4,5-dihydroxyocta-2,6-dienedioate (155)



(2*E*,2'*E*)-dimethyl 3,3'-((4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)diacrylate **154** (1g, 3.7mmol, 1 eq.) was put in solution in 20mL THF and 20mL H_2O at rt. HCl (fuming 37%, 5mL was added to the solution (inner temperature raised up to 30°C). Afte 2h, another 5mL of HCl (fuming 37%) was slowly added to the solution. After 4h, the reaction was quenched with addition of 20mL10N K_2CO_3. The resulting mixture was saturated with 20mL NaCl and extracted with 3x 50mL TBME. The organic phases were put together and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Product crystallized by addition of a minimum of CH_2Cl_2. The white solid was filtered, washed with hexane and put in the oven to dry to afford the desired product (white solid, 0.7506g, 88% yield).

^{1}H NMR (600 MHz, DMSO-d_6) δ ppm 3.65 (s, 6 H) 4.31 (br. s., 2 H) 5.55 (d, *J*=4.02 Hz, 2 H) 5.99 (dd, *J*=15.73, 1.10 Hz, 2 H) 6.90 (dd, *J*=15.73, 3.66 Hz, 2 H)

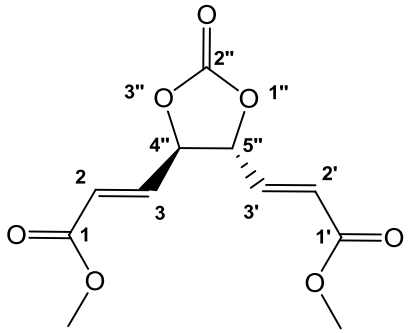
^{13}C NMR (151 MHz, DMSO-d_6) δ ppm 51.33 (CH_3) 72.29 (C_4 and C_5) 120.27 (C_2 and C_7) 148.54 (C_3 and C_6) 166.00 (C_1 and C_8)

HR-MS: calculated 231.08632 $[M+H]^+$, 248.11287 $[M+NH_4]^+$, 253.06826 $[M+Na]^+$; found 231.08623 $[M+H]^+$, 248.11275 $[M+NH_4]^+$, 253.06811 $[M+Na]^+$; Δm = 0.4-0.6 ppm

FTIR: 3390 (OH), 3279 (OH), 2997 (CH), 2955(CH), 2916 (CH), 2855 (CH), 1714 (C=O ester), 1666 (C=C), 1445, 1318 (C-O), 1279 (C-O), 1201 (C-O), 1178 (C-O), 1020 (C-O), 982 (δ CH trans C=C) cm^{-1}

m_p: 88.5-90.5 °C

(2*E*,2'*E*)-dimethyl 3,3'-[(4''*R*,5''*R*)-2''-oxo-1'',3''-dioxolane-4'',5''-diyl]diacrylate (156)



(2*E*,4*R*,5*R*,6*E*)-dimethyl 4,5-dihydroxyocta-2,6-dienedioate **155** (0.4g, 1.737mmol, 1 eq.) was put in solution in 15mL CH_2Cl_2 at rt. Pyridine (0.7mL, 8.685mmol, 5 eq.) was added at rt and the reaction mixture was cooled down at 0°C. Trisphosgen (0.773g, 2.606mmol, 1.5 eq.) diluted in 7mL CH_2Cl_2 was slowly added to the mixture during 10min (inner temperature +1-2°C). After 1h, the reaction was quenched with 40mL NH_4Cl at 0°C and was allowed to come at rt. The organic phase was separated and the aqueous phase was extracted with 3x 30mL TBME. The organic phases were put together and extracted with 1x 100mL $NaHCO_3$ sat., 1x 100mL NaCl sat. and dried over $MgSO_4$. The solvent was evaporated under reduced pressure.

Flash chromatography of the crude (1:1 HXF : ESTP) afforded the desired product (white powder, 0.423g, 95% yield)

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 3.71 (s, 6 H) 5.30 - 5.36 (m, 2 H) 6.24 (d, *J*=15.81 Hz, 2 H) 6.94 - 7.04 (m, 2 H)

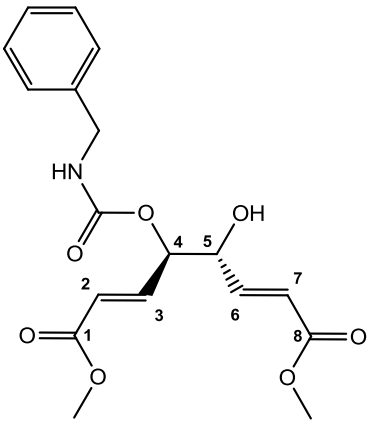
^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 51.80 (CH_3) 78.54 ($C_{4''}$ and $C_{5''}$) 124.68 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 140.09 (C_2 and $C_{2'}$ or C_3 and $C_{3'}$) 153.01 (C=O) 164.99 (C=O)

HR-MS: calculated 257.06558 $[M+H]^+$, 274.09213 $[M+NH_4]^+$, 279.04753 $[M+Na]^+$; found 257.06558 $[M+H]^+$, 274.09201 $[M+NH_4]^+$, 279.04745 $[M+Na]^+$; Δm: < 0.1-0.4 ppm

IR: 3073 (υ(CH) arom. olef. CH), 3001 (υ(CH) arom. olef. CH), 2956 (υ_{as}(CH3)), 2849 (υ_s(CH3)), 1822 (υ(C=O) carbonate), 1720 (υ(C=O) ester), 1670 (υ(C=C)), 1436 (δ(CH)), 1389 (δ(CH)), 1327, 1271 (υ(C-O)), 1201 (υ(C-O)), 1063 (C-O), 989 (δ(CH) CH=CH trans), 746 cm^{-1}

m_p: 78.8-79.9°C

(2*E*,4*R*,5*R*,6*E*)-dimethyl 4-((benzylcarbamoyl)oxy)-5-hydroxyocta-2,6-dienedioate (157)



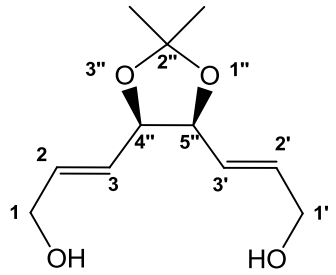
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 3.74 (s, 6 H) 4.35 (m, 3H) 4.50 (br. s., 1 H) 5.45 (m, 1 H) 5.51 - 5.57 (m, 1 H) 6.04 - 6.21 (m, 2 H) 6.92 (dt, *J*=15.75, 4.55 Hz, 2 H) 7.23 - 7.38 (m, 5 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 45.13 (*C*H_2 amide) 51.72 (*C*H_3) 51.79 (*C*H_3) 71.63 (C_4 or C_5) 74.82 (C_4 or C_5) 122.65 (C_2 or C_3 or C_6 or C_7) 123.26 (C_2 or C_3 or C_6 or C_7) 127.41 - 128.69 (aromatic *C*H) 137.76 (quaternary C) 141.88 (C_2 or C_3 or C_6 or C_7) 144.79 (C_2 or C_3 or C_6 or C_7) 155.21 (C=O) 166.13 (C=O) 166.46 (C=O)

HR-MS: calculated 364.13908 $[M+H]^+$, 381.16563 $[M+NH_4]^+$, 386.12103 $[M+Na]^+$; found 364.13925 $[M+H]^+$, 381.16590 $[M+NH_4]^+$, 386.12101 $[M+Na]^+$; Δm: < 0.1-0.7 ppm

IR: 3437 (γ(NH) + γ(OH)), 3420 (γ(NH) + γ(OH)), 3032 (γ(CH) arom. CH), 1721 (γ(C=O)), 1700 (γ(C=O)), 1660 (γ(C=O)), 1515 (amide II) cm^{-1}

(2*E*,2'*E*)-3,3'-[(4''*R*,5''*S*)-2'',2''-dimethyl-1'',3''-dioxolane-4'',5''-diyl]bis(prop-2-en-1-ol) (161)



$LiAlH_4$ (pellet, 0.043g, 1.133mmol, 3.4 eq.) was put in solution in 4mL THF at rt and the solution was cooled down at -78°C. *n*-BuBr (0.155g, 1.133mmol, 3.4 eq.) diluted in 1mL THF was slowly added and after the end of addition, the mixture was allowed to come at rt to react. After16h, the mixture was cooled down at -78°C and (2*E*,2'*E*)-diethyl 3,3'-((4*R*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)diacrylate **142** (0.1g, 0.335mmol, 1 eq.) was added dropwise during 15min. After 3h, the reaction mixture was allowed to come at 0°C. After 1h at 0°C, the reaction was finished and 0.07mL NaOH 1M was slowly added at 0°C and left to stir for 15min. A grey gel was formed which is filtered through a short pad of cellflock and washed with 40mL ESTP. The solvent was evaporated under reduced pressure. Flash

chromatography of the crude (eluent: ESTP) afforded the desired product (0.055g, 77% yield).

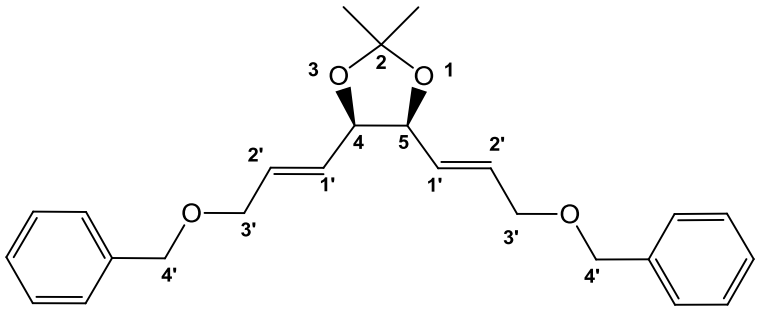
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.41 (s, 3 H) 1.54 (s, 3 H) 1.80 (br. s., 2 H) 4.16 (dd, *J*=5.02, 1.51 Hz, 4 H) 4.63 - 4.71 (m, 2 H) 5.61 - 5.71 (m, 2 H) 5.91 (dt, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 25.41 (CH_3-$C_{2''}$) 27.95 (CH_3-$C_{2''}$) 62.61 (C_1 and $C_{1'}$) 78.88 ($C_{4''}$ and $C_{5''}$) 108.86 ($C_{2''}$) 127.24 (C_3 and $C_{3'}$) 133.33 (C_2 and $C_{2'}$)

HR-MS: calculated 215.12779 $[M+H]^+$, 232.15434 $[M+NH_4]^+$; found 215.12772 $[M+H]^+$, 232.15425 $[M+NH_4]^+$; Δm = 0.3-0.4 ppm

FTIR: 3381 (υ(OH)), 2988 (υ(CH) aliph. CH), 2934 (υ(CH) aliph. CH), 2871 (υ(CH) aliph. CH), 1676 (υ(C=C)), 1456 (δ(CH)), 1381 (δ(CH)), 1372 (δ(CH)), 1247 (υ(C-O)), 1217 (υ(C-O)), 1165 (υ(C-O)), 1094 (υ(C-O)), 1041 (υ(C-O)), 974 (δ_{oop}(CH), trans CH=CH) cm^{-1}

(4*R*,5*S*)-4,5-bis-[(*E*)-3'-(benzyloxy)prop-1'-en-1'-yl]-2,2-dimethyl-1,3-dioxolane (162)



NaH (55-65% in mineral oil, 0.367g, 8.4mmol, 3 eq.) was put in solution in 15mL THF at rt forming a white/grey suspension. (2*E*,2'*E*)-3,3'-((4*R*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(prop-2-en-1-ol) **161** (0.6g, 2.8mmol, 1 eq.) diluted in 15mL THF was slowly added to the suspension during 10min. 3mL of DMF was added to the reaction mixture followed by

BnBr (1.149g, 6.72mmol, 2.4 eq.). After 3h30, the reaction was quenched with 10mL ammonium chloride sat and 5mL water. The water phase was extracted with 2x 40mL ESTP. The organic phases were put together, washed with 50mL NaCl sat and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (8:2 HXF:ESTP) afforded the desired product (0.723g, 65% yield)

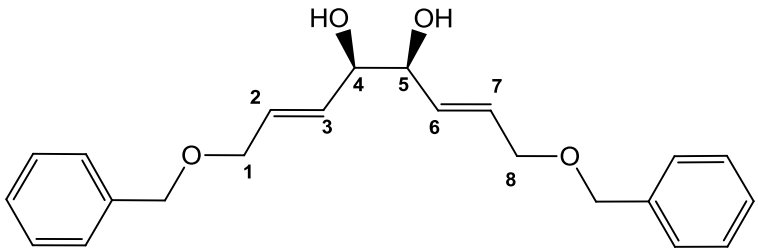
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.41 (s, 3 H) 1.54 (s, 3 H) 4.04 (d, *J*=5.52 Hz, 4 H) 4.48 (s, 4 H) 4.64 - 4.70 (m, 2 H) 5.65 - 5.75 (m, 2 H) 5.84 - 5.93 (m, 2 H) 7.25 - 7.36 (m, 10 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 25.49 (*C*H_3) 28.02 (*C*H_3) 69.72 ($C_{3'}$) 71.95 ($C_{4'}$) 79.01 (C_4 and C_5) 108.86 (C_2) 127.59 – 128.69 (aromatic *C*H + $C_{1'}$ or $C_{2'}$) 130.86 ($C_{1'}$ or $C_{2'}$) 138.17 (quaternary C, 2 C)

HR-MS: calculated 412.24824 $[M+NH_4]^+$, 417.20363 $[M+Na]^+$, 433.17757 $[M+K]^+$; found 412.24850 $[M+NH_4]^+$, 417.20355 $[M+Na]^+$, 433.17755 $[M+K]^+$; Δm = 0.6-0.7 ppm

FTIR: 3325 (υ(OH)), 3063 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2988 (υ(CH) aliph. CH)), 2934 (υ(CH) aliph. CH)), 2858 (υ(CH) aliph. CH)), 1605 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1371 (δ(CH)), 1247 (υ(C-O)), 1216 (υ(C-O)), 1115 (υ(C-O)), 1042 (υ(C-O)), 972 (δ(CH) C=C trans), 739 (δ(CH) arom. CH), 699 (δ(Ph)) cm^{-1}

(2*E*,4*R*,5*S*,6*E*)-1,8-bis-(benzyloxy)octa-2,6-diene-4,5-diol (163)



(4*R*,5*S*)-4,5-bis((*E*)-3-(benzyloxy)prop-1-en-1yl)-2,2-dimethyl-1,3-dioxolane **162** (0.688g, 1.744mmol, 1 eq.) was put in solution in 40mL THF and 15mL water at rt. HCl (fuming 37%, 5mL) was slowly added to the solution. After 3h, the reaction was quenched with 10mL K_2CO_3 10N and 20mL NaCl sat. The water phase was extracted with 3x 50mL TBME and the organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (1:1 HXF:ESTP) afforded the desired product (0.545g, 88% yield)

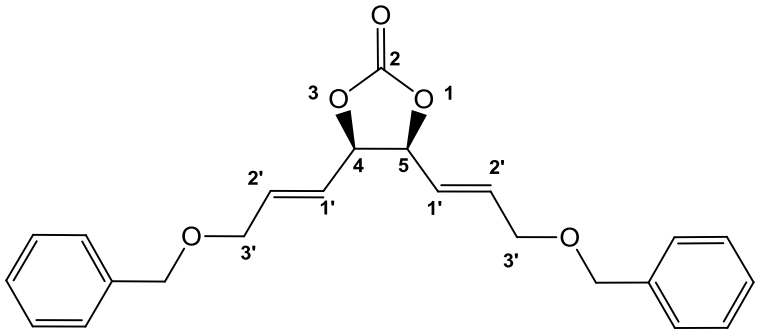
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.69 (br. s., 2 H) 4.05 (d, *J*=5.27 Hz, 4 H) 4.21 - 4.26 (m, 2 H) 4.52 (s, 4 H) 5.76 - 5.84 (m, 2 H) 5.88 - 5.97 (m, 2 H) 7.28 - 7.38 (m, 10 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 69.91 (C_1 and C_8) 72.27 (CH_2 ether) 74.66 (C_4 and C_5) 127.67 (aromatic *C*H) 127.74 (aromatic *C*H) 128.40 (aromatic *C*H) 130.10 (C_2 and C_7 or C_3 and C_6) 130.45 (C_2 and C_7 or C_3 and C_6) 138.12 (aromatic quaternary C)

HR-MS: calculated 355.19039 $[M+H]^+$, 372.21694 $[M+NH_4]^+$, 377.17233 $[M+Na]^+$; found 372.21686 $[M+NH_4]^+$, 377.17209 $[M+Na]^+$; Δm = 0.2 ppm

FTIR: 3063 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2861 (υ(CH) aliph. CH), 1586 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1101 (υ(C-O)), 1068 (υ(C-O)), 974 (δ(CH) C=C trans) 741 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

(4*R*,5*S*)-4,5-bis-[(*E*)-3'-(benzyloxy)-prop-1'-en-1'-yl]-1,3-dioxolan-2-one (164)



(2*E*,4*R*,5*S*,6*E*)-1,8-bis-(benzyloxy)octa-2,6-diene-4,5-diol **163** (0.52g, 1.47mmol, 1 eq.) was put in solution in 40mL CH_2Cl_2 at rt, pyridine (0.61mL, 7.48mmol, 5.1 eq.) was added at rt and then cooled down at 0°C. Trisphosgen (0.653g, 2.2mmol, 1.5 eq.) diluted in 10mL CH_2Cl_2 was slowly added to the reaction mixture during 15min. After 15min, the reaction was quenched with 20mL ammonium chloride sat and extracted with 3x 60mL CH_2Cl_2. The collected organic phases was extracted with 1x 60mL $NaHCO_3$ sat and 1x 60mL NaCl sat. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (6:4 HXF:ESTP) afforded the desired product (0.543g, 97% yield).

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 4.07 (dd, 4 H) 4.51 (s, 4 H) 5.16 - 5.23 (m, 2 H) 5.70 - 5.81 (m, *J*=15.53, 5.49, 1.78, 1.78, 1.78 Hz, 2 H) 6.02 (dt, *J*=15.81, 4.89 Hz, 2 H) 7.27 - 7.39 (m, 10 H)

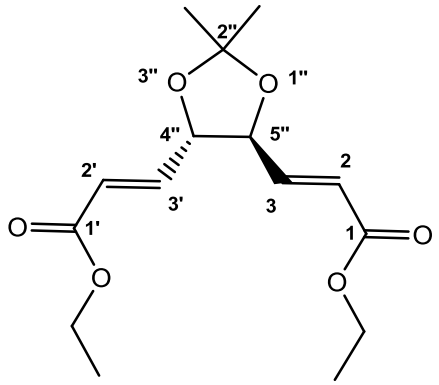
^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 68.90 ($C_{3'}$) 72.50 (CH_2 ether) 79.71 (C_4 and C_5) 123.10 ($C_{1'}$) 127.65 (aromatic *C*H) 127.81 (aromatic *C*H) 128.46 (aromatic *C*H) 134.43 ($C_{2'}$) 137.77 (aromatic quaternary C) 154.07 (C_2)

HR-MS: calculated 398.19620 $[M+NH_4]^+$, 403.15160 $[M+Na]^+$, 419.12553 $[M+K]^+$; found 398.19629 $[M+NH_4]^+$, 403.15147 $[M+Na]^+$, 419.12540 $[M+K]^+$,; Δm = 0.2-0.3 ppm

FTIR: 3088 (υ(CH) arom. CH), 3063 (υ(CH) arom. CH), 3031 (υ(CH) arom. CH), 2855 (υ(CH) aliph. CH), 1800 (υ(C=O) carbonate), 1678 (υ(C=C)), 1605 (υ(Ph)), 1496 (υ(Ph)),

1454 (υ(Ph)), 1176 (υ(C-O)), 1115 (υ(C-O)), 1040 (υ(C-O)), 968 (δ(CH) CH=CH trans), 739 (δ(CH) Ph), 699 (δ(Ph)) cm^{-1}

(2*E*,2'*E*)-diethyl 3,3'-[(4''*S*, 5''*S*)-2''-2''-dimethyl-1'',3''-dioxolane-4'',5''diyl]diacrylate (167)



(-)-Dimethyl 2,3-*O*-isopropylidene-*L*-tartrate (21g, 96.237mmol, 1 eq.) was put in solution in 400mL toluene and the solution was cooled down at -78°C. DIBAL (1M in toluene, 193mL, 193 mmol, 2 eq.) was slowly added to the reaction mixture during 30min and left to react during 3h (inner temperature went up to -70°C). In the meantime, sodio triethyl phosphonoacetate was prepared by dissolving NaH (55-65% in mineral oil, 10.5g, 240.6 mmol, 2.5 eq.) in 70mL DME. The mixture was cooled down at 0°C and triethyl phosphonoacetate (53.94g, 240.6, 2.5 eq.) diluted in 30mL DME was added at 0°C. After the end of addition, the yellow solution with some white suspension was allowed to come at rt and the mixture was stirred during 45min at rt. The sodio triethyl phosphonoacetate was added to the DIBAL solution during 15min (inner temperature -70°C) and was then allowed to come at rt. After 3h, the reaction was quenched with 200mL H_2O. The formed grey gel was filtered through a small pad of cellflock and washed with ESTP. The filtrate was extracted with 2x 200mL H_2O and the organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (9:1 HXF:ESTP) afforded the desired product (colorless oil, 17.291g, 60%).

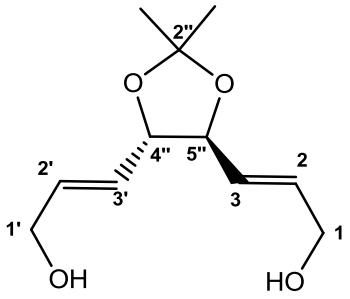
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.31 (t, *J*=7.15 Hz, 6 H) 1.48 (s, 6 H) 4.22 (q, *J*=7.28 Hz, 4 H) 4.27 - 4.33 (m, 2 H) 6.12 - 6.18 (m, 2 H) 6.83 - 6.91 (m, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 14.17 (*C*H_3 ethyl) 26.77 (*C*H_3-$C_{2''}$) 60.72 (*C*H_2 ethyl) 79.70 ($C_{4''}$ and $C_{5''}$) 110.81 ($C_{2''}$) 123.70 (C_2 and $C_{2''}$) 141.78 (C_3 and $C_{3''}$) 165.64 (C_1 and $C_{1''}$)

HR-MS: calculated 299.14892 $[M+H]^+$, 316.17547 $[M+NH_4]^+$; found 299.14887 $[M+H]^+$, 316.17551 $[M+NH_4]^+$

FTIR: 2986 (υ(CH) aliph. CH), 2939 (υ(CH) aliph. CH), 1724 (υ(C=O)), 1664 (υ(C=C)), 1448 (δ(CH)), 1180 (υ(C-O)), 1165 (υ(C-O)), 979 (δ(CH) C=C trans) cm^{-1}

(2*E*,2'*E*)-3,3'-[(4S'', 5S'')-2'',2''-dimethyl-1'',3''-dioxolane-4'',5''-diyl]bis(prop-2-en-1-ol) (168)



$LiAlH_4$ (pellets, 7.63g, 201.12mmol, 6 eq.) was put in solution in 350mL THF and stirred to dissolve the pellets. The grey suspension was then cooled down at -78°C. *n*-BuBr (27.56g, 201.12, 6 eq.) was added to the grey suspension (inner temperature -70°C). After the end of addition, the reaction mixture was allowed to come at rt. After 16h, the reaction mixture was cooled down at -78°C and (2*E*,2'*E*)-diethyl 3,3'-((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)diacrylate **167** (10g, 33.52mmol, 1 eq.) diluted in 40mL THF was slowly added during 15min. 1h30 after the end of addition, the reaction mixture was allowed to come at 0°C after 30min at 0°C, the reaction was finished. The mixture was slowly quenched with 20mL NaOH (1M) at 0°C and left to stir for 1h. The grey gel formed was filtered through a small pad of cellflock and washed with ESTP (500mL). The solvent was evaporated under reduced

pressure. Flash chromatography (eluent: ESTP) afforded the desired product (oil, 4.29g, 60% yield)

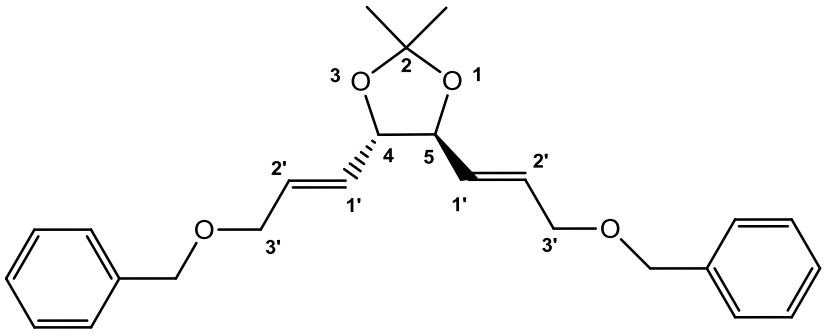
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.45 (s, 6 H) 1.92 (s, 2 H) 4.14 (dd, *J*=4.89, 1.88 Hz, 2 H) 4.17 (dd, *J*=5.14, 1.63 Hz, 4 H) 5.67 - 5.74 (m, 2 H) 5.98 (dt, *J*=15.69, 4.96 Hz, 2 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 26.99 (CH_3-$C_{2''}$) 62.59 (C_1 and $C_{1'}$) 81.34 ($C_{4''}$ and $C_{5''}$) 109.10 ($C_{2''}$) 126.47 (C_3 and $C_{3'}$) 134.39 (C_2 and $C_{2'}$)

HR-MS: calculated 259.11842 [M+$HCOO^-$]; found 259.11865 [M+$HCOO^-$]

FTIR: 3397 (υ(OH)), 2987 (υ(CH) aliph. CH), 2934 (υ(CH) aliph. CH), 2872 (υ(CH) aliph. CH), 1683 (υ(C=C)), 1455 (δ(CH) aliph. CH), 1373 (δ(CH) aliph. CH), 1236 (υ(C-O)), 1054 (υ(C-OH)), 971 (δ(CH) C=C trans) cm^{-1}

(4*S*,5*S*)-4,5-bis[(*E*)-3'-(benzyloxy)prop-1'-en-1'-yl]-2,2-dimethyl-1,3-dioxolane (169)



NaH (55-65% in mineral oil, 0.754g, 17.268mmol, 3.7 eq.) was put in solution in 50mL THF at rt. (2*E*,2'*E*)-3,3'-((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(prop-2-en-1-ol) **168** (1g, 4.667mmol, 1 eq.) diluted in 20mL THF was slowly added during 5min at rt. Afer 1h30, 10mL DMF and BnBr (1.92g, 11.2mmol, 2.4 eq.) were added to the brawn solution. After 3h, the reaction was quenched with 20mL ammonium chloride sat. and 20mL H_2O. The water phase was extracted with 2x 40mL ESTP and the collected organic phases were dried over

$MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (8:2 HXF:ESTP) afforded the desired product (0.999g, 54% yield)

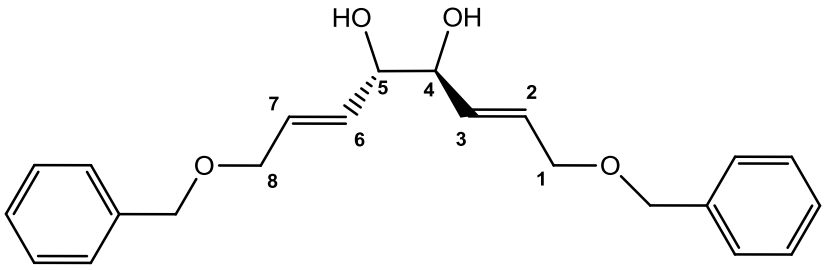
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 1.46 (s, 6 H) 4.06 (dd, *J*=5.27, 1.51 Hz, 4 H) 4.12 - 4.19 (m, 2 H) 4.52 (s, 4 H) 5.70 - 5.80 (m, 2 H) 5.94 (dt, 2 H) 7.27 - 7.38 (m, 10 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 27.01 (*C*H_3-C_2) 69.72 ($C_{3'}$) 72.22 (*C*H_2 benzyloxy) 81.40 (C_4 and C_5) 109.09 (C_2) 127.64 (aromatic *C*H, 2C) 127.71 (aromatic *C*H, 4C) 128.12 ($C_{1'}$) 128.40 (aromatic *C*H, 4C) 131.47 ($C_{2'}$) 138.10 (aromatic quaternary C, 2C)

HR-MS: calculated 412.24824 $[M+NH_4]^+$, 417.20363 $[M+Na]^+$; found 412.24830 $[M+NH_4]^+$, 417.20327 $[M+Na]^+$; Δm = 0.2 ppm

FTIR: 3088 (υ(C-H) arom. CH), 3031 (υ(C-H) arom. CH), 2986 (υ(C-H) arom. CH), 2933 (υ(C-H) aliph. CH), 2858 (υ(C-H) aliph. CH), 1605 (υ(Ph)), 1496 (υ(Ph)), 1455 (υ(Ph)), 1239 (υ(C-O)), 1118 (υ(C-O)), 1054 (υ(C-O)), 970 (δ(CH) C=C trans), 739 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

(2*E*,4*S*,5*S*,6*E*)-1,8-bis(benzyloxy)octa-2,6-diene-4,5-diol (170)



(4*S*,5*S*)-4,5-bis((*E*)-3-(benzyloxy)prop-1-en-1-yl)-2,2-dimethyl-1,3-dioxolane **169** (0.429g, 1.089mmol, 1 eq.) was put in solution in 25mL THF and 9mL H_2O at rt. HCl (fuming 37%, 3.5mL) was slowly added to the solution. After 6h, 1ml HCl fuming was slowly added again at rt. 2h after the second addition, the reaction was quenched with 7mL 10N K_2CO_3 and

saturated with 20mL NaCl sat. The aqueous phase was extracted with 3x 50mL TBME and the organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (1:1 HXF:ESTP) afforded the desired product (0.35g, 91% yield).

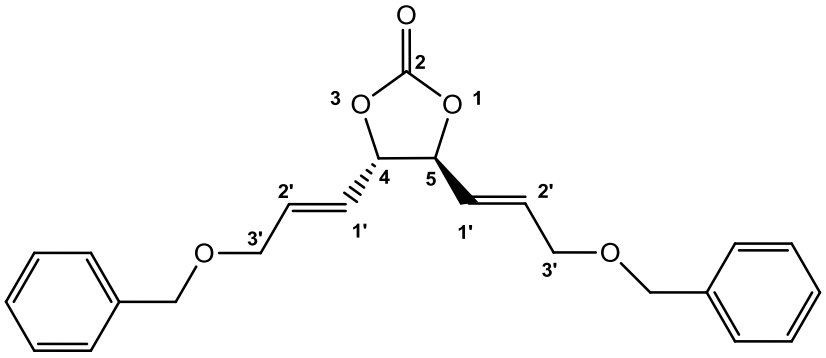
^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 2.14 (br. s., 2 H) 4.05 (dd, *J*=5.14, 1.13 Hz, 6 H) 4.52 (s, 4 H) 5.75 - 5.84 (m, 2 H) 5.94 (dt, *J*=15.80 Hz, 2 H) 7.27 - 7.38 (m, 10 H)

^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 69.89 (C_1 and C_8 or C_4 and C_5) 72.29 (*C*H_2 benzyloxy) 74.92 (C_1 and C_8 or C_4 and C_5) 127.66 (aromatic *C*H, 2C) 127.73 (aromatic *C*H, 4C) 128.39 (aromatic *C*H, 4C) 129.86 (C_2 and C_7 or C_3 and C_6) 131.07 (C_2 and C_7 or C_3 and C_6) 138.11 (aromatic quaternary C)

HR-MS: calculated 372.21694 $[M+NH_4]^+$, 377.17233 $[M+Na]^+$; found 372.21712 $[M+NH_4]^+$, 377.17216 $[M+Na]^+$; Δm = 0.5ppm

FTIR: 3392 (υ(OH)), 3063 (υ(C-H) arom. CH), 3031 (υ(C-H) arom. CH), 2859 (υ(C-H) aliph. CH), 1605 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1097 (υ(C-O)), 1065 (υ(C-O)), 1028 (δ(CH) mono-sub.), 973 (δ(CH) C=C trans) 740 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

(4*S*,5*S*)-4,5-bis[(*E*)-3'-(benzyloxy)prop-1'-en-1'-yl)]-1,3-dioxolan-2-one (171)



(2*E*,4*S*,5*S*,6*E*)-1,8-bis(benzyloxy)octa-2,6-diene-4,5-diol **170** (0.1g, 0.282mmol, 1 eq.) was put in solution in 8mL CH_2Cl_2 at rt. Pyridine (0.114mL, 1.438mmol, 5.1 eq.) was added to the solution at rt and the reaction mixture was cooled down at 0°C. Trisphogen (0.126g, 0.423mmol, 1.5 eq.) diluted in 2mL CH_2Cl_2 was slowly added to the reaction mixture. After 1h, the reaction was quenched with 3.5mL ammonium chloide sat. and 2mL H_2O at 0°C. The solution was then allowed to come at rt and the aqueous phase was extracted with 3x 10mL CH_2Cl_2. The collected organic phases were extracted with 1x 25mL $NaHCO_3$ sat. and 1x 25mL NaCl sat. The solvent was evaporated under reduced pressure. Flash chromatography of the crude (6:4 HXF:ESTP) afforded the desired product

^{1}H NMR (400 MHz, $CDCl_3$-*d*) δ ppm 4.08 (dd, *J*=4.77, 1.76 Hz, 4 H) 4.55 (s, 4 H) 4.72 - 4.79 (m, 2 H) 5.78 - 5.88 (m, 2 H) 6.03 (dt, *J*=15.81 Hz, 2 H) 7.28 - 7.41 (m, 10 H)

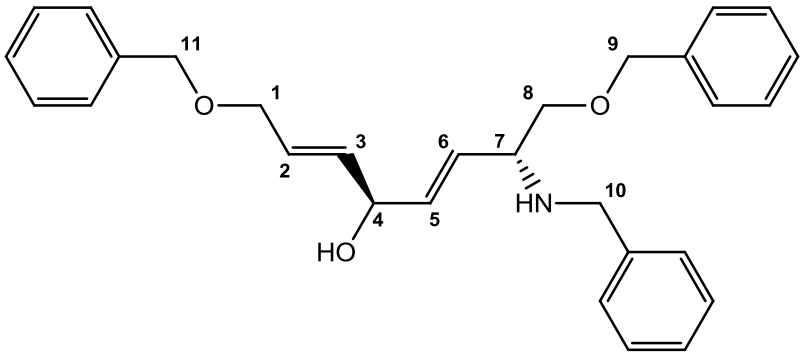
^{13}C NMR (101 MHz, $CDCl_3$-*d*) δ ppm 68.87 ($C_{3'}$) 72.80 (*C*H_2 benzyloxy) 82.02 (C_4 and C_5) 124.14 ($C_{1'}$) 127.72 (aromatic *C*H, 4C) 127.87 (aromatic *C*H, 2C) 128.49 (aromatic *C*H, 4C) 134.64 ($C_{2'}$) 137.66 (aromatic quaternary C) 153.90 (C_2)

HR-MS: calculated 398.19620 $[M+NH_4]^+$, 403.15160 $[M+Na]^+$; found 398.19625 $[M+NH_4]^+$, 403.15136 $[M+Na]^+$

FTIR: 3088 (υ(C-H) arom. CH), 3063 (υ(C-H) arom. CH), 3030 (υ(C-H) arom. CH), 2921 ((υ(C-H) aliph. CH), 2854 (υ(C-H) aliph. CH), 1800 (υ(C=O)), 1678 (υ(C=C)), 1605 (υ(Ph)),

1496 (υ(Ph)), 1454 (υ(Ph)), 1178 (υ(C-O)), 1114 (υ(C-O)), 1024 (υ(C-O)), 967 (δ(CH) C=C trans), 737 (δ(CH) mono subst.), 698 (δ(CH) mono subst.) cm^{-1}

(2*E*,4*R*,5*E*,7*R*)-7-(benzylamino)-1,8-bis(benzyloxy)octa-2,5-dien-4-ol (172)



The empty flask was evacuated and refilled with argon in a cycle of 3x (5min vacuum/5min argon). (*R*,*R*)-Trost ANDEN (0.01g, 0.0126mmol, 0.24 eq.) diluted in 0.5mL toluene and $[Pd(ally)Cl]_2$ (0.0015g, 0.0042mmol, 0.08 eq.) diluted in 0.5mL toluene were added to the flask. The unclear yellow solution was left to stir for 15min then (4S,5S)-4,5-bis((E)-3-(benzyloxy)prop-1-en-1-yl)-1,3-dioxolan-2-one **171** (0.02g, 0.0526mmol, 1 eq.) diluted in 0.5mL toluene was added. EDIPA (0.0068g, 0.0526mmol, 1 eq.) diluted in 0.5mL toluene and BnNH2 (0.0113g, 0.1052mmol, 2eq) were added to the reaction mixture at rt. After 2h, BnNH2 (6µL) was added again. After 72h, the reaction mixture was filtered over silica (1.4g) and washed with a solution of 80mL TBME and 0.3mL Et_3N. The solvents were evaporated under reduced pressure. Flash chromatography of the crude (7:3 ESTP:HXF) afforded the desired product (0.0088g, 38% yield)

^{1}H NMR: (600 MHz, $CDCl_3$-*d*) δ ppm 3.49 - 3.63 (m, 3 H) 3.78 - 4.01 (m, 2 H) 4.06 (d, *J*=5.49 Hz, 2 H) 4.49 - 4.59 (m, 6 H) 4.68 (t, *J*=5.85 Hz, 1 H) 5.80 (dd, *J*=14.64, 5.49 Hz, 2 H) 5.86 (m, *J*=4.94, 4.94 Hz, 2 H) 7.29 - 7.41 (m, 15 H)

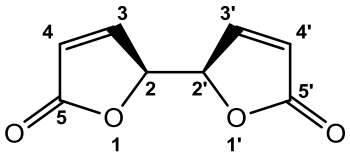
^{13}C NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 51.32 (C_{11}) 59.34 (C_5) 70.00 (C_1) 72.34 (C_9 or C_{10}) 72.45 (C_4) 73.16 (C_9 or C_{10}) 73.19 (C_8) 126.86 – 128.40 (aromatic *C*H + 1 C allyl) 130.82 (C_2

or C_3 or C_6 or C_7) 133.87 (C_2 or C_3 or C_6 or C_7) 134.45 (C_2 or C_3 or C_6 or C_7) 138.05 (quaternary C) 138.16 (quaternary C) 140.41 (quaternary C)

HR-MS: calculated 444.25332 $[M+H]^+$; found 444.25327 $[M+H]^+$, Δm = 0.1ppm

FTIR: 3327 (υ(NH) + υ(OH)), 3062 (υ(CH) arom. CH), 3029 (υ(CH) arom. CH), 2919 (υ(CH) aliph. CH), 2853 (υ(CH) aliph. CH), 1604 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1097 (υ(C-O)), 1074 (υ(C-O)), 1028 (δ_{ip}(CH) mono-sub.), 974 (δ(CH) C=C trans), 738 (δ(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

[2,2'-bifuran]-5,5'(2H,2'H)-dione (173)



(4*S*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic (5g, 22.914mmol, 1 eq.) was put in solution in 70mL toluene and the solution was cooled down at -78°C. DIBAL (1M in toluene, 46mL, 45.827mmol, 2 eq.) was slowly added to the solution during 20min at -70°C. Methyl triphenylphosphonoanylidene acetate diluted in 250mL MeOH was added to the reaction mixutre during 30min. After end of addition, the solution was allowed to come at rt. After 3h, 10mL of water was slowly added to quench the reaction. The formed gel was filtered and washed with TBME. The solvents were evaporated under reduced pressure. 40mL H_2O was added to the crude and extracted with 70mL TBME. The collected organic phases were dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. A white precipitate was formed which corresponded to triphenylphosphine oxide. To remove it, the mixture was stirred with pentane (300mL) and filtered off to afford a crude product (5.254g).

Ethanol (1.023g, 22.2mmol, 1.2 eq.) and methansulfonic acid (0.711g, 7.4mmol, 0.4 eq.) were added to the crude. 270mL DME and 27mL H_2O were added to the reaction mixture and put at reflux. Afer 6h, the reaction mixture was cooled down at rt and the solvent were evaporated

under reduced pressure. Hexane was then added to the crude and left to precipitate during 15h in the fridge. The precipitate was then filtered and dried in the oven. ESTP was added the precipitate, heated up to dissolve, cooled down at rt. The precipiate was filtered and dried in the oven to afford the desired product (0.2769g, 7% yield).

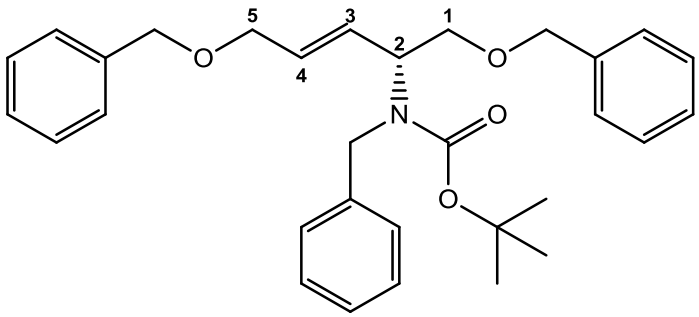
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 5.58 - 5.65 (m, 2 H) 6.41 (dd, *J*=5.77, 1.51 Hz, 2 H) 7.74 (dd, *J*=5.90, 0.88 Hz, 2 H)

^{13}C NMR (101 MHz, DMSO-d_6) δ ppm 81.21 (C_2 and $C_{2'}$) 123.05 (C_3 and $C_{3'}$ or C_4 and $C_{4'}$) 153.21 (C_3 and $C_{3'}$ or C_4 and $C_{4'}$) 172.00 (C_5 and $C_{5'}$)

HR-MS: found 165.01918 $[M-H]^-$

FTIR: 3098 (υ(CH)), 2943 (υ(CH)), 1791 (υ(C=O) lactone), 1751 (υ(C=O) lactone), 1600 (υ(C=C)), 1165 (υ(C-O)), 1097 (υ(C-O)), 1038 (υ(C-O)) cm^{-1}

(*R*,*E*)-*tert*-butyl benzyl(1,5-bis(benzyloxy)pent-3-en-2-yl)carbamate (177)



(*E*)-*N*-benyzl-1,5-bis(benzyloxy)pent-3-en-2-amine **80** (product from enantioselective allylic substitution with (*R*,*R*)-Trost ANDEN ligand) (0.2g, 0.516mmol, 1 eq.) was put in solution in 3mL CH_2Cl_2. DMAP (0.0063g, 0.0516mmol, 0.1 eq.) was added to the solution. Di-tert-butyl dicarbonate was diluted in 1mL CH_2Cl_2 and added drop wise to the reaction mixture. The

reaction was quenched with 2mL water and the aqueous layer was extracted with 2x 5mL CH_2Cl_2. The combined organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Flash chromatography of the crude in 9:1 HXF:ESTP afforded the desired product (colorless oil, 0.2213g, 87% yield).

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 1.13 - 1.47 (m, 9 H) 3.49 - 3.68 (m, 2 H) 3.92 (br. s., 2 H) 4.25 - 4.47 (m, 6 H) 4.79 (m, 1 H) 5.53 - 5.84 (m, 2 H) 7.16 - 7.41 (m, 15 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 27.91 (CH_3 ^{t}Bu) 48.52 (CH_2 benzylamine) 56.64 (C_2) 69.36 (C_5) 70.95 (C_1) 71.82 (CH_2 benzylether) 79.11 (quternary C) 126.62 - 128.20 (aromatic *C*H and C_3 and C_4) 138.19 (quaternary C) 138.36 (quaternary C) 154.88 (C=O)

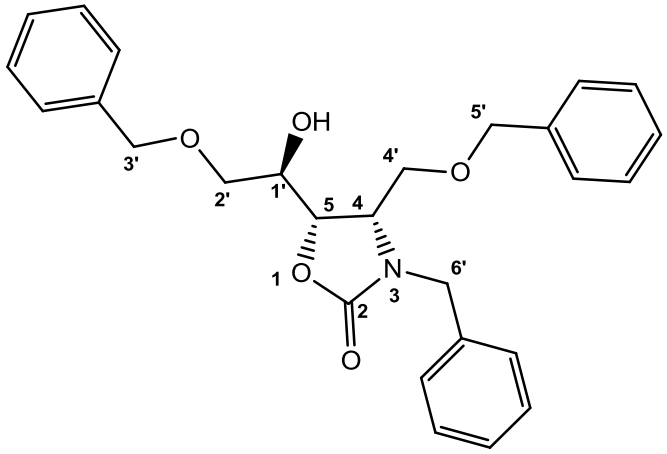
Confirmation of rotamers with ROESY

HR-MS: calculated 488.2801 $[M+H]^+$, found: 488.2798 $[M+H]^+$, Δm = 0.6ppm

IR: 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2975 (υ(CH) aliph. CH), 2929 (υ(CH) aliph. CH), 2858 (υ(CH) aliph. CH), 1692 (υ(C=O)), 1605 (υ(Ph)), 1454 (υ(Ph)), 1404 (C-N), 1365 (δ$(CH_3)_3$), 1167 (υ(C-O) boc), 1104 (υ(C-O-C)), 1028 (δ_{ip}(CH) arom. CH), 972 (δ(CH) C=C trans), 736 (δ(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 3 (1 mL/min, 30°C), ee = 87%, t_R = 11.1 min ((*R*)-**177**), t_R = 14.9 min ((*S*)-**177**)

(4*S*,5*S*)-3-benzyl-5-((*R*)-2'-(benzyloxy)-1'-hydroxyethyl)-4-((benzyloxy)methyl)oxazolidin-2-one (178)



(*R,E*)-*tert*-butyl benzyl(1,5-bis(benzyloxy)pent-3-en-2-yl)carbamate **177** (0.12g, 0.246mmol, 1 eq.) was put in solution in 10mL CH_2Cl_2 at rt. *m*-CPBA (70% purity, 0.57g, 2.31mmol, 9.4 eq.) was added to the solution at rt. After 24h, 10mL CH_2Cl_2 was added and the reaction mixutre was extracted with 1x 15mL $Na_2S_2O_3$ sat, 1x 15mL $NaHCO_3$ and 1x 15mL H_2O. The organic phase was dried over $MgSO_4$ and the solvent evaporated under reduced pressure. Flash chromatography of the crude (6:4 HXF: ESTP) afforded the desired product (colorless oil, 0.0429g, 39% yield) and the second diastereoisomer **179** (colorless oil, 0.0452g, 41% yield).

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 2.93 (d, *J*=5.02 Hz, 1 H) 3.61 - 3.73 (m, 4 H) 3.74 - 3.80 (m, 1 H) 3.96 (d, *J*=15.31 Hz, 1 H) 4.10 (dd, *J*=8.28, 4.02 Hz, 1 H) 4.40 - 4.45 (m, 1 H) 4.45 - 4.63 (m, 4 H) 4.81 (d, *J*=15.31 Hz, 1 H) 7.19 (dd, *J*=7.40, 1.88 Hz, 2 H) 7.28 - 7.42 (m, 13 H)

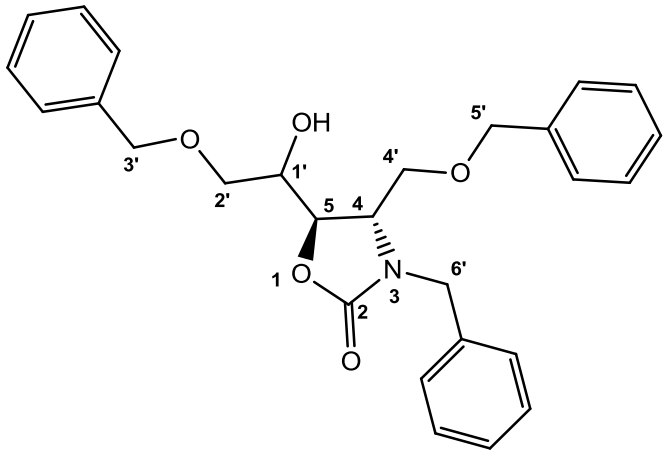
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 46.32 ($C_{6'}$) 56.08 ($C_{4'}$) 64.86 ($C_{2'}$) 67.88 ($C_{1'}$) 70.77 (C_4) 73.43 ($C_{3'}$ or $C_{5'}$) 73.65 ($C_{3'}$ or $C_{5'}$) 74.83 (C_5) 126.85 - 129.88 (aromatic *C*H) 136.01 (quaternary C) 136.95 (quaternary C) 137.59 (quaternary C) 157.60 (C=O)

HR-MS: calculated 448.2124 $[M+H]^+$, found: 448.2123 $[M+H]^+$, Δm = 0.2ppm

IR: 3430 (υ(OH)), 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2923 (υ(CH) aliph. CH), 2865 (υ(CH) aliph. CH), 1752 (υ(C=O)), 1586 (υ(Ph)), 1496 (υ(Ph)), 1454 (υ(Ph)), 1421 (C-N), 1221 (υ(C-O)), 1205 (υ(C-O)), 1090 (υ(C-O)), 1074 (υ(C-O)), 1028 (δ_{ip}(CH) arom. CH), 739 (δ(CH) mono-sub.), 701 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), ee = 88%, t_R = 30.8 (major enantiomer), t_R =36.6 (minor enantiomer)

(4*S*,5*R*))-3-benzyl-5-(2-(benzyloxy)-1-hydroxyethyl)-4-((benzyloxy)methyl)oxazolidin-2-one (179)



The same procedure as for the other diastereoisomer **178** (yield of **179** = 0.0452g, 41% yield).

^{1}H-NMR: (400 MHz, $CDCl_3$-*d*) δ ppm 2.49 (d, *J*=6.02 Hz, 1 H) 3.39 - 3.53 (m, 2 H) 3.56 - 3.66 (m, 2 H) 3.71 - 3.76 (m, 1 H) 3.76 - 3.80 (m, 1 H) 4.14 (d, *J*=15.31 Hz, 1 H) 4.30 (dd, *J*=7.28, 5.02 Hz, 1 H) 4.39 - 4.48 (m, 2 H) 4.48 - 4.56 (m, 2 H) 4.74 (d, *J*=15.06 Hz, 1 H) 7.19 - 7.24 (m, 2 H) 7.28 - 7.40 (m, 13 H)

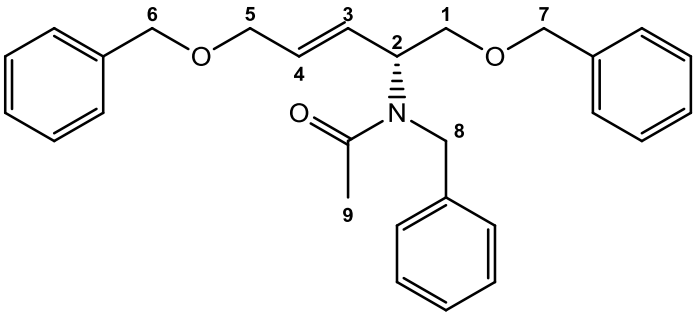
^{13}C-NMR: (101 MHz, $CDCl_3$-*d*) δ ppm 46.47 ($C_{6'}$) 56.43 (C_4) 68.96 ($C_{4'}$) 69.85 ($C_{2'}$) 70.83 ($C_{1'}$) 73.23 ($C_{3'}$ or $C_{5'}$) 73.64 ($C_{3'}$ or $C_{5'}$) 75.08 (C_5) 127.43 - 128.92 (aromatic *C*H) 135.96 (quaternary C) 137.39 (quaternary C, 2 C) 157.70 (C=O)

HR-MS: calculated 448.2124 $[M+H]^+$, found: 448.2124 $[M+H]^+$, Δm < 0.1 ppm

IR: 3405 (υ(OH)), 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2921 (υ(CH) aliph. CH), 2863 (υ(CH) aliph. CH), 1733 (υ(C=O)), 1586 (υ(Ph)), 1496 (υ(Ph)), 1453 (υ(Ph)), 1253 (υ(C-O)), 1205 (υ(C-O)), 1099 (υ(C-O)), 1076 (υ(C-O)), 739 (δ(CH) mono-sub.), 700 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), ee = 88%, t_R = 17.3 (major enantiomer), t_R =18.3 (minor enantiomer)

(*R, E*)-*N*-benzyl-*N*-(1,5-bis(benzyloxy)pent-3-en-2-yl)acetamide (183)



(*E*)-*N*-benyzl-1,5-bis(benzyloxy)pent-3-en-2-amine **80** (product from enantioselective allylic substitution with (*R,R*)-Trost ANDEN ligand) (0.2g, 0.516mmol, 1 eq.) was put in solution in 4mL CH_2Cl_2 at rt. DMAP (0.0032g, 0.026mmol, 0.05 eq.) and Et_3N (0.1566g, 1.548mmol, 3 eq.) were added to the solution and cooled down at 0°C. Acetylchlorid (70µL, 1.032mmol, 2 eq.) was slowly added to the reaction mixture. After 15min, the reaction was finished, the solvent was evaporated and the crude was purified with flash chromatography (1:1 ESTP:HXF) to afford the desired product (yellow oil, 0.157g, 71% yield)

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 1.92 (s, 3 H) 2.17 (s, 3 H) 3.55 - 3.65 (m, 2 H) 3.92 (br. s., 2 H) 4.34 - 4.38 (m, 4 H) 4.39 - 4.64 (m, 2 H) 4.71 - 4.78 (m, 1 H) 5.07 - 5.13 (m, 1 H) 5.65 - 5.81 (m, 2 H) 7.15 - 7.38 (m, 15 H)

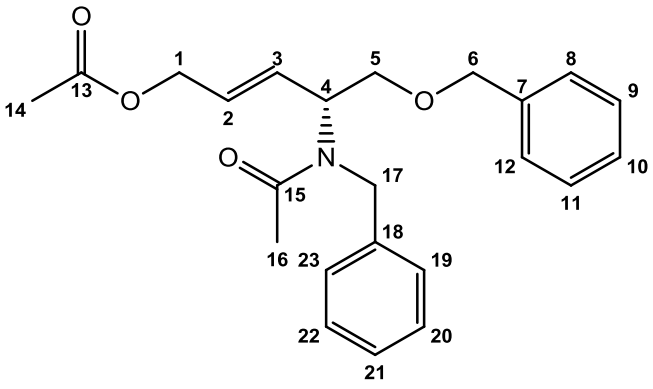
mixture of rotamers (ROESY)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 22.13 (C_9) 44.53 (C_8) 58.64 (C_2) 69.31 (C_5) 71.11 (C_1) 71.88 (C_6 or C_7) 72.02 (C_6 or C_7) 126.11 - 128.67 (aromatic *C*H + C_3 and C_4) 129.82 (quaternary C) 130.08 (quaternary c) 170.69 (C=O)

HR-MS: calculated 430.2382 $[M+H]^+$, found: 430.2381 $[M+H]^+$, Δm = -0.2 ppm

IR: 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2926 (υ(CH) aliph. CH), 2857 (υ(CH) aliph. CH), 1648 (υ(C=O) amide), 1496 (υ(Ph)), 1453 (υ(Ph)), 1412 (υ(C-N) amide) 1104 (υ(C-O)), 1028 (δ_{ip}(CH) mono-sub.), 975 (δ(CH) C=C trans), 735 (δ_{oop}(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

(*E*)-4-(*N*-benzylacetamido)-5-(benzyloxy)pent-2-en-1yl acetate (185)



(*E*)-*N*-benyzl-1,5-bis(benzyloxy)pent-3-en-2-amine **80** (product from enantioselective allylic substitution with (*R,R*)-Trost ANDEN ligand) (0.3g, 0.774mmol, 1 eq.) was weighted in a reaction flask. Acetic acid (12mL) then acetic acid anhydride (12mL) were added at rt. HBr,

33% in acetic acid (12mL) was added to the reaction mixture. After 32h, the reaction was finished. To quench the reaction, 500mL $NaHCO_3$ sat was cooled down at 0°C then the reaction mixture was slowly (drop by drop) added to the this cooled stirring solution at 0°C (the amount of $NaHCO_3$ has to be enough to quench the whole reaction). The aqueous phase was extracted with 3x 300mL CH_2Cl_2 and the collected organic phase was dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the crude was purified with flash chromatography (1:1 HXF:ESTP) to afford the desired product (oil, 0.2377g, 81%)

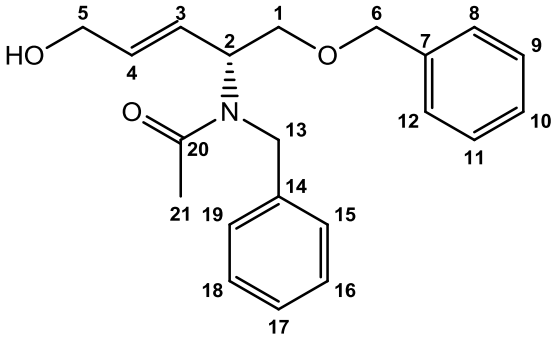
^{1}H-NMR: (400 MHz, DMSO-d_6) δ ppm 1.95 (s, 3 H) 2.02 (br. s., 3 H) 3.53 - 3.66 (m, 2 H) 4.36 (d, *J*=5.14 Hz, 2 H) 4.42 (d, *J*=4.40 Hz, 2 H) 4.51 (m, *J*=10.51 Hz, 2 H) 4.81 (br. s., 1 H) 5.71 (m, *J*=4.03 Hz, 2 H) 7.14 - 7.33 (m, 10 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 20.62 (CH_3) 22.10 (CH_3) 49.04 (C_{17}) 58.45 (C_4) 63.38 (C_1) 69.64 (C_5) 71.93 (C_6) 125.75 - 130.74 (aromatic *C*H + C_2 and C_3) 138.63 (quaternary C) 139.53 (quaternary C) 169.94 (C=O) 170.74 (C=O)

HR-MS: calculated 382.2018 $[M+H]^+$, found: 382.2022 $[M+H]^+$, Δm = 1 ppm

IR: 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2933 (υ(CH) aliph. CH), 2864 (υ(CH) aliph. CH), 1739 (υ(C=O)), 1649 (υ(C=O) amide), 1496 (υ(Ph)), 1453 (υ(Ph)), 1413 (C-N amide), 1364 (δ(CH_3) acetate), 1236 (υ(C-O) acetate), 1100 (υ(C-O-C) ether), 1028 (δ_{ip}(CH) mono-sub.), 974 (δ(CH) C=C trans), 733 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

(*E*)-*N*-benzyl-*N*-(1-(benzyloxy)-5-hydroxypent-3-en-2yl)acetamide (186)



(*E*)-4-(*N*-benzylacetamido)-5-(benzyloxy)pent-2-en-1yl acetate **185** (0.2g, 0.524mmol, 1 eq.) was put in solution in 15mL MeOH at rt. K_2CO_3 was added to the solution. After 30min, the reaction mixture was filtered through a syringe filter (PTFE, 0.45µm) and washed with 20mL MeOH. The solvent was reduced under reduced pressure and the crude was purified with flash chromatography (8:2 ESTP: HXF) to afford the desired product (0.0723g, 41%)

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 1.90 (s, 1 H) 2.16 (s, 1 H) 3.42 - 3.64 (m, 2 H) 3.90 (d, *J*=4.39 Hz, 5 H) 4.20 - 4.40 (m, 3 H) 4.47 - 4.65 (m, 2 H) 4.70 (br. s., 1 H) 5.09 (br. s., 1 H) 5.58 - 5.81 (m, 10 H)

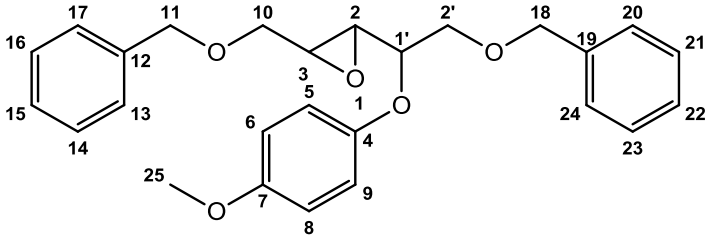
Rotamers (ROESY)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 22.24 (C_{21}) 48.87 (C_{13}) 58.73 (C_2) 60.82 (C_6) 70.04 (C_1) 71.91 (C_5) 125.16 (C_3 or C_4) 125.65 - 129.51 (aromatic *C*H) 133.96 (C_3 or C_4) 138.14 (quaternary C) 139.59 (quaternary C) 170.70 (C=O)

HR-MS: calculated 340.19072 $[M+H]^+$, 362.17267 $[M+Na]^+$, found: 340.19067 $[M+H]^+$, 362.17239 $[M+Na]^+$

IR: 3395 (υ(OH)), 3062 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2925 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1627 (υ(C=O)), 1496 (υ(Ph)), 1452 (C-N), 1417 (C-N), 1099 (υ(C-O)), 1028 (δ_{ip}(CH) arom. CH), 976 (δ_{oop}(CH) olefinic CH), 732 (δ_{oop}(CH) mono-sub.), 698 (δ(Ph) mono-sub.) cm^{-1}

2-(2-(benzyloxy)-1-(4-methoxyphenoxy)ethyl)-3-((benzyloxy)methyl)oxirane (187)



(*E*)-(((4-(4-methoxyphenoxy)pent-2-ene-1,5-diyl)bis(oxy))bis(methylene))dibenzene **114** (product from enantioselective allylic substitution with (*R*,*R*)-Trost ANDEN ligand) (0.345g, 0.853mmol, 1 eq.) was put in solution in 5mL CH_2Cl_2 at rt. *m*-CPBA (70%, 0.58g, 2.352mmol, 2.8 eq.) was added to the solution at rt. After 7h, 10mL of 10% MeOH in CH_2Cl_2 was added to the reaction mixture and extracted with 1x 15mL $Na_2S_2O_3$ sat and 1x 15mL $NaHCO_3$ sat and 1x 15mL H_2O. The organic phase was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. Flash chromatography of the crude (8:2 HXF:ESTP) afforded the desired product (oil, 0.1394g, 40%)

^{1}H-NMR: (600 MHz, DMSO-d_6) δ ppm 3.20 (s, 1 H) 3.37 - 3.43 (m, 1 H) 3.65 - 3.73 (m, 6 H) 4.23 (q, *J*=5.49 Hz, 1 H) 4.36 (q, *J*=4.51 Hz, 1 H) 4.47 - 4.58 (m, 4 H) 6.81 - 6.87 (m, 2 H) 6.92 - 6.98 (m, 2 H) 7.25 - 7.38 (m, 10 H)

^{13}C-NMR: (101 MHz, DMSO-d_6) δ ppm 53.88 (C_2) 55.30 (C_{25}) 69.27 (C_{10} or $C_{2'}$) 69.49 (C_{10} or $C_{2'}$) 72.04 (C_{11} or C_{18}) 72.35 (C_{11} or C_{18}) 76.57 (C_3) 77.88 ($C_{1'}$) 114.49 (C_6 and C_8) 117.18 (C_5 and C_9) 127.26 - 128.23 (aromatic *C*H) 151.62 (quaternary C) 151.78 (quaternary C) 153.79 (quaternary C) 153.97 (quaternary C)

HR-MS: calculated 438.22750 $[M+H]^+$, 443.18290 $[M+Na]^+$, found: 438.22762 $[M+H]^+$, 443.18265 $[M+Na]^+$, Δm = 0.3-0.6 ppm

IR: 3063 (υ(CH) arom. CH), 3030 (υ(CH) arom. CH), 2913 (υ(CH) aliph. CH), 2860 (υ(CH) aliph. CH), 1506 (υ(Ph)), 1454 (υ(Ph)), 1227 (Ph-O), 1105 (υ(C-O)), 1036 (υ(C-O)), 826 (δ(CH) para-disub.), 740 (δ(CH) mono-sub.), 699 (δ(Ph) mono-sub.) cm^{-1}

HPLC: C-HPLC 5 (1 mL/min, 30°C), t_R = 19.0 (major diastereoisomer), t_R =21.9 (minor diastereoisomer)

5.3 General procedures for allylic substitutions

General procedure for the racemic allylic substitutions

The empty reaction flask was first degassed through 3 cycles of (5 min vacuum/ 5 min argon). The chosen solvent (2 mL) was added and again 3 short cycles of vacuum/argon were performed. Triphenylphosphine (0.24 eq.) and $[Pd(allyl)Cl]_2$ or $[Pd_2(dba)_3]\cdot CHCl_3$ (0.08 eq.) were added at room temperature and left to stir for 15 min. Substrate (100 mg) diluted in 0.5mL of the chosen solvent was added and depending on the temperature cooled down or heated up. The chosen nucleophile was then added (2 eq.). The reaction was followed by HPLC and after completion, filtered through a short pad of silica (1 g for 0.1 g of substrate) and washed with a solution of 80 mL TBME and 0.3 mL Et_3N. The solvent was evaporated under reduced pressure. Flash column chromatography of the crude gave the corresponding product.

General procedure for enantioselective allylic substitutions without addition of a base

The empty reaction flask was degassed through 3x (5 min vacuum/ 5 min argon cycles) then the desired solvent (2 mL) was added and again 3 short cycles of vacuum/argon were performed. The chosen ligand (0.24 eq.) and $[Pd(allyl)Cl]_2$ or $[Pd_2(dba)_3]CHCl_3$ (0.08 eq.) were added at room temperature and left to stir during 15 min. Substrate (100 mg) diluted in 0.5 mL of the chosen solvent and then the nucleophile (2 eq.) were added to the reaction mixture. The reaction was followed by HPLC and after completion, was filtered through a short pad of silica (1 g for 0.1 g of substrate) and washed with a mixture of TBME (80 mL) and triethylamine (0.3 mL). The solvent was evaporated under reduced pressure. Flash column chromatography of the crude gave the corresponding product.

General procedure for enantioselective allylic substitutions with addition of a base

The empty reaction flask was degassed through 3x (5 min vacuum/ 5 min argon cycles) then the desired solvent (2 mL) was added and again 3 short cycles of vacuum/argon were performed. The chosen ligand (0.24 eq.) and $[Pd(allyl)Cl]_2$ or $[Pd_2(dba)_3]CHCl_3$ (0.08 eq.) were added at room temperature and left to stir during 15 min. Substrate (100 mg) diluted in 0.5 mL of the chosen solvent and then the base (1 eq.) were added to the reaction mixture. The nucleophile (2 eq.) was then added to the reaction mixture. The reaction was followed by HPLC and after completion, was filtered through a short pad of silica (1 g for 0.1 g of substrate) and washed with a mixture of TBME (80 mL) and triethylamine (0.3 mL). The solvent was evaporated under reduced pressure. Flash column chromatography of the crude gave the corresponding product.

Chapter 6

Appendix

6. Appendix

6.1 Abbreviations

2,2-DMP	2,2-Dimethoxypropane	DYKAT	Dynamic Kinetic Asymmetric Transformation
Ac_2O	Acetic anhydride		
AcOH	Acetic acid	EDIPA	Ethyldiisopropylamine
ALI	90% ethanol, 5% *i*PrOH, 5% water	ee	Enantiomeric excess
		eq.	Equivalent
Aliph.	Aliphatic	ESTP	Ethyl acetat, tech.
Arom.	Aromatic	Et_3N	Triethylamine
Art.-Nr.	Articel number	EtOH	Ethanol
Bn	Benzyl	FC	Flash Chromatography
BOC	*tert*-Butyloxycarbonyl	h	Hours
BSA	*N, O*-bis(trimethylsilyl) acetamide	HPLC	High Pressure Liquid Chromatography
Cellflock	Cellulose	HR	High Resolution
d	Day	HPTF	Heptan fraction, tech.
dba	Dibenzylidenacetone	HXF	Hexan fraction, tech.
DBU	1,8-diazabicyclo [5.4.0]undec-7-ene	IR	Infrared Spectroscopy
		J	Coupling constant
DIBAL	Diisobutylaluminium hydride	LC	Liquid Chromatography
		LDA	Lithium Diisopropylamine
DIOP	*O*-isopropylidene-2,3-dihydroxy-1,4-bis (diphenylphosphino)butan	LG	Leaving group
		$LiAlH_4$	Lithium Aluminium Hydride
DMAP	4-(dimethylamino)pyridine	Ln	Ligand
DME	Dimethoxyethane	LTMP	Lithium-2,2,6,6-tetramethylpiperidine
DMF	Dimethylformamide		
DPPBA	2-(diphenylphosphino) benzoic acid	*m*-CPBA	*meta*-Chloroperoxybenzoic acid

MED	Dichloromethane, tech.	PTSA	*para*-Toluenesulfonic acid
Min	Minute	rt	Room temperature
m_p	Melting point	SM	Starting material
MS	Mass Spectroscopy	TBME	*tert*-butylmethyl ether
NBS	*N*-Bromsuccinimide	Tech.	Technic
NMR	Nuclear Magnetic	T	Temperature
	Resonance	TFA	Trifluoroacetic acid
NuH	Nucleophile	THF	Tetrahydrofuran
Pd	Palladium	TMP	2,2,6,6-
Pd/C	Palladium on carbon		Tetramethylpiperidine
Ph	Phenyl	UPLC	Ultra Performance Liquid
PHOX	Chiral phosphinooxazoline		Chromatography
Phth	Phthalimide	UV	Ultraviolet
PMP	*para*-Methoxyphenyl	*β*-H	*β*-Hydride

Chapter 7

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7. References

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