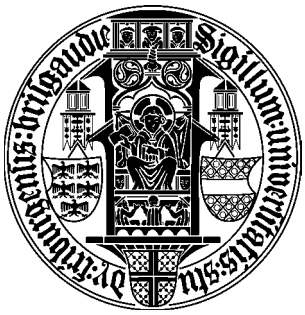
ortho-Diphenylphosphanylbenzoyl-Directed Palladium Catalyzed Allylic Substitution with Soft Nucleophiles



Inaugural-Dissertation

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Порядочный химик в двадцать раз полезнее всякого поэта.

(A decent chemist is twenty times more useful than any poet.)

Fathers and Sons

Ivan S. Turgenev

Acknowledgment

I would especially like to thank Prof. Dr. Bernhard Breit for the opportunity to come to University of Freiburg and make a research in his lab. Without his help and guidance this work would not be possible. The topic seemed to be a tough nut to crack but we managed that.

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Everyone in our group I thank for good working atmosphere, their help in the lab, scientific discussions and fun we had during and out of the lab. I would like to say my special thanks to Alexander Schuschkovski and Anita Weidner for their help organizing my first days in Freiburg, Christian Grünanger for his courage to visit cold Russia, Tomislav Reiss for his scientific and personal care, Marc Awenius as my private trainer, Susanne Kemme and Ulrich Breuninger for being good friends and Ippei Usui for lots of funny stories he told me.

And the last but not the least thanks to my family and friends out of Freiburg. Despite huge distance between us, their support was vital for me.

Herzlichen Dank!!!

Content

A. Theoretical part

Abbreviations

Ac	acetyl
BINAP	2,2´-bis(diphenylphosphino)-1,1´-binaphthyl
BINAPO	2,2´-bis(diphenylphosphinooxy)-1,1´-binaphthyl
BIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
bp	boiling point
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
CDG	catalyst directing group
CH	cyclohexane
cod	1,5-cyclooctadiene
dba	*E*,*E*-dibenzylidene acetone
dppb	diphenylphosphinobutane
dppe	diphenylphosphinoethane
dppf	diphenylphosphinoferrocene
DCC	dicyclohexylcarbodiimide
DIBAL	Di-*iso*-butylaluminium hydrid
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
o-DPPB	*ortho*-diphenylphosphinobenzoate
o-DPPBA	*ortho*-diphenylphosphinobenzoic acid
o-DPPFA	*ortho*-diphenylphosphinoferrocene-carboxylic acid
EE	ethyl acetate
ee	enentiomeric excess
EI	electronic ionisation masspectroscopy
eq	equivalent(s)
GC	gas chromatography
h	hour(s)
HMDS	hexamethyldisilazane (or silazide)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
HWE	Horner-Wadsworth-Emmons olefination
J	coupling constant
min	minute
mp	melting point
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
Ns	nosyl
Nu	nucleophile
PCC	pyridinium chlorochromate
PE	petrolether
phth	phthalimide
PPTS	pyridinium *p*-toluenesulfonate
Py	pyridine
RDG	reagent directing group
rs	regioselectivity
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBME	*tert*-butylmethylether
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
TsOH	*p*-toluenesulfonic acid
UV	ultra-violet

A. Theoretical part

1. Introduction

Inventing new methods for carbon-carbon and carbon-heteroatom bond formation becomes more and more important in modern Organic chemistry, and it is surely transition metal catalysis that provides us nowadays with novel approaches towards new molecules. These methods rapidly become applied for synthetic purposes after being the subject of academic knowledge and purely scientific discussions.

Only the last decade gave two Nobel Prices in Chemistry for catalytic methods: for stereoselective reduction and oxidation to W.S. Knowles, R. Noyori and K.B. Sharpless (2001), and for metathesis to Y. Chauvin, R.H. Grubbs and R.R. Schrock (2005). There is no doubt that the whole batch of palladium-catalyzed methods is expected to be also awarded soon.

What are the criteria for elaborating new approaches for organic synthesis? B.M. Trost wrote:

"*In defining strategies and reactions to construct complex molecules we require synthetic methods that can (i) perform a wanted structural change and none other (that is be chemo-selective), (ii) orient the reaction partners in a correct fashion (be regioselective), (iii) create the correct orientation of the various parts of the molecule with respect to each other (be diastereo-selective), and (iv) enable the formation of a molecule of one handedness or a mirror image isomer (be enantioselective). Such extraordinary demands are exciting challenges.*" [1]

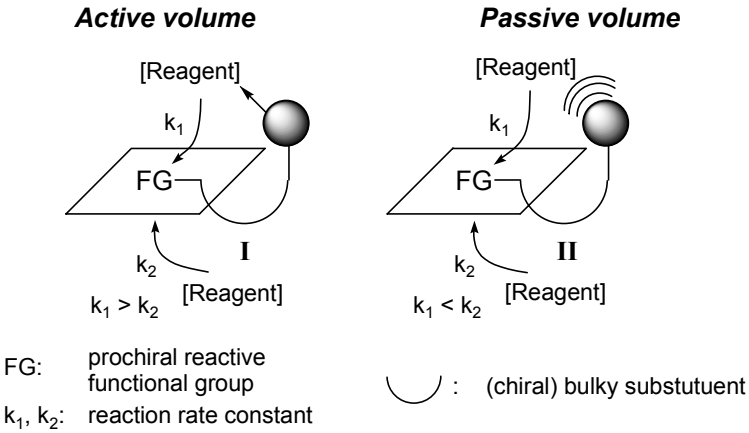
Such high demands make the catalytic systems more sophisticated. From metal black and metal sponges for hydrogenations and aluminum silicates (to say simply, clay or brick-stone) for the first catalytic cracking we come to elegant structures which are mostly complexes of noble metals with chiral ligands (active but expensive).

There is a definite trend in public concern for the environment (that led to the rise of *green chemistry*), in chemical perfectionism (that led to the rise of the strategy of *atom economy*), and surely vulgar economics (that led to numerous technological improvements such as recycling of solvents and catalysts, process optimization, energy saving). Not all the processes satisfy the mentioned requirements, but one should keep in mind the long, intellectually intensive way from primary invention via first applications to a completely ideal process in use.

2. Background

2.1. Directing groups in Organic chemistry

Directing groups have found wide application in Organic chemistry. [2]
A directing effect can proceed via either active or passive substrate control (Scheme 1). The former implies coordination of the reagent to the directing group that favors the attack of the substrate from the side proximal to the directing group; the latter means that the bulky directing group blocks the proximal side and favors the attack from the opposite side.



Scheme 1: Active and passive substrate control in diastereoselective synthesis.

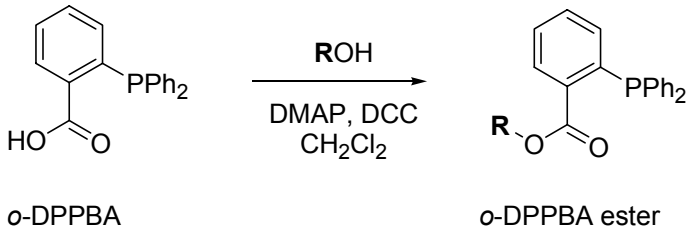
The same mechanism as for a reagent directing group proceeds for a catalyst directing group when a catalyst precursor coordinates to the directing group to facilitate the reaction.
Depending on the substrate this approach allows to combine chemoselectivity (only the functional group proximal to the directing group), regioselectivity (only the side of multiple bond or allylic system proximal to the directing group), diastereoselectivity (the attack by the reagent happens from the diastereotopic face where the directing group is located in the most reactive conformer).
The *ortho*-diphenylphosphanylbenzoate (*o*-DPPB) directing group represents a catalyst directing group with active substrate control.

2.2. *o*-Diphenylphosphanylbenzoates as substrates with directing group

o-DPPB as a directing group has been successfully developed in Breit's research group. The first breakthrough in *o*-DPPB directed reactions has been achieved in hydroformylation reaction

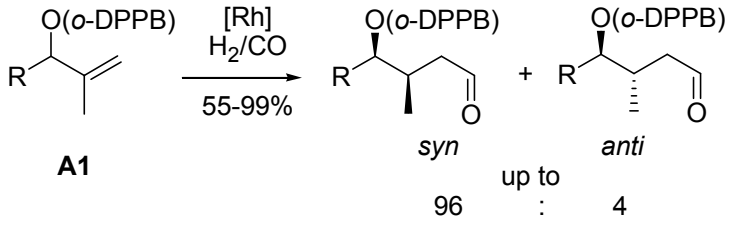
which represents one of the most important industrial processes relying on homogeneous catalysis. [3]

Normally, the *o*-DPPB directing group is installed via esterification under Steglich conditions (Scheme 2). This reaction proceeds with up to quantitative yields providing often crystalline, easy handleable compounds. [4]



Scheme 2: Synthesis of substrates with *o*-DPPB directing group (Steglich conditions).

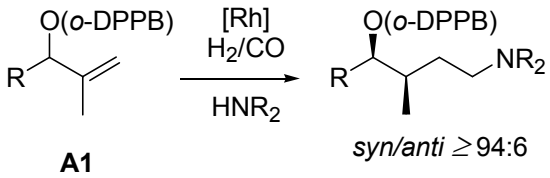
The hydroformylation of the methallylic *o*-DPPB esters **A1** provided the corresponding *syn*-aldehydes with diastereoselectivities up to 96:4 and in good to excellent yields (Scheme 3).



Scheme 3: *Syn*-diastereoselective hydroformylation with *o*-DPPB directing group.

Removal and recycling of the *o*-DPPB group is possible upon alkaline hydrolysis of the aldehydes providing quantitative yields of the both lactols and *ortho*-diphenylphosphanylbenzoic acid. [5]

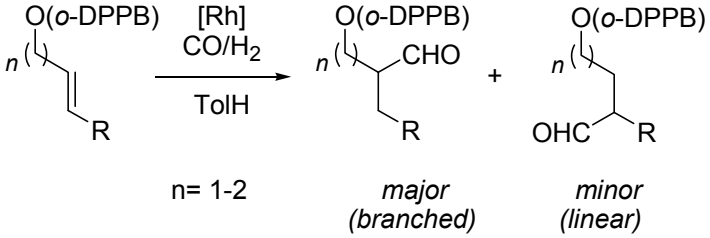
The same methallylic *o*-DPPB ester **A1** under hydroformylation conditions in the presence of either primary or secondary amines can be converted into the product of hydroaminomethylation (Scheme 4). The corresponding tertiary or secondary amine products were isolated in good yields and diastereomer ratios up to 94:6 (*syn*:*anti*). [6]



Scheme 4: *o*-DPPB directed hydroaminomethylation.

Aldehydes formed in hydroformylation reaction can participate in subsequent chemical modification providing numerous domino processes: hydroformylation-Wittig olefination-hydrogenation [7], hydroformylation-Knoevenagel reaction-hydrogenation [8], hydroformyilation-cuprate addition [9].

Allylic and homoallylic alcohols bearing an *o*-DPPB directing group give in hydroformylation the branched products with high regioselectivity (up to 97:3) (Scheme 5).

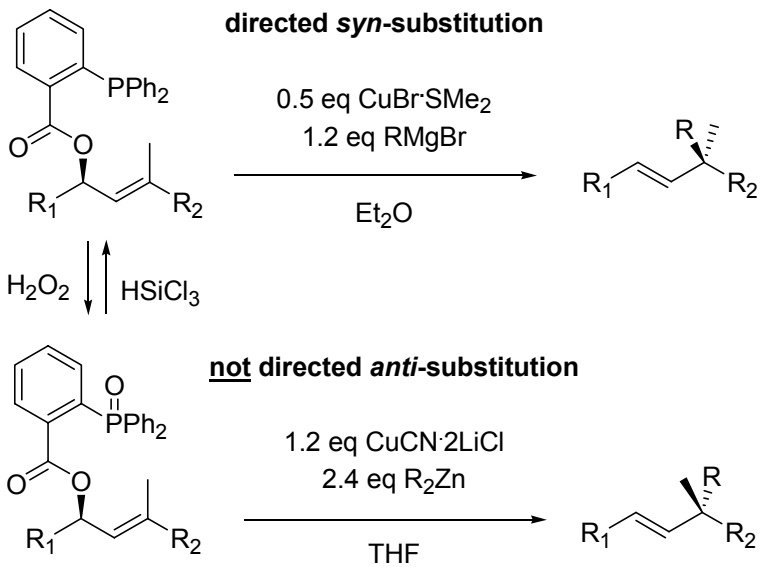


Scheme 5: Directed hydroformylation of allylic and homoallylic *o*-DPPB esters.

It is also important to note that the *o*-DPPB group accelerates the rate of hydroformylation. That allowed carrying out hydroformylation with trisubstituted olefins which are known as tough substrates for the reaction. [10]

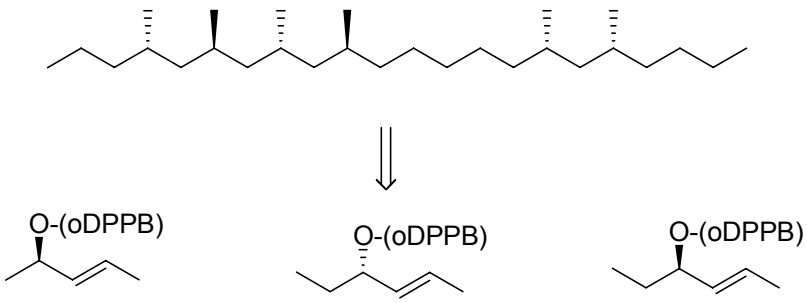
Another opportunity to use the same directing group has been found for copper mediated allylic substitution with *o*-DPPB as a directing leaving group. [11] The reaction proceeds via coordination of copper to the phosphorous atom of the directing group and a subsequent *syn*-S_N2'-attack (Scheme 6).

o-DPPB has been proven to be a switchable directing group. Oxidation of the phosphine moiety to the phosphine oxide reverses the selectivity into *anti*-substitution (Scheme 6). [12]



Scheme 6: Allylic substitution with switchable directing group.

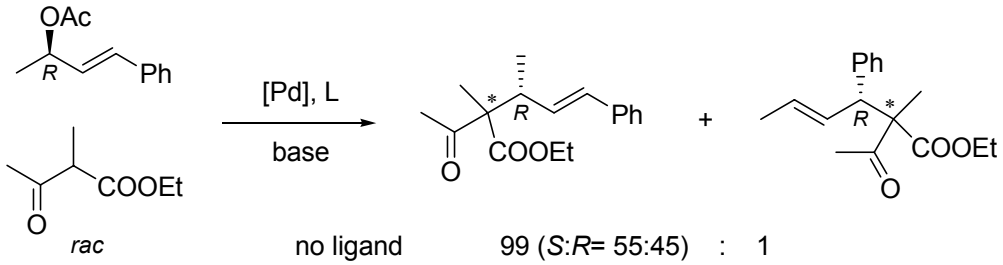
The directed copper mediated allylic substitution has been applied for the synthesis of desoxypoly-propionate unit containing natural compounds. Thus, 4,6,8,10,16,18-hexamethyldocosane, pheromone from *Antitrogus parvulus*, has been synthesized (Scheme 7). [13]



Scheme 7: Synthesis of 4,6,8,10,16,18-hexamethyldocosane from *Antitrogus parvulus*.

(*R*,*R*,*R*)-α-Tocopherol has been also synthesized applying the concept of reagent directing group. [14] Other total synthesis efforts are being under investigation in the Breit's group at the moment (Borrelidin, TMC-151).

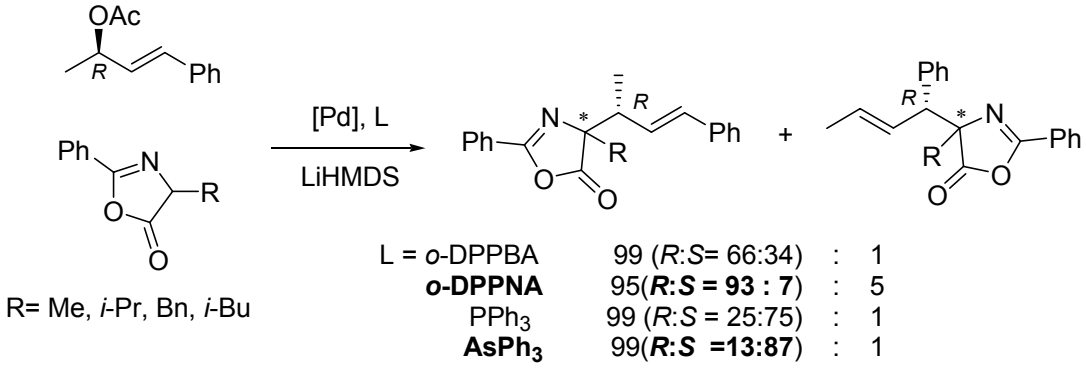
Alternatively, *o*-DPPBA has been used as a ligand without covalent binding to the substrates. The palladium-catalyzed regio- and diastereoselective allylic alkylation of allyl acetates with enolate as carbon nucleophile has been described (Scheme 8). The stereochemistry was highly controlled by the palladium catalyst with *ortho*-(diphenylphosphino)benzoic acid as a ligand. Vicinal quaternary and tertiary carbon centers were constructed. It has been proven that other ligands (Ph_3P, 1,2-bis-(diphenylphosphanyl)ethane) gave nearly racemic mixtures of allylic substitution products. [15]



no ligand	99 (*S*:*R*= 55:45)	:	1
L = PPh_3	99 (*S*:*R*= 55:45)	:	1
dppe	95 (*S*:*R*= 51:49)	:	5
***o*-DPPBA**	99 (***S*:*R*= 94:6**)	:	1

Scheme 8: Regio- and diastereoselective allylic alkylation with enolate.

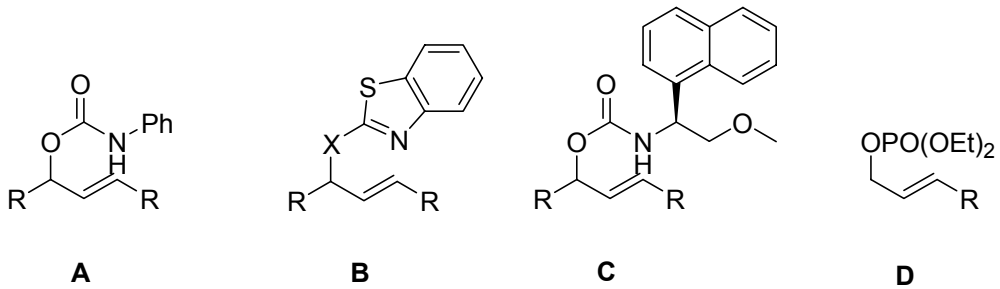
But this system is not universal. The same authors published earlier that allylic alkylation with azolactones as carbon nucleophiles was not effective with *o*-DPPBA as a ligand (Scheme 9), but other ligands provided high stereoselectivity: 2-(diphenylphosphino)-1-naphthoic acid (*o*-DPPNA, *R*:*S*= 93:7), more over it was possible to reverse selectivity with triphenylarsine (*R*:*S*= 13:87). Stereoselectivity could be considerably increased with bulkier leaving groups. [16]



Scheme 9: Regio- and diastereoselective allylic alkylation with azalactone.

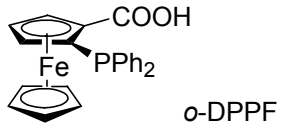
2.3. *o*-DPPB analogues as directing groups

o-DPPB is known as a directing leaving group for allylic substitution with cuprates. [11-14]
Recent reviews of Breit [17] and Alexakis [18] cover the field of copper mediated allylic substitution broadly.
Besides *o*-DPPB a large variety of directing groups is known. Among them carbamates (Scheme 10, **A**) [19], benzothiazoles (**B**) [20], (*S*)-α-naphthylglycine derivatives (**C**) [21] and phosphates (**D**) [22] have been proven useful.



Scheme 10: Substrates for directed copper mediated allylic substitution.

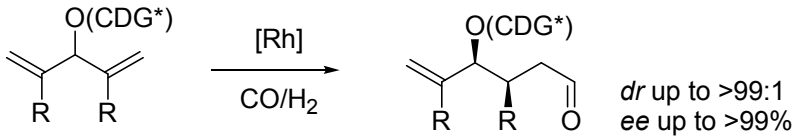
ortho-Diphenylphosphinoferrocenecarboxylic acid, *o*-DPPFA (Scheme 11), can be used instead of *o*-DPPBA as a planar chiral catalyst-directing group.



o-DPPF

Scheme 11: *ortho*-Diphenylphosphinoferrocenecarboxylic acid.

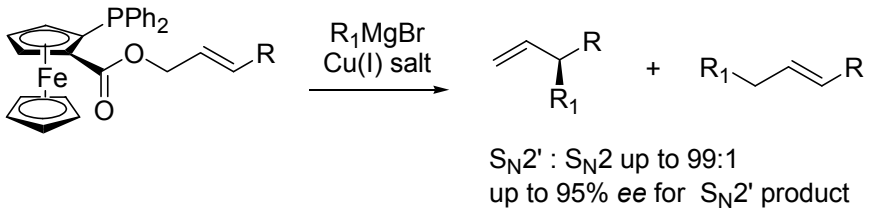
It has been used in desymmetrizing hydroformylation of prochiral bisalkenylcarbinols and bisallylcarbinols (Scheme 12). The *o*-DPPF group enables to achieve hydroformylation with excellent level of stereocontrol. [23-24]



CDG*= (S_p)- or (R_p)-o-DPPF

Scheme 12: Desymmetrizing hydroformylation of bisalkenylcarbinols with *o*-DPPF as a directing group.

Enantioselective copper-mediated allylic substitution with Grignard reagents with *o*-DPPF as a planar chiral reagent directing leaving group has also been carried out in Breit's laboratory (Scheme 13).



S_N2' : S_N2 up to 99:1
up to 95% *ee* for S_N2' product

Scheme 13: Enantioselective copper-mediated allylic substitution with *o*-DPPF as a chiral reagent directing leaving group.

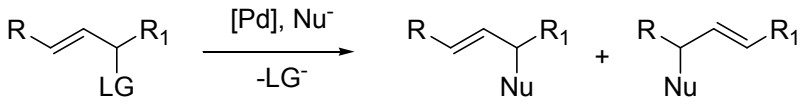
This approach provides the S_N2' product with excellent regio- and good stereoselectivity. [25]

2.4. Palladium catalyzed allylic substitution

2.4.1. General information

Palladium catalyzed allylic substitution (Scheme 14) is one of the most popular catalyzed reactions in organic chemistry. Under mild conditions a large variety of allylic substrates can be reacted with a number of nucleophiles, both carbon and heteroatom nucleophiles. Due to the fact

that the reaction has been thoroughly studied by chemists over the last decades, general means to predict or to tune chemo-, regio- and stereoselectitities have been broadly described as well as synthetic application for the reaction. [26]

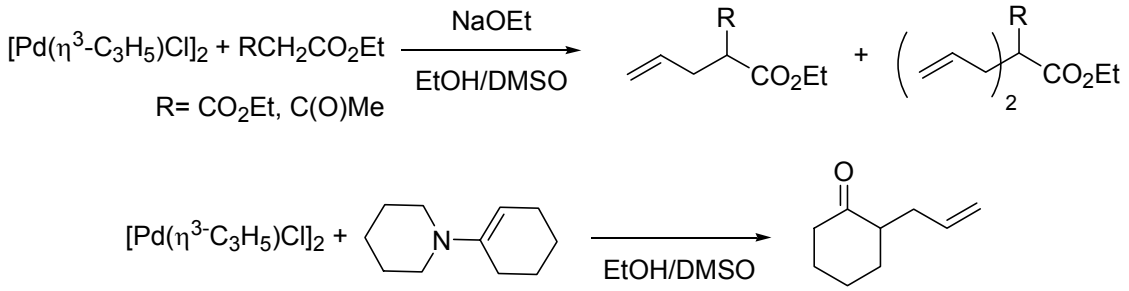


Scheme 14: Palladium catalyzed allylic substitution.

For the sake of chemical logic in the overview about allylic substitution chronological order is kept only at the very beginning of the survey. For the same reason several facts, as application of chiral ligands or other metals as catalyst precursors, are just mentioned (with literature references) since they are not closely connected with the project. Most of the mechanism issues are described in detail to clarify main problems one can face starting this chemistry.

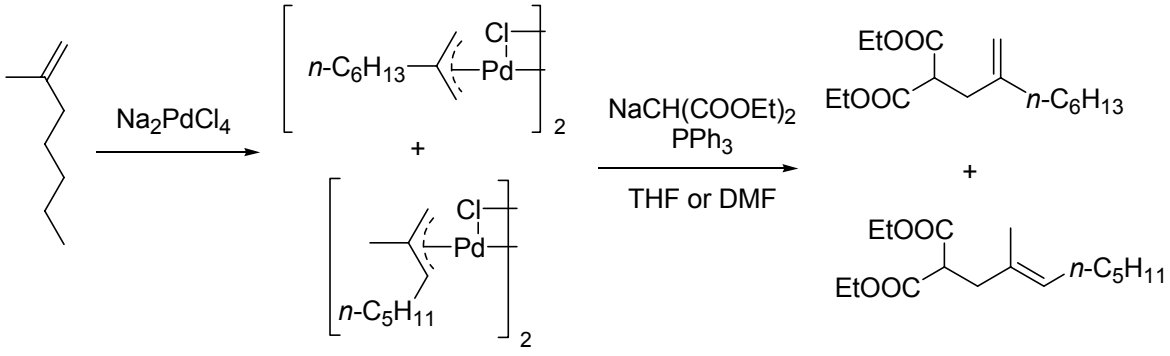
2.4.2. History of the reaction

The first example of stoichometric allylic substitution was reported by Tsuji in 1965 (Scheme 15). [27]



Scheme 15: First example of stoichometric allylic substitution by Tsuji.

Then Trost published another stoichometric allylic alkylation where he especially underlined the importance of triphenylphosphine for the reaction to proceed (Scheme 16). [28]

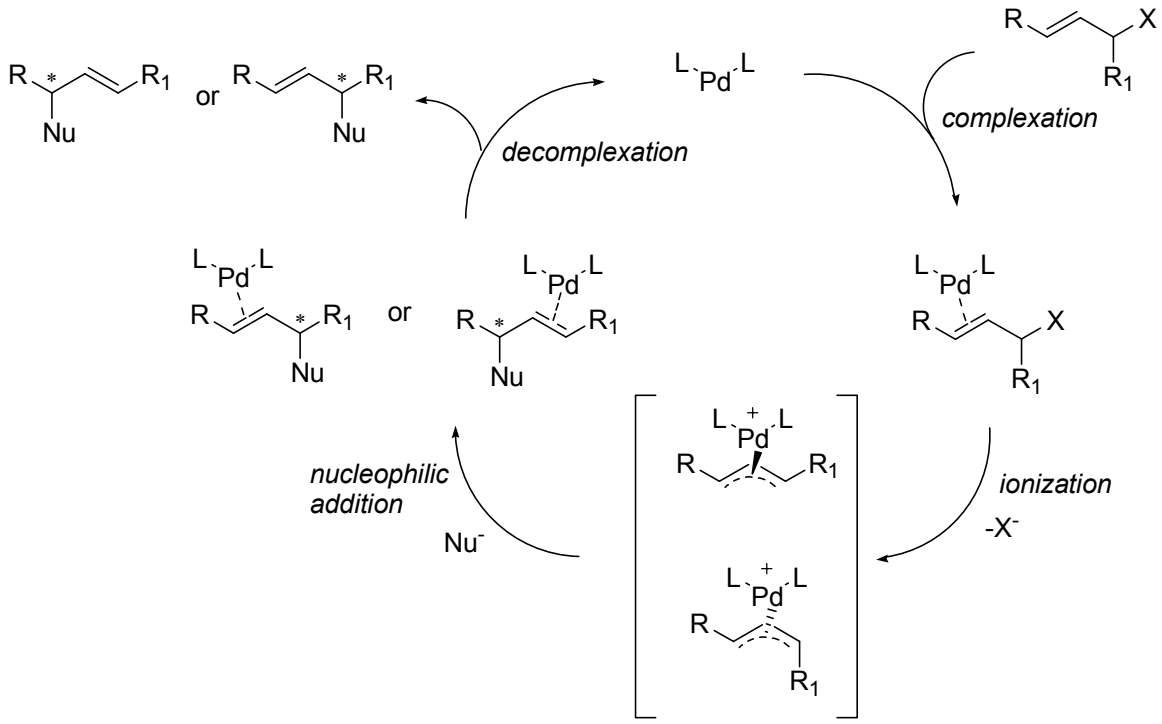


Scheme 16: First example of stoichometric allylic substitution by Trost.

Since then numerous publications broadened the scope of palladium catalyzed allylic substitution, explained mechanism of the reaction, elaborated different approaches to influence chemo-, regio- and stereoselectitities. Nowadays palladium catalyzed allylic substitution is frequently applied in total synthesis and stays one of the first choices for testing newly invented ligands.

2.4.3. Mechanism

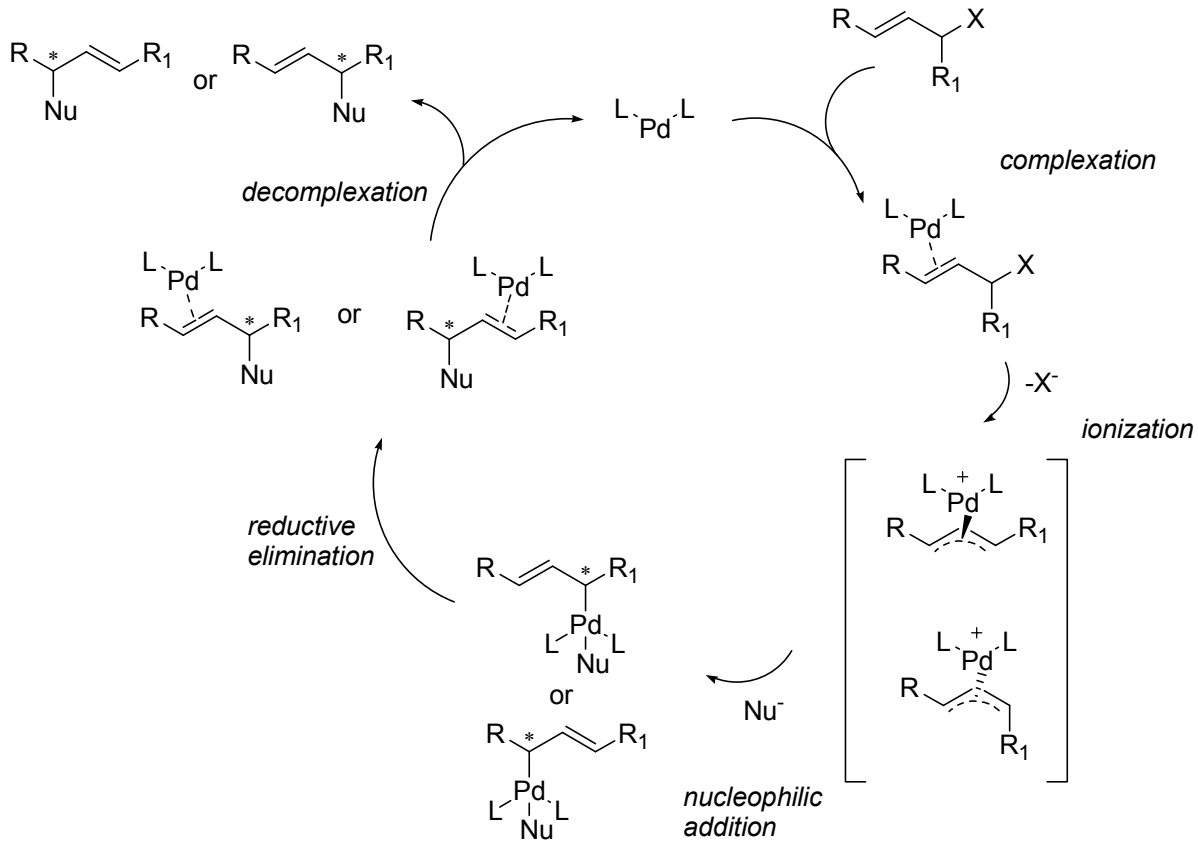
The general mechanism of the reaction consists of complexation, oxidative addition, nucleophile attack and reductive elimination. The step of nucleophilic addition is highly dependent on the type of nucleophile. Soft nucleophiles: malonates, enolates, primary and secondary amines and their anions, thiolates and alcoholates (pK_a<20) – attack carbon atom of allyl-palladium complex (Scheme 17).



Scheme 17: Mechanism of allylic substitution with soft nucleophiles.

Hard nucleophiles such as Grignard reagents, cuprates, zincates and other metalo-organics (pK_a>20) attack the palladium atom at first (Scheme 18). This difference results in an opposite stereochemical outcome: soft nucleophiles lead to double inversion and therefore net retention of

the stereocenter, while hard nucleophiles give rise to net inversion. More detailed description of the phenomenon for soft nucleophiles is given below.



Scheme 18: Mechanism of allylic substitution with hard nucleophiles.

Kinetics and thermodynamics of palladium catalyzed allylic substitution (as many other cross-coupling reactions) have been thoroughly investigated in the group of C. Amatore and A. Jutand. First two steps, coordination (formation of π-allyl-Pd complex) and ionization (formation of η^3-allyl-Pd complex), are reversible for the reaction of $Pd(dba)_2$ or $Pd(PPh_3)_4$ with allylic acetates. It was also shown for the reaction in DMF that complexation is considerably faster, than ionization. Under similar experiment conditions the formation of cationic $[(\eta^3$-PhCHCHCHPh)Pd(dppb)$]^+$ is considerably slower than formation of the unsubstituted allylic complex $[(\eta^3$-$CH_2CHCH_2)Pd(dppb)]^+$. [29]

The acetate ion does not act as a simple leaving group, but acts as a nucleophile capable of attacking π-allyl-Pd(+2) complex reproducing allylic acetate. The process may be responsible for the isomerisation of chiral acetates. In DMF no significant ion pairing occurs and free ions are formed. In THF almost complete ion pairing occurs and therefore almost no free ions are produced. [30]

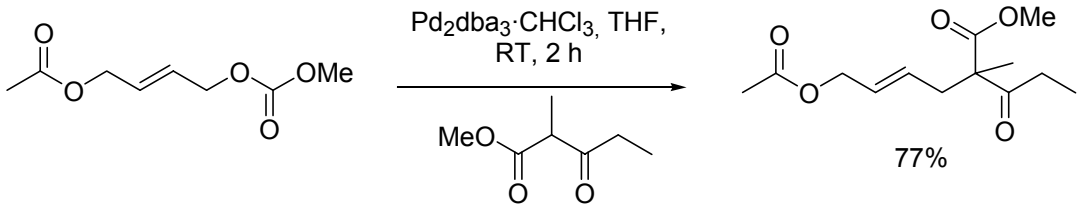
The reaction proceeds via the neutral intermediate complex $[(\eta^2$-$CH{=}CHCH_2OAc)Pd(0)L_2]$ to give the cationic $[(\eta^3$-allyl)$Pd(+2)L_2]^+$ complex. The overall equilibrium from [*solvent*·PdL_2] to

the cationic complex is more favorable with bidentate phosphines compared to triphenylphosphine. [31]

The following order of overall equilibrium constant in DMF has been established: 1,4-bis-(diphenylphosphanyl)butane > bis-(diphenylphosphanyl)ferrocene > PPh_3. [32]

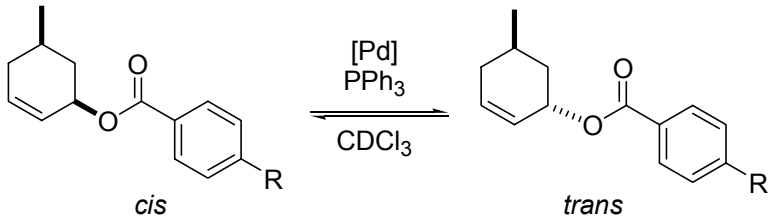
Kinetics of the first two steps is strongly dependent on the leaving group. For allyl chloroacetates and allyl benzoates (substituted) the coordination step stays faster than the ionization as in the case of unsubstituted acetates. Very good leaving groups (carbonates, trifluoroacetate) make the oxidative addition step faster, than the coordination step. [33-34]

This fact makes it possible to carry out substitution of allylic carbonate in the presence of allylic acetate selectively with very good yield (Scheme 19). [35]



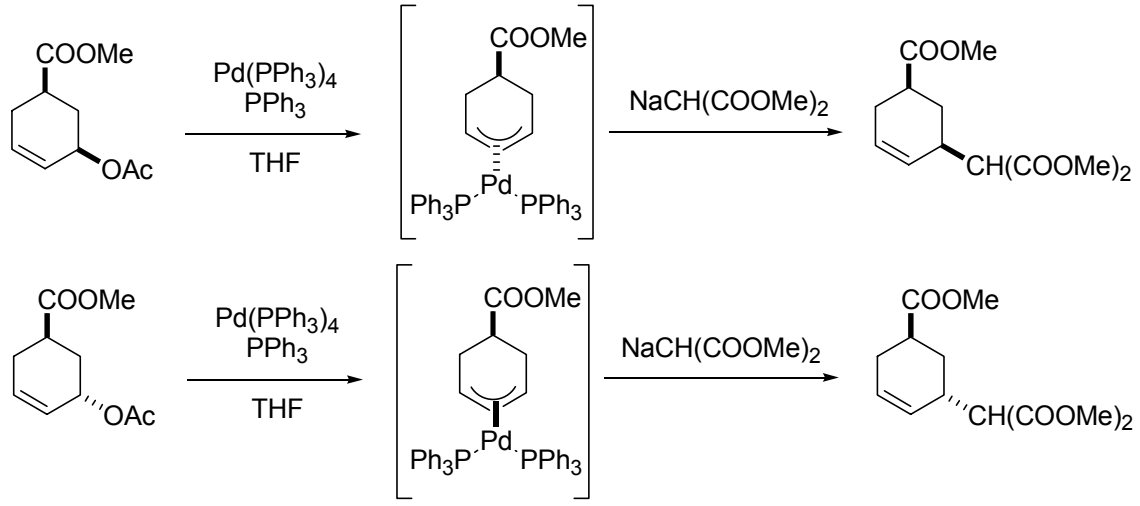
Scheme 19: Selective allylic substitution of carbonate in the presence of acetate.

Cis-trans isomerisation of cyclic allylic benzoates proceeds according to a similar mechanism. The isomerisation with $Pd(PPh_3)_4$ as a precursor is faster than with $[Pd(dba)_2+2PPh_3]$. Palladium (0) precursors are not "innocent" and play an important role in kinetics of nucleophilic substitution. A substituent at *para*-position of benzoate, which is a leaving group and a nucleophile at the same time, also influences the isomerisation considerably. For the given precursors the reaction rate follows the same order as given for the leaving groups: 4-NO_2-C_6H_4-COO^- > 4-Cl-C_6H_4-COO^- > C_6H_5-COO^- > 4-CH_3-C_6H_4-COO^- > 4-CH_3O-C_6H_4-COO^- (Scheme 20). [36]



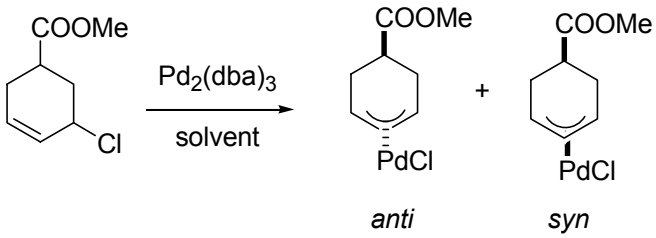
Scheme 20: *Cis-trans* isomerisation of cyclic allylic benzoates.

As it was mentioned above, soft nucleophiles cause net retention of the configuration via double net inversion. First it was demonstrated for *syn*- and *anti*-substituted cyclic allyl acetates (Scheme 21). [37]



Scheme 21: Net retention in allylic substitution with *syn*- and *anti*-substituted cyclic allyl acetates.

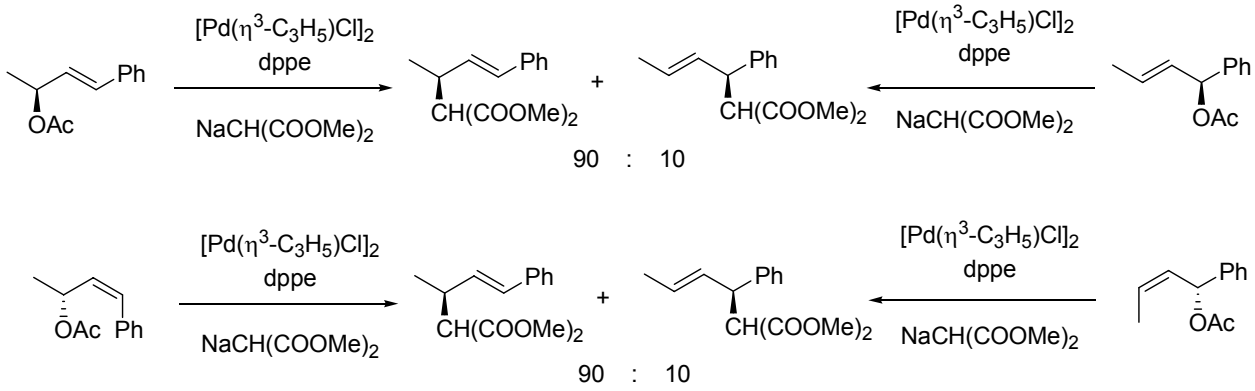
It is also known that *syn*/*anti* equilibrium of substituted cyclic allyl-palladium complexes is highly dependent on the solvent (Scheme 22, table 1). [38]



Scheme 22 and table 1: *Syn*- and *anti*-allyl-palladium complexes, solvent effect.

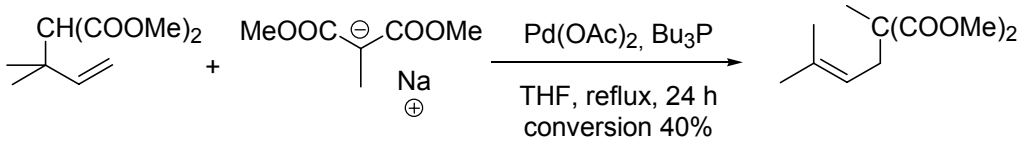
entry	solvent	ratio: *anti*/*syn*
1	benzene	100/0
2	dichloromethane	94/6
3	THF	95/5
4	acetone	75/25
5	DMF	29/71
6	acetonitrile	5/95
7	DMSO	3/97

All the examples mentioned above are with *E*-allylic substrates. *Z*-compounds also participate in palladium catalyzed allylic alkylation: besides double net inversion one more structural change happens. After the first inversion the double bond isomerizes via single bond rotation in the σ-palladium complex. Thus, (*S*,*Z*)- and (*R*,*E*)-allyl acetates result in the same product with high regioselectivity (Scheme 23). [39]



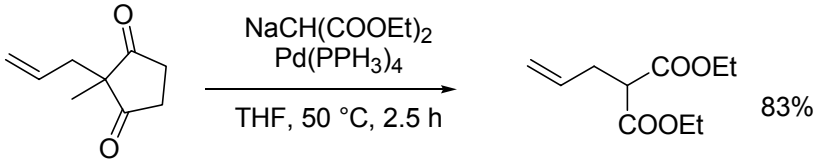
Scheme 23: Reaction with *Z*- and *E*-allylic acetates

The last step of allylic substitution, that is addition of a nucleophile, is also reversible. In this case carbanions as well as phthalimide anion can function as a leaving group (Scheme 24). [40]



Scheme 24: Malonate anion as a leaving group in allylic substitution.

The second example shows higher conversion under milder conditions with a different catalytic system and a cyclic malonate analogue as a leaving group (Scheme 25). [41]

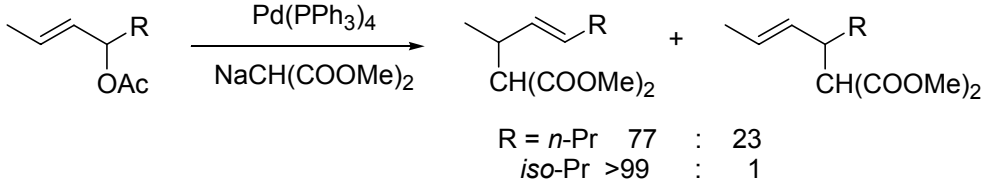


Scheme 25: Carbanion as a leaving group in allylic substitution with diethylmalonate.

2.4.4. Regioselectivity

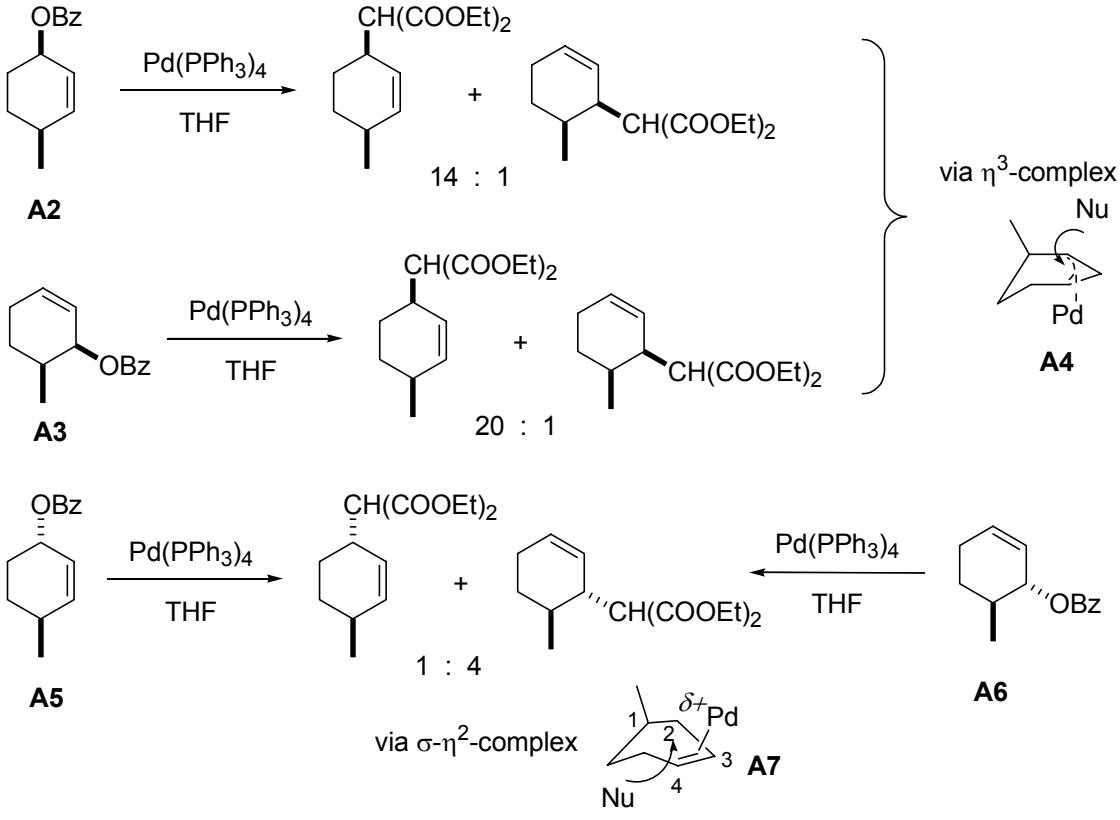
There are two positions for the attack of a nucleophile: S_N2 and S_N2'. The choice between the two possibilities is connected with the bulkiness of the substituents on the both sides of allylic system and therefore sterical hindrance for nucleophile addition step. The greater the difference in the substituent size is, the higher is the selectivity for the attack from the less hindered side

(Scheme 26). Thus, palladium catalyzed allylic substitution with unsymmetrical substrates normally leads to linear products. [42]



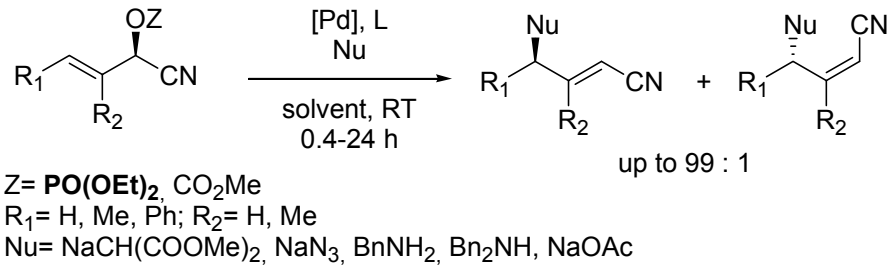
Scheme 26: Steric effects on regioselectivity.

Also in cyclic systems regioselection depends on stereosurrounding. The reaction of *syn*-substrates **A2** and **A3** gave no surprise: the major product formed was the less hindered one (Scheme 27). The reaction proceeds via η^3-allyl-palladium complex **A4**; the nucleophile prefers to attack the distant carbon atom of the allyl system. *Anti*-substrates **A5** and **A6** lead mainly to the hindered product via unsymmetrical σ-η^2-allyl-palladium complex **A7** where steric repulsion between palladium and methyl group causes localization of a partial positive charge at C2 and formation of η^2-Pd-complex. [43]



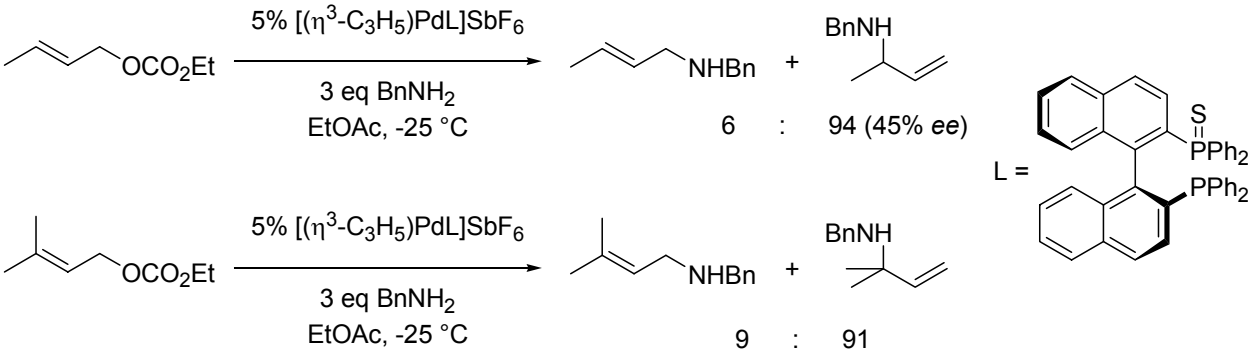
Scheme 27: Steric factors in *syn*- and *anti*-cyclic substrates.

Another ground of regioselection appears from electronic effects. The nitrile group as a group with a strong –M-effect destabilizes a partial positive charge at S_N2 position and therefore facilitates the S_N2' reaction (Scheme 28). The best *syn*/*anti*-selectivity was observed with palladium acetate as a catalyst precursor and phosphate as a leaving group. [44]



Scheme 28: Reaction of allylic systems bearing nitrile group.

Some ligands can switch regioselectivity normally linear for the palladium catalyzed reaction to untypical branched one (Scheme 29). [45]



Scheme 29: Unusual regioselectivity for Pd-catalyzed reaction facilitated with the ligand.

Other metals can be also effectively used as catalysts for allylic substitution: iridium $[Ir(COD)Cl]_2$ [46], rhodium $[RhCl(PPh_3)_3 + P(OMe)_3]$ with retention of absolute configuration [47], molybdenum $[Mo(CO)_3(EtCN)_3$ + ligands] [48], tungsten $[W(CO)_3(EtCN)_3$ + phox-ligand] [49], ruthenium $[Cp^*Ru(CH_3CN)_3PF_6]$ [50]. All these metals favor the branched products.

2.4.5. Stereoselectivity

Trost pioneered the application of chiral ligands: first in stoichometric version with (+)-2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane {(+)-DIOP }, (+)-*o*-anisyl-cyclohexylmethylphosphine {(+)-ACMP }, (-)-dimenthylisopropylphosphine {(-)-DMIP } and (-)-sparteine as ligands with maximal about 25% *ee*, [51] and then in catalytic version with 0.75

mol.% $Pd(Ph_3P)_4$ and 10 mol.% of (+)-DIOP giving considerable selectivity increase to 35-46% *ee*. [52]

Additionaly to the reaction of allyl acetates and 1,3-dienes known as sources of allyl-palladium species, 1,3-diene monoepoxides and allyl carbonates were published by Tsuji to be reactive with 1-5 mol.% of palladium catalyst. [53]

Next step in stereoselectivity improvement was made by Trost applying other chiral ligands: (-)-chiraphos, (+)-BIOP, (-)-BINAP, (-)-BINAPO. With (-)-BINAPO modified with Me_3Si-groups 69% *ee* was first reached. To rationalize the participation of the chiral ligands in stereoselection step the concept of *chiral pocket* was suggested. It implies orientation of the substituents of the allylic system in allyl-palladium complex out of bulkiness of the chiral ligand. [54]

A new series of ligands from C_2-symmetric diols and diamines (including Trost ligand) was published in early 90-s, reaching the very limit of stereoselectivity, reserving nearly no gap for future improvement. [55]

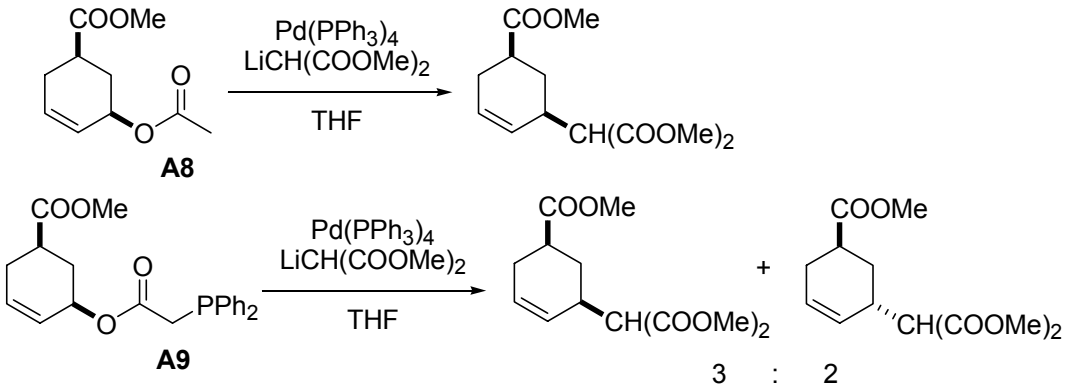
Nonetheless, one should keep in mind that in most of the cases chiral ligands are applied for symmetrical allylic systems. This structural simplification releases from the significant problem of regioselection. There have been plenty of ligands tested in palladium catalyzed allylic substitution. In a recent review more than 200 ligands for the reaction have been listed. [56]

2.4.6. Effect of directing groups

2.4.6.1. Directing leaving groups

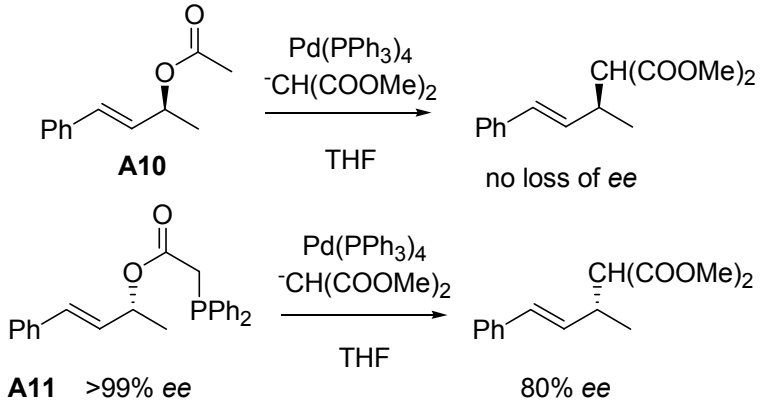
There are a few examples in literature of palladium catalyzed allylic substitution probing catalyst directing groups. There two types of directing groups known for palladium catalyzed allylic substitution – leaving and non-leaving directing groups.

Normally, palladium catalyzed allylic substitution proceeds via double net inversion. If a leaving group contains a moiety capable of binding with palladium, it can force the metal attack preferably from the same side where the leaving group is skipping therefore one net inversion step. Thus, *syn*-4-methoxycarbonyl-1-diphenylphosphinoacetyl-cyclohex-2-ene **A9** led to 40% of the inverted product opposite to acetate **A8** which provided the sole product of double inversion (Scheme 30). [57]



Scheme 30: Influence of Pd-coordinating group on stereochemistry in cyclic substrates.

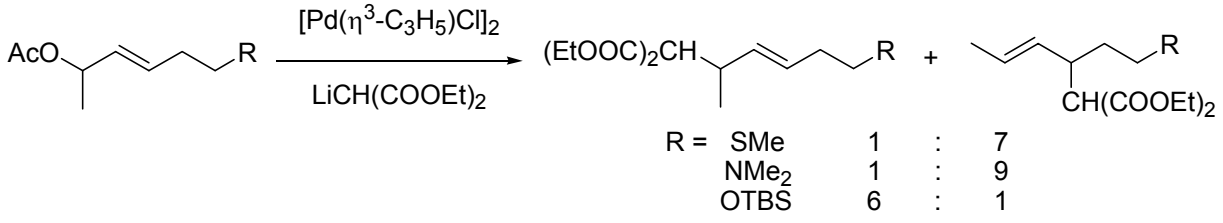
A similar effect was observed for acyclic allylic substitution employing a potentially directing leaving group: allylic substitution of acetate **A10** proceeded without loss of stereo-information. Substituted acetate **A11** shows partial racemization (Scheme 31).



Scheme 31 Influence of Pd-coordinating group on stereochemistry in linear substrates.

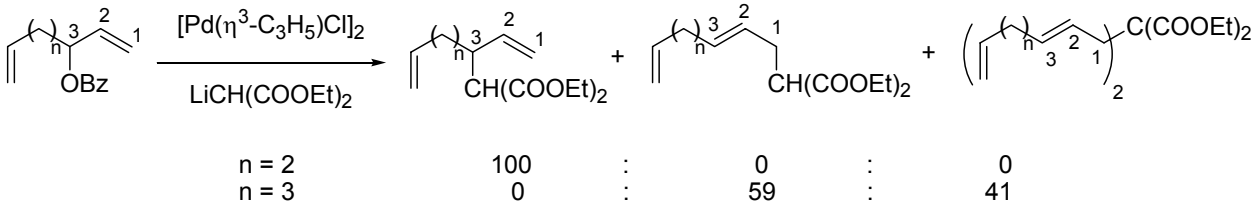
2.4.6.2. Non leaving directing groups

In the example published by Krafft methylsulfide group and dimethylamine group assisted formation of the branched product with linear/branched ratio 1:7 and 1:9, respectively (Scheme 32). *tert*-Butyldimethylsilyl group incapable of binding with palladium diverts the nucleophile to less hindered position providing linear/branched ratio 6:1. [58]



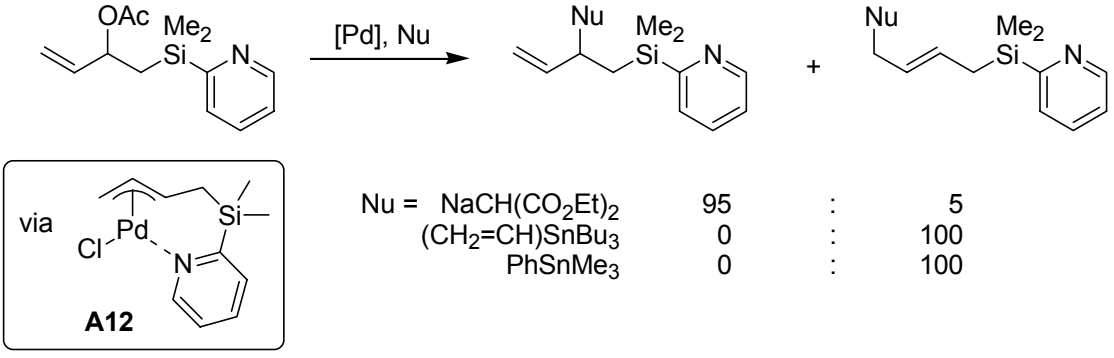
Scheme 32: Sulfide and amine as directing groups in allylic substitution.

Several years later the same research group published allylic alkylation directed by double bond moiety. Depending on the distance from the reactive center it was possible to tune the regio-selectivity. When n=2 the directing effect was observed and only the branched product was isolated (Scheme 33). When n=3 the directing ability was weaker, than natural inclination towards the linear product. In this case only linear product was formed. [59]



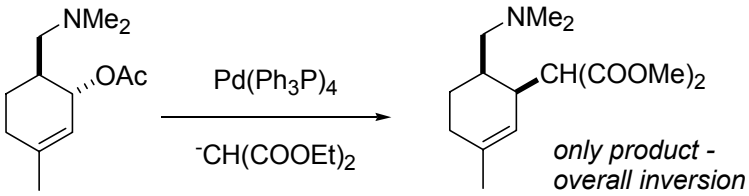
Scheme 33: Alkene-directed and non-directed Pd-catalyzed allylic substitution.

Another directing group containing nitrogen capable of coordinating with palladium is 2-pyridyldimethylsilyl group. The reaction (Scheme 34) proceeds via allyl-palladium complex **A12** isolated and characterized by X-ray crystallographic analysis. The opposite selectivity comes from different mechanisms for hard and soft nucleophiles (Chapter 2.4.3, schemes 17 and 18). In the case of malonate, substitution of chlorine atom with phosphine ligand in **A12** happens and that causes distortion of the allyl-palladium complex and therefore the nucleophile attacks from the less hindered side. In the case of organotin compound, the attack of the nucleophile occurs directly on the palladium atom (trans-metalation) from less hindered side and reductive elimination results in the linear product. [60]



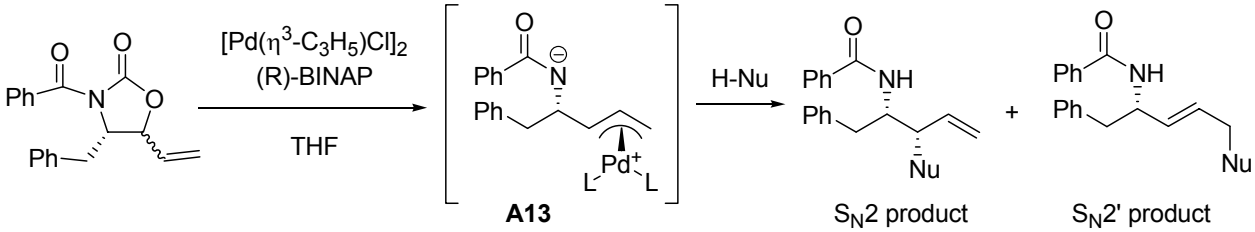
Scheme 34: Invertibility of regioselectivity with 2-pyridyldimetylsilyl group.

There is one more example of a directing group influence on stereochemical outcome (Scheme 35). It is a dimethylamine group which coordinates to palladium and as result to cause overall net inversion. [58]

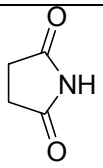
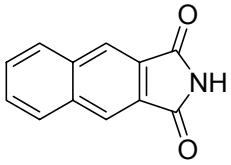
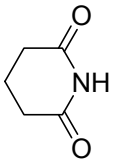
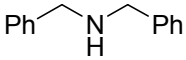
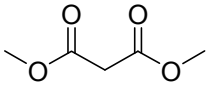
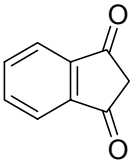


Scheme 35: Amine as a Pd-coordinating group allylic substitution.

Palladium catalyzed allylic substitution of 5-vinyloxazolidinones favors branched (S_N2) product for nitrogen nucleophiles and linear (S_N2') product for carbon nucleophiles (Scheme 36 and table 2). After decarboxylation under the reaction conditions allyl-palladium complex **A13** bearing the imide anion as a directing group is formed.



Scheme 36 and table 2: Allylic substitution of 5-vinyloxazolidinones.

entry	H-Nu	S_N2 / S_N2'	Yield, %
1		97:3	95
2		95:5	94
3		83:17	55
4		0:100	97
5		0:100	90
6		0:100	83
7		0:100	91

Nitrogen nucleophiles are deprotonated by the imide and hydrogen bond between obtained amide and oxygen of phthalimide anion (and alike structures) can be formed. This structural interconvertion provides the explanation of the directing effect towards branched products (Table 2, entries 1-3). Carbon nucleophiles were beforehand deprotonated with sodium hydride and lead to linear product because of electrostatic repulsion of two negative charges (Table 2, entries 6-7). Similar selectivity was obtained with dibenzylamine and pyrrolidine incapable of the hydrogen bond formation (Table 2, entries 4-5). [61]

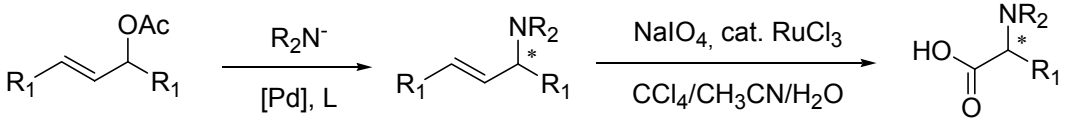
Thus, directing groups can be responsible not only for regioselectivity, but can also switch the usual net retention for palladium catalyzed allylic substitution with soft nucleophiles into net inversion.

2.5. Nitrogen nucleophiles in allylic substitution

2.5.1. Unusual reactivity of nitrogen nucleophiles

Nitrogen nucleophiles represent an especially interesting type of nucleophiles for palladium catalyzed allylic substitution. [62] It is one of few opportunities in Organic chemistry to build carbon-nitrogen bond stereoselectively applying means of transition metal catalysis.

There is one more good reason for the concern in palladium catalyzed allylic amination: two step synthesis from commercially available or relatively simply synthesizable allylic acetates results in a chiral (natural or not natural) α-aminoacid (Scheme 37). [63]

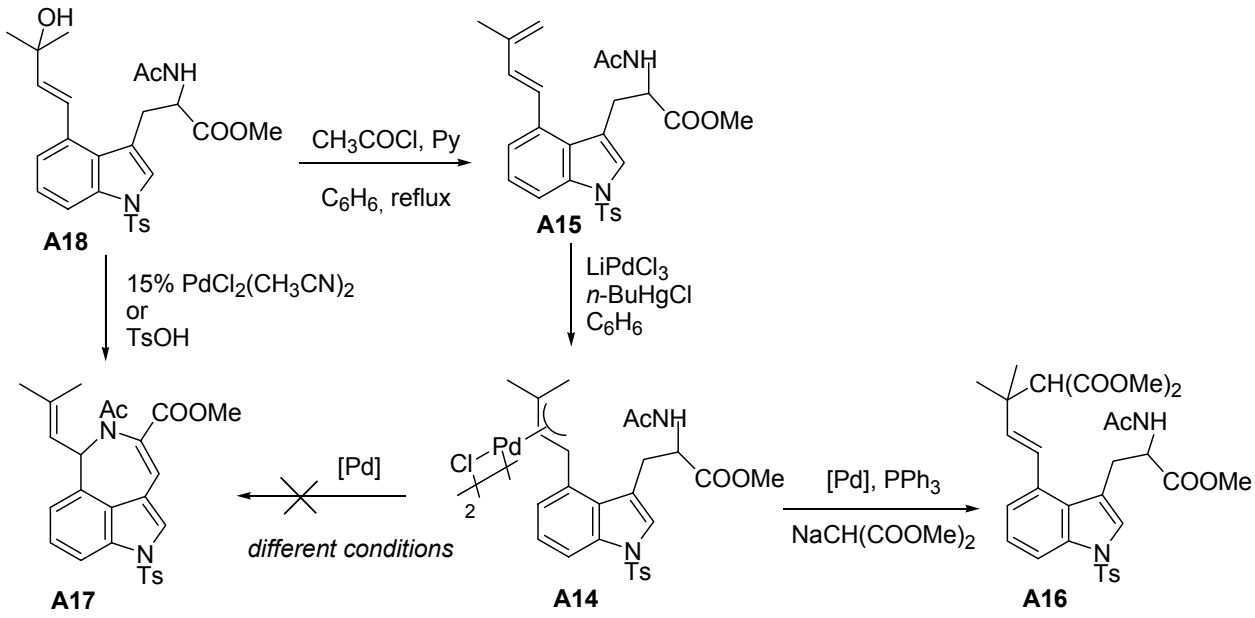


Scheme 37: Synthetic approach towards chiral α-aminoacids.

General mechanism of allylic subsitution is depicted above (Chapter 2.4.3, scheme 17). Mechanistic details of the reaction of secondary amines with cationic palladium complexes as $[(\eta^3\text{-PhCHCHCHPh})Pd(PPh_3)_2]^+BF_4^-$ has been investigated in DMF. The reaction is irreversible with monodentate ligands such as triphenylphosphine, whereas it is reversible with bidentate ligands such as dppb. In all cases, piperidine is more reactive than morpholine. The rate and equilibrium constants have been determined in DMF. [64]

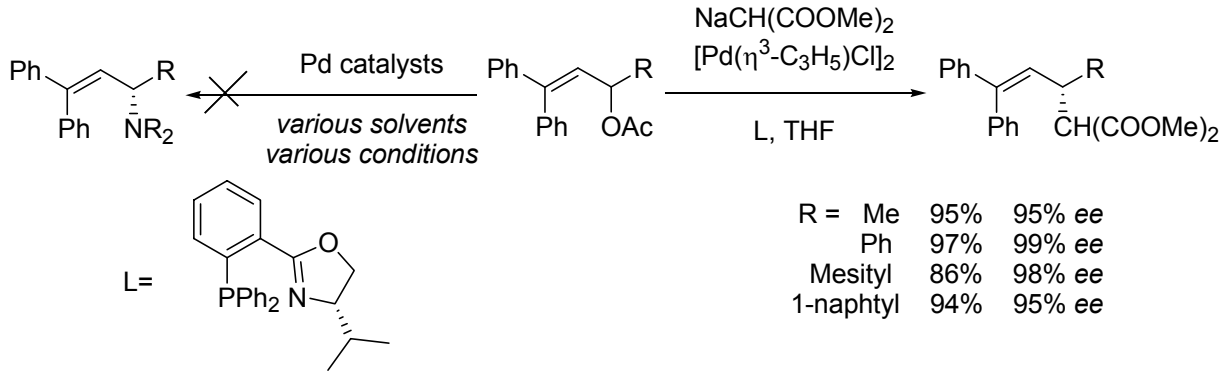
It is important to note here, that despite the mechanism of allylic substitution is described as the same for both carbon and nitrogen nucleophiles, there are sometimes particular differences in the outcome – in selectivity and especially in reactivity. These issues are very often omitted in reviews and even publications (when a more or less suitable solution is found). Nonetheless, sometimes these problems can be barely surmountable.

Allyl-palladium complex **A14** prepared from diene **A15** reacts easily with sodium dimethyl-malonate forming the product **A16** (Scheme 38). Different conditions were attempted for intra-molecular allylic amination to get the target compound **A17** from the complex **A14** with no success. Only roundabout way via allylic alcohol **A18** allowed formation of the desired product **A17** via palladium or acid catalysis. [65]



Scheme 38: Different reactivity of allyl-palladium system with C- and N-nucleophiles.

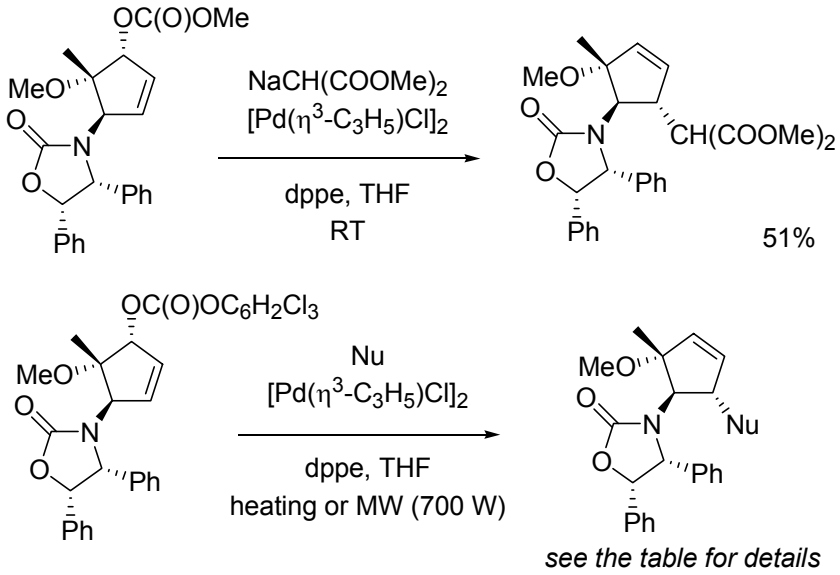
Similar problem arose in palladium catalyzed allylic substitution with the trisubstituted allylic acetates and catalytic system based on phox-ligand (Scheme 39). Various nitrogen nucleophiles under various conditions were not reactive, while a malonate nucleophile gave the substitution product. [66]



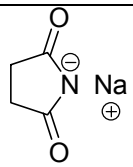
Scheme 39: Allylic alkylation and allylic amination of trisubstituted substrates.

Pfaltz and Helmchen reported Pd-catalyzed allylic substitution with chiral phosphino-oxazoline ligands and different nitrogen nucleophiles (benzylamine, sodium salts of *p*-toluenesulfonamide, benzoylhydrazine and dibenzylamine). It is noted that these reactions were found to be slower, than analogous allylic alkylation with dimethyl malonate or related stabilized anions, proceeding smoothly at room temperature. The nitrogen nucleophiles demanded heating to 40-60 °C and longer reaction times for achieving satisfactory yields. [67]

Using potassium phthalimide aa a nucleophile in palladium catalyzed allylic substitution Trost recognized that the reaction was slow (probably because of low solubility of phthalimide) and required a short initial period of sonication in the presence of tetra-*n*-hexylammonium bromide to facilitate the reaction with cyclic allylic acetate (opposite to highly reactive malonate). [68]

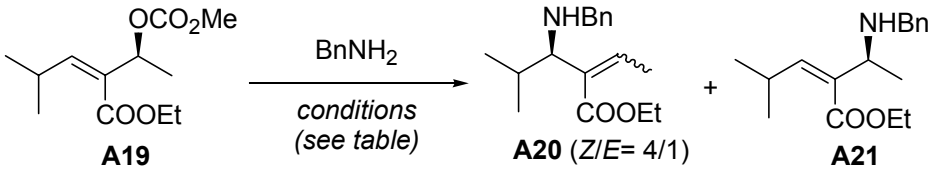


Scheme 40 and table 3: Microwave assisted allylic substitution with N-nucleophiles.

entry	Nu	conventional heating, dppf/THF			MW heating, dppe/DMSO		MW heating, dppf/THF	
		T, °C	time, h	Yield, %	time, min	Yield, %	time, min	Yield, %
1		70-120	48	8	5	29	5 × 2	0
2	Ac_2NNa	70	48	3	2	46	6	24
3	Ts(Bn)NNa	40-90	36	4	5	37	6	86
4	K-phthalimide	60	24	0	5	63	0	0

Microwave heating also made allylic substitution proceed with N-nucleophiles while the reaction under conventional heating (up to 120 °C) during 1–2 days resulted in 0–8% yield (Scheme 40, table 3). [69]

Allylic carbonate **A19** can undergo allylic amination with benzylamine in both refluxing THF and refluxing acetonitrile without any catalyst leading to amines **A20** (with *Z*/*E* = 4/1) and **A21** with high S_N2'-selectivity (Scheme 41, table 4). Application of a palladium catalyst gives opposite selectivity for the two solvents. In THF amine **A20** is formed as a major product and in acetonitrile amine **A21** is a major product. [70]



Scheme 41 and table 4: Solvent effect on catalyzed and not catalyzed allylic substitution.

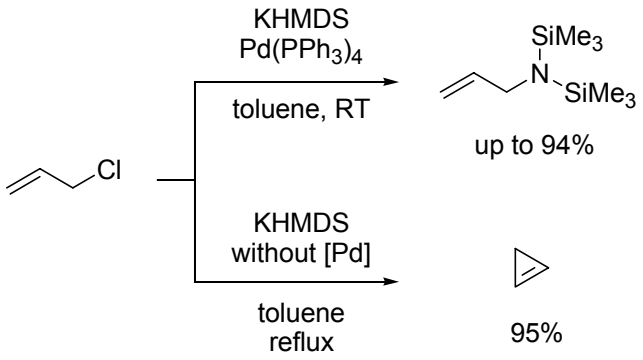
entry	catalyst	solvent (reflux)	ratio **A20**/**A21**
1	no	THF	99/1
2	no	CH_3CN	99/1
3	$Pd_2(dba)_3$	THF	90/10
4	$Pd_2(dba)_3$	CH_3CN	20/80

2.5.2. Ammonia surrogates

Ammonia surrogates represent the most interesting class of nitrogen-nucleophiles as they can be converted into free amino-group, that means synthesis of chiral primary amines. There are some examples where ammonia itself was used as a nucleophile, but problems with di- and tri-alkylation always arose. Moreover, application of gaseous (or even liquid) ammonia as a reagent for laboratory purposes is connected with inevitable excess of the reagent and that is not always compatible with sensitive compounds in use.

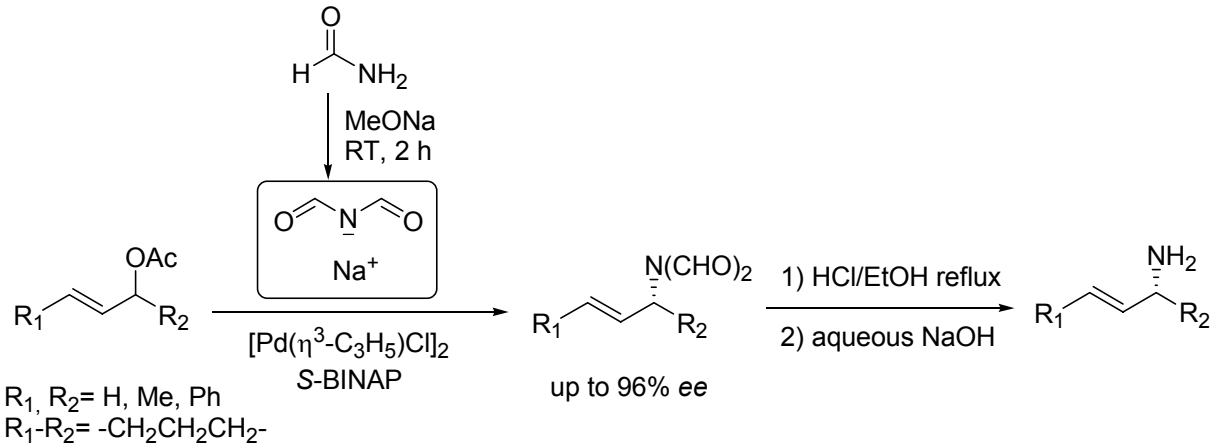
There are plenty of ammonia surrogates. The most known of them, which is also used in Gabriel synthesis, is potassium phthalimide. [71] Standard removal of phthalimide group (with NH_2NH_2) has been known for a long time.

Bis(trimethylsilyl)amide was used as an effective ammonia surrogate in palladium catalyzed reaction with allyl chloride in toluene. The product can be easily converted into primary amine under acidic conditions. This reaction broadens the scope of bulk commercially available reagent. [72] Similar conditions without palladium give rise to cyclopropene as a product (Scheme 42). [73]



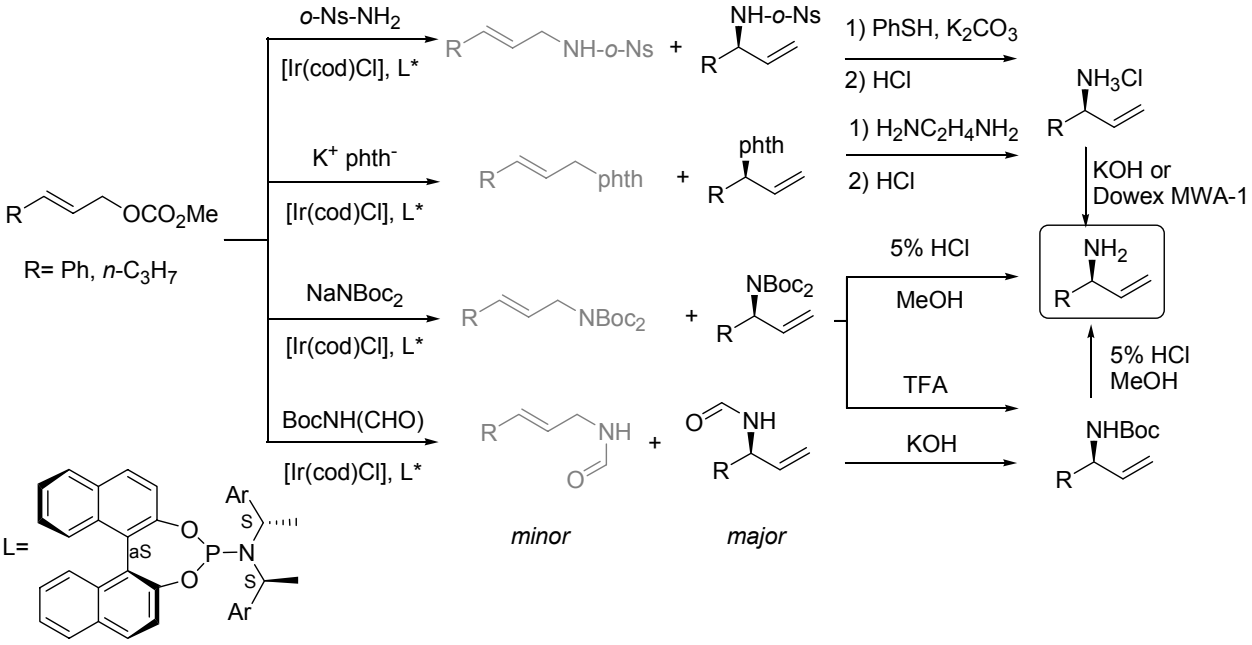
Scheme 42: Reaction of allyl chloride with KHMDS.

The next ammonia surrogate is sodium diformylamide. It is synthesized from formamide in one step (Scheme 43). The best solvent for the reaction was $ClCH_2CH_2Cl$, the reaction proceeded with high yield and very good enantioselectivity with (*S*)-BINAP as a chiral ligand at 0 °C. In other solvents (acetonitrile, DMF, DMSO, toluene) stirring at room temperature or higher was necessary and the reaction led to both lower selectivity and worse yield. Formyl-groups can be removed under acidic conditions. [74]



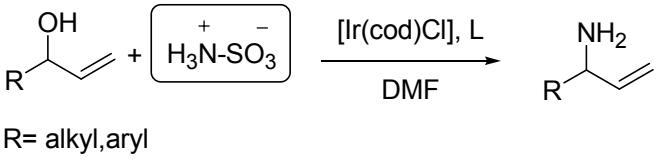
Scheme 43: Allylic amination with sodium diformylamide.

Helmchen reported iridium-catalyzed allylic substitution with different ammonia surrogates: *o*-nosylamide, potassium phthalimide, sodium bis-(*tert*-butyloxycarbonyl)amide, *N*-(*tert*-butyl-oxycarbonyl)-*N*-formylamine (Scheme 44). [75]



Scheme 44: Allylic amination with different ammonia surrogates.

Sulfamic acid has been recently published to be an effective ammonia surrogate in iridium catalyzed allylic substitution with free allylic alcohol leading to free primary amine as a product (Scheme 45).



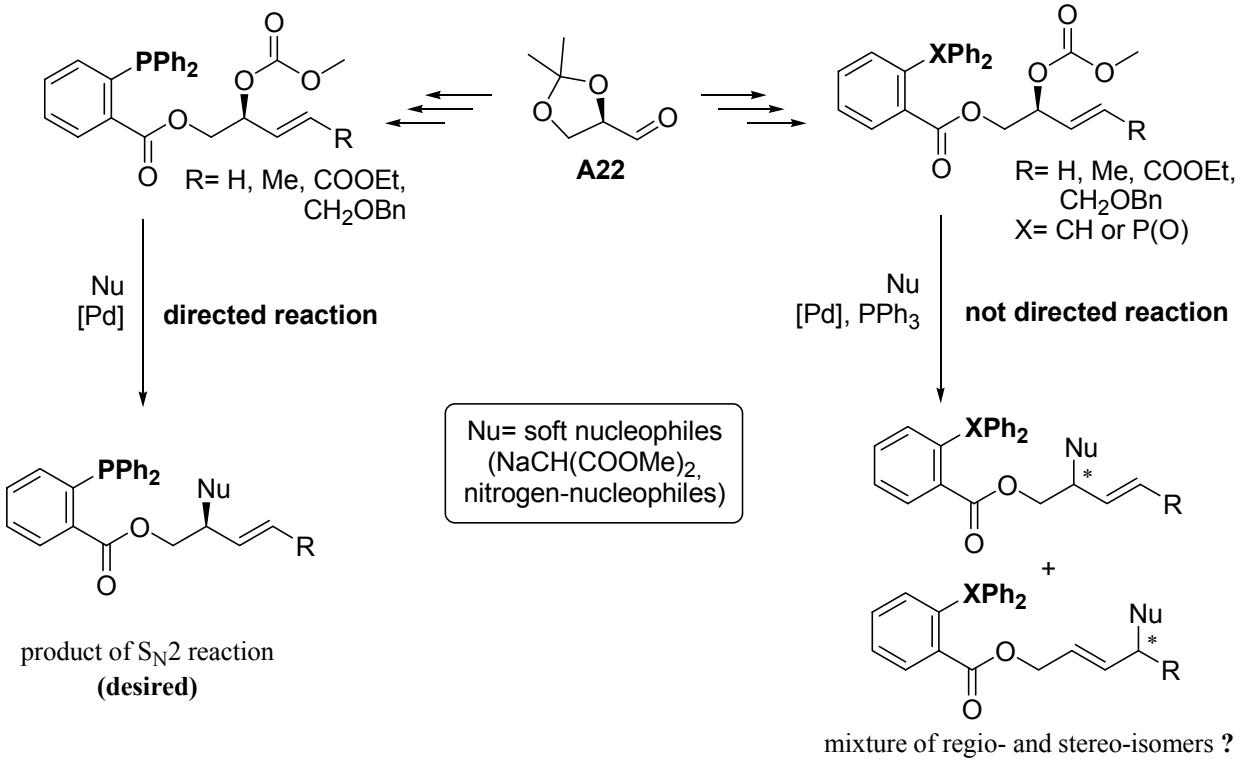
Scheme 45: Sulfamic acid as ammonia surrogate.

It has been suggested that *N*,*N*-dimethylformamide undergoes interaction with sulfamic acid to form a Vilsmeier-like intermediate and free ammonia which reacts subsequently as a nucleophile with allyl-iridium species formed from the Vilsmeier-like intermediate. [76]

3. Goal

Palladium catalyzed allylic substitution with soft nucleophiles is a valuable synthetic method. So far problematic is the control of regiochemistry which usually prefers substitution at the less hindered allyl terminus. Furthermore, it is known that the reaction occurs with overall retention of configuration. In the course of this project we wanted to learn how the *o*-DPPB catalyst-directing group being a part of the substrate can alter intrinsic regio- and stereochemical preferences.

As a first allylic system bearing *o*-DPPB directing group and methylcarbonate as a leaving group for palladium catalyzed allylic substitution with soft nucleophiles we selected the substrates depicted on Scheme 46. These compounds can be synthesized from 2,3-*O*-isopropyliden-glyceraldehyde (**A22).**



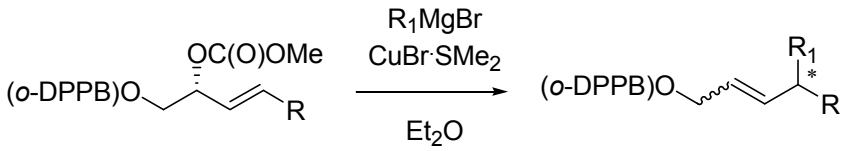
Scheme 46: Preliminary goal.

Allylic substrates with different substituents on the opposite allyl terminus (H, Me, COOEt, CH_2OBn) would allow to evaluate their influence on the reaction (steric and electronic effects).

Application of non-directing moiety: *ortho*-diphenylphosphanylbenzoate-oxide (X= P(O)) and *ortho*-benzhydrylbenzoate (X= CH) – would enable distinguishing the directing group effect in the presence of the same steric surrounding.

Different soft nucleophiles should be used for the reaction. Application of nitrogen nucleophiles in the reaction is of great interest as a way towards chiral amines and chiral α-aminoacids.

Hard nucleophiles as cuprates can be also applied for allylic substitution. Thus, carbonate serves as a leaving group and *o*-DPPB stays in the molecule (Scheme 47).



Scheme 47: Copper mediated allylic substitution with o-DPPB as non-leaving directing group.

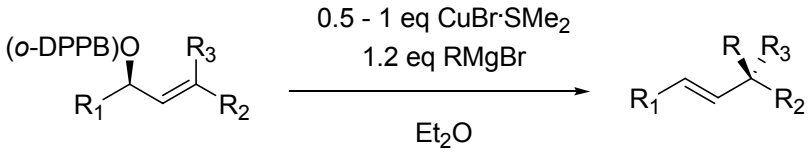
This work should provide an approach to a solution of selectivity problem for palladium catalyzed allylic substitution with soft nucleophiles and unsymmetrical allylic substrates applying the concept of a catalyst directing group.

4. Results and discussion

4.1. *o*-DPPB as a leaving directing group

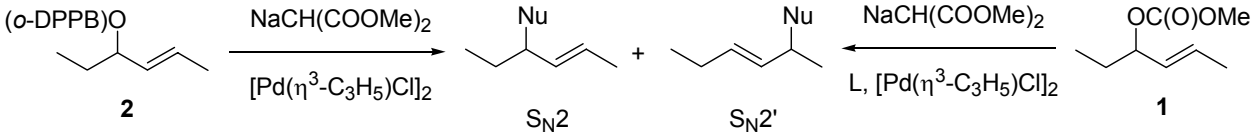
4.1.1. Allylic substitution with *o*-DPPB as a leaving directing group

Allylic esters and carbonates are known as substrates for a variety of allylic substitution reactions. Our laboratory has published a highly regioselective copper mediated reaction with *o*-DPPB esters of substituted allylic alcohols (Scheme 48). [12,13]



Scheme 48: Allylic substitution of *o*-DPPB esters with cuprates.

Having good experience with copper mediated chemistry of *o*-DPPB ester of hex-2-en-4-ol in hand, we have supposed that *o*-DPPB could serve as a good directing leaving group in the case of palladium catalyzed allylic substitution (Scheme 49). Palladium catalyzed allylic substitution is known to proceed via η^3-allylpalladium complex. And therefore a regioselectivity problem can arise. Predominant formation of a single product was observed mostly when substituents on both allyl termini had considerable difference in their bulkiness (see *Background*).



Scheme 49: Palladium catalyzed allylic substitution.

Nonetheless, palladium catalyzed allylic substitution with *o*-DPPB ester **1** resulted in S_N2'/S_N2 selectivity of only 2:1 (Scheme 51 and table 5). The reaction seems to form nearly symmetrical η^3-allylpalladium complex as there is no considerable bulkiness difference between methyl and ethyl groups.

The substrate without a directing group, the carbonate **2**, results in similarly low S_N2'/S_N2 selectivity of 1.5:1 and 3:1 for triphenylphosphine and *o*-DPPBA as extra ligands, respectively.

Comparison of regioselectivity of palladium catalyzed allylic substitution with the non-directing substrate **2** and the directing substrate **1** brings to the conclusion that *o*-DPPB as a leaving

directing group does not have any influence on the regioselectivity outcome in palladium catalyzed allylic substitution and behaves like a common leaving group.

Table 5: Palladium catalyzed reaction of hept-2-en-4-ol derivatives with malonate.[a]

entry	substrate	ligand	conversion [b], %	ratio [b] S_N2'/S_N2
1	**1**	-	100	2:1
2	**2**	PPh_3	100	1.5:1
3	**2**	*o*-DPPBA	100	3:1

a) $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), ligand (10 mol.%), NaH (2 eq), $CH_2(COOMe)_2$ (2.5 eq), stirring 19 h at room temperature; b) determined by NMR from crude reaction mixture.

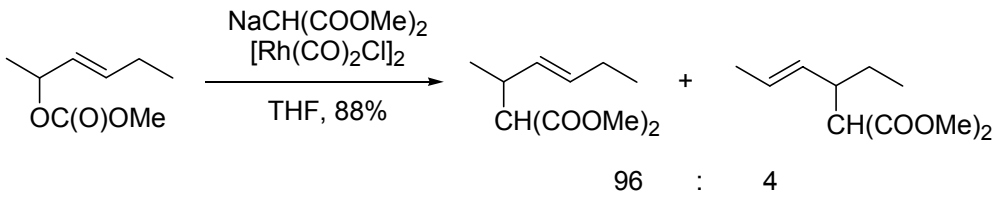
To broaden the scope of the reaction nitrogen nucleophiles were also used in palladium catalyzed allylic substitution. Nitrogen nucleophiles are known to be less reactive and sometimes lead to different selectivity, than carbon nucleophiles (see *Background*). Thus, nitrogen nucleophiles demonstrate similar regioselectivity in palladium catalyzed allylic substitution with *o*-DPPB ester **1** in the range of 1.6:1 for piperidine to 7:1 for morpholine (Scheme 49, table 6).

Table 6: Palladium catalyzed reaction of *o*-DPPB ester **1** with nitrogen nucleophiles.[a]

entry	Nu	conversion [b], %	ratio [b] S_N2'/S_N2
1	piperidine	68	1.6:1
2	morpholine	100	7:1
3	pyrrolidine	85	6:1
4	allylamine	100	6:1

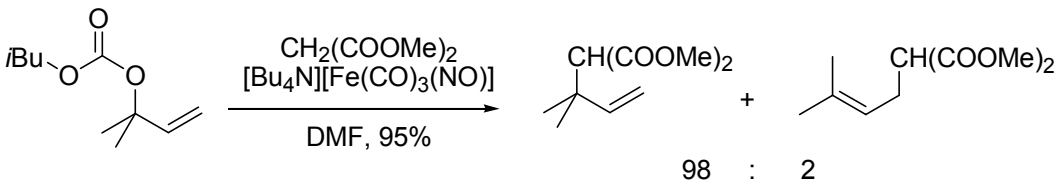
a) $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), *n*-Bu_4NBr (20 mol.%), nucleophile (4.0 eq) stirring 19 h at room temperature; b) determined by NMR from crude reaction mixture.

Other transition metals are also known as catalysts in allylic substitution with soft nucleophiles. Martin and co-workers used a rhodium catalyst for allylic substitution with carbon nucleophiles. [77] The allylic carbonate led to a mixture of regioisomeric products with S_N2/S_N2' ratio of 96:4 (Scheme 50).



Scheme 50: Rhodium catalyzed allylic substitution.

Tetra-*n*-butylammonium nitrosotricarbonylferrate was also proved to be effective as a catalyst for allylic substitution with dimethylmalonate. [78] High regioselectivity has been achieved by Plietker in the reaction with the iron complex (Scheme 51). Application of bulky leaving groups was essential for the reaction.

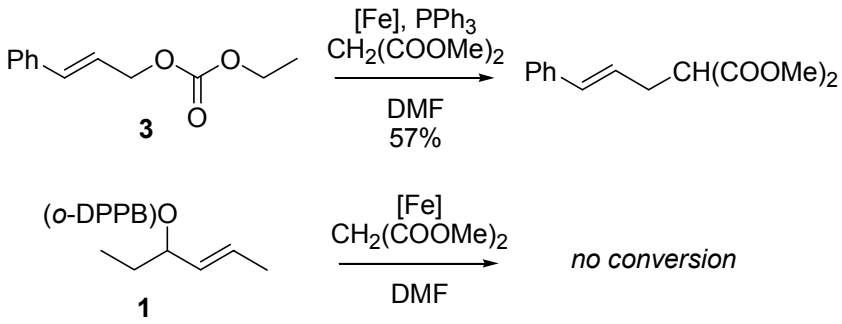


Scheme 51: Iron catalyzed allylic substitution.

The two reactions mentioned above imply the intermediates with σ-coordinated metals. That explains high S_N2 regioselectivity for both rhodium and iron catalyzed reactions.

Nonetheless, application of other metals for the reaction of the *o*-DPPB ester **1** with dimethylmalonate was not successful. Thus, rhodium catalyzed allylic substitution under the conditions described by Martin with 5 mol.% of $[Rh(CO)_2Cl]_2$ led to 58% of conversion and similarly low regioselectivity with S_N2'/S_N2 ratio of 1:2.

The iron complex seems to be effective only for bulky carbonates which serve as very good leaving groups. The ethyl carbonate **3** under Plietker's conditions (no base, DMF as a solvent, high concentration, triphenylphosphine as a ligand, heating at 80 °C) gave 57% conversion (Scheme 52).



Scheme 52: Iron catalyzed allylic substitution.

Same conditions for the *o*-DPPB ester **1** (both in the presence and without NaH as a base) led to no conversion, while the carbonate **2** gave 13% conversion after 24 h.

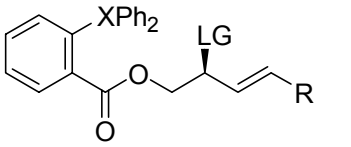
4.1.2. Conclusion

All the attempts to conduct regioselective palladium catalyzed allylic substitution with *o*-DPPB as a leaving directing group led to low S_N2'/ S_N2 selectivities in the range from 7:1 for morpholine to 1.5:1 for malonate. These experiments show that *o*-DPPB can not act as a directing leaving group in palladium catalyzed allylic substitution. Therefore we decided to synthesize substrates with *o*-DPPB as a purely directing group and employing carbonates or acetates as leaving groups.

4.2. System based on 2,3-*O*-isopropyliden-glyceraldehyde

4.2.1. Synthesis of the substrates

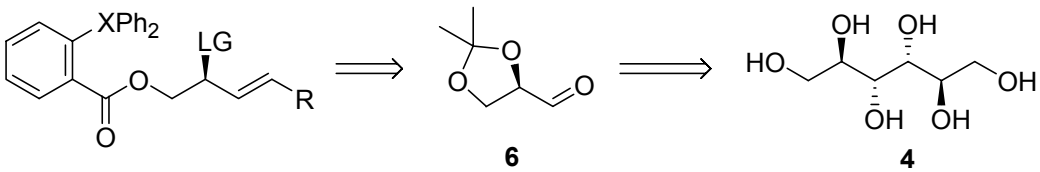
The substrate for the directed palladium catalyzed allylic substitution was designed to bear *o*-DPPB as a directing group, methylcarbonate or acetate as a leaving group, and one more substituent (R) on the allylic system which allows estimating sterical and electronic influence of the substituent on the reaction (Scheme 53). To evaluate a directing ability of *o*-DPPB group, non-directing analogues with groups incapable of binding to palladium were synthesized. 2-Benzhydrylbenzoate (X= CH) or 2-(diphenylphosphoryl)benzoate (X= P(O), *o*-DPPBA-oxide) can be used as non-directing groups.



R = H, Me, COOEt, CH_2OBn
LG = OC(O)OMe, OAc
X = P, CH, P(O)

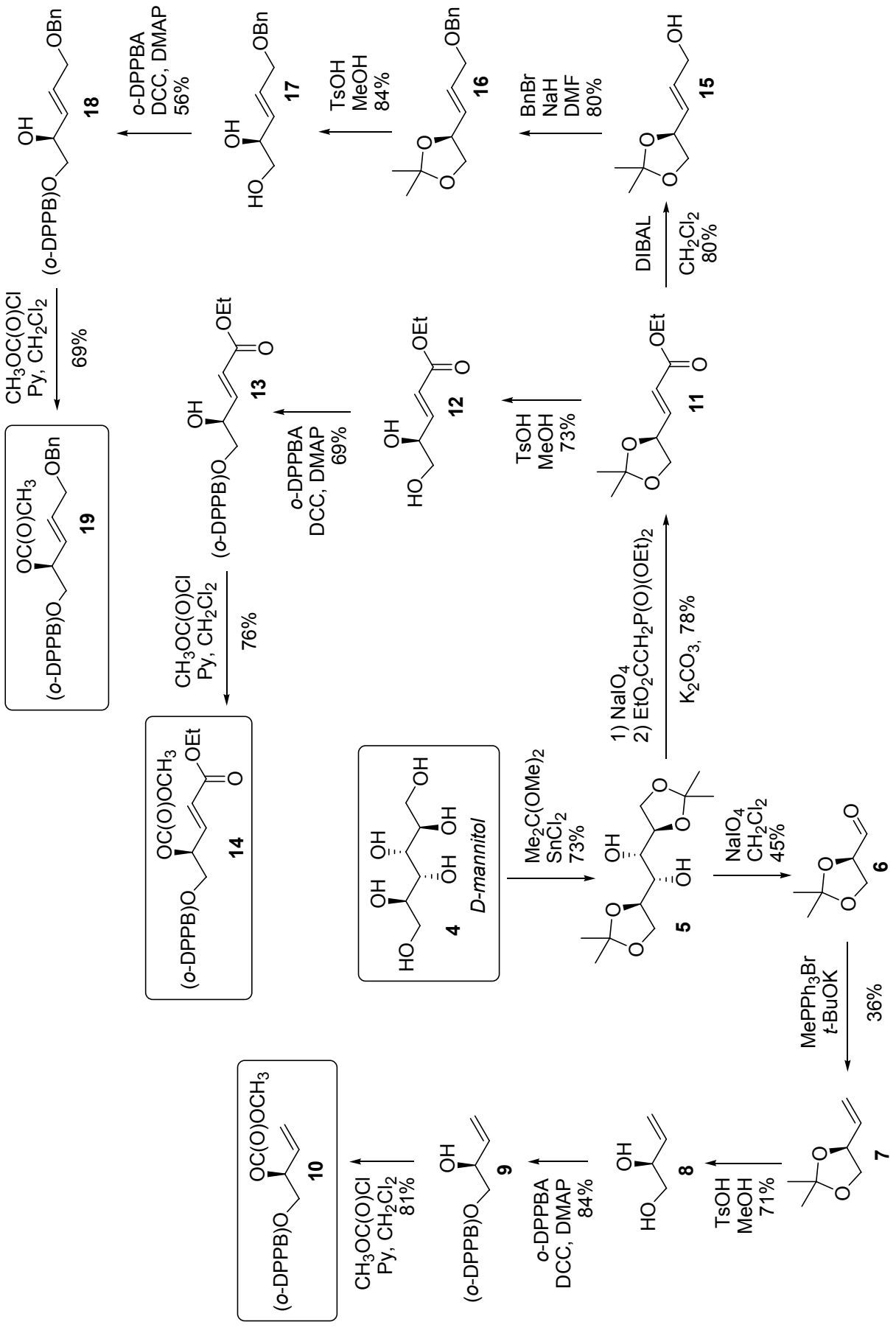
Scheme 53: General structure of the substrates based on 2,3-*O*-isopropyliden-glyceraldehyde.

Retrosynthetic analysis of the substrates brings us to (*S*)-2,3-*O*-isopropyliden-glyceraldehyde (**6**) as a key intermediate and D-mannitol (**4**) as a commercially available starting material (Scheme 54). Application of D-mannitol (**4**) enabled chiral pool synthesis of the substrates for directed allylic substitution.



6 **4**

Scheme 54: Retrosynthetic analysis of the substrates for directed allylic substitution.



Scheme 55: Synthesis of the substrates based on (*S*)-2,3-*O*-isopropyliden-glyceraldehyde.

Selective diol bis-protection of D-mannitol (**4**) and subsequent glycol oxidative cleavage with sodium periodate led to (*S*)-2,3-*O*-isopropyliden-glyceraldehyde (**6**) (Scheme 55). The aldehyde **6** can participate in the following olefination reaction. Horner-Wadsworth-Emmons reaction of the aldehyde **6** with triethyl phosphonoacetate and potassium carbonate as a base was carried out in a one-pot procedure with glycol cleavage in water as a solvent resulting in (*S*,*E*)-3-[(4′)-2′,2′-dimethyl-1′,3′-dioxolane-4′-yl]-prop-2-enoic acid ethyl ester (**11**).

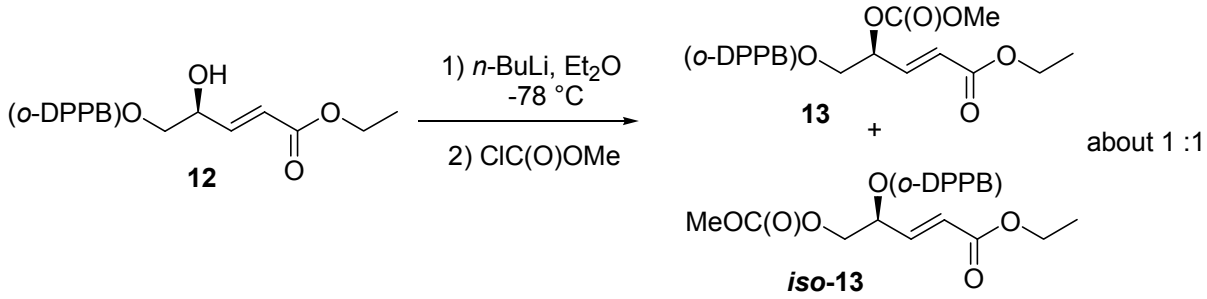
Wittig reaction of the aldehyde **6** and methyltriphenylphosphonium halogenide (bromide or iodide) and potassium *tert*-butoxide as a base furnished the terminal alkene **7**.

Reduction of ester **11** with DIBAL provided allylic alcohol **15** which was then protected with benzyl group to give compound **16**.

Deprotection of the acetonide group can be carried out either in ethanol in the presence of 2 M hydrochloric acid (2 eq) or in methanol with a catalytic amount of *para*-toluenesulfonic acid. Both methods provided good yields. The second method is considered to be more preferable because of simpler work-up: only evaporation of the solvent is necessary without the need to get rid of water. Deprotection of all the three acetonide protected compounds **7**, **11** and **16** led to the 1,2-diols **8**, **12** and **17**, respectively.

Esterification of the primary alcohol group in the diols **8**, **12** and **17** with *o*-DPPBA was carried out under Steglich conditions at 0 °C in the presence of 1 equivalent of dicyclohexyl-carbodiimide (DCC) and catalytic amounts of 4-dimethylaminopyridine (DMAP). Thus, the *ortho*-diphenylphosphanylbenzoates **9**, **13** and **18** were formed, respectively.

The next step, formation of carbonates, required choice of an appropriate base. When a strong base such as *n*-butyllithium was used for deprotonation of the alcohol **12**, a transfer of the *o*-DPPB group from the primary alcohol function to the secondary one occurred. This transesterification results in a nearly 1:1 mixture of regioisomers **13** and ***iso*-13** (Scheme 56). The regioisomers are hardly separable by means of ordinary column chromatography.

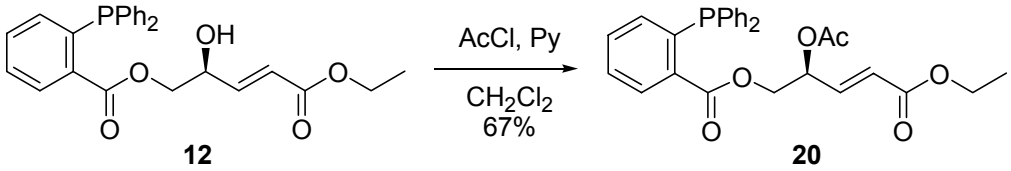


Scheme 56: Formation of regioisomeric carbonates with *n*-butyllithium as a base.

It was pyridine that allowed formation of the single desired carbonate **13** (Scheme 55). Under the same conditions (3 eq of pyridine, 1.1 eq of methylchloroformate and dichloromethane as a

solvent at 0 °C) the other carbonates for palladium catalyzed allylic substitution, as **10** and **19**, were obtained.

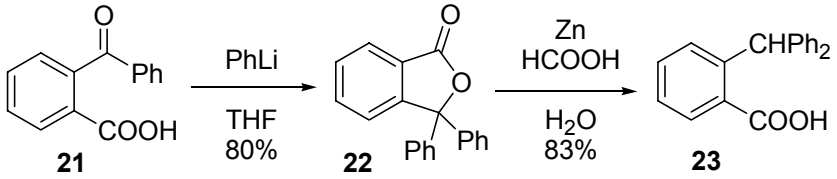
The substrate **20** with acetate as a leaving group was synthesized analogously to the synthesis of the carbonates with acetylchloride instead of methylchloroformate. Pyridine was also used as a base (Scheme 57).



Scheme 57: Synthesis of the substrate **20** with acetate as a leaving group.

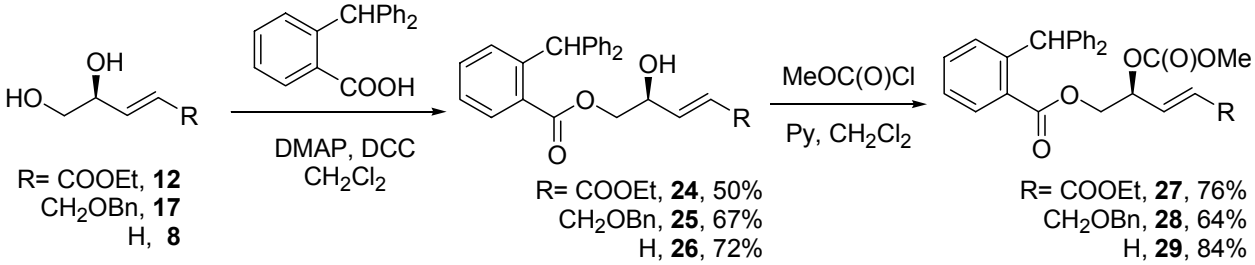
Non-directing carbon analogue of *o*-DPPBA, *ortho*-benzhydrylbenzoic acid (**23**), was prepared from *ortho*-benzoylbenzoic acid (**21**) according to a literature procedure (Scheme 58). [79,80] First, *ortho*-benzoylbenzoic acid (**21**) reacted with phenyllithium to give 3,3-diphenylphtalyde (**22**) which then after reductive ring opening with zinc in formic acid led to the desired *ortho*-benzhydrylbenzoic acid (**23**) in good yield.

The is a second method for reducing 3,3-diphenylphtalyde (**22**) described in literature. It proceeds in the presence of zinc in ethanol solution of sodium hydroxide. Nonetheless, this approach leads to low conversion.



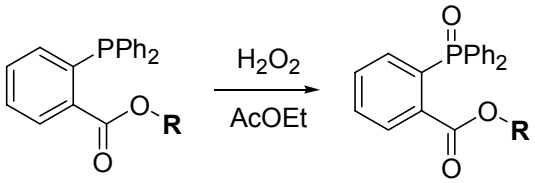
Scheme 58: Synthesis of 2-benzhydrylbenzoic acid.

Esterification reaction of the primary alcohol group in the diols **8**, **12** and **17** with 2-benzhydryl-benzoic acid (**23**) proceeded similarly to esterification with *o*-DPPBA under Steglich conditions with DCC and DMAP (Scheme 59). Then the obtained mono-esters **24**, **25** and **26** were converted into the carbonates **27**, **28** and **29**, respectively, according to a similar procedure as described for the synthesis of the substrates bearing *o*-DPPB directing group.



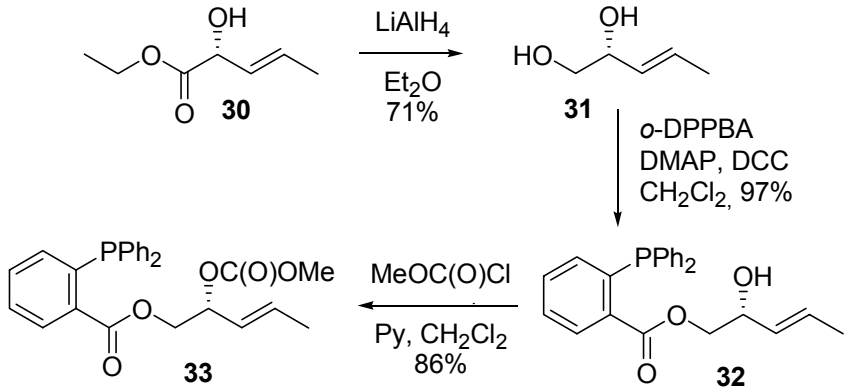
Scheme 59: Synthesis of 2-benzhydrylbenzoic acid esters.

An alternative probe is to use the *o*-DPPB-oxides which has the same steric demand of the *o*-DPPB group but lacks the ability to bind to the metal center. These compounds were synthesized by oxidation of the corresponding *o*-DPPB esters with hydrogen peroxide in ethyl acetate (Scheme 60). The same procedure for the phosphine group oxidation was applied for HPLC-analysis of the products of palladium catalyzed allylic substitution to prevent oxidation process on the column which sometimes occurred and therefore gave rise to broad overlapping peaks incapable of being clearly interpreted.



Scheme 60: Synthesis of the substrates bearing *o*-DPPB-oxide.

The substrate **33** with a methyl group on the allylic terminus was prepared from 2-hydroxypent-3-enoic acid ethyl ester (**30**) available in our laboratory (Scheme 61). This compound is synthesized via enzymatic addition of hydrogen cyanide to crotonaldehyde and a subsequent Pinner reaction [81]. Reduction of the α-hydroxyester **30** with lithiumaluminium hydride furnished the diol **31**. Esterification of the primary hydroxyl group in the diol **31** with *o*-DPPBA gave the ester **32**, which was treated with methylchloroformate to yield carbonate **33**.

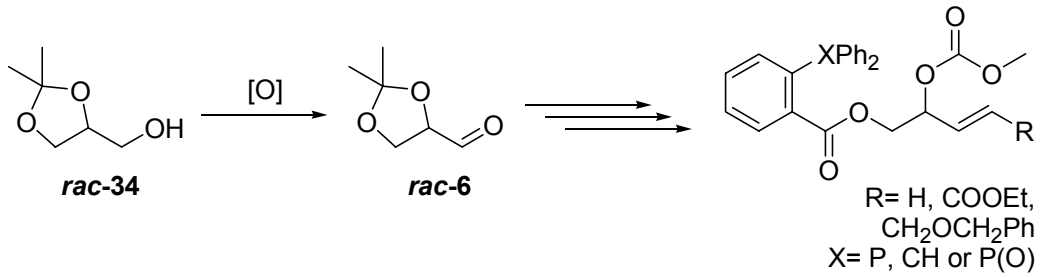


Scheme 61: Synthesis of the substrate **33** with R= Me.

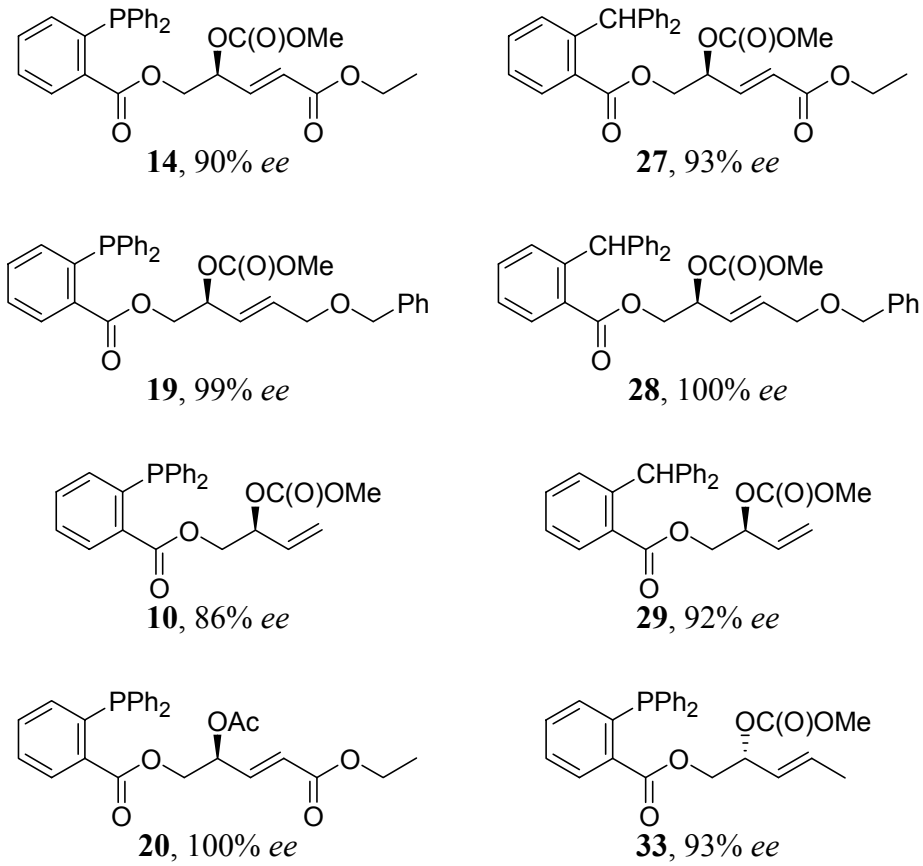
The racemic substrates were synthesized in analogous manner (Scheme 55, 57, 59 and 61). For the synthesis of the substrates ***rac*-14** and ***rac*-19** solketal (***rac*-34**) was used as a starting material (Scheme 62). Swern oxidation was carried out to obtain *rac*-2,3-*O*-isopropylidenglyceraldehyde (***rac*-6**), which then underwent Horner-Wadsworth-Emmons olefination with triethyl

phosphonoacetate and potassium carbonate as a base in a one-pot procedure in water as the solvent providing the ester ***rac*-11** with 78% overall yield.

For the synthesis of the "unsubstituted" allylic substrate ***rac*-10** commercially available *rac*-but-3-ene-1,2-diol (***rac*-8**) was used (Scheme 55). The racemic substrate ***rac*-33** with methyl group on allylic terminus was synthesized from *rac*-2-hydroxypent-3-enoic acid ethyl ester (***rac*-30**) (Scheme 61).



Scheme 62: Synthesis of racemic substrates.



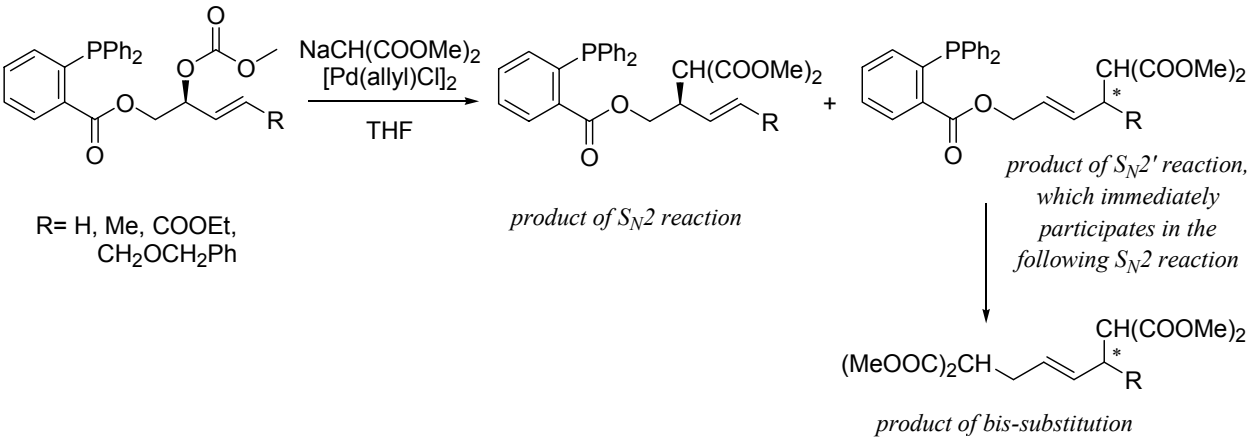
Scheme 63: Enantiopurity of the substrates.

The racemic substrates were used to elaborate methods of HPLC analysis. Enantiopurity of the chiral substrates for palladium catalyzed allylic substitution was determined by HPLC (enantiomeric excess of acetate **20** was measured for its oxide, **20-oxide**) is in the range of 90-100% *ee* (Scheme 63).

The racemic substrates were also used in palladium catalyzed allylic substitution reaction to obtain the racemic products (also for HPLC method elaboration).

4.2.2. Palladium catalyzed allylic substitution with carbon nucleophiles

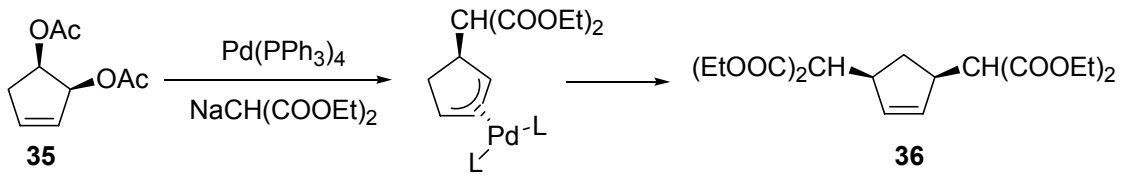
Palladium catalyzed allylic substitution proceeds via an η^3-allylpalladium complex which has two reactive centers. As a result two regioisomers may form: the S_N2 product when a nucleophile attacks at the same carbon atom at which the leaving group was attached and S_N2' when the opposite terminus of the allylic system is attacked (Scheme 64).



Scheme 64: Palladium catalyzed allylic substitution with sodium dimethylmalonate.

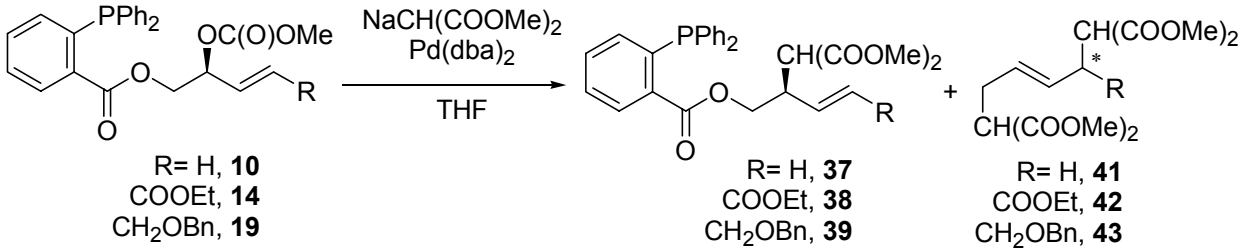
The product of S_N2'pathway has the *o*-DPPB group now in allylic position. This may allow a second allylic substitution to furnish the corresponding bis-substitution product (Scheme 64). It was always the product of the bis-substitution obtained as a result of S_N2' reaction.

Similarly, bis-substitution for palladium catalyzed allylic alkylation has been described in the literature for *syn*-3,4-diacetoxycyclopent-1-en (**35**). [82] The reaction with 2 equivalents of diethylmalonate results in the symmetrical product **36** (Scheme 65).



Scheme 65: Subsequent bis-substitution.

Different conditions and palladium precursors known for palladium catalyzed allylic substitution were tested in the reaction with the *o*-DPPB substrates **10**, **14** and **19**. Initially, $Pd(dba)_2$ was studied as palladium catalyst precursor for *o*-DPPB-directed allylic substitution (Scheme 66 and table 7).



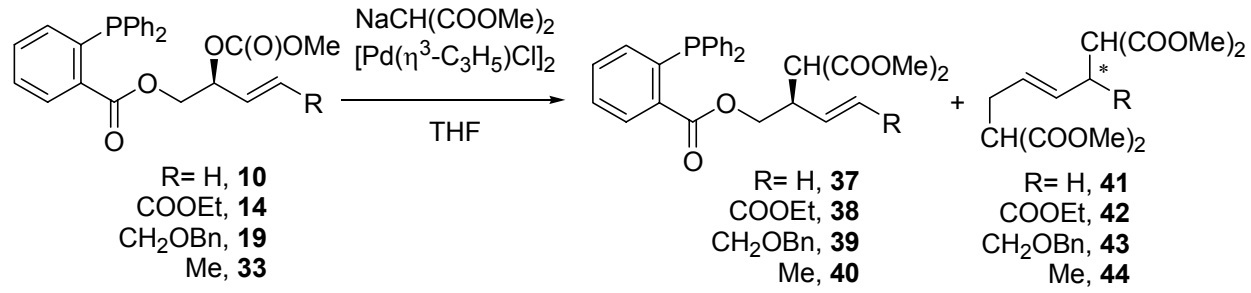
Scheme 66 and table 7: *o*-DPPB-directed allylic substitution with $Pd(dba)_2$.[a]

entry	R=	% yield [b] of S_N2 product	% *ee* (% *ct* [d]) of S_N2 product	% yield [b] of S_N2' product
1	COOEt	60	97 (100) [e]	n.d. [c]
2	CH_2OBn	53	81 (81) [e]	n.d. [c]
3	H	n.d. [c]	- [e]	12

a) allylic substrate (0.198 mmol), $Pd(dba)_2$ (5 mol.%), dimethylmalonate (1.6 eq), NaH (1.5 eq), THF (2 ml), stirring 19 h at room temperature; b) separated yield; c) not detected; d) determined by HPLC; e) *o*-DPPBA methyl ester as a side product (about 20 % in all the cases).

In all three cases (Table 7, entry 1-3) formation of ca 20% a side product was noted, which could be identified as the *o*-DPPBA methyl ester. This compound can be formed as a product of a transesterification reaction, when the carboxylic group of *o*-DPPB is attacked by methoxide, formed from methylcarbonate after carbon dioxide elimination.

Next $[Pd(\eta^3\text{-allyl})Cl]_2$ was checked as an alternative palladium source for the *o*-DPPB-directed allylic substitution, since *E*,*E*-dibenzylidene acetone (dba) as a ligand is known to slow down palladium catalyzed allylic substitution (see *Background*) and some other palladium catalyzed reactions as well (Scheme 67 and table 8).



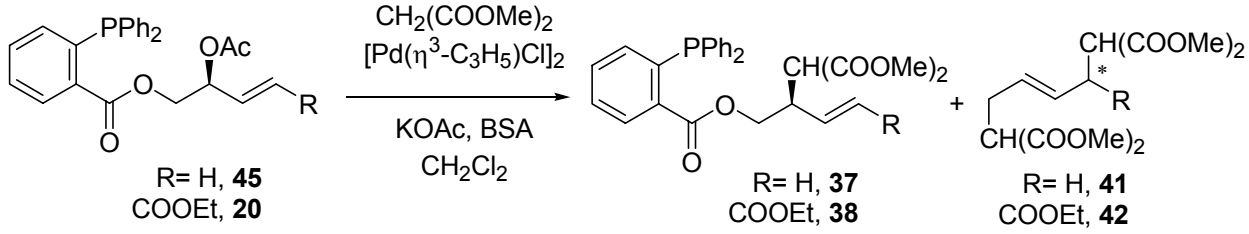
Scheme 67 and table 8: *o*-DPPB-directed allylic substitution with $[Pd(\eta^3\text{-allyl})Cl]_2$.[a]

entry	R=	% yield [b] of S_N2 product	% *ee* (% *ct* [d]) of S_N2 product	rs (S_N2:S_N2') [e]	% yield [b] of S_N2' product
1	COOEt	52	97 (100)	4:1	n.d.[c]
2	CH_2OBn	62	97 (98)	3.5:1	20
3	CH_3	33	93 (99.8)	1:1	46 (70 % ct [d])
4	H	n.d. [c]	-	0:100	16
5 [f]	COOEt	0	-	-	0

a) allylic substrate (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), dimethylmalonate (1.6 eq), NaH (1.5 eq), THF (2 ml), stirring 19 h at room temperature; b) separated yield; c) not detected; d) determined by HPLC; e) determined by NMR for crude mixture; f) reaction without a base – no conversion.

Application of $[Pd(\eta^3\text{-allyl})Cl]_2$ as a palladium precursor and NaH as a base led to excellent chirality transfers for the S_N2 products (Table 8, entries 1-3). Smaller substutuents on the other terminus of the allylic system led to larger amounts of the S_N2' products (Table 8, entries 3-4). In the case of the mono-substituted allylic system the S_N2 product was not observed at all. In all cases the directed palladium catalyzed allylic substitution required the presence of a base (Table 8, entry 5).

BSA-protocol is known to be frequently used for palladium catalyzed allylic substitution. In this method *N*,*O*-bis(trimethylsilyl)acetamide is used as a base. We applied these conditions (with dichloromethane as a solvent) to test selectivity of the *o*-DPPB-directed reaction as well (Scheme 68 and table 9).



Scheme 68 and table 9: *o*-DPPB-directed allylic substitution with $[Pd(\eta^3\text{-allyl})Cl]_2$, BSA-KOAc-dimethylmalonate protocol.[a]

entry	R=	% yield [b] of S_N2 product	% ee (% *ct* [d]) of S_N2 product	% yield [b] of S_N2' product
1	COOEt	54	99.7 (99.7)	14
2	H	n.d. [c]	-	54

a) allylic substrate (0.2 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), dimethylmalonate (3 eq), KOAc (c.a. 1 mg), BSA (3 eq), CH_2Cl_2 (1.5 ml), stirring 19 h at room temperature; b) separated yield; c) not detected; d) determined by HPLC.

All three methods used led to moderate yields of the S_N2 products, but excellent chirality transfer (up to 100% *ct*). Application of $Pd(dba)_2$ as a catalyst precursor provided considerably lower enantiopurity of the product **39** (R= CH_2OCH_2Ph, 81% *ct*; Table 7, entry 2) while allylic substitution with $[Pd(\eta^3\text{-allyl})Cl]_2$ as a catalyst resulted in very high enantioselectivity for the substrate (98% *ct*; Table 8, entry 2).

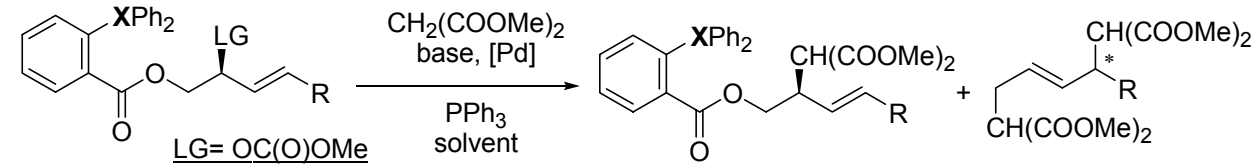
Different conditions used for directed palladium catalyzed allylic substitution (a source of palladium, a base) do not influence enantioselectivity of the reaction crucially. Nonetheless, application of $Pd(dba)_2$ as a catalyst precursor led to the side reaction of *o*-DPPBA methyl ester formation. This product was not found under other conditions.

Employing the BSA-protocol with acetate as a leaving group (Table 9) seems to result in no significant difference in regio- and stereoselectivity of the allylic substitution with dimethylmalonate as a nucleophile in comparison with the reaction when sodium hydride was used as a base and methylcarbonate as a leaving group (Table 8). What can be considered as a disadvantage of the BSA-protocol, that makes a scale-up of the reaction problematic, is that it demands the same weight of BSA and the allylic substrate while handling with low molecular weight sodium hydride is simpler. Moreover, sodium hydride is cheaper. Consequently the method with sodium dimethylmalonate (Table 8) was taken for the majority of the following reactions as being the most effective and practically convenient.

One more peculiarity of the reaction selectivity is connected with the size of substituent R at allylic terminus: the larger the substituent R was the more S_N2 product was formed. Unsubstituted allylic system (R= H) results in only S_N2' product (bis-substitution). The methyl substituted allylic system led to formation of both regioisomers in equimolar ammount (Table 8, entry 3).

It should be also noted that chirality transfer for the S_N2' product is lower than for the S_N2 product. This fact can be explained as follows: (1) the directing group stabilizes both positions of η^3-allyl-palladium complex (not symmetrical η^3-allyl-palladium complex allows nonetheless formation of the both products), (2) the second palladium species (very bulky species, as it is coordinated with *o*-DPPB group of another substrate molecule) may attack the less hindered S_N2'-position easier, than S_N2-position. It leads to one more possible net inversion and therefore partial loss of chirality transfer for overall S_N2' (bis-substitution) product.

To ensure the directing effect of *o*-DPPB group palladium catalyzed allylic substitution with the substrates bearing non-directing group (*o*-DPPB-oxide or 2-benzhydrylbenzoyl) was carried out (Scheme 69 and table 10). Different protocols were tested for the non-directed reaction.



LG= OC(O)OMe
R= COOEt, X= CH, **27**
R= COOEt, X= P(O), **14-oxide**
R= CH_2OBn, X= CH, **28**
R= H, X= CH, **29**
LG= OAc
R= COOEt, X= CH, **47**
R= H, X= CH, **46**

R= H, X= CH
R= COOEt, X= P(O), **38-oxide**
R= COOEt, X= CH, **48**
R= CH_2OBn, X= CH, **49**

R= H, **41**
COOEt, **42**
CH_2OBn, **43**

Scheme 69 and table 10: Non-directed allylic substitution.[a]

entry	substrate	[Pd]	base	% yield [b] (% *ct* [d]) of S_N2 product	% yield [b] (% *ct* [d]) of S_N2' product
1 [e]	**27**	$Pd(dba)_2$	NaH	n.d. [c]	n.d. [c]
2 [f]	**27**	$[Pd(\eta^3\text{-allyl})Cl]_2$	NaH	n.d. [c]	n.d. [c]
3 [g]	**47**	$[Pd(\eta^3\text{-allyl})Cl]_2$	BSA	n.d. [c]	n.d. [c]
4 [f]	**14-oxide**	$[Pd(\eta^3\text{-allyl})Cl]_2$	NaH	n.d. [c]	n.d. [c]
5 [f]	**28**	$[Pd(\eta^3\text{-allyl})Cl]_2$	NaH	39 (75)	48 (63)
6 [f]	**29**	$[Pd(\eta^3\text{-allyl})Cl]_2$	NaH	n.d. [c]	54
7 [e]	**46**	$Pd(dba)_2$	NaH	n.d. [c]	36
8 [g]	**46**	$[Pd(\eta^3\text{-allyl})Cl]_2$	BSA	n.d. [c]	84

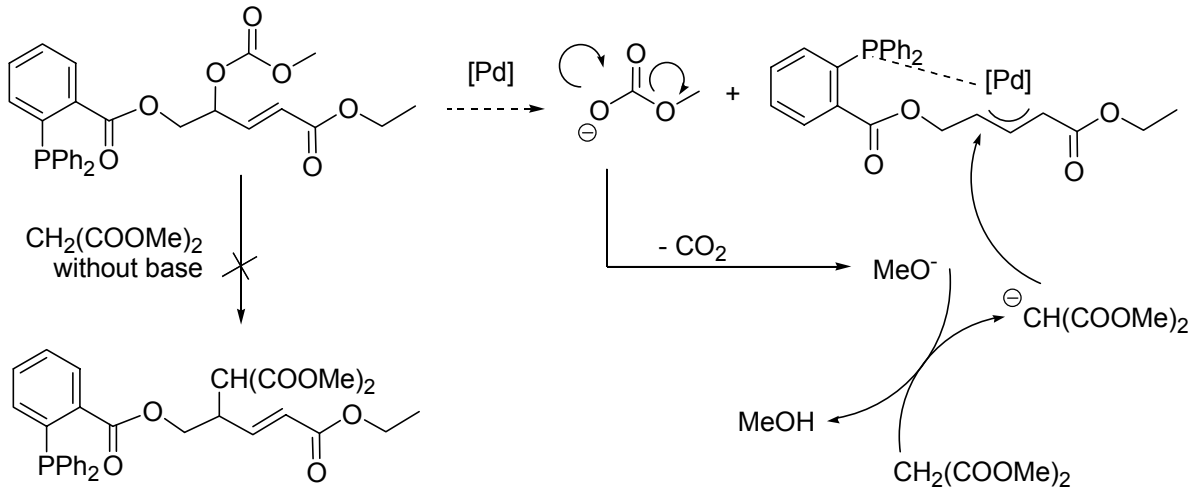
a) allylic substrate (0.198 mmol), [Pd] (5 mol.%), PPh_3 (5.2 mg, 0.02 mmol, 10 mol.%), dimethylmalonate, stirring 19 h at room temperature; b) separated yield; c) not detected; d) determined by HPLC; e) for conditions see table 7; f) for conditions see table 8; g) for conditions see table 9.

In the case of the substrates with ethyl ester functionality (R= COOEt, entries 1-4, table 10) none of the expected products (namely, **38-oxide** or **48** as an S_N2-product and **42** as an S_N2' product) were formed. A new labile compound was observed instead. According to NMR experiment it contains the non-directing group, but does not contain any double bond. It may be presumably a cyclization product. Although the structure of this compound was not evaluated because of its instability, it is interesting to underline, that *o*-DPPB group makes the directed palladium catalyzed allylic substitution faster than the side reaction. This side reaction happens to be the dominant process in the case of the non-directing substrates.

In the case of the non-directing substrate with R= CH_2OBn, a mixture of S_N2 and S_N2' products in the ratio 39:48 was obtained (entry 5, table 10).

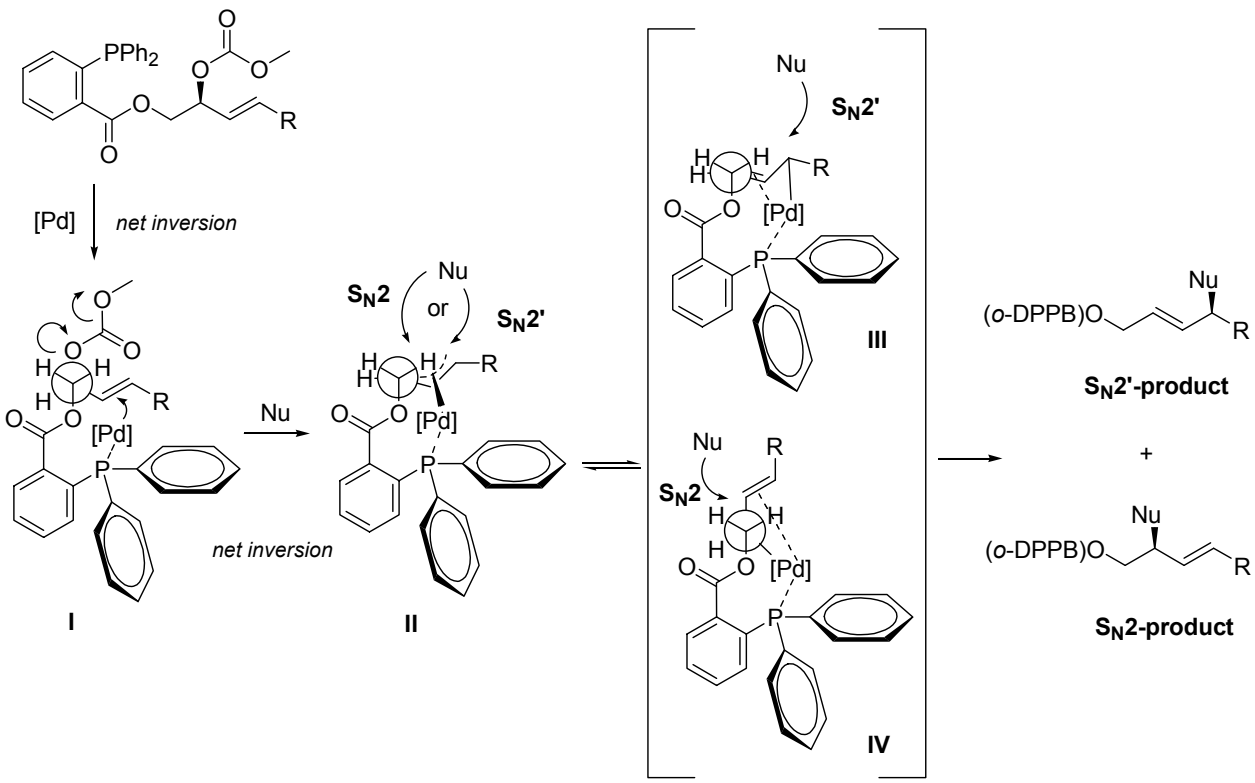
Unsubstituted allylic system bearing the non-directing group (R= H; Table 10, entries 6-8) only led to the S_N2' product (bis-substitution) as in the case of the reaction with the substrate bearing o-DPPB directing group (Table 7, entry 3; table 8, entry 4 and table 9 entry 2).

Although, it is known that methylcarbonate being a leaving group dissociates into carbon dioxide and a methoxide anion which can serve as an inner base in the system, the reaction does not proceed without extra base (Scheme 70 and table 8, entry 5). Only the starting material was separated.



Scheme 70: No reaction without extra base.

The participation of the directing group can be speculated as follows. The phosphorus atom of *o*-DPPB group being the strongest ligand in the system coordinates with palladium (Scheme 71).



Scheme 71: Regioselectivity of palladium catalyzed allylic substitution with *o*-DPPB directing group.

Then coordination of palladium with double bond happens providing η^2-allyl-palladium-phosphine complex (**I**). After carbonate eliminating η^3-allyl-palladium-phosphine complex **II** is formed (the first net inversion). This complex **II** can be either attacked by a nucleophile or equilibrated with the two σ-allyl-palladium-phosphine complexes **III** and **IV**. Nuchleophilic attack of complex **II** can proceed in two fashions: S_N2 and S_N2'.

The cyclic σ-allyl-palladium-phosphine complexe **IV** (S_N2-like) is more stable, than distorted complexes **III (**S_N2'-like**)**, because of smaller, less strained ring system formation. This supposition counts in favor of S_N2 product formation.

The σ-allyl complexes **III** and **IV** are, additionally, differently stabilized by electronic effect of the substituent R. Steric bulkiness of substituent R favors formation of the S_N2 product in both η^3-allyl-complex **II** and σ-allyl complexes **III** (Scheme 71).

The rigid construction with *o*-DPPB group should also prevent loss of stereoinformation which normally happens via attack of outer palladium species onto the formed allyl-palladium complexes.

4.2.3. Conclusion of palladium catalyzed allylic substitution with malonate

According to our expectations *o*-DPPB works as a directing group in palladium catalysed allylic substitution with dimethylmalonate as a nucleophile. The substances bearing a non-directing analogue of *o*-DPPB group lead to either lower regio- and enantioselectivity (R= CH_2OBn) or did not give any allylic substitution product at all (R= COOEt).

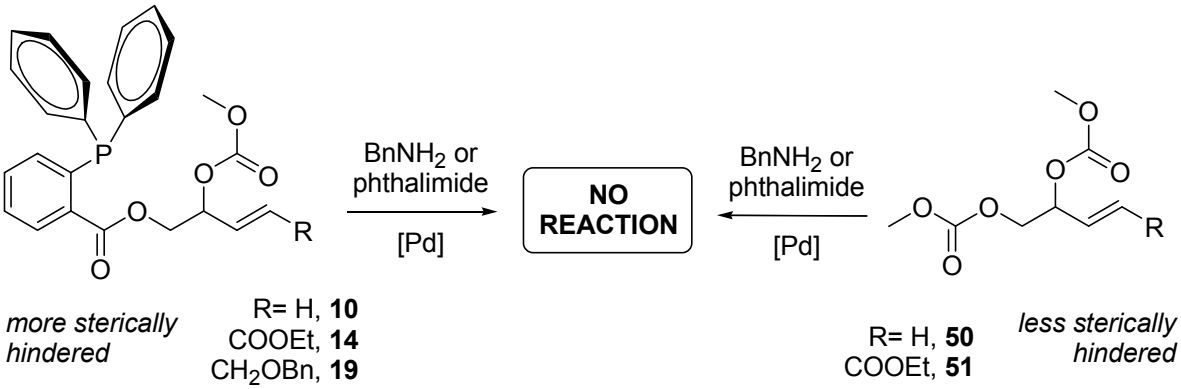
Unfortunately, the directing group does not function with unsubstituted double bond (R= H) and the steric factor preponderates the directing ability. In this case, always product of bis-substitution: S_N2' reaction followed by immediate S_N2-reaction with *o*-DPPB as a leaving group was observed.

Absolute configuration of the products could not be determined. We suppose overall retention of configuration as it typical for palladium catalyzed allylic substitution and as it was proved later for the compounds with a longer tether between the *o*-DPPB directing group and the allylic system.

4.2.4. Reactivity problem with nitrogen nucleophiles

To broaden the scope of the *o*-DPPB directed reaction, palladium catalyzed allylic substitution with nitrogen nucleophiles was attempted. Benzylamine and phthalimide are normally taken as typical nucleophiles for the reaction (see *Background*). These nucleophiles lead to formation of allylic amines which can be easily converted into chiral α-aminoacids (after oxidative double bond cleavage). [63]

Benzylamine and phthalimide were investigated as nucleophiles for directed palladium catalyzed allylic substitution with our substrates. Nonetheless no reaction was observed with the *o*-DPPB esters **10**, **14** and **19**, respectively (Scheme 72).



Scheme 72: Palladium catalyzed allylic substitution with nitrogen nucleophiles.

It is known from literature precedents that nitrogen nucleophiles are less reactive in some cases (see *Background*). But there are very few examples described when there was no way to overcome the reactivity problem.

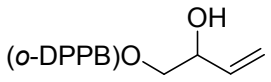
To understand better the origin of the problem and at the same time not to spend the complex substrate bearing *o*-DPPB group, bis-carbonates were used for the reaction. The bis-carbonates **50** (R= H) and **51** (R= COOEt) we prepared from the diols **8** and **12**, respectively (Scheme 72). The carbonate substituent has a similar electronic influence on the allylic system but is considerably less bulky. Reaction with the bis-carbonates (if one happened) would explain the lack of reactivity with sterical hindrance of the *o*-DPPB group.

Moreover, compound **51** is known to react with dimethylmalonate under palladium catalyzed conditions, although a complicated inseparable mixture of products was observed [83].

Unfortunately, the allylic substrates with both huge *o*-DPPB and smaller methylcarbonate moieties were found to be completely unreactive towards benzylamine and potassium salt of phthalimide as nucleophiles (Scheme 72).

The bis-carbonates were taken as a test system for palladium catalyzed allylic amination. Tuning of the conditions was carried out according to literature known precedent of reactivity improvement, namely:

- increasing of phthalimide solubility: application of phthalimide (as well as a combination of phthalimide and cesium carbonate as a base);
- addition of tertiary ammonium salt (TBAB) combined with sonication;
- application of various solvents (THF, CH_2Cl_2, DME, DMSO);
- protocol with BSA;
- application of various palladium sources: $[Pd(\eta^3\text{-allyl})Cl]_2$, $Pd(dba)_2$, $Pd(PPh_3)_4$, $Pd(OAc)_2$;
- other metals as catalysts: $Mo(CO)_6$, $[Ir(1,5\text{-}C_8H_{16})Cl]_2$;
- heating;
- microwave irradiation;
- other nucleophiles: $NaN(CHO)_2$ [84], BnNHNa [85], C_3H_5SH, Bn_2NH, allylamine;
- allylic alcohol bearing *o*-DPPB ***rac*-9** (Scheme 73) as a starting material [86] in different solvents (THF, ethyl acetate, water- ethyl acetate 1:1);
- addition of copper salts (known to facilitate rhodium-catalyzed allylic substitution of enolates [87] and alkoxydes [88]).



***rac*-9**

Scheme 73: Allylic alcohol bearing *o*-DPPB as a substrate for allylic substitution.

All variations gave either no conversion at all or decomposition of the starting material.

Application of azide nucleophiles (sodium azide, $TMSN_3$) as alternative nitrogen nucleophile can not be realized for the directed allylic substitution because of a potential Staudinger reaction with the phosphine directing group.

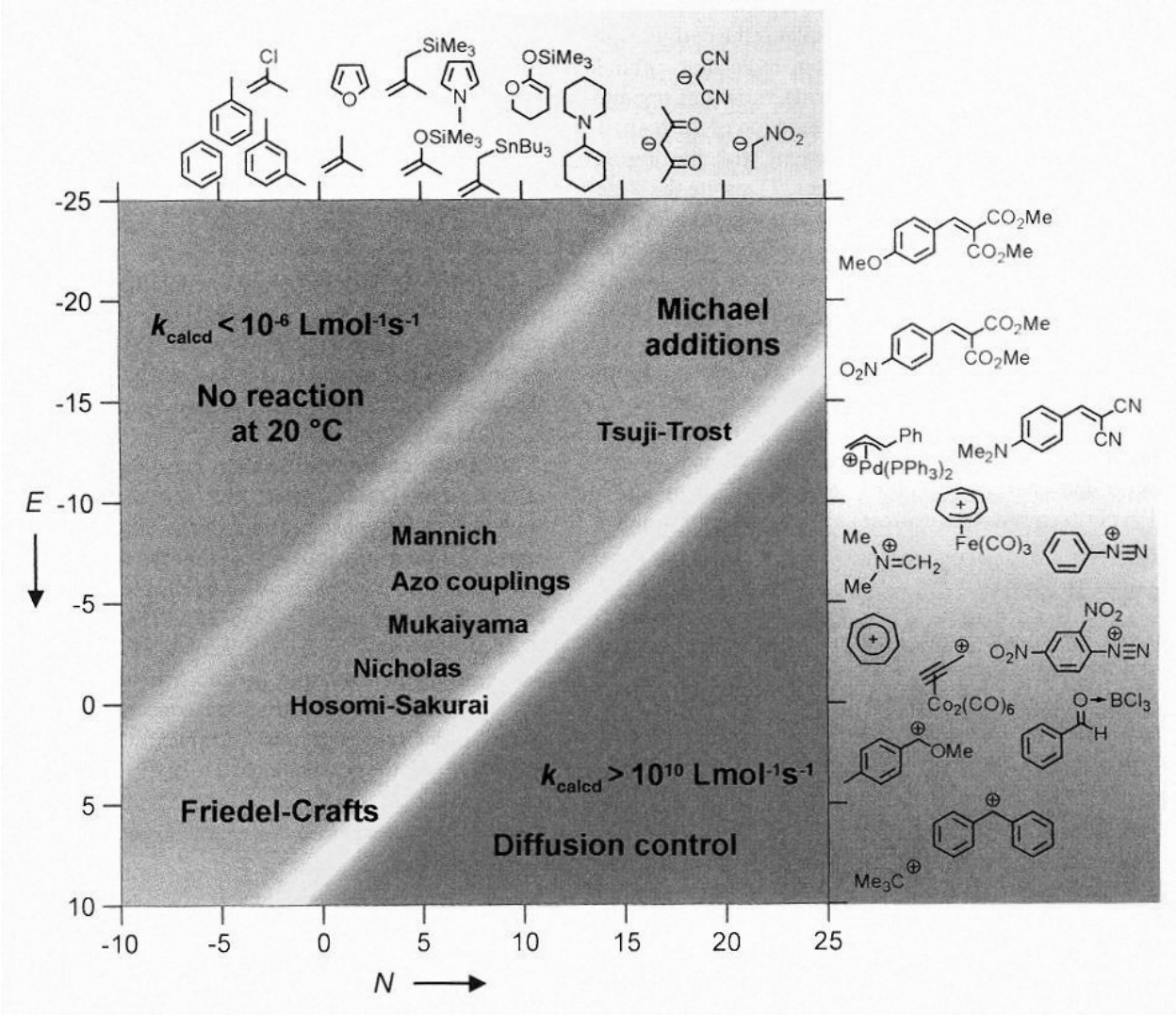
This fundamental lack of reactivity with nitrogen nucleophiles seems to have its origin in a non-matching situation regarding with ratio of electrophilicity and nucleophilicity of the reaction partners.

4.2.5. Possible explanation of lacking reactivity of the substrates and reaction with pyrrolidine

Electrophilicity and nucleophilicity parameters as activity measure are a topic of investigation in the Mayr's group from [89]. These parameters are evaluated from kinetics. The rate constant (k) is described by three parameters: nucleophilicity parameter (N), nucleophile specific slope parameter (s) and electrophilicity parameter (E):

$$\log k = s\,(N + E) \qquad (\mathbf{1}).$$

It is necessary to have N + E > –5 to observe a reaction at room temperature. [90]

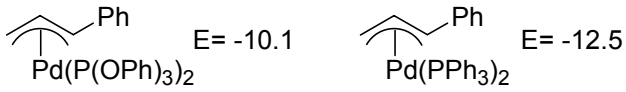


Scheme 74: Nucleophilicity and electrophilicity parameters in a comprehensive model of organic reactivity. [91]

Equation (**1**) allows to display the reactivity dependence on nucleophilicity and electrophilicity in a more clear graphical way (Scheme 74). [91] Nucleophilicity values on abscissa and

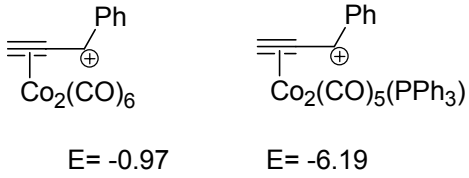
electophilicity values on ordinate compose the zone in the middle part of the diagram area responsible for different organic reactions.

E-values of metal complexes can be influenced by a ligand surrounding. Thus, a change of triphenylphosphine to stronger π-acceptor ligand triphenylphosphite in the allyl-palladium complexes results in 2.4 units of electrophilicity increase (Scheme 75). [92]



Scheme 75: Ligand influence onto E-values of allyl-palladium complexes.

An even strong ligand dependence on the E-value was observed for cobalt-alkyne complexes: triphenylphosphine instead of a carbonyl ligand decreases electrophilicity by nearly 5 units (Scheme 76).



Scheme 76: Ligand influence onto E-values of alkynyl-cobalt complexes

Unfortunately, this option of electrophilicity tuning is not applicable for the systems with the directing group: *o*-DPPB group is covalently bound to the substrate. Thus, it is only possible to change reactivity of the particular substrate with *o*-DPPB group in directed palladium catalyzed allylic substitution by appropriate choice of a nucleophile.

Table 11: pK_a and N-values for different nucleophiles

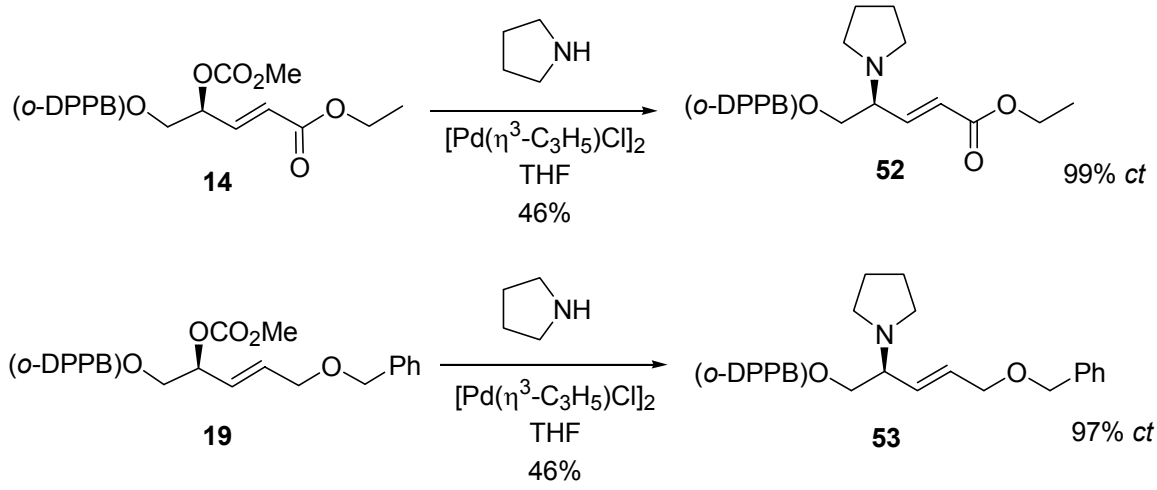
Nucleophile	**N (20°C)**	**pK_a (H_2O)**
phthalimide	- [a]	8.30
allylamine	13.21 [b]	9.69
$BnNH_2$	13.44 [b], 13.46 [c]	9.34
Bn_2NH ≈diallylamine	- [a]	9.34
piperidine	18.13 [b], 15.63 [c]	11.22
pyrrolidine	17.21 [b], 15.97 [c]	11.27
dimethylmalonate	18.24 [d]	13

a) not known from literature; b) in water; c) in methanol/acetonitrile 91/9; d) in methanol.

Nucleophilicity-values (hence, reaction rate) of common nitrogen nucleophiles [93] as well as pK_a values increase in the table top-down (Table 11).

Our experiments with several nitrogen nucleophiles (potassium phthalimide, allylamine, benzylamine, dibenzylamine) led to no conversion. The last chance to observe the *o*-DPPB-directed allylic substitution was to use one of the strongest nitrogen nucleophiles – that is pyrrolidine.

Pyrrolidine as a N-nucleophile participated in *o*-DPPB-directed palladium catalyzed allylic substitution with the substrates **14** and **19** to provide the products **52** and **53**, respectively, with moderate yield and excellent chirality transfer (Scheme 77). No S_N2' product was observed in the case.



Scheme 77: Palladium catalyzed directed allylic substitution with pyrrolidine.

There is a definite disadvantage of pyrrolidine as a nucleophile in comparison with, for example, phthalimide or benzylamine, that it can not be modified into primary amine to give rise to different chiral amines or chiral α-aminoacids.

Piperidine, which has a very similar N-value compared to pyrrolidine, did not react with the substrate **14** under palladium catalyzed conditions.

As mentioned above, N + E > –5 for a reaction to occur. It would mean that electrophilicity value of the allyl-palladium complex, formed from the substrate **14** and the bis-carbonates **50** and **51**, is about -20. This frontier value for allyl-palladium complexes participating in Tsuji-Trost reaction would provide the reaction with the most reactive soft nucleophiles, leaving aside the main batch of nitrogen nucleophiles.

Thus, pyrrolidine was the only nitrogen nucleophile reacted with the allylic carbonates bearing *o*-DPPB-directing group under palladium catalyzed conditions.

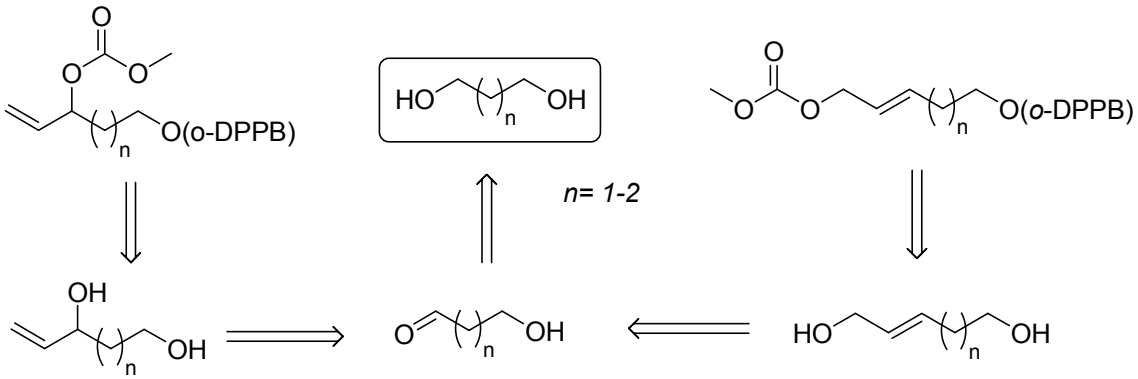
4.2.6. Conclusion

The series of allylic carbonates bearing *o*-DPPB-directing group was synthesized from D-mannitol. Palladium catalyzed allylic substitution with sodium dimethylmalonate proved high dependence on the substituent on the opposite terminus of the allylic system. The smaller substituents lead to greater extent of S_N2' reaction with carbonate (or acetate as a leaving group). The S_N2' product immediately undergoes the second S_N2 reaction with *o*-DPPB as a leaving group to give the bis-substitution product. The allylic substrates with bulkier substituents (with both electron-withdrawing and donating groups) led mainly to the S_N2 product with excellent chirality transfer but in moderate yield. Allylic substitution with the non-directing substrates led to poor selectivity or side reactions. This fact proves the effectiveness of *o*-DPPB as a directing group. Application of nitrogen nucleophiles despite excellent chirality transfer is limited to the reaction with pyrrolidine.

4.3. Substrates with allylic system separated from the directing group by 2 or 3 carbon atoms

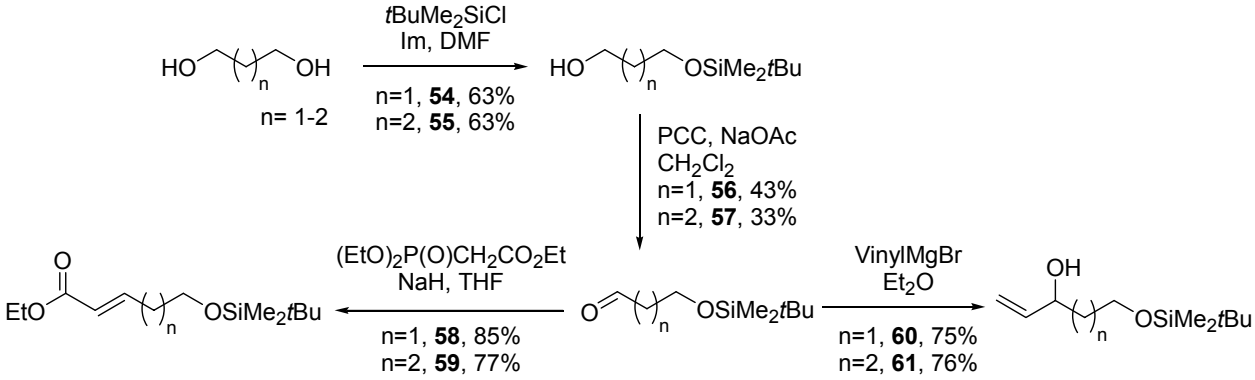
4.3.1. Synthesis of the substrates

In order to learn about the influence of the location of the directing *o*-DPPB group as well as to probe substrate scope a series of substrates was designed (Scheme 78). Thus, acyclic allylic carbonate systems were selected with different tether lengths between the potentially directing *o*-DPPB group and the allylic system. Both the linear and the branched allylic substrates can be synthesized from the respective diols: propan-1,3-diol for n = 1 and butan-1,4-diol for n = 2 (Scheme 78).



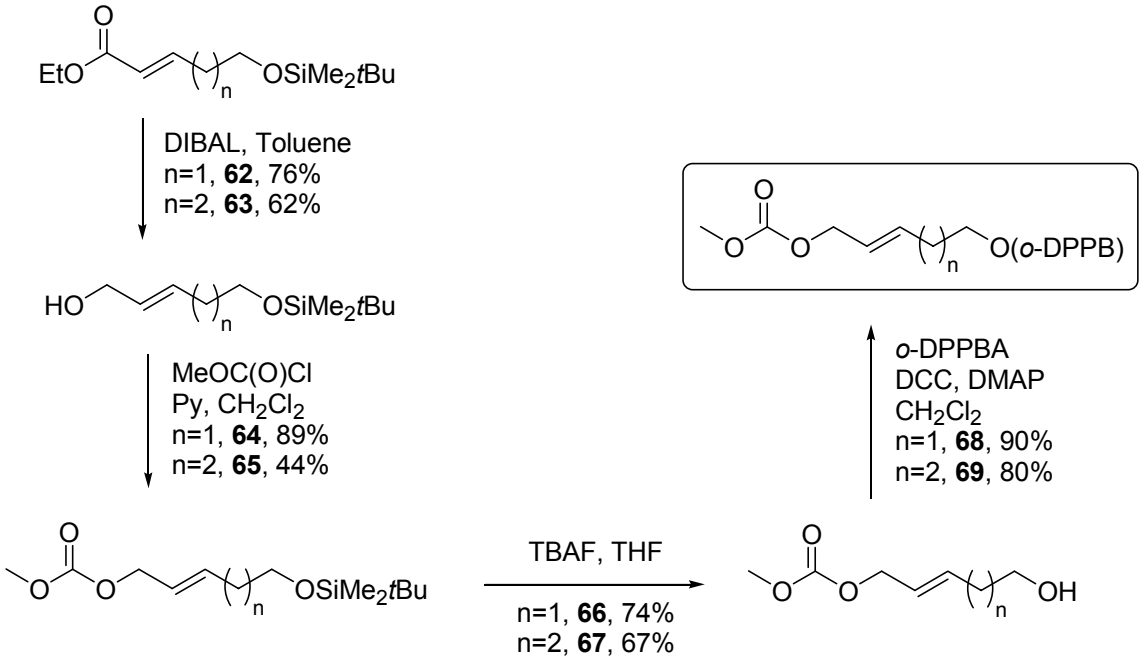
Scheme 78: Retrosynthetic analysis of the substrates with the allylic system separated from the directing group by 2 or 3 carbon atoms.

Propan-1,3-diol and butan-1,4-diol were first mono-protected with *tert*-butyldimethylsilyl group to give the alcohols **54** and **55**, which were oxidized with pyridinium chlorochromate providing aldehydes **56** and **57**, respectively (Scheme 79). These aldehydes gave rise to both the linear and the branched substrates. Horner-Wadsworth-Emmons reaction of the aldehydes **56** and **57** with triethyl phosphonoacetate led to acrylic esters **58** and **59**, respectively.



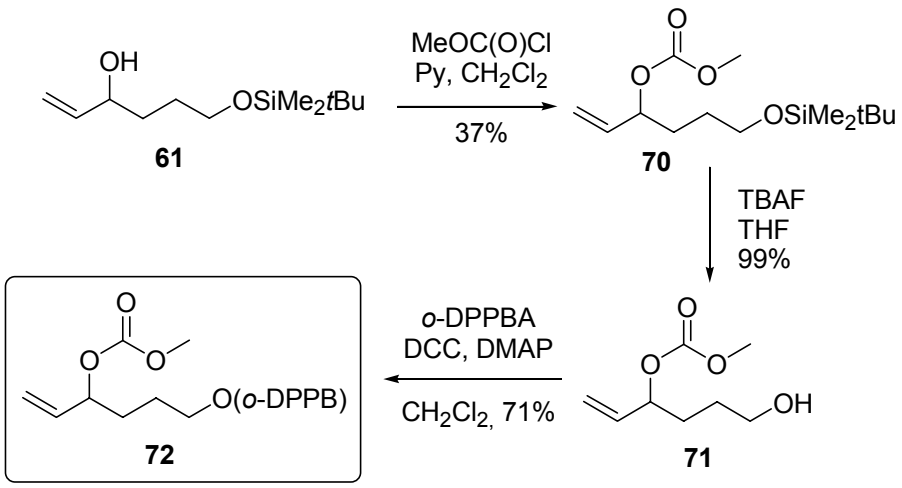
Scheme 79: Synthesis of the precursors for the linear and branched substrates.

Reaction of the aldehydes **56** and **57** with vinylmagnesiumbromide provided the allylic alcohols **60** and **61**, respectively. Reduction of the esters **58** and **59** with di-*iso*-butylaluminium hydride furnished the allylic alcohols **62** and **63** (Scheme 80). Subsequent reaction with methylchloroformate gave the allylic carbonates **64** and **65**, which were deprotected with tetra-*n*-butylammonium fluoride providing alcohols **66** and **67**, respectively. Esterification under Steglich conditions with *o*-DPPB led to the desired allylic substrates **68** and **69**.



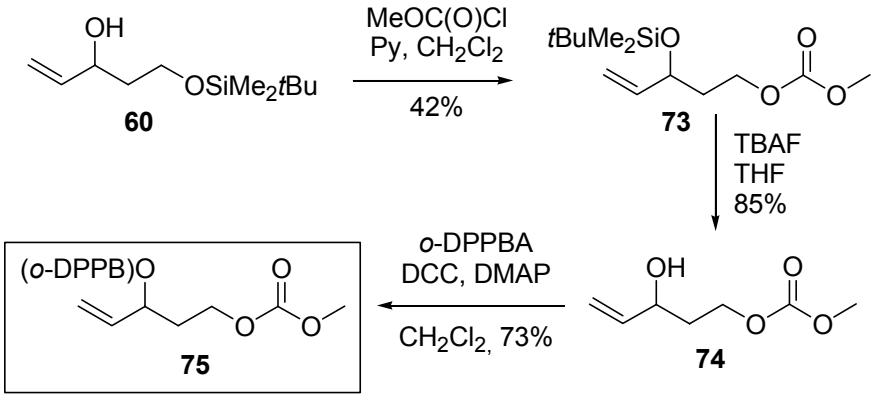
Scheme 80: Synthesis of the linear allylic substrates with the allylic system separated from the directing group by 2 or 3 carbon atoms.

In a similar manner, reaction of the allylic alcohol **61** with methyl-chloroformate, followed by *tert*-butyldimethylsilyl group deprotection and *o*-DPPB ester formation under Steglich conditions led to the desired allylic substrates **72** (Scheme 81).



Scheme 81: Synthesis of the branched allylic substrate with the allylic system separated from the directing group by 3 carbon atoms.

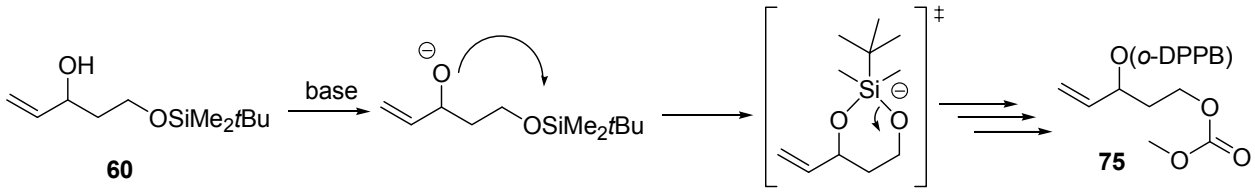
Interestingly, the same reaction sequence carried out with the "shorter" allylic alcohol **60** resulted in the regioisomeric compound **75**. The *o*-DPPB group in the product is bound to the secondary allylic alcohol, and methylcarbonate was attached to the primary OH-group (Scheme 82).



Scheme 82: Synthesis which led to the regioisomer of the desired branched allylic substrate with the allylic system separated from the directing group by 2 carbon atoms.

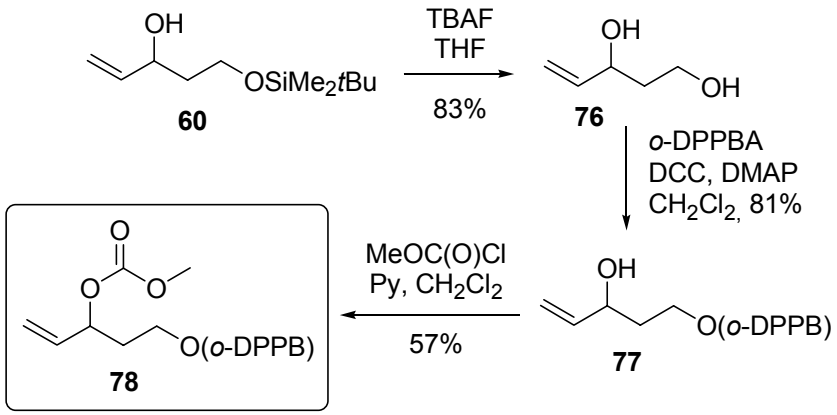
This trans-silylation could happen via a transposition of the *tert*-butyldimethylsilyl protecting group from the primary to the secondary alcohol in the presence of a base (Scheme 83). After

deprotonation the secondary alkoxide anion attacks silicon atom to form a 6-membered cyclic intermediate. This intermediate can either give the primary alcohol under protic conditions or react with methylchloroformate to give the primary carbonate. Such rearrangements have precedents in the literature. [94]



Scheme 83: Machanism of *tert*-butyldimethylsilyl group migration.

Finally, the desired product **78** could be obtained starting from the allylic alcohol **60** which was first deprotected with tetra-*n*-butylammonium fluoride to give the diol **76** (Scheme 84).



Scheme 84: Synthesis of the branched allylic substrate with the allylic system separated from the directing group by 2 carbon atoms.

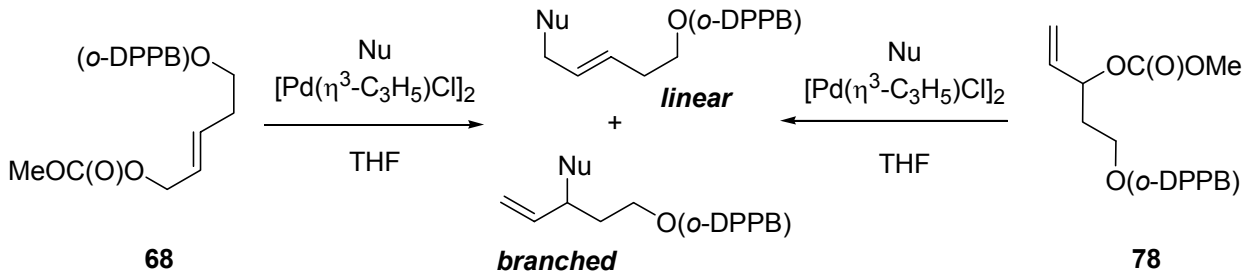
Selective esterification of the primary OH-group of the diol **76** with *o*-DPPBA under Steglich conditions led to ester **60**. Reaction of ester **60** with methylchloroformate provided the desired allylic substrate **78**.

4.3.2. Palladium catalyzed allylic substitution

Palladium catalyzed allylic substitution was carried out in THF with $[Pd(\eta^3\text{-allyl})Cl]_2$ as the catalyst precursor and sodium dimethylmalonate, benzylamine or potassium phthalimide as a

nucleophile. The nucleophile was used in quantities ranging from 1.2 equivalents for potassium phthalimide to 3 equivalents for benzylamine.

First, palladium catalyzed allylic substitution was carried out with o-DPPB esters **68** and **78**, respectively. In these compounds the directing group is separated from the allylic system by two carbon atoms (Scheme 85 and table 12).



Scheme 85 and table 12: Palladium catalyzed allylic substitution with substrates where the allylic system separated from the directing group by 2 carbon atoms. [a]

Substrate		Nucleophile		
		$NaCH(COOMe)_2$	$BnNH_2$	K^+phthalimide$^-$
68	Yield (%) [b]	61	46	62
	linear:branched ratio [c]	only linear	8 : 1	2.3 : 1
78	Yield (%) [b]	88	39	75
	linear:branched ratio [c]	1.2 : 1	9 : 1	1 : 1

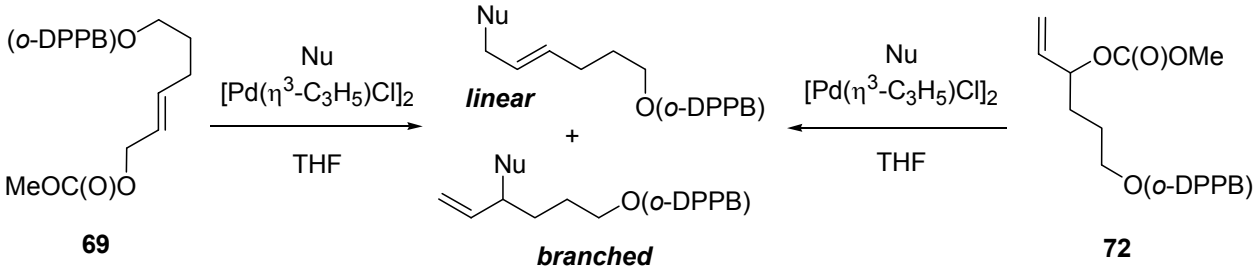
a) allylic substrate (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), nucleophile (1.2-3 eq), THF (2 ml), stirring 19 h at room temperature; b) separated yield; c) determined by NMR for crude mixture.

As it was supposed, these substrates were reactive towards benzylamine and potassium phthalimide. The yields ranged from moderate to good. In all cases a preference for the linear product was observed. This is in accord with the general observation that in palladium catalyzed allylic alkylation the sterically less hindered regioisomer is formed preferably. Obviously, the presence of a potentially directing group would not overcome this intrinsic regioselectivity.

One could notice a memory effect (conservation of higher linear/branched ratio for linear substrates and lower for branched) in the case of the more reactive malonate nucleophiles. Less reactive nitrogen nucleophiles demonstrate no memory effect. It seems that the allyl-palladium complex equilibrates to a more stable and less sterically hindered complex before a nitrogen nucleophile attacks.

Memory effect is known from literature to retain both stereo- and regio-information of the starting material. The effect is known to be highly dependent on a solvent and a ligands in use. [95]

The next palladium catalyzed allylic substitution was carried out with the substrates **69** and **72**. In this case the directing group is separated from the allylic system by three carbon atoms (Scheme 86 and table 13).



Scheme 86 and table 13: Palladium catalyzed allylic substitution with substrates where the allylic system separated from the directing group by 3 carbon atoms. [a]

Substrate		Nucleophile		
		$NaCH(COOMe)_2$	$BnNH_2$	K^+phthalimide$^-$
69	Yield (%) [b]	55	47 [d]	21 [d]
	linear:branched ratio [c]	13 : 1	6 : 1	1 : 2
72	Yield (%) [b]	47	52	62
	linear:branched ratio [c]	only linear	only linear	1.5 : 1

a) allylic substrate (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), nucleophile (1.2-3 eq), THF (2 ml), stirring 19 h at room temperature; b) separated yield; c) determined by NMR for crude mixture; d) heating at 60 °C.

The substrates **69** and **72** are reactive with all the nucleophiles in use (sodium dimethylmalonate, benzylamine and potassium phthalimide). In this case even less directing effect than for the substrates synthesized from propan-1,3-diol was observed.

4.3.3. Conclusion

The substrates where the directing group is withdrawn from the allylic system by two or three carbon atoms were synthesized starting from propan-1,3-diol and butan-1,4-diol, respectively. All the substrates are reactive with both carbon and nitrogen nucleophiles: sodium dimethyl-

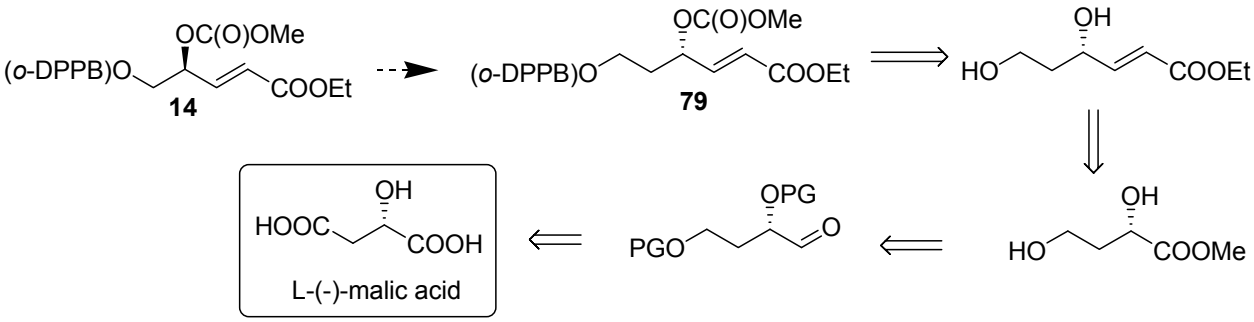
malonate, benzylamine and potassium phthalimide. Regioselectivity is highly linear because of affinity of nucleophiles in the palladium catalyzed reaction to attack the less hindered terminus. The presence of the potentially directing *o*-DPPB group could not overcome this intrinsic regioselectivity.

The memory effect observed for the reaction with malonate as a nucleophile can be explained with the difference in reaction rates for malonate and nitrogen nucleophiles. Malonate reacting faster provides less time for allyl-palladium complex equilibration and leads to a greater amount of the substrate-like product. While nitrogen nucleophiles reacting slower allow formation of a more stable allyl-palladium complex resulting preferably in the linear product.

4.4. System based on malic acid

4.4.1. Synthesis of the substrates

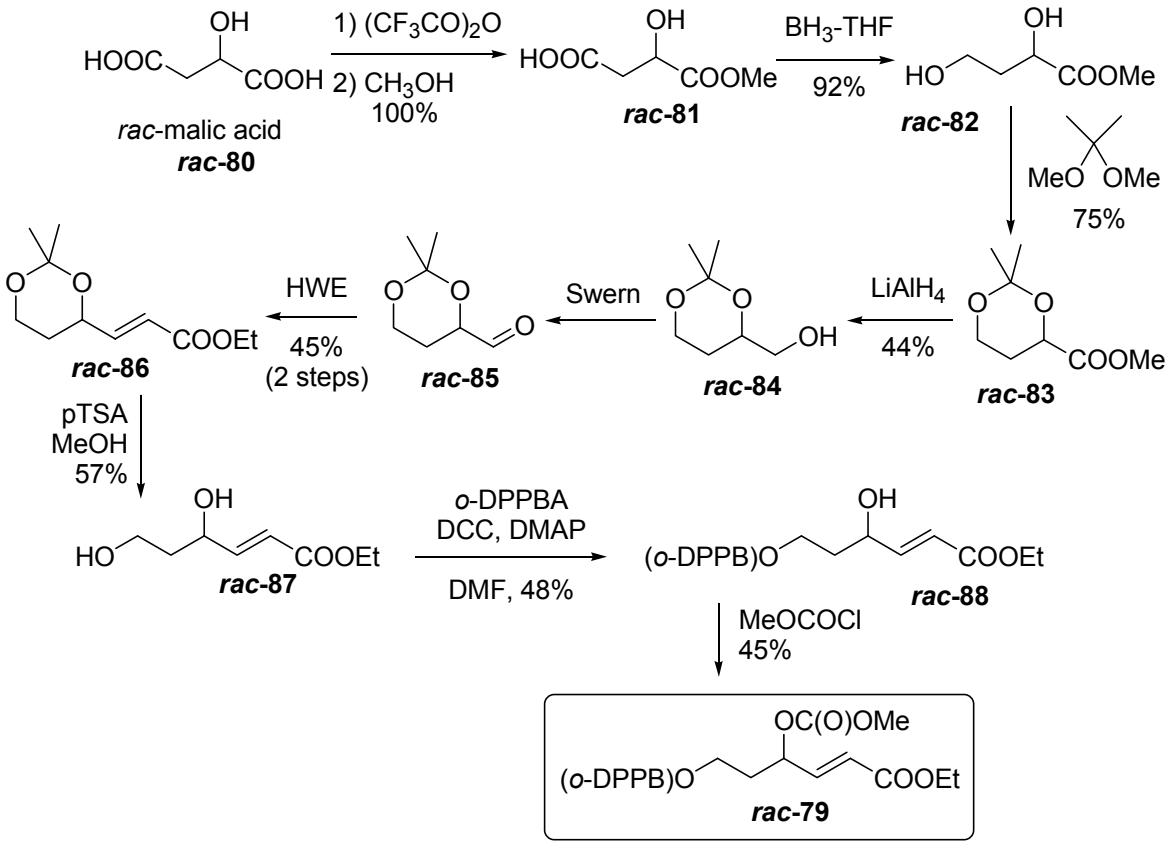
The higher reactivity observed for the substrates in which the directing group is withdrawn from the allylic system by two or three carbon atoms inspired us to synthesize a chiral allylic substrate with both allylic termini substituted. Taking the allylic substrate **14** as an example, a new compound **79** was designed with the hope that it would maintain high stereoselectivity observed for the substrate **14** and high reactivity observed for the substrates with the distinct directing group, described in the previous chapters (Scheme 87). Retrosynthetic analysis of compound **79** identified L-(-)-malic acid as an ideal starting material.



Scheme 87: Retrosynthetic analysis of the substrates for the directed allylic substitution.

Racemic malic acid (***rac*-80**) after the reaction with trifluoroacetic anhydride and methanolic work-up provided mono-ester ***rac*-81** (Scheme 88). Then the free carboxylic group of the mono-ester ***rac*-81** was selectively reduced with borane to give the diol ***rac*-82**. The following sequence was realized in analogy to the synthesis of the substrate **14** (Scheme 55). Protection of the diol

***rac*-82** as the acetonide led to the ester ***rac*-83** which was subsequently reduced to furnish alcohol ***rac*-84**. The following one-pot procedure including Swern oxidation which provided the aldehyde ***rac*-85** and Horner-Wadsworth-Emmons reaction with triethyl phosphonoacetate and potassium carbonate as a base in aqueous media gave the ester ***rac*-86**. Deprotection of acetonide group results in the diol ***rac*-87**, which after mono-esterification of the primary alcohol with *o*-DPPBA under Steglich conditions provided allylic alcohol ***rac*-88**. Opposite to the other Steglich esterifications described above which were carried out in dichloromethane as a solvent, dimethylformamide was used as a solvent in this case to diminish the formation of the undesired di-ester. In dichloromethane exclusively the bis-*o*-DPPB ester was formed. Finally, the compound ***rac*-88** was transferred upon reaction with methylchloroformate into the desired allylic substrate ***rac*-79** (Scheme 88).

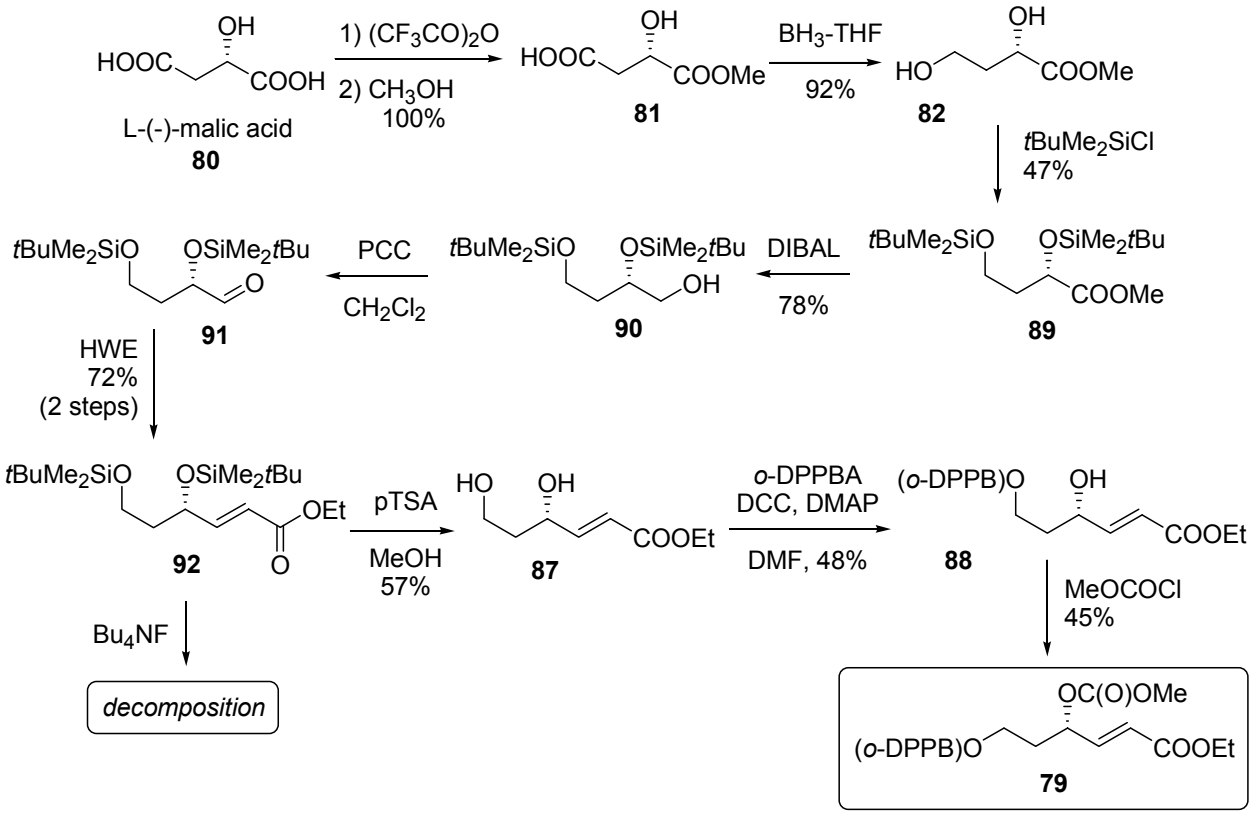


Scheme 88 Synthesis of the racemic allylic substrate.

The attempt to use the same protocol to synthesize the chiral allylic substrate led to complete epimerization. It could happen during Swern oxidation in the presence of one of the bases (triethylamine and potassium carbonate) participating in a one-pot procedure of Swern oxidation-Horner-Wadsworth-Emmons olefination in water as a solvent at room temperature. Interestingly, the same method, used for the synthesis of the allylic substrate **14** (with a shorter linker) did not

cause any considerable loss of stereoinformation; enantiopurity of the substrates is in the range 90-100% *ee* (Scheme 63).

A new synthetic route was suggested. To avoid an appearance of the aldehyde under basic conditions and therefore to avoid epimerization, oxidation with pyridinium chlorochromate was carried out. This acidic oxidant is not compatible with acetonide protecting group. Thus, a *tert*-butyldimethylsilyl-protecting group was chosen instead. Horner-Wadsworth-Emmons olefination was carried out with triethyl phosphonoacetate and sodium hydride as a base in tetrahydrofurane at -78 °C (Scheme 89).



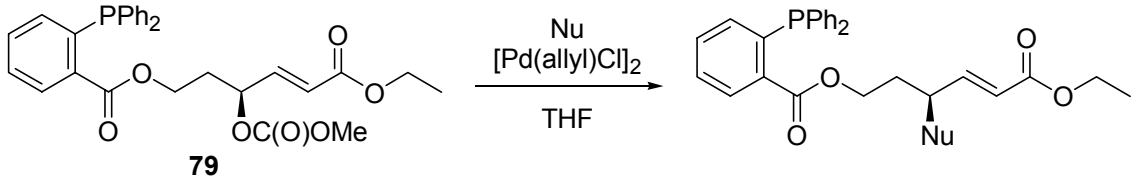
Scheme 89: Synthesis of the chiral allylic substrate.

All further steps of the synthesis toward the chiral allylic substrate **79** were carried out according to the synthesis of the racemic substrate ***rac*-79**. Enantiopure product (100% *ee*) was obtained according to this approach.

4.4.2. Palladium catalyzed allylic substitution

The substrate **79** was applied for palladium catalyzed allylic substitution with $[Pd(\eta^3\text{-allyl})Cl]_2$ as a catalyst precursor and sodium dimethylmalonate, benzylamine, dibenzylamine or potassium phthalimide as a nucleophile. Nucleophiles were used in the quantities in the range from

1.2 equivalents for potassium phthalimide up to 3 equivalents for benzylamine and dibenzylamine (Scheme 90).



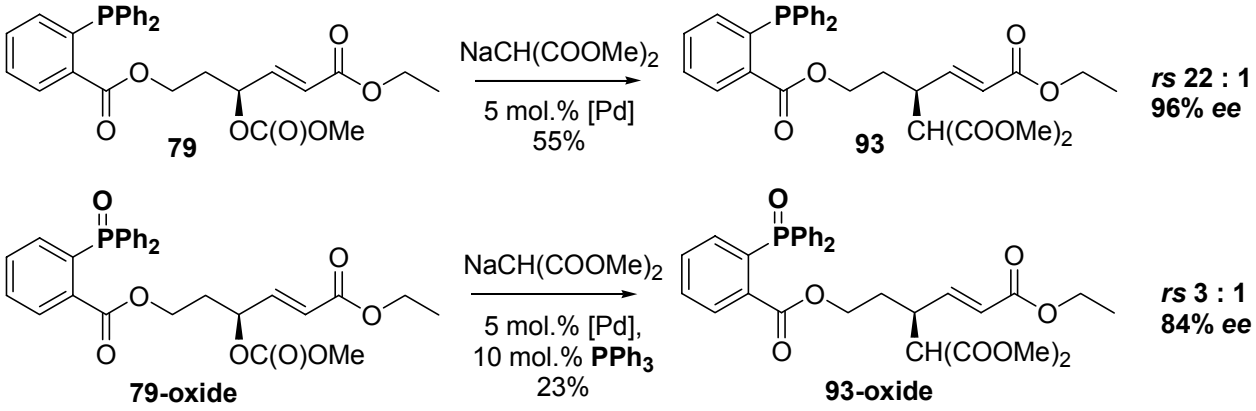
Scheme 90 and table 14: *o*-DPPB-directed allylic substitution with $[Pd(\eta^3\text{-allyl})Cl]_2$.[a]

Nu	yield (%) [b]	*rs* (S_N2:S_N2') [c]	*ct* % [d]
$NaCH(COOMe)_2$	55	>22:1	96
$BnNH_2$	58	100:0	91
Bn_2NH	73	100:0	95
K^+phthalimide$^-$	81	100:0	88

a) allylic substrate **79** (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%), nucleophile (1.2-3 eq), THF (2 ml), stirring 19 h at room temperature; b) separated yield; c) determined by NMR for crude mixture; d) determined by HPLC (in this case % *ct* = % *ee* as the substrate was enantiopure).

The allylic substrate **79** is reactive against both carbon and nitrogen nucleophiles. The yields are still moderate, but higher, than in the case of the substrate **14**, synthesized from D-mannitol. The reaction provided excellent regio- and stereoselectivity (Table 14).

To clarify the influence of the directing group, comparative allylic substitution with the oxidized *o*-DPPB group was carried out (Scheme 91).

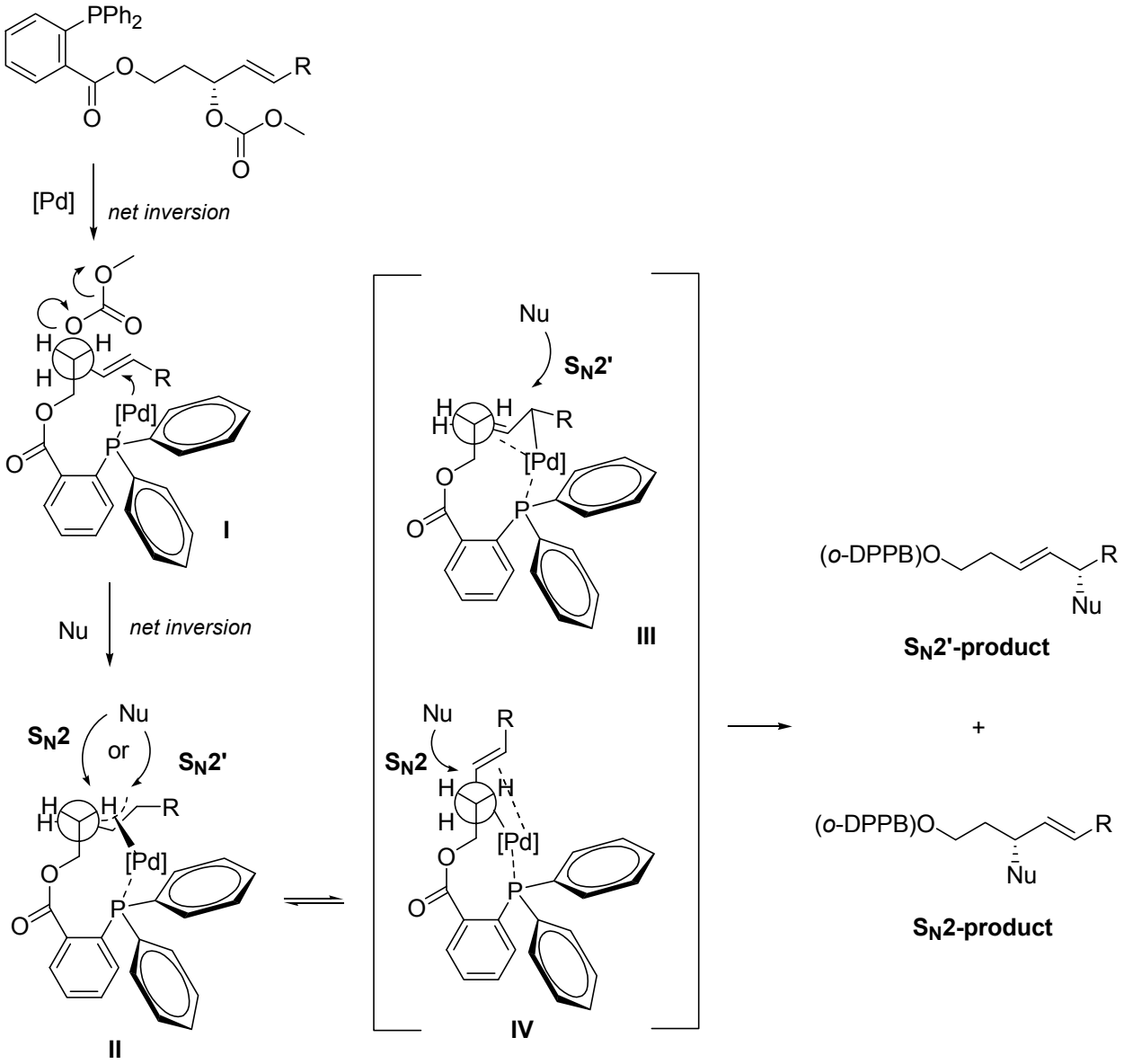


Scheme 91: Comparison of allylic substitution with directing *o*-DPPB and non-directing *o*-DPPB-oxide group.

Palladium catalyzed allylic substitution with the non-directing group led to considerably reduced regio- and stereoselectivity. Regioselectivity dropped from the ratio of 22:1 to 3:1, and stereoselectivity dropped from 96% *ee* to 84% *ee*.

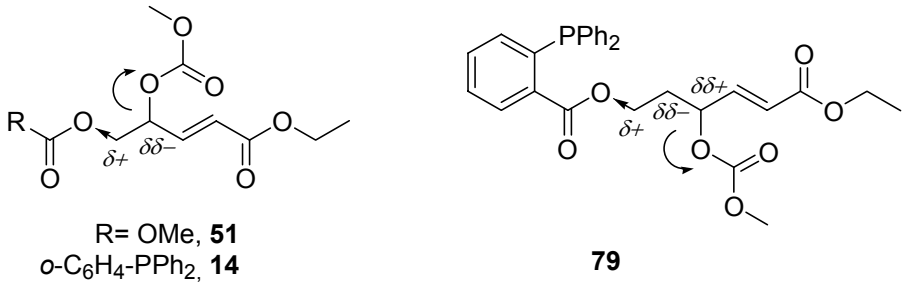
Schematically regio- and stereoselectivity of the reaction can be explained similarly to the reaction with the substrate **14** described above. Coordination of palladium species to phosphorus atom of *o*-DPPB group first happens, then η^2-allyl-palladium complex **I** is produced which rearranges into η^3-allyl-palladium complex **II** after the leaving group cleavage (Scheme 92). This complex can equilibrate with both the S_N2-like complex **III** and the S_N2'-like complex **IV.**

The cyclic σ-allyl-palladium-phosphine complex **IV** is presumably more stable, than distorted complexes **III**, because of smaller, less strained ring system formation. This supposition counts in favor of S_N2 product formation.



Scheme 92: Regioselectivity of palladium catalyzed allylic substitution with *o*-DPPB directing group.

It is interesting to compare the two types of allylic substrates discussed above (Scheme 93). The only difference is in the length of the tether binding the leaving group and the directing group: shorter in the substrate **14** and longer in the substrate **79**. The substituent at the other terminus of the allylic system is the same for the both substrates (R= COOEt). Nonetheless, the former substrate **14** (as well as bis-carbonate **51**) does not react with less nucleophilic nitrogen nucleophiles, while the latter does react with nitrogen nucleophiles. The difference in reactivity could only be explained with the –I-effect of carboxylic group of *o*-DPPB. It is known that electronegative groups result in charge alternation along a carbon chain rather than steady charge decay. [96] Thus, a partial negative charge on the "S_N2" carbon atom (and therefore the whole allylic system) in the case of the substrate **14** make the compound less electrophilic, that prevents the reaction with nitrogen nucleophiles. The substrate **79** bearing a partial positive charge appears to be more reactive.

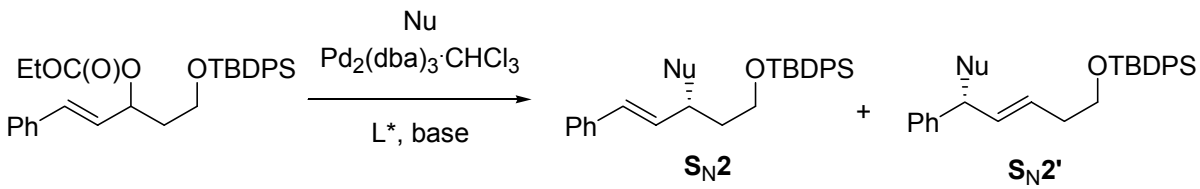


Scheme 93: Comparison of the two allylic systems.

If to come back to the explanation of reactions in terms of interaction between an electrophile and a nucleophile, given by Mayr, application of the substrates with different tethers between the leaving group and the directing group allowed tuning electrophilicity parameter of the substrates while the other possibility, which is a change of phosphine ligand, was excluded because of the system with fixed *o*-DPPB as a directing group.

Despite this electronic peculiarity and therefore arising reactivity difference, the both compounds (when reacted) **14** and **79** provide equally high stereoselectivity.

A compound with similar structure has been published by Hoberg in palladium catalyzed allylic substitution. The selectivity issue was worked out with a help of chiral ligands (Scheme 94 and table 15). [97]



Scheme 94 and table 15: Analogous system known from literature. [97]

entry	Nu	Ligand	Base	Yield, %	Ratio $S_N2/S_N2´$	*ee*, %
1	$CH_2(COOMe)_2$	*S*-BINAP	NaH	88	1.5:1	nd [a]
2	$CH_2(COOMe)_2$	*S*-BINAP	Cs_2CO_3	93	2.2:1	nd [a]
3	phenol	*S*-BINAP	Cs_2CO_3	94	>99:1	92
4	aniline	*S*-BINAP	Cs_2CO_3	52	>1:99	98

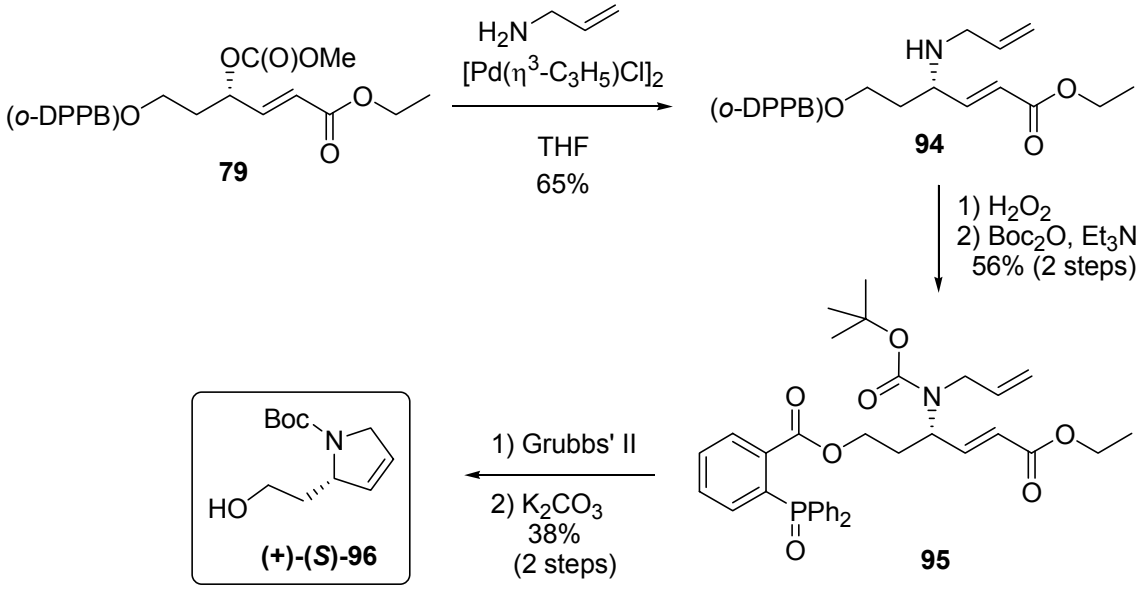
[a] not detected.

Interestingly, in this reaction regioselectivity is highly S_N2 in the case of phenol and highly $S_N2´$ in the case of aniline as nucleophiles and very low in the case of dimethylmalonate. Enantioselectivity problem was solved applying chiral ligands while regioselectivity was substrate controlled. Our approach for similar molecules is advantageous as it allows to solve both selectivity problems with a help of a catalyst directing group.

4.4.3 Determination of absolute configuration. Formal total synthesis of enantiomeric *cis*-hexahydropyrrolo[3,2-*b*]pyrrol-3-ones

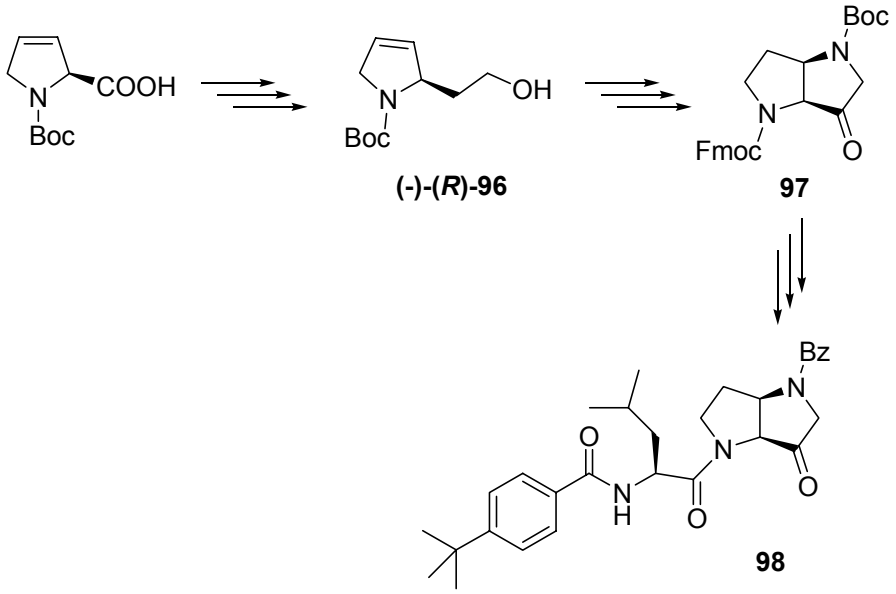
Palladium catalyzed allylic substitution is known to proceed with double inversion of configuration, that leads to overall retention of configuration. To clarify the role of the directing group on the stereochemical course of the palladium catalyzed allylic substitution, the absolute configuration of the directed allylic substitution product had to be determined. For the purpose we decided to do an allylic substitution with allylamine, and to transform the substitution product to the known dihydropyrrole **96**.

First palladium catalyzed allylic substitution of the substrate **79** was performed with allylamine as a nucleophile to furnish product **94** (Scheme 95). Then *o*-DPPB group was oxidized with hydrogen peroxide to give the phosphine-oxide (to avoid possible problems with the extra ligand at the following metathesis step) and amino group was protected with Boc-protecting group in a reaction with di-*tert*-butyl dicarbonate providing the compound **95**.



Scheme 95: Evaluation of the directed allylic substitution stereo-outcome.

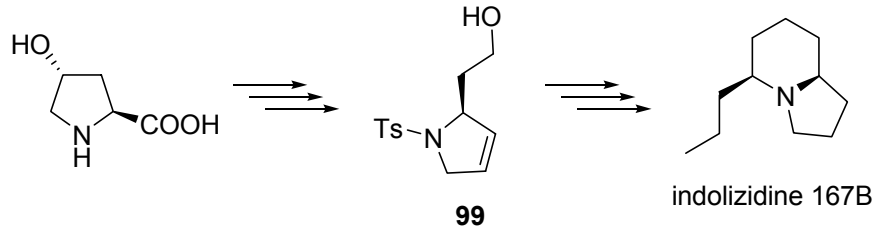
A ring closing metathesis reaction employing the Grubbs' II catalyst was carried out with compound **95** followed by saponification of *o*-DPPB ester with potassium carbonate leading to furnish the desired dihydropyrrol **96** (Scheme 95). Determination of optical rotary power of the compound **96** proved obtaining of the *dextro* stereoisomer. Its optical antipode, the *leva* isomer **(–)-(*R*)-96**, has been published as an intermediate in the synthesis of functionalized *cis*-hexahydropyrrolo[3,2-*b*]pyrrol-3-ones (**97**) which represents an interesting scaffold in total synthesis (Scheme 96). The published modification of pyrrolone **97** leads to product **98**, which is a potent and selective inhibitor of human cathepsin K with osteoporosis as the main therapeutic indication. [98]



Scheme 96: Synthesis of functionalized *cis*-hexahydropyrrolo[3,2-*b*]pyrrol-3-ones.

Thus, our approach represents a formal total synthesis towards a number of enantiomers of bioactive *cis*-hexahydropyrrolo[3,2-*b*]pyrrol-3-ones.

The analog (substance **99)** of the compound **96** with tosyl protecting group on nitrogen atom instead of Boc-group has been reported in a total synthesis of indolizidine 167B (Scheme 97).

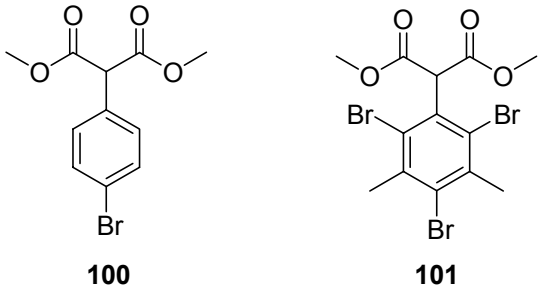


Scheme 97: Synthesis of indolizidine 167B.

This alkaloid, indolizidine 167B, has been detected as a minor trace component in *dendrobatidae* frogs found in a single population. [99]

4.4.4. Bulky malonates

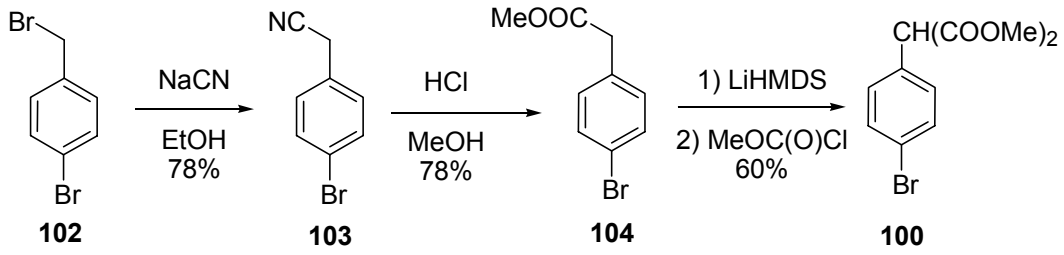
Synthesis of bulky malonates (Scheme 98) was attempted as the last available tuning of the reaction: to find out bulkiness limitations for nucleophiles in use and to obtain crystalline allylic substitution products since all the reaction products are oily viscous waxes. X-ray analysis of the products could be carried out as an additional proof of stereochemistry.



Scheme 98: Bulky malonates.

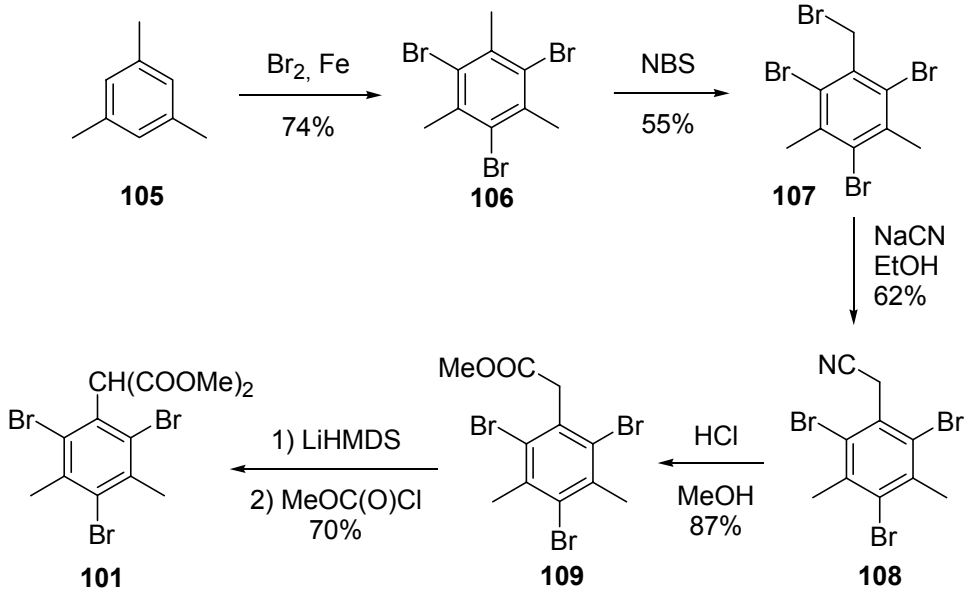
The synthesis of the malonate **100** commenced with nucleophilic substitution of benzylic bromide in commercially available *para*-bromobenzylbromide (**102**) with cyanide providing the nitrile **103** (Scheme 99). Pinner reaction of the nitrile **103** led to the methyl ester **104**.

Deprotonation of the ester with lithium hexamethyldisilazide forming carbanion which reacted with methylchloroformate resulted in the *para*-bromophenyl-substituted malonate **100**.



Scheme 99: Synthesis of *para*-bromophenyl-substituted malonate.

The more bulky malonate **101**, was synthesized from mesitylene (**105**). Aromatic tribromination of mesitylene in the presence of an iron catalyst led to the compound **106**, which was then involved into radical bromination with N-bromosuccinimide to form the benzylbromide **107** (Scheme 100). The following steps - nucleophilic substitution with sodium cyanide, Pinner reaction, deprotonation and condensation with methylchloroformate - were carried out analogously to the above described synthesis of the *para*-bromophenyl-substituted malonate **100**.

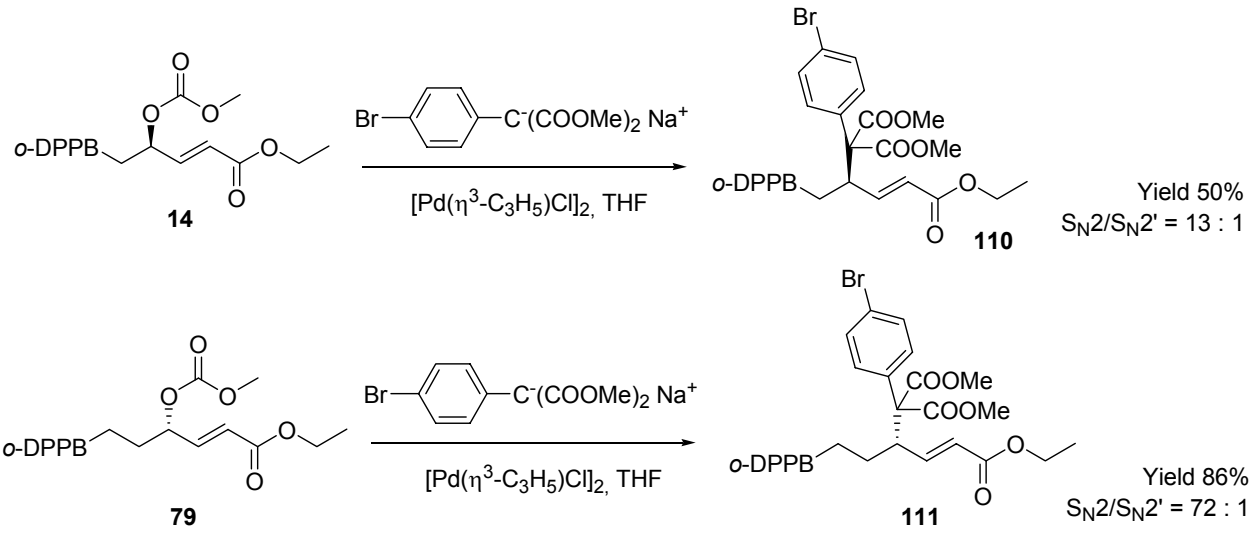


Scheme 100: Synthesis of 2,4,6-tribromo-3,5-dimethylphenyl-substituted malonate.

The last step of the both syntheses is very sensitive to the choice of the base and the electrophile. Sodium hydride, potassium *tert*-butoxide and lithium di-*iso*-propylamide as bases led to only partial deprotonation. It was lithium hexamethyldisilazide that provided quantitative deprotonation. Several electrophiles: dimethyloxalate, dimethyl carbonate or methylchloroformate – could be taken for the condensation with the carbanion. But only

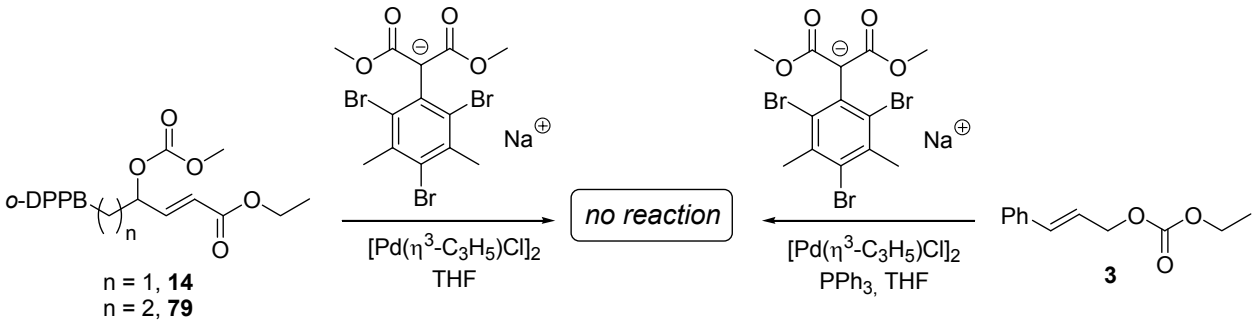
methylchloroformate was effective in the reaction. Moreover, addition of equimolar amount of both the base and the electrophile is essential for conversion of the ester **104** to the *para*-bromophenyl-substituted malonate **100**; otherwise in the case of the excess reagents bis-acetylation happens providing 2-(4-bromo-phenyl)-2-methoxycarbonyl-malonic acid dimethyl ester.

Palladium catalyzed allylic substitution with the substrates **14** and **79** where the directing *o*-DPPB group is separated from the leaving group with the tether of two and three carbons long, respectively, was carried out with the *para*-bromophenyl-substituted malonate **100** (Scheme 101). The reaction led to moderate up to good yields with high regioselectivity (stereoselectivity was not evaluated). As in the case of the reaction with nitrogen nucleophiles, the substrate with the longer tether was more reactive. The allylic substrate led to 50% separated yield, while the substrate **79** led to 86% isolated yield.



Scheme 101: Directed allylic substitution with *para*-bromophenyl-substituted malonate.

The products **110** and **111** are crystalline. These compounds are the first non-oil-like allylic substitution products. Unfortunately, all attempts to grow proper crystals for X-ray analysis failed.



Scheme 102: No reaction with 2,4,6-tribromo-3,5-dimethylphenyl-substituted malonate.

The more bulky malonate **101** is not reactive in palladium catalyzed allylic substitution (Scheme 102). It gives no reaction not only in the case of the sterically hindered substrates bearing *o*-DPPB group, but also in the case of a simpler 3-phenylallyl-ethylcarbonate (**3**).

4.4.5. Conclusion

The chiral allylic substrate with *o*-DPPB directing group separated from the carbonate leaving group with a tether built up of three carbon atoms was synthesized. This compound reacts under conditions of palladium catalysis with both more reactive sodium dimethylmalonate and less reactive nitrogen nucleophiles: potassium phthalimide, allylamine, benzylamine and dibenzylamine. All the directed reactions provide excellent regio- and stereoselectivity. Reaction with the substrate bearing oxidized *o*-DPPB group leads to a considerable drop of both regio- and stereoselectivity.

A short reaction sequence with the product of palladium catalyzed allylic substitution of the substrate with allylamine resulting in the literature known alcohol **96** allowed determination of absolute configuration of the product. Thus, overall retention of configuration, typical for palladium catalyzed allylic substitution without a directing group was proved. This sequence represents a formal total synthesis towards a number of enantiomers of bioactive *cis*-hexahydropyrrolo[3,2-*b*]pyrrol-3-ones and can be used as well in a total synthesis of indolizidine 167B.

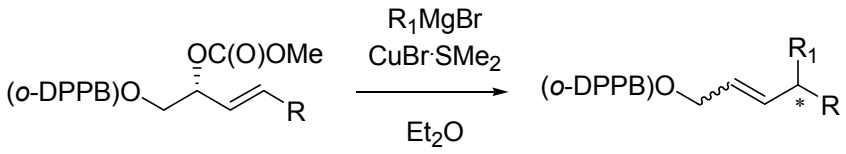
4.5. Copper mediated directed allylic substitution

4.5.1. Copper mediated allylic substitution of carbonates bearing *o*-DPPB directing group

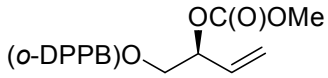
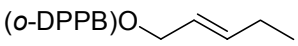
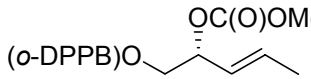
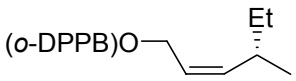
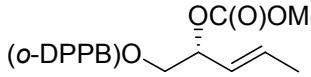
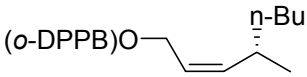
o-DPPB-directed copper mediated allylic substitution has been published by our laboratory. [12,13] In that case the *o*-DPPB group served as a directing leaving group. The reaction proceeds S_N2' regioselectively with *syn*-attack of the cuprate (from the side of the directing group).

It was interesting to test our substrates (used for palladium catalyzed allylic substitution with soft nucleophiles) in the reaction with hard nucleophiles where *o*-DPPB acts as a directing group and methylcarbonate becomes a leaving group.

The same reaction conditions as for allylic substitution with *o*-DPPB as a leaving-directing group were taken for the reaction: 0.8 equivalents of copper bromide, 1.1 equivalent of Grignard reagent (Scheme 103 and table 16).



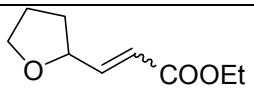
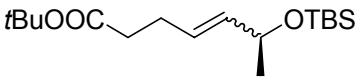
Scheme 103 and table 16: Copper mediated *o*-DPPB-directed allylic substitution. [a]

entry	Substrate	Grignard reagent	Product	Yield, % [b]	*ct*, %
1		MeMgBr		75	-
2		EtMgBr		52	86 [c]
3		*n*-BuMgBr		55	87 [d]

[a] allylic substrate (0.2 mmol), $CuBr{\cdot}SMe_2$ (0.8 eq.), Grignard reagent (1.1 eq.), THF (2 ml) stirred at 0 °C for 3-7 h; [b] separated yield; [c] determined by HPLC for phosphine-oxide of the product; [d] detected after transformation into alcohol via ozonolysis

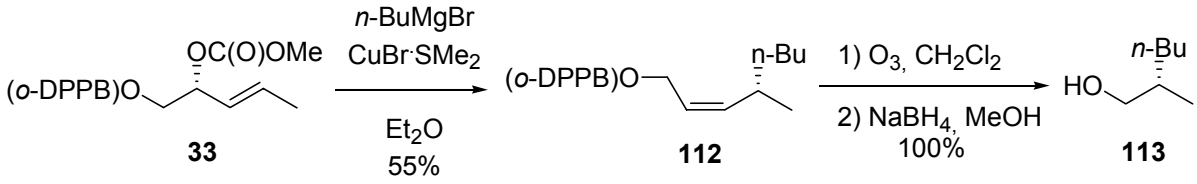
Only S_N2' product, which is the product of attack on the less hindered terminus, was obtained in all the reactions. In the case of unsubstituted allylic substrate **10** (Table 16, entry 1) *E*-olefin is formed (*J*= 15.4 Hz); in the case of substituted allylic substrate **33** (Table 16, entries 2-3) *Z*-olefin is observed (*J*= 10.9-11.0 Hz). This assumption is in a good agreement with the coupling constant values for *E*- and *Z*-olefins known from literature (Table 17). [100,101]

Table 17: Coupling constants for *E*- and *Z*-olefins.

entry	Compound	J_Z, Hz	J_E, Hz	Reference
1		10.8	15.6	[100]
2		11.2	15.5	[101]

Chirality transfer is good (86-87%), but still *lower* than for palladium catalyzed allylic substitution with soft nucleophiles and *lower* than for copper mediated allylic substitution with *o*-DPPB as a leaving directing group.

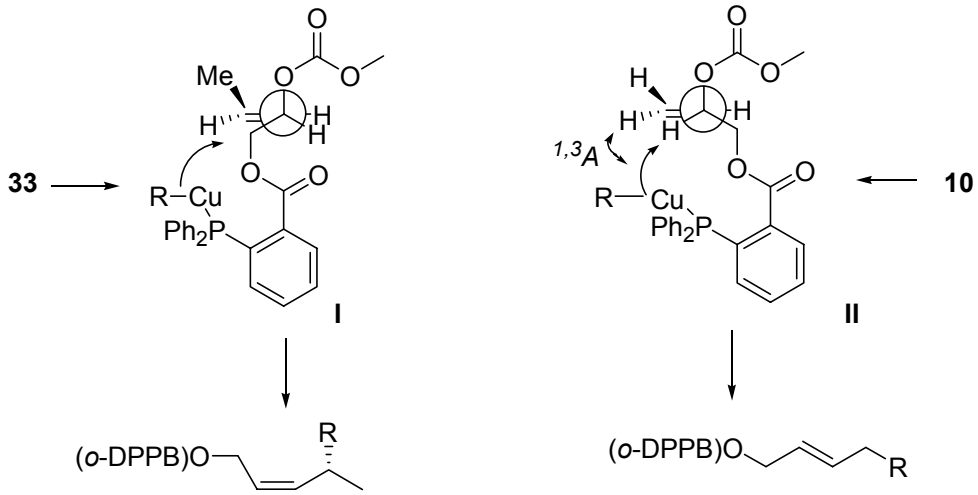
Absolute stereochemistry was proved by means of ozonolysis of the product **112** of allylic substitution reaction with the substrate **33** and *n*-butylmagnesiumbromide (Scheme 104). Reductive work-up with sodium borohydride led to literature known (*S*)-2-methylhexan-1-ol (**113**).



Scheme 104: Evaluation of the directed allylic substitution stereo-outcome.

This experiment proved retention of configuration during the reaction.

Different intermediates are supposed to be formed from substituted and unsubstituted substrates (Scheme 105).



Scheme 105: Speculated intermediate for copper mediated allylic substitution with *o*-DPPB-directing group.

In the case of the substitute **33** the reaction proceeds via more stable intermediate **I**, while the substrate **10** leads to mole labile intermediate **II** containing allylic strain. Intermediate **I** provides the *cis*-products, and intermediate **II** furnishes the *trans*-products. Nonetheless, there is no good explanation for the observation.

Formation of *S*-alcohol **113** from the substitute **33** also correlates good with suggested intermediate **I**.

To evaluate the directing effect of *o*-DPPB group, phosphine moiety in the substrate **33** was oxidized providing the non-directing substrate **33-oxide**. Copper mediated allylic substitution with **33-oxide** in the presence of triphenylphosphine as a ligand led to no expected (S_N2' or S_N2) product. Only reduced *o*-DPPB moiety as a product of Grignard reagent (or cuprate) attack on the carboxylic group was registered.

4.5.2. Conclusion

Copper mediated allylic substitution with the substrates bearing *o*-DPPB as a directing group and methylcarbonate as a leaving group leads to the product resulting from an S_N2' attack with retention of configuration in good stereoselectivity (about 90% *ee*). In the case of unsubstituted allylic substrate *E*-product is formed, in the case of substituted allylic substrate *Z*-product is observed.

Stereoselectivity is lower than for palladium catalyzed allylic substitution with soft nucleophiles and lower than for copper mediated allylic substitution with *o*-DPPB as a leaving directing group.

However, when *o*-DPPB was oxidized no allylic substitution took place. We consider that coordination of copper with *o*-DPPB is essential for the reaction to occur.

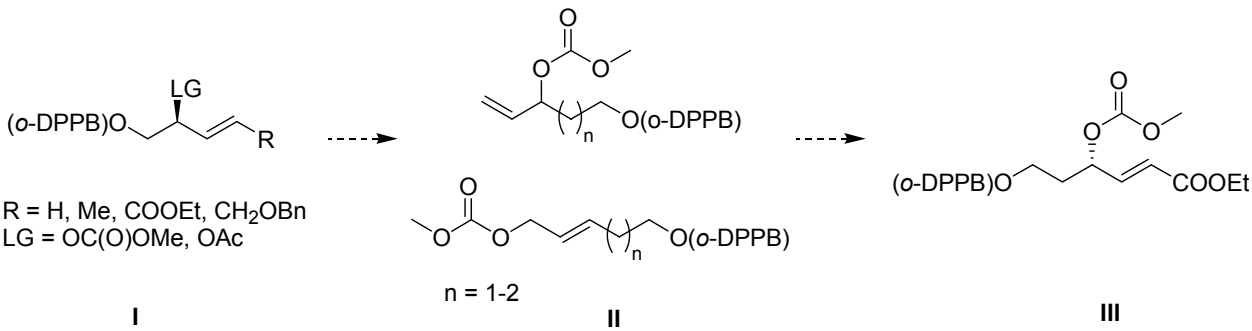
5. Summary

Palladium catalyzed allylic substitution with soft nucleophiles represents a very important class of reactions which are very often used in synthesis. The main strategy for solving selectivity problems of the reaction implies application of chiral ligands. Nonetheless, this concept normally keeps regioselectivity problem unsolved, as either only symmetrical substrates are usually taken for testing new ligands or the product is often planned according to the natural affinity of the reaction towards an attack of less sterically hindered position.

There are very few examples in scientific literature when directing effect was used for palladium catalyzed allylic substitution to tune regioselectivity. Having great experience with *o*-DPPB as a directing leaving group for copper mediated allylic substitution, we decided to apply *o*-DPPB directing group for palladium catalyzed allylic substitution with soft nucleophiles.

Unfortunately, there is no way to apply *o*-DPPB as a directing leaving group for palladium catalyzed allylic substitution. Because of mechanistic peculiarities, namely formation of nearly symmetrical η^3-allylpalladium complex as a reactive intermediate, unsatisfactory S_N2'/S_N2 regioselectivity was obtained. These experiments led us explore substrates with *o*-DPPB as a purely directing group and carbonate or acetate moiety as leaving groups.

Such allylic substrates (**I**, Scheme 106) bearing *o*-DPPB directing group separated from the leaving group with a tether built of two carbon atoms were synthesized starting from D-mannitol. Regioselectivity of palladium catalyzed allylic substitution with sodium dimethylmalonate was proved to be highly dependent on the substituent on the distal terminus of the allylic system. The smaller the substituent is, the more S_N2' product is obtained in the reaction.



Scheme 106: Substrates for allylic substitution.

The allylic substrates with bulkier substituents at the allyl terminus (**I**, R= COOEt, CH_2OBn) lead preferably to S_N2 product with excellent chirality transfer.

Application of nitrogen nucleophiles for the substrates **I** is disappointing as it is limited to the reaction with the most nucleophilic N-nucleophile pyrrolidine (despite excellent chirality transfer).

That is why a family of the substrates **II** where the directing group is withdrawn from the allylic system by a longer tether of two or three carbon atoms was synthesized starting from propan-1,3-diol and butan-1,4-diol, respectively. All the substrates are reactive with both carbon and nitrogen nucleophiles. Regioselectivity is highly linear because of affinity of nucleophiles in the palladium catalyzed reaction to attack the less hindered terminus.

Being convinced that a longer tether between *o*-DPPB directing group and the carbonate leaving group makes the compounds reactive with a wide range of soft nucleophiles, the chiral allylic substrate **III** was synthesized. This compound reacts under conditions of palladium catalysis with more reactive sodium dimethylmalonate and less reactive nitrogen nucleophiles: potassium phthalimide, allylamine, benzylamine and dibenzylamine. All the directed reactions provided excellent regio- and stereoselectivity.

A short modification of the product, obtained in palladium catalyzed allylic substitution with allylamine, allowed estimating overall retention of configuration, typical for palladium catalyzed allylic substitution with soft nucleophiles.

Explanation of reactivity difference between the substrates **I** and **III** was given in terms of nucleophilicity and electrophilicity developed by Mayr: the particular electrophile reacts with the nucleophiles only within a limited range of their nucleophilicity value.

Copper mediated allylic substitution with the substrates bearing *o*-DPPB as a directing group and methylcarbonate as a leaving group (**I**, R= CH_3) furnished the *cis*-olefin as a product of S_N2' attack with retention of configuration. In the case of the unsubstituted substrate (**I**, R= H) *trans*-olefin was formed. Stereoselectivity of the directed copper mediated reaction with carbonate as a leaving group is lower than for palladium catalyzed allylic substitution with soft nucleophiles and lower than for copper mediated allylic substitution with *o*-DPPB as a directing leaving group.

For all the allylic substitutions (with both soft and hard nucleophiles) non-directing analogues with either oxidized *o*-DPPB moiety or with 2-benzhydrylbenzoate (CH instead of P-atom) proves the effect of the directing group in the reactions. Non directing substrates lead either to considerably lower selectivity or side reactions (which are overcome in the presence of the *o*-DPPB directing group).

Thus, *ortho*-diphenylphosphanylbenzoyl can be used as a directing group for palladium catalyzed allylic substitution with soft (as well as hard) nucleophiles to regulate regioselectivity of the reaction and to keep excellent chirality transfer from the substrate to the product.

B. Experimental part

1. General Procedures

1.1. General

All manipulations with oxygen- and moisture-sensitive materials were performed using oven-dried glassware under atmosphere of purified argon. Air- and moisture-sensitive liquids and solutions were transferred via syringe.
Organic solutions were concentrated under reduced pressure by rotary evaporation.

1.2. Chromatography

Thin-layer chromatography was performed using TLC-ready charts by Merck (aluminium sheets with silica gel Si 60 with fluorescent indicator F_{254}). UV-active substances were detected in UV-light with wavelength λ = 254 nm. Colouring was afforded via dipping into a colouring agent followed by heating with a heat-gun.
Colouring agent for TLC: 3 g $KMnO_4$, 20 g K_2CO_3, 5 ml 5% aqueous solution of NaOH, 300 ml distilled water.
Chromatographic purification of products was accomplished using flash column chromatography on Kieselgel 60 (40-63 μm, 230-400 mesh) as a stationary phase from Merck company.

1.3. Melting points

Melting points were measured on a Dr. Tottoli (Büchi) apparatus and were not corrected.

1.4. Elemental analysis

Elemental analysis were measured by the analytic department of Institut für Organische Chemie und Biochemie der Universität Freiburg on an apparatus VarioEL (Elementaranalysen-Systeme Gmbh).

1.5. NMR spectroscopy

NMR spectra were recorded on Bruker DRX 500 (500 MHz), Avance II 400 (400 MHz) and Varian Mercury 300 HFCP (300 MHz) spectrometers at 300 K. Chemical shifts are reported in ppm with tetramethylsilane (δ = 0 ppm) as internal standard. In the absence of tetramethylsilane residual solvent peak was used as internal standard for ^{1}H and ^{13}C-NMR, respectively: in deuterochloroform ($CHCl_3$, δ = 7.26 and 77.1 ppm), in deuterobenzene (C_6H_6, δ = 7.16 and 128.0 ppm). Data are reported as follows: s = singlet, d = dublet, t = triplet, q = quartet, q = quintet, m= multiplet, m_c = centrosymmetric multiplet, b = broad signal, dd = doubled dublet, dt = doubled triplet, dm = doubled multiplet, p = pseudo; coupling constant(s) in Hz; integration; assignment.

1.6. Mass spectrometry

Electronic ionization (EI): TSQ 700 and MAT 95XL, Fa. THERMO; ionization energy 70 eV, source temperature 200 °C.
Chemical ionization (CI): TSQ 700 and MAT 95XL, Fa. THERMO; ionization energy 110 eV, source temperature 200 °C. Reaction gasses: ammonia or *iso*-butane.
High-resolution mass spectroscopy (HRMS): MAT 95XL, EI or CI, M/δ M=10000.
GC/MS (EI and CI): TSQ 700 with VARIAN 3400.
Electrospray ionization (ESI) and ambient pressure chemical ionization (APCI): LCQ Advantage and TSQ 7000, Fa. THERMO.
LC/MS: LCQ Advantage with Surveyor LC-System.

1.7. Gas chromatography and HPLC

Gass chromatography: 6890N der Fa. AGILENT TECHNOLOGIES (column: 24079, Supelcowax 10, 30.0 m × 0.25 mm × 0.25 µm, Fa. SUPELCO).
Analytical HPLC:
Fa. MERCK-HITACHI, L-7100 (pump), D-7000 (detector), L-7360 (oven),
Fa. MERCK-HITACHI, L-6200A (pump), L-4000 (detector),
Fa. DIONEX, P580 (pump), UVD170S (detector).

1.8. Optical-rotary power

Optical rotation was measured using Perkin-Elmer 241 polarimeter with sodium-vapor lamp (λ = 589 nm). The following equation was used for calculations of the optical-rotary power:

$$[\alpha]_{\lambda}^{T} = \frac{\alpha \cdot 100}{c \cdot d}$$

T : temperature [°C], d : length of the cuvette [dm], α : optical-rotary power [°], c : concentration [g / 100 ml], λ : wavelength [nm]

1.9. Dry Solvents

Et_2O	dried by distillation from potassium – sodium alloy with benzophenon as indicator
CH_2Cl_2	dried by distillation from CaH_2
THF	dried by distillation from potassium with benzophenon as indicator
Toluene	dried by distillation from sodium with benzophenon as indicator
Et_3N	dried by distillation from CaH_2

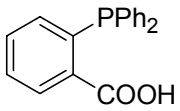
Acetone, benzene, dimethyl solfoxide (DMSO), *N,N*-dimethylformamide (DMF), ethanol, methanol, ethyl acetate (EE) and some others were purchased in the form of analytical reagents and were stored over activated molecular sieves 4Å and under Ar.

1.10. Organometallic reagents

The concentration of organolithium reagents was determined with the method of Suffert [direct titration with *N*-pivaloyl-*o*-toluidine (*n*-BuLi) or with N-pivaloyl-*o*-benzylaniline (PhLi)].
[102]

2. Synthesis of basic starting materials

2.1. Synthesis of 2-diphenylphosphanylbenzoic acid



Synthesized according to literature. [103]

2.2. Synthesis of $[Pd(\eta^3\text{-allyl})Cl]_2$

The allyl palladium complex was synthesized according to literature. [104] Recrystalliation from CH_2Cl_2/PE. Yield 89%.

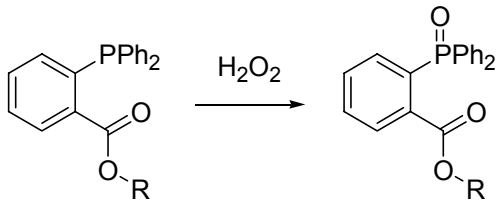
2.3. Synthesis of $Bu_4N[Fe(CO)_3NO]$

Synthesized according to literature. [105] $Fe(CO)_5$ (7.89 ml, 60 mmol) in degassed dichloromethane (20 ml) was added to solution of Bu_4NBr (19.32 g, 60 mmol) and $NaNO_2$ (4.14 g, 60 mmol) in degassed water (20 ml). The reaction was stirred under argon at room temperature for 2 h, yellow solution turns brown. The organic layer was separated, washed with water and dried over Na_2SO_4. The solvent was evaporated to give yellow solid (63%). It was used for analysis and reactions without further purification.

mp= 46 °C

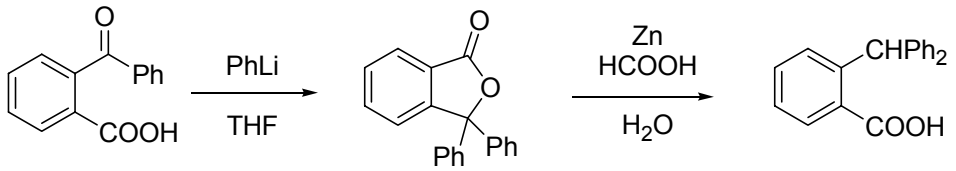
Elemental analysis	$C_{19}H_{36}FeN_2O_4$	M_r= 412.20	
Calculated, %:	C 55.34	H 8.80	N 6.79
Found, %:	C 55.34	H 9.00	N 6.55

2.4. Oxidation of *o*-DPPBA esters



To a solution of *o*-DPPBA ester (c.a. 10 mg) in ethyl acetate a drop of hydrogen peroxide (30%) was added, the reaction mixture was stirred for 10 minutes, then excess of the oxidant was reduced with sodium thiosulfate pentahydrate. The mixture was dried over Na_2SO_4 and filtrated through a shot silica gel pad and evaporated. The obtained phosphine oxide was used (for HPLC-analysis or reactions) without further purification.

2.5. Synthesis of 2-benzhydrylbenzoic acid (23)



21 **22** **23**

[W. Wykypiel, J.-J. Lohmann, D. Seebach, *Helv. Chim. Acta*, **1981**,64, 1344] [79]

To a solution of o-benzoylbenzoic acid (**21**) (10.6 g, 47 mmol) in of THF (150 ml) at -78°C a solution of PhLi (20% solution in Bu_2O, ~ 1.8 M, 62 ml, 111 mmol) was added. The reaction mixture was stirring at the temperature during 2 h. After water addition the extraction with Et_2O (3×50 ml) was carried out. Concentrated hydrochloric acid added to water layer caused 3,3-diphenylphtalyde (**22**) precipitation. The solid was dissolved in Et_2O, dried over $MgSO_4$. Ether was evaporated giving 10.7 g (80% yield) of 3,3-diphenylphtalyde (**22**).

[R.L. Letsinger, J.D. Jamison, A.S. Hussey, *J. Org. Chem.*, **1961**, 26, 97-102] [80]

A mixture of of 3,3-diphenylphtalyde (**22**) (11.5g , 40.2 mmol), of formic acid (96 g, 2.09 mol), of zinc (23 g, 352 mmol) and of water (23 ml) were refluxed for 5 h and then poured into water. The precipitate was separated and dissolved in alcohol. After the filtration to remove unreacted zinc, excess ethanol was distilled and the residue recrystallised from ethanol-water to give 9.5 g (83% yield) of 2-benzhydrylbenzoic acid (**23**).

mp=148 °C

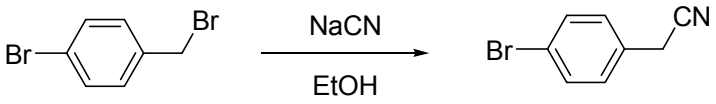
Yield= 66% (for 2 steps).

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 6.74 (s, 1H, C<u>H</u>Ph$_2$), 7.05-7.10 (m, 5H, ArH), 7.17-7.39 (m, 7H, ArH), 7.47 (ddd, J = 7.6, 1.6, 1.6 Hz, 1H, ArH), 8.04 (dd, J = 7.8, 1.5 Hz, 1H, ArH).

2.6. Synthesis of substituted malonates

2.6.1. Synthesis of (4-bromophenyl)acetonitrile (103)



102 **103**

The compound was synthesized according to literature. [106] Into a 100 ml flask 1-bromo-4-bromomethylbenzene (2.56 g, 10.2 mmol), sodium cyanide (0.50 g, 10.2 mmol, 1 eq) and ethanol (35 ml) were placed, refluxed 2 h and then cooled to room temperature. Water was added, the reaction mixture was extracted with ethyl acetate (3×20 ml), dried over Na_2SO_4, filtered, the solvent was evaporated.

Flash-column chromatography (silica gel, PE/TBME = 20:1 to 5:1).

R_f = 0.16 (PE/TBME 5:1).

Yield 1.56 g (78%).

^{1}H-NMR (400.130 MHz, C_6D_6):

δ = 2.51 (s, 2H, C<u>H</u>$_2$CN), 6.44 (d, J = 8.7 Hz, 2H, ArH), 7.06 (d, J = 8.6 Hz, 2H, ArH).

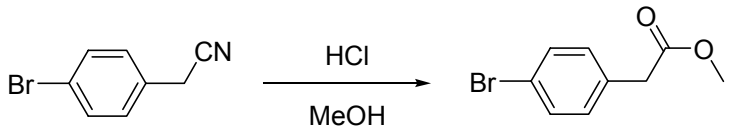
^{13}C-NMR (100.620 MHz, C_6D_6):

δ = 22.2 (CH_2), 117.1 (CN), 121.9 (Ar), 129.6 (Ar), 132.1 (Ar).

MS, GC-EI: C_8H_6NBr m/z=194.1 (40, M), 115.9 (100, M-Br).

Analytical data are in a good agreement with literature. [106]

2.6.2. Synthesis of (4-bromophenyl)acetic acid methyl ester (104)



103 **104**

The compound was synthesized according to literature. [107] Methanol (50 ml) was saturated with gaseous hydrogen chloride, then (4-bromophenyl)-acetonitrile (1.56 g, 7.96 mmol) was added and refluxed overnight. The solvent was evaporated.

Flash-column chromatography (silica gel, PE/TBME = 5:1).

R_f = 0.56 (CH/EE 1:1).

Yield 1.41 g (78%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.58 (s, 2H, C$\underline{H_2}$COO), 3.69 (s, 3H, COOC$\underline{H_3}$), 7.15 (d, J = 8.7 Hz, 2H, ArH), 7.44 (d, J = 8.5 Hz, 2H, ArH).

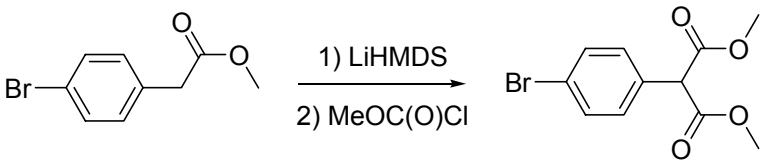
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 40.6 (CH_2), 52.2 (Me), 121.3 (Ar), 131.1 (Ar), 131.8 (Ar), 133.0 (Ar), 171.5 ($\underline{C}$OOMe).

MS, GC-EI: $C_9H_9BrO_2$ m/z=227.9 (67, M), 170.8 (100, M-CO_2Me).

Analytical data are in a good agreement with literature. [107

2.6.3. Synthesis of 2-(4-bromophenyl)malonic acid dimethyl ester (100)



104 **100**

At 0 °C *n*-BuLi (3.8 ml, 6.08 mmol, 1.eq, 1.6 M solution in hexanes) was dropwise added to a solution of hexamethyldisilazane (1.35 ml, 1.04 g, 6.44 mmol, 1.05 eq) in abs. THF. The reaction mixture was stirred 1 h at room temperature and then cooled to 0 °C and (4-bromophenyl)acetic acid methyl ester (1.41, 6.18 mmol, 1.02 eq) was added as a solid, stirred 30 min

and followed by adding methylchloroformate (0.57 ml, 0.69 g, 7.38 mmol, 1.2 eq). After 4 h stirring at room temperature the solvent was evaporated.

Flash-column chromatography (silica gel, PE/EtOH = 97:3).

R_f = 0.54 (CH/EE 1:1).

Yield 60%, yellow liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.53 (s, 6H, COOC<u>H</u>$_3$), 4.38 (s, 1H, C<u>H</u>(COOCH$_3$)$_2$), 7.06 (d, J = 8.3 Hz, 2H, ArH), 7.27 (d, J = 8.6 Hz, 2H, ArH).

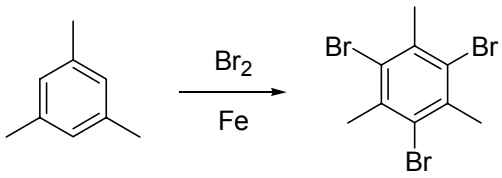
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 53.1 (<u>C</u>H(COOMe)$_2$), 57.0 (CH(COO<u>Me</u>)$_2$), 122.7 (Ar), 131.0 (Ar), 131.6 (Ar), 131.9 (Ar), 168.2 (CH(<u>C</u>OOMe)$_2$).

MS, GC-EI: $C_{11}H_{11}BrO_4$ m/z=287.8 (100, M+1), 228.8 (77, M-CO_2Me).

Analytical data are in a good agreement with literature. [108]

2.6.4. Synthesis of 1,3,5-tribromo-2,4,6-trimethylbenzene (106)



105 **106**

The compound was synthesized according to literature. [109] To the flask fitted with vents for high quantities of HBr evaluating and containing iron powder (0.649 g, 11.6 mmol, 0.32 eq) and bromine (10.1 ml, 31.5 g, 196.9 mmol, 5.47 eq) 1,3,5-trimethylbenzene (5 ml, 4.32 g, 36.0 mmol) was dropwise added at room temperature. The reaction mixture was ventilated with air stream, sodium thiosulfate was added, stirred, the mixture was filtered and the product was recrystallised from $CHCl_3$ to give white needles.

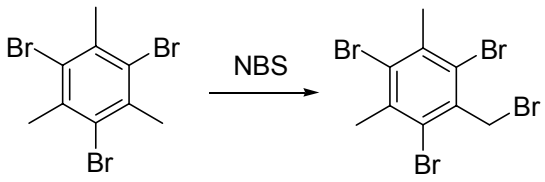
Yield 9.47 g (74%).

^{1}H-NMR (300.064 MHz, $CDCl_3$+C_6D_6):

δ = 2.58 (s, 9H, CH_3×3).

Analytical data are in a good agreement with literature. [109]

2.6.5. Synthesis of 1,3,5-tribromo-2-bromomethyl-4,6-dimethylbenzene (107)



106 **107**

The compound was synthesized according to literature. [110] 2,4,6-Tribromomesitylene (17.93 g, 50.2 mmol) and NBS (7.6 g, 42.7 mmol, 0.85 eq) in tetrachloromethane (200 ml) was refluxed 3 h under irradiation with 200 W lamp. The succinimide was filtered from the hot solution, the solvent was evaporated. Recrystallisation from $CHCl_3$.

Yield 14.9 g (impured with ~ 20% of starting material), white powder; that gives 12.2 g (55%) of pure product.

^{1}H-NMR (400.130 MHz, C_6D_6):

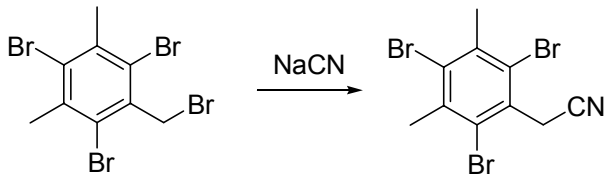
δ = 2.30 (s, 6H, CH_3×2), 4.59 (s, 2H, CH_2Br).

^{13}C-NMR (100.620 MHz, C_6D_6):

δ = 25.9 (CH_3), 36.9 (CH_2), 125.4 (Ar), 128.4 (Ar), 136.0 (Ar), 138.1 (Ar).

Analytical data are in a good agreement with literature. [110]

2.6.6. Synthesis of (2,4,6-tribromo-3,5-dimethyl-phenyl)-acetonitrile (108)



107 **108**

The nitrile **108** was synthesized analogously to **103** (see chapter 2.6.1.) starting from the compound **107** (12.2 g, 27.87 mmol).

Flash-column chromatography (silica gel, PE/TBME = 10:1).

R_f = 0.41 (PE/TBME 5:1).

Yield 6.59 g (62%), white crystals (mp 117 °C).

^{1}H-NMR (400.130 MHz, C_6D_6):

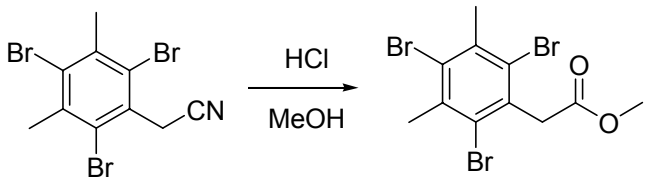
δ = 2.25 (s, 6H, CH_3×2), 3.44 (s, 2H, CH_2CN).

^{13}C-NMR (100.620 MHz, C_6D_6):

δ = 26.0 (CH_3), 28.0 (CH_2), 115.2 (CN), 124.9 (Ar), 128.7 (Ar), 138.2 (Ar).

HRMS, EI:	calculated	378.820679
$C_{10}H_8Br_3N$	found	378.820398

2.6.7. Synthesis of (2,4,6-tribromo-3,5-dimethylphenyl)acetic acid methyl ester (109)



108 **109**

The ester **109** was synthesized analogously to **104** (see chapter 2.6.3.) starting from the nitrile **108** (0.802 g, 2.10 mmol).

Flash-column chromatography (silica gel, PE/TBME = 10:1).

R_f = 0.68 (CH/EE 1:1) and R_f = 0.54 (PE/TBME 5:1).

Yield 0.759 g (87%).

^{1}H-NMR (400.130 MHz, C_6D_6+DMSO):

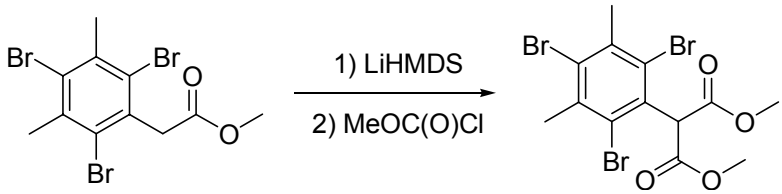
δ = 2.43 (s, 6H, CH_3×2), 3.48 (s, 3H, COOMe), 4.16 (s, 2H, $C\underline{H}_2$COOMe).

^{13}C-NMR (100.620 MHz, C_6D_6+DMSO):

δ = 26.1 (CH_3), 44.7 (CH_2), 52.0 (COO<u>Me</u>), 126.0 (Ar), 127.0 (Ar), 134.4 (Ar), 137.5 (Ar), 169.3 (<u>C</u>OOMe).

HRMS, CI (NH_3):	calculated	429.865284
$C_{11}H_{11}Br_3O_2$ (M+NH_4)	found	429.864702

2.6.8. Synthesis of 2-(2,4,6-tribromo-3,5-dimethyl-phenyl)-malonic acid dimethyl ester (101)



109 **101**

The malonate **101** was synthesized analogously to **100** (see chapter 2.6.3.) starting from the ester **109** (0.26 g, 0.63 mmol).

It is described in literature [108] for *p*-bromophenylmalonic acid dimethyl ester that LDA was used as a base to deprotonate α-proton of the ester, nonetheless for this compound only lithium hexamethyldisilazide proved to be the only effective one for tribromoderivative. Screening of electrophiles among the three (methylchloroformate, dimethylcarbonate and dimethyloxalate) also led to the one effective – MeOC(O)Cl.

Flash-column chromatography (silica gel, PE/TBME = 10:1).

R_f = 0.33 (PE/TBME 5:1).

Yield 0.21 g (70%), white crystalline powder.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 2.69 (s, 6H, CH_3×2), 3.78 (s, 6H, COOMe×2), 5.80 (s, 1H, C<u>H</u>(COOMe)$_2$).

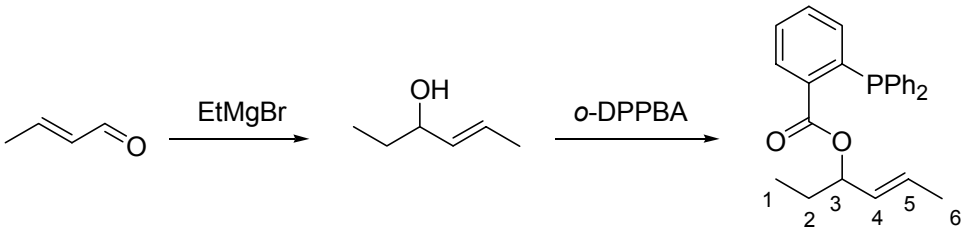
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 26.8 (CH_3), 53.1 (CH(COO<u>Me</u>)$_2$), 60.2 (<u>C</u>H(COOMe)$_2$), 126.1 (Ar), 128.3 (Ar), 133.8 (Ar), 138.3 (Ar), 166.6 (CH(<u>C</u>OOMe)$_2$).

HRMS, CI (NH_3):	calculated	470.844215
$C_{13}H_{13}Br_3O_4$ (M+H)	found	470.844298

3. Substrates with *o*-DPPB as a leaving group

3.1. Synthesis of *rac,trans*-4-[2-(diphenylphosphanyl)benzoyloxy]-2-hexene (1)



2

The compound **1** was synthesised as it is described in the thesis of C. Herber. [111]

Flash-column chromatography (silica gel, CH/EE = 10:1 to 6:1).

R_f = 0.79 (CH/EE 1:1).

Recrystallisation from PE. White crystals.

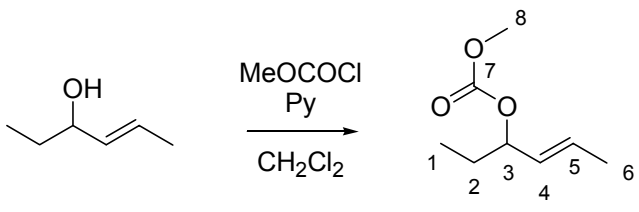
Yield 54%.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 0.83 (t, J = 7.5 Hz, 3H, CH_3-C_1), 1.50-1.65 (m, 2H, CH_2-C_2), 1.64 (dd, J = 6.9, 1.5 Hz, 3H, CH_3-C_6), 5.23-5.35 (m, 2H, CH-C_3 and CH-C_4), 5.61-5.72 (dq, J = 14.1, 6.5 Hz, 1H, CH-C_5), 6.90-6.94 (m, 1H, Ar-H), 7.25-7.42 (m, 12H, Ar-H), 8.06-8.11(m, 1H, Ar-H).

Analytical data are in a good agreement with literature. [111]

3.2. Synthesis of *rac*-3-methoxycarbonyloxy-4-hexene (2)



1

The compound was synthesized according to literature procedure for carbonate synthesis. [112]

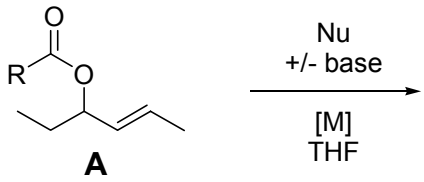
To a stirred solution of hex-2-en-4-ol (381.5 mg, 3.8 mol) and pyridine (0.9 ml, 0.88 g, 11.1 mmol, 3 eq) in CH_2Cl_2 (15 ml) was added dropwise methyl chloroformate (0.32 ml, 0.39 g, 4.1 mmol, 1.1 eq) at 0 °C, and stirring was continued for 1 h at the same temperature.
Flash-column chromatography (silica gel, PE/Et_2O = 4:1).
R_f = 0.47 (CH/EE 1:1 and same for PE/Et_2O = 4:1).
Yield 43%.

^{1}H-NMR (300.064 MHz, $CDCl_3$):
δ = 0.87 (t, J = 7.4 Hz, 3H, CH_3-C_1), 1.51-1.65 (m, 2H, CH_2-C_2), 1.68 (ddd, J = 6.9, 1.6, 0.5 Hz, 3H, CH_3-C_6), 3.72 (s, 3H, CH_3-C_8), 4.90 (q, J = 7.0 Hz, 1H, CH-C_3), 5.40 (ddq, J = 15.3, 7.62, 1.6 Hz, 1H, CH-C_4), 5.75 (ddq, J = 19.5, 6.5, 0.88 Hz, 1H, CH-C_5).

Analytical data are in a good agreement with literature. [77b]

3.3. Allylic substitution with the substrate with *o*-DPPB as a leaving group

3.3.1. General method for allylic substitution



A

R= OMe, *o*-Ph_2P-C_6H_4
M = Pd, Rh

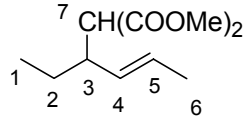
A solution of allylic substrate **A** (1 mmol), [Pd(η^3-allyl)Cl]$_2$ (9 mg, 5 mol.%) or [Rh(CO)$_2$Cl]$_2$ (10 mg, 5 mol.%), PPh_3 (only for carbonate, 26 mg, 10 mol.%), Bu_4NBr (64.4 mg, 20 mol.%) and with or without NaH (60% in oil, 8 mg, 20 mol.) in THF (5 ml) was stirred under argon 0.5 h. Then under a stream of argon the nucleophile was added (via a syringe for liquids or a funnel for solids (1-4 eq)). The reaction mixture was stirred at room temperature. Flash chromatography (silica gel, eluent CH_2Cl_2/acetone= 10:1). The compound was separated as a mixture of regioisomers (and unreacted starting material).

3.3.2. Allylic substitution with iron catalyst

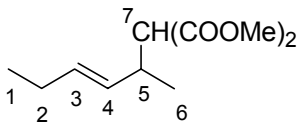
$Bu_4N[Fe(CO)_3NO]$ (21.2 mg, 5 mol%) and the substrate **A** (776.8 mg, 2 mmol) in DMF (13 ml) were stirred under argon 0.5 h at 80 °C.

Then dimethylmalonate (200 µl, 2 mmol) was added. The reaction was heated overnight at 80 °C. After cooling to room temperature dichloromethane (5 ml) was added, the organic layer was washed with water (2 × 5 ml), dried over Na_2SO_4. Flash chromatography (d=2 cm; silica gel, l=8 cm; eluent CH_2Cl_2/acetone= 10:1). Only starting material was observed. No conversion was registered.

3.3.3. Products of allylic substitution with dimethylmalonate as a nucleophile; *rac*-2-(1-Ethylbut-2-enyl)-malonic acid dimethyl ester (S_N2 product) and *rac*-2-(1-methylpent-2-enyl)-malonic acid dimethyl ester (S_N2' product)



S_N2



S_N2'

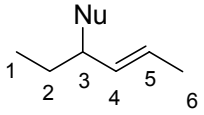
^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 0.84 (t, *J* = 7.3 Hz, 3H, CH_3-C_1, **S_N2**), 0.93 (t, *J* = 7.5 Hz, 3H, CH_3-C_1, **S_N2'**), 1.05 (d, *J* = 6.7 Hz, 3H, CH_3-C_6, **S_N2'**), 1.64 (dd, *J* = 6.5, 1.6 Hz, 3H, CH_3-C_6, **S_N2**), 1.92-2.02 (m, 2H, CH_2-C_2, **S_N2 and S_N2'**), 2.56-2.67 (m, 1H, CH-C_3, **S_N2**), 2.82-2.94 (m, 1H, CH-C_5, **S_N2'**), 3.26 (d, *J* = 9.2 Hz, 1H, CH-C_7, **S_N2'**), 3.33 (d, *J* = 9.1 Hz, 1H, CH-C_7, **S_N2**), 3.67 and 3.71 (s and s, 6H, CH_3OOC, **S_N2**), 3.68 and 3.72 (s and s, 6H, CH_3OOC, **S_N2'**), 5.2-5.6 and 5.5-5.6 (m, signals of double bond protons).

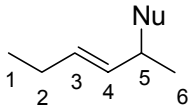
The spectrum for **S_N2'** productis in good agreement with [77].

3.3.4. Products of allylic substitution with other nucleophiles

The products were not separated. Regioselectivity was determined via NMR of the crude reaction mixtures. Only characteristic signals in ^{1}H-NMR are presented for the products in the table below.



S_N2-product



S_N2'-product

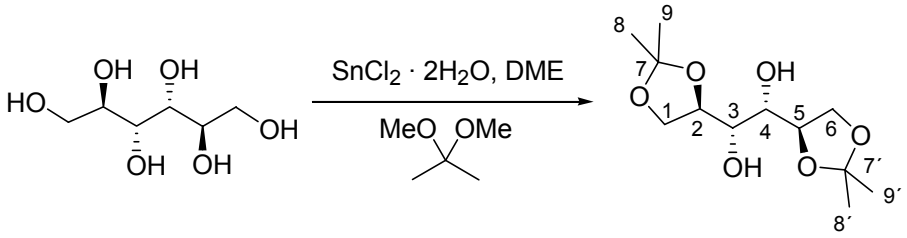
entry	Nucleophile	t, CH_3-C_1, **S_N2'**, δ, J; (d, CH_3-C_6, **S_N2'**, δ, J)	t, CH_3-C_1, **S_N2**, δ, J; (dd, CH_3-C_6, **S_N2**, δ, J)
1	$CH_2(COOMe)_2$	0.93 ppm, 7.5 Hz; (1.05 ppm, 6.7 Hz)	0.84 ppm, 7.3 Hz; (1.64 ppm, 6.5, 1.6 Hz)
2	$CH_2(CN)_2$	0.99 ppm, 7.4 Hz; (1.29 ppm, 6.9 Hz)	0.93 ppm, 7.3 Hz; (1.74 ppm, 6.6, 1.6 Hz)
3	piperidine	0.97 ppm, 7.5 Hz; (1.25 ppm, 6.7 Hz)	0.81 ppm, 7.4 Hz; (1.73 ppm, 6.3, 1.7 Hz)
4	morpholine	0.97 ppm, 7.5 Hz; (1.13 ppm, 6.5 Hz)	0.83 ppm, 7.4 Hz; (1.70 ppm, 6.4, 1.5 Hz)
5	pyrrolidine	1.02 ppm, 7.5 Hz; (1.60 ppm, 6.7 Hz)	0.90 ppm, 7.5 Hz; (1.80 ppm, 6.4, 1.5 Hz)
6	allylamine	0.96 ppm, 7.5 Hz; (1.12 ppm, 6.7 Hz)	0.83 ppm, 7.4 Hz; (1.67 ppm, 6.5, 1.5 Hz)

4. System based on 2,3-*O*-isopropyliden-glyceraldehyde

4.1. Synthesis of carbonates bearing *o*-DPPB directing group

4.1.1. Synthesis of (+)-1,2:5,6-Di-*O*-isopropyliden-D-mannitol (5)

Method 1

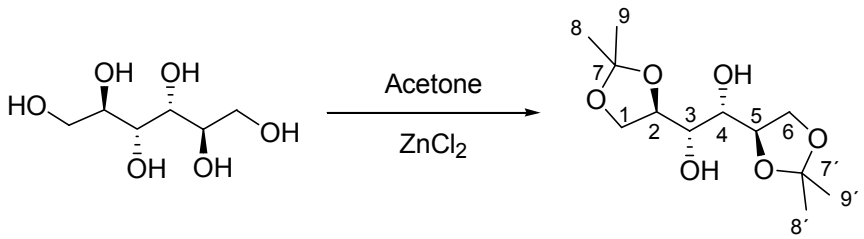


4 **5**

To a mixture of D-mannitol (25.7 g, 141 mmol) and $SnCl_2 \cdot 2H_2O$ (50 mg, 0.22 mmol) in DMF (60 ml) 2,2-dimethoxypropane (40 ml, 33.6 g, 323 mmol, 2.4 eq) was added and the reaction mixture was refluxed 2 h (clear solution formed). Then pyridine (0.5 ml) was added, the olvent was evaporated. The solid was dissolved in CH_2Cl_2, filtered and after CH_2Cl_2 evaporation the solid was recrystallized from Bu_2O (110 ml).

Yield 24.5 g (73%).

Method 2



4 **5**

$ZnCl_2$ (20.4 g, 150 mmol, 2.5 eq) was dissolved in dry acetone (106 ml, 83.5 g, 1.44 mol, 24 eq), the exothermic reaction was stirred 0.5 h at room temperature. D-mannitol (10.9 g, 60 mmol) was added and the reaction mixture was stirred overnight. Then potassium carbonate (27 g) in water (300 ml) was added, precipitate was filtered, the filtrate was extracted with CH_2Cl_2 (3×30 ml), the combined organic layers were washed with saturated aqueous NaCl solution (30 ml), the solvent was evaporated. The solid was dissolved in CH_2Cl_2, filtered. PE was added to the solution. White precipitate was filtered and dried in vacuum.

Yield 5.89 g (38%).

^{1}H-NMR (300.064 MHz, C_6D_6):

δ = 1.35 (s, 6H, CH_3-$C_{8/8'}$), 1.40 (s, 6H, CH_3-$C_{9/9'}$), 2.71 (d, J = 6.4 Hz, 2H, OH), 3.73 (dd, J = 6.2, 6.2 Hz, 2H, CH-$C_{3/4}$), 3.96 (dd, J = 5.4, 8.3 Hz, 2H, CH_A-$C_{1/6}$), 4.07-4-21 (m, 4H, CH_B-$C_{1/6}$ and CH-$C_{2/5}$).

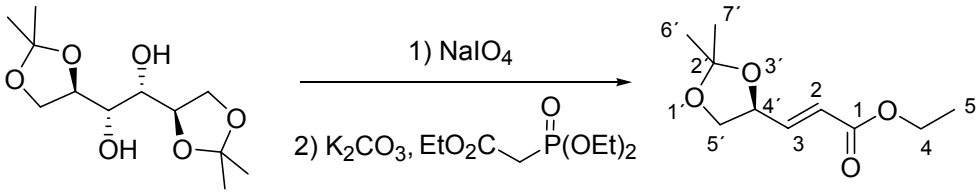
^{13}C-NMR (75.451 MHz, C_6D_6):

δ = 25.5 ($C_{8/8'}$), 27.0 ($C_{9/9'}$), 67.1, 71.5, 76.5, 109.7 ($C_{7/7'}$).

$[\alpha]_D^{21}$ = 1.5 ° (c = 1.215, MeOH).

Analytical data are in a good agreement with literature. [113]

4.1.2. Synthesis of (*S*,*E*)-3-[(4′)-2′,2′-dimethyl-1′,3′-dioxolane-4′-yl]-prop-2-enic acid ethyl ester (11)



5 **11**

To a suspension of protected D-mannitol (**5**) (3.57 g, 13.6 mmol) in saturated aqueous $NaHCO_3$ solution (59 ml) at 0 °C $NaIO_4$ (3.78 g, 17.7 mmol) was added slowly. After 10 min the ice-bath was removed and the reaction mixture was stirred for 4 h at room temperature. Then solid K_2CO_3 (76 g, 551 mmol) and triethyl phosphonoacetate (10.9 ml, 12.3 g, 54.9 mmol, 4.0 eq) were added one after another and stirred at room temperature overnight. After addition of water (till all the salts dissolve) the organic phase was separared, the water phase was extracted with Et_2O (4×80 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.60 (CH/EE 1:1).

Yield 4.29 g (78%), viscous liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3-C_5), 1.40 (s, 3H, CH_3-$C_{6'/7'}$), 1.45 (s, 3H, CH_3-$C_{6'/7'}$), 3.67 (dd, J = 8.2, 7.3 Hz, 1H, CH_A-$C_{5'}$), 4.13 (dd, J = 8.2, 6.6 Hz, 1H, CH_B-$C_{5'}$), 4.16 (q, J = 7.1 Hz, 2H, CH_2-C_4), 4.66 (dddd, J = 6.9, 6.9, 6.9, 1.3 Hz, 1H, CH-$C_{4'}$), 6.10 (dd, J = 15.7, 1.5 Hz, 1H, CH-C_2), 6.88 (dd, J = 15.9, 5.6 Hz, 1H, CH-C_3).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

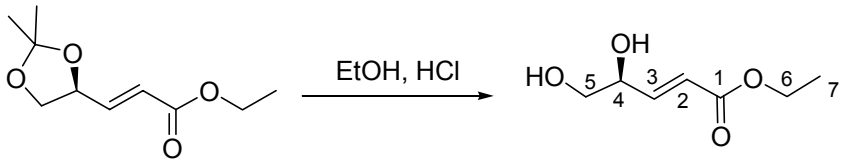
δ = 14.2 (C_5), 25.8 ($C_{6'/7'}$), 26.5 ($C_{6'/7'}$), 60.5 (C_4), 68.9 ($C_{5'}$), 75.0 ($C_{4'}$), 110.2 ($C_{2'}$), 122.5 (C_2), 144.7 (C_3), 166.0 (C_1).

$[\alpha]_D^{20}$ = 41.3° (c = 1.29, $CHCl_3$).

Analytical data are in a good agreement with literature. [114]

4.1.3. Synthesis of (*S*,*E*)-4,5-dihydroxy-pent-2-enoic acid ethyl ester (12)

Method 1



11 **12**

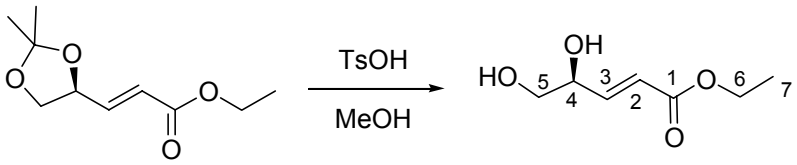
The compound was synthesized according to literature. [115] To the solution of compound **11** (1.90 g, 9.5 mmol) in ethanol (20 ml) hydrochloric acid (2 M, 9.5 ml, 18.9 mmol) was added. After 2.5 h stirring at room temperature the reaction mixture was neutralized with $NaHCO_3$ and the solvent was evaporated. The solid was washed with ethyl acetate (3×30 ml) and dried over $MgSO_4$, then the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 2:1 to EE).

R_f = 0.14 (CH/EE 1:1).

Yield 1.0 g (67%).

Method 2



11 **12**

The compound was synthesized according to literature procedure for acetonide group cleavage. [116] To the solution of compound **11** (2.44 g, 12.2 mmol) in methanol (23 ml) several crystals of TsOH were added at 0 °C. Overnight stirring at room temperature. Methanol was evaporated. Flash-column chromatography (silica gel, CH/EE = 2:1 to EE).

R_f = 0.14 (CH/EE 1:1).

Yield 1.43 g (73%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.26 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.45-3.93 (bs × 2, 2H, OH), 3.51 (dd, J = 11.2, 6.9 Hz, 1H, CH_A-C_5), 3.71 (dd, J = 11.4, 3.2 Hz, 1H, CH_B-C_5), 4.17 (q, J = 7.0 Hz, 2H, CH_2-C_6), 4.38 (m_c, 1H, CH-C_4), 6.10 (dd, J = 15.7, 1.8 Hz, 1H, CH-C_2), 6.87 (dd, J = 15.7, 4.5 Hz, 1H, CH-C_3).

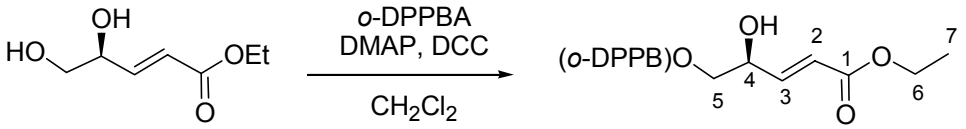
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.2 (C_7), 60.8 (C_6), 65.6 (C_5), 71.7 (C_4), 122.0 (C_2), 146.3 (C_3), 166.6 (C_1).

$[\alpha]_D^{20}$ = -10.1° (c = 1.615, $CHCl_3$).

Analytical data are in a good agreement with literature. [115]

4.1.4. Synthesis of (*S*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-hydroxy-pent-2-enoic acid ethyl ester (13)



12 **13**

The compound was synthesized according to literature. [83]

To the solution containing diol **$$3** (0.45 g, 2.8 mmol), *o*-DPPBA (0.89 g, 2.9 mmol, 1.03 eq) and DMAP (67.8 mg, 0.56 mmol, 0.2 eq) in dichloromethane (5 ml) solution of DCC (0.572 g, 2.8, 1 eq) was dropwise added at 0 °C. After stirring at room temperature overnight the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 10:1 to 2:1).

R_f = 0.53 (CH/EE 1:1).

Yield 0.85 g (69%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.18 (bs, 1H, OH), 4.07 (dd, J = 11.3, 8.1 Hz, 1H, CH_A-C_5), 4.20 (q, J = 7.1 Hz, 2H, CH_2-C_6), 4.32 (dd, J = 11.3, 3.0 Hz, 1H, CH_B-C_5), 4.46 (m_c, 1H, CH-C_4), 6.16 (dd, J = 15.7, 1.9 Hz, 1H, CH-C_2), 6.83 (dd, J = 15.6, 4.2 Hz, 1H, CH-C_3), 6.94-7.00 (m, 1H, Ar-H), 7.21-7.43 (m, 12H, Ar-H), 8.05-8.10 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.2 (C_7), 60.5 (C_6), 68.3 ($C_{4/5}$), 69.1 ($C_{4/5}$), 122.8 (C_2), 128.7 (d, $J_{C,P}$ = 7.3 Hz), 128.7, 129.1 (d, $J_{C,P}$ = 5.8 Hz), 131.3 (d, $J_{C,P}$ = 4.4 Hz), 132.4, 133.8 (d, $J_{C,P}$ = 18.8 Hz), 134.0 (d, $J_{C,P}$ = 18.9 Hz), 135.0, 136.9 (d, $J_{C,P}$ = 5.8 Hz), 137.0 (d, $J_{C,P}$ = 5.8 Hz), 144.1 (C_3), 166.1 (C_1), 167.1 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}O_2$R).

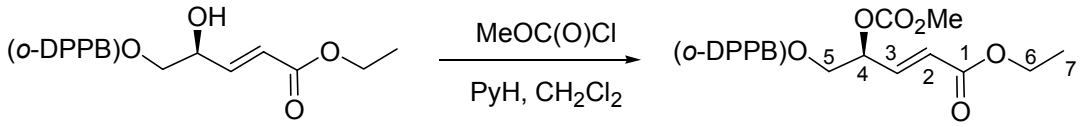
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.64.

Elemental analysis for **13**	$C_{26}H_{25}O_5P$	M_r= 448.45
Calculated, %:	C 69.64	H 5.62
Found, %:	C 68.67	H 5.79

$[\alpha]_D^{20}$ = 4.2° (c = 1.95, CH_2Cl_2).

4.1.5. Synthesis of (*S*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-methoxycarbonyloxy-pent-2-enoic acid ethyl ester (13)



13 **14**

The compound was synthesized according to literature procedure for carbonate synthesis. [112] To a stirred solution of the ester **13** (799 mg, 1.8 mol) and pyridine (0.5 ml, 5.4 mmol, 3 eq) in CH_2Cl_2 (17 ml) was added dropwise methyl chloroformate (0.14 ml, 2 mmol, 1.1 eq) at 0 °C, and stirring was continued for 1 h at the same temperature. The reaction mixture was evaporated and was chromatographed on silica gel (CH/EE = 10:1 to 5:1) as eluent to give allylic carbonate **14** (685 mg, 76%) as a yellowish oil.

R_f = 0.56 (CH/EE 1:1).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.79 (s, 3H, OMe), 4.21 (q, J = 7.5 Hz, 2H, CH_2-C_6), 4.24 (dd, J = 12.0, 6.7 Hz, 1H, CH_A-C_5), 4.40 (dd, J = 11.9, 3.9 Hz, 1H, CH_B-C_5), 5.51 (m_c, 1H, CH-C_4), 6.11 (dd, J = 15.8, 1.5 Hz, 1H, CH-C_2), 6.84 (dd, J = 15.8, 5.2 Hz, 1H, CH-C_3), 6.92-6.97 (m, 1H, Ar-H), 7.23-7.42 (m, 12H, Ar-H), 8.00-8.07 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.2 (C_7), 55.2 (OMe), 60.8 (C_6), 64.6 (C_5), 74.0 (C_4), 124.3 (C_2), 128.3, 128.5 (d, $J_{C,P}$ = 1.8 Hz), 128.6 (d, $J_{C,P}$ = 1.8 Hz), 128.7 (d, $J_{C,P}$ = 1.8 Hz), 130.9 (d, $J_{C,P}$ = 2.6 Hz), 132.3, 133.5 (d, $J_{C,P}$ = 19.0 Hz), 133.9 (d, $J_{C,P}$ = 20.7 Hz), 134.0 (d, $J_{C,P}$ = 20.7 Hz), 134.4, 137.7 (d, $J_{C,P}$ = 2.6 Hz), 137.8 (d, $J_{C,P}$ = 2.9 Hz), 140.1 (C_3), 141.1 (d, $J_{C,P}$ = 27.4 Hz), 154.7 (RO<u>C</u>O_2R´), 165.4 (C_1), 166.1 (d, $J_{C,P}$ = 2.0 Hz, Ar<u>C</u>O_2R).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

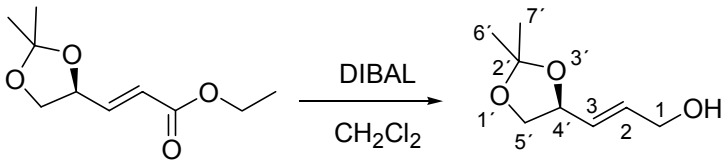
δ = -4.30.

Elemental analysis for **14**	$C_{28}H_{27}O_7P$	M_r= 506.48
Calculated, %:	C 66.40	H 5.37
Found, %:	C 66.13	H 5.23

$[\alpha]_D^{20}$ = -4.4° (c = 2.230, CH_2Cl_2).

Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 90/10, room temperature, 0.8 ml/min, 230 nm):
R_T[(*S*)-**14**]= 15.2 min,
R_T[(*R*)-**14**]= 13.5 min.

4.1.6. Synthesis of (*S*,*E*)-3-[(4´)-2´,2´-dimethyl-1´,3´-dioxolan-4´-yl]-prop-2-en-1-ol (15)



11 **15**

The compound was synthesized according to literature. [114] To the cooled to -78 °C solution of the ester **11** (2.64 g, 13.2 mmol) in CH_2Cl_2 (70 ml) was slowly added DIBAL-H (4.7 g, 5.9 ml, 33 mmol, 2.51 eq) in CH_2Cl_2 (20 ml). After 2.5 h stirring at the temperature saturated aqueous solution of K/Na-tartrate (20 ml) was added and stirred at room temperature till clear solution was formed, then extracted with CH_2Cl_2 (5×40 ml) and dried over Na_2SO_4, then the solvent was evaporated.
Flash-column chromatography (silica gel, CH/EE = 2:1 to 1:2).
R_f = 0.21 (CH/EE 1:1).
Yield 1.65 g (80%).

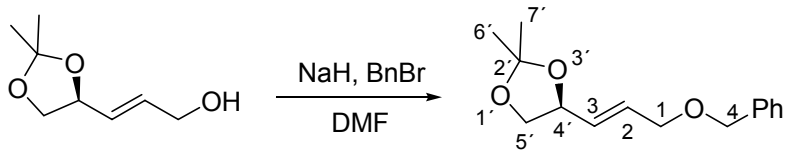
^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 1.39 (s, 3H, CH_3-$C_{6'/7'}$), 1.43 (s, 3H, CH_3-$C_{6'/7'}$), 3.60 (dd, *J* = 7.9, 7.9, 1H, CH_A-$C_{5'}$), 4.10 (dd, *J* = 8.2, 6.2 Hz, 1H, CH_B-$C_{5'}$), 4.17 (d, *J* = 4.7 Hz, 2H, CH_2-C_1), 4.54 (ddd, *J* = 7.0, 7.0, 7.0 Hz, 1H, CH-$C_{4'}$), 5.72 (ddt, *J* = 15.5, 7.3, 1.5 Hz, 1H, CH-C_3), 5.96 (dtd, *J* = 15.4, 5.1, 0.6 Hz, 1H, CH-C_2).

^{13}C-NMR (100.620 MHz, $CDCl_3$):
δ = 25.9 ($C_{6'/7'}$), 26.7 ($C_{6'/7'}$), 62.6 (C_1), 69.4 ($C_{5'}$), 76.5 ($C_{4'}$), 109.4 ($C_{2'}$), 128.5 ($C_{2/3}$), 133.5 ($C_{2/3}$).

$[\alpha]_D^{22}$ = 30.8° (c = 2.305, $CHCl_3$).

Analytical data are in a good agreement with literature. [114]

4.1.7. Synthesis of (*S*,*E*)-3-[(4´)-2´,2´-dimethyl-1´,3´-dioxolan-4´-yl]-prop-2-en-1-yl-benzylether (16)



15 **16**

The compound was synthesized according to literature. [114] To the suspension of NaH (60%, 511 mg, 12.8 mmol, 1.5 eq) in DMF (15 ml) at -60 °C the solution of the alcohol **15** (1.35 g, 8.5 mmol) in DMF (15 ml) was added dropwise. After stirring at -30 °C for 1 h BnBr (1.42 ml, 2.04 g, 12.0 mmol, 1.4 eq) was added and stirred overnight at room temperature. Then saturated aqueous solution of NaCl (110 ml) was added, extracted with Et_2O (4×100 ml) and dried over Na_2SO_4, then the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 6:1 to 4:1).

R_f = 0.58 (CH/EE 1:1).

Yield 1.69 g (80%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.40 (s, 3H, CH_3-$C_{6'/7'}$), 1.43 (s, 3H, CH_3-$C_{6'/7'}$), 3.60 (dd, J = 8.1, 7.8, 1H, CH_A-$C_{5'}$), 4.04 (d, J = 5.3 Hz, 2H, CH_2-C_1), 4.09 (dd, J = 8.1, 6.2 Hz, 1H, CH_B-$C_{5'}$), 4.49-4.56 (m, 3H, CH-$C_{4'}$ and CH_2-C_4), 5.74 (dd, J = 15.5, 7.2 Hz, 1H, CH-C_3), 5.91 (dt, J = 15.5, 5.3 Hz, 1H, CH-C_2), 7.24-7.36 (m, 5H, Ar-H).

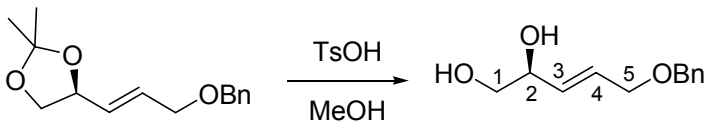
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 26.0 ($C_{6'/7'}$), 26.8 ($C_{6'/7'}$), 69.5, 69.9, 72.4, 76.6, 109.4 ($C_{2'}$), 127.7, 127.8, 128.5, 130.2, 130.7, 138.2 (C_3).

$[\alpha]_D^{20}$ = 26.5° (c = 2.490, $CHCl_3$).

Analytical data are in a good agreement with literature. [114]

4.1.8. Synthesis of (*S*,*E*)-5-benzyloxypent-3-en-1,2-diol (17)



16 **17**

The compound **17** was synthesized analogously to **12** (see chapter 4.1.3.) starting from the protected diol **16** (1.69 g, 6.81 mmol).

R_f = 0.09 (CH/EE 1:1).

Yield 1.20 g (84%), clear oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

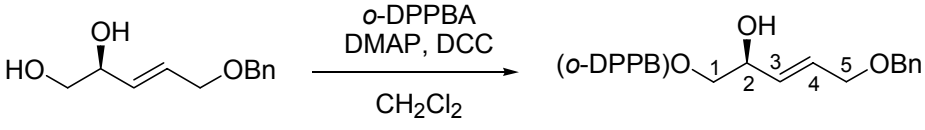
δ = 2.60 (bs, 1H, OH), 2.78 (bs, 1H, OH), 3.47 (dd, J = 11.4, 7.1 Hz, 1H, CH_A-C_1), 3.62 (dd, J = 11.2, 3.0 Hz, 1H, CH_B-C_1), 4.02 (d, J = 5.6 Hz, 2H, CH_2-C_5), 4.23 (m_c, 1H, CH-C_2), 4.51 (s, 2H, CH_2Ph), 5.73 (ddt, J = 15.5, 5.7, 1.4 Hz, 1H, CH-C_3), 5.90 (dtd, J = 15.7, 5.6, 1.3 Hz, 1H, CH-C_4), 7.26-7.37 (m, 5H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 66.3, 70.1, 72.5, 72.6, 127.8 (Ar-C), 127.9 (Ar-C), 128.5 (Ar-C), 129.0, 131.6, 138.1 (Ar-C).

$[\alpha]_D^{20}$ = 4.24 (2.335, $CHCl_3$).

4.1.9. Synthesis of (*S*,*E*)-5-benzyloxy-1-[2-(diphenylphosphanyl)benzoyloxy]-pent-3-en-2-ol (18)



17 **18**

The compound **18** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the diol **17** (0.59 g, 2.83 mmol).

R_f = 0.46 (CH/EE 1:1).

Yield 0.78 g (56%), light-yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.00 (bs, 1H, OH), 4.01 (d, J = 5.2 Hz, 2H, CH_2-C_5), 4.08 (dd, J = 11.0, 8.0 Hz, 1H, CH_A-C_1), 4.25 (dd, J = 11.2, 3.0 Hz, 1H, CH_A-C_1), 4.33 (m_c, 1H, CH-C_2), 4.48 (s, 2H, C$\underline{H_2}$Ph), 5.70 (dd, 1H, J = 15.5, 5.6 Hz, CH-C_3), 5.92 (dt, 1H, J = 15.5, 5.4 Hz, CH-C_4), 6.94-7.00 (m, 1H, Ar-H), 7.24-7.42 (m, 12H, Ar-H), 8.06-8.11 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 69.0, 69.6, 69.8, 72.1, 127.5, 127.6, 128.3, 128.6 (d, $J_{C,P}$ = 7.3 Hz), 128.8 (d, $J_{C,P}$ = 4.4 Hz), 129.4, 129.9, 131.1 (d, $J_{C,P}$ = 2.9 Hz), 132.1, 133.7 (d, $J_{C,P}$ = 20.3 Hz), 133.9 (d, $J_{C,P}$ = 20.4 Hz), 134.5, 134.7 (d, $J_{C,P}$ = 20.3 Hz), 137.1 (d, $J_{C,P}$ = 8.7 Hz), 137.2 (d, $J_{C,P}$ = 8.7 Hz), 138.2, 139.9 (d, $J_{C,P}$ = 23.3 Hz), 166.9 ($ArCO_2R$).

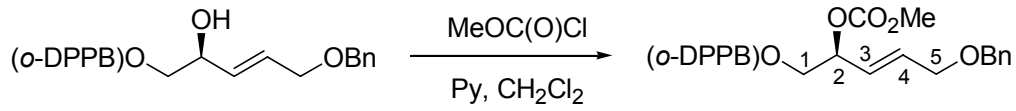
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.70.

Elemental analysis for **18**	$C_{26}H_{25}O_5P$	M_r= 496.53
Calculated, %:	C 74.99	H 5.89
Found, %:	C 74.66	H 5.90

$[\alpha]_D^{20}$ = 4.4° (c = 1.67, CH_2Cl_2).

4.1.10. Synthesis of (*S*,*E*)-5-benzyloxy-1-[2-(diphenylphosphanyl)benzoyloxy]-2-methoxy-carbonyloxypent-3-en (19)



18 **19**

The carbonate **19** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **18** (0.42 g, 0.84 mmol).

R_f = 0.72 (CH/EE 1:1).

Yield 0.32 g (69%), light-yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.77 (s, 3H, OCOMe), 4.01 (ddd, J = 5.2, 1.6, 0.9 Hz, 2H, CH_2-C_5), 4.23 (dd, J = 12.0, 7.2 Hz, 1H, CH_A-C_1), 4.36 (dd, J = 12.0, 3.8 Hz, 1H, CH_B-C_1), 4.49 (s, 2H, CH_2Ph), 5.39 (m_c, 1H, CH-C_2), 5.74 (ddt, 1H, J = 15.7, 6.7, 1.6 Hz, CH-C_3), 5.97 (dtd, 1H, J = 15.7, 5.2, 1.1 Hz, CH-C_4), 6.91-6.96 (m, 1H, ArH), 7.22-7.40 (m, 12H, ArH), 8.02-8.08 (m, 1H, ArH).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 55.0 (OCOMe), 65.5 (C_1), 69.5 (C_5), 72.4 (CH_2Ph), 75.5 (C_2), 125.6 (C_3), 127.76, 127.78, 128.3, 128.4, 128.5 (d, $J_{C,P}$ = 7.0 Hz), 128.6 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.9 (d, $J_{C,P}$ = 2.7 Hz), 132.3 (C_4), 132.4, 133.7 (d, $J_{C,P}$ = 18.8 Hz), 133.9 (d, $J_{C,P}$ = 20.8 Hz), 134.0 (d, $J_{C,P}$ = 20.8 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 10.9 Hz), 138.0 (d, $J_{C,P}$ = 11.4 Hz), 138.1, 141.1 (d, $J_{C,P}$ = 27.3 Hz), 155.0, 166.1 (d, $J_{C,P}$ = 2.2 Hz, ArCO).

Signal assignment from 2D-NMR experiment.

HRMS, CI (NH_3):	calculated	555.193653
$C_{33}H_{31}O_6P$ (M+H)	found	555.193797

^{31}P-NMR (161.984 MHz, $CDCl_3$):

δ = -4.66.

Elemental analysis for **19**	$C_{26}H_{25}O_5P$	M_r= 554.57
Calculated, %:	C 71.47	H 5.63
Found, %:	C 71.33	H 5.70

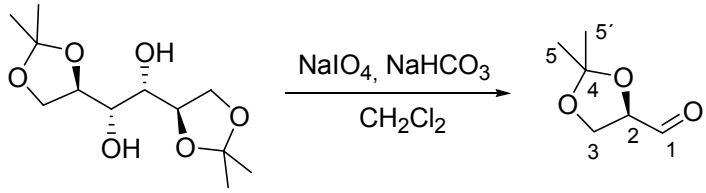
$[\alpha]_D^{20}$ = 5.1° (c = 0.545, $CHCl_3$).

Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 85/15, room temperature, 0.8 ml/min, 270 nm):

R_T[(*S*)-**19**]= 15.2 min,

R_T[(*R*)-**19**]= 13.5 min.

4.1.11. Synthesis of (*R*)-2,3-*O*-isopropyliden-glyceraldehyde (6)



5 **6**

The compound was synthesized according to literature. [113] To the solution of protected D-mannitol (**5**) (5.50 g, 20.9 mmol) in CH_2Cl_2 (50 ml) at 0 °C saturated aqueous $NaHCO_3$ solution (2 ml) was added. Then solid $NaIO_4$ (8.8 g, 41.1 mmol) was slowly added while stirring. After 2 h stirring at room temperature $MgSO_4$ was added, filtered, washed with CH_2Cl_2 (2×70 ml) and the solvent was evaporated. Kugelrohr distillation (70 °C at 10 mbar).

Yield 2.46 g (45%), viscous liquid.

It is very important to keep the product under argon excluding from moisture and air.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.29 (s, 3H, CH_3-$C_{5/5'}$), 1.36 (s, 3H, CH_3-$C_{5/5'}$), 3.88-3.92 (m, 2H, CH_2-C_3), 4.07-4.14 (m, 1H, CH_1-C_2), 9.52 (d, J = 1.8 Hz, 1H, CH-C_1).

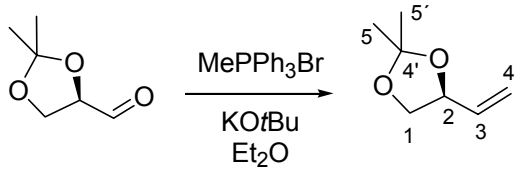
^{13}C-NMR (100.620 MHz, C_6D_6):

δ = 25.1 ($C_{5/5'}$), 26.2 ($C_{5/5'}$), 65.3 (C_3), 80.0 (C_2), 111.0 (C_4), 200.8 (C_1).

$[\alpha]_D^{21}$ = 42.5° (c = 1.63, $CHCl_3$).

Analytical data are in a good agreement with literature. [113]

4.1.12. Synthesis of (*S*)-2,2-dimethyl-4-vinyl-[1,3]dioxolane (7)



6 **7**

The compound was synthesized according to literature. [117] *t*-BuOK (650 mg, 5.83 mmol) in Et_2O (8 ml) at 0 °C under argon was added to $MePPh_3Br$ (2.1g, 5.88 mmol). After 1.5 h of stirring a solution of the aldehyde **6** (750 mg, 5.77 mmol) in of anhydrous Et_2O (3 ml) was added and stirred 3 h. The reaction mixture was quenched with Et_2O and water. The organic phase was separated, washed, dried with $MgSO_4$ and concentrated. Kugelrohr-distillation (50°C at 50 mmHg).

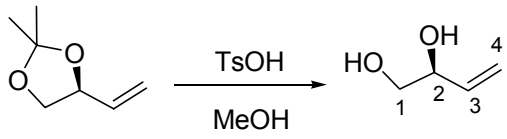
Yield 0.87 g (36%).

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.30 (s, 3H, CH_3-$C_{5/5'}$), 1.34 (s, 3H, CH_3-$C_{5/5'}$), 3.50 (dd, J = 8.2, 8.2 Hz, 1H, CH_A-C_1), 4.01 (dd, J = 8.2, 6.3 Hz 1H, CH_B-C_1), 4.41 (m_c, 1H, CH-C_2), 5.12 (bd, J = 10.3 Hz, 1H, CH_A-C_4), 5.25 (bd, J = 17.2 Hz, 1H, CH_B-C_4), 5.74 (ddd, J = 17.2, 10.3, 7.0 Hz, 1H, CH-C_3).

Analytical data are in a good agreement with literature. [117]

4.1.13. Synthesis of (*S*)-but-3-ene-1,2-diol (8)



7 **8**

The diol **8** was synthesized analogously to **12** (see chapter 4.1.3.) starting from the compound **7** (0.76 g, 5.9 mmol).

R_f = 0.09 (CH/EE 1:1).

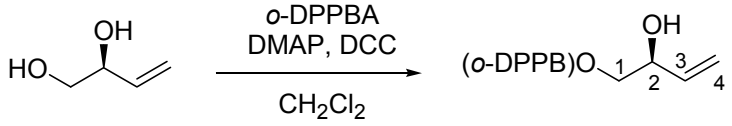
Yield 0.37 g (71%), colourless liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 3.40 (dd, J = 11.3, 7.6 Hz, 1H, CH_A-C_1), 3.48 (dd, J = 11.3, 3.4 Hz, 1H, CH_B-C_1), 3.65-3.70 (bs×2, 2H, OH), 4.16 (m_c, 1H, CH-C_2), 5.12 (bd, J = 10.6 Hz, 1H, CH_A-C_4), 5.27 (bd, J = 17.3 Hz, 1H, CH_B-C_4), 5.77 (ddd, J = 17.3, 10.6, 5.6 Hz, 1H, CH-C_3).

Analytical data are in a good agreement with literature. [118]

4.1.14. Synthesis of 2-(diphenylphosphanyl)benzoic acid (*S*)-2-hydroxybut-3-en-1-yl ester (9)



8 **9**

The compound **9** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the diol **8** (0.83 g, 9.48 mmol).

R_f = 0.48 (CH/EE 1:1).

Yield 2.98 g (84%), light-yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 2.90 (m_c, 1H, CH-C_2), 4.07 (dd, J = 11.1, 8.1 Hz, 1H, CH_A-C_1), 4.26 (dd, J = 11.2, 3.0 Hz, 1H, CH_B-C_1), 4.30 (bs, 1H, OH), 5.19 (ddd, J = 10.5, 1.5, 1.5 Hz, 1H, CH_A-C_4), 5.36 (ddd, J = 17.3, 1.5, 1.5 Hz, 1H, CH_B-C_4), 5.78 (ddd, J = 17.3, 10.6, 5.3 Hz, 1H, CH-C_3), 6.93-6.99 (m, 1H, Ar-H), 7.23-7.45 (m, 12H, Ar-H), 8.06-8.12 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 69.4 (C_1), 70.5 (C_2), 117.2, 128.7 (d, $J_{C,P}$ = 7.0 Hz), 129.0 (d, $J_{C,P}$ = 5.8 Hz), 131.3 (d, $J_{C,P}$ = 3.4 Hz), 132.3, 133.8 (d, $J_{C,P}$ = 20.0 Hz), 133.9 (d, $J_{C,P}$ = 20.0 Hz), 134.7, 134.9, 135.5, 137.0 (d, $J_{C,P}$ = 8.7 Hz), 137.2 (d, $J_{C,P}$ = 9.7 Hz), 139.0 (d, $J_{C,P}$ = 23.4 Hz), 167.1 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>O).

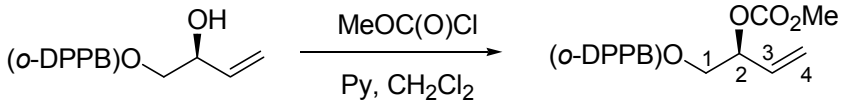
^{31}P-NMR (161.984 MHz, $CDCl_3$):

δ = -4.94.

HRMS, CI (NH_3):	calculated	377.13066
$C_{23}H_{21}O_3P$ ($M+NH_4$)	found	377.13060

Elemental analysis for **9**	$C_{23}H_{21}O_3P$	M_r=376.38
Calculated, %:	C 73.39	H 5.62
Found, %:	C 73.22	H 5.68

4.1.15. Synthesis of 2-(diphenylphosphanyl)benzoic acid (*S*)-2-methoxycarbonyloxy-but-3-enyl ester (10)



9 **10**

The carbonate **10** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **9** (0.46 g, 1.23 mmol).

R_f = 0.65 (CH/EE 1:1).

Yield 0.43 g (81%), light-yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.78 (s, 3H, OCOMe), 4.23 (dd, J = 12.0, 7.2 Hz, 1H, CH_A-C_1), 4.37 (dd, J = 12.0, 3.7 Hz, 1H, CH_B-C_1), 5.29 (ddd, J = 10.6, 1.1, 1.1 Hz, 1H, CH_A-C_4), 5.35 (m_c, 1H, CH-C_2), 5.40 (ddd, J = 17.2, 1.1, 1.1 Hz, 1H, CH-C_4), 5.79 (ddd, J = 17.2, 10.6, 6.3 Hz, 1H, CH-C_3), 6.91-6.96 (m, 1H, ArH), 7.23-7.41 (m, 12H, ArH), 8.03-8.08 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 55.0 (OCOMe), 65.3 (C_1), 76.1 (C_2), 119.6, 128.3, 128.5 (d, $J_{C,P}$ = 6.3 Hz), 128.7, 130.9 (d, $J_{C,P}$ = 2.7 Hz), 131.8, 132.3, 133.7 (d, $J_{C,P}$ = 18.8 Hz), 133.9 (d, $J_{C,P}$ = 20.8 Hz), 134.0 (d, $J_{C,P}$ = 20.5 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 11.1 Hz), 138.0 (d, $J_{C,P}$ = 11.3 Hz), 141.0 (d, $J_{C,P}$ = 27.3 Hz), 155.0, 166.1 (d, $J_{C,P}$ = 2.2 Hz, ArCO).

^{31}P-NMR (161.984 MHz, $CDCl_3$):

δ = -4.63.

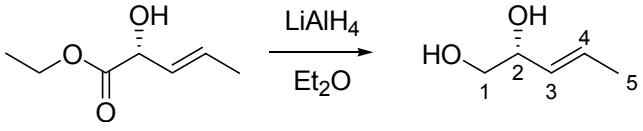
$[\alpha]_D^{20}$ = -12.0° (c = 0.2, $CHCl_3$).

HRMS, CI (NH_3):	calculated	435.136138
$C_{25}H_{23}O_5P$ (M+H)	found	435.135100

Elemental analysis for **10**	$C_{25}H_{23}O_5P$	M_r=434.42
Calculated, %:	C 69.12	H 5.34
Found, %:	C 69.36	H 5.39

Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 90/10, room temperature, 0.8 ml/min, 230 nm):
R_T[(*S*)-**10**]= 10.2 min,
R_T[(*R*)-**10**]= 9.2 min.

4.1.16. Synthesis of (*R*,*E*)-pent-3-ene-1,2-diol (31)



30 **31**

2-Hydroxy-pent-3-enoic acid ethyl ester (**30**) is synthesized in our lab. [81] The α-hydroxy ester **30** (0.963 g, 6.7 mmol) was added dropwise to suspension of $LiAlH_4$ (0.254 g, 0.67 mmol) in abs. ether (20 ml). After stirring 1 h at room temperature saturated aqueous solution of Na_2SO_4 was added until no more bubbles of hydrogen were evaluated, then solid Na_2SO_4 was added, filtered, washed with ether (~ 60 ml). The solvent was evaporated.
Flash-column chromatography (silica gel, CH/EE = 1:1 to EE).
R_f = 0.05 (CH/EE 1:1).
Yield 0.462 g (71%), colourless liquid.

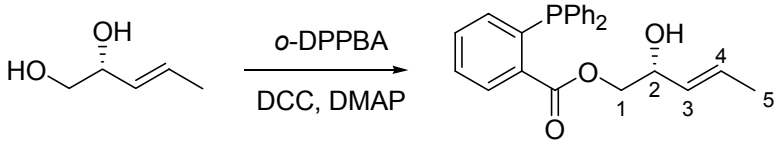
^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 1.67 (ddd, *J* = 6.6, 0.9, 1.6 Hz, 3H, CH_3-C_5), 3.40 (dd, *J* = 11.4, 7.8 Hz, 1H, CH_A-C_1), 3.55 (dd, *J* = 11.4, 3.3 Hz, 1H, CH_B-C_1), 3.70 (s, 2H, OH), 4.12 (m_c, 1H, CH-C_2), 5.40 (ddq, *J* = 15.4, 6.7, 1.6 Hz, 1H, CH-C_3), 5.72 (dqd, *J* = 15.4, 6.6, 1.3 Hz, 1H, CH-C_4).

^{13}C-NMR (100.620 MHz, $CDCl_3$):
δ = 14.3 ($\underline{C}H_3CH_2$), 46.7 (C_4), 53.1 (COO$\underline{Me}$), 53.2 (COO$\underline{Me}$), 60.6 ($CH_3\underline{C}H_2$), 64.47 (C_5), 64.49 ($\underline{C}(COOMe)_2$), 122.6, 126.0 (C_2).

$[\alpha]_D^{20}$ = -22.8° (c = 1.56, $CHCl_3$).

HRMS, CI (NH_3):	calculated	120.102454
$C_5H_{10}O_2$ ($M+NH_4$)	found	120.102197

4.1.17. Synthesis of (*R*,*E*)-1-[2-(diphenylphosphanyl)benzoyloxy]-2-hydroxypent-3-en (32)



31 **32**

The ester **32** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the doil **31** (0.426 g, 4.18 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.55 (CH/EE 1:1).

Yield 1.71 g (97%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.69 (d, J = 6.3 Hz, 3H, CH_3-C_5), 2.63 (bs, 1H, OH), 3.93 (dd, J = 11.6, 9.1 Hz, 1H, CH-C_2), 4.21-4.27 (m, 2H, CH_2-C_1), 5.40 (dd, J = 15.5, 6.3 Hz, 1H, CH-C_3), 5.78 (dq, J = 15.5, 6.6 Hz, 1H, CH-C_4), 6.93-6.98 (m, 1H, Ar-H), 7.23-7.47 (m, 12H, Ar-H), 8.08-8.12 (m, 1H, Ar-H).

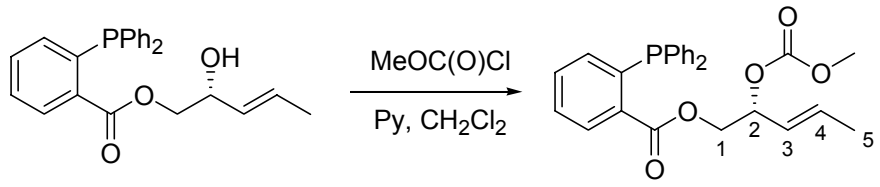
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 17.9 (C_5), 69.5, 70.3, 128.3, 128.6, 128.7 (d, $J_{C,P}$ = 6.5 Hz), 129.0 (d, $J_{C,P}$ = 7.5 Hz), 129.3, 131.3 (d, $J_{C,P}$ = 3.2 Hz), 132.3, 133.8 (d, $J_{C,P}$ = 19.3 Hz), 134.0 (d, $J_{C,P}$ = 20.4 Hz), 134.7, 134.9 (d, $J_{C,P}$ = 21.5 Hz), 137.1, 137.1 (d, $J_{C,P}$ = 18.3 Hz), 138.8 (d, $J_{C,P}$ = 23.6 Hz), 167.1 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>OO).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.85.

4.1.18. Synthesis of (*R*,*E*)-1-[2-(diphenylphosphanyl)benzoyloxy]-2-methoxycarbonyloxy-pent-3-en (33)



32 **33**

The carbonate **33** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the ester **32** (1.59 g, 4.08 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.65 (CH/EE 1:1).

Yield 1.57 g (86%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.71 (ddd, J = 6.6, 1.6, 0.6 Hz, 3H, CH_3-C_5), 3.77 (s, 3H, C$\underline{H}_3$OCO), 4.20 (dd, J = 11.9, 7.5 Hz, 1H, CH_A-C_1), 4.33 (dd, J = 12.0, 3.6 Hz, 1H, CH_B-C_1), 5.30 (ddd, J = 7.6, 7.6, 3.6 Hz, 1H, CH-C_2), 5.44 (ddq, J = 15.4, 7.6, 1.6 Hz, 1H, CH-C_3), 5.88 (dqd, J = 15.4, 6.6, 0.9 Hz, 1H, CH-C_4), 6.92-6.95 (m, 1H, Ar-H), 7.23-7.41 (m, 12H, Ar-H), 8.04-8.07 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 18.0 (C_5), 54.9 ($\underline{C}H_3OCO$), 65.7 (C_1), 76.4 (C_2), 124.7 (C_3), 128.3, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.9 (d, $J_{C,P}$ = 2.7 Hz), 132.1 (d, $J_{C,P}$ = 13.0 Hz), 132.2 (C_4), 132.6, 133.7, 134.0 (d, $J_{C,P}$ = 20.5 Hz), 134.1 (d, $J_{C,P}$ = 20.5 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 2.9 Hz), 138.0 (d, $J_{C,P}$ = 2.9 Hz), 141.0 (d, $J_{C,P}$ = 27.5 Hz), 155.1 ($CH_3O\underline{C}O$), 166.2 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (161.968 MHz, $CDCl_3$):

δ = -4.70.

$[\alpha]_D^{20}$ = -7.1° (c = 0.24, $CHCl_3$).

HRMS, CI (NH_3):	calculated	449.151788
$C_{26}H_{25}O_5P$ (M+H)	found	449.152298

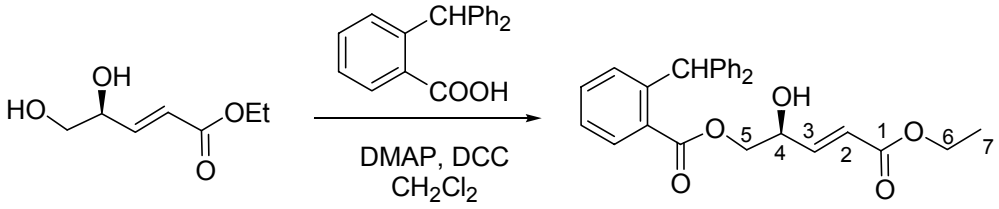
Chiral HPLC (Chiracel OD-H, n-heptane/*iso*-propanol 90/10, room temperature, 0.8 ml/min, 230 nm):

R_T[(*S*)-**33**]= 12.8 min,

R_T[(*R*)-**33**]= 13.9 min.

4.2. Synthesis of carbonatesbearing carbon analogue of o-DPPBA

4.2.1. Synthesis of 2-(benzhydryl)benzoic acid (*S*,*E*)-4-ethoxycarbonyl-2-hydroxybut-3-enyl ester (24)



12 **24**

The compound **24** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the compound **12** (0.37 g, 2.33 mmol).

R_f = 0.54 (CH/EE 1:1).

Yield 0.51 g (50%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.28 (t, *J* = 7.1 Hz, 3H, CH_3-C_7), 2.05 (d, *J* = 4.7 Hz, 1H, OH), 4.03 (dd, *J* = 11.4, 7.1 Hz, 1H, CH_A-C_5), 4.19 (q, *J* = 7.1 Hz, 2H, CH_2-C_6), 4.28 (dd, *J* = 11.4, 3.3 Hz, 1H, CH_B-C_5), 4.35 (m_c, 1H, CH-C_4), 4.29 (dd, *J* = 11.8, 3.1 Hz, 1H, CH_B-C_5), 6.12 (dd, *J* = 15.7, 1.9 Hz 1H, CH-C_2), 6.48 (s, 1H, C<u>H</u>Ph_2), 6.83 (dd, *J* = 15.7, 4.3 Hz, 1H, CH-C_3), 6.97-7.07 (m, 5H, ArH), 7.17-7.31 (m, 7H, ArH), 7.40 (ddd, *J* = 7.6, 7.6, 1.5 Hz, 1H, ArH), 7.81 (dd, *J* = 7.7, 1.4 Hz, 1H, ArH).

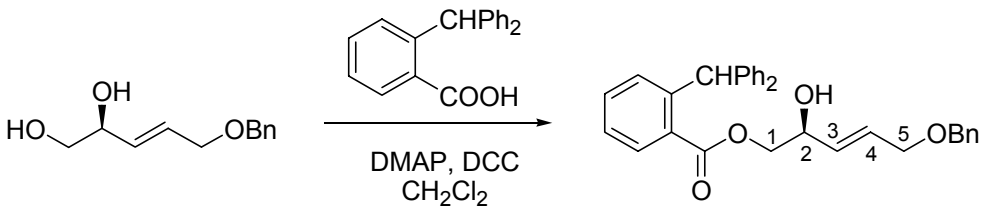
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.3 (C_7), 52.7 (Ph_2<u>C</u>HAr), 60.7 (C_6), 67.8 (C_5), 69.5 (C_4), 122.8, 126.4, 126.5, 128.40, 128.41, 129.8, 130.5, 131.1, 131.9, 143.6, 143.8, 144.5, 144.6, 166.1 (C_1), 168.0 (Ar<u>C</u>O_2).

HRMS, EI:	calculated	430.17802
$C_{27}H_{26}O_5$	found	430.17710

Elemental analysis for **24**	$C_{27}H_{26}O_5$	M_r=430.49
Calculated, %:	C 75.33	H 6.09
Found, %:	C 74.85	H 6.09

4.2.2. Synthesis of 2-(benzhydryl)benzoic acid (*S*,*E*)-5-benzyloxy-2-hydroxypent-3-enyl ester (25)



17 **25**

The compound **25** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the compound **17** (0.61 g, 2.93 mmol).

R_f = 0.56 (CH/EE 1:1).

Yield 0.93 g (67%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.81 (d, J = 4.0 Hz, 1H, OH), 4.00 (m_c, 1H, CH_A-C_5), 4.02 (m_c, 1H, CH_B-C_5), 4.04 (dd, J = 12.2, 3.8 Hz, 1H, CH_A-C_1), 4.22 (dd, J = 12.2, 3.3 Hz, 1H, CH_B-C_1), 4.25 (m_c, 1H, CH-C_2), 4.49 (s, 2H, C$\underline{H}_2$Ph), 5.69 (ddt, J = 15.5, 5.7, 1.5 Hz, 1H, CH-C_3), 5.89 (dtd, J = 15.5, 5.6, 1.4 Hz, 1H, CH-C_4), 6.52 (s, 1H, C$\underline{H}$Ph$_2$), 7.00 (bd, J = 7.8 Hz, 1H, ArH), 7.04-7.07 (m, 4H, ArH), 7.18-7.36 (m, 12H, ArH), 7.39 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H, ArH), 7.83 (ddd, J = 7.7, 1.5, 0.4 Hz, 1H, ArH).

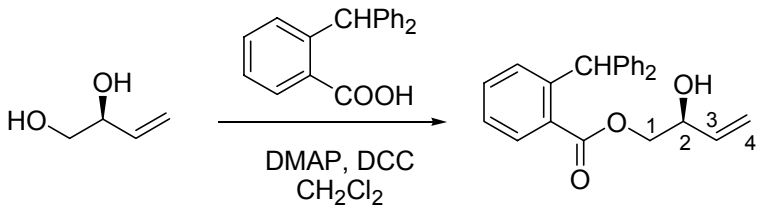
^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 52.6 (Ph$_2$C$\underline{H}$Ar), 68.6 (C_2), 70.1, 70.2, 72.4, 126.4 126.5, 127.7, 127.8, 128.3, 128.4, 128.5, 129.6, 129.8, 130.3, 130.5, 130.7, 131.1, 131.7, 138.2, 143.7, 143.9, 144.5, 168.0 (Ar$\underline{C}$O$_2$).

$[\alpha]_D^{20}$ = 14.9° (c = 0.565, $CHCl_3$).

HRMS, CI (NH_3):	calculated	496.248784
$C_{32}H_{30}O_4$ (M+NH_4)	found	496.248303

4.2.3. Synthesis of 2-(benzhydryl)benzoic acid (*S*)-2-hydroxybut-3-en-1-yl ester (26)



8 **26**

The compound **26** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the compound **8** (0.48 g, 5.49 mmol).

R_f = 0.56 (CH/EE 1:1).

Yield 1.41 g (72%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

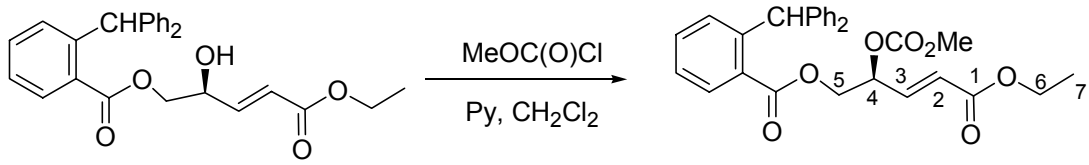
δ = 1.91 (d, J = 4.4 Hz 1H, OH), 4.05 (dd, J = 12.1, 8.1 Hz, 1H, CH_A-C_1), 4.22 (m_c, 1H, CH-C_2), 4.24 (dd, J = 12.1, 3.3 Hz, 1H, CH_B-C_1), 5.19 (ddd, J = 10.5, 1.3, 1.3 Hz, 1H, CH_A-C_4), 5.32 (ddd, J = 17.2, 1.4, 1.4 Hz, 1H, CH_B-C_4), 5.77 (ddd, J = 17.2, 10.5, 5.3 Hz, 1H, CH-C_3), 6.53 (s, 1H, C<u>H</u>Ph_2), 7.00-7.08 (m, 5H, ArH), 7.17-7.30 (m, 7H, ArH), 7.38 (ddd, J = 7.7, 7.7, 1.6 Hz, 1H, ArH), 7.84 (dd, J = 7.7, 1.5 Hz, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 55.0 (<u>C</u>HPh_2), 65.0 (C_1), 76.1 (C_2), 119.7, 126.31, 126.35, 128.3, 129.73, 129.77, 130.1, 130.8, 131.2, 131.8, 143.8, 145.1, 155.1 (CH_3O<u>C</u>O), 167.2 (Ar<u>C</u>O_2).

HRMS, CI (NH_3):	calculated	376.19127
$C_{24}H_{22}O_3$ (M+NH_4)	found	376.19170

4.2.4. Synthesis of 2-(benzhydryl)benzoic acid (*S*,*E*)-4-ethoxycarbonyl-2-methoxy-carbonyloxy-but-3-enyl ester (27)



24 **27**

The cabbonate **27** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **24** (0.20 g, 0.46 mmol).

R_f = 0.77 (CH/EE 1:1).

Yield 0.17 g (76%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.28 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.78 (s, 3H, $OCO_2C\underline{H}_3$), 4.19 (q, J = 7.1 Hz, 2H, CH_2-C_6), 4.20 (dd, J = 12.0, 6.6 Hz, 1H, CH_A-C_5), 4.37 (dd, J = 12.0, 3.8 Hz, 1H, CH_B-C_5), 5.50 (m_c, 1H, CH-C_4), 6.10 (dd, J = 15.8, 1.6 Hz, 1H, CH-C_2), 6.54 (s, 1H, $C\underline{H}Ph_2$), 6.83 (dd, J = 15.8, 5.2 Hz, 1H, CH-C_3), 7.00-7.07 (m, 5H, ArH), 7.17-7.31 (m, 7H, ArH), 7.40 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H, ArH), 7.86 (dd, J = 7.7, 1.4 Hz, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.2 (C_7), 52.4 ($\underline{C}HPh_2$), 55.3 ($\underline{Me}OCO$), 60.9 (C_6), 64.4 (C_5), 74.1 (C_4), 124.3 (C_2), 126.4, 128.3, 129.73, 129.76, 129.8, 130.7, 131.2, 131.9, 140.2 (C_3), 143.70, 143.72, 145.1, 154.8 (MeO$\underline{C}$O), 165.4, 167.0.

Signal assignment from 2D-NMR experiment.

$[\alpha]_D^{20}$ = 0.48° (c = 0.415, $CHCl_3$).

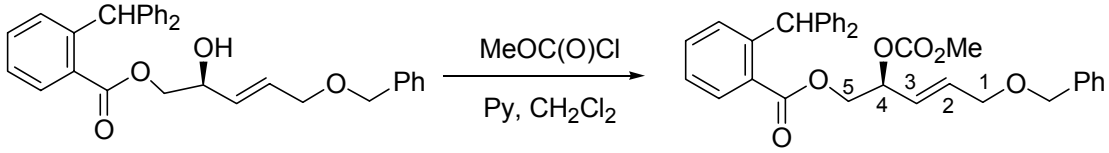
HRMS, CI (NH_3):	calculated	506.217879
$C_{29}H_{28}O_7$ (M+NH_4)	found	506.218404

Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 97/3, room temperature, 0.8 ml/min, 230 nm):

R_T[(*S*)-**27**]= 24.5 min,

R_T[(*R*)-**27**]= 22.1 min.

4.2.5. Synthesis of 2-(benzhydryl)benzoic acid (*S*,*E*)-5-benzyloxy-2-methoxycarbonyloxy-pent-3-enyl ester (28)



25 **28**

The compound **28** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **25** (0.93 g, 1.95 mmol).

R_f = 0.74 (CH/EE 1:1).

Yield 0.67 g (64%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.74 (s, 3H, C<u>H</u>$_3$OCO), 4.00 (m_c, 1H, CH_A-C_1), 4.02 (m_c, 1H, CH_B-C_1), 4.18 (dd, J = 12.0, 7.2 Hz, 1H, CH_A-C_5), 4.29 (dd, J = 12.0, 3.8 Hz, 1H, CH_B-C_5), 4.48 (s, 2H, C<u>H</u>$_2$Ph), 5.40 (m_c, 1H, CH-C_4), 5.73 (ddt, J = 15.7, 6.7, 1.6 Hz, 1H, CH-C_3), 5.97 (dtd, J = 15.7, 5.2, 1.0 Hz, 1H, CH-C_4), 6.57 (s, 1H, C<u>H</u>Ph$_2$), 7.00-7.07 (m, 5H, ArH), 7.15-7.35 (m, 12H, ArH), 7.39 (ddd, J = 9.2, 9.2, 1.5 Hz, 1H, ArH), 7.85 (dd, J = 7.8, 1.5 Hz, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 52.3 (<u>Me</u>OCO), 55.0 (<u>C</u>HPh$_2$), 65.2, 69.5, 72.5, 75.5 (C_4), 125.5, 126.3, 126.4, 127.8, 128.3, 128.5, 129.7, 129.8, 130.1, 130.8, 131.2, 131.8, 132.4, 138.1, 143.8, 145.1, 155.0 (MeO<u>C</u>O), 167.2 (Ar<u>C</u>O).

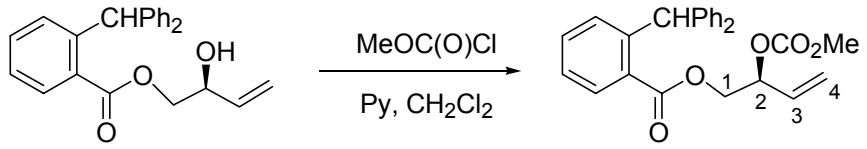
HRMS, CI (NH_3):	calculated	554.254264
$C_{34}H_{32}O_6$ (M+NH_4)	found	554.254604

Chiral HPLC (Chiracel OD-H, n-heptane/iso-propanol 97/3, room temperature, 0.8 ml/min, 230 nm):

R_T[(*S*)-**28**]= 33.7 min,

R_T[(*R*)-**28**]= 39.0 min.

4.2.6. Synthesis of 2-benzhydryl-benzoic acid (*S*)-2-methoxycarbonyloxy-but-3-enyl ester (29)



26 **29**

The compound **29** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **26** (0.58 g, 1.63 mmol).

R_f = 0.73 (CH/EE 1:1).

Yield 0.57 g (84%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.68 (s, 3H, C$\underline{H}_3$OCO), 4.12 (dd, *J* = 12.7, 7.1 Hz, 1H, CH_A-C_1), 4.22 (dd, *J* = 11.9, 3.7 Hz, 1H, CH_B-C_1), 5.22 (ddd, *J* = 10.6, 1.1, 1.1 Hz, 1H, CH-C_4), 5.28 (m_c, 1H, CH-C_2), 5.33 (ddd, *J* = 17.2, 1.2, 1.1 Hz, 1H, CH-C_4), 5.70 (ddd, *J* = 17.2, 10.7, 6.3 Hz, 1H, CH-C_3), 6.51 (s, 1H, C$\underline{H}$Ph$_2$), 6.93-7.01 (m, 5H, ArH), 7.08-7.22 (m, 7H, ArH), 7.31 (dddd, *J* = 7.3, 7.3, 1.5, 0.4 Hz, 1H, ArH), 7.85 (ddd, *J* = 7.8, 1.5, 0.4 Hz, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 52.3 (C$\underline{H}_3$OCO), 55.0 (C$\underline{H}$Ph$_2$), 65.0 (C_1), 76.1 (C_2), 119.7, 126.31, 126.35, 128.3, 129.73, 129.77, 130.1, 130.8, 131.2, 131.8, 143.8, 145.1, 155.1 ($CH_3O\underline{C}O$), 167.2 (Ar$\underline{C}O_2$).

$[\alpha]_D^{20}$ = -6.1° (c = 0.38, $CHCl_3$).

HRMS, CI (NH_3):	calculated	434.196749
$C_{26}H_{24}O_5$ (M+NH_4)	found	434.197101

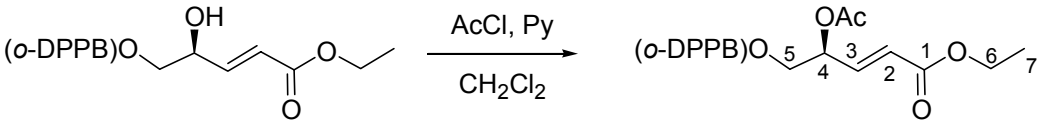
Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 95/5, room temperature, 0.8 ml/min, 230 nm):

R_T[(*S*)-**29**]= 9.3 min,

R_T[(*R*)-**29**]= 8.5 min.

4.3. Synthesis of allylic substrates bearing acyl as a leaving group

4.3.1. Synthesis of (*S*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-acetoxypent-2-enoic acid ethyl ester (20)



12 **20**

The compound was synthesised analogously to synthesis of **14** (see chapter 4.1.5.) using AcCl (1.1 eq) instead of MeOC(O)Cl from the compound **12** (0.58 g, 1.63 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).
R_f = 0.58 (CH/EE 1:1).
Yield 1.69 g (67%).

^{1}H-NMR (400.132 MHz, C_6D_6):
δ = 0.93 (t, J = 7.2 Hz, 3H, CH_3-C_7), 1.54 (s, 3H, C(O)CH_3), 3.85 (dd, J = 12.5, 6.5 Hz, 1H, CH_A-C_5), 3.95 (q, J = 7.1 Hz, 2H, CH_2-C_6), 4.07 (dd, J = 11.9, 3.8 Hz, 1H, CH_B-C_5), 5.49 (m, 1H, CH-C_4), 6.01 (dd, J = 15.8, 2.2 Hz, 1H, CH-C_2), 6.77 (dd, J = 15.7, 5.5 Hz, 1H, CH-C_3), 6.87-7.42 (m, 13H, ArH), 8.03-8.06 (m, 1H, ArH).

^{13}C-NMR (100.612 MHz, C_6D_6):
δ = 14.1 (C_7), 20.2 ($\underline{C}H_3C(O)$), 60.4 (C_6), 64.7 (C_5), 70.3 (C_4), 123.8 (C_2), 128.3, 128.7 (d, $J_{C,P}$ = 2.4 Hz), 128.8 (d, $J_{C,P}$ = 2.4 Hz), 131.0 (d, $J_{C,P}$ = 2.7 Hz), 132.2, 134.2 (d, $J_{C,P}$ = 20.8 Hz), 134.3 (d, $J_{C,P}$ = 21.0 Hz), 134.4 (d, $J_{C,P}$ = 19.6 Hz), 138.8 (d, $J_{C,P}$ = 12.3 Hz), 138.9 (d, $J_{C,P}$ = 12.8 Hz), 141.4 (C_3), 141.7 (d, $J_{C,P}$ = 29.2 Hz), 165.2 (C_1), 166.0 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}O_2$), 169.0 ($CH_3\underline{C}(O)$).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, C_6D_6):
δ = -3.98.

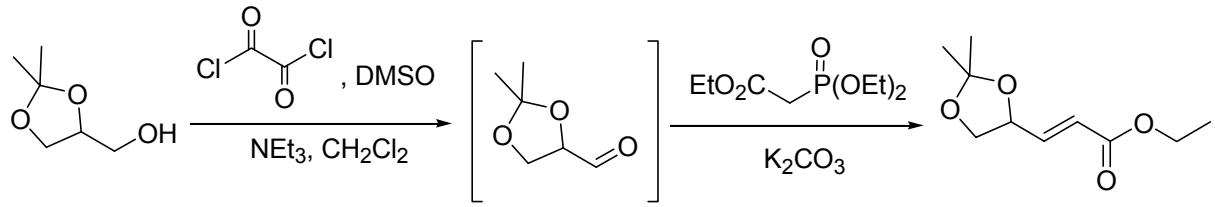
HRMS, CI (NH_3):	calculated	491.162353
$C_{28}H_{27}O_6P$ (M+H)	found	491.161102

Elemental analysis for **20**	$C_{28}H_{27}O_6P$	M_r=490.15
Calculated, %:	C 68.56	H 5.55
Found, %:	C 68.07	H 5.66

Chiral HPLC (Chiracel OD-H, n-heptane/ethanol 90/10, room temperature, 0.8 ml/min, 230 nm):
R_T[(*S*)-**20**-oxide]= 23.6 min,
R_T[(*R*)-**20**-oxide]= 26.8 min.

4.4. Synthesis of racemic compounds

4.4.1. Synthesis of *rac*-(*E*)-3-[(4´)-2´,2´-dimethyl-1´,3´-dioxolane-4´-yl]-prop-2-enic acid ethyl ester (*rac*-11)



***rac*-34** ***rac*-6** ***rac*-11**

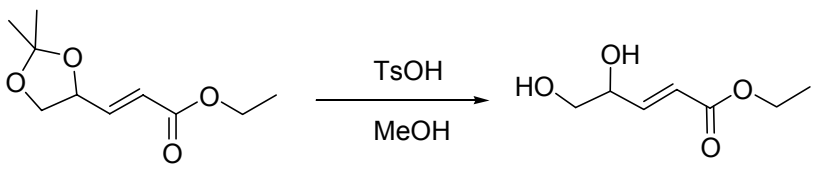
The compound was synthesized according to procedure developed in our laboratory. [83] To a stirred solution of oxalylchloride (2.73 ml, 4.04 g, 31.8 mmol, 1.2 eq) in CH_2Cl_2 (60ml) at -60 °C DMSO (4.52 ml, 4.97 g, 63.6 mmol, 2.4 eq) was slowly added. In 10 minutes a solution of Solketal (***rac*-34**) (3.50 g, 26.5 mmol) in CH_2Cl_2 (40 ml) was slowly added. After stirring during 20 minutes at -60°C triethylamine (18.4 ml, 13.4 g, 133 mmol, 5.0 eq) was added and cooling bath was replaced by ice-bath. After 1.5 h stirring at 0 °C saturated solution of K_2CO_3 (100 ml), solid $NaHCO_3$ (45 g, 0.53 mol, 20 eq), H_2O (20 ml) and triethyl phosphonoacetate (13.3 ml, 14.9 g, 66.3 mmol, 2.5 eq) were slowly added and after 10 minutes at 0°C the reaction mixture was stirred for 20 h at room temperature. Water (400 ml) was added to the suspension, phases were separated, aqueous phase was extracted with CH_2Cl_2 (2×200 ml). The combined organic phases were dried over Na_2SO_4.

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

Yield 78%.

Analytical data are described above for the ester **11**.

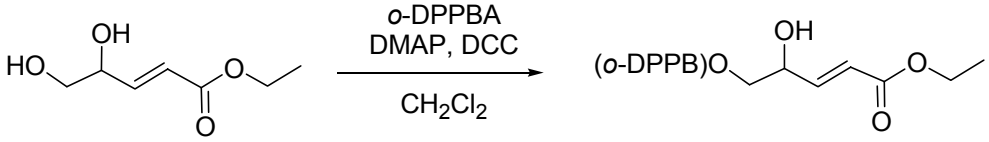
4.4.2. Synthesis of *rac*-(*E*)-4,5-dihydroxypent-2-enoic acid ethyl ester (*rac*-12)



***rac*-11** ***rac*-12**

The synthesis was performed analogously to synthesis of the diol **12**.
Analytical data are described above for **12**.

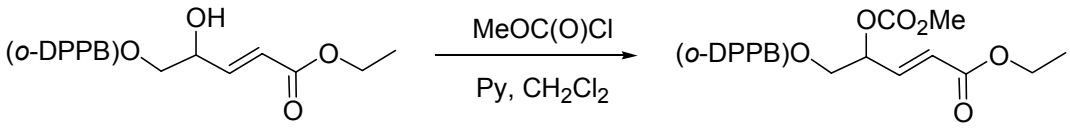
4.4.3. Synthesis of *rac*-(*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-hydroxypent-2-enoic acid ethyl ester (*rac*-13)



***rac*-12** ***rac*-13**

The synthesis was performed analogously to synthesis of **13**.
Analytical data are described above for **13**.

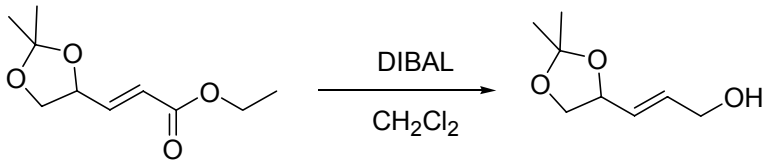
4.4.4. Synthesis of *rac*-(*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-methoxycarbonyloxy-pent-2-enoic acid ethyl ester (*rac-14*)



***rac*-13** ***rac*-14**

The synthesis was performed analogously to synthesis of **14**.
Analytical data are described above for **14**.

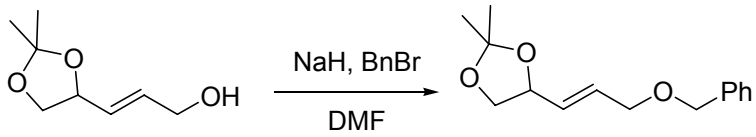
4.4.5. Synthesis of *rac*-(*E*)-3-[(4′)-2′,2′-dimethyl-1′,3′-dioxolan-4′-yl]-prop-2-en-1-ol (*rac*-15)



***rac*-11** ***rac*-15**

The synthesis was performed analogously to synthesis of **15**.
Analytical data are described above for **15**.

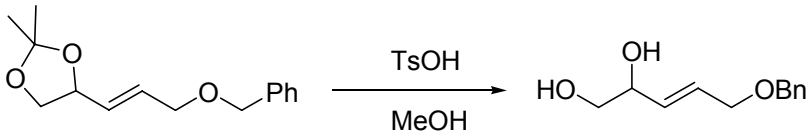
4.4.6. Synthesis of *rac*-(*E*)-3-[(4´)-2´,2´-dimethyl-1´,3´-dioxolan-4´-yl]-prop-2-en-1-ylbenzylether (*rac*-16)



***rac*-15** ***rac*-16**

The synthesis was performed analogously to synthesis of **16**.
Analytical data are described above for **16**.

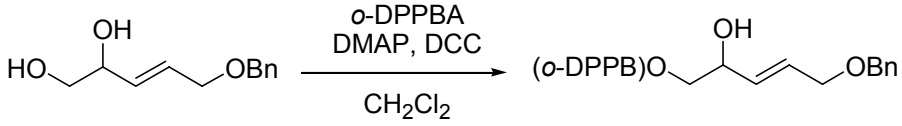
4.4.7. Synthesis of *rac*-(*E*)-5-benzyloxypent-3-en-1,2-diol (*rac*-17)



***rac*-16** ***rac*-17**

The synthesis was performed analogously to synthesis of **17**.
Analytical data are described above for **17**.

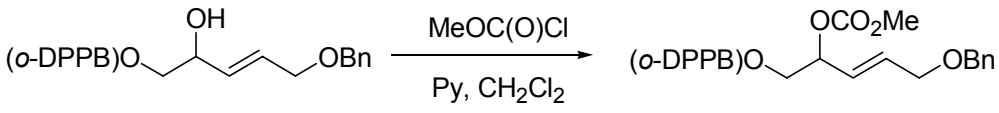
4.4.8. Synthesis of *rac*-(*E*)-5-benzyloxy-1-[2-(diphenylphosphanyl)benzoyloxy]pent-3-en-2-ol (*rac*-18)



***rac*-17** ***rac*-18**

The synthesis was performed analogously to synthesis of **18**.
Analytical data are described above for **18**.

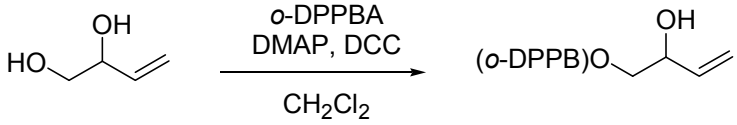
4.4.9. Synthesis of *rac*-(*E*)-5-benzyloxy-1-[2-(diphenylphosphanyl)benzoyloxy]-2-methoxycarbonyloxypent-3-en (*rac*-19)



***rac*-18** ***rac*-19**

The synthesis was performed analogously to synthesis of **19**.
Analytical data are described above for **19**.

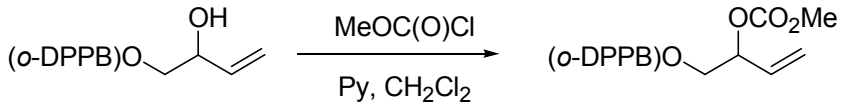
4.4.10. Synthesis of 2-(diphenylphosphanyl)benzoic acid *rac*-2-hydroxybut-3-enyl ester (*rac*-9)



***rac*-8** ***rac*-9**

The synthesis was performed analogously to synthesis of **9** (see chapter 4.1.14.) from commercially available *rac*-but-3-ene-1,2-diol (***rac*-8**).
Analytical data are described above for **8**.

4.4.11. Synthesis of 2-(diphenylphosphanyl)benzoic acid *rac*-2-methoxycarbonyloxybut-3-enyl ester (*rac*-10)

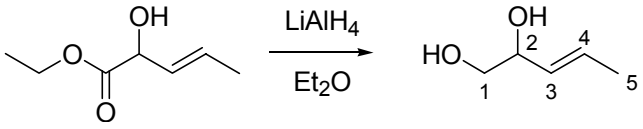


***rac*-9** ***rac*-10**

The synthesis was performed analogously to synthesis of **10**.

Analytical data are described above for **10**.

4.4.12. Synthesis of *rac*-(*E*)-pent-3-ene-1,2-diol (*rac*-31)

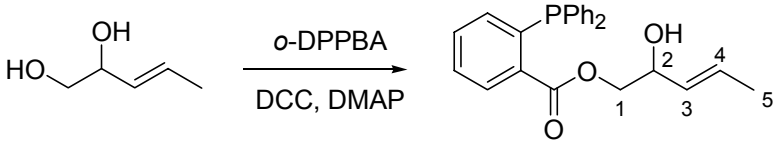


***rac*-30** ***rac*-31**

The synthesis was performed analogously to synthesis of **31**.

Analytical data are described above for **31**.

4.4.13. Synthesis of *rac*-(*E*)-1-[2-(diphenylphosphanyl)benzoyloxy]-2-hydroxypent-3-en (*rac*-32)

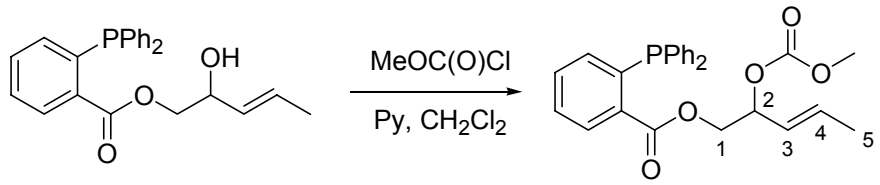


***rac*-31** ***rac*-32**

The synthesis was performed analogously to synthesis of **32**.

Analytical data are described above for **32**.

4.4.14. Synthesis of *rac*-(*E*)-1-[2-(diphenylphosphanyl)benzoyloxy]-2-methoxycarbonyloxypent-3-en (*rac*-33)

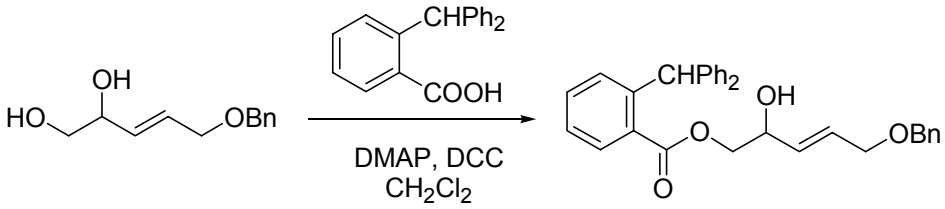


***rac*-32** ***rac*-33**

The synthesis was performed analogously to synthesis of **33**.

Analytical data are described above for **33**.

4.4.15. Synthesis of 2-(benzhydryl)benzoic acid *rac*-(*E*)-5-benzyloxy-2-hydroxypent-3-enyl ester (*rac*-25)

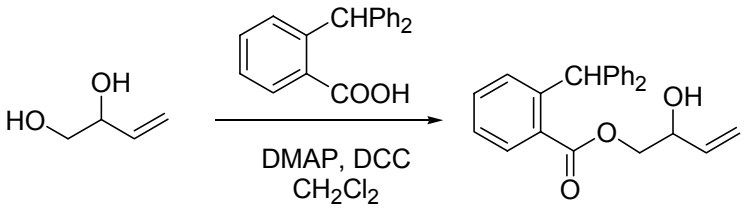


***rac*-17** ***rac*-25**

The synthesis was performed analogously to synthesis of **25**.

Analytical data are described above for **25**.

4.4.16. Synthesis of 2-(benzhydryl)benzoic acid *rac*-2-hydroxybut-3-enyl ester (*rac*-26)

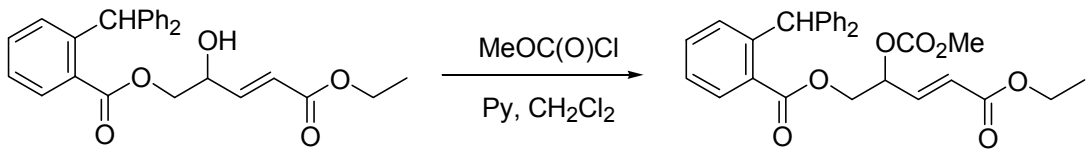


***rac*-8** ***rac*-26**

The synthesis was performed analogously to synthesis of **26**.

Analytical data are described above for **26**.

4.4.17. Synthesis of 2-(benzhydryl)benzoic acid *rac*-(*E*)-4-ethoxycarbonyl-2-methoxycarbonyloxy-but-3-enyl ester (*rac*-24)

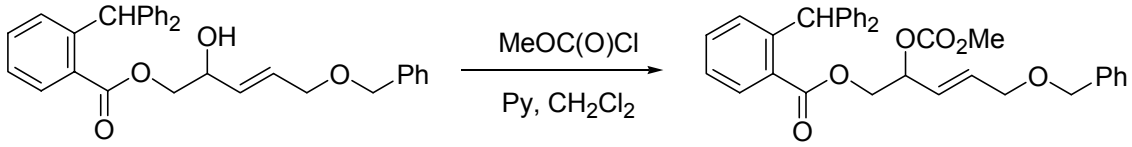


***rac*-12** ***rac*-24**

The synthesis was performed analogously to synthesis of **24**.

Analytical data are described above for **24**.

4.4.18. Synthesis of 2-(benzhydryl)benzoic acid *rac*-(*E*)-5-benzyloxy-2-methoxycarbonyloxypent-3-enyl ester (*rac*-28)

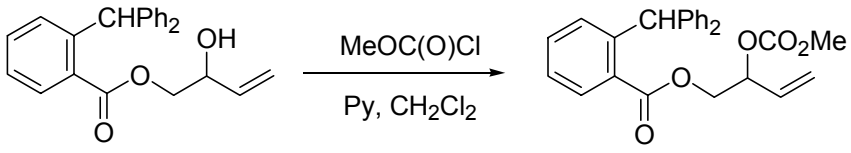


***rac*-25** ***rac*-28**

The synthesis was performed analogously to synthesis of **28**.

Analytical data are described above for **28**.

4.4.19. Synthesis of 2-(benzhydryl)benzoic acid *rac*-2-methoxycarbonyloxybut-3-enyl ester (*rac*-29)

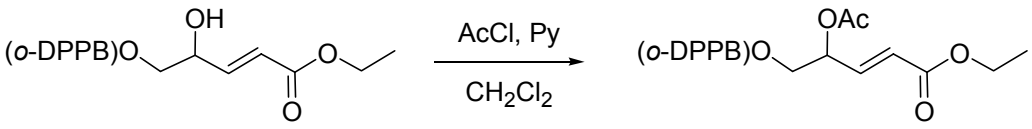


***rac*-26** ***rac*-29**

The synthesis was performed analogously to synthesis of **29**.

Analytical data are described above for **29**.

4.4.20. Synthesis of *rac*-(*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-acetoxypent-2-enoic acid ethyl ester (*rac*-27)

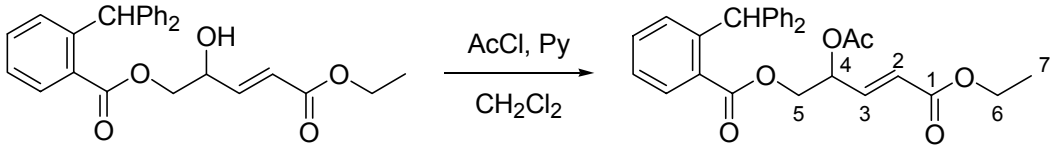


***rac*-24** ***rac*-27**

The synthesis was performed analogously to synthesis of **27**.

Analytical data are described above for **27**.

4.4.21. Synthesis of 2-(benzhydryl)benzoic acid *rac*-(*E*)-4-ethoxycarbonyl-2-acetoxybut-3-enyl ester (*rac*-47)



***rac*-24** ***rac*-47**

The acetate ***rac*-47** was synthesized analogously to **20** (see chapter 4.3.1.) starting from the compound ***rac*-24** (0.88 g, 2.01 mmol).

R_f = 0.58 (CH/EE 1:1).

Yield 0.82 g (97%), colourless oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 1.29 (t, J = 7.2 Hz, 3H, CH_3-C_7), 2.07 (s, 3H, C(O)C$\underline{H}_3$), 4.18-4.23 (dd, J = 11.9, ? Hz, 1H, CH_A-C_5 and q, J = 7.2 Hz, 2H, CH_2-C_6), 4.33 (dd, J = 11.9, 4.0 Hz, 1H, CH_B-C_5), 5.67 (m_c, 1H, CH-C_4), 6.05 (dd, J = 15.8, 1.8 Hz, 1H, CH-C_2), 6.57 (s, 1H, C$\underline{H}Ph_2$), 6.85 (dd, J = 15.8, 5.1 Hz, 1H, CH-C_3), 7.02-7.08 (m, 5H, ArH), 7.17-7.31 (m, 7H, ArH), 7.31 (ddd, J = 7.6, 7.6, 1.5 Hz, 1H, ArH), 7.83 (dd, J = 7.8, 1.5 Hz, 1H, ArH).

^{13}C-NMR (100.612 MHz, $CDCl_3$):

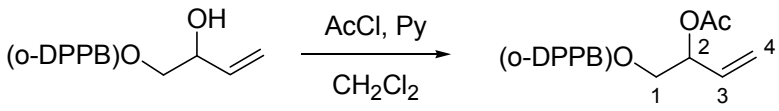
δ = 14.2 (C_7), 20.9 ($\underline{C}H_3C(O)$), 52.3 ($Ph_2\underline{C}H$), 60.8 (C_6), 64.4 (C_5), 70.2 (C_4), 123.8 (C_2), 126.35, 126.42, 128.3, 129.71, 129.73, 129.9, 130.6, 131.2, 131.9, 141.0 (C_3), 143.7, 145.1, 165.5, 167.0, 169.7.

Signal assignment from 2D-NMR experiment.

HRMS, CI (NH_3):	calculated	490.222964
$C_{29}H_{28}O_6$ ($M+NH_4$)	found	490.223195

Elemental analysis for ***rac*-47**	$C_{29}H_{28}O_6$	M_r=472.19
Calculated, %:	C 73.71	H 5.97
Found, %:	C 73.86	H 6.25

4.4.22. Synthesis of 2-(diphenylphosphanyl)benzoic acid *rac*-2-acetoxybut-3-enyl ester (*rac*-45)



***rac*-9** ***rac*-45**

The acetate ***rac*-45** was synthesized analogously to **20** (see chapter 4.3.1.) starting from the compound ***rac*-9** (2.18 g, 5.80 mmol).

R_f = 0.69 (CH/EE 1:1).

Yield 1.91 g (79%), yellowish oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 1.97 (s, 3H, C(O)C$\underline{H}_3$), 4.16 (dd, J = 11.8, 7.0 Hz, 1H, CH_A- C_1), 4.26 (dd, J = 11.8, 3.7 Hz, 1H, CH_B- C_1), 5.18 (ddd, J = 10.6, 1.3, 1.3 Hz, 1H, CH_A-C_4), 5.26 (ddd, J = 17.3, 1.3,1.3 Hz, 1H, CH_B-C_4), 5.45 (m_c, 1H, CH-C_2), 5.70 (ddd, J = 17.3, 10.6, 6.1 Hz, 1H, CH-C_3), 6.84-6.89 (m, 1H, ArH), 7.15-7.35 (m, 12H, ArH), 7.95-7.98 (m, 1H, ArH).

^{13}C-NMR (100.612 MHz, $CDCl_3$):

δ = 21.1 (C(O)<u>C</u>H$_3$), 65.4 (C$_1$), 72.1 (C$_2$), 118.9, 128.4, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7 (d, $J_{C,P}$ = 1.9 Hz), 130.8 (d, $J_{C,P}$ = 2.7 Hz), 132.3 (d, $J_{C,P}$ = 14.2 Hz), 133.7, 133.9 (d, $J_{C,P}$ = 20.8 Hz), 134.0 (d, $J_{C,P}$ = 20.8 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 10.93 Hz), 138.0 (d, $J_{C,P}$ = 11.1 Hz), 142.0 (d, $J_{C,P}$ = 27.0 Hz), 166.2 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>O), 170.1 (<u>C</u>(O)CH$_3$).

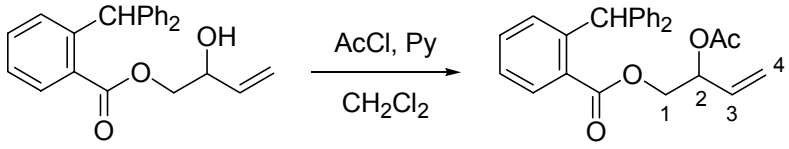
^{31}P-NMR (161.984 MHz, CDCl$_3$):

δ = -4.73.

HRMS, CI (NH_3):	calculated	419.141223
$C_{25}H_{23}O_4P$ (M+H)	found	419.141798

Elemental analysis for ***rac*-45**	$C_{25}H_{23}O_4P$	M_r=418.13
Calculated, %:	C 71.76	H 5.54
Found, %:	C 71.99	H 5.72

4.4.23. Synthesis of 2-(benzhydryl)benzoic acid *rac*-2-acetoxy-but-3-enyl ester (*rac*-46)



***rac*-26** ***rac*-46**

The acetate ***rac*-46** was synthesized analogously to **20** (see chapter 4.3.1.) starting from the compound ***rac*-26** (0.81 g, 2.27 mmol).

R_f = 0.70 (CH/EE 1:1).

Yield 0.78 g (86%), colourless oil.

^{1}H-NMR (400.132 MHz, CDCl$_3$):

δ = 1.96 (s, 3H, C(O)C<u>H</u>$_3$), 4.12 (dd, J = 11.8, 6.8 Hz, 1H, CH$_A$- C$_1$), 4.19 (dd, J = 11.8, 3.9 Hz, 1H, CH$_B$-C$_1$), 5.18 (ddd, J =10.6, 1.3, 1.3 Hz, 1H, CH$_A$-C$_4$), 5.26 (d, J = 17.2, 1.3, 1.3 Hz, 1H, CH$_B$-C$_4$), 5.45 (m$_c$, 1H, CH-C$_2$), 5.70 (ddd, J = 17.3, 10.6, 6.1 Hz, 1H, CH-C$_3$), 6.52 (s, 1H, C<u>H</u>Ph$_2$), 6.93-7.00 (m, 5H, ArH), 7.08-7.22 (m, 7H, ArH), 7.31 (ddd, J = 7.7 7.7, 1.5 Hz, 1H, ArH), 7.77 (ddd, J = 7.8, 1.5, 0.4 Hz, 1H, ArH).

^{13}C-NMR (100.612 MHz, $CDCl_3$):

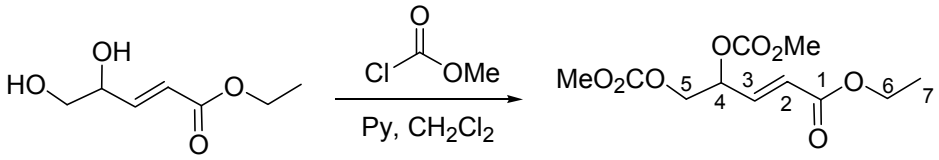
δ = 21.1 (C(O)C<u>H</u>$_3$), 52.2 (Ph_2C<u>H</u>), 65.2 (C_1), 72.1 (C_2), 126.3, 126.4, 128.3, 129.7, 129.8, 130.1, 130.7, 131.2, 131.8, 132.4, 143.8, 145.1, 167.2 (Ar<u>C</u>O), 170.0 (<u>C</u>(O)CH_3).

HRMS, CI (NH_3):	calculated	418.201834
$C_{26}H_{24}O_4$ (M+NH_4)	found	418.201504

Elemental analysis for ***rac*-46**	$C_{26}H_{24}O_4$	M_r=400.17
Calculated, %:	C 77.98	H 5.99
Found, %:	C 77.98	H 6.04

4.5. Synthesis of bis-carbonates

4.5.1. Synthesis of *rac*-(*E*)-4,5-bis-(methoxycarbonyloxy)pent-2-enoic acid ethyl ester (*rac*-51)



***rac*-12** ***rac*-51**

The bis-carbonate ***rac*-51** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the diol ***rac*-12** (207 mg, 1.38 mol) with 2.2 eq of methylchloroformate.

R_f = 0.48 (CH/EE 1:1).

Yield 243 mg (67%), colourless viscous liquid.

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 1.26 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.77 (s, 3H, OCO<u>Me</u>), 3.79 (s, 3H, OCO<u>Me</u>), 4.18 (q, J = 7.1 Hz, 2H, CH_2-C_6), 4.21 (dd, J = 11.9, 6.8 Hz, 1H, CH_A-C_5), 4.37 (dd, J = 11.9, 3.7 Hz, 1H, CH_B-C_5), 5.49 (m_c, 1H, CH-C_4), 6.10 (dd, J = 15.8, 1.6 Hz, 1H, CH-C_2), 6.81 (dd, J = 15.8, 5.2 Hz, 1H, CH-C_3).

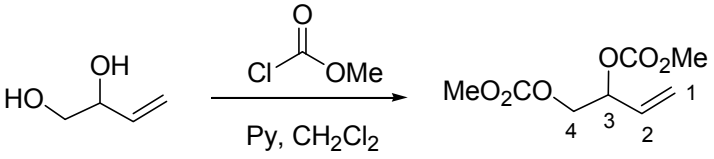
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.2 (C_7), 55.2 (OCO<u>Me</u>), 55.3 (OCO<u>Me</u>), 60.9 (C_6), 67.1 (C_5), 73.9 (C_4), 124.6 (C_2), 139.6 (C_3), 154.7 (O<u>C</u>OMe), 155.3 (O<u>C</u>OMe), 165.3 (C_1).

HRMS, CI (NH_3):	calculated	294.118894
$C_{11}H_{16}O_8$ (M+NH_4)	found	294.118700

Elemental analysis for ***rac*-51**	$C_{11}H_{16}O_8$	M_r= 276.24
Calculated, %:	C 47.83	H 5.84
Found, %:	C 47.68	H 5.77

4.5.2. Synthesis of *rac*-3,4-bis-(methoxycarbonyloxy)but-1-en (*rac*-50)



***rac*-8** ***rac*-50**

The compound ***rac*-50** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound ***rac*-8** (0.63 g, 4.12 mmol) with 2.2 eq of methylchloroformate.

R_f = 0.59 (CH/EE 1:1).

Yield 0.55 g (65%), colourless liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 3.78 (s, 6H, OCO<u>Me</u>×2), 4.18 (dd, J =11.8 Hz, 7.4 Hz, 1H, CH_A-C_4), 4.31 (dd, J =11.8 Hz, 3.6 Hz, 1H, CH_B-C_4), 5.30-5.38 (bd, J =10.4 Hz, 1H, CH_A-C_1 and m_c, 1H, CH-C_3), 5.44 (bd, J =18.3 Hz, 1H, CH_B-C_1), 5.76-5.87 (m_c, 1H, CH-C_2).

^{13}C-NMR (75.442 MHz, $CDCl_3$):

δ = 55.0 (OCO$_2$<u>Me</u>), 55.1 (OCO$_2$<u>Me</u>), 68.0 (C_4), 75.9 (C_3), 120.0 (C_1), 131.4 (C_2), 155.0 (O<u>C</u>O$_2$Me), 155.5 (O<u>C</u>O$_2$Me).

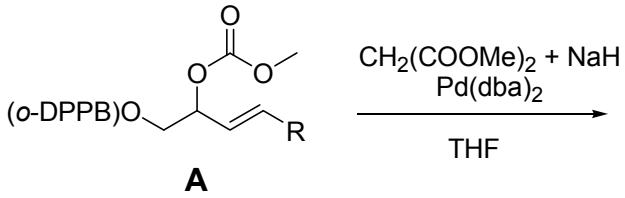
Elemental analysis for ***rac*-50**	$C_8H_{12}O_6$	M_r= 204.18
Calculated, %:	C 47.06	H 5.92
Found, %:	C 47.09	H 5.71

Analytical data are in a good agreement with literature. [119]

4.6. Palladium catalyzed allylic substitution

4.6.1. General procedure

4.6.1.1. Method I (dba-NaH-THF)

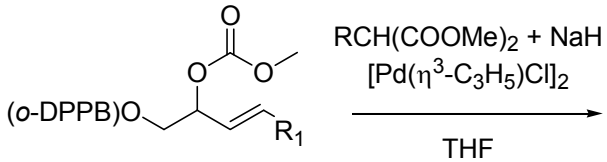


A

R= H, COOEt, CH_2OBn

A solution of allylic substrate **A** (0.198 mmol), $Pd(dba)_2$ (5.6 mg, 5 mol.%) in THF (1 ml) was stirred under argon 0.5 h. Then cooled to 0°C THF (1 ml) sodium dimethylmalonate solution (prepared by reaction of NaH (60% in mineral oil, 11.9 mg, 1,5 eq) and dimethylmalonate (36µl, 41.9 mg, 1.6 eq) in THF (1 ml)) was added. The reaction mixture was stirred at room temperature for 19 h. Flash chromatography (silica gel, CH/EE= 10:1 to 4:1).

4.6.1.2. Method II (allyl-NaH-THF)

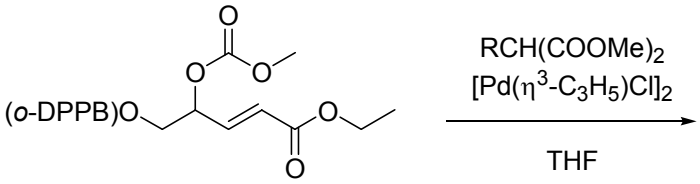


B

R_1 = H, COOEt, CH_2OBn;
R = H, p-Br-C_6H_4

A solution of allylic substrate **B** (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (1.8 mg, 5 mol.%) in THF (1 ml) was stirred under argon 0.5 h. Then of cooled to 0°C THF (1 ml) sodium dimethylmalonate solution (prepared by reaction of NaH (60% in mineral oil, 11.9 mg, 1.5 eq) and dimethylmalonate (36µl, 41.9 mg, 1.6 eq) in THF (1 ml)) was added. The reaction mixture was stirred at room temperature for 19 h. Flash chromatography (silica gel, CH/EE= 10:1 to 4:1).

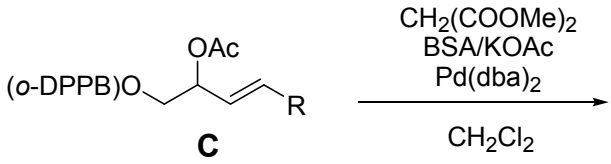
4.6.1.3.Method III (allyl-without base-THF)



A solution of allylic substrate **6** (100 mg, 0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (1.8 mg, 5 mol.%) in THF (2 ml) was stirred under argon 0.5 h. Then dimethylmalonate (36µl, 41.9 mg, 1.6 eq) was added. The reaction mixture was stirred at room temperature for 19 h. Flash chromatography (silica gel, CH/EE= 10:1 to 4:1).

No conversion was detected by NMR-analysis, only the stating material was separated.

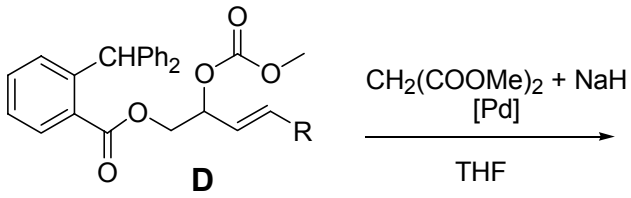
4.6.1.4.Method IV (allyl-BSA-KOAc-dichloromethane)



R= H, COOEt

A solution of allylic substrate **C** (0.2 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (1.8 mg, 5 mol.%), KOAc (c.a. 1 mg) in CH_2Cl_2 (1.5 ml) was stirred under argon 0.5 h. Then dimethylmalonate (69 µl, 3 eq) and BSA (148 µl, 3 eq) were added. The reaction mixture was stirred at room temperature for 19 h. Flash chromatography (silica gel, CH/EE= 10:1 to 4:1).

4.6.1.5.Method V (dba or allyl-carbon analog-NaH-THF)

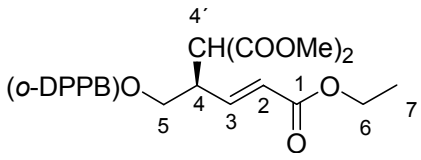


R= H, COOEt, CH_2OBn

A solution of allylic substrate **D** (0.198 mmol), $[Pd(\eta^3\text{-allyl})Cl]_2$ (1.8 mg, 5 mol.%) or $Pd(dba)_2$ (5.6 mg, 5 mol.%), PPh_3 (5.2 mg, 0,02 mmol, 10 mol.%) in THF (1 ml) was stirred under argon 0.5 h. Then 1 ml of cooled to 0°C THF sodium dimethylmalonate solution (prepared by reaction of NaH (60% in mineral oil, 11.9 mg, 1.5 eq) and diethylmalonate (36µl, 41.9 mg, 1.6 eq) in THF (1 ml)) was added. The reaction mixture was stirred at room temperature for 19 h. Flash chromatography (silica gel, CH/EE= 10:1 to 4:1).

4.6.2. Analytics for allylic substitution products

4.6.2.1. Synthesis of (*R*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-(di-(methoxycarbonyl)-methyl)-pent-2-enoic acid ethyl ester (38)



38

R_f = 0.54 (CH/EE 1:1).

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 1.28 (t, J = 7.1 Hz, 3H, CH_3-C_7), 3.34 (m_c, 1H, CH-C_4), 3.66 (d, J = 8.1 Hz, 1H, CH-$C_{4'}$), 3.69 (s, 3H, CH(COO<u>Me</u>)$_2$), 3.70 (s, 3H, CH(COO<u>Me</u>)$_2$), 4.18 (q, J = 7.2 Hz, 2H, CH_2-C_6), 4.24 (dd, J = 11.4, 5.6 Hz, 1H, CH_A-C_5), 4.34 (dd, J = 11.4, 5.9 Hz, 1H, CH_B-C_5), 5.93 (dd, J = 15.4, 0.7 Hz, 1H, CH-C_2), 6.90 (dd, J = 15.8, 8.9 Hz, 1H, CH-C_3), 6.91-6.97 (m, 1H, Ar-H), 7.21-7.43 (m, 12H, Ar-H), 7.96-8.04 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ =14.2 (C_7), 41.1 (C_4), 52.6, 52.7, 52.9, 60.6 (C_6), 64.8 (C_5), 125.0 (C_2), 128.4, 128.5, 128.6, 128.7, 130.7 (d, $J_{C,P}$ = 2.9 Hz), 132.3, 133.8 (d, $J_{C,P}$ = 18.9 Hz), 133.9 (d, $J_{C,P}$ = 20.4 Hz), 134.5, 137.8, 137.9 (d, $J_{C,P}$ = 2.9 Hz), 141.9 (d, 26.2 $J_{C,P}$ = Hz), 143.5 (C_3), 165.7 (C_1), 166.2 ($ArCO_2R$), 167.6 (<u>C</u>O_2Me), 167.7 (<u>C</u>O_2Me).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.76.

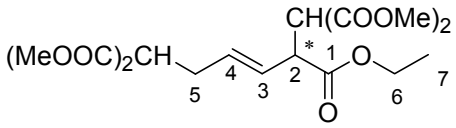
Elemental analysis for **38**	$C_{31}H_{31}O_8P$	M_r= 562.55
Calculated, %:	C 66.19	H 5.55
Found, %:	C 65.65	H 5.57

HRMS, CI (NH_3):	calculated	563.183483
$C_{31}H_{31}O_8P$ (M+H)	found	563.183601

$[\alpha]_D^{20}$ = 6.8° (c = 1.33, CH_2Cl_2).

Chiral HPLC (Chirapak AD-H, n-heptane/ethanol 40/60, room temperature, 0.8 ml/min, 230 nm):
R_T[(*major*)-**38**-oxide]= 12.1 min,
R_T[(*minor*)-**38**-oxide]= 15.6 min.

4.6.2.2.Synthesis of (*E*)-4,5-(di-(methoxycarbonyl)-methyl)-pent-2-enoic acid ethyl ester (42)

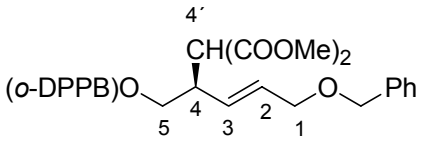


42

R_f = 0.64 (CH/EE 1:1).

^{1}H-NMR (300.064 MHz, $CDCl_3$):
δ = 1.26 (t, *J* = 7.1 Hz, 3H, CH_3-C_7), 1.71 (dd, *J* = 8.9, 5.0 Hz, 1H, CH_A-C_5), 1.81 (dd, *J* = 7.3, 5.0 Hz, 1H, CH_B-C_5), 2.66 (m_c, 1H, CH-C_2), 3.74 (s, 6H, CH(COO<u>Me</u>)$_2$), 3.76 (s, 6H, CH(COO<u>Me</u>)$_2$ and d, 1H, C<u>H</u>(COOMe)$_2$), 3.87-4.04 (m, 1H, C<u>H</u>(COOMe)$_2$), 4.17 (q, *J* = 7.1 Hz, 2H, CH_2-C_6), 6.05 (dd, *J* = 15.5, 0.6 Hz, 1H, CH-$C_{2/3}$), 6.45 (dd, *J* = 15.5, 9.8 Hz, 1H, CH-$C_{2/3}$).

4.6.2.3.Synthesis of (*R*,*E*)-1-benzyloxy-5-[2-(diphenylphosphanyl)benzoyloxy]-4-(di-(methoxycarbonyl)methyl)-pent-2-ene (39)



39

R_f = 0.66 (CH/EE 1:1).

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 3.28 (m_c, 1H, CH-C_4), 3.66 (d, J = 8.2 Hz, 1H, CH-$C_{4'}$), 3.70 (s × 2, 6H, 2 × CO_2Me), 3.98 (d, J = 4.6 Hz, 2H, CH_2-C_1), 4.26 (dd, J = 11.2, 5.9 Hz, 1H, CH_A-C_5), 4.36 (dd, J = 11.0, 5.8 Hz, 1H, CH_B-C_5), 4.46 (s, 2H, C$\underline{H}_2$Ph), 5.72 (dd, J = 15.5, 7.6 Hz, 1H, CH-C_3), 5.77 (dt, J = 15.5, 5.3 Hz, 1H, CH-C_2), 6.94-7.00 (m, 1H, Ar-H), 7.25-7.42 (m, 17H, Ar-H), 8.03-8.07 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 41.8 (C_4), 52.5 (OMe), 52.7 (OMe), 53.3 ($C_{4'}$), 65.6 (C_5), 70.1 (C_1), 71.8 ($\underline{C}H_2$Ph), 127.6, 127.8, 128.38, 128.43, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 129.3 (C_3), 130.7 (d, $J_{C,P}$ = 2.7 Hz), 131.3 (C_2), 132.2, 133.8 (d, $J_{C,P}$ = 20.5 Hz), 133.9 (d, $J_{C,P}$ = 20.5 Hz), 134.0 (d, $J_{C,P}$ = 19.1 Hz), 134.5, 137.8 (d, $J_{C,P}$ = 10.9 Hz), 138.3, 140.8 (d, $J_{C,P}$ = 26.6 Hz), 166.3 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}O_2$), 168.1 ($\underline{C}O_2$Me), 168.2 ($\underline{C}O_2$Me).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.58.

Elemental analysis for **39**	$C_{36}H_{35}O_7P$	M_r= 610.64
Calculated, %:	C 70.81	H 5.78
Found, %:	C 70.28	H 5.92

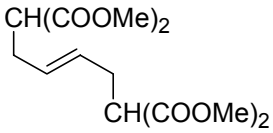
MS, CI (NH_3): $C_{36}H_{35}O_7P$ m/z=611.3 (100, M+H).

Chiral HPLC (Chiracel OD-H with OD-H pre-column, n-heptane/iso-propanol 75/25, 40°C, 0.5 ml/min, 230 nm):

R_T[(*major*)-**39**-oxide]= 36.0 min,

R_T[(*minor*)-**39**-oxide]= 39.9 min.

4.6.2.4.Synthesis of 2,7-bis-(methoxycarbonyl)-oct-4-enedioic acid dimethyl ester (41)



41

R_f = 0.70 (CH/EE 1:1).

^{1}H-NMR (400.132 MHz, $CDCl_3$):

δ = 2.56 (m, 4H, CHC<u>H</u>$_2$CH), 3.37 (t, J = 7.5 Hz, 2H, C<u>H</u>(COOMe)$_2$), 3.72 (s, 6H, CH(COO<u>Me</u>)$_2$), 5.48 (m, 2H, -C<u>H</u>=C<u>H</u>-).

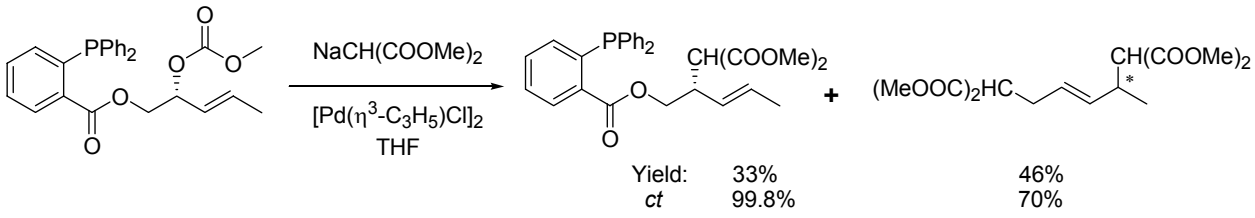
^{13}C-NMR (100.612 MHz, $CDCl_3$):

δ = 31.7 (CH<u>C</u>H$_2$CH), 51.7 (<u>C</u>H(COOMe)$_2$), 52.6 (CH(COO<u>Me</u>)$_2$), 128.9 (-<u>C</u>H=<u>C</u>H-), 169.2 (CH(<u>C</u>OOMe)$_2$).

MS, CI (NH_3): $C_{14}H_{20}O_8$ m/z=334.1 (100, M+NH_4), 317.1 (41, M+H).

Elemental analysis for **41**	$C_{14}H_{20}O_8$	M_r=316.12
Calculated, %:	C 53.16	H 6.37
Found, %:	C 53.03	H 6.07

4.6.2.5.Synthesis of 2-(diphenylphosphanyl)benzoic acid (*S*,*E*)-2-(di-(methoxycarbonyl)-methyl)-pent-3-enyl ester (40) and (*E*)-3-methyl-2,7-di-(methoxycarbonyl)-oct-4-ene-1,8-dioic acid dimethyl ester (44)

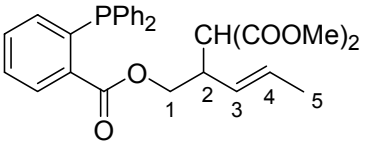


33 **40** **44**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **33** (74.9 mg, 0.167 mmol) with 1.6 eq of the malonate (solution in THF).

Flash-column chromatography (silica gel, CH/EE = 30:1).

Yield 27.9 mg (33%, 93% *ee*, 99.8% *ct*), R_f = 0.62 (CH/EE 1:1) and 25.3 mg (46%, 66% *ee*, 70% *ct*), R_f = 0.48 (CH/EE 1:1).



40

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.63 (dd, J = 6.4, 1.6 Hz, 1H, CH-C_5), 3.15 (m_c, 1H, CH-C_2), 3.58 (d, J = 8.3 Hz, 1H, C<u>H</u>(COOMe)$_2$), 3.66 (s, 3H, COO<u>Me</u>), 3.67 (s, 3H, COO<u>Me</u>), 4.18 (dd, J = 11.2, 6.2 Hz, 1H, CH_A-C_1), 4.28 (dd, J = 11.2, 5.7 Hz, 1H, CH_B-C_1), 5.38 (ddq, J = 15.2, 9.0, 1.6 Hz, 1H, CH-C_3), 5.61 (dqd, J = 15.2, 6.4, 0.8 Hz, 1H, CH-C_4), 6.92 (m, 1H, ArH), 7.24-7.43 (m, 12H, ArH), 8.01-8.04 (m, 1H, ArH).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 18.1 (C_5), 42.2 (C_2), 52.4 (COO<u>Me</u>), 52.6 (COO<u>Me</u>), 53.6 (<u>C</u>H(COOMe)$_2$), 66.1 (C_1), 126.8 (C_3), 128.3, 128.6 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.1 (C_4), 130.7 (d, $J_{C,P}$ = 2.9 Hz), 132.1, 134.0 (d, $J_{C,P}$ = 20.8 Hz), 134.2, 134.5, 137.9 (d, $J_{C,P}$ = 10.9 Hz), 138.0 (d, $J_{C,P}$ = 10.9 Hz), 140.8 (d, $J_{C,P}$ = 26.8 Hz), 166.3 (d, $J_{C,P}$ = 1.9 Hz, Ar<u>C</u>O), 168.4 (<u>C</u>OOMe), 168.5 (<u>C</u>OOMe).

Signal assignment from 2D-NMR experiment.

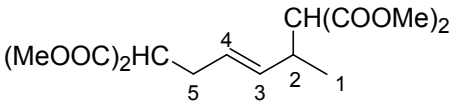
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.60.

Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 90/10, room temperature, 0.8 ml/min, 230 nm):

R_T[(*major*)-**40**]= 11.8 min,

R_T[(*minor*)-**40**]= 15.0 min.



44

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.04 (d, J = 6.8 Hz, 1H, CH-C_1), 2.54-2.57 (m, 2H, CH_2-C_5), 2.88 (m_c, 1H, CH-C_2), 3.25 (d, J = 8.8 Hz, 1H, C<u>H</u>(COOMe)$_2$), 3.38 (d, J = 7.5 Hz, 1H, C<u>H</u>(COOMe)$_2$), 3.69 (COO<u>Me</u>), 3.71 (COO<u>Me</u>), 3.72 (COO<u>Me</u>), 3.73 (COO<u>Me</u>), 5.41-5.51 (m, 2H, CH-C_3 and CH-C_4).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 18.5 (C_1), 31.7 (C_5), 37.2 (C_2), 51.8 (<u>C</u>H(COOMe)$_2$), 52.3 (COO<u>Me</u>), 52.4 (COO<u>Me</u>), 52.5 (COO<u>Me</u>), 52.6 (COO<u>Me</u>), 57.7 (<u>C</u>H(COOMe)$_2$), 126.8 ($C_{3/4}$), 134.9 ($C_{3/4}$), 168.6 (<u>C</u>OOMe), 168.7 (<u>C</u>OOMe), 169.2 (<u>C</u>OOMe), 169.3 (<u>C</u>OOMe).

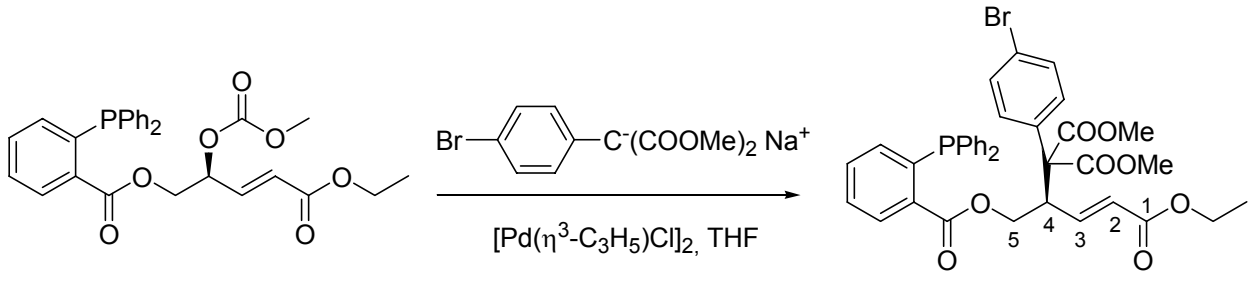
Signal assignment from 2D-NMR experiment.

Chiral HPLC (Chiralpak OD-H, n-heptane/*iso*-propanol 90/10, room temperature, 0.5 ml/min, 210 nm):

R_T[(*minor*)-**44**]= 22.3 min,

R_T[(*major*)-**44**]= 23.6 min.

4.6.2.6.Synthesis of (*R*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-[(4-bromophenyl)-di-(methoxycarbonyl)methyl]-pent-2-enoic acid ethyl ester (110)



14 **110**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **14** (60.5 mg, 0.120 mmol) with 1.2 eq of the malonate (solution in THF).

Flash-column chromatography (silica gel, PE/TBME = 20:1 to 4:1).

R_f = 0.41 (CH/EE 1:1).

Yield 43.0 mg (50%), regioselectivity (via NMR) = 100 : 7.5, white powder.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.26 (t, J = 7.1 Hz, 3H, C<u>H</u>$_3$CH$_2$), 3.67 (m$_c$, 1H, CH-C$_4$), 3.72 (s, 3H, COO<u>Me</u>), 3.75 (s, 3H, COO<u>Me</u>), 4.08 (dd, J = 11.3, 8.6 Hz, 1H, CH$_A$-C$_5$), 4.17 (q, J = 7.1 Hz, 2H, CH$_3$C<u>H</u>$_2$), 4.32 (dd, J = 11.3, 4.0 Hz, 1H, CH$_B$-C$_5$), 5.80 (dd, J = 15.7, 0.9 Hz, 1H, CH-C$_2$), 6.75 (dd, J = 15.7, 9.2 Hz, 1H, CH-C$_3$), 6.89-6.93 (m, 1H, Ar-H), 7.15-7.49 (m, 16H, Ar-H), 7.84-7.88 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

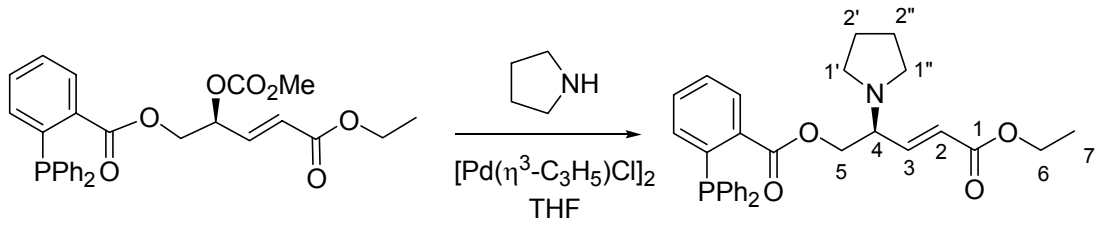
δ = 14.3 (<u>C</u>H$_3$CH$_2$), 46.7 (C$_4$), 53.1 (COO<u>Me</u>), 53.2 (COO<u>Me</u>), 60.6 (CH$_3$<u>C</u>H$_2$), 64.47 (C$_5$), 64.49 (<u>C</u>(COOMe)$_2$), 122.6, 126.0 (C$_2$), 128.4, 128.5 (d, $J_{C,P}$ = 1.9 Hz), 128.6 (d, $J_{C,P}$ = 1.9 Hz), 128.7 (d, $J_{C,P}$ = 1.7 Hz), 130.2, 130.7 (d, $J_{C,P}$ = 2.9 Hz), 131.7, 132.2, 133.5, 133.8 (d, $J_{C,P}$ = 8.9 Hz), 134.1 (d, $J_{C,P}$ = 9.2 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 10.4 Hz), 140.8 (d, $J_{C,P}$ = 27.0 Hz), 143.5 (C$_3$), 165.7 (<u>C</u>OOEt), 166.1 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>OO), 168.9 (<u>C</u>OOMe), 169.2 (<u>C</u>OOMe).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.82.

4.6.3. Allylic amination with pyrrolidin

4.6.3.1. Synthesis of (*S*,*E*)-5-[2-(diphenylphosphanyl)benzoyloxy]-4-(pyrrolidin-1-yl)-pent-2-enoic acid ethyl ester (52)



14 **52**

Allylic amination was carried out according to the general procedure II (see chapter 4.6.1.2.) with $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%) starting from the carbonate **14**. The reaction proceded in the presence of both NaH (20 mol.%) as a base and without base with tetra(*n*-butyl)ammonium bromide (20 mol.%) with 44% and 43% yield respectively and 99% chirality transfer.

R_f = 0.36 (CH/EE 1:1).

^{1}H-NMR (400.136 MHz, $CDCl_3$):
δ = 1.29 (t, J = 7.1 Hz, 3H, CH_3-C_7), 1.78 (bs, 4H, CH_2-$C_{1'}$ and CH_2-$C_{1''}$), 2.59 (bs, 4H, CH_2-$C_{2'}$ and CH_2-$C_{2''}$), 4.20 (q, J = 7.1 Hz, 2H, CH_2-C_6), 4.24 (dd, J = 12.0, 6.7 Hz, 1H, CH_A-C_5), 4.40 (dd, J = 11.9, 3.9 Hz, 1H, CH_B-C_5), 5.51 (m, 1H, CH-C_4), 5.97 (d, J = 15.8 Hz, 1H, CH-C_2), 6.89 (d, J = 8.8 Hz, 1H, CH-C_3), 6.90-6.95 (m, 1H, Ar-H), 7.23-7.43 (m, 12H, Ar-H), 7.98-8.03 (m, 1H, Ar-H).

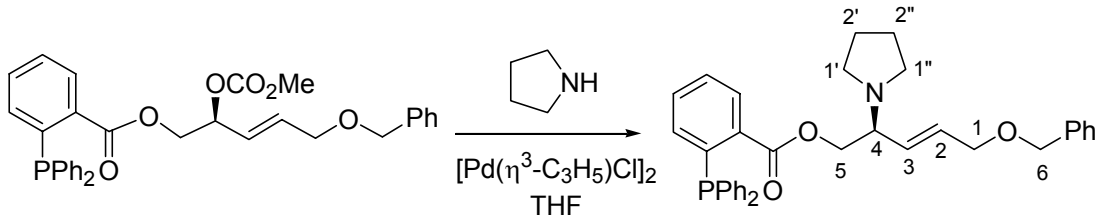
^{13}C-NMR (100.620 MHz, $CDCl_3$):
δ = 14.3 (C_7), 23.3 ($C_{1'}$ and $C_{1''}$), 27.0 ($C_{2'}$ and $C_{2''}$), 51.9 (C_5), 60.7 (C_6), 64.3 (C_4), 128.4 (C_2), 128.5 (d, $J_{C,P}$ = 1.9 Hz), 128.6 (d, $J_{C,P}$ = 2.2 Hz), 128.7 (d, $J_{C,P}$ = 1.7 Hz), 128.8 (d, $J_{C,P}$ = 2.4 Hz), 132.0, 132.3 (C_3), 134.0 (d, $J_{C,P}$ = 20.0 Hz), 134.4 (C_1), 166.4 (d, $J_{C,P}$ = 2.1 Hz, $ArCO_2R$).

^{31}P-NMR (121.468 MHz, $CDCl_3$):
δ = -3.64.

Elemental analysis for **52**	$C_{30}H_{32}NO_4P$	M_r= 501.55	
Calculated, %:	C 71.84	H 6.43	N 2.79
Found, %:	C 70.96	H 6.6	N 2.01

Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 80/20, room temperature, 0.5 ml/min, 230 nm):
R_T[(*major*)-**52**]= 11.5 min,
R_T[(*minor*)-**52**]= 12.8 min.

4.6.3.2.Synthesis of (*S*,*E*)-1-benzyloxy-5-[2-(diphenylphosphanyl)benzoyloxy]-4-(pyrrolidin-1-yl)-pent-2-ene (53)



19 **53**

Allylic amination was carried out according to the general procedure II (see chapter 4.6.1.2.) with $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%) starting from the carbonate **19**. The reaction worked in the presence of tetra(*n*-butyl)ammonium bromide (20 mol.%) with 46% yield 97% chirality transfer.

R_f = 0.19 (CH/EE 1:1).

^{1}H-NMR (400.136 MHz, $CDCl_3$):

δ = 1.75 (bs, 4H, CH_2-$C_{1'}$ and CH_2-$C_{1"}$), 2.57 (bs, 4H, CH_2-$C_{2'}$ and CH_2-$C_{2"}$), 3.05 (m_c, 1H, CH-C_4), 4.01 (d, J = 4.8 Hz, 2H, CH_2-C_1), 4.21 (dd, J = 11.0, 7.0 Hz, 1H, CH_A-C_5), 4.37 (dd, J = 11.1, 5.1 Hz, 1H, CH_B-C_5), 4.46 (s, 2H, CH_2-C_6), 5.67-5.80 (m, 2H, CH-C_2 and CH-C_3), 6.90-6.94 (m, 1H, Ar-H), 7.23-7.37 (m, 17H, Ar-H), 8.01-8.04 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 23.3 ($C_{1'}$ and $C_{1"}$), 52.0 ($C_{2'}$ and $C_{2"}$), 65.5 (C_4), 66.6 (C_5), 70.3 (C_1), 72.0 (C_6), 127.6, 127.8, 128.3, 128.4, 128.5 (d, $J_{C,P}$ = 1.0 Hz), 128.6 (d, $J_{C,P}$ = 0.7 Hz), 128.7, 130.7 (d, $J_{C,P}$ = 2.6 Hz, C_2 or C_3), 132.0 (C_2 or C_3), 132.9 (d, $J_{C,P}$ = 1.7 Hz), 134.1 (d, $J_{C,P}$ = 1.5 Hz), 134.4.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -3.79.

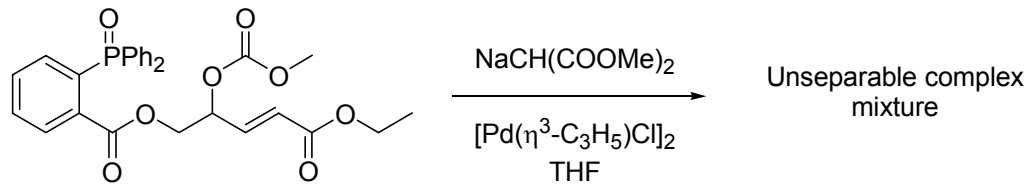
Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 90/10, room temperature, 0.8 ml/min, 230 nm):

R_T[(*major*)-**53**]= 8.9 min,

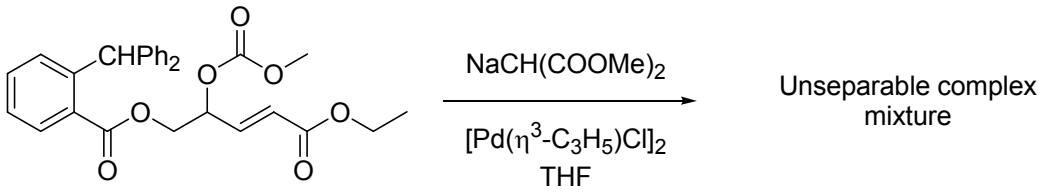
R_T[(*minor*)-**53**]= 9.4 min.

3.6.4. Not directed reactions

3.6.4.1. Reaction with (*E*)-5-[2-(diphenylphosphoryl)benzoyloxy]-4-methoxycarbonyloxy-pent-2-enoic acid ethyl ester (14-oxide) and 2-(benzhydryl)benzoic acid (*E*)-4-ethoxycarbonyl-2-methoxycarbonyloxy-but-3-enyl ester (27)



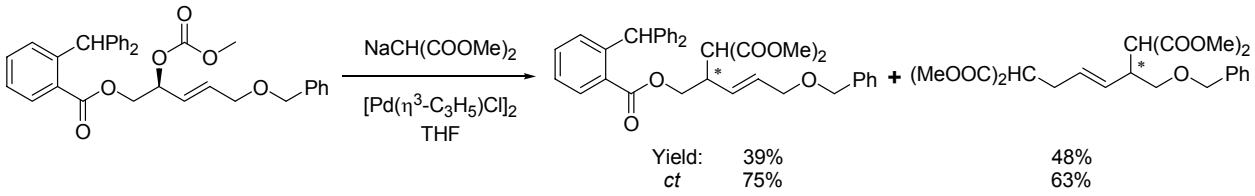
14-oxide



27

Not directed reactions with these substrates carried out according to the general procedure V (see chapter 4.6.1.5.) with $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%) and triphenylphosphine as a ligand and gave complex unseparable mixtures. It seems that some cyclization process happens as there is minor signal of double bond registered in NMR spectrum.

3.6.4.2. Synthesis of 2-(benzhydryl)benzoic acid (*E*)-5-benzyloxy-2-(di-(methoxy-carbonyl)-methyl)-pent-3-enyl ester (49) and (*E*)-3-benzyloxymethyl-2,7-di-(methoxycarbonyl)-oct-4-ene-1,8-dioic acid dimethyl ester (43)

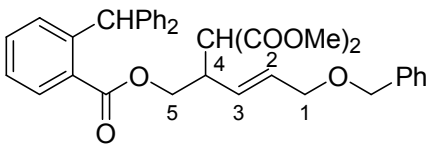


28 **49** **43**

Allylic substitution reaction was carried out according to the general procedure V (see chapter 4.6.1.2.) with $[Pd(\eta^3\text{-allyl})Cl]_2$ (5 mol.%) and triphenylphosphine as a ligand starting from the substrate **28** (95.0 mg, 0.177 mmol) with 1.6 eq of the malonate (solution in THF).

Flash-column chromatography (silica gel, PE/TBME = 10:1 to 4:1).

Yield of **49** 40.3 mg (39%, 75% *ee*, 75% *ct*), R_f = 0.61 (CH/EE 1:1) and of **43** 36.7 mg (48%, 63% *ee*, 63% *ct*), R_f = 0.46 (CH/EE 1:1).



49

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 3.24 (m_c, 1H, CH-C_4), 3.55 (d, J = 8.2 Hz, 1H, CH_A-C_5), 3.66 (s, 3H, COO<u>Me</u>), 3.67 (s, 3H, COO<u>Me</u>), 3.70 (m_c, 1H, CH_B-C_5), 3.95 (d, J = 5.2 Hz, 1H, C<u>H</u>(COOMe)$_2$), 4.18 (dd, J = 11.2, 5.9 Hz, 1H, CH_A-C_1), 4.26 (dd, J = 11.2, 5.9 Hz, 1H, CH_B-C_1), 4.44 (s, 2H, OC<u>H</u>$_2$Ph), 5.64-5.79 (m, 2H, C_2 and C_3), 6.58 (s, 1H, Ph$_2$C<u>H</u>Ar), 7.02-7.08 (m, 5H, ArH), 7.17-7.41 (m, 13H, ArH), 7.83 (dd, J = 7.8, 1.3 Hz, 1H, ArH).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

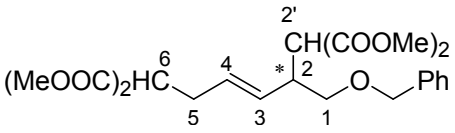
δ = 41.8 (C_4), 52.2 (Ph$_2$<u>C</u>HAr), 52.6 (COO<u>Me</u>), 52.7 (COO<u>Me</u>), 53.3 (C_5), 65.3 (C_1), 70.1 (<u>C</u>H(COOMe)$_2$), 71.9 (O<u>C</u>H$_2$Ph), 126.3, 126.4, 127.7, 127.8, 128.3, 128.4, 129.2 ($C_{2/3}$), 129.7, 127.8, 130.3, 130.5, 131.2 ($C_{2/3}$), 131.3, 131.7, 138.3, 143.7, 143.8, 145.0, 167.2 (Ar<u>C</u>OO), 168.1 (<u>C</u>OOMe), 168.2 (<u>C</u>OOMe).

MS, CI (NH_3): $C_{37}H_{36}O_7$ m/z=610.3 (100, M+NH_4).

Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 80/20, 25 C, 0.8 ml/min, 230 nm):

R_T[(*minor*)-**49**]= 15.4 min,

R_T[(*major*)-**49**]= 22.9 min.



43

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 2.58 (dd, *J* = 7.5, 5.6 Hz, 2H, CH_2-C_5), 3.08 (m_c, 1H, CH-C_2), 3.38 (t, *J* = 7.6 Hz, 1H, CH-C_6), 3.46 (dd, *J* = 9.5, 6.7 Hz, 1H, CH_A-C_1), 3.51 (dd, *J* = 9.6, 5.2 Hz, 1H, CH_B-C_1), 3.64 (s, 3H, COOMe), 3.65 (d, *J* = 8.2 Hz, 2H, CH-$C_{2'}$), 3.67 (s, 3H, COOMe), 3.70 (s, 3H, COOMe), 3.72 (s, 3H, COOMe), 4.44 (s, 2H, OCH_2Ph), 5.50-5.62 (m, 2H, C_3 and C_4), 7.24-7.35 (m, 5H, ArH).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 31.8 (C_5), 43.0 (C_2), 51.7 (C_6), 52.3 (COOMe), 52.4 (COOMe), 52.55 (COOMe), 52.58 (COOMe), 53.4 ($C_{2'}$), 71.3 (C_1), 73.2 (Ph_2CHAr), 127.68, 127.72, 128.4, 129.5, 130.4, 138.1, 168.6 (COOMe), 168.8 (COOMe), 169.18 (COOMe), 169.22 (COOMe).

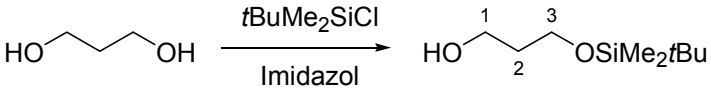
HRMS, EI:	calculated	436.173335
$C_{22}H_{28}O_9$	found	436.172301

Chiral HPLC (Chiralpak AD-H, n-heptane/*iso*-propanol 90/10, 15 C, 1.0 ml/min, 210 nm):
R_T[(*minor*)-**43**]= 31.6 min,
R_T[(*major*)-**43**]= 33.9 min.

5. The substrates with allylic system separated from the directing group by 2 or 3 carbon atoms

5.1. Syntheis of linear substrate with allylic system separated from the directing group by 2 carbon atoms

5.1.1. Synthesis of 3-(*tert*-butyldimethylsilyloxy)-propan-1-ol (54)



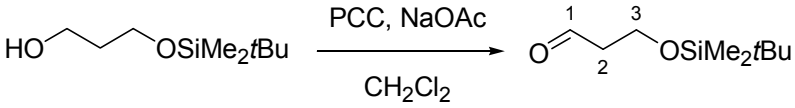
54

Propan-1,3-diol (9.69 g, 128 mmol, 2.40 eq) and imidazole (7.52 g, 106 mmol, 1.99 eq) were dissolved in anhydrous DMF (30 ml) at 0 °C. Then *tert*-butyldimethylsilylchloride (8.00 g, 53.1 mmol, 1 eq) was added. The reaction mixture was tirred overnight at room temperature. Then 100 ml of petroleum ether (30-50) was added and the organic phase was washed with water (6×20 ml), dried over $MgSO_4$. The solvent was evaporated. The product **54** (6.38 g, 63%) as a colourles oily liquid was used without further purification (contained 20% of bis-protected diol, 1,3-di-(*tert*-butyldimethylsilyloxy)propane).

^{1}H-NMR (300.064 MHz, $CDCl_3$):
δ = 0.03 and 0.04 (s and s, 6H, $Si(CH_3)_2$), 0.06 and 0.07 (s and s, 6H, $Si(CH_3)_2$), 0.89 (m, 9H, $Si(C(CH_3)_3)$), 1.76 (ddd, J= 11.3, 5.7, 0.6 Hz, 2H, CH_2-C_3), 2.54 (bs, 1H, OH), 3.76-3.83 (m, 4H, CH_2-C_1 and CH_2-C_3).

Analytical data are in a good agreement with literature. [120]

5.1.2. Synthesis of 3-(*tert*-butyldimethylsilyloxy)-propanal (56)



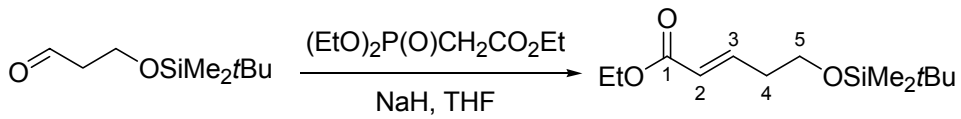
54 **56**

The alcohol **54** (6.38 g, 33.6 mmol) and sodium acetate (2.45 g, 30.0 mmol, 0.89 eq) were added into anhydrous dichlormethan (120 ml) and pyridiniumchlorochromate (10.9 g, 50.4 mmol, 1.50 eq) was then added slowly (during 30 min) at 0 °C and stirred 3 h. Then the solvent was evaporated and the mixture was filtered through silica gel column with Et_2O. Diethylether was evaporated. Flash-column chromatography (silica gel, PE/TBME = 10:1 to 2:1).
R_f = 0.70 (Et_2O).
Yield 1.36 g (25%), colourless liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):
δ = 0.06 (m, 6H, $Si(CH_3)_2$), 0.89 (m, 9H, $Si(C(CH_3)_3)$), 2.54 (td, J = 6.1, 2.1 Hz, 2H, CH_2-C_2), 3.97 (t, J = 6.0 Hz, 2H, CH_2-C_3), 9.75 (t, J = 2.1 Hz, 1H, CH-C_1).

Analytical data are in a good agreement with literature. [120]

5.1.3. Synthesis of (*E*)-5-(*tert*-butyldimethylsilyloxy)-pent-2-enoic acid ethyl ester (58)



56 **58**

To the suspenion of NaH (60% in mineral oil, 0.332 g, 8.31 mmol, 1.1 eq) in anhydrous THF (15 ml) triethylphosphonoacetate (1.86 g, 2.08 ml, 8.31 mmol, 1.1 eq) was added slowly at 0 °C and stirred 40 min. Then the reaction mixture was cooled to -78 °C and the aldehyde **56** (1.36 g, 7.55 mmol) dissolved in anhydrous THF (5 ml) was slowly added, stirred 30 min and warmed up to room temperature, quentched with satutared aqueous solution of potassium-sodium tartrate (10 ml), the organic phase was washed with water (4×5 ml), dried over Na_2SO_4. After filtration and solvent evaporation, flash-column chromatography (silica gel, CH/EE = 10:1).
R_f = 0.71 (CH/EE 1:1).
Yield 1.65 g (85%), colourless liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.89 (m, 9H, $Si(C(CH_3)_3)$), 1.23 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2$), 2.41 (dtd, J = 6.4, 1.5, 1.6 Hz, 2H, CH_2-C_4), 3.72 (t, J = 6.6 Hz, 2H, CH_2-C_5), 4.19 (q, J = 7.1 Hz, 2H, $CH_3C\underline{H}_2$), 5.86 (dt, J = 15.7, 1.6 Hz, 1H, CH-C_2), 6.91 (ddd, J = 15.7, 7.1 Hz, CH-C_3).

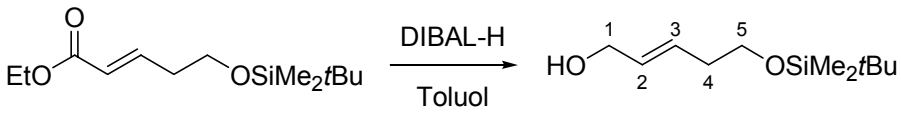
^{13}C-NMR (100.613 MHz, $CDCl_3$:

δ = -5.2, 14.4, 18.4, 26.0, 35.8, 60.2, 61.7, 123.1, 145.9, 166.6.

HRMS, EI:	calculated	201.094699
$C_9H_{17}O_3Si$	found	201.094203

Analytical data are in a good agreement with literature. [121]

5.1.4. Synthesis of (*E*)-5-(*tert*-butyldimethylsilyloxy)-pent-2-en-1-ol (62)



58 **62**

To the cooled to 0 °C solution of the ester **58** (1.65 g, 6.49 mmol) in toluene (10 ml) was slowly added DIBAL-H (2.28 g, 2.85 ml, 16.04 mmol, 2.51 eq) in toluene (10 ml). After 30 min saturated aqueous solution of Na_2SO_4 was added until no more bubbles of hydrogen were evaluated, then solid Na_2SO_4 was added, filtered, washed with ether (~ 60 ml). The solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 4:1 to EE).

R_f = 0.68 (CH/EE 1:1).

Yield 1.05 g (76%), colourless oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

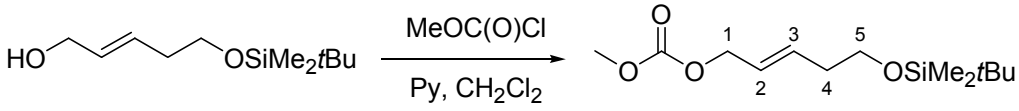
δ = 0.05 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 1.46 (bs, 1H, OH), 2.24-2.30 (m, 2H, CH_2-C_4), 3.65 (t, J = 6.7, 2H, CH_2-C_1), 4.08-4.10 (m, 2H, CH_2-C_5), 5.69-5.71 (m, 2H, CH-C_2 and CH-C_3).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.2, 18.4, 26.0, 35.9, 62.8, 63.8, 129.6, 131.1.

Analytical data are in a good agreement with literature. [122]

5.1.5. Synthesis of (*E*)-5-(*tert*-butyldimethylsilyloxy)-1-methoxycarbonyloxypent-2-ene (64)



62 **64**

The carbonate **64** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the alcohol **62** (1.05 g, 4.89 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1).

R_f = 0.84 (CH/EE 1:1).

Yield 1.19 g (89%), colourless oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

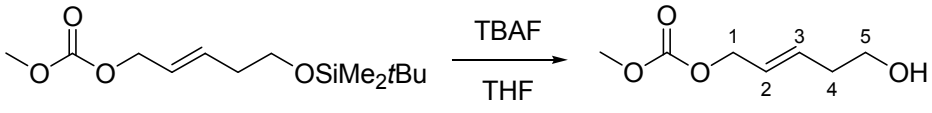
δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 2.28 (dddd, J = 6.8, 2.2, 0.9 Hz, 2H, CH_2-C_4), 3.65 (t, J = 6.6 Hz, 2H, CH_2-C_5), 3.78 (s, 3H, CH_3OCO), 4.58 (ddd, J = 6.4, 1.9, 0.9 Hz, 2H, CH_2-C_1), 5.65 (dddt, J = 15.4, 12.8, 6.4, 1.3 Hz, 1H, CH-C_3), 5.82 (dddt, J = 15.4, 13.6, 6.8, 1.1 Hz, 1H, CH-C_2).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.2, 18.4, 26.0, 35.9, 54.8, 62.5, 68.6, 125.3 (C_2 and C_3), 133.7.

HRMS, CI (NH_3):	calculated	275.167864
$C_{13}H_{27}O_4Si$ (M+H)	found	275.167602

5.1.6. Synthesis of (*E*)-1-methoxycarbonyloxypent-2-en-5-ol (66)



64 **66**

To the solution of the carbonate **64** (1.19 g, 4.54 mmol) in THF (12 ml) tetra-*n*-butylammoniumflourid trihydrat (1.58 g, 5.00 mmol, 1.1 eq) and stirred at room temperature 30 min. The solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 4:1).

R_f = 0.24 (CH/EE 1:1).

Yield 0.57 g (74%), colourless oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

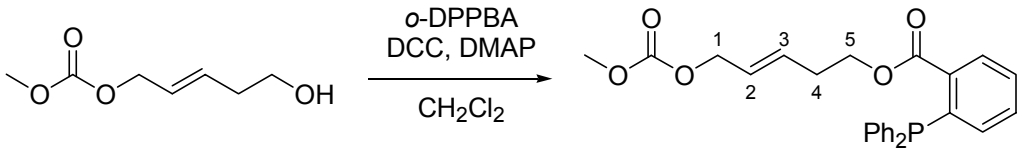
δ = 1.50 (bs, 1H, OH), 2.34 (dddd, J = 13.0, 6.6, 1.9, 0.8 Hz, 2H, CH_2-C_4), 3.69 (t, J = 6.3 Hz, 2H, CH_2-C_5), 3.78 (s, 3H, CH_3OCO), 4.60 (ddd, J = 6.1, 2.0, 0.8 Hz, 2H, CH_2-C_1), 5.71 (dddt, J = 15.4, 12.3, 5.9, 1.0 Hz, 1H, CH-C_3), 5.82 (dddt, J = 15.4, 13.5, 6.7, 1.0 Hz, 1H, CH-C_2).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 35.7, 54.9, 61.7, 68.3, 126.4, 132.8, 155.7.

HRMS, CI (NH_3):	calculated	178.107934
$C_7H_{12}O_4$ (M+NH_4)	found	178.108298

5.1.7. Synthesis of (*E*)-5-(2-(diphenylphosphanyl)benzoyloxy)-1-methoxycarbonyloxy-pent-2-ene (68)



66 **68**

The compound **68** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the alcohol **66** (0.537 g, 3.38 mmol).

Flash-column chromatography (silica gel, CH/EE = 9:1 to 4:1).

R_f = 0.61 (CH/EE 1:1).

Yield 1.37 g (90%), colourless oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 2.34 (dtd, J = 13.1, 6.7, 0.9 Hz, 2H, CH_2-C_4), 3.77 (s, 3H, CH_3OCO), 4.20 (t, J = 6.8 Hz, 2H, CH_2-C_5), 4.54 (dd, J = 6.2, 0.8 Hz, 2H, CH_2-C_1), 5.59-5.76 (m, 2H, CH-C_3 and CH-C_2), 6.91-6.94 (m, 1H, Ar-H), 7.23-7.42 (m, 12H, Ar-H), 8.01-8.04 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 31.5, 54.8, 64.0, 68.2, 126.1, 128.3, 128.5, 128.6, 128.7, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 132.0 (d, $J_{C,P}$ = 1.9 Hz), 133.9, 134.1, 134.5, 137.9 (d, $J_{C,P}$ = 10.9 Hz), 140.3 (d, $J_{C,P}$ = 26.3 Hz), 155.7, 166.8 (d, $J_{C,P}$ = 2.2 Hz).

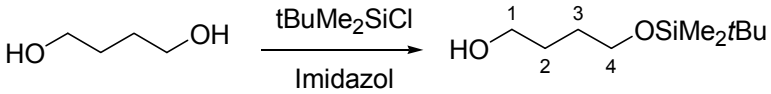
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.41.

HRMS, CI (NH_3):	calculated	449.151788
$C_{26}H_{25}O_5P$ (M+H)	found	449.151699

5.2. Synthesis of linear substrate with allylic system separated from the directing group by 3 carbon atoms

5.2.1. Synthesis of 4-(*tert*-butyldimethylsilyloxy)-butan-1-ol (55)



55

The compound **55** was synthesized analogously to **54** (see chapter 5.1.1.) starting from butan-1,4-diol (**$$r33**) (0.537 g, 3.38 mmol).

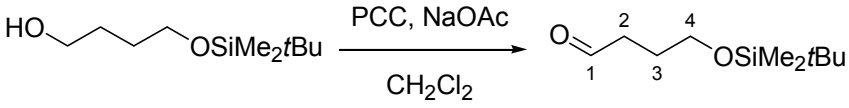
Yield 9.64 g (64%), colourless oily liquid, was used without further purification (contained 20% of bis-protected diol, 1,4-di-(*tert*-butyldimethylsilyloxy)butane).

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 0.06 (m, 6H, $Si(CH_3)_2$), 0.89 (m, 9H, $Si(C(CH_3)_3)$), 1.63 (m, 4H, CH_2-C_2, CH_2-C_3), 2.50 (bs, 1H, OH), 3.61-3.67 (m, 4H, CH_2-C_1, CH_2-C_4).

Analytical data are in a good agreement with literature. [123]

5.2.2. Synthesis of 4-(*tert*-butyldimethylsilyloxy)-butanal (57)



55 **57**

The compound **57** was synthesized analogously to **56** (see chapter 5.1.2.) starting from the alcohol **55** (2.45 g, 12.01 mmol).

Flash-column chromatography (silica gel, CH/EE = 9:1 to 4:1).

R_f = 0.72 (Et_2O).

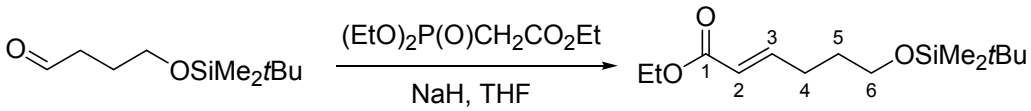
Yield 3.19 g (33%), light-yellow oily liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 0.01 (s, 6H, $Si(CH_3)_2$), 0.86 (s, 9H, $Si(C(CH_3)_3)$), 1.83 (m_c, 2H, CH_2-C_3), 2.47 (td, J = 7.0, 1.8 Hz, 2H, CH_2-C_2), 3.62 (t, J = 6.0, 1.0 Hz, 2H. CH_2-C_4), 9.76 (t, J = 1.8 Hz, 1H, CH-C_1).

Analytical data are in a good agreement with literature. [123]

5.2.3. Synthesis of (*E*)-6-(*tert*-butyldimethylsilyloxy)-hex-2-enoic acid ethyl ester (59)



57 **59**

The compound **59** was synthesized analogously to **58** (see chapter 5.1.3.) starting from the alcohol **57** (1.60 g, 7.89 mmol).

Flash-column chromatography (silica gel, CH/EE = 9:1 to 4:1).

R_f = 0.75 (CH/EE 1:1).

Yield 1.42 g (77%), light-yellow oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (m, 9H, $Si(C(CH_3)_3)$), 1.28 (t, J = 7.1 Hz, 3H, $C\underline{H}_3CH_2$), 1.67 (m_c, 2H, CH_2-C_5), 2.27 (m_c, 2H, CH_2-C_4), 3.62 (t, J = 6.2 Hz, 2H, CH_2-C_6), 4.18 (q, J = 7.2 Hz, 2H, $CH_3C\underline{H}_2$), 5.83 (dt, J = 15.7, 1.6 Hz, 1H, CH-C_2), 6.94 (td, J = 15.7, 7.0 Hz, 1H, CH-C_3).

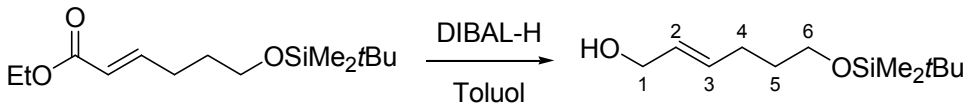
^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.2, 14.4, 18.4, 26.0, 28.8, 31.2, 60.2, 62.3, 121.6, 149.0, 166.8.

HRMS, EI:	calculated	215.110349
$C_{10}H_{19}O_3Si$	found	215.110198

Analytical data are in a good agreement with literature. [123]

5.2.4. Synthesis of (*E*)-6-(*tert*-butyldimethylsilyloxy)-hex-2-en-1-ol (63)



59 **63**

The compound **63** was synthesized analogously to **62** (see chapter 5.1.4.) starting from the ester **59** (1.44 g, 5.50 mmol).

R_f = 0.84 (CH/EE 1:1).

Yield 0.785 g (62%), light-yellow oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

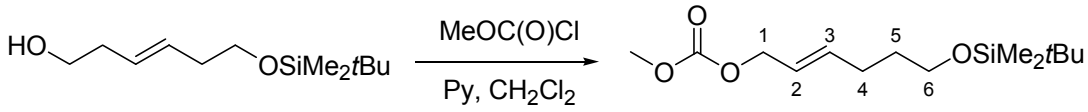
δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 1.44 (bs, 1H, OH), 1.57-1.65 (m, 2H, CH_2-C_5), 2.10 (m_c, 2H, CH_2-C_4), 3.61 (t, J = 6.4 Hz, 2H, CH_2-C_6), 4.08 (d, J = 5.3 Hz, 2H, CH_2-C_1), 5.60-5.75 (m, 2H, CH-C_2 and CH-C_3).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.2, 18.4, 26.0, 28.6, 32.3, 62.6, 63.9, 129.3, 133.0.

Analytical data are in a good agreement with literature. [123]

5.2.5. Synthesis of (*E*)-6-(*tert*-butyldimethylsilyloxy)-1-methoxycarbonyloxyhex-2-ene (65)



63 **65**

The compound **65** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the alcohol **63** (0.785 g, 3.42 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.69 (CH/EE 1:1).

Yield 3.19 g (33%), light-yellow oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

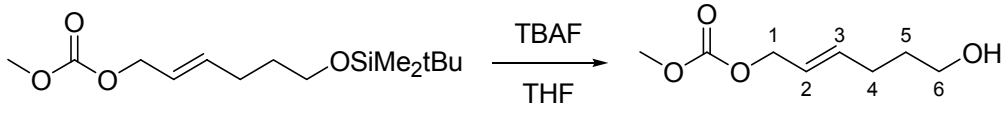
δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $Si(C(CH_3)_3)$), 1.57-1.64 (m, 2H, CH_2-C_5), 2.09-2.16 (m, 2H, CH_2-C_4), 3.60 (t, J = 6.4 Hz, 2H, CH_2-C_6), 3.78 (s, 3H, CH_3OCO), 4.57 (ddd, J = 6.4, 1.0, 1.0 Hz, 2H, CH_2-C_1), 5.60 (dddt, J = 13.0, 6.5, 6.5, 1.5 Hz, 1H, CH-C_2), 5.82 (dddt, J = 13.4, 6.7, 6.7, 1.1 Hz, 1H, CH-C_3).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.2, 18.4, 26.0, 28.7, 32.0, 54.8, 62.5, 68.7, 123.6, 137.0, 155.8.

HRMS, CI (NH_3):	calculated	289.183514
$C_{14}H_{29}O_4Si$ (M+H)	found	289.183903

5.2.6. Synthesis of (*E*)-1-methoxycarbonyloxyhex-2-en-6-ol (67)



65 **67**

The compound **67** was synthesized analogously to **66** (see chapter 5.1.6.) starting from the carbonate **65** (0.430 g, 1.49 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.26 (CH/EE 1:1).

Yield 0.172 g (67%), yellow oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

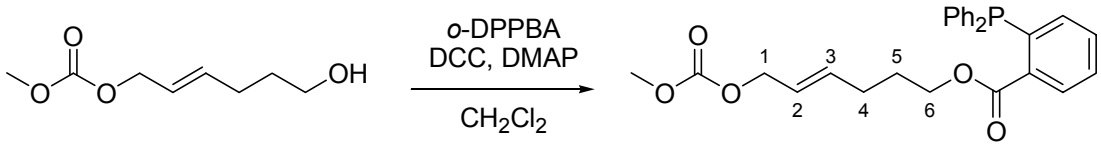
δ = 1.41 (bs, 1H, OH), 1.66 (m_c, 2H, CH_2-C_5), 2.15 (m_c, 2H, CH_2-C_4), 3.64 (t, J = 6.4 Hz, 2H, CH_2-C_6), 3,77 (s, 3H, CH_3OCO), 4.56 (ddd, J = 6.4, 1.0, 1.0 Hz, 2H, CH_2-C_1), 5.60 (dddt, J = 12.9, 6.4, 6.4, 1.5 Hz, 1H, CH-C_2), 5.82 (dddt, J = 13.4, 6.7, 6.7, 1.1 Hz, 1H, CH-C_3).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 28.6, 31.8, 54.8, 62.3, 68.6, 124.0, 136.5, 155.8.

HRMS, CI (NH_3):	calculated	192.123584
$C_8H_{14}O_4$ ($M+NH_4$)	found	192.123798

5.2.7. Synthesis of (*E*)-6-[2-(diphenylphosphanyl)benzoyloxy]-1-methoxycarbonyloxy-hex-2-ene (69)



67 **69**

The compound **69** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the carbonate **67** (0.172 g, 0.988 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.60 (CH/EE 1:1).

Yield 0.365 g (80%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.68 (m_c, 2H, CH_2-C_5), 2.07 (m_c, 2H, CH_2-C_4), 3,78 (s, 3H, CH_3OCO), 4.16 (t, J = 6.5 Hz, 2H, CH_2-C_6), 4.55 (ddd, J = 6.4, 1.0, 1.0 Hz, 2H, CH_2-C_1), 5.57 (dddt, J = 12.9, 6.4, 6.4, 1.4 Hz, 1H, CH-C_2), 5.82 (dddt, J = 13.3, 6.7, 6.7, 1.1 Hz, 1H, CH-C_3), 6.91-6.94 (m, 1H, Ar-H), 7.23-7.42 (m, 12H, Ar-H), 8.01-8.05 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 27.7, 28.7, 54.8, 64.6, 68.4, 124.2, 128.3, 128.5 (d, $J_{C,P}$ = 7.0 Hz), 128.7, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 132.0, 134.1 (d, $J_{C,P}$ = 20.5 Hz), 134.5, 134.7 (d, $J_{C,P}$ = 19.3 Hz), 135.8, 138.0 (d, $J_{C,P}$ = 11.1 Hz), 140.3 (d, $J_{C,P}$ = 26.6 Hz), 155.7, 167.0 (d, $J_{C,P}$ = 2.2 Hz).

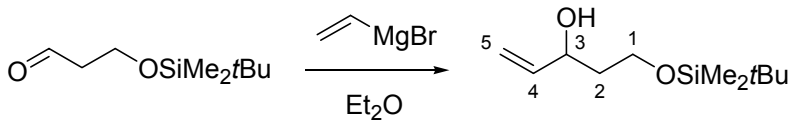
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.71.

HRMS, CI (NH_3):	calculated	463.167438
$C_{27}H_{27}O_5P$ (M+H)	found	463.168397

5.3. Synthesis of branched substrate with allylic system separated from the directing group by 2 carbon atoms

5.3.1. Synthesis of 1-(*tert*-butyldimethylsilyloxy)-pent-4-en-3-ol (60)



56 **60**

The compound was synthesized according to the procedure elaborated in our group. [124] To vinylmagnesiumbromid (4.31 ml, 1.93 M in Et_2O, 8.31 mmol, 1.10 eq) dissolved in anhydrous diethylether (10 ml) aldehyde **56** (1.36 g, 7.55 mmol) in anhydrous diethylether (8 ml) was added at -78 °C during 30 min and then stirred at the temperature for 1.5 h, quentched with satutared aqueous solution of potassium-sodium tartrate (5 ml) and stirred for about 5 min, filtrated; the organic phase was extracted with ether (3 × 10 ml), the combined organic phase were washed with satutared aqueous solution of NaCl, dried over $MgSO_4$. After filtration and solvent evaporation, flash-column chromatography (silica gel, CH/EE = 10:1).

R_f = 0.64 (CH/EE 1:1).

Yield 1.16 g (71%), light-yellow liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

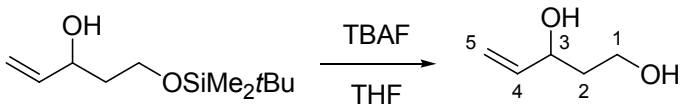
δ = 0.08 (s and s, 6H, $Si(CH_3)_2$), 0.90 (s, 9H, $Si(C(CH_3)_3)$), 1.67-1.83 (m, 2H, CH_2-C_2), 3.29 (bs, 1H, OH), 3.80 (ddd, J = 10.2, 7.6, 4.6 Hz, 1H, CH_A-C_1), 3.89 (ddd, J = 10.2, 6.1, 4.4 Hz, 1H, CH_B-C_1), 4.35 (m_c, 1H, CH-C_3), 5.10 (ddd, J = 10.5, 1.6, 1.5 Hz, 1H, CH-C_5), 5.28 (ddd, J = 17.2, 1.6, 1.6 Hz, 1H, CH-C_5), 5.88 (ddd, J = 15.9, 10.5, 5.4 Hz, 1H, CH-C_4).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.5 (2×s), 18.2, 25.9, 38.4, 62.0, 72.5, 114.2, 140.7.

Analytical data are in a good agreement with literature. [125]

5.3.2. Synthesis of pent-4-en-1,3-diol (76)



60 **76**

The diol **76** was synthesized analogously to **66** (see chapter 5.1.6.) starting from the compound **60** (1.16 g, 5.37 mmol).

Flash-column chromatography (silica gel, CH/EE = 4:1 to EE).

R_f = 0.25 (CH/EE 1:1).

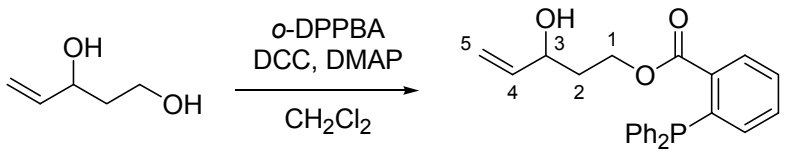
Yield 0.455 g (83%), colourless liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.66-1.87 (m, 2H, CH_2-C_2), 3.39 (bs, 2H, C_3-OH and C_1-OH), 3.81 (m_c, 2H, CH_2-C_1), 4.36 (m_c, 1H, CH-C_3), 5.12 (dd, J = 10.4, 1.3 Hz, 1H, CH-C_5), 5.26 (dd, J = 17.1, 1.5 Hz, 1H, CH-C_5), 5.89 (dddd, J = 16.3, 10.4, 5.7, 0.7 Hz, 1H, CH-C_4).

HRMS, CI (NH_3):	calculated	120.102454
$C_5H_{10}O_2$ ($M+NH_4$)	found	120.102500

5.3.3. Synthesis of 1-(2-(diphenylphosphanyl)benzoyloxy)-3-hydroxypent-4-ene (77)



76 **77**

The ester **76** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the diol **$$r41** (0.455 g, 4.48 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.46 (CH/EE 1:1).

Yield 1.42 g (81%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.69-1.85 (m, 2H, CH_2-C_2), 2.44 (bs, 1H, C_3-OH), 4.11 (m_c, 1H, CH-C_3), 4.24 (ddd, J = 11.5, 5.8, 5.8 Hz, 1H, CH_A-C_1), 4.38 (ddd, J = 11.2, 7.8, 5.7 Hz, 1H, CH_A-C_1), 5.08 (ddd, J = 10.5, 1.4, 1.4 Hz, 1H, CH-C_5), 5.19 (dt, J = 17.2, 1.5, 1.5 Hz, 1H, CH-C_5), 5.79 (ddd, J = 163, 10.5, 5.8 Hz, 1H, CH-C_4), 6.91-6.94 (m, 1H, Ar-H), 7.23-7.42 (m, 12H, Ar-H), 8.03-8.06 (m, 1H, Ar-H).

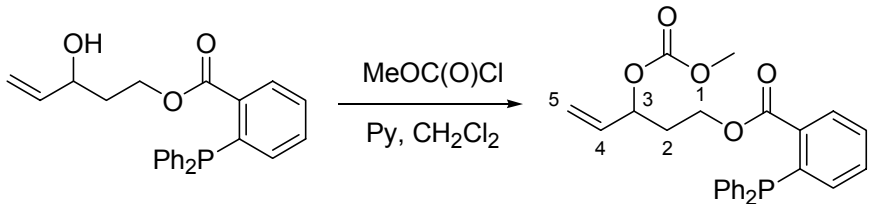
^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 35.8, 62.1, 69.5, 114.8, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.7 (d, $J_{C,P}$ = 2.9 Hz), 132.0, 133.8 (d, $J_{C,P}$ = 4.4 Hz), 134.0 (d, $J_{C,P}$ = 4.4 Hz), 134.3, 134.6, 137.8 (d, $J_{C,P}$ = 4.1 Hz), 137.9 (d, $J_{C,P}$ = 3.9 Hz), 140.4, 167.1 (d, $J_{C,P}$ = 2.4 Hz).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.32.

5.3.4. Synthesis of 1-(2-(diphenylphosphanyl)benzoyloxy)-3-methoxycarbonyloxypent-4-ene (78)



77 **78**

The compound **78** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the ester **77** (1.42 g, 3.64 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.59 (CH/EE 1:1).

Yield 0.93 g (57%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$)

δ = 1.87-2.02 (m, 2H, C_2-CH_2), 3.75 (s, 3H, CH_3OCO), 4.24 (m_c, 2H, C_1-CH_2), 5.17 (m_c, 1H, C_3-CH), 5.22 (d, J = 10.5 Hz, 1H, CH-C_5), 5.30 (d, J = 17.2 Hz, 1H, CH-C_5), 5.76 (dddd, J = 17.2, 10.5, 6.6, 0.5 Hz, 1H, C_4-CH), 6.90-6.95 (m, 1H, Ar-H), 7.22-7.43 (m, 12H, Ar-H), 8.03-8.08 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 33.1, 54.8, 61.1, 75.9, 118.1, 128.3, 128.5 ($J_{C,P}$ = 7.2 Hz), 128.7 ($J_{C,P}$ = 0.7 Hz), 130.7, ($J_{C,P}$ = 2.7 Hz), 132.0, 133.9, ($J_{C,P}$ = 20.8 Hz), 134.4, 135.2, 137.9, ($J_{C,P}$ = 2.9 Hz), 138.0 ($J_{C,P}$ = 2.9 Hz), 140.4 ($J_{C,P}$ = 26.6 Hz), 155.1, 166.7 ($J_{C,P}$ = 2.2 Hz).

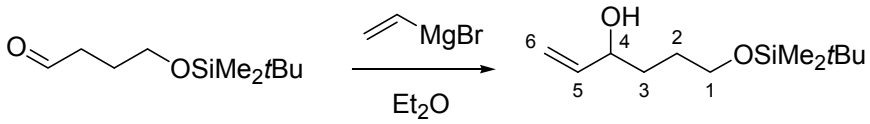
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.38.

HRMS, CI (NH_3):	calculated	449.151788
$C_{26}H_{25}O_5P$ (M+H)	found	449.150901

5.4. Synthesis of branched substrate with allylic system separated from the directing group by 3 carbon atoms

5.4.1. Synthesis of 1-(*tert*-butyldimethylsilyloxy)-hex-5-en-4-ol (61)



57 **61**

The compound **61** was synthesized analogously to **60** (see chapter 5.3.1.) starting from the aldehyde **57** (1.59 g, 7.87 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.68 (CH/EE 1:1).

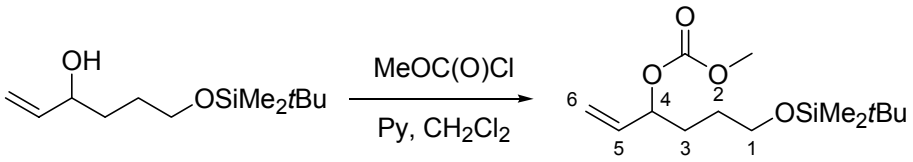
Yield 1.37 g (76%), light-yellow liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 0.06 and 0.07 (s×2, 6H, $Si(CH_3)_2$), 0.83 (s×2, 9H, $Si(C(CH_3)_3)$), 1.54-1.72 (m, 4H, CH_2-C_2 and CH_2-C_3), 2.59 (bs, 1H, OH), 3.66 (m_c, 2H, CH_2-C_1), 4.13 (m_c, 1H, CH-C_4), 5.09 (ddd, J = 10.4, 1.3, 1.2 Hz, 1H, CH-C_6), 5.23 (ddd, J = 17.3, 1.6, 1.5 Hz, 1H, CH-C_6), 5.87 (dddd, J = 17.3, 10.4, 5.9, 0.9 Hz, 1H, CH-C_5).

Analytical data are in a good agreement with literature. [126]

5.4.2. Synthesis of 1-(*tert*-butyldimethylsilyloxy)-4-methoxycarbonyloxy-hex-5-ene (73)



60 **73**

The carbonate **73** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **60** (1.37 g, 5.96 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.73 (CH/EE 1:1).

Yield 0.631 g (37%), light-yellow liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

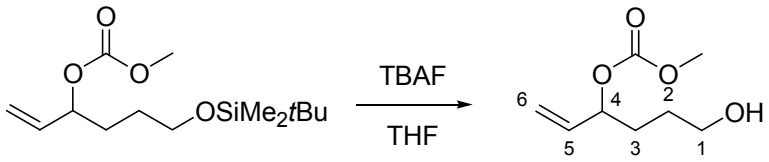
δ = 0.04 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $Si(C(CH_3)_3)$), 1.49-1.64 (m, 2H, CH_2-C_2), 1.66-1.79 (m, 2H, CH_2-C_3), 3.61 (td, J = 6.3, 1.9 Hz, 2H, CH_2-C_1), 3.77 (s, 3H, CH_3OCO), 5.08 (m_c, 1H, CH-C_4), 5.21 (dt, J = 10.5, 1.1, 1.1 Hz, 1H, CH-C_6), 5.30 (ddd, J = 17.3, 1.3, 1.3 Hz, 1H, CH-C_6), 5.79 (ddd, J = 17.2, 10.5, 6.7 Hz, 1H, CH-C_5).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = -5.3, 18.4, 26.0, 28.3, 30.7, 54.7, 62.7, 79.0, 117.6, 136.1, 155.3.

HRMS, CI (NH_3):	calculated	289.183514
$C_{14}H_{29}O_4Si$ (M+H)	found	289.183501

5.4.3. Synthesis of 4-methoxycarbonyloxyhex-5-en-1-ol (74)



73 **74**

The compound **74** was synthesized analogously to **66** (see chapter 5.1.6.) starting from the compound **73** (0.560 g, 1.94 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.47 (CH/EE 1:1).

Yield 0.334 g (99%), light-yellow liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

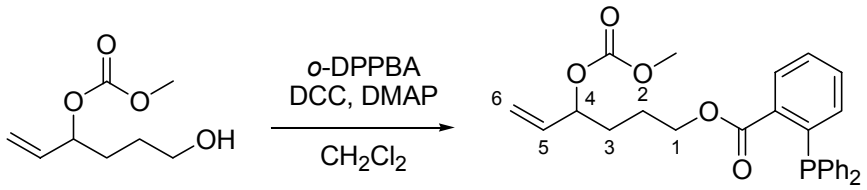
δ = 1.58-1.68 (m, 2H, CH_2-C_3), 1.68-1.82 (m, 2H, CH_2-C_2), 3.65 (t, J = 6.4 Hz, 2H, CH_2-C_1), 3.76 (s, 3H, CH_3OCO), 5.08 (m_c, 1H, CH-C_4), 5.21 (ddd, J = 10.6, 1.1, 1.1 Hz, 1H, CH-C_6), 5.30 (ddd, J = 17.3, 1.3, 1.3 Hz, 1H, CH-C_6), 5.79 (ddd, J = 17.2, 10.5, 6.7 Hz, 1H, CH-C_5).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 28.1, 30.6, 54.7, 62.4, 78.9, 117.7, 135.8, 155.3.

HRMS, CI (NH_3):	calculated	192.123584
$C_8H_{14}O_4$ (M+NH_4)	found	192.123396

5.4.4. Synthesis of 1-(2-(diphenylphosphanyl)benzoyloxy)-4-methoxycarbonyloxyhex-5-ene (75)



74 **75**

The ester **75** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the compound **74** (0.334 g, 1.92 mmol).

Flash-column chromatography (silica gel, CH/EE = 20:1 to 4:1).

R_f = 0.63 (CH/EE 1:1).

Yield 0.629 g (71%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.59-1.77 (m, 4H, CH_2-C_2 and CH_2-C_3), 3.77 (s, 3H, CH_3OCO), 4.17 (t, J = 6.3 Hz, 2H, CH_2-C_1), 5.02 (m_c, 1H, CH-C_4), 5.22 (ddd, J = 10.5, 1.1, 1.1 Hz, 1H, CH-C_6), 5.29 (ddd, J = 17.3, 1.3, 1.3 Hz, 1H, CH-C_6), 5.75 (ddd, J = 17.2, 10.5, 6.7 Hz, 1H, CH-C_5), 6.90-6.95 (m, 1H, Ar-H), 7.23-7.43 (m, 12H, Ar-H), 8.01-8.06 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 24.3, 30.8, 54.7, 64.8, 78.6, 117.9, 128.3, 128.5 ($J_{C,P}$ = 7.2 Hz), 128.7, 130.7 ($J_{C,P}$ = 2.9 Hz), 132.0, 134.0 (($J_{C,P}$ = 20.8 Hz), 134.5, 134.8, 135.6, 138.0 ($J_{C,P}$ = 11.4 Hz), 140.3 ($J_{C,P}$ = 26.6 Hz), 155.2, 167.0 ($J_{C,P}$ = 2.2 Hz).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

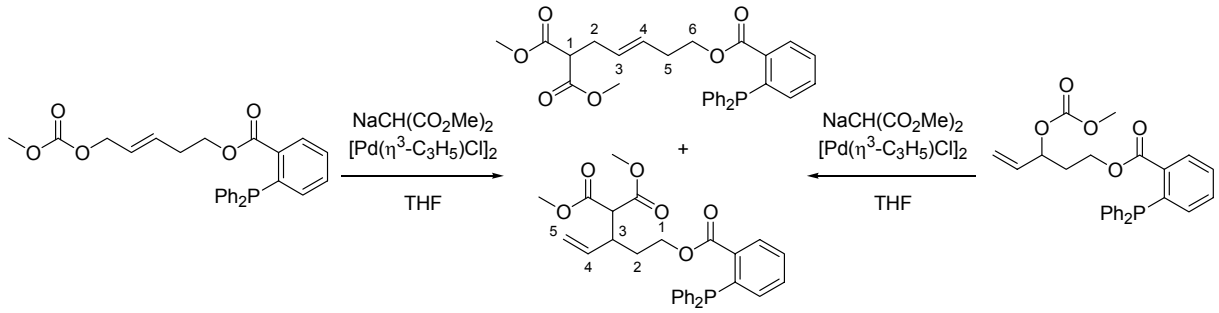
δ = -4.43.

HRMS, CI (NH_3):	calculated	463.167438
$C_{27}H_{27}O_5P$ (M+H)	found	463.166803

5.5. Palladium catalysed allylic substitution

5.5.1. Palladium catalyzed allylic substitution with substrates with allylic system separated from the directing group by 2 carbon atoms

5.5.1.1. Reaction with sodiodimethylmalonate. Synthesis of (*E*)-6-[2-(diphenylphosphanyl)-benzoyloxy]-1,1-[di-(methoxycarbonyl)]-hex-3-ene (114) and 1-[2-(diphenyl-phosphanyl)-benzoyloxy]-3-[di-(methoxycarbonyl)-methyl]-pent-4-ene (115)



68 **114** **115** **78**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **68** (75.3 mg, 0.170 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).
R_f = 0.61 (CH/EE 1:1).
Yield 61%, mixture **114/115** = 30:1, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate **78** (67.5 mg, 0.151 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).
R_f = 0.61 (CH/EE 1:1).
Yield 88%, mixture **114/115** = 1.2:1, yellow oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$)

114: δ = 2.27 (m_c, 2H, C_2-CH_2), 2.57 (m_c, 2H, C_5-CH_2), 3.40 (t, J = 7.6 Hz, 1H, C_1-CH), 3.70 (s, 6H, $(CH_3OOC)_2$), 4.14 (t, J = 6.8 Hz, 2H, C_6-CH_2), 5.38-5.52 (m, 2H, C_4-CH and C_3-CH), 6.90-6.95 (m, 1H, Ar-H), 7.23-7.43 (m, 12H, Ar-H), 8.01-8.06 (m, 1H, Ar-H).

115: only olefin and malonate signals:

δ = 3.75 (s, 6H, $(CH_3OOC)_2$), 5.07 (m_c, 1H, C_5-CH), 5.12 (m_c, 1H, C_5-CH), 5.66 (m_c, 1H, C_4-CH).

^{13}C-NMR (100.613 MHz, $CDCl_3$): both regioisomers

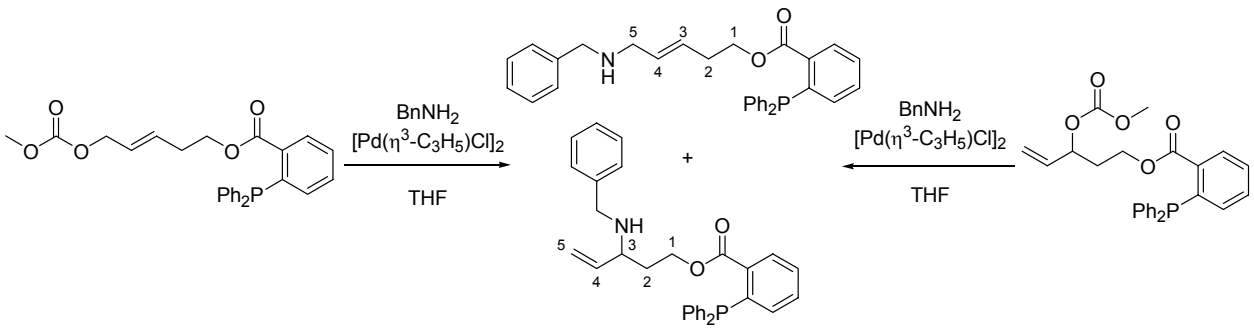
δ = 31.8, 31.9, 51.8, 52.5, 64.5, 128.3 ($J_{C,P}$ = 1.7 Hz), 128.6 ($J_{C,P}$ = 7.2 Hz), 128.7, 129.1, 130.7 ($J_{C,P}$ = 2.7 Hz), 132.0, 134.0 ($J_{C,P}$ = 20.8 Hz), 134.6 ($J_{C,P}$ = 19.3 Hz), 134.4, 138.0 ($J_{C,P}$ =11.1 Hz), 166.8 ($J_{C,P}$ = 2.2 Hz), 169.4; minor signals 32.0, 52.6, 140.4 ($J_{C,P}$ = 26.8 Hz).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.50 (linear) and -4.42 (branched).

HRMS, EI:	calculated	520.165093
$C_{29}H_{29}O_7P$	found	520.165001

5.5.1.2. Reaction with benzylamine. Synthesis of (*E*)-1-[2-(diphenylphosphanyl)-benzoyloxy]-5-(benzylamino)-pent-3-ene (116) and 1-[2-(diphenylphosphanyl)-benzoyloxy]-3-(benzylamino)-pent-4-ene (117)



68 **116** **117** **78**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **68** (74.7 mg, 0.167 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.03 (CH/EE 1:1).

Yield 46%, mixture **116/117** = 8:1, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate **78** (57.4 mg, 0.128 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.03 (CH/EE 1:1).

Yield 39%, mixture **116/117** = 9:1, yellow oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$)

116: δ = 1.48 (bs, 1H, NH), 2.32 (ddd, J = 13.3, 6.7, 1.0 Hz, 2H, C_2-CH_2), 3.22 (dd, J = 5.9, 1.1 Hz, 2H, C_5-CH_2), 3.77 (s, 2H, NHC$\underline{H_2}$Ph), 4.21 (t, J = 6.8 Hz, 2H, C_1-CH_2), 5.64 (dtt, J = 15.4, 6.7, 1.3 Hz, 1H, $C_{3/4}$-CH), 5.63 (dtt, J = 15.4, 6.1, 1.1 Hz, 1H, $C_{3/4}$-CH), 6.92-6.97 (m, 1H, Ar-H), 7.23-7.41 (m, 17H, Ar-H), 8.04-8.09 (m, 1H, Ar-H).

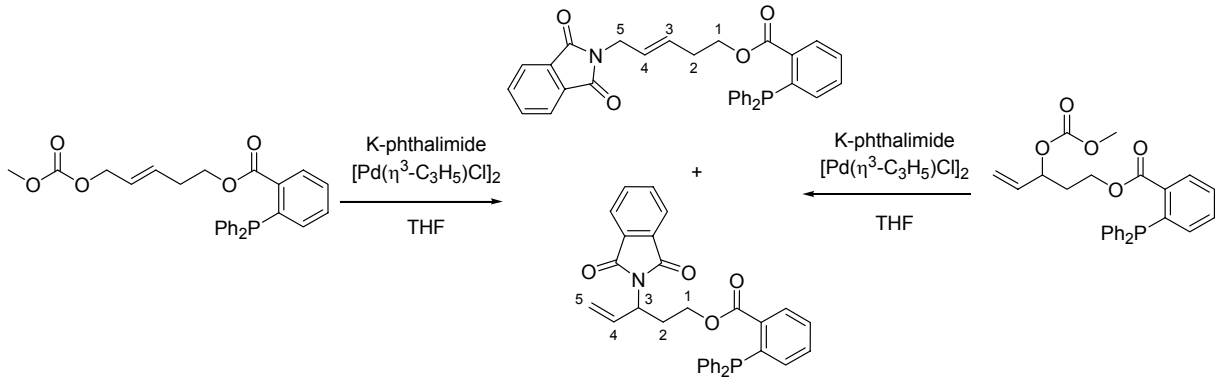
^{13}C-NMR (100.613 MHz, $CDCl_3$):

116: δ = 31.7, 51.0, 53.3, 64.6, 127.0, 127.7, 128.2, 128.3, 128.5 ($J_{C,P}$ = 4.4 Hz), 128.6, 128.7, 130.7 ($J_{C,P}$ = 2.9 Hz), 131.3, 131.9, 134.0 ($J_{C,P}$ = 20.8, Hz), 134.4, 134.7 ($J_{C,P}$ = 19.3 Hz), 138.1 ($J_{C,P}$ = 11.1 Hz), 140.3, 140.4 ($J_{C,P}$ = 26.6 Hz), 166.8 ($J_{C,P}$ = 2.2 Hz).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.58 (linear) and -4.43 (branched).

5.5.1.3. Reaction with potassium phthalimide. Synthesis of (*E*)-1-[2-(diphenylphosphanyl)-benzoyloxy]-5-(phthalimido)-pent-3-ene (118) and 1-[2-(diphenylphosphanyl)-benzoyloxy]-3-(phthalimido)-pent-4-ene (119)



118

68 **119** **78**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **68** (63.4 mg, 0.133 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.57 (CH/EE 1:1).

Yield 62%, mixture **118/119** = 2.3:1, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate ***iso*-68** (63.4 mg, 0.133 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.57 (CH/EE 1:1).

Yield 62%, mixture **118/119** = 1:1, yellow oil.

^{1}H-NMR (300.064 MHz, $CDCl_3$)

118: δ = 2.32 (q, J = 6.7 Hz, 2H, C_2-CH_2), 3.20 (d, J = 5.8 Hz, 2H, C_5-CH_2), 4.19 (t, J = 6.8 Hz, 2H, C_1-CH_2), 5.52 (dt, J = 15.5, 6.5 Hz, 1H, $C_{3/4}$-CH), 5.62 (dt, J = 15.5, 5.9 Hz, 1H, $C_{3/4}$-CH), 6.90-6.94 (m, 1H, Ar-H), 7.22-7.39 (m, 16H, Ar-H), 8.02-8.07 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

118: δ = 31.8 (C_2), 50.9 (C_5), 64.6 (C_1), 127.1, 128.0, 128.3, 128.4, 128.5, 128.6, 128.7, 130.7 ($J_{C,P}$ = 2.9 Hz), 131.0, 132.0, 133.9 ($J_{C,P}$ = 20.7 Hz), 134.5, 138.1 ($J_{C,P}$ = 11.1 Hz), 140.2, 166.8, 166.9 ($J_{C,P}$ = 2.4 Hz).

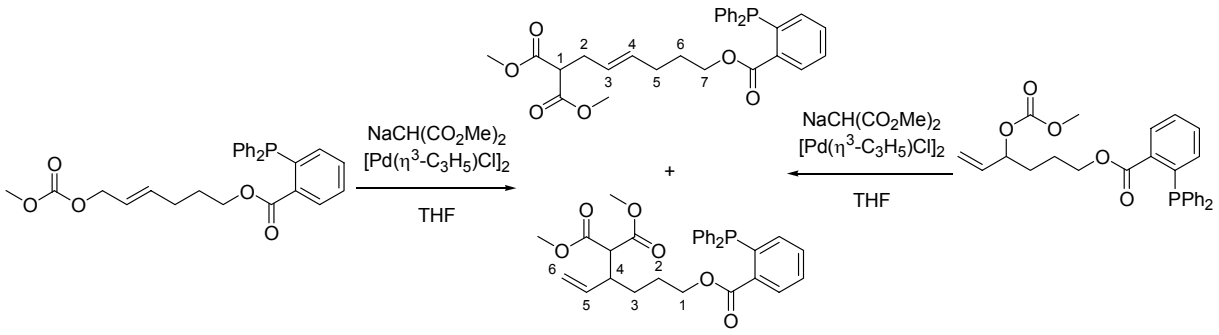
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.43 (linear) and -4.48 (branched).

HRMS, EI:	calculated	535.154862
$C_{32}H_{26}NO_5P$	found	535.155002

5.5.2. Palladium catalyzed allylic substitution with substrates with allylic system separated from the directing group by 3 carbon atoms

5.5.2.1. Reaction with sodiodimethylmalonate. Synthesis of (*E*)-7-[2-(diphenylphosphanyl)-benzoyloxy]-1,1-[di-(methoxycarbonyl)]-hept-3-ene (120) and 1-[2-(diphenyl-phosphanyl)-benzoyloxy]-4-[di-(methoxycarbonyl)-methyl]-hex-5-ene (121)



69 **120** **121** **72**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **69** (60.5 mg, 0.132 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.55 (CH/EE 1:1).

Yield 61%, mixture **120/121** = 13:1, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate **72** (69.7 mg, 0.132 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.55 (CH/EE 1:1).

Yield 47%, the only linear product **120**, yellow oil.

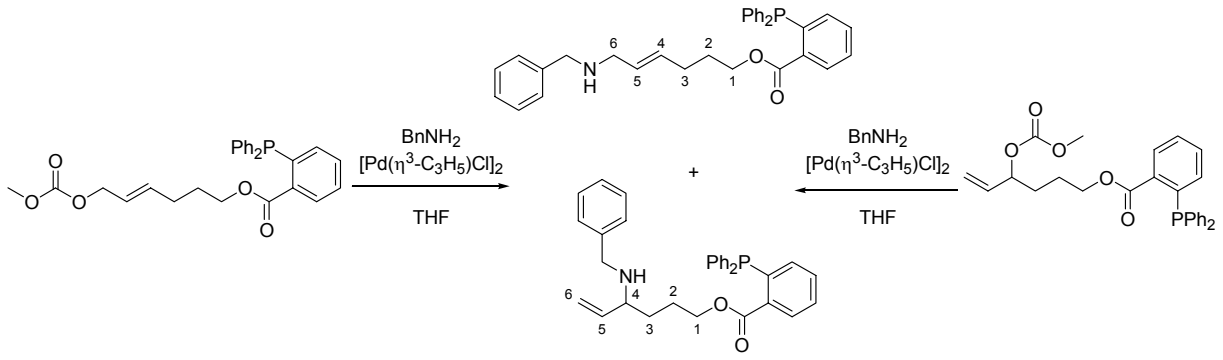
^{1}H-NMR (400.132 MHz, $CDCl_3$)

120: δ = 1.59-1.66 (m, 2H, C_6-CH_2), 1.99 (m_c, 2H, C_5-CH_2), 2.57 (ddd, J = 6.8, 6.8, 1.1 Hz, 2H, C_2-CH_2), 3.40 (t, J = 7.6 Hz, 1H, C_1-CH), 3.71 (s, 6H, C<u>H</u>$_3$OOC), 4.13 (t, J = 6.6 Hz, 2H, C_7-CH_2), 5.35 (dtt, J = 15.3, 6.7, 1.1 Hz, 2H, $C_{3/4}$-CH), 5.48 35 (dtt, J = 15.3, 6.6, 1.1 Hz, 2H, $C_{3/4}$-CH), 6.90-6.94 (m, 1H, Ar-H), 7.23-7.42 (m, 12H, Ar-H), 8.02-8.05 (m, 1H, Ar-H).
121: δ = 3.47 (t, J = 7.6 Hz, 2H, C<u>H</u>(COOMe)$_2$), 5.04-5.15 (m, 2H, C_6-CH_2), 5.77 (m_c, 1H, C_4-CH).

^{13}C-NMR (100.613 MHz, $CDCl_3$)
120: δ = 28.1, 28.9, 31.9, 51.9, 52.5, 64.6, 126.3, 128.3, 128.5 ($J_{C,P}$ = 7.0 Hz), 128.6, 130.6 ($J_{C,P}$ = 2.9 Hz), 131.9, 132.6, 133.9 ($J_{C,P}$ = 20.8 Hz), 134.4, 134.7 ($J_{C,P}$ = 19.3 Hz), 138.0 ($J_{C,P}$ = 11.1 Hz), 140.2 ($J_{C,P}$ = 26.6 Hz), 166.9 ($J_{C,P}$ = 1.9 Hz), 169.4.

^{31}P-NMR (121.468 MHz, $CDCl_3$):
δ = -4.44 (linear) and -4.42 (branched).

5.5.2.2. Reaction with benzylamine. Synthesis of (*E*)-1-[2-(diphenylphosphanyl)-benzoyloxy]-6-(benzylamino)-hex-4-ene (122) and 1-[2-(diphenylphosphanyl)-benzoyloxy]-4-(benzylamino)-hex-5-ene (123)



69 **122** **123** **72**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **69** (79.3 mg, 0.167 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).
R_f = 0.03 (CH/EE 1:1).
Yield 47%, mixture **122/123** = 6:1, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate **72** (62.8 mg, 0.136 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).

R_f = 0.03 (CH/EE 1:1).

Yield 52%, the only linear product **122**, yellow oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$)

122: δ = 1.67 (m_c, 2H, C_2-CH_2), 2.05 (m_c, 2H, C_3-CH_2), 3.21 (m_c, 2H, C_6-CH), 3.77 (s, 2H, $C\underline{H}_2$Ph), 4.17 (t, J = 6.6 Hz, 2H, C_1-CH_2), 5.51-5.58 (m, 2H, C_4-CH and C_5-CH), 6.90-6.95 (m, 1H, Ar-H), 7.23-7.67 (m, 17H, Ar-H), 8.02-8.07 (m, 1H, Ar-H).

123: δ = 3.93 (t, J = 6.7 Hz, 2H, C_1-CH_2), 5.08-5.23 and 5.41-5.46 (double bond).

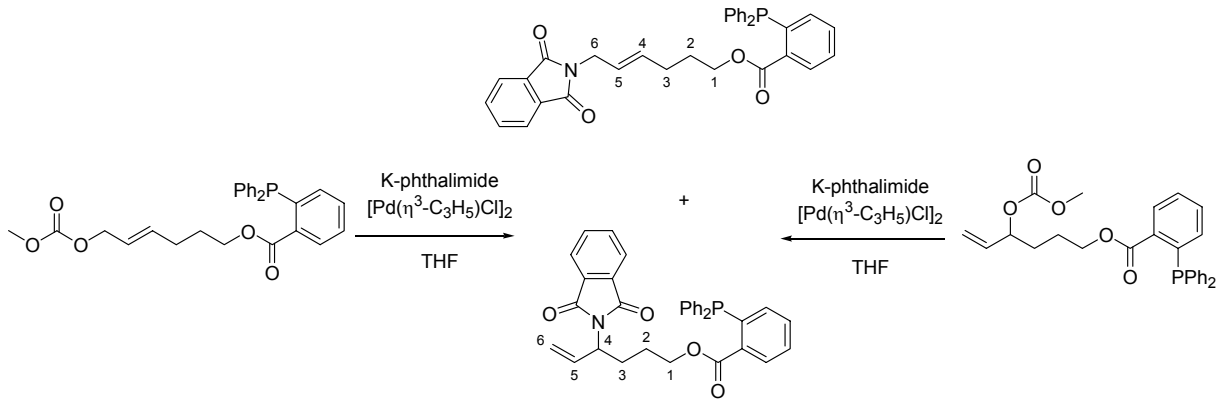
^{13}C-NMR (100.613 MHz, $CDCl_3$)

122: δ = 28.2, 28.8, 51.1, 53.4, 64.8, 126.7, 128.3, 128.5 ($J_{C,P}$ = 3.1 Hz), 128.6, 128.7, 129.3, 130.7 ($J_{C,P}$ = 2.7 Hz), 131.3, 131.9, 133.9 ($J_{C,P}$ = 20.5 Hz), 134.4, 134.8 ($J_{C,P}$ = 19.3 Hz), 138.1 ($J_{C,P}$ = 11.4 Hz), 140.2, 140.5, 167.0 ($J_{C,P}$ = 2.2 Hz).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.58 (linear) and -4.54 (branched).

5.5.2.3. Reaction with potassium phthalimide. Synthesis of (*E*)-1-[2-(diphenylphosphanyl)-benzoyloxy]-6-(phthalimido)-hex-4-ene (124) and 1-[2-(diphenylphosphanyl)-benzoyloxy]-4-(phthalimido)-hex-5-ene (125)



69 **124** **125** **72**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the linear substrate **69** (81.5 mg, 0.176 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).
R_f = 0.63 (CH/EE 1:1).
Yield 49%, mixture **124/125** = 1:1.7, yellow oil.

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the branched substrate **72** (79.1 mg, 0.171 mmol).
Flash-column chromatography (silica gel, CH/EE = 10:1 to 1:1).
R_f = 0.63 (CH/EE 1:1).
Yield 62%, mixture **124/125** = 1:1, yellow oil.

^{1}H-NMR (400.132 MHz, $CDCl_3$)
124 and **125**: δ = 1.44-1.71 (m, 2H, $C_{2/3}$-CH_2), 1.86-2.10 (m, 2H, $C_{2/3}$-CH_2), 6.86-6.90 (m, 1H, Ar-H), 7.18-7.38 (m, 12H, Ar-H), 7.64-7.69 (m, 2H, Ar-H in phthalimide), 7.77-7.83 (m, 2H, Ar-H in phthalimide), 7.97-8.01 (m, 1H, Ar-H).

124: δ = 4.10 (t, J = 6.6 Hz, 1H, C_1-CH_2), 4.19 (dd, J = 6.1, 1.1 Hz, 2H, C_6-CH_2), 5.46 (dtt, J = 15.3, 6.2, 1.4 Hz, 1H, $C_{4/5}$-CH), 5.65 (dtt, J = 15.3, 6.6, 1.2 Hz, 1H, $C_{4/5}$-CH);

125: δ = 4.13 (t, J = 6.6 Hz, 1H, C_1-CH_2), 4.66 (dddd, J = 15.3, 7.7, 1.0, 1.0 Hz, C_4-CH), 5.15 (ddd, J = 10.2, 1.1, 1.1 Hz, 1H, C_6-CH), 5.20 (ddd, J = 17.2, 1.2, 1.2 Hz, 1H, C_6-CH), 6.15 (ddd, J = 17.2, 10.2, 7.7 Hz, 1H, C_5-CH).

^{13}C-NMR (100.613 MHz, $CDCl_3$)
124 and **125**: δ = 25.7, 27.8, 28.6, 39.5, 53.8, 64.6,64.7, 117.9, 123.27, 123.29, 124.1, 128.25, 128.28, 128.5 ($J_{C,P}$ = 7.2 Hz), 128.6, 130.6 ($J_{C,P}$ = 2.9 Hz), 130.7 ($J_{C,P}$ = 2.7 Hz), 131.8 ($J_{C,P}$ = 3.1 Hz), 131.9 ($J_{C,P}$ = 2.7 Hz), 132.2, 133.7, 133.8, 133.9, 134.0, 134.4, 134.6 ($J_{C,P}$ = 19.6 Hz), 134.7 ($J_{C,P}$ = 19.6 Hz), 135.4, 138.0 ($J_{C,P}$ = 2.4 Hz), 138.1 ($J_{C,P}$ = 2.4 Hz), 140.2 ($J_{C,P}$ = 26.6 Hz), 166.9 ($J_{C,P}$ = 2.2 Hz, branched), 167.0 ($J_{C,P}$ = 1.9 Hz, linear), 168.0 (linear), 168.2 (branched).

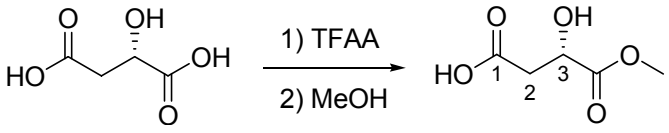
^{31}P-NMR (121.468 MHz, $CDCl_3$):
δ = -4.40 (linear) and -4.38 (branched).

HRMS, CI (NH_3):	calculated	534.183422
$C_{33}H_{28}NO_4P$ (M+H)	found	534.184497

6. System based on malic acid

6.1. Synthesis of chiral substrates

6.1.1. Synthesis of (*S*)-3-hydroxy-4-methoxy-4-oxobutanoic acid (81)



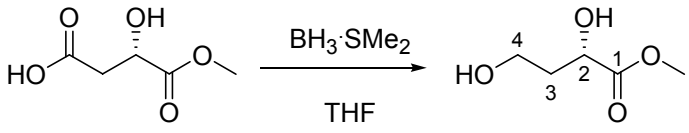
80 **81**

L-(–)-Malic acid (3.02 g, 22.54 mmol) was dissolved in trifluoroacetic anhydride (7.5 ml, 11.3 g, 53.9 mmol, 2.4 eq) at 0 °C. After 3 h stirring at room temperature the formed clear solution was evacuated to get rid of excess anhydride. Anhydrous methanol (12.0 ml, 9.5 g, 295.9 mmol, 13.1 eq) was added to the solid, stirred 30 min and the solvent was evaporated. The product **81** was isolated as a white crystalline compound (3.34 g, 100%), which was used in the following steps without further purification.

^{1}H-NMR (300.064 MHz, $CDCl_3$):
δ = 2.84 (dd, J = 16.8, 6.0 Hz, 1H, C_2-CH_A), 2.94 (dd, J = 16.8, 4.4 Hz, 1H, C_2-CH_B), 3.82 (s, 3H, $COOCH_3$), 4.54 (dd, J = 6.2, 4.4 Hz, 1H, C_3-CH).

Analytical data are in a good agreement with literature. [127]

6.1.2. Synthesis of (*S*)-2,4-dihydroxybutanoic acid methyl ester (82)



81 **82**

To the solution of (*S*)-malic acid monomethyl ester **81** (3.34 g, 22.54 mmol) in anhydrous THF (18 ml) at -30 °C dropwise boron dimethylsulfide complex (94%, 4.55 ml, 3.64 g, 45.08 mmol, 2 eq) was added, the reaction was stirred at room temperature overnight. Water (15 ml) was slowly

added to the reaction mixture at 0 °C, THF was evaporated and the mixture was extracted with ethyl acetate (4×20 ml), the combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated.

The product **82** (2.79 g, 92%), yellow oil, was used in the following steps without further purification.

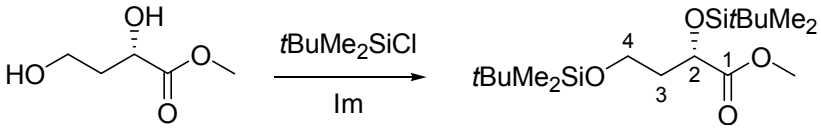
^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.73-1.81 (m, 1H, C_3-CH_A), 1.82-1.97 (m, 1H, C_3-CH_B), 3.73 (s, 3H, $COOCH_3$), 3.86 (m_c, 1H, C_2-CH), 3.98 (ddd, J = 11.8, 5.4, 2.0 Hz, 1H, C_4-CH_A), 4.50 (ddd, J = 11.8, 3.2, 3.2 Hz, 1H, C_4-CH_B).

Analytical data are in a good agreement with literature. [128]

6.1.3. Synthesis of (*S*)-2,4-di-(*tert*-buthyldimethylsilyloxy)-butanoic acid methyl ester (89)

Method 1



82 **89**

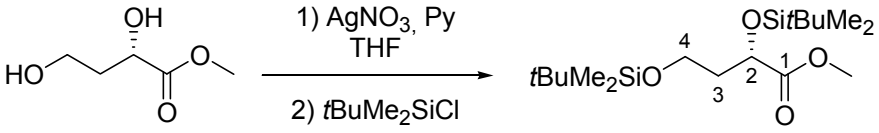
To a solution of the diol **82** (4.57 g, 34.1 mmol) in DMF (20 ml) imidazole (9.7 g, 142.4 mmol, 4.2 eq) was added at 0 °C. Then tBuMe$_2$SiCl (10.3 g, 68.3 mmol, 2.0 eq) was added at 0 °C. After stirring at room temperature overnight ether (40 ml) was added to the reaction mixture, it was washed with water (4×20 ml), dried over Na_2SO_4, the solvent was evaporated.

Flash-column chromatography (silica gel, PE to PE/TMBE = 3:1).

R_f = 0.72 (CH/EE 1:1).

Yield 3.9 g (32%).

Method 2



82 **89**

The compound was synthesized according to literature known procedure of silylation [129] To a solution of the diol **82** (5.02 g, 37.5 mmol) in THF (21 ml) silver nitrate (15.3 g, 90.0 mmol), then pyridine (30 ml, 29.3 mg, 370.9 mmol) was added. After 10 minutes stirring at room temperature without access of light *t*BuMe$_2$SiCl (14.3 g, 94.8 mmol, 2.5 eq) was added. After stirring at room temperature for 2h the reaction mixture was filtrated, filter-cake was washed with ether.

Flash-column chromatography (silica gel, PE to PE/TMBE = 3:1).

R_f = 0.72 (CH/EE 1:1).

Yield 6.39 g (47%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

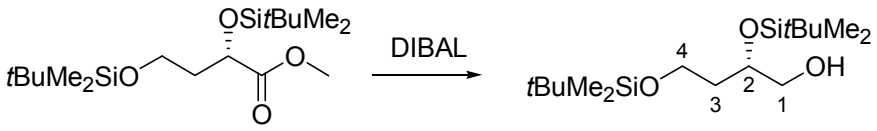
δ = 0.04 (s, 6H, *t*BuMe$_2$Si), 0.06 (s, 6H, *t*BuMe$_2$Si), 0.89 (s, 9H, *t*BuMe$_2$Si), 0.91 (s, 9H, *t*BuMe$_2$Si), 1.84 (ddddd, *J* = 19.3, 13.5, 8.1, 5.3, 5.3 Hz, 1H, CH_B-C_3), 1.93 (ddddd, *J* = 19.3, 13.6, 7.8, 6.2, 4.3 Hz, 1H, CH_A-C_3), 3.66-3.77 (m, 2H, CH_2-C_4), 3.71 (s, 3H, COOMe), 4.39 (dd, *J* = 8.1, 4.3 Hz, 1H, CH-C_2).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = -5.36 (*t*BuMe$_2$Si), -5.29 (*t*BuMe$_2$Si), -5.26 (*t*BuMe$_2$Si), -4.89 (*t*BuMe$_2$Si), 18.37 (C(CH$_3$)$_3$), 18.40 (C(CH$_3$)$_3$), 26.0 (C(CH$_3$)$_3$), 26.8 (C(CH$_3$)$_3$), 38.2 (C_3), 51.8 (COOMe), 58.7 (C_4), 69.0 (C_2), 174.6 (COOMe).

HRMS, EI:	calculated	305.160443
$C_{13}H_{29}O_4Si_2$	found	305.160299

6.1.4. Synthesis of (*S*)-2,4-di-(*tert*-buthyldimethylsilyloxy)-butan-1-ol (90)



89 **90**

To the solution of the protected diol **89** (3.76 g, 10.4 mmol) in toluene (25 ml) solution of DIBAL-H (4.0 ml, 3.19 g, 22.5 mmol, 2.2 eq) in toluene (25 ml) was added at 0 °C. After 1.5 h the reaction mixture was warmed up to room temperature and saturated aqueous solution of

Na_2SO_4 was added until no more bubbles of hydrogen were evaluated, then solid Na_2SO_4 was added, filtered, washed with ether. The solvent was evaporated. The compound was used without further purification.

Yield 2.79 g (78%), colourless oily liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

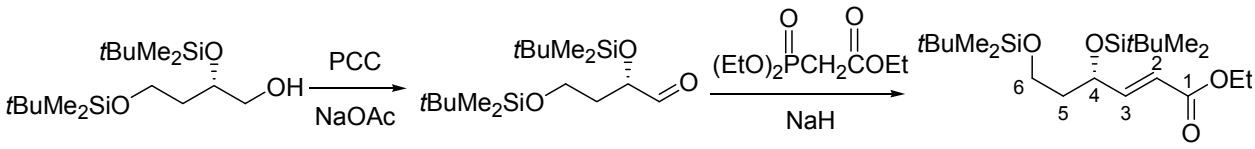
δ = 0.06 (s, 6H, *t*Bu$\underline{Me}_2$Si), 0.08 (s, 6H, *t*Bu$\underline{Me}_2$Si), 0.89 (s, 9H, *t*$\underline{Bu}$Me$_2$Si), 0.90 (s, 9H, *t*$\underline{Bu}$Me$_2$Si), 1.66-1.82 (m, 2H, CH_2-C_3), 3.65 (ddd, J = 10.4, 7.1, 4.9 Hz, 1H, CH_A-C_4), 3.71 (ddd, J = 10.4, 6.7, 5.1 Hz, 1H, CH_B-C_4), 3.93 (m_c, 1H, CH-C_2).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = -5.33 (*t*Bu$\underline{Me}_2$Si, 2×C), -4.59 (*t*Bu$\underline{Me}_2$Si), -4.53 (*t*Bu$\underline{Me}_2$Si), 18.2 ($\underline{C}(CH_3)_3$), 18.3 ($\underline{C}(CH_3)_3$), 25.9 (C($\underline{C}H_3)_3$), 26.0 (C($\underline{C}H_3)_3$), 37.5 (C_3), 59.4 (C_4), 66.6 (C_2), 70.5 (C_1).

HRMS, EI:	calculated	303.217563
$C_{15}H_{35}O_2Si_2$	found	303.217297

6.1.5. Synthesis of (*S*,*E*)-4,6-di-(*tert*-buthyldimethylsilyloxy)-hex-2-enoic acid ethyl ester (92)



90 **91** **92**

To mixture of the alcohol **90** (2.78 g, 8.3 mmol) and sodium acetate (0.56 g, 6.8 mmol, 0.82 eq) in CH_2Cl_2 (20 ml) at 0 °C PCC (3.72 g, 17.3 mmol, 2.08 eq) was slowly added. After 40 min at the temperature the solvent was evaporated, ether was added to the residue and the mixture was filtered through a short silica gel column, washed with ether. The solvent was evaporated and the aldehyde was dissolved in abs. THF (5 ml).

Triethyl phophonoacetate (1.7 ml, 1.92 g, 8.6 mmol) was added into a suspension of NaH (60% in mineral oil, 0.34 g, 8.5 mmol) in THF (18 ml) at -78 °C and stirred 1 h at room temperature, cooled again to -78 °C, and the solution of aldegyde in THF was added. Afrer 30 min stirring the reaction mixture was warmed up to room temperature. After addition of water the organic phase

was separated, the water phase was extracted with CH_2Cl_2 (3×100 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated.

Flash-column chromatography (silica gel, PE/TMBE = 10:0 to 3:1).

R_f = 0.72 (CH/EE 1:1).

Yield 2.4 g (72%), viscous liquid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

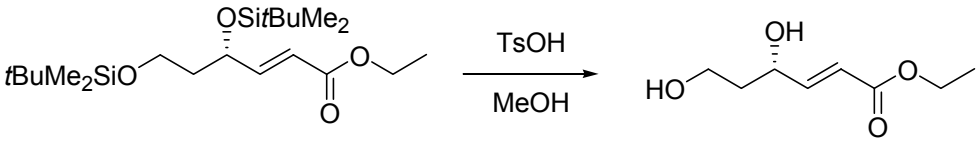
δ = 0.00 (s, 6H, *t*Bu$\underline{Me}_2$Si), 0.02 (s, 6H, *t*Bu$\underline{Me}_2$Si), 0.85 (s, 9H, *t*$\underline{Bu}$Me$_2$Si), 0.87 (s, 9H, *t*$\underline{Bu}$Me$_2$Si), 1.25 (t, J = 7.1 Hz, 3H, $CH_2C\underline{H}_3$), 1.66-1.72 (m, 2H, CH_2-C_5), 3.58-3.71 (m, 2H, CH_2-C_6), 4.16 (q, J = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.45 (m_c, 1H, CH-C_4), 5.93 (dd, J = 15.5, 1.6 Hz, 1H, CH-C_2), 6.91 (dd, J = 15.5, 4.9 Hz, 1H, CH-C_3).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = -5.26 (*t*Bu$\underline{Me}_2$Si, 2×C), -4.9 (*t*Bu$\underline{Me}_2$Si), -4.5 (*t*Bu$\underline{Me}_2$Si), 14.4 ($CH_2\underline{C}H_3$), 18.27 ($\underline{C}(CH_3)_3$), 18.30 ($\underline{C}(CH_3)_3$), 25.9 ($C(\underline{C}H_3)_3$), 26.0 ($C(\underline{C}H_3)_3$), 40.6 (C_5), 59.0 (C_6), 60.4 ($\underline{C}H_2CH_3$), 68.8 (C_4), 119.7 (C_2), 151.2 (C_3), 166.8 ($\underline{C}$OOEt).

HRMS, EI:	calculated	345.191743
$C_{16}H_{33}O_4Si_2$	found	345.192099

6.1.6. Synthesis of (*S*,*E*)-4,6-dihydroxyhex-2-enoic acid ethyl ester (87)



92 **87**

The protected diol **92** (0.63 g, 1.6 mmol) was dissolved in methanol (15 ml), several crystals of TsOH were added. After 2 h stirring the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 3:0 to EE).

R_f = 0.10 (CH/EE 1:1).

Yield 0.15 g (57%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.30 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.59 (bs, 1H, OH), 1.79 (dddd, J = 14.7, 8.2, 7.3, 4.0 Hz, 1H, 5-CH_A), 1.92 (dddd, J = 14.7, 7.0, 4.0, 3.7 Hz, 1H, 5-CH_B), 2.89 (d, J = 3.9 Hz, 1H, C_4-OH), 3.83-3.96 (m, 2H, 6-CH_2), 4.21 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.60 (m_c, 1H, 4-CH), 6.11 (dd, J = 15.7, 1.8 Hz, 1H, 2-CH), 6.96 (dd, J = 15.7, 4.4 Hz, 1H, 3-CH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.3, 37.5, 60.6, 61.2, 70.9, 120.6, 149.5, 166.6.

HRMS, CI (NH_3):	calculated	192.123584
$C_8H_{14}O_4$ (M+NH_4)	found	192.123396

6.1.7. Synthesis of (*S*,*E*)-4-hydroxy-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (88)

87 **88**

The ester **88** was synthesized analogously to **13** (see chapter 4.1.4.) starting from the diol **87** (0.675 g, 3.88 mmol) in DMF as a solvent.

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.51 (CH/EE 1:1).

Yield 0.89 g (48%), yellow oil.

Additionally bis-(*o*-DPPBA) ester was separated.

R_f = 0.78 (CH/EE 1:1).

Yield 0.89 g (30%), yellowish solid.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.28 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.64-1.75 (m, 1H, C_5-CH_A), 1.79-1.90 (m, 1H, C_5-CH_B), 2.55 (d, J = 4.8 Hz, 1H, OH), 4.17-4.22 (m, 1H, C_4-CH), 4.19 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.22-4.28 (m, 1H, C_6-CH_A), 4.41-4.49 (m, 1H, C_6-CH_B), 6.02 (dd, J = 15.7, 1.8 Hz, 1H, C_2-CH),

6.83 (dd, J = 15.7, 4.5 Hz, 1H, C_3-CH), 6.90-6.96 (m, 1H, Ar-H), 7.24-7.44 (m, 12H, Ar-H), 8.02-8.09 (m, 1H, Ar-H).

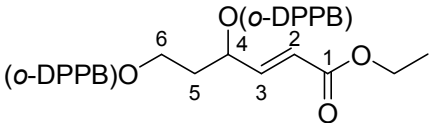
^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.3 ($OCH_2\underline{C}H_3$), 35.5 (C_5), 60.5 ($O\underline{C}H_2CH_3$), 61.6 (C_6), 67.6 (C_4), 120.5, 128.39, 128.7 (d, $J_{C,P}$ = 7.5 Hz), 128.9, 131.0 (d, $J_{C,P}$ = 2.9 Hz), 132.2, 133.9 (d, $J_{C,P}$ = 7.7 Hz), 134.1 (d, $J_{C,P}$ = 8.0 Hz), 134.4, 137.8 (d, $J_{C,P}$ = 9.9 Hz), 140.1 (d, $J_{C,P}$ = 26.1 Hz), 149.3, 166.5, 167.4 (d, $J_{C,P}$ = 2.2 Hz).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.08.



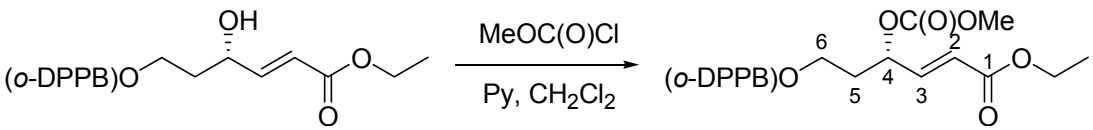
^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.27 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.50-1.85 (m, 2H, C_5-CH_2), 3.54 (m, 1H, C_6-CH_A), 3.80 (m, 1H, C_6-CH_B), 4.15 (q, J = 7.1 Hz, $OC\underline{H}_2CH_3$), 5.61 (m_c, 1H, C_4-CH) 5.90 (dd, J = 15.7, 1.5 Hz, 1H, C_2-CH), 6.74 (dd, J = 15.7, 5.3 Hz, 1H, C_3-CH), 6.90-6.96 (m, 2H, Ar-H), 7.15-7.41 (m, 24H, Ar-H), 7.95-8.10 (m, 2H, Ar-H).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.23 and -4.32.

6.1.8. Synthesis of (*S*,*E*)-4-(methoxycarbonyloxy)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (79)



88 **79**

The compound **79** was synthesized analogously to **14** (see chapter 4.1.5.) starting from the compound **88** (2.4 g, 5.2 mmol).

Flash-column chromatography (silica gel, CH/EE = 10:1 to 4:1).

R_f = 0.59 (CH/EE 1:1).

Yield 1.16 g (45%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.28 (t, J = 7.1 Hz, 3H, $OCH_2C\underline{H}_3$), 1.93-2.00 (m, 2H, C_5-CH_2), 3.77 (s, 3H, $OCOOCH_3$), 4.19 (q, J = 7.1 Hz, 2H, $OC\underline{H}_2CH_3$), 4.22-4.29 (m, 2H, C_6-CH_2), 5.31 (ddd, J = 6.0, 1.5, 1.5 Hz, 1H, C_4-CH), 5.98 (dd, J = 15.7, 1.5 Hz, 1H, C_2-CH), 6.78 (dd, J = 15.7, 5.4 Hz, 1H, C_3-CH), 6.91-6.94 (1H, Ar-H), 7.24 -7.42 (m, 12H, Ar-H), 8.02-8.05 (m, 1H, Ar-H).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.2 ($OCH_2\underline{C}H_3$), 32.8 (C_5), 55.1 ($\underline{C}H_3OCO$), 60.4 ($O\underline{C}H_2CH_3$), 60.7 (C_6), 73.6 (C_4), 122.5, 128.6 (d, $J_{C,P}$ = 7.2 Hz), 128.7 (d, $J_{C,P}$ = 2.2 Hz), 130.7 (d, $J_{C,P}$ = 2.9 Hz), 132.1, 133.8 (d, $J_{C,P}$ = 2.7 Hz), 134.1 (d, $J_{C,P}$ = 2.9 Hz), 134.4, 138.0 (d, $J_{C,P}$ = 2.7 Hz), 140.4 (d, $J_{C,P}$ = 26.6 Hz), 143.8, 154.9, 165.7, 166.7 (d, $J_{C,P}$ = 1.9 Hz, Ar$\underline{C}$OO), 171.7 ($CH_3O\underline{C}O$).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.35.

$[\alpha]_D^{20}$ = -12.2° (c = 0.475, $CHCl_3$).

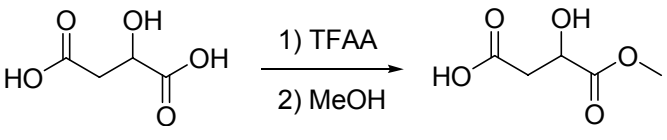
Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 95/5, room temperature, 0.8 ml/min, 230 nm):

R_T[(*R*)-**79**]= 18.6 min,

R_T[(*S*)-**79**]= 20.0 min.

6.2. Syntheis of racemic substrates

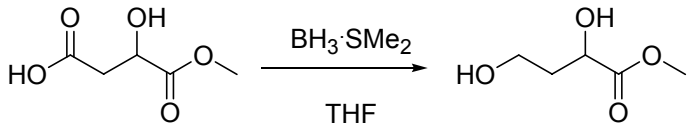
6.2.1. Synthesis of *rac*-3-hydroxy-4-methoxy-4-oxobutanoic acid (*rac*-81)



***rac*-80** ***rac*-81**

The synthesis was performed analogously to synthesis of **81**.
Analytical data are described above for **81**.

6.2.2. Synthesis of rac-2,4-dihydroxybutanoic acid methyl ester (*rac*-82)

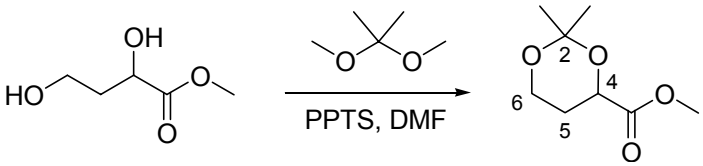


***rac*-81** ***rac*-82**

The synthesis was performed analogously to synthesis of **82**.
Analytical data are described above for **82**.

6.2.3. Synthesis of *rac*-2,2-dimethyl-[1,3]-dioxane-4-carboxylic acid methyl ester (*rac*-83)

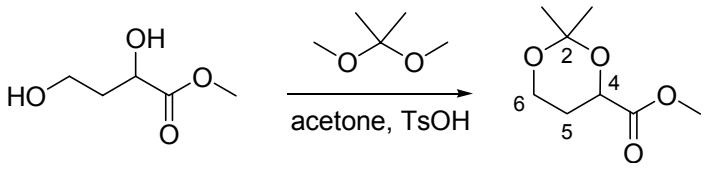
<u>In DMF mit PPTS</u>



***rac*-82** ***rac*-83**

To the solution of diol ***rac*-82** (2.52 g, 18.82 mmol) in DMF 2,2-dimethoxypropane (10.0 ml, 8.5 g, 81.6 mmol, 4.3 eq) and PPTS (cat. amount) were added. After stirring overnight water (20 ml) was added, the mixture was extracted with CH_2Cl_2 (3×20 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated.
It gives a mixture of product (1.06 g, 2.03 mmol, 11%) / DMF = 2:1.

<u>In Aceton mit TsOH</u>



***rac*-82** ***rac*-83**

The diol ***rac*-82** (2.79 g, 20.79 mmol) was dissolved in acetone (10 ml), then 2,2-dimethoxy-propane (11.0 ml, 9.4 g, 90.2 mmol, 4.3 eq) and TsOH (cat. amount) were added, stirred overnight. The solvent was evaporated and the residue was filtered through a silica gel pad (CH/EE = 1:1 + 2% vol. NEt_3). After solvent evaporation the product ***rac*-83** was obtained (2.7 g, 75%) as yellow oil. The product was used without further purification.

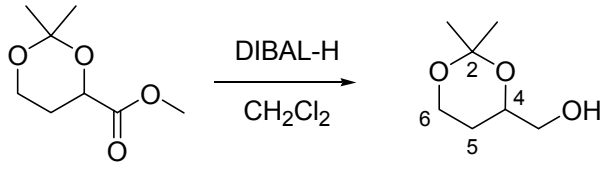
^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.47 (s, 3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 1.75-1.82 (m, 1H, C_5-CH_A), 1.85-1.99 (m, 1H, C_5-CH_B), 3.76 (s, $COOCH_3$), 3.89 (ddd, J = 11.9 , 5.6, 2.3 Hz, 1H, C_6-CH_A), 4.00 (ddd, J = 11.9, 11.9, 3.2 Hz, C_6-CH_B), 4.52 (dd, J = 11.8, 3.2 Hz, 1H, C_4-CH).

Analytical data are in a good agreement with literature. [130]

6.2.4. Synthesis of (2,2-dimethyl-[1,3]dioxan-4-yl)-methanol (*rac*-84)

Reduction with DIBAL-H



***rac*-83** ***rac*-84**

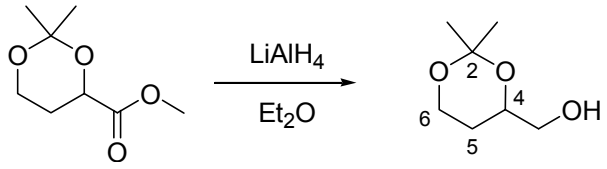
To the cooled to -78 °C solution of the ester ***rac*-83** (2.70 g, 15.5 mmol) in dichloromethane (10 ml) was slowly added di-isobutylaluminiumhydride (6.9 ml, 5.7 g, 40.2 mmol, 2.6 eq) in dichloromethane (10 ml). After 2.5 h the reaction mixture was warmed up to room temperature and saturated aqueous solution of Na_2SO_4 was added until no more bubbles of hydrogen were evaluated, then solid Na_2SO_4 was added, filtered, washed with ether. The solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 2:1 + 2% vol. NEt_3).

R_f = 0.19 (CH/EE 1:1).

Yield 0.85 g (38%), colourless oily liquid.

Reduction with LAH



***rac*-83** ***rac*-84**

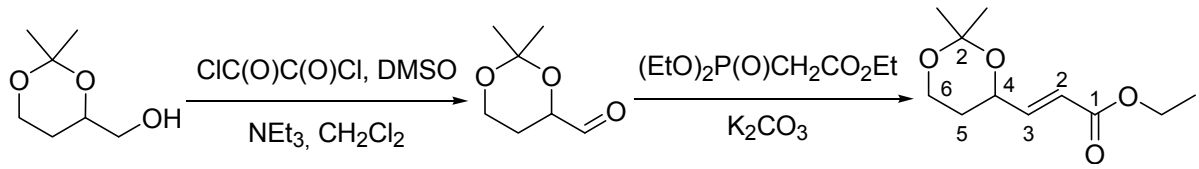
To suspension of $LiAlH_4$ (9.5 g, 250 mmol, 4 eq) in Et_2O (150 ml) at 0 °C solution of the ester ***rac*-83** (10.8 g, 62.3 mmol) in Et_2O (150 ml) was slowly added, stirred 1 h at room temperature. Saturated aqueous solution of Na_2SO_4 was added until no more bubbles of hydrogen were evaluated, then solid Na_2SO_4 was added, filtered, washed with ether. The solvent was evaporated. The product was used in the following steps without further purification.

Yield 4.0 g (44%), colourless oily liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.39 (s, 3H, $C(CH_3)_2$), 1.46 (s, 3H, $C(CH_3)_2$), 1.68 -1.85 (m, 2H, C_5-CH_2), 3.47-3.63 (m, 2H, $C\underline{H_2}OH$), 3.86 (ddd, J = 11.7, 5.7, 1.8 Hz, C_6-CH_A), 3.97 (dd, J = 11.8, 2.9 Hz, C_6-CH_A), 4.03 (m_c, 1H, C_4-CH).

6.2.5. Synthesis of *rac*-(*E*)-3-(2,2-Dimethyl-1,3-dioxan-4-yl)acryl acid ethyl ester (*rac*-86)



***rac*-84** ***rac*-84** ***rac*-86**

To solution of oxalylchloride (1.9 ml, 2.8 g, 21.9 mmol, 1.2 eq) in CH_2Cl_2 (40 ml) at -78 °C DMSO (3.1 ml, 3.4 g, 43.9 mmol, 2.4 eq) was slowly added. After 10 min at the temperature alcohol ***rac*-84** (2.66 g, 18.2 mmol) in CH_2Cl_2 (30 ml) was added dropwise. After additional 20 min of stirring triethylamine (12.7 ml, 9.3 g, 91.8 mmol, 5 eq) was added and the reaction mixture

was allowed to warm up to 0°C. Then saturated aqueous solution of K_2CO_3 (70 ml), solid $NaHCO_3$ (31 g) and triethyl phophonoacetate (9.1 ml, 10.3 g, 45.7 mmol, 2.5 eq) were added one after another and stirred at room temperature overnight. After addition of water (till all the salts dissolve) the organic phase was separated, the water phase was extracted with CH_2Cl_2 (3×100 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 4:1 + 1% vol. NEt_3).

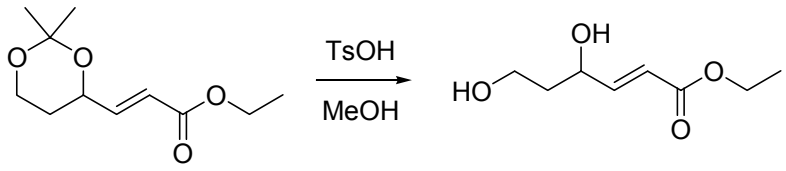
R_f = 0.53 (CH/EE 1:1).

Yield 1.75 g (45%), viscous liquid.

^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.27 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.42 (s, 3H, $C(CH_3)_2$), 1.48 (s, 3H, $C(CH_3)_2$), 1.53-1.61 (m, 1H, C_5-CH_A), 1.62-1.76 (m, 1H, C_5-CH_B), 3.87 (ddd, J = 5.3, 1.8, 1.8 Hz, 1H, C_6-CH_A), 4.02 (ddd, J = 12.0, 9.1, 3.1 Hz, 1H, C_6-CH_B), 4.19 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.54 (m_c, 1H, C_4-CH), 6.04 (dd, J = 15.7, 1.5 Hz, 1H, C_2-CH), 6.86 (dd, J = 15.7, 4.4 Hz, 1H, C_3-CH).

6.2.6. Synthesis of *rac*-(*E*)-4,6-dihydroxyhex-2-enoic acid ethyl ester (*rac*-87)



***rac*-86** ***rac*-87**

The protected diol ***rac*-86** (1.75 g, 8.18 mmol) was dissolved in MeOH (20 ml). TsOH (cat. amount) was added and the reaction mixture was stirred 2.5 h, then the solvent was evaporated.

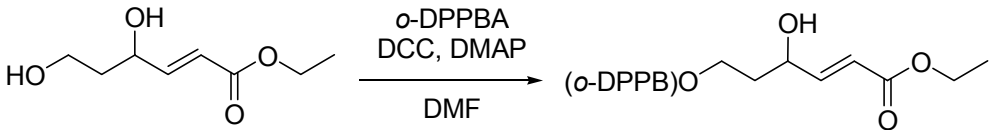
Flash-column chromatography (silica gel, CH/EE = 4:1 to 1:1).

R_f = 0.05 (CH/EE 1:1).

Yield 1.11 g (80%), viscous colourless liquid.

Analytical data are described above for **87**.

6.2.7. Synthesis of *rac*-(*E*)-4-hydroxy-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (*rac*-88)

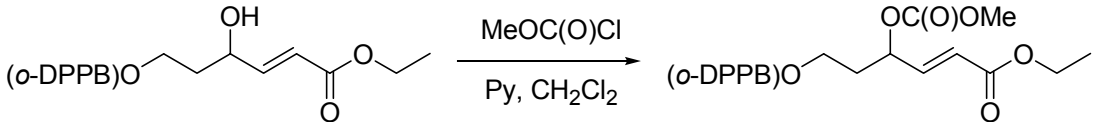


***rac*-87** ***rac*-88**

The synthesis was performed analogously to synthesis of **88**.

Analytical data are described above for **88**.

6.2.8. Synthesis of *rac*-(*E*)-4-(methoxycarbonyloxy)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (*rac*-79)



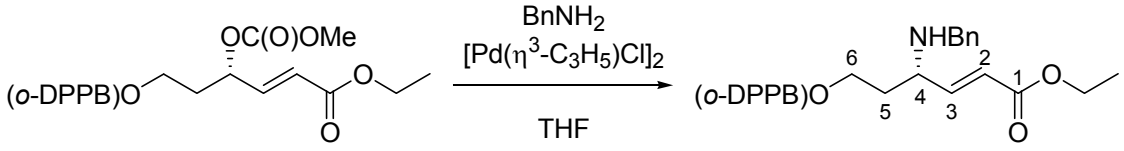
***rac*-88** ***rac*-79**

The synthesis was performed analogously to synthesis of **79**.

Analytical data are described above for **79**.

6.3. Palladium catalyzed allylic substitution

6.3.1. Synthesis of (*S*,*E*)-4-(benzylamino)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (126)



79 **126**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (58.5 mg, 0.11 mmol) with 3.1 eq of benzylamine.
Flash-column chromatography (silica gel, CH/EE = 10:1).
R_f = 0.50 (CH/EE 1:1).
Yield 35.2 mg (49%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 1.30 (t, J = 7.2 Hz, 3H, $OCH_2\underline{C}H_3$), 1.63 (bs, 1H, NH), 1.78 (ddd, J = 6.4, 6.4, 6.4 Hz, 2H, C_5-CH_2), 3.29 (m_c, 1H, C_4-CH), 3.58 (d, J = 13.1 Hz, 1H, $NHC\underline{H}_APh$), 3.77 (d, J = 13.1 Hz, 1H, $NHC\underline{H}_BPh$), 4.19 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.18-4.23 (m, 1H, C_6-CH_A), 4.27-4.33 (m, 1H, C_6-CH_B), 5.89 (dd, J = 15.7, 1.0 Hz, 1H, C_2-CH), 6.72 (dd, J = 15.7, 8.0 Hz, 1H, C_3-CH), 6.86-6.94 (m, 1H, ArH), 7.19-7.40 (m, 17H, ArH), 7.91-7.97 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):
δ = 14.3 ($OCH_2\underline{C}H_3$), 34.0 (C_5), 51.3 ($\underline{C}H_2Ph$), 56.1 (C_4), 60.5 ($O\underline{C}H_2CH_3$), 62.1 (C_6), 122.4, 127.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.7, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 132.0, 133.8 (d, $J_{C,P}$ = 2.4 Hz), 134.0 (d, $J_{C,P}$ = 2.2 Hz), 134.4, 134.6, 138.0 (d, $J_{C,P}$ = 11.4 Hz), 140.0, 140.3 (d, $J_{C,P}$ = 26.3 Hz), 149.6, 166.3, 166.8 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO).
Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):
δ = -4.36.

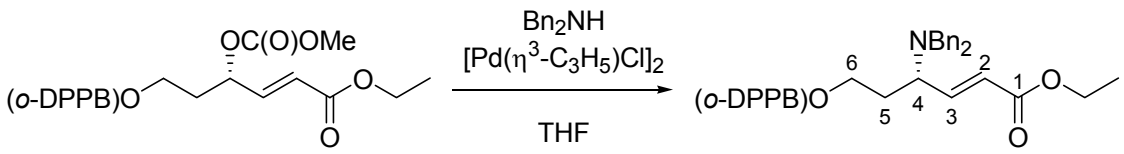
MS, ESI: $C_{34}H_{34}NO_4P$ m/z=552.2 (100, M+H).

Chiral HPLC (Chiralpak IA, n-heptane/ethanol 50/50, 15 °C, 0.6 ml/min, 230 nm):

R_T[(*minor*)-**126**]= 13.4 min,

R_T[(*major*)-**126**]= 15.1 min.

6.3.2. Synthesis of (*S*,*E*)-4-(dibenzylamino)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (127)



79 **127**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (55.2 mg, 0.11 mmol) with 1.9 eq of dibenzylamine.

Flash-column chromatography (silica gel, CH/EE = 10:1).

R_f = 0.68 (CH/EE 1:1).

Yield 51.7 mg (73%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.30 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 1.72 (ddd, J = 6.4, 6.4, 6.4 Hz, 1H, C_5-CH_A), 1.99 (m_c, 1H, C_5-H_B), 3.37 (d, J = 13.8, 2H, $NC\underline{H}_2Ph$), 3.58 (m_c, 1H, C_4-CH), 3.78 (d, J = 13.6 Hz, 2H, $NC\underline{H}_2Ph$), 4.11-4.22 (m, 1H, C_6-CH_A), 4.24 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.25-4.32 (m, 1H, C_6-CH_B), 5.82 (dd, J = 15.8, 1.0 Hz, 1H, C_2-CH), 6.87-6.90 (m, 1H, ArH), 6.97 (dd, J = 15.8, 8.3 Hz, 1H, C_3-CH), 7.13-7.38 (m, 22H, ArH), 7.66-7.69 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.4 ($OCH_2\underline{C}H_3$), 27.0 (C_5), 53.9 ($\underline{C}H_2Ph$), 55.6 (C_4), 60.6 ($O\underline{C}H_2CH_3$), 62.3 (C_6), 124.2, 127.1, 128.2, 128.3, 128.4, 128.46, 128.53 (d, $J_{C,P}$ = 2.7 Hz), 128.57 (d, $J_{C,P}$ = 2.7 Hz), 128.6, 128.7, 128.8, 128.9, 130.8, 131.9, 133.9 (d, $J_{C,P}$ = 6.5 Hz), 134.1 (d, $J_{C,P}$ = 6.8 Hz), 134.3, 139.3, 145.7, 166.2, 166.7 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO).

Signal assignment from 2D-NMR experiment.

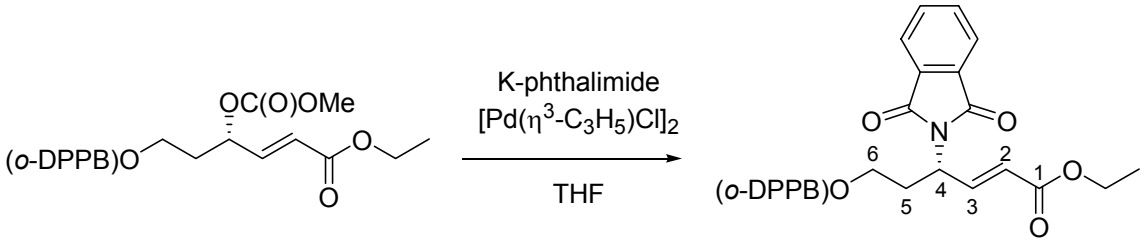
^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.27.

HRMS, EI:	calculated	550.214722
$C_{34}H_{33}NO_4P$	found	550.214304

Chiral HPLC (Chiralpak OD-H, n-heptane/ethanol 93/7, room temperature, 0.8 ml/min, 230 nm):
R_T[(*major*)-**127**-oxide]= 20.0 min,
R_T[(*minor*)-**127**-oxide]= 27.0 min.

6.3.3. Synthesis of (*S*,*E*)-4-(phthalimido)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (128)



79 **128**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (58.5 mg, 0.11 mmol) with 1.2 eq of potassium phthalimide.
Flash-column chromatography (silica gel, CH/EE = 10:1).
R_f = 0.54 (CH/EE 1:1).
Yield 52.8 mg (81%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 1.27 (t, J = 7.2 Hz, 3H, $OCH_2C\underline{H}_3$), 2.23 (m_c, 1H, C_5-CH_A), 2.56 (m_c, 1H, C_5-CH_B), 4.13-4.18 (m, 1H, C_6-CH_A), 4.18 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.18-4.23 (m, 1H, C_6-CH_B), 5.05 (ddd, J = 9.9, 5.9, 1.5 Hz, 1H, C_4-CH), 5.82 (dd, J = 15.7, 1.5 Hz, 1H, C_2-CH), 6.87-6.92 (m, 1H, ArH), 7.07 (dd, J = 15.8, 6.4 Hz, 1H, C_3-CH), 7.22-7.38 (m, 12H, ArH), 7.72 (dd, J = 5.6, 3.0 Hz, 2H, ArH), 7.82 (dd, J = 5.6, 3.0 Hz, 2H, ArH), 7.96-8.01 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):
δ = 14.3 ($OCH_2\underline{C}H_3$), 30.2 (C_5), 48.8 (C_4), 60.8 (C_6), 61.8 ($O\underline{C}H_2CH_3$), 123.5, 123.6, 123.7, 128.4, 128.5 (d, $J_{C,P}$ = 3.4 Hz), 128.6 (d, $J_{C,P}$ = 3.6 Hz), 128.7 (d, $J_{C,P}$ = 5.1 Hz), 130.7 (d, $J_{C,P}$ =

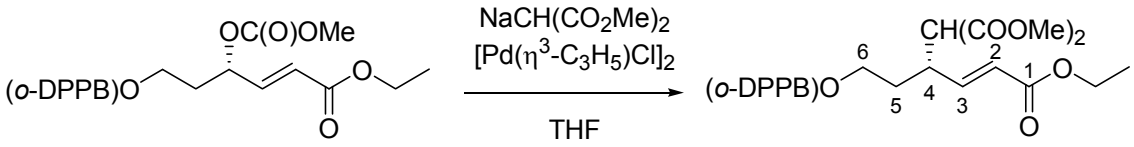
2.7 Hz), 131.8, 133.9 (d, $J_{C,P}$ = 20.0 Hz), 134.3, 134.4, 137.9 (d, $J_{C,P}$ = 6.0 Hz), 138.0 (d, $J_{C,P}$ = 6.0 Hz), 140.3, 140.5, 165.8 166.6 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>OO), 167.7.
Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):
δ = -4.47.

$[\alpha]_D^{20}$ = -1.0° (c = 0.29, $CHCl_3$).

Chiral HPLC (Chiralpak AD-H, n-heptane/*iso*-propanol 40/60, 35 °C, 0.7 ml/min, 230 nm):
R_T[(*minor*)-**128**-oxide]= 17.1 min,
R_T[(*major*)-**128**-oxide]= 18.5 min.

6.3.4. Synthesis of (*S*,*E*)-6-(2-(diphenylphosphanyl)benzoyl)-4-[bis-(methoxycarbonyl)-methyl]-hex-2-enoic acid ethyl ester (93)



79 **93**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (103 mg, 0.20 mmol) with 1.6 eq of sodiodimethylmalonate (solution in THF).
Flash-column chromatography (silica gel, CH/EE = 10:1).
R_f = 0.59 (CH/EE 1:1).
Yield 69.2 mg (55%), yellow oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 1.26 (t, J = 7.2 Hz, 3H, $OCH_2\underline{C}H_3$), 1.75 (m_c, 1H, C_5-CH_A), 1.89 (m_c, 1H, C_5-CH_B), 3.08 (m_c, 1H, C_4-CH), 3.46 (d, J = 8.0 Hz, 1H, C<u>H</u>$(COOMe)_2$), 3.69 (s, 3H, CH(COO<u>Me</u>)$_2$), 3.73 (s, 3H, CH(COO<u>Me</u>)$_2$), 4.03-4.09 (m, 1H, C_6-CH_A), 4.15 (q, J = 7.2 Hz, 2H, $OC\underline{H}_2CH_3$), 4.16-4.23 (m, 1H, C_6-CH_B), 5.85 (dd, J = 15.7, 0.8 Hz, 1H, C_2-CH), 6.77 (dd, J = 15.9, 9.7 Hz, 1H, C_3-CH), 6.91-6.94 (m, 1H, ArH), 7.24-7.42 (m, 12H, ArH), 8.02-8.05 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.3 ($OCH_2\underline{C}H_3$), 30.7 (C_5), 39.4 (C_4), 52.6 ($CH(COO\underline{Me})_2$), 52.7 ($CH(COO\underline{Me})_2$), 55.6 ($\underline{C}H(COOMe)_2$), 60.5 ($O\underline{C}H_2CH_3$), 62.6 (C_6), 124.5, 128.3, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 134.0 (d, $J_{C,P}$ = 5.1 Hz), 134.2, 134.3, 134.4, 138.0 (d, $J_{C,P}$ = 10.9 Hz), 140.5 (d, $J_{C,P}$ = 26.6 Hz), 146.0, 166.8, 166.6 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO), 167.8 ($CH(\underline{C}OOMe)_2$), 167.9 ($CH(\underline{C}OOMe)_2$).

Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.36.

$[\alpha]_D^{20}$ = 6.9° (c = 0.375, $CHCl_3$).

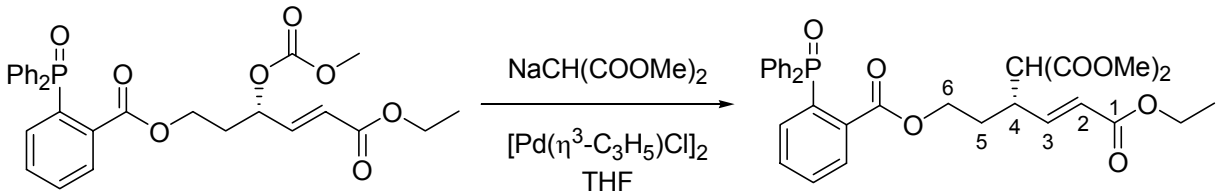
HRMS, EI:	calculated	592.186223
$C_{32}H_{33}O_9P$	found	592.186698

Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 50/50, room temperature, 0.8 ml/min, 230 nm):

R_T[(*minor*)-**93**-oxide]= 20.1 min,

R_T[(*major*)-**93**-oxide]= 33.1 min.

6.3.5. Not directed reaction Synthesis of (*S*,*E*)-6-(2-(diphenylphosphoryl)benzoyl)-4-[bis-(methoxycarbonyl)-methyl]-hex-2-enoic acid ethyl ester (93-oxide)



79-oxide **93-oxide**

Allylic substitution reaction was carried out according to the general procedure V (see chapter 4.6.1.2.) with [Pd(η^3-allyl)Cl]$_2$ (5 mol.%) and triphenylphosphine as a ligand starting from the

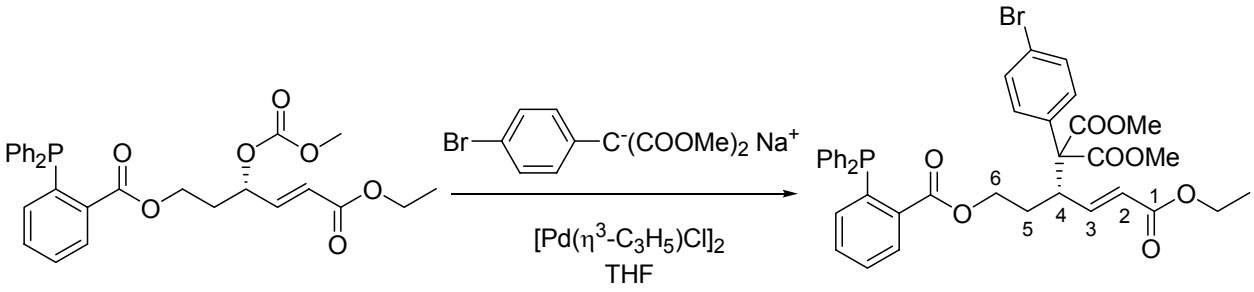
substrate **79-oxide** (69.0 mg, 0.129 mmol) with 1.6 eq of sodiodimethylmalonate (solution in THF).

Flash-column chromatography (silica gel, CH/EE = 10:1).

R_f = 0.58 (EE).

Yield 17.8 mg (23%), ratio of regioiomers: 3:1, *ee* = *ct* =84%.

6.3.6. Synthesis of (*S*,*E*)-6-[2-(diphenylphosphanyl)benzoyloxy]-4-[(4-bromophenyl)-di-(methoxycarbonyl)methyl]-hex-2-enoic acid ethyl ester (111)



79 **111**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (75.5 mg, 0.145 mmol) with 1.2 eq of the malonate (solution in THF).

Flash-column chromatography (silica gel, PE/TBME = 20:1 to 4:1).

R_f = 0.61 (CH/EE 1:1).

Yield 91 mg (86%), regioselectivity (via NMR) = 100:1.4, white powder.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.26 (t, *J* = 7.1 Hz, 3H, $C\underline{H}_3CH_2$), 1.36 (m_c, 1H, CH_A-C_5), 2.00 (dddd, *J* = 14.0, 8.6, 6.7, 1.9 Hz, 1H, CH_B-C_5), 3.41 (m_c, 1H, CH-C_4), 3.74 (s, 3H, COO$\underline{Me}$), 3.75 (s, 3H, COO$\underline{Me}$), 3.97 (m_c, 1H, CH_A-C_6), 4.13 (q, *J* = 7.1 Hz, 2H, $CH_3C\underline{H}_2$), 4.16 (m_c, 1H, CH_B-C_6), 5.79 (dd, *J* = 15.7, 0.8 Hz, 1H, CH-C_2), 6.75 (dd, *J* = 15.5, 10.0 Hz, 1H, CH-C_3), 6.91-6.94 (m, 1H, Ar-H), 7.15-7.51 (m, 16H, Ar-H), 8.00-8.03 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.3 ($\underline{C}H_3CH_2$), 29.3 (C_5), 45.0 (C_4), 52.9 (COO$\underline{Me}$), 53.0 (COO$\underline{Me}$), 60.5 ($CH_3\underline{C}H_2$), 62.9 (C_6), 66.2 ($\underline{C}$(COOMe)$_2$), 122.3, 125.6 (C_2), 128.3, 128.5 (d, $J_{C,P}$ = 1.7 Hz), 128.6 (d, $J_{C,P}$ = 1.7

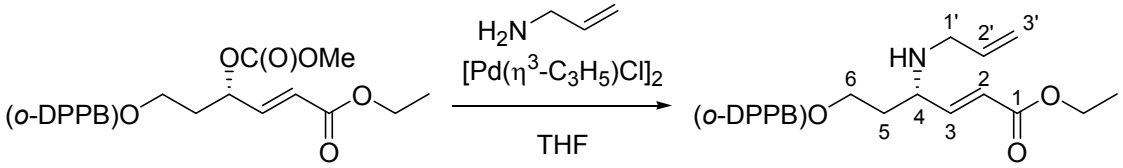
Hz), 128.7, 130.4, 130.8 (d, $J_{C,P}$ = 2.4 Hz), 131.5, 132.1, 133.8 (d, $J_{C,P}$ = 5.1 Hz), 134.0, 134.1 (d, $J_{C,P}$ = 5.1 Hz), 134.2 (d, $J_{C,P}$ = 19.1 Hz), 134.5, 137.9 (d, $J_{C,P}$ = 6.3 Hz), 138.0 (d, $J_{C,P}$ = 6.3 Hz), 140.6 (d, $J_{C,P}$ = 26.8 Hz), 145.4 (C_3), 165.7 (COOEt), 166.5 (d, $J_{C,P}$ = 2.2 Hz, ArCOO), 169.3 (COOMe), 169.5 (COOMe).

^{31}P-NMR (161.984 MHz, $CDCl_3$):

δ = -4.70

MS, CI (NH_3): $C_{38}H_{36}BrO_8P$ m/z=731.2 (4, M+H).

6.3.7. Synthesis of (*S*,*E*)-4-(allylamino)-6-(2-(diphenylphosphanyl)benzoyl)-hex-2-enoic acid ethyl ester (94)



79 **94**

Allylic substitution reaction was carried out according to the general procedure II (see chapter 4.6.1.2.) starting from the substrate **79** (160 mg, 0.31 mmol) with 2.0 eq of allylamine.
Flash-column chromatography (silica gel, TBME/PE = 15:1).
R_f = 0.32 (CH/EE 1:1).
Yield 100.0 mg (65%), yellowish oil.

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.29 (t, J = 7.1 Hz, 3H, OCH_2CH_3), 1.41 (bs, 1H, NH), 1.77 (m_c, 2H, C_5-CH_2), 3.05 (ddd, J = 14.0, 6.3, 1.4 Hz, 1H, $C_{1'}$-CH_A), 3.21 (ddd, J = 14.0, 5.6, 1.5 Hz, 1H, $C_{1'}$-CH_B), 3.29 (m_c, 1H, C_4-CH), 4.18 (q, J = 7.1 Hz, 2H, OCH_2CH_3), 4.21 (m_c, 1H, C_6-CH_A), 4.28 (m_c, 1H, C_6-CH_B), 5.07 (ddd, J = 10.2, 3.0, 1.4 Hz, 1H, $C_{3'}$-CH_A), 5.14 (ddd, J = 17.2, 3.4, 1.7 Hz, 1H, $C_{3'}$-CH_B), 5.82 (dddd, J = 17.2, 10.2, 6.3, 5.6 Hz, 1H, $C_{2'}$-CH), 5.86 (dd, J = 15.7, 1.0 Hz, 1H, C_2-CH), 6.67 (dd, J = 15.7, 8.1 Hz, 1H, C_3-CH), 6.91-6.95 (m, 1H, ArH), 7.23-7.43 (m, 12H, ArH), 7.98-8.03 (m, 1H, ArH).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 14.3 ($OCH_2\underline{C}H_3$), 34.0 (C_5), 49.8 ($\underline{C}H_2NH$), 56.2 (C_4), 60.5 ($O\underline{C}H_2CH_3$), 62.1 (C_6), 116.2 ($C_{3'}$), 122.5 (C_2), 128.3, 128.6, 128.7 (d, $J_{C,P}$ = 12.1 Hz), 130.7 (d, $J_{C,P}$ = 2.7 Hz), 132.1, 132.3, 134.0 (d, $J_{C,P}$ = 20.5 Hz), 134.5, 134.6 (d, $J_{C,P}$ = 11.8Hz), 136.6 ($C_{2'}$), 138.0 (d, $J_{C,P}$ = 11.1 Hz), 140.3 (d, $J_{C,P}$ = 26.6 Hz), 149.5 (C_3), 166.3, 166.9 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO).

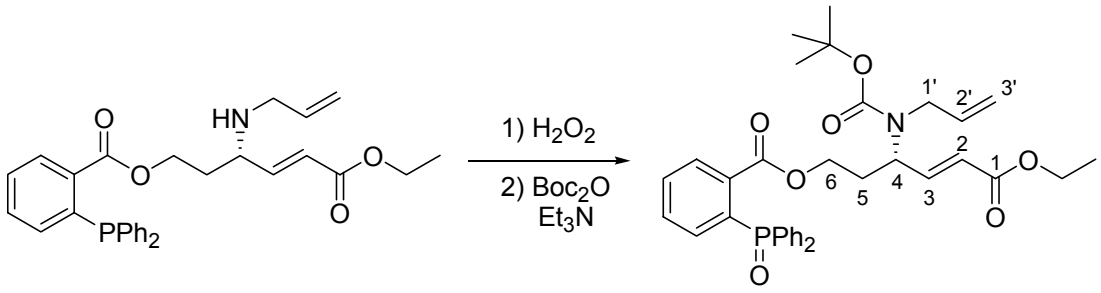
Signal assignment from 2D-NMR experiment.

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.64.

HRMS, CI (NH_3):	calculated	502.21472
$C_{30}H_{32}NO_4P$ (M+H)	found	502.21450

6.3.8. Synthesis of (*S*,*E*)-4-(*N*-*tert*-butyloxycarbonyl-*N*-allyl-amino)-6-(2-(diphenyl-phosphoryl)-benzoyl)-hex-2-enoic acid ethyl ester (95)



94 **95**

To the solution of **94** (90.2 mg, 0.186 mmol) in ethylacetate 0.4 ml of hydrogen peroxide (30%) was added. After 10 minutes stirring at room temperature sodium thiosulfate was added to reduce hydrogen peroxide. After drying with sodium sulfate the reaction mixture was filtered over the short pad of silica gel and the solvent was evaporated. The resulting oily compound was disolved in dichloromethane (3 ml) and triethylamine (75 µl, 54.6 mg, 0.54 mmol, 3 eq) and Boc_2O (77 µl, 78.5 mg, 0.34 mmol, 2 eq) were added. The reaction mixture was stirred overnight at room temperature. Then the solvent was evaporated.

Flash-column chromatography (silica gel, CH/EE = 3:1 to EE).

R_f = 0.45 (EE).

Yield 63.7 mg (56% over 2 steps), yellowish oil.

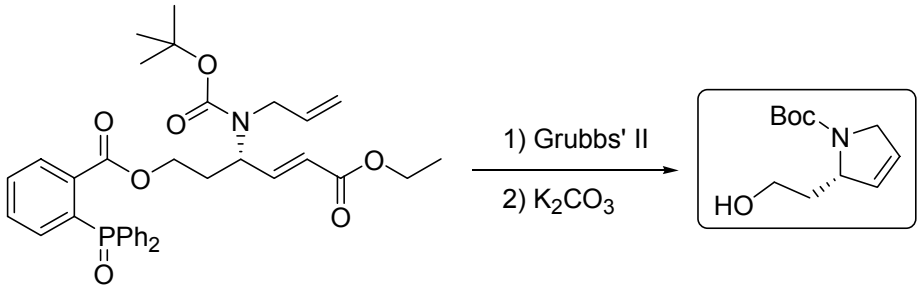
^{1}H-NMR (300.064 MHz, $CDCl_3$):

δ = 1.26 (t, J = 7.2 Hz, 3H, OC$\underline{H}_3$CH$_2$), 1.42 (s, 9H, (C$\underline{H}_3$)$_3$C), 1.63 (m$_c$, 1H, C$_5$-CH$_A$), 1.82 (m$_c$, 1H, C$_5$-CH$_B$), 3.45-3.57 (m, 1H, C$_{1'}$-CH$_A$), 3.64-3.79 (m, 1H, C$_{1'}$-CH$_B$), 3.88-4.08 (m, 3H, C$_6$-CH$_2$ and C$_4$-CH), 4.20 (q, J = 7.2 Hz, 2H, OC$\underline{H}_2$CH$_3$), 5.01 (m$_c$, 1H, C$_{3'}$-CH$_A$), 5.07 (m$_c$, 1H, C$_{3'}$-CH$_B$), 5.17 (m$_c$, 1H, C$_{2'}$-CH), 5.72 (dd, J = 15.8, 1.4 Hz, 1H, C$_2$-CH), 5.76 (dd, J = 15.8, 5.6 Hz, 1H, C$_3$-CH), 7.42-7.68 (m, 13H, ArH), 7.89-7.93 (m, 1H, ArH).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = 31.44.

6.3.9. Synthesis of (+)-(*S*)-2-(2-hydroxyethyl)-2,5-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (96)



95 **96**

To a solution of **95** (63.7 mg, 0.10 mmol) in dichloromethane Grubbs' II catalyst (4.4 mg, 5 mol.%) was added [99]. After overnight stirring at room temperature the solvent was evaporated. Methanol (5 ml) and potasium carbonate (1 g) were added. After overnight stirring at room temperature the solvent was evaporated.

Flash-column chromatography (silica gel, TBMEH/PE = 20:1).

R_f = 0.32 (CH/EE 1:1).

Yield 8.4 mg (38% over 2 steps).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 1.45-1-51 (bs, 10H, C(C$\underline{H}_3$)$_3$ and C$\underline{H}_A$CH$_2$OH), 1.86-1.95 (m, 1H, C$\underline{H}_B$CH$_2$OH), 3.61-3.69 (m, 2H, C$\underline{H}_2$OH), 3.92-4.04 (m, BocNCH$_2$), 4.59-4.76 (m, 1H, BocNC$\underline{H}$), 5.68-5.73 (m, 1H, -C$\underline{H}$=), 5.74-5.79 (m, 1H, -C$\underline{H}$=).

^{13}C-NMR (100.613 MHz, $CDCl_3$):

δ = 28.5 ($C(\underline{C}H_3)_3$), {37.6} 38.9 ($\underline{C}H_2CH_2OH$), {53.4} 53.7 ($N\underline{C}H_2$), 59.4 {59.7} ($O\underline{C}H_2$), 61.3 {62.0} (BocN$\underline{C}$H), {79.9} 80.2 ($O\underline{C}(CH_3)_3$), 124.6 {125.4} (CH=$\underline{C}$H), {130.4} 131.3 (CH=$\underline{C}$H), {154.5} 156.1 ($N\underline{C}O_2$).

Minor signals of the other conformer are given in braces. The NMR spectra are in good agreement with literature. [98]

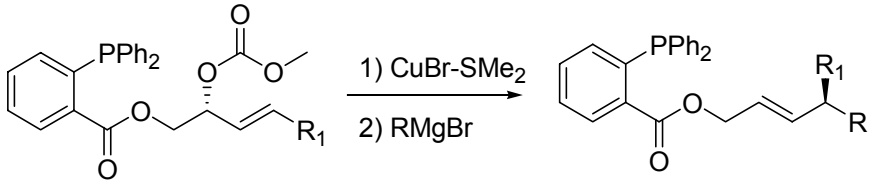
$[\alpha]_D^{20}$ = 76.5° (c = 0.85, $CHCl_3$).

Literature value for (–)-(*R*)-isomer $[\alpha]_D^{22}$ = - 127° (c = 1.0, $CHCl_3$). [98]

HRMS, CI (NH_3):	calculated	214.14432
$C_{11}H_{19}NO_3$ (M+H)	found	214.14460

7. Allylic substitution with cuprates

7.1. General procedure

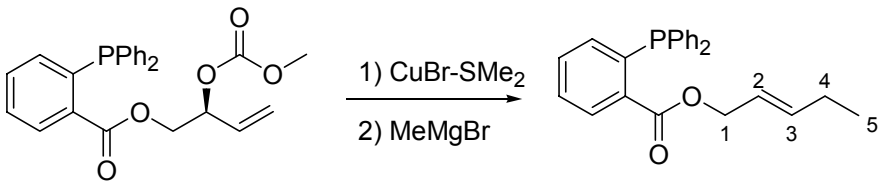


A

R= H, Me;
R_1= Me, Et, *n*-Bu

To a stirred solution of carbonate **A** (0.1-0.2 mmol, 1 eq) CuBr·Me_2S (0.8 eq) was added. The reaction mixture was stirred 30 min at room temperature, then it was cooled down to 0 °C, and the solution Grignard reagent in ether (1 M, 1.1 eq) was dropwise added. After 1 h stirring at the temperature aqueous ammonia solution (25%, 1 ml) and saturated aqueous solution of ammonia chloride (2 ml) were added, and the mixture was extracted with CH_2Cl_2 (4×3 ml). The combined organic phases were dried over Na_2SO_4 and the solvent was evaporated. Purification via flash-column chromatography (silica gel, PE/TBME = 20:1).

7.2. Synthesis of 2-(diphenylphosphanyl)benzoic acid (*E*)-4-pent-2-enyl ester (129)



10 **129**

Allylic substitution reaction was carried out according to general procedure (chapter 7.1.) starting from the compound **10** (69.5 mg, 0.160 mmol).

Flash-column chromatography (silica gel, PE/TBME = 20:1).

R_f = 0.72 (CH/EE 1:1).

Yield 44 mg (75%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 0.97 (t, J = 7.5 Hz, 3H, CH_3-C_5), 2.03 (m_c, 1H, CH-C_4), 4.59 (dd, J = 6.6, 1.1 Hz, 1H, CH-C_1), 5.46 (dddt, J = 15.4, 6.6, 6.6, 1.5 Hz, 1H, CH-$C_{2/3}$), 5.76 (dddt, J = 15.4, 6.2, 6.2, 1.3 Hz, 1H, CH-$C_{2/3}$), 6.90-6.94 (m, 1H, Ar-H), 7.25-7.40 (m, 12H, Ar-H), 8.05-8.08 (m, 1H, Ar-H).

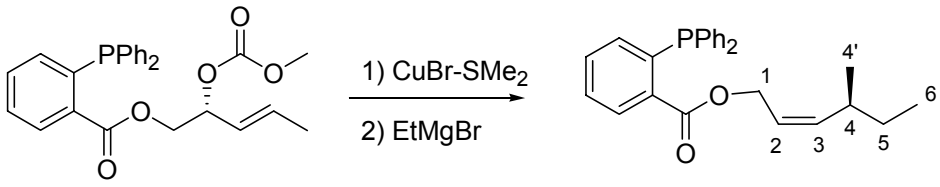
^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 13.1 (C_5), 25.3 (C_4), 66.0 (C_1), 122.7 ($C_{2/3}$), 128.2, 128.4 (d, $J_{C,P}$ = 7.2 Hz), 128.6, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 131.8, 133.9 (d, $J_{C,P}$ = 20.8 Hz), 134.3, 134.6 (d, $J_{C,P}$ = 19.1 Hz), 138.0 ($C_{2/3}$), 138.1 (d, $J_{C,P}$ = 11.1 Hz), 140.3 (d, $J_{C,P}$ = 26.6 Hz), 166.7 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>OO).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.39.

7.3. Synthesis of 2-(diphenylphosphanyl)benzoic acid *rac*-(*S*,*Z*)-4-methylhex-2-enyl ester (130)



33 **130**

Allylic substitution reaction was carried out according to general procedure (chapter 7.1.) starting from the compound **33** (69.5 mg, 0.155 mmol).

Flash-column chromatography (silica gel, PE/TBME = 20:1).

R_f = 0.73 (CH/EE 1:1).

Yield 32 mg (52%).

^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 0.73 (t, J = 7.4 Hz, 3H, CH_3-C_6), 0.85 (d, J = 6.6 Hz, 3H, CH_3-$C_{4'}$), 1.12 (m_c, 1H, CH_A-C_5), 1.18 (m_c, 1H, CH-C_4), 1.26 (dtd, J = 15.0, 7.6, 5.7 Hz, 1H, CH_B-C_5), 4.60 (dddd, J = 19.3, 12.6, 6.7, 1.3 Hz, 1H, CH_A-C_1), 4.65 (dddd, J = 19.6, 12.6, 6.8, 1.3 Hz, 1H, CH_B-C_1), 5.27 (dddd, J = 11.0, 9.9, 1.3, 1.3 Hz, 1H, CH-C_3), 5.37 (dddd, J = 11.0, 6.8, 6.8, 0.7 Hz, 1H, CH-C_2), 6.84-6.87 (m, 1H, Ar-H), 7.17-7.33 (m, 12H, Ar-H), 7.96-8.00 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 11.9 (C_6), 20.9 ($C_{4'}$), 30.0 (C_5), 34.0 (C_4), 61.5 (C_1), 122.0, 128.3, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.7, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 131.9, 134.0 (d, $J_{C,P}$ = 20.8 Hz), 134.4, 134.6 (d, $J_{C,P}$ = 19.1 Hz), 138.0 (d, $J_{C,P}$ = 10.9 Hz), 140.4 (d, $J_{C,P}$ = 26.3 Hz), 141.3, 166.8 (d, $J_{C,P}$ = 2.2 Hz, Ar<u>C</u>OO).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

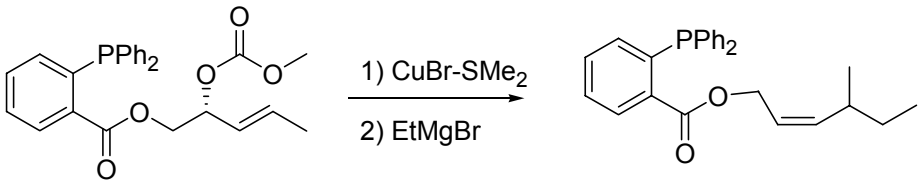
δ = -4.37.

Chiral HPLC (Chiralpak AD-H, n-heptane/ethanol 97/3, 40 °C, 1.0 ml/min, 230 nm):

R_T[(*minor*)-**130**]= 29.0 min,

R_T[(*major*)-**130**]= 30.7 min.

7.4. Synthesis of 2-(diphenylphosphanyl)benzoic acid *rac*-(*Z*)-4-methylhex-2-enyl ester (*rac*-130)

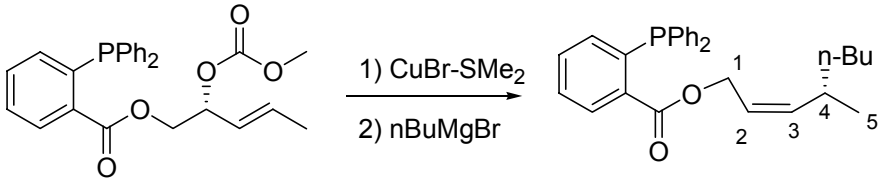


***rac*-33** ***rac*-130**

The synthesis was performed analogously to synthesis of ***rac*-130**.

Analytical data are described above for ***rac*-130**.

7.5. Synthesis of 2-(diphenylphosphanyl)benzoic acid (*S*,*Z*)-4-methyloct-2-enyl ester (112)



33 **112**

Allylic substitution reaction was carried out according to general procedure (chapter 7.1.) starting from the compound **33** (105 mg, 0.235 mmol).

Flash-column chromatography (silica gel, PE/TBME = 20:1).

R_f = 0.76 (CH/EE 1:1).

Yield 56 mg (55%).

^{1}H-NMR (400.130 MHz, C_6D_6):

δ = 0.80 (d, J = 6.7 Hz, 3H, CH_3-C_5), 0.84 (t, J = 7.1 Hz, 3H, $C\underline{H_3}CH_2CH_2CH_2$), 1.01-1.24 (m, 6H, $CH_3C\underline{H_2}\underline{CH_2}\underline{CH_2}$), 2.25 ($m_c$, 1H, CH-$C_4$), 4.64 (ddd, J = 12.5, 6.8, 1.4 Hz, 1H, CH_A-C_1), 4.68 (ddd, J = 12.5, 7.1, 1.3 Hz, 1H, CH_A-C_1), 5.18 (dddd, J = 10.9, 10.2, 1.4, 1.4 Hz, 1H, CH-C_3), 5.44 (dddd, J = 10.9, 7.0, 7.0, 0.9 Hz, 1H, CH-C_2), 6.90-7.14 (m, 9H, Ar-H), 7.39-7.44 (m, 4H, Ar-H), 8.09-8.13 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, C_6D_6):

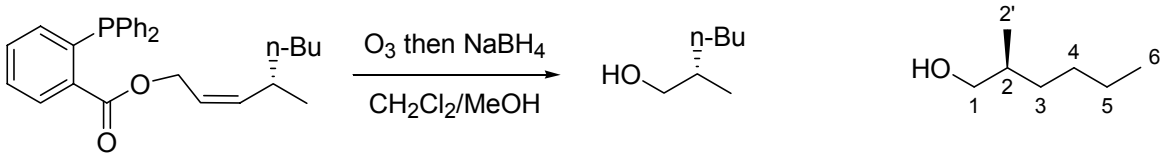
δ = 14.3, 21.3, 23.1, 29.9, 32.4, 37.2, 61.3 (C_1), 122.5, 128.7, 128.8 (d, $J_{C,P}$ = 7.0 Hz), 131.0 (d, $J_{C,P}$ = 2.7 Hz), 131.9, 134.4 (d, $J_{C,P}$ = 21.0 Hz), 134.5 (d, $J_{C,P}$ = 21.0 Hz), 134.7, 135.4 (d, $J_{C,P}$ = 19.8 Hz), 139.1 (d, $J_{C,P}$ = 12.6 Hz), 141.3 (d, $J_{C,P}$ = 28.7 Hz), 141.4, 142.0, 166.5 (d, $J_{C,P}$ = 2.2 Hz, Ar$\underline{C}$OO).

^{31}P-NMR (121.468 MHz, C_6D_6):

δ = -4.16.

HRMS, CI (NH_3):	calculated	431.213993
$C_{28}H_{31}O_2P$ (M+H)	found	431.214497

7.6. Synthesis of (*S*)-2-methylhexan-1-ol (113)



112 **113**

The compound was synthesized according to the procedure elaborated in our group. [131]

Through the solution of *o*-DPPBA ester (46.2 mg, 0.107 mmol) in CH_2Cl_2 (3 ml) ozone was bubbled at -78 °C until the reaction mixture became blue, then argon was bubbled through the solution; sodium borohydride (41 mg, 1.08 mmol) and MeOH (5 ml) were added at -78 °C and

the reaction mixture was allowed to warm up to room temperature with stirring overnight. Satutared aqueous solution of ammonium chloride (8 ml) was added, extraction with TBME (4 × 10 ml), after solvent evaporation, flash-column chromatography (silica gel, PE/TBME = 10:1).
R_f = 0.49 (CH/EE 1:1).
Yield quant., colourless liquid (80% *ee*, 86% *ct*).

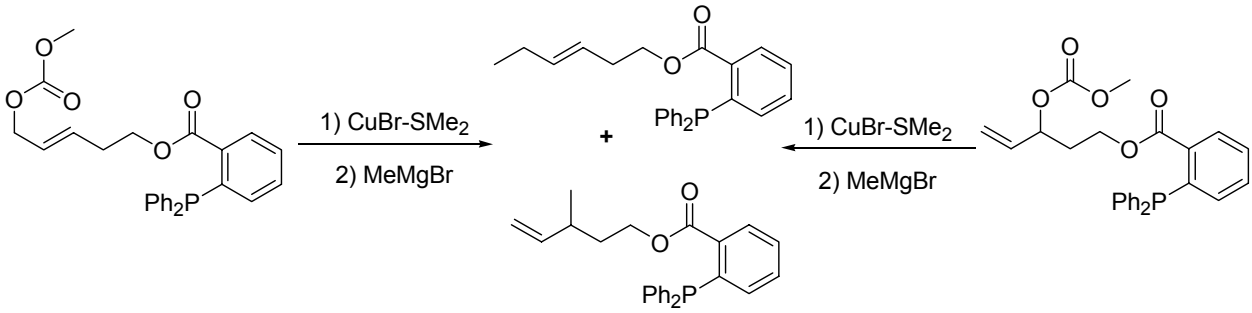
^{1}H-NMR (400.130 MHz, $CDCl_3$):
δ = 0.92 (d, J = 6.7 Hz, 3H, CH_3-$C_{2'}$), 1.19 (d, J = 9.9 Hz, 3H, CH_3-C_6), 1.23-1.36 (d, J = 6.7 Hz, 3H, CH_2-C_3, CH_2-C_4 and CH_2-C_5), 1.61 (m_c, 1H, CH-C_2), 3.42 (dd, J = 10.5, 6.6 Hz, 1H, CH_A-C_1), 3.51 (dd, J = 10.5, 5.8 Hz, 1H, CH_B-C_1).

^{13}C-NMR (100.620 MHz, $CDCl_3$):
δ = 14.2 (C_6), 16.7 ($C_{2'}$), 22.8, 29.3, 33.0, 35.9 (C_2), 68.5 (C_1).

Chiral GC (isotherm, 65°C, 1.3 bar He):
τ_1 (+) = 27.1 min,
τ_2 (–) = 28.7 min.

MS, GC-CI: $C_7H_{16}O$ m/z=134.1 (100, M+NH_4).

7.7. Synthesis of 2-(diphenylphosphanyl)benzoic acid (*E*)-hex-3-enyl ester (131) and 2-(diphenylphosphanyl)benzoic acid 3-methylpent-4-enyl ester (132)



68 **131** **132** **78**

Allylic substitution reaction was carried out according to general procedure (chapter 7.1.) starting from the linear substrate **68** (96.7 mg, 0.216 mmol).

Flash-column chromatography (silica gel, PE/TBME = 20:1).

R_f = 0.76 (CH/EE 1:1).

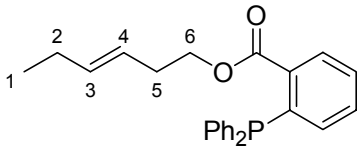
Yield 26.7 mg (61%), mixture **131/132** = 3.6:1.

Allylic substitution reaction was carried out according to general procedure starting from the branched substrate ***iso*-68** (88.9 mg, 0.198 mmol).

Flash-column chromatography (silica gel, PE/TBME = 20:1).

R_f = 0.76 (CH/EE 1:1).

Yield 47.3 mg (62%), mixture **131/132** = 5.6:1.

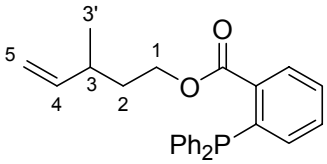


^{1}H-NMR (400.130 MHz, $CDCl_3$):

δ = 0.94 (t, J = 7.5 Hz, 3H, CH_3-C_1), 2.01 (m_c, 1H, CH_2-C_2), 2.31 (m_c, 1H, CH_2-C_5), 4.14 (t, J = 7.1 Hz, 3H, CH_2-C_6), 5.26 (dtt, J = 10.8, 7.3, 1.5 Hz, 1H, CH-$C_{3/4}$), 5.46 (dtt, J = 10.8, 7.2, 1.6 Hz, 1H, CH-$C_{3/4}$), 6.90-6.94 (m, 1H, Ar-H), 7.24-7.41 (m, 12H, Ar-H), 8.02-8.07 (m, 1H, Ar-H).

^{13}C-NMR (100.620 MHz, $CDCl_3$):

δ = 14.3 (C_1), 26.7 (C_2), 31.9 (C_5), 64.7 (C_6), 123.7 ($C_{3/4}$), 128.2, 128.5 (d, $J_{C,P}$ = 7.2 Hz), 128.6, 130.7 (d, $J_{C,P}$ = 2.7 Hz), 131.9, 133.9 (d, $J_{C,P}$ = 20.8 Hz), 134.4 (d, $J_{C,P}$ = 16.2 Hz, $C_{3/4}$), 135.1, 138.1 (d, $J_{C,P}$ = 11.1 Hz), 140.3 (d, $J_{C,P}$ = 26.8 Hz), 143.4, 166.9 (d, $J_{C,P}$ = 1.9 Hz).



selected signals:

^{1}H-NMR (400.130 MHz, $CDCl_3$):

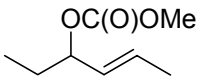
δ = 4.91 (ddd, J = 10.4, 1.8, 1.0 Hz, 1H, CH-C_4), 4.95 (ddd, J = 17.2, 1.8, 1.1 Hz, 1H, CH-C_4), 5.63 (ddd, J = 17.9, 10.4, 7.7 Hz, 1H, CH-C_4).

^{31}P-NMR (121.468 MHz, $CDCl_3$):

δ = -4.44 (minor) and -4.50 (major).

HRMS, EI:	calculated	388.159218
$C_{25}H_{25}O_2P$	found	388.159002

Structure index



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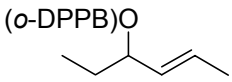

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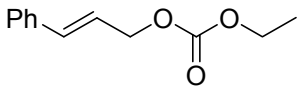

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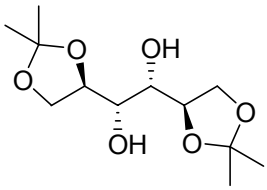

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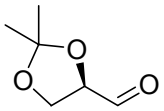

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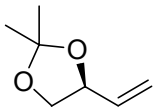

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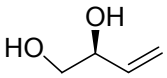

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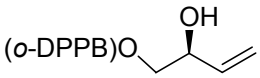

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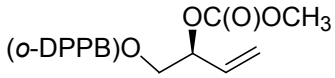

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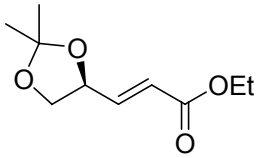

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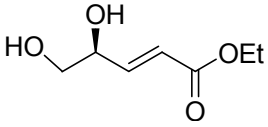

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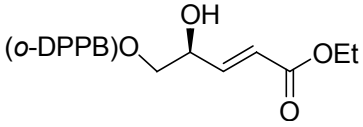

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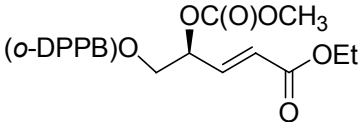

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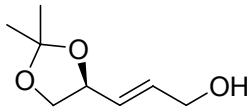

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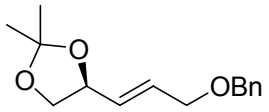

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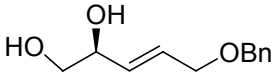

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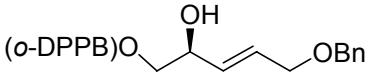

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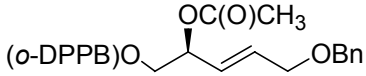

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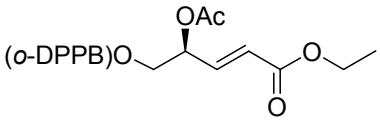

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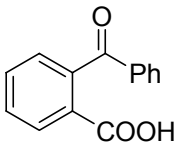

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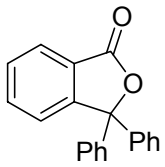

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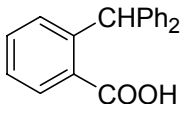

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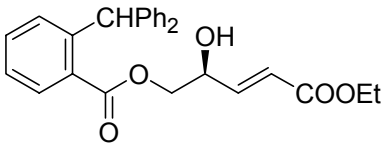

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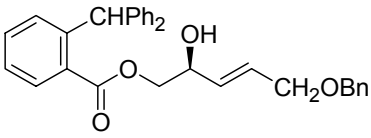

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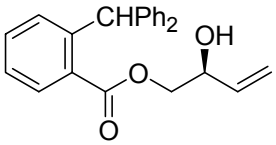

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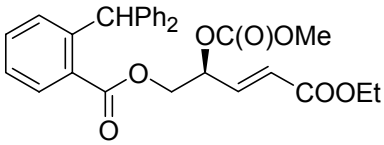

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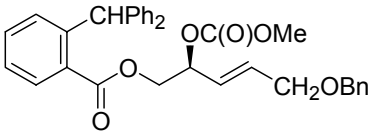

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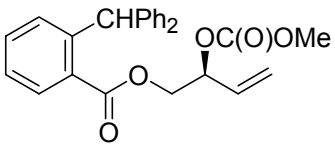

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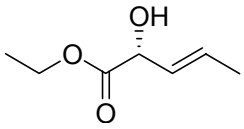

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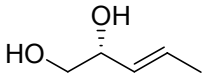

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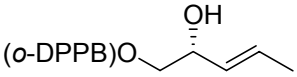

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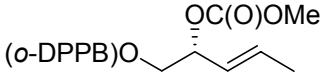

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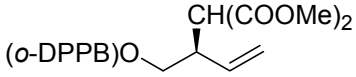

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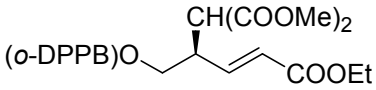

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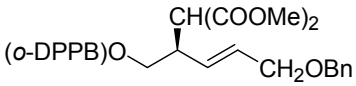

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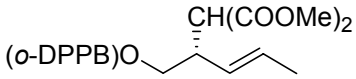

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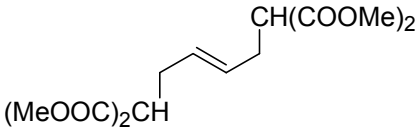

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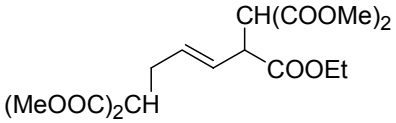

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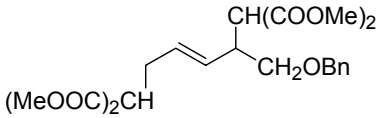

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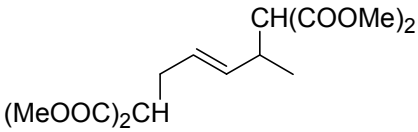

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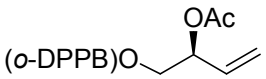

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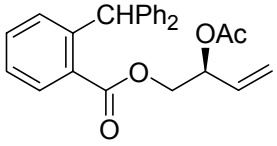

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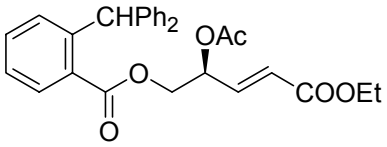

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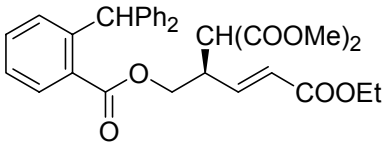

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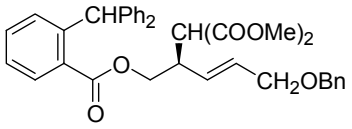

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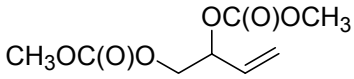

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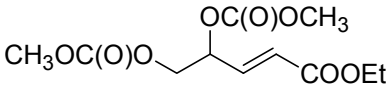

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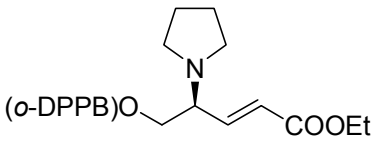

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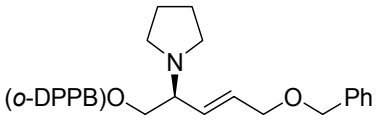

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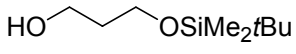

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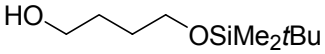

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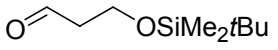

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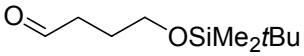

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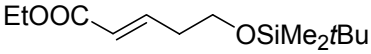

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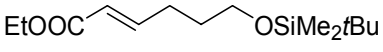

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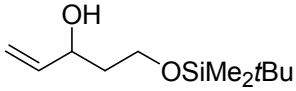

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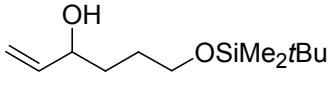

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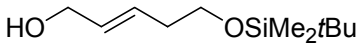

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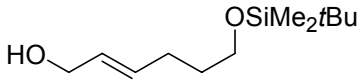

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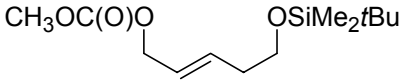

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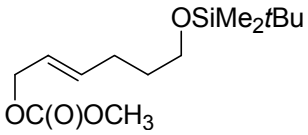

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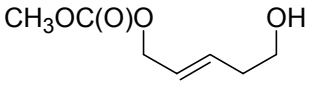

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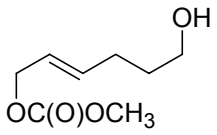

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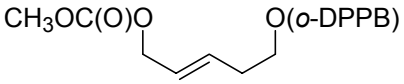

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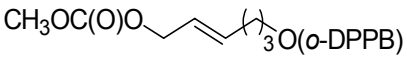

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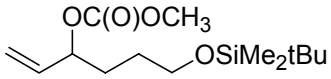

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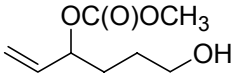

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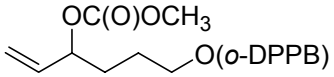

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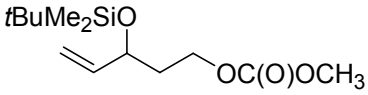

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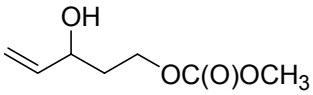

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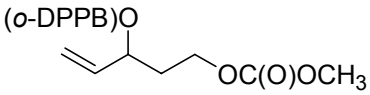

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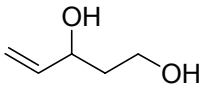

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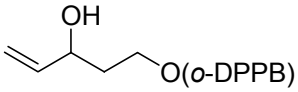

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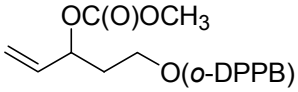

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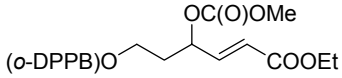

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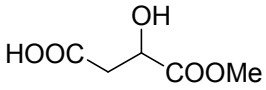

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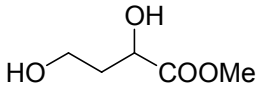

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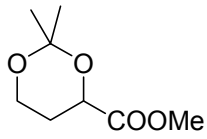

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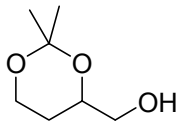

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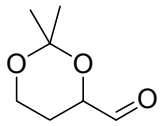

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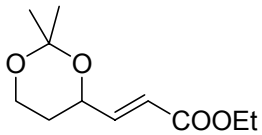

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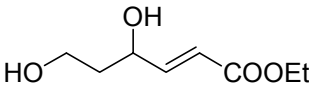

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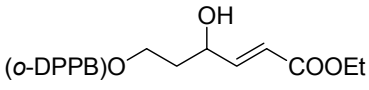

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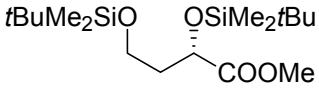

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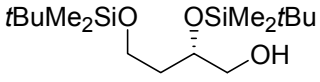

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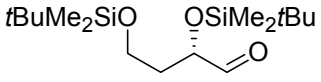

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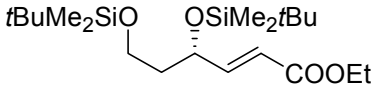

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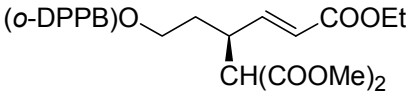

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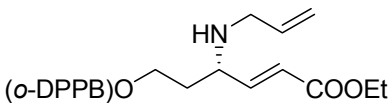

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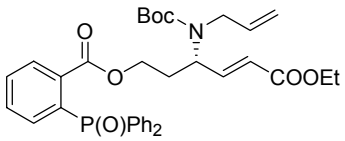

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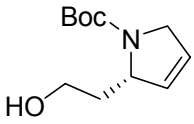

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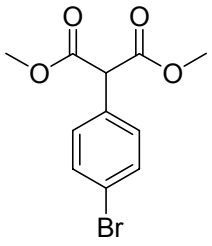

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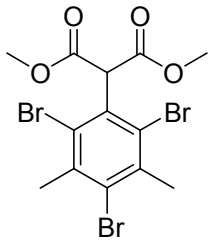

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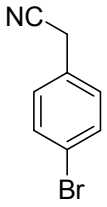

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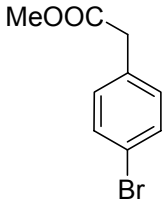

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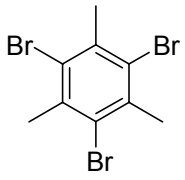

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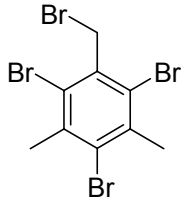

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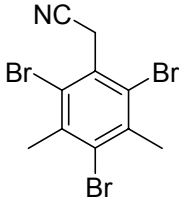

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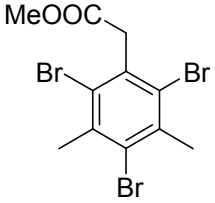

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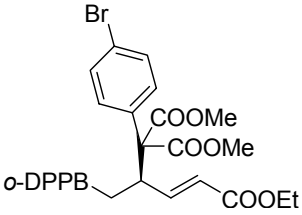

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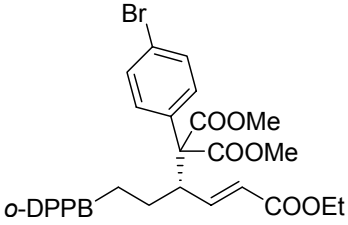

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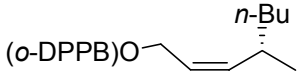

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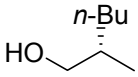

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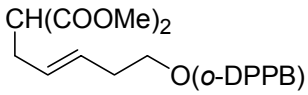

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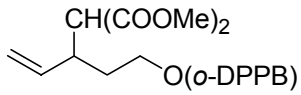

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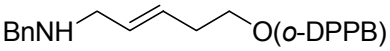

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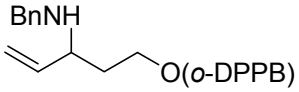

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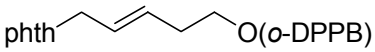

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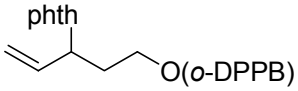

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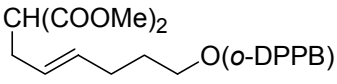

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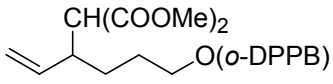

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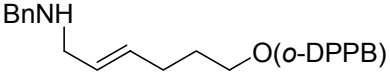

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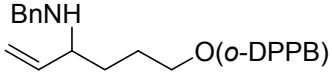

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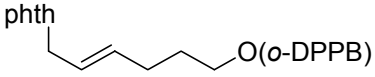

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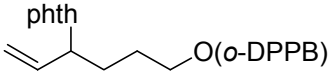

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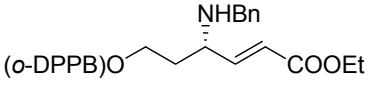

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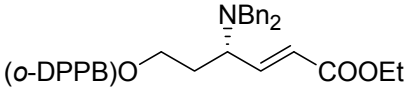

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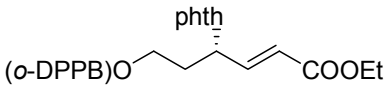

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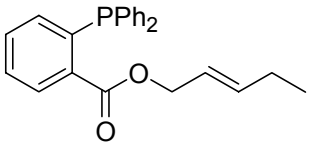

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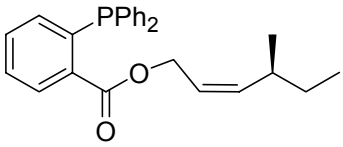

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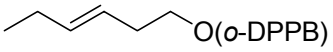

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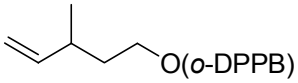

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