Heck reactions of Crotonaldehyde

and

Organocatalytic, asymmetric Mannich reactions of

N-Boc and related imines

Inaugural-Dissertation

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Meinen Eltern

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List of abbreviations

Å	angstrom
Ac	acyl
Ar	aryl
BAIB	[bis(acetoxy)iodo]benzene
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
BINOL	1,1'-bi-2-naphthol
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOX	bisoxazoline
*n*Bu	butyl
*t*Bu	*tert*-butyl
Bz	benzoyl
c	concentration
CAN	ceric ammonium nitrate
Cbz	carbobenzyloxy
Cy	cyclohexyl
dba	dibenzylideneacetone
DBU	1,8-diazabicycloundec-7-ene
DCM	dichloromethane
decomp.	decomposition
DERA	deoxyribose-5-phosphate aldolase
DIBAL	diisobutylaluminium hydride
dm	decimeter
DMAc	dimethylacetamide
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DPC	dipyridin-2-yl carbonate
Dpp	diphenylphosphinyl
dppe	1,2-bis(diphenylphosphino)ethane
dr	diastereomeric ratio
EA	ethylacetate
EE	ethoxyethyl
EI	electron impact
equiv	equivalents
er	enantiomeric ratio
ESI	electron spray ionization
Et	ethyl
EWG	electron withdrawing group
Fmoc	(9H-fluoren-9-yl)methyloxycarbonyl
g	gram
GC	gas chromatography
GC-MS	gas chromatography coupled with mass detection
h	hour
Hal	halogen
HEH	Hantzsch dihydropyridine
HMDS	hexamethyldisilazane

HPLC	high throughput liquid chromatography
HRMS	high resolution mass spectrometry
Hex	hexane
J	coupling constant
L	liter
LDA	lithium diisopropyl amide
Lit.	literature
m	meter
mbar	millibar
MCPBA	*meta*-chloro perbenzoic acid
Me	methyl
mg	milligram
MHz	megahertz
min	minute
mL	milliliter
mm	millimeter
MS	molecular sieves
MTBE	methyl *tert*-butyl ether
m/z	atomic mass units per charge
naph	naphthyl
n.d.	not determined
nm	nanometer
NMI	*N*-methylimidazole
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methylpyrrolidinone
NMR	nuclear magnetic resonance spectroscopy
Nu	nucleophile
PCC	pyridinium chlorochromate
Pg	protecting group
Ph	phenyl
Piv	pivaloyl
PMP	*para*-methoxyphenyl
PPL	*porcine pancreatic* lipase.
ppm	parts per million
n-Pr	propyl
i-Pr	isopropyl
py	pyridine
rac	racemic
R_f	retention factor
RT	room temperature
SEGPHOS	5,5′-bis(diphenylphosphino)-4,4′-bi-1,3-benzodioxole
TBS	*tert*-butyldimethylsilyl
temp.	temperature
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxyl
TPAP	tetra-*n*-propyl ammonium perruthenate
Tf	trifluoromethanesulfonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
tol	toluene

TRIP	3,3’-bis-(2,4,6-tristriisopropylphenyl)-1,1’-binaphtholphosphate
Ts	*para*-toluenesulfonyl
*o*Ts	*ortho*-toluenesulfonyl
UV	ultraviolet
v/v	volume/volume

Abbreviations used for NMR data

arom	aromatic proton
b	broad signal
CH_{Ar}	aromatic carbon
Cq_{Ar}	aromatic, quaternary carbon
d	doublet
dd	doublet of doublets
dq	doublet of quartets
dqq	doublet of quartet of quartets
dt	doublet of triplets
ddd	doublet of doublet of doublets
m	multiplet
q	quartet
qd	quartet of doublets
s	singlet
t	triplet
tq	triplet of quartets
tt	triplet of triplets

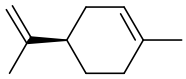
1. Introduction

When one is talking about modern organic synthesis, the area of catalysis deserves mentioning as one of the pillars of the field. Catalysis has dramatically changed not only the chemist's world and works, but the world as a whole. Many of the materials encountered in daily life are made by catalytic processes, such as many types of plastics; and in a more obvious manner, barely any car is found nowadays that is not equipped with a catalytic converter.
Catalysts are, by definition, species that participate in a reaction and enhance its rate. They may undergo several chemical transformations, but are not consumed in the process. Catalysts accelerate reactions by providing an alternative reaction pathway with lower activation energy.

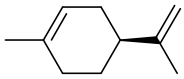
Catalysis can be divided into two main areas: heterogeneous and homogenous catalysis. In the case of heterogeneous catalysis, the catalyst acts in a different phase than the reactants. In many cases it is a solid, with the substrates being liquid or gaseous. Heterogeneous catalysts are often supported, that is, dispensed on a second material, which may affect the catalytic activity by interaction of the materials, or simply increase the surface area of the catalyst.
The great advantage of heterogeneous catalysis is the ease of separation of the reaction mixture from the catalyst, as it is simply a phase separation. These catalysts are therefore widely employed in industry, especially in the synthesis of bulk chemicals, with ammonia and sulfur trioxide being prominent examples of catalytically generated compounds. The disadvantages, however, are that only the surface is able to interact with the substrates, and that the phase transitions required by the reactants reduce the overall reaction rate.
Homogeneous catalysis is taking place when the catalyst functions in the same phase as the reactants. Higher reaction rates as compared to heterogeneous catalysis can usually be realized since the catalyst is evenly distributed in the reaction medium and no phase transition is required prior to the reaction. Moreover, every molecule of the catalyst employed can actively participate in the reaction and not only the surface layer. The disadvantage of homogeneous catalysis is that usually a purification step is required to remove the catalyst from the products. This can also influence the reusability of the catalyst.

Another distinction between different kinds of catalysis can be made when the product of a catalyzed reaction is chiral. A compound is chiral when it is not superimposable on its mirror image; the two compounds are then called enantiomers. These compounds are similar in most

of their physical properties as well as their reactivity when in symmetric surroundings but differ significantly when brought into a chiral environment. Biological systems commonly distinguish between enantiomeric forms of molecules since they are themselves made up of chiral molecules. Thus, two different enantiomers of the same compound may have distinctly different effects on a given biological system. The two enantiomeric forms of limonene are examples for chiral compounds (Scheme 1). While (*R*)-(+)-limonene (**1**) smells of oranges, its enantiomer (*S*)-(–)-limonene (*ent*-**1**) has a piney, turpentine-like odor.



(*R*)-(+)-limonene
1



(*S*)-(−)-limonene
ent-**1**

Scheme 1: Enantiomers of limonene.

When two or more achiral compounds are reacted to yield a chiral molecule under the influence of an achiral catalyst, this product will be obtained as a 1:1 mixture of its enantiomers, which is a racemate. This can be called non-asymmetric catalysis. However, the goal of chemistry is usually to obtain one particular compound and not mixtures, and strictly spoken a racemate comprises a mixture of 50% of the desired product or enantiomer and 50% of the undesired enantiomer which has to be separated using methods of kinetic or dynamic kinetic resolution. These separations are generally much more tedious than separations of compounds that are not enantiomers. Moreover, the formation of the undesired enantiomer makes the process less atom-economic.

One solution to these problems is to employ methods of asymmetric catalysis, in which a small quantity of a chiral catalyst will convert a large amount of chiral or achiral starting materials into enantiomerically pure or enriched products. Nowadays asymmetric catalysis is divided into three areas: biocatalysis, metal catalysis, and organocatalysis.

Biocatalysis is based on the use of enzymes, catalysts consisting of proteins and often metallic cofactors. They can be employed both as isolated compounds as well as in form of whole cells. Enzymes are usually very selective with regard to chemo-, diastereo-, and enantioselectivity due to their complex three-dimensional structure, which allows only specific target molecules to interact with the active site of the enzyme. Biocatalysis is the oldest known principle for asymmetric catalysis.[1] Enzymes are unsurpassed in enhancing reaction rates as well as in their selectivity. Problems may arise with the low tolerance of changes in operational

parameters, such as pH value or temperature, the preference for water as the reaction medium, and the often encountered strict dependence on their natural cofactor, which is often too costly for stoichiometric use. Another drawback for the use of enzymes is that they are provided by nature in only one enantiomeric form, and their antipodes cannot simply be made from all-D amino acids to yield the opposite stereoisomer in a given, chemical transformation.[2]

The second major field of asymmetric catalysis is based on the use of chiral complexes derived from metal centers and chiral ligands. While the basic idea of using a non-enzymatic catalyst to achieve an asymmetric reaction was known for a long time,[3] it was not until after the pioneering work of *Knowles* [4] and *Noyori* [5] in the late 1960s that it was widely employed in chemistry. Their contribution to the development of this powerful concept was awarded with the Nobel Prize in chemistry in 2001 together with *Sharpless*. The field has seen tremendous growth since its beginnings in both academic as well as industrial context. *Noyori* stated in 1995 that the synthesis of (–)-menthol at Takasago International Corporation, Japan, in which the key step is promoted by a chiral rhodium catalyst, was "[…] the world's biggest application of asymmetric catalysis, allowing for an annual production of about 1500 tons of menthol […]".[6] However, one major disadvantage for the industrial use of organometallic compounds in asymmetric synthesis is the need for removing trace amounts of catalyst especially in food and drug related context due to the requisition to offer products that are free from even traces of heavy metals.

The third and youngest area of asymmetric synthesis is the field of organocatalysis, in which small molecules not containing any metals in the active center act as catalysts. While sporadic examples of asymmetric organocatalysis where long known,[3, 7-10] it was not until the early 2000s and the seminal works of *List* [11] and *MacMillan* [12] and the ensuing boom in the area that the statement of *Nicolaou* and *Sorensen* that "[in] a catalytic asymmetric reaction, a small amount of an enantiomerically pure catalyst, either an enzyme or a synthetic, soluble transition metal complex, is used to produce large quantities of an optically active compound from a precursor that may be chiral or achiral," as found in "Classics in Total Synthesis" from 1996,[13] was made obsolete before the publication of a second volume.

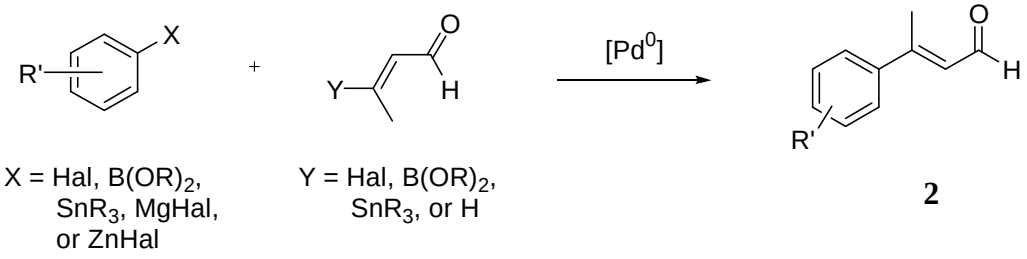
2. Concept

The work described in this thesis pursued two main goals in different areas of catalysis. First, a new, efficient, and short route to β,β-disubstituted, α,β-unsaturated aldehydes was to be found. The second goal was to develop the chemistry of *N*-Boc-imines and related carbamate- and amide-protected preformed imines in an organocatalyzed Mannich reaction.

2.1. Development of an efficient route to β,β-disubstituted, α,β-unsaturated aldehydes through palladium-mediated catalysis

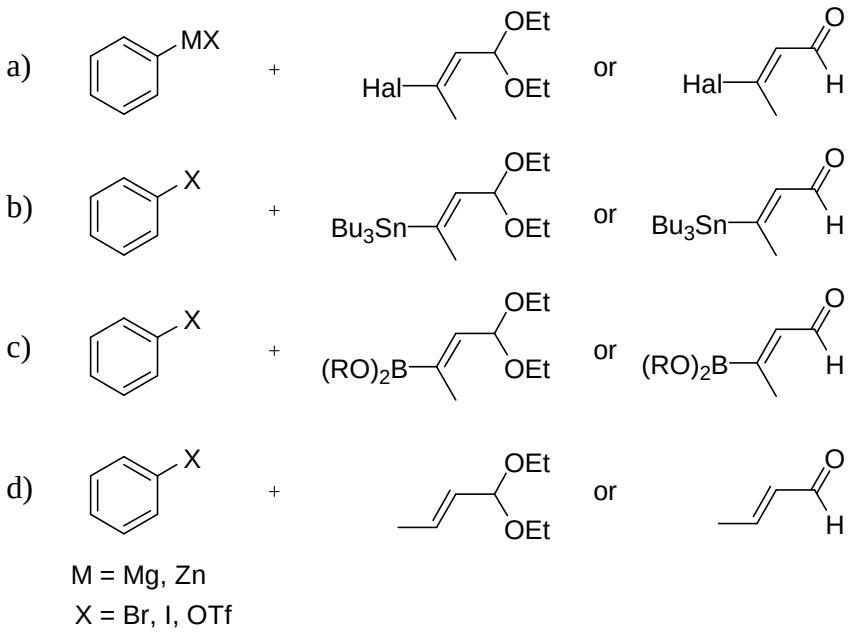
β,β-Disubstituted, α,β-unsaturated aldehydes have turned out to be viable substrates for a variety of transformations, but they are also interesting substances with regard to industrial application, as many of these compounds are fragrances. However, no general and simple access to this class of compound was known.

It was one goal of this thesis to establish a palladium-catalyzed route to the target molecules **2** (Scheme 2).



Scheme 2: General idea to obtain β,β-disubstituted, α,β-unsaturated aldehydes through a Pd-mediated reaction.

The development of this method was mainly focused on aldehydes with an aromatic as well as an aliphatic substituent. The choice to use a palladium-catalyzed route to the targeted compounds was made due to the large number of potential reactions available as well as the vast amount of substrates, many of which are commercially available (Scheme 3).

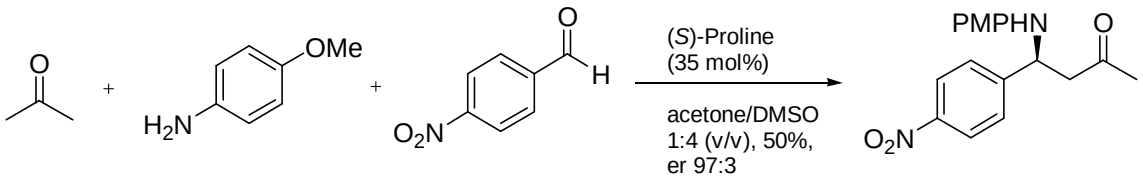


Scheme 3: Possible Pd-catalyzed reactions yielding β,β-disubstituted, α,β-unsaturated aldehydes.

Negishi and Kumada (a), Stille (b), or Suzuki couplings (c) are possible reactions leading to the desired products. They require the synthesis of functionalized unsaturated aldehydes or acetals. Unmodified, unsaturated aldehydes or acetals are substrates for the Heck reaction (d).

2.2. Development of an organocatalytic Mannich reaction of preformed *N*-Boc and related imines

The second goal of this thesis was to develop the chemistry of preformed *N*-Boc, *N*-Cbz, *N*-Fmoc, and *N*-Bz-imines in an organocatalyzed Mannich reaction. The proline-catalyzed three-component Mannich reaction developed by *List* in 2000 had shown that proline was capable of catalyzing the reaction between enolizable carbonyl compounds and imines (Scheme 4).[14]



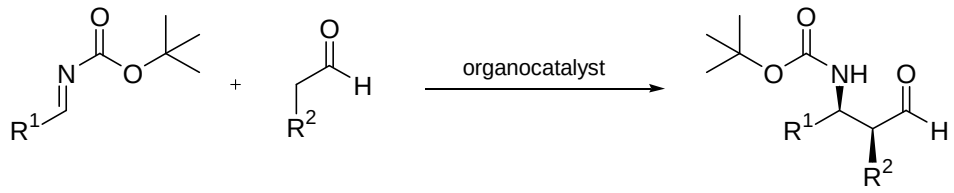
Scheme 4: Organocatalyzed three-component Mannich reaction discovered by *List*.

The major drawback of the method is the removal of the PMP-protecting group from nitrogen. The standard method for this transformation is oxidative cleavage using ceric ammonium nitrate (CAN), a procedure which is not suitable for some substrates due to the strongly oxidiz-

ing conditions employed, and which typically is accompanied by product loss.[15] Moreover, *p*-anisidine is highly toxic, and ceric ammonium nitrate is toxic and too expensive for industrial use.

In contrast to this, the Boc group is one of the standard and most widely employed protecting groups for nitrogen in organic and especially in peptide synthesis. Due to the ease of its removal, a Mannich reaction with *N*-Boc-protected-imines would deliver valuable β-amino carbonyl building blocks. However, it was known that the reaction between hydroxyacetone, which had become a standard reagent in aldol and Mannich reactions, and a preformed *N*-Boc-imine under proline catalysis was not observed.[16]

As part of this thesis a method should therefore be developed by which unmodified aldehydes could be reacted with preformed *N*-Boc-imines (Scheme 5).

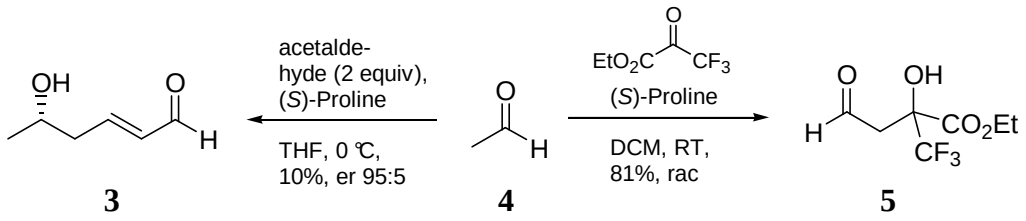


Scheme 5: General outline for an organocatalyzed Mannich reaction of *N*-Boc-imines.

A further goal was to explore the reaction with different carbamate and amide protecting groups. This is of great importance for the use of the resulting products in organic synthesis, as many of the protecting groups can be cleaved selectively under specific conditions. The development of the chemistry of imines with different protecting group would allow for a direct access to suitably protected building blocks.

2.3. Development of an organocatalytic transformation of acetaldehyde

Acetaldehyde, the smallest enolizable aldehyde, is a valuable two carbon donor. Its use in synthesis leads to unbranched addition products, which are otherwise only accessible by indirect methods, such as by using enol ethers,[17-19] but it has long been elusive in organic transformations. This is due to its inherent reactivity and also the reactivity of these unbranched products. *Córdova et al.* described the formation of trimers **3** when they reacted acetaldehyde (**4**) under proline catalysis (Scheme 6, left).[20]

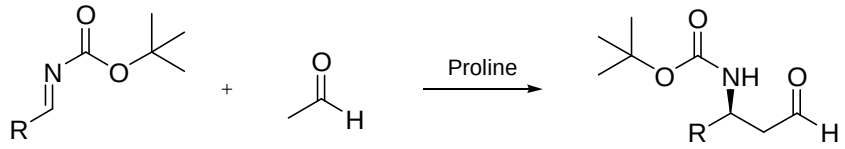


3 **4** **5**

Scheme 6: Previous attempts at proline-catalyzed reactions of acetaldehyde.

While the enantiomeric ratio of 95:5 was found to be very high, the yield of the product was only 10%. When the group of *Jørgensen* attempted another aldol reaction with a rather engineered acceptor, they faced the complementary problem of high yields of a racemic product (**5**) (Scheme 6, right).[21]

Through the aforementioned literature it was known that proline can act as a catalyst for reactions of acetaldehyde, but no high yielding, enantioselective, and controllable reaction had so far been developed. As part of this thesis it was a goal to find out whether the proline-catalyzed Mannich reaction of *N*-Boc-imines is a suitable reaction to allow for the first use of acetaldehyde in a reaction that could lead in reasonable yields to monoaddition products of acetaldehyde with high enantiopurity (Scheme 7).

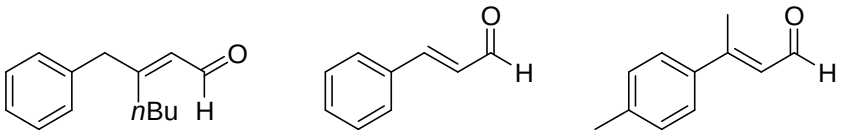


Scheme 7: Outline for the reaction of acetaldehyde with *N*-Boc-imines.

3. Background

3.1. Synthetic routes to β,β-disubstituted, α,β-unsaturated aldehydes

α,β-Unsaturated aldehydes play important roles as fragrances (**6**),[22] food additives (**7**),[23] and starting materials for organic synthesis (**8**, Scheme 8).[24]



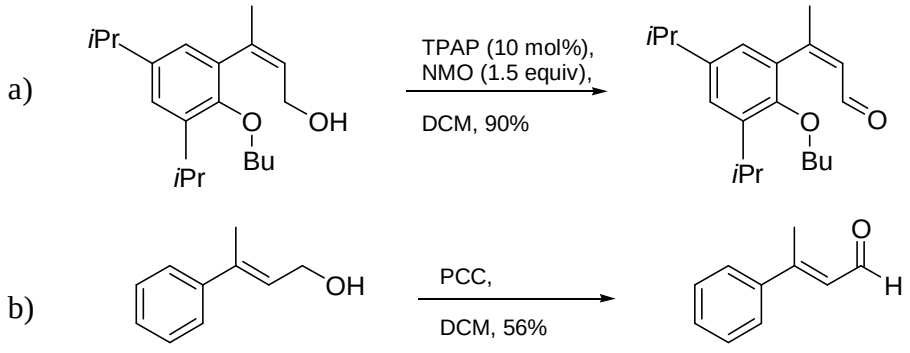
6 **7** **8**

Scheme 8: Examples of α,β-unsaturated aldehydes.

The synthesis of this class of compound has therefore been the focus of considerable research. The following chapter will provide an overview of the methods available to synthesize β,β-disubstituted, α,β-unsaturated aldehydes.

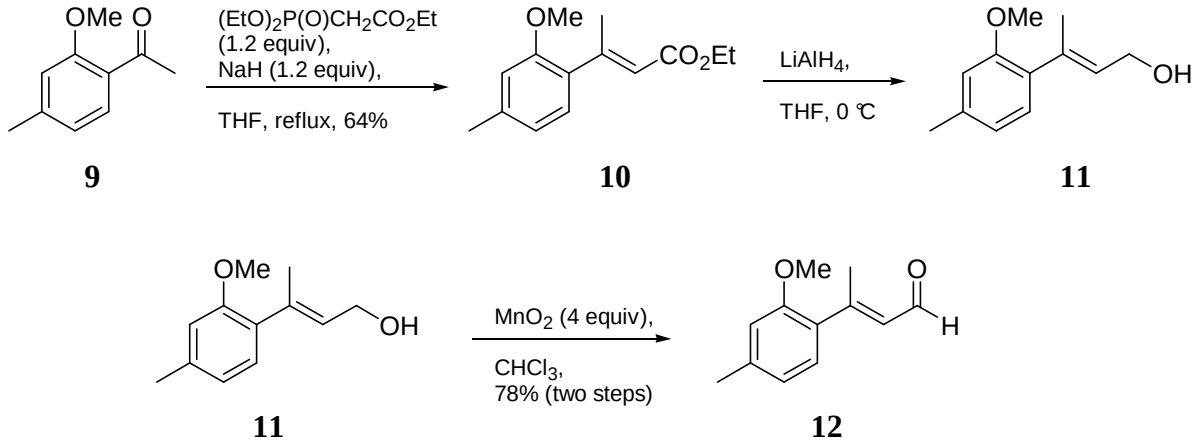
3.1.1. Oxidative methods

The oxidation of an alcohol to an aldehyde is one of the basic transformations in organic chemistry, and numerous methods have been developed. It is possible to oxidize allylic alcohols as well, which leads to α,β-unsaturated aldehydes. Some of the methods that have successfully been used are exemplified below. Typical oxidants are the combination of tetra-*n*-propyl ammonium perruthenate (TPAP) and *N*-methylmorpholine-*N*-oxide (NMO) (Scheme 9a),[25] pyridinium chlorochromate (PCC) (Scheme 9b),[26] or manganese dioxide (Scheme 10).[27]



Scheme 9: Literature-known examples of allylic alcohol oxidations to α,β-unsaturated aldehydes.

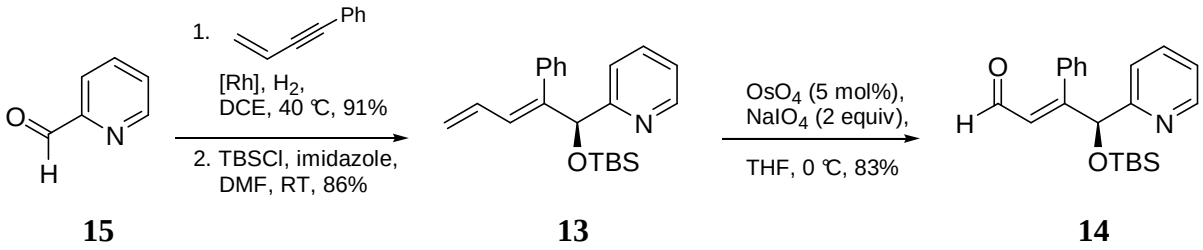
The problem of this synthetic method is not the actual oxidation step, but the necessity to obtain suitably substituted alcohols. *Fuganti* and *Serra*, for example, started from ketone **9**, which was converted in a Horner-Wadsworth-Emmons reaction to the unsaturated ester **10** in an approximate ratio of 5:1 in favor of the *E*-isomer (Scheme 10).[27] Since it is generally not possible to reduce α,β-unsaturated esters selectively to α,β-unsaturated aldehydes, the ester was reduced to allylic alcohol **11**, which was subsequently re-oxidized to the desired aldehyde **12**.



Scheme 10: α,β-unsaturated aldehydes *via* Horner-Wadsworth-Emmons reaction.

Despite the apparent drawback of a lengthy synthesis this method actually offers the broadest access to β,β-disubstituted, α,β-unsaturated aldehydes, as many of the starting ketones are commercially available or can be synthesized.

Transforming an alcohol to an aldehyde is not the only possibility to obtain α,β-unsaturated aldehydes *via* oxidation of the starting material. *Krische* transformed diene **13** to aldehyde **14** through osmium tetroxide/sodium periodate oxidative olefin cleavage (Scheme 11).[28]

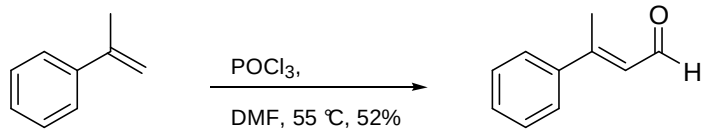


Scheme 11: Oxidative cleavage of dienes to yield α,β-unsaturated aldehydes.

Aldehyde **15** was the starting point for the rhodium-catalyzed preparation of the diene. A number of dienes have been synthesized by the method, but the compounds are all substituted

by a γ-hydroxy group. It is not mentioned that the other olefin geometric isomer was observed. The focus of *Krische*'s work did not lie in obtaining the aldehydes, of course.

The extension of an existing olefin to an α,β-unsaturated aldehyde is possible *via* the Vilsmeier-Haak formylation.[29] α-Methylcinnamaldehyde **16** was obtained from α-methylstyrene **17** in 52% by this method (Scheme 12).[30]



17 **16**

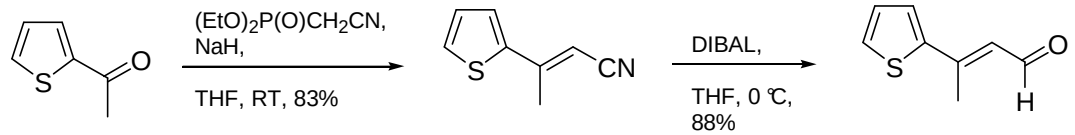
Scheme 12: Vilsmeier-Haak formylation of α-methylstyrene **17**.

Instead of styrenes it is also possible to use tertiary alcohols which are dehydrated to an olefin *in situ*.[31] The drawback of the Vilsmeier-Haak formylation is the use of phosphoryl chloride, which is both corrosive and toxic. Moreover, it is highly reactive, which renders it incompatible with substrates such as alcohols and amides.

3.1.2. Reductive methods

Carboxylic acid esters can often be reduced selectively to the corresponding aldehydes with DIBAL at –78 °C. While the corresponding reaction of α,β-unsaturated esters yields mixtures of aldehyde and alcohol, the reduction of unsaturated nitriles and Weinreb-amides to the aldehydes is possible.

Watanabe's group has used a two-step synthesis starting from a ketone like **18** to obtain the unsaturated nitrile **19** which was then reduced to the desired aldehyde **20** (Scheme 13).[32]

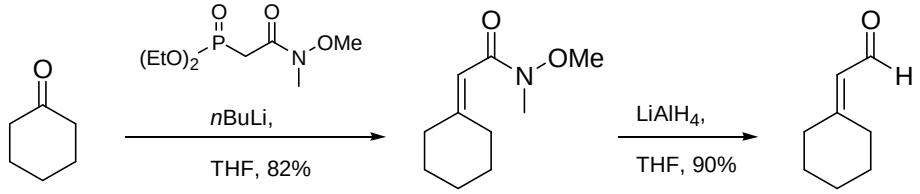


18 **19** **20**

Scheme 13: Synthetic sequence *via* unsaturated nitriles.

This method also employs a Horner-Wadsworth-Emmons reaction, which allows for the same broad substrate scope as in the case of *Serra* described above (Scheme 10).

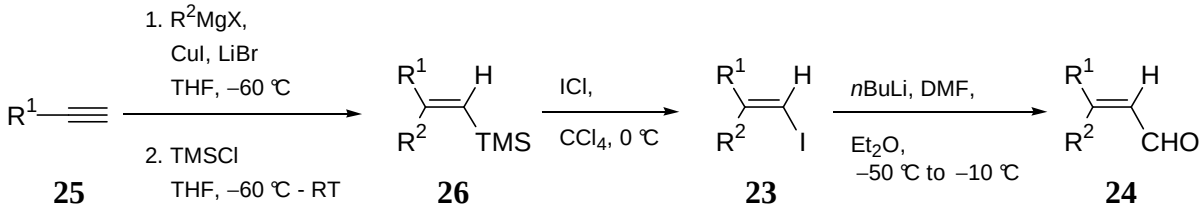
Nuzillard, *Boumendjel*, and *Massiot* also employed a Horner-Wadsworth-Emmons reaction to obtain the unsaturated Weinreb-amide **21**.[33] The amide was then reduced to the corresponding aldehyde **22** with lithium aluminium hydride (Scheme 14).



Scheme 14: Partial reduction of a Weinreb-amide.

A number of other aldehydes and ketones could be employed in the reaction sequence with typically good yields.

Chou et al. converted vinyl iodides **23** to α,β-unsaturated aldehydes **24** (Scheme 15).[34]

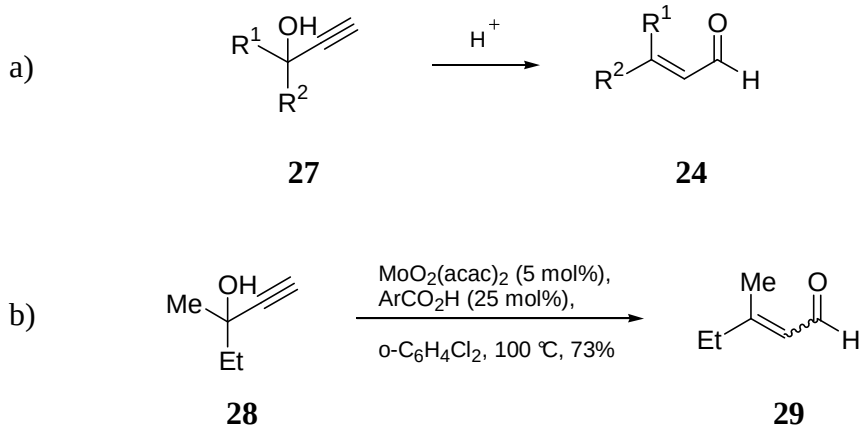


Scheme 15: Substitution of iodine with DMF.

A yield of 67% of **24** was obtained when R^1 was ethyl and R^2 was phenyl in **23**. The addition of a cuprate to alkynes **25** allows for an interesting substrate scope. Moreover, the geometry in **23** could be inverted when **26** was treated with MCPBA and HI instead of ICl.

3.1.3. Rearrangements

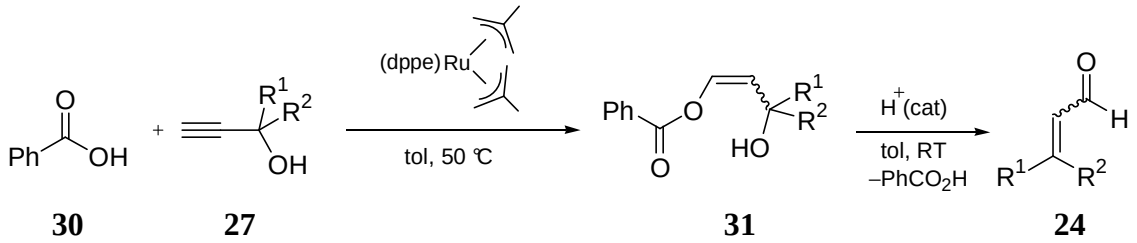
The Meyer-Schuster rearrangement is a reaction which transfers a tertiary, propargylic alcohol **27** into an α,β-unsaturated aldehyde **24** (Scheme 16a).[35]



Scheme 16: The Meyer-Schuster rearrangement.

Its use is limited by the strongly acidic conditions necessary. Moreover, if the substrate contains hydrogen in α-position, the Rupe rearrangement leading to an α,β-unsaturated ketone is the dominant reaction pathway.[35] However, under metal catalysis the Meyer-Schuster rearrangement can be predominant even for substrates with α-hydrogen atoms. For example, a molybdenum complex catalyzed the rearrangement of propargylic alcohol **28** to aldehyde **29** in good yield of 73%. However, the product was obtained as a mixture of *E*- and *Z*-isomers (Scheme 16b).[36]

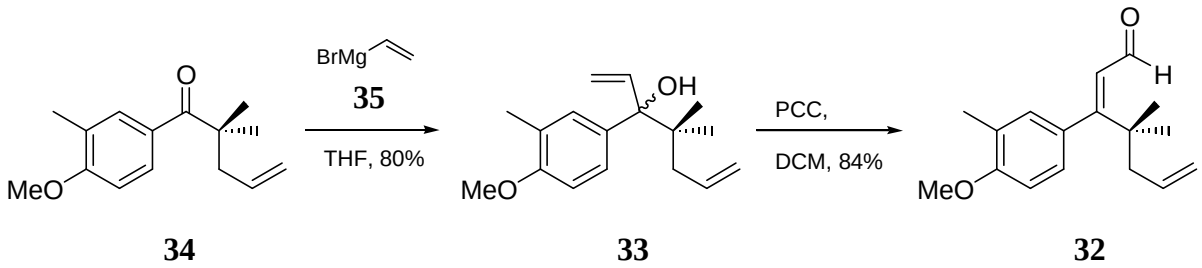
Bruneau developed a method to circumvent the problems associated with the Meyer-Schuster rearrangement (Scheme 16).[37] The addition of benzoic acid (**30**) to propargylic alcohols **27** under ruthenium catalysis leads to 3-hydroxy-1-propen-1-yl benzoates **31**. In an acid-catalyzed process the hydroxy group rearranges and benzoic acid is eliminated to yield aldehydes **24** (Scheme 17).



Scheme 17: Two-step isomerization of propargylic alcohols *via* benzoates.

The advantage of this method is that milder conditions can be employed in the second step. The yields are usually good to very good for both steps, while the ratio of isomers seems to depend on the conditions employed and ranges from 90:10 to 67:33.

The oxidative rearrangement of tertiary, allylic alcohols with PCC also leads to α,β-unsaturated aldehydes.[38] Unlike in the Meyer-Schuster rearrangement, the starting material may also contain hydrogen in α-position to the alcohol. *Srikrishna* made use of this reaction to access aldehyde **32** from tertiary alcohol **33** as an intermediate in the synthesis of β-herbertenol (Scheme 18).[39]



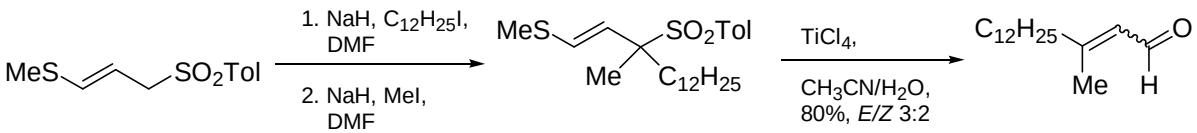
34 **33** **32**

Scheme 18: Rearrangement of a tertiary, allylic alcohol.

A suitably substituted ketone (**34**) was treated with vinyl Grignard reagent **35** to obtain the necessary tertiary alcohol. The driving force for the rearrangement is the irreversible oxidation of the primary alcohol/chromium intermediate that is formed during the reaction. The reaction also uses ketones as starting materials, which opens up the same broad substrate scope as mentioned above.

3.1.4. Eliminations

3-Methylthio-2-propenyl *p*-tolylsulfone (**36**) was introduced as a general reagent for the synthesis of α,β-unsaturated aldehydes by *Ogura*.[40] Twofold alkylation allows for the introduction of a variety of substituents in the β-position. The methyl sulfide in **37** was displaced with water under Lewis acid catalysis, and the hydroxide tautomerized to the saturated aldehyde. The tosyl group either eliminates under Lewis acid catalysis at this stage or after subsequent treatment with a base (Scheme 19).

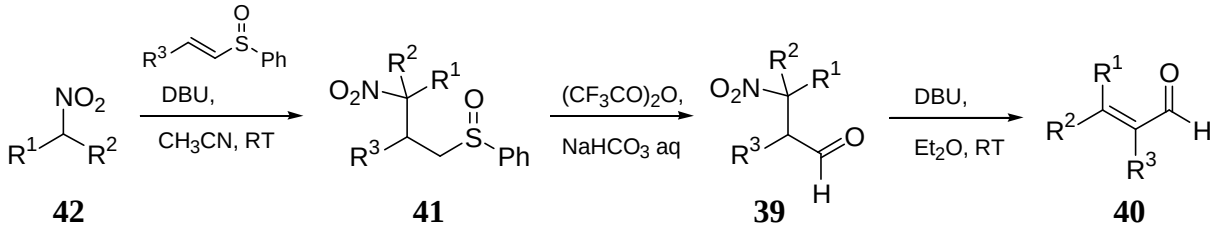


36 **37** **38**

Scheme 19: Synthesis of α,β-unsaturated aldehydes by a methyl sulfide displacement/elimination sequence.

38 was obtained in good overall yield (80%), but with a low *E*/*Z*-selectivity (3:2). The scope is naturally limited to alkyl- or allyl-disubstituted α,β-unsaturated aldehydes.

Ono reported the elimination of the nitro group from compounds **39** to form the corresponding α,β-unsaturated aldehydes **40** (Scheme 20).[41]

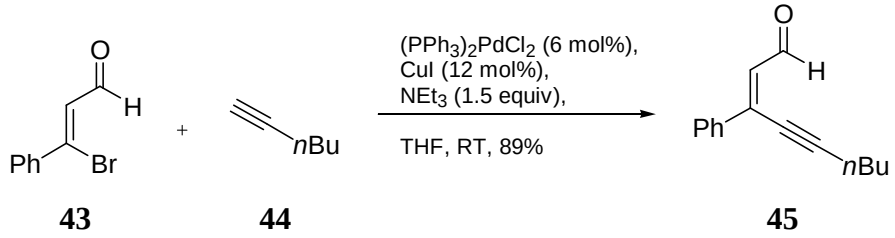


Scheme 20: Michael addition/elimination sequence.

The yields of **40** were good (52-82%), but only aliphatic nitro compounds **41** made from nitro alkanes **42** were used. Moreover, the *E*/*Z*-selectivity was low (typically 65:35).

3.1.5. Palladium-mediated syntheses

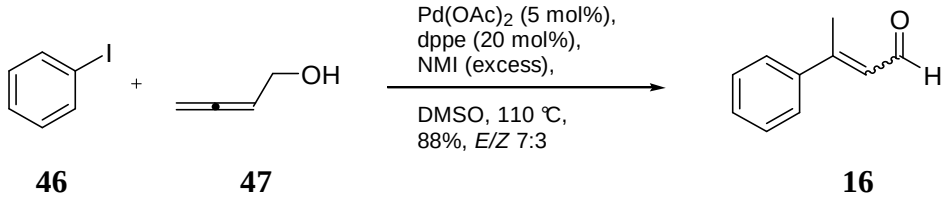
Herndon showed the synthesis of a β-alkyne-substituted, α,β-unsaturated aldehyde starting from bromoaldehyde **43**. The Sonogashira coupling with hexyne (**44**) gave 3-phenyl-2-nonen-4-ynal (**45**) in 89% yield.[42]



Scheme 21: Sonogashira coupling to obtain an alkyne-substituted aldehyde from bromoaldehyde **43**.

Aldehyde **43** was prepared from acetophenone *via* a Vilsmeier-type reaction. The method has later been extended to the palladium(0)-catalyzed Ullmann cross-coupling [43] and the Suzuki coupling.[44]

The synthesis of β-methyl substituted α,β-unsaturated aldehydes was exemplified by *Tsuji* in the palladium(0)-catalyzed reaction of iodobenzene (**46**) with 1,2-diene **47** (Scheme 22).[45]

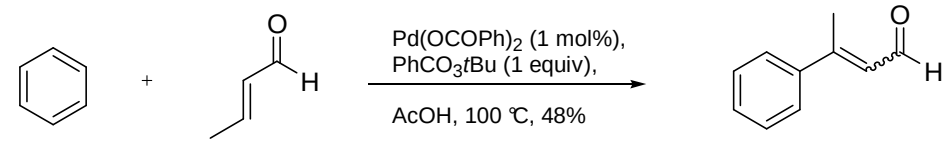


46 **47** **16**

Scheme 22: Arylation of a 1,2-diene.

The yield of 88% was very good, but product **16** was obtained as a diastereomeric mixture. Moreover, **47** must be synthesized, which limits the usability of the reaction.

The oxidative, palladium(II)-mediated coupling of crotonaldehyde (**48**) with benzene (**49**) was also reported by *Tsuji* (Scheme 23).[46]



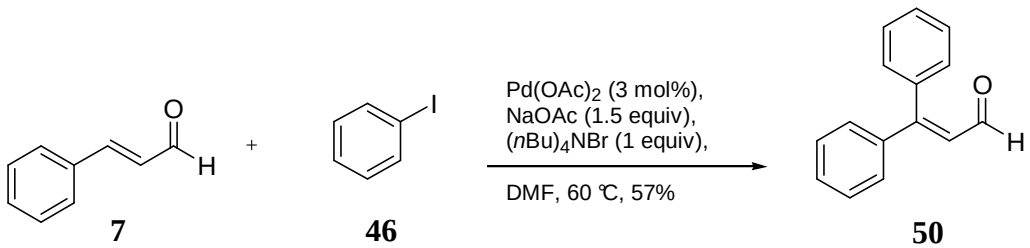
49 (excess) **48** **16**

Scheme 23: Oxidative coupling of crotonaldehyde with benzene.

A stoichiometric amount of a perester was necessary to re-oxidize the catalyst. **16** was obtained in moderate yield of 48% and as a mixture of *E*- and *Z*-isomers. It was reported that no regioselectivity was observed when substituted benzenes were used, which limits the potential of the method.

Another example of this chemistry used cinnamaldehyde as the olefin and *tert*-butylhydroperoxide as the stoichiometric oxidant in a reaction with benzene. The product was obtained in 36% yield.[47]

Cacchi has reported the synthesis of 3,3-diphenylacrylaldehyde (**50**) through the Heck reaction of cinnamaldehyde (**7**) and phenyliodide (**46**).[48]

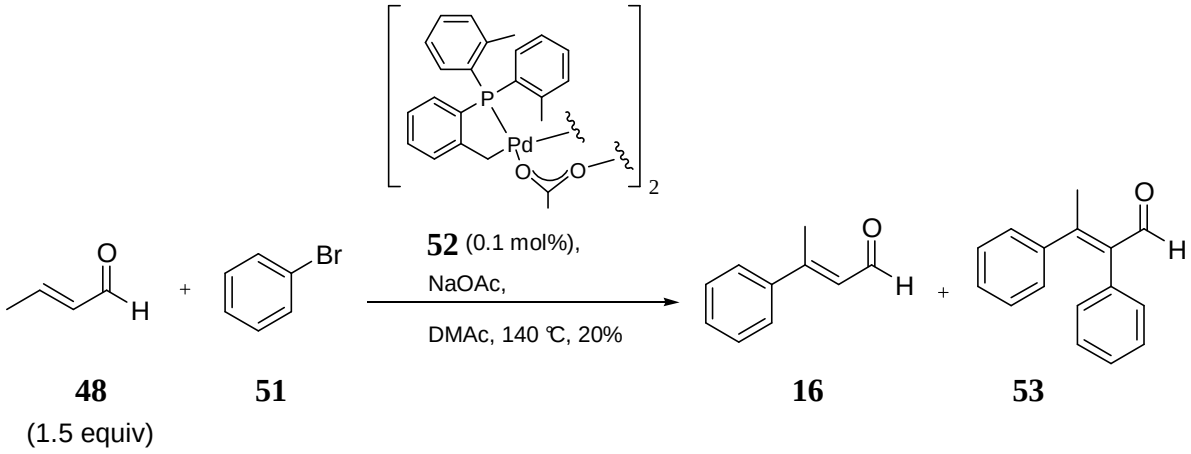


7 **46** (1.5 equiv) **50**

Scheme 24: Heck reaction of cinnamaldehyde.

The yields were moderate to high (46-84%) when other aromatic halides were employed, and the ratios of *E*- and *Z*-isomers ranged from 63:37 to 87:13.
The conditions were later improved by *Aggarwal*, who obtained **50** in 89% yield.[49]

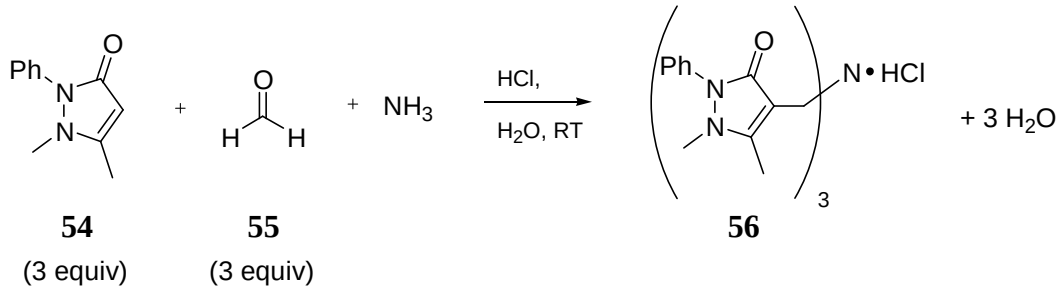
Crotonaldehyde (**48**) has also been used in the Heck reaction, but only one example has been described in the literature.[50] In the work of *Djakovitch* it was arylated with bromobenzene (**51**) under catalysis of palladium-complex **52** in low yields of only 20% of the desired product (**16**) and a further 8% of diarylation product **53** (Scheme 25).



Scheme 25: Heck reaction of crotonaldehyde.

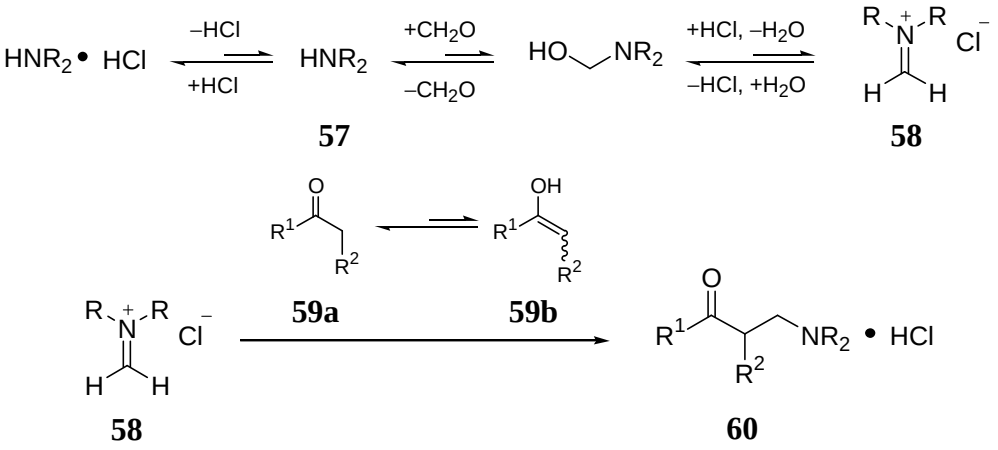
3.2. The Mannich reaction

In 1912 *Mannich* and *Krösche* described an aminomethylation reaction between phenazone (**54**), formaldehyde (**55**), and ammonia that occurred under acidic conditions and gave **56** (Scheme 26).[51] It would in later years become known as the Mannich reaction.



Scheme 26: First Mannich reaction.

In practice, enolizable aldehydes and ketones soon became the most important nucleophiles, and the combination of formaldehyde and an amine hydrochloride the predominant acceptors. A generalized mechanism is shown below (Scheme 27).

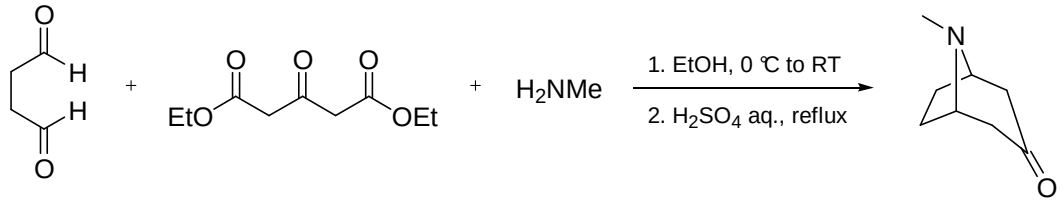


Scheme 27: Simplified reaction mechanism.

According to this mechanism the free amine **57**, which is in equilibrium with its hydrochloride, will undergo a sequence of equilibrium reactions with formaldehyde to give iminium ion **58** *via* an N,O-acetal. An equilibrium also exists between carbonyl compound **59a** and its enol form **59b**. The enol reacts with **58** to yield the hydrochloride of **60**.

The products of the reaction are usually β-amino aldehydes and ketones, also called Mannich bases. They are of interest due to the possible further transformations, such as the elimination of the amine yielding Michael acceptors or manipulations of the carbonyl group.

The reaction is particularly interesting because of the incorporation of nitrogen in the products, which is often present in natural products and drugs. In fact, the Mannich reaction was already used only five years after its discovery, in 1917, as key step in *Robinson*'s total synthesis of tropinone (**61**).[52] In this reaction succinaldehyde (**62**), diethyl acetonedicarboxylate (**63**), and methylamine (**64**) gave the desired product after twofold decarboxylation in a synthesis that is nowadays recognized as a classic in total synthesis (Scheme 28).



62 **63** **64** **61**

Scheme 28: Total synthesis of tropinone according to *Robinson*.

In the years since its discovery the Mannich reaction was developed into one of the most versatile carbon-carbon bond forming reactions and allows access to a variety of different building blocks and alkaloids.[53-56]

3.2.1. Diastereoselective variants

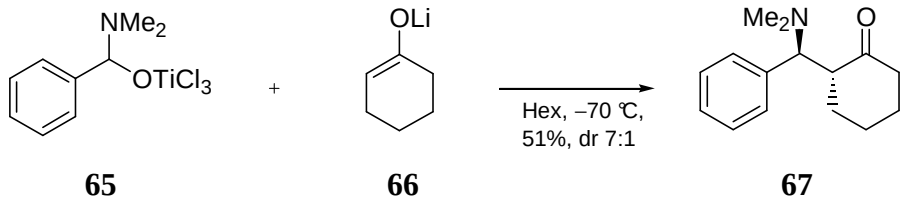
As with every chemical transformation selectivity is an important issue, and the development of diastereoselective variants of the Mannich reaction has been an early focus of research. Diastereoselectivity can be achieved by two principles. One possibility is to use the geometry of the enolate of the starting materials, as *E*- and *Z*-enolates will often give different diastereomers in a reaction.

The other possibility is the use of chiral starting materials, as the diastereomeric distribution of the products can be influenced by the chiral element already present. This concept is widely employed in chemistry and can be extended to the use of achiral starting materials by the introduction of chiral auxiliaries.

3.2.1.1. Simple diastereoselectivity

Several ways to induce simple diastereoselectivity, that is, preference for one particular diastereomer resulting from the reaction of achiral starting materials, have been devised, and the examples given in this chapter will highlight some of the approaches.

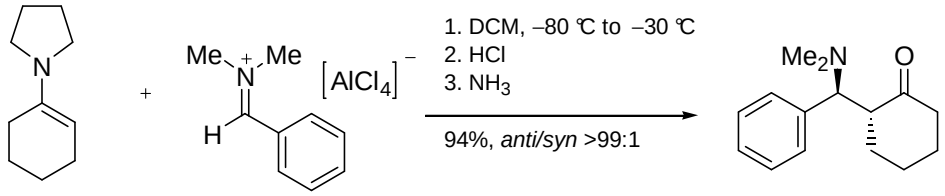
Seebach explored the reaction of titanium-reagents with lithium enolates. As an example, **65** was reacted with **66** to yield Mannich base **67** in 51% yield and with a dr of 7:1 in favor of the *anti* product (Scheme 29).[57]



65 **66** **67**

Scheme 29: Diastereoselective Mannich reaction with lithium enolates.

Perfect diastereoselectivity has been reported for the reaction of *E*-enamine **68** with ternary iminium salt **69** also leading to Mannich base **67** (Scheme 30).[58]

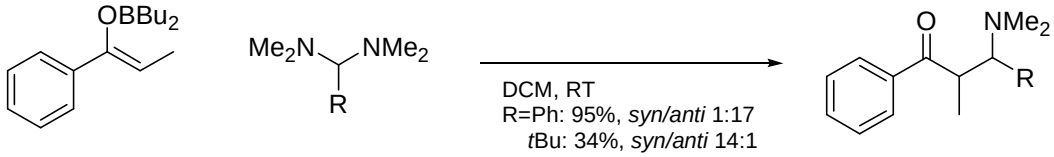


68 **69** **67**

Scheme 30: Diastereoselective reaction of enamines with iminium ions.

The reaction also works with similarly high yield and diastereoselectivity for a range of other substrates including open-chain enamines.

Nolen reacted boron enolates **70** with aminals **71**.[59] It was found that preference for the *syn* or *anti* product **72** depended on the aminal used (Scheme 31).



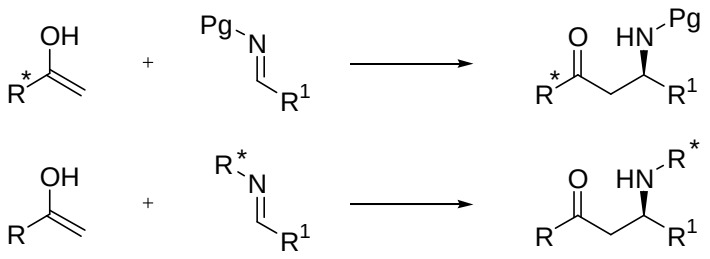
70 **71** **72**

Scheme 31: Diastereoselectivity with boron enolates and aminals.

The examples presented so far show that control of the diastereoselectivity can be efficiently achieved with achiral starting materials, which allows for a fast and simple access to the target β-amino compounds. The drawback, however, is that the products will always be obtained as racemates.

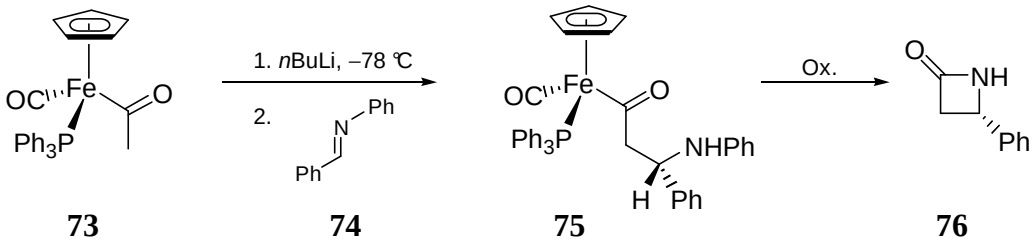
3.2.1.2. Auxiliary-induced diastereoselectivity

Important progress was made with the introduction of chiral auxiliaries to the Mannich reaction. Starting from enantiomerically pure auxiliaries, enantiomerically pure diastereoisomers can be obtained which greatly improved the synthetic value of the Mannich reaction (Scheme 32). Auxiliaries can be introduced on both the nucleophile as well as the electrophile.



Scheme 32: General scheme for auxiliary-based strategies. R^* = chiral auxiliary.

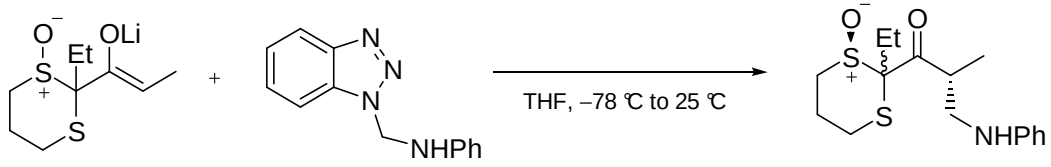
This concept was first employed in the Mannich reaction by *Broadley* and *Davies* in 1984.[60] When the lithium enolate of cyclopentadienyl iron-complex **73** was reacted with imine **74**, complex **75** was obtained with a diastereoselectivity of 99:1 (Scheme 33).



Scheme 33: Diastereoselective Mannich reaction with a chiral auxiliary.

The product could be converted into β-lactam **76** by oxidation. **73** was employed as a racemate, but the authors pointed out that it could be easily separated, which opens up the possibility to synthesize enantiopure products.

Another approach with racemic starting materials was described by *Page et al.*, who used β-keto sulfoxides as auxiliaries (Scheme 34).[61] For example, *syn* and *anti* enolates **77** reacted with **78** to give the ethyl-epimers of product **79** with a dr of >54:1 and >48:1, respectively, and with good yields (61% and 72%).

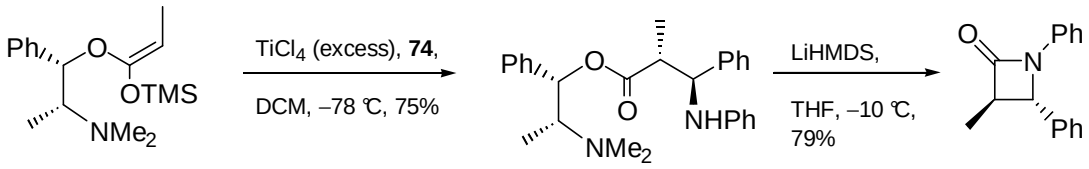


77 **78** **79**

Scheme 34: Use of sulfoxide as auxiliary.

Depending on the imine equivalent employed high diastereoselectivity could be achieved, but the reaction is hampered by a rather lengthy synthesis of the enolate.

The synthesis of enantiopure β-lactams was put into practice by *Gennari* and coworkers. With the help of an excess of $TiCl_4$, silyl ketene acetal **80** was converted to Mannich product **81** (Scheme 35).[62] The four possible diastereoisomers of **81** were obtained in a ratio of 38:3.7:1:0.

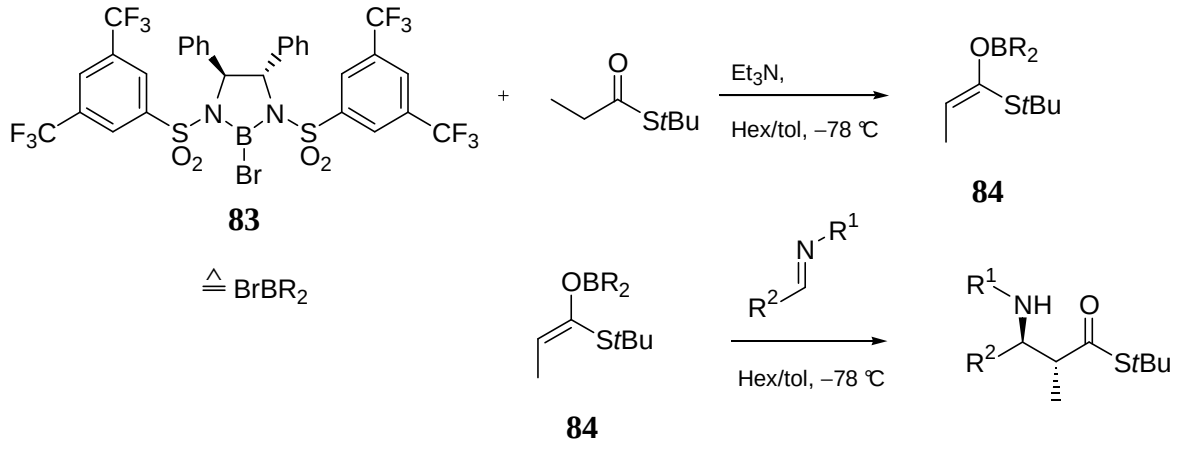


80 **81** **82**

Scheme 35: Synthesis of a β-lactam with an enantiopure starting material.

The reaction was not perfectly diastereoselective. However, direct conversion of the mixture to **82** led to a diastereomeric mixture of >10:1 (or 38:3.7) in favor of the *anti* product, which was obtained with an er of 97.5:2.5 (or 38:1).

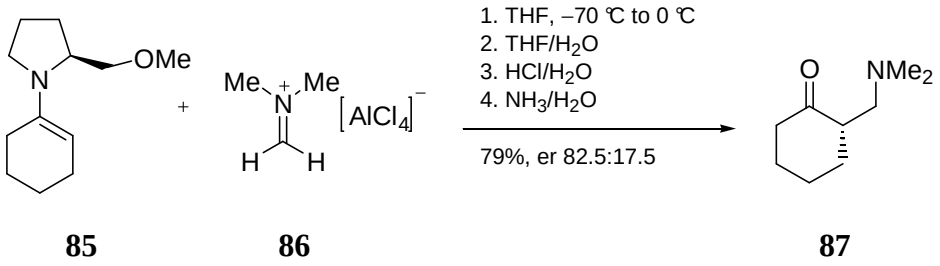
Boron enolates have been developed into a source of chirality in the Mannich reaction by *Corey* (Scheme 36).[63]



Scheme 36: Chiral boron enolate **84** in the Mannich reaction.

83 was transformed to enolate **84**, which was reacted with different imines in yields ranging from 67-77% and with diastereomeric ratios from 92:8 to >99:1.

Chiral enamines **85** have been employed by *Risch*.[64] They yield the products of the aminomethylation with **86** in good yields, but only moderate enantiomeric excesses (Scheme 37).

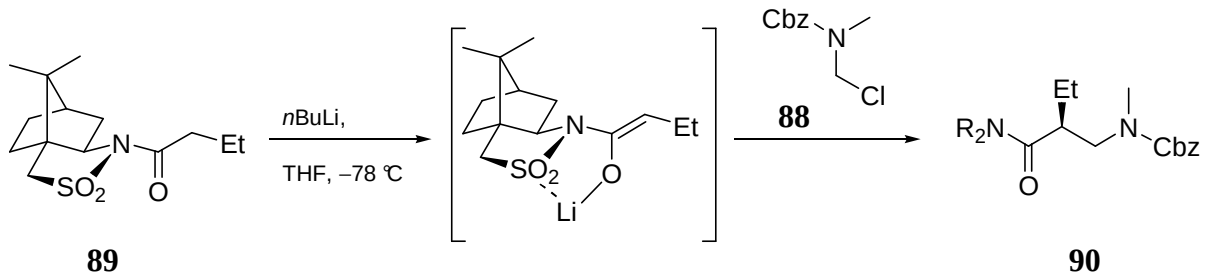


85 **86** **87**

Scheme 37: Aminomethylation of chiral enamines.

Later research indicated that the low enantiomeric purity of **87** may be due to racemization during workup rather than low selectivity.[65]

The alkylation of imine equivalent **88** has been reported by the group of *Oppolzer* as part of their investigation of camphorsulfonic acid-derived reagent **89** (Scheme 38).[66]

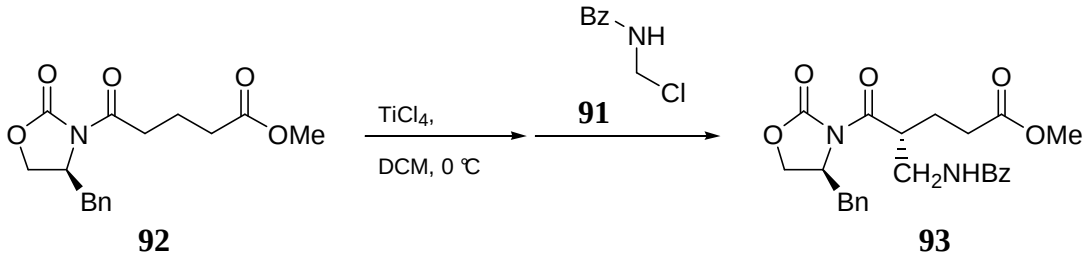


89 **90**

Scheme 38: Camphorsulfonic acid derivative **89** as source of chirality.

90 was obtained in 47% yield, yet at a conversion of only ~50%. The dr was 94.5:5.5 but could be increased to >99:1 by crystallization.

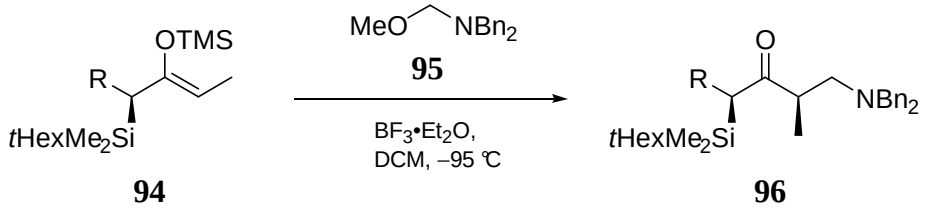
A similar alkylating agent (**91**) has been used by *Evans* (Scheme 39).[67]



Scheme 39: Evans-auxiliary in an alkylation with imine equivalent **91**.

The reaction of **92** and **91** was similarly diastereoselective as in the case of *Oppolzer*'s system with a dr of 96:4, but the yield of 87% of **93** was much higher.

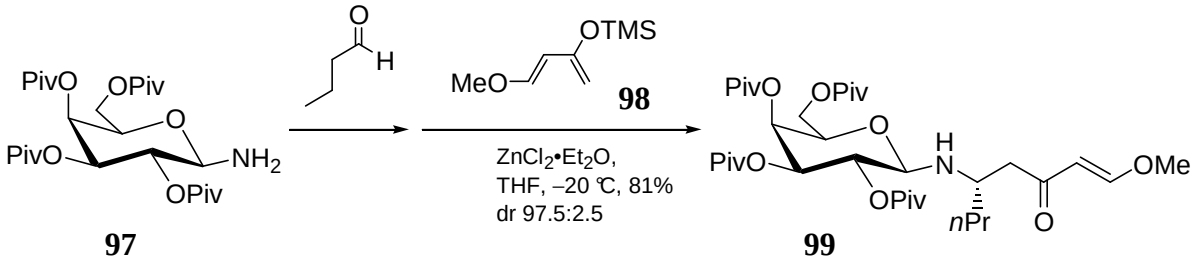
Enders used chiral α-silylketones as starting materials for a highly diastereoselective Mannich reaction. The corresponding O-*Z*-silylenol ethers **94** were reacted with N,O-acetal **95** in excellent yields of up to 95% and with very high diastereoselectivities ranging from 96:4 to 98:2 (Scheme 40).[68]



Scheme 40: Silicon as directing group in *Ender*'s Mannich reaction. *t*HexMe$_2$ = 1,1,2-trimethylpropyl.

The silyl group in the products **96** could be removed easily and in high yields by treatment with ammonium fluoride.

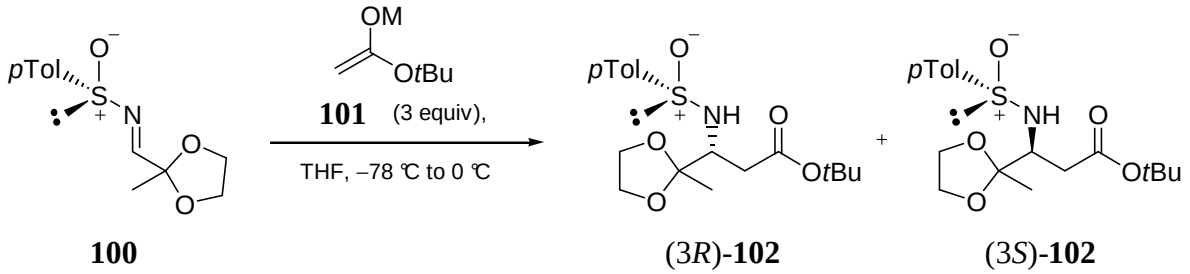
While the chirality was usually introduced through the nucleophile, *Kunz* described a different approach with 2,3,4,6-tetra-*O*-pivaloyl-β-D-galactopyranosylamine (**97**). The reaction with an aldehyde led to a chiral imine, which was then reacted with silyl enol ether **98** (Scheme 41).[69]



Scheme 41: Diastereoselective reaction employing a sugar as chiral auxiliary. Piv = *t*BuCO.

99 was obtained in a diastereomeric ratio of 97.5:2.5 and high yields when one equivalent of $ZnCl_2$ was used. It was found that the opposite diastereomer is obtained when two equivalents of the Lewis acid were used. **99** could be converted into enantiopure (*S*)-coniine in a few steps.

Chirality on sulfur could also be used to generate a chiral electrophile. *Fujisawa et al.* used imine **100**, which was prepared in 5 steps from (*S*)-(–)-menthyl-*p*-toluene sulfinate, in a reaction with metal ketene acetals **101** to obtain optically active products (3*R*)-**102** and (3*S*)-**102** (Scheme 42).[70]

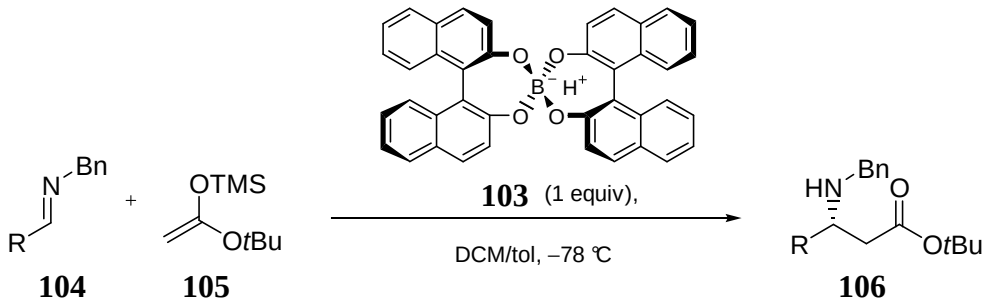


100 (3*R*)-**102** (3*S*)-**102**

Scheme 42: Mannich reactions with chiral sulfur imines. M = Li, K, Ti, or Al.

Depending on the choice of the metal in **101** both diastereoisomers were accessible in diastereomeric ratios of up to 96:4 and in very good yields of up to 89%. The auxiliary could be cleaved off by treatment with trifluoroacetic acid.

A new concept was introduced to the Mannich chemistry by *Yamamoto* in 1994.[71] The chiral Brønsted-acid assisted Lewis acid **103** used by his group is not covalently bound to either nucleophile or electrophile (Scheme 43). It is assumed to activate the imine *via* coordination of the nitrogen to the boron atom. However, it was used in stoichiometric amount. It is not mentioned whether catalytic amounts were tested.



104 **105** **106**

Scheme 43: Use of a non-covalently bound Lewis acid as source of chirality.

Imines **104** react with silyl ketene acetal **105** to give β-amino acid esters **106** with moderate yields (35-58%), but with excellent enantioselectivities (er 97.5:2.5 to 99:1). High optical

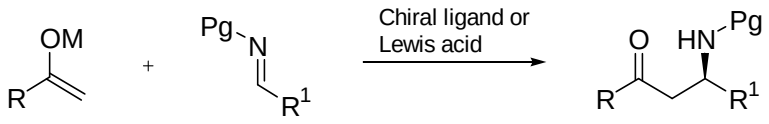
purity could only be achieved with aryl imines. The obvious advantage of this concept is that it is not necessary to prepare chiral starting materials, but that the chirality can simply be "added" to the reaction *via* the Lewis acid. This development was also a major step towards a catalytic variant of the Mannich reaction.

3.2.2. Metal-catalyzed, asymmetric Mannich reactions

While the approaches presented in chapter 3.2.1 have been developed to give high diastereoselectivities, the need to separate the racemates obtained from simply diastereoselective reactions or the handling of auxiliaries, which adds several steps to any reaction sequence, was a driving force to develop catalytic, enantioselective reactions. The first successful examples of this concept were developed with metal catalysts.

3.2.2.1. Indirect Mannich reactions

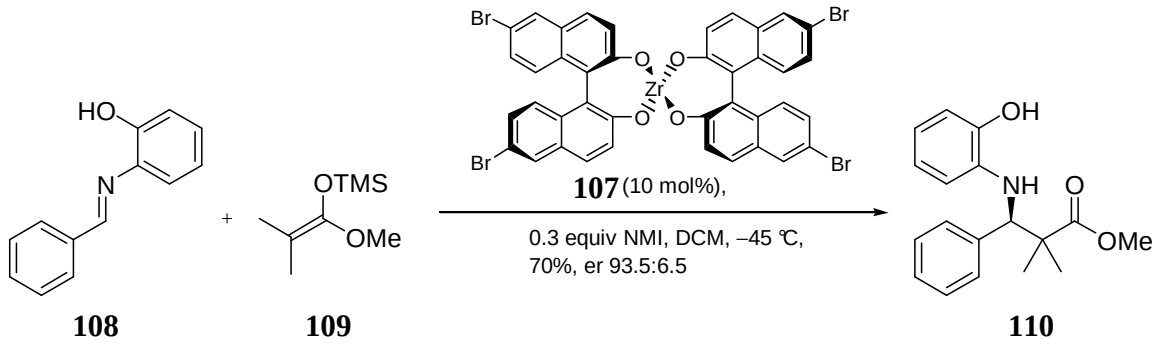
A number of highly diastereo- and enantioselective indirect Mannich reactions have been developed to date. Silyl enol ethers and silyl ketene acetals have emerged as highly reactive intermediates for this type of reaction (Scheme 44).



Scheme 44: General concept for the enantioselective, indirect, organometallic Mannich reaction. M = metal.

Chirality can be either introduced through chiral ligands that directly coordinate the enolate, or by activation through a chiral Lewis acid. This chapter summarizes the development in this important area.

In 1997 *Kobayashi* published the first highly enantioselective, catalytic Mannich-type reaction of (O,O)- and (O,S)-silyl ketene acetals and preformed imines.[72] Catalyst **107** made use of the chirality of BINOL as in the case of *Yamamoto* (see Scheme 43), but zirconium as the metal center allowed for a catalytic amount to be used.



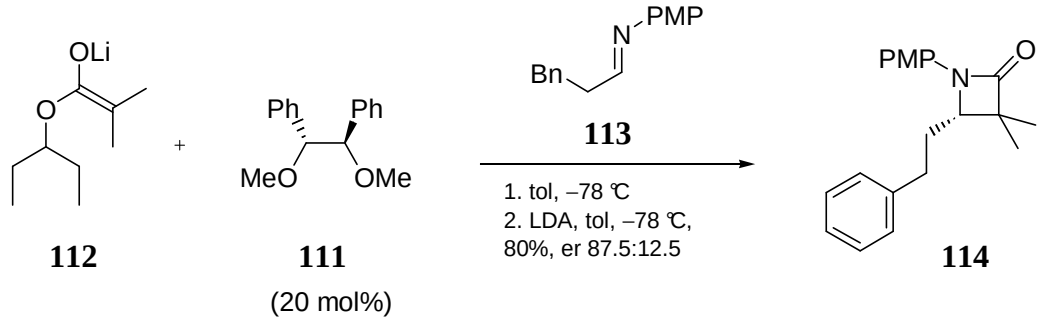
Scheme 45: Example of the first highly enantioselective, catalytic Mannich reaction. NMI = *N*-methylimidazole.

In the above example (Scheme 45), imine **108** reacts with **109** to give product **110** in a yield of 70% and with a ratio of enantiomers of 93.5:6.5. Several other aromatic as well as an aliphatic imine were tested, and the products were always obtained with high yield and enantioselectivity.

The use of 2-aminophenol derived imines is crucial for the reaction. *Kobayashi* postulated a hexavalent zirconium in the transition state bound to both nitrogen and oxygen of the imine. *N*-methylimidazole is speculated to generate monomers of the catalyst.

In a later expansion the same group found that both *syn* and *anti* β-amino alcohols were accessible when *E*- or *Z*-trisubstituted silyl ketene acetals were used.[73]

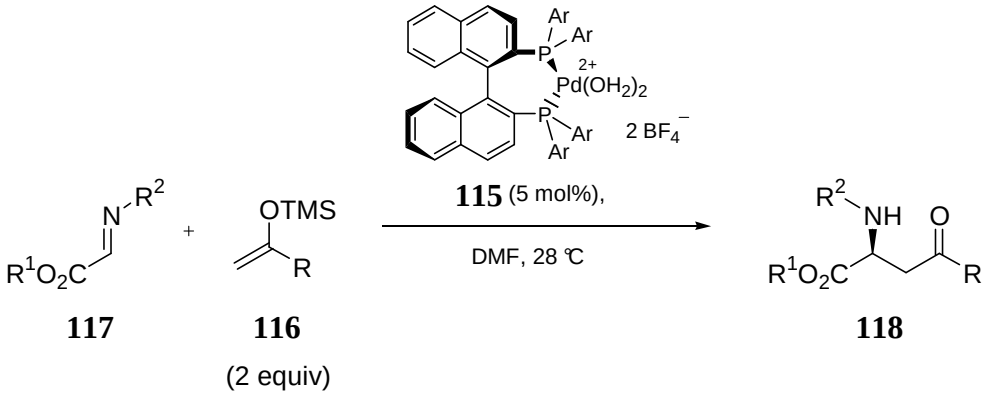
In the same year *Tomioka* and coworkers used chiral ether **111** in a catalytic amount (20 mol%) to allow for the enantioselective reaction of lithium ester enolate **112**, which was generated *in situ* from the corresponding ester and lithium diisopropylamide, with *N-para*-methoxyphenyl (PMP) imine **113**.[74]



Scheme 46: Chiral ether **111** as catalyst for the Mannich reaction of lithium enolates.

The reaction proceeded with reasonable enantioselectivity and yield. Under the reaction conditions the initial Mannich product cyclized to β-lactam **114**. The authors had originally used stoichiometric amounts of the ether before turning to a catalytic process. A drawback of the reaction is the fourfold excess of LDA used.

Sodeoka and co-workers used chiral BINAP (Ar = Ph) and tol-BINAP (Ar = *para*-tolyl) palladium complexes **115** to add silyl enol ethers **116** to imino esters **117** in an enantioselective fashion (Scheme 47).[75]

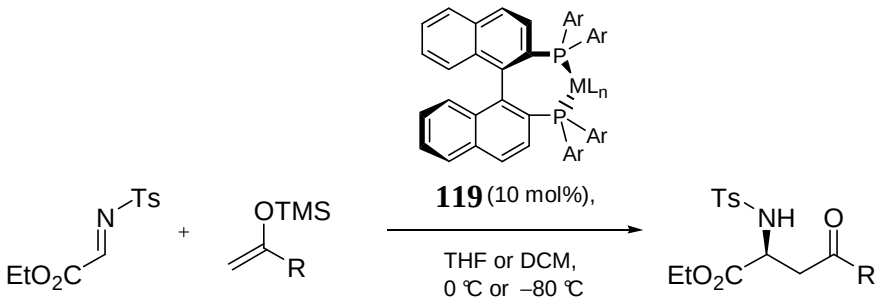


117 **116** (2 equiv) **118**

Scheme 47: Palladium-complex **115** yields protected amino acid esters **118**. Ar = Ph or *para*-tolyl.

The yields of **118** were usually above 80% and the ratios of enantiomers were between 80:20 and 95:5, thereby offering a useful approach to γ-keto amino acids.

Lectka developed the same reaction while focusing on a variety of different metals (silver, palladium, copper, and nickel) in chiral BINAP and tol-BINAP complexes **119** to obtain amino acid esters **120** from the reaction of imine ester **121** with different silyl enol ethers **116** (Scheme 48).[76]



121 **116** **120**

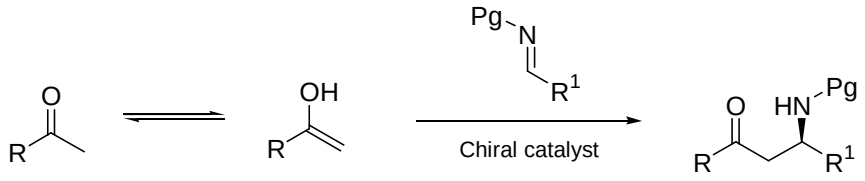
Scheme 48: Synthesis of chiral γ-keto amino esters. Ar = Ph or *para*-tolyl, M = Ag, Pd, Cu, or Ni.

The best results were obtained with silver and copper catalysts. Very high yields of up to 95% were achieved for a number of different silyl enol ethers, and only a few examples gave enantiomeric ratios below 90:10. This might be attributed to the lower temperatures as compared to the studies of *Sodeoka* (Scheme 47).

This methodology was later extended to include trisubstituted silyl enol ethers, which gave diastereoselectivities of up to 25:1. The products had *syn* or *anti* configuration dependent on the geometry of the enol ether.[77]

3.2.2.2. Direct Mannich reactions

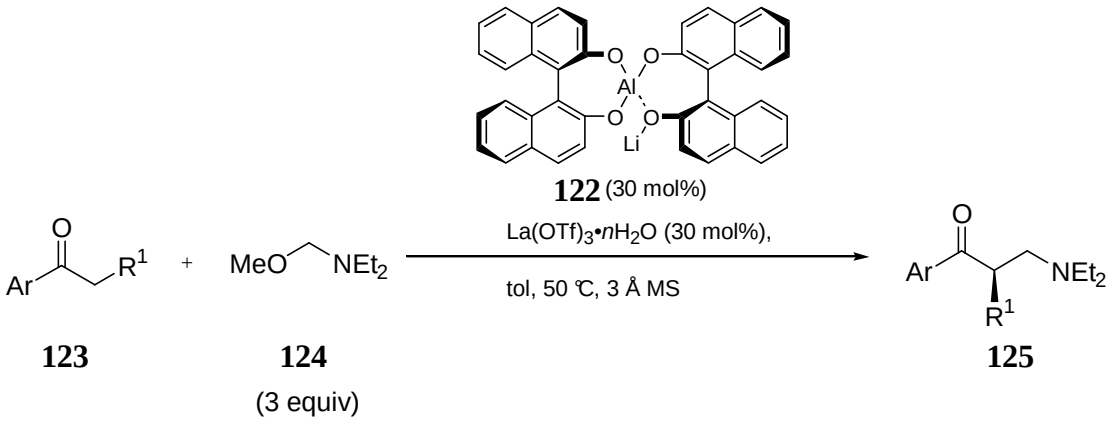
In contrast to the reactions discussed in chapter 3.2.2.1, direct Mannich reactions are reactions that employ unmodified nucleophiles such as aldehydes, ketones, or carboxylic acid esters. Reactions of this kind are generally preferable as they do not require extra steps to preform the enolate or enolate equivalents (Scheme 49).



Scheme 49: General scheme for the direct enantioselective, metal-catalyzed Mannich reaction.

Higher reaction temperatures are commonly employed as compared to the reactions described in the previous chapter because the starting materials are less reactive.

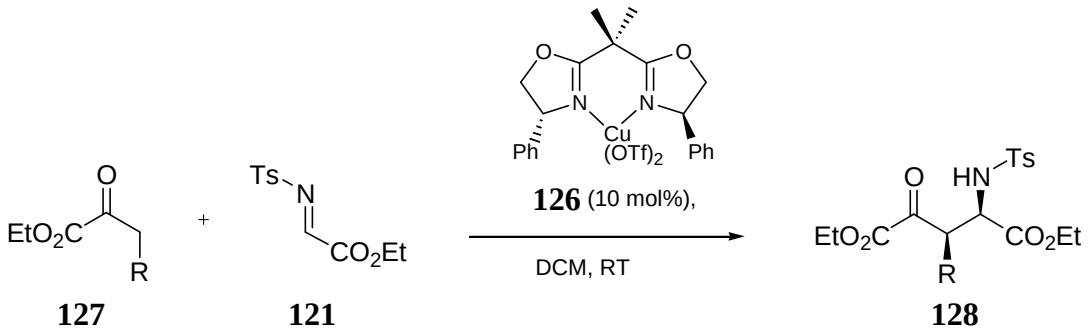
The first example of a direct asymmetric Mannich reaction of ketones was described by *Shibasaki* in 1999.[78] Aluminium *bis*-BINOL complex **122** in combination with Lewis acidic lanthanum triflate mediated the reaction between aryl ketones **123** and imine equivalent **124** (Scheme 50).



Scheme 50: First example of an enantioselective, direct, catalytic Mannich reaction of ketones.

The yields of products **125** obtained in this reaction were good (61-76%), but the enantioselectivity was only moderate, and the enantiomeric ratios ranged between 65.5:34.5 and 72:28. The substrate scope of this initial study was narrow, and high catalyst loadings had to be used. However, this first example proved that such direct Mannich reactions were possible and stimulated further research in this area.

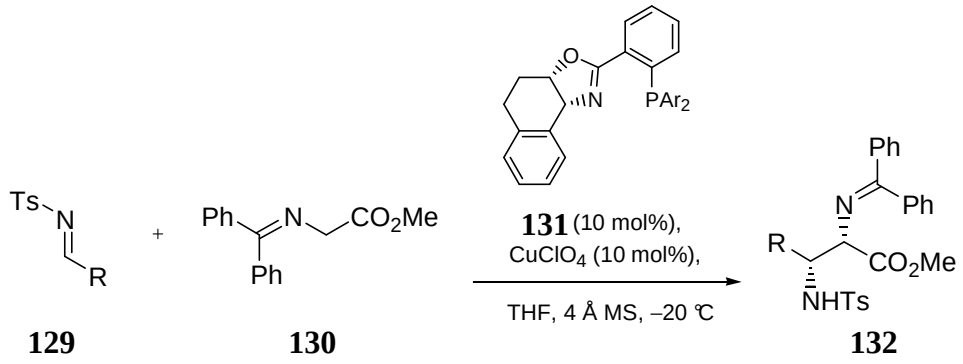
Soon thereafter Ph-BOX-Cu(OTf)$_2$ (**126**) was found to be an efficient catalyst in the enantio- and diastereoselective Mannich reaction of α-carbonyl esters **127** and *N*-tosyl-α-imino ester **121** by the group of *Jørgensen* (Scheme 51).[79]



Scheme 51: Copper(II)-BOX as catalyst system. Ts = *para*-toluenesulfonyl.

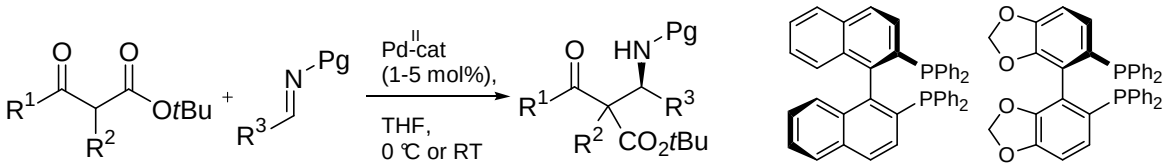
The products **128** were obtained in yields from 71-98%, diastereomeric ratios of >10:1, and high enantiomeric ratios from 89:11 to >99:1. The reaction time was usually 40 h. Besides hydrogen and aliphatic substituents, R could also be bromine. Nonetheless, the substrate scope presented was very limited. It was later expanded to malonates and β-keto esters.[80]

The same group also explored the reaction of *N*-Ts-imines **129** with imino glycine esters **130**.[81] While an analogue of catalyst **126** gave only racemic products, ligand **131** in combination with 10 mol% of copper(I) perchlorate was found to usually achieve high yields of >90% and very good enantiomeric ratios of >95:5, albeit in some cases with little diastereoselectivity (Scheme 52). The *syn* product **132** was generally favored.



Scheme 52: Synthesis of α,β-diamino acid derivatives **132** with a copper catalyst. Ar = 2,4,6-$Me_3C_6H_2$.

β-Keto esters were thoroughly researched as nucleophiles by *Sodeoka* and coworkers, who used BINAP (**133**) and SEGPHOS (**134**) as ligands for palladium(II).[82] In the study, several β-keto esters **135** were reacted with imines with different substitution patterns **136** (Scheme 53).

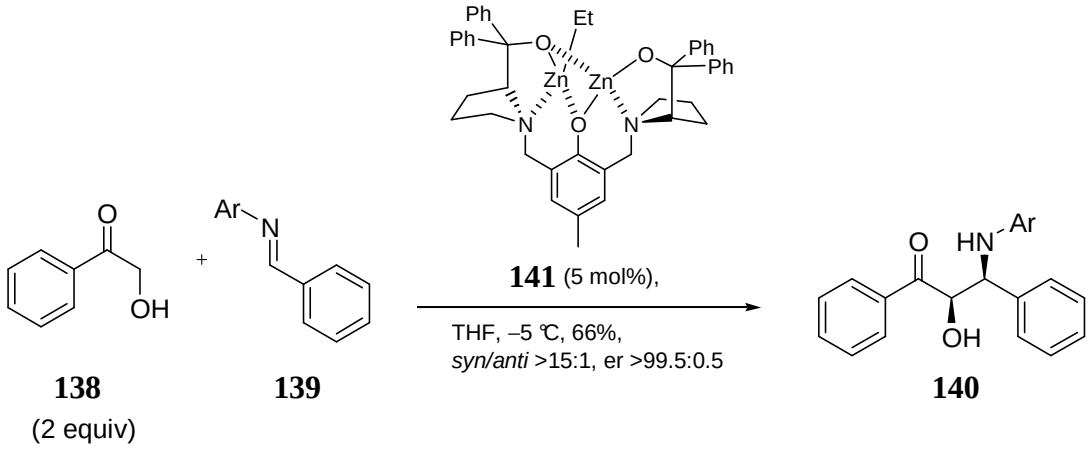


135 **136** **137** **133** **134**

Scheme 53: Study of β-keto esters as nucleophiles for the direct Mannich reaction.

Products **137** were obtained in good to very good yields and mostly very high enantiopurity, but the diastereoselectivity varied between 50:50 and >95:5. The same study also presented an example of a three-component reaction between *para*-methoxyaniline, ethyl-glyoxylate, and a β-keto ester, which gave the product in 61% yield, with an er of 98:2, and a dr of 70:30.

Trost introduced a dinuclear zinc-catalyst which gave extraordinarily high enantiomeric ratios.[83] As an example, α-hydroxyketone **138** was reacted with imine **139** to give **140** in good yield and with excellent stereoselectivity (Scheme 54).

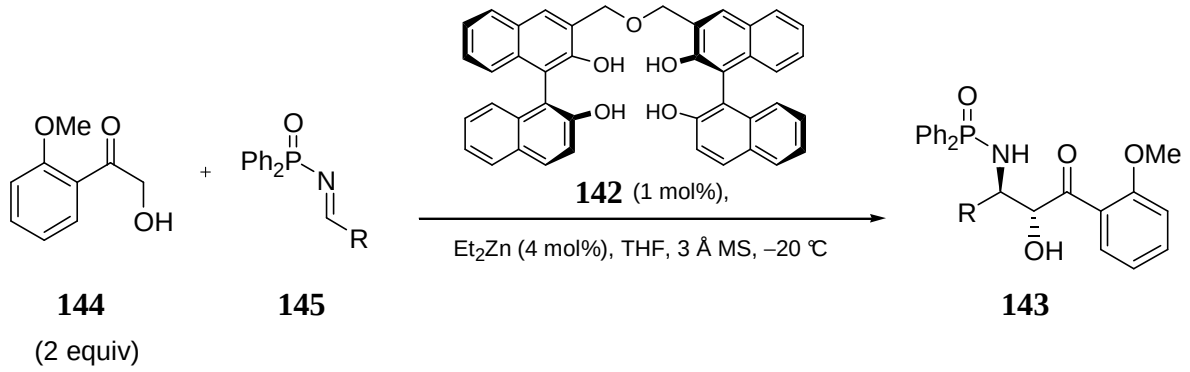


138 (2 equiv) **139** **140**

Scheme 54: Mannich reaction with a dinuclear zinc catalyst. Ar = 2-$MeOC_6H_4$.

5 mol% of catalyst **141** were sufficient to obtain high selectivity. It was also possible to use α-imino esters as substrates, which gives direct access to α-amino acid derivatives. While the enantioselectivity was excellent for all of the tested substrates, the diastereoselectivity was found to vary greatly with the imine, and was in the worst case only 1.7:1.

Shibasaki used a combination of diethylzinc with linked BINOL-ligand **142** to obtain *anti* Mannich products **143** in the reaction of α-hydroxyketone **144** with different *N*-diphenylphosphinyl (Dpp) protected imines **145** (Scheme 55).[84]

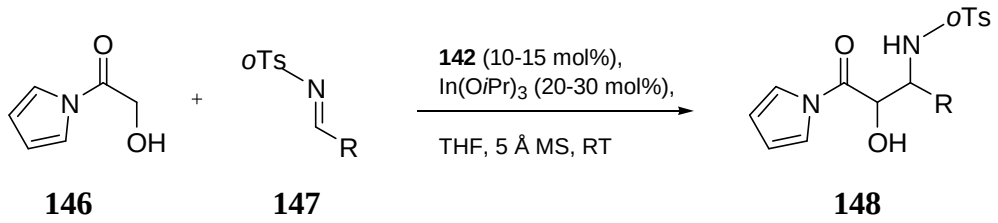


Scheme 55: *anti* Selective direct Mannich reaction.

The reaction is very selective (>94:6) for the *anti* products for a variety of aromatic substituents R, but the selectivity drops when R is cyclopropyl or cinnamyl. However, the enantioselectivities are outstanding, as they are 99:1 or higher in all cases. The same is true for yields, which were found to be 95% or higher for all substrates tested. In addition to that, the small catalyst loading of only 1 mol% is another striking feature of this reaction.

Shibasaki's group also found that the choice of the protecting group allowed to switch between *syn* and *anti* products.[85] When they used *N*-Boc-protected imines instead of *N*-Dpp-imines, the products were obtained in poor to good diastereoselectivities ranging from 58:42 to 95:5 in favor of the *syn* products. Outstanding enantiomeric ratios of >99:1 as well as very high yields were obtained in almost all cases, with only one example below 79% yield. *Trost* later showed that catalyst **141** was able to catalyze very similar reactions, but with a focus on aliphatic imines.[86] It also allowed to switch between *anti* and *syn* products by using *N*-Dpp- and *N*-Boc-imines, respectively. Good yields of up to 90% and enantiomeric ratios of up to >99.5:0.5 were achieved, but the diastereomeric ratios never exceeded 6:1.

Another valuable extension of the substrate scope of catalysts based on **142** was achieved with the introduction of *N*-(2-hydroxyacetyl)pyrrole (**146**) as nucleophile (Scheme 56).[87]



Scheme 56: Masked carboxylic acid as donor in the Mannich reaction.

The reaction with *N*-*o*Ts-imines **147** leads to products **148** that can be converted into a variety of carboxylic acid derivatives. The yields are good to high (68-98%) and the enantiomeric ratios are in no case lower than 94.5:5.5, but the diastereoselectivity ranges from good to al-

most non-existent. Moreover, the selectivity for *syn* or *anti* products depends on the imine employed. Aromatic imines preferentially yield *anti* products, while alkenyl imines yield *syn* products. In addition, the substrates were much less reactive compared to the previously employed ketones and required higher catalyst loadings of up to 30 mol% of metal and 15 mol% of ligand.

3.2.3. Organocatalytic, asymmetric Mannich reactions

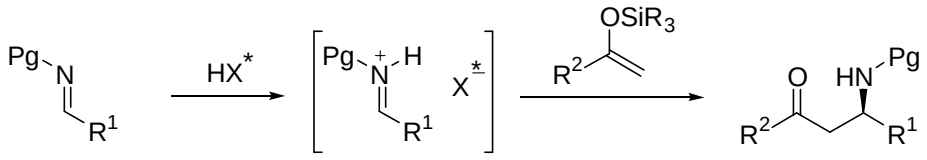
The organocatalytic approach directed at selectivity in the Mannich reactions differs from the approaches described in the previous chapters in that it was not a slow evolution from diastereoselective to enantioselective, or from auxiliary-based to catalytic versions with ever increasing selectivities for the desired products. Instead, already the first organocatalytic Mannich reaction, published by *List* only three years after *Kobayashi*'s initial discovery of the first highly enantioselective Mannich reaction, featured aspects that organometallic approaches could not compete with easily, such as a direct three-component reaction in a highly enantioselective reaction.

This chapter is therefore organized according to the mode of activation of the catalyst rather than their chronological development and will highlight the organocatalytic methods developed for the Mannich reaction.

3.2.3.1. Indirect Mannich reactions

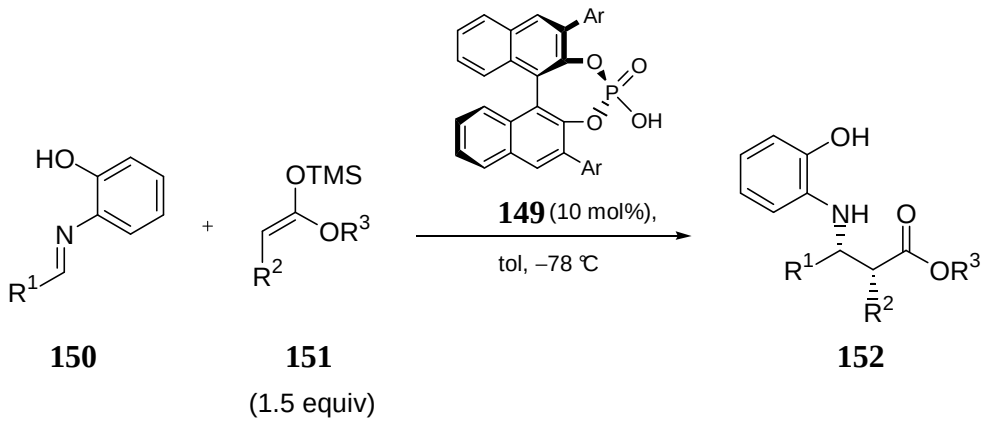
Brønsted acid catalysts

Brønsted acids are able to catalyze Mannich reactions through activation of the imine. Imines can be protonated by Brønsted acids, and an iminium ion is formed as an intermediate in the reaction.[88] If the acid is chiral, the corresponding anion can form a chiral ion pair with the iminium ion and lead to stereocontrol in the addition step (Scheme 57).



Scheme 57: General reaction scheme for the Brønsted acid catalyzed indirect Mannich reaction.

Akiyama et al. reported the use of chiral phosphoric acid **149** as a catalyst in an indirect Mannich reaction similar to the reactions examined by *Kobayashi* (see Scheme 45). The reaction of aliphatic and cinnamyl imines **150** with different trisubstituted silyl ketene acetals **151** led to products **152** in high yields of up to 100%, high diastereoselectivities of up to a dr of >99:1, and high enantiopurity of up to an er of 98:2 (Scheme 58).[88] The authors reasoned that the imine is protonated by the acid and is thereby activated towards the nucleophile.

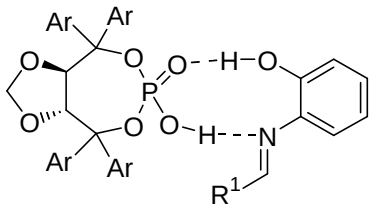


150 **151** (1.5 equiv) **152**

Scheme 58: Chiral phosphoric acid **149** as catalyst for the indirect asymmetric Mannich reaction. Ar = 4-NO_2-C_6H_4.

The enantioselectivity of the reaction decreased from 98:2 to only 70:30 when the *ortho* hydroxyphenyl group on the nitrogen was substituted by a phenyl group. The *ortho* hydroxyphenyl group is not a common protecting group for nitrogen and has to be removed in two steps.

The same group also developed catalyst **153** based on the TADDOL scaffold for the same reaction.[89] In comparison to **149** it could be employed with lower catalyst loading (5 mol%) and gave similarly high enantiomeric ratios. High selectivity could again only be achieved with *ortho* hydroxyphenyl protecting groups on the nitrogen, which is reasoned to be due to the bifunctional nature of the phosphate in **153** (Scheme 59).

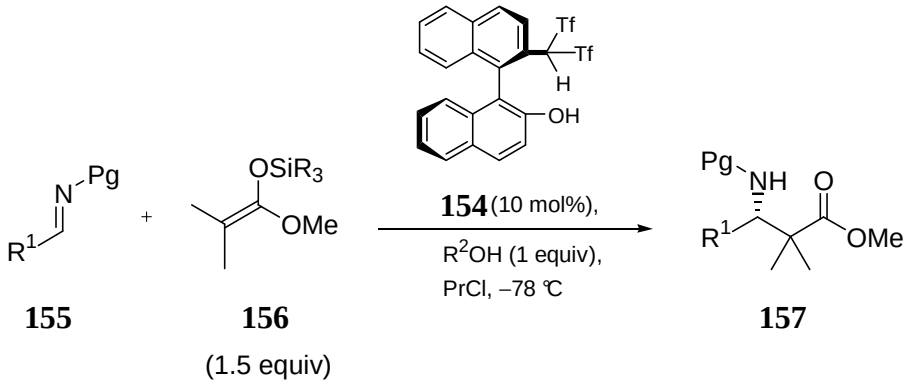


153

Scheme 59: Activation of *ortho* hydroxyphenyl imines by **153**. Ar = *p*-$CF_3C_6H_4$.

A serious drawback of the method is the narrow substrate scope, as only tetrasubstituted silyl ketene acetals have been employed.

Yamamoto developed Brønsted acid assisted Brønsted acid catalyst **154**.[90] It is also based on the BINOL backbone but is not C_2-symmetric. **154** catalyzes the reaction of *N*-phenyl- and *N*-(diphenylmethyl)aldimines **155** with tetrasubstituted silyl ketene acetals **156** to β-amino esters **157** in good to high yields and moderate to good enantioselectivity, which was in most cases between 80:20 and 88.5:11.5 (Scheme 60).

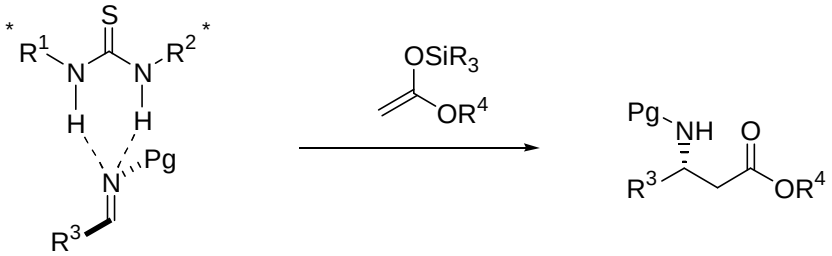


Scheme 60: Brønsted acid assisted Brønsted acid catalyst in the Mannich reaction. Pg = Ph or $CHPh_2$.

It was necessary to add a proton source to accomplish a catalytic cycle. The reaction was also limited to tetrasubstituted silyl ketene acetals.

Thiourea catalysis

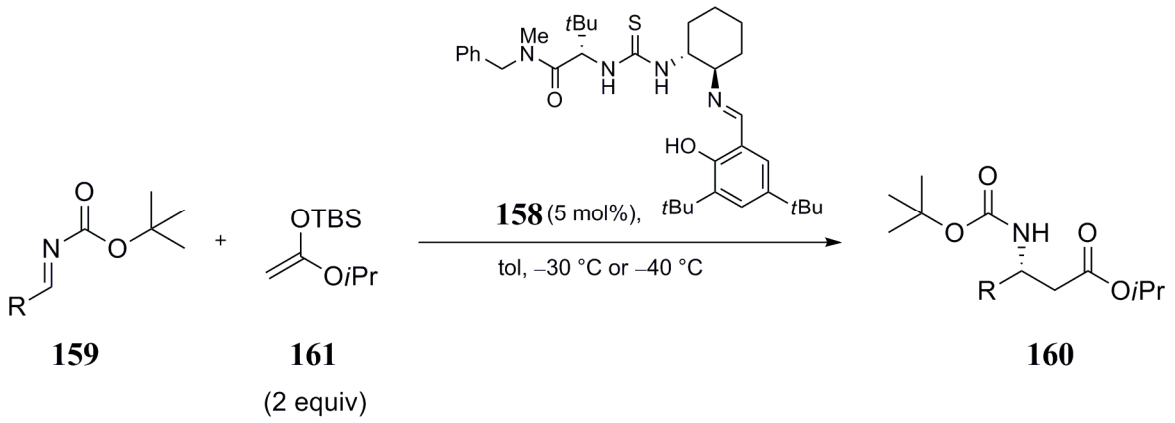
According to *Jacobsen*, thioureas are able to activate imines through hydrogen bonding (Scheme 61).[91]



Scheme 61: General mode of activation of imines through hydrogen bonding.

Chirality can be introduced *via* the substituents on nitrogen.

The introduction of thiourea-based catalyst **158** to the Mannich reaction by *Jacobsen* was not only remarkable because of the catalyst motif, but also because it showed the first use of pre-formed *N*-Boc-imines **159** in a highly enantioselective catalytic Mannich reaction (Scheme 62).[92]



Scheme 62: Thiourea-derivative **158** as catalyst in the indirect Mannich reaction.

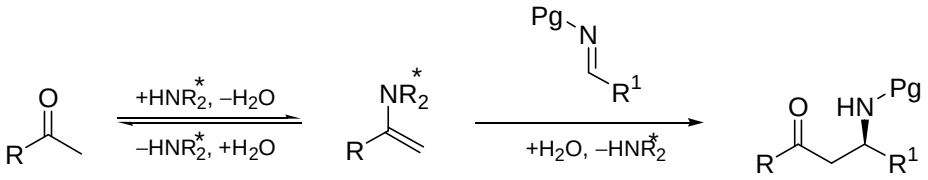
The reaction gave products **160** in generally very high yields (84-99%) and with enantiomeric ratios of >93:7 in all cases. Silyl ketene acetals other than **161** have been investigated and gave somewhat lower enantioselectivity. It is also notable that an *N*-Cbz-imine tested under the same conditions gave an er of only 63:37, while the product of an *N*-Ts-imine was racemic.

Jacobsen's method allowed for an access to *N*-Boc-protected β^3-amino acid esters in very high yields and selectivities. The use of a Boc-group renders this transformation a very valuable synthetic method to obtain β^3-amino acids for peptide synthesis. Aliphatic imines could not be tested, as there was no method known for their synthesis at the time the study was conducted.

3.2.3.2. Direct Mannich reactions

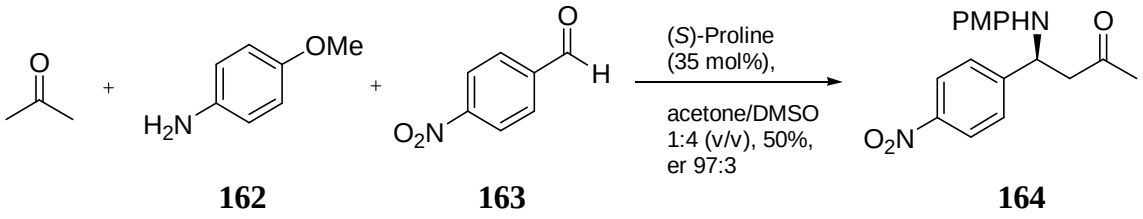
syn-Selective enamine catalysts

Carbonyl groups can often be efficiently activated towards electrophiles by the addition of primary or secondary amines. The *in situ* formation of the corresponding enamines leads to a more nucleophilic species. Moreover, if the amine is chiral, asymmetric induction can occur (Scheme 63).



Scheme 63: Outline for the direct asymmetric Mannich reaction based on enamine catalysis. The imine may be preformed or generated *in situ*.

The first example of a direct organocatalytic asymmetric Mannich reaction described by *List* can be regarded as a prototype of this kind of activation.[14] It made use of (*S*)-proline as chiral amine in the reaction of an aldehyde, an amine, and a ketone in one pot in a reminiscence of the original Mannich concept. *para*-Methoxyaniline (**162**) was chosen as a very reactive amine, acetone as the nucleophile, and several different aliphatic and aromatic aldehydes were used as electrophiles. In the example given below *para*-nitrobenzaldehyde (**163**) gave the corresponding PMP-imine *in situ* and reacted to product **164** under proline-catalysis in 50% yield and with excellent stereoselectivity (Scheme 64).



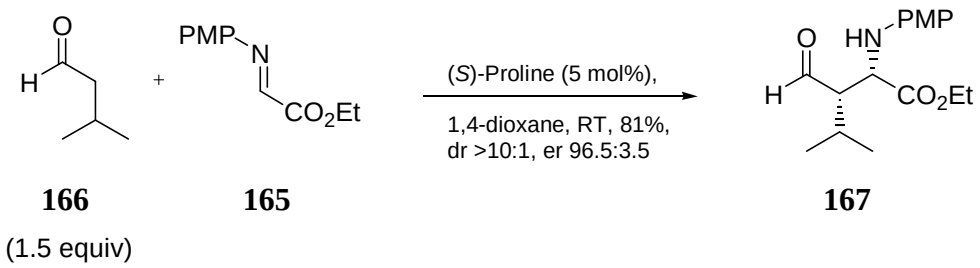
Scheme 64: Example of the first direct, highly enantioselective three-component Mannich reaction.

Only traces of the aldol product were found under the reaction conditions. This reaction provided the starting point for intense research on other organocatalytic protocols for the Mannich reaction, as it showed the use of convenient reaction conditions and a simple catalyst leading very selectively to valuable compounds. The only real drawback of the reaction is that the products are PMP-protected, and PMP is not an ideal protecting group due to the oxidative and sometimes low-yielding removal.

The same group also showed that branched ketones gave products with high *syn* selectivity (95:5).[14, 93] Similar results were published by *Barbas* and coworkers, who also demonstrated the use of preformed α-imino esters as starting materials.[94, 95] These esters are direct precursors of α-amino acids.

The *Barbas* group made an important contribution to the development of the proline-catalyzed Mannich reaction by introducing aldehydes as donors.[96] As an example, *N*-PMP-

protected α-imino ester **165** was reacted with a small excess of 1.5 equivalents of isovaleraldehyde (**166**) to yield protected α-amino acid ester **167** (Scheme 65).

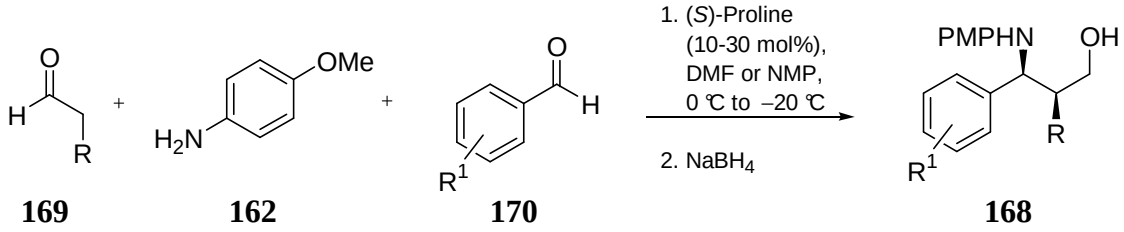


166 (1.5 equiv) **165** **167**

Scheme 65: First use of unmodified aldehydes in the proline-catalyzed Mannich reaction.

The diastereomeric ratio was higher with increased steric bulk on the aldehyde. It was noted that some products epimerized upon purification by column chromatography.

The development of a three-component, proline-catalyzed cross-Mannich reaction of two unmodified aldehydes and *para*-methoxyaniline (**162**) was reported independently by the groups of *Hayashi*,[97] *Barbas*,[98] and *Córdova*.[99] While the three methods differ slightly, all used dimethylformamide or *N*-methylpyrrolidinone as solvent and employed a temperature range of 0 °C to –20 °C. In many cases the products were reduced *in situ* to the corresponding β-amino alcohols **168** (Scheme 66).

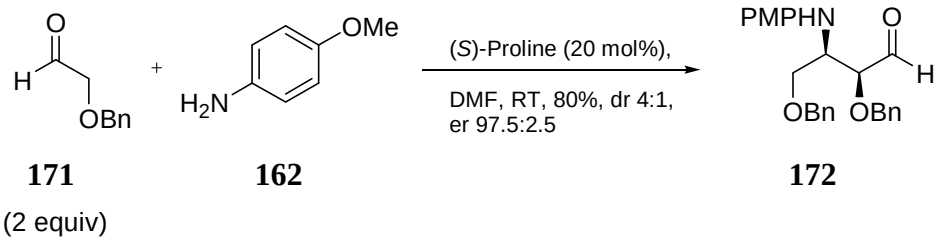


169 **162** **170** **168**

Scheme 66: Enantioselective three-component cross-Mannich reaction with unmodified aldehydes.

A variety of aldehydes **169** could be employed as donor. The reactions proceeded with good selectivity. Diastereomeric ratios were typically >95:5, and only very few examples had enantiomeric ratios below 95:5. In addition, the reactions gave good to high yields (70-90%) in most cases. While aromatic aldehydes **170** were mostly used as acceptors, *Barbas* also reported the self-Mannich reaction between two aliphatic aldehydes. The products were generally formed with lower selectivities, with diastereomeric ratios around 5:1 and enantiomeric ratios ranging from 90.5:9.5 to 93.5:6.5. The product derived from isovaleraldehyde (**166**) as the bulkiest aldehyde in this screening was formed with an er of only 59:41.

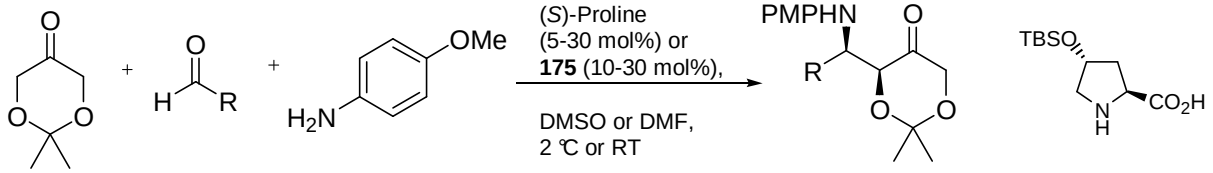
A later study focused on the use of benzyl-protected glycolaldehyde **171** as both donor and acceptor. The reaction provides access to amino-tetrose **172** in one step (Scheme 67).[100]



Scheme 67: One-step synthesis of 3-amino-tetrose **172**.

Preformed *N*-PMP-protected α-imino esters and *N*-PMP-aryl aldimines could also be employed. The enantiomeric ratio was higher than 88:12 in all cases and the yields were good, but the diastereoselectivity was low, and the ratio of diastereoisomers was typically between 1:1 and 7:1.

The organocatalytic entry to amino sugars *via* the Mannich reaction has been broadened by the groups of *Córdova*,[101] *Westermann*,[102] and *Enders* [103] with the use of protected dihydroxyacetone **173** (Scheme 68).



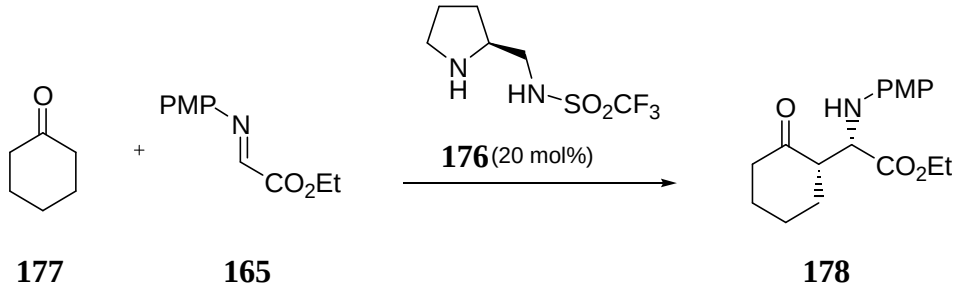
Scheme 68: Synthesis of aminoketoses through Mannich reaction.

The yields of amino sugars **174** were typically found to be good to high, and both enantio- and diastereoselectivities were high, too. The group of *Westermann* used preformed imines, while both *Córdova* and *Enders* developed three-component reactions. Moreover, *Enders* reported TBS-protected 4-hydroxyproline (**175**) to be a superior catalyst due to the better solubility.

It can be seen from the literature reviewed so far that proline has emerged as a catalyst of broad utility for the Mannich reaction. Apart from its high selectivity, easy handling, and non-toxicity, it has the additional advantage of being cheap and available in both enantiomeric forms. However, several researchers have been interested in finding different catalysts. *List* [93] and *Barbas* [98] have researched pyrrolidine-derived catalysts for the reaction of ketones and aldehydes in the Mannich reaction, but proline remained the catalyst of choice. *Córdova*

screened acyclic amino acids such as alanine or serine, which also catalyzed the Mannich reaction with good selectivities.[104]

Wang and coworkers disclosed the use of pyrrolidine-sulfonamide **176** as an alternative to proline.[105] As an example, it was used in the reaction of cyclohexanone (**177**) with **165** in protic and aprotic solvents with yields varying from 76% to 90% (Scheme 69).

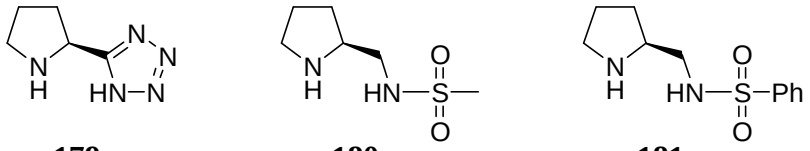


177 **165** **178**

Scheme 69: Pyrrolidine-sulfonamide **176** as an alternative catalyst to proline.

Product **178** was obtained with high selectivity in all cases, with enantiomeric ratios of >98.5:1.5 and diastereomeric ratios of >95:5 in favor of the *syn* product.

Ley chose the same reaction (Scheme 69) to evaluate catalysts **179**, **180**, and **181** (Scheme 70).[106]



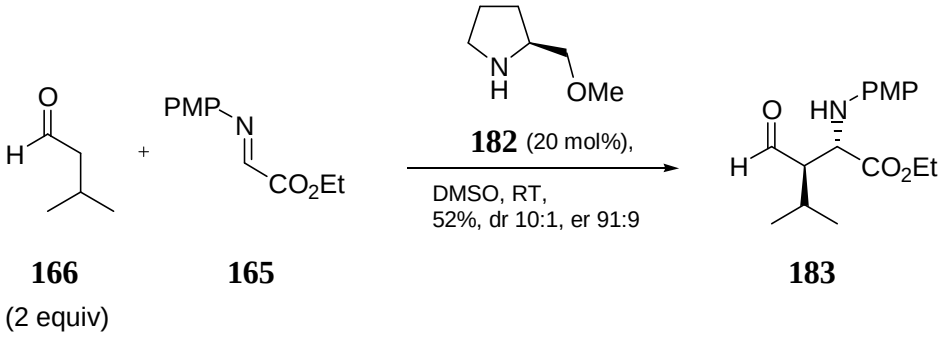
179 **180** **181**

Scheme 70: Improved catalysts for the Mannich reaction.

Ley's survey focused mainly on the use of less polar solvents. While proline-catalysis is usually conducted in highly polar solvents such as DMSO or DMF due to the low solubility of proline in less polar solvents, the new catalysts were found to be efficient even in DCM or THF, and product **178** was obtained in all cases with diastereomeric ratios of >95:5 and with high enantiomeric ratios of >97.5:2.5 in most cases. It was furthermore demonstrated that even a catalyst loading of only 1 mol% of **179** was enough to catalyze the reaction efficiently and without loss of enantioselectivity.

anti Selective enamine catalysts

The first *anti* selective organocatalytic Mannich reaction was published by *Barbas* in 2002.[107] 20 mol% of (*S*)-2-methoxymethylpyrrolidine (**182**) served as catalyst in a reaction that is exemplified by the reaction of **166** and **165** to yield **183** (Scheme 71).

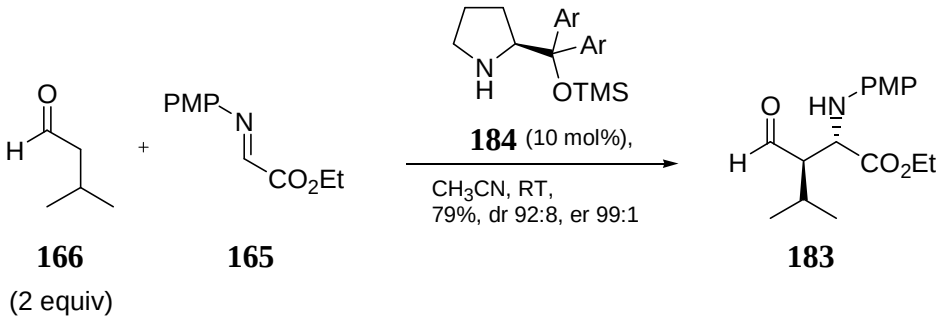


166 (2 equiv) **165** **183**

Scheme 71: First *anti* selective organocatalytic Mannich reaction.

Different aldehydes were employed in the initial screening. The diastereoselectivity was typically higher than 90:10, but when a very small aldehyde like *n*-butanal was used, it dropped to 1:1. Moreover, the yields only ranged from 44-78% and the enantioselectivity was mostly between 87:13 and 91:9.

Jørgensen's group later used α,α-diarylprolinol silyl ether **184** as catalyst in the same reaction (Scheme 72).[108]

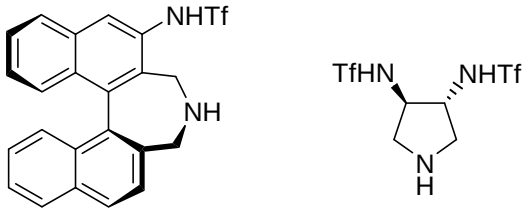


166 (2 equiv) **165** **183**

Scheme 72: α,α-Diarylprolinol silyl ether **184** as catalyst for the *anti* selective Mannich reaction. Ar = 3,5-$(CF_3)_2C_6H_3$.

While the diastereoselectivity was not improved much, both the yield and enantioselectivity were significantly better with **184**. In addition, it could also be used for small, unbranched aldehydes such as propionaldehyde without significant loss of selectivity.

Maruoka introduced a new motif to chiral enamine-based catalysts with **185**.[109] Unlike proline and its derivatives, the catalyst is based on a seven-membered ring. The chirality is derived from the BINOL-backbone.



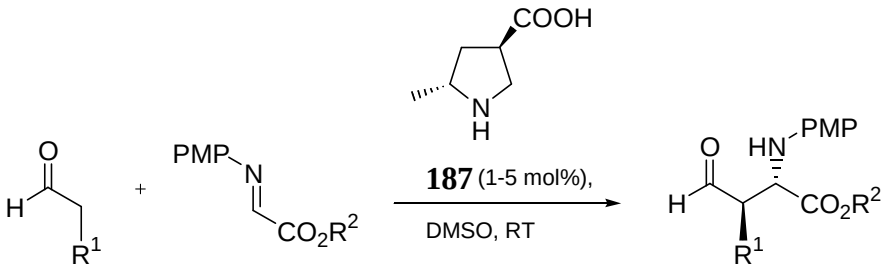
185 **186**

Scheme 73: Axially chiral BINOL-derived catalyst **185** and C_2-symmetric catalyst **186** developed by *Maruoka*. Tf = SO_2CF_3.

The catalyst was tested in the same reaction as *Barbas*' and *Jørgensen's* (Scheme 71 & Scheme 72), but with 1,4-dioxane as the solvent. 82-99% yield was achieved, but a bulky aldehyde gave significantly lower yield (42%). The enantiomeric ratios were between 98.5:1.5 and >99.5:0.5, while the dr ranged between 11:1 and >20:1. **185** also proved to be superior with regard to the activity, as it could be used with catalyst loadings of 0.2 to 5 mol%.

To obtain a more reactive catalyst for bulky aldehydes, the same group synthesized C_2-symmetric catalyst **186**.[110] Higher yields were indeed obtained, and the catalyst was also suitable to activate ketones. While the diastereoselectivity remained as high as before, the enantiomeric ratios were a little lower as compared to **185** (95:5 to 97.5:2.5).

From a combined effort of computational and synthetic chemistry *Barbas* and *Houk* disclosed the highly selective catalyst **187**.[111] In the same test reaction as in all other cases discussed in this section, aldehydes **169** were reacted with different *N*-PMP-imino esters **188** (Scheme 74).



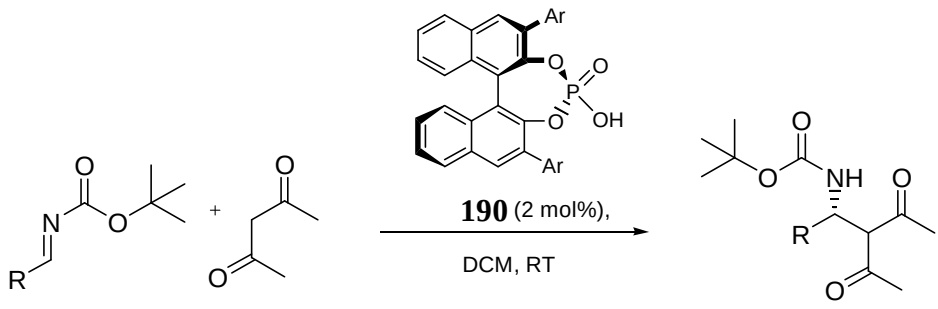
169 (2 equiv) **188** **189**

Scheme 74: Designer amino acid **187** as highly active, *anti* selective catalyst.

Products **189** were obtained in excellent diastereoselectivities ranging from 94:6 to 98:2 and enantioselectivities from >98.5:1.5 to >99.5:0.5. Moreover, the reaction proceeded fast, gave good to very high yields of 54-92%, and used small amounts of catalyst.

Brønsted acid catalysis

Uraguchi and *Terada* used chiral BINOL-derived phosphoric acid **190** as catalyst in a direct Mannich reaction between different aromatic *N*-Boc-imines **159** and acetylacetone (**191**) (Scheme 75).[112]



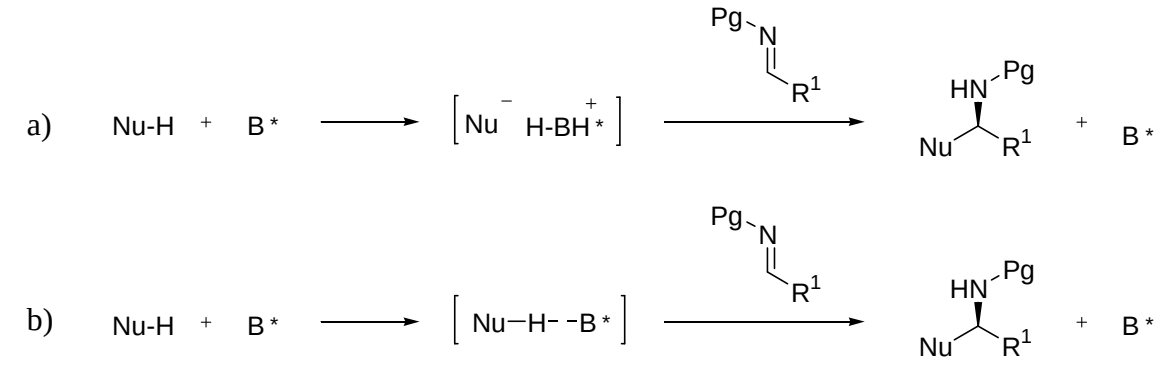
159 **191** **192**

Scheme 75: Chiral phosphoric acid **190** as catalyst for the direct asymmetric Mannich reaction of *N*-Boc-imines. Ar = 4-(β-naph)-C_6H_4.

Products **192** were obtained in very high yields (>90%) and excellent enantiomeric excesses (er 95:5 or higher). The synthesis of an *N*-Boc-protected α-amino acid ester from one of the products in four steps and an overall yield of 46% was exemplified.

Brønsted base catalysts

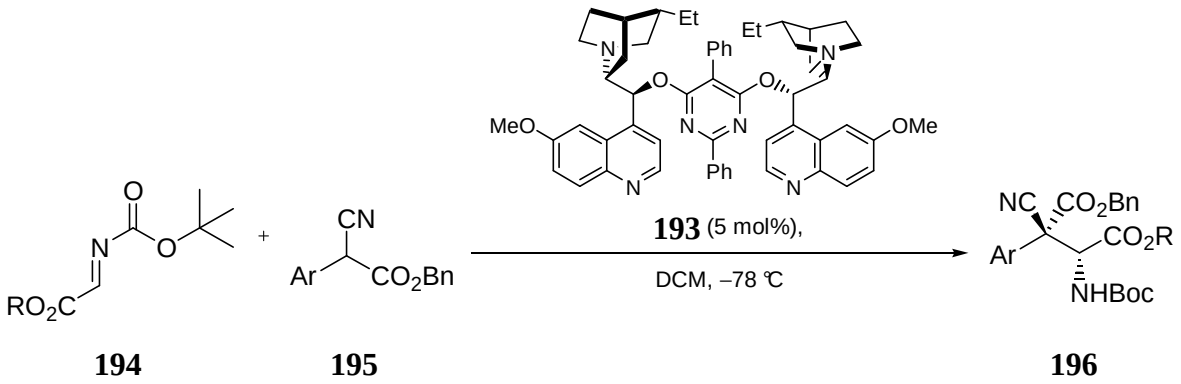
Brønsted bases can be used as catalysts with sufficiently acidic nucleophiles. After deprotonation by the Brønsted base the nucleophile can attack the imine, and the developing negative charge on the imine nitrogen will abstract a proton from the Brønsted base, thereby completing the catalytic cycle (Scheme 76a). The protonated base can form an ion pair with the deprotonated nucleophile. If the base is chiral, the chirality of the ion pair can be transferred to the product.



Scheme 76: General schemes for the Brønsted base catalyzed Mannich reaction.

Another possibility is that the base activates the nucleophile *via* a hydrogen bond (Scheme 76b).

Jørgensen used commercially available hydroquinidine-2,5-diphenyl-4,6-pyrimidinediyl diether $(DHQD)_2Pyr$ (**193**) as a chiral base in a reaction of *N*-Boc-protected imino esters **194** with different benzyl α-aryl cyanoacetates **195** (Scheme 77).[113]



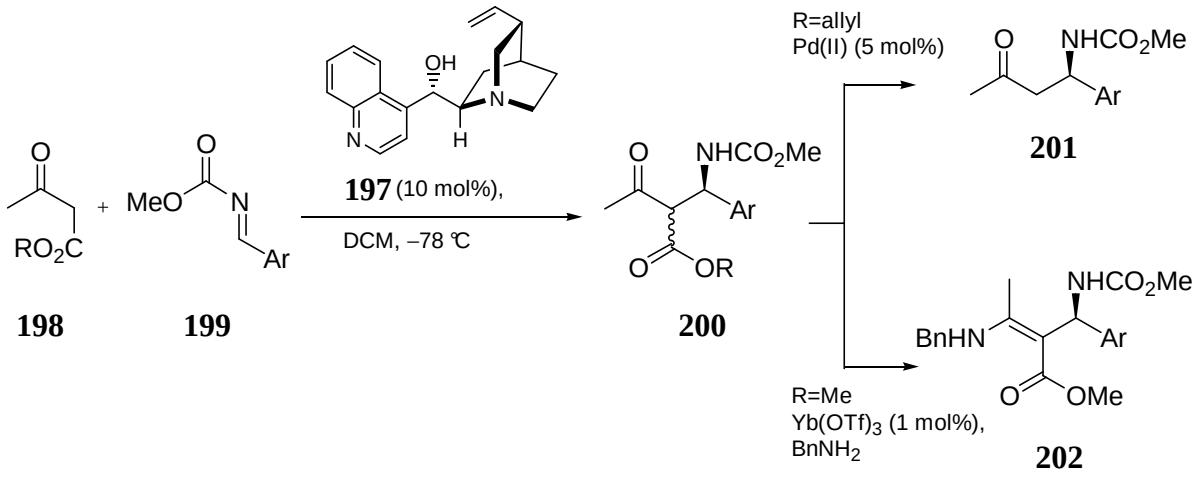
194 **195** **196**

Scheme 77: $(DHQD)_2Pyr$ (**193**) as Brønsted basic catalyst.

Very good yields between 89% and 99% of products **196** were reported. The reaction also proceeded in a highly enantioselective fashion with enantiomeric ratios ranging from 95.5:4.5 to 99:1, but the diastereoselectivity was only moderate and ranged from 80:20 to 98:2. Nonetheless this method allows for a very efficient entry into quaternary stereocenters with excellent enantiomeric excesses.

The idea of cinchona-alkaloid derived catalyst **193** was taken back to the parent compound cinchonine (**197**) by *Schaus* and coworkers.[114] It was found that the reaction of β-keto esters **198** and acyl imines **199** led to products with high yield and high enantiomeric purity, but

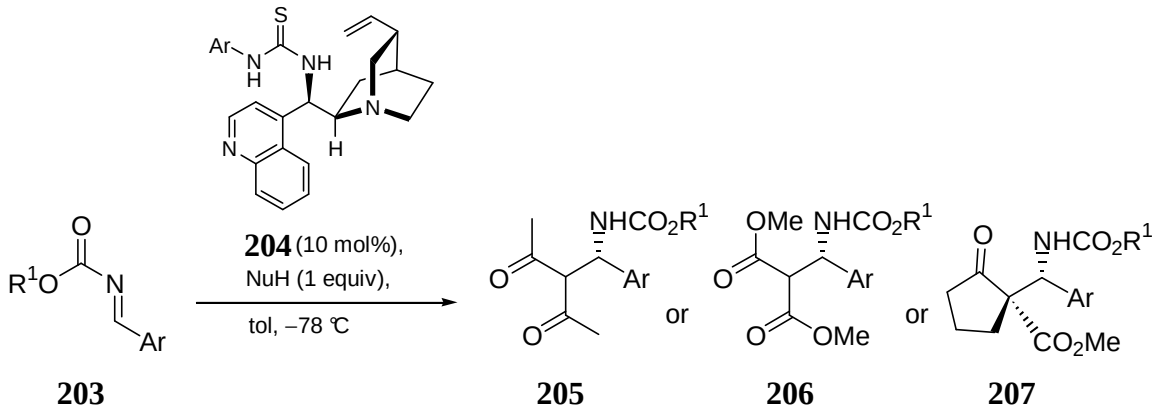
often without diastereoselectivity. The initial products **200** were therefore transformed to products **201** or **202** depending on the ester functionality (Scheme 78).



Scheme 78: Cinchonine (**197**) catalyzing the reaction of acyl imines with β-keto esters.

The scope was extended in a subsequent publication to cyclic β-keto esters and β-diketones.[115] The corresponding quaternary products were obtained in excellent selectivities for both enantiomeric ratios and diastereomeric ratios of up to 99.5:0.5 and with almost quantitative yield.

Dixon used the combination of a cinchona alkaloid as a chiral base and a thiourea moiety to activate *N*-Boc- and *N*-Cbz-imines **203** towards the addition of β-diketones, malonates, and cyclic β-keto esters (Scheme 79).[116]

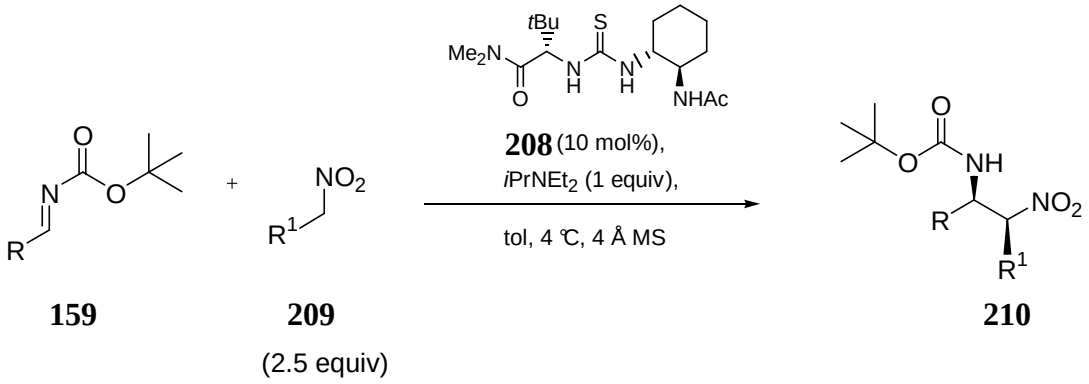


Scheme 79: Combined thiourea/chiral base catalyst **204**. Ar = 3,5-$(CF_3)_2C_6H_3$.

Catalyst **204** gave the corresponding products **205**, **206**, and **207** usually in good to high enantiomeric ratios and in very good yields.

Thiourea catalysis

Thiourea-based catalyst **208** was used in the direct Mannich reaction of nitroalkanes **209** and *N*-Boc-imines **159** (Scheme 80).[117]



Scheme 80: Thiourea-catalyzed, *syn* selective Mannich reaction.

The products of this reaction are β-amino nitroalkanes **210** that were obtained with high yields and enantiomeric ratios generally above 96:4, but with varying diastereoselectivities between 2:1 and 16:1.

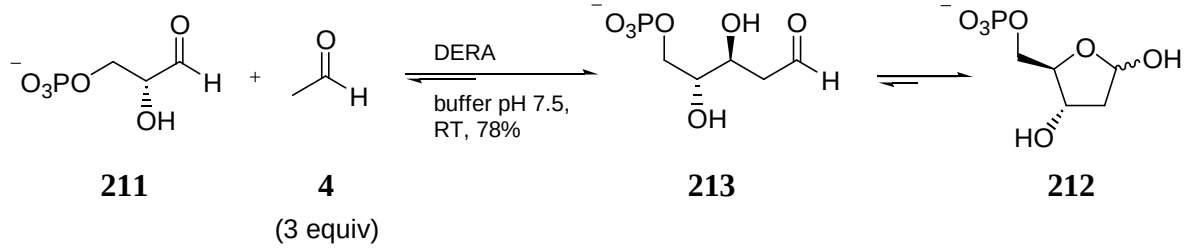
3.3. Acetaldehyde in asymmetric synthesis

Acetaldehyde is a compound of potentially high value for synthetic chemistry. It is very cheap and accessible in large quantities. In chemical terms, it is a two-carbon donor, at the 2-position through its enol form as well as at the 1-position through umpolung, but also a good acceptor because of the carbonyl group. Moreover, it is very reactive because little steric hindrance occurs due to the lack of substituents.

Because of the problems associated with the high and ambivalent reactivity acetaldehyde has not found widespread use as donor in asymmetric catalytic reactions as of yet. All of the few known examples are aldol reactions. This chapter reviews the approaches to the use of acetaldehyde in asymmetric catalysis.

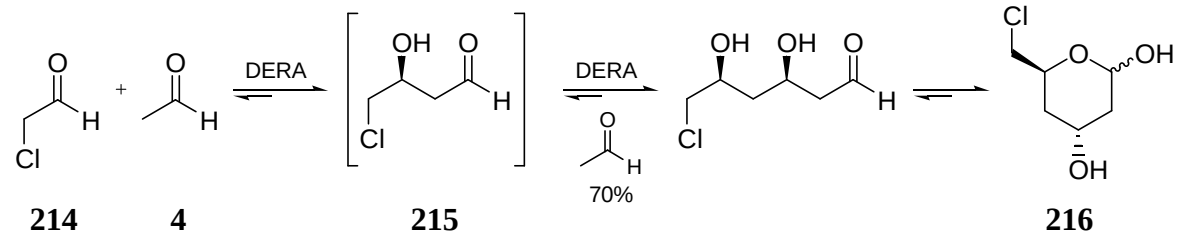
3.3.1. Biocatalysis

Deoxyribose-5-phosphate aldolase (DERA) is an enzyme that catalyzes the aldol reaction between two aldehydes,[118] and also catalyzes aldol reactions with acetaldehyde, for example with phosphate **211**. It was first employed to obtain 5-membered rings **212**, which are in equilibrium with the initial reaction product **213** (Scheme 81).[119]



Scheme 81: DERA-catalyzed aldol reaction with acetaldehyde as donor.

DERA was also able to catalyze the reaction between two molecules of acetaldehyde and one molecule of another aldehyde as well as the trimerization of acetaldehyde (Scheme 82).[120]

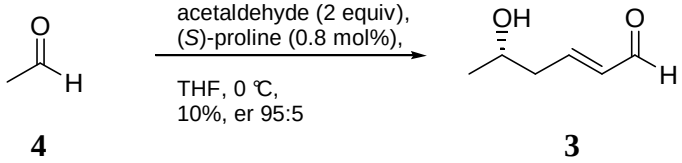


Scheme 82: Tandem aldol reaction of chloroacetaldehyde with acetaldehyde.

In the example above chloroacetaldehyde (**214**) was reacted with acetaldehyde under catalysis by DERA. The initial product **215** was again attacked by a molecule of acetaldehyde. Cyclization led to the final product **216**, which was not susceptible to further nucleophilic attack. **216** was obtained in 70% yield, but the self-aldol-aldol reaction sequence of three molecules of acetaldehyde gave the corresponding product in only 20% yield. Moreover, the reaction conditions employed, stirring for 6 d at room temperature under argon and in the dark, are clearly not optimal.

3.3.2. Organocatalysis

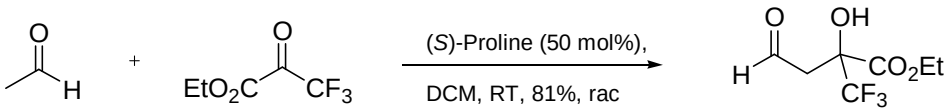
Two publications have been dealing with acetaldehyde as donor in organocatalytic reactions. *Barbas* and coworkers observed product **3** in an aldol reaction/Mannich-type reaction sequence (Scheme 83).[20]



Scheme 83: First organocatalytic, highly enantioselective reaction of acetaldehyde.

This example showed that proline is able to induce high stereocontrol in the reaction of even the smallest enolizable aldehyde. However, it was not possible to stop the reaction at the aldol stage, and a trimerization was observed. The low yield is another drawback of this reaction.

Jørgensen found the reaction of acetaldehyde (**4**) and highly activated acceptor **217** to proceed with high yield (81%), but proline was unable to induce stereoselectivity in this case (Scheme 84).[21]



4 **217** **5**

Scheme 84: High-yielding, proline catalyzed aldol reaction of acetaldehyde.

A high load of proline was necessary to obtain good conversion. Even though **5** was obtained as racemate, this reaction showed that the reactivity of acetaldehyde can indeed be controlled as the major product was the result of the monoaddition.

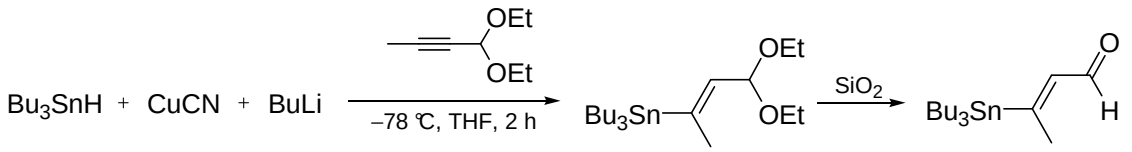
4. Results and discussion

4.1. Heck reactions of α,β-unsaturated aldehydes

A number of palladium-mediated reactions have the potential to give α,β-unsaturated aldehydes or acetals from their respective precursors. It was initially assessed which reaction was the most suitable and the conditions were then optimized. The efficiency of this new method was demonstrated in the shortest asymmetric synthesis of Florhydral® reported to date.

4.1.1. Orienting experiments to compare the different palladium-mediated reactions available

The utilization of the Heck reaction in the synthesis of α,β-unsaturated aldehydes has been discouraged in the years after the discovery of this reaction by one of its pioneers, *Richard F. Heck* himself, when he found that "[r]eactions carried out between bromobenzene and acrolein, crotonaldehyde, and 3-buten-2-one at 60 to 100 °C […] never contained more than 5-10% of the 3-phenylcarbonyl product".[121] This is potentially due to polymerization reactions.
Alongside the investigation of the Heck reaction for the desired transformation other palladium-mediated carbon-carbon bond forming reactions were evaluated, most notably the Stille coupling. For the Stille coupling it was necessary to synthesize a suitable precursor, which was possible in a two-step sequence described by *Lipshutz* [122] and *Quintard* [123] in 80% yield (Scheme 85).

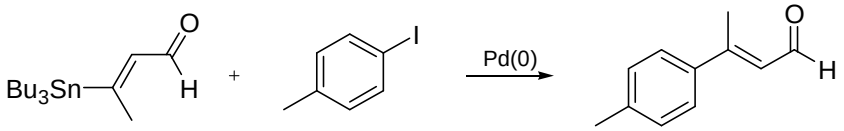


218

Scheme 85: Synthesis of tin-precursor **218**.

218 was tested in a reaction with 4-iodotoluene (**219**), but the yields of α,β-unsaturated aldehyde **8** obtained under different conditions were poor (Table 1).

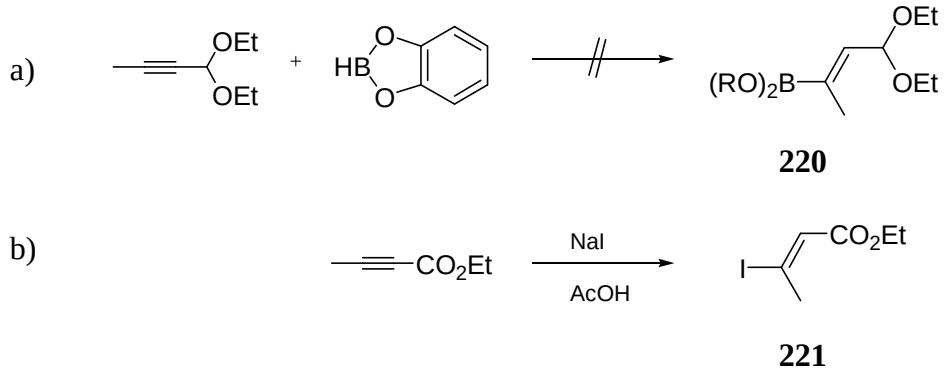
Table 1: Stille coupling of **226**.



218 **219** **8**

Entry	**219** (equiv)	CuI (equiv)	Additive (equiv)	$Pd(PPh_3)_4$	Tempera-ture	Reaction time	Yield
1	2	1	Et_3N (1.0)	4.5 mol%	RT	12 h	12%
2	0.9	0.1	CsF (2.6)	6.1 mol%	45 °C	2.5 h	37%
3	1.5	0.2	CsF (4.0)	4.5 mol%	42 °C	2 h	24%

The synthesis of precursors for the Suzuki reaction failed completely (**220**, Scheme 86a). Vinyl iodide **221**, which could have been used with different coupling partners, was accessible (Scheme 86b), but was found to be very unstable. This route was therefore not pursued further, since the project should lead to a bench-stable aldehyde precursor.

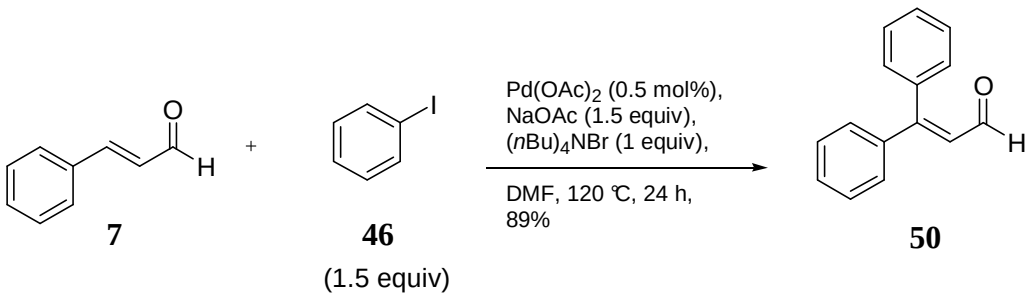


220

221

Scheme 86: Syntheses of precursors for palladium-mediated reactions.

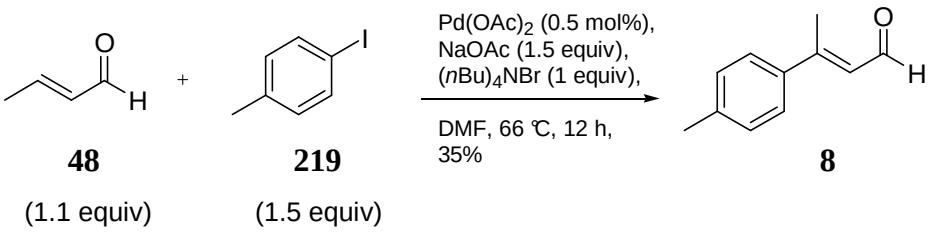
While these studies were conducted, *Aggarwal* had reported the synthesis of 3,3-diphenylacrylaldehyde (**50**) through Heck reaction of cinnamaldehyde (**7**) and phenyliodide (**46**) (Scheme 87).[49]



7 **46** (1.5 equiv) **50**

Scheme 87: Synthesis of **50** reported by *Aggarwal*.

The use of similar conditions in the Heck reaction of crotonaldehyde (**48**) (Scheme 88) led to results comparable to those of the best Stille conditions (Table 1). The lower reaction temperature was chosen to account for the lower boiling point of **48**.



48 (1.1 equiv) + **219** (1.5 equiv) → **8**

Scheme 88: Heck reaction of crotonaldehyde using modified *Aggarwal* conditions.

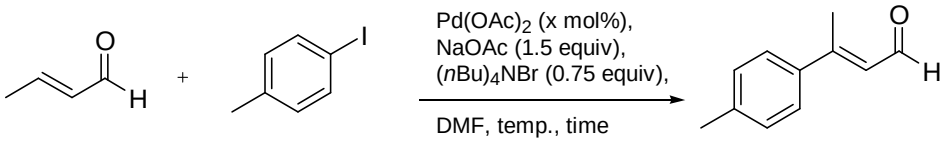
The orienting experiments showed that the synthesis of aldehyde precursors for palladium mediated reactions was only possible in the case of the tributyl-tin derivative **218**, thereby ruling out reactions other than the Stille and the Heck coupling for the desired transformation. However, in addition to the necessity to synthesize **218**, the Stille coupling suffers from the use and release of highly toxic trialkyl-tin compounds, and is therefore not an ideal reaction. With the results for the Heck and the Stille reaction in terms of yield being rather similar, the Heck reaction was chosen for development because of the inherent advantages of using unmodified aldehydes and much less harmful chemicals.

4.1.2. Optimization of the reaction conditions

The initial change in conditions as compared to *Aggarwal* was that owing to the abundance of crotonaldehyde a twofold excess was used for further reactions. With less than two equivalents the reaction became slower, while three or more equivalents did not lead to increased yield, but rather increased side-product formation. Moreover, crotonaldehyde always remained in the reaction mixture after the reaction was finished. This shows that polymerization and loss of crotonaldehyde does not lead to decreased yields, as there is always crotonaldehyde available for the arylation.

Catalyst loading and temperature were screened next (Table 2).

Table 2: Screening of temperature and catalyst loading.



48 (2 equiv) **219** **8**

Entry	Catalyst loading	Temperature	Reaction time	Conversion[a] based on **219**
1	1.3 mol%	66 °C	24 h	~ 70%
2	1.3 mol%	80 °C	24 h	~ 90%
3	1.3 mol%	90 °C	12 h	>90%
4	1.0 mol%	90 °C	24 h	full
5	1.5 mol%	90 °C	12 h	>90%
6	2.0 mol%	90 °C	12 h	full

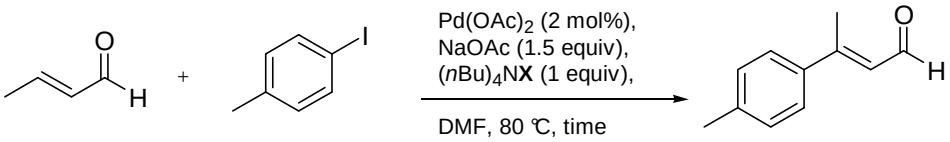
a) Determined by GC. Samples taken after 12 and 24 h.

The reaction temperature was limited to a maximum of 90 °C in this screening because of the low boiling point of crotonaldehyde (104 °C).

It was found that the reaction proceeds faster at higher temperatures and the conversion was also better (entries 1 - 3). The screening of different catalyst loadings revealed that with 2 mol% a reasonable time to achieve full conversion was achieved (entry 6).

Aggarwal employed a modification of *Jefferies*' phase-transfer conditions,[124] which were developed to allow for the use of inorganic bases rather than the amines originally employed by *Heck*. Since in the original publication tetrabutylammonium chloride was used and a variety of other counteranions are available the effect of the anion was screened (Table 3). The reactions were run at 80 °C to better observe any accelerating effect.

Table 3: Effect of the tetrabutylammonium counteranion.



48 (2 equiv) **219** **8**

Entry	**X**	Reaction time	Conversion[a] based on **219**	Side product[a]
1	Br^-	12 h	~ 80%	no
2	Cl^-	4 h	full	no
3	I^-	12 h	~ 70%	no
4	OAc^-	4 h	full	predominant
5	*p*-Tol-SO_3^-	4 h	>90%	considerable
6	$H_2PO_4^-$	12 h	~ 80%	much
7	NO_3^-	4 h	>90%	considerable
8	BF_4^-	8 h	>90%	considerable
9	HSO_4^-	12 h	~ 50%	considerable

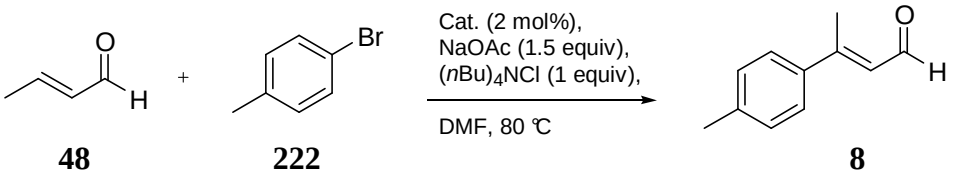
a) Determined by GC. Samples taken after 4, 8, and 12 h.

It was revealed that the halides gave a cleaner reaction, with chloride increasing the reaction rate much more than bromide and iodide (entries 1-3). In all other cases, an unidentified aromatic side product was formed, which even became the predominant product when acetate or dihydrogenphosphate were used (entries 4 & 6).

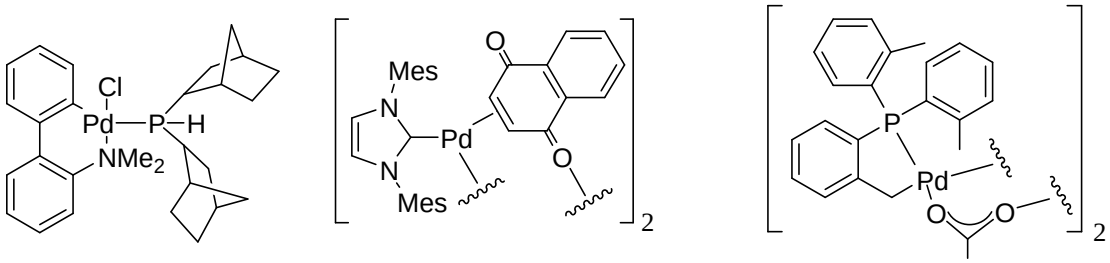
At this stage **8** was formed in a yield of 75-80% at full conversion and with a ratio of *E*/*Z* of 2.8:1. However, the corresponding reaction with 4-bromotoluene (**222**) did not go to full conversion. The following optimizations were therefore undertaken with **222** as a model substrate for bromoarenes (Table 4).

The initial screening was undertaken to find a more active catalyst. Palladium acetate is a good catalyst precursor as it is bench-stable and can be easily handled. However, in recent years many catalysts for palladium mediated reactions became commercially available. A variety has been tested for the transformation of **222** under the conditions developed so far (Table 4).

Table 4: Catalyst screening.



48 (2 equiv) **222** **8**



223 **224** **52**

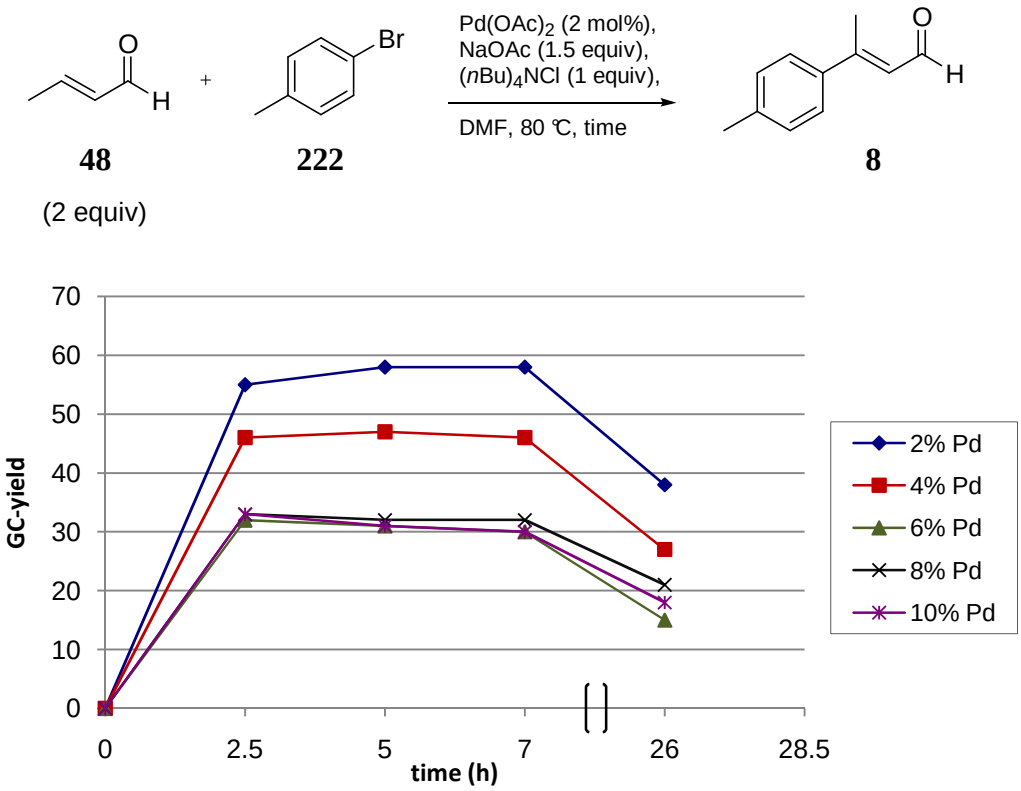
Entry	Catalyst	Reaction time	Yield[a]
1	$Pd(OAc)_2$	3 h	55%
2	$Pd(PPh_3)_4$	5 h	0%
3	$Pd(P(t\text{-}Bu)_3)_2$	1.5 h	58%
4	$Pd(P(Cy)_3)_2$	4 h	9%
5	$Pd(P(Cy)_3)_2Cl_2$	4 h	0%
6	$Pd_2dba_3/P(furyl)_3$	3 h	5%
7	**223**	5 h	2%
8	**224**	5 h	42%
9	**52**	3 h	42%

a) Determined by GC.

The catalyst screening revealed that only bis(tri-*tert*-butylphosphine) palladium(0) (entry 3) gave results comparable to palladium acetate. Due to the much higher sensitivity of this catalyst and the prerequisite to handle it under argon it was decided to continue the optimization process with palladium acetate.

The effect of the catalyst loading on the yield was also studied in the case of bromoarenes (Scheme 89), and samples were taken after 2.5, 5, 7, and 26 h. However, it was found that higher amounts of catalyst actually lead to lower yields. This observation is probably due to

the precipitation of catalytically inactive palladium black, which is more likely to occur when the catalyst concentration is higher.

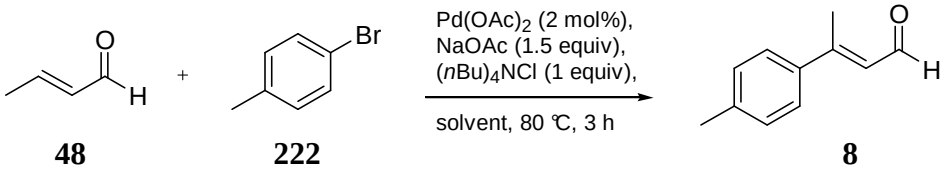


Scheme 89: Development of the yield over time with different amounts of palladium acetate.

It also turned out that the reaction was complete in much shorter time than expected and the product decomposes upon prolonged heating. The addition of further palladium acetate after 3 h reaction time had no effect on the yield.

It was finally tried to increase the yield by screening some other solvents commonly employed in Heck reactions (Table 5).

Table 5: Screening of solvents.



48 (2 equiv) **222** **8**

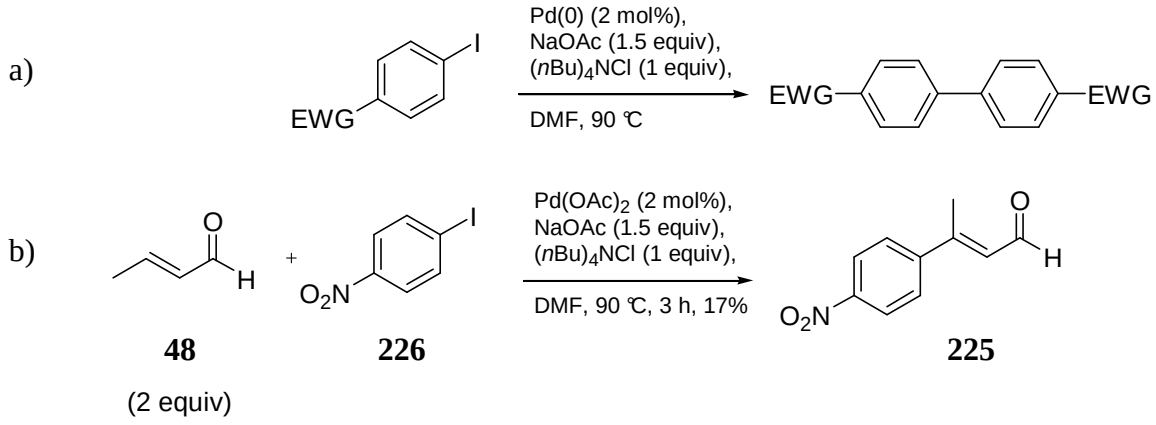
Entry	Solvent	Yield[a]
1	DMF	55%
2	DMAc	57%
3	NMP	68%

a) Determined by GC.

Slight improvement was observed when DMAc was used, but the yield was significantly better with NMP, which was therefore chosen as solvent for the reaction.

Finally the solvent was deoxygenated before the reaction, and the reactions were run under argon. While this procedure increased the yields slightly by about 2% and was subsequently employed, the reaction can also be run without using protective gas techniques.

A problem observed with the conditions employed so far was that arenes substituted with an electron withdrawing group (EWG) did not yield primarily the desired Heck products, but rather gave Ullmann-type homocoupling products (Scheme 90a). As a result of this competing reaction pathway, the yields of desired products such as **225** produced from 1-iodo-4-nitrobenzene (**226**) were very low, even when the best conditions found so far were employed (Scheme 90b).



48 (2 equiv) **226** **225**

Scheme 90: Homocoupling (a) and best results for an electron-deficient iodoarene (b).

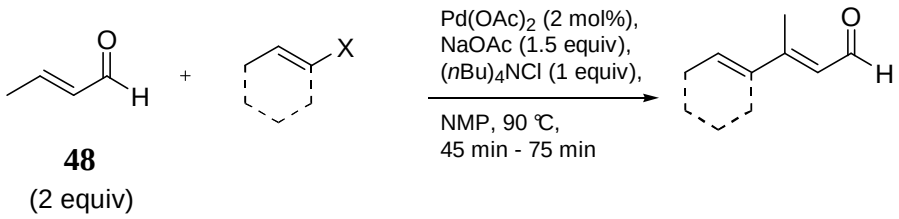
The reaction was also tested with all catalysts given above (Table 4), but in no case was any yield exceeding 17% of the desired product found.

It was assumed that bromides or even chlorides as leaving groups would be beneficial to use, but no significant enhancement of yields was observed with bromides, while chlorides proved to be completely unreactive. It was finally tested whether the slow addition of aryl bromide or aryl iodide to a solution of crotonaldehyde and palladium acetate would drive the reaction towards the Heck product, but also in these cases no GC-measured yield exceeding 15% was measured.

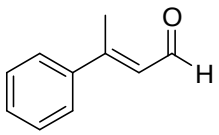
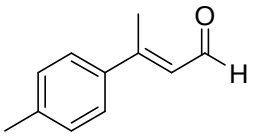
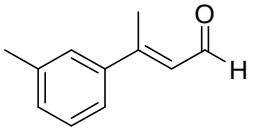
4.1.3. Substrate scope and limitations

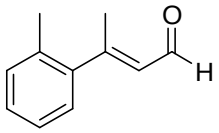
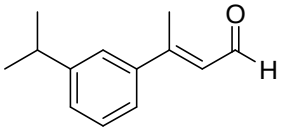
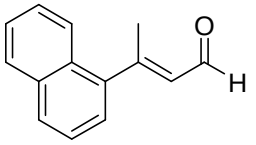
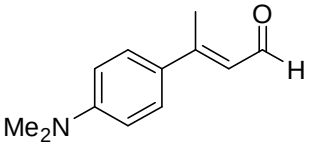
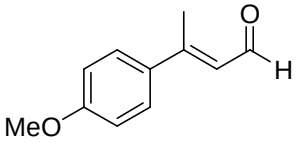
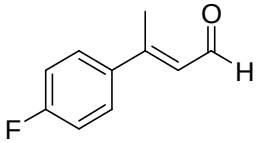
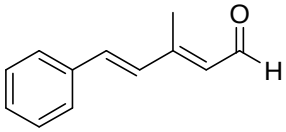
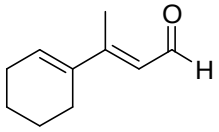
With the optimal conditions in hand the scope with regard to different aryl and vinyl bromides and iodides was explored in the reaction with crotonaldehyde.

Table 6: Substrate scope.



48
(2 equiv)

Entry	Product	Yield (X=Br)	Yield (X=I)	*E*/*Z*[a]
1	 **16**	50%	68%	2.8:1
2	 **8**	70%	77%	2.8:1
3	 **227a**	70%	70%	3.0:1

Entry	Product	Yield (X=Br)	Yield (X=I)	*E*/*Z*[a]
4	 **227b**	46%	55%	1:2.9
5	 **227c**	65%	–[b]	2.5:1
6	 **227d**	71%	43%	1:2.1
7	 **227e**	76%	87%	4:1[c]
8	 **227f**	73%	92%	3.3:1
9	 **227g**	40%	44%	3.0:1
10	 **227h**	74%	60%	1.7:1
11	 **227i**	44%	–[b]	6.7:1

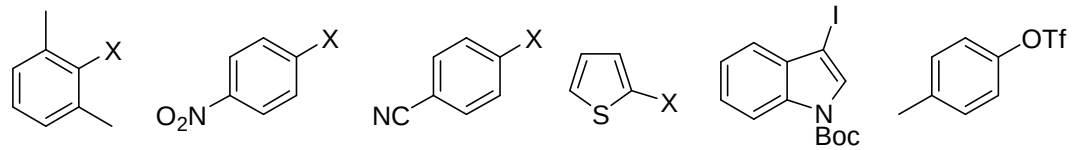
a) Determined by GC analysis of the crude reaction mixture; b) not attempted; c) determined by ^{1}H-NMR after column chromatography.

The reaction was initially evaluated with regard to the substitution on the arene. Both *para* and *meta* substitution gave very good yields (entries 2 & 3), while they were slightly lower with a substituent in *ortho* position (entry 4). Moreover, the *ortho* product was obtained with a higher preference for the *Z*-isomer, which was also found in the case of 1-naphthyl halides (entry 6). If both *ortho* positions were occupied in the starting material the reaction yielded almost no product at all (Scheme 91, **228**). In contrast to that, increased steric bulk in *meta* position was well tolerated (entry 5).

With regard to the electronic properties of the aryl halide it was found that the reaction proceeds better with electron-rich substituents (entries 7 & 8), which also give better *E*/*Z*-ratios. This also explains why the least sterically hindered phenylbromide gave lower yields as compared to *meta*- and *para*-tolylbromide (entries 1-3). With increasing electron-with-drawing properties of the arene the yield decreases (entry 9).

It was furthermore possible to employ vinyl halides as substrates (entries 10 & 11). The yield was found to be only moderate for **227i**, but it showed the best *E*/*Z* ratio observed in the study.

The reaction limitations are shown below (Scheme 91). Apart from sterically too hindered substrates (**228**) and electron-poor aromatic compounds (**229**, **230**) the reaction did also not proceed with 2-halothiophenes **231**, which also predominantly gave the homocoupling product, and indole-derivative **232**, which was found to be unstable during the preparation and decomposed very quickly under the reaction conditions.



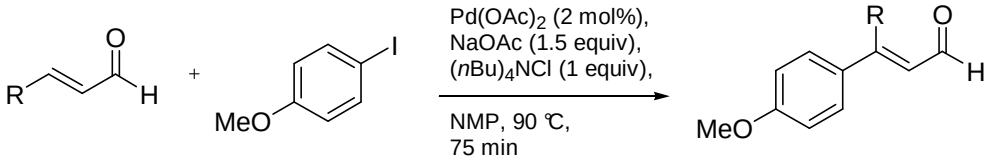
228 **229** **230** **231** **232** **233**

Scheme 91: Substrates that could not be coupled successfully or in reasonable yields. X = Br, I.

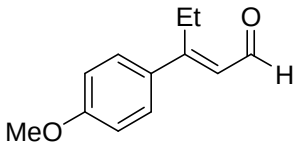
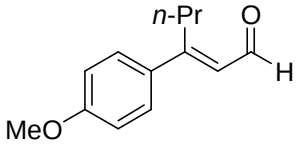
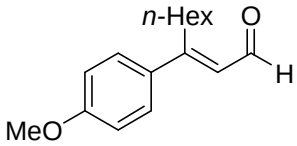
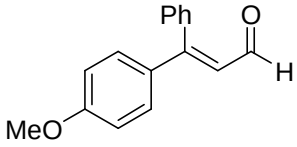
Triflate **233** reacted very slowly as compared to bromide and iodide, with barely any conversion observed after 2 h, and still very low conversion after 5 h.

With the scope probed with regard to different halides, it was next investigated what aldehydes could be employed in the reaction with 4-iodoanisole (**234**) (Table 7).

Table 7: Scope with regard to different aldehydes.



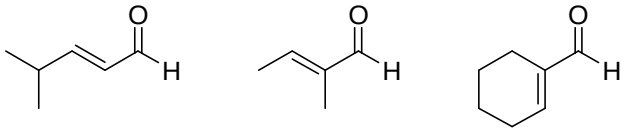
(2 equiv) **234** **235**

Entry	Product	Yield	*E*/*Z*[a]
1	 **235a**	61%	1.4:1
2	 **235b**	80%	1.6:1
3	 **235c**	65%	1.4:1
4	 **235d**	52%	1.7:1

a) Determined by GC analysis of the crude reaction mixture.

Several linear α,β-unsaturated aldehydes could be reacted in good to very good yields (entries 1-3), but the diastereomeric ratios observed were lower as compared to crotonaldehyde. It was further possible to employ aryl-conjugated cinnamaldehyde (**7**), giving the product in good yield (entry 4).

The limitation with regard to aldehydes also lies with the steric hindrance of the starting material (Scheme 92).

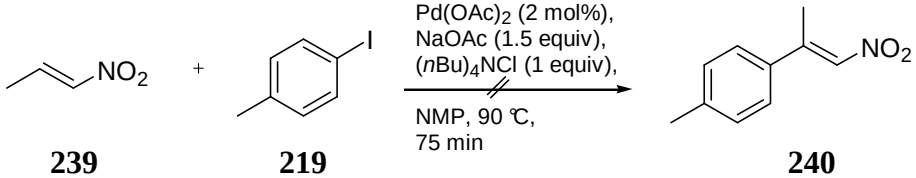


236 **237** **238**

Scheme 92: Aldehydes that could not be coupled successfully.

Using branched aldehydes like 4-methyl-2-pentanal (**236**) led to only trace amounts of the desired product being formed. The use of α-substituted aldehyde **237** as well as its fused analogue **238** also only led to trace amounts of product.

It was briefly investigated whether the conditions for the Heck reaction with crotonaldehyde could also be used to form nitro olefins. This was tested by the reaction of 1-nitropropene (**239**) with **219** (Scheme 93).



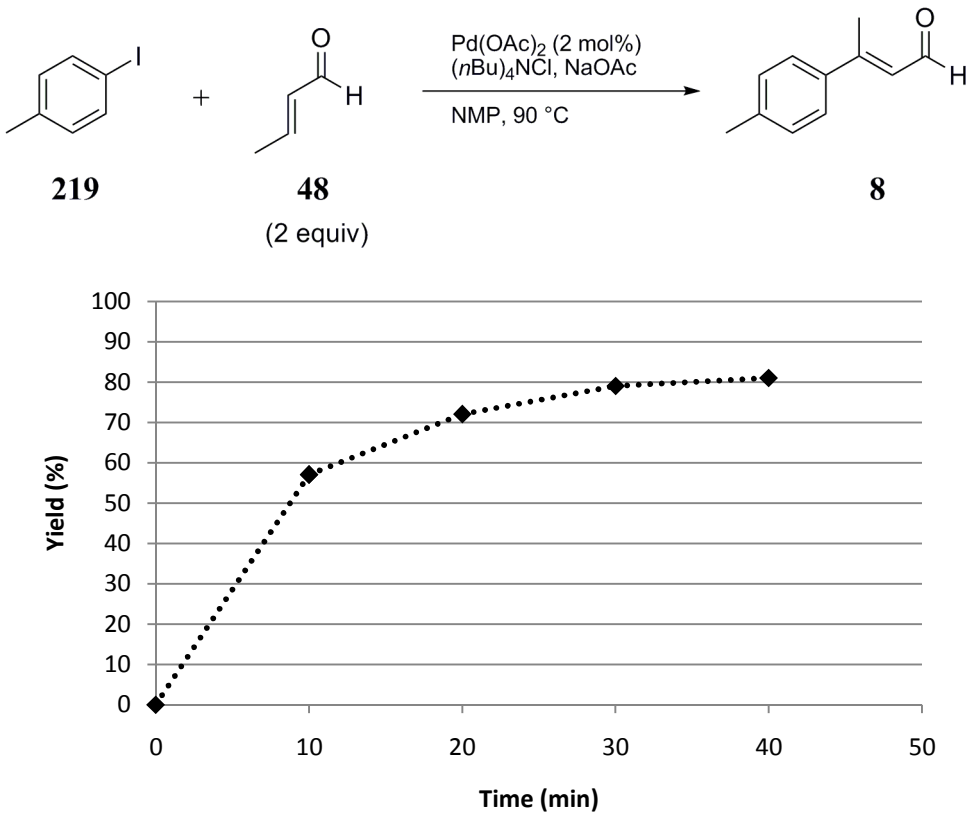
239 (2 equiv) **219** **240**

Scheme 93: Attempted extension of the method to nitro olefins.

Under the conditions employed for the Heck reaction of unsaturated aldehydes no reaction to the desired nitro olefin **240** took place.

4.1.4. Discussion

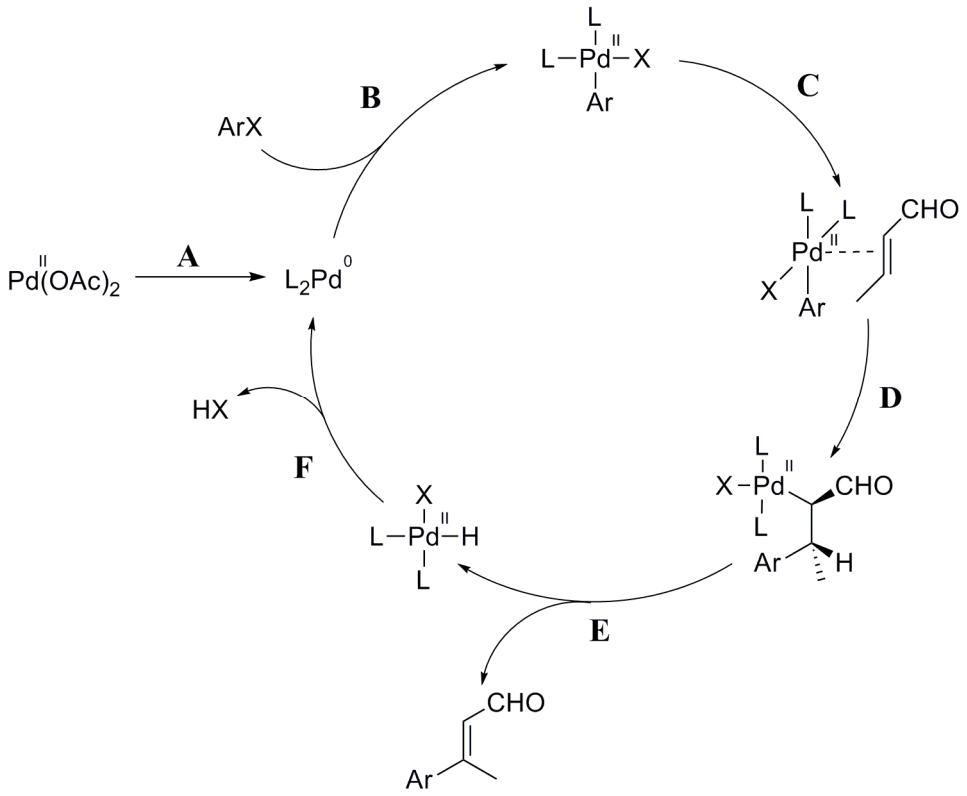
With the best conditions in hand a small kinetic study was conducted on the reaction of **219** with crotonaldehyde (**48**). Samples were taken every 10 min and the yield determined by GC is plotted over time in Scheme 94.



Scheme 94: Kinetic study of the reaction.

It can be seen from the results of this study that the reaction was finished very quickly, with most of the product already formed in the first 10 min of the reaction. The dotted line does not represent real data, as there is usually an induction period in which the active catalyst is formed, and which could not be observed on the timescale chosen for these measurements.

The mechanism of the Heck reaction is both well explored and little understood at the same time due to the multitude of reaction conditions developed so far. The outcome of the reaction often depends on the starting material, and no single catalyst or system has yet emerged that is of universal use. The mechanism given below is therefore simplified and shows the most important steps in the catalytic cycle (Scheme 95). More detailed discussions go far beyond the scope of this thesis, but can be found for example from *Beletskaya* and *Cheprakov* [125] or *Knowles* and *Whiting*.[126]

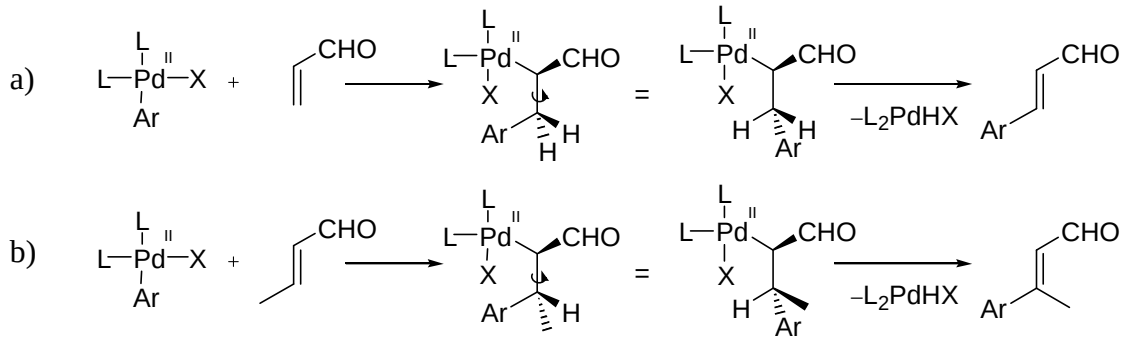


Scheme 95: Catalytic cycle of the Heck reaction.

The reaction sequence starts with the formation of the active catalyst from palladium acetate by reduction. In the absence of the common reducing agents for Heck reactions, phosphines, the reduction is likely to be brought about by the olefin, which is in turn oxidized in a Wacker-type oxidation (Step **A**). The halide then undergoes an oxidative addition to the palladium (step **B**). Coordination of the olefin on a free site of the palladium (**C**) is the prerequisite for the carbopalladation step (**D**). β-Hydride elimination (**E**) liberates the product, and the catalyst is recycled through a reductive elimination (**F**). The acid formed in this step is quenched by the added base.

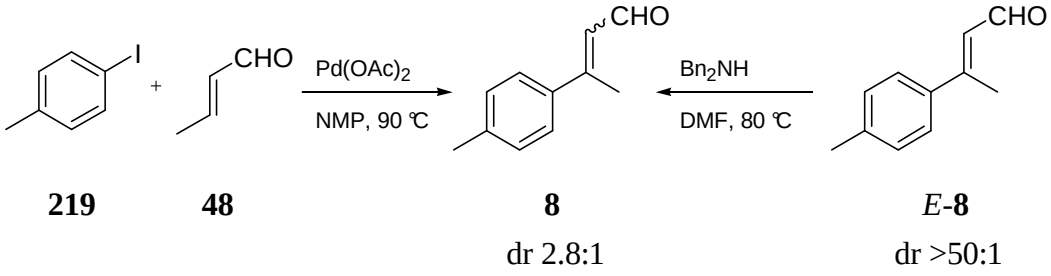
The Heck reaction is *trans*-selective in the case of β-unsubstituted olefins, as product control during the β-hydride elimination (Scheme 96a) will favor the formation of the thermodynamically favored olefin with an *E*-configured double bond.

The Heck reaction of crotonaldehyde can yield only one product with regard to the olefin geometry, and it is defined by the geometry present in crotonaldehyde (Scheme 96b). This is because both the carbopalladation step and the β-hydride elimination are *syn*.



Scheme 96: β-Hydride elimination and resulting product.

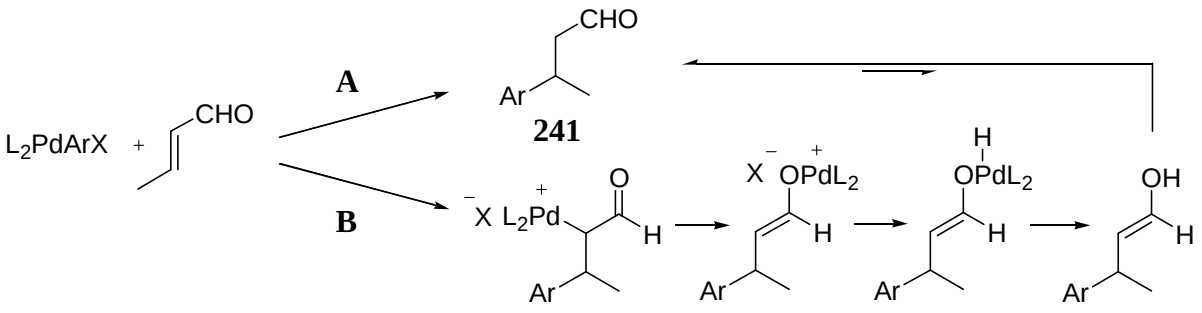
However, mixtures of *E*- and *Z*-olefins were observed in all cases. To explore this problem pure *E*-3-(4-methylphenyl)-2-butenal (*E*-**8**) was subjected to isomerization conditions and it turned out that the Heck reaction yields the thermodynamic mixture of olefin isomers (Scheme 97).



Scheme 97: Comparison of the Heck reaction and an isomerization experiment with *E*-**8**.

It is assumed that the isomerization is brought about *via* a nucleophilic pathway. It is also possible that the reaction product re-inserts into the palladiumhydride, but with the opposite regiochemistry. With two hydrogen atoms now ready for the β-hydride elimination this pathway will also lead to thermodynamic mixtures. Moreover, aldehydes of this type are generally prone to undergo isomerization. While this is certainly a drawback of the reaction, the isomers are separable by column chromatography, and methods are available to isomerize the undesired olefin geometry.

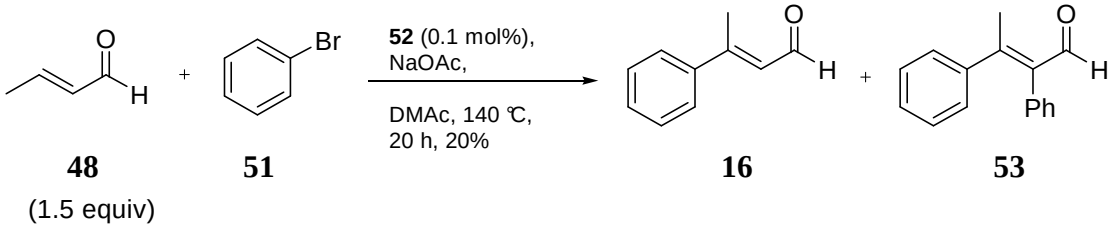
Common side products obtained in the Heck reaction were the saturated aldehydes **241** corresponding to the desired products. They can be either formed through a conjugate addition to the olefin rather than a carbopalladation (Scheme 98, path **A**), or by a mechanism involving an enolate (path **B**).



Scheme 98: Plausible pathways leading to the observed saturated aldehydes.

Both pathways are more favored under conditions differing from the ones described. Conjugate addition is usually observed in a larger amount when triethylamine is used as base, while bromide ions inhibit this reaction. Pathway **B**, however, needs an external hydride source, as the palladium-enolate cannot eliminate.[125] No further studies were undertaken to determine the source of the saturated aldehydes obtained, but it was concluded that a one-pot Heck reaction/ asymmetric transfer hydrogenation, for example for the synthesis described in chapter 4.1.5., will not be possible since the saturated aldehyde is formed as a racemate during the Heck reaction.

At the time this study was undertaken there were examples known employing acrolein as the substrate in Heck reactions,[124, 127-133] but there was only one example described by *Nejjar et al.* in which crotonaldehyde was arylated with bromobenzene **51** in low yields of only 20% of the desired product **16** and a further 8% of diarylation product **53** (Scheme 99).[50]



Scheme 99: Heck reaction of crotonaldehyde previously described.

It was possible to increase the yields to 50% starting from bromobenzene (**51**) and to obtain 68% product starting from iodobenzene. Moreover, a much less sophisticated and cheaper catalyst could be employed, the reaction conditions were significantly less harsh, and the reaction proceeded much faster than in the case reported by *Nejjar*.

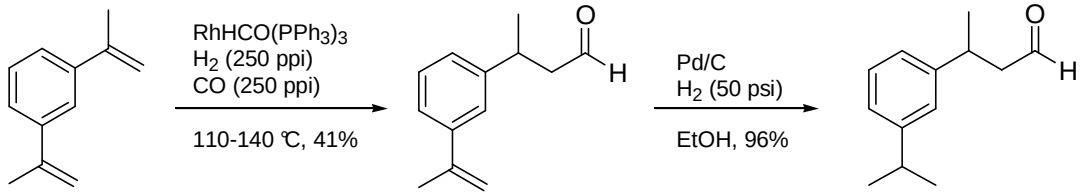
Another use of crotonaldehyde was published by *Li* during the course of this study, which featured very good *E*-selectivity when employing silver carbonate as the base in the reaction of crotonaldehyde with a vinyl iodide.[134] When the same conditions were applied to the aryla-

tion of crotonaldehyde with 4-iodotoluene (**219**), a good dr of ~10:1 was observed, albeit at low conversion.

In conclusion, it was found that palladium acetate is a suitable catalyst precursor for the arylation and vinylation of crotonaldehyde and related α,β-unsaturated aldehydes to form β,β-disubstituted products. It is both one of the cheapest sources of palladium as well as stable under air and at room temperature. The conditions found, employing tetrabutylammonium chloride as the phase transfer catalyst and sodium acetate as an inexpensive inorganic base, with *N*-methylpyrrolidinone as the solvent, provides quick access to the target compounds in good to very good yields and only employs reagents readily available in any chemical laboratory. Moreover, the operational simplicity of the process described makes it easy for every practitioner of chemistry to obtain the products. While the low *E*/*Z* ratios obtained in this synthesis are clearly not ideal, the reaction was initially intended to offer quick access to the starting materials for organocatalytic transfer hydrogenations.[135] It meets this criterion very well, as the transfer hydrogenations are enantioconvergent and both olefin geometric isomers are converted to the same enantiomer.[24, 136, 137] The usefulness of the reaction in this context is exemplified with a short synthesis of Florhydral® in the following chapter.

4.1.5. Asymmetric synthesis of (+)-3-(3-isopropylphenyl)butanal (Florhydral®)

Florhydral® (**242**) is a chiral fragrance that is marketed as a racemate by Givaudan.[138, 139] It can be prepared from *m*-diisopropenylbenzene (**243**) in two steps by a hydroformylation/hydrogenation sequence (Scheme 100).

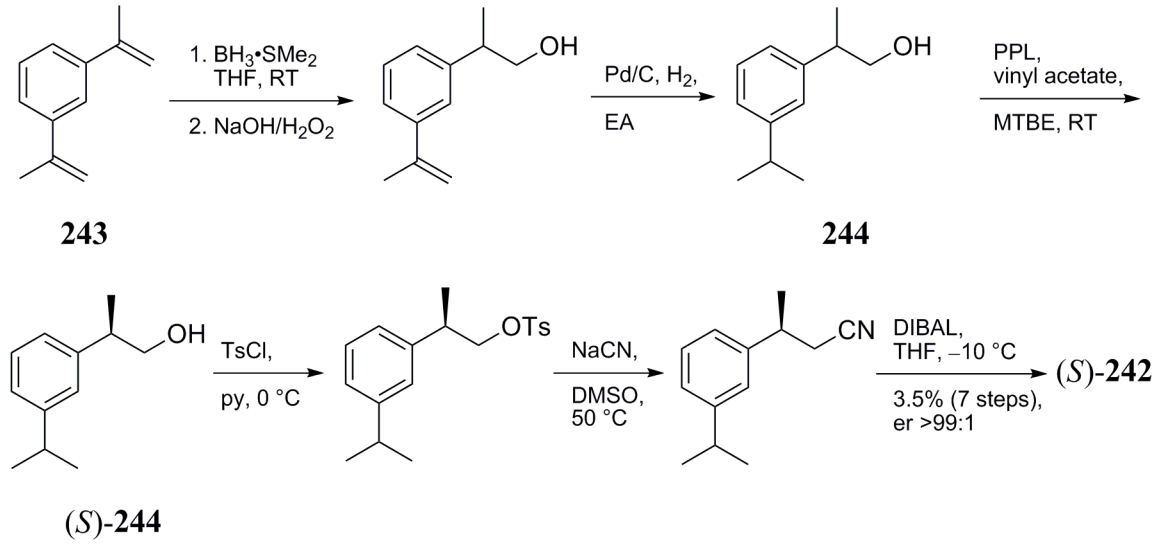


243 **242**

Scheme 100: Racemic synthesis of Florhydral®.

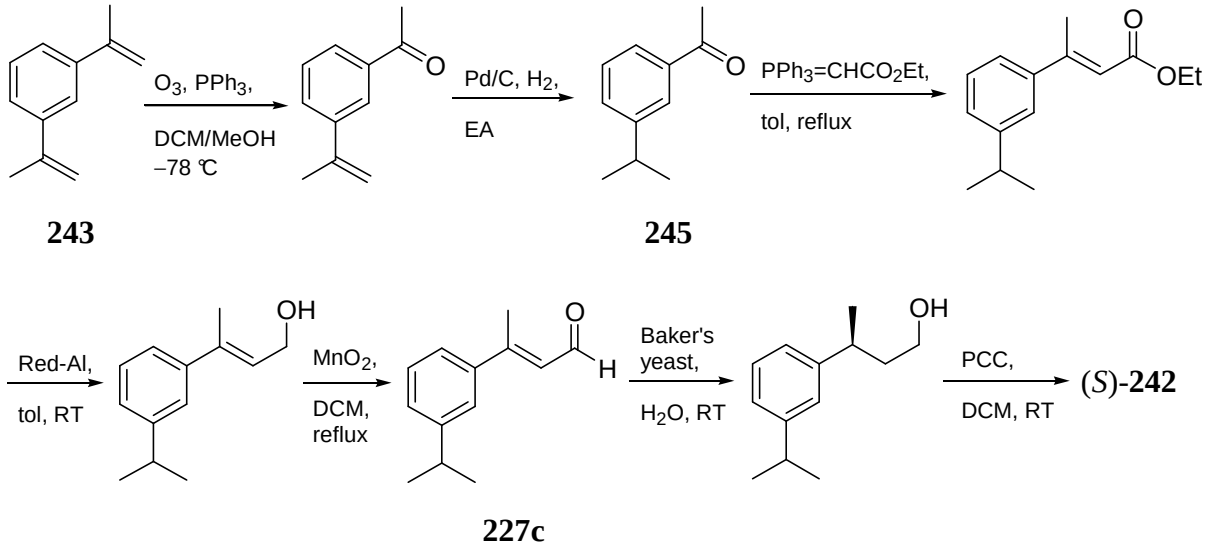
It was first synthesized in a highly enantioselective fashion by *Abate et al.*,[140] who presented two methods. The first synthesis uses racemic alcohol **244**, which is subjected to a kinetic resolution with *porcine pancreatic* lipase (PPL), to give key intermediate (*S*)-**244** (Scheme

101). The synthesis of (*S*)-**242** is completed in three more steps. Since the kinetic resolution had to be repeated to obtain high enantiomeric excesses the overall yield for this synthesis is 3.5% with an er of >99:1.



Scheme 101: Synthesis of Florhydral®, relying on a kinetic resolution as the key step. PPL = *porcine pancreatic* lipase.

The second route employs ketone **245**, which is made from **243** through partial ozonolysis and subsequent reduction of the remaining olefinic double bond. It is transferred in three steps through a Wadsworth-Horner-Emmons reaction, reduction, and reoxidation sequence into α,β-unsaturated aldehyde **227c**. This key intermediate is then reduced by Baker's yeast, which shows low chemoselectivity and also reduces the aldehyde in the process, and must be reoxydized to yield (*S*)-**242** in an overall yield of 2.6% and an er of 98.5:1.5.

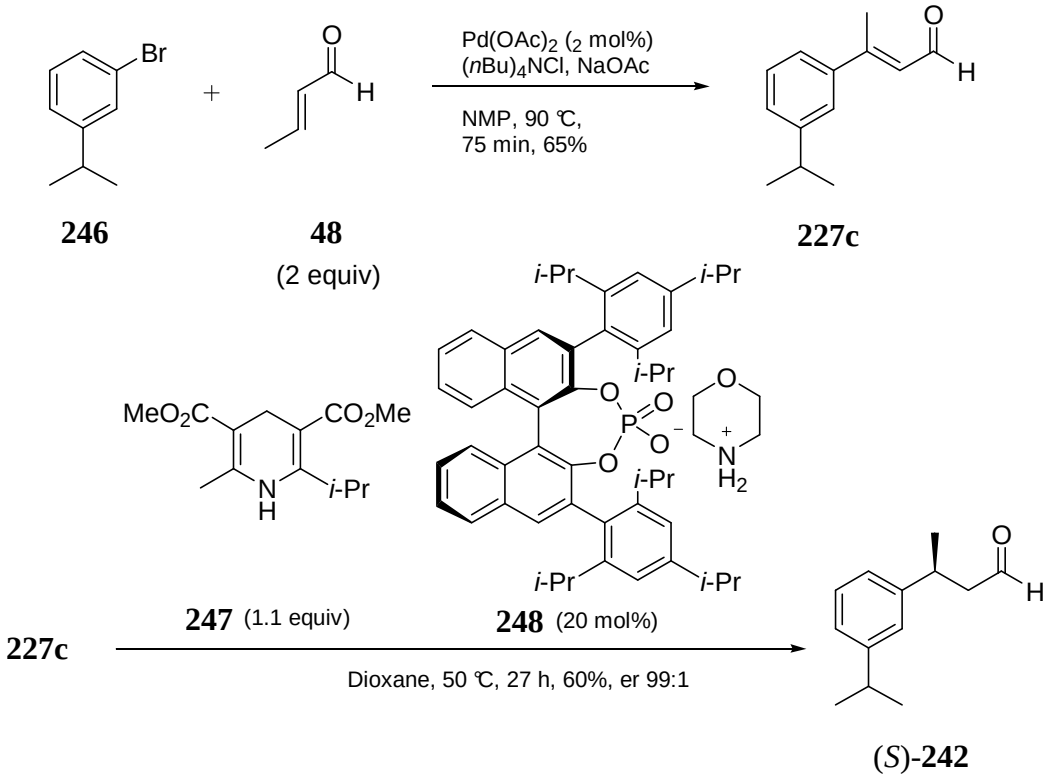


Scheme 102: Synthesis of Florhydral®, relying on an enzymatic reduction as the key step.

The latter method is not only low in yield, but the key reduction step is conducted on a 9 g scale of **227c**, which was transformed by 1.5 kg of baker's yeast in a beaker containing 1 kg of glucose and 5 L of water, clearly no ideal conditions for a large-scale synthesis. In addition to that, the yeast was found to only reduce the *E*-isomer.

Another approach was reported by *Paganelli et al.*, who used chiral ligands in the hydroformylation step.[141] (*R*)-BINAP was found to be the best ligand for the rhodium catalyst employed in their research, and gave the product in a very low enantiomeric ratio of 52.5:47.5.

The synthesis developed for this thesis made use of the Heck reaction of crotonaldehyde to access key intermediate **227c** from *Abate*'s work in only one step instead of the five previously necessary. This is possible because *m*-isopropylbromobenzene (**246**) is a commercially available substrate. As was already stated before, it could be used to arylate crotonaldehyde (**48**) in 65% combined yield of a 2.5:1 mixture of *E*- and *Z*-isomers (Scheme 103).



Scheme 103: Synthesis of Florhydral® using Heck reaction and transfer hydrogenation.

The synthesis was completed using the methodology developed by *Mayer* and *List* for the asymmetric counteranion directed organocatalytic transfer hydrogenation of enals to saturated

aldehydes.[24] Both isomers of **227c** could be employed in this enantioconvergent reaction and were converted to the product.
In this reaction Hantzsch ester **247** serves as the reducing agent, while the TRIP-morpholine salt **248** activates **227c** through iminium ion formation. The reaction was finished after 27 h with a good yield of 60% and an outstanding enantiomeric ratio of 99:1.

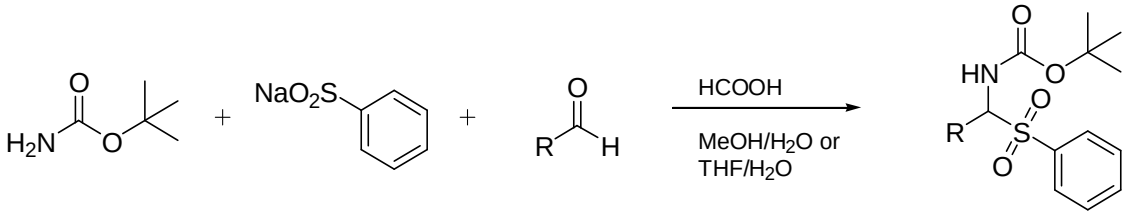
The method described here provides rapid access to the almost enantiomerically pure forms of Florhydral® in an overall yield of 39% as compared to the low yielding seven step syntheses described previously. It is by far the shortest synthesis published to obtain Florhydral® in high enantiomeric excess, and it is possible to produce both enantiomers.

4.2. Mannich reactions of *N*-Boc-imines

The reactions described in this chapter have been developed in cooperation with Dr. Jung Woon Yang, who discovered the initial highly selective Mannich reaction. The compounds **249e** and **f**, **159e** and **f**, **258a**, **b**, **f** and **l**, and **264** have been synthesized by Dr. Yang.

4.2.1. Synthesis of the starting materials

The starting materials for the experiments have been synthesized following a two-step protocol first outlined by *Kanazawa*, *Denis*, and *Greene*.[142] In the first step, the stable sulfones **249a-i** are prepared, which are subsequently transferred to the corresponding imine by elimination. Several methods [92, 142, 143] have been used to obtain the required sulfone compounds **249a-i** in yields of 22-81% from *tert*-butyl carbamate **250**, benzenesulfinic acid sodium salt **251**, and the corresponding aldehyde (**252a-h**, **7**) (Scheme 104).



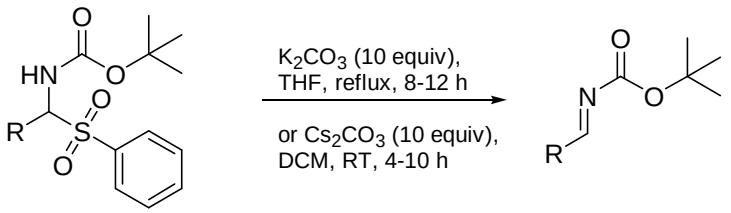
250	**251**	**252a**,	R = Ph	**249a**,	81%[a]
		252b,	R = 2-Furyl	**249b**,	46%[a]
		252c,	R = 2-Naphthyl	**249c**,	22%[b]
		252d,	R = 4-$CF_3C_6H_4$	**249d**,	67%[c]
		252e,	R = 4-ClC_6H_4	**249e**,	57%[c]
		252f,	R = 4-$MeOC_6H_4$	**249f**,	78%[a]
		252g,	R = *i*-Bu	**249g**,	22%[d]
		252h,	R = Et	**249h**,	24%[d]
		7,	R = (*E*)-PhCH=CH	**249i**,	48%[c]

Scheme 104: Synthesis of sulfone compounds **249a-i**. Conditions employed: a) MeOH/H_2O (1:2, v/v), RT; b) MeOH/H_2O (1:2, v/v), 65 °C; c) THF/H_2O (2:5, v/v), RT; d) MeOH/H_2O (1:10, v/v), 65 °C.

The products generally precipitated from the reaction mixture and are purified simply by washing with water and diethyl ether. However, in some cases it was necessary to recrystall-

ize. Crotonaldehyde and 2,2,2-trichloroacetaldehyde failed to give the desired product when subjected to the reaction conditions.

The sulfones were then converted into the corresponding imines **159a-i** by treatment with base, either according to the conditions of *Kanazawa et al.*[142] for aromatic and unsaturated substituents or according to *Deng* [144] for aliphatic compounds. In most cases the product was pure after filtering off the insoluble inorganic salts, giving satisfying to very good yields (64-98%, Scheme 105). When necessary, they could be purified by bulb-to-bulb distillation.



249a,	R = Ph	**159a**,	91%[a]
249b,	R = 2-Furyl	**159b**,	80%[a]
249c,	R = 2-Naphthyl	**159c**,	94%[a]
249d,	R = 4-$CF_3C_6H_4$	**159d**,	90%[a]
249e,	R = 4-ClC_6H_4	**159e**,	95%[a]
249f,	R = 4-$MeOC_6H_4$	**159f**,	98%[a]
249g,	R = *i*-Bu	**159g**,	n.d.[b]
249h,	R = Et	**159h**,	n.d.[b]
249i,	R = (*E*)-PhCH=CH	**159i**,	64%[a]

Scheme 105: Synthesis of imines **159a-i**. Conditions employed: a) K_2CO_3, THF, 65 °C; b) Cs_2CO_3, DCM, RT.

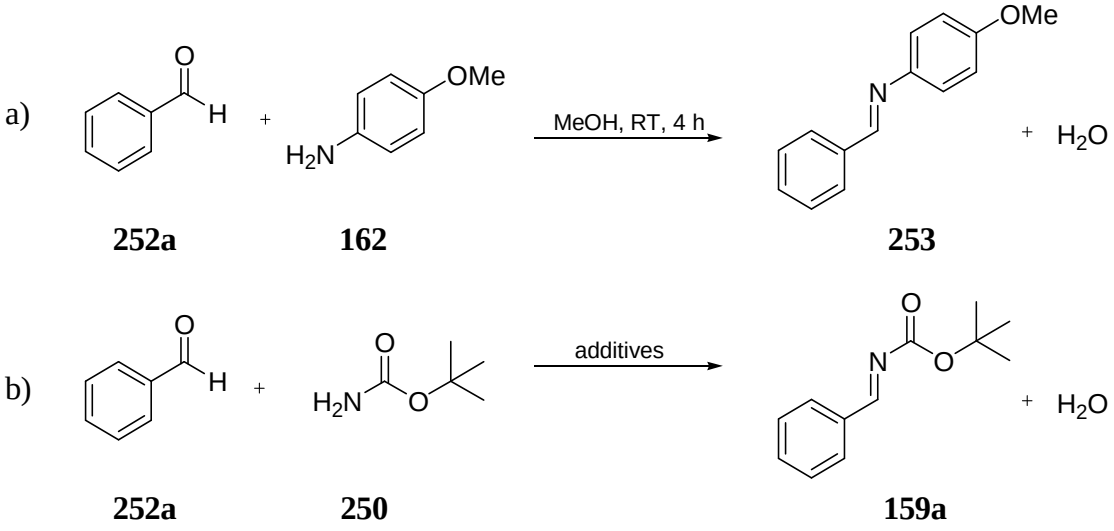
Aliphatic imines were found to be very unstable and completely decomposed within a day even at –18 °C. It is believed that this instability is due to the possibility of tautomerization to the more stable ene carbamate.[145] Compounds **159g** and **h** were therefore directly used in the subsequent Mannich reaction, while the other imines could be stored for prolonged times under argon in a freezer.

Though several attempts were made, it was not possible to obtain the formaldehyde-derived imine from its sulfone precursor. These imines have been prepared *in situ* and used in addition reactions before,[146, 147] but have not been isolated.

4.2.2. Attempts directed towards a one-step protocol for the synthesis of the starting materials

While the synthesis following the two-step sequence is an acceptable way to obtain the required starting materials in multigram amounts, it still suffers from several drawbacks. First, the reaction sequence is time consuming, with the first step usually run for 48 h and the second step up to 12 h. Second, it is not atom-economic due to the use of the sulfinic acid salt and the subsequent use of large amounts of base. Finally, on an industrial scale the precipitation of large amounts of products in the first step, their collection by filtration, and the necessity to stir even higher amounts of insoluble organic bases in the second step make this method problematic for large-scale synthesis. It was therefore attempted to develop a one-step protocol.

The synthesis of imines in one step from the corresponding aldehyde and a proper source of nitrogen is widely employed. For example, the condensation of *p*-anisidine (**162**) and benzaldehyde (**252a**) proceeds smoothly to yield the corresponding *N*-PMP-protected imine (**253**, Scheme 106a), even without removal of the formed water.



Scheme 106: a) Synthesis of benzaldehyde derived ***N***-PMP-imine **253**; b) attempted one-step synthesis of **159a**.

Both the syntheses of *N*-Boc-sulfones **249** as well as that of *N*-PMP-imines commence with an attack of the nitrogen on the carbonyl group under elimination of water. While the *N*-PMP-imine is stable enough towards hydrolysis to tolerate the water, *N*-Boc-imines are easily hydrolyzed, and the equilibrium lies on the left. The initially formed *N*-Boc-imine is therefore intercepted by the sulfinate.

It was tried to circumvent the hydrolysis by removing the water, either by adding Na_2SO_4 (Table 8, entry 1) or molecular sieves 4 Å (entry 2) or by employing a Dean-Stark water con-

denser (entry 3), and to shift the equilibrium to the product side. However, no product formation was observed by GC in these cases.

Table 8: Reaction conditions employed for the one-step synthesis of **159a**

Entry	Additive	Reaction conditions	Result
1	Na_2SO_4	toluene (0.15 M), reflux	no reaction
2	molecular sieves 4 Å	acetonitrile (0.25 M), 50 °C	no reaction
3	/	Dean-Stark water condenser, toluene (0.15 M), reflux	no reaction
4	20 mol% (*R*)-proline, molecular sieves 4 Å	acetonitrile (0.25 M), 18 °C and 50 °C	no reaction
5	10 mol% BNDHP[a)], molecular sieves 4 Å	acetonitrile (0.25 M), 50 °C	low conversion
6	20 mol% TFA, molecular sieves 4 Å	acetonitrile (0.25 M), RT, then 50 °C	low conversion
7	40 mol% 3,3,3-trifluoropropionic acid	$CHCl_3$ (0.5 M), reflux, Dean-Stark water condenser	product and byproducts, medium conversion

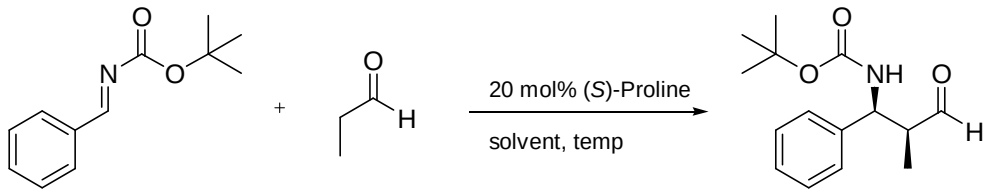
a) 1,1'-Binaphthalene-2,2'-diyl phosphoric acid.

With *tert*-butyl carbamate (**250**) being a much weaker nucleophile as compared to **162**, it was then tried to accelerate the reaction by activating the carbonyl group through acid catalysis (Table 8, entries 4-7). Proline was not acidic enough to affect the desired reaction (entry 4), while a phosphoric acid and trifluoroacetic acid (TFA) gave low conversion even after 24 h (entries 5 & 6). 3,3,3-Trifluoropropionic acid was chosen as being of similar pKa, but higher boiling point then formic acid, but even though the conversion under these conditions was better, the reaction never went to completion (entry 7). Moreover, the reaction was not clean and side products were observed, potentially deriving from the attack of a second unit of carbamate to the imine.

So far no reaction conditions leading to satisfying yields have been developed.

4.2.3. Optimization of the reaction conditions

Proline was known to be an excellent catalyst for the Mannich reaction,[14] and has since been used in numerous reactions *via* enamine intermediates. It was therefore chosen as the initial catalyst for the reaction of *N*-Boc-imines with unmodified aldehydes. The model reaction of **159a** with propionaldehyde (**254**) is shown below (Scheme 107).



159a **254** (2 equiv) **255a**

Scheme 107: Model reaction for the proline-catalyzed reaction of *N*-Boc-imines with unmodified aldehydes.

In an orienting solvent screen including DMSO, 1,4-dioxane, chloroform, and acetonitrile, it was found that the reaction proceeded well in DMSO, chloroform and acetonitrile and gave full conversion after 4 h (Table 9, entries 1, 3 & 4), while it was sluggish and not very clean in dioxane (entry 2). Acetonitrile was chosen over the other solvents because it gave excellent enantiomeric ratios, combined with a very clean reaction. Moreover, as a unique feature, the product precipitated when the reaction mixture was poured into water, which could later be used in a very simple and elegant workup/purification procedure.

Table 9: Effect of solvents and temperature

Entry	Solvent	Tem-perature	Reaction time	Conversion[a]	dr	er
1	DMSO	RT	4 h	full	n.d.	n.d.
2	1,4-dioxane	RT	4 h	~ 50%	n.d.	n.d.
3	chloroform	RT	4 h	full	n.d.	n.d.
4	acetonitrile	RT	4 h	full	5.4:1	99:1
5	acetonitrile	0 °C	8 h	full	>99:1	>99:1

a) Estimated by TLC.

It was next investigated if conditions could be found which led to better diastereomeric ratios. Gratifyingly, the dr was found to be mostly dependent on the temperature, and simply carrying out the reaction at 0 °C was enough to lead to very high levels of diastereoselectivity (Table 9, entry 5).

Further attempts to improve the reaction conditions were not successful (Table 10).

Table 10: Reaction conditions screened

Entry	Molarity	Temperature	Catalyst loading	Conversion[a]	Equiv. aldehyde	dr	er
1	0.1	0 °C	10 mol%	~60%	2	96:4	99:1
2	0.2	0 °C	10 mol%	~70%	2	97:3	97:3
3	0.1	0 °C	10 mol%	full	5	95:5	>99:1
4	0.1	0 °C	20 mol%	full	5	8.4:1	>99:1

Reaction conditions: 0.2 mmol imine, acetonitrile, 0 °C, reaction time 8 h; a) estimated by TLC.

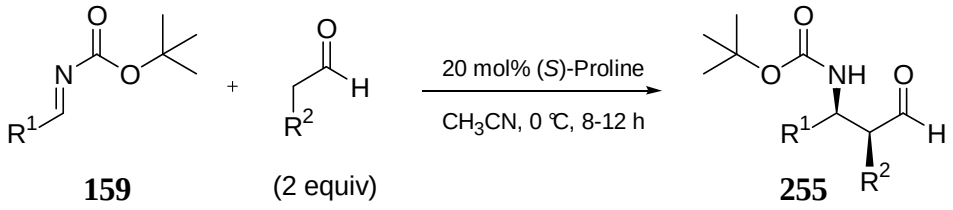
Lowering the catalyst loading led to a sluggish reaction and the formation of side products, presumably due to decomposition of the starting material (Table 10, entry 1). This effect could not be compensated by a higher molarity, which led to a lower enantioselectivity and increased aldol formation (entry 2). An increase in the amount of aldehyde was also not beneficial as the diastereoselectivity was eroding and the reaction was less clean (entries 3 & 4).

As was mentioned before, the product precipitated upon pouring the reaction mixture into water and could be isolated by filtration. This precipitate usually contained a small amount of the aldehyde impurity as detected by TLC, which could be removed by triturating the solid with hexanes precooled to –78 °C.

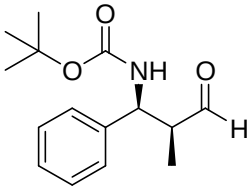
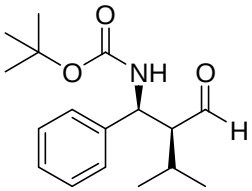
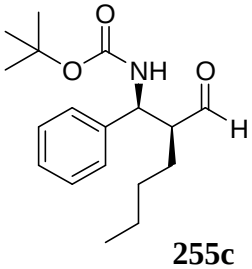
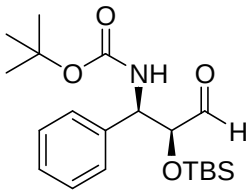
4.2.4. Reaction scope and limitations

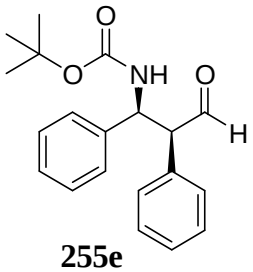
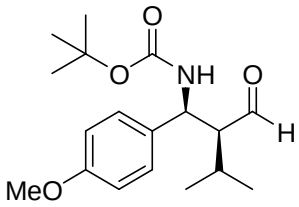
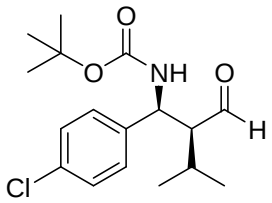
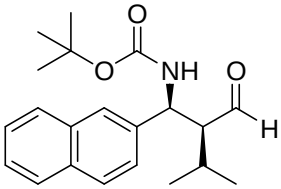
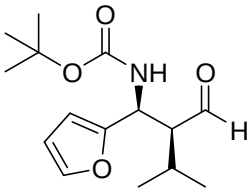
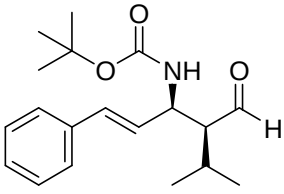
The substrate scope was evaluated with regard to different donor carbonyls as well as different imines.

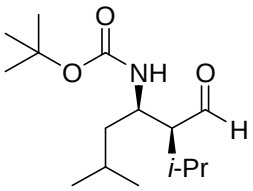
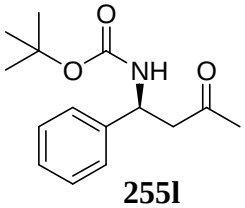
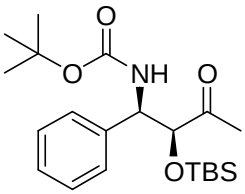
Table 11: Substrate scope



159 (2 equiv) **255**

Entry	Product	Yield	dr	er
1	 **255a**	91%	>99:1	>99:1
2	 **255b**	88%	>99:1	>99:1
3	 **255c**	84% (75%)[a]	>99:1	>99:1 (99:1)[b]
4[c]	 **255d**	69%	95:5	99:1

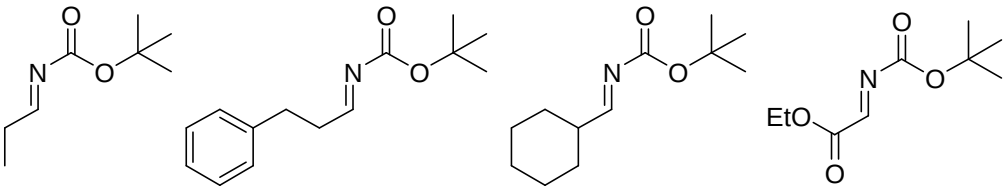
Entry	Product	Yield	dr	er
5	 **255e**	76%	98:2	>99:1
6	 **255f**	80%	>99:1	>99:1
7	 **255g**	59%	99:1	99:1
8	 **255h**	82%	99:1	99:1 (96:4)[b]
9	 **255i**	74%	97:3	99:1
10	 **255j**	64%	95:5	>99:1

Entry	Product	Yield	dr	er
11[c]	 **255k**	36%[d]	11:1	98:2
12[c,e]	 **255l**	73%	–	>99:1
13[c]	 **255m**	20%	17:1	99:1

a) Reaction run on a 50 mmol scale; b) er of the crude product; c) reaction run at RT; d) yield from the corresponding sulfone; e) reaction run in acetone.

The reaction of unmodified aldehydes was first evaluated using benzaldehyde-derived imine **159a** with several α-unbranched aldehydes (Table 11, entries 1-5). The yields were very good to excellent in all cases, with almost perfect selectivities for the *syn* product. The next investigation covered the electronic properties of the acceptor for imines derived from aromatic and heteroaromatic precursors. The reaction proceeded with excellent selectivities regardless of the electronic nature of the imine (entries 6-9), albeit at reduced yield for electron-deficient *p*-chloro substituted imine **159e** (entry 7). It was also possible to use cinnamaldehyde-derived imine **159i**, which led to the unsaturated compound **255j** (entry 10). The reaction was initially believed to be unable to yield products from aliphatic imines, as several had been tested and failed to give the desired transformation (see below for the limitations). However, after the discovery that aliphatic imines are viable substrates for the Mannich reaction of *N*-Boc-imines with acetaldehyde (see chapter 4.3.2), one example was also successfully employed under the original conditions (entry 11) with excellent enantioselectivity but only moderate yield. The use of ketones as donors was finally demonstrated with acetone and TBS-protected hydroxyacetone, with the latter also giving rather low yields (entries 12 & 13).

While the reaction was found to be of broad utility, it failed to give the desired product in some cases, most notably for aliphatic imines **159h**, **j**, and **k**, which presumably decomposed to the more stable but under these conditions unreactive enamines.

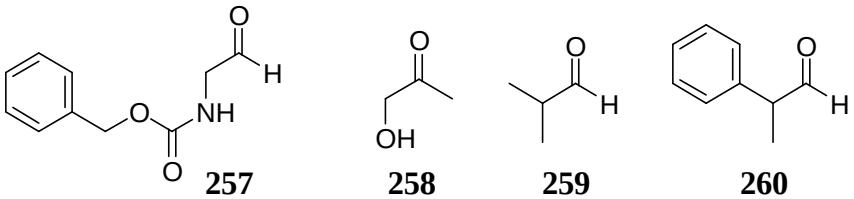


159h **159j** **159k** **256**

Scheme 108: Reaction limitations with regard to acceptors.

Another class of potential substrates are α-imino esters **256**. These unstable compounds can be accessed *via* a bromination/elimination reaction sequence from *N*-Boc glycine esters [148] and were immediately subjected to the Mannich reaction conditions. However, only trace amounts of aldehydes were obtained.

Some donors could also not be employed. No desired reaction was observed when Cbz-protected α-aminoaldehyde **257** was used as donor, which would have led to a formal diamination. The reaction with unmodified hydroxyacetone **258** only led to decomposition of the starting imine.



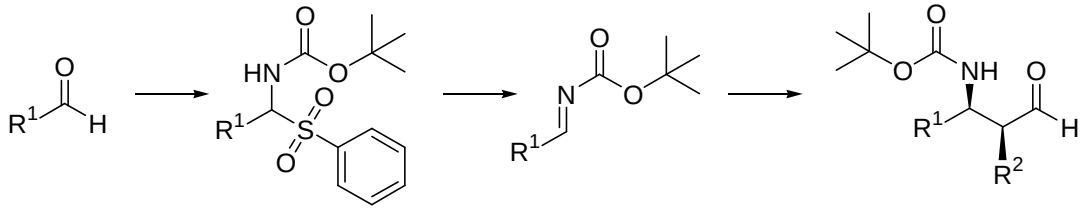
257 **258** **259** **260**

Scheme 109: Reaction limitations with regard to donors.

α,α-Disubstituted aldehydes **259** and **260** could also not be activated towards the reaction by proline and consequently no reaction was observed.

4.2.5. Experiments towards a two-step, one-pot protocol

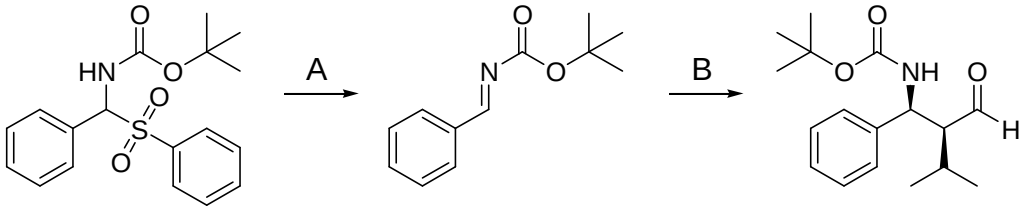
With the development of the Mannich reaction up to this point three reaction and three workup steps needed to be conducted to obtain the final product (Scheme 110).



Scheme 110: Route to Mannich products.

It was therefore tested whether it would be possible to conduct the two final steps in one pot. In the model reaction sulfone **249a** should be transformed to the imine and then directly converted to the corresponding Mannich product **255b** through reaction with isovaleraldehyde (**166**) without workup. The conditions tested are given below (Table 12).

Table 12: Experiments towards a one-pot protocol



249a **159a** **255b**

Entry	Conditions employed	Solvent	Yield	dr	er
1	Step A: 1.2 equiv Cs_2CO_3, 20 mol% (*S*)-proline, 2 equiv **166** Step B: 0 °C, 48 h	CH_3CN	0%	n.d.	n.d.
2	Step A: 1.2 equiv NEt_3, 20 mol% (*S*)-proline, 2 equiv **166** Step B: 0 °C, 48 h	CH_3CN	<5%	n.d.	n.d.
3	Step A: 1.2 equiv CsOH, 20 mol% (*S*)-proline, 2 equiv **166** Step B: 0 °C, 44 h	CH_3CN /H_2O	0%	n.d.	n.d.
4	Step A: 1.2 equiv Na_2CO_3, 20 mol% (*S*)-proline, 2 equiv **166** Step B: 0 °C, 44 h	CH_3CN /H_2O	0%	n.d.	n.d.
5	Step A: 1.0 equiv Cs_2CO_3, RT, 6 h Step B: 20 mol% (*S*)-proline, 2 equiv **166**, 0 °C, 12 h	DCM	~20%	95:5	97:3
6	Step A: 10.0 equiv Cs_2CO_3, RT, 6 h Step B: 20 mol% (*S*)-proline, 2 equiv **166**, 0 °C, 12 h	DCM	0%	n.d.	n.d.

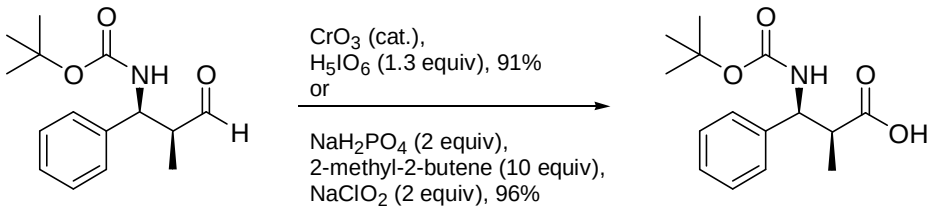
Initially all compounds were mixed and left stirring in the solvent indicated (entries 1-4). Different bases were tried for the first step, but only in the reaction using triethylamine was some product formed. This problem probably arose due to the lower temperature (0 °C or RT) as compared to the temperatures usually employed for the imine preparation (65 °C), and the imine is probably not formed in sufficient quantities. It was next undertaken to separate the imine formation from the Mannich reaction. Elevating the temperature in the first step led to formation of the imine, and after addition of proline and the aldehyde at again lowered temperature, about 20% of product was obtained in selectivities comparable to the original reaction (entry 5). However, an additional 20% of starting material was also recovered during workup, so the product needed to be purified by column chromatography. To drive the imine formation to completion a higher amount of base was used (entry 6), but this resulted in no Mannich product being formed, most likely due to deprotonation and thereby deactivation of proline.

The experiments showed some potential for a one-pot sequence, but since the products were obtained in lower yields and needed to be purified the original protocol was deemed superior.

4.2.6. Conversion to a $\beta^{2,3}$-amino acid and determination of the absolute configuration

The products of the Mannich reaction, protected amino aldehydes, are viable substrates for further manipulation. Their most prominent derivatives are possibly *N*-Boc-protected β-amino acids, which can be accessed *via* simple oxidation.

255a could be transformed into acid **261** by oxidation with catalytic amounts of chromium(VI)oxide and periodic acid or sodium chlorite as oxidizing agents in high yields and with complete conservation of the stereochemical information (Scheme 111).

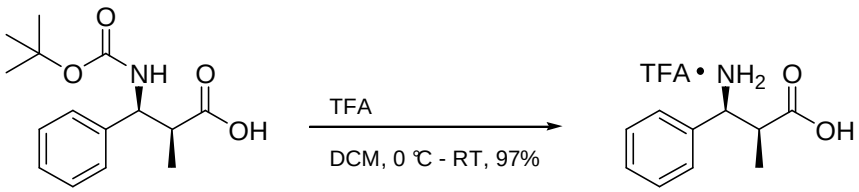


255a **261**

Scheme 111: Oxidation reactions to yield an *N*-Boc-protected β-amino acid.

To obtain the free amino acid, **261** was treated with acid according to standard methods. Both HCl and TFA could be used for this step, but the reaction was cleaner and proceeded faster

with TFA (Scheme 112).[149] The compound was obtained as the pure product after simply evaporating the volatile side products, dissolving it in water, and washing this solution with diethyl ether.



261 **262**•TFA

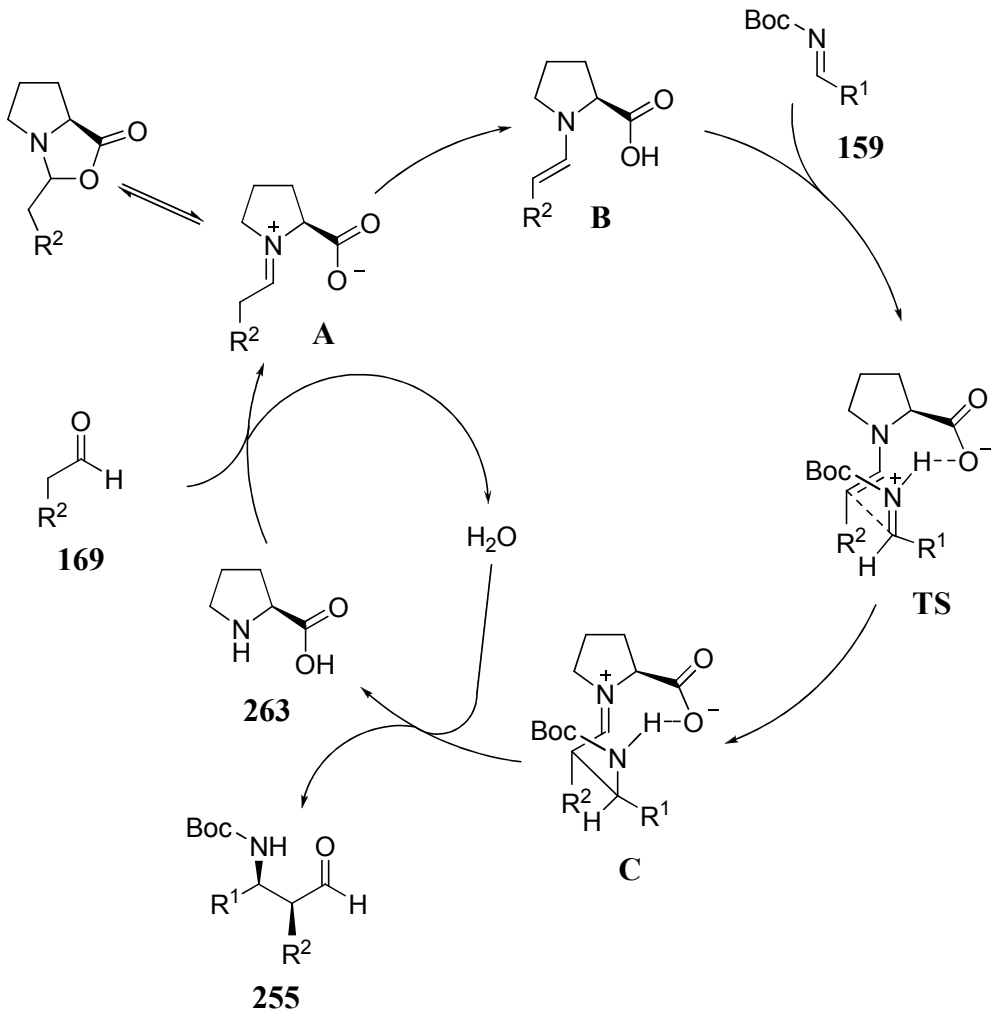
Scheme 112: Deprotection to the free amino acid.

To confirm the absolute configuration of the products, **261** was deprotected to **262**·HCl with 1 M HCl in diethyl ether. **262**·HCl was previously synthesized by *Davies et al*. and the absolute configuration determined to be (2*S*,3*S*).[150] The specific optical rotation measured was $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –4.7 (*c* = 0.91, H_2O), which has the same sign as the compound described by *Davies* ($[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ –1.7(*c* = 1.06, H_2O)), thereby confirming the expected absolute configuration. The re-protection of **262** with Boc-anhydride and the comparison with HPLC data from **261** showed no loss of enantiopurity during the oxidation.

4.2.7. Discussion

Proline was found to be an excellent mediator for the Mannich reaction of several *N*-Boc protected imines with a variety of aldehydes and ketones. The use of proline as catalyst is beneficial because it is inexpensive, available in both enantiomeric forms, can be stored for long times on the shelf, and is non-toxic.

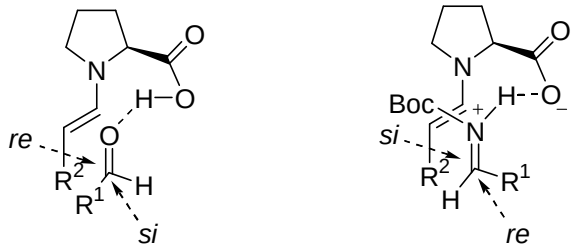
The reaction is presumed to proceed through an enamine intermediate, with proline acting as a bifunctional catalyst. This reasoning is in agreement with previous work on the mechanism of the proline-catalyzed intra- and intermolecular aldol reactions [151] as well as work on the Mannich reaction.[93, 152] The proposed catalytic cycle starts with the condensation of proline (**263**) and an enolizable aldehyde **169**, which leads to iminium ion intermediate **A** and liberates one molecule of water (Scheme 113).



Scheme 113: Proposed catalytic cycle.

Possibly with the aid of the carboxylate, **A** tautomerizes to the uncharged enamine **B**. **B** then coordinates a molecule of imine **159**. In the transition state (**TS**) the iminium ion is held in place by a hydrogen bond to the carboxylate. The imine is forced in a position so that the *si*-side is facing the enamine, and the reaction proceeds to give iminium ion **C**. The catalytic cycle is completed by the hydrolytic liberation of proline and the amino aldehyde **255**, which shows the observed absolute configuration.

With the outcome of the Mannich reaction being *syn*, the selectivity is opposite as compared to the proline-catalyzed aldol reaction. This is a result of the different transition state geometry which is possible for the aldol reaction (Scheme 114).

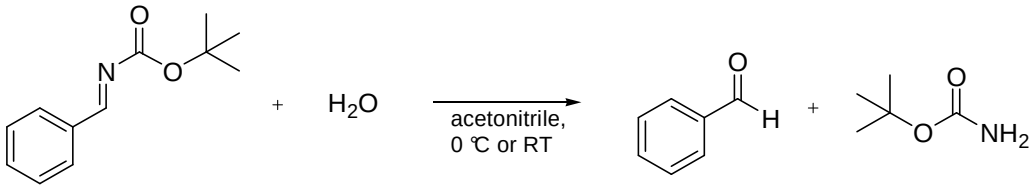


TS-A **TS-B**

Scheme 114: Transition states of the aldol (**TS-A**) and Mannich reaction (**TS-B**).

While in both cases the enamine can reach an energetically favorable pseudo-equatorial position, transition state **TS-B** shows both the Boc group as well as R^1 in pseudo-axial positions.[152] This is necessary to allow for the formation of the hydrogen bond with the carboxylate and leads to a nucleophilic attack on the *si*-side. In transition state **TS-A** for the aldol reaction, however, a hydrogen bond can be formed with either lone pair on the carbonyl oxygen, and the acceptor can therefore attain an energetically lower geometry in which R^1 is in pseudo-equatorial position, leading to the observed *re*-selectivity.

The proline-catalyzed Mannich reaction features high yields and almost perfect selectivities especially for simple carbonyl compounds, such as propionaldehyde or acetone. The reactions were generally driven to completion in reasonable times. While small amounts of aldol reaction and aldol condensation side products could be detected by TLC, the only major side reaction was hydrolysis of the imine to the parent aldehyde and *tert*-butyl carbamate (Scheme 115). It is possible that the carboxylic acid moiety of proline activates the imine towards the nucleophilic attack of water. Though the use of dried solvents can prevent this to some extent, there will always be some water in the reaction mixture due to the formation of the reactive enamine.



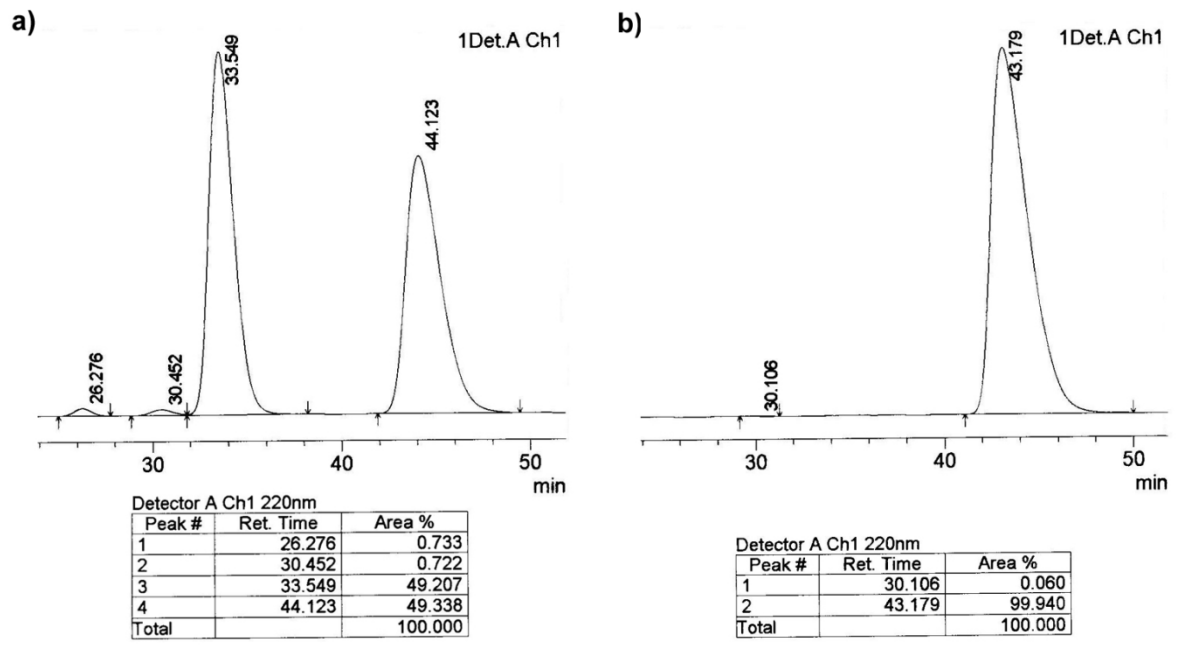
159a **252a** **97**

Scheme 115: Hydrolysis of starting material.

In many cases the product of the Mannich reaction precipitated directly from the reaction mixture or during an aqueous workup, which, in combination with the clean course the reactions ran, led to simple product collection (Scheme 116).

Scheme 116: Preparation of **255h**; a) reaction mixture after adding all components; b) Reaction mixture after completion of the reaction.

The products, generally colorless solids, could easily be collected by filtration and were pure after simple washing with cool hexanes without the necessity of further purification. Moreover, they were typically also obtained enantio- and diastereomerically pure (Scheme 117). This is a great advantage of this method which is especially interesting in an industrial context, where column chromatographic purification is cost intense and avoided if possible. A small enrichment in enantiopurity was sometimes observed due to the precipitation. Chromatographic purification became necessary when either the carbonyl donor or the imine was unstable, for example in the case of aliphatic imines or α-oxygenated carbonyls, or the product did not precipitate.



Detector A Ch1 220nm

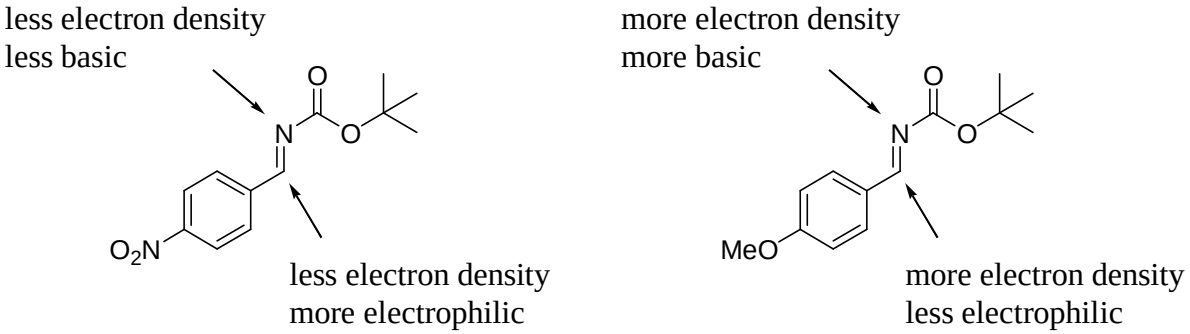
Peak #	Ret. Time	Area %
1	26.276	0.733
2	30.452	0.722
3	33.549	49.207
4	44.123	49.338
Total		100.000

Detector A Ch1 220nm

Peak #	Ret. Time	Area %
1	30.106	0.060
2	43.179	99.940
Total		100.000

Scheme 117: HPLC traces of **255c** (Chiralpak AS-H column, 2% *i*-PrOH/heptane, 0.50 mL/min, 220 nm); a) reaction run with racemic proline at RT; b) reaction run with (*S*)-proline at 0 °C.

In extension of the originally published results, which indicated a rather narrow substrate scope,[153, 154] the Mannich reaction was shown to have broad utility with regard to both donor and acceptor. The majority of products are derived from aromatic aldehydes. It was found that the electronic properties of the aromatic ring play a role in the reactivity of the imine. While electron-rich or neutral substituents led to good reactivity, electron-poor substituents like chlorine led to a lowered yield when the same reaction conditions were employed. This observation became even more obvious during the study of the Mannich reaction of *N*-Boc-imines with acetaldehyde (see chapter 4.3.2), where substrates bearing even stronger electron acceptors like a nitro or trifluoromethyl group would not react at 0 °C at all. This also offers an explanation why α-imino ester **266** (see Scheme 108), in which the imine is also substituted with a strong electron withdrawing group, did not react. The observed reactivity is counter-intuitive as the electron-deficient substrates should be more reactive towards a nucleophilic attack. However, through the conjugated system the nitrogen atom of the imine should be less basic when substituted by an electron-deficient group. Since the transition state involves an iminium ion, it would be higher in energy as compared to the more basic electron-rich imines, which leads to the observed lower reactivity (Scheme 118).



Scheme 118: Consequences of the different electronic properties of the aromatic part.

Due to the aforementioned problems associated with aliphatic imines, it was initially believed they would not undergo the Mannich reaction at all. However, it turned out that, provided the imine is sufficiently stable, the Mannich reaction can indeed take place and yield the desired product even under the original conditions. At this moment, however, the yields are poor, and further research into these starting materials will be necessary. Particularly interesting is the possibility of generating the imines *in situ* as pioneered by *Deng* and coworkers,[145] which limits the problem of imine decomposition during the reaction.

With regard to the donor it was shown that a variety of different carbonyl functions can be employed. Apart from the use of aliphatic aldehydes it was possible to employ phenylacetaldehyde, the Mannich product of which should be prone to undergo epimerization. However, it was isolated in excellent isomeric purity, thereby demonstrating the mildness of the reaction conditions. Moreover, α-oxygenated aldehydes and ketones could be used, and the products of this reaction complement the asymmetric aminohydroxylations described by *Sharpless*.[155] α-Oxygenated aldehydes were found to be less reactive than carbon-substituted and required higher temperatures and longer reaction times. The corresponding reaction with α-aminated aldehyde **257** was not observed. Another limitation is that α,α-disubstituted aldehydes could not be activated by proline, which excludes the formation of quaternary carbons directly through this methodology. The reason is probably a too strong steric interaction between the pyrrolidine and the substituent in *Z*-position of the required enamine. On the other hand, this non-reactivity of proline is a prerequisite to obtain the observed high *syn*/*anti* ratios, which would be lower if proline could form an enamine with α,α-disubstituted aldehydes, as the product of the Mannich reaction is also an aldehyde of this type.

The use of two cyclic ketones as donors in this reaction was already reported by *Enders* and coworkers during the time this research was carried out.[156, 157] It was demonstrated in this thesis that acyclic ketones are also donors for the Mannich reaction. Their reactivity is lower as compared to aldehydes due to the lowered electrophilicity of the carbonyl carbon atom, which

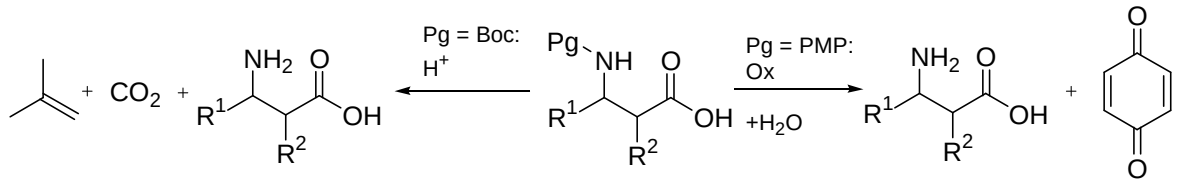
results in higher reaction temperatures being required. The combination of a ketone with an α-oxygen seems to mark the limitation with regard to donor reactivity. Only low yields could be obtained with the rest of the starting imine being hydrolyzed.

It was possible to scale the reactions up from 0.5 mmolar to 50 mmolar without loss of selectivity, albeit at a longer reaction time of 24 h as compared to 8 h on a small scale and somewhat reduced yields of 75% instead of 84%. Both these observations may be explained by problems intermixing the reactants, which would lead to prolonged reaction time and therefore higher starting material decomposition. However, this experiment showed that the reaction can easily be run at much larger than usual laboratory scales.[158]

The described process does not require protective gas techniques, since all components employed are stable to air. Due to the nature of the starting material it is necessary to limit the amount of water in the reaction mixture.

The usefulness of the products for further synthetic manipulation was shown with the easy transformation to a $\beta^{2,3}$-amino acid in two high-yielding steps. However, the carbonyl group is not only limited to oxidations, but is readily subjected to a wide range of reactions which open the door to a variety of products that can be made from these aminoaldehydes. The products of the Mannich reaction of *N*-Boc-imines are therefore valuable chiral building blocks with diverse substitution patterns (see also chapter 4.3.3).

Even though the Mannich reaction of *N*-Boc protected imines results in excellent yields and selectivities and offers access to stable, crystalline products, it has a distinct disadvantage over the already known organocatalytic, proline-catalyzed three-component Mannich reaction already discovered in 2000 [14] in that it is necessary to pre-form the imine, which is both unattractive in terms of atom economy as well as increasing the number of steps to obtain the final product. The major advantage of the new method, however, lies in the protecting group employed. While the *para*-methoxyphenyl (PMP) nitrogen protecting group is cleaved under oxidative conditions, the Boc-protecting group can be removed by treatment with acid (Scheme 119).



Scheme 119: Removal of *N*-Boc and *N*-PMP protecting groups.

The removal of the protecting group is the major drawback in any synthesis containing PMP-protected amines. Even though new methods for the deprotection have been developed [159, 160] the PMP-group is most commonly deprotected with ceric ammonium nitrate (CAN), which is toxic, too expensive for industrial use, and not suitable for functional groups prone to undergo oxidation. Moreover, PMP-deprotections are often reported with yields of 70% - 80%,[15] while especially the deprotection step in a synthesis should not consume considerable portions of the valuable product. The Boc group in contrast is usually cleaved under mild acidic conditions, typically in high or even quantitative yields.[15] As an additional benefit, only gases are formed during the Boc deprotection, allowing for an easy purification. In conclusion, while the preparations for the Mannich reaction of *N*-Boc-imines require more work, the final products are of greater value, rendering this a highly useful method to synthesize β-amino carbonyls and derivatives thereof.

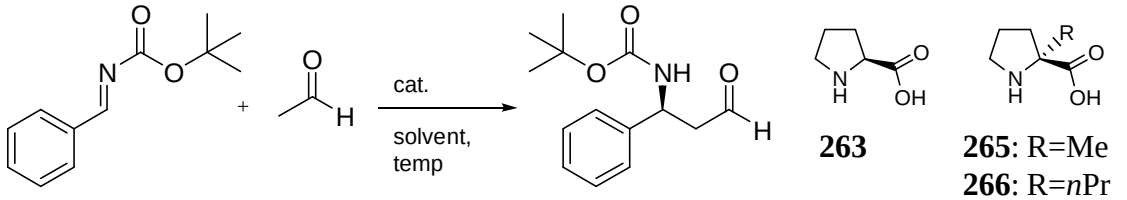
4.3. Mannich reactions of acetaldehyde

The Mannich reaction of acetaldehyde was developed together with Dr. Yang, who synthesized compounds **264a**, **d**, and **f**. Dr. Carley Chandler joined for the further development of the chemistry of aliphatic imines in this reaction and synthesized compounds **264b** and **h**. Daniela Kampen worked on the functionalization of the Mannich products that is briefly discussed in chapter 4.3.3 and will be described in detail in her thesis.

4.3.1. Development of reaction conditions

Since the Mannich reaction of *N*-Boc-imines proved to be a very clean and efficient reaction it was chosen as the model for attempts to use acetaldehyde in a first practical, controlled, and asymmetric chemical transformation. In the initial reaction, *N*-Boc-imine **159a** was to be reacted with acetaldehyde (**4**) to give β-amino aldehyde **264a** (Table 13). It was known from studies towards a proline-catalyzed aldol reaction of acetaldehyde that it is very reactive in the presence of proline and is quickly converted, presumably in a selfaldol condensation, to colored oligo- and polymers. Orange to red solutions of these compounds have been observed until the reaction temperature was lowered to –20 °C. Low temperatures where therefore initially chosen for the Mannich reaction to limit the side reactions.

Table 13: Screening of conditions



159a **4** **264a** **263**

265: R=Me
266: R=*n*Pr
267: R=allyl

Entry	Solvent	Temperature	Equiv **4**	Catalyst	Reaction time	Yield[a]	er
1	CH_3CN	–18 °C	2	20 mol% **263**	13 h	<5%	n.d.
2	CH_3CN	–30 °C	2	20 mol% **263**	30 h	<5%	n.d.
3	CH_3CN	–40 °C	2	20 mol% **263**	60 h	<5%	n.d.
4	THF	–72 °C	2	20 mol% **263**	30 h	0%	n.d.
5	CH_3CN	–20 °C	2	20 mol% **263**	4 d	~10%	n.d.
6	CH_3CN	–20 °C	2	50 mol% **263**	4 d	<5%	n.d.

Entry	Solvent	Temper-ature	Equiv **4**	Catalyst	Reaction time	Yield[a]	er
7	CH_3CN	–32 °C	2	20 mol% **263**	16 d	~20%	n.d.
8	CH_3CN	–26 °C	2	20 mol% **263**	4.5 d	~10%	99.8:0.2
9	CH_3CN	0 °C	5	20 mol% **265**	2 d	~30%	n.d.
10	CH_3CN	0 °C	5	20 mol% **266**	2 d	0%	n.d.
11	CH_3CN	0 °C	5	20 mol% **257**	2 d	0%	n.d.
12	CH_3CN	–10 °C	5	10 mol% **265**	2 d	<5%	n.d.
13	CH_3CN	–10 °C	5	20 mol% **265**	2 d	<10%	n.d.
14	CH_3CN	0 °C	5	20 mol% **263**	3 h	~50%	>99:1

a) Determined by TLC or GC

Toujas et al. had previously described **264a** as unstable during column chromatography [161] which could be disproved during this study.

The reaction was initially explored with regard to the temperature, using proline (**263**) as the catalyst. While the product was detected until –40 °C, no desired reaction was observed at –72 °C even after 30 h (Table 13, entries 1-4). Prolonged reaction times improved the yield slightly, but an increase in catalyst loading had detrimental effects (entries 5 & 6). The best result with regard to the yield was obtained at very low temperatures, but at extremely long reaction time (entry 7), and also an excellent er was measured (entry 8).

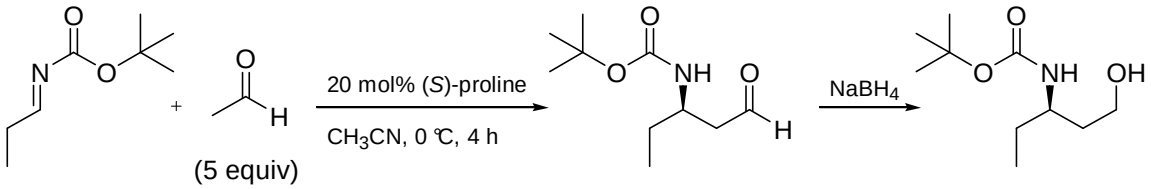
Dr. Yang joined the project at this stage and explored a different approach using α-methyl proline **265** as catalyst. **265** had previously been used in the intramolecular α-alkylation of aldehydes [162] but was hampered towards the aldol reaction. It was therefore believed to suppress the side reactions of acetaldehyde in the Mannich reaction. Moreover, a higher amount of acetaldehyde was employed, which should increase the overall reaction rate, but also help suppress the potential follow-up Mannich reaction between **265a** and another equivalent of **159a**.

The initial experiment gave promising results at zero degrees (entry 9), while structurally similar catalysts **266** and **267** did not yield the desired product (entries 10 & 11). No coloring of the solution was found even though the amount of acetaldehyde was increased to five equivalents.

The yields were drastically reduced when the reaction was run at lower temperature as the reaction become sluggish (entries 12 & 13). With these encouraging results and the knowledge that five equivalents of the aldehyde are beneficial, it was finally tried to use proline under the same conditions, which turned out to give acceptable yields (entry 14). It was also

discovered that the order of addition is important. When proline is added to a solution of the imine in acetonitrile and then a solution of acetaldehyde in the same solvent is added, an oligomerization of the aldehyde is not observed.

These conditions worked well for aromatic imines, and since the reactions with acetaldehyde were faster as compared to other aldehydes, aliphatic imines were investigated as substrates for this reaction. It was found that it is indeed possible to use **159h** to obtain the first example of an aliphatic, *N*-Boc protected Mannich product under proline catalysis (Scheme 120).



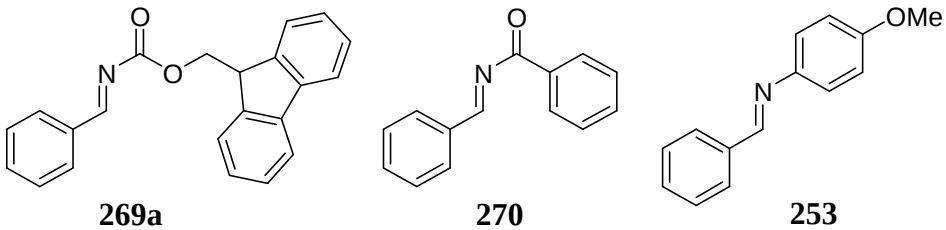
159h **4** **264b** **268**

Scheme 120: First synthesis of an aliphatic product of the Mannich reaction.

A solvent screen revealed yields of 6-11% of **268** in acetonitrile, dichloromethane, and 1,4-dioxane/tetrahydrofuran mixtures, but with an excellent er of 98.5:1.5. The reduction step was deemed necessary due to initial problems with isolating the product, and concerns regarding the product stability. However, it could soon be shown that the aldehyde **264b** is also stable and could be isolated.

As was mentioned before (see chapter 4.2.4), the stability of the imine was discovered to be an important factor for the outcome of the reaction. Dr. Chandler joined the search for better reaction conditions and succeeded in improving the yields by using a solution of aliphatic imine and acetaldehyde in acetonitrile, cooled to –10 °C, which was added slowly to a slurry of proline in acetonitrile at the reaction temperature of 0 °C. The imine had a longer lifetime due to the cooling and the yields could be increased to a maximum of 23% of **264b**.

The reaction was also attempted with different imine protecting groups (Scheme 121).



269a **270** **253**

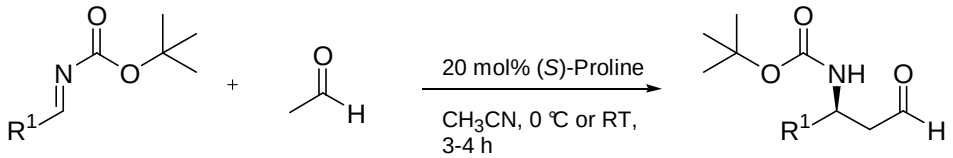
Scheme 121: Additionally screened imines.

The reaction with *N*-Fmoc-protected imine **269a** never reached complete conversion under the conditions found above, and at the same time the products could not be obtained pure (also see chapter 4.5.3). The attempts at reacting acetaldehyde with *N*-benzoyl-protected imine **270** at room temperature failed completely, as there was an immediate decomposition of the starting material, and the solution became orange. The reason for this decomposition became apparent during the later research into this class of imines as an acid-catalyzed reaction of the starting material (chapter 4.6.4). The group of *Hayashi* later showed that the Mannich reaction with acetaldehyde is indeed possible with this class of imine under proline catalysis.[163] PMP-protected imine **253** was finally found to be much less reactive even at room temperature, and the reaction led to a multitude of products as observed by TLC. Since both the products of the Mannich reactions of **270** and **253** would have been protected with non-optimal protecting groups it was decided to explore the reaction with a Boc-protecting group following these orienting experiments.

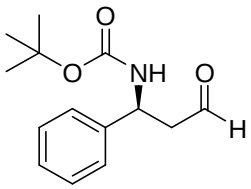
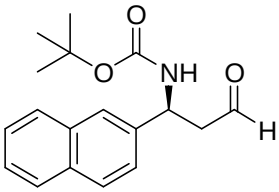
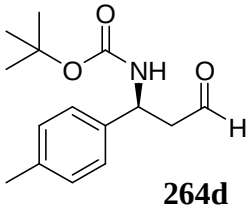
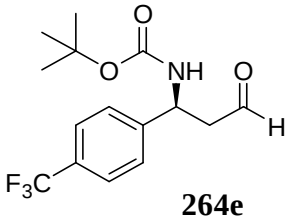
4.3.2. Reaction scope and limitations

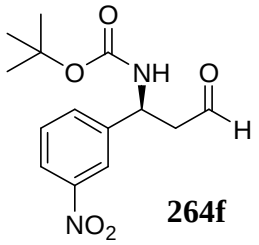
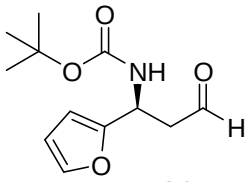
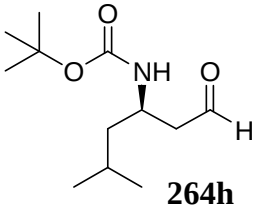
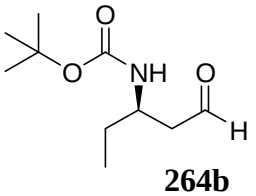
The Mannich reaction of acetaldehyde was evaluated with regard to different acceptors. Both aromatic as well as aliphatic imines could be used (Table 14).

Table 14: Substrate scope



159 **4** (5-10 equiv) **264**

Entry	Product	Yield	er
1	 **264a**	54%	>99:1
2	 **264c**	40%	>99:1
3	 **264d**	58%	98:2
4[a]	 **264e**	42%	99:1

Entry	Product	Yield	er
5[a,b]	 **264f**	42%	>99:1
6	 **264g**	30%	99:1
7	 **264h**	55%	>99:1
8	 **264b**	23%	>99:1

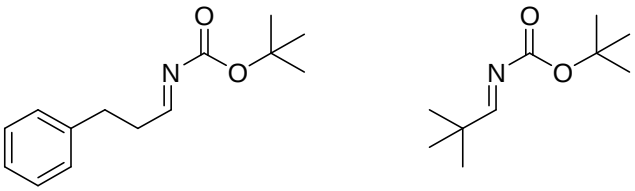
a) Reaction run at RT; b) yield and er determined after *in situ* reduction with $NaBH_4$.

The Mannich reaction of acetaldehyde with *N*-Boc-imines showed the same broad substrate spectrum as was described for other enolizable aldehydes (chapter 4.2). The enantioselectivity was again found to be outstanding, but the yields were only moderate to good.

The substituents of the aromatic ring were governing the reactivity of the imine. Phenyl and naphthyl substituted imines as well as an imine with an electron donating substituent were reacting at low temperatures in the desired way (Table 14, entries 1-3). Electron-poor imines were found to be of lower reactivity, but could be reacted in satisfying yields at room temperature (entries 4 & 5). **264f** had to be reduced *in situ* to alcohol **271** because it was prone to undergo elimination. Slightly lower yields were obtained for a heteroaromatic substituent (entry 6).

It was also possible to demonstrate the use of aliphatic imines in the Mannich reaction of *N*-Boc-imines for the first time, with yields strongly dependent on the stability of the parent imine (entries 7 & 8).

Apart from the somewhat low yields, the limitation of the reaction lies with the imines, and the very unreactive aliphatic imines **159j** and **l** could not be converted to the desired products (Scheme 122).

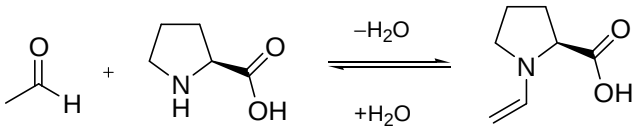


159j **159l**

Scheme 122: Imines that could not be successfully employed in the reaction with acetaldehyde.

4.3.3. Discussion

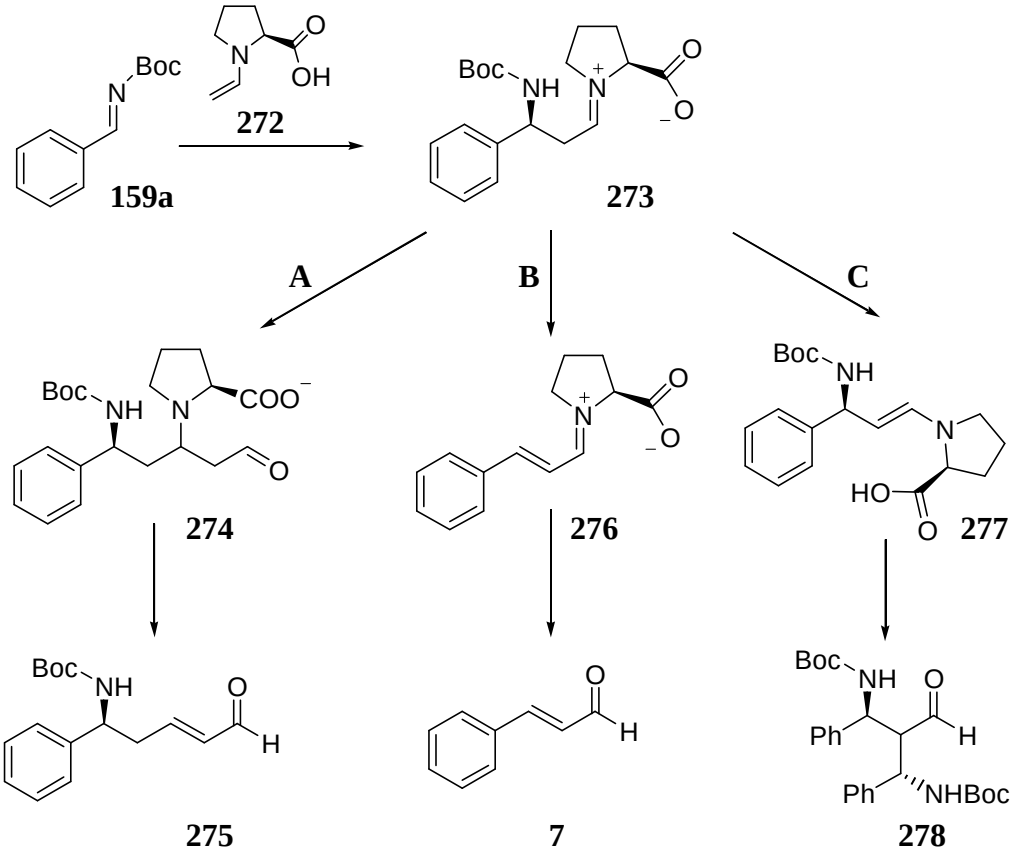
In the course of this work and at the same time the research of *Hayashi* and coworkers on the aldol reaction of acetaldehyde [164] it was demonstrated for the first time that acetaldehyde can indeed be used directly as a nucleophile in organic synthesis in a controlled manner. The challenge here lay with the reactivity of acetaldehyde **4** and its enamine formed with proline (**272**, Scheme 123).



4 **263** **272**

Scheme 123: Acetaldehyde and its proline enamine (**272**).

Because of the substitution with only a methyl group the carbonyl function of acetaldehyde is a better acceptor than most other aliphatic aldehydes, rendering it prone to undergo self-aldol reactions. The reaction products of acetaldehyde are themselves also potential nucleophiles and electrophiles for further transformations. Apart from the possibility of aldol reactions between two molecules of acetaldehyde the products of the Mannich reaction may also undergo several follow-up reactions to account for the low yields (Scheme 124).



Scheme 124: Potential overreactions of the initial addition product.

Pathway **A** shows the initial product **273** undergo another Mannich reaction with an additional equivalent of acetaldehyde to form intermediate **274**, which would then eliminate to α,β-unsaturated aldehyde **275**. This Mannich-Mannich reaction sequence is analogous to the explanation of *Córdova et al.* for the formation of the trimer of acetaldehyde in the self-aldol reaction.[20] Some hints were found that this reaction is taking place with the discovery of the typical signal set for α,β-unsaturated aldehydes in crude NMR measurements, and which could be neither attributed to cinnamaldehyde **7** nor crotonaldehyde. However, this compound could not be isolated.

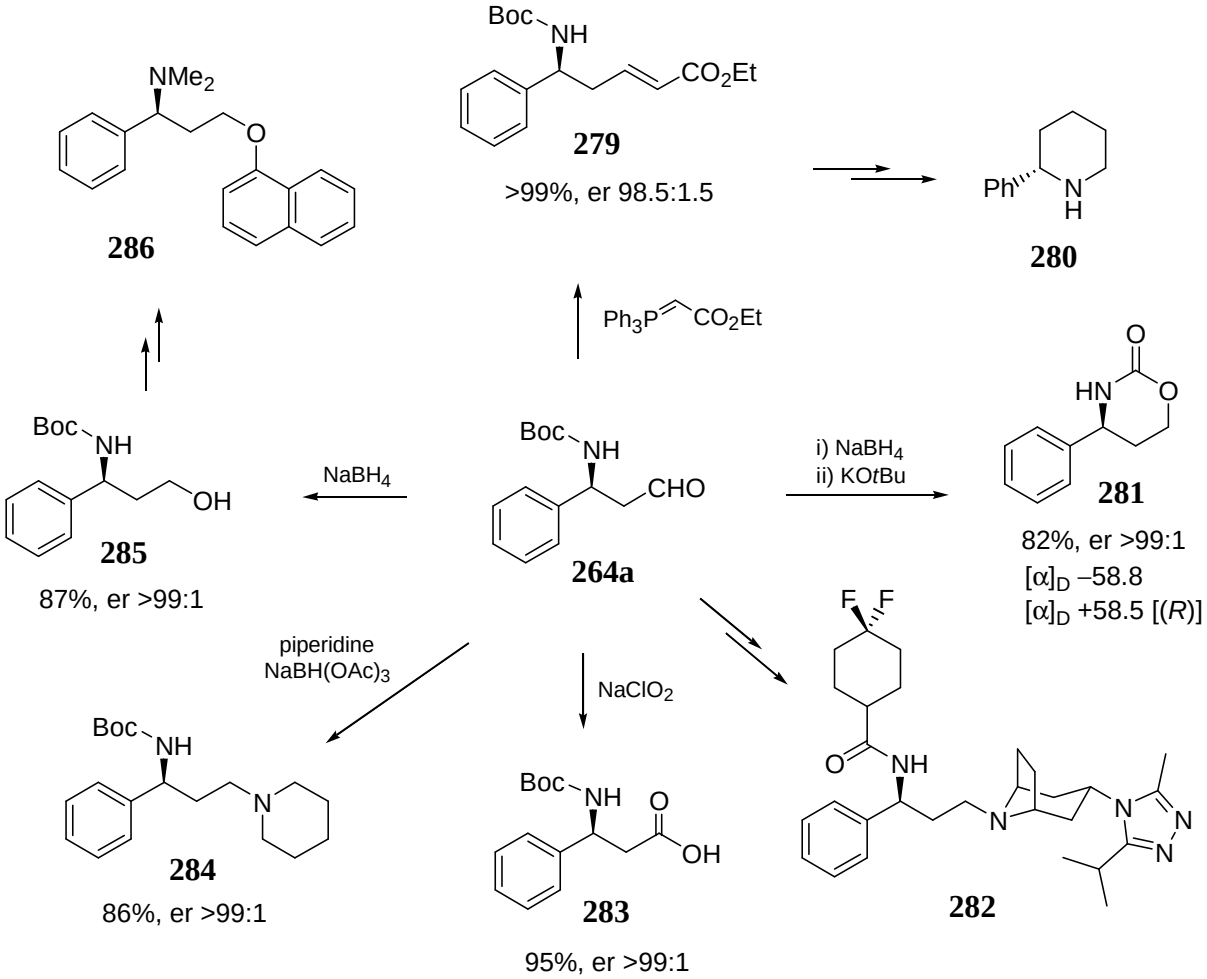
Another elimination is possible directly from **273** to yield iminium ion **276** (Scheme 124, pathway **B**), which would hydrolyze to cinnamaldehyde **7**. As an alternative pathway, **264a** may eliminate the carbamate to yield the same product.

Both reaction pathways proceed *via* iminium ion **273**, and are in competition with the hydrolysis to **264a**. Little influence can be taken on this competition, as an increase in the water concentration which would increase the rate of the hydrolysis would also lead to decomposition of the starting material. Gratifyingly, however, the hydrolysis is faster under the chosen conditions than the undesired follow-up reactions.

Pathway **C** shows the tautomerization of **273** to enamine **277**. This can then react with a further equivalent of **159a** in a second Mannich reaction, yielding double Mannich product **278**.[165] This reaction pathway can be suppressed by using a large excess of acetaldehyde.

The manipulation of the products of the Mannich reaction was not part of this thesis, but is covered by Daniela Kampen in detail in her thesis. The following paragraph will therefore only briefly sum up the results already published to show the synthetic potential deriving from the Mannich reaction.[166]

The synthetic utility was exemplified with **264a**, which can be reacted in a Wittig reaction to yield **279**, an intermediate in the synthesis of 2-phenylpiperidine (**280**) (Scheme 125).[167]

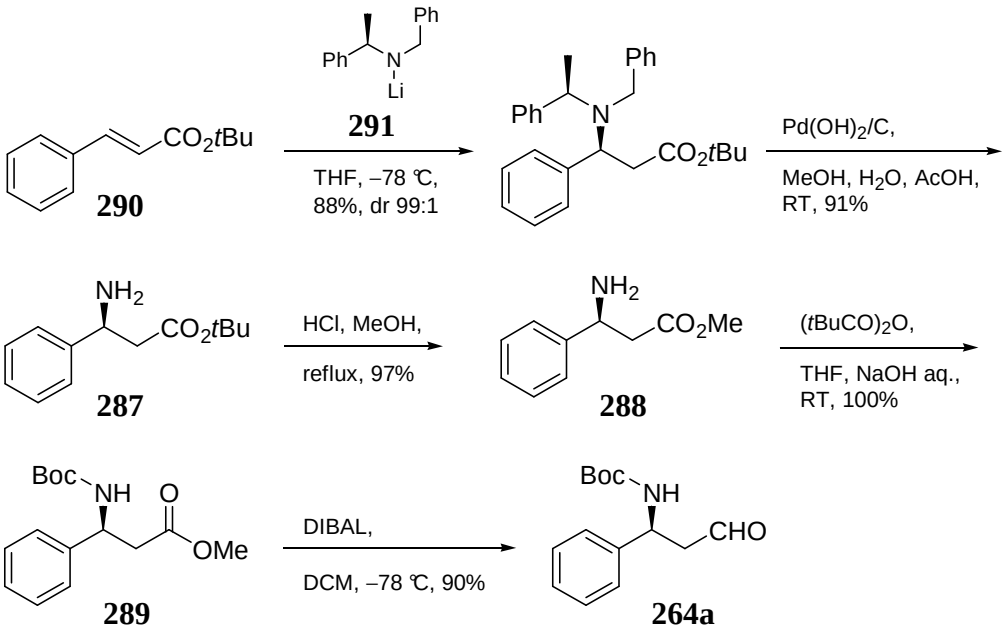


Scheme 125: Possible transformations of **264a**.

It could also be reduced and cyclized to **281**, and the absolute configuration of the product could be determined by comparison with the optical rotation of the known (*R*)-enantiomer.[168] **264a** is a known intermediate in the synthesis of UK-427,857 (**282**), a recently approved CCR5 inhibitor for the treatment of AIDS,[169, 170] can be oxidized to the corresponding *N*-Boc-

protected β^3-amino acid **283**, and reductively aminated to **284** in very high yields. Finally, simple reduction of the aldehyde to alcohol **285** gives a known intermediate in the synthesis of serotonin reuptake inhibitor (*S*)-Dapoxetine (**286**).[171, 172]

The advantage of the new methodology presented herein can be demonstrated by comparison with the previously reported synthesis of **264a** in the patent of Pfizer concerning the synthesis of **282** (Scheme 126).



Scheme 126: Known synthetic route to **264a**.

Pfizer's patent starts from ester **287**, which is converted into **264a** via transesterification to **288**, Boc-protection to **289**, and finally a DIBAL-reduction.[173] **287** can be prepared from cinnamic ester **290** in two steps.[174] This synthesis does not only employ several more reaction, workup, and purification steps as compared to the new synthesis presented here, but it also relies on the use of a stoichiometric amount of a chiral amine (**291**) to introduce the chirality of the molecule. Moreover, several steps are conducted at –78 °C, which is preferentially avoided in industry because of economic reasons.

In the course of the study reported in this chapter it could not only be shown that acetaldehyde is indeed a useful nucleophile in asymmetric, catalytic reactions, but also that this reaction directly leads to a variety of interesting follow-up products through transformations that can be undertaken starting from an essentially enantiopure starting material. It has, together with the research on the aldol reaction by *Hayashi* and co-workers,[164] thus opened the way to further explore the chemistry of this smallest enolizable carbonyl compound by proving that it is

in fact not as uncontrollable as was believed for a long time. The use of acetaldehyde has already been extended to the Michael-reaction,[175, 176] and other approaches to the Mannich reaction have already been reported.[163, 177] The value of this discovery lies therefore not only in the products that can be obtained, but in opening the door for the future exploration of the chemistry of acetaldehyde.

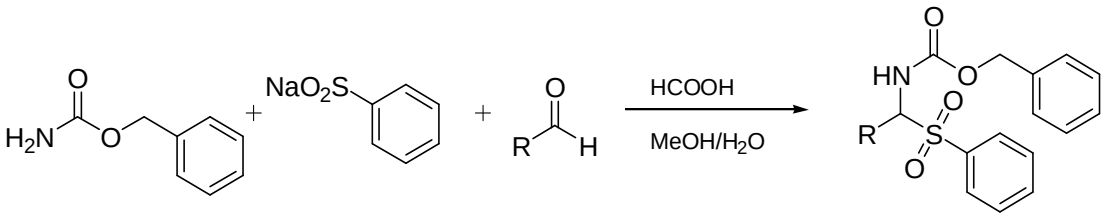
4.4. Mannich reactions of *N*-Cbz-imines

With the chemistry of *N*-Boc-imines established in the Mannich reactions of unmodified aldehydes under proline catalysis, the development of the similar reaction with *N*-Cbz-imines was undertaken.

The Cbz group is orthogonal to the Boc group in the protection of the amino function since it is able to withstand the mild acidic conditions leading to the cleavage of the Boc group, but is itself cleaved under hydrogenolytic conditions which are tolerated by Boc.

4.4.1. Synthesis of the starting materials

The starting imines have been prepared in a two step synthesis following *Kanazawa*, *Denis*, and *Greene*,[142] which was first extended to *N*-Cbz-protected imines *via* their sulfones by *Tillman*, *Ye*, and *Dixon* .[116]



292 **251** **252a**, R = Ph **293a**, 50%

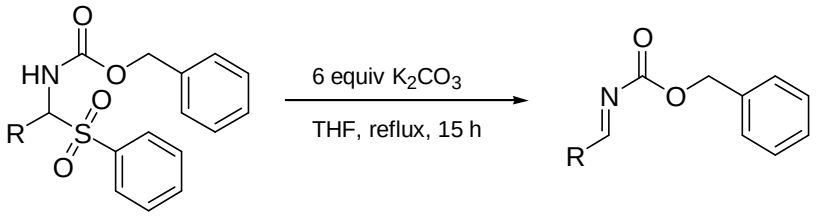
252j, R = 4-MeC_6H_4 **293b**, 30%

252d, R = 4-$CF_3C_6H_4$ **293c**, 34%

Scheme 127: Synthesis of the starting sulfone compounds.

The reactions were conducted as described in chapter 4.2.1 with benzylcarbamate **292** as the amine compound, giving sulfones **293a - c** in rather low yields (Scheme 127). Nonetheless, enough of the products could be obtained for further transformations since the reactions could be run on a large scale. *Tillman* described the use of the tosylsulfinic acid sodium salt instead of **251**, and a much better yield of 97% for the tosyl-analogue of **293a** was reported.[116] The use of a stronger nucleophile is obviously beneficial in this reaction.

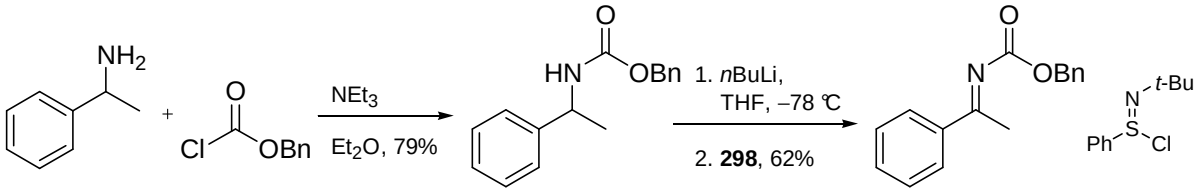
The elimination step was also possible according to the reaction previously described (chapter 4.2.1) and proceeded to give the required imines in high yields, which could either be directly employed in the subsequent Mannich reaction (**294a**), or were purified by bulb-to-bulb distillation (**294b** & **c**, Scheme 128).



293a,	R = Ph	**294a**,	94%
293b,	R = 4-MeC_6H_4	**294b**,	87%
293c,	R = 4-$CF_3C_6H_4$	**294c**,	96%

Scheme 128: Synthesis of the imines.

Apart from imines derived from aldehydes, a ketimine was also synthesized following a procedure by *Matsuo* and *Ishibashi* (Scheme 129).[178]



295 **296** **297** **299** **298**

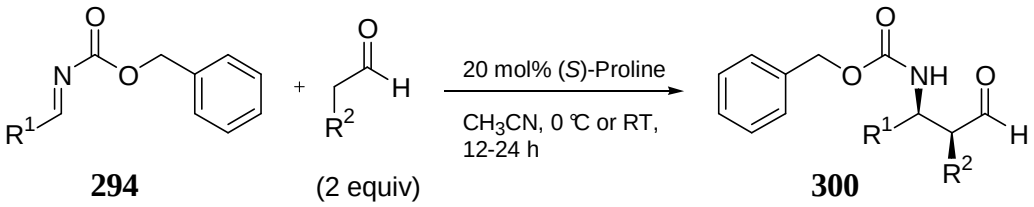
Scheme 129: Synthesis of an *N*-Cbz-ketimine.

In this synthesis, phenylethylamine (**295**) is protected with Cbz-chloride (**296**). Protected amine **297** is deprotonated with *n*BuLi and oxidized with *N*-*tert*-butyl benzenesulfinimidoyl chloride (**298**) to yield the ketimine **299** in good overall yield.

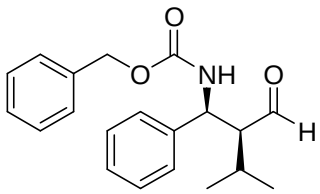
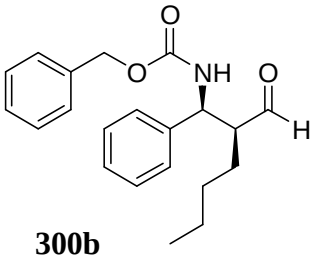
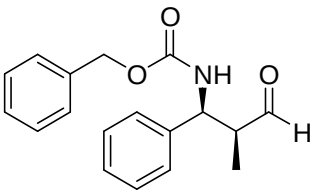
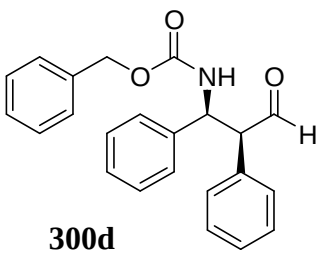
4.4.2. Reaction scope and limitations

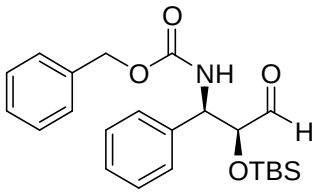
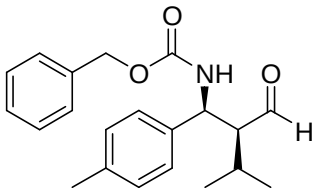
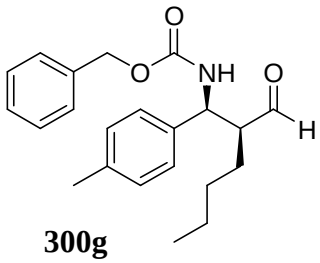
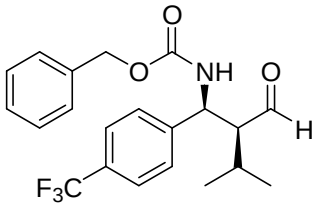
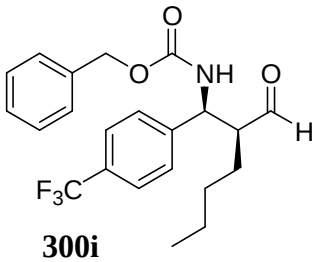
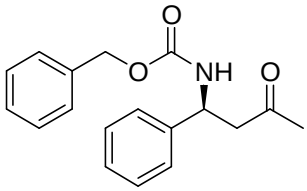
There were no further optimizations undertaken as compared to the Mannich reaction with *N*-Boc-imines. The scope was evaluated with regard to three different imines and a variety of different carbonyl functions (Table 15). The absolute configuration has been assigned in analogy to the absolute configuration of the *N*-Boc protected products.

Table 15: Substrate scope for the Mannich reaction of *N*-Cbz-imines



294 (2 equiv) **300**

Entry	Product	Yield	dr	er
1	 **300a**	57%	49:1	90.5:9.5
2	 **300b**	57%	19:1	>98:2
3[a]	 **300c**	33%	14:1	89:11
4[a]	 **300d**	49%	8.8:1	>99:1

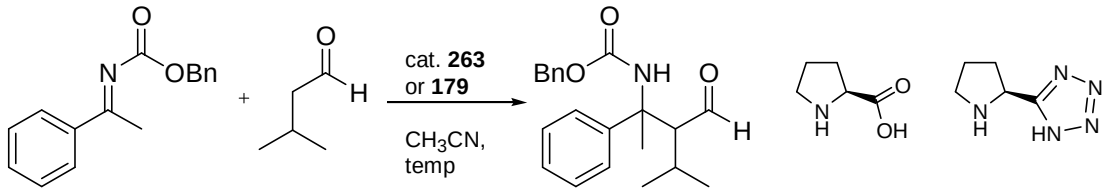
Entry	Product	Yield	dr	er
5[b]	 **300e**	57%	39:1	>99:1
6	 **300f**	81%	29:1	91.7:8.3
7	 **300g**	94%	19:1	>99:1
8[c]	 **300h**	54%	5:1	88:12
9[c]	 **300i**	69%	7:1	97:3
10[c,d]	 **300j**	55%	–	96:4

a) Yield and er determined after *in situ* reduction with $NaBH_4$; b) reaction run at 15 °C for 48 h; c) reaction run at RT; d) reaction run in acetone.

Different aldehydes could be employed in this reaction, giving products of very high to excellent diastereomeric and optical purity, with the yields being somewhat lower as compared to the Mannich reaction of *N*-Boc-imines (Table 15, entries 1-5). Some products were epimerizing during column chromatography and therefore had to be reduced to the corresponding alcohols before the workup (entries 3 & 4).
It was further possible to show the use of electron-rich (entries 6 & 7) as well as electron-poor aromatic imines (entries 8 & 9). The yields were found to be better for the electron rich imines. The reactivity of the electron-poor imines was found to be reduced and the reactions had to be run at room temperature.

Ketimine **299** was investigated as potential substrate for the Mannich reaction (Table 16).

Table 16: Attempts at reacting an *N*-Cbz-ketimine



Entry	Temperature	Catalyst	Reaction time	Yield	er
1	RT	50 mol% **263**	46 h	n.d.	n.d.
2	40 °C	30 mol% **263**	26 h	n.d.	n.d.
3	RT	20 mol% **179**	19 h	n.d.	n.d.

However, it was found that proline could not activate the ketimine at room temperature (entry 1) even at higher than usual catalyst loading, and an increase in the temperature lead to unidentified side reactions, but not to the formation of any desired product (entry 2). Tetrazole-derivative **179** was investigated as a potentially more active catalyst due to its better solubility, but the major product in this case was the conversion to the enamide corresponding to **299** (entry 3), and the desired product **301** was not observed in any case.

4.4.3. Discussion

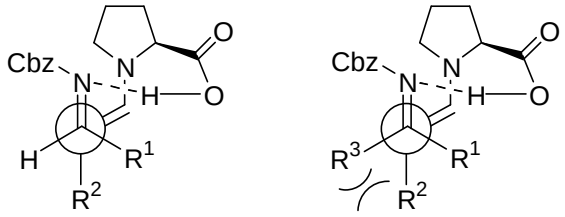
The products of the Mannich reaction of *N*-Cbz-imines were typically also precipitating at least during the aqueous workup and are stable, crystalline compounds. However, unlike in the corresponding reactions of *N*-Boc-imines, simple filtration and washing was not sufficient to isolate the pure products, and column chromatographic purification was necessary. This is due to the lower amount of product formation, which allows for the appearance of side products, but also due to the different solubility of the benzoyl carbamate formed through hydrolysis which has to be removed.

The reaction of **294a** with propionaldehyde was previously reported by *Córdova*,[154] who found that treating the imine with propionaldehyde in DMF at 4 °C gave **300c** in an enantiomeric ratio of 86:14 and a diastereomeric ratio of 4:1. The results of the study presented here suggest that the reaction is in fact of higher diastereoselectivity, but product epimerization occurs during column chromatography, as the dr found during this study was 14:1 after *in situ* reduction, but was considerably lower when the isolation of **300c** was attempted by chromatography. This instability of some products made it necessary to reduce them *in situ* before attempting workup and chromatographical purification. On a larger scale this can possibly be circumvented by the use of crystallization for purification.

The yields were found to be lower as compared to the corresponding reactions with *N*-Boc-imines, but were still good to very good in almost all cases. This is probably due to a higher rate of decomposition of the starting material.

It was also observed that the optical purity is not in all cases as good as for the *N*-Boc-imines. While several aldehydes, both bulky as well as long-chain aliphatic aldehydes, gave almost perfect enantiomeric ratios, β-substituted isovaleraldehyde as well as the small propionaldehyde gave lower selectivities. The Cbz group seems to disrupt the transition state geometry in contrast to the Boc group.

Extending the substrate scope to ketimines was so far not found possible. Ketimines are expected to be much less reactive as compared to aldimines because of the steric interaction of the enamine and the additional substituent on the imine carbon atom in the transition state (Scheme 130). The transition state geometries [93] shown are based on the lowest energy states in the calculations by *Bahmanyar* and *Houk* on the reaction of the *N*-phenyl imine of acetaldehyde with acetone under proline catalysis.[152]



TS-A **TS-B**

Scheme 130: Transition states for aldimine (**TS-A**) and ketimine (**TS-B**).

It was found that proline cannot activate the imine towards the nucleophilic attack of the enamine. Attempts at using the tetrazole derivative **179** also proved not fruitful, because the ketimine has another reaction pathway under these conditions in tautomerizing to the corresponding ene carbamate.

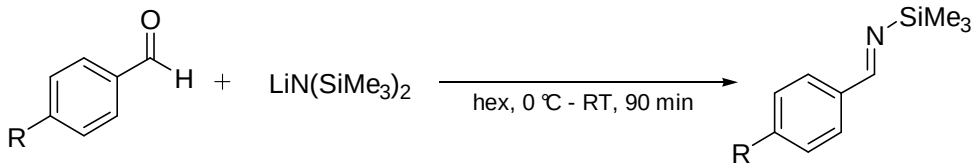
The Mannich reaction of *N*-Cbz-imines accepted the same substrates as the corresponding Mannich reaction of *N*-Boc-imines, albeit at sometimes reduced yields. The selectivities were found to be very good with larger aldehyde donors, but are somewhat lowered with small aldehydes. It can be seen as complementary to the reaction of *N*-Boc-imines with regard to the protecting group and its removal.

4.5. Mannich reactions of *N*-Fmoc-imines

The last of the three most important carbamate protecting groups is the Fmoc group. It is orthogonal to the previously described Boc and Cbz groups in that it is cleaved under mild basic conditions, but is able to withstand acidic conditions that remove a Boc group as well as hydrogenolytic conditions that liberate Cbz-protected amines. The chemistry of *N*-Fmoc-imines in the Mannich reaction was therefore also explored.

4.5.1. Synthesis of the starting materials

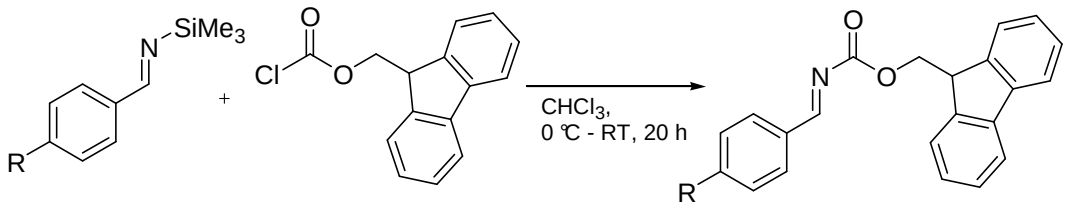
The synthesis of *N*-Fmoc-imines is also a two-step process. Due to the instability of the Fmoc group under basic conditions, a different approach to this kind of imine was used, based on the conversion of silanamines to carbamates that was introduced by *Würthwein*.[179] The required silanamines **302a - c** could be obtained in good to very good yields through the reaction of the corresponding aldehydes with lithium hexamethyldisilazane (**303**) according to a procedure described by *Hart et al.*[180] (Scheme 131) and were purified by distillation.



252a,	**303**	R = Ph	**302a**,	83%
252j,		R = 4-MeC_6H_4	**302b**,	54%
252d,		R = 4-$CF_3C_6H_4$	**302c**,	69%

Scheme 131: Preparation of the starting silanamines.

The silanamines were converted into the corresponding Fmoc-protected imines **269a - c** by reaction with Fmoc chloride (**304**). The compounds were purified by crystallization to give the products in acceptable yields (Scheme 132).



302a,	**304**	R = Ph	**269a**,	65%
302b,		R = 4-MeC_6H_4	**269b**,	n.d.
302c,		R = 4-$CF_3C_6H_4$	**269c**,	37%

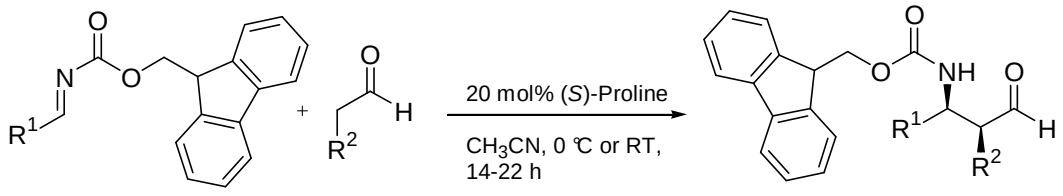
Scheme 132: Preparation of the *N*-Fmoc-imines.

269b was found to be very unstable and decomposed upon any kind of attempted purification as well as upon storage at –18 °C. The same instability was found for the 4-methoxyphenyl imine.

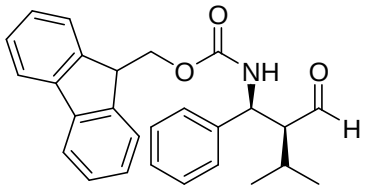
4.5.2. Reaction scope and limitations

The scope of the reaction was evaluated under the same conditions as for the previously reported Mannich reactions (see chapter 4.2.3). Due to the instability of the electron-rich imines this class of starting materials was not tested, as the starting materials could not be purified, and no trustworthy data could therefore be expected. The absolute configuration has been assigned in analogy to the absolute configuration of the *N*-Boc protected products.

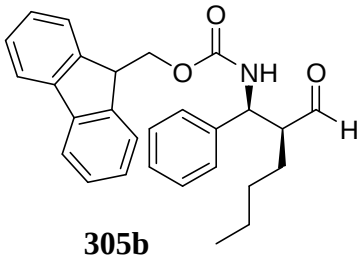
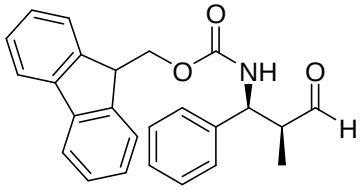
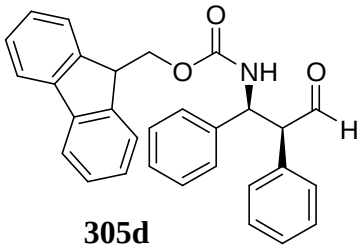
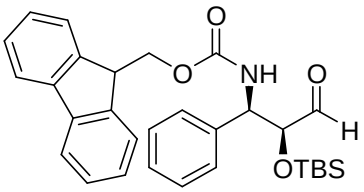
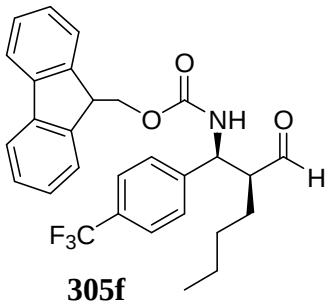
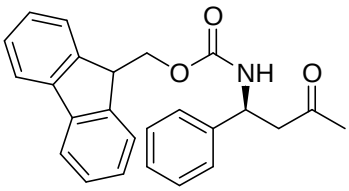
Table 17: Substrate scope of the Mannich reaction of *N*-Fmoc-imines



269 (2 equiv) **305**

Entry	Product	Yield	dr	er
1		61%	2.8:1	93:7

305a

Entry	Product	Yield	dr	er
2	 **305b**	59%	2.2:1	84:16
3[a]	 **305c**	45%	2.5:1	>99:1
4[a]	 **305d**	67%[b]	n.d.	99:1
5[c]	 **305e**	61%	44:1	>99:1
6[d]	 **305f**	57%	2.2:1	92:8
7[d,e]	 **305g**	38%	–	93.5:6.5

a) Yield and er determined after *in situ* reduction with $NaBH_4$; b) yield of single isomer; c) reaction run at 15 °C for 48 h; d) reaction run at RT; e) reaction run in acetone.

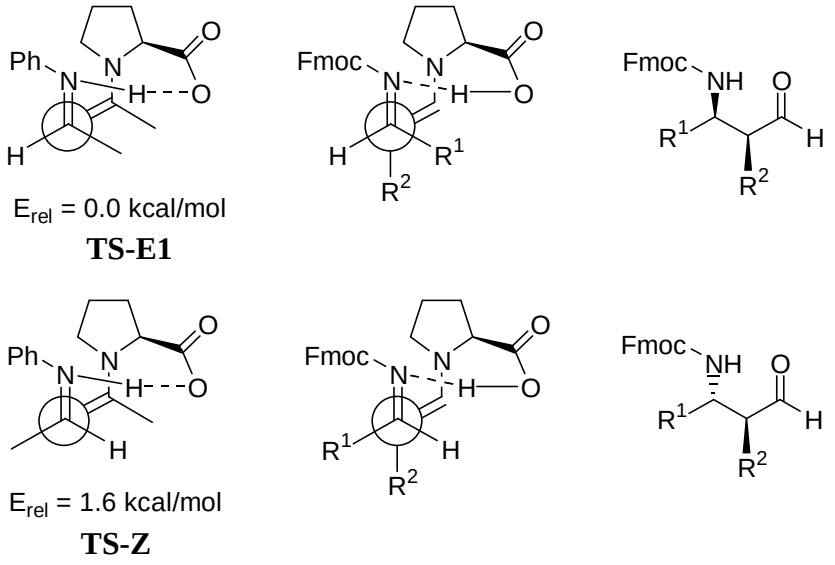
The yields were good with various carbonyl compounds except acetone (entry 7). A good yield was also obtained for an electron deficient imine (entry 6). The enantiomeric purity of the products was better when bulkier aldehydes were used, but was generally high to excellent. However, the diastereomeric ratios were poor in all cases except for the α-oxygenated product **305e** (entry 5).

4.5.3. Discussion

The Mannich reaction of *N*-Fmoc-imines shows results similar to the reaction of *N*-Cbz-imines with regard to the yields and enantiomeric excesses obtained. It was also observed that larger donors lead to better enantioselectivities (Table 17, entries 4 & 5), with the difference that hexanal reacted with lower selectivity. The most pronounced difference to the chemistry of *N*-Boc- and *N*-Cbz-imines, however, is the very low diastereoselectivity obtained in the reaction of *N*-Fmoc-imines.

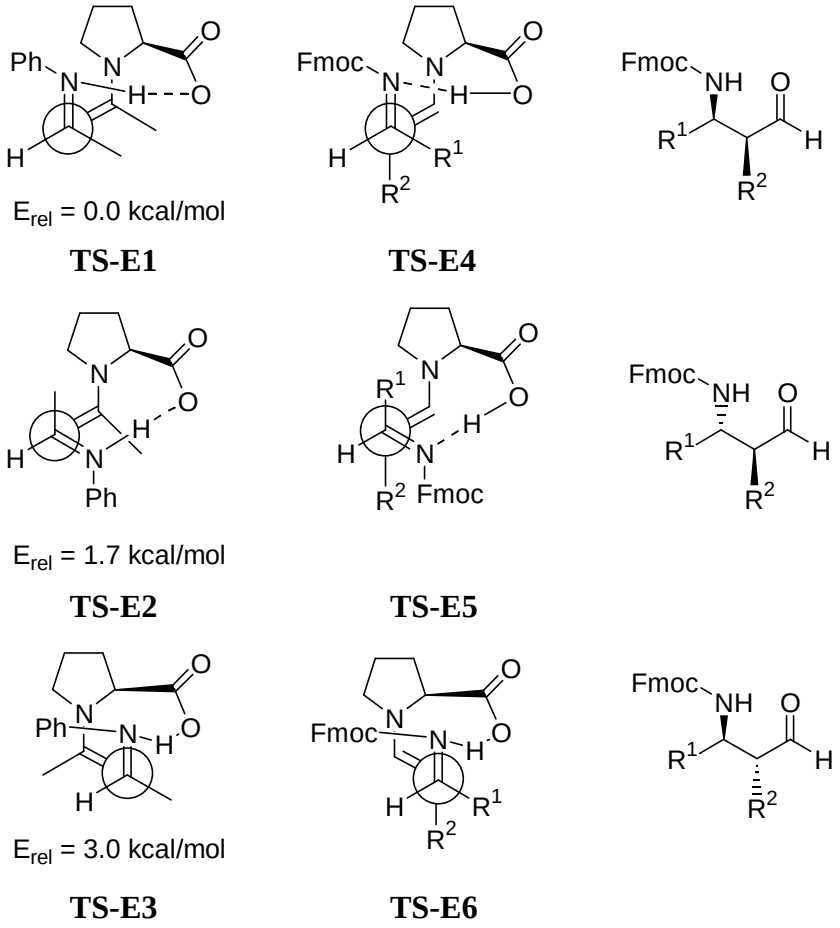
Three explanations for the low diastereomeric ratios can be discussed. First, the diastereomeric ratio can decrease during the reaction as a result of epimerization. Epimerization occurred during column chromatography of **305c** and **d**, but the other products were found to be stable on silica. Moreover, in all other Mannich reactions described so far, no epimerization took place under the reaction conditions, so this is most likely not responsible for the low dr in the products.

A second possibility is the involvement of *Z*-imines. During the synthesis of the substrates it was observed that sometimes another imine peak was detected by NMR, which is probably from the *Z*-configured imine. *Z*-imines have been studied in calculations regarding the transition states of Mannich reactions, but are usually not considered to be the dominant species because the corresponding *E*-imines are more stable. Based on the results for the lowest energy transition states by *Houk* in the reaction of the *N*-phenyl imine of acetaldehyde with acetone (Scheme 133, left), the two transition states differ by only 1.6 kcal/mol and TS-Z is therefore energetically accessible.[152] If the same concept is applied to the Fmoc-imines and it is assumed that the energy difference is no bigger than in the calculated case, this can explain an erosion of the dr if sufficient *Z*-configured imine is present during the reaction (Scheme 133, middle and right). The required *Z*-imine would then have to be formed during the reaction by a nucleophilic mechanism.



Scheme 133: Plausible transition states for *E*-(**TS-E1**) and *Z*-imines (**TS-Z**); left: calculations by *Houk*;[152] middle: corresponding transition state for *N*-Fmoc-imines; right: corresponding products.

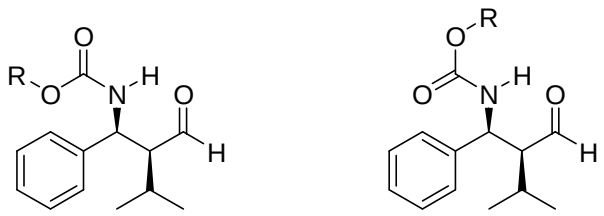
The third possible explanation deals with the transition states invoking an *E*-imine (Scheme 134).



Scheme 134: Plausible transition states in the Mannich reaction for an *E*-imine based on those calculated by *Houk.*

The relative energies are again referring to the reaction of the *N*-phenyl imine of acetaldehyde with acetone. *Houk* found that **TS-E1** and **TS-E2**, in which the enamine double bond is oriented away from or *anti* to the carboxylate, are lower in energy than **TS-E3** with the double bond on the same side or *syn* to the carboxylate (Scheme 134, left row). It can be assumed that the corresponding transition state **TS-E6** for an aldehyde is even higher in energy because of the steric interaction between the double bond and the carboxylate, which does not occur in the corresponding transition states **TS-E4** and **TS-E5** (Scheme 134, middle row). In fact, *Hayashi* and co-workers have calculated the difference in energy between *anti* and *syn* conformations of the enamine of acetaldehyde with α-methylpyrrolidine to be 0.7 kcal/mol.[163]
The two predominant transition states should therefore be **TS-E4** and **TS-E5**. To account for the lower selectivity the steric interaction between the Fmoc group and the substituent R^2 in transition state **TS-E5** is assumed to be lower as compared to the Mannich reaction of *N*-Boc-imines. This can also explain why a much higher dr was found in the case of the sterically more demanding TBS-ether (**305e**), as this would increase the unfavorable interaction between R^2 and the Fmoc protecting group.

During the characterization of the products the existence of rotamers was observed, which do not interconvert on the NMR timescale at room temperature and give two sets of signals (Scheme 135). This was also found for compounds **255d** and **k** with a Boc group and **300e** with a Cbz group, respectively.

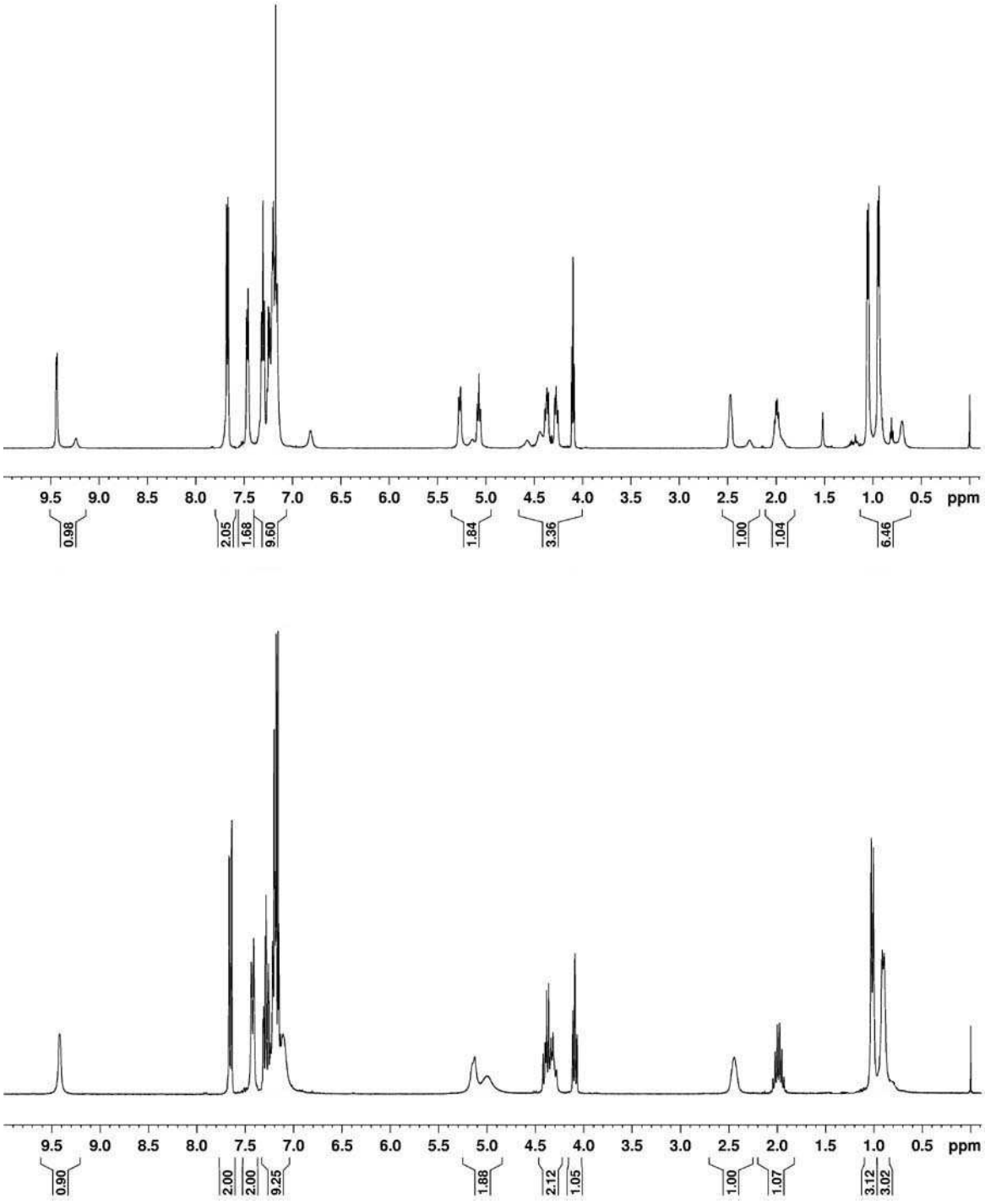


syn *anti*

R = (9H-fluoren-9-yl)methyl

Scheme 135: Rotamers of **305a**.

At 333 K the rotamers were interchangeable and only one set of signals was observed in NMR measurements (Scheme 136).



Scheme 136: NMR spectra of **305a** in $CDCl_3$. Top: measured at 293 K (500 MHz); bottom: measured at 333 K (300 MHz).

The Mannich reaction of *N*-Fmoc-imines was found to be less rewarding than the previously discussed Mannich reactions of *N*-Boc- and *N*-Cbz-imines. Although precipitation occurs during the reaction, the collection of the pure product was not possible by simple filtration. This is due to the formation of the Fmoc-carbamate which results from the hydrolysis of the starting material and has to be removed by chromatographical methods.

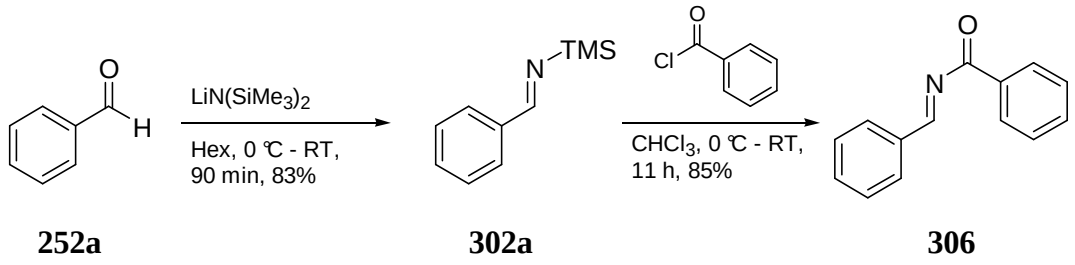
Moreover, the reaction yields mixtures of diastereoisomers which are usually difficult to separate and sometimes required two or more columns with different eluents for purification. While the yields obtained are good, they are still lower than in the comparable reaction with *N*-Boc imines. Nonetheless, the Fmoc protected aminoaldehydes may well serve as building blocks in synthesis, and separation of the diastereomers will not necessarily be difficult at a later stage in a desired synthesis. In addition to that, β-amino acids derived from these products are especially valuable for solid phase synthesis, for example of peptides, because the reactions can be monitored by following the UV-absorption of the Fmoc-group.

4.6. Mannich reactions of an *N*-benzoyl-imine

The benzoyl group is an example for a non-carbamate group and was chosen to investigate if the Mannich reaction also works with an amide substituent on nitrogen. Its cleavage requires much harsher acidic conditions for removal than the Boc group, such as refluxing 6N HCl or HBr in acetic acid.[15] It is also more electrophilic compared to the carbamates.
Furthermore, the reaction of the *N*-benzoyl-imine of benzaldehyde with a suitably protected α-hydroxyaldehyde offers a direct approach to the side chain of paclitaxel (taxol).

4.6.1. Synthesis of the starting material

N-benzylidenebenzamide **306** was synthesized in the same reaction sequence as described before (chapter 4.5.1) for the synthesis of the *N*-Fmoc-imines from benzaldehyde in very good yields and could be purified by bulb-to-bulb distillation (Scheme 137).



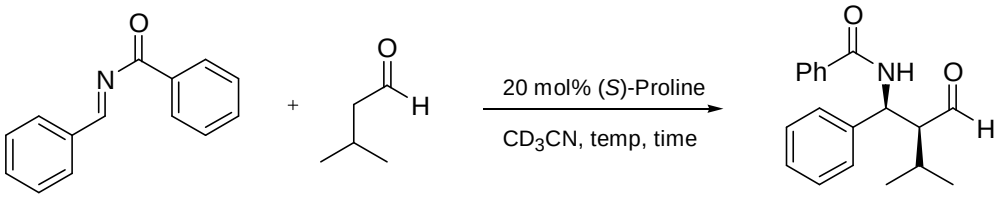
252a **302a** **306**

Scheme 137: Synthesis of *N*-benzylidenebenzamide **306**.

4.6.2. Optimization of the reaction conditions

The major factor to be investigated in the Mannich reaction of *N*-benzylidenebenzamide (**306**) was the reaction temperature. It was found that the *N*-benzoyl-imine reacted very slow at reduced temperatures, which is in accordance with the observations for electron-poor imines in the previously described reactions. Moreover, it can be hydrolyzed to benzaldehyde or potentially react with itself under inclusion of one molecule of water in an acid-catalyzed process (see chapter 4.6.4). The latter could be avoided by stirring the starting materials over base for 10 min prior to use.
In the model reaction *N*-benzylidenebenzamide **306** was reacted with isovaleraldehyde (**166**) to yield **307a**. Several temperatures where investigated and the reaction progress monitored by NMR (Table 18).

Table 18: Optimization of temperature and reaction time



306 **166** (2 equiv) **307a**

Entry	Temper-ature	Reaction time	dr[a]	Result[a,b]
1	0 °C	78 h	n.d.	~ 70% conversion, decomposition starting
2	10 °C	52 h	n.d.	~ 90% conversion, decomposition starting
3	21 °C	19 h	3.4:1	full conversion
4	30 °C	7.5 h	2.2:1	full conversion

a) Determined by NMR; b) decomposition refers to the acid-catalyzed process becoming observable. Decomposition to yield benzaldehyde can be seen from the beginning of the reaction.

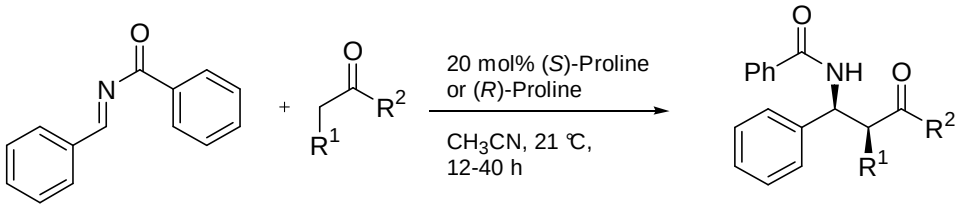
The reaction was found to be sluggish at 0 °C and 10 °C (Table 18, entries 1 & 2). The starting material was never consumed completely, and after three and two days, respectively, the decomposition of the starting material to the dimer was observed, probably due to oxidation of the formed benzaldehyde to benzoic acid, which then catalyzed the other decomposition pathway.

Raising the temperature to 21 °C led to an acceptable reaction time. It was even shorter at 30 °C, yet at the cost of lower diastereoselectivity and an approximate 1:1 rate of product to benzaldehyde (entries 3 & 4).

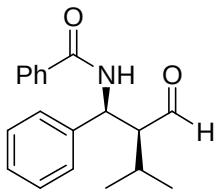
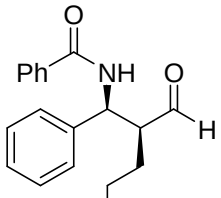
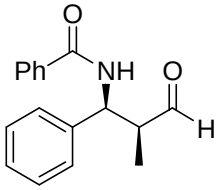
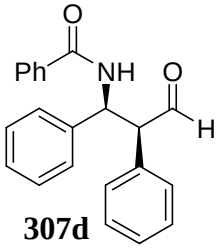
4.6.3. Reaction scope and limitations

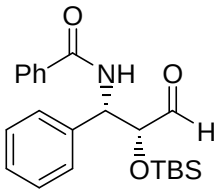
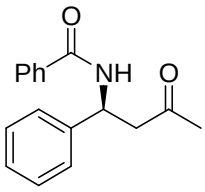
A number of aldehydes were investigated as donors for the reaction with **306** (Table 19).

Table 19: Substrate scope



306 (2 equiv) **307**

Entry	Product	Yield	dr	er
1	 **307a**	73%	3.4:1	93:7
2	 **307b**	69%	2.8:1	98.8:1.2
3	 **307c**	67%	3.5:1	>99:1
4[a]	 **307d**	54%	2:1	98:2

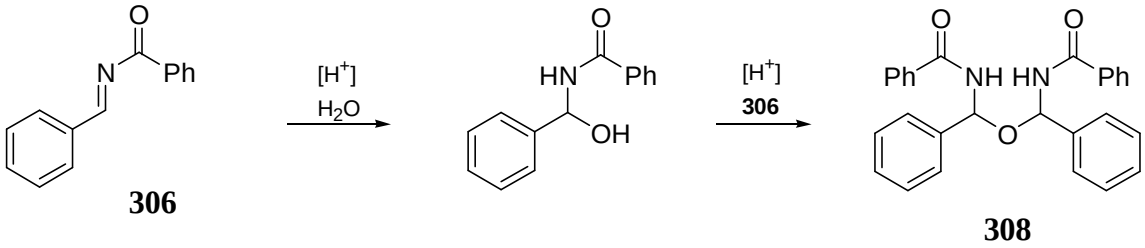
Entry	Product	Yield	dr	er
5	 **307e**	57%[b]	5:1	98:2
6[c]	 **307f**	47%	–	76:24

a) Yield and er determined after *in situ* reduction with $NaBH_4$; b) yield of single isomer; c) reaction run in acetone.

The yields for the Mannich reaction were found to be good in all cases. Due to the higher reaction temperature, the diastereoselectivities were low, with the best being 5:1 for TBS-protected α-hydroxy acetaldehyde (**307e**, entry 5), a result that was also found for the Mannich reaction of the corresponding *N*-Fmoc-imines. Isovaleraldehyde was found to give a slightly lower er compared to the other aldehydes, which gave excellent results. Unlike in all previously reported cases, however, acetone was found to be a rather unselective nucleophile, leading to the lowest er observed in the whole study.

4.6.4. Discussion

N-benzylidenebenzamide **306** was found to be less stable under the reaction conditions than the *N*-Boc-imines and was hydrolyzed faster, which accounts for the lower yields obtained in the reactions. It was also found that it is absolutely necessary to work in acid-free conditions, as the starting material quickly decomposes in an acid-catalyzed process. Based on mass spectrometric and NMR measurements, **308** is suggested as the potential, undesired product, which could be formed according to the mechanism given below (Scheme 138).



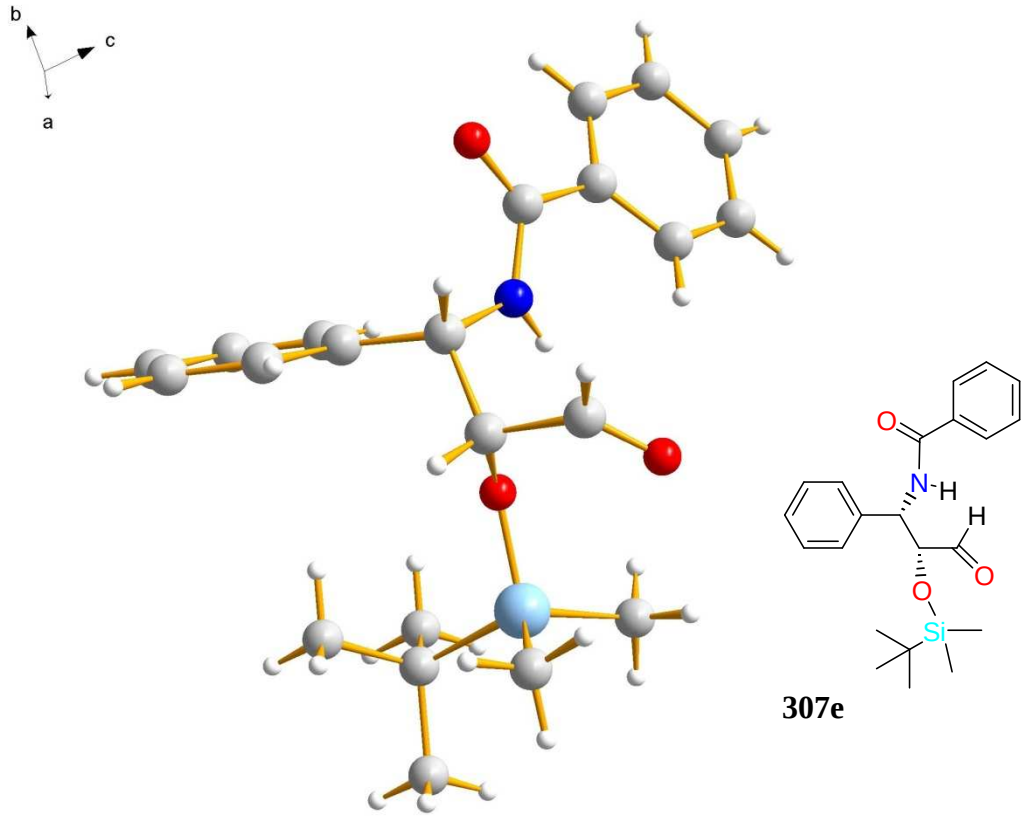
306 **308**

Scheme 138: Decomposition product **308** and proposed mechanism for its formation.

This decomposition was sometimes even observed despite the use of freshly distilled or prepared starting materials. A simple and reliable method to circumvent this problem was therefore needed. It turned out that this side reaction could be completely suppressed when solutions of the starting compounds where stirred over K_2CO_3 for 10 min immediately prior to use.

In many cases, the Mannich product precipitated from the reaction mixture or upon treatment with water. However, it was not possible to isolate the pure products, as the precipitate contained mixtures of *syn* and *anti* products as well as benzamide formed during the hydrolysis of the starting material. Column chromatography was therefore necessary to obtain the pure products. The products were stable to chromatographic purification with the exception of **307d**, which had to be reduced to the aldehyde to prevent epimerization. The reaction accepted the same nucleophiles as did the previously reported Mannich reactions and gave the corresponding products in good yields and typically very good enantioselectivities, but at low diastereoselectivities. This is due to the higher reaction temperatures required to overcome the lower reactivity of the imine.

It was possible to obtain crystals suitable for X-ray diffraction measurements by slow diffusion of pentane into a solution of **307e** in dichloromethane at 8 °C. The measurement confirmed the preference for the *syn* product in the Mannich reaction (Scheme 139).



307e

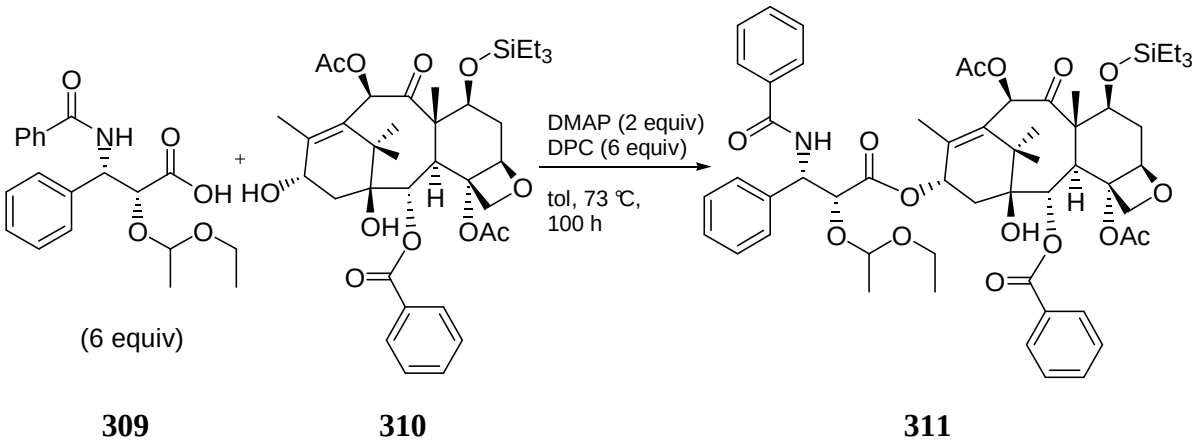
Scheme 139: Crystal structure of **307e** showing the relative geometry. The absolute configuration is assigned arbitrarily.

The use of an *N*-benzoyl-imine shows that not only carbamate-protected imines are viable substrates for the proline-catalyzed Mannich reactions, but also amide-based protecting groups are suitable. It was shown that a more electron-demanding protecting group is also lowering the reactivity of the imine in this kind of reaction. The removal of the benzoyl group from nitrogen requires harsher conditions than that of the Boc group, which will likely make it less useful in the synthesis of β-amino acids, but allows for the direct introduction of a sturdy protecting group early on in any synthesis using *N*-benzoyl Mannich products as chiral building blocks. The synthesis of paclitaxel described in the following chapter will illustrate this point.

4.6.5. Semisynthesis of paclitaxel

To demonstrate the use of the Mannich reaction of *N*-benzylidenebenzamide **306** as the key step in a semisynthesis of paclitaxel it was decided to prepare key intermediate **309** of the

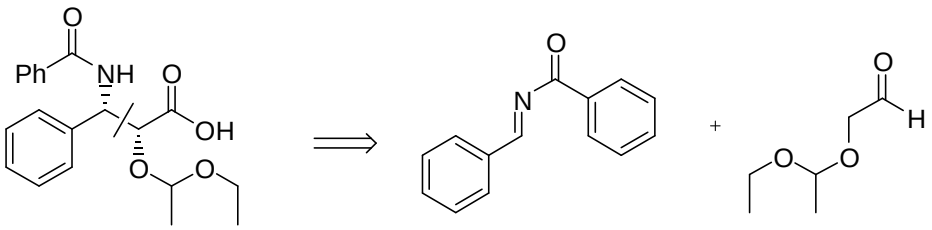
paclitaxel-synthesis from 7-TES-baccatin III (**310**) developed by *Greene* and *Guéritte-Voegelein* in 1988 (Scheme 140).[181]



309 **310** **311**

Scheme 140: Synthesis of protected paclitaxel-precursor **311** from acid **309** and 7-TES-baccatin III (**310**) developed by *Greene* and *Guéritte-Voegelein.*

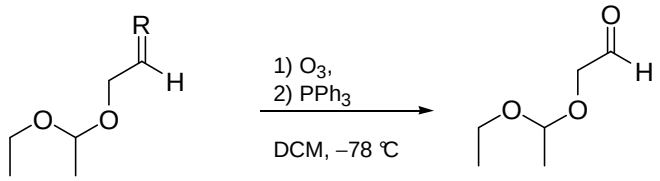
It was envisioned to install the correct absolute stereochemistry of **309** *via* an organocatalytic Mannich reaction according to the scheme below (Scheme 141).



309 **306** **312**

Scheme 141: Retrosynthetic analysis of **309**.

The synthesis of paclitaxel began with the search for a suitable method to produce the required aldehyde **312** through ozonolysis (Scheme 142). This aldehyde should already have the proper ethoxyethyl (EE) protecting group at the α-oxygen.

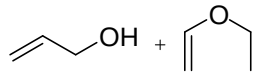
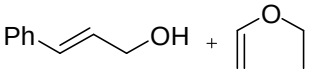
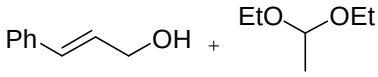
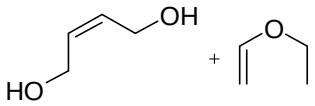
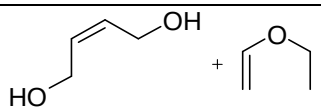


312

Scheme 142: Outline for the preparation of **312**.

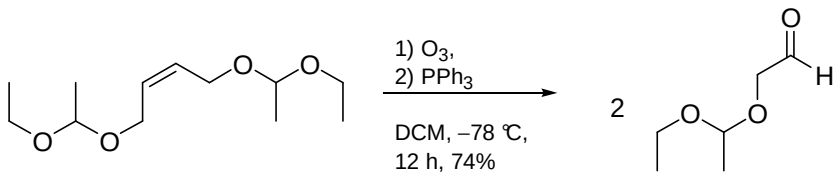
The different reactions tried are shown in the table below (Table 20). Several allylic alcohols were tested in the addition reaction to ethylvinylether (**313**) or a substitution on 1,1-diethoxyethane (**314**).

Table 20: Reagents and conditions tried for the synthesis of an aldehyde precursor

Entry	Reagents	Catalyst	Reaction time	Conditions	Yield
1	 **315** **313**	$CoCl_2$	18 h	DCM, RT	2%
2	 **316** **313**	$CoCl_2$	18 h	CH_3CN, RT	0%
3	 **316** **314**	HCl	6 h	neat, 110 °C	0%
4	 **317** **313**	TFA	3 h	neat, RT	93%
5	 **317** **313**	*p*-TsOH	3 h	neat, RT	80%

The reactions of both allylic alcohol (**315**) and cinnamyl alcohol (**316**) with ethylvinylether (**313**) or 1,1-diethoxyethane (**314**) were found to be low yielding under $CoCl_2$ and HCl-catalysis (Table 20, entries 1-3). *cis*-1,4-Butendiol (**317**), however, was found to give the desired double-protected product in high yield under both TFA as well as *p*-TsOH-catalysis. TFA proved to be superior, as *p*-TsOH presumably also catalyzed the polymerization of the starting materials and the solution was colored after the reaction.

With a high yielding synthesis for a suitable precursor in hand the ozonolysis was undertaken next (Scheme 143).



318 **312**

Scheme 143: Ozonolysis of **318** to give required aldehyde **312**.

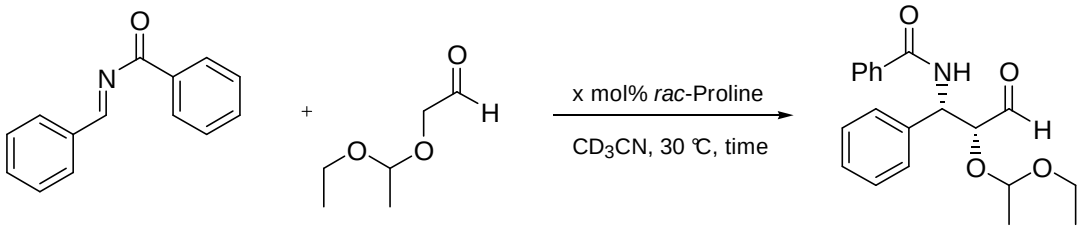
The ozonolysis of protected alcohol **318** proceeded smoothly at –78 °C, and the desired aldehyde was formed by addition of triphenylphosphine. After warming to room temperature and removal of the solvent the aldehyde was obtained by direct distillation from the reaction ves-

sel in a yield of 55% or by column chromatography in 74%. The lower yield in the distillation may be due to the precipitation of triphenylphosphine with ongoing removal of **312** which possibly trapped some of the product. This reaction is perfectly atom-economic with respect to the starting olefin.

312 was found to be rather unstable and even storage under argon and at –78 °C did not ensure a long lifetime. It is therefore more convenient to store **318** and prepare the aldehyde freshly prior to use.

The optimal conditions to perform the key step in the designed synthesis were determined with regard to temperature, catalyst loading, and ratios of the reactants (Table 21).

Table 21: Conditions for the key step converting **306** to **319**



306 **312** (y equiv) **319**

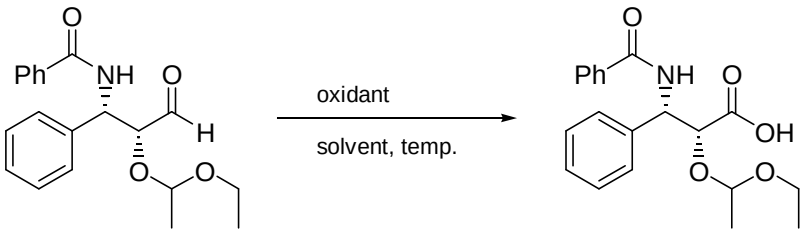
Entry	Catalyst	Equiv. **312**	Reaction time	Yield[a]
1	5 mol%	2	8	17%
2	10 mol%	2	8	41%
3	15 mol%	2	8	49%
4	20 mol%	2	6	51%
5	30 mol%	2	6	48%
6	40 mol%	2	6	39%
7	20 mol%	0.8	10	40%
8	20 mol%	1.0	10	45%
9	20 mol%	1.5	7	47%
10	20 mol%	4	6	47%
11	20 mol%	6	6	38%

a) Determined by NMR. Yields refer to the combined methyl epimers of the desired *syn* product.

The reaction was found to proceed sluggish at 20 °C, but fast enough when the temperature was increased to 30 °C. A maximum yield was found with a catalyst loading of 20 mol% while becoming lower when much less (entries 1 & 2) or much more catalyst was employed (entry 6). It was also established that the best result was obtained when two equivalents of aldehyde were used. Lower yields with higher amounts of aldehyde are possibly due to a parasitic equilibrium between proline and the aldehyde leading to oxazolidinones.[182]
Under the optimal conditions (entry 4) and using (*R*)-proline as the catalyst, **319** was obtained as an approximately one to one mixture of methyl epimers with a *syn*/*anti* ratio of 8:1 which is consistent with the previous observation that bulky aldehydes give better diastereoselectivity. The *syn* and *anti* isomers could be separated by column chromatography and the desired *syn* isomer was finally obtained in 52% yield.

The oxidation of **319** to **309** was also tried under different conditions (Table 22). The conditions used previously to oxidize the Mannich products to protected β-amino acids turned out to be not suitable, as the product was not clean after the workup (entry 1), and it was observed that column chromatographical purification was not possible due to the sensitivity of **309**.

Table 22: Oxidation of **319** to **309**



319 **309**

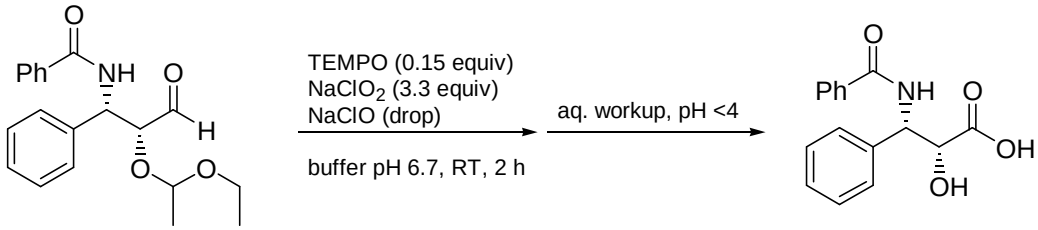
Entry	Oxidant	Solvent (v/v)	Temperature	Result
1	$NaClO_2$	2-methyl-2-butene, *t*BuOH, H_2O (1:1:1)	0 °C	product not clean
2	$NaClO_2$	2-methyl-2-butene, *t*BuOH, H_2O (5:1:1)	0 °C	product not clean
3	BAIB/ cat. TEMPO	CH_3CN/H_2O (1:1)	RT	product not clean
4	$NaClO_2$, cat. TEMPO, cat. NaClO	aqueous buffer (pH 6.7)/ CH_3CN (5:3)	RT	77% yield

An increase in 2-methyl-2-butene to more effectively scavenge the sodium hypochlorite formed during the reaction did not lead to a cleaner product, and the same result was observed for the BAIB/TEMPO system (entries 2 & 3). Finally the mixture of sodium chlorite, sodium

hypochlorite and TEMPO in an aqueous buffer as described by *Zhao et al.*[183] for the direct oxidation of alcohols to carboxylic acids turned out to give the product in 77% yield and without significant loss of diastereoselectivity (dr >20:1).

A major problem during this optimization study turned out to be the sensitivity of **309**, as the ethoxyethyl protecting group will be very easily cleaved under acidic conditions. The workup of **309**, as with many acids prepared in a similar way, is to basify the reaction medium and extract all organic compounds with diethyl ether in the first step. It is then acidified to protonate the acid and make it soluble in an organic solvent for a second extraction with ethyl acetate. In the case of **309** this was the only means of purification possible. It was therefore necessary to control the pH-value very strictly during the workup, as **309** is stable to a pH of 4.5, but will very quickly be deprotected at a pH below 4. The acid was found to be so unstable that it would even decompose when it was dissolved in neutralized chloroform and the solvent removed on a rotary evaporator at room temperature.

The deprotection of **309**, however, gave the opportunity to check the enantiomeric ratio of the compound as well as its absolute configuration, as **320** was described by *Jacobsen* [184] before (Scheme 144).

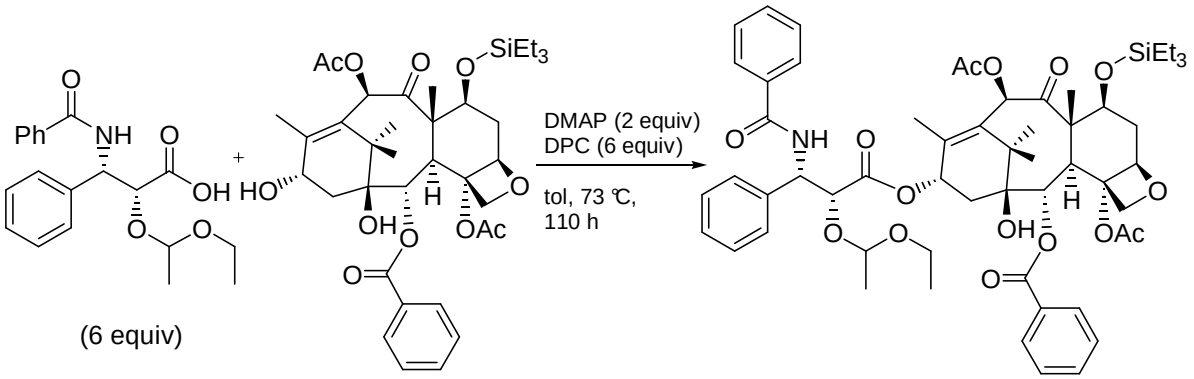


319 **320**

Scheme 144: Oxidation and *in situ* deprotection to acid **320**.

On this stage the er of **320** was determined by HPLC to be 99.6:0.4 and by comparison of the specific rotation measured for **320** and the literature-known results the desired absolute configuration of the product was confirmed ($[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –26.9 [*c* = 0.22, EtOH]; Lit.[185] $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{25}}$ –35.9 [*c* = 0.565, EtOH]).

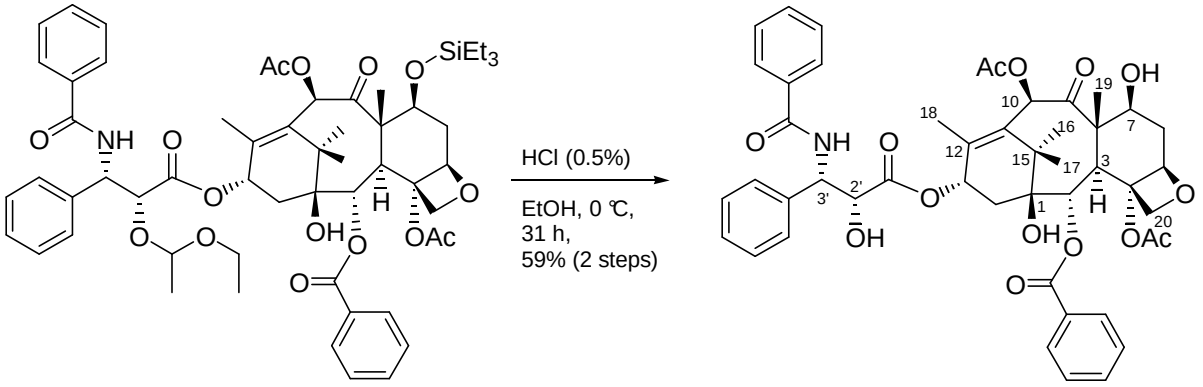
With **309** in hand the coupling with suitably protected 7-TES-baccatin III (**310**) could be undertaken with dipyridin-2-yl carbonate (DPC) as the coupling reagent. **310** was obtained from Toronto Research Chemicals, Inc. (TRC). The reaction was conducted according to the procedure by *Greene* and *Guéritte-Voegelein* (Scheme 145).[181]



309 **310** **311**

Scheme 145: Coupling of **309** and **310**. DPC = dipyridin-2-yl carbonate.

After 110 h the reaction was worked up and 53% of **310** were recovered by column chromatography. **311** was not obtained very pure but was directly employed in the final step of the synthesis, which was the deprotection of the hydroxy groups in 7 and 2' positions which could be brought about in one step with diluted hydrochloric acid in ethanol.

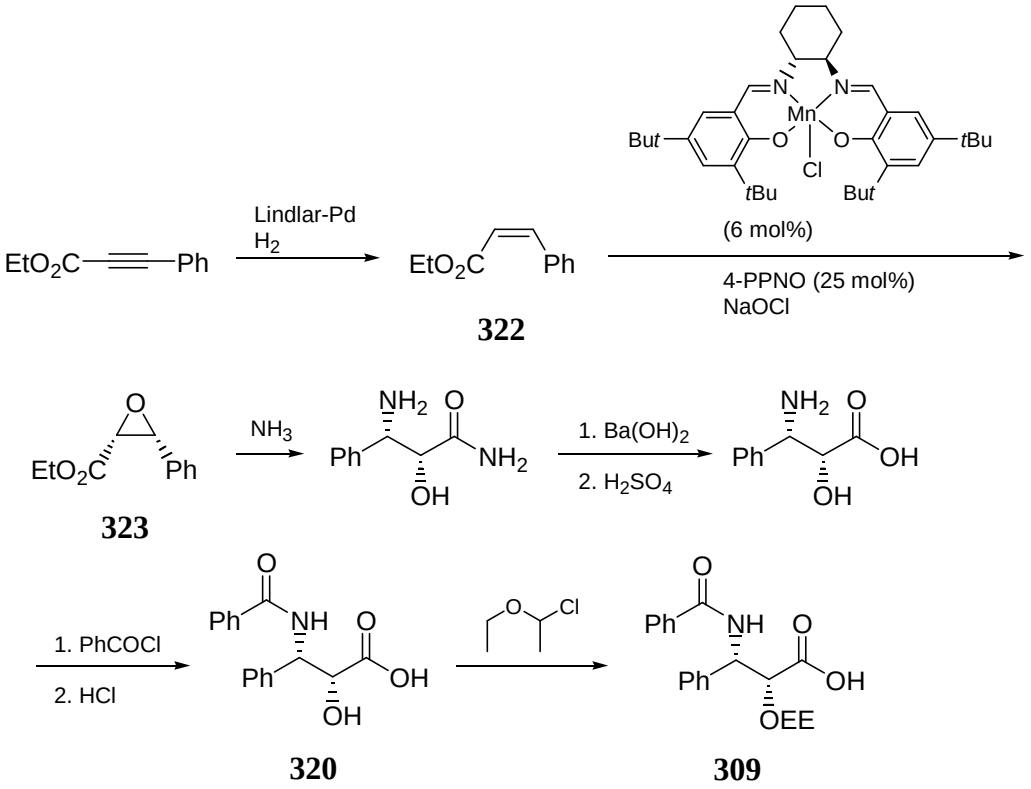


311 **321**

Scheme 146: Completion of the synthesis of paclitaxel (**321**).

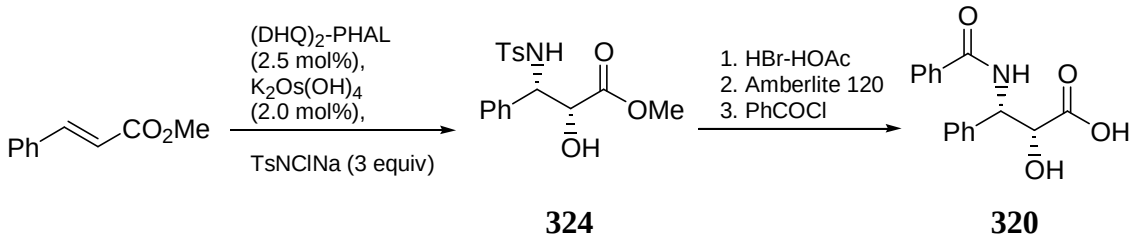
The product was isolated by column chromatography and further purified by preparative scale HPLC to give pure paclitaxel in 59% yield over two steps (based on 47% conversion in the first step), which is slightly lower than the 71% reported by *Greene* and *Guéritte-Voegelein*.

Paclitaxel (taxol) was and is one of the proving grounds for organic synthesis. Especially the synthesis of the side chain has naturally received much attention, and some of the best catalytic asymmetric methods have been explored in its synthesis. The synthesis by *Jacobsen*, for example, relying on the asymmetric epoxidation of *cis*-cinnamic acid ester **322**, gives **323** in 56% yield and with enantiomeric ratios from 97.5:2.5 up to 98.5:1.5 (Scheme 147). **320** is obtained in 25% overall yield but needs to be protected in an additional step to give **309**.[184, 185]



Scheme 147: Synthesis of **309** through Jacobsen asymmetric epoxidation.[185] 4-PPNO = 4-phenylpyridine *N*-oxide

In the patent of *Sharpless* regarding the asymmetric aminohydroxylation a method for the synthesis of the paclitaxel side chain is described (Scheme 148).[186]



Scheme 148: Paclitaxel side chain synthesis using asymmetric aminohydroxylation.

Key intermediate **324** was obtained in only moderate enantiopurity and was therefore recrystallized several times, which gave a total yield of only 35% of a material having an er >99.5:0.5. **320** was therefore obtained in only 17.5% overall yield and is still one step short of a suitably protected acid.

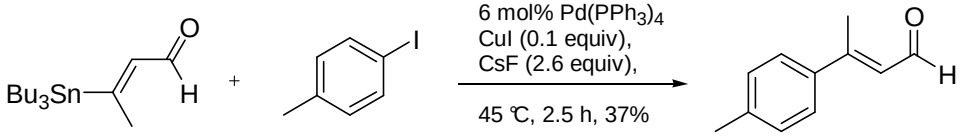
In comparison to these results, the methodology developed in this thesis yields **309** in 28% starting from benzaldehyde and with an enantiomeric ratio of 99.6:0.4 in a total of 6 steps.

As the manufacturing of paclitaxel is nowadays based on fermentation and the side-chain production for semisynthetic approaches according to *Holton* [187] is firmly established, the metho-

dology described in our synthesis will likely not have a great impact on the production of the drug. It does, however, show the potential of the method and also organocatalysis in the whole. Together with the baccatin III and paclitaxel total synthesis of *Danishefsky*,[188] in which the complete stereochemistry of the baccatin III-core of the molecule is based on the Wieland-Miescher-ketone (which is produced through proline catalysis), our organocatalytic asymmetric synthesis of the paclitaxel side chain shows that all the stereochemistry in such a complex molecule can be derived from as simple a catalyst as proline.

5. Summary

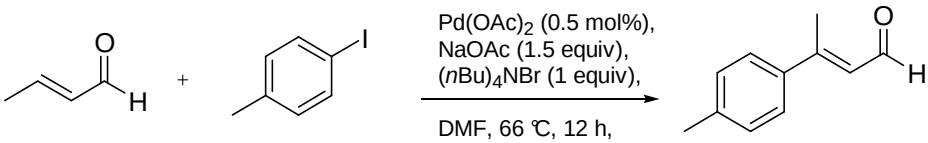
The palladium-catalyzed reaction of aryl and vinyl halides with α,β-unsaturated aldehydes or their respective precursors was initially studied with regard to the most promising reactions. It was possible to identify the Stille coupling as a potential reaction for development, and a suitable tin-substituted aldehyde precursor was prepared. The test reaction between aldehyde surrogate **218** and 4-iodotoluene (**219**) under catalysis of tetrakis-triphenylphosphine palladium(0) gave the desired product, 3-(4-methylphenyl)-2-butenal (**8**), in 37% yield (Scheme 149).



218 **219** **8**

Scheme 149: Stille coupling to yield α,β-unsaturated aldehyde **8**.

Since **218** was found to be rather stable and could be stored for longer times, the Stille coupling could have been developed into a method for obtaining the desired products. However, similar yields were obtained in the initial experiments for the Heck reaction (Scheme 150). In this case crotonaldehyde (**48**) was directly arylated by **219**.

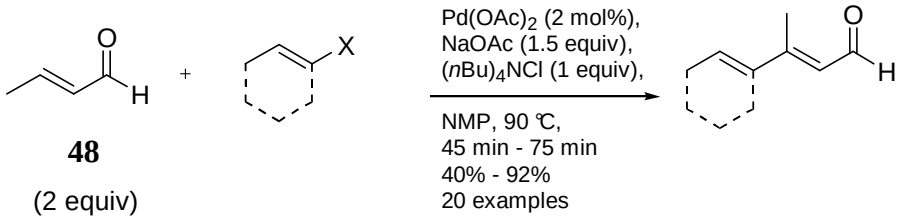


48 (1.1 equiv) **219** (1.5 equiv) **8**

Scheme 150: Initial Heck reaction to yield α,β-unsaturated aldehydes.

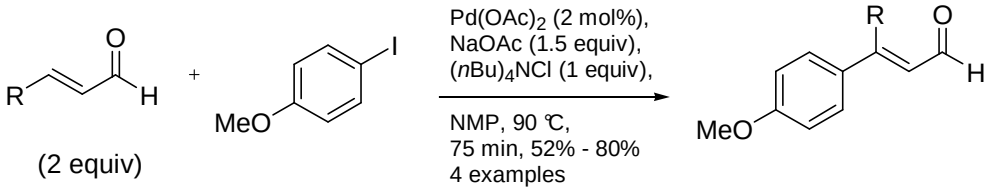
The Heck reaction has obvious advantages over the Stille reaction since unmodified aldehydes can be used, and there are no toxic tin-species involved. It was therefore chosen for further development.

After optimizing the reaction conditions, several aryl and vinyl bromides and iodides were tested (Scheme 151).



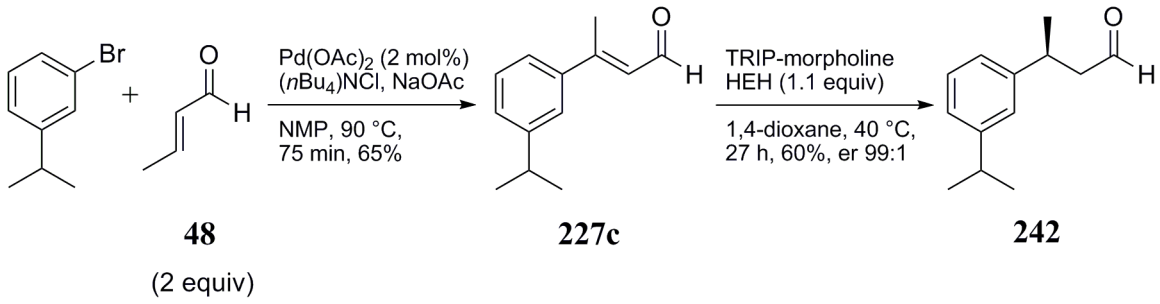
Scheme 151: Substrate scope of the Heck reaction of crotonaldehyde.

The reaction was found to give the desired products in good to very good yields ranging from 40% to 92%, usually as thermodynamic mixtures of *E*- and *Z*-isomers. It tolerates aryl and vinyl halides. Strongly electron-deficient arenes were found to be unsuitable for the reaction. It was next evaluated with regard to different aldehydes and again the products were obtained in good to high yields of 52% to 80% (Scheme 152).



Scheme 152: Different aldehydes in the Heck reaction.

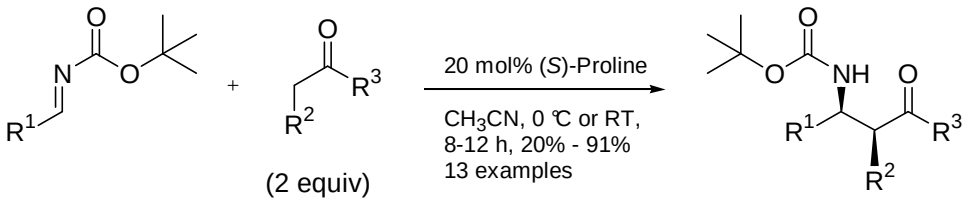
With the newly developed reaction a practical application was undertaken. Florhydral® (**242**), a saturated aldehyde serving as a fragrance, was previously synthesized in an enantiopure fashion in poor yields in seven step syntheses. Employing the newly discovered Heck reaction and the previously developed reduction of α,β-unsaturated aldehydes [24] it was possible to cut the synthesis to only two steps and obtain a good yield of 39% of a highly enantiopure product (Scheme 153).



Scheme 153: Synthesis of Florhydral®.

This short synthesis also demonstrates the speed with which chemical sciences evolve; a mere five years lay between the aforementioned long synthesis and the one presented here.

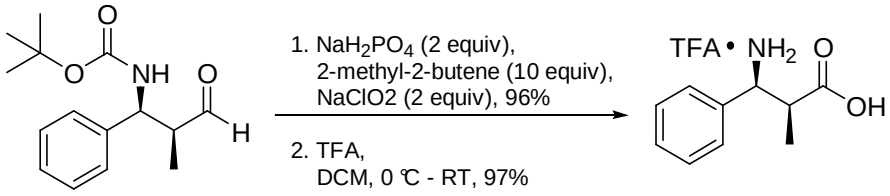
The second part of this thesis concerned the development of an asymmetric Mannich reaction between *N*-Boc and related imines and unmodified aldehydes or ketones. It could quickly be established that proline was a viable catalyst for the reaction (Scheme 154).



Scheme 154: Mannich reaction of *N*-Boc-imines and unmodified aldehydes or ketones catalyzed by proline.

With the exception of very demanding substrates like aliphatic imines, the yields for the expected *syn* amino carbonyl compounds were found to be good to very high. Moreover, in most cases the desired product precipitated during the reaction or upon treatment with water, and could be collected by filtration without the need for additional purification. The products were also obtained in very high optical and diastereomeric purity of up to >99:1.

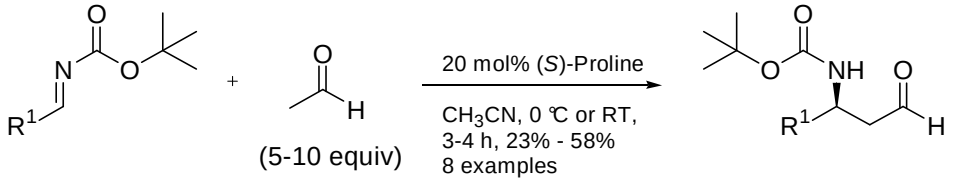
The benefit of the Boc group as compared to the known PMP-protecting group was shown by a high-yielding two step transformation of the Mannich product into a $\beta^{2,3}$-amino acid by oxidation and deprotection (Scheme 155).



255a **262**•TFA

Scheme 155: Transformation of the *N*-Boc aminoaldehyde to the amino acid salt.

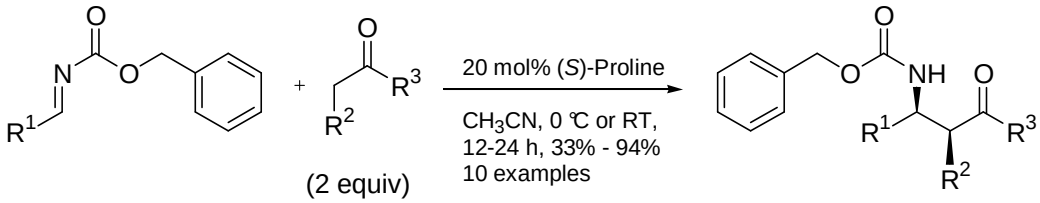
Based on the chemistry of *N*-Boc-imines with unmodified aldehydes the use of acetaldehyde was explored. It turned out that this aldehyde could also be used as donor with a variety of substrates. Moderate to good yields from 23% to 58% were realized and the products were again obtained in excellent optical purity of up to >99:1 (Scheme 156).



Scheme 156: First organocatalyzed Mannich reaction of acetaldehyde.

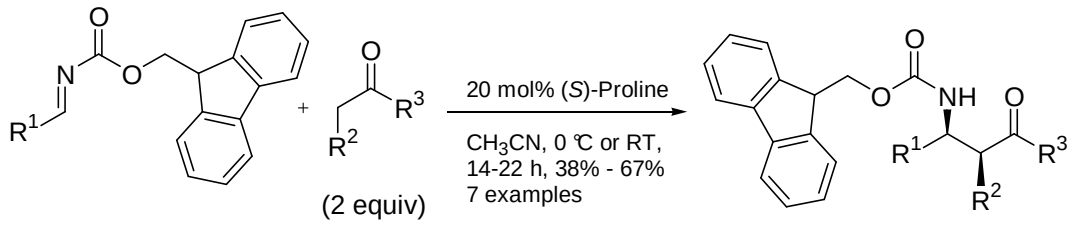
Together with the work of *Hayashi* [164] on the aldol reaction of acetaldehyde the results obtained during the research for this thesis show the first use of acetaldehyde as donor in a controlled addition reaction leading to high optical induction with good yields.

Apart from the Boc-group several other protecting groups could be used. *N*-Cbz-imines were found to generally give good to high yields between 33% and 94%, and also optical purity and diastereoselectivity were usually high with diastereomeric ratios ranging from 5:1 to 49:1 and enantiomeric ratios from 88:12 to >99:1 (Scheme 157).



Scheme 157: Mannich reaction of *N*-Cbz-imines and unmodified aldehydes catalyzed by proline.

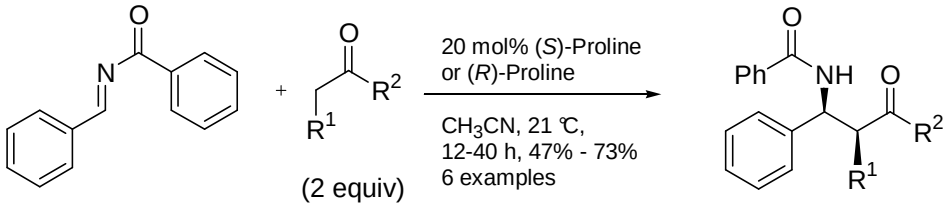
The third carbamate protecting group of general use is the Fmoc group. *N*-Fmoc-imines were next investigated for the Mannich reaction. Under similar conditions as before the reaction proceeded with moderate to good yields of 38% - 67% and with high enantioselectivity of 84:16 to >99:1, but the diastereoselectivity, which was usually around 2.5:1, was very low as compared to the other carbamate protecting groups (Scheme 158).



Scheme 158: Mannich reaction of *N*-Fmoc-imines and unmodified aldehydes catalyzed by proline.

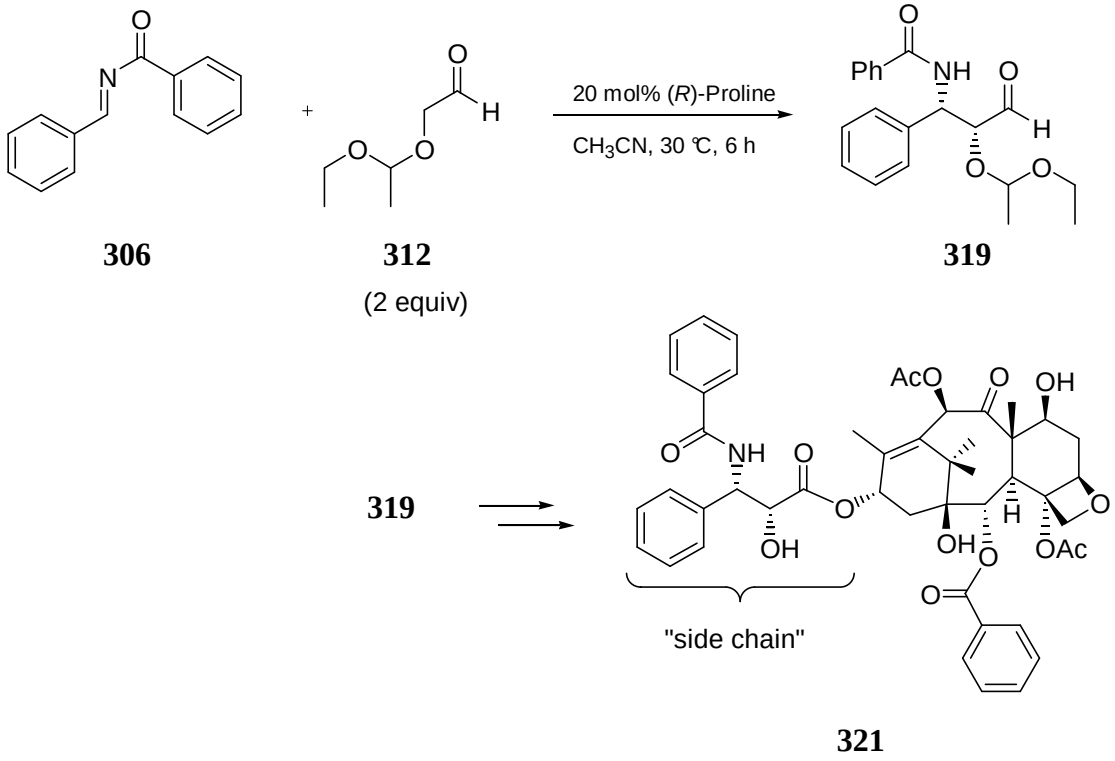
Moreover, in some cases it was difficult to separate the mixture of isomers.

Finally, the Mannich reaction of an *N*-Bz-imine was developed, a protecting group of the amide type. It was found that the imine was less reactive than the corresponding carbamate-protected imines, and higher reaction temperatures had to be used. The yields were good to high (47% - 73%) with typically high optical purities (er in almost all cases >93:7), but higher temperature was found to be detrimental for the diastereoselectivity, and the diastereomeric ratios range from 2:1 to 5:1 (Scheme 159).



Scheme 159: Mannich reaction of an *N*-Bz-imine and unmodified aldehydes catalyzed by proline.

The utility of the last reaction was shown when it was employed as the key step in a semisynthesis of paclitaxel (**321**). A protected and esterification-ready paclitaxel side chain can be obtained by oxidation of **319**, which is in turn available from a Mannich reaction of **306** and **312** in a yield of 52% of the major isomer and with excellent enantiopurity of >99:1 (Scheme 160).



Scheme 160: Semisynthesis of paclitaxel (**321**) with a Mannich key step.

This approach compares very well to established, “classical” methods of asymmetric catalysis, such as the Sharpless asymmetric aminohydroxylation or the Jacobsen epoxidation, which have both previously been used to obtain the side chain of paclitaxel.

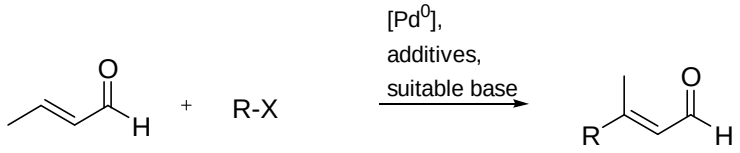
Parts of the results presented in this thesis have already been published.[153, 158, 166, 189]

6. Outlook

6.1. Heck reactions of crotonaldehyde

There are two major problems unsolved for this reaction, the low *E*/*Z* ratios and the inability to use electron-deficient arenes. The *E*/*Z* ratios did not pose a problem for the intended use of the products as starting materials for asymmetric, organocatalytic transfer hydrogenations, as they are enantioconvergent. While the reaction was originally developed to give quick access to such starting materials in high yields, it is now desirable to find ways to selectively obtain one isomer.

A possible starting point has already been mentioned with the use of the conditions employed by *Li*,[134] which are themselves modified conditions of *Overman*.[190] The use of silver or thallium salts, for example, is known to prevent the loss of chirality in asymmetric Heck reactions due to their ability to suppress the re-insertion of the reaction products into the palladium-hydride bond.[126] If this re-insertion is causing the erosion of isomeric excess, an addition of silver or thallium salts may circumvent this problem.



Scheme 161: General scheme for development of the Heck reaction

Since the conversion in the arylation of crotonaldehyde was low when *Li*'s conditions were employed, it would be necessary to find suitable conditions, for example by using phase-transfer-catalysts, to again achieve good conversions and high yields.

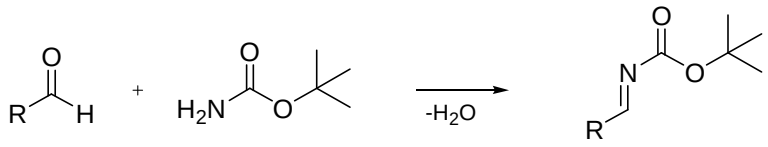
No good solution is currently at hand for the second problem, the inability to efficiently couple electron-deficient arenes under the conditions screened. The Ullmann coupling is known to proceed under palladium catalysis, and has been described for 4-iodobenzene by *Dyker* under very similar conditions to the ones given here for the Heck reaction.[191] From the results obtained during the work on this thesis it seems that the Pd(II)-species obtained after the oxidative addition is much less reactive towards crotonaldehyde than the corresponding ones from electron-rich arenes.

Future work in this area will therefore have to find out whether it is possible to couple these intermediates with electron-richer or electron-poorer olefins and to draw conclusions from

this. It will also be possible to use different ligands on palladium to tune the electronic properties of the intermediate.

6.2. Mannich reactions of *N*-Boc and related imines

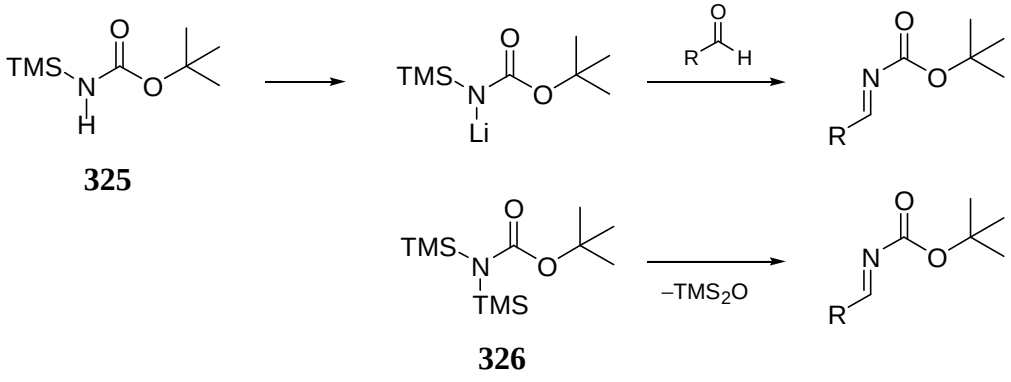
One of the main drawbacks of the organocatalyzed Mannich reaction of *N*-Boc and related imines is the necessity to synthesize the starting materials in two steps. While this sequence usually allows for good yields of the starting materials and is usable on a multigram scale, it is nonetheless desirable to develop a one-step protocol (Scheme 162).



Scheme 162: One-step synthesis of Boc-imines.

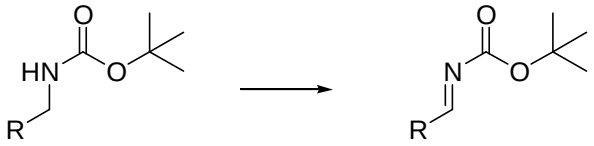
Ideally and in the most atom-economic manner this reaction will, in a condensation reaction of the aldehyde and Boc-carbamate, release the imine. One problem in this case is that the carbamate is not very nucleophilic, which requires the aldehyde to be activated by an acid. The other problem is that the carbamate may also attack the imine as a nucleophile. During the course of this thesis, some acids were screened. It was shown that the activation of the imine by an acid was necessary to activate it towards nucleophilic attack. A careful screening of acids of different pKa-values may enable the selective formation of the imine, and concurrent removal of the formed water should drive the reaction to completion.

Another possibility is the synthesis of a HMDS-analogue compound with one silyl- and one Boc group (**325**). It could then be lithiated and used in a similar fashion as LiHMDS to generate imines directly from the corresponding aldehydes (Scheme 163).



Scheme 163: Synthesis of Boc-imines *via* **325** and **326**.

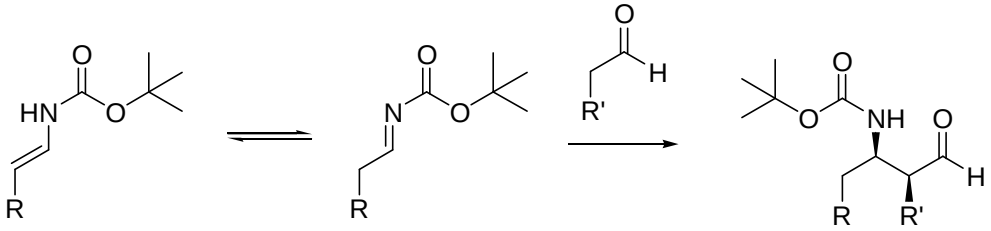
The same reaction would also be possible with **326**. While this is not the perfect solution, it would at least eliminate the necessity to prepare the sulfones for every single aldehyde.
Another option could be the use of *N*-Boc-protected amines, many of which are commercially available. If suitable conditions can be found, an oxidation would lead to the desired *N*-Boc-imine (Scheme 164).



Scheme 164: Possible route to imines *via* oxidation.

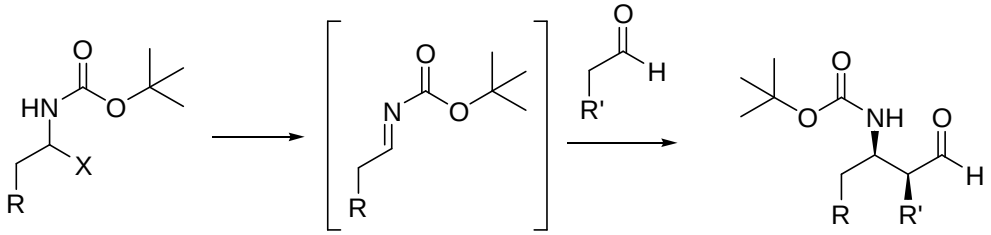
The reaction could be explored using anodic oxidation.

On the side of the Mannich reaction it is desirable to find better conditions for the use of aliphatic imines. These imines may undergo tautomerization to the corresponding enamides, which is unreactive under the conditions described. A plausible solution would be the use of additional acid to equilibrate enamide and imine forms (Scheme 165).



Scheme 165: Enamide-imine equilibrium.

This could also be brought about when using proline derivatives that are stronger acids.
Another possibility to obtain higher yields with aliphatic imines is to prepare them *in situ*.

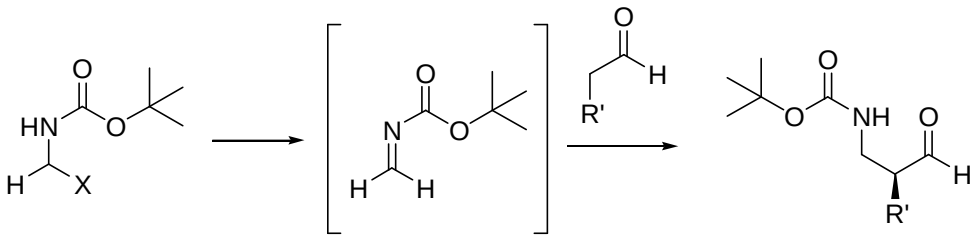


Scheme 166: *In situ* preparation of aliphatic imines.

The *in situ* formation of imines has been described by *Deng* [145] and later by *Melchiorre*,[192] where the latter states that aliphatic imines react very slowly under the conditions employed. The problem here lies with the need to employ basic conditions for the imine formation and

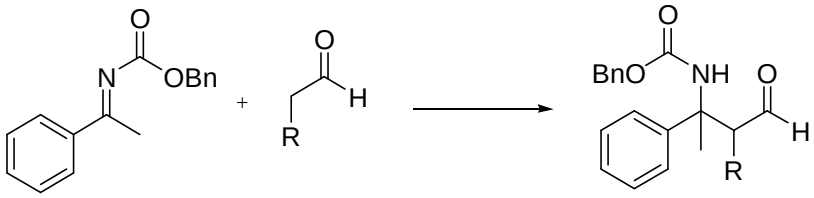
an acidic catalyst to activate the imine. A possible solution to this could be the use of a Lewis-acidic instead of a Brønsted acidic catalyst.

This thesis dealt with methods to form β^3- and $\beta^{2,3}$-aminocarbonyl compounds. It was so far not possible to use the *N*-Boc-imine of formaldehyde, even though the precursor was synthesized. In this case it might also be possible to make the reaction work with *in situ* generation of the imine, as the failure to obtain the products so far is likely due to the high reactivity of the imine which prevented its isolation (Scheme 167).



Scheme 167: *In situ* generation of formaldehyde-derived imine and Mannich reaction.

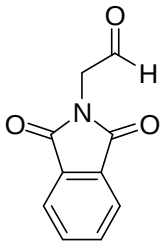
Another interesting development would be the Mannich reaction with ketimines. The problem of the imine-enamide tautomerism could be solved in analogy to the problem described for aliphatic imines if a suitable catalyst for the equilibration is available (Scheme 168).



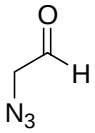
Scheme 168: Mannich reaction with ketimines.

This reaction could probably be catalyzed by a combination of a strong acid and a chiral secondary amine of the type used by *Jørgensen* (see Scheme 72).

Finally, an important extension would be the use of α-amino aldehydes as donors. This reaction would give direct access to 1,2 diamino compounds. The use of a Cbz-protected amino aldehyde failed, but it is possible to use different protecting groups, for example phthalimide **327**, or a different source of nitrogen such as azide **328** in this reaction (Scheme 169).



327



328

Scheme 169: Potential nitrogen-containing donors.

7. Experimental part

7.1. General experimental conditions

Solvents and reagents

All solvents were purified by distillation before use following standard procedures. Absolute diethyl ether, tetrahydrofuran and toluene were obtained by distilling over sodium, using benzophenone as indicator. Absolute chloroform and dichloromethane were obtained by distillation over calcium hydride. Ethanol, *iso*-propanol and methanol were dried by distilling over magnesium. *N*-Methylpyrrolidine was commercially available and used as received. Acetonitrile was refluxed over a 60% suspension of sodium hydride in mineral oil for 10 min, distilled, refluxed over phosphorous(V)-oxide for 10 min and distilled again. Acetaldehyde was freshly distilled prior to use. Other commercial reagents were obtained from various sources and used as received unless indicated otherwise.

Inert gas atmosphere

Air and moisture-sensitive reactions were conducted under an argon atmosphere. Argon was obtained from *Air Liquide* with higher than 99.5% purity.

Thin layer chromatography (TLC)

Materials: *Macherey-Nagel* MN POLYGRAM Sil G/UV_{254} plates (0.20 mm thickness). The spots were visualized with UV-light (λ = 254 nm) and/or by staining with vanillin, anisaldehyde, or bromocresol green.

Preparative scale TLC was conducted on *Macherey-Nagel* glass plates with a thickness of 0.25, 1, or 2 mm silica gel, respectively.

Flash column chromatography

Materials: Silicagel 60 (*Merck* 60 Å, 230-400 mesh 0.040-0.063 mm). Separations were either performed at slightly elevated pressure in a glass column or using the automated Sepacore Flash system from *Büchi*, consisting of fraction collector C-660, UV-photometer C-635, and pump module C-605.

Gas chromatography (GC)

Gas chromatography was conducted with an *Agilent Technology* GC 6890 N (Carrier gas: helium or hydrogen) with flame ionization detector (FID) and a HP 6890 Series Injector, em-

ploying HP-5 (30 m, 0.25 mm ID, 0.25 μm film thickness) or MN Optima® 5 (30 m, 0.25 mm ID, 0.25 μm film thickness) columns.

GC-MS-couplings were performed on an *Agilent Technology* GC 6890 Series and MSD 5973 (Carrier gas: helium) with HP6890 Series Injector, employing an MN Optima® 5 column. The mass spectra were recorded with an *Agilent Technology* 5973 Network MSD.

High performance liquid chromatography (HPLC)

Analytical HPLC was carried out on a *Shimadzu* LC-2010C HPLC-system equipped with a spectrophotometric detector or diode array. Columns employed were *Daicel* Chiralpak AS-H (0.46 cm × 25 cm), OD-H (0.46 cm × 25 cm), AD-H (0.46 cm × 25 cm) and IA (0.46 cm × 25 cm). Commercial HPLC-grade solvents were employed.

Preparative scale HPLC was performed on a Shimadzu LC-8A/10A apparatus with SPD-10A detector. The column was a 150 mm YMC, 20 mm internal diameter column packed with YMC Pack ODS-A, 5 μm.

All measurements were conducted at 20 °C.

Nuclear magnetic resonance spectroscopy (NMR)

Spectra were recorded on *Bruker* DPX 300 (^{1}H: 300 MHz, ^{13}C: 75.5 MHz), *Bruker* AV 400 (^{1}H: 400 MHz, ^{13}C: 100.8 MHz), and *Bruker* AV 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz) spectrometers. The spectra were recorded at room temperature (298 K) unless otherwise stated. Chemical shifts for protons and carbons are reported in parts per million (ppm) relative to tetramethylsilane as internal standard or to the residual signal of the NMR solvents ($CDCl_3$: δ_H 7.26 ppm, δ_C 77.16 ppm; CD_3CN: δ_H 1.94 ppm, δ_C 118.26 ppm; DMSO-d_6: δ_H 2.50 ppm, δ_C 39.52 ppm; CD_3OD: δ_H 3.31 ppm, δ_C 49.00 ppm; acetone-d_6: δ_H 2.05 ppm, δ_C 29.84 ppm). The coupling constants (*J*) are reported in Hertz (Hz). The signals have been assigned using 1D and 2D experiments.

Mass spectrometry (MS)

Mass spectra were measured on a Finnigan MAT 8200 (70 eV) or MAT 8400 (70 eV) by electron ionization, chemical ionization, of fast atom/ion bombardment techniques. High resolution masses were determined on a Bruker APEX III FT-MS (7 T magnet). All masses are given in atomic units/elementary charge (*m/z*) and reported in percentage relative to the basic peak.

Melting point (MP)

All melting points were measured on a *Büchi* 540 Melting Point apparatus in open glass capillaries. The values are given in °C and are uncorrected.

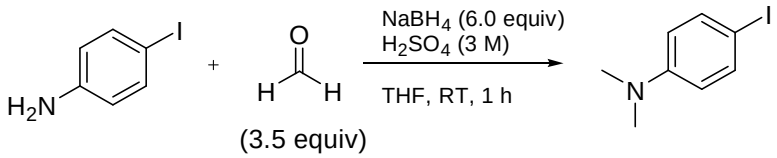
Specific rotation ([α])

Optical rotations were measured on a *Perkin Elmer* 343 polarimeter using a 1 mL cell with a path length of 1 dm at the temperature and wavelength indicated, with “D” referring to the sodium D-line wavelength (589 nm). Concentrations are given in g/100 mL.

7.2. Heck reactions of α,β-unsaturated aldehydes

7.2.1. Synthesis of starting materials

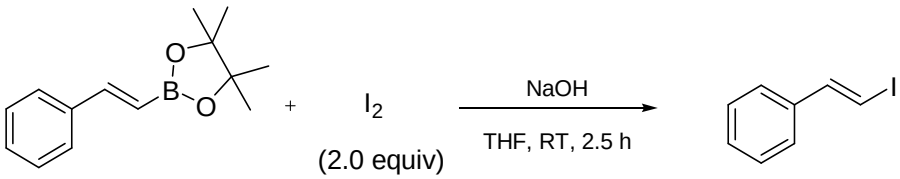
7.2.1.1. 4-Iodo-*N*,*N*-dimethylaniline



A literature-known procedure was followed.[193] 2.5 g (11.4 mmol, 1.0 equiv) of 4-Iodoaniline were mixed with 2.51 g (66.5 mmol, 5.8 equiv) of finely powdered $NaBH_4$ and suspended in 21 mL of tetrahydrofuran. This mixture was slowly added (about 20 min) to a mixture of 21 mL tetrahydrofuran, 3.3 mL of aqueous formaldehyde (37% formaldehyde by weight) and 3 mL 3 M H_2SO_4. After approximately half the aniline was added, another 3 mL of 3 M H_2SO_4 were added and the slow addition of aniline continued. When the addition was complete, the mixture was left stirring for 1 h at room temperature. It was then diluted by addition of water, basified with NaOH, and extracted twice with diethyl ether. The green product obtained after evaporation of the solvent was purified by column chromatography to yield a colorless solid. The NMR data was in agreement with the literature.[194]

Chemical Formula	$C_8H_{10}IN$ (247.08 g/mol)
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/ hexane (5/95 – 25/75 v/v)
Yield	1.75 g (67%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 2.92 (s, 6H, C*H*$_3$), 6.50 (d, *J* = 8.9 Hz, 2H, arom), 7.47 (d, *J* = 8.9 Hz, 2H, arom);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 40.4 (*C*H$_3$), 77.0 (*C*I), 114.7 (*C*H$_{Ar}$), 137.5 (*C*H$_{Ar}$), 150.0 (*C*q$_{Ar}$);

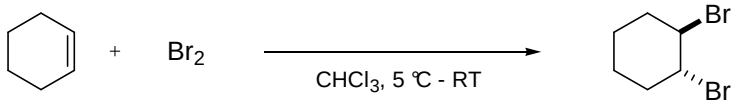
7.2.1.2. (*E*)-(2-Iodovinyl)benzene



A literature-known procedure was followed.[195] (*E*)-1-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethane (525 mg, 2.28 mmol) was dissolved in 5.5 mL of tetrahydrofuran and introduced into flask filled with argon. 270 mg (6.75 mmol) of sodium hydroxide in 2.2 mL of water was added and the mixture left stirring for 10 min. 1.11 g (4.37 mmol, 2.0 equiv) of iodine was dissolved in 23 mL of tetrahydrofuran and added to the reaction mixture slowly, so that the mixture would turn from reddish-brown to yellow before further addition of iodine. When the color stayed red, the reaction was quenched by addition of an aqueous solution of sodium thiosulfate. The reaction mixture was extracted with diethyl ether (3 times) and dried over anhydrous magnesium sulfate. The product was purified by column chromatography. The NMR data was in agreement with the literature.[195]

Chemical Formula	C_8H_7I (230.05 g/mol)
Purification	column chromatography on silica gel, eluting with hexane
Yield	416 mg (79%, Lit.[195] 99%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 6.83 (d, *J* = 15.0 Hz, 3H, PhCH=C*H*I), 7.22-7.38 (m, 5H, arom), 7.43 (d, *J* = 14.9 Hz, 1H, PhC*H*=CHI);

7.2.1.3. *trans*-1,2-Dibromocyclohexane



A literature-known procedure was followed.[196] 8.2 g (0.10 mol) of cyclohexene were dissolved in 30 mL of chloroform and cooled to 5 °C. 14.4 g (0.09 mol) of bromine, dissolved in 10 mL of chloroform were then added, and the temperature was kept at 5 °C. After completion of the addition the reaction was warmed to room temperature and stirred over night. The

solvent was removed on a rotary evaporator and the residue was distilled to yield a slightly yellow oil. The NMR was in agreement with the literature.[197]

Chemical Formula $C_6H_{10}Br_2$ (241.95 g/mol)

Boiling point 80 °C (2 mbar)

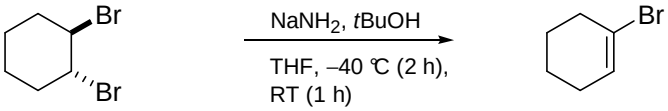
Purification distillation

Yield 19.2 g (88%, Lit.[196] 95%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.43-1.60 (m, 2H, C*H*$_2$CH$_2$CHBr), 1.70-1.95 (m, 4H, C*H*'$_2$CH$_2$CHBr and C*H*$_2$CHBr), 2.38-2.53 (m, 2H, C*H*'$_2$CHBr), 4.45 (t, *J* = 2.3 Hz, 2H, C*H*Br);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 22.4 (*C*H$_2$), 31.9 (br, *C*H$_2$), 55.2 (*C*HBr);

7.2.1.4. 1-Bromocyclohex-1-ene



A literature-known procedure was employed.[198] 22.4 g (0.57 mol) of sodium amide were added to 230 mL of tetrahydrofuran and cooled to –40 °C. 23.8 g (0.32 mol) *tert*-butanol were added dropwise over a period of 5 min. The resulting mixture was stirred for 1 h at –40 °C, then a solution of 19.2 g (0.079 mol) of *trans*-1,2-dibromocyclohexane in 70 mL tetrahydrofuran was added dropwise over 1 h. After stirring for an additional hour the solution was warmed to room temperature and stirred for 75 min. The solution was filtered and the tetrahydrofuran removed on a rotary evaporator. The residue was taken up in 200 mL of diethyl ether, washed with water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent evaporated. The residue was purified by distillation. The NMR was in agreement with the literature.[199]

Chemical Formula C_6H_9Br (161.04 g/mol)

Boiling point 60-62 °C (25 mbar)

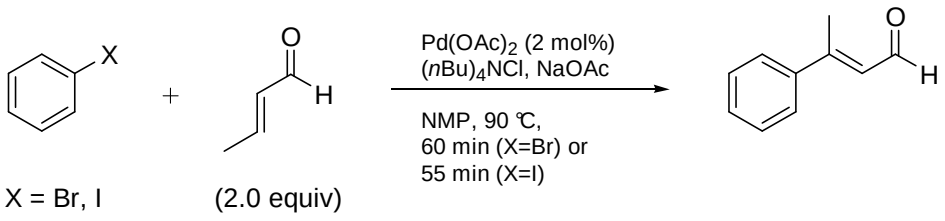
Purification distillation

Yield 1.41 g (11%, Lit.[198] 63%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.54-1.65 (m, 2H), 1.65-1.80 (m, 2H), 2.00-2.14 (m, 2H), 2.35-2.48 (m, 2H), 5.98-6.08 (m, 1H);

7.2.2. Products of the Heck reaction

7.2.2.1. 3-Phenyl-2-butenal (16)



48 **16**

Phenylbromide (239.4 mg, 1.5 mmol) or phenyliodide (304.9 mg, 1.5 mmol), tetrabutylammonium chloride (420 mg, 1.5 mmol), and sodium acetate (148 mg, 1.8 mmol) were suspended in 8 mL of NMP. Palladium acetate (6.8 mg, 0.03 mmol) was dissolved in 4 mL of NMP and added, followed by crotonaldehyde (250 µl, 3 mmol). Oxygen was removed by two cycles of freeze-pump-thaw. The mixture was then heated at an oil bath temperature of 90 °C for 60 min. After being cooled, the reaction mixture was poured into a half-concentrated aqueous solution of sodium bicarbonate (80 mL) and extracted three times with dichloromethane (120 mL in total). The combined organic fractions were washed with brine once, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting solution in NMP was directly loaded onto a column packed with silica gel and eluted with diethyl ether/pentane (12/88, then 15/85 v/v) to give fractions of pure *E*- and *Z*-isomers as yellow oils.

Chemical Formula $C_{10}H_{10}O$ (146.19 g/mol)

TLC R_f = 0.49 and 0.55 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (12/88, then 15/85 v/v)

Yield **X=Br:** 111 mg (50%)

X=I: 146 mg (68%)

Diastereomeric ratio *E/Z* = 2.8:1

^{1}H-NMR ***E*-isomer** (300 MHz, $CDCl_3$): δ = 2.57 (d, *J* = 1.2 Hz, 3H, CH_3), 6.40 (dq, *J* = 7.7, 1.3 Hz, 1H, =CH), 7.40-7.44 (m, 3H, arom), 7.53-7.56 (m, 2H, arom), 10.18 (d, *J* = 7.8 Hz, 1H, CHO);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.31 (d, *J* = 1.4 Hz, 3H, CH_3), 6.13 (dq, *J* = 8.2, 1.4 Hz, 1H, =CH), 7.28-7.33 (m, 2H, arom), 7.39-7.43 (m, 3H, arom), 9.47 (d, *J* = 8.0 Hz, 1H, CHO);

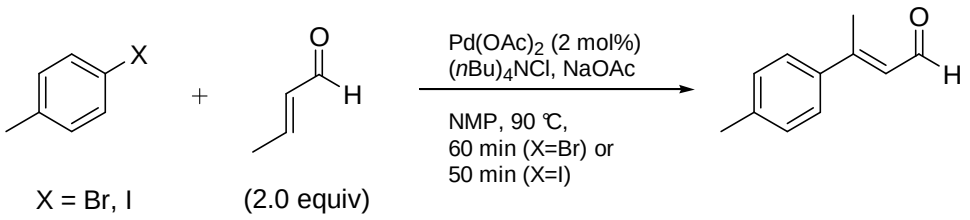
^{13}C-NMR ***E*-isomer** (75.5 MHz, $CDCl_3$): δ = 16.4 (*C*H_3), 126.3 (*C*H_{Ar}), 127.3 (*C*HCHO), 128.8 (*C*H_{Ar}), 130.1 (*C*H_{Ar}), 140.6 (*C*q_{Ar}), 157.6 (Ar*C*CH_3=), 191.2 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 26.4 (*C*H_3), 128.4 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 129.2 (*C*H_{Ar}), 129.2 (*C*HCHO), 138.5 (*C*q_{Ar}), 162.1 (Ar*C*CH_3=), 193.4 (*C*HO);

Mass *m/z* (%) (DE) 145 (M-H, 100), 131 (M-CH_3, 25), 115 (36), 103 (15), 91 (18), 78 (13);

HRMS (ESIpos) calculated for $C_{10}H_{11}O$ (M+H) 147.080988; found 147.080836;

7.2.2.2. 3-(4-Methylphenyl)-2-butenal (8)



X = Br, I (2.0 equiv)

48 **8**

The procedure of 7.2.2.1 was followed. The *E*-isomer was obtained as a slightly yellow solid, the *Z*-isomer as a yellowish oil.

Chemical Formula $C_{11}H_{12}O$ (160.21 g/mol)

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (12/88, then 15/85 v/v)

Yield **X=Br:** 167 mg (70%)

X=I: 182 mg (77%)

Diastereomeric ratio *E/Z* = 2.8:1

^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H, C*H*$_3$), 2.54 (d, *J* = 1.2 Hz, 3H, C*H*$_3$), 6.40 (dq, *J* = 7.9, 1.2 Hz, 1H, =C*H*), 7.20-7.22 (m, 2H, arom), 7.44-7.47 (m, 2H, arom), 10.16 (d, *J* = 7.9 Hz, 1H, C*H*O);

***Z*-isomer** (400 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 1.3 Hz, 3H, C*H*$_3$), 2.39 (s, 3H, C*H*$_3$), 6.10 (dq, *J* = 8.1, 1.3 Hz, 1H, =C*H*), 7.18-7.25 (m, 4H, arom), 9.49 (d, *J* = 8.1 Hz, 1H, C*H*O);

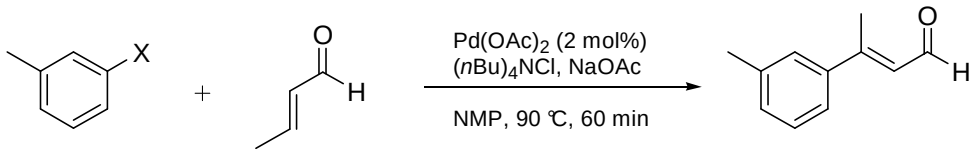
^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 16.2 (*C*H_3), 21.3 (Ar*C*H_3), 126.2 (*C*HAr), 126.5 (*C*HCHO), 129.5 (*C*HAr), 137.5 (*C*q_{Ar}), 140.5 (*C*q_{Ar}), 157.5 (Ar*C*CH_3=), 191.3 (*C*HO);

***Z*-isomer** (100 MHz, $CDCl_3$): δ = 21.3 (Ar*C*H_3), 26.4 (*C*H_3), 128.5 (*C*HAr), 129.0 (*C*HAr), 129.1 (*C*HCHO), 135.5 (*C*q_{Ar}), 139.4 (*C*q_{Ar}), 162.2 (Ar*C*CH_3=), 193.6 (*C*HO);

Mass *m/z* (%) (EI) 159 (M-H, 27), 145 (M-CH_3, 100), 131 (6), 115 (32), 103 (2), 91 (27);

HRMS (ESIpos) calculated for $C_{11}H_{12}O$ (M) 160.088819; found 160.088651;

7.2.2.3. 3-(3-Methylphenyl)-2-butenal (227a)



X = Br, I (2.0 equiv)

48 **227a**

The procedure of 7.2.2.1 was followed. Both *E*- and *Z*-isomer were obtained as slightly yellow solids.

Chemical Formula $C_{11}H_{12}O$ (160.21 g/mol)

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (12/88, then 15/85 v/v)

Yield **X=Br:** 169 mg (70%)

X=I: 168 mg (70%)

Diastereomeric ratio *E/Z* = 3.0:1

^{1}H-NMR ***E*-isomer** (300 MHz, $CDCl_3$): δ = 2.38 (s, 3H, C*H*$_3$), 2.54 (d, *J* = 1.2 Hz, 3H, C*H*$_3$), 6.37 (dq, *J* = 7.9, 1.2 Hz, 1H, =C*H*), 7.21-7.23 (m, 1H, arom), 7.25-7.29 (m, 1H, arom), 7.30-7.34 (m, 2H, arom), 10.16 (d, *J* = 7.9 Hz, 1H, C*H*O);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 1.3 Hz, 3H, C*H*$_3$), 2.38 (s, 3H, C*H*$_3$), 6.11 (dq, *J* = 8.2, 1.4 Hz, 1H, =C*H*), 7.08-7.11 (m, 2H, arom), 7.20-7.23 (m, 1H, arom), 7.27-7.32 (m, 1H, arom), 9.47 (d, *J* = 8.2 Hz, 1H, C*H*O);

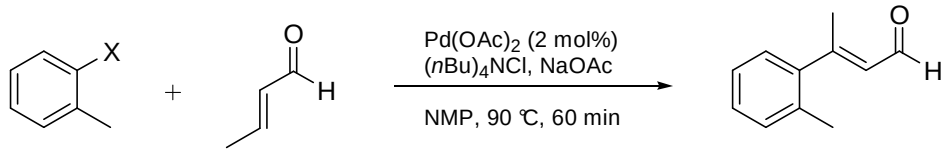
^{13}C-NMR ***E*-isomer** (75.5 MHz, $CDCl_3$): δ = 16.5 (*C*H$_3$), 21.5 (Ar*C*H$_3$), 123.4 (*C*HAr), 127.0 (*C*HAr), 127.2 (*C*HCHO), 128.7 (*C*HAr), 130.9 (*C*HAr), 138.4 (*C*q$_{Ar}$), 140.6 (*C*q$_{Ar}$), 157.8 (Ar*C*CH$_3$=), 191.2 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 21.4 (Ar*C*H_3), 26.5 (*C*H_3), 125.5 (*C*HAr), 128.3 (*C*HAr), 129.0 (*C*HAr), 129.1 (*C*HCHO), 138.2 (*C*q_{Ar}), 138.4 (*C*q_{Ar}), 162.4 (Ar*C*CH_3=), 193.5 (*C*HO);

Mass *m/z* (%) (EI) 160 (M, 35), 145 (M-CH_3, 100), 131 (9), 115 (31), 103 (2), 91 (27);

HRMS (ESIpos) calculated for $C_{11}H_{13}O$ (M+H) 161.096637; found 161.096484;

7.2.2.4. 3-(2-Methylphenyl)-2-butenal (227b)



X = Br, I (2.0 equiv)

48 **227b**

The procedure of 7.2.2.1 was followed. Both *E*-and *Z*-isomer were obtained as slightly yellow oils.

Chemical Formula $C_{11}H_{12}O$ (160.21 g/mol)

TLC R_f = 0.46 and 0.52 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (10/90, then 15/85 v/v)

Yield **X=Br:** 109 mg (46%)

X=I: 133 mg (55%)

Diastereomeric ratio *E/Z* = 1:2.9

^{1}H-NMR ***E*-isomer** (400 MHz): δ = 2.31 (s, 3H, C*H*$_3$), 2.46 (d, *J* = 1.4 Hz, 3H, C*H*$_3$), 5.95 (dq, *J* = 7.9, 1.4 Hz, 1H, =C*H*), 7.09-7.11 (m,

1H, arom), 7.18-7.27 (m, 3H, arom), 10.16 (d, *J* = 7.9 Hz, 1H, C*H*O);

***Z*-isomer** (400 MHz, $CDCl_3$): δ = 2.23 (d, *J* = 1.4 Hz, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.14 (dq, *J* = 8.3, 1.4 Hz, 1H, =C*H*), 7.08-7.10 (m, 1H, arom), 7.20-7.29 (m, 3H, arom), 9.21 (d, *J* = 8.3 Hz, 1H, C*H*O);

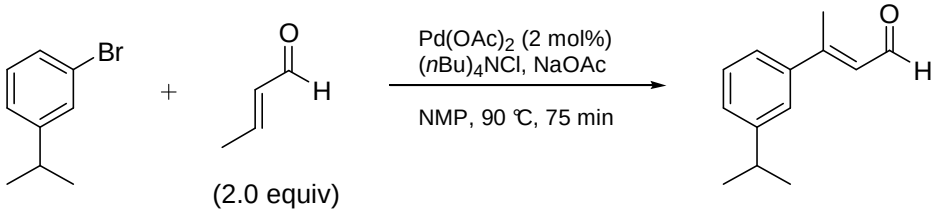
^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 19.3 (*C*H_3), 19.8 (Ar*C*H_3), 125.9 (*C*H_{Ar}), 126.7 (*C*H_{Ar}), 128.3 (*C*H_{Ar}), 130.1 (*C*HCHO), 130.7 (*C*H_{Ar}), 133.6 (*C*q_{Ar}), 142.7 (*C*q_{Ar}), 161.0 (Ar*C*CH_3=), 191.1 (*C*HO);

***Z*-isomer** (100 MHz, $CDCl_3$): δ = 19.5 (Ar*C*H_3), 26.7 (*C*H_3), 125.9 (*C*H_{Ar}), 127.8 (*C*H_{Ar}), 128.3 (*C*H_{Ar}), 129.6 (*C*HCHO), 130.4 (*C*H_{Ar}), 134.3 (*C*q_{Ar}), 138.5 (*C*q_{Ar}), 163.4 (Ar*C*CH_3=), 193.5 (*C*HO);

Mass *m/z* (%) (EI) 159 (M-H, 6), 145 (M-CH_3, 100), 115 (30), 91 (22);

HRMS (ESIpos) calculated for $C_{11}H_{13}O$ (M+H) 161.096637; found 161.096454;

7.2.2.5. 3-(3-Isopropylphenyl)-2-butenal (227c)



(2.0 equiv)

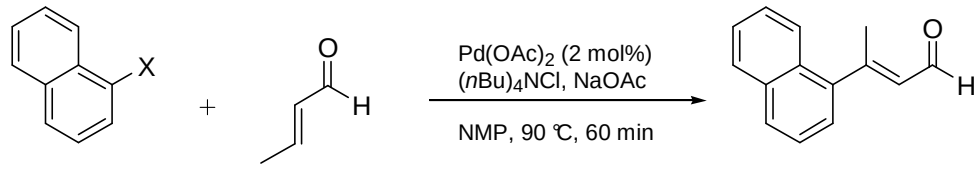
48 **227c**

The procedure of 7.2.2.1 was followed. The isomers were not separated and obtained as yellowish oil.

Chemical Formula $C_{13}H_{16}O$ (188.27 g/mol)

TLC	R_f = 0.49 and 0.55 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with dichloromethane/hexane (50/50, then 80/20 v/v)
Yield	192 mg (65%)
Diastereomeric ratio	*E/Z* = 2.5:1
^{1}H-NMR	***E*-isomer** (400 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 6.9 Hz, 6H, $CH(CH_3)_2$), 2.51 (d, *J* = 1.2 Hz, 3H, CH_3), 2.93-2.96 (septet, *J* = 6.9 Hz, 1H, $CH(CH_3)_2$), 6.40 (dq, *J* = 7.9, 1.2 Hz, 1H, =CH) 7.10-7.48 (m, 4H, arom), 10.18 (d, *J* = 7.9 Hz, 1H, CHO); ***Z*-isomer** (400 MHz, $CDCl_3$): δ = 1.26 (d, *J* = 7.0 Hz, 6H, $CH(CH_3)_2$), 2.31 (d, *J* = 1.4 Hz, 3H, CH_3), 2.93-2.96 (m, 1H, $CH(CH_3)_2$), 6.12 (dq, *J* = 8.2, 1.3 Hz, 1H, =CH), 7.10-7.48 (m, 4H, arom), 9.47 (d, *J* = 8.2 Hz, 1H, CHO);
^{13}C-NMR	***E*-isomer** (100 MHz, $CDCl_3$): δ = 16.5 (CH_3), 24.0 (CH_3), 123.9 (CHAr), 124.4 (CHAr), 127.2 (CHAr), 128.3 (CHAr), 128.7 (CHCHO), 140.7 (Cq_{Ar}), 149.4 (Cq_{Ar}), 158.1 ($ArCCH_3$=), 191.3 (CHO); ***Z*-isomer** (100 MHz, $CDCl_3$): δ = 26.5 (CH_3), 34.2 (CH_3), 125.8 (CHAr), 126.6 (CHAr), 127.3 (CHAr), 128.4 (CHAr), 129.1 (CHCHO), 138.5 (Cq_{Ar}), 149.2 (Cq_{Ar}), 162.6 ($ArCCH_3$=), 193.6 (CHO);
Mass	*m/z* (%) (EI) 187 (M-H, 6), 173 (M-CH_3, 4), 145 (100), 117 (16), 115 (15), 91 (9);
HRMS	(ESIpos) calculated for $C_{13}H_{16}O$ (M) 188.120116; found 188.120170;

7.2.2.6. 3-(1-Naphthalenyl)-2-butenal (227d)



X = Br, I (2.0 equiv)

48 **227d**

The procedure of 7.2.2.1 was followed. The *E*-isomer was obtained as a colorless solid, the *Z*-isomer as a yellowish oil.

Chemical Formula $C_{14}H_{12}O$ (196.24 g/mol)

TLC R_f = 0.43 and 0.51 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (30/70, then 40/60, then 50/50 v/v)

Yield **X=Br:** 205 mg (71%)

X=I: 128 mg (43%)

Diastereomeric ratio *E/Z* = 1:2.1

^{1}H-NMR ***E*-isomer** (300 MHz, $CDCl_3$): δ = 2.65 (d, *J* = 1.4 Hz, 3H, C*H*$_3$), 6.18 (dq, *J* = 7.9, 1.3 Hz, 1H, =C*H*) 7.32 (dd, *J* = 7.0, 1.1 Hz, 1H, arom), 7.43-7.56 (m, 3H, arom), 7.82-7.92 (m, 3H, arom), 10.29 (d, *J* = 7.9 Hz, 1H, C*H*O);

***Z*-isomer** (400 MHz, $CDCl_3$): δ = 2.40 (d, *J* = 1.4 Hz, 3H, C*H*$_3$), 6.36 (dq, *J* = 8.3, 1.3 Hz, 1H, =C*H*), 7.32 (dd, *J* = 7.0, 1.1 Hz, 1H, arom), 7.47-7.56 (m, 3H, arom), 7.77-7.81 (m, 1H, arom), 7.85-7.91 (m, 2H, arom), 9.18 (d, *J* = 8.3 Hz, 1H, C*H*O);

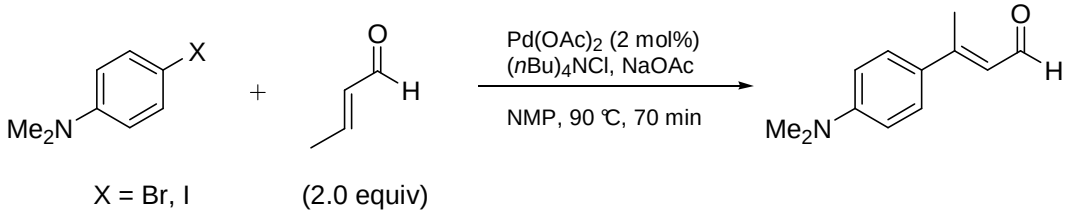
^{13}C-NMR ***E*-isomer** (75.5 MHz, $CDCl_3$): δ = 20.1 (*C*H$_3$), 124.1 (*C*HCHO), 125.0 (*C*H$_{Ar}$), 125.2 (*C*H$_{Ar}$), 126.2 (*C*H$_{Ar}$), 126.6 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 129.6 (*C*q$_{Ar}$), 131.2 (*C*H$_{Ar}$), 133.8 (*C*q$_{Ar}$), 140.9 (*C*q$_{Ar}$), 159.8 (Ar*C*CH$_3$=), 191.0 (*C*HO);

***Z*-isomer** (100 MHz, $CDCl_3$): δ = 27.4 (*C*H_3), 125.0 (*C*HCHO), 125.1 (*C*H_{Ar}), 125.4 (*C*H_{Ar}), 126.4 (*C*H_{Ar}), 126.9 (*C*H_{Ar}), 128.6 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 130.7 (*C*q_{Ar}), 130.9 (*C*H_{Ar}), 133.6 (*C*q_{Ar}), 136.6 (*C*q_{Ar}), 162.0 (Ar*C*CH_3=), 193.3 (*C*HO);

Mass *m/z* (%) (EI) 196 (M, 44), 195 (M-H, 47) 181 (M-CH_3, 100), 167 (46), 152 (58), 128 (18), 115 (6), 83 (16);

HRMS (ESIpos) calculated for $C_{14}H_{12}O$ (M) 196.088813; found 196.088607;

7.2.2.7. 3-(4-(Dimethylamino)phenyl)-2-butenal (227e)



X = Br, I (2.0 equiv)

48 **227e**

The procedure of 7.2.2.1 was followed. Both *E*- and *Z*-isomer were obtained as yellow-orange solids.

Chemical Formula $C_{12}H_{15}NO$ (189.25 g/mol)

TLC R_f = 0.25 and 0.31 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 v/v)

Yield **X=Br:** 219 mg (76%)

X=I: 249 mg (87%)

Diastereomeric ratio *E/Z* = 4:1

^{1}H-NMR ***E*-isomer** (300 MHz): δ = 2.53 (d, *J* = 1.0 Hz, 3H, C*H*$_3$), 3.03 (s, 3H, C*H*$_3$), 6.42 (dq, *J* = 8.1, 1.1 Hz, 1H, =C*H*), 6.67-6.73 (m,

2H, arom), 7.50-7.57 (m, 2H, arom), 10.12 (d, *J* = 8.0 Hz, 1H, C*H*O);

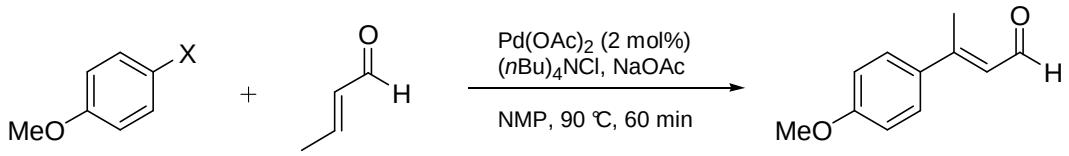
***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.29 (d, *J* = 1.1 Hz, 3H, CH_3), 3.02 (s, 3H, CH_3), 6.04 (dq, *J* = 8.1, 1.2 Hz, 1H, =C*H*), 6.67-6.73 (m, 2H, arom), 7.21-7.26 (m, 2H, arom), 9.56 (d, *J* = 8.0 Hz, 1H, C*H*O);

^{13}C-NMR ***E*-isomer** (75.5 MHz, $CDCl_3$): δ = 15.6 (*C*H_3), 40.1 (*C*H_3), 111.6 (*C*H_{Ar}), 123.3 (*C*H_{Ar}), 126.6 (*C*HCHO), 127.7 (*C*q_{Ar}), 151.9 (*C*q_{Ar}), 157.4 (Ar*C*CH_3=), 191.2 (*C*HO);

Mass *m/z* (%) (EI) 189 (M, 100), 174 (M-CH_3, 31), 160 (M-CHO, 23), 146 (24), 121 (58), 115 (21), 91 (9), 77 (11);

HRMS (ESIpos) calculated for $C_{12}H_{15}NO$ (M) 189.115366; found 189.115343;

7.2.2.8. 3-(4-Methoxyphenyl)-2-butenal (227f)



X = Br, I (2.0 equiv)

48 **227f**

The procedure of 7.2.2.1 was followed. The *E*-isomer was obtained as a yellowish solid, the *Z*-isomer as a yellowish oil.

Chemical Formula $C_{11}H_{12}O_2$ (176.21 g/mol)

TLC R_f = 0.27 and 0.35 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with diethyl ether/pentane (15/85 v/v)

Yield **X=Br:** 197 mg (71%)

X=I: 242 mg (92%)

Diastereomeric ratio *E/Z* = 3.3:1

^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 2.54 (d, *J* = 1.2 Hz, 3H, C*H*$_3$), 3.85 (s, 3H, C*H*$_3$), 6.38 (dq, *J* = 7.9, 1.1 Hz, 1H, =C*H*), 6.91-6.95 (m, 2H, arom), 7.52-7.56 (m, 2H, arom), 10.15 (d, *J* = 7.9 Hz, 1H, C*H*O);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 1.4 Hz, 3H, C*H*$_3$), 3.85 (s, 3H, C*H*$_3$), 6.10 (dq, *J* = 8.1, 1.3 Hz, 1H, =C*H*), 6.90-6.96 (m, 2H, arom), 7.24-7.29 (m, 2H, arom), 9.50 (d, *J* = 8.1 Hz, 1H, C*H*O);

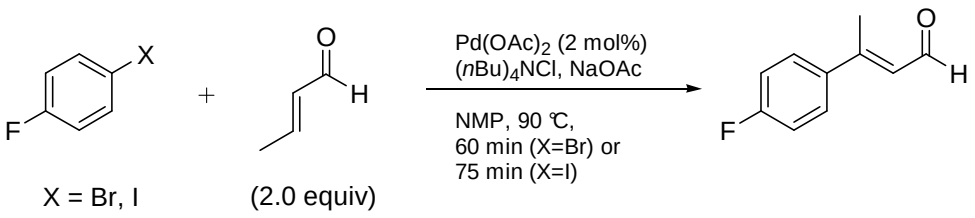
^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 16.1 (*C*H$_3$), 55.4 (O*C*H$_3$), 114.1 (*C*HAr), 125.6 (*C*HCHO), 127.9 (*C*HAr), 132.5 (*C*qAr), 156.9 (*C*qAr), 161.4 (Ar*C*CH$_3$=), 191.2 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 26.2 (*C*H$_3$), 55.4 (O*C*H$_3$), 113.8 (*C*HAr), 128.7 (*C*HCHO), 130.1 (*C*HAr), 130.7 (*C*qAr), 160.6 (*C*qAr), 161.6 (Ar*C*CH$_3$=), 193.5 (*C*HO);

Mass *m/z* (%) (EI) 175 (M-H, 100), 161 (M-CH$_3$, 84), 145 (86), 133 (35), 115 (33), 108 (26), 91 (28), 77 (37);

HRMS (ESIpos) calculated for $C_{11}H_{12}O_2$ (M) 176.083733; found 176.083741;

7.2.2.9. 3-(4-Fluorophenyl)-2-butenal (227g)



X = Br, I (2.0 equiv)

48 **227g**

The procedure of 7.2.2.1 was followed. The *E*-isomer was obtained as a slightly yellow solid, the *Z*-isomer as a yellowish oil.

Chemical Formula $C_{10}H_9FO$ (164.18 g/mol)

Diastereomeric ratio *E/Z* = 3.0:1

TLC R_f = 0.31 and 0.39 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)

Yield **X=Br:** 100 mg (40%)

X=I: 108 mg (44%)

^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 2.55 (d, *J* = 1.2 Hz, 3H, C*H*$_3$), 6.35 (dq, *J* = 7.7, 1.2 Hz, 1H, =C*H*), 7.08-7.13 (m, 2H, arom), 7.51-7.57 (m, 2H, arom), 10.16 (d, *J* = 7.8 Hz, 1H, C*H*O);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.30 (d, *J* = 1.3 Hz, 3H, C*H*$_3$), 6.14 (dq, *J* = 8.1, 1.4 Hz, 1H, =C*H*), 7.08-7.15 (m, 2H, arom), 7.27-7.32 (m, 2H, arom), 9.47 (d, *J* = 8.1 Hz, 1H, C*H*O);

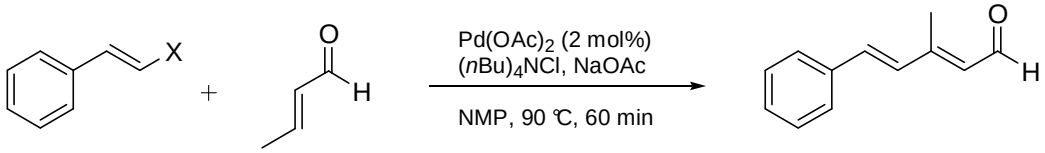
^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 16.4 (*C*H_3), 115.8 (d, $^2J_{CF}$ = 21.7 Hz, *C*H_{Ar}), 127.1 (=*C*H), 128.2 (d, $^3J_{CF}$ = 8 Hz, *C*H_{Ar}), 136.6 (d, $^4J_{CF}$ = 4.0 Hz, *C*q_{Ar}), 156.2 (=*C*Ar), 163.9 (d, $^1J_{CF}$ = 249.5 Hz, *C*q_{Ar}), 191.1 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 26.5 (*C*H_3), 115.6 (d, $^2J_{CF}$ = 21 Hz, *C*H_{Ar}), 129.5 (=*C*H), 130.2 (d, $^3J_{CF}$ = 8 Hz, *C*H_{Ar}), 134.4 (d, $^4J_{CF}$ = 3 Hz, *C*q_{Ar}), 160.7 (=*C*Ar), 163.2 (d, $^1J_{CF}$ = 249.3 Hz, *C*q_{Ar}), 193.0 (*C*HO);

Mass *m/z* (%) (EI) 163 (M-H, 100), 149 (M-CH_3, 34), 145 (10), 133 (30), 115 (25), 109 (21);

HRMS (ESIpos) calculated for $C_{10}H_9FO$ (M) 164.063742; found 164.063574;

7.2.2.10. 3-Methyl-5-phenyl-2,4-pentadienal (227h)



X = Br, I (2.0 equiv)

48 **227h**

The procedure of 7.2.2.1 was followed. Both *E*- and *Z*-isomers were obtained as yellowish liquids.

Chemical Formula $C_{12}H_{12}O$ (172.22 g/mol)

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)

Yield **X=Br:** 194 mg (74%)

X=I: 140 mg (60%)

Diastereomeric ratio *E/Z* = 1.7:1

^{1}H-NMR ***E*-isomer** (300 MHz, $CDCl_3$): δ = 2.39 (d, *J* = 1.1 Hz, 3H, C*H*$_3$), 6.09 (d, *J* = 8.0 Hz, 1H, =C*H*CHO), 6.90 (d, *J* = 16.2 Hz, 1H, PhCH=C*H*R), 7.09 (d, *J* = 16.1 Hz, 1H, PhC*H*=CHR), 7.29-7.42 (m, 3H, arom), 7.47-7.54 (m, 2H, arom),10.17 (d, *J* = 8.0 Hz, 1H, C*H*O);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 2.21 (d, *J* = 1.1 Hz, 3H, C*H*$_3$), 5.96 (dd, *J* = 7.8, 0.7 Hz, 1H, =C*H*CHO), 6.98 (d, *J* = 15.9 Hz, 1H, PhCH=C*H*R), 7.83 (d, *J* = 15.9 Hz, 1H, PhC*H*=CHR), 7.30-7.43 (m, 3H, arom), 7.49-7.55 (m, 2H, arom),10.30 (d, *J* = 7.8 Hz, 1H, C*H*O);

^{13}C-NMR

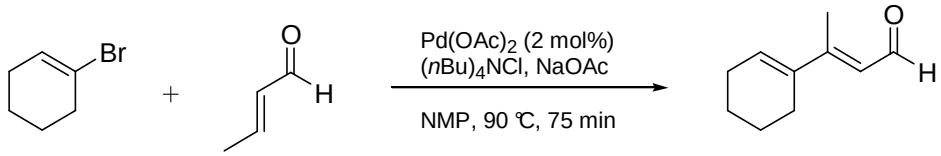
***E*-isomer** (75.5 MHz, $CDCl_3$): δ = 13.1 (*C*H_3), 127.4 (*C*H), 128.9 (*C*H), 129.3 (*C*H), 130.1 (*C*H), 131.4 (*C*H), 135.7 (*C*H), 135.9 (*C*q_{Ar}), 154.2 (CH*C*CH_3=), 191.2 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 21.3 (*C*H_3), 123.4 (*C*H), 127.4 (*C*H), 128.8 (*C*H), 129.0 (*C*H), 129.3 (*C*H), 136.0 (*C*H), 136.9 (*C*q_{Ar}), 154.1 (CH*C*CH_3=), 189.9 (*C*HO);

Mass *m/z* (%) (DE) 172 (M-H, 100), 157 (M-CH_3, 49), 143 (M-CHO, 22), 129 (83), 115 (22), 95 (M-C_6H_5, 25), 77 (19);

HRMS (ESIpos) calculated for $C_{12}H_{12}O$ (M) 172.088816; found 172.088595;

7.2.2.11. 3-Cyclohex-1-enyl-2-butenal (227i)



(2.0 equiv)

48 **227i**

The procedure of 7.2.2.1 was followed. Only the *E*-isomer was isolated and obtained as colorless oil.

Chemical Formula $C_{10}H_{14}O$ (150.22 g/mol)

TLC R_f = 0.49 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anis-aldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 v/v)

Yield 100 mg (44%)

Diastereomeric ratio *E/Z* = 6.7:1

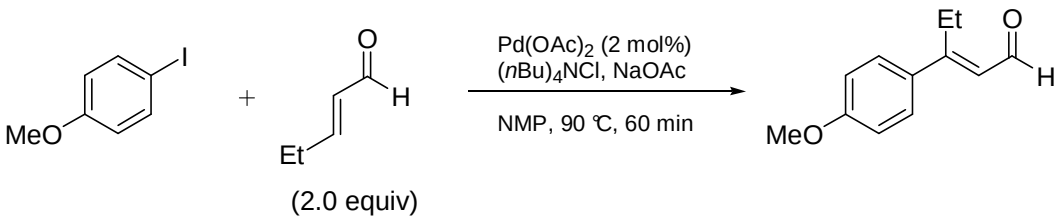
^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 1.60-1.62 (m, 2H), 1.70-1.72 (m, 2H), 2.17-2.28 (m, 4H), 2.29 (d, *J* = 0.8 Hz, 3H, C*H*$_3$), 6.04 (d, *J* = 8.0 Hz, 1H, =C*H*CHO), 6.44 (m, 1H, =C*H*$_{cyclohex}$), 10.15 (d, *J* = 7.9 Hz, 1H, C*H*O);

^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 13.9 (*C*H$_3$), 21.7 (*C*H$_2$), 22.6 (*C*H$_2$), 25.6 (*C*H$_2$), 26.6 (*C*H$_2$), 124.2 (*C*H), 133.0 (*C*HCOH), 137.3 (*C*q), 157.1 (CH*C*CH$_3$=), 192.3 (*C*HO);

Mass *m/z* (%) (EI) 149 (M-H, 20), 135 (M-CH$_3$, 33), 121 (100), 107 (18), 91 (28), 79 (45);

HRMS (ESIpos) calculated for $C_{10}H_{14}O$ (M) 150.104463; found 150.104295;

7.2.2.12. 3-(4-Methoxyphenyl)-2-pentenal (235a)



242 **235a**

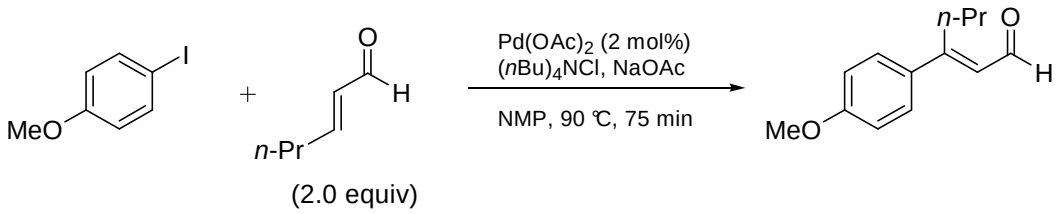
The procedure of 7.2.2.1 was followed. Both *E*- and *Z*-isomers were obtained as slightly yellow oils.

Chemical Formula $C_{12}H_{14}O_2$ (190.24 g/mol)

TLC R_f = 0.38 and 0.44 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (8/92 v/v)
Yield	173 mg (61%)
Diastereomeric ratio	*E/Z* = 1.4:1
^{1}H-NMR	***E*-isomer** (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.6 Hz, 3H, CH_2CH_3), 3.04 (q, *J* = 7.6 Hz, 2H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 6.25 (d, *J* = 8.0 Hz, 1H, =C*H*), 6.92-6.95 (m, 2H, arom), 7.48-7.52 (m, 2H, arom), 10.13 (d, *J* = 8.0 Hz, 1H, C*H*O); ***Z*-isomer** (400 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 2.59 (qd, *J* = 7.4 Hz, 1.3 Hz, 2H, CH_2CH_3), 3.85 (s, 3H, OCH_3), 6.08 (dt, *J* = 8.0, 1.3 Hz, 1H, =C*H*), 6.91-6.95 (m, 2H, arom), 7.20-7.24 (m, 2H, arom), 9.48 (d, *J* = 8.0 Hz, 1H, C*H*O);
^{13}C-NMR	***E*-isomer** (100 MHz, $CDCl_3$): δ = 15.2 (CH_3), 23.0 (CH_2), 55.4 (OCH_3), 114.3 (CH_{Ar}), 125.3 (*C*HCHO), 128.2 (CH_{Ar}), 131.3 (Cq_{Ar}), 161.3 (Cq_{Ar}), 164.0 ($ArCCH_2$=), 191.0 (*C*HO); ***Z*-isomer** (100 MHz, $CDCl_3$): δ = 12.3 (CH_3), 32.5 (CH_2), 55.4 (OCH_3), 113.8 (CH_{Ar}), 127.1 (CH_{Ar}, *C*HCHO), 130.1 (Cq_{Ar}), 160.4 (Cq_{Ar}), 167.5 ($ArCCH_2$=), 193.9 (*C*HO);
Mass	*m/z* (%) (EI) 190 (M, 100), 175 (M-CH_3, 29), 161 (M-CHO, 47), 147 (16), 135 (20), 121 (16), 108 (17), 91 (17);
HRMS	(ESIpos) calculated for $C_{12}H_{14}NaO_2$ (M+Na) 213.088597; found 213.088879;

7.2.2.13. 3-(4-Methoxyphenyl)-2-hexenal (235b)



242 **235b**

The procedure of 7.2.2.1 was followed. Both *E*- and *Z*-isomers were obtained as slightly yellow oils.

Chemical Formula $C_{13}H_{16}O_2$ (204.26 g/mol)

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 v/v)

Yield 245 mg (80%)

Diastereomeric ratio *E/Z* = 1.6:1

^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.56 (tq, *J* = 7.5, 7.5 Hz, 2H, $CH_2CH_2CH_3$), 2.99 (t, *J* = 7.6 Hz, 2H, $CH_2CH_2CH_3$), 3.85 (s, 3H, OCH_3), 6.30 (d, *J* = 8.0 Hz, 1H, =C*H*), 6.91-6.95 (m, 2H, arom), 7.46-7.50 (m, 2H, arom), 10.11 (d, *J* = 8.1 Hz, 1H, C*H*O);

***Z*-isomer** (300 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.4 Hz, 3H, $CH_2CH_2CH_3$), 1.56 (tq, *J* = 7.5, 7.5 Hz, 2H, $CH_2CH_2CH_3$), 2.55 (td, *J* = 7.3, 1.0 Hz, 2H, $CH_2CH_2CH_3$), 3.84 (s, 3H, OCH_3), 6.07 (dt, *J* = 8.0, 1.0 Hz, 1H, =C*H*), 6.90-6.95 (m, 2H, arom), 7.20-7.24 (m, 2H, arom), 9.47 (d, *J* = 8.0 Hz, 1H, C*H*O);

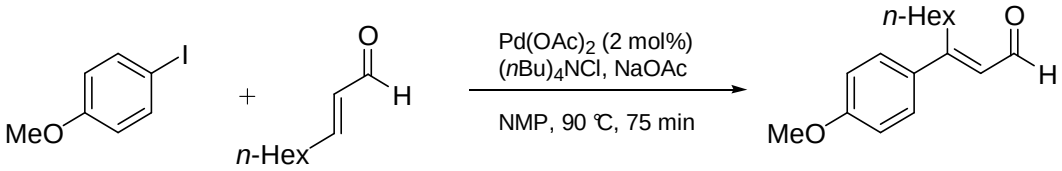
^{13}C-NMR ***E*-isomer** (100 MHz, $CDCl_3$): δ = 13.8 (CH_3), 23.4 (CH_2), 31.4 (CH_2), 55.4 (OCH_3), 114.2 (CH_{Ar}), 126.4 (*C*HCHO), 128.2 (CH_{Ar}), 131.7 (Cq_{Ar}), 161.2 (Cq_{Ar}), 162.3 (Ar*C*CH_2=), 191.0 (*C*HO);

***Z*-isomer** (75.5 MHz, $CDCl_3$): δ = 13.6 (*C*H_3), 20.9 (*C*H_2), 41.5 (*C*H_2), 55.4 (O*C*H_3), 113.8 (*C*H_{Ar}), 128.2 (*C*HCHO), 129.9 (*C*H_{Ar}), 130.2 (*C*q_{Ar}), 160.4 (*C*q_{Ar}), 166.0 (Ar*C*CH_2=), 193.8 (*C*HO);

Mass *m/z* (%) (DE) 204 (M, 100), 189 (M-CH_3, 22), 175 (M-CHO, 18), 173 (M-OMe, 36), 161 (65), 148 (23), 133 (21), 121 (22), 91 (19), 77 (19);

HRMS (ESIpos) calculated for $C_{13}H_{16}NaO_2$ (M+Na) 227.104248; found 227.104164;

7.2.2.14. 3-(4-Methoxyphenyl)-2-nonenal (235c)



(2.0 equiv)

242 **235c**

The procedure of 7.2.2.1 was followed. The isomers have not been separated.

Chemical Formula $C_{16}H_{22}O_2$ (246.34 g/mol)

TLC R_f = 0.46 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (8/92 v/v)

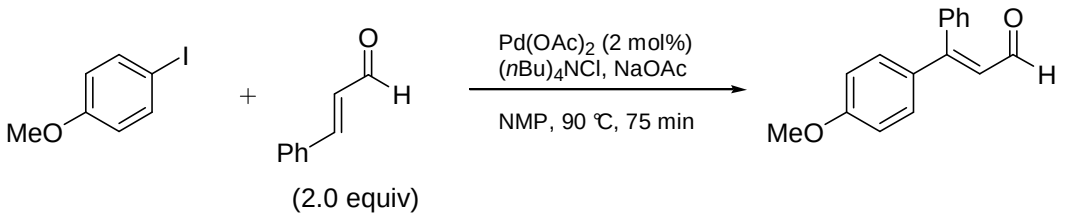
Yield 238 mg (65%)

Diastereomeric ratio *E/Z* = 1.4:1

^{1}H-NMR ***E*-isomer** (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.9 Hz, 3H, $CH_2CH_2(CH_2)_3CH_3$), 1.18-1.46 (m, 6H, $CH_2CH_2(CH_2)_3CH_3$), 1.47-1.56 (m, 2H, $CH_2CH_2(CH_2)_3CH_3$), 3.00 (t, *J* = 7.7 Hz, 2H,

	C*H*$_2$CH$_2$(CH$_2$)$_3$CH$_3$), 3.83 (s, 3H, OC*H*$_3$), 6.27 (d, *J* = 8.0 Hz, 1H, =C*H*), 6.91-6.95 (m, 2H, arom), 7.46-7.50 (m, 2H, arom), 10.12 (d, *J* = 8.0 Hz, 1H, C*H*O);
	***Z*-isomer** (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 3H, CH$_2$(CH$_2$)$_4$C*H*$_3$), 1.18-1.46 (m, 8H, CH$_2$ (C*H*$_2$)$_4$CH$_3$), 2.56 (td, *J* = 7.5, 1.0 Hz, 2H, C*H*$_2$(CH$_2$)$_4$CH$_3$), 3.83 (s, 3H, OC*H*$_3$), 6.07 (dt, *J* = 8.0, 1.0 Hz, 1H, =C*H*), 6.91-6.95 (m, 2H, arom), 7.20-7.23 (m, 2H, arom), 9.48 (d, *J* = 8.1 Hz, 1H, C*H*O);
^{13}C-NMR	***E*-isomer** (100 MHz, $CDCl_3$): δ = 13.6 (*C*H$_3$), 22.1 (*C*H$_2$), 28.8 (*C*H$_2$), 29.2 (*C*H$_2$), 29.9 (*C*H$_2$), 31.1 (*C*H$_2$), 55.0 (O*C*H$_3$), 113.8 (*C*H$_{Ar}$), 125.7 (*C*H$_{Ar}$), 127.8 (*C*HCHO), 129.8 (*C*q$_{Ar}$), 160.8 (*C*q$_{Ar}$), 162.3 (Ar*C*CH$_2$=), 190.6 (*C*HO);
	***Z*-isomer** (100 MHz, $CDCl_3$): δ = 13.6 (*C*H$_3$), 22.1 (*C*H$_2$), 27.3 (*C*H$_2$), 28.4 (*C*H$_2$), 31.1 (*C*H$_2$), 39.1 (*C*H$_2$), 54.9 (O*C*H$_3$), 113.4 (*C*H$_{Ar}$), 127.7 (*C*HCHO), 129.5 (*C*H$_{Ar}$), 131.2 (*C*q$_{Ar}$), 160.0 (*C*q$_{Ar}$), 165.9 (Ar*C*CH$_2$=), 193.4 (*C*HO);
Mass	*m/z* (%) (DE) 246 (M, 94), 231 (M-CH$_3$, 6), 215 (M-OMe, 22), 203 (36), 189 (71), 176 (M-C$_5$H$_{11}$, 82), 161 (M-C$_6$H$_{13}$, 53), 148 (100), 133 (25), 121 (53), 108 (23), 91 (21), 77 (17);
HRMS	(ESIpos) calculated for C$_{16}$H$_{22}$NaO$_2$ (M+Na) 269.151201; found 269.151315;

7.2.2.15. 3-(4-Methoxyphenyl)-3-phenyl-propenal (235d)



242 **235d**

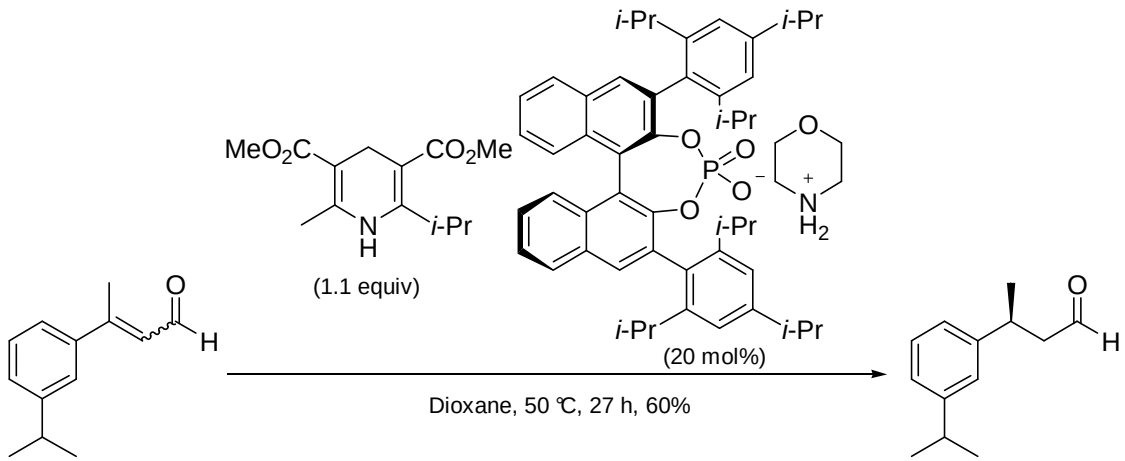
The procedure of 7.2.2.1 was followed. The isomers have not been separated and the mixture was obtained as a slightly yellow oil.

Chemical Formula	$C_{16}H_{14}O_2$ (238.28 g/mol)
TLC	R_f = 0.24 (SiO_2, dichloromethane), stained dark purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with dichloromethane/hexane (50/50, then 100/0 v/v)
Yield	186 mg (52%)
Diastereomeric ratio	1.7:1
^{1}H-NMR	**major isomer** (400 MHz, $CDCl_3$): δ = 3.82 (s, 3H, OC*H*$_3$), 6.56 (d, *J* = 8.0 Hz, 1H, =C*H*), 6.88 (m, 2H, arom), 7.20-7.50 (m, 7H, arom), 9.45 (d, *J* = 8.0 Hz, 1H, C*H*O); **minor isomer** (400 MHz, $CDCl_3$): δ = 3.86 (s, 3H, OC*H*$_3$), 6.51 (d, *J* = 7.9 Hz, 1H, =C*H*), 6.95 (m, 2H, arom), 7.20-7.50 (m, 7H, arom), 9.56 (d, *J* = 8.0 Hz, 1H, C*H*O);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 55.4 (O*C*H$_3$), 113.8 (*C*H$_{Ar}$), 114.1 (*C*H$_{Ar}$), 125.6 (*C*HCHO), 127.0 (*C*HCHO), 128.5 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 129.3 (*C*H$_{Ar}$), 130.3 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 130.6 (*C*H$_{Ar}$), 131.8 (*C*H$_{Ar}$), 132.5 (*C*H$_{Ar}$), 136.9 (*C*q$_{Ar}$), 140.3 (*C*q$_{Ar}$), 160.9 (*C*q$_{Ar}$), 161.7 (*C*q$_{Ar}$), 161.9 (Ar$_2$*C*=), 162.2 (Ar$_2$*C*=), 193.4 (*C*HO), 193.5 (*C*HO);

Mass *m/z* (%) (DE) 238 (M, 100), 223 (M-CH_3, 12), 207 (M-CHO, 30), 165 (26), 135 (12), 102 (15);

HRMS (ESIpos) calculated for $C_{16}H_{14}NaO_2$ (M+Na) 261.088597; found 261.088521;

7.2.3. Synthesis of (+)-3-(3-isopropylphenyl)butanal (Florhydral®) (242)



227c **247** **248** **242**

The reaction was performed employing a literature-known procedure.[24] The isomeric mixture of 3-(3-isopropylphenyl)-2-butenal (**227c**) (92.0 mg, 0.5 mmol) was dissolved in 1,4-dioxane (5 mL), heated to 50 °C, and the morpholine salt **248** of 3,3'-bis(2,4,6-triisopropylphenyl)-1,1'-binaphthyl-2,2'-diyl hydrogen phosphate (TRIP) was added (84.0 mg, 0.1 mmol). The mixture was allowed to stir for 5 min before addition of dimethyl 2-isopropyl-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate **247** (142 mg, 0.55 mmol). After stirring for 27 h the reaction mixture was allowed to cool to room temperature, poured into 15 mL of distilled water, and extracted twice with 15 mL of dichloromethane. The combined organic fractions were washed with brine once, dried over magnesium sulfate, and the solvent was removed under reduced pressure. The product was purified by column chromatography with 50/50 dichloromethane/hexane (v/v) as the eluent. The product was obtained as a colorless oil.

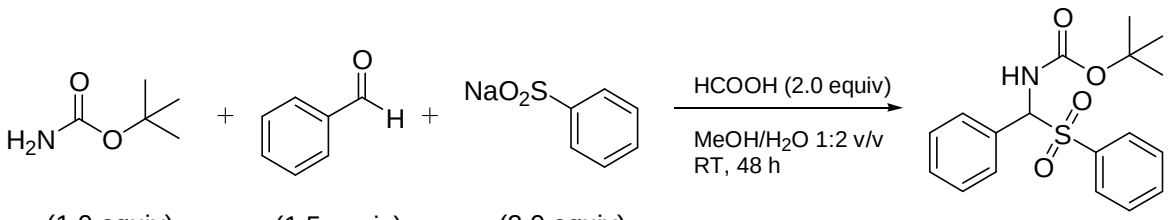
Chemical Formula $C_{13}H_{18}O$ (190.28 g/mol)

TLC	R_f = 0.55 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with dichloromethane/hexane (50/50 v/v)
Yield	56 mg (60%)
Enantiomeric ratio	99:1
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ +34.7 (*c* = 1.45, $CHCl_3$), Lit.[140] $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ +30.7 (*c* = 1.39, $CHCl_3$)
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 7.0 Hz, 6H, CH(C*H*$_3$)$_2$), 1.32 (d, *J* = 7.0 Hz, 3H, CHC*H*$_3$), 2.65 (ddd, *J* = 16.6, 7.8, 2.3 Hz, CHC*H*$_2$CHO), 2.75 (ddd, *J* = 16.5, 6.7, 1.8 Hz, CHC*H*$_2$CHO), 2.88 (septet, *J* = 6.9 Hz, 1H, C*H*(CH$_3$)$_2$), 3.29-3.39 (m, 1H, C*H*CH$_3$), 7.01-7.11 (m, 3H, arom), 7.21-7.27 (m, 1H, arom), 9.71 (t, *J* = 2.0 Hz, 1H, C*H*O);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 22.2 (*C*H$_3$), 24.0 (*C*H$_3$), 34.2 (*C*H), 34.4 (*C*HNH), 51.8 (*C*H$_2$COH), 124.1 (*C*H$_{Ar}$), 124.6 (*C*H$_{Ar}$), 125.1 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 145.4 (*C*q$_{Ar}$), 149.3 (*C*q$_{Ar}$), 202.1 (*C*HO);
Mass	*m/z* (%) (DE) 190 (M, 60), 175 (M-CH$_3$, 11), 147 (M-CHO, 100), 133 (27), 119 (21), 105 (77), 91 (38);
HRMS	(ESIpos) calculated for $C_{13}H_{18}O$ (M) 190.135761; found 190.135807;
GC	$\boldsymbol{\tau_R}$ 29.71 min (major enantiomer) $\boldsymbol{\tau_R}$ 30.01 min (minor enantiomer) (Ivadex-1/PS-86 column 25 m (80 °C, 1.5 °C/min until 130 °C, 20 °C/min until 220 °C, 10 min at 320 °C, 0.7 bar H_2 as carrier gas));

7.3. Mannich reactions of *N*-Boc-imines

7.3.1. Synthesis of *N*-Boc-imines

7.3.1.1. (Benzenesulfonyl-phenylmethyl)-carbamic acid *tert*-butyl ester (249a)



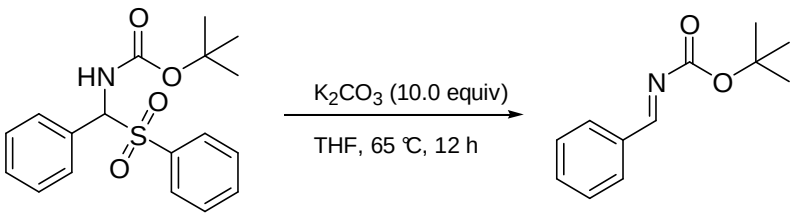
(1.0 equiv) (1.5 equiv) (2.0 equiv)

250 **252a** **251** **249a**

A literature procedure was followed.[92] To a stirred solution of *tert*-butyl carbamate (10.2 g, 87.1 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (28 g, 170.6 mmol, 2.0 equiv) in methanol/water (83 mL/167 mL) was added benzaldehyde (13 mL, 128.6 mmol, 1.5 equiv) in one portion, followed by formic acid (6.4 mL). The mixture was stirred at room temperature for 48 h, during which a colorless precipitate occurred. The solid was filtered, washed with water and diethyl ether and dried *in vacuo*. The NMR data was in agreement with the literature.[92]

Chemical Formula	$C_{18}H_{21}NO_4S$ (347.43 g/mol)
Purification	washing with water and diethyl ether
Yield	24.6 g (81%; Lit.[92] 80%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, C(CH_3)$_3$), 5.83 (d, J = 9.8 Hz, 1H, CHN*H*), 5.94 (d, J = 10.5 Hz, 1H, C*H*NH), 7.38-7.48 (m, 5H, arom), 7.49-7.57 (m, 2H, arom), 7.60-7.68 (m, 1H, arom), 7.87-7.95 (m, 2H, arom);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 28.0 (C(CH_3)$_3$), 73.9 (*C*NH), 81.3 (*C*(CH_3)$_3$), 128.8 (CH_{Ar}), 128.9 (CH_{Ar}), 129.0 (CH_{Ar}), 129.5 (CH_{Ar}), 129.9 (CH_{Ar}), 129.9 (CH_{Ar}), 134.0 (Cq_{Ar}), 137.0 (Cq_{Ar}), 153.5 (CO_2);

7.3.1.2. Phenylmethylene-carbamic acid *tert*-butyl ester (159a)

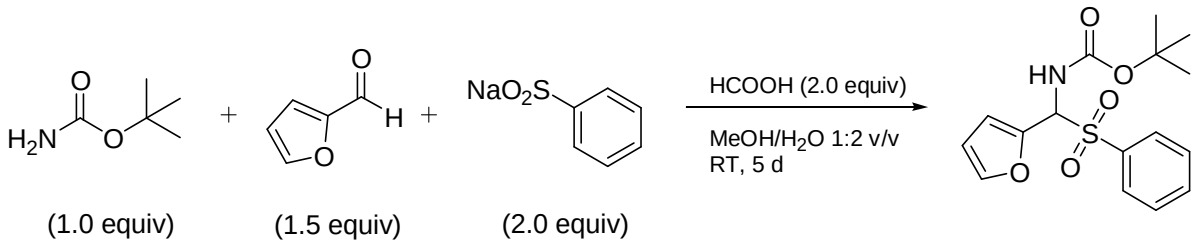


249a **159a**

For this synthesis a modified literature procedure was employed.[92] A 250 mL round-bottomed flask was charged with 21 g of K_2CO_3 (150 mmol, 10.0 equiv) which was then flame dried under vacuum. After cooling, 5.2 g of (Benzenesulfonyl-phenylmethyl)-carbamic acid benzyl ester (15 mmol, 1.0 equiv) were added and the flask was charged with argon. After addition of 140 mL of dry tetrahydrofuran the reaction mixture was heated to reflux for 12 h under an atmosphere of argon. After cooling the mixture was filtered through a glass frit and the solvent evaporated to give a colorless oil.

Chemical Formula	$C_{12}H_{15}NO_2$ (205.25 g/mol)
Purification	Usually the product was sufficiently pure and was directly used in subsequent reactions. If impurities were detected the compound was distilled with a bulb-to-bulb distillation apparatus at 120 °C/0.01 mbar
Yield	2.08 g (91%; Lit.[92] 100%)
^{1}H-NMR	(300 MHz, acetone-d6): δ = 1.54 (s, 9H, C(C*H*$_3$)$_3$), 7.49-7.58 (m, 2H, arom), 7.59-7.66 (m, 1H, arom), 7.91-7.99 (m, 2H, arom), 8.80 (C*H*=N);
^{13}C-NMR	(75.5 MHz, acetone-d6): δ = 28.1 (C(*C*H$_3$)$_3$), 82.0 (*C*(CH$_3$)$_3$), 129.9 (*C*H$_{Ar}$), 130.5 (*C*H$_{Ar}$), 134.1 (*C*H$_{Ar}$), 135.6 (*C*q$_{Ar}$), 163.4 (*C*O$_2$), 168.4 (*C*HN);

7.3.1.3. (Benzenesulfonyl-furan-2-ylmethyl)-carbamic acid *tert*-butyl ester (249b)



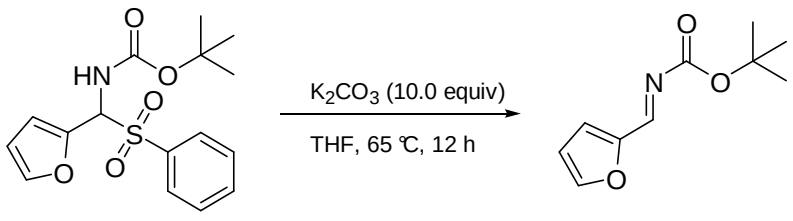
(1.0 equiv) (1.5 equiv) (2.0 equiv)

250 **252b** **251** **249b**

The aldehyde was freshly distilled prior to use, and the procedure of 7.3.1.1 was followed. The ^{1}H-NMR of the product, obtained as a colorless solid, was in full agreement with the literature.[92]

Chemical Formula	$C_{16}H_{19}NO_5S$ (337.39 g/mol)
Purification	washing with water and diethyl ether
Yield	4.7 g (46%; Lit.[92] 55%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.28 (s, 9H, C(C*H*$_3$)$_3$), 5.82 (d, *J* = 10.8 Hz, CHN*H*), 6.03 (d, *J* = 10.6 Hz, C*H*NH), 6.44 (dd, *J* = 3.4, 1.9 Hz, 1H, C*H*$_{Fur}$), 6.58 (d, *J* = 3.3 Hz, 1H, C*H*$_{Fur}$), 7.48 (s, 1H, C*H*$_{Fur}$), 7.50-7.57 (m, 2H, C*H*$_{Ar}$), 7.60-7.69 (m, 1H, C*H*$_{Ar}$), 7.89 (d, *J* = 7.4 Hz, 2H, C*H*$_{Ar}$);

7.3.1.4. Furan-2-ylmethylene-carbamic acid *tert*-butyl ester (159b)



249b **159b**

The procedure of 7.3.1.2 was followed. The product was obtained as a yellow oil. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula $C_{10}H_{13}NO_3$ (195.22 g/mol)

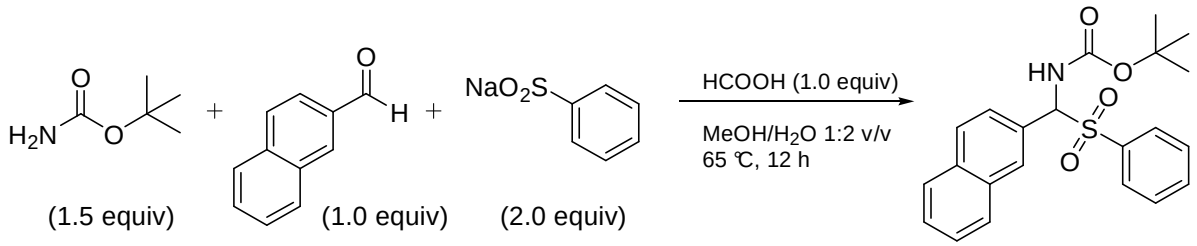
Purification The product was directly used in the next step without purification

Yield 2.16 g (80%; Lit.[92] 95%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.57 (s, 9H, C(C*H*$_3$)$_3$), 6.60 (dd, *J* = 3.6, 1.7 Hz, 1H, C*H*$_{Fur}$), 7.23 (d, *J* = 3.5 Hz, 1H, C*H*$_{Fur}$), 7.69 (s, 1H, C*H*$_{Fur}$), 8.78 (s, 1H, C*H*=N);

^{13}C-NMR (75.5 MHz, acetone-d6): δ = 28.0 (C(*C*H$_3$)$_3$), 81.8 (*C*(CH$_3$)$_3$), 113.8 (*C*H$_{Fur}$), 121.9 (*C*H$_{Fur}$), 149.2 (*C*H$_{Fur}$), 152.0 (*C*q$_{Fur}$), 156.6 (*C*O$_2$), 163.4 (*C*H=N);

7.3.1.5. (Benzenesulfonyl-naphthalen-2-ylmethyl)-carbamic acid *tert*-butyl ester (249c)



(1.5 equiv) (1.0 equiv) (2.0 equiv)

250 **252c** **251** **249c**

4.4 g (26.9 mmol, 1.0 equiv) of 2-naphthaldehyde, 4.7 g (40.4 mmol, 1.5 equiv) of *tert*-butyl carbamate and 8.8 g (53.8 mmol, 2.0 equiv) of benzenesulfinic acid sodium salt were dissolved in methanol/water (22 mL/44 mL). Formic acid (1.35 mL, 1.0 equiv) was added and the mixture heated to 65 °C for 12 h. After cooling, the precipitate was filtered, washed with water and diethyl ether and then dried *in vacuo*. It was purified by crystallization from chloroform at –40 °C to yield a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

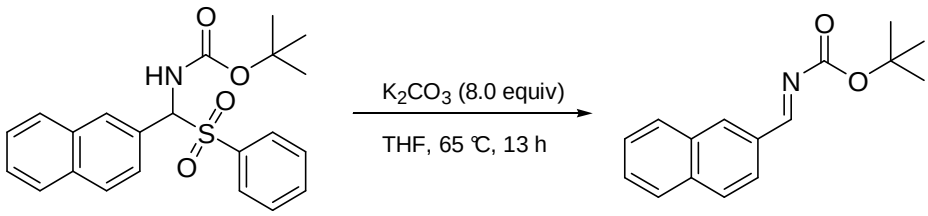
Chemical Formula $C_{22}H_{23}NO_4S$ (397.49 g/mol)

Purification crystallization from chloroform

Yield 2.37 g (22%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.24 (s, 9H, C(C*H*$_3$)$_3$), 6.22 (d, *J* = 10.8 Hz, CHN*H*), 7.53-7.78 (m, 6H, C*H*$_{Ar}$ and CHN*H*), 7.82 (dd, *J* = 8.7, 1.8 Hz, 1H, C*H*$_{Ar}$),7.90-8.00 (m, 5H, C*H*$_{Ar}$), 8.21 (s, 1H, C*H*$_{Ar}$);

7.3.1.6. Naphthalen-2-ylmethylene-carbamic acid *tert*-butyl ester (159c)



249c **159c**

The procedure of 7.3.1.2 was followed. The product was obtained as a yellow solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula $C_{16}H_{17}NO_2$ (255.31 g/mol)

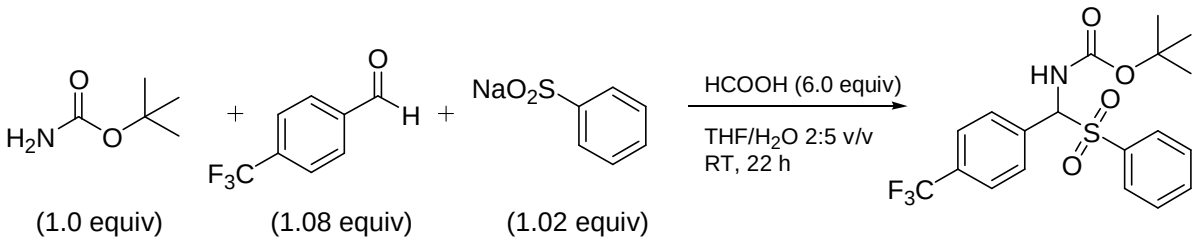
Purification The product was directly used in the next step without purification

Yield 752 mg (94%; Lit.[92] 100%)

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.62 (s, 9H, C(C*H*$_3$)$_3$), 7.53-7.63 (m, 2H, CH$_{Ar}$), 7.89 (t, *J* = 8.3 Hz, 2H, CH$_{Ar}$), 7.94 (d, *J* = 8.1 Hz, 1H, CH$_{Ar}$), 8.09 (dd, *J* = 8.6, 1.6 Hz, 1H, C*H*$_{Ar}$), 8.29 (s, 1H, CH$_{Ar}$), 9.05 (s, 1H, C*H*=N);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.1 (C(*C*H$_3$)$_3$), 82.4 (*C*(CH$_3$)$_3$), 124.2 (*C*H$_{Ar}$), 127.0 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 129.0 (*C*H$_{Ar}$), 129.3 (*C*H$_{Ar}$), 132.0 (*C*q$_{Ar}$), 132.9 (*C*q$_{Ar}$), 134.3 (*C*H$_{Ar}$), 136.2 (*C*q$_{Ar}$), 162.8 (*C*O$_2$), 170.0 (*C*H=N);

7.3.1.7. [Benzenesulfonyl-4-(trifluoromethyl)phenyl-methyl]-carbamic acid *tert*-butyl ester (249d)



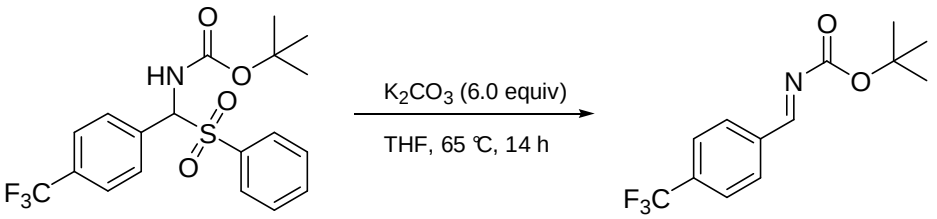
(1.0 equiv) (1.08 equiv) (1.02 equiv)

250 **252d** **251** **249d**

The compound was obtained according to 7.3.1.1 as a colorless solid.

Chemical Formula	$C_{19}H_{20}F_3NO_4S$ (415.43 g/mol)
Purification	The product was directly used in the next step without purification
Yield	2.79 g (67%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.25 (s, 9H, C(CH_3)$_3$), 5.85 (d, J = 10.4 Hz, 1H, C*H*NH), 6.01 (d, J = 10.9 Hz, 1H, CHN*H*), 7.52-7.63 (m, 4H, arom), 7.64-7.74 (m, 3H, arom), 7.93 (d, J = 7.7 Hz, 2H, arom);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 28.0 (C(*C*H_3)$_3$), 73.3 (*C*HNH), 81.7 (*C*(CH$_3$)$_3$), 123.8 (q, $^1J_{CF}$ = 273.0 Hz, *C*F$_3$), 125.7 (q, $^3J_{CF}$ = 3.9 Hz, (*C*H)$_2$CCF$_3$), 129.3 (*C*H$_{Ar}$), 129.4 (*C*H$_{Ar}$), 129.5 (*C*H$_{Ar}$), 131.9 (q, $^2J_{CF}$ = 32.7 Hz, (CH)$_2$*C*CF$_3$), 133.9 (*C*q$_{Ar}$), 134.3 (*C*H$_{Ar}$), 136.6 (*C*q$_{Ar}$), 153.4 (*C*O$_2$);

7.3.1.8. 4-(Trifluoromethyl)phenylmethylene-carbamic acid *tert*-butyl ester (159d)

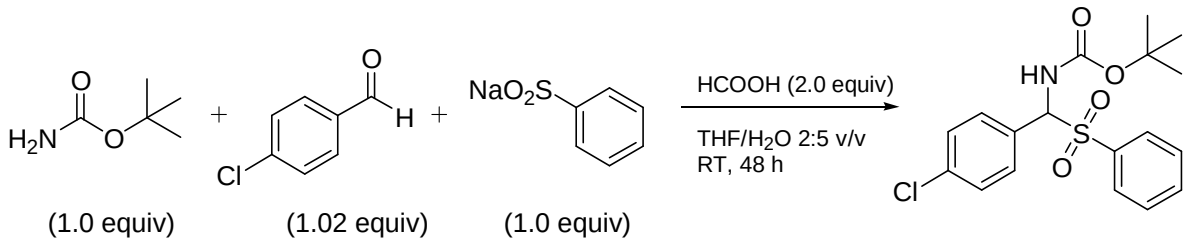


249d **159d**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula	$C_{13}H_{14}F_3NO_2$ (273.25 g/mol)
Purification	The product was directly used in the next step without purification
Yield	832 mg (90%)
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 1.60 (s, 9H, C(C*H*$_3$)$_3$), 7.73 (d, *J* = 8.3 Hz, 2H, arom), 8.02 (d, *J* = 8.2 Hz, 2H, arom), 8.86 (s, 1H, C*H*=N);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 27.9 (C(*C*H$_3$)$_3$), 82.9 (*C*(CH$_3$)$_3$), 123.2 (q, $^{1}J_{CF}$ = 272.0 Hz, *C*F$_3$), 125.9 (q, $^{3}J_{CF}$ = 4.0 Hz, (*C*H)$_2$CCF$_3$), 130.2 (*C*H$_{Ar}$), 134.7 (q, $^{2}J_{CF}$ = 32.4 Hz, (CH)$_2$*C*CF$_3$), 137.3 (*C*q$_{Ar}$), 162.2 (*C*O$_2$), 167.5 (*C*H=N);

7.3.1.9. (Benzenesulfonyl-4-chlorophenylmethyl)-carbamic acid *tert*-butyl ester (249e)



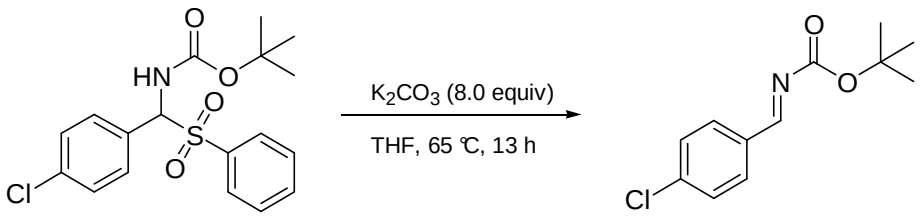
(1.0 equiv) (1.02 equiv) (1.0 equiv)

250 **252e** **251** **249e**

The reaction was performed according to 7.3.1.1. The product was obtained as a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula	$C_{18}H_{20}ClNO_4S$ (381.87 g/mol)
Purification	crystallization from chloroform
Yield	7.6 g (57%)
^{1}H-NMR	(300 MHz, acetone-d6): δ = 1.21 (s, 9H, C(C*H*$_3$)$_3$), 6.07 (d, *J* = 10.9 Hz, 1H, C*H*NH), 7.44-7.50 (m, 2H, arom), 7.58-7.67 (m, 3H, CHN*H* and arom), 7.68-7.78 (m, 3H, arom), 7.89-7.97 (m, 2H, arom);
^{13}C-NMR	(75.5 MHz, acetone-d6): δ = 28.2 (C(*C*H$_3$)$_3$), 74.6 (*C*HNH), 80.6 (*C*(CH$_3$)$_3$), 129.3 (*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 130.4 (*C*H$_{Ar}$), 130.8 (*C*q$_{Ar}$), 132.2 (*C*H$_{Ar}$), 134.8 (*C*H$_{Ar}$), 135.9 (*C*q$_{Ar}$), 138.5 (*C*q$_{Ar}$), 154.8 (*C*O$_2$);

7.3.1.10. 4-Chlorophenylmethylene-carbamic acid *tert*-butyl ester (159e)

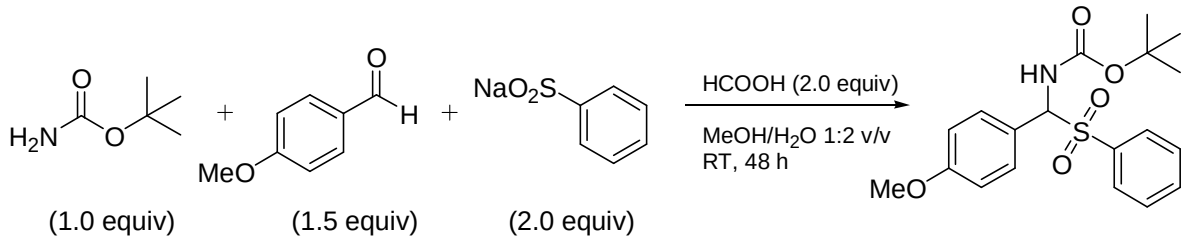


249e **159e**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula	$C_{12}H_{14}ClNO_2$ (239.70 g/mol)
Purification	The product was directly used in the next step without purification
Yield	1.79 g (95%)
^{1}H-NMR	(400 MHz, acetone-d6): δ = 1.54 (s, 9H, C(CH_3)$_3$), 7.56-7.61 (m, 2H, arom), 7.93-7.99 (m, 2H, arom), 8.79 (s, 1H, C*H*=N);
^{13}C-NMR	(100 MHz, acetone-d6): δ = 28.1 (C(*C*H$_3$)$_3$), 82.2 (*C*(CH$_3$)$_3$), 130.1 (*C*H$_{Ar}$), 132.0 (*C*H$_{Ar}$), 134.4 (*C*q$_{Ar}$), 139.6 (*C*q$_{Ar}$), 163.1 (*C*O$_2$), 167.2 (*C*H=N);

7.3.1.11. (Benzenesulfonyl-4-methoxyphenylmethyl)-carbamic acid *tert*-butyl ester (249f)



(1.0 equiv) (1.5 equiv) (2.0 equiv)

250 **252f** **251** **249f**

The reaction was performed according to 7.3.1.1. The product was obtained as a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula $C_{19}H_{23}NO_5S$ (377.45 g/mol)

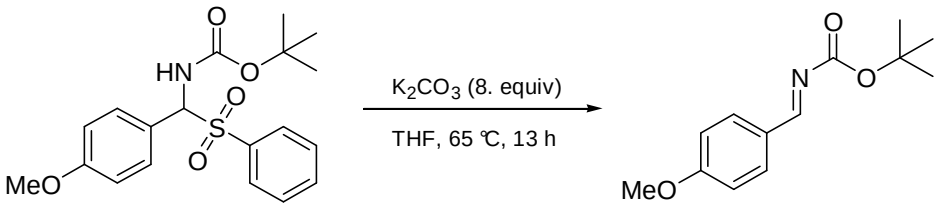
Purification the compound was directly employed in the next step without further purification

Yield 3.5 g (78%; Lit.[92] 80%)

^{1}H-NMR (300 MHz, acetone-d6): δ = 1.21 (s, 9H, C(C*H*$_3$)$_3$), 3.83 (s, 3H, OC*H*$_3$), 5.97 (d, *J* = 10.7 Hz, 1H, C*H*NH), 6.92-7.02 (m, 2H, arom), 7.50 (d, *J* = 10.7 Hz, 1H, CHN*H*), 7.54-7.67 (m, 4H, arom), 7.67-7.77 (m, 1H, arom), 7.87-7.95 (m, 2H, arom);

^{13}C-NMR (75.5 MHz, acetone-d6): δ = 28.3 (C(*C*H$_3$)$_3$), 55.7 (O*C*H$_3$), 74.9 (*C*HNH), 80.4 (*C*(CH$_3$)$_3$), 114.5 (*C*H$_{Ar}$), 123.6 (*C*H$_{Ar}$), 129.8 (*C*H$_{Ar}$), 130.3 (*C*H$_{Ar}$), 131.8 (*C*H$_{Ar}$), 134.5 (*C*q$_{Ar}$), 138.9 (*C*q$_{Ar}$), 154.9 (*C*O$_2$), 161.6 (*C*q$_{Ar}$ OCH$_3$);

7.3.1.12. 4-Methoxyphenylmethylene-carbamic acid *tert*-butyl ester (159f)



249f **159f**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid. The ^{1}H-NMR was in full agreement with the literature.[92]

Chemical Formula $C_{13}H_{17}NO_3$ (235.28 g/mol)

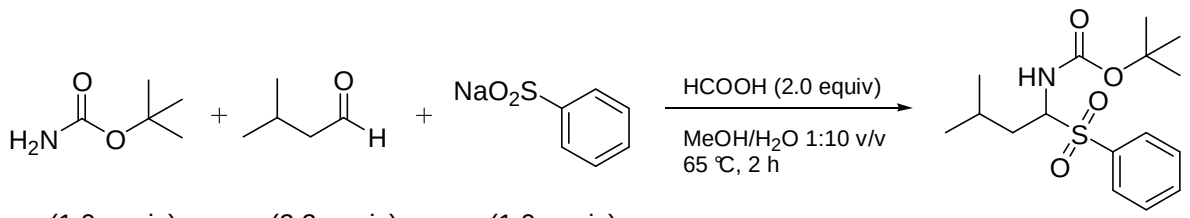
Purification The product was directly used in the next step without purification

Yield 2.14 g (98%; Lit.[92] 98%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.53 (s, 9H, C(C*H*$_3$)$_3$), 3.90 (s, 3H, OC*H*$_3$), 7.05-7.12 (m, 2H, arom), 7.88-7.95 (m, 2H, arom), 8.76 (s, 1H, C*H*=N);

^{13}C-NMR (75.5 MHz, acetone-d6): δ = 28.1 (C(*C*H$_3$)$_3$), 56.0 (O*C*H$_3$), 81.5 (*C*(CH$_3$)$_3$), 115.3 (*C*H$_{Ar}$), 128.3 (Cq$_{Ar}$), 132.7 (*C*H$_{Ar}$), 163.6 (*C*O$_2$), 165.0 (*C*q$_{Ar}$OCH$_3$), 168.3 (*C*H=N);

7.3.1.13. (1-Benzenesulfonyl-3-methylbutyl)-carbamic acid *tert*-butyl ester (249g)



(1.0 equiv) (2.2 equiv) (1.0 equiv)

250 **252g** **251** **249g**

A modified literature procedure was followed.[200] To a stirred solution of *tert*-butyl carbamate (2.5 g, 21 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (3.45 g, 21 mmol, 1.0 equiv) in methanol/water (2 mL/21 mL) was added isovaleraldehyde (5 mL, 46.2 mmol, 2.2 equiv) in one portion, followed by formic acid (2 mL). The mixture was stirred at 65 °C for 2 h, during which a colorless precipitate occurred. The solid was filtered, washed with water and diethyl ether and dried *in vacuo*. The material thus obtained was not pure and was recrystallized from diethyl ether/hexane to yield colorless crystals.

Chemical Formula $C_{16}H_{25}NO_4S$ (327.44 g/mol)

Purification recrystallization from diethyl ether/hexane

Yield 2.37 g (22%)

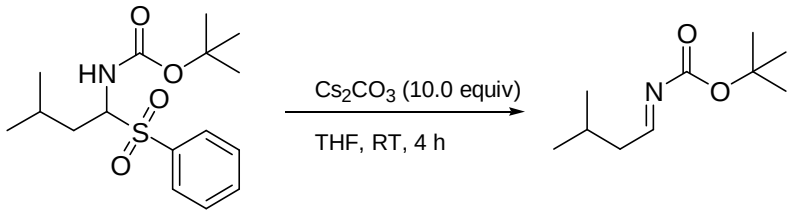
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 6.5 Hz, 3H, C*H*$_3$), 0.99 (d, *J* = 6.5 Hz, 3H, C*H*$_3$), 1.19 (s, 9H, C(C*H*$_3$)$_3$), 1.65-1.85 (m, 2H, C*H*$_2$), 1.92-2.08 (m, 1H, C*H*(CH$_3$)$_2$), 4.91 (td, *J* = 11.0, 3.0 Hz, 1H, C*H*NH), 5.01 (d, *J* = 11.0, 1H, CHN*H*), 7.48-7.69 (m, 3H, arom), 7.88-7.95 (m, 2H, arom);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 21.2, 23.3, 24.9, 28.1 ($C(CH_3)_3$), 34.7 (CH_2), 69.7 (*C*HNH), 80.8 ($C(CH_3)_3$), 129.1 (CH_{Ar}), 129.5 (CH_{Ar}), 133.9 (CH_{Ar}), 137.1 (Cq_{Ar}), 153.8 (CO_2);

Mass *m/z* (%) (EI) 210 (M-$C_5H_{10}NO_2$-H, 2), 186 ($PhSO_2$, 21), 130 (186-*t*Bu+H, 84), 86 (186-$C_5H_9O_2$+H, 83), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{16}H_{25}NNaO_4Si$ (M+Na) 350.139651; found 350.139674;

7.3.1.14. 3-Methylbutylidene-carbamic acid *tert*-butyl ester (159g)



249g **159g**

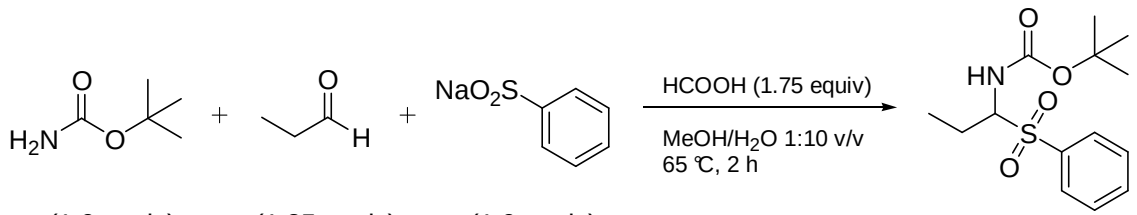
The product was obtained following a literature-known procedure.[144] 1.625 g (5 mmol, 10 equiv) of Cs_2CO_3 were introduced into a 25 mL round-bottomed flask and flame dried under high vacuum. After cooling, 163 mg (0.5 mmol, 1 equiv) of (1-benzenesulfonyl-3-methylbutyl)-carbamic acid *tert*-butyl ester were added and the solids suspended in 5 mL of dry tetrahydrofuran. After stirring at room temperature for 4 h, the mixture was cooled to 0 °C, diluted with pre-cooled pentane (5 mL), washed with water (0 °C) twice and with brine (0 °C) once. The organic phase was dried over magnesium sulfate and the solvent removed on a rotary evaporator while being kept at 0 °C. The colorless oil thus obtained was used immediately in the Mannich reaction.

Chemical Formula $C_{10}H_{19}NO_2$ (185.26 g/mol)

Purification The product was directly used in the next step without purification

^{1}H-NMR (500 MHz, CD_3CN): δ = 0.89 (d, *J* = 6.7 Hz, 6H, CH_3), 1.41 (s, 9H, $C(CH_3)_3$), 1.85-1.89 (m, 2H, CH_2), 2.06-2.08 (m, 1H, $CH(CH_3)_2$), 8.06 (s, 1H, C*H*=N);

7.3.1.15. (1-Benzenesulfonylpropyl)carbamic acid *tert*-butyl ester (249h)



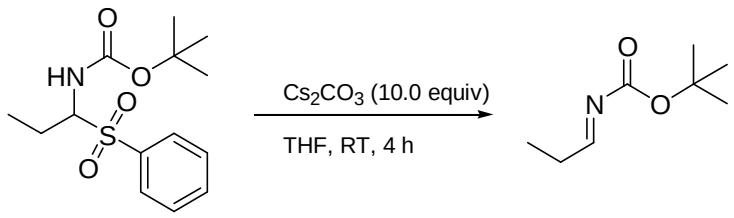
(1.0 equiv) (1.35 equiv) (1.0 equiv)

250 **252h** **251** **249h**

A modified literature procedure was followed.[200] To a stirred solution of *tert*-butyl carbamate (3.5 g, 29.9 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (5.0 g, 30.0 mmol, 1.0 equiv) in methanol/water (3 mL/30 mL) was added propionaldehyde (2.35 g, 40.4 mmol, 1.35 equiv) in one portion, followed by formic acid (3 mL). The mixture was stirred at 65 °C for 2 h, during which a colorless precipitate occurred. The solid was filtered, washed with water and diethyl ether and dried *in vacuo*. The material thus obtained was not pure and was recrystallized from chloroform to yield colorless crystals.

Chemical Formula	$C_{14}H_{21}NO_4S$ (299.39 g/mol)
Purification	crystallization from chloroform
Yield	2.18 g (24%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.09 (t, *J* = 7.5 Hz, 3H, CH_2CH_3), 1.22 (s, 9H, $C(CH_3)_3$), 1.71-1.87 (m, 1H, CH_2CH_3), 2.24-2.39 (m, 1H, CH_2CH_3), 4.78 (td, *J* = 10.5, 3.6 Hz, 1H, CHNH), 4.95 (d, *J* = 11.0, 1H, CHNH), 7.50-7.57 (m, 2H, arom), 7.59-7.68 (m, 1H, arom), 7.88-7.95 (m, 2H, arom);
HRMS	(ESIpos) calculated for $C_{14}H_{22}NO_4S$ (M+H) 300.126955; found 300.127069;

7.3.1.16. Propylidenecarbamic acid *tert*-butyl ester (159h)



249h **159h**

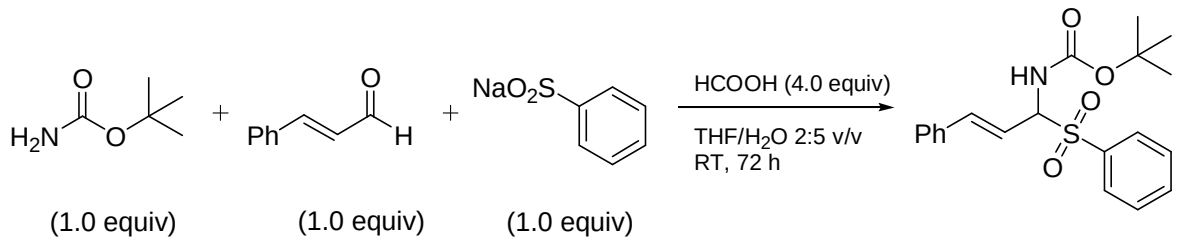
The product was obtained according to 7.3.1.14. The NMR was in agreement with the literature.[144] The colorless oil thus obtained was used immediately in the Mannich reaction.

Chemical Formula $C_8H_{15}NO_2$ (157.21 g/mol)

Purification The product was directly used in the next step without purification

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 (t, *J* = 7.4 Hz, 3H, CH_2CH_3), 1.53 (s, 9H, $C(CH_3)_3$), 2.37-2.50 (m, 2H, CH_2CH_3), 8.30 (bs, 1H, C*H*=N);

7.3.1.17. (1-Benzenesulfonyl-3-phenylallyl)carbamic acid *tert*-butyl ester (249i)



(1.0 equiv) (1.0 equiv) (1.0 equiv)

250 **7** **251** **249i**

A modified literature procedure was followed.[143] To a stirred solution of *tert*-butyl carbamate (586 mg, 5 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (821 mg, 5.0 mmol, 1.0 equiv) in tetrahydrofuran/water (2 mL/5 mL) was added cinnamaldehyde (0.68 mL, 4.9 mmol, 0.98 equiv) in one portion, followed by formic acid (1.2 mL). The mixture was stirred at room temperature for 72 h, during which a colorless precipitate occurred. The solid was filtered, washed with water and diethyl ether, dried *in vacuo*, and recrystallized from chloroform.

Chemical Formula $C_{20}H_{23}NO_4S$ (373.47 g/mol)

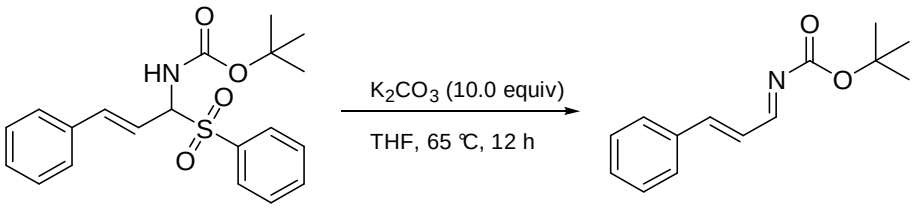
Purification recrystallization from chloroform

Yield 901 mg (48%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.44 (s, 9H, C(C*H*$_3$)$_3$), 4.61 (m, 1H), 5.40 (m, 1H), 6.43 (m, 1H), 6.67 (m, 1H), 7.15-7.21 (m, 2H, arom), 7.21-7.30 (m, 3H, arom), 7.36-7.42 (m, 2H, arom), 7.50-7.62 (m, 3H, arom);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 28.2 (C(*C*H$_3$)$_3$), 73.5 (*C*HNH), 81.1 (*C*(CH$_3$)$_3$), 98.7 (ArCH=*C*H), 128.6 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 129.2 (*C*H$_{Ar}$), 129.4 (*C*H$_{Ar}$), 131.5 (Ar*C*H=CH), 132.9 (*C*q$_{Ar}$), 133.5 (*C*H$_{Ar}$), 137.3 (*C*q$_{Ar}$), 152.1 (*C*O$_2$);

7.3.1.18. 3-Phenylallylidenecarbamic acid *tert*-butyl ester (159i)



249i **159i**

The product was obtained according to 7.3.1.2 as a pale yellow oil after bulb-to-bulb distillation.

Chemical Formula $C_{14}H_{17}NO_2$ (231.29 g/mol)

Purification bulb-to-bulb distillation (165-175 °C, $5\cdot10^{-2}$ mbar)

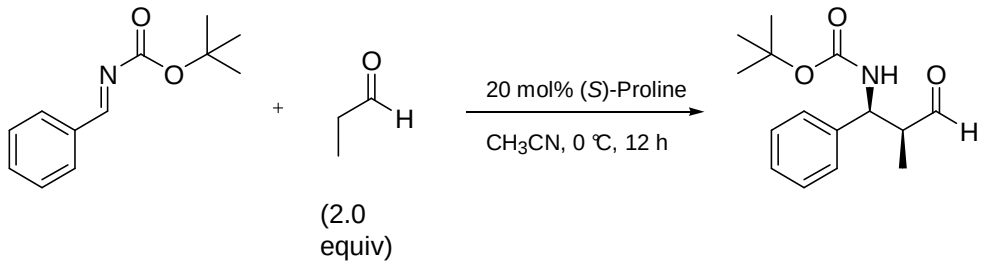
Yield 178 mg (64%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.57 (s, 9H, C(C*H*$_3$)$_3$), 6.98 (dd, *J* = 16.0, 9.2 Hz, 1H, C*H*=CHAr), 7.36 (d, *J* = 15.8 Hz, 1H, CH=C*H*Ar), 7.40-7.47 (m, 3H, arom), 7.51-7.60 (m, 2H, arom), 8.69 (d, *J* = 9.4 Hz, 1H, C*H*=N);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 28.1 (C(*C*H_3)$_3$), 82.1 (*C*(CH$_3$)$_3$), 127.0 (*C*H=CHAr), 128.3 (*C*H$_{Ar}$), 129.2 (*C*H$_{Ar}$), 130.9 (*C*H$_{Ar}$), 134.9 (*C*q$_{Ar}$), 150.7 (CH=*C*HAr), 162.5 (*C*O_2), 171.7 (*C*H=N);

7.3.2. Products of the Mannich reaction

7.3.2.1. *tert*-Butyl-(1*S*,2*S*)-2-methyl-3-oxo-1-phenylpropylcarbamate (255a)



159a **255a**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

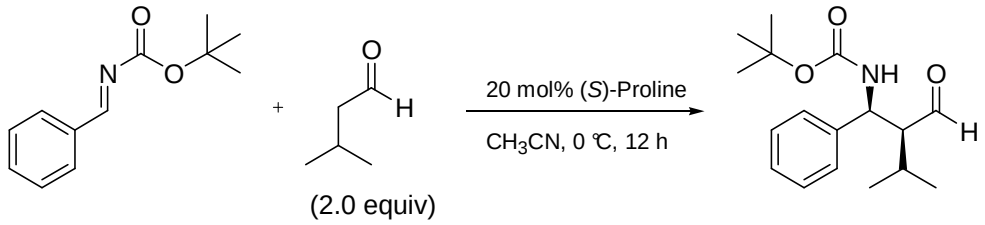
Chemical Formula	$C_{15}H_{21}NO_3$ (263.33 g/mol)
TLC	R_f = 0.33 (SiO_2, ethyl acetate/hexane 15/85 v/v), stained with anisaldehyde
Purification	The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)
Yield	120.2 mg (91%)
Diastereomeric ratio	>99:1
Enantiomeric ratio	>99:1
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ +11.5 (*c* = 1.00, $CHCl_3$)
Melting point	133-135 °C
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 7.0 Hz, 3H, CH_3), 1.41 (s, 9H, C(CH_3)$_3$), 2.80-2.94 (m, 1H, C*H*CHO), 5.04-5.24 (m, 2H, C*H*NH and CHN*H*), 7.37-7.24 (m, 5H, arom), 9.71 (s, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 9.3 (CH*C*H$_3$), 28.3 (C(*C*H$_3$)$_3$), 51.6 (*C*HCOH), 54.7 (*C*HNH), 80.1 (*C*(CH$_3$)$_3$), 126.7 (*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 139.7 (*C*q$_{Ar}$), 155.1 (*C*O$_2$), 203.0 (*C*HO);

Mass *m/z* (%) (EI) 206 (M-C_3H_5O, 39), 150 (206-*t*Bu+H, 97), 118 (20), 106 (150-CO_2, 92), 91 (CH_2Ph, 16), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{15}H_{21}NNaO_3$ (M+Na) 286.141350; found 286.141365;

HPLC τ_R 44.7 min (minor enantiomer)
τ_R 60.5 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);

7.3.2.2. *tert*-Butyl-(1S,2S)-2-formyl-3-methyl-1-phenylbutylcarbamate (255b)



159a **255b**

102.5 mg (0.5 mmol, 1.0 equiv) of phenylmethylene-carbamic acid *tert*-butyl ester were dissolved in 5 mL of anhydrous acetonitrile. 86.1 mg (1.0 mmol, 2.0 equiv) of isovaleraldehyde were then added and the mixture cooled to 0 °C. 11.5 mg (0.01 mmol, 20 mol%) of (*S*)-proline were added and the mixture stirred for 12 h. Upon completion of the reaction, the mixture was poured into water, and a colorless solid precipitated. The precipitate was collected *via* filtration and then triturated with cold hexanes (–78 °C) to give the pure product as a colorless solid.

Chemical Formula $C_{17}H_{25}NO_3$ (291.39 g/mol)

TLC R_f = 0.45 (SiO_2, ethyl acetate/hexane 15/85 v/v), stained with anisaldehyde

Purification The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)

Yield 128.5 mg (88%)

Diastereomeric ratio >99:1

Enantiomeric ratio >99:1

Optical rotation $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –70.9 (*c* = 0.81, $CHCl_3$)

Melting point 141-142 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.13 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 2.14-2.08 (m, 1H C*H*(CH$_3$)$_2$), 2.47-2.53 (m, 1H, C*H*CHO), 5.01-5.20 (m, 2H, C*H*NH and CHN*H*), 7.21-7.34 (m, 5H, arom), 9.49 (d, *J* = 4.2 Hz, 1H, C*H*O);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 19.1 (*C*H(CH$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 27.0 (CH(*C*H$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 53.5 (*C*HNH), 62.0 (*C*H-CHO), 79.8 (*C*(CH$_3$)$_3$), 127.2 (*C*H$_{Ar}$), 127.8 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 139.9 (*C*q$_{Ar}$), 155.0 (*C*O$_2$), 204.9 (*C*HO);

Mass *m/z* (%) (EI) 235 (M-*t*Bu+H, 1), 206 (M-C_5H_9O, 38), 150 (206-*t*Bu+H, 100), 106 (150-CO_2, 96), 91 (CH_2Ph, 11), 57 (*t*Bu, 99);

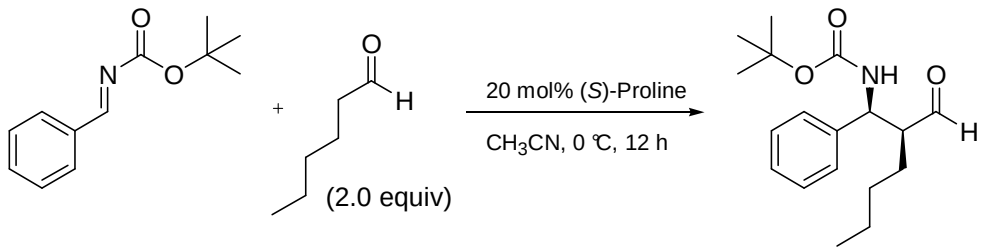
HRMS (ESIpos) calculated for $C_{17}H_{25}NNaO_3$ (M+Na) 314.172600; found 314.172661;

HPLC

$\boldsymbol{\tau_R}$	33.4 min	(minor enantiomer)
$\boldsymbol{\tau_R}$	54.7 min	(major enantiomer)

(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);

7.3.2.3. *tert*-Butyl-(1*S*,2*S*)-2-formyl-1-phenylhexylcarbamate (255c)



159a **255c**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

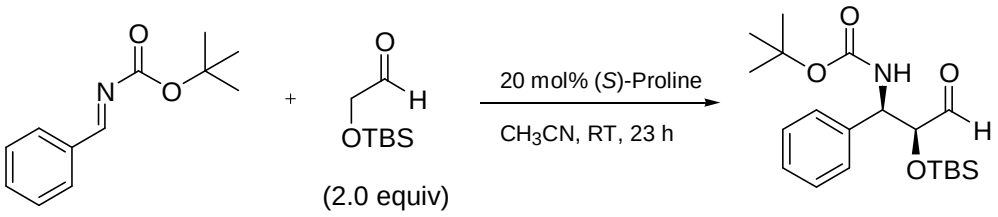
Chemical Formula	$C_{18}H_{27}NO_3$ (305.41 g/mol)
TLC	R_f = 0.43 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde
Purification	The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)
Yield	131 mg (84%)
Diastereomeric ratio	>99:1
Enantiomeric ratio	>99:1
Optical rotation	$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –14.2 (*c* = 1.01, $CHCl_3$)
Melting point	139-140 °C
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.41 (s, 9H, C(C*H*$_3$)$_3$), 1.18-1.53 (m, 5H), 1.63-1.76 (m, 1H), 2.65-2.74 (m, 1H, C*H*CHO), 5.00-5.10 (m, 1H, C*H*NH), 5.10-5.21 (m, 1H, CHN*H*), 7.21-7.29 (m, 3H, arom), 7.32-7.36 (m, 2H, arom), 9.59 (d, *J* = 2.4 Hz, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 13.8 (CH_2CH_3), 22.7 (CH_2), 25.3 (CH_2), 28.3 (C(CH_3)$_3$), 29.6 (CH_2), 54.7 (*C*HNH), 56.7 (*C*HCOH), 80.0 (*C*(CH_3)$_3$), 126.9 (CH_{Ar}), 127.7 (CH_{Ar}), 128.8 (CH_{Ar}), 139.7 (Cq_{Ar}), 155.0 (CO_2), 203.7 (*C*HO);

Mass *m/z* (%) (EI) 249 (M-*t*Bu+H, 1), 206 (M-$C_6H_{11}O$, 39), 204 (249-CO_2, 1), 189 (204-CH_3, 6), 150 (206-*t*Bu+H, 100), 106 (150-CO_2, 80), 91 (CH_2Ph, 10), 57 (*t*Bu, 67);

HRMS (ESIpos) calculated for $C_{18}H_{27}NNaO_3$ (M+Na) 328.188606; found 328.188316;

HPLC τ_R 35.5 min (minor enantiomer)
τ_R 44.1 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);

7.3.2.4. *tert*-Butyl-(1*R*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylpropylcarbamate (255d)



159a **255d**

The reaction was performed according to 7.3.2.2, but with a different workup: The solution was poured into water and extracted with dichloromethane (3x). The combined organic fractions were washed with brine, dried over magnesium sulfate, and the solvent was removed on a rotary evaporator. The product was obtained as a colorless oil.

Chemical Formula $C_{20}H_{33}NO_4Si$ (379.57 g/mol)

TLC R_f = 0.15 (SiO_2, diethyl ether/pentane 20/80 v/v), stained pink with anisaldehyde

Purification flash column chromatography on silica gel, eluting with diethyl ether/pentane (8/92 v/v)

Yield 132 mg (69%)

Diastereomeric ratio >95:5

Enantiomeric ratio 99:1

^{1}H-NMR (400 MHz, $CDCl_3$): δ = –0.33 (s, 3H, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), –0.16 (s, 3H, Si(CH$_3$)$_A$(C*H*$_3$)$_B$), 0.79 (s, 9H, C(C*H*$_3$)$_3$), 1.42 (s, 9H, C(C*H*$_3$)$_3$), 4.13-4.28 (m, 1H, C*H*COH), 5.10-5.27 (m, 1H, C*H*NH), 5.35-5.50 (m, 1H, CHN*H*), 7.21-7.29 (m, 3H, arom), 7.29-7.38 (m, 2H, arom), 9.70 (s, 1H, C*H*O);

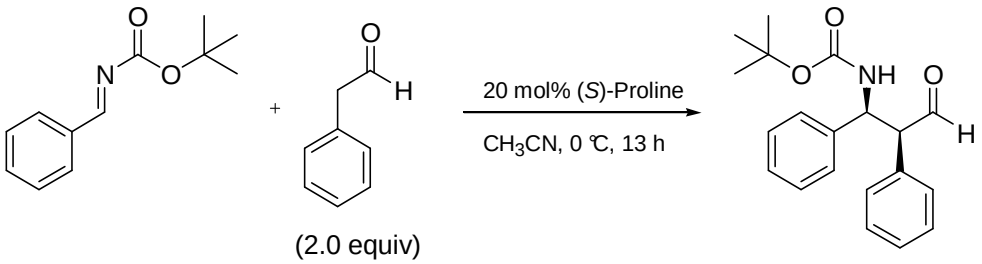
^{13}C-NMR (100 MHz, $CDCl_3$): δ = –5.6 (Si(*C*H$_3$)$_A$(CH$_3$)$_B$), –5.1 (Si(CH$_3$)$_A$(*C*H$_3$)$_B$), 18.3 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 28.5 (C(*C*H$_3$)$_3$), 55.6 (*C*HNH), 80.2 (*C*q), 81.6 (*C*q), 126.6 (*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 139.5 (*C*q$_{Ar}$), 155.1 (*C*O$_2$NH), 201.6 (*C*HO);

Mass *m/z* (%) (EI) 306 (M-*t*BuO, 6), 206 (M-$C_8H_{17}O_2Si$, 26), 150 (206-*t*Bu+H, 100), 106 (150-CO_2, 42), 57 (*t*Bu, 28);

HRMS (ESIpos) calculated for $C_{20}H_{33}NNaO_4Si$ (M+Na) 402.207104; found 402.207409;

HPLC τ_R 17.8 min (minor enantiomer)
τ_R 29.3 min (major enantiomer)
(AD-H, 0.5 mL/min, *i*PrOH/*n*-heptane 3/97);

7.3.2.5. *tert*-Butyl-(1*S*,2*S*)-3-oxo-1,2-diphenylpropylcarbamate (255e)



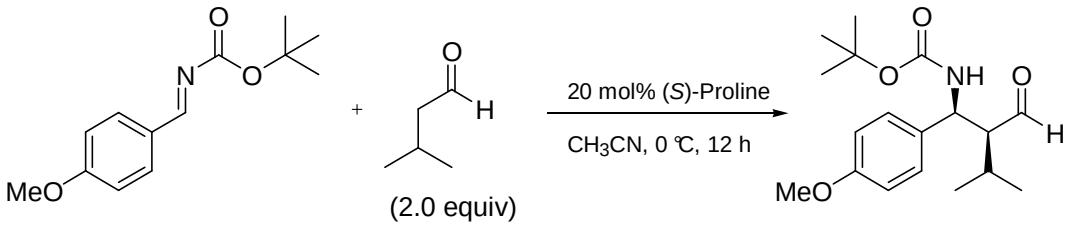
159a **255e**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

Chemical Formula $C_{20}H_{23}NO_3$ (325.40 g/mol)

TLC	R_f = 0.37 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained green-blue with anisaldehyde
Purification	The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)
Yield	127 mg (76%)
Diastereomeric ratio	98:2
Enantiomeric ratio	>99:1
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 1.31 (s, 9H, C(C*H*$_3$)$_3$), 4.00 (d, *J* = 7.6 Hz, 1H, C*H*CHO), 4.87-5.10 (m, 1H, CHN*H*), 5.42 (t, *J* = 7.6 Hz, 1H, C*H*NH), 7.08-7.14 (m, 2H, arom), 7.15-7.20 (m, 2H, arom), 7.23-7.37 (m, 6H, arom), 9.72 (d, *J* = 1.8 Hz, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 28.2 (C(*C*H$_3$)$_3$), 54.9 (*C*HNH), 64.5 (*C*HCHO), 80.0 (*C*(CH$_3$)$_3$), 127.2 (*C*H$_{Ar}$), 127.4 (*C*H$_{Ar}$), 127.7 (*C*q$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 129.0 (*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 135.5 (*C*q$_{Ar}$), 154.9 (*C*O$_2$), 198.6 (*C*HO);
Mass	*m/z* (%) (EI) 206 (M-C_8H_7O, 39), 181 (12), 150 (206-*t*Bu+H, 99), 120 (C_8H_7O+H, 25), 106 (150-CO_2, 100), 91 (CH_2Ph, 15), 77 (Ph, 8), 57 (*t*Bu, 96);
HRMS	(ESIpos) calculated for $C_{20}H_{23}NNaO_3$ (M+Na) 348.157014; found 348.156602;
HPLC	τ_R 26.7 min (minor enantiomer) τ_R 35.7 min (major enantiomer) (AD-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.3.2.6. *tert*-Butyl-(1*S*,2*S*)-2-formyl-1-(4-methoxyphenyl)-3-methylbutyl-carbamate (255f)



159f **255f**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

Chemical Formula	$C_{18}H_{27}NO_4$ (321.41 g/mol)
TLC	R_f = 0.30 (SiO_2, ethyl acetate/hexane 15/85 v/v), stained with anisaldehyde
Purification	The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)
Yield	128.9 mg (80%)
Diastereomeric ratio	>99:1
Enantiomeric ratio	>99:1
Optical rotation	$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –95.2 (*c* = 1.01, $CHCl_3$)
Melting point	151-152 °C
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.11 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 2.07-2.13 (m, 1H C*H*(CH$_3$)$_2$), 2.44-2.50 (m, 1H, C*H*CHO), 3.77 (s, 3H, OC*H*$_3$), 5.00-5.15 (m, 2H, C*H*NH and CHN*H*), 6.83 (d, *J* = 8.6 Hz, 2H, arom), 7.15 (d, *J* = 8.6 Hz, 2H, arom), 9.49 (d, *J* = 4.2 Hz, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 19.0 (*C*H(CH$_3$)$_2$), 21.2 (CH(*C*H$_3$)$_2$), 27.1 (CH(*C*H$_3$)$_2$), 28.4 (C(*C*H$_3$)$_3$), 52.9 (O*C*H$_3$), 55.3 (*C*HNH),

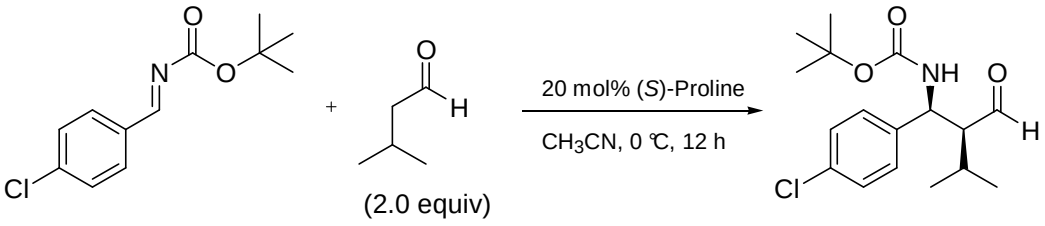
62.1 (*C*HCHO), 79.8 (*C*(CH$_3$)$_3$), 114.2 (*C*H$_{Ar}$), 128.4 (*C*H$_{Ar}$), 132.0 (*C*q$_{Ar}$), 155.0 (*C*O$_2$), 159.1 (*C*q$_{Ar}$OMe), 205.1 (*C*HO);

Mass *m/z* (%) (EI) 264 (M-*t*Bu, 3), 236 (M-C$_5$H$_9$O, 21), 180 (236-*t*Bu+H, 100), 136 (180-CO$_2$, 44), 57 (*t*Bu, 43);

HRMS (ESIpos) calculated for C$_{18}$H$_{27}$NNaO$_4$ (M+Na) 344.183209; found 344.183224;

HPLC τ_R 28.2 min (minor enantiomer)
τ_R 58.4 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 5/95);

7.3.2.7. *tert*-Butyl-(1*S*,2*S*)-2-formyl-1-(4-chlorophenyl)-3-methylbutyl-carbamate (255g)



159e **255g**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

Chemical Formula C$_{17}$H$_{24}$ClNO$_3$ (325.83 g/mol)

TLC R_f = 0.42 (SiO$_2$, ethyl acetate/hexane 15/85 v/v), stained with anisaldehyde

Purification The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)

Yield 96 mg (59%)

Diastereomeric ratio 99:1

Enantiomeric ratio 99:1

Optical rotation $[\alpha]_D^{20}$ –90.5 (*c* = 1.04, $CHCl_3$)

Melting point 137-140 °C

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.13 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 2.03-2.17 (m, 1H C*H*(CH$_3$)$_2$), 2.45-2.54 (m, 1H, C*H*CHO), 4.96-5.18 (m, 2H, C*H*NH and CHN*H*), 7.18 (d, *J* = 8.3 Hz, 2H, arom), 7.25-7.32 (m, 3H, arom), 9.50 (d, *J* = 3.9 Hz, 1H, C*H*O);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 19.2 (*C*H(CH$_3$)$_2$), 21.3 (CH(*C*H$_3$)$_2$), 27.1 (CH(*C*H$_3$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 53.0 (*C*HNH), 61.9 (*C*HCHO), 80.2 (*C*(CH$_3$)$_3$), 128.8 (*C*H$_{Ar}$), 129.1 (*C*H$_{Ar}$), 133.8 (*C*q$_{Ar}$), 138.7 (*C*q$_{Ar}$), 155.0 (*C*O$_2$), 204.7 (*C*HO);

Mass *m/z* (%) (EI) 269 (M-*t*Bu+H, 1), 240 (M-C_5H_9O, 20), 184 (269-C_5H_9O, 54), 140 (150-CO_2, 47), 57 (*t*Bu, 100);

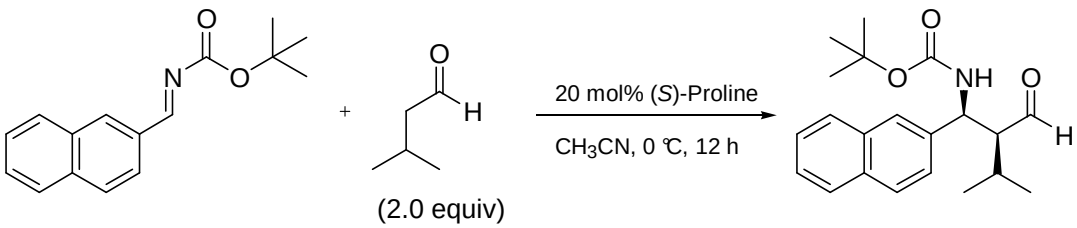
HRMS (ESIpos) calculated for $C_{17}H_{24}ClNNaO_3$ (M+Na) 348.133388; found 348.133693;

HPLC

τ_R	16.1 min	(minor enantiomer)
τ_R	28.7 min	(major enantiomer)

(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 7/93);

7.3.2.8. *tert*-Butyl-(1*S*,2*S*)-2-formyl-3-methyl-1-(naphthalene-2-yl)-butyl-carbamate (255h)



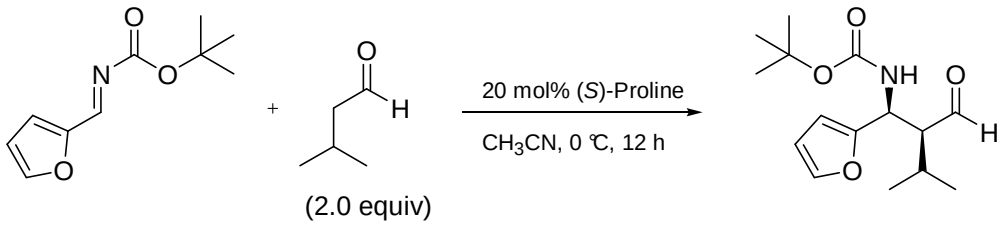
159c **255h**

The reaction was performed according to 7.3.2.2. The product was obtained as a colorless solid.

Chemical Formula	$C_{21}H_{27}NO_3$ (341.44 g/mol)
TLC	R_f = 0.36 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde
Purification	The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)
Yield	136 mg (82%)
Diastereomeric ratio	99:1
Enantiomeric ratio	99:1 (crude: 96:4)
Optical rotation	$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –81.8 (*c* = 1.02, $CHCl_3$)
Melting point	177-180 °C (decomp.)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.04 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.17 (d, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.40 (s, 9H, C(C*H*$_3$)$_3$), 2.10-2.25 (m, 1H C*H*(CH$_3$)$_2$), 2.55-2.65 (m, 1H, C*H*CHO), 5.10-5.35 (m, 2H, C*H*NH and CHN*H*), 7.35 (dd, *J* = 8.3, 1.5 Hz, 1H, arom), 7.43-7.51 (m, 2H, arom), 7.70 (brs, 1H), 7.77-7.84 (m, 3H, arom), 9.54 (d, *J* = 4.1 Hz, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 19.1 (*C*H(CH$_3$)$_2$), 21.3 (CH(*C*H$_3$)$_2$), 27.1 (CH(*C*H$_3$)$_2$), 28.3 (C(*C*H$_3$)$_3$), 53.6 (*C*HNH), 62.0 (*C*H-CHO), 79.9 (*C*(CH$_3$)$_3$), 125.0 (*C*H$_{Ar}$), 126.2 (*C*H$_{Ar}$), 126.3 (*C*H$_{Ar}$), 126.4 (*C*H$_{Ar}$), 127.6 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 132.9 (*C*q$_{Ar}$), 133.2 (*C*q$_{Ar}$), 137.3 (*C*q$_{Ar}$), 155.0 (*C*O$_2$), 204.9 (*C*HO);
Mass	*m/z* (%) (EI) 341 (M, 2), 285 (M-*t*Bu+H, 6), 256 (M-C_5H_9O, 25), 200 (285-C_5H_9O, 100), 156 (200-CO_2, 60), 127 (naph, 7), 57 (*t*Bu, 47);
HRMS	(ESIpos) calculated for $C_{21}H_{27}NNaO_3$ (M+Na) 364.188025; found 364.188315;

HPLC	τ_R	37.5 min	(minor enantiomer)
	τ_R	73.5 min	(major enantiomer)
	(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);		

7.3.2.9. *tert*-Butyl-(1*S*,2*S*)-2-formyl-1-(furan-2-yl)-3-methylbutylcarbamate (255i)



159b **255i**

The reaction was performed according to 7.3.2.2, but a different workup had to be employed since the product did not precipitate after adding the reaction mixture to water. Instead, the aqueous layer was extracted three times with diethyl ether, and the combined organic phases were washed with brine once and dried over Na_2SO_4. The product was obtained as a colorless solid after purification by column chromatography.

Chemical Formula	$C_{15}H_{23}NO_4$ (281.35 g/mol)
TLC	R_f = 0.40 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 v/v)
Yield	103 mg (74%)
Diastereomeric ratio	97:3
Enantiomeric ratio	99:1
Optical rotation	$[\alpha]_D^{20}$ –104.1 (*c* = 1.01, $CHCl_3$)
Melting point	62-64 °C

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.97 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.06 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.43 (s, 9H, C(C*H*$_3$)$_3$), 1.90-2.07 (m, 1H C*H*(CH$_3$)$_2$), 2.39-2.50 (m, 1H, C*H*CHO), 5.06-5.24 (m, 2H, C*H*NH and CHN*H*), 6.21-6.25 (d, *J* = 3.0 Hz, 1H, C*H*$_{Fur}$), 6.29 (dd, *J* = 3.4, 1.9 Hz, 1H, C*H*$_{Fur}$), 7.32 (dd, *J* = 1.9, 0.8 Hz, 1H, C*H*$_{Fur}$), 9.60 (d, *J* = 3.9 Hz, 1H, C*H*O);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 20.1 (*C*H(CH$_3$)$_2$), 20.6 (CH(*C*H$_3$)$_2$), 26.7 (CH(*C*H$_3$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 47.7 (*C*HNH), 61.1 (*C*H-CHO), 80.2 (*C*(CH$_3$)$_3$), 108.0 (*C*H$_{Fur}$), 110.5 (*C*H$_{Fur}$), 142.3 (*C*H$_{Fur}$), 152.2 (*C*q$_{Fur}$), 154.9(*C*O$_2$), 204.8(*C*HO);

Mass *m/z* (%) (EI) 281 (M, 1), 225 (M-*t*Bu+H, 37), 196 (M-C_5H_9O, 12), 182 (225-C_3H_7, 29), 165 (182-O, 13), 140 (182-C_2H_2O, 100), 96 (140-CO_2, 78), 57 (*t*Bu, 65);

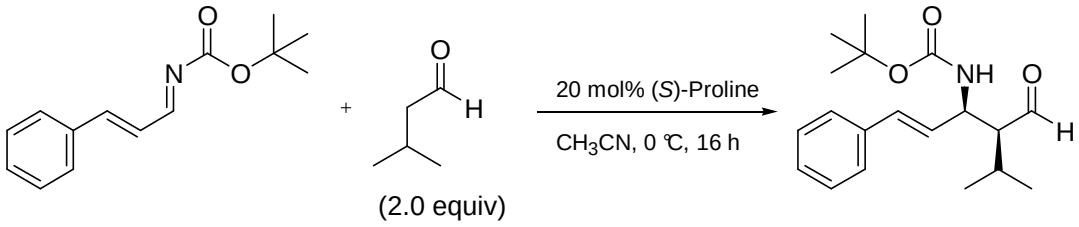
HRMS (ESIpos) calculated for $C_{15}H_{23}NNaO_4$ (M+Na) 304.151806; found 304.151928;

HPLC

τ_R	22.4 min	(minor enantiomer)
τ_R	39.7 min	(major enantiomer)

(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 3/97);

7.3.2.10. *tert*-Butyl-(3*R*,4*S*,*E*)-4-formyl-5-methyl-1-phenylhex-1-en-3-yl-carbamate (255j)

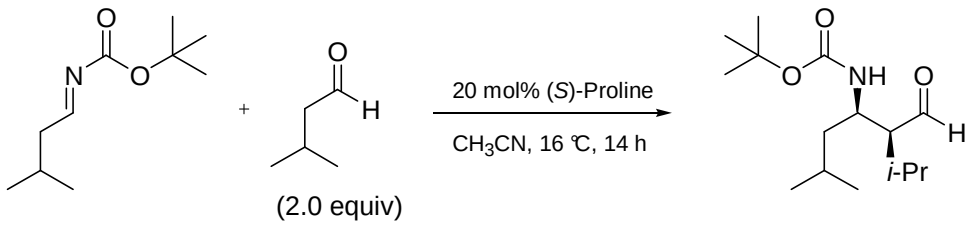


159i **255j**

The reaction was performed according to 7.3.2.9, but dichloromethane was used for the extraction. The product was obtained as a colorless solid after column chromatographical purification.

Chemical Formula	$C_{19}H_{27}NO_3$ (317.42 g/mol)
TLC	R_f = 0.43 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained green-blue with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/pentane (10/90 – 20/80 v/v)
Yield	100.8 mg (64%)
Diastereomeric ratio	95:5
Enantiomeric ratio	>99:1
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 0.99 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 1.06 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 1.38 (s, 9H, (C(C*H*$_3$)$_3$), 2.00-2.14 (m, 1H, C*H*(CH$_3$)$_2$), 2.28-2.36 (m, 1H, C*H*CHO), 4.51-4.68 (m, 1H, C*H*NH), 4.85-5.02 (m, 1H, CHN*H*), 6.10 (dd, *J* = 15.8, 7.6 Hz, 1H, ArCH=C*H*), 6.51 (d, *J* = 15.8 Hz, 1H, ArC*H*=CH), 7.14-7.30 (m, 5H, arom), 9.70 (d, *J* = 3.1 Hz, 1H, C*H*O);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 20.4 (*C*H$_3$), 21.0 (*C*H$_3$), 27.0 (C*H*), 28.5 (C(*C*H$_3$)$_3$), 52.1 (C*H*NH), 62.0 (*C*HCHO), 80.0 (*C*(CH$_3$)$_3$), 126.7 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 131.6 (*C*q$_{Ar}$), 132.7 (ArCH=*C*H), 136.5 (Ar*C*H=CH), 155.1 (*C*O$_2$), 205.9 (*C*HO);
Mass	*m/z* (%) (EI) 317 (M, 2), 261 (M-*t*Bu+H, 18), 232 (M-C_5H_9O, 4), 200 (M-$C_5H_{10}NO_2$-H, 63), 176 (261-C_5H_9O, 100), 132 (232-$C_5H_9O_2$+H, 34), 115 (132-NH, 48), 91 (Bz, 12), 77 (Ph, 4), 57 (*t*Bu, 54);
HRMS	(ESIpos) calculated for $C_{19}H_{27}NNaO_3$ (M+Na) 340.188310; found 340.188470;
HPLC	τ_R 25.9 min (major enantiomer) τ_R 31.2 min (minor enantiomer) (OD-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);

7.3.2.11. *tert*-Butyl-(3*S*,4*R*)-3-formyl-2,6-dimethylheptan-4-ylcarbamate (255k)



159g **255k**

The reaction was performed according to 7.3.2.4. The imine was employed in the reaction immediately after preparation. The product was obtained as a colorless solid.

Chemical Formula	$C_{15}H_{29}NO_3$ (271.40 g/mol)
TLC	R_f = 0.32 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 v/v)
Yield	48.5 mg (36% over two steps)
Diastereomeric ratio	11:1
Enantiomeric ratio	98:2
Melting point	50-56 °C
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = 0.91 (d, *J* = 6.7 Hz, 3H, CH_2CH-(CH_3)$_A$(CH_3)$_B$), 0.93 (d, *J* = 6.6 Hz, 3H, $CH_2CH(CH_3)_A(CH_3)_B$), 1.03 (d, *J* = 6.7 Hz, 3H, $CHCH(CH_3)_A(CH_3)_B$), 1.06 (d, *J* = 6.8 Hz, 3H, $CHCH(CH_3)_A(CH_3)_B$), 1.22-1.32 (m, 2H, CH_2), 1.44 (s, 9H, $C(CH_3)_3$), 1.61-1.79 (m, 2H, $CH_2CH(CH_3)_2$), 2.08 (dqq, *J* = 6.8, 6.8, 6.8 Hz, 1H, $CHCH(CH_3)_2$), 2.21 (ddd, *J* = 7.5, 6.5, 3.4 Hz, 1H, $CHCH(CH_3)_2$), 3.98-4.13 (m, 1H, CHNH), 4.32-4.54 (m, 1H, CHN*H*), 9.75 (dd, *J* = 3.4, 0.4 Hz, 1H, CHO);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 20.2 (CH_3), 20.6 (CH_3), 21.3 (CH_3), 23.8 (CH_3), 25.0 (CH), 26.6 (CH), 28.4 ($C(CH_3)_3$), 41.2 (CH_2),

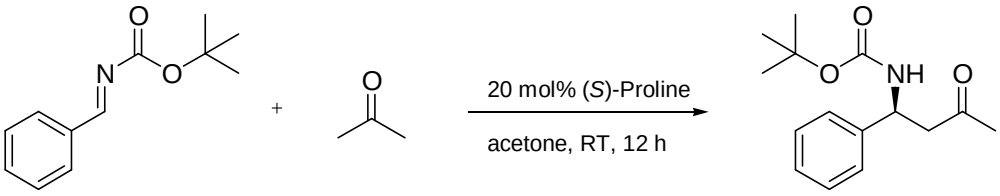
47.9 (C*H*NH), 62.6 (*C*HCHO), 79.3 (*C*$(CH_3)_3$), 155.4 (*C*O_2), 206.3 (*C*HO);

Mass *m/z* (%) (EI), 214 (M-*t*Bu, 2), 200 (214-CH_3, 1), 186 (214-CHO+H, 26), 170 (214-CO_2, 1), 158 (214-*t*Bu+H, 7), 130 (214-C_5H_9O+H, 77), 86 (C_5H_9O+H, 96), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{15}H_{29}NNaO_3$ (M+Na) 294.203959; found 294.203784;

HPLC τ_R 11.4 min (minor enantiomer)
τ_R 13.7 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 8/92);

7.3.2.12. (*S*)-*tert*-Butyl-3-oxo-1-phenylbutylcarbamate (255l)



159a **255l**

The reaction was performed according to 7.3.2.2, albeit in acetone as the solvent and at room temperature to account for the lower reactivity of the ketone. The product was obtained as a colorless solid.

Chemical Formula $C_{15}H_{21}NO_3$ (263.33 g/mol)

TLC R_f = 0.20 (SiO_2, ethyl acetate/hexane 15/85 v/v), stained with anisaldehyde

Purification The colorless solid obtained in the workup was triturated with cold hexanes (–78 °C)

Yield 96.2 mg (73%)

Enantiomeric ratio >99:1

Optical rotation $[\alpha]_D^{20}$ –23.8 (*c* = 1.02, $CHCl_3$)

Melting point 106-107 °C (decomp.)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, $C(CH_3)_3$), 2.08 (s, 3H, $COCH_3$), 2.90 (dd, *J* = 16.2, 4.5 Hz, 1H, CH_AH_BCOMe), 3.03 (dd, *J* = 14.9, 3.2 Hz, 1H, CH_AH_BCOMe), 5.00-5.14 (m, 1H), 5.30-5.52 (m, 1H), 7.20-7.37 (m, 5H, arom);

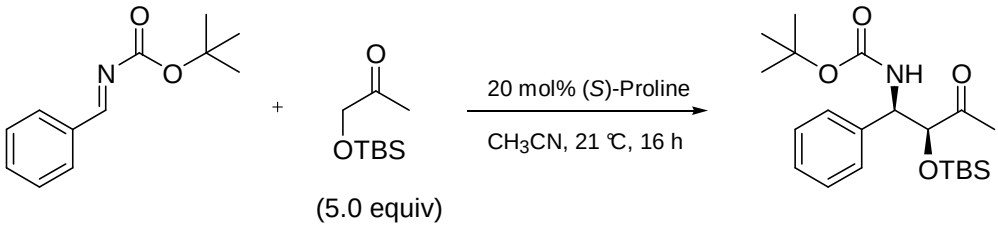
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 28.5 ($C(CH_3)_3$), 30.7 ($COCH_3$), 49.5 (CH_2COH), 51.2 (*C*HNH), 79.8 ($C(CH_3)_3$), 126.3 (CH_{Ar}), 127.5 (CH_{Ar}), 128.8 (CH_{Ar}), 141.7 (Cq_{Ar}), 155.3 (CO_2), 207.0 (*C*HO);

Mass *m/z* (%) (EI) 207 (M-*t*Bu+H, 85), 162 (M-CO_2, 43), 150 (207-C_3H_5O, 55), 106 (150-CO_2, 99), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{15}H_{21}NNaO_3$ (M+Na) 286.141260; found 286.141359;

HPLC τ_R 20.5 min (minor enantiomer)
τ_R 27.1 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.3.2.13. *tert*-Butyl-(1*R*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylbutyl-carbamate (255m)



159a **255m**

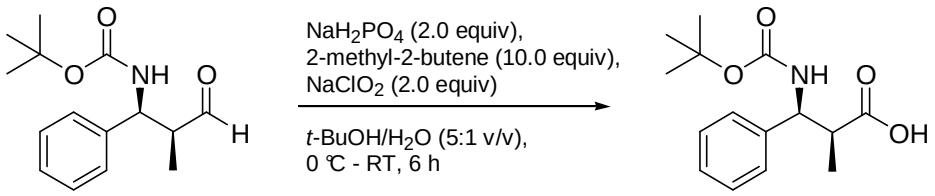
The reaction was performed according to 7.3.2.2, albeit at room temperature to account for the lower reactivity of the ketone. The product was obtained as a colorless oil.

Chemical Formula $C_{21}H_{35}NO_4Si$ (393.59 g/mol)

TLC	R_f = 0.44 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained orange with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/hexane (8/92 v/v)
Yield	40.4 mg (20%)
Diastereomeric ratio	17:1
Enantiomeric ratio	99:1
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = –0.35 [rotamer: bs, –0.54] (s, 3H, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), –0.13 (s, 3H, Si(CH$_3$)$_A$(C*H*$_3$)$_B$), 0.81 (s, 9H, Si(C*H*$_3$)$_3$), 1.42 [rotamer: bs, 1.26] (s, 9H, C(C*H*$_3$)$_3$), 2.15 [rotamer: bs, 2.23] (s, 3H, COCH$_3$), 4.24 [rotamer: bs, 4.10] (s, 1H, C*H*CO), 5.12 [rotamer: bs, 4.90] (d, *J* = 9.4 Hz, 1H, C*H*NH), 5.50 [rotamer: bs, 5.27] (d, *J* = 9.1 Hz, 1H, CHN*H*), 7.22-7.28 (m, 3H, arom), 7.29-7.35 (m, 2H, arom);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = –5.7 (Si*C*H$_3$), –5.2 (Si*C*H$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 26.9 (CO*C*H$_3$), 28.5 (C(*C*H$_3$)$_3$), 56.9 (*C*HNH), 80.0 (*C*(CH$_3$)$_3$), 82.0 (*C*OTBS), 126.7 (*C*H$_{Ar}$), 127.6 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 139.5 (*C*q$_{Ar}$), 155.1 (*C*O$_2$), 209.6 (*C*OCH$_3$);
Mass	*m/z* (%) (EI) 393 (M, 1), 320 (M-*t*BuO, 5), 206 (M-$C_9H_{19}O_2Si$, 29), 188 ($C_9H_{19}O_2Si$+H, 4), 150 (206-*t*Bu+H, 100), 131 ($C_6H_{15}OSi$, 12), 106 (150-CO_2, 48), 57 (*t*Bu, 22);
HRMS	(ESIpos) calculated for $C_{21}H_{35}NNaO_4Si$ (M+Na) 416.222759; found 416.223148;
HPLC	τ_R 9.3 min (minor enantiomer) τ_R 10.8 min (major enantiomer) (OD-H, 0.5 mL/min, *i*PrOH/*n*-heptane 2/98);

7.3.3. Conversion of the Mannich product to a β[2,3]-amino acid

7.3.3.1. (2*S*,3*S*)-3-(*tert*-butoxycarbonylamino)-2-methyl-3-phenylpropanoic acid (261)



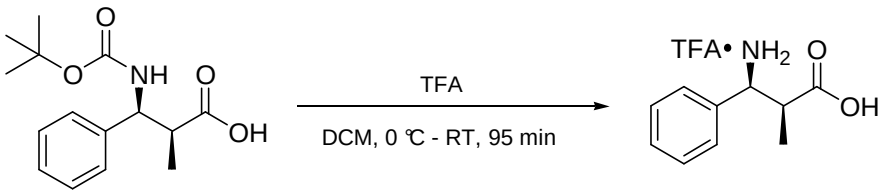
255a **261**

500 mg (1.9 mmol, 1.0 equiv) of *tert*-Butyl-(1*S*,2*S*)-2-methyl-3-oxo-1-phenylpropyl-carbamate, 524.4 mg (3.8 mmol, 2.0 equiv) NaH_2PO_4 and 1.33 g (19 mmol, 10.0 equiv) 2-methyl-2-butene were dissolved in a mixture of water and *tert*-butanol (1:5, v/v) and cooled to 0 °C. $NaClO_2$ was then added and the solution allowed to warm to room temperature. After vigorous stirring for 6 h, the reaction was quenched by adding a saturated solution of $Na_2S_2O_3$. Ethyl acetate was added, the phases separated, and the organic layer was washed with aqueous HCl (10%) and water and then dried over magnesium sulfate. The product was obtained as a colorless solid after column chromatography.

Chemical Formula	$C_{15}H_{21}NO_4$ (279.33 g/mol)
TLC	R_f = 0.41 (SiO_2, ethyl acetate/hexane 40/60 v/v),
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 – 50/50 v/v)
Yield	509.1 mg (96%)
^{1}H-NMR	(400 MHz, DMSO-d6): δ = 1.11 (d, *J* = 6.9 Hz, 3H, CHC*H*$_3$), 1.36 (s, 9H, C(C*H*$_3$)$_3$), 2.68-2.78 (m, 1H, C*H*CH$_3$), 4.68 (t, *J* = 9.5 Hz, 1H, C*H*NH), 7.17-7.24 (m, 1H, arom), 7.28 (m, 4H, arom), 7.37 (d, *J* = 9.8 Hz, 1H, CHN*H*), 12.06 (s, 1H, COOH);
^{13}C-NMR	(100 MHz, DMSO-d6): δ = 14.4 (CH*C*H$_3$), 28.2 (C(*C*H$_3$)$_3$), 45.2 (*C*HCH$_3$), 56.4 (*C*HNH), 77.9 (*C*(CH$_3$)$_3$), 126.9 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 142.2 (*C*q$_{Ar}$), 155.2 (N*C*O$_2$), 175.2 (*C*OOH);

HPLC	τ_R	22.4 min	(minor enantiomer)
	τ_R	30.1 min	(major enantiomer)
	(AD-H, 0.5 mL/min, *i*PrOH/*n*-heptane/TFA 10/90/0.1);		

7.3.3.2. (2*S*,3*S*)-3-amino-2-methyl-3-phenylpropanoic acid trifluoroacetic acid salt (262)



261 **262 · TFA**

The Boc-protected amino acid (50.1 mg, 0.18 mmol) was dissolved in 1 mL of dichloromethane und cooled to 0 °C. 0.14 mL of trifluoroacetic acid were then added dropwise and the mixture was allowed to warm to room temperature after complete addition. The solution was stirred for 70 min and the solvent was removed under reduced pressure. The residue was taken up in dichloromethane, evaporated again, and then dried under high vacuum for 16 h at room temperature. After this, it was dissolved in 4 mL of H_2O, washed with 2 mL of diethyl ether once, and the aqueous phase was evaporated and dried under high vacuum to give the product as a colorless solid.

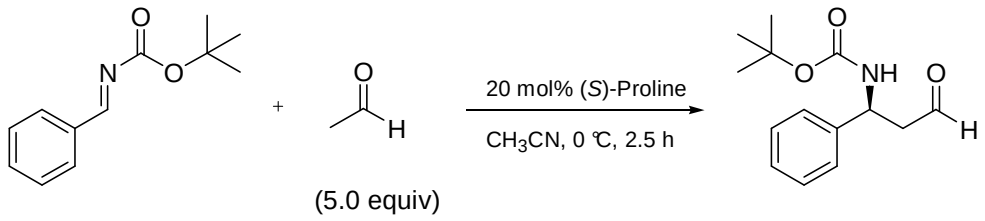
Chemical Formula	$C_{12}H_{14}F_3NO_4$ (293.24 g/mol)
Purification	washing with diethyl ether
Yield	51.2 mg (97%)
Diastereomeric ratio	>99:1
Enantiomeric ratio	>99:1 (determined after Boc-protection)
Optical rotation	$[\alpha]_D^{20}$ –4.7 (*c* = 0.91, H_2O); Lit.[150] $[\alpha]_D^{25}$ –1.7 (*c* = 1.06, H_2O); both values refer to the corresponding HCl-salt.

^{1}H-NMR (400 MHz, CD_3OD): δ = 1.31 (d, *J* = 7.1 Hz, 3H, CHC*H*$_3$), 3.06-3.16 (m, 1H, C*H*CH_3), 4.49 (d, *J* = 7.7 Hz, 1H, C*H*NH_2), 7.41-7.46 (m, 5H, arom);

^{13}C-NMR (100 MHz, CD_3OD): δ = 14.3 (CH*C*H_3), 44.8 (*C*HCH_3), 58.3 (*C*HNH), 117.8 (q, $^{1}J_{CF}$ = 291.0 Hz, *C*F_3), 128.7 (*C*H_{Ar}), 130.2 (*C*H_{Ar}), 130.5 (*C*H_{Ar}), 136.6 (*C*q_{Ar}), 162.2 (q, $^{2}J_{CF}$ = 36.3 Hz, CF_3*C*OOH), 175.8 (*C*OOH);

7.4. Mannich reactions of acetaldehyde

7.4.1. (*S*)-*tert*-Butyl-3-oxo-1-phenylpropylcarbamate (264a)



159a **264a**

A 0.74 M stock solution was prepared from 0.63 mL of freshly distilled acetaldehyde and 14.37 mL of acetonitrile. 9.5 mL (7 mmol acetaldehyde, 5.0 equiv) of this solution were added to 287.4 mg (1.4 mmol, 1.0 equiv) of Phenylmethylene-carbamic acid *tert*-butyl ester and cooled to 0 °C. 32.2 mg (0.28 mmol, 0.2 equiv) of (*S*)-proline were added and the mixture stirred for 2.5 h. The reaction was quenched with water and extracted three times with dichloromethane. The combined organic fractions were washed with brine, dried over Na_2SO_4, and the solvent evaporated under reduced pressure. The product was obtained as a colorless solid after column chromatography.

Chemical Formula	$C_{14}H_{19}NO_3$ (249.31 g/mol)
TLC	R_f = 0.24 (SiO_2, ethyl acetate/hexane 20/80 v/v), stained purple with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 v/v)
Yield	188.2 mg (54%)
Enantiomeric ratio	>99:1
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.42 (s, 9H, C(C*H*$_3$)$_3$), 2.85-3.05 (m, 2H, C*H*$_2$CHO), 4.97-5.13 (m, 1H, CHN*H*), 5.13-5.27 (m, 1H, C*H*NH), 7.24-7.39 (m, 5H, arom), 9.75 (dd, *J* = 2.2, 1.5 Hz, 1H, C*H*O);

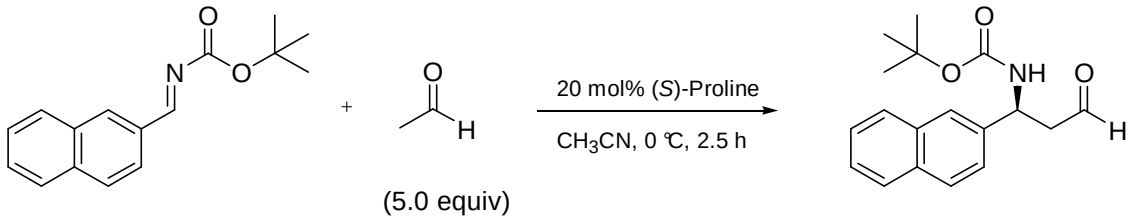
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 28.2 ($C(CH_3)_3$), 49.8, 50.0, 79.8 ($C(CH_3)_3$), 126.2 (CH_{Ar}), 127.6 (CH_{Ar}), 128.7 (CH_{Ar}), 140.9 (Cq_{Ar}), 155.0 (CO_2), 200.2 (CHO);

Mass *m/z* (%) (EI) 206 (M-C_2H_3O, 5), 193 (M-*t*Bu+H, 46), 150 (206-*t*Bu+H, 43), 106 (150-CO_2, 54), 77 (Ph, 25), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{14}H_{19}NNaO_3$ (M+Na) 272.125716; found 272.125418;

GC τ_R 72.6 min (minor enantiomer)
τ_R 73.4 min (major enantiomer)
(Ivadex-7/PS086 column 25 m (100 °C, 0.7 °C/min until 160 °C, 20 °C/min until 220 °C, 10 min at 320 °C, 0.5 bar H_2 as carrier gas));

7.4.2. (*S*)-*tert*-Butyl-1-(naphthalene-2-yl)-3-oxopropylcarbamate (264c)



159c **264c**

The product was obtained as a colorless solid according to the procedure described in 7.4.1.

Chemical Formula $C_{18}H_{21}NO_3$ (299.36 g/mol)

TLC R_f = 0.27 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue-green with anisaldehyde

Purification column chromatography on silica gel, eluting with methanol/dichloromethane (1.5/98.5 v/v)

Yield 70 mg (40%)

Enantiomeric ratio >99:1

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H, C(C*H*$_3$)$_3$), 2.96-3.12 (m, 2H, C*H*$_2$CHO), 5.09-5.25 (m, 1H, CHN*H*), 5.29-5.42 (m, 1H, C*H*NH), 7.42 (dd, *J* = 8.5, 1.8 Hz, 1H, arom), 7.44-7.51 (m, 2H, arom), 7.72-7.75 (m, 1H, arom), 7.78-7.86 (m, 3H, arom), 9.78 (dd, *J* = 2.3, 1.5 Hz, 1H, C*H*O);

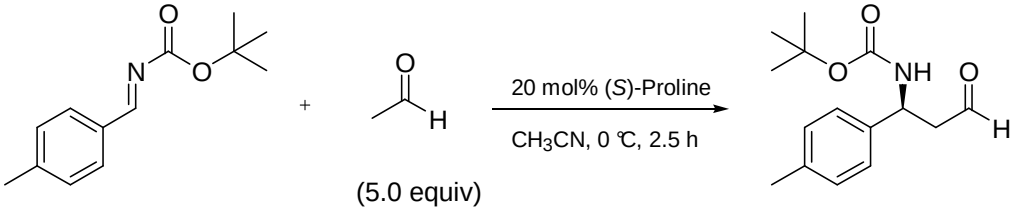
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 28.4 (C(*C*H$_3$)$_3$), 49.8, 49.8, 80.2 (*C*(CH$_3$)$_3$), 124.4 (*C*H$_{Ar}$), 125.1 (*C*H$_{Ar}$), 126.2 (*C*H$_{Ar}$), 126.5 (*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 132.9 (*C*q$_{Ar}$), 133.3 (*C*q$_{Ar}$), 138.4 (*C*q$_{Ar}$), 155.1 (*C*O$_2$), 200.1 (*C*HO);

Mass *m/z* (%) (EI) 299 (M, 7), 256 (M-C_2H_3O, 1), 243 (M-*t*Bu+H, 100), 200 (243-C_2H_3O, 90), 198 (243-H-CO_2, 28), 183 (198-NH, 19), 156 (47), 154 (183-CHO, 31), 129 ($C_6H_{11}NO_2$, 17), 127 (naphth., 10), 57 (*t*Bu, 41);

HRMS (ESIpos) calculated for $C_{18}H_{21}NNaO_3$ (M+Na) 322.141361; found 322.141369;

HPLC τ_R 26.8 min (minor enantiomer)
τ_R 34.1 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.4.3. (*S*)-*tert*-Butyl-1-(4-methylphenyl)-3-oxo-propylcarbamate (264d)



264d

The product was obtained as a colorless solid according to the procedure described in 7.4.1.

Chemical Formula $C_{15}H_{21}NO_3$ (263.33 g/mol)

TLC R_f = 0.34 (SiO_2, ethyl acetate/hexane 20/80 v/v), stained with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 – 20/80 v/v)

Yield 214.7 mg (58%)

Enantiomeric ratio 98:2

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.42 (s, 9H, C(CH_3)$_3$), 2.33 (s, 3H, ArCH_3), 2.87 (ddd, *J* = 16.4, 6.3, 1.0 Hz, 1H, CH_AH_BCHO), 2.97 (ddd, *J* = 16.5, 7.2, 2.5 Hz, 1H, CH_AH_BCHO), 4.92-5.09 (m, 1H, CHN*H*), 5.09-5.25 (m, 1H, C*H*NH), 7.12-7.21 (m, 4H, arom), 9.73 (dd, *J* = 2.3, 1.9 Hz, 1H, C*H*O);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 21.1 (ArCH_3), 28.4 (C(CH_3)$_3$), 49.9, 50.0, 80.0 (*C*(CH_3)$_3$), 126.2 (*C*H_{Ar}), 129.6 (*C*H_{Ar}), 137.6 (*C*q_{Ar}), 138.0 (*C*q_{Ar}), 155.0 (*C*O_2), 200.3 (*C*HO);

Mass *m/z* (%) (EI) 220 (M-C_2H_3O, 7), 207 (M-*t*Bu+H, 69), 189 (13), 164 (207-C_2H_3O, 83), 162 (M-*t*BuCO_2, 25), 147 (162-NH, 20), 131 (147-CH_3-H, 13), 120 (72), 118 (147-CHO, 38), 91 (CH_2Ph, 18), 77 (Ph, 5), 57 (*t*Bu, 100);

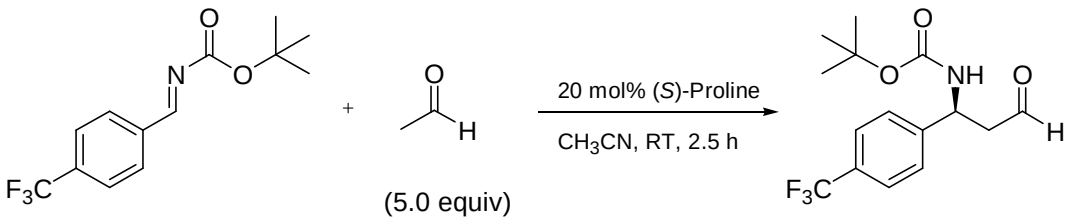
HRMS (ESIpos) calculated for $C_{15}H_{21}NNaO_3$ (M+Na) 286.141364; found 286.141227;

GC

τ_R	68.7 min	(minor enantiomer)
τ_R	69.0 min	(major enantiomer)

(Ivadex-1/PS086 column 25 m (100 °C, 1.2 °C/min until 220 °C, 5 min at 320 °C, 0.5 bar H_2 as carrier gas);

7.4.4. (*S*)-*tert*-Butyl-3-oxo-1-(4-trifluoromethylphenyl)propylcarbamate (264e)



105d **264e**

The product was obtained as a colorless solid according to the procedure described in 7.4.1.

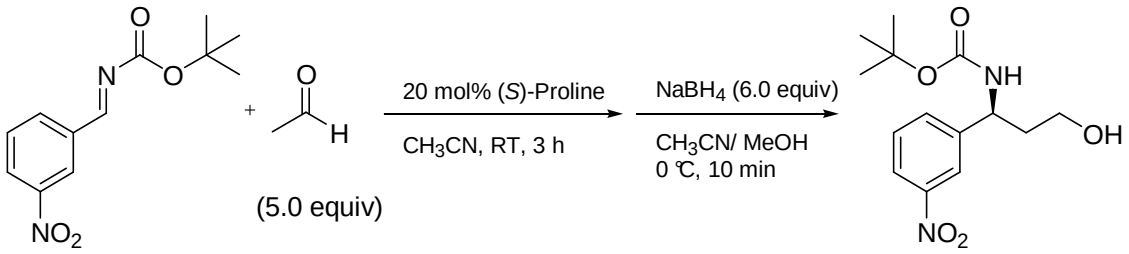
Chemical Formula	$C_{15}H_{18}F_3NO_3$ (317.30 g/mol)
TLC	R_f = 0.26 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue-green with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85, then 20/80 v/v)
Yield	185.7 mg (42%)
Enantiomeric ratio	99:1
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 1.42 (s, 9H, C(CH_3)$_3$), 2.88-3.08 (m, 2H, CH_2), 5.16-5.31 (m, 2H, CHN*H* and C*H*NH), 7.43 (d, *J* = 8.2 Hz, 2H, arom), 7.60 d, *J* = 8.1 Hz, 2H, arom), 9.74 (dd, *J* = 1.8, 1.1 Hz, 1H, C*H*O);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 28.3 (C(*C*H_3)$_3$), 49.5, 49.8, 80.3 (*C*(CH$_3$)$_3$), 124.0 (q, $^1J_{CF}$ = 272.7 Hz, *C*F_3), 125.8 (q, $^3J_{CF}$ = 4.1 Hz, (*C*H)$_2$CCF$_3$), 126.7 (*C*H$_{Ar}$), 130.0 (q, $^2J_{CF}$ = 32.5 Hz, (CH)$_2$*C*CF$_3$), 145.3 (*C*q$_{Ar}$), 155.0 (*C*O$_2$), 199.5 (*C*HO);
Mass	*m/z* (%) (EI) 274 (M-C_2H_3O, 3), 261 (M-*t*Bu+H, 35), 218 (261-C_2H_3O, 25), 174 (29), 172 (M-$C_7H_4F_3$, 25), 145 ($C_7H_4F_3$, 5), 57 (*t*Bu, 100);
HRMS	(ESIpos) calculated for $C_{15}H_{18}F_3NNaO_3$ (M+Na) 340.113096; found 340.113416;

GC τ_R 76.2 min (major enantiomer)

τ_R 76.9 min (minor enantiomer)

(Ivadex-1/PS086 column 25 m (100 °C, 1.0 °C/min until 220 °C, 10 min at 320 °C, 0.6 bar H_2 as carrier gas);

7.4.5. (*S*)-*tert*-Butyl-3-hydroxy-1-(3-nitrophenyl)propylcarbamate (271)



271

The Mannich reaction was performed according to the procedure described in 7.4.1, albeit at room temperature to compensate for the lower reactivity of the imine. After the Mannich reaction, 3 mL of methanol were added, the solution was cooled to 0 °C, and the excess of acetaldehyde removed under reduced pressure. 90.8 mg (2.4 mmol, 6.0 equiv) of sodium borohydride were added and the reaction left stirring for 10 min. It was then quenched by addition of saturated ammonia chloride solution and extracted three times with ethyl acetate. Column chromatographical purification gave the product as a colorless solid.

Chemical Formula $C_{14}H_{20}N_2O_5$ (296.32 g/mol)

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80, then 30/70, then 50/50 v/v)

Yield 360.4 mg (42%)

Enantiomeric ratio >99:1

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.41 (s, 9H, $C(CH_3)_3$), 1.77-1.96 (m, 1H, $CH_AH_BCH_2OH$), 1.98-2.20 (m, 1H, $CH_AH_BCH_2OH$), 2.38 (brs, 1H, OH), 3.62-3.74 (m, 2H, CH_2OH), 4.84-5.09 (m, 1H, CHNH), 5.34-5.59 (m, 1H, CHNH), 7.50 (t, *J* = 7.9 Hz, 1H,

arom), 7.65 (d, *J* = 7.9 Hz, 1H, arom), 8.07-8.14 (m, 1H, arom), 8.15-8.20 (m, 1H, arom);

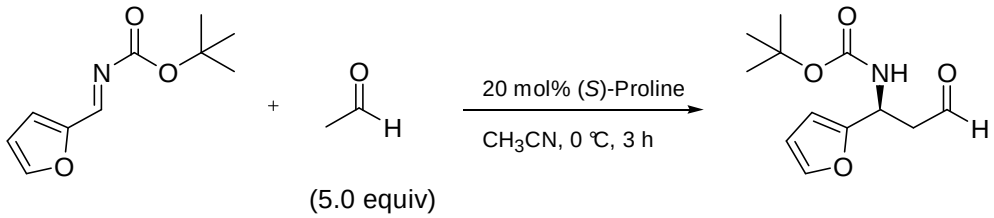
^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 28.3 ($C(CH_3)_3$), 38.6 (CH_2CH_2OH), 51.8 (*C*HNH), 59.0 (CH_2OH), 80.4 ($C(CH_3)_3$), 121.2 (CH_{Ar}), 122.4 (CH_{Ar}), 129.6 (CH_{Ar}), 132.8 (CH_{Ar}), 144.8 (Cq_{Ar}), 148.5 ($Cq_{Ar}NO_2$), 155.9 (CO_2);

Mass *m/z* (%) (EI) 296 (M, 1), 251 (M-C_2H_5O, 25), 240 (M-*t*Bu+H, 5), 223 (M-C_4H_9O, 5), 195 (223-CO, 36), 179 (195-NH_2, 12), 151 (52), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{14}H_{20}N_2NaO_5$ (M+Na) 319.126445; found 319.126559;

HPLC τ_R 45.4 min (minor enantiomer)
τ_R 51.3 min (major enantiomer)
(OJ-H, 0.5 mL/min, *i*PrOH/*n*-heptane 5/95);

7.4.6. (*S*)-*tert*-Butyl-1-(furan-2-yl)-3-oxo-propylcarbamate (264g)



159b **264g**

The product was obtained as a colorless oil according to the procedure described in 7.4.1.

Chemical Formula $C_{12}H_{17}NO_4$ (239.27 g/mol)

TLC R_f = 0.32 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with methanol/dichloromethane (2/98, v/v)

Yield 92 mg (30%)

Enantiomeric ratio 99:1

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.44 (s, 9H, C(CH_3)$_3$), 2.89-3.03 (m, 2H, CH_2), 5.00-5.19 (m, 1H, CHN*H*), 5.19-5.35 (m, 1H, C*H*NH), 6.20-6.22 (m , 1H, CH_{Fur}), 6.31 (dd, *J* = 3.3, 1.8 Hz, 1H, CH_{Fur}), 7.34 (dd, *J* = 1.8, 0.8 Hz, 1H, CH_{Fur}), 9.77 (dd, *J* = 1.8, 1.8 Hz, 1H, C*H*O);

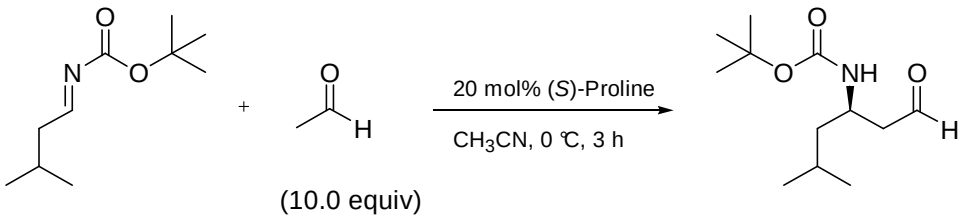
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 28.4 (C(*C*H_3)$_3$), 44.5 (*C*HNH), 47.5 (*C*H_2), 80.3 (*C*(CH_3)$_3$), 106.5 (*C*H_{Fur}), 110.6 (*C*H_{Fur}), 142.2 (*C*H_{Fur}), 153.3 (*C*q$_{Fur}$), 155.0 (*C*O_2), 199.9 (*C*HO);

Mass *m/z* (%) (EI) 239 (M, 1), 183 (M-*t*Bu+H, 99), 154 (183-CHO, 18), 139 (183-C_2H_2O, 50), 138 (M-$C_5H_9O_2$, 43), 123 (138-NH, 45), 110 (138-CHO+H, 22), 96 (110-CH, 92), 94 (123-CHO, 47), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{12}H_{17}NNaO_4$ (M+Na) 262.104978; found 262.105062;

GC τ_R 51.9 min (major enantiomer)
τ_R 52.4 min (minor enantiomer)
(Lipodex E column 25 m (120 °C, 0.5 °C/min until 160 °C, 18 °C/min until 220 °C, 10 min at 320 °C, 0.5 bar H_2 as carrier gas));

7.4.7. (*R*)-*tert*-Butyl-5-methyl-1-oxohexan-3-ylcarbamate (264g)



159g **264g**

A solution of 3-methylbutylidene-carbamic acid *tert*-butyl ester, freshly prepared from 163.7 mg (0.5 mmol, 1.0 equiv) of (1-benzenesulfonyl-3-methylbutyl)-carbamic acid

tert-butyl ester, was immediately dissolved in acetonitrile (4 mL) and cooled to –10 °C. Redistilled acetaldehyde (300 mL, 5.3 mmol, 10.0 equiv) was added and the mixture was transferred to an addition funnel equipped with a cooling system set at –10 °C. In a separate round-bottomed flask a solution of (*S*)-proline (11.5 mg, 0.1 mmol, 0.2 equiv) in acetonitrile (4 mL) was cooled to 0 °C. The above mixture was added to the catalyst solution over 2 h, then the addition funnel was rinsed with 1 mL acetonitrile into the reaction flask, and the mixture stirred an additional 30 min at 0 °C after complete addition. The reaction was poured into a separation funnel containing water (30 mL) and extracted with dichloromethane (3x25 mL). The combined organic fractions were dried over Na_2SO_4, filtered, and the solvent was removed under vacuum. Purification by column chromatography on silica gel (10% ethyl acetate in hexane) gave the corresponding product as a colorless solid.

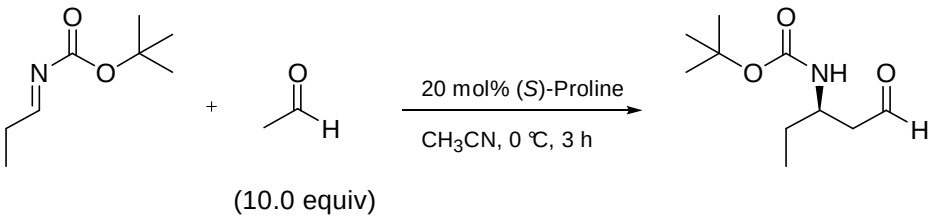
Chemical Formula	$C_{12}H_{23}NO_3$ (229.32 g/mol)
TLC	R_f = 0.53 (SiO_2, ethyl acetate/hexane 30/70 v/v), stained greenish-blue with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90, v/v)
Yield	63.5 mg (55% over two steps)
Enantiomeric ratio	>99:1
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 0.91 (d, *J* = 3.4 Hz, 3H, $CH(CH_3)_A(CH_3)_B$), 0.93 d, *J* = 3.4 Hz, 3H, $CH(CH_3)_A(CH_3)_B$), 1.19-1.34 (m, 2H, $CHCH_2$), 1.43 (s, 9H, $C(CH_3)_3$), 1.58-1.74 (m, 1H, $(CH_3)_2CHCH_2$), 2.47-2.68 (m, 2H, CH_2CHO), 3.99-4.18 (m, 1H, CHNH), 4.58 (d, *J* = 7.1 Hz, 1H, CHNH), 9.76 (dd, *J* = 2.0, 2.0 Hz, 1H, CHO);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 22.2 (CH_3), 23.1 (CH_3), 25.1 (CH), 28.5 ($C(CH_3)_3$), 44.4 ($CHCH_2$), 44.9 (CHNH), 49.9 (CH_2CHO), 79.6 ($C(CH_3)_3$), 155.5 (CO_2), 201.4 (CHO);
Mass	*m/z* (%) (EI) 214 ($M-CH_3$, 1), 201 (M+H-CHO, 1) 186 ($M-C_2H_3O$, 1), 173 (M-*t*Bu+H, 10), 172 ($M-C_4H_9$, 9), 130

(186+H-C_4H_9, 11), 116 (172-C_4H_9, 14), 86 (18), 72 (33), 57 (*t*Bu, 100);

HRMS (ESIpos) calculated for $C_{12}H_{23}NNaO_3$ (M+Na) 252.157010; found 252.156743;

GC τ_R 36.1 min (major enantiomer)
τ_R 37.3 min (minor enantiomer)
(HYDRODEX-β-TBDAc column 25 m (120 °C isotherm, 0.6 bar H_2 as carrier gas));

7.4.8. (*R*)-*tert*-Butyl-1-oxopentan-3-ylcarbamate (264b)



159h **264b**

The compound was obtained according to 7.4.7 as a colorless solid.

Chemical Formula $C_{10}H_{19}NO_3$ (201.26 g/mol)

TLC R_f = 0.52 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained green with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90, v/v)

Yield 22.8 mg (23% over two steps)

Enantiomeric ratio >99:1

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, *J* = 7.4 Hz, 3H, CH_3), 1.42 (s, 9H, C(CH_3)$_3$), 1.50-1.60 (m, 2H, CH_3CH_2), 2.54 (ddd, *J* = 16.4, 7.0, 2.6 Hz, 1H, CH_AH$_B$CHO), 2.58-2.66 (m, 1H, CH$_A$$H_B$CHO), 3.89-4.02 (m, 1H, C*H*NH), 4.53-4.72 (m, 1H, CHN*H*), 9.76 (dd, *J* = 2.3, 1.8 Hz, 1H, C*H*O);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 10.6 (*C*H_3), 28.2 (*C*H_2CH$_3$), 28.5 (C(*C*H_3)$_3$), 48.0 (*C*HNH), 49.0 (*C*H_2CHO), 79.7 (*C*(CH$_3$)$_3$), 155.6 (*C*O_2), 201.4 (*C*HO);

Mass *m/z* (%) (EI) 172 (M-C_2H_5, 5), 145 (M-*t*Bu+H, 10), 116 ($C_5H_{10}NO_2$, 9), 102 (116-N, 7), 72 (23), 57 (*t*Bu, 100);

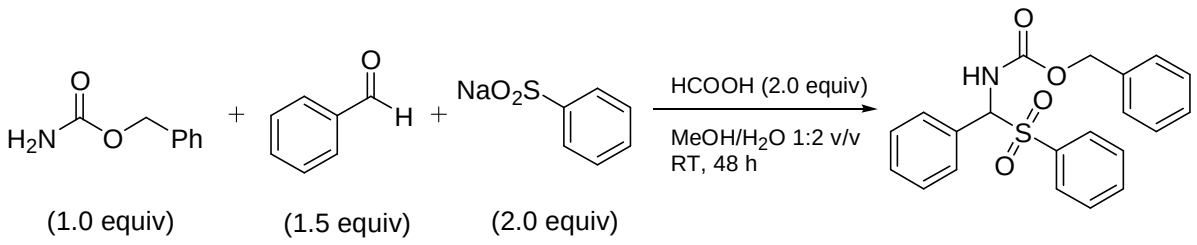
HRMS (ESIpos) calculated for $C_{10}H_{20}NO_3$ (M+H) 202.144319; found 202.144152;

GC τ_R 58.4 min (major enantiomer)
τ_R 61.0 min (minor enantiomer)
(HYDRODEX-β-TBDAc column 25 m (110 °C isotherm, 0.6 bar H_2 as carrier gas));

7.5. Mannich reactions of *N*-Cbz-imines

7.5.1. Preparation of *N*-Cbz-imines

7.5.1.1. (Benzenesulfonyl-phenylmethyl)-carbamic acid benzyl ester (293a)



(1.0 equiv) (1.5 equiv) (2.0 equiv)

292 **252a** **251** **293a**

A modified literature procedure was followed.[116] To a stirred solution of benzyl carbamate (5.7 g, 37.7 mmol, 1.0 equiv) and benzenesulfinic acid sodium salt (12.3 g, 74.9 mmol, 2.0 equiv) in methanol/water (37 mL/74 mL) was added benzaldehyde (5.7 mL, 56.4 mmol, 1.5 equiv) in one portion, followed by formic acid (2.9 mL, 2.0 equiv). The mixture was stirred at room temperature for 72 h, during which a colorless precipitate occurred. The solid was filtered, washed with water (50 mL) and diethyl ether (50 mL) and then dried *in vacuo*.

Chemical Formula $C_{21}H_{19}NO_4S$ (381.45 g/mol)

Purification washing with water and diethyl ether

Yield 7.2 g (50%; Lit.[116] 97%)

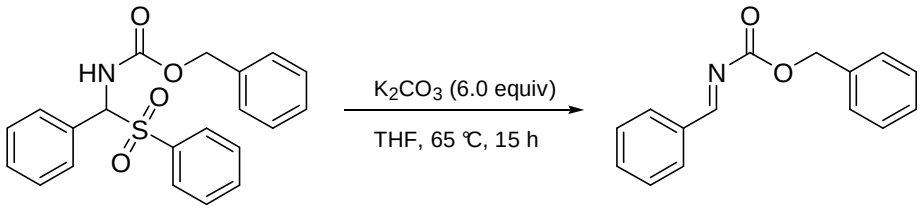
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.91 (d, *J* = 12.0 Hz, 1H, OC*H*$_A$H$_B$), 4.95 (d, *J* = 12.0 Hz, 1H, OCH$_A$*H*$_B$), 5.96 (d, *J* = 10.6 Hz, 1H, C*H*NH), 6.02 (d, *J* = 10.6 Hz, 1H, CHN*H*), 7.18-7.25 (m, 2H, arom), 7.30-7.48 (m, 10H, arom), 7.60 (t, *J* = 7.5 Hz, 1H, arom), 7.83 (d, *J* = 7.6 Hz, 1H, arom);

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 67.9 (CO_2CH_2), 74.6 (NH*C*H), 128.7 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 129.0 (*C*H$_{Ar}$), 129.0 (*C*H$_{Ar}$), 129.2 (*C*H$_{Ar}$), 129.6 (*C*H$_{Ar}$), 130.0 (*C*H$_{Ar}$), 130.2 (*C*H$_{Ar}$), 134.4 (*C*q$_{Ar}$), 135.7 (*C*q$_{Ar}$), 136.7 (*C*q$_{Ar}$), 154.8 (*C*O$_2$CH$_2$);

Mass *m/z* (%) (EI) 240 (M-SO_2Ph, 19), 239 (240-H, 24), 196 (240-CO_2, 14), 142 (SO_2Ph+H, 11), 132 (11), 107 (OBn, 34), 91 (CH_2Ph, 100), 77 (Ph, 32);

HRMS (ESIpos) calculated for $C_{21}H_{19}NNaO_4S$ (M+Na) 404.092698; found 404.092622;

7.5.1.2. Phenylmethylene-carbamic acid benzyl ester (294a)



293a **294a**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid.

Chemical Formula $C_{15}H_{13}NO_2$ (239.27 g/mol)

Purification the product was sufficiently pure and was directly used in subsequent reactions.

Yield 1.47 g (94%)

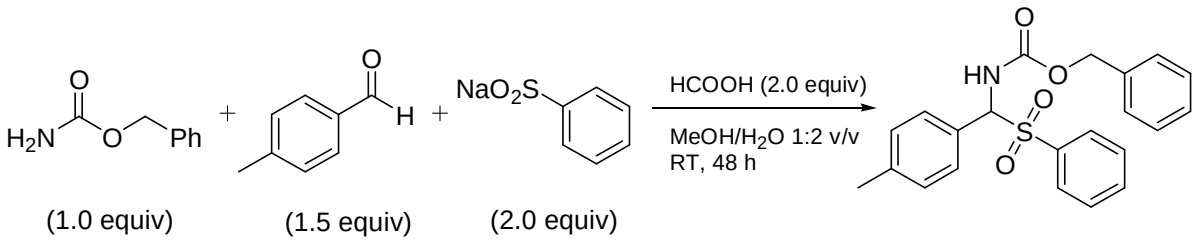
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 5.32 (s, 2H, OC*H*$_2$), 7.34-7.41 (m, 3H, arom), 7.44-7.50 (m, 4H, arom), 7.56-7.60 (m, 1H, arom), 7.92 (d, *J* = 7.7 Hz, 2H, arom), 8.95 (s, 1H, N=C*H*);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 67.9 (CO_2CH_2), 127.5 (CH_{Ar}), 127.6 (CH_{Ar}), 127.6 (CH_{Ar}), 127.9 (CH_{Ar}), 129.4 (CH_{Ar}), 132.8 (CH_{Ar}), 132.9 (Cq_{Ar}), 134.3 (Cq_{Ar}), 162.7 (NCO_2), 170.2 (Ph*C*N);

Mass *m/z* (%) (EI) 239 (M, 49), 194 (18), 132 (M-OBn, 20), 107 (OBn, 67), 91 (CH_2Ph, 100), 77 (Ph, 22);

HRMS (ESIpos) calculated for $C_{15}H_{13}NNaO_2$ (M+Na) 262.083847; found 262.083931;

7.5.1.3. (Benzenesulfonyl-4-methylphenyl-methyl)-carbamic acid benzyl ester (293b)



(1.0 equiv) (1.5 equiv) (2.0 equiv)

292 **252j** **251** **293b**

The procedure of 7.5.1.1 was followed. The product was obtained as a colorless solid.

Chemical Formula $C_{22}H_{21}NO_4S$ (395.49 g/mol)

Purification washing with water and diethyl ether

Yield 2.64 g (30%)

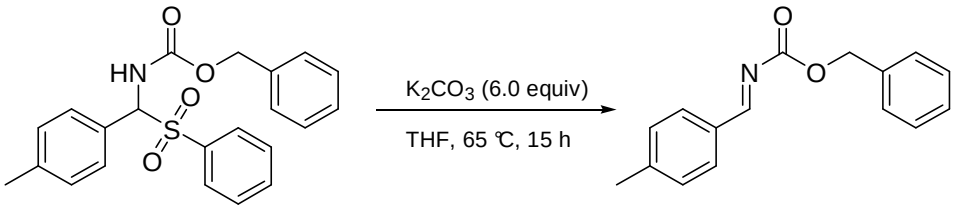
^{1}H-NMR (500 MHz, acetone-d6): δ = 2.35 (s, 3H, CH_3), 4.87 (d, J = 12.4 Hz, 1H, OCH_AH_B), 4.91 (d, J = 12.4 Hz, 1H, OCH_AH_B), 6.03 (d, J = 10.9 Hz, 1H, CHNH), 7.21-7.26 (m, 4H, arom), 7.29-7.37 (m, 3H, arom), 7.53 (d, J = 8.0 Hz, 2H, arom), 7.57 (t, J = 7.9 Hz, 2H, arom), 7.72 (t, J = 7.8 Hz, 1H, arom), 7.87 (d, J = 7.4 Hz, 2H, arom), 7.92 (d, J = 12.0 Hz, 1H, NH);

^{13}C-NMR (125.8 MHz, DMSO-d6): δ = 20.8 (CH_3), 66.0 (CO_2CH_2), 74.7 (NHCH), 127.1 (CH_{Ar}), 127.6 (CH_{Ar}), 127.9 (CH_{Ar}), 128.3 (CH_{Ar}), 128.7 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 (CH_{Ar}), 129.5 (CH_{Ar}), 134.1 (Cq_{Ar}), 136.3 (Cq_{Ar}), 136.7 (Cq_{Ar}), 138.9 (Cq_{Ar}), 155.2 (CO_2CH_2);

Mass *m/z* (%) (EI) 254 (M-SO_2Ph, 7), 238 (43), 208 (10), 146 (23), 142 (SO_2Ph+H, 15), 107 (OBn, 53), 91 (CH_2Ph, 100), 77 (Ph, 31);

HRMS (ESIpos) calculated for $C_{22}H_{22}NO_4S$ (M+H) 396.126954; found 396.126626;

7.5.1.4. [(4-Methylphenyl)methylene]-carbamic acid benzyl ester (294b)

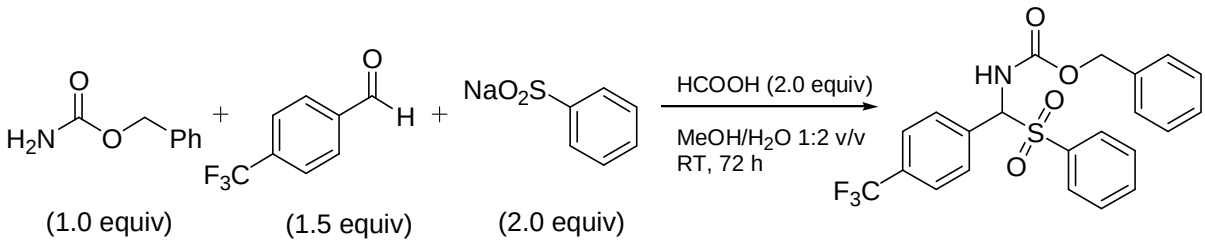


293b **294b**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid.

Chemical Formula	$C_{16}H_{15}NO_2$ (253.30 g/mol)
Purification	bulb-to-bulb distillation (165-175 °C, $4 \cdot 10^{-2}$ mbar)
Yield	578 mg (87%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 2.42 (s, 3H, C*H*$_3$), 5.31 (s, 2H, OC*H*$_2$), 7.26-7.30 (m, 2H, arom), 7.33-7.41 (m, 3H, arom), 7.42-7.48 (m, 2H, arom), 7.82 (d, *J* = 8.1Hz, 2H, arom), 8.94 (s, 1H, N=C*H*);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 21.9 (*C*H$_3$), 68.8 (CO$_2$*C*H$_2$), 128.1 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 129.2 (*C*H$_{Ar}$), 129.8 (*C*H$_{Ar}$), 130.6 (*C*q$_{Ar}$), 131.4 (*C*q$_{Ar}$), 135.5 (*C*q$_{Ar}$), 163.9 (N*C*O$_2$), 171.5 (Ph*C*N);
Mass	*m/z* (%) (EI) 253 (M, 10), 238 (M-CH$_3$, 48), 208 (9), 146 (M-OBn, 25), 107 (OBn, 58), 91 (CH$_2$Ph, 100);
HRMS	(ESIpos) calculated for $C_{16}H_{15}NNaO_2$ (M+Na) 276.099495; found 276.099419;

7.5.1.5. [Benzenesulfonyl-4-(trifluoromethyl)phenyl-methyl]-carbamic acid benzyl ester (293c)



(1.0 equiv) (1.5 equiv) (2.0 equiv)

292 **252d** **251** **293c**

The procedure of 7.5.1.1 was followed. The product was obtained as a colorless solid.

Chemical Formula $C_{22}H_{18}F_3NO_4S$ (449.44 g/mol)

Purification washing with water and diethyl ether

Yield 3.40 g (34%)

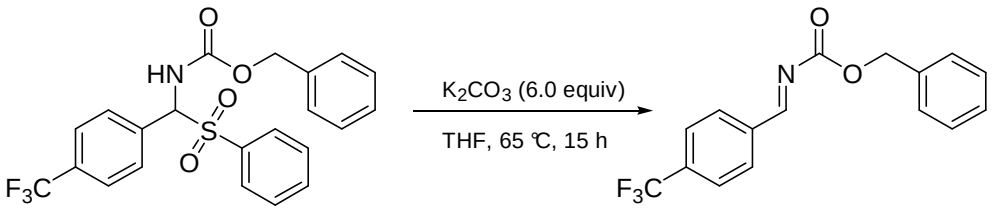
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 4.83 (d, *J* = 12.8 Hz, 1H, OCH_AH_B), 4.89 (d, *J* = 12.7 Hz, 1H, OCH_AH_B), 6.31 (d, *J* = 10.8 Hz, 1H, CHNH), 7.15-7.22 (m, 2H, arom), 7.30-7.36 (m, 3H, arom), 7.57-7.65 (m, 2H, arom), 7.73-7.83 (m, 3H, arom), 7.85-7.94 (m, 4H, arom), 9.27 (d, *J* = 10.7 Hz, 1H, NH);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 66.50 (CO_2CH_2), 74.51 (NHCH), 124.38 (q, $^1J_{CF}$ = 272.1 Hz, CF_3), 125.40 (q, $^3J_{CF}$ = 3.9 Hz, $(CH)_2CCF_3$), 128.04 (CH_{Ar}), 128.31 (CH_{Ar}), 128.72 (CH_{Ar}), 129.50 (CH_{Ar}), 129.54 (CH_{Ar}), 130.14 (q, $^2J_{CF}$ = 31.7 Hz, $(CH)_2CCF_3$), 130.88 (CH_{Ar}), 134.74 (CH_{Ar}), 135.22 (Cq_{Ar}), 136.58 (Cq_{Ar}), 136.71 (Cq_{Ar}), 155.49 (CO_2CH_2);

Mass *m/z* (%) (EI) 308 (M-SO_2Ph, 13), 264 (308-CO_2, 10), 200 (8), 142 (SO_2Ph+H, 9), 107 (OBn, 39), 91 (CH_2Ph, 100), 77 (Ph, 22);

HRMS (ESIpos) calculated for $C_{22}H_{19}F_3NO_4S$ (M+H) 450.098695; found 450.098932;

7.5.1.6. [(4-Trifluoromethylphenyl)methylene]-carbamic acid benzyl ester (294c)

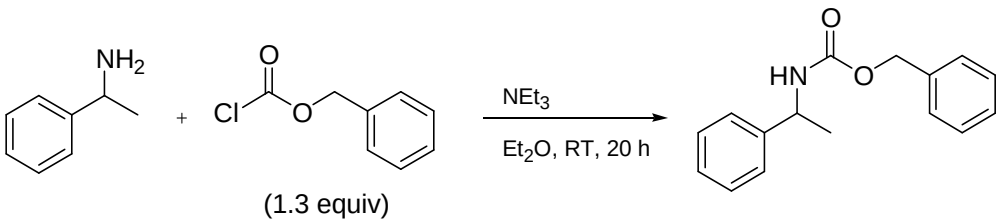


293c **294c**

The procedure of 7.3.1.2 was followed. The product was obtained as a colorless solid.

Chemical Formula	$C_{16}H_{12}F_3NO_2$ (307.27 g/mol)
Purification	bulb-to-bulb distillation (120-125 °C, $1.3 \cdot 10^{-2}$ mbar)
Yield	778 mg (96%)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 5.32 (s, 2H, OC*H*$_2$), 7.33-7.40 (m, 3H, arom), 7.43-7.47 (m, 2H, arom), 7.72 (d, *J* = 8.2 Hz, 2H, arom), 8.01 (d, *J* = 8.2 Hz, 2H, arom), 8.91 (s, 1H, N=C*H*);
^{13}C-NMR	(125.7 MHz, $CDCl_3$): δ = 69.2 (CO_2CH_2), 123.5 (q, $^1J_{CF}$ = 272.5 Hz, CF_3), 125.9 (q, $^3J_{CF}$ = 3.6 Hz, $(CH)_2CCF_3$)), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 130.4 (CH_{Ar}), 134.9 (q, $^2J_{CF}$ = 32.1 Hz, $(CH)_2CCF_3$), 135.1 (Cq_{Ar}), 136.9 (Cq_{Ar}), 163.2 (NCO_2), 169.1 (*p*-CF_3Ph*C*HN);
Mass	*m/z* (%) (EI) 307 (M, 55), 262 (M-H-CO_2, 16), 238 (M-CF_3, 5), 200 (M-OBn, 17), 173 (M+H-CO_2Bn, 9), 145 (CF_3Ph, 22), 107 (OBn, 91), 91 (CH_2Ph, 100);
HRMS	(ESIpos) calculated for $C_{16}H_{13}F_3NO_2$ (M+H) 308.0892289; found 308.089121;

7.5.1.7. Benzyl-1-phenylethylcarbamate (297)

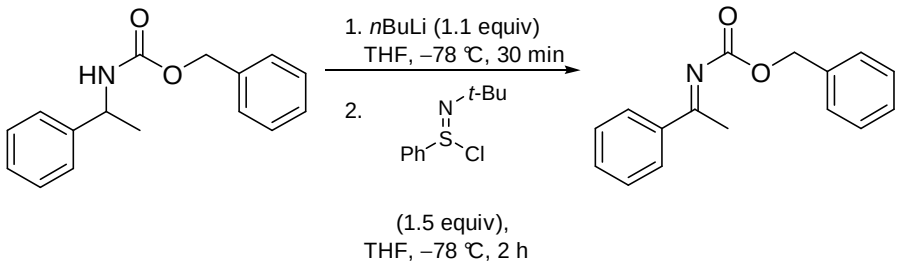


295 **296** **297**

A solution of 0.86 g (7.1 mmol, 1.0 equiv) phenylethylamine and 3 mL of triethylamine in 250 mL of diethyl ether was treated with 1.5 mL (9.2 mmol, 1.3 equiv) of Cbz chloride over 5 min and left stirring for 20 h. 40 mL of a 1 M aqueous HCl was added. The phases were separated, the aqueous layer extracted with ether once, and the combined organic fractions washed with brine and dried over magnesium sulfate. After column chromatographical purification the product was obtained as a colorless solid. The ^{1}H-NMR was in agreement with the literature.[201]

Chemical Formula	$C_{16}H_{17}NO_2$ (255.31 g/mol)
Purification	column chromatography on silica, eluting with ethyl acetate/Hex 20/80, v/v
Yield	1.44 g (79%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.48 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 4.78-4.92 (m, 1H, C*H*NH), 4.96-5.04 (m, 1H, CHN*H*), 5.05 (d, *J* = 12.2 Hz, 1H, C*H*$_A$CH$_B$O), 5.12 (d, *J* = 12.2 Hz, 1H, CH$_A$C*H*$_B$O), 7.16-7.46 (m, 10H, arom);

7.5.1.8. Benzyl-1-phenylethylidenecarbamate (299)



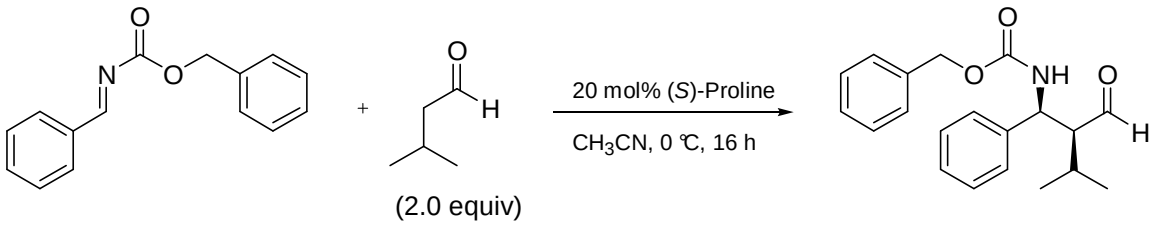
297 **298** **299**

The product was obtained following a literature known procedure.[178] 198.3 mg (0.78 mmol) of benzyl-1-phenylethylcarbamate were dissolved in 4 mL dry tetrahydrofuran and cooled to –78 °C. 0.35 mL of a 2.5 M solution of BuLi in hexane (0.87 mmol, 1.1 equiv) where added within five min, and the mixture left stirring for 30 min. After that time, a solution of 259 mg (1.32 mmol, 1.5 equiv) of *N*-*tert*-butyl benzenesulfinimidoyl chloride in tetrahydrofuran was added portion wise at –78 °C and stirred for an additional 2 h. The reaction was quenched by adding 10 mL of a saturated solution of $NaHCO_3$, extracted with ethyl acetate three times, washed with brine, and dried over Na_2SO_4. The product was obtained as a slightly yellow oil after purification on preparative scale TLC. The ^{1}H-NMR was in agreement with the data published.

Chemical Formula	$C_{15}H_{15}NO_2$ (253.30 g/mol)
TLC	R_f = 0.38 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained orange with anisaldehyde
Purification	preparative scale TLC on silica, eluting with ethyl acetate/Hex 25/75, v/v
Yield	123 mg (62%, Lit.[178] 97%)
^{1}H-NMR	(400 MHz, $CDCl_3$): δ = 2.37 (s, 3H, C*H*$_3$), 5.30 (s, 2H, OC*H*$_2$), 7.30-7.46 (m, 8H, arom), 7.88 (d, *J* = 7.5 Hz, 2H, arom);

7.5.2. Products of the Mannich reaction

7.5.2.1. Benzyl-(1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutylcarbamate (300a)



294a **300a**

The reaction was performed according to 7.3.2.2, but with a different workup: The solution was poured into water and extracted with dichloromethane (3x). The combined organic fractions were washed with brine, dried over magnesium sulfate, and the solvent removed on a rotary evaporator. The product was obtained as a colorless oil. The product was obtained as a colorless solid after column chromatographical purification.

Chemical Formula	$C_{20}H_{23}NO_3$ (325.40 g/mol)
TLC	R_f = 0.35 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue-green with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)
Yield	94.5 mg (57%)
Diastereomeric ratio	49:1
Enantiomeric ratio	90.5:9.5
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –46.1 (*c* = 0.91, $CHCl_3$)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 1.13 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 2.06-2.16 (m, 1H, C*H*$(CH_3)_2$), 2.50-2.56 (m, C*H*COH), 5.03 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$H$_B$), 5.10 (d, *J* = 12.2 Hz, 1H, OCH$_A$*H*$_B$), 5.16 (dd, *J* = 8.2 Hz, 1H, C*H*NH), 5.36 (d, *J* = 8.4 Hz, 1H, N*H*), 7.21-7.37 (m, 10H, arom), 9.51 (d, *J* = 3.5 Hz, 1H, C*H*O);

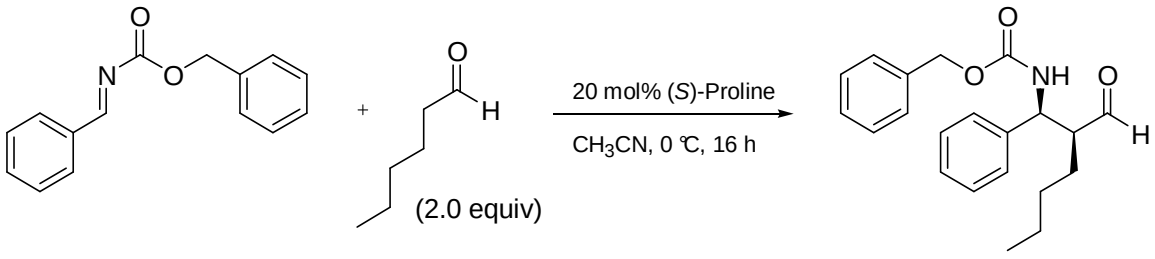
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 19.0 (*C*H(CH_3)$_2$), 21.2 (*C*H_3), 27.0 (*C*H_3), 54.0 (*C*HNH), 61.8 (*C*HCHO), 67.0 (O*C*H_2), 127.3 (*C*H_{Ar}), 128.1 (*C*H_{Ar}), 128.2 (*C*H_{Ar}), 128.2 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.9 (*C*H_{Ar}), 136.2 (*C*q$_{Ar}$), 139.4 (*C*q$_{Ar}$), 155.5 (*C*O_2), 204.7 (*C*HO);

Mass *m/z* (%) (EI) 240 (M-C_5H_9O, 37), 196 (240-CO_2, 28), 91 (CH_2Ph, 100), 77 (Ph, 3);

HRMS (ESIpos) calculated for $C_{20}H_{23}NNaO_3$ (M+Na) 348.157011; found 348.156691;

HPLC τ_R 33.80 min (minor enantiomer)
τ_R 53.78 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.5.2.2. Benzyl-(1*S*,2*S*)-2-formyl-1-phenylhexylcarbamate (300b)



294a **300b**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula $C_{21}H_{25}NO_3$ (339.43 g/mol)

TLC R_f = 0.37 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)

Yield 94.5 mg (57%)

Diastereomeric ratio 19:1

Enantiomeric ratio >98:2

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.0 Hz, 3H, C*H*$_3$), 1.19-1.35 (m, 4H), 1.44-1.53 (m, 1H), 1.64-1.73 (m, 1H), 2.72 (m, 1H, C*H*CHO), 5.04 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$H$_B$Ph), 5.04-5.12 (m, 1H, C*H*NH), 5.10 (d, *J* = 12.2 Hz, 1H, OCH$_A$*H*$_B$Ph), 5.52 (t, *J* = 8.4 Hz, 1H, CHN*H*), 7.20-7.24 (m, 2H, arom), 7.24-7.29 (m, 2H, arom), 7.29-7.37 (m, 6H, arom), 9.56 (s, 1H, C*H*O);

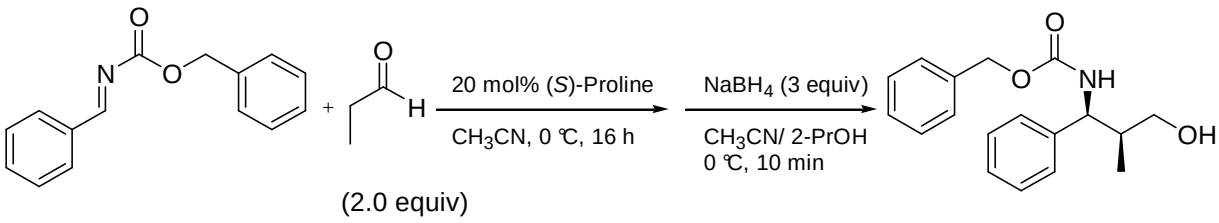
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 13.8 (*C*H$_3$), 22.6 (*C*H$_2$), 25.5 (*C*H$_2$), 29.5 (*C*H$_2$), 55.3 (*C*HNH), 56.4 (*C*HCHO), 67.1 (O*C*H$_2$), 127.0 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 136.2 (*C*q$_{Ar}$), 139.2 (*C*q$_{Ar}$), 155.6 (NH*C*O$_2$), 203.7 (*C*HO);

Mass *m/z* (%) (EI) 240 (M-C$_6$H$_{11}$O, 26), 196 (240-CO$_2$, 25), 91 (CH$_2$Ph, 100), 77 (Ph, 3);

HRMS (ESIpos) calculated for $C_{21}H_{25}NNaO_3$ (M+Na) 362.172664; found 362.172084;

HPLC τ_R 16.45 min (minor enantiomer)
τ_R 20.02 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.5.2.3. Benzyl-(1*S*,2*S*)-3-hydroxy-2-methyl-1-phenylpropylcarbamate (329)



294a **329**

The reaction was performed according to 7.5.2.1. After the Mannich reaction was finished, 2-3 mL of 2-propanol were added to the solution, followed by 59 mg (1.5 mmol, 3 equiv) of $NaBH_4$. The solution was stirred for 10 min, then 5 mL of water were added and the mixture extracted 3 times with dichloromethane. The combined organic layers were washed with brine, dried over anhydrous magnesium sulfate, and the solvent was evaporated. The crude mixture was purified by flash column chromatography on silica gel, eluting with 20/80 - 50/50 ethyl acetate/hexanes, to yield 47.6 mg of a colorless solid.

Chemical Formula	$C_{18}H_{21}NO_3$ (299.36 g/mol)
TLC	R_f = 0.23 (SiO_2, ethyl acetate/hexane 50/50 v/v), stained with vanillin
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 – 50/50 v/v)
Yield	47.6 mg (33% over two steps)
Diastereomeric ratio	14:1
Enantiomeric ratio	89:11
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = 0.77 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 2.12-2.26 (m, 1H, C*H*CH$_3$), 2.40 (bs, 1H, O*H*), 3.36-3.52 (m, 2H, C*H*$_2$OH), 4.94-5.04 (m, 1H, C*H*NH) , 5.06 (d, *J* = 12.3 Hz, 1H, OC*H*$_A$H$_B$), 5.12 (d, *J* = 12.3 Hz, 1H, OCH$_A$*H*$_B$), 5.54 (d, *J* = 9.1 Hz, CHN*H*), 7.21-7.36 (m, 10H, arom);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 11.3 (*C*H$_3$), 40.7 (*C*H$_2$CH$_2$OH), 55.7 (*C*HNH), 64.9 (CH$_2$*C*H$_2$OH), 67.2 (O*C*H$_2$), 126.6 (*C*H$_{Ar}$), 127.2

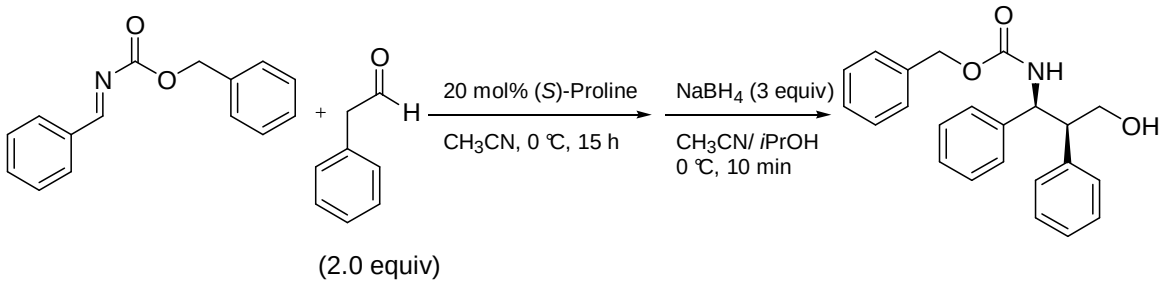
(CH_{Ar}), 128.2 (CH_{Ar}), 128.3 (CH_{Ar}), 128.4 (CH_{Ar}), 128.6 (CH_{Ar}), 136.3 (Cq_{Ar}), 140.0 (Cq_{Ar}), 156.8 ($NHCO_2$);

Mass *m/z* (%) (EI) 299 (M, 1), 240 (M-C_3H_7O, 35), 196 (240-CO_2, 25), 91 (CH_2Ph, 100), 77 (Ph, 3);

HRMS (ESIpos) calculated for $C_{18}H_{21}NNaO_3$ (M+Na) 322.141365; found 322.141426;

HPLC τ_R 23.10 min (major enantiomer)
τ_R 27.52 min (minor enantiomer)
(IA, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.5.2.4. Benzyl-(1*S*,2*S*)-3-hydroxy-1,2-diphenylpropylcarbamate (330)



(2.0 equiv)

294a **330**

The reaction was performed according to 0. The product was obtained as a colorless solid.

Chemical Formula $C_{23}H_{23}NO_3$ (361.43 g/mol)

TLC R_f = 0.34 (SiO_2, methanol/dichloromethane 2/98 v/v), stained yellow-green with vanillin

Purification flash column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 – 50/50 v/v)

Yield 87.5 mg (49%, only major isomer)

Diastereomeric ratio 8.8:1

Enantiomeric ratio >99:1

Optical rotation $[\alpha]_D^{20}$ –11.9 (*c* = 0.91, $CHCl_3$)

Melting point 146-148 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.68 (s, 1H, O*H*), 3.13-3.20 (m, 1H, C*H*CH_2OH), 3.70 (dd, *J* = 11.1, 5.7 Hz, 1H, CH_AH_BOH), 3.78-3.86 (m, 1H, CH_AH_BOH), 5.02 (d, *J* = 12.4 Hz, 1H, OCH_AH_BPh), 5.07 (d, *J* = 12.4 Hz, 1H, OCH_AH_BPh), 5.24-5.31 (m, 1H, C*H*NH), 5.33 (d, *J* = 8.3 Hz, 1H, CHN*H*), 6.90-7.08 (m, 4H, arom), 7.19-7.37 (m, 11H, arom);

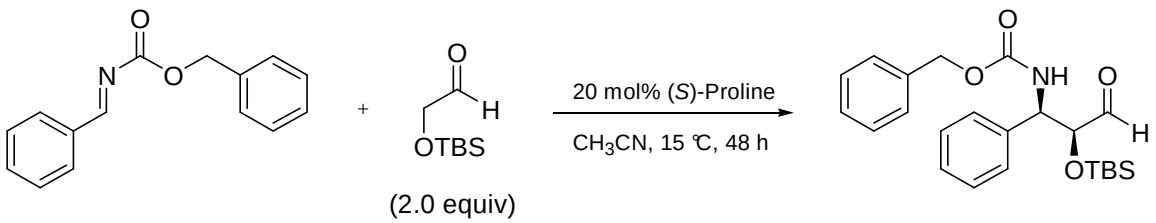
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 54.0 (*C*HCH_2OH), 55.6 (*C*HNH), 63.3 (CH*C*H_2OH), 67.1 (O*C*H_2), 126.8 (*C*H_{Ar}), 127.4 (*C*H_{Ar}), 128.1 (*C*H_{Ar}), 128.2 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.9 (*C*H_{Ar}), 136.2 (*C*q_{Ar}), 137.5 (*C*q_{Ar}), 140.2 (*C*q_{Ar}), 156.4 (N*C*O_2);

Mass *m/z* (%) (EI) 240 (M-C_8H_9O, 45), 196 (240-CO_2, 28), 121 (M-240, 3), 104 (121-OH, 17), 91 (CH_2Ph, 100), 77 (Ph, 8);

HRMS (CI) calculated for $C_{23}H_{24}NO_3$ (M+H) 362.175617; found 362.175304;

HPLC τ_R 34.15 min (major enantiomer)
τ_R 45.29 min (minor enantiomer)
(IA, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.5.2.5. Benzyl-(1*R*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylpropyl-carbamate (300e)

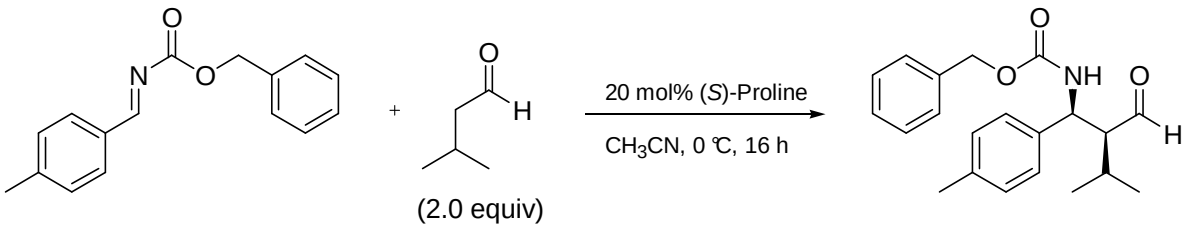


294a **300e**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless oil.

Chemical Formula	$C_{23}H_{31}NO_4Si$ (413.58 g/mol)
TLC	R_f = 0.34 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 to 30/70 v/v)
Yield	116.8 mg (57%)
Diastereomeric ratio	39:1
Enantiomeric ratio	>99:1
Optical rotation	$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –11.3 (*c* = 2.41, $CHCl_3$)
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = –0.30 (s, 3H, Si(CH_3)$_A$(CH_3)$_B$), –0.13 (s, 3H, Si(CH_3)$_A$(CH_3)$_B$), 0.80 (s, 9H, C(CH_3)$_3$), 4.20 (m, 1H, C*H*COH), 5.07 (s, 2H, OCH_2), 5.23 (d, *J* = 9.0 Hz, 1H, C*H*NH), 5.61 (d, *J* = 8.0 Hz, 1H, CHN*H*), 7.21-7.36 (m, 10H, arom), 9.68 (d, *J* = 1.0 Hz, 1H, C*H*NH);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = –5.6 (Si(*C*H_3)$_A$(CH_3)$_B$), –5.2 (Si(CH_3)$_A$(*C*H_3)$_B$), 18.3 (Si*C*(CH_3)$_3$), 25.7 (SiC(*C*H_3)$_3$), 56.0 (*C*HNH), 67.4 (*C*H_2O), 81.4 (*C*HCHO), 126.6 (*C*H_{Ar}), 127.9 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 136.2 (*C*q$_{Ar}$), 139.0 (*C*q$_{Ar}$), 155.6 (*C*O_2NH), 201.7 (*C*HO);
Mass	*m/z* (%) (EI) 356 (M-*t*Bu, 2), 240 (M-$C_8H_{17}O_2Si$, 37), 196 (240-CO_2, 31), 91 (CH_2Ph, 100), 77 (Ph, 2);
HRMS	(ESIpos) calculated for $C_{23}H_{31}NNaO_4$ (M+Na) 436.191454; found 436.191958;
HPLC	$\boldsymbol{\tau_R}$ 27.16 min (minor enantiomer) $\boldsymbol{\tau_R}$ 45.97 min (major enantiomer) (IA, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.5.2.6. Benzyl-(1*S*,2*S*)-2-formyl-3-methyl-1-(4-methylphenyl)butylcarbamate (300f)



294b **300f**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula	$C_{21}H_{25}NO_3$ (339.43 g/mol)
TLC	R_f = 0.31 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)
Yield	136.5 mg (81%)
Diastereomeric ratio	29:1
Enantiomeric ratio	91.7:8.3
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –59.9 (*c* = 1.35, $CHCl_3$)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.4 Hz, 3H, C*H*$_3$), 1.11 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 2.05-2.15 (m, 1H, C*H*$(CH_3)_2$), 2.31 (s, 3H, *p*-C*H*$_3$), 2.47-2.54 (m, C*H*COH), 5.02 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$H$_B$), 5.09 (d, *J* = 12.2 Hz, 1H, OCH$_A$*H*$_B$), 5.12 (dd, *J* = 8.4 Hz, 1H, C*H*NH), 5.35 (d, *J* = 8.5 Hz, 1H, N*H*), 7.07-7.16 (m, 4H, arom), 7.26-7.37 (m, 5H, arom), 9.49 (d, *J* = 3.1 Hz, 1H, C*H*O);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 18.9 (*C*H$(CH_3)_2$), 21.1 (Ar*C*H$_3$), 21.2 (*C*H$_3$), 27.1 (*C*H$_3$), 53.7 (*C*HNH), 61.8 (*C*HCOH), 67.0 (O*C*H$_2$), 127.2 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 129.6

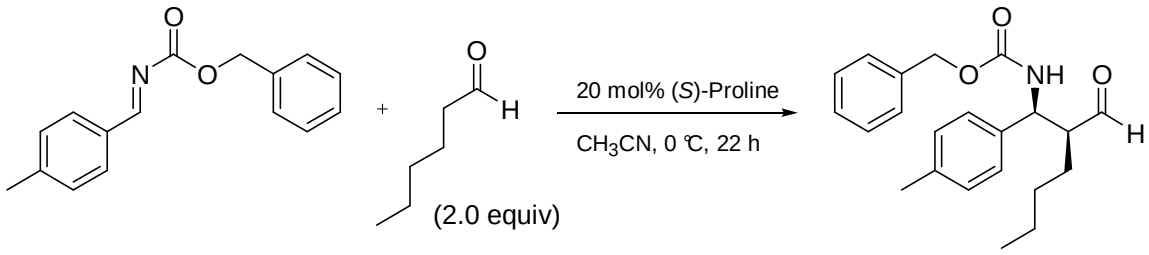
(*C*H$_{Ar}$), 136.2 (*C*q$_{Ar}$), 136.4 (*C*q$_{Ar}$), 137.8 (*C*q$_{Ar}$), 155.5 (*C*O$_2$), 204.9 (*C*HO);

Mass *m/z* (%) (EI) 254 (M-C$_5$H$_9$O, 38), 248 (M-Bn, 2), 210 (254-CO$_2$, 35), 91 (CH$_2$Ph, 100);

HRMS (ESIpos) calculated for $C_{21}H_{25}NNaO_3$ (M+Na) 362.172662; found 362.172456;

HPLC τ_R 24.41 min (minor enantiomer)
τ_R 42.16 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.5.2.7. Benzyl-(1*S*,2*S*)-2-formyl-1-(4-methylphenyl)hexylcarbamate (300g)



294b **300g**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula $C_{22}H_{27}NO_3$ (353.45 g/mol)

TLC R_f = 0.40 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification flash column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 - 15/85 v/v)

Yield 165.2 mg (94%)

Diastereomeric ratio 19:1

Enantiomeric ratio >99:1

Optical rotation $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –22.6 (*c* = 0.9315, $CHCl_3$)

Melting point 99-101 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 6.7 Hz, 3H, CH_2CH_3), 1.20-1.36 (m, 4H), 1.44-1.53 (m, 1H), 1.63-1.73 (m, 1H), 2.32 (s, 3H, CH_3), 2.66-2.74 (m, 1H, C*H*CHO), 4.98-5.07 (m, 1H, C*H*NH), 5.05 (d, *J* = 12.1 Hz, 1H, OCH_AH_B), 5.10 (d, *J* = 12.1 Hz, 1H, OCH_AH_B), 5.40 (d, *J* = 7.7 Hz, 1H, N*H*), 7.06-7.16 (m, 4H, arom), 7.27-7.38 (m, 5H, arom), 9.56 (s, 1H, CHO);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 13.8 (CH_3), 21.1 (CH_2), 22.6 (CH_2), 25.7 (CH_2), 29.5 (CH_2), 55.1 (*C*HNH), 56.4 (*C*HCOH), 67.1 (OCH_2), 126.9 (CH_{Ar}), 128.2 (CH_{Ar}), 128.2 (CH_{Ar}), 128.6 (CH_{Ar}), 129.5 (CH_{Ar}), 136.2 (Cq_{Ar}), 137.7 (Cq_{Ar}), 155.6 ($NHCO_2$), 203.9 (*C*HO);

Mass *m/z* (%) (EI) 254 (M-$C_6H_{11}O$, 44), 210 (254-CO_2), 91 (CH_2Ph, 100);

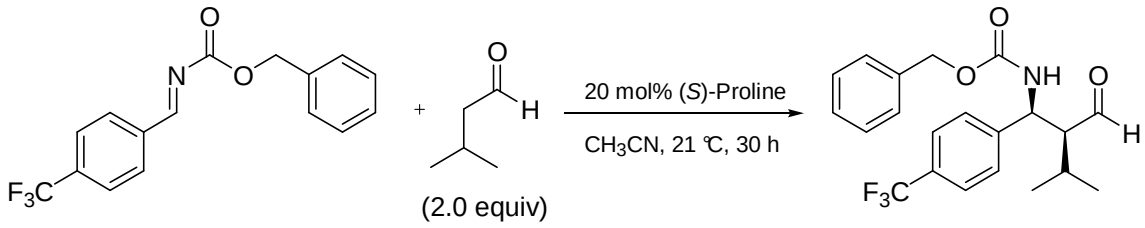
HRMS (ESIpos) calculated for $C_{22}H_{27}NNaO_3$ (M+Na) 376.188310; found 376.188569;

HPLC

$\boldsymbol{\tau_R}$	17.24 min	(minor enantiomer)
$\boldsymbol{\tau_R}$	21.81 min	(major enantiomer)

(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.5.2.8. Benzyl-(1*S*,2*S*)-2-formyl-3-methyl-1-(4-trifluoromethylphenyl)-butyl-carbamate (300h)



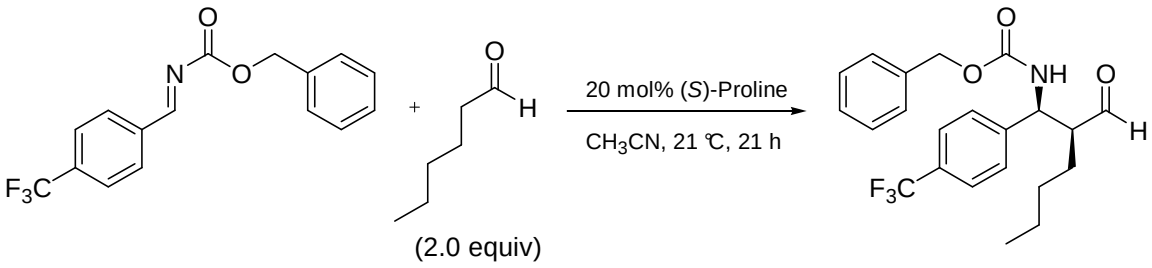
294c **300h**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula	$C_{21}H_{22}F_3NO_3$ (393.40 g/mol)
TLC	R_f = 0.35 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)
Yield	106.0 mg (54%)
Diastereomeric ratio	5:1
Enantiomeric ratio	88:12
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –52 (*c* = 0.07, $CHCl_3$)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 1.02 (d, *J* = 6.6 Hz, 3H, C*H*$_3$), 1.15 (d, *J* = 7.0 Hz, 3H, C*H*$_3$), 2.07-2.18 (m, 1H, C*H*$(CH_3)_2$), 2.56-2.63 (m, C*H*COH), 5.02 (d, *J* = 12.2 Hz, 1H, OC*H*$_A$H$_B$), 5.10 (d, *J* = 12.2 Hz, 1H, OCH$_A$*H*$_B$), 5.19 (dd, *J* = 8.2 Hz, 1H, C*H*NH), 5.49 (d, *J* = 8.3 Hz, 1H, N*H*), 7.24-7.36 (m, 5H, arom), 7.39 (d, *J* = 7.5 Hz, 2H, arom), 7.57 (d, *J* = 7.5 Hz, 2H, arom), 9.52 (d, *J* = 2.5 Hz, 1H, C*H*O);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 18.9 (*C*H$(CH_3)_2$), 21.2 (*C*H$_3$), 27.0 (*C*H$_3$), 53.5 (*C*HNH), 61.4 (*C*HCOH), 67.2 (O*C*H$_2$), 123.9 (q, $^1J_{CF}$ = 272.1 Hz, *C*F$_3$), 125.8 (m, (*C*H)$_2$CCF$_3$), 127.8 (*C*H$_{Ar}$),

	128.2 (*C*H$_{Ar}$), 128.3 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 130.2 (q, $^2J_{CF}$ = 32.4 Hz, (CH)$_2$*C*CF$_3$), 136.0 (*C*q$_{Ar}$), 143.7 (*C*q$_{Ar}$), 155.5 (NH*C*O$_2$), 204.1 (*C*HO);
Mass	*m/z* (%) (EI) 308 (M-C$_5$H$_9$O, 28), 264 (308-CO$_2$, 18), 91 (CH$_2$Ph, 100);
HRMS	(ESIpos) calculated for C$_{21}$H$_{22}$F$_3$NNaO$_3$ (M+Na) 416.144397; found 416.144359
HPLC	τ_R 8.21 min (minor enantiomer) τ_R 12.31 min (major enantiomer) (AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 40/60);

7.5.2.9. Benzyl-(1*S*,2*S*)-2-formyl-1-(4-trifluoromethylphenyl)-hexylcarbamate (300i)



294c **300i**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula	C$_{22}$H$_{24}$F$_3$NO$_3$ (407.43 g/mol)
TLC	R_f = 0.37 (SiO$_2$, ethyl acetate/hexane 25/75 v/v), stained green with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/pentane (10/90 – 20/80 v/v)
Yield	146.0 mg (69%)
Diastereomeric ratio	7:1

Enantiomeric ratio 97:3

Optical rotation $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –13.2(*c* = 0.07, $CHCl_3$)

Melting point 122-124 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.15-1.32 (m, 4H), 1.35-1.44 (m, 1H), 1.58-1.67 (m, 1H), 2.67 (m, 1H, C*H*COH), 4.97 (d, *J* = 12.0 Hz, 1H, OC*H*$_A$H$_B$Ph), 5.03 (d, *J* = 12.0 Hz, 1H, OCH$_A$*H*$_B$Ph), 5.07 (dd, *J* = 6.7 Hz, 1H, C*H*NH), 5.51 (d, *J* = 7.7 Hz, 1H, CHN*H*), 7.21-7.34 (m, 7H, arom), 7.53 (d, *J* = 8.1 Hz, 2H, arom), 9.51 (s, 1H, C*H*O);

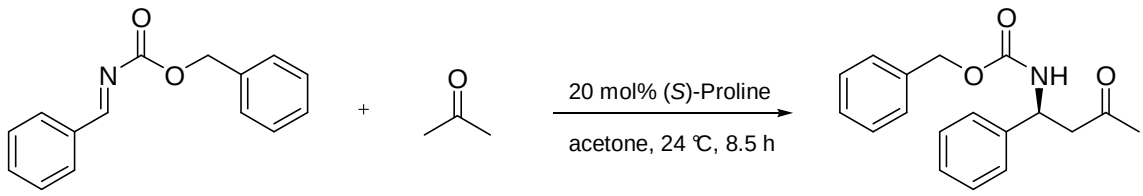
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 13.8 (*C*H$_3$), 22.6 (*C*H$_2$), 25.5 (*C*H$_2$), 29.5 (*C*H$_2$), 54.8 (*C*HNH), 55.9 (*C*HCOH), 67.3 (O*C*H$_2$), 123.9 (q, $^1J_{CF}$ = 272.0 Hz, *C*F$_3$), 125.8 (q, $^3J_{CF}$ = 4.0 Hz, (*C*H)$_2$CCF$_3$), 127.5 (*C*H$_{Ar}$), 128.2 (*C*H$_{Ar}$), 128.4 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 130.1 (q, $^2J_{CF}$ = 32.1 Hz, (CH)$_2$*C*CF$_3$), 136.0 (*C*q$_{Ar}$), 143.4 (*C*q$_{Ar}$), 155.6 (NH*C*O$_2$), 203.3 (*C*HO);

Mass *m/z* (%) (EI) 407 (M, 1), 308 (M-C$_6$H$_{11}$O, 17), 264 (308-CO$_2$, 12), 172 (264-BnCO$_2$-H, 7), 107 (BnCO$_2$-CO, 6), 91 (CH$_2$Ph, 100);

HRMS (EI) calculated for $C_{22}H_{24}F_3NO_3$ (M) 407.170829; found 407.171111;

HPLC
$\boldsymbol{\tau_R}$ 13.55 min (minor enantiomer)
$\boldsymbol{\tau_R}$ 16.35 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.5.2.10. Benzyl-(1*S*)-3-oxo-1-phenylbutylcarbamate (300j)



294a **300j**

The reaction was performed according to 7.5.2.1, albeit at higher temperature to account for the lower reactivity of the ketone. The product was obtained as a colorless solid.

Chemical Formula $C_{18}H_{19}NO_3$ (297.35 g/mol)

TLC R_f = 0.12 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained orange-red with anisaldehyde

Purification column chromatography on silica gel, eluting with ethyl acetate/hexane (30/70 v/v)

Yield 82.4 mg (55%)

Enantiomeric ratio 96:4

Optical rotation $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –12.7 (*c* = 0.565, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.07 (s, 3H, CH_3), 2.91 (dd, *J* = 16.4, 5.4 Hz, 1H, CHCH_AH$_B$COMe), 3.07 (d, *J* = 14.4, 1H, CHCH$_A$$H_B$COMe), 5.06 (d, *J* = 12.3 Hz, 1H, OCH_AH$_B$Ph), 5.10 (d, *J* = 12.3 Hz, 1H, OCH$_A$$H_B$Ph), 5.14 (ddd, *J* = 13.5, 6.5 Hz, 1H, C*H*NH), 5.76 (bs, 1H, CHN*H*), 7.22-7.37 (m, 10H, arom);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 30.7 (*C*H$_3$), 48.9 (*C*H$_2$COCH$_3$), 51.5 (*C*HNH), 66.8 (O*C*H$_2$), 126.3 (*C*H$_{Ar}$), 127.6 (*C*H$_{Ar}$), 128.1 (*C*H$_{Ar}$), 128.5 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 136.4 (*C*q$_{Ar}$), 141.1 (*C*q$_{Ar}$), 155.6 (NH*C*O$_2$), 206.8 (*C*OCH$_3$);

Mass *m/z* (%) (EI) 297 (M, 2), 240 (M-C_3H_5O, 3), 206 (M-CH_2Ph, 31), 196 (240-CO_2, 9), 162 (206-CO_2, 45), 148 (162-NH+H, 12), 120 (30), 107 (C_7H_7O, 13), 91 (CH_2Ph, 100), 77 (Ph, 5);

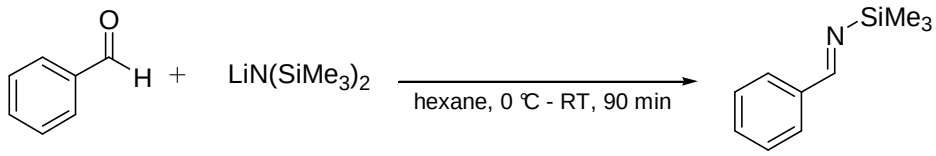
HRMS (ESIpos) calculated for $C_{18}H_{19}NNaO_3$ (M+Na) 320.125709; found 320.125610;

HPLC τ_R 32.60 min (minor enantiomer)
τ_R 46.57 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.6. Mannich reactions of *N*-Fmoc-imines

7.6.1. Preparation of *N*-Fmoc-imines

7.6.1.1. 1,1,1-Trimethyl-*N*-(phenylmethylene)-silanamine (302a)



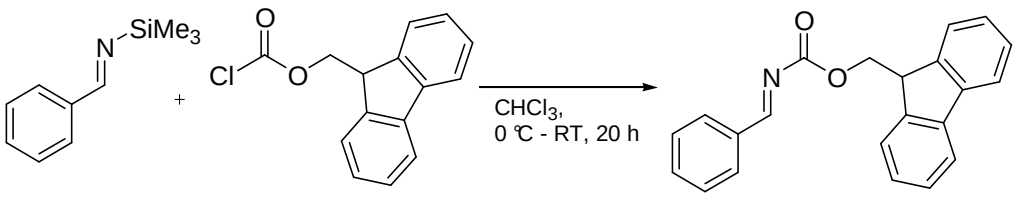
252a **302a**

The product was obtained following a procedure by Hart et al.[180]. A 50 mL two-neck flask was evacuated and flame dried. It was charged with argon and 33 mL of a 1 M solution of lithium hexamethyldisilazane (33 mmol) in hexanes. The solution was cooled to 0 °C, and 3.3 mL (33 mmol) of benzaldehyde was added portion wise over 30 min. The mixture was stirred at 0 °C for 1 h, then the solvent was evaporated. The resulting yellow solution was distilled at 70 °C/ 1 mbar to yield 4.37 g of a yellow oil, which was sensitive to air and moisture.

In an alternative procedure lithium hexamethyldisilazane was freshly prepared by adding 13.2 mL of a 2.5 M solution (33.75 mmol) of *n*-butyllithium in hexanes to a solution of 7 mL (33.8 mmol) of hexamethyldisilazane in dry pentane, kept at 0 °C in a flame-dried 50 mL two-neck flask, over approximately 5 min. The addition of the aldehyde and subsequent treatment were similar to the above described.

Chemical Formula	$C_{10}H_{15}NSi$ (177.32 g/mol)
Purification	distillation (70 °C/1 mbar)
Yield	4.37 g (83%; Lit.[180] 89%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 0.28 (s, 9H, Si(C*H*$_3$)$_3$), 7.42-7.47 (m, 3H, arom), 7.79-7.85 (m, 2H, arom), 9.00 (s, 1H, N=C*H*);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = –1.0 (Si(*C*H$_3$)$_3$), 128.6 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 131.4 (*C*H$_{Ar}$), 139.0 (*C*q$_{Ar}$), 168.6 (N=*C*H);

7.6.1.2. Phenylmethylene-carbamic acid (9H-fluoren-9-yl)methyl ester (269a)



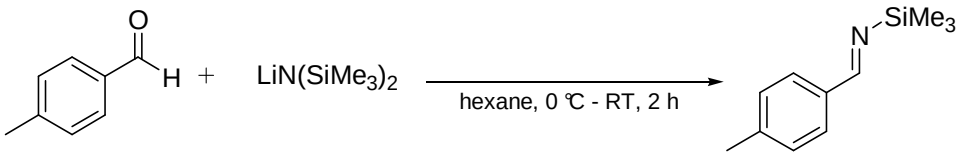
302a **269a**

The compound was prepared by extension of a literature-known procedure.[179] 1.04 g (5.6 mmol) of 1,1,1-trimethyl-N-(phenylmethylene)-silanamine were introduced into a flame-dried Schlenk flask and dissolved in 10 mL of dry chloroform, which was passed through a plug of neutral aluminium oxide immediately before use. The solution was cooled to 0 °C. 1.43 g (5.6 mmol) of 9-fluorenylmethyl chloroformate were dissolved in 5 mL of chloroform treated as above and added drop wise over a period of 20 min. After the addition was complete, the ice bath was removed and the mixture left stirring for 20 h. The solvent was removed on a rotary evaporator and the residue was recrystallized from tetrahydrofuran/pentane to yield 1.28 g of a colorless solid.

Chemical Formula	$C_{22}H_{17}NO_2$ (327.38 g/mol)
Purification	recrystallization from tetrahydrofuran/pentane
Yield	1.28 g (65%)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 4.38 (t, *J* = 7.4 Hz, 1H, C*H*CH_2), 4.57 (d, *J* = 7.4 Hz, 2H, CHC*H*$_2$), 7.33 (td, *J* = 7.6, 1.0 Hz, 2H, arom), 7.42 (t, *J* = 7.6 Hz, 2H, arom), 7.51 (t, *J* = 8.9 Hz, 2H, arom), 7.61 (tt, *J* = 7.4, 1.7 Hz, 1H, arom), 7.67 (d, *J* = 7.7 Hz, 2H, arom), 7.78 (d, *J* = 7.5 Hz, 2H, arom), 7.96 (d, *J* = 7.0 Hz, 2H, arom), 8.90 (s, 1H, C*H*N);
^{13}C-NMR	(100 MHz, $CDCl_3$): δ = 46.4 (*C*HCH_2), 68.7 (O*C*H_2), 119.7 (*C*H_{Ar}), 124.9 (*C*H_{Ar}), 126.8 (*C*H_{Ar}), 127.5 (*C*H_{Ar}), 128.3 (*C*H_{Ar}), 128.6 (*C*H_{Ar}), 130.1 (*C*H_{Ar}), 133.6 (*C*q_{Ar}), 141.0 (*C*q_{Ar}), 143.2 (*C*q_{Ar}), 163.6 (O*C*(O)N), 170.7 (*C*HN);
Mass	*m/z* (%) (EI) 327 (M, 2), 179 (M-$C_8H_6NO_2$, 16), 178 (179-H, 100), 165 (178-CH, 15), 132 ($C_8H_6NO_2$-O, 11), 77 (Ph, 4);

HRMS (ESIpos) calculated for $C_{22}H_{17}NNaO_2$ (M+Na) 350.115150; found 350.115310;

7.6.1.3. 1,1,1-Trimethyl-*N*-(4-methylphenylmethylene)-silanamine (302b)



252j **302b**

The product was obtained following the alternative procedure described in 7.6.1.1. The product was obtained as a yellow oil.

Chemical Formula $C_{11}H_{17}NSi$ (191.34 g/mol)

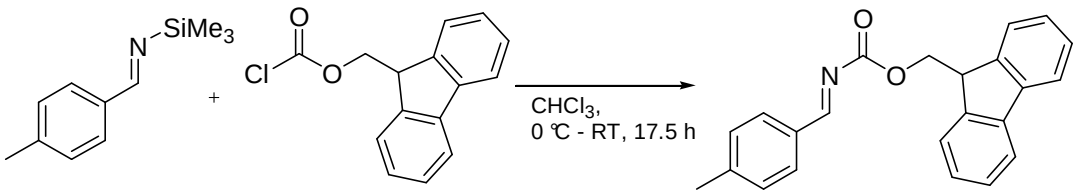
Purification distillation (88-90 °C/1 mbar)

Yield 3.4 g (54%)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.25 (s, 9H, Si(C*H*$_3$)$_3$), 2.39 (s, 3H, C*H*$_3$), 7.23 (d, *J* = 7.9 Hz, 2H, arom), 7.69 (d, *J* = 7.9 Hz, 2H, arom), 8.94 (s, 1H, C*H*=N);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = –1.0 (Si(*C*H$_3$)$_3$), 21.7 (C*C*H$_3$), 126.5 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 136.6 (*C*q$_{Ar}$), 141.8 (*C*q$_{Ar}$), 168.7 (*C*H=N);

7.6.1.4. 4-Methylphenylmethylene-carbamic acid (9H-fluoren-9-yl)methyl ester (269b)



302b **269b**

The procedure of 7.6.1.2 was followed. The product was obtained as a yellow solid. Every attempt at purification (distillation and crystallization) led to product decomposition.

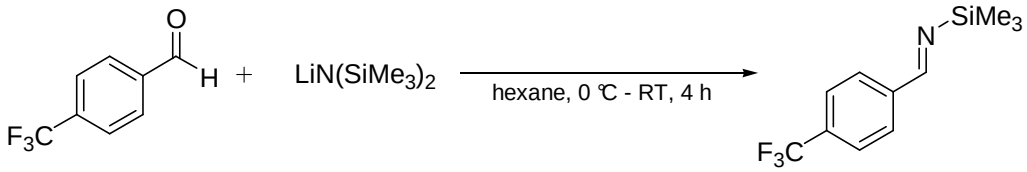
Chemical Formula $C_{23}H_{19}NO_2$ (341.40 g/mol)

Purification not possible

Yield not determined

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.45 (s, 3H, CH_3), 4.38 (t, *J* = 7.4 Hz, 1H, C*H*CH_2O), 4.56 (d, *J* = 7.4 Hz, 2H, CHC*H*$_2$O), 7.33 (t, *J* = 7.5 Hz, 4H, arom), 7.41 (t, *J* = 7.5 Hz, 2H, arom), 7.68 (d, *J* = 7.4 Hz, 2H, arom), 7.78 (d, *J* = 7.5 Hz, 2H, arom), 7.86 (d, *J* = 8.0 Hz, 2H, arom), 8.91 (s, 1H, C*H*=N);

7.6.1.5. 1,1,1-Trimethyl-*N*-(4-trifluoromethylphenylmethylene)-silanamine (302c)



252d **302c**

The product was obtained following the alternative procedure described in 7.6.1.1. The product was obtained as a slightly yellow oil as a 4.5:1 mixture of *E*- and *Z*-isomers.

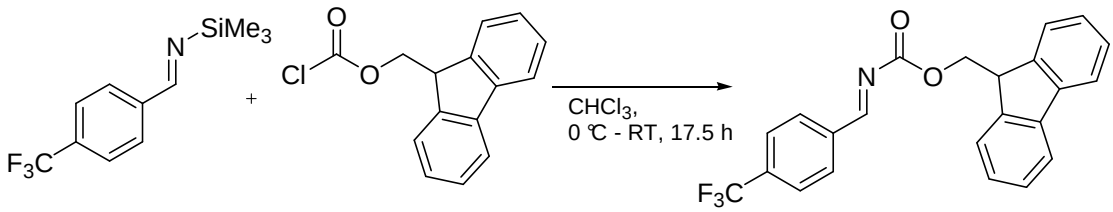
Chemical Formula $C_{11}H_{14}F_3NSi$ (245.32 g/mol)

Purification distillation (105 °C oil bath temperature/1 mbar; Lit.[202] 47-57 °C/0.1 mbar)

Yield 3.64 g (69%; Lit.[202] 55%)

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 0.27 (s, 9H, $Si(CH_3)_3$), 7.69 (d, *J* = 8.4 Hz, 2H, arom), 7.91 (d, *J* = 8.1 Hz, 2H, arom), 9.00 (s, 1H, N=C*H*);

7.6.1.6. 4-Trifluorophenylmethylene-carbamic acid (9H-fluoren-9-yl)methyl ester (269c)



302c **269c**

The procedure of 7.6.1.2 was followed. The product was obtained as a colorless solid.

Chemical Formula $C_{23}H_{16}F_3NO_2$ (395.37 g/mol)

Purification recrystallization from tetrahydrofuran/pentane

Yield 2.17 g (37%)

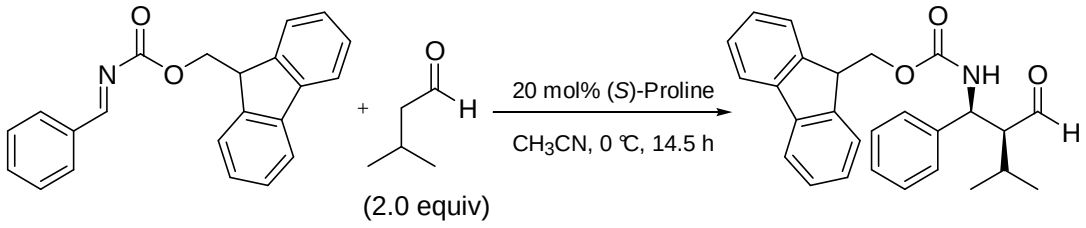
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 4.37 (t, *J* = 7.3 Hz, 1H, C*H*CH_2), 4.60 (d, *J* = 7.3 Hz, 2H, CHC*H*$_2$), 7.34 (td, *J* = 7.7, 0.8 Hz, 2H, arom), 7.43 (t, *J* = 7.5 Hz, 2H, arom), 7.66 (d, *J* = 7.6 Hz, 2H, arom), 7.78 (t, *J* = 7.4 Hz, 4H, arom), 7.67 (d, *J* = 7.7 Hz, 2H, arom), 7.78 (d, *J* = 7.5 Hz, 2H, arom), 8.07 (d, *J* = 8.2 Hz, 2H, arom), 8.86 (s, 1H, C*H*N);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 46.8 (*C*HCH_2), 69.2 (O*C*H_2), 120.1 (*C*H_{Ar}), 123.5 (q, $^1J_{CF}$ = 272.8 Hz, *C*F_3), 125.2 (*C*H_{Ar}), 126.0 (q, $^3J_{CF}$ = 3.7 Hz, (*C*H)$_2$CCF_3)), 127.2 (*C*H_{Ar}), 128.0 (*C*H_{Ar}), 130.4 (*C*H_{Ar}), 135.0 (q, $^2J_{CF}$ = 32.4 Hz, (CH)$_2$*C*CF_3), 136.9 (*C*q_{Ar}),

	141.4 (*C*q$_{Ar}$), 143.4 (*C*q$_{Ar}$), 163.4 (N*C*O$_2$), 168.9 (*p*-CF$_3$Ph*C*HN);
Mass	*m/z* (%) (EI) 395 (M, 3), 200 (M-C$_{14}$H$_{11}$O, 6), 179 (M-C$_9$H$_5$F$_3$NO$_2$, 17), 178 (179-H, 100), 165 (178-CH, 22);
HRMS	(ESIpos) calculated for C$_{23}$H$_{16}$F$_3$NNaO$_2$ (M+Na) 418.102535; found 418.102054;

7.6.2. Products of the Mannich reaction

7.6.2.1. (9H-fluoren-9-yl)methyl-(1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutyl-carbamate (305a)



269a **305a**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula	$C_{27}H_{27}NO_3$ (413.51 g/mol)
TLC	R_f = 0.26 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 – 20/80 v/v)
Yield	124.4 mg (61%)
Diastereomeric ratio	2.8:1
Enantiomeric ratio	93:7
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –51 (*c* = 0.1745, $CHCl_3$)
Melting point	165-167 °C
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = 0.91 (d, *J* = 6.2 Hz, 3H, C*H*$_3$), 1.02 (d, *J* = 6.7 Hz, 3H, C*H*$_3$), 1.90-2.08 (m, 1H, C*H*$(CH_3)_2$), 2.38-2.51 (m, 1H, C*H*CHO), 4.09 (dd, *J* = 6.8, 6.8 Hz, 1H, C*H*-CH_AH_B), 4.31 (dd, *J* = 10.8, 6.5 Hz, 1H, CHC*H*$_A$H$_B$), 4.40 (dd, *J* = 10.8, 6.6 Hz, 1H, CHCH$_A$*H*$_B$), 4.83-5.07 (m, 1H, C*H*NH), 5.07-5.22 (d, *J* = 6.4 Hz, 1H, CHN*H*), 7.03-7.33 (m, 9H, arom),

7.39-7.47 (m, 2H, arom), 7.62-7.69 (m, 2H, arom), 9.42 (s, 1H, C*H*O);

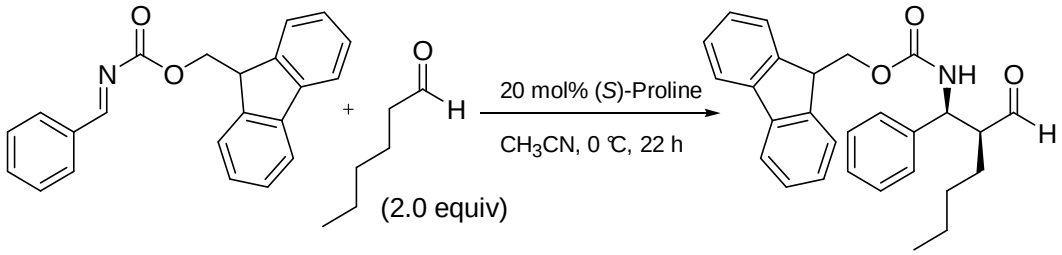
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 18.9 (*C*H(CH_3)$_2$), 21.2 (*C*H_3), 27.1 (*C*H_3), 47.3 (*C*HCH_2), 53.9 (*C*HNH), 61.6 (*C*HCOH), 66.7 (CH*C*H_2O), 120.0 (*C*H_{Ar}), 125.0 (*C*H_{Ar}), 127.1 (*C*H_{Ar}), 127.3 (*C*H_{Ar}), 127.7 (*C*H_{Ar}), 128.1 (*C*H_{Ar}), 128.9 (*C*H_{Ar}), 139.5 (*C*q_{Ar}), 141.3 (*C*q_{Ar}), 143.8 (*C*q_{Ar}), 155.5 (NH*C*O_2), 204.7 (*C*HO);

Mass *m/z* (%) (EI) 328 (M-C_5H_9O, 1), 179 (328-$C_8H_7NO_2$, 25), 178 (179-H, 100), 165 (178-CH, 6);

HRMS (ESIpos) calculated for $C_{27}H_{27}NNaO_3$ (M+Na) 436.188314; found 436.187994;

HPLC τ_R 20.83 min (minor enantiomer)
τ_R 48.17 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.6.2.2. (9H-fluoren-9-yl)methyl-(1*S*,2*S*)-2-formyl-1-phenylhexylcarbamate (305b)



269a **305b**

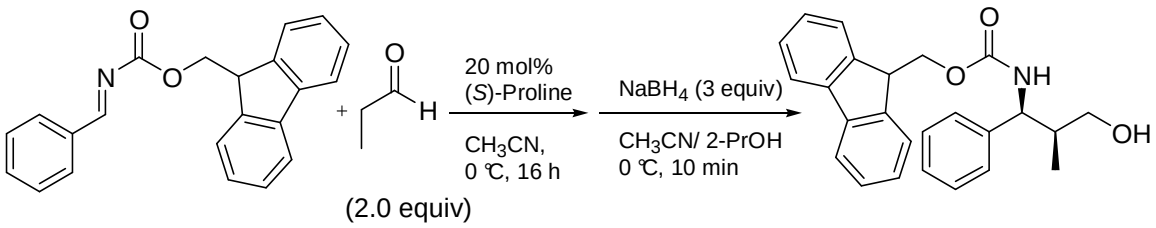
The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula $C_{28}H_{29}NO_3$ (427.53 g/mol)

TLC R_f = 0.30 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 – 20/80 v/v); diastereoisomers separated by column chromatography on silica gel, eluting with methanol/dichloromethane (0.3/99.7 v/v);
Yield	130.6 mg (59%)
Diastereomeric ratio	2.2:1
Enantiomeric ratio	84:16
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –14 (*c* = 0.265, $CHCl_3$)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 0.79 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.12-1.27 (m, 4H), 1.33-1.46 (m, 1H), 1.51-1.67 (m, 1H), 2.55-2.69 (m, 1H, C*H*COH), 4.11 (t, *J* = 6.6 Hz, 1H, C*H*CH$_A$H$_B$O$_2$C), 4.33 (dd, *J* = 10.8, 6.5 Hz, 1H, CHC*H*$_A$H$_B$O$_2$C), 4.39 (dd, *J* = 10.8, 6.8 Hz, 1H, CHCH$_A$*H*$_B$O$_2$C), 4.85-5.01 (m, 1H, C*H*NH), 5.15-5.30 (m, 1H, CHN*H*), 7.06-7.14 (m, 2H, arom), 7.15-7.33 (m, 7H, arom), 7.44 (d, *J* = 7.1 Hz, 2H, arom), 7.66 (dt, *J* = 7.6, 0.8 Hz, 2H, arom), 9.47 (s, 1H, C*H*O);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 13.8 (*C*H$_3$), 22.6 (*C*H$_2$), 25.6 (*C*H$_2$), 29.5 (*C*H$_2$), 47.3 (*C*HCH$_2$O$_2$C), 55.3, 56.2, 66.8 (CH*C*H$_2$O$_2$C), 120.0 (*C*H$_{Ar}$), 125.0 (*C*H$_{Ar}$), 127.0 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 139.1 (*C*q$_{Ar}$), 141.3 (*C*q$_{Ar}$), 143.8 (*C*q$_{Ar}$), 155.6 (*C*O$_2$), 203.8 (*C*HO);
Mass	*m/z* (%) (EI) 328 (M-C$_6$H$_{11}$O, 2), 179 (328-C$_8$H$_7$NO$_2$, 26), 178 (179-H, 100), 165 (178-CH, 7), 91 (CH$_2$Ph, 3);
HRMS	(ESIpos) calculated for $C_{28}H_{29}NNaO_3$ (M+Na) 450.203959; found 450.204333;
HPLC	$\boldsymbol{\tau_R}$ 28.31 min (minor enantiomer) $\boldsymbol{\tau_R}$ 46.69 min (major enantiomer) (AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.6.2.3. (9H-fluoren-9-yl)methyl-(1*S*,2*S*)-3-hydroxy-2-methyl-1-phenylpropyl-carbamate (331)



269a **331**

The reaction was performed according to 7.5.2.3. The product was obtained as a colorless solid.

Chemical Formula	$C_{25}H_{25}NO_3$ (387.47 g/mol)
TLC	R_f = 0.20 (SiO_2, methanol/dichloromethane 2/98 v/v), stained yellow-green with vanillin
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/pentane (25/75 – 55/45 v/v).
Yield	88 mg (45%)
Diastereomeric ratio	2.5:1
Enantiomeric ratio	>99:1
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 0.70 (d, *J* = 6.8 Hz, 3H, C*H*$_3$), 2.19 (m, 1H, C*H*CH$_2$OH), 2.64 (bs, 1H, O*H*), 3.30 (dd, *J* = 9.8, 9.8 Hz, 1H, CHC*H*$_A$CH$_B$OH), 3.44 (dd, *J* = 11.5, 4.8 Hz, 1H, CHCH$_A$C*H*$_B$OH), 4.19 (t, *J* = 6.4 Hz, 1H, C*H*CH$_A$CH$_B$O$_2$C), 4.39 (dd, *J* = 10.2, 6.6 Hz, 1H, CHC*H*$_A$CH$_B$O$_2$C), 4.48 (dd, *J* = 10.6, 7.3 Hz, 1H, CHCH$_A$C*H*$_B$O$_2$C), 4.97-5.03 (m, 1H, C*H*NH), 5.76 (d, *J* = 9.4 Hz, 1H, CHN*H*), 7.19-7.40 (m, 9H, arom), 7.55-7.59 (m, 2H, arom), 7.71-7.76 (m, 2H, arom);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 11.3 (*C*H$_3$), 40.6 (*C*H$_2$CH$_2$OH), 47.4 (*C*HCH$_2$O$_2$C), 55.6 (*C*HNH), 64.9 (CH$_2$*C*H$_2$OH), 66.7 (O*C*H$_2$), 120.0 (*C*H$_{Ar}$), 124.9 (*C*H$_{Ar}$), 125.0 (*C*H$_{Ar}$), 126.6 (*C*H$_{Ar}$), 127.1

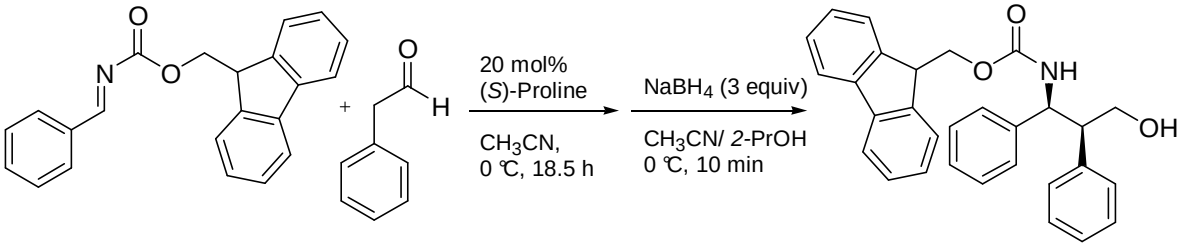
(CH_{Ar}), 127.2 (CH_{Ar}), 127.7 (CH_{Ar}), 128.5 (CH_{Ar}), 140.0 (Cq_{Ar}), 141.3 (Cq_{Ar}), 143.8 (Cq_{Ar}), 143.9 (Cq_{Ar}), 156.8 ($NHCO_2$);

Mass *m/z* (%) (EI) 328 (M-C_3H_7O, 35), 196 (328-C_8H_7NO+H, 4), 179 (196-O, 37), 178 (179-H, 100), 165 (178-CH, 16), 91 (CH_2Ph, 8), 77 (Ph, 2);

HRMS (EI) calculated for $C_{25}H_{25}NO_3$ (M) 387.183440; found 387.183509;

HPLC τ_R 5.71 min (minor enantiomer)
τ_R 7.66 min (major enantiomer)
(50 mm Zorbax XDB-C18, 1 mL/min, CH_3CN/H_2O 60/40, then 150 mm CelluCoat RP 1 mL/min, CH_3CN/H_2O 80/20);

7.6.2.4. (9H-fluoren-9-yl)methyl-(1*S*,2*S*)-3-hydroxy-1,2-diphenylpropyl-carbamate (332)



269a **332**

The reaction was performed according to 7.5.2.3. The product was obtained as a colorless solid.

Chemical Formula $C_{30}H_{27}NO_3$ (449.54 g/mol)

TLC R_f = 0.37 (SiO_2, methanol/dichloromethane 2/98 v/v), stained yellow-green with vanillin

Purification flash column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 – 50/50 v/v)

Yield 152.3 mg (67%, only major isomer)

Diastereomeric ratio not determined

Enantiomeric ratio 99:1

Optical rotation $[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –42.3 (*c* = 0.989, $CHCl_3$)

Melting point 168-171 °C

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 2.19 (bs, 1H, OH), 3.14 (m, 1H, C*H*CH_2OH), 3.59-3.74 (m, 2H, C*H*$_2$OH), 4.15 (t, *J* = 6.4 Hz, 1H, C*H*$CH_AH_BO_2C$), 4.30 (dd, *J* = 10.8, 6.4 Hz, 1H, $CHCH_AH_BO_2C$), 4.57 (dd, *J* = 10.8, 6.3 Hz, 1H, $CHCH_AH$-$_BO_2C$), 5.03 (d, *J* = 9.0 Hz, 1H, CHN*H*), 5.17 (m, 1H, C*H*NH), 6.87-6.94 (m, 2H, arom), 6.98-7.05 (m, 2H, arom), 7.19-7.31 (m, 8H, arom), 7.34-7.41 (m, 2H, arom), 7.42-7.51 (m, 2H, arom), 7.72-7.77 (m, 2H, arom);

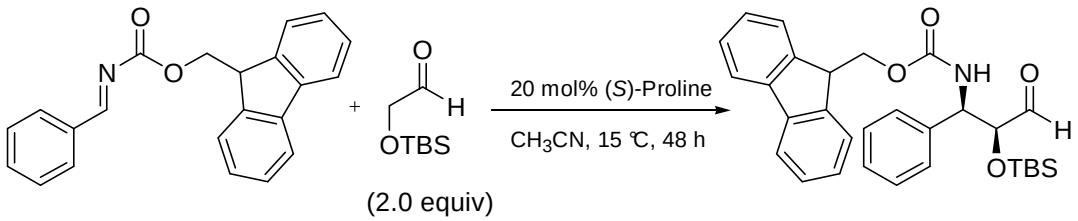
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 47.5 (*C*HCH_2O_2C), 54.2, 55.0, 63.1 (CH_2OH), 66.3 ($CHCH_2O_2C$), 119.9 (*C*H_{Ar}), 120.0 (*C*H_{Ar}), 124.8 (*C*H_{Ar}), 125.1 (*C*H_{Ar}), 126.7 (*C*H_{Ar}), 127.1 (*C*H_{Ar}), 127.1 (*C*H_{Ar}), 127.4 (*C*H_{Ar}), 127.7 (*C*H_{Ar}), 127.8 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 128.5 (*C*H_{Ar}), 129.0 (*C*H_{Ar}), 137.3 (*C*q_{Ar}), 140.1 (*C*q_{Ar}), 141.4 (*C*q_{Ar}), 143.6 (*C*q_{Ar}), 143.9 (*C*q_{Ar}), 156.5 (N*C*O_2);

Mass *m/z* (%) (EI) 328 (M-C_8H_9O, 53), 284 (328-CO_2, 5), 196 ($C_{14}H_{11}O$+H, 9), 179 (196-O-H, 100), 178 (179-H, 83), 165 (178-CH, 32), 104 (C_8H_9O-OH, 34), 91 (CH_2Ph, 6), 77 (Ph, 6);

HRMS (EI) calculated for $C_{30}H_{27}NO_3$ (M) 449.199090; found 449.198900;

HPLC $\boldsymbol{\tau_R}$ 17.37 min (major enantiomer)
$\boldsymbol{\tau_R}$ 19.39 min (minor enantiomer)
(IA, 0.5 mL/min, *i*PrOH/*n*-heptane 40/60);

7.6.2.5. (9H-fluoren-9-yl)methyl-(1*R*,2*S*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylpropylcarbamate (305e)



269a **305e**

The reaction was performed according to 7.5.2.1. The product was obtained as a colorless solid.

Chemical Formula	$C_{30}H_{35}NO_4Si$ (501.69 g/mol)
TLC	R_f = 0.30 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained with anisaldehyde
Purification	flash column chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 to 30/70 v/v)
Yield	153 mg (61%, only major isomer)
Diastereomeric ratio	44:1
Enantiomeric ratio	>99:1
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = –0.28 (s, 3H, Si(C*H*$_3$)$_A$(CH$_3$)$_B$), –0.11 (s, 3H, Si(CH$_3$)$_A$(C*H*$_3$)$_B$), 0.83 (s, 9H, C(C*H*$_3$)$_3$), 4.06-4.28 (m, 2H, C*H*COH and C*H*CH$_2$O), 4.28-4.47 (m, 2H, OC*H*$_2$), 5.20 (d, *J* = 7.8 Hz, 1H, C*H*NH), 5.60 (d, *J* = 8.0 Hz, 1H, N*H*), 7.15-7.59 (m, 11H, arom), 7.66-7.76 (m, 2H, arom), 9.66 (d, *J* = 1.0 Hz, 1H, C*H*O);
^{13}C-NMR	(75.5 MHz, $CDCl_3$, 333 K): δ = –5.5 (Si(*C*H$_3$)$_A$(CH$_3$)$_B$), –5.1 (Si(CH$_3$)$_A$(*C*H$_3$)$_B$), 18.2 (Si*C*(CH$_3$)$_3$), 25.7 (SiC(*C*H$_3$)$_3$), 47.4 (*C*HCH$_2$O$_2$C), 56.4 (*C*HNH), 67.3 (CH*C*H$_2$O$_2$C), 81.3 (*C*H-CHO), 120.0 (*C*H$_{Ar}$), 125.1 (*C*H$_{Ar}$), 126.6 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.7 (*C*H$_{Ar}$), 127.8 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 139.2

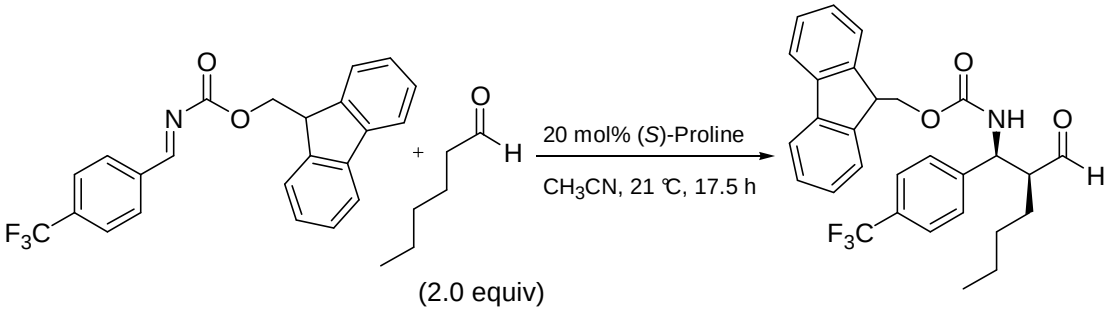
(Cq_{Ar}), 141.4 (Cq_{Ar}), 144.0 (Cq_{Ar}), 155.5 (CO_2NH), 201.3 (*C*HO);

Mass *m/z* (%) (EI) 444 (M-*t*Bu, 5), 328 (M-$C_8H_{17}O_2Si$, 41), 284 (328-CO_2, 7), 205 (M-OTBS-$C_{13}H_9$, 10), 179 ($C_{14}H_{11}$, 100), 178 (179-H, 66), 165 (179-CH_2, 7), 150 (19), 106 (10);

HRMS (ESIpos) calculated for $C_{30}H_{35}NNaO_4Si$ (M+Na) 524.222759; found 524.222828;

HPLC τ_R 15.40 min (minor enantiomer)
τ_R 41.34 min (major enantiomer)
(IA, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.6.2.6. (9H-fluoren-9-yl)methyl-(1*S*,2*S*)-2-formyl-1-(4-trifluoromethylphenyl)-hexylcarbamate (305f)



269c **305f**

The reaction was performed according to 7.5.2.1, albeit at a higher temperature due to the lower reactivity of the imine. The product was obtained as a colorless solid.

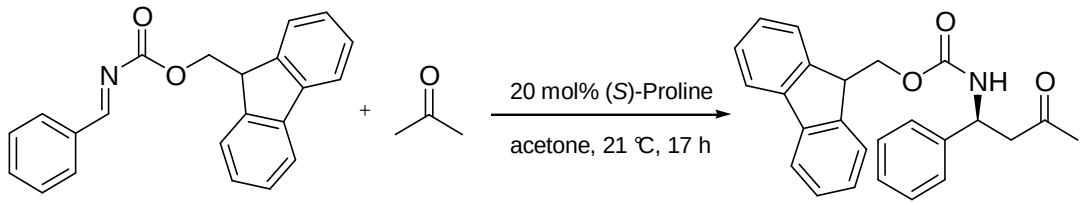
Chemical Formula $C_{29}H_{28}F_3NO_3$ (495.53 g/mol)

TLC R_f = 0.27 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained green with vanillin

Purification flash column chromatography on silica gel, eluting with ethyl acetate/pentane (10/90 – 20/80 v/v); diastereomers separated by flash column chromatography on silica gel, eluting with methanol/dichloromethane (0.5/99.5 v/v);

Yield	140.9 mg (57%)
Diastereomeric ratio	2.2:1
Enantiomeric ratio	92:8
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = 0.86 (t, *J* = 6.8 Hz, 3H, C*H*$_3$), 1.19-1.50 (m, 5H), 1.58-1.75 (m, 1H), 2.62-2.75 (m, 1H, C*H*COH), 4.16 (t, *J* = 6.3 Hz, 1H, C*H*CH_2O_2C), 4.42-4.52 (m, 2H, CHC*H*$_2O_2C$), 4.86-5.15 (m, 1H, C*H*NH), 5.28-5.43 (m, 1H, CHN*H*), 7.21-7.30 (m, 4H, arom), 7.33-7.40 (m, 2H, arom), 7.44-7.62 (m, 4H, arom), 7.69-7.77 (m, 2H, arom), 9.53 (s, 1H, C*H*O);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 13.8 (*C*H_3), 22.6 (*C*H_2), 25.5 (*C*H_2), 29.5 (*C*H_2), 47.3 (*C*HCH_2O_2C), 54.7 (*C*HNH), 55.8 (*C*HCOH), 66.8 (O*C*H_2), 120.0 (*C*H_{Ar}), 123.9 (q, *J* = 272.5 Hz, *C*F_3), 124.9 (*C*H_{Ar}), 125.0 (*C*H_{Ar}), 125.8 (m, (*C*H)$_2$CCF_3), 127.1 (*C*H_{Ar}), 127.4 (*C*H_{Ar}), 127.7 (*C*H_{Ar}), 130.1 (m, (CH)$_2$*C*CF_3), 141.4 (*C*q_{Ar}), 143.3 (*C*q_{Ar}), 143.6 (*C*q_{Ar}), 143.7 (*C*q_{Ar}), 143.8 (*C*q_{Ar}), 155.6 (NH*C*O_2), 203.3 (*C*HO);
Mass	*m/z* (%) (EI) 396 (M-$C_6H_{11}O$, 17), 200 (396-$C_{14}H_{11}O$, 2), 179 (M-$C_{15}H_{17}F_3NO_3$, 23), 178 (179-H, 100), 165 (178-CH, 9);
HRMS	(EI) calculated for $C_{29}H_{28}F_3NNaO_3$ (M+Na) 518.191347; found 518.191110;
HPLC	τ_R 33.84 min (minor enantiomer) τ_R 78.54 min (major enantiomer) (AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 10/90);

7.6.2.7. (9H-fluoren-9-yl)methyl-(1*S*)-3-oxo-1-phenylbutylcarbamate (305g)



269a **305g**

The reaction was performed according to 7.5.2.1, albeit at a higher temperature due to the lower reactivity of the imine. The product was obtained as a colorless solid.

Chemical Formula	$C_{25}H_{23}NO_3$ (385.46 g/mol)
TLC	R_f = 0.71 (SiO_2, ethyl acetate/dichloromethane 20/80 v/v), stained orange with anisaldehyde
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 to 40/60 v/v) and ethyl acetate/dichloromethane (5/95 to 10/90 v/v)
Yield	75.1 mg (38%)
Enantiomeric ratio	93.5:6.5
Optical rotation	$[\boldsymbol{\alpha}]_{\mathbf{D}}^{\mathbf{20}}$ –10.1 (*c* = 1.0, $CHCl_3$)
Melting point	143-144 °C
^{1}H-NMR	(300 MHz, $CDCl_3$, 333 K): δ = 1.97 (s, 3H, C*H*$_3$), 2.80 (dd, *J* = 6.0, 16.6 Hz, 1H, C*H*$_A$H$_B$COMe), 2.94 (dd, *J* = 16.3, 6.3 Hz, 1H, CH$_A$*H*$_B$COMe), 4.10 (t, *J* = 6.7 Hz, 1H, C*H*CH$_2$O), 4.32 (d, *J* = 6.5 Hz, 2H, CHC*H*$_2$O), 5.02 (dd, *J* = 14.0, 6.3 Hz, 1H, C*H*NH), 5.48 (d, *J* = 7.1 Hz, 1H, N*H*), 7.10-7.32 (m, 9H, arom), 7.37-7.49 (m, 2H, arom), 7.61-7.69 (m, 2H, arom);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 30.6 (*C*H$_3$), 47.2 (*C*H), 48.8 (*C*H$_2$COMe), 51.4 (*C*NH), 66.7 (*C*H$_2$O), 120.0 (*C*HAr), 125.0 (*C*HAr), 126.2 (*C*HAr), 127.1 (*C*HAr), 127.6 (*C*HAr), 127.7

(*C*HAr), 128.7 (*C*HAr), 141.3 (*C*qAr), 143.8 (*C*qAr), 143.9 (*C*qAr), 155.7 (O*C*ON), 207.0 (*C*OMe);

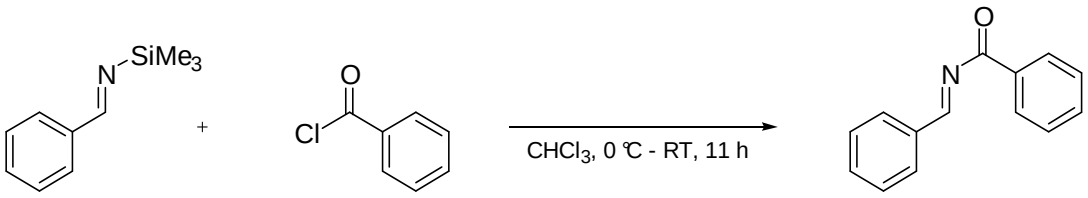
Mass *m/z* (%) (EI) 179 (M-$C_{11}H_{11}NO_3$, 17), 178 (179-H, 100), 165 (178-CH, 8);

HRMS (ESIpos) calculated for $C_{25}H_{23}NNaO_3$ (M+Na) 408.157013; found 408.157433;

HPLC τ_R 54.06 min (minor enantiomer)
τ_R 75.96 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.7. Mannich reactions of an *N*-benzoyl-imine

7.7.1. Preparation of *N*-benzylidenebenzamide (306)



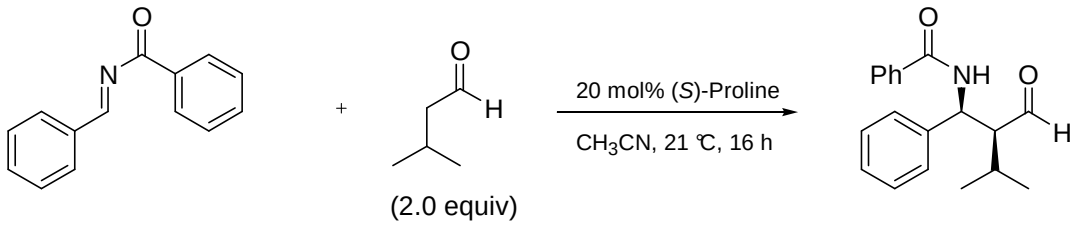
302a **306**

4.1 g (23.1 mmol) of 1,1,1-trimethyl-N-(phenylmethylene)-silanamine were introduced into a flame-dried Schlenk flask and dissolved in 30 mL of dry chloroform, which was passed through a plug of neutral aluminium oxide immediately before use. The solution was cooled to 0 °C. 2.7 mL (23.1 mmol) of benzoyl chloride were dissolved in 25 mL of chloroform treated as above and added dropwise over a period of 30 min. After the addition was completed, the ice bath was removed and the mixture left stirring for 11 h. The solvent was removed on a rotary evaporator and the residue was distilled with a bulb-to-bulb distillation apparatus at 150 °C-160 °C/6.5·10^{-2} mbar to yield 4.1 g (19.6 mmol) of a yellow oil which solidified upon cooling. The compound obtained was found to be very unstable in even slightly acidic media.

Chemical Formula	$C_{14}H_{11}NO$ (209.24 g/mol)
Purification	distillation (150 °C-160 °C/6.5·10^{-2} mbar)
Yield	4.1 g (85%)
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 7.44-7.63 (m, 6H, arom), 7.96-8.00 (m, 2H, arom), 8.14-8.19 (m, 2H, arom), 8.78 (s, 1H, N=C*H*);
^{13}C-NMR	(75.5 MHz, $CDCl_3$): δ = 128.5 (*C*HAr), 129.0 (*C*HAr), 130.0 (*C*HAr), 130.2 (*C*HAr), 133.3 (*C*HAr), 133.4 (*C*HAr), 133.5 (*C*qAr), 134.6 (*C*qAr), 164.5 (*C*H=N), 181.0 (C=O);
Mass	*m/z* (%) (EI) 209 (M, 17), 105 (M-PhCHN, 100), 77 (Ph, 46);
HRMS	(EI) calculated for $C_{14}H_{11}NO$ (M) 209.084067; found 209.083967;

7.7.2. Products of the Mannich reaction

7.7.2.1. *N*-((1*S*,2*S*)-2-formyl-3-methyl-1-phenylbutyl)benzamide (307a)



306 **307a**

The product was obtained as a colorless solid following the procedure of 7.5.2.1, albeit at higher temperature due to the lower reactivity of the imine. To avoid decomposition through acid catalysis, both aldehyde and imine were stirred over K_2CO_3 in acetonitrile for 10 min immediately prior to use.

Chemical Formula	$C_{19}H_{21}NO_2$ (295.38 g/mol)
TLC	R_f = 0.23 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained blue with anisaldehyde
Purification	flash-chromatography on silica gel, eluting with ethyl acetate/hexane (15/85 v/v)
Yield	106.2 mg (73%)
Diastereomeric ratio	3.4:1
Enantiomeric ratio	93:7
^{1}H-NMR	(300 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 6.8 Hz, 3H, *C*H_3), 1.18 (d, *J* = 6.8 Hz, 3H, *C*H_3), 2.06-2.19 (m, 1H, C*H* (CH_3)$_2$), 2.60 (ddd, *J* = 7.1, 7.1, 3.8 Hz, 1H, C*H*CHO), 5.64 (dd, *J* = 7.5, 7.5 Hz, 1H, C*H*NH), 6.90 (d, *J* = 8.0 Hz, 1H, N*H*CO_2), 7.26-7.35 (m, 5H, arom), 7.40-7.51 (m, 3H, arom), 7.75-7.81 (m, 2H, arom), 9.64 (d, 3.8 Hz, 1H, C*H*O);
^{13}C-NMR	(75 MHz, $CDCl_3$): δ = 19.6 (C*H*(CH_3)$_2$), 21.2 (CH(C*H*$_3$)$_2$), 27.0 (CH(C*H*$_3$)$_2$), 52.6 (*C*HNH), 61.5 (*C*HCOH), 127.0 (*C*H_{Ar}), 127.6 (*C*H_{Ar}), 128.1 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 129.0 (*C*H_{Ar}), 131.7

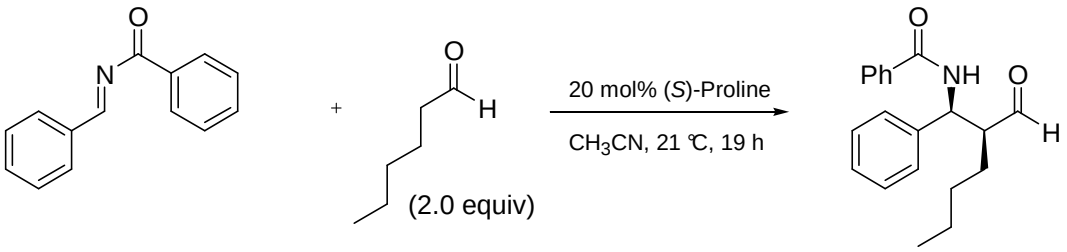
(*C*H$_{Ar}$), 134.2 (*C*q$_{Ar}$), 139.0 (*C*q$_{Ar}$), 166.3 (NH*C*O), 206.0 (*C*HO);

Mass *m/z* (%) (EI) 295 (M, 4), 252 (M-*i*Pr, 5), 210 (M-C_5H_9O, 46), 105 (PhC=O, 100), 77 (Ph, 26);

HRMS (ESIpos) calculated for $C_{19}H_{21}NNaO_2$ (M+Na) 318.146447; found 318.146378;

HPLC τ_R 15.84 min (minor enantiomer)
τ_R 19.53 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 25/75);

7.7.2.2. *N*-((1*S*,2*S*)-2-formyl-1-phenylhexyl)benzamide (307b)



306 **307b**

The procedure of 7.7.2.1 was followed, the product was obtained as a colorless solid.

Chemical Formula $C_{20}H_{23}NO_2$ (309.40 g/mol)

TLC R_f = 0.27 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification flash-chromatography on silica gel, eluting with ethyl acetate/hexane (8/92 - 15/85 v/v)

Yield 105 mg (69%)

Diastereomeric ratio 2.8:1

Enantiomeric ratio 98.8:1.2

Optical rotation $[\alpha]_D^{20}$ +12 (*c* = 0.28, $CHCl_3$)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.9 Hz, 3H, C*H*$_3$), 1.26-1.44 (m, 4H), 1.52-1.60 (m, 1H), 1.72-1.81 (m, 1H), 2.81-2.87 (m, 1H, C*H*COH), 5.53 (dd, *J* = 8.4, 6.2 Hz, 1H, C*H*NH), 7.06 (d, *J* = 8.2 Hz, 1H, CHN*H*), 7.26-7.36 (m, 5H, arom), 7.44 (t, *J* = 7.9 Hz, 2H, arom), 7.51 (tt, *J* = 6.4, 2.2 Hz, 1H, arom), 7.77-7.80 (m, 5H, arom), 9.66 (d, *J* = 2.3 Hz, 1H, C*H*O);

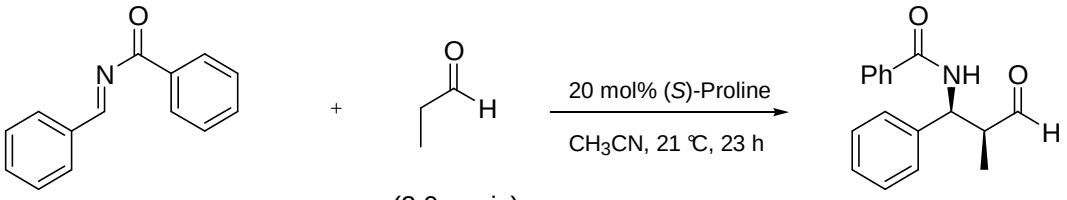
^{13}C-NMR (125 MHz, $CDCl_3$): δ = 13.8 (*C*H$_3$), 22.6 (*C*H$_2$), 26.1 (*C*H$_2$), 29.7 (*C*H$_2$), 53.9 (*C*HCHO), 55.7 (*C*HNH), 127.0 (*C*H$_{Ar}$), 127.4 (*C*H$_{Ar}$), 128.0 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 131.8 (*C*H$_{Ar}$), 134.1 (*C*q$_{Ar}$), 138.8 (*C*q$_{Ar}$), 166.5 (*C*ON), 205.0 (*C*HO);

Mass *m/z* (%) (EI) 309 (M, 4), 280 (M-CHO, 2), 252 (M-Bu, 1), 210 (M-$C_6H_{11}O$, 44), 105 (PhC=O, 100), 77 (Ph, 26);

HRMS (ESIpos) calculated for $C_{20}H_{23}NNaO_2$ (M+Na) 332.162098; found 332.161839;

HPLC τ_R 24.91 min (minor enantiomer)
τ_R 50.47 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.7.2.3. *N*-((1*S*,2*S*)-2-formyl-1-phenylpropyl)benzamide (307c)



(2.0 equiv)

306 **307c**

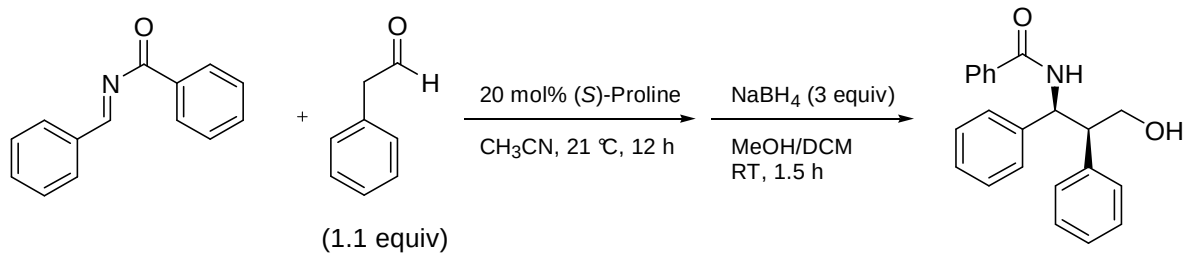
The product was obtained as a colorless solid following the procedure of 7.7.2.1.

Chemical Formula $C_{17}H_{17}NO_2$ (267.32 g/mol)

TLC R_f = 0.11 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained purple with anisaldehyde

Purification	flash-chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 v/v)
Yield	90.1 mg (67%)
Diastereomeric ratio	3.5:1
Enantiomeric ratio	>99:1
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ +22 (*c* = 1.05, $CHCl_3$)
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 1.13 (d, *J* = 7.2 Hz, 3H, C*H*$_3$), 2.93-3.01 (m, 1H, C*H*CH_3), 5.54 (dd, *J* = 8.6, 6.8 Hz, 1H, C*H*NH), 6.88 (d, *J* = 8.2 Hz, 1H, CHN*H*), 7.20-7.32 (m, 5H, arom), 7.37 (t, *J* = 7.8 Hz, 2H, arom), 7.42-7.47 (m, 1H, arom), 7.69-7.73 (m, 2H, arom), 9.68 (s, 1H, C*H*O);
^{13}C-NMR	(100.5 MHz, $CDCl_3$): δ = 10.4 (*C*H_3), 50.7 (*C*HNH), 54.2 (*C*HCOH), 127.0 (*C*H_{Ar}), 127.2 (*C*H_{Ar}), 128.0 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 128.9 (*C*H_{Ar}), 131.8 (*C*H_{Ar}), 134.1 (*C*q_{Ar}), 138.9 (*C*q_{Ar}), 166.8 (*C*ON), 203.9 (*C*OH);
Mass	*m/z* (%) (EI) 267 (M, 6), 238 (M-CHO, 2), 210 (M-C_3H_5O, 28), 105 (PhC=O, 100), 77 (Ph, 32);
HRMS	(ESIpos) calculated for $C_{17}H_{17}NNaO_2$ (M+Na) 290.115151; found 290.114937;
HPLC	$\boldsymbol{\tau_R}$ 28.08 min (minor enantiomer) $\boldsymbol{\tau_R}$ 40.43 min (major enantiomer) (AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.7.2.4. *N*-((1*S*,2*S*)-3-hydroxy-1,3-diphenyl-propyl)benzamide (333)



306 **333**

The Mannich reaction was performed according to 7.7.2.1, but the aldehyde was filtered over neutral alox instead of stirring over K_2CO_3. After the Mannich reaction was complete, the reaction mixture was poured into water, filtered and the solids dissolved in 10 mL methanol/dichloromethane (1/1, v/v). 65 mg of $NaBH_4$ were added and the solution stirred for 1.5 h. HCl was then added until the evolution of hydrogen gas seized. The mixture was diluted with water and extracted with dichloromethane (3x). The combined organic fractions were washed with brine once, dried over Na_2SO_4 and the solvent removed on a rotary evaporator. The product was obtained as a colorless solid after column chromatography.

Chemical Formula	$C_{22}H_{21}NO_2$ (331.41 g/mol)
TLC	R_f = 0.34 (SiO_2, methanol/dichloromethane 2/98 v/v), stained yellow-green with vanillin
Purification	flash column chromatography on silica gel, eluting with methanol/dichloromethane (0.5/99.5 – 1/99 v/v), then preparative scale TLC on silica gel, using methanol/chloroform (5/95 v/v) as mobile phase
Yield	89.5 mg (54%)
Diastereomeric ratio	2:1
Enantiomeric ratio	98:2
Melting point	168-169 °C
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 3.16-3.21 (m, 1H, C*H*CH_AH_BOH), 3.92 (dd, *J* = 11.5, 4.1 Hz, 1H, CHC*H*$_A$$H_BOH$), 4.03 (dd, *J* = 11.5, 3.8 Hz, 1H, $CHCH_AH_B$OH), 5.61 (dd, *J* = 8.5, 8.5 Hz, 1H,

C*H*NH), 7.11-7.24 (m, 10H, arom), 7.32 (d, *J* = 7.7 Hz, 1H, CHN*H*), 7.41 (t, *J* = 7.7 Hz, 2H, arom), 7.50 (t, *J* = 7.4 Hz, 1H, arom), 7.77 (d, *J* = 7.5 Hz, 2H, arom);

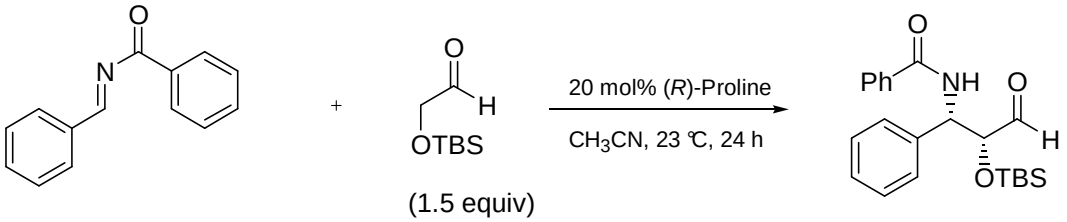
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 52.8 (*C*H), 56.5 (*C*HNH), 64.1 (*C*OH), 126.8 (*C*H_{Ar}), 127.0 (*C*H_{Ar}), 127.2 (*C*H_{Ar}), 127.5 (*C*H_{Ar}), 128.4 (*C*H_{Ar}), 128.6 (*C*H_{Ar}), 128.6 (*C*H_{Ar}), 128.7 (*C*H_{Ar}), 131.8 (*C*H_{Ar}), 134.0 (*C*q_{Ar}), 139.8 (*C*q_{Ar}), 140.5 (*C*q_{Ar}), 167.5 (*C*ON);

Mass *m/z* (%) (EI) 301 (M-CH_3O+H, 1), 211 (M-PhCONH, 13), 210 (M-C_8H_9O, 74), 180 (211-CH_3O, 16), 105 (PhC=O, 100), 77 (Ph, 25);

HRMS (CI) calculated for $C_{22}H_{21}NNaO_2$ (M+Na) 354.146450; found 354.146282;

HPLC τ_R 29.42 min (minor enantiomer)
τ_R 37.06 min (major enantiomer)
(OD-H, 0.5 mL/min, *i*PrOH/*n*-heptane 15/85);

7.7.2.5. *N*-((1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylpropyl)benzamide (307e)



306 **307e**

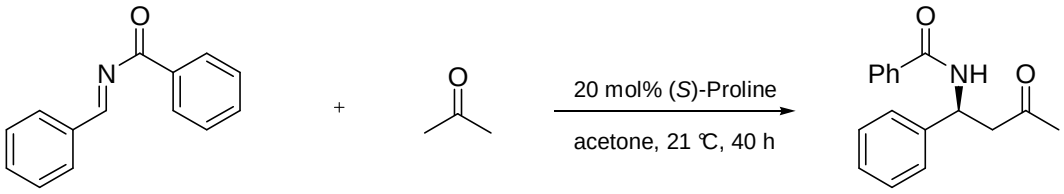
The procedure of 7.7.2.1 was followed; the product was obtained as a colorless solid.

Chemical Formula $C_{22}H_{29}NO_3Si$ (383.56 g/mol)

TLC R_f = 0.24 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained pink with anisaldehyde

Purification	flash-chromatography on silica gel, eluting with ethyl acetate/hexane (15/85, then 25/75 v/v)
Yield	109 mg (57%, only major)
Diastereomeric ratio	5:1
Enantiomeric ratio	98:2
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = –0.27 (s, 3H, Si(C*H*$_3$)$_A$(CH_3)$_B$), –0.06 (s, 3H, Si(CH_3)$_A$(C*H*$_3$)$_B$), 0.85 (s, 9H, C(C*H*$_3$)$_3$), 4.39-4.41 (m, 1H, C*H*COH), 5.72 (dd, *J* = 8.8, 2.1 Hz, 1H, C*H*NH), 7.10 (d, *J* = 8.7 Hz, 1H, CHN*H*), 7.26-7.39 (m, 5H, arom), 7.43-7.57 (m, 3H, arom), 7.76-7.81 (m, 2H, arom), 9.75 (d, *J* = 2.3 Hz, 1H, C*H*O);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = –5.5 (Si(*C*H_3)$_A$(CH_3)$_B$), –4.9 (Si(CH_3)$_A$(*C*H_3)$_B$), 18.3 (Si*C*(CH_3)$_3$), 25.8 (SiC(*C*H_3)$_3$), 54.1 (*C*HNH), 81.4 (*C*HCHO), 126.7 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.9 (*C*H$_{Ar}$), 132.0 (*C*H$_{Ar}$), 134.2 (*C*q$_{Ar}$), 138.8 (*C*q$_{Ar}$), 166.7 (*C*ON), 201.3 (*C*HO);
Mass	*m/z* (%) (EI) 354 (M-CHO, 2), 326 (M-*t*Bu, 7), 324 (354-PhCON, 4), 210 (M-$C_8H_{17}O_2Si$, 44), 205 (25), 105 (PhC=O, 100), 77 (Ph, 20);
HRMS	(ESIpos) calculated for $C_{22}H_{29}NNaO_3Si$ (M+Na) 406.180899; found 406.180891;
HPLC	τ_R 19.04 min (major enantiomer) τ_R 34.93 min (minor enantiomer) (IA, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.7.2.6. (*S*)-*N*-(3-oxo-1-phenylbutyl)benzamide (307f)



306 **307f**

The imine (105.2 mg, 0.5 mmol) was dissolved in 3.4 mL of acetone and added to a suspension of 11.5 mg of (*S*)-proline in 1.6 mL of acetone at a rate of 4.2 µl/min to suppress the addition of a second equivalent of imine to the initial reaction product.

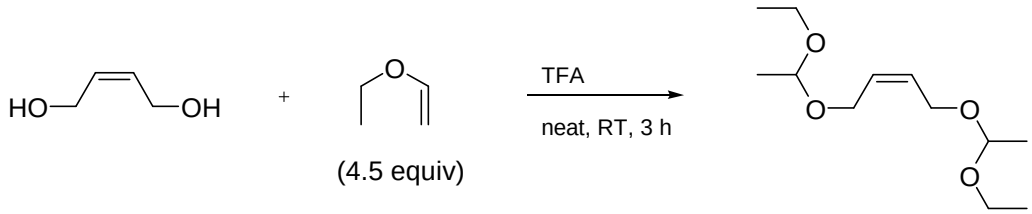
Chemical Formula	$C_{17}H_{17}NO_2$ (267.32 g/mol)
TLC	R_f = 0.07 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained orange with anisaldehyde
Purification	flash-chromatography on silica gel, eluting with ethyl acetate/hexane (20/80 – 34/66 v/v)
Yield	63.2 mg (47%)
Enantiomeric ratio	76:24
^{1}H-NMR	(500 MHz, $CDCl_3$): δ = 2.13 (s, 3H, C*H*$_3$), 3.03 (dd, *J* = 16.6, 5.8 Hz, 1H, C*H*$_A$H$_B$COMe), 3.24 (dd, *J* = 16.7, 5.4 Hz, 1H, CH$_A$*H*$_B$COMe), 5.58-5.63 (ddd, *J* = 8.1, 5.7, 5.7 Hz, 1H, C*H*-CH$_A$H$_B$), 7.24-7.28 (m, 1H, CHN*H*), 7.31-7.37 (m, 4H, arom), 7.40-7.46 (m, 2H, arom), 7.46-7.53 (m, 2H, arom), 7.79-7.83 (m, 2H, arom);
^{13}C-NMR	(125.8 MHz, $CDCl_3$): δ = 31.0 (*C*H$_3$), 47.9 (*C*H$_2$), 50.0 (*C*HNH), 126.4 (*C*H$_{Ar}$), 127.0 (*C*H$_{Ar}$), 127.6 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 131.7 (*C*H$_{Ar}$), 134.2 (*C*q$_{Ar}$), 140.8 (*C*q$_{Ar}$), 166.6 (*C*ON), 208.2 (*C*OMe);
Mass	*m/z* (%) (EI) 267 (M, 4), 224 (M-COMe, 3), 210 (M-C_3H_5O, 3), 162 (M-PhC=O, 68), 105 (PhC=O, 100), 77 (Ph, 34), 43 (COMe, 8);

HRMS (ESIpos) calculated for $C_{17}H_{17}NNaO_2$ (M+Na) 290.115146; found 290.114925;

HPLC τ_R 30.71 min (minor enantiomer)
τ_R 45.36 min (major enantiomer)
(AS-H, 0.5 mL/min, *i*PrOH/*n*-heptane 20/80);

7.7.3. Semisynthesis of paclitaxel

7.7.3.1. 4,11-Dimethyl-3,5,10,12-tetraoxatetradec-7-ene (318)



317 **313** **318**

A modified literature procedure was employed.[203] 877 mg (10 mmol, 1.0 equiv) of *cis*-2-buten-1,4-diol and 3.29 g (45 mmol, 4.5 equiv) of ethylvinylether were treated dropwise with approximately 10 drops of TFA while being vigorously stirred. Stirring was continued for 3 h, then the volatiles were removed on a rotary evaporator, and the residue was purified by column chromatography to give a colorless oil.

Chemical Formula $C_{12}H_{24}O_4$ (232.32 g/mol)

TLC R_f = 0.43 (SiO_2, ethyl acetate/hexane 25/75 v/v), decolorizes $KMnO_4$

Purification flash-chromatography on silica gel, eluting with ethyl acetate/hexane (10/90 v/v)

Yield 2.16 g (93%)

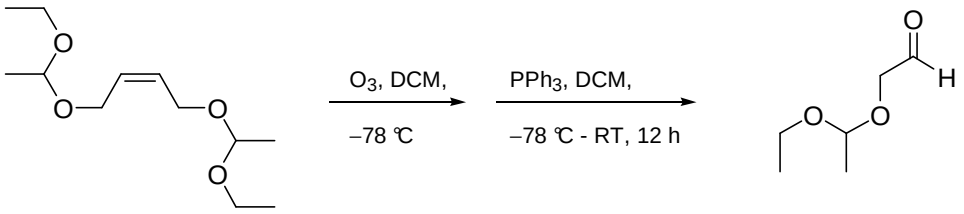
^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.32 (d, *J* = 5.3 Hz, 3H, $CHCH_3$), 3.49 (dq, *J* = 9.4, 7.0 Hz, 1H, $CH_AH_BCH_3$), 3.63 (dq, *J* = 9.3, 7.0 Hz, 1H, $CH_AH_BCH_3$), 4.05-4.13 (m, 1H, $=CHCH_AH_B$), 4.13-4.21 (m, 1H, $=CHCH_AH_B$), 4.73 (q, *J* = 5.3 Hz, 1H, $CHCH_3$), 5.69-5.72 (m, 2H, =CHC);

^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 15.3 (CH_2CH_3), 19.8 ($CHCH_3$), 60.6 ($=CHCH_AH_B$), 60.8 (CH_2CH_3), 99.1 ($CHCH_3$), 129.1 (=CHC);

Mass *m/z* (%) (EI) 159 ($M-C_4H_9O$, 1), 113 ($159-C_2H_6O$, 1), 99 ($113-CH_3+H$, 2), 73 (C_4H_9O, 100), 45 (C_2H_5O, 62);

HRMS (ESIpos) calculated for $C_{12}H_{24}NaO_4$ (M+Na) 255.156678; found 255.156655;

7.7.3.2. 2-(1-Ethoxyethoxy)acetaldehyde (312)



318 **312**

A modified literature procedure was employed.[204] 2.16 g (9.3 mmol) of 4,11-dimethyl-3,5,10,12-tetraoxatetradec-7-ene were dissolved in 94 mL of dichloromethane and cooled to –78 °C. Ozone was bubbled through this solution until the color changes to light blue. The solution was then purged with oxygen until it was decolorized, and a solution of 6.1 g (23.2 mmol, 2.5 equiv) of PPh_3 in 70 mL of dichloromethane was added dropwise over 2 h. After complete addition the cooling bath was removed and the reaction allowed to warm to room temperature. Stirring was continued for an additional 12 h, then the solvent was removed on a rotary evaporator and the product purified by distillation at 1 mbar and 23 °C to yield a clear oil.

Chemical Formula $C_6H_{12}O_3$ (132.16 g/mol)

Purification distillation (1 mbar, 23 °C)

Yield 1.355 g (55% by distillation, 74% by column chromatography)

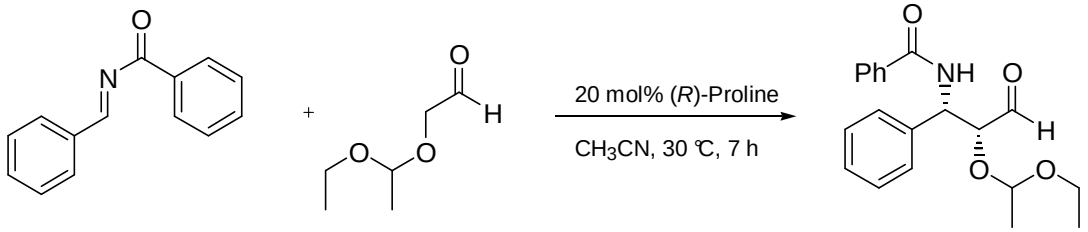
^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.19 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.36 (d, *J* = 5.5 Hz, 3H, $CHCH_3$), 3.52 (dq, *J* = 9.3, 7.2 Hz, 1H, $CH_AH_BCH_3$), 3.65 (dq, *J* = 9.3, 7.2 Hz, 1H, $CH_AH_BCH_3$), 4.11-4.13 (m, 2H, CH_2CHO), 4.81 (q, *J* = 5.3 Hz, 1H, $CHCH_3$), 9.73 (t, *J* = 1.0 Hz, 1H, CHO);

^{13}C-NMR (75.5 MHz, $CDCl_3$): δ = 15.2 (CH_2CH_3), 19.6 ($CHCH_3$), 61.6 (CH_2CH_3), 70.2 (CH_2CHO), 100.1 ($CHCH_3$), 200.8 (CHO);

Mass *m/z* (%) (EI) 117 (M-CH_3, 3), 103 (M-C_2H_5, 3) 89 (117-CH_2, 4), 87 (103-O, 16), 73 (C_4H_9O, 70), 59 (M-C_4H_9O, 15), 45 (C_2H_5O, 100), 43 (C_2H_3O, 44);

HRMS (ESIpos) calculated for $C_6H_{13}O_3$ (M+H) 133.086469; found 133.086217;

7.7.3.3. *N*-((1*S*,2*R*)-2-(1-ethoxyethoxy)-3-oxo-1-phenylpropyl)benzamide (319)



(2.0 equiv)

306 **312** **319**

The procedure of 7.7.2.1 was followed; after column chromatography, the product was obtained as a 1:1 mixture of methyl epimers.

Chemical Formula $C_{20}H_{23}NO_4$ (341.40 g/mol)

TLC R_f = 0.32 (SiO_2, ethyl acetate/hexane 25/75 v/v), stained with anisaldehyde

Purification flash-chromatography on silica gel, eluting with ethyl acetate/hexane (30/70 v/v) and with ethyl acetate/dichloromethane (10/90 v/v)

Yield 180 mg (52%, only major)

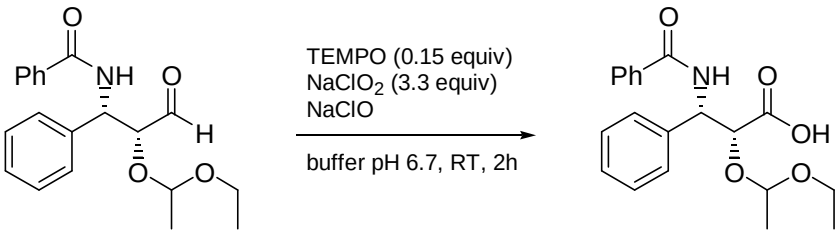
Diastereomeric ratio 8:1 (*syn*:*anti*)

Enantiomeric ratio 99.6:0.4 (determined after oxidation and deprotection, see 7.7.3.5)

^{1}H-NMR **epimer 1** (500 MHz, $CDCl_3$): δ = 1.05 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.27 (d, *J* = 5.3 Hz, 3H, $CHCH_3$), 3.30-3.43 (m, 2H,

	C*H*$_2$CH$_3$), 4.27 (dd, *J* = 1.8, 1.8 Hz, 1H, C*H*CHO), 4.54 (q, *J* = 5.3 Hz, 1H, C*H*CH$_3$), 5.69 (dd, *J* = 9.0, 2.2 Hz, 1H, C*H*NH), 7.11 (d, *J* = 9.3 Hz, 1H, CHN*H*), 7.26-7.31 (m, 1H, arom), 7.32-7.42 (m, 4H, arom), 7.46 (t, *J* = 7.7 Hz, 2H, arom), 7.53 (t, *J* = 7.2 Hz, 1H, arom), 7.79-7.83 (m, 2H, arom), 9.75 (s, 1H, C*H*O); **epimer 2** (500 MHz, CDCl$_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.24 (d, *J* = 5.4 Hz, 3H, CH$_2$C*H*$_3$), 3.03-3.11 (m, 1H, C*H*$_A$H$_B$CH$_3$), 3.36-3.43 (m, 1H, CH$_A$*H*$_B$CH$_3$), 4.50 (m, 1H, C*H*CHO), 4.83 (q, *J* = 5.4 Hz, 1H, C*H*CH$_3$), 5.76 (dd, *J* = 8.6, 2.4 Hz, 1H, C*H*NH), 7.11 (d, *J* = 9.3 Hz, 1H, CHN*H*), 7.26-7.31 (m, 1H, arom), 7.32-7.42 (m, 4H, arom), 7.46 (t, *J* = 7.7 Hz, 2H, arom), 7.53 (t, *J* = 7.2 Hz, 1H, arom), 7.79-7.83 (m, 2H, arom), 9.76 (s, 1H, C*H*O);
^{13}C-NMR	**epimer 1** (125.8 MHz, CDCl$_3$): δ = 15.0 (CH$_2$*C*H$_3$), 20.1 (CH*C*H$_3$), 53.6 (*C*HNH), 61.8 (*C*H$_2$CH$_3$), 83.0 (*C*HCHO), 101.6 (*C*HCH$_3$), 126.7 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 131.8 (*C*q$_{Ar}$), 134.0 (*C*q$_{Ar}$), 138.6 (*C*q$_{Ar}$), 166.6 (*C*O$_2$), 202.1 (*C*HO); **epimer 2** (125.8 MHz, CDCl$_3$): δ = 15.0 (CH$_2$*C*H$_3$), 19.7 (CH*C*H$_3$), 53.0 (*C*HNH), 60.8 (*C*H$_2$CH$_3$), 81.2 (*C*HCHO), 99.7 (*C*HCH$_3$), 126.8 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.8 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 131.8 (*C*q$_{Ar}$), 134.0 (*C*q$_{Ar}$), 138.5 (*C*q$_{Ar}$), 166.8 (*C*O$_2$), 200.6 (*C*HO);
Mass	*m/z* (%) (EI) 240 (6), 210 (M-C$_6$H$_{11}$O$_3$, 71), 105 (PhC=O, 100), 77 (Ph, 20), 73 (C$_4$H$_9$O, 23), 45 (C$_2$H$_5$O, 20);
HRMS	(ESIpos) calculated for C$_{20}$H$_{23}$NNaO$_4$ (M+Na) 364.151931; found 364.152114;

7.7.3.4. (2*R*,3*S*)-3-Benzamido-2-(1-ethoxyethoxy)-3-phenylpropanoic acid (309)



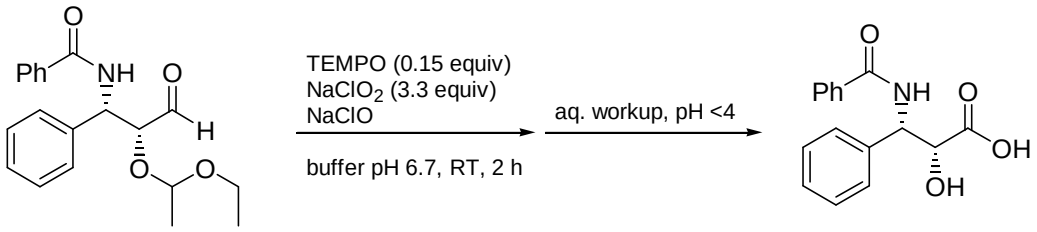
319 **309**

A literature-known synthesis was employed.[183] 20.5 mg (0.06 mmol) of *N*-((1*S*,2*R*)-2-(1-ethoxyethoxy)-3-oxo-1-phenylpropyl)benzamide were dissolved in 0.7 mL of a phosphorous buffer at pH 6.7. 23 mg (0.2 mmol, 3.3 equiv) of $NaClO_2$ (80%) were dissolved in 0.13 mL of water and added together with a solution of 1.4 mg (0.009 mmol, 0.15 equiv) TEMPO in 0.5 mL of acetonitrile. To this solution was added a drop of an aqueous solution of NaClO and the mixture stirred for 2 h. 3 mL water were added and the pH adjusted to 8 with 1 M aqueous NaOH. The mixture was cooled to 10-15 °C before addition of 1.3 mL of a solution of 33 mg Na_2SO_3 in water, precooled to 0 °C. After stirring for 45 min the mixture was washed with diethyl ether once, brought to pH 4.5 by careful (!) addition of aqueous HCl (0.1 M), and extracted three times with ethyl acetate. The combined ethyl acetate-fractions were washed with brine once, dried over magnesium sulfate, and the solvent was removed on a rotary evaporator and under high vacuum. The product was obtained as colorless solid. Note: The product was found to be very sensitive to acid; if the pH was lowered below 4 during the workup the protecting group was removed. The same would also happen if the product was dissolved in chloroform and the solvent was removed on a rotary evaporator at 30 °C.

Chemical Formula	$C_{20}H_{23}NO_5$ (357.40 g/mol)
Purification	The product was directly used in the next step
Yield	16 mg (77%, average of two runs)
Diastereomeric ratio	>20:1 (*syn*:*anti*)
Enantiomeric ratio	99.6:0.4 (determined after deprotection, see 7.7.3.5)
^{1}H-NMR	**epimer 1** (500 MHz, $CDCl_3$): δ = 1.15 (t, *J* = 7.1 Hz, 3H, CH_2CH_3), 1.29 (d, *J* = 5.2 Hz, 3H, $CHCH_3$), 3.43-3.53 (m, 2H,

	C*H*$_2$CH$_3$), 4.51 (d, *J* = 3.4 Hz, 1H, C*H*COOH), 4.66 (q, *J* = 5.1 Hz, 1H, C*H*CH$_3$), 5.74-5.79 (m, 1H, C*H*NH), 7.24-7.31 (m, 1H, arom), 7.32-7.48 (m, 7H, arom and CHN*H*), 7.49-7.55 (m, 1H, arom), 7.81-7.86 (m, 2H, arom); **epimer 2** (500 MHz, CDCl$_3$): δ = 0.96 (t, *J* = 7.1 Hz, 3H, CH$_2$C*H*$_3$), 1.33 (d, *J* = 5.2 Hz, 3H, CHC*H*$_3$), 3.00-3.07 (m, 1H, C*H*$_A$H$_B$CH$_3$), 3.33-3.41 (m, 1H, CH$_A$*H*$_B$CH$_3$), 4.64-4.68 (m, 1H, C*H*COOH), 4.86 (q, *J* = 5.4 Hz, 1H, C*H*CH$_3$), 5.74-5.79 (m, 1H, C*H*NH), 7.24-7.31 (m, 1H, arom), 7.32-7.48 (m, 7H, arom and CHN*H*), 7.49-7.55 (m, 1H, arom), 7.81-7.86 (m, 2H, arom);
^{13}C-NMR	**epimer 1** (125.8 MHz, CDCl$_3$): δ = 15.1 (CH$_2$*C*H$_3$), 19.7 (CH*C*H$_3$), 55.1 (*C*HNH), 62.4 (*C*H$_2$CH$_3$), 76.9 (*C*HCOOH), 101.7 (*C*HCH$_3$), 126.9 (*C*H$_{Ar}$), 127.4 (*C*H$_{Ar}$), 127.9 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 128.7 (*C*H$_{Ar}$), 132.0 (*C*q$_{Ar}$), 133.9 (*C*q$_{Ar}$), 138.4 (*C*q$_{Ar}$), 167.8 (*C*O$_2$), 172.8 (*C*OOH); **epimer 2** (125.8 MHz, CDCl$_3$): δ = 14.3 (CH$_2$*C*H$_3$), 19.6 (CH*C*H$_3$), 55.3 (*C*HNH), 59.8 (*C*H$_2$CH$_3$), 75.8 (*C*HCOOH), 99.3 (*C*HCH$_3$), 126.8 (*C*H$_{Ar}$), 127.1 (*C*H$_{Ar}$), 127.8 (*C*H$_{Ar}$), 128.6 (*C*H$_{Ar}$), 128.8 (*C*H$_{Ar}$), 132.1 (*C*q$_{Ar}$), 134.0 (*C*q$_{Ar}$), 138.8 (*C*q$_{Ar}$), 167.9 (*C*O$_2$), 172.7 (*C*OOH);
HRMS	(ESIpos) calculated for C$_{20}$H$_{23}$NNaO$_5$ (M+Na) 380.146840; found 380.146634;

7.7.3.5. (2*R*,3*S*)-3-Benzamido-2-hydroxy-3-phenylpropanoic acid (320)

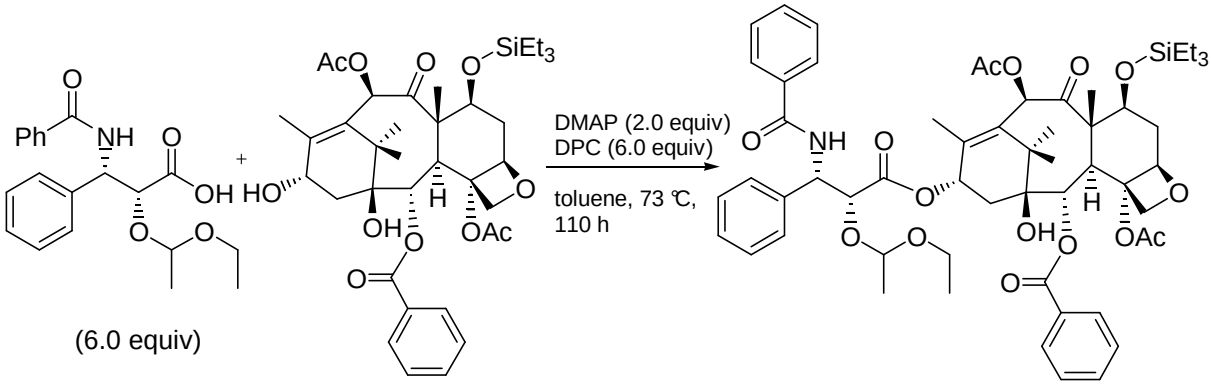


319 **320**

The procedure of 7.7.3.4 was followed, but the solution was acidified to pH < 4 before extraction with ethyl acetate. The product was obtained as a colorless solid. The NMR-data was in agreement with the literature.[205]

Chemical Formula	$C_{16}H_{15}NO_4$ (285.29 g/mol)
Yield	5.45 mg (71%)
Diastereomeric ratio	>20:1 (*syn*:*anti*)
Enantiomeric ratio	99.6:0.4
Optical rotation	$[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{20}}$ –26.9 (*c* = 0.22, EtOH); Lit.[185] $[\boldsymbol{a}]_{\mathbf{D}}^{\mathbf{25}}$ –35.9 (*c* = 0.565, EtOH);
^{1}H-NMR	(500 MHz, DMSO-d6): δ = 4.38 (d, *J* = 3.6 Hz, 1H, C*H*COOH), 5.47 (dd, *J* = 9.0, 4.4 Hz, 1H, C*H*NH), 5.55 (bs, 1H, OH), 7.22-7.27 (m, 1H, arom), 7.30-7.35 (m, 2H, arom), 7.39-7.43 (m, 2H, arom), 7.48-7.52 (m, 2H, arom), 7.54-7.58 (m, 1H, arom), 7.83-7.87 (m, 2H, arom), 8.57 (d, *J* = 8.8 Hz, 1H, CHN*H*), 12.74 (bs, 1H, COO*H*);
HPLC	$\boldsymbol{\tau_R}$ 13.47 min (major enantiomer) $\boldsymbol{\tau_R}$ 21.51 min (minor enantiomer) (AD-H, 0.5 mL/min, *i*PrOH/*n*-heptane /TFA 20/80/0.1);

7.7.3.6. (α*R*,β*S*)-Benzenepropanoic acid, β-(benzoylamino)-α-(1-ethoxyethoxy)-(2a*R*,4*S*,4a*S*,6*R*,9*S*,11*S*,12*S*,12a*R*,12b*S*)-6,12b-bis(acetyloxy)-12-(benzoyloxy)-2a,3,4,4a,5,6,9,10,11,12,12a,12b-dodecahydro-11-hydroxy-4a,8,13,13-tetramethyl-5-oxo-4-[(triethylsilyl)oxy]-7,11-methano-1H-cyclodeca[3,4]benz[1,2-b]oxet-9-yl ester (311)

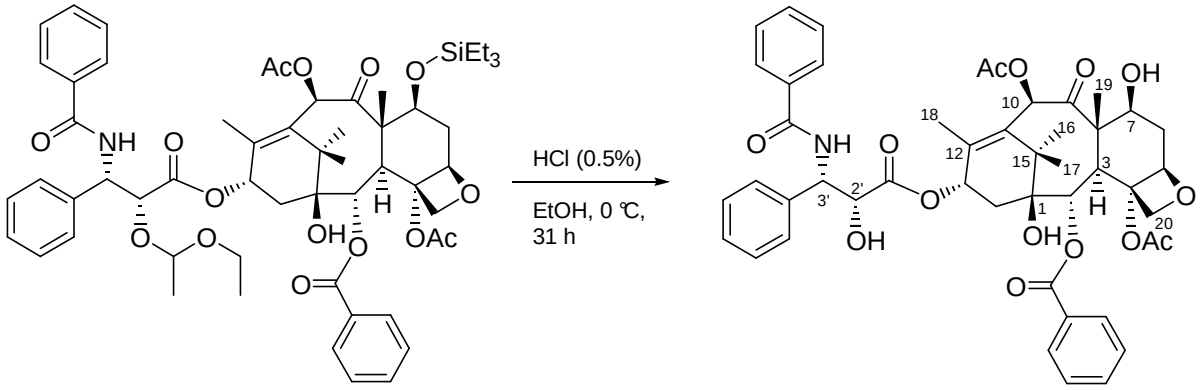


309 **310** **311**

According to the procedure of *Denis et al.*,[181] 8.9 mg (0.0127 mmol, 1.0 equiv) of 7-TES-baccatin III were introduced into a flame-dried, argon-purged flask and dissolved in 0.6 mL dry toluene. 28 mg (0.082 mmol, 6.0 equiv) of (2*R*,3*S*)-3-benzamido-2-(1-ethoxyethoxy)-3-phenylpropanoic acid were added, followed by 17.3 mg (0.08 mmol, 6.0 equiv) of dipyridin-2-yl carbonate (DPC) and 3.4 mg (0.028 mmol, 2.0 equiv) of DMAP. The mixture was then heated at 73 °C for 110 h. After this time, the mixture was diluted with 2 mL ethyl acetate, washed 3 times with saturated aqueous $NaHCO_3$ (3 mL in total), 2 times with water (2 mL), and once with brine. The organic layer was dried over Na_2SO_4 before removal of the solvent. The major impurities were removed by column chromatography to yield the not-pure title compound, which was employed in the next step without further purification. 4.2 mg of 7-TES-baccatin III were recovered (53% conversion).

Chemical Formula	$C_{57}H_{73}NO_{15}Si$ (1040.27 g/mol)
Purification	column chromatography on silica gel, eluting with ethyl acetate/hexane (15/85, then 20/80 v/v)
Yield	n.d.

7.7.3.7. Paclitaxel (taxol) (321)



311 **321**

The deprotection was performed as described by *Denis et al.*[181] 10.18 mg of the material obtained in the previous step were treated with 1 mL of pre-cooled (0 °C) HCl (0.5% in EtOH) and stirred at 0 °C for 31 h. After this time, 5 mL of water were added, and the mixture was extracted with 10 mL of ethyl acetate. The organic layer was washed 5 times with water (12.5 mL in total, 0 °C), twice with brine (5 mL in total), dried over Na_2SO_4, and the solvent removed on a rotary evaporator. The product was purified by column chromatography and preparative-scale HPLC.

Chemical Formula $C_{47}H_{51}NO_{14}$ (853.91 g/mol)

Purification column chromatography on silica gel, eluting with methanol/dichloromethane (2/98, then 3/97 v/v), and preparative-scale HPLC (150 mm YMC, 20 mm internal diameter column packed with YMC Pack ODS-A, 5 µm; eluting with methanol/water 70/30 v/v)

Yield 3.0 mg (59% over two steps, based on 47% conversion, Lit.[181] 71% based on 50% conversion)

^{1}H-NMR (500 MHz, $CDCl_3$): δ = 1.14 (s, 3H, 17-CH_3), 1.24 (s, 3H, 16-CH_3), 1.68 (s, 3H, 19-CH_3), 1.70 (s, 1H, 1-O*H*), 1.79 (d, *J* = 1.4 Hz, 3H, 18-CH_3), 1.88 (ddd, *J* = 14.8, 11.0, 2.4 Hz, 1H, 6-CH_AH_B), 2.24 (s, 3H, OAc), 2.28 (dd, *J* = 15.4, 9.2 Hz, 1H, 14-CH_AH_B), 2.35 (dd, *J* = 15.5, 9.0 Hz, 1H, 14-CH_AH_B), 2.39 (s, 3H, OAc), 2.46 (d, *J* = 4.2 Hz, 1H, 7-O*H*), 2.55 (ddd, *J* = 14.8,

9.7, 6.8 Hz, 1H, 6-CH_AH_B), 3.52 (d, *J* = 5.3 Hz, 1H, 2'-O*H*), 3.79 (d, *J* = 7.1 Hz, 1H, 3-H), 4.19 (dd, *J* = 8.5, 0.9 Hz, 1H, 20-CH_AH_B), 4.31 (bd, *J* = 8.5 Hz, 1H, 20-CH_AH_B), 4.38-4.43 (m, 1H, 7-H), 4.79 (dd, *J* = 5.2, 2.7 Hz, 1H, 2'-H), 4.95 (dd, *J* = 9.6, 2.0 Hz, 1H, 5-H), 5.67 (d, *J* = 7.1 Hz, 1H, 2-H), 5.79 (dd, *J* = 8.8, 2.6 Hz, 1H, 3'-H), 6.23 (dt, *J* = 8.9, 1.4 Hz, 1H, 13-H), 6.26 (s, 1H, 10-H), 6.97 (d, *J* = 8.9 Hz, 1H, N*H*), 7.36 (tt, *J* = 6.7, 1.3 Hz, 1H, arom), 7.39-7.44 (m, 4H, arom), 7.47-7.53 (m, 5H, arom), 7.62 (tt, *J* = 7.0, 1.3 Hz, 1H, arom), 7.73-7.76 (m, 2H, arom), 8.12-8.15 (m, 2H, arom); [assignment of peaks according to *Nicolaou et al.* [206]]

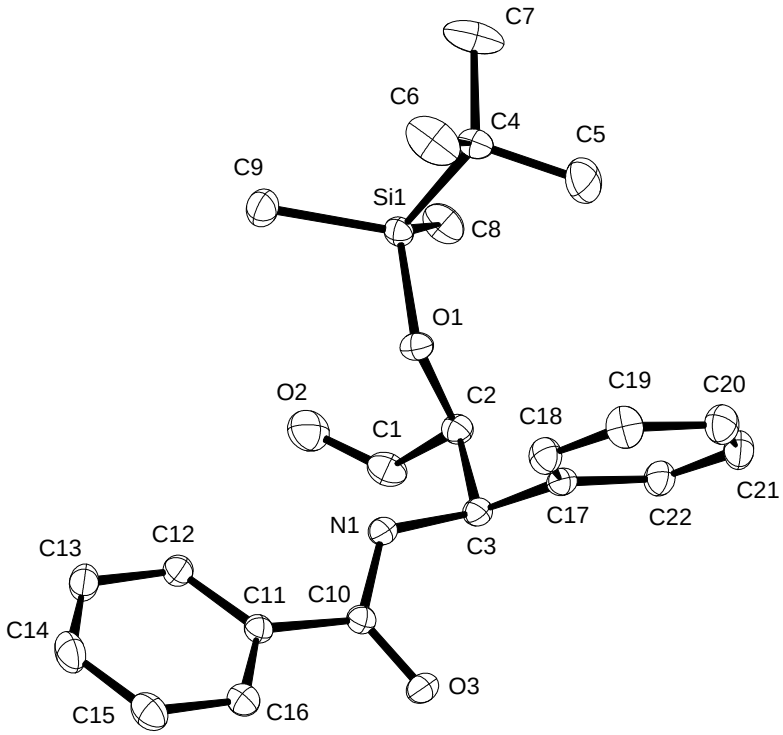
^{13}C-NMR (125.8 MHz, $CDCl_3$): δ = 9.5 (C-19), 14.9 (C-18), 20.9 (10-O_2CCH_3), 21.8 (C-16), 22.7 (4-O_2CCH_3), 26.9 (C-17), 35.6 (C-6), 35.6 (C-14), 43.1 (C-15), 45.6 (C-3), 55.0 (C-3'), 58.6 (C-8), 72.2 (C-7), 72.4 C-13), 73.2 (C-2'), 74.8 (C-2), 75.5 (C-10), 76.5 (C-20), 79.0 (C-1), 81.1 (C-4), 84.4 (C-5), 127.0 (CH_{Ar}), 127.0 (CH_{Ar}), 128.4 (CH_{Ar}), 128.7 (CH_{Ar}), 128.7 (CH_{Ar}), 129.0 (CH_{Ar}), 129.1 (Cq_{Ar}), 130.2 (CH_{Ar}), 132.0 (CH_{Ar}), 133.1 (Cq_{Ar}), 133.5 (CH_{Ar}), 133.8 (C-11), 137.9 (Cq_{Ar}), 142.0 (C-12), 167.0 (*C*=O of 3'-N-Bz), 167.0 (*C*=O of 2-O-Bz), 170.4 (CH_3CO_2 at C-4), 171.3 (CH_3CO_2 at C-10), 172.7 (C-1'), 203.7 (C-9); [assignment of peaks according to *Baker* [207]]

Mass *m/z* (%) (EI) 568 (M-$C_{16}H_{14}NO_4$ [side-chain]-H, 1), 508 (568-HOAc, 1), 446 (568-PhCOOH, 1), 386 (446-HOAc, 3), 326 (386-HOAc, 3), 268 (M-$C_{31}H_{37}O_{11}$ [baccatin III], 5), 240 (268-CO, 4), 222 (240-H_2O, 10), 210 (240-CH_2O, 20), 121 (PhCOO, 3) 105 (C_7H_5O, 100), 91 ($PhCH_2$, 5), 77 (Ph, 25) 43 (Ac, 13);

HRMS (ESIpos) calculated for $C_{47}H_{51}NNaO_{14}$ (M+Na) 876.320176; found 876.320207;

7.8. Crystallographic data

N-((1*S*,2*R*)-2-(*tert*-butyldimethylsilyloxy)-3-oxo-1-phenylpropyl)benzamide (307e)



Crystal data and structure refinement.

Identification code	5715	
Empirical formula	$C_{22}H_{29}NO_3Si$	
Color	colorless	
Formula weight	383.55 g · mol^{-1}	
Temperature	100 K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	**$P2_1/n$, (no. 14)**	
Unit cell dimensions	a = 12.3199(2) Å	α= 90°.
	b = 9.66240(10) Å	β= 107.8590(10)°.
	c = 18.9307(4) Å	γ = 90°.
Volume	2144.92(6) Å^3	
Z	4	
Density (calculated)	1.188 Mg · m^{-3}	
Absorption coefficient	0.130 mm^{-1}	
F(000)	824 e	
Crystal size	0.08 x 0.06 x 0.04 mm^3	
θ range for data collection	3.09 to 31.50°.	

Index ranges	$-18 \leq h \leq 18, -14 \leq k \leq 14, -27 \leq l \leq 27$	
Reflections collected	50668	
Independent reflections	7119 [$R_{int} = 0.0610$]	
Reflections with $I>2\sigma(I)$	5923	
Completeness to $\theta = 31.50°$	99.9 %	
Absorption correction	Gaussian	
Max. and min. transmission	1.00 and 0.99	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7119 / 0 / 253	
Goodness-of-fit on F^2	1.038	
Final R indices [$I>2\sigma(I)$]	$R_1 = 0.0395$	$wR^2 = 0.1056$
R indices (all data)	$R_1 = 0.0532$	$wR^2 = 0.1163$
Largest diff. peak and hole	0.417 and -0.615 e · Å^{-3}	

Selected bond lengths [Å]

C(1)-C(2)	1.5200(15)
C(2)-O(1)	1.4045(12)
C(2)-C(3)	1.5391(14)
C(3)-N(1)	1.4559(12)

Selected bond angles [°]

O(2)-C(1)-C(2)	123.94(10)
O(1)-C(2)-C(3)	107.88(8)
N(1)-C(3)-C(17)	114.09(8)
C(2)-O(1)-Si(1)	127.02(6)
C(1)-C(2)-C(3)	109.30(8)

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9. Appendix

9.1. Abstract

This thesis is divided into two major parts. The first part deals with the development of conditions for a Heck reaction to introduce aryl and vinyl substituents to the β-position of crotonaldehyde and related α,β-unsaturated aldehydes. The reaction provides very fast (<1 h) access to the desired β,β-disubstituted, α,β-unsaturated aldehydes in typically good to very high yields. The methodology is furthermore employed in shortening the formerly lengthy synthesis of enantiopure Florhydral®.

The second and larger part concerns the development of the chemistry of *N*-Boc, *N*-Cbz, *N*-Fmoc, and *N*-Bz-imines in proline-catalyzed Mannich reactions of unmodified aldehydes and ketones. The reactions are usually good to high in yield and with high to excellent levels of enantioselectivity. It also describes the first use of acetaldehyde as donor in an organocatalyzed reaction, leading to defined single-addition products of extremely high enantiopurity. Finally, the newly developed methodology was employed to synthesize the side chain of paclitaxel (taxol), and the semisynthesis thereof is presented.

Die vorliegende Arbeit gliedert sich in zwei Teile. Der erste Teil behandelt die Entwicklung von Bedingungen für die Heck-Reaktion, mittels derer Aryl- und Vinylsubstituenten in die β-Position von Crotonaldehyd und verwandten, α,β-ungesättigten Aldehyden eingeführt werden können. Die Reaktion ermöglicht einen sehr schnellen (<1 h) Zugang zu den gewünschten β,β-disubstituierten, α,β-ungesättigten Aldehyden in zumeist guten bis sehr guten Ausbeuten. Weiterhin wird die entwickelte Methode angewendet, um die vormals lange Synthese von enantiomerenreinem Florhydral® zu verkürzen.

Im zweiten und größeren Teil wird die Entwicklung der Chemie von *N*-Boc, *N*-Cbz, *N*-Fmoc, und *N*-Bz-Iminen in Prolin-katalysierten Mannich-Reaktionen mit unmodifizierten Aldehyden und Ketonen beschrieben. Die Produkte werden meist in guten bis sehr guten Ausbeuten und in hoher bis exzellenter Enantiomerenreinheit erhalten. Daneben wird zudem zum ersten Mal die Verwendung von Acetaldehyd als Donor in einer organokatalytischen Reaktion beschrieben, die zu definierten Produkten von hoher optischer Reinheit führt. Schließlich wurde die neuentwickelte Methode in der Semisynthese von Paclitaxel (Taxol) angewendet.

9.2. Erklärung

"Ich versichere, dass ich die von mir vorgelegte Dissertation selbständig angefertigt, die benutzten Quellen und Hilfsmittel vollständig angegeben und die Stellen der Arbeit - einschließlich Tabellen, Karten und Abbildungen-, die anderen Werken im Wortlaut oder dem Sinn nach entnommen sind, in jedem Einzelfall als Entlehnung kenntlich gemacht habe; dass diese Dissertation noch keiner anderen Fakultät oder Universität zur Prüfung vorgelegen hat; dass sie noch nicht veröffentlicht worden ist, sowie, dass ich eine solche Veröffentlichung vor Abschluss des Promotionsverfahrens nicht vornehmen werde. Die Bestimmungen der Promotionsordnung sind mir bekannt. Die von mir vorgelegte Dissertation ist von Herrn Professor Dr. Benjamin List betreut worden."

Mülheim an der Ruhr, April 2009

Bisher sind folgende Teilpublikationen veröffentlicht worden:

- Jung Woon Yang, Michael Stadler, Benjamin List
  Proline-Catalyzed Mannich Reaction of Aldehydes with *N*-Boc-Imines.
  Angew. Chem. Int. Ed. **2007**, *46*, 609-611

- Jung Woon Yang, Michael Stadler, Benjamin List
  Practical Proline-catalyzed asymmetric Mannich reaction of aldehydes with *N*-Boc-imines.
  Nat. Protocols **2007**, *2(8)*, 1937-1942

- Michael Stadler, Benjamin List
  Heck Reactions of Crotonaldehyde.
  Synlett **2008**, 597-599

- Jung Woon Yang, Carley Chandler, Michael Stadler, Daniela Kampen, Benjamin List
  Proline-catalysed Mannich reactions of acetaldehyde.
  Nature **2008**, *452*, 453-455

9.3. Lebenslauf

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