Thesis submitted in fulfilment of the requirements for the Degree of Doctor of Philosophy

New Strategies for Pinacol Cross-Couplings and Alkenation Reactions

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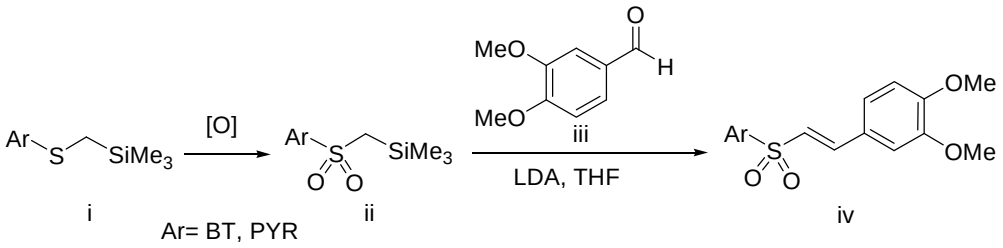
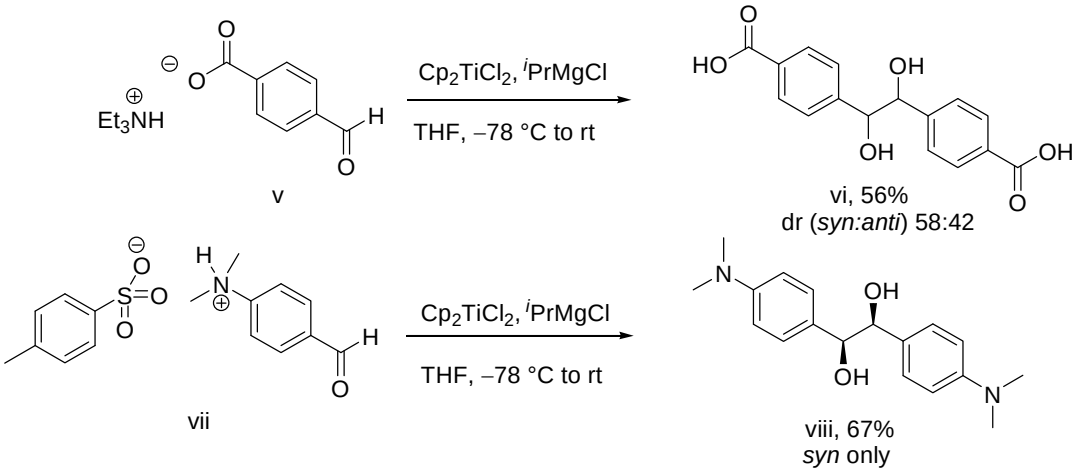
Abstract

The research described herein involves the study of new approaches to alkenation and pinacol cross-coupling.

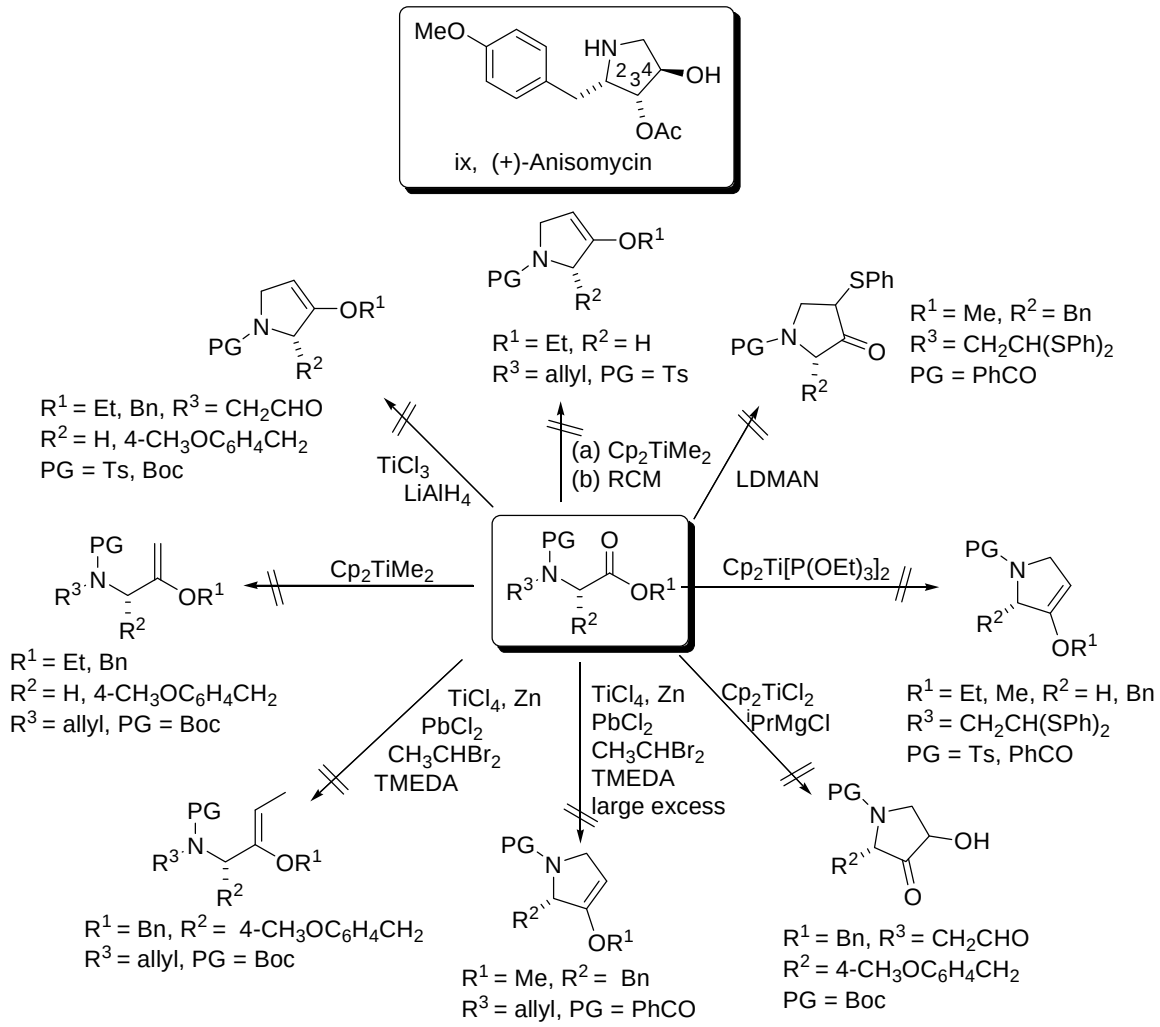
The competition between modified Julia alkenation and Peterson alkenation was studied. Heterocyclic sulfides (i) were oxidised to sulfones (ii) by dimethyldioxirane, generated *in situ* from oxone® and acetone. Reactions between sulfones (ii) and aldehyde (iii) gave vinyl sulfones (iv) in good yields, rather than vinyl silanes, confirming that the Peterson alkenation is preferred in this system.



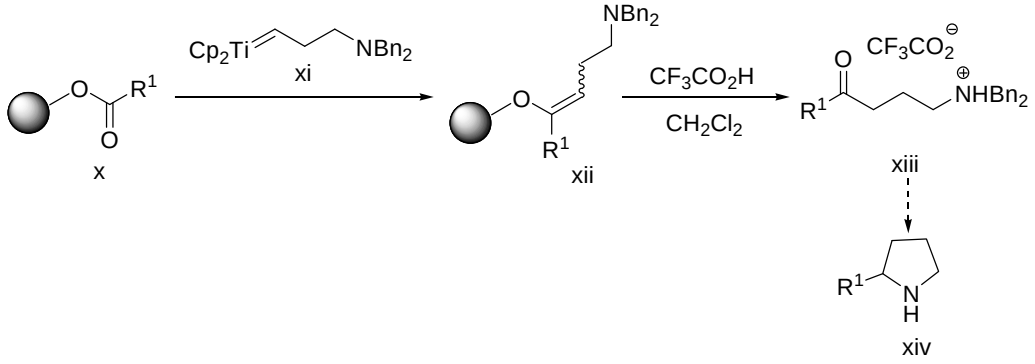
Pinacol cross-coupling between an aldehyde or ketone in solution and a more easily reduced aldehyde immobilised on resin was attempted, but proved unsuccessful. However, aldehydes (v) and (vii) bearing the salts of tertiary amines were found to be good substrates for pinacol homo-coupling giving diols (vi) and (viii), respectively. The formation of salt (v) avoided unwanted reduction of the aldehyde to a primary alcohol.



A wide range of approaches to anisomycin (ix) using titanium reagents were investigated. These were based on the formation of the bond between C-3 and C-4 by alkylidenation of esters and ring-closing metathesis (RCM) or intramolecular alkylidenation or radical cyclization. The presence and position of the nitrogen atom proved an insurmountable obstacle to this strategy.



The solid-phase synthesis of 4-amino-ketones (xiii) was achieved. Resin-bound esters (x) were alkylidenated using a novel titanium reagent (xi) generated *in situ* by reduction of a thioacetal with a low valent titanium reagent. Treating the resulting enol ethers (xii) with acid gave ketones in good yield and high purity because of the switch in the nature of the linker from acid-stable to acid-sensitive (a chameleon catch strategy). Amino-ketones (xiii) are potential precursors of pyrrolidines (xiv).



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Special thanks to my family for their love and support. It has been a long journey since my first year at the Uni and you have always been there, by my side.

To Matthieu. Thanks for supporting my speeches for long, long hours every day. Your patience, your strength and your love made me feel stronger every day for the last 5 years and will for the next 50 years of our life.

Author's Declaration

This thesis represents the original work of Guilaine Francine Blanc unless explicitly stated otherwise in the text. No part of this thesis has been previously submitted for a degree at the University of Glasgow or any other University. The research was carried out at the University of Glasgow in the Loudon laboratory under the supervision of Dr Richard Hartley during the period of October 2006 to September 2009.

Abbreviations

[α]	specific rotation
Å	angstrom
AA	amino acid
Ac	acetyl
AcOH	acetic acid
aq	aqueous
Alk	alkyl
Ar	Aryl
atm	atmosphere (pressure)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyldicarbonate
Bu	butyl
^{n}Bu	normal butyl
^{sec}Bu	secondary butyl
^{t}Bu	*tert*-butyl
b.p.	boiling point
BT	benzothiazole
br d	broad doublet (NMR spectroscopy)
br s	broad singlet (NMR spectroscopy)
Bz	benzoyl
°C	degrees Celsius
cat	catalytic
$CDCl_3$	deuterated chloroform
CI	chemical ionisation
cm	centimetre
cm^{-1}	wavenumber
conc	concentrated
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift (NMR spectroscopy)
d	doublet (NMR spectroscopy)
dd	doublet of doublets (NMR spectroscopy)

ddd	doublet of doublet of doublets (NMR spectroscopy)
dt	doublet of triplets (NMR spectroscopy)
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	*N,N'*-dicyclohexylcarbodiimide
DCM	dichloromethane
DCU	dicyclohexylurea
DEAD	diethyl azodicarboxylate
DEPT	distortionless enhancement by polarization transfer
DHQ-CLB	*O*-(4-chlorobenzoyl)hydroquinine
DIAD	diisopropyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DIPEA	diisopropylethylamine
DIPT	diisopropyltartrate
DMAP	*N,N*-dimethyl-4-aminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DMT	dimethyltitanocene
DVB	divinyl benzene
dr	diastereomeric ratio
EI	electron impact ionisation
eq	equivalent(s)
Et	ethyl
FAB	fast atom bombardment
g	gram
h	hour(s)
Hz	Hertz
HCl	hydrochloric acid
HMPA	hexamethylphosphoramide
HRMS	high-resolution mass spectroscopy
HWE	Horner-Wadsworth-Emmons reaction
IR	infra-red
J	NMR spectra coupling constant
Kg	kilogram
KHz	kiloHertz

L	litre
µL	microlitre
LAH	lithium aluminium hydride
LDA	lithium diisopropylamide
LDBB	lithium 4,4'-di-*tert*-butylbiphenylide
LDMAN	lithium dimethylamino naphthalenide
lit.	literature value
LN	lithium naphthalenide
m	multiplet
M	molar
$M^{+\cdot}$	parent molecular ion
m-CPBA	*meta*-chloroperoxybenzoic acid
MALDI-TOF	matrix assisted laser desoprtion ionisation-time of flight
MAOS	microwave assisted organic synthesis
MAS-NMR	magic angle spinning-nuclear magnetic resonance
Me	methyl
MHz	megaHertz
mequiv	milliequivalent
mg	milligram
mL	millilitre
min(s)	minute(s)
mmol	millimole
mol	moles(s)
MOM	methoxymethyl chloride
m.p.	melting point
MP-TsOH	macroporous polystyrene-tosic acid resin
Ms	mesyl (methanesulfonyl)
MS	molecular sieves
MTBD	1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-*a*]pyrimidine
MW	microwave irradiations
m/z	mass-to-charge ratio
N	normal
4-NBP	4-nitrobenzylpyridine
NIS	*N*-iodosuccinimide
NMR	nuclear magnetic resonance

ODB	2-dichlorobenzene
o/n	overnight
Oxone®	potassium peroxymonosulfate ($2KHSO_5.KHSO_4.K_2SO_4$)
PCC	pyridinium chlorochromate
PEG	polyethylene glycol
PG	protecting group
Ph	phenyl
phth	phthalimido group
ppm	part(s) per million
PPTS	pyridinium toluene-*p*-sulfonate
Pr	propyl
^{i}Pr	isopropyl
Pyr	pyridine
q	quartet (NMR spectroscopy)
qn	quintet (NMR spectroscopy)
RCM	ring closing metathesis
R_f	retention factor
rt	room temperature
s	singlet
sat	saturated
SET	single electron transfer
SM	starting material
SPOS	solid-phase organic synthesis
t	triplet (NMR spectroscopy)
td	triplet of doublets (NMR spectroscopy)
TBAI	tetrabutylammonium iodide
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
TBDMSCl	*tert*-butyldimethylsilyl chloride
TBHP	*tert*-butyl hydroperoxide
TBS	*tert*-butyldimethylsilyl chloride
TCE	trichloroethyl
Tf	triflate
TFA	trifluoroacetic acid
T_g	glass transition temperature

THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N,N*-tetramethyl-ethane-1,2-diamine
TMS	trimethylsilyl
TNBS	2,4,6-trinitrobenzenesulfonic acid
TOF-SIMS	Time of Flight- Secondary Ion Mass Spectrometry
TPA	triphosgene
p-tosic	*para*-toluenesulfonic
Ts	tosyl (*para*-toluenesulfonyl)
p-TsOH	*para*-toluenesulfonic acid
p-TsCl	*para*-toluenesulfonyl chloride
UV	ultraviolet
v/v	volume per unit volume
w/w	weight per unit weight
Z	benzyloxycarbonyl group

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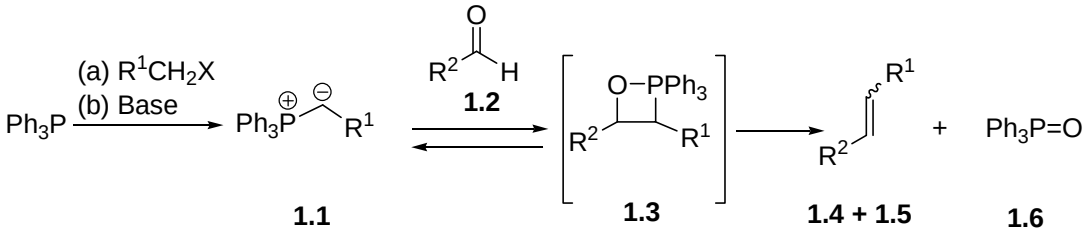
Part A

1. Classical Alkenation Reactions

Alkenation of carbonyl compounds to produce carbon-carbon double bonds is one of the most fundamental reactions in organic chemistry due to the reactive nature of the double bond. Wittig, Horner-Wadsworth-Emmons, Julia (and modified Julia) and Peterson reactions are among the most widely used reactions developed to accomplish this transformation. A brief description of these classical alkenation reactions will be provided in this section and although alkenation reactions can also be promoted by titanium complexes, the discussion relevant to this titanium chemistry will be given in chapter 6.

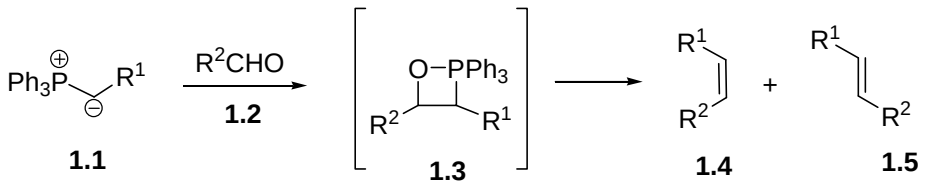
1.1. Wittig and Horner-Wadsworth-Emmons (HWE) reactions

Discovered in 1954[1] and recognised by the Nobel Prize in 1979, the Wittig reaction is one of the most effective and general methods for the preparation of alkenes from carbonyl compounds. Before Wittig's discovery, the synthesis of alkenes from carbonyl compounds generally involved nucleophilic attack followed by elimination; the double bond position and geometry were difficult to control. Wittig described a reaction which involves the addition of an aldehyde or ketone **1.2** to a preformed phosphorus ylide **1.1** producing alkenes **1.4** and **1.5** and phosphine oxide **1.6** *via* an oxaphosphacyclobutane **1.3** (Scheme 1.1).



Scheme 1.1: Wittig reaction

The stereochemistry of the alkene is defined by the nature of R^1. With an unstabilised ylide (R^1 = alkyl), the formation of the oxaphosphetane **1.3** being *syn* selective and the elimination step being stereospecific, the *Z*-alkene **1.4** (kinetic product) is favoured while an ylide stabilised by an electron-withdrawing group (R^1 = CHO, CO_2R, COR) will produce the *E*-alkene **1.5** (thermodynamic product) (Scheme 1.2).[2]



Scheme 1.2: Mechanism of Wittig reaction

Recently, Aggarwal and co-workers[3] have demonstrated that a dipole–dipole interaction between the two reactants controlled the transition state structures (TS) and explains the *E*-selectivity in triphenylphosphine stabilized ylides, as well as 1,2- and 1,3-steric interactions already described by Vedejs' models (Figure 1.1).[4,5] Indeed, unstabilized ylides react with aldehydes in a way to minimize 1,2 and 1,3-steric interactions in the early TS and hence the *cis*-TS is favored, leading to the *Z*-alkene. For stabilized ylides, the high *E*-selectivity is due to a strong polar interaction at the addition TS added to minimised 1,2-interactions which favors the *trans*-TS and therefore formation of the *E*-product.

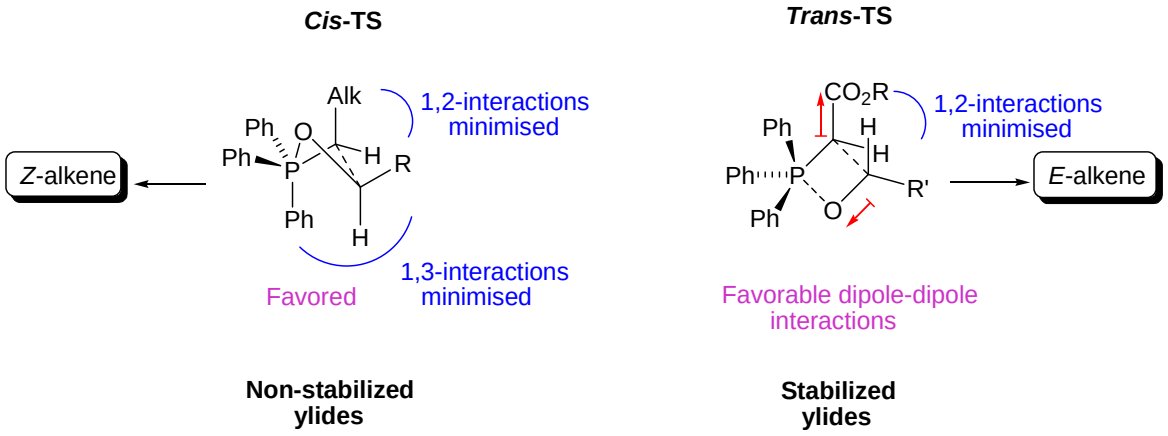
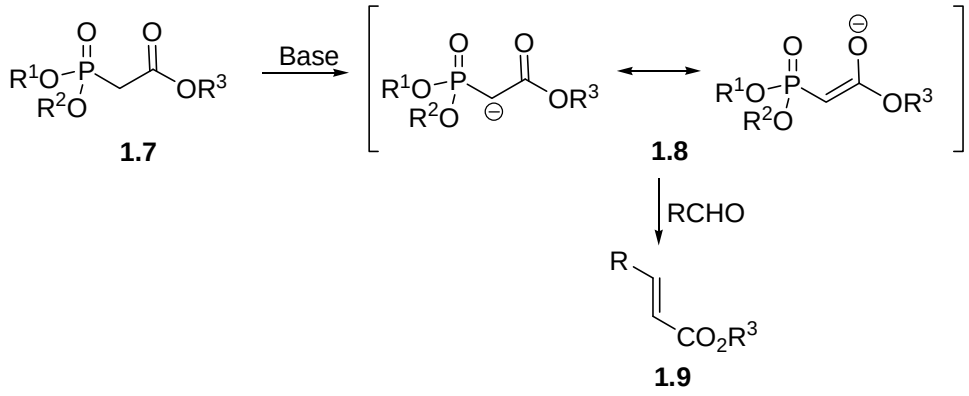


Figure 1.1: Aggarwal and co-workers' TS structure model

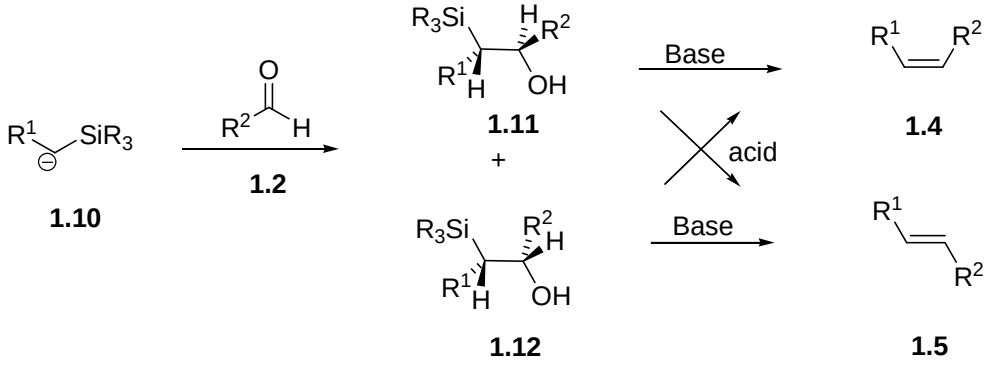
However, stabilised ylides are rather unreactive and phosphonate esters **1.7**, more nucleophilic reagents, are often used instead of phosphorus ylides. This reaction is called the Horner-Wadsworth-Emmons reaction (HWE) and normally produces the *E*-alkene **1.9** (Scheme 1.3). However by altering R^1 or R^2 groups, a Z-alkene can be accessed.[6] The HWE reaction has proven to be effective with hindered ketones that are unreactive in the classical Wittig reaction.[7]



Scheme 1.3: HWE reaction

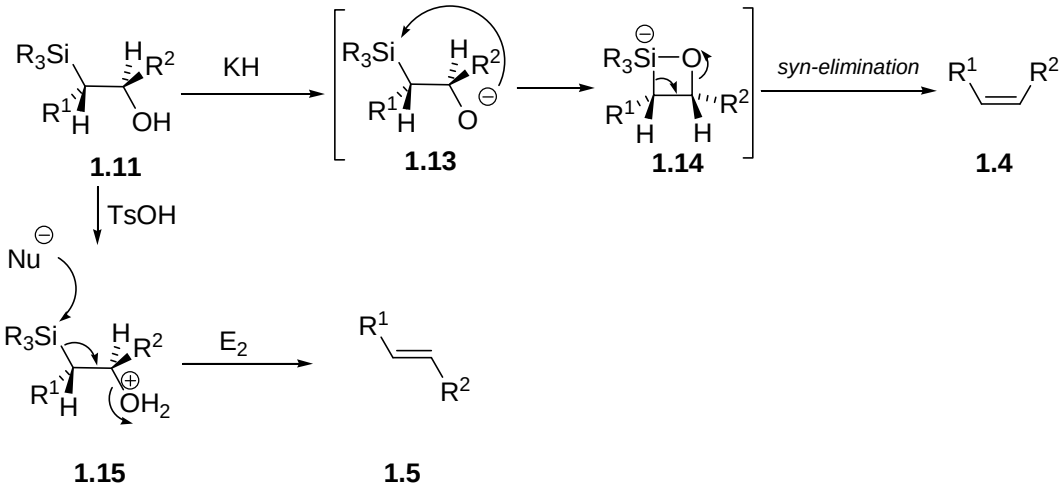
1.2. Peterson reaction

The silicon-based alternative to the Wittig reaction is the Peterson alkenation. This is the reaction of an α-silyl carbanion **1.10** with a carbonyl compound **1.2** to give β-hydroxysilyl intermediates **1.11** and **1.12** (Scheme 1.4). Treated with either acid or base, these intermediates produce alkenes **1.4** or **1.5**.



Scheme 1.4: Peterson reaction

Under basic conditions, *syn*-elimination of *anti*-diastereomer **1.11** occurs through the formation of the intermediates **1.13** and **1.14** to yield the *Z*-alkene **1.4** while elimination in acid follows an E2 mechanism and produces the other isomer **1.5**, stereospecifically (Scheme 1.5)**.** Consequently, the control of alkene geometry depends on the ability to make intermediates **1.11** or **1.12** as single diastereoisomers.[2]

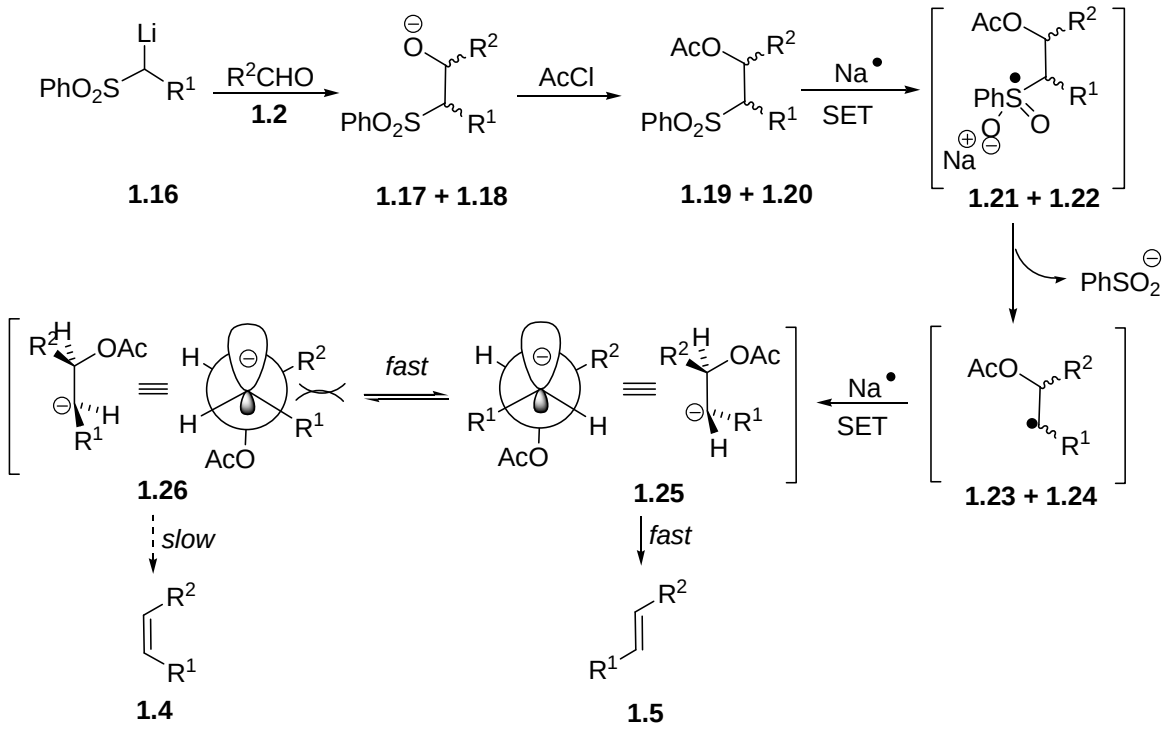


Scheme 1.5: Mechanism of the Peterson reaction

1.3. Julia and modified Julia reactions

Introduced in 1973 by Marc Julia,[8] the Julia reaction is a reaction of a lithiated sulfone derivative **1.16** with a carbonyl compound **1.2** to give the oxyanions **1.17** and **1.18** which are converted into β-acyloxysulfones **1.19** and **1.20** (Scheme 1.6). Reduction with a single electron transfer (SET) reagent gives radicals **1.21** and **1.22** and this is followed by elimination of phenyl sulfone to give radicals **1.23** and **1.24**. A second reduction provides conformers **1.25** and **1.26** with the acyl group arranged *anti*-periplanar to the lone pair. The geometry of the alkene is independent of the relative configuration of the intermediate β-acyloxysulfones **1.19** or **1.20** but depends on the bulk of R^1 and R^2 groups. In the carbanion conformer **1.25**, the substituents are arranged so that steric interactions are minimised and this leads to the formation of the *E*-alkene **1.5** occuring rapidly. On the other hand, the *Z*-alkene **1.4** is disfavoured by interactions between R^1 and R^2. Furthermore, interconversion between carbanions **1.25** and **1.26** takes place very rapidly resulting predominantly in the

formation of the *E*-isomer regardless of which diastereoisomeric sulfone **1.19** or **1.20** is used. The Julia reaction is stereoselective.



Scheme 1.6: Julia reaction

A *one-pot* version of the Julia reaction has been developed by Sylvestre Julia[9] and has been reviewed by Blakemore.[10] This reaction requires a heteroarylsulfone and four heterocyclic activators have been identified which provide useful levels of stereoselectivity under certain conditions (Figure 1.2):[10] benzothiazol-2-yl (BT), pyridin-2-yl (PYR), 1-phenyl-1H-tetrazol-5-yl (PT) and 1-*tert*-butyl-1H- tetrazol-5-yl (TBT).

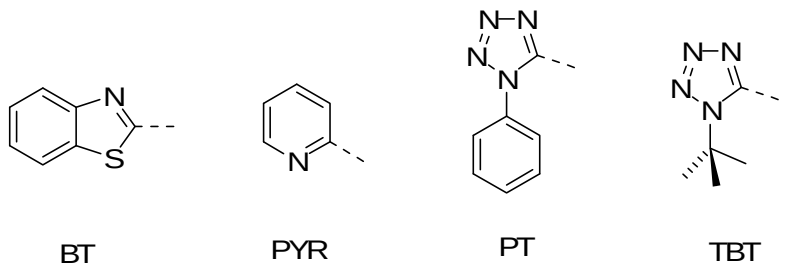
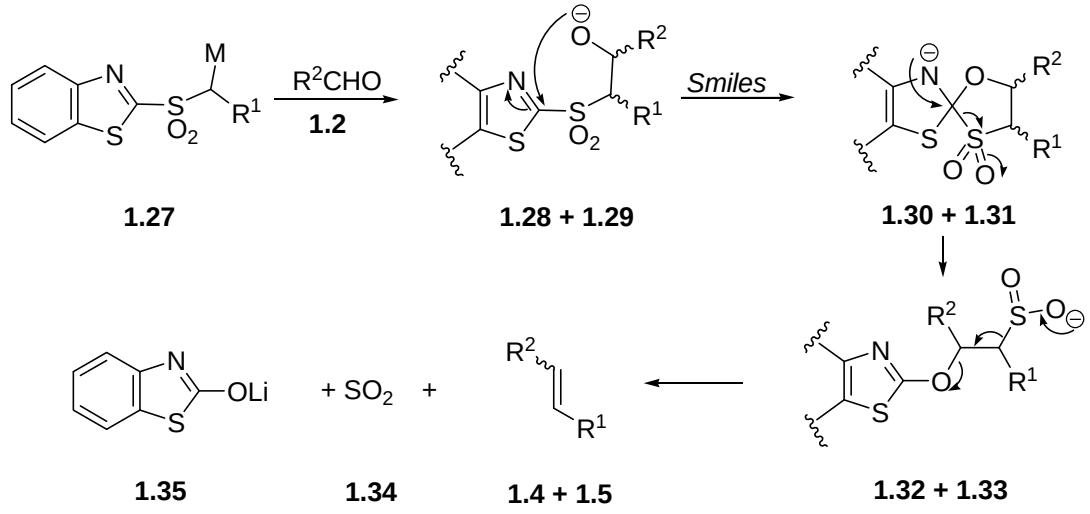


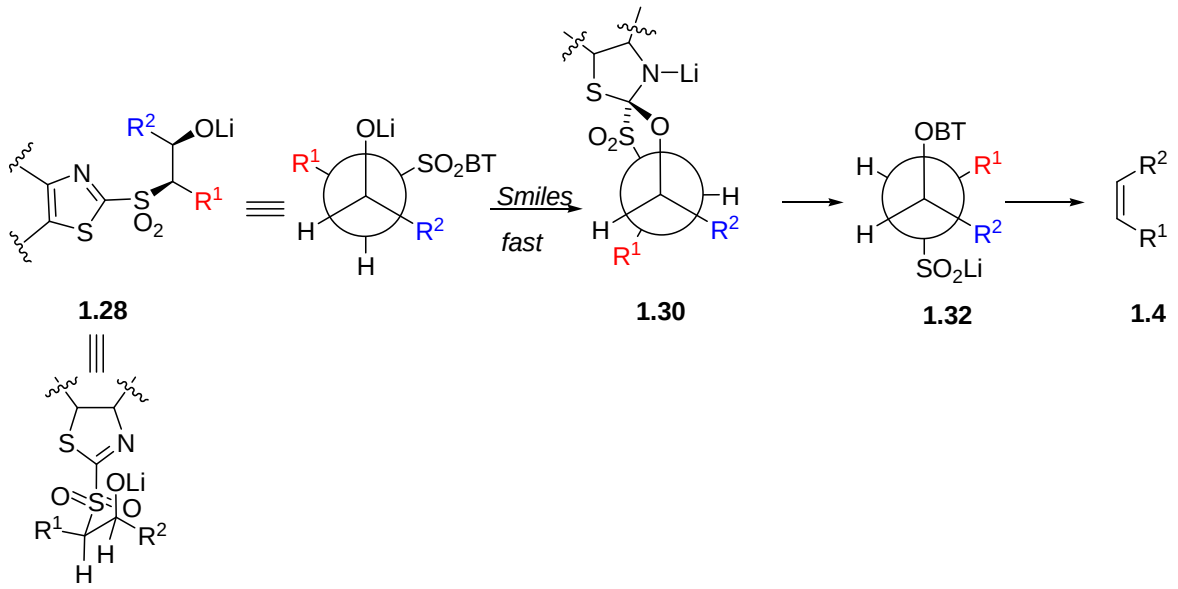
Figure 1.2: Heterocyclic activators of the modified Julia olefination

BT-sulfones and PYR-sulfones are commonly used for their stereoselectivity. The presence of an imine-like moiety in the molecule controls their reactivity. Like the classical Julia, addition of the lithiated sulfone **1.27** to an aldehyde **1.2** generates unstable β-alkoxysulfones **1.28** and **1.29** which rearrange *via* Smiles rearrangement to give sulfinate salts **1.32** and **1.33** (Scheme 1.7). Then spontaneous elimination (E2 like) of sulfur dioxide **1.34** and lithium benzothiazolone **1.35** yields alkenes **1.4** and **1.5**. The geometry of the alkene is then controlled by the geometry of sulfones **1.28** and **1.29** and by the reaction conditions.

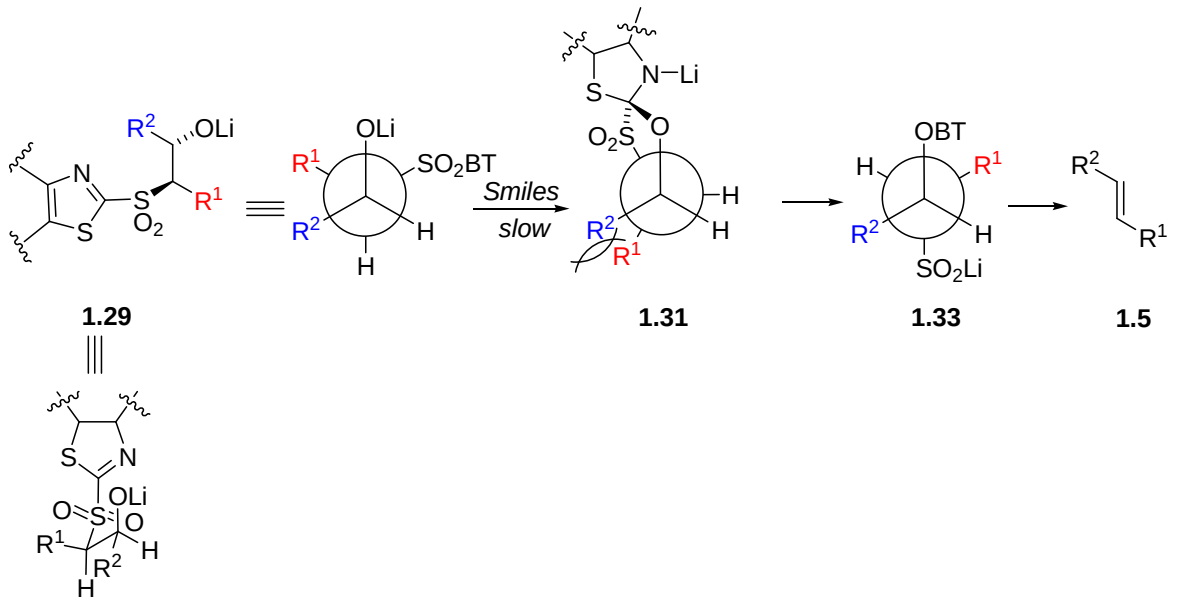


Scheme 1.7: Modified Julia reaction mechanism

Indeed, the elimination of β-alkoxy-BT-sulfones **1.28** and **1.29** is stereospecific. The *syn*-diastereoisomer **1.28** yields the *Z*-alkene **1.4** (Scheme 1.8) as an *anti*-periplanar arrangement of BTO- and SO_2Li is required in the final elimination step whereas the *anti*-diastereoisomer **1.29** produces the *E*-alkene **1.5** (Scheme 1.9). Then the ratio of *Z*/*E* alkenes **1.4/1.5** should reflect the ratio of *syn*/*anti* sulfones **1.28/1.29** formed after the nucleophilic addition.



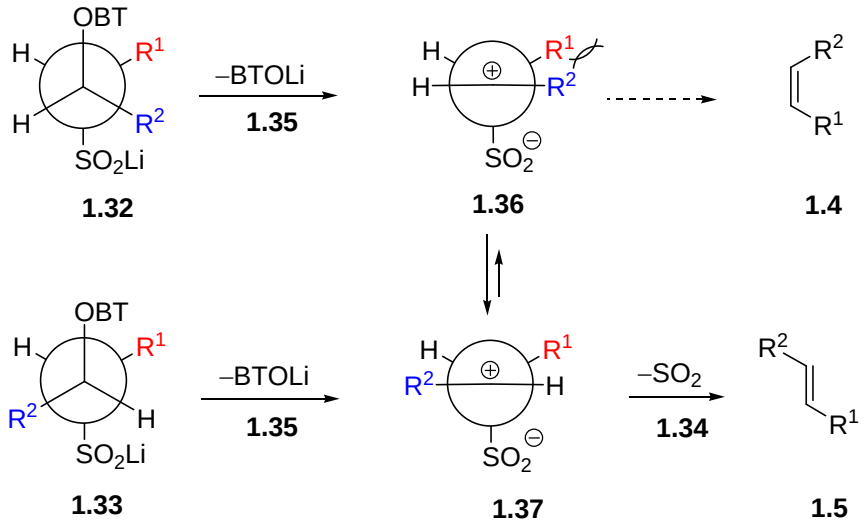
Scheme 1.8: Synthesis of *Z*-alkene 1.4



Scheme 1.9: Synthesis of *E*-alkene 1.5

However, It has been reported by Smith and co-workers[11] that the use of α,β-unsaturated aldehydes and aryl aldehydes improves the *E*-stereoselectivity regardless of the ratio of β-alkoxysulfones **1.28** and **1.29**. Julia and co-workers[12] proposed that the reaction followed a E1 mechanism (Scheme 1.10). The loss of benzothiazolone **1.35** from diastereoisomers **1.32** and **1.33** would produce zwitterionic conformers **1.36** and **1.37**. The carbocation is stabilized by the α,β-unsaturation of R^2. Interconversion would then occur rapidly to form the

more stable conformer **1.37** followed by the loss of sufur dioxide **1.34** to yield the *E*-alkene **1.5**.

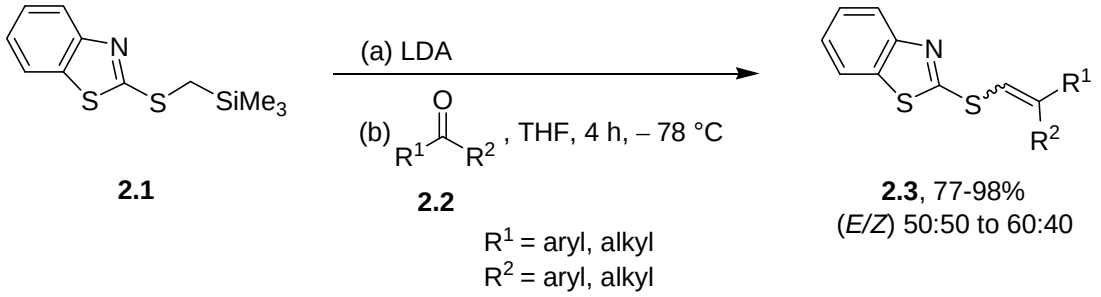


Scheme 1.10: ***E*-stereoselectivity**

These alkenations reactions became popular because of their wide applicability. A large variety of carbonyl compounds are suitable and the number of examples of their application in total synthesis of natural compounds is vast.

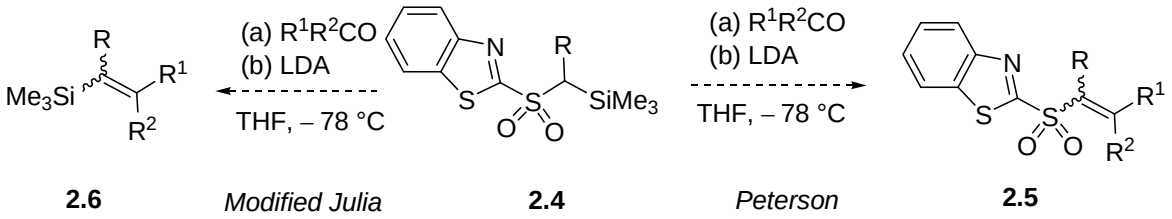
2. Peterson *versus* Modified Julia or Stereocontrolled Synthesis of Alkenes

Katritzky *et al.*[13] described the lithiation of α-silyl BT-sulfide **2.1** and its reaction with carbonyl compounds **2.2** (Scheme 2.1). Naturally, a Peterson reaction took place and he observed elimination of the silyl group leading to the formation of a mixture of *E* and *Z*-vinyl sulfides **2.3**. The reaction was not stereoselective.



Scheme 2.1: Peterson reaction with a α-silyl BT-sulfide

But what if instead of the BT-sulfide, we had a BT-sulfone **2.4**? Would we observe elimination of the silyl group (**2.5**) *via* a Peterson reaction or elimination of the sulfone (**2.6**) *via* a modified Julia reaction (Scheme 2.2)?

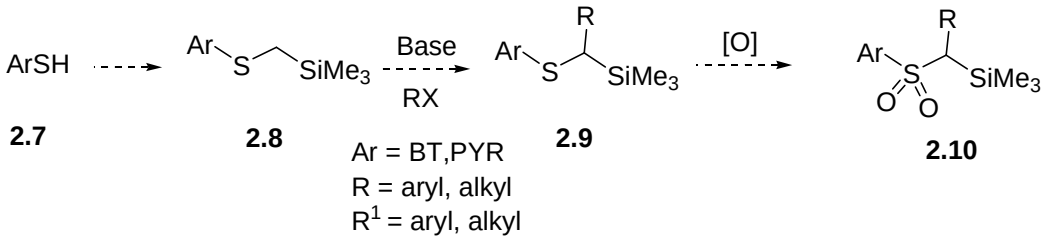


Scheme 2.2: Modified Julia *versus* Peterson reactions

The increased electrophilicity of the BT moiety bearing a sulfonyl group might favour the Modified Julia to give the vinyl silane **2.6**. Alternatively, the vinyl sulfone **2.5** might be produced.

Having the works of Julia and Katritzky in mind, we proposed the following short sequence to access α-silyl sulfones (Scheme 2.3). The synthesis would start from

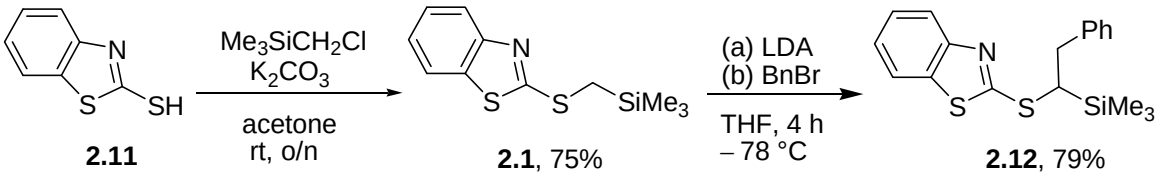
the appropriate heterocyclic thiol **2.7**; the silyl derivative **2.8** would be prepared, then alkylation followed by oxidation of the alkyl sulfide **2.9** would produce the desired sulfone **2.10**.



Scheme 2.3: Proposed route to sulfone 2.10

2.1. Benzothiazol-2-yl sulfone derivatives

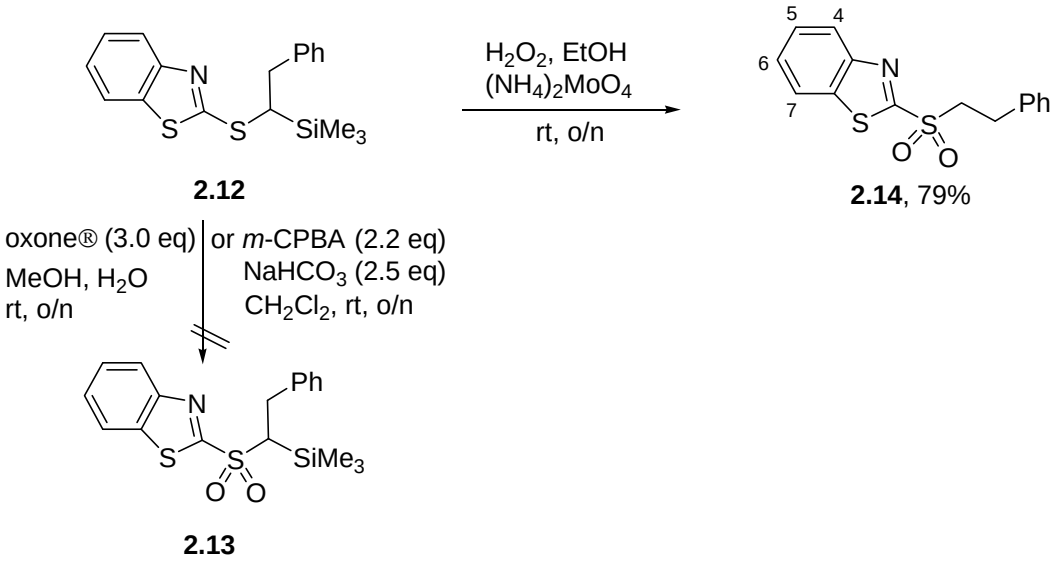
According to Katritzky's procedure,[13] the silyl derivative **2.1** was prepared in good yield by reaction of (chloromethyl)trimethylsilane with benzothiazol-2-thiol **2.11** and potassium carbonate in acetone (Scheme 2.4). Deprotonation of silyl derivative **2.1** with equimolar LDA (generated *in situ*) afforded an α-lithio derivative which was alkylated with benzyl bromide.[13] After purification, the sulfide **2.12** was isolated in good yield.



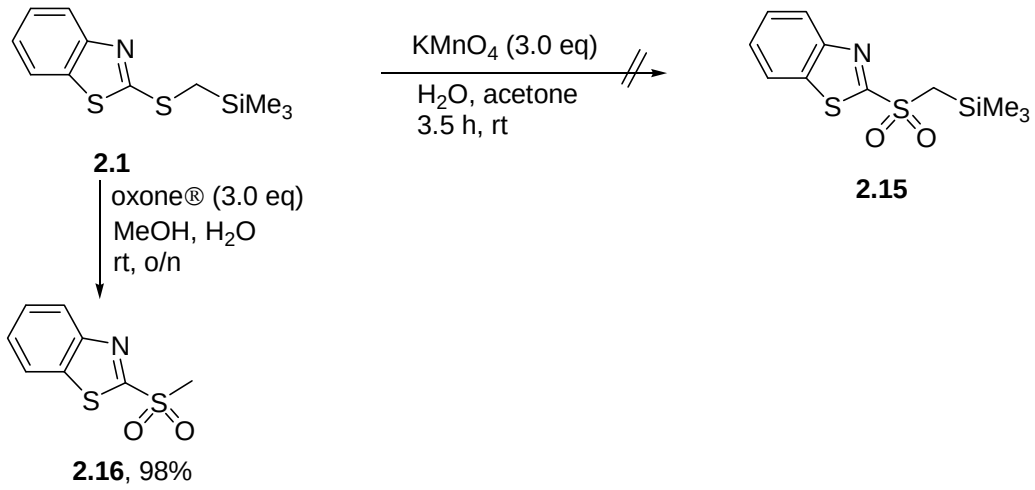
Scheme 2.4: Preparation of sulfide 2.12

Molybdate catalysed oxidation is the most popular method to access heteroaryl sulfones. However, treatment of thioether **2.12** with $(NH_4)_2MoO_4$ (10 mol%) and H_2O_2 in ethanol did not lead to the formation of sulfone **2.13** (Scheme 2.5). ^{1}H NMR analysis of the crude mixture showed the formation of the sulfone **2.14** resulting from the loss of the trimethylsilyl group. [**^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.05 (2H, t, *J* 8.4 Hz, CH_2), 3.65 (2H, t, *J* 8.6 Hz, CH_2), 7.00-7.11 (5H, m, Ar-H), 7.43 (1H, dt, *J* 1.4 and 7.9 Hz, H5 or H6), 7.48 (1H, dt, *J* 1.5 and 7.8 Hz, H5 or H6), 7.85 (1H, ddd, *J* 0.9, 1.4 and 7.9 Hz, H4 or H7), 8.05 (1H, ddd, *J* 0.8, 1.5

and 8.0 Hz, H4 or H7)]. Oxidation conditions were obviously too harsh to allow the presence of the silyl group on the molecule. Therefore, several classical oxidising systems were investigated on either sulfide **2.1** or sulfide **2.12** in order to obtain sulfones. Although peracid reagents (particularly *m*-CPBA) have been extensively employed for the oxidation of heteroaryl thioethers,[14] the reaction of sulfide **2.12** with *m*-CPBA in the presence of sodium hydrogenocarbonate in CH_2Cl_2 [15] did not proceed and we recovered starting material. Moreover, reaction using potassium permanganate in acetone at rt performed with the substrate **2.1** led to recovery of starting material (Scheme 2.6). After reaction of sulfide **2.12** with oxone® (potassium peroxomonosulfate) in methanol at rt,[16] we observed decomposition of the α-silyl sulfide and among these by-products we detected traces of the sulfone **2.14** from the ^{1}H NMR analysis of the crude mixture (Scheme 2.5). The loss of the silyl group was highlighted again and the result was further confirmed by the oxidation reaction of the sulfide **2.1** which provided the sulfone **2.16** in excellent yield (Scheme 2.6).

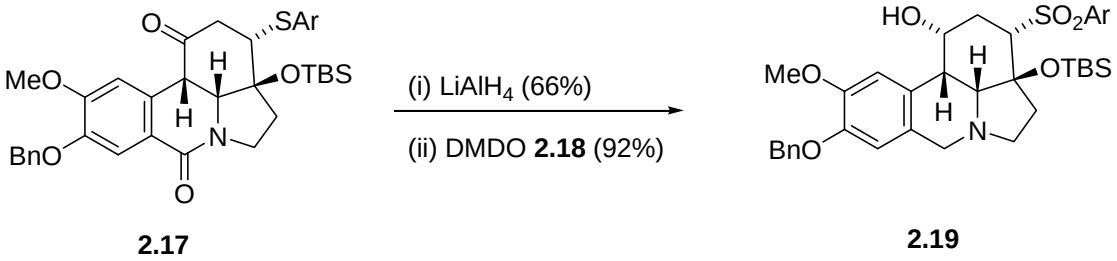


Scheme 2.5: Oxidation reactions



Scheme 2.6: Oxidation of sulfide 2.1

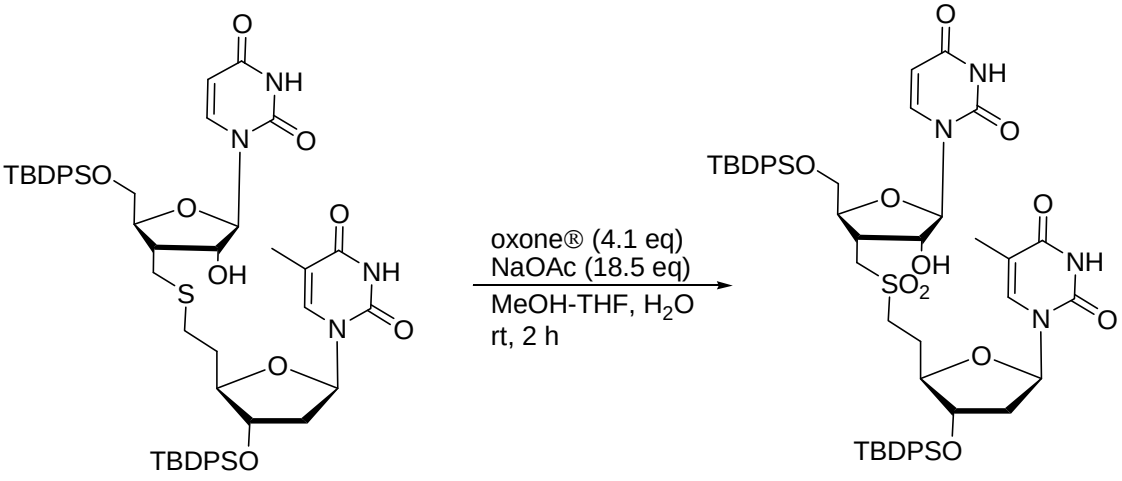
An interesting oxidising system based on the use of oxone® attracted our attention as it was reported in the total synthesis of (±)-Fortucine (Scheme 2.7).[17] The use of 2,2-dimethyldioxirane (DMDO) **2.18** in presence of TFA (to protect the amine) allows the oxidation of sulfide **2.17** into sulfone **2.19** in excellent yield and tolerates the silyl protection of the alcohol.



2.17 **2.19**

Scheme 2.7: Towards the total synthesis of (±)-Fortucine

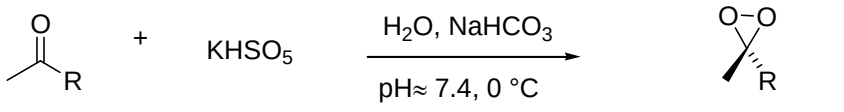
Similarly, Baeschlin *et al.*[18] reported oxidation of thioether **2.20** to give sulfone **2.21** using oxone® and sodium acetate in methanol-THF (Scheme 2.8). The silyl protection of alcohols survived these conditions.



2.20 **2.21**

Scheme 2.8: Oxidation using oxone®- NaOAc

Dioxiranes , such as 2,2-dimethyldioxirane (DMDO) **2.18** or trifluoromethyl dioxirane (TFDO) **2.23**, are a class of powerful oxidants which exhibit electrophilic oxygen transfer to nucleophilic substrates as well as oxidation of unactivated alkanes.[19] First reported in 1979,[20] dioxiranes are easily accessed by the reaction of simple ketones **2.22** with potassium peroxymonosulfate (*also called* oxone® or caroat®, $2KHSO_5.KHSO_4.K_2SO_4$) at pH close to neutrality (Scheme 2.9). The fact that they perform a variety of versatile oxidations, exhibit unusual reactivity and conduct oxygen transfer highly chemo-, regio- and stereoselectively is responsible for the popularity of these reagents. The oxidation reaction is carried out either with the isolated solution of dioxirane in acetone or with the *in situ* generated dioxirane. The *in situ* generated dioxirane allows the reaction to be carried out on larger scale and can not be applied to substrates that are water-sensitive.



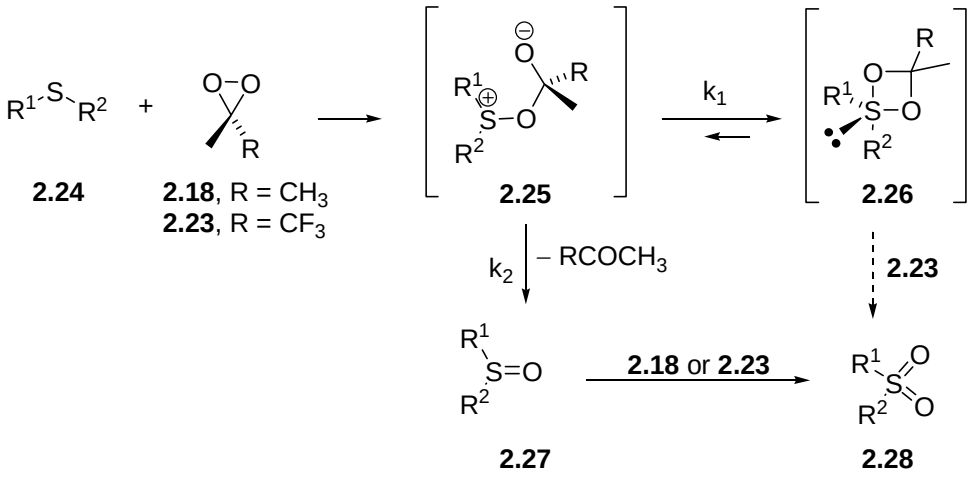
2.22

2.18, R = CH_3
2.23, R = CF_3

Scheme 2.9: Formation of dioxiranes

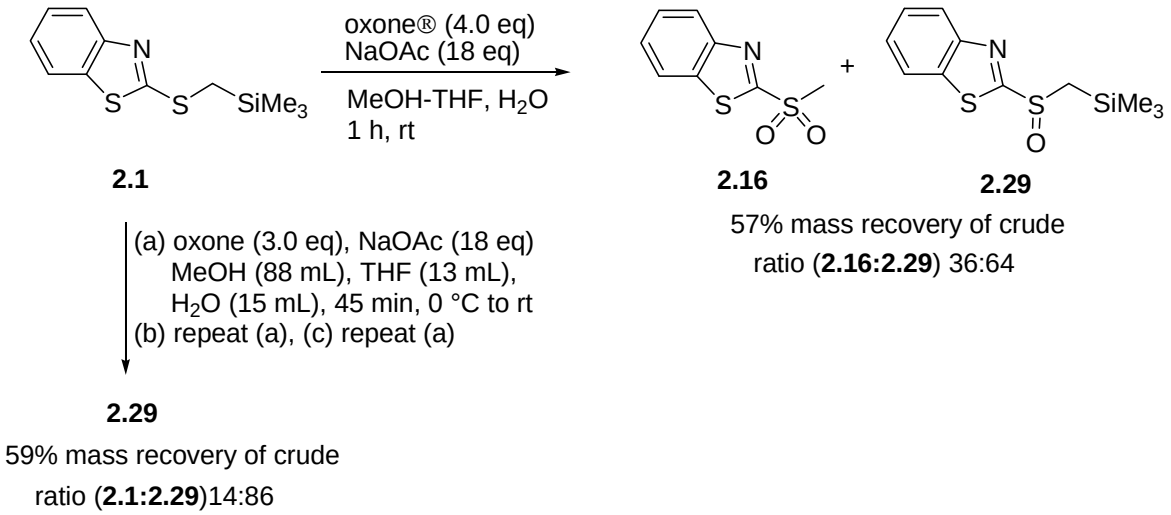
Sulfides **2.24** may be oxidised to sulfoxides **2.27** or sulfones **2.28** depending on the number of equivalent of the oxidant used. However sulfides **2.24** are more

easily oxidised than sulfoxides **2.27** due to the electrophilic character of the reagent. Details of the mechanism of sulfide oxidation with dioxiranes are not clear. González-Núñez *et al*.[21] reported a mechanistic study where they showed that the first step is an electrophilic attack of dioxiranes **2.18** or **2.23** on the sulfur atom to give the zwitterionic species **2.25** which undergoes a reversible cyclisation step to generate the sulfurane intermediate **2.26** (Scheme 2.10). However, elimination of acetone from the species **2.25** occurs faster than the cyclisation and provides the sulfoxide **2.27**. Indeed, the use of a polar solvent such as acetone solvates the zwitterionic intermediate **2.25** shifting the equilibrium away from sulfurane **2.26** and so favours the formation of sulfoxide **2.27**. González-Núñez reported β-elimination from sulfurane **2.26** to give sulfone **2.28** only in the case of the use of TFDO **2.23**.



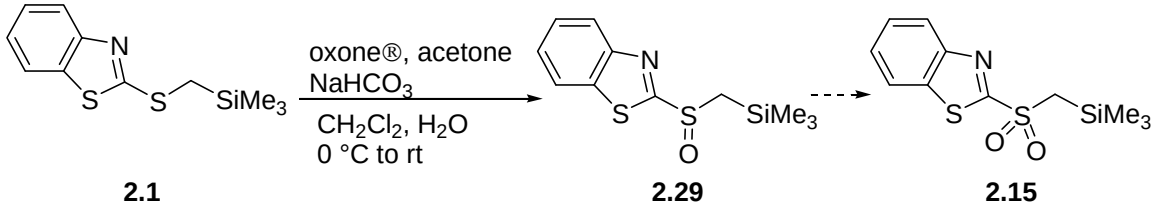
Scheme 2.10: Mechanism of oxidation

Applying this procedure to thioether **2.1** led to the formation of methyl sulfone **2.16** and sulfoxide **2.29** (Scheme 2.11). Since the desilylated sulfoxide was not observed, we concluded that loss of the silyl group occurred after oxidation to the sulfone. Careful addition of the oxidising system in 3 batches avoided the formation of the methyl sulfone **2.16**. ^{1}H NMR analysis of the crude mixture showed the exclusive formation of sulfoxide **2.29**.



Scheme 2.11: Oxidation with oxone®-NaOAc

Thus, reaction of sulfide **2.1** with DMDO **2.18** [generated *in situ* from oxone® (3.0 eq) and acetone (5.6 eq) in water] and $NaHCO_3$ in dichloromethane provided the sulfoxide **2.29** (Scheme 2.12). However, the reaction did not go to completion (Table 2.1, entry 1). After several attempts, it appeared that a large excess of DMDO **2.18** (entries 2 and 3) as well as a longer reaction time [entry 4(i)] did not improve the reaction as the unstable reagent decomposed before reacting. On the other hand, after a first overnight reaction we isolated sulfoxide **2.29** [entry 4(i)] which was put back into the reaction with DMDO **2.18** for 2 h [entry 4(ii)]. After usual work up, we then observed traces of sulfone **2.15**. As predicted by González-Núñez,[21] it proved to be necessary to add DMDO **2.18** in several batches in order to displace the reaction to the sulfone (entries 4 and 5).

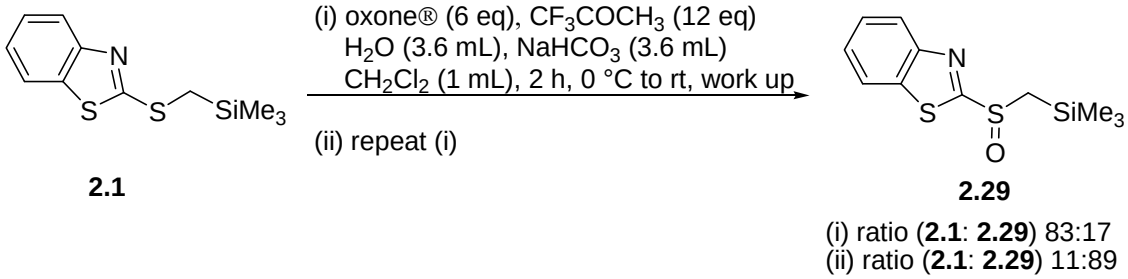


Scheme 2.12: Oxidation with DMDO

Entry	Acetone (eq)	Oxone® (eq)	Time	Ratio (**2.1**: **2.29**: **2.15**)
1	5.6	3.0	2.5 h	36:64:0
2	6.0	6.0	3 h	35:65:0
3	30	20	2 h	100:0:0
4	(i) 5.7	3.0	o/n	59:41:0
	(ii) 5.7	3.0	2 h	0:81:19
5	5.6 x 7	2.0 x 7	6 h	0:85:15

Table 2.1: Oxidation conditions with DMDO

At the same time, the oxidation was attempted using *in situ* generated TFDO **2.23** (Scheme 2.13). A first reaction with 6 eq of oxone® and 12 eq of 1,1,1-trifluoroacetone provided mainly starting silyl sulfide **2.1** and traces of sulfoxide **2.29**. The crude mixture was submitted to similar conditions a second time. The sulfoxide **2.29** was the major product of the reaction but the reaction never went on to form the sulfone.



2.1 **2.29**

(i) ratio (**2.1**: **2.29**) 83:17
(ii) ratio (**2.1**: **2.29**) 11:89

Scheme 2.13: Oxidation with TFDO

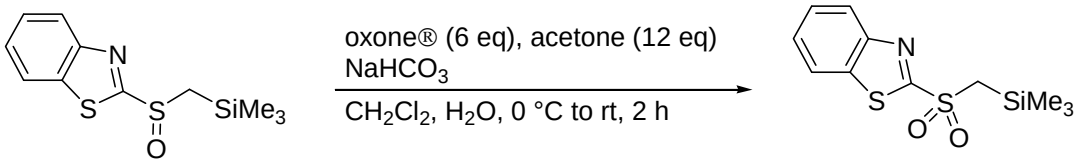
The formation of sulfoxide **2.29** using DMDO **2.18** not being optimal, we decided to study the impact of two parameters on its formation: the number of equivalent of acetone and the concentration of the reaction (Scheme 2.12, Table 2.2). Standard conditions are reported in entry 1 for a proper comparison. The use of twice the amount of acetone (entry 2) improved considerably the advancement of the reaction but it was still incomplete. Also, doubling the concentration of the reaction led to an improvement compared to standard conditions (entry 3). Consequently, the next logical step was to use 6.0 eq of oxone®, 12 eq of acetone and half the volume of CH_2Cl_2 (entry 4). We were able to isolate the sulfoxide **2.29** in 57%.

Entry	Acetone (eq)	Oxone® (eq)	Conc of sulfide **2.1** in CH_2Cl_2 (mol. L^{-1})	Time	Ratio (**2.1**: **2.29**)
1	5.6	6.0	0.23	2 h	91:9
2	11.9	6.0	0.25	2 h	56:44
3	5.6	6.0	0.49	2 h	70:30
4	12.0	6.0	0.47	2 h	16:84 (57%)[a]

[a]: isolated yield of sulfoxide **2.29**

Table 2.2: Determination of conditions for an optimum formation of sulfoxide 2.29

Synthesis of the sulfone **2.15** was investigated from this isolated sulfoxide **2.29** (Scheme 2.14). Thus, after 2 h of reaction of sulfoxide **2.29** with DMDO **2.18**, the sulfone **2.15** was finally accessible and isolated in a modest yield.

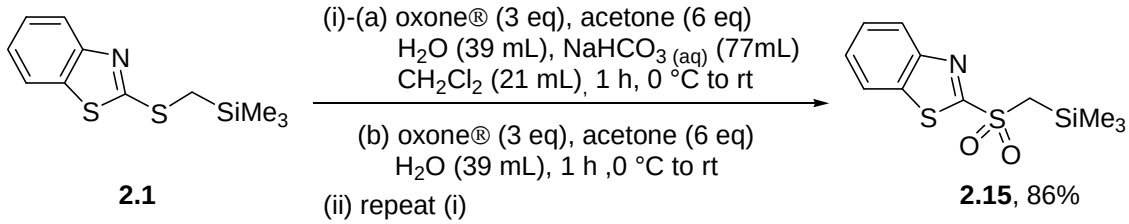


2.29 **2.15**, 48%

Scheme 2.14: Formation of the sulfone 2.15

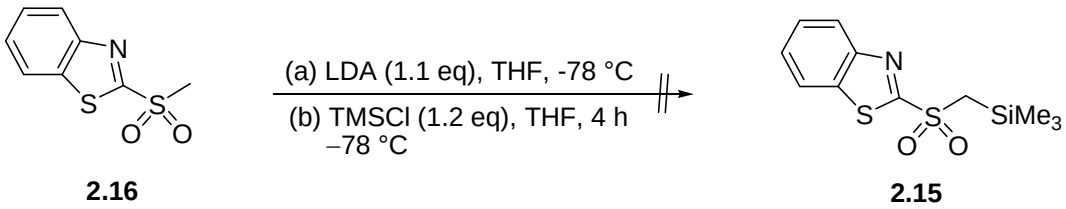
From those two series of reactions, we obtained important information. The sulfoxide **2.29** is an intermediate in the synthesis of the sulfone **2.15** which we can reach only by the addition of several batches of oxidising system. Optimum conditions to obtain the sulfoxide **2.29** were established with 12 eq of acetone, 6.0 eq of oxone® in presence of $NaHCO_3$ and with a concentration of sulfide in CH_2Cl_2 about 0.5 M. With this information in hand, we finally optimised the synthesis of the sulfone **2.15** (Scheme 2.15). A first addition of oxidising agent (6 eq acetone: 3 eq oxone® in water) to the sulfide **2.1** dissolved in CH_2Cl_2 and $NaHCO_3$ was done at 0 °C and the reaction was left for 1 h at rt. Then another addition (6 eq: 3 eq in water) was performed and the reaction was left for another hour. After this time and in order to keep a high concentration, the reaction was stopped, organic materials were extracted and after removal of the solvent, the crude mixture was submitted to the same oxidation procedure. Then, after a total of 24 eq of acetone, 12 eq of oxone® in 4 batches and after

4 h of reaction, we isolated a clean sulfone **2.15** in very good yield. No purification was required.



Scheme 2.15: Synthesis of the sulfone 2.15

In an attempt to access the sulfone **2.15** from the methyl sulfone **2.16**, we carried out the reaction of the lithiated sulfone and trimethylsilyl chloride in THF (Scheme 2.16). Unfortunately, this reaction was unsuccessful; we recovered starting sulfone **2.16**.



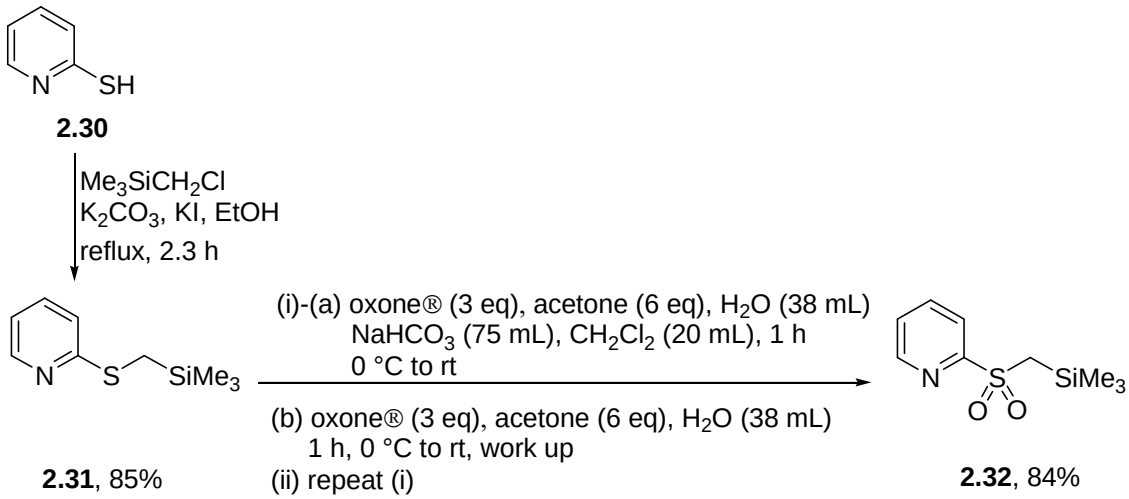
Scheme 2.16: Attempt of formation of sulfone 2.15

Naturally, the oxidation of α-silyl sulfide **2.12** was undertaken following the optimum conditions just established. After 4 h at rt, the sulfone **2.13** was obtained in poor yield.

Since the sequence towards the synthesis of the sulfone intermediate was well established, we prepared the pyridine-2-yl sulfone **2.32**.

2.2. Pyridin-2-yl sulfones derivatives

First following Kohra's procedure,[22] *S*-alkylation of thiol **2.30** with (chloromethyl)trimethylsilane gave the thioether **2.31** in excellent yield. Oxidation of sulfide **2.31** with DMDO **2.18**, generated *in situ*, provided the sulfone **2.32** in excellent yield (Scheme 2.17).



Scheme 2.17: Synthesis of sulfone 2.32

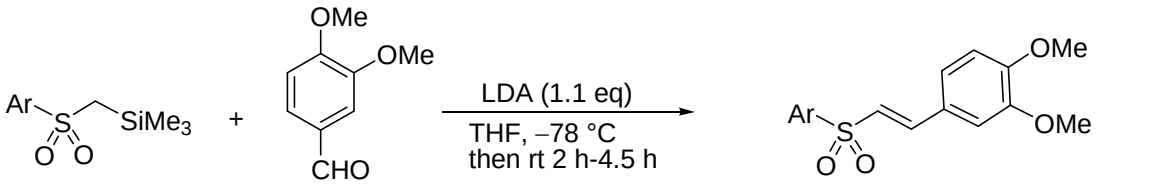
With three different heterocyclic sulfone intermediates **2.13**, **2.15** and **2.32** in hand, alkenation was naturally the next target reaction.

2.3. Modified Julia *versus* Peterson

Modified Julia reactions are particularly successful between alkyl BT-sulfones and electron-rich conjugated aldehydes and are highly *E*-stereoselective.[10] This reaction was found to be extremely water-sensitive and care had to be taken to ensure the absence of water. Every substrate needed to be dried prior to the reaction. BT-sulfones are particularly sensitive to nucleophilic attack at C2 and participate in *ipso* substitution reactions. To avoid that, the deprotonation of the sulfone must be done with non-nucleophilic bases (e.g. LDA). Moreover, self-condensation side reactions usually occur with non-sterically hindered sulfones and thus the process can be improved by adopting Barbier conditions (the base is added to a mixture of sulfone and aldehyde). On the other hand, PYR-sulfones

are less susceptible to *ipso* substitutions. The lack of electrophilicity of PYR moiety results in a better stability of the lithiated PYR-sulfone and then self condensations are avoided.

Modified Julia *versus* a Peterson reaction was investigated with sulfone **2.15** and veratraldehyde **2.33** and thus gave only the *E*-vinyl sulfone **2.34**, isolated in good yield. Similarly the *E*-vinyl sulfone **2.35** resulted from reaction of PYR-sulfone **2.32** and veratraldehyde **2.33** under Barbier conditions (Scheme 2.18). The conclusion is clear: Peterson alkenation is faster than the modified Julia reaction in direct competition.



2.15, Ar = BT
2.32, Ar = PYR

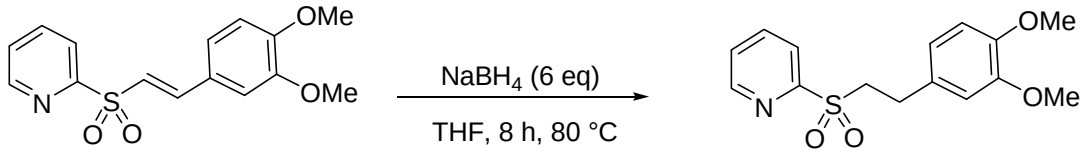
2.33

2.34, 63%, Ar = BT, *E*-alkene only
2.35, 58%, Ar = PYR, *E*-alkene only

Scheme 2.18: Peterson wins

Before making further attempts to form various vinyl sulfones, we had to think about how useful our discovery was and what scope we saw for this sequence. Vinyl sulfones are reversible inhibitors of cysteine proteases and more specifically are effective inhibitors against cruzain, a cysteine protease that plays a crucial role in the life cycle of *Trypanosoma cruzi*.[23] Vinyl sulfones have also been exploited as inhibitors of *Staphylococcus aureus* sortase and HIV-1 integrase.[23] For chemists, vinyl sulfones play an important role acting as efficient Michael acceptors and as dienophiles in Diels-Alder and related reactions and have been reviewed by Simpkins.[24]

We decided to investigate first an easy transformation with the reduction of the double bond in order to allow access to alkyl sulfones (Scheme 2.19). Attempts to reduce vinyl sulfone **2.35** using sodium borohydride in methanol were unsuccessful but reaction of PYR-sulfone **2.35** with $NaBH_4$ in THF provided alkyl sulfone **2.36**. Conditions were unsuccessful with BT-sulfone **2.34**.



2.35 **2.36**, 49%

Scheme 2.19: Formation of alkanes

2.4. Conclusion

A short route to heterocyclic vinyl sulfones was developed and it has been demonstrated that a silyl substituent is more reactive than the heterocyclic sulfones so that Peterson alkenation is more favourable than Modified Julia reaction. Since an alternative route to similar vinyl sulfones using the HWE reaction[25] appears more straightforward than our Peterson alkenation, the reaction was not studied further.

Part B

3. Solid-Phase Synthesis

3.1. Background

Since Merrifield's pioneering work[26] in solid-phase peptide synthesis, which gave him a Nobel Prize in 1984, solid-phase organic synthesis (SPOS) has experienced constant popularity and development. At the end of the 70's, Fréchet[27] and Leznoff[28,29] introduced the concept of solid-phase synthesis for the synthesis of small molecules by doing organic reactions where a substrate, reagent or catalyst was loaded on an insoluble polymer support. Since then a large number of organic reactions have been translated to the solid phase with success and this was the origin of the development of combinatorial chemistry in the 90's.

In SPOS, starting materials are attached to an insoluble support (polymer bead) by a linker that can later be cleaved under specific reaction conditions.[30] The support-bound intermediates are exposed to solutions of the desired reagents. Stoichiometric excesses can be used to obtain completion of the reaction. The excess reagents and by-products formed are removed by simply rinsing the solid supports with various solvents. Finally, the products are cleaved from the solid supports and subjected to purification (Figure 3.1).

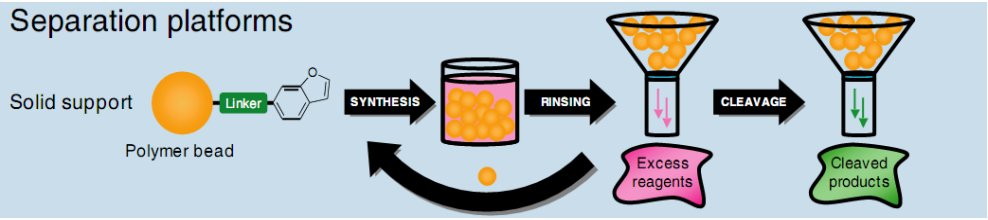


Figure 3.1: Solid-phase synthesis concept[30]

SPOS, which can be automated, proved to be quick and simple, providing time and labour advantages over the corresponding syntheses in solution phase.[31] Moreover, the yields and quality of products were improved by using an excess of the reagents. SPOS worked well for small scale reactions. This chemistry limits the use of toxic and flammable solvents as the only purification step

consists of a filtration, and therefore reduces waste. The polymer is also potentially recyclable and reactions are less harmful and dangerous due to the high chemical and physical stability of supports. Therefore SPOS holds a full place in the new concept of *green chemistry*. For all these reasons, SPOS is now recognized as an important methodology for constructing libraries of biologically active small molecules.[32]

3.2. Insoluble supports

Supports of different macroscopic shape have been used in SPOS.[33] Although the supports can take the shape of small discs or sheets, they are most commonly shaped as beads. The general requirements for a support are mechanical stability and chemical inertness under the reaction conditions to be used. The support is functionalized to allow the substrate to be attached to the support *via* a linker. Two major classes of solid support have been designed for SPOS: polystyrene (Figure 3.2) and polyacrylamide supports. Styrene polymers are crosslinked with divinyl benzene (styrene-DVB) in order to hold the long chains of polystyrene together in a spherical bead. Styrene-DVB is one of the most common support[33] (Figure 3.2) and was the one we used through our work in solid-phase chemistry.

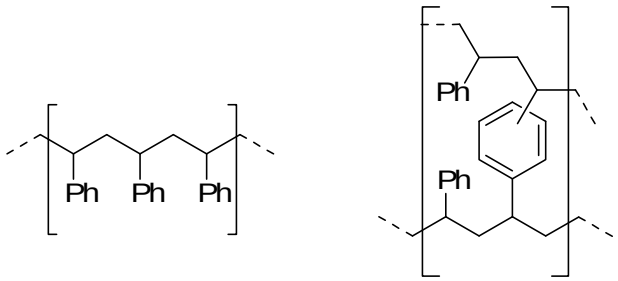


Figure 3.2: Polystyrene supports

3.3. Linkers

The linker is the connection between the molecule being synthesized and the solid support that is cleaved to release the desired molecule (Figure 3.3).

Figure 3.3: Connection of the substrate to polymer

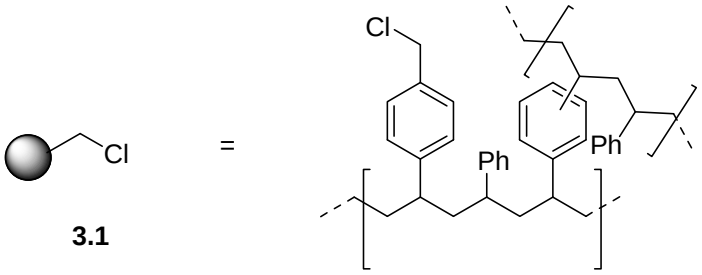
It is attached to the substrate through a functional group that is labile to the cleavage conditions (e.g. silyl ether, esters, carbamates, etc.) and orthogonal to reaction conditions. It is linked to the solid-phase polymer through a covalent stable bond (e.g. carbon-carbon, ether or thioether). The linker is then considered as a sort of supported protecting group. The ideal linker would fulfil a number of important criteria. It would be cheap and readily available. The attachment of the starting material would be achieved in high yield. The linker would be stable to the chemistry used in the synthesis. Cleavage would be efficient under conditions that do not damage the final product. The cleavage method should be easy to apply and should not introduce impurities that are difficult to remove.[34]

All linkers must survive the reaction conditions; therefore the choice of the synthetic route may determine the choice of the linker. A large variety of linkers[34] has been reported in the literature to allow a correct selection and a successful synthesis.

Three specific linkers have been used through my work: Wang and Merrifield linkers and a *p*-toluenesulfonic acid linker.

- *Merrifield linker (chloromethylated polystyrene)*

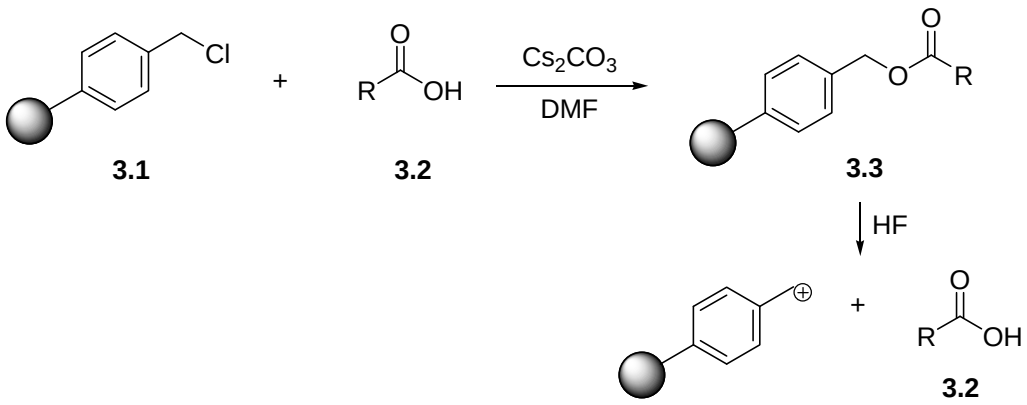
Merrifield Resin **3.1** is a polystyrene resin based on a copolymer of styrene and chloromethylstyrene cross-linked with DVB (up to 5%)(Figure 3.4).[26]



3.1

Figure 3.4: Merrifield resin

Carboxylic acids **3.2** are attached to the support **3.1** as esters **3.3** *via* the formation of their corresponding cesium carboxylate salts using Gisin's method[35] and acidic cleavage leads to the regeneration of the carboxylic acid **3.2** (Scheme 3.1).



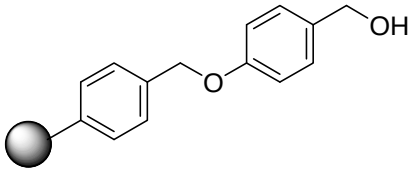
3.1 **3.2** **3.3** **3.2**

Scheme 3.1: Loading and cleavage of Merrifield resin

The lability of this linker depends on the stability of the generated carbocation. The cation formed in this case is relatively unstable making the linker-substrate bond really strong. Consequently a strong acid (HF) is required for the cleavage from resin which is the major inconvenience of this resin.

- *Wang linker (hydroxymethylphenoxy linker)*

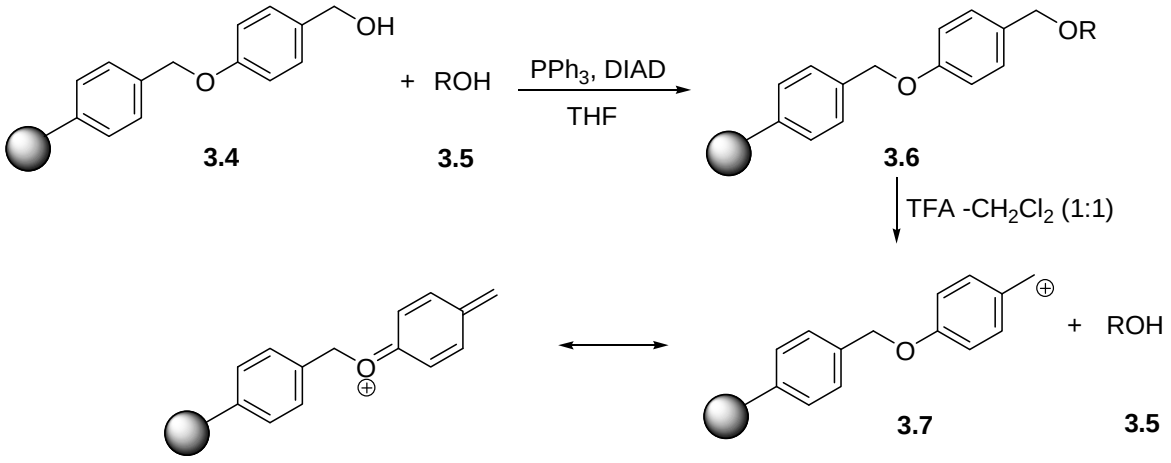
Wang resin **3.4**, first described in 1973 by Wang,[36] is the most popular support for SPOS (Figure 3.5).



3.4

Figure 3.5: Wang resin

Developed for the attachment of carboxylic acids, the Wang resin **3.4** can be used for the attachment of alcohols **3.5** as ethers **3.6** under Mitsunobu conditions (Scheme 3.2). The Wang resin **3.4** has a greater acid lability compared to Merrifield resin **3.1** due to the formation upon cleavage of a carbocation **3.7** stabilized by resonance. Therefore, cleavage is accomplished by TFA/CH_2Cl_2 (50-95%) treatment and leads to the regeneration of alcohol **3.5**.



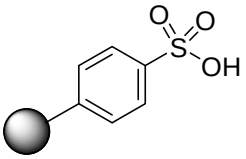
3.4 **3.5** **3.6** **3.7** **3.5**

Scheme 3.2: Loading and cleavage of Wang resin

- *p-Toluenesulfonic acid linker (MP-TsOH)*

MP-TsOH **3.8** is a sulfonated polystyrene resin that is a resin-bound equivalent of the strong acid, *p*-toluenesulfonic acid (TsOH) (Figure 3.6). It is a strong acid cation exchange resin. Ion exchange is the process in which ions, held by electrostatic forces to charged functional groups on the surface of an ion

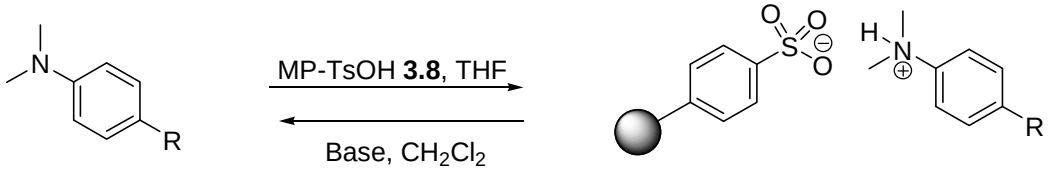
exchange resin, are exchanged for ions of similar charge from the solution in which the resin is immersed.



3.8

Figure 3.6: MP-TsOH resin

Resin **3.8** is used to perform capture and release of amine derivatives **3.9** in solution (Scheme 3.3). The cleavage proceeds by treatment with a base (Et_3N or NaOH) in CH_2Cl_2, nevertheless the resin **3.8** can be regenerated by contact with a strongly acidic solution.



3.9 **3.10**

Scheme 3.3: Loading of MP-TsOH

3.4. IRORI MacroKan™ technology

In my research, prior to the synthesis, the resin beads are loaded into a polypropylene reactor called an IRORI MacroKan™ (Figure 3.7). This is then sealed with a cap and the Kan is introduced into the glassware where the synthesis takes place as reagents flow through the porous reactor. The MacroKan™ has an internal volume of 2.4 mL and a pore size of 74 μm, and allows easier handling of the solid support. It is suitable for use with standard laboratory glassware and standard conditions (heating, cooling, mixing, etc.). The MacroKan™ can be filled with a maximum of 300 mg of resin.

Figure 3.7: IRORI MacroKans™

3.5. Site-site isolation or site-site interaction?

Among the many advantages of SPOS one unique property is the pseudo-dilution effect.[37] In an ideal representation of a resin support, the reactive groups are bound to the insoluble rigid polymer and so they have restricted motion. Intramolecular reactions between reactive groups are minimized, and the situation is approaching infinite dilution while the "concentration" of reactive groups is still relatively high. This notion is defined as "site-site isolation" or pseudo-dilution effect (Figure 3.8). In reality, the structural mobility of a polymer support is controlled by numerous factors such as cross-linking, loading, solvent, temperature and reagent concentrations. Site-site interactions can occur when the polymer support is very flexible or the sites are close in space.

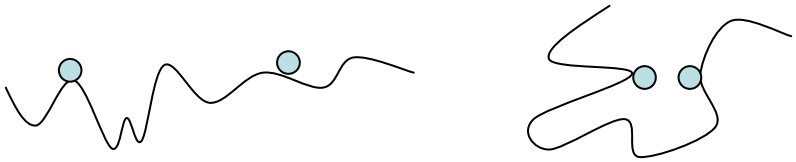


Figure 3.8: Site-site isolation and site-site interaction

Considering the pinacol coupling reaction between a supported aldehyde **3.11** and an aldehyde **3.12** in solution, the pseudo-dilution effect would favour the formation of the 1,2-diols **3.14** whereas homo-dimer **3.13** would be formed in the case of site-site interactions (Figure 3.9). It may be necessary to suppress site-site interactions to get the desired cross-pinacol products **3.14**.

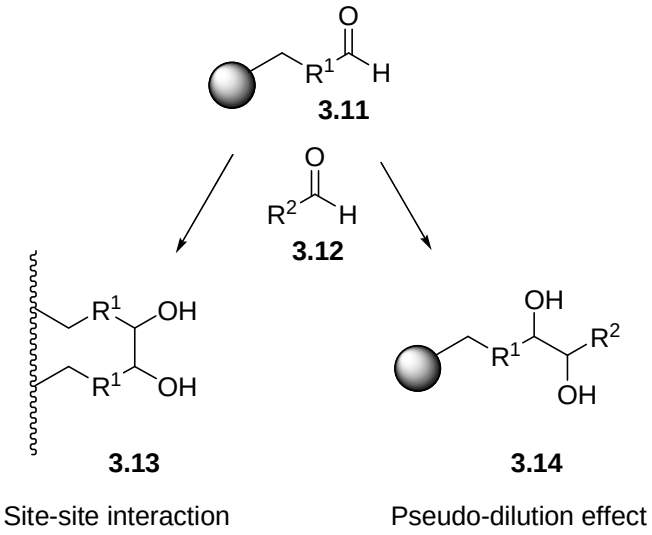


Figure 3.9: Pseudo-dilution effect or site-site interaction

These interactions can be limited by choosing a polymer with a high level of covalent cross-linking, and site-site interactions are further reduced by selecting a lower resin loading or a solvent that does not swell the resin to its maximum or by using lower reaction temperatures. Several reports[37,38,39,40] provided evidence that site-site isolation can be enhanced by low reaction temperatures without being really able to explain the phenomenon. Crosby and Kato[38] suggested that low temperatures (close to the polymer glass transition temperature T_g) result in relatively rigid polymer chains as observed in the dry state. More and more investigations have proved that site-site isolation and site-site interactions are in a dynamic equilibrium.[37] By controlling these parameters, site-site interactions can be reduced so that the desired intermolecular reaction dominates.

3.6. Monitoring the progress of solid-phase synthesis

Various methods have been developed for analyses of solid support-bound intermediates as alternatives to the cleavage of intermediates from the support and their characterization in solution. These techniques are fully described in Zaragoza's work[33] and an overview of the most common analytical methods is given in this paragraph.

Combustion analysis: this is mainly used to determine the amount of halogens, nitrogen or sulfur present in samples. The information allows an estimation of

the loading of a support and to verify complete displacement of a halide. The technique is destructive, not really precise and not fast enough to allow reaction monitoring.

Colorimetric assays: this is widely used in solid-phase synthesis of peptides and the technique allows detection of even small amounts of amines [Kaiser test, TNBS (2,4,6-trinitrobenzenesulfonic acid), etc.], alcohols [4-NBP (4-nitrobenzyl pyridine), etc.], thiols (Ellman's reagent).

IR spectroscopy: the method is fast, easy and cheap for the detection of certain functional groups on insoluble supports. However, IR spectroscopy is only sensitive to some functional groups and therefore not well suited to quantitative measurements.

MS analysis has proven useful for the analysis of resin-bound molecules. Carrasco *et al*.[41] developed a simple and general method by MALDI-TOF (**M**atrix-**A**ssisted **L**aser **D**esorption **I**onisation- **T**ime **o**f **F**light) allowing direct analysis of support–bound intermediates. The method relies on the use of a derivatised resin that incorporates a dual linker strategy and an ionization sequence (Figure 3.10). A photocleavable linker is used to attach an ionization sequence to the resin while a chemically cleavable linker is used to allow release of the target molecule and the desired final product can be isolated free of the linker sequences. The photocleavable linker and the ionization sequence allow better detection of small molecules as the global mass is increased, identification of the resin-bound products regardless of the presence of potential protonation sites on the molecule at any stage of the synthesis and without interfering with isolation of the products released into solution. This sensitive method requires a few mg of resin and appropriate equipment and skills.

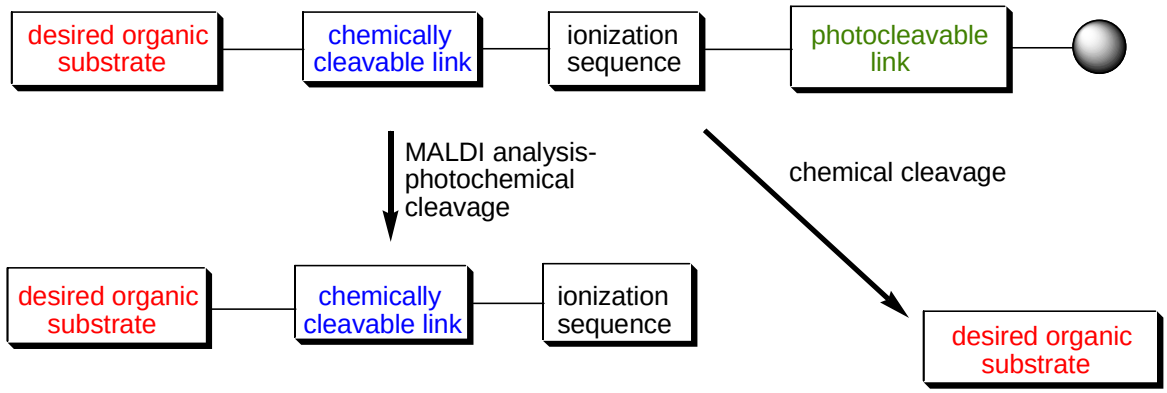


Figure 3.10: Representation of a chemical and a photochemical cleavage of a resin-bound molecule[41]

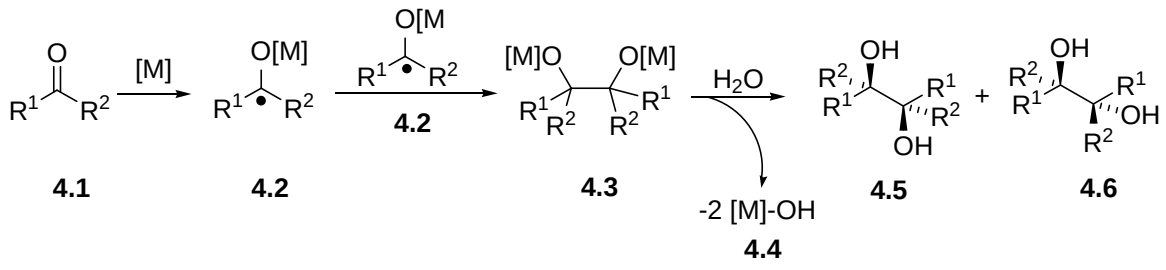
Alternatively, the analysis of non-photolabile linkers can be done with TOF-SIMS (**T**ime **o**f **F**light- **S**econdary **I**on **M**ass **S**pectrometry).[42] This technique is particularly adequate for analysis of supported peptides.

NMR analysis: MAS-NMR (**M**agic **A**ngle **S**pinning-NMR) has been especially adapted for recording NMR spectra of support-bound compounds. Cross-linked polymers have anisotropic physical properties. The magnetic field is intermittent at the interface of the polymer, which explains the broadness of spectra and the decrease in the resolution in the NMR spectra. This technique consists in keeping a sample of swollen solid support spinning at 1-2 KHz at the 'magic angle' (54.7° relative to the orientation of the magnetic field) in order to erase this discontinuity. The method enables the recording of much better resolved spectra (^{1}H NMR, 2D-NMR). However, it requires specific apparatus and skills.

Indirect analysis: this method consists in cleavage of the bound material from the solid support and analysis of the filtrate. The technique relies on sampling as release of the material from resin terminates synthesis but it does not require any specific equipment.

4. Pinacol Coupling Reactions

Many pharmacologically active substances contain the 1,2-diol structural motif and 1,2-diols can also serve as key intermediates in total synthesis, in chiral ligands or auxiliaries. A powerful way of setting up 1,2-diols is to form the C-C bond between the two hydroxyl groups by means of a pinacol reaction.[43] This involves the reduction of ketones or aldehydes **4.1** by a metal or compound containing a metal in a low oxidation state to give ketyl radicals **4.2**, which then homo-couple to give 1,2-*syn*-diols **4.5** and/or 1,2-*anti*-diols **4.6**, after quenching (Scheme 4.1). Although a very wide range of metals or low-valent metal ions can be used, including group 1 metals and samarium(II) ions,[44] my work focuses on the use of low valent titanium complexes in the synthesis of 1,2-diols. Therefore, a short review of this reaction follows concentrating on the use of titanium reagents rather than other metal-mediated pinacol reactions. Pinacol reactions can be divided into three categories: homo-coupling reactions, intramolecular reactions and cross-coupling reactions and these will be dealt with in turn. While the first two of these involve diastereocontrol, the last of these, cross-coupling reactions, presents the additional challenge of pairing up different coupling partners and it is this challenge that I tried to address in my research.



Scheme 4.1: Pinacol Coupling Reactions

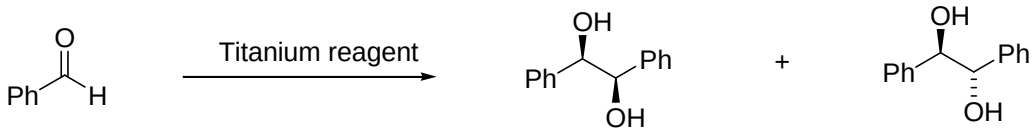
4.1. Homo-coupling reactions

Homo-coupling involves two molecules of the same carbonyl compound coupling to give 1,2-diols (Scheme 4.2). Studies have been devoted to the search for a low-valent titanium compound that would be suitable for the synthesis of

pinacols with high stereoselectivity. They will be presented in the following section and a comparison will be done based on benzaldehyde.

One of the most efficient systems was developed by Corey *et al*.[45] in 1976 (Table 4.1, entry 1). He found that aldehydes (e.g. benzaldehyde **4.7**) and ketones (e.g. cyclohexanone) could be homo-coupled to give the corresponding pinacols by treatment with a stoichiometric amount of $TiCl_4$ and magnesium amalgam at 0 °C in THF. Yields were excellent compared with previously reported methods (Mukaiyama,[46] Tyrlik[47]). Clerici *et al*. showed that pinacols **4.8** and **4.9** were quantitatively formed but with poor stereoselectivity [ratio(*syn*:*anti*) 1.3] by coupling benzaldehyde **4.7** with aqueous $TiCl_3$ in basic media (30% NaOH solution)[48] (entry 2) but with anhydrous $TiCl_3$ solution in CH_2Cl_2 the reaction was highly diastereoselective (entry 3).[49]

A few other examples of pinacol coupling mediated by titanium compounds have been reported. Handa and Inanaga[50] reported a highly stereoselective pinacol homo-coupling of aromatic aldehydes and of α,β-unsaturated aldehydes mediated by titanium(III)-magnesium systems such as $Cp_2TiCl_2/^{i}PrMgI$ or $Cp_2TiCl_2/^{sec}BuMgCl$ (entries 4,5). The 1,2-*syn*-stereoselectivity in the pinacol coupling of benzaldehyde **4.7** strongly depends on the reducing agent used for reduced titanocene dichloride. Moreover, aromatic aldehydes having less electron-donating group showed lower reactivity and selectivity when $Cp_2TiCl_2/^{sec}BuMgCl$ is used.



4.7 rac-**4.8** *syn* meso-**4.9** *anti*

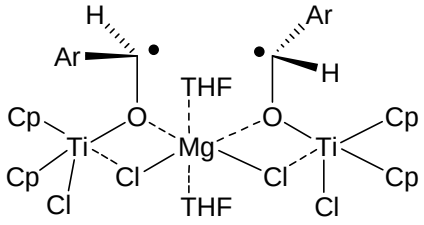
Scheme 4.2: Homo-coupling reaction titanium mediated

Entry	Titanium reagent + conditions	Yield[a]	Ratio (*syn*:*anti*) **4.8**: **4.9**
1	$TiCl_4$, Mg(Hg), THF, −10 °C to 0 °c, 0.5 h	84% 93%[b]	*Not reported*
2	15% aq ac $TiCl_3$, MeOH, 30% aq NaOH, pH 10, rt	100%	1.3
3	$TiCl_3$, CH_2Cl_2, rt, 0.5 h	65%	200:1
4	Cp_2TiCl_2, ^{i}PrMgI, THF, −78 °C to rt, 0.5 h	*Not reported*	80:1
5	Cp_2TiCl_2, ^{sec}BuMgCl, THF, −78 °C to rt, 1 h	96%[c]	100:1
6	Cp_2TiCl_2, ^{i}PrMgCl, PhMe, −78 °C to rt, 0.5 h	46%	97:3
7	Cp_2TiCl_2, ^{i}PrMgCl, PhMgBr, PhMe, −78 °C to rt, 1 h	94%	67:33
8	Cp_2TiCl(THF), excess NaCl, THF: H_2O (80:20), 0 °C to rt, 1 h	84%	94:6
9	3 mol% Cp_2TiCl_2, Zn, $MgBr_2$, Me_3SiCl, rt, 2 h	79%	92:8
10	3 mol% Cp_2Ti(Ph)Cl, Zn, Me_3SiCl, THF, rt, 1.2 h	88%	71:29

[a]: reactions based on benzaldehyde, [b]: cyclohexanone as substrate, [c]: anisaldehyde as substrate

Table 4.1: Reactions conditions

It has been proposed by Handa and Inanaga[50] that the high *syn*-selectivity for homo-coupling of aromatic aldehydes is due to the formation of a dimer of ketyl radicals **4.10** oriented in a manner which minimizes steric interactions between the phenyl groups (Figure 4.1).



4.10

Figure 4.1: Titanium(III)-complex responsible for selectivity

In accordance with these results, Yamamoto *et al.*[51] developed a system based on titanium(III) that gave similar selectivity. The treatment of Cp_2TiCl_2 with ^{i}PrMgCl followed by addition of benzaldehyde **4.7** provided the 1,2-diols **4.8** and **4.9** with excellent diastereoselectivity (Table 4.1, entry 6). On the other hand, Cp_2TiPh generated *in situ* by treatment of Cp_2TiCl_2 with ^{i}PrMgCl and then PhMgBr

converted benzaldehyde **4.7** into 1,2-diols **4.8** and 4.**9** with lower selectivity but in higher yield (entry 7).

Barden and Schwartz[52] reported a stereoselective pinacol coupling reaction of benzaldehyde **4.7** using Cp_2TiCl in THF in the presence of saturated aqueous sodium chloride; the diastereoselectivity was very high (entry 8).

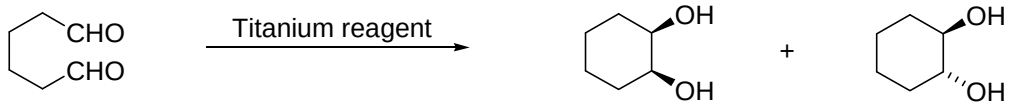
Various other reagent combinations employing stoichiometric amounts of titanium complexes have been used for diastereoselectivity in pinacol coupling [e.g. Cp_2TiCl_2/SmI_2 [50] and $Ti(O^iPr)_4/EtMgBr$[53]]. However, a catalytic version of the highly diastereoselective stoichiometric protocols established for pinacol homo-coupling was highly desirable for economic and environmental reasons. Recent studies have revealed that pinacol coupling reactions can be rendered stereoselective and catalytic in titanium with the use of additives or modified ligands. Maury *et al.*[54] reported the first pinacol coupling reaction that was catalytic in titanium, by using the $TiCl_4$, Li(Hg) system in the presence of $AlCl_3$, a transmetallation reaction of the titanium pinacolate intermediates with $AlCl_3$ regenerated the pre-catalyst $TiCl_4$ and gave aluminium diolates which were inert towards the reducing agent and not transformed into the alkene.

At the same time, Gansäuer[55] reported that the pinacol homo-coupling of benzaldehyde **4.7** could be catalyzed by a low valent complex derived from titanocene dichloride in the presence of Me_3SiCl and $MgBr_2$ as additives, and Zn as a reducing agent to give the racemic 1,2–diols **4.8** and **4.9** in very good yield and with excellent diastereoselectivity [ratio (*syn: anti)* > 96:4] (entry 9). Another example of a catalytic system was described by Yamamoto *et al.*[51,56] who used $Cp_2Ti(Ph)Cl/Zn/Me_3SiCl$ system in the homo-coupling of benzaldehyde **4.7** (entry 10). However, the diastereoselectivity was not as good as other systems.

4.2. Intramolecular pinacol coupling

Intramolecular pinacol reactions have received less attention compared to the intermolecular couplings of aldehydes. The use of the powerful low valent

titanium system developed by Corey *et al*.[45] in 1976 for intermolecular pinacol homo-couplings has already been discussed. This system proved to be even better when applied to intramolecular couplings. *Syn*-selectivity is total and yields varied from modest for a 6-membered ring (32%) (Scheme 4.3, Table 4.2) to very good for the formation of a 4-membered ring (81%).



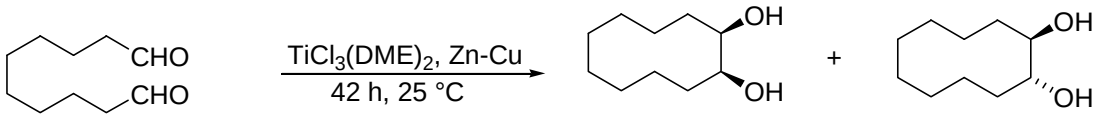
4.11 **4.12** **4.13**

Scheme 4.3: Titanium(II)-mediated pinacol coupling

Entry	Reaction conditions	Yield	Ratio (*syn*: *anti*) **4.12**:**4.13**
1	$TiCl_4$, Mg(Hg)	32%	*Syn* only
2	$TiCl_3(DME)_2$, Zn-Cu, 42 h, 25 °C	85%	*Syn* only
3	10 mol % $Cp_2Ti(Ph)Cl$, Zn, Me_3SiCl, THF, rt, 14 h	60%	1:99

Table 4.2: Intramolecular couplings yielding 6-membered rings

$TiCl_3$, Zn-Cu introduced by McMurry and Rico[57] was used successfully for the intramolecular coupling of various aldehydes (Scheme 4.3). It appeared that the 1,2-*syn*-isomer dominated for 6-membered ring and smaller (Table 4.2, entry 2), whereas the 1,2-*anti*-isomer became predominant with rings containing 8 or more carbons (Scheme 4.4). In comparison to the results obtained by Corey with $TiCl_4$, Mg(Hg), yields are much higher.

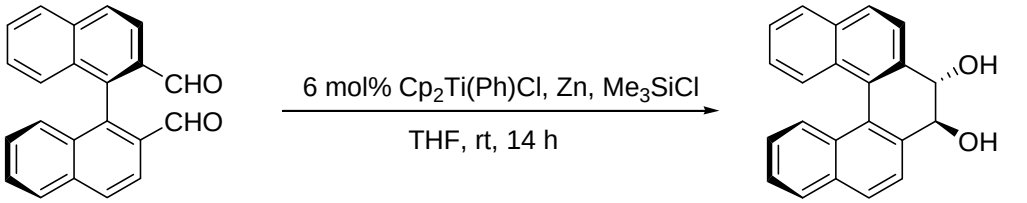


4.14 **4.15** 80% **4.16**
ratio (*syn:anti*) 25:75

Scheme 4.4: Formation of large ring using pinacol coupling reaction

With the idea of promoting *anti*-selectivity, Yamamoto *et al*.[51] used his sterically bulky complex, $Cp_2Ti(Ph)Cl$. In the presence of 6-10 mol% $Cp_2Ti(Ph)Cl$, dials **4.11** and **4.17** were reduced at ambient temperature to afford 1,2-diols **4.12/4.13**

and **4.18** with excellent *anti*-selectivity (Scheme 4.3, Table 4.2, entry 3 and Scheme 4.5).



4.17

4.18, 78%
ratio (*syn*: *anti*) 0:100
99.5% ee

Scheme 4.5: Titanium(III)-mediated catalytic pinacol coupling

The high *anti*-selectivity observed with this cyclic substrate **4.17** was explained as follows (Figure 4.2). The bulky titanium-bound ketyl can combine only if the $Cp_2(Ph)TiO$ moieties occupy axial positions in order to minimize steric repulsion, and this then favours a 1,2-*anti*-relationship.

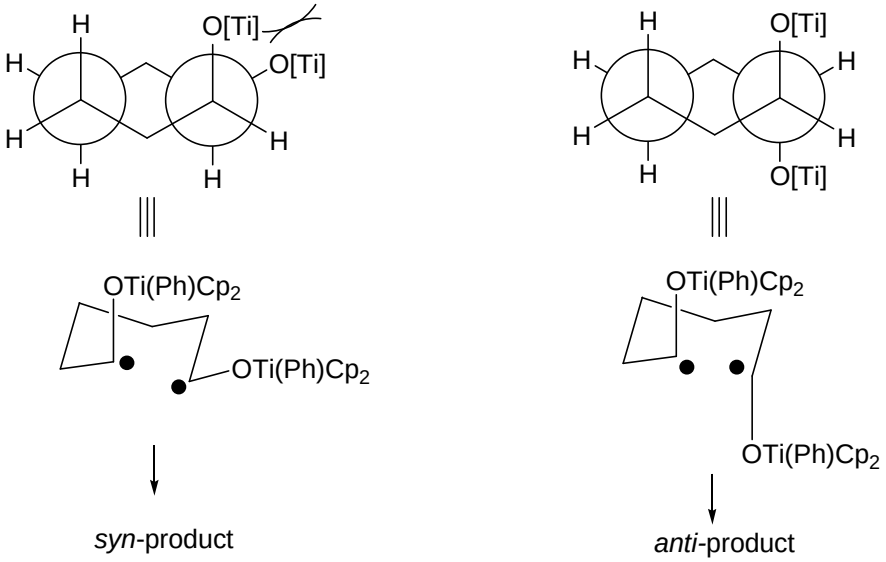
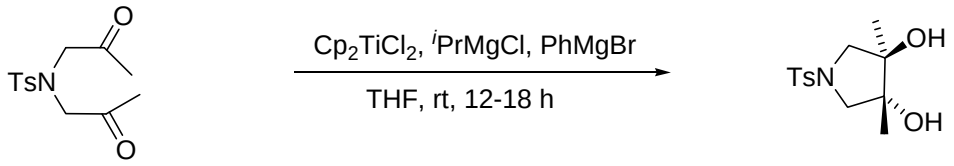


Figure 4.2: Mechanism of stereoselection

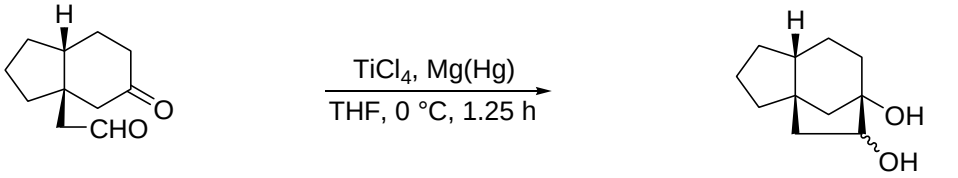
Following Yamamoto's results, Handa *et al*.[58] published the first successful diastereoselective pinacol coupling of dicarbonyl species to produce *N*-protected heterocyclic 1,2-diols e.g. diketones **4.19** gave diols **4.20** in high yield (Scheme 4.6).



4.19 **4.20**, 64%
anti only

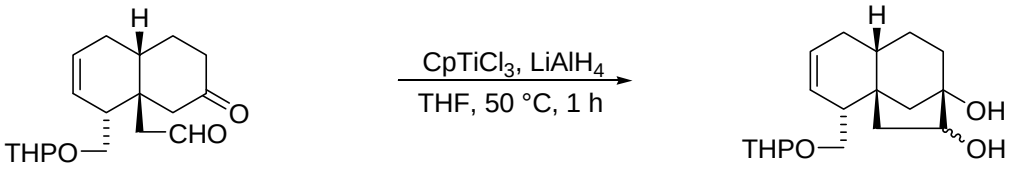
Scheme 4.6: Formation of heterocyclic 1,2-diols using pinacol coupling

Intramolecular pinacol reactions are not restricted to the use of symmetrical dialdehydes. Corey *et al*.[45] tested his system on unsymmetrical aldehyde **4.21** and observed excellent yield and good diastereoselectivity (Scheme 4.7). Nevertheless the system proved to be totally ineffective for a related cyclisation and had to be modified to $CpTiCl_3$-$LiAlH_4$ (Scheme 4.8).



4.21 **4.22**, 90%
ratio (*syn:anti*) 80:20

Scheme 4.7: Titanium(II)-mediated cross-coupling reaction



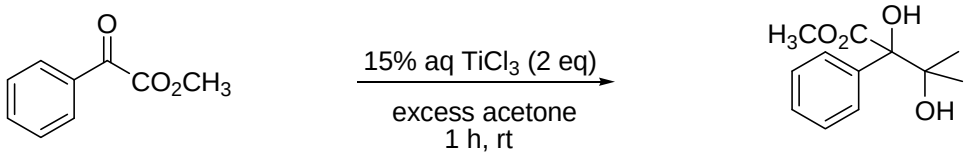
4.23 **4.24**, 55%
ratio (*syn:anti*) 71:29

Scheme 4.8: Intramolecular cross-coupling reaction

4.3. Pinacol cross-coupling reactions

The synthesis of unsymmetrical pinacols by pinacol cross-coupling remains a challenge as only a few examples have been reported in the literature and they are dependant upon the structural or electronic differences between the two reactants and on the low-valent titanium species used. Clerici and Porta[59]

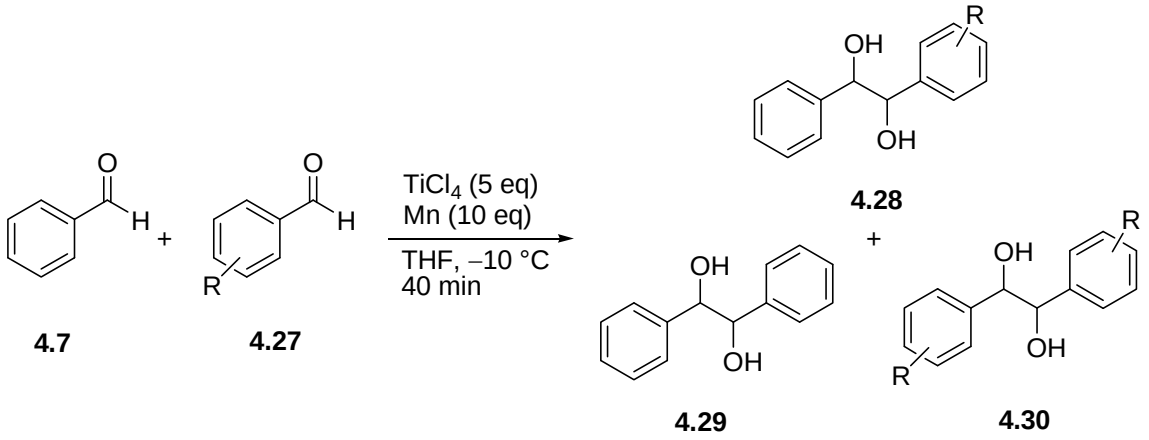
reported a pinacol cross-coupling between ketone **4.25** and acetone using aqueous titanium trichloride and acetone as co-solvent (Scheme 4.9). Ketone **4.25** will be reduced in preference to acetone because it produces a more stable radical. Presumably, the large excess of acetone prevented significant homo-coupling of ketone **4.25**.



4.25 **4.26**, 85%

Scheme 4.9: Titanium(III)-mediated pinacol cross-coupling reaction

Recently, Duan *et al.*[60] reported a study on the synthesis of unsymmetrical pinacols by coupling of structurally similar aromatic aldehydes in the presence of low-valent titanium species. They chose benzaldehyde **4.7** and *p*-anisaldehyde as substrates and studied the effect of the low-valent titanium species (nature and amount), the solvent and the temperature on the formation of the cross-pinacol. It was observed that the reactions initiated by $TiCl_4$, Mn species afforded the cross-pinacol products in good yield. The best selectivity was obtained with 5 eq of titanium species and additives and temperature had no significant effect on the transformation however the solvent did. The reaction gave alkenes in acetonitrile while no reaction was observed in dichloromethane. Under the optimized reaction conditions, a variety of unsymmetrical pinacols **4.28** were efficiently prepared from benzaldehyde **4.7** and substituted benzaldehyde **4.27** (Scheme 4.10, Table 4.3). Results showed that the cross-couplings proceeded with high selectivity when substrates containing nitrogen or oxygen-atom functional groups were used (i.e. OH, OMe, NMe_2, NHCOPh). On the contrary, reaction with substrates **4.27** containing F or Me substituents gave a mixture of the three possible pinacols which were inseparable by chromatography. Both electron-donating and electron-withdrawing aromatic aldehydes gave moderate to good yields and they observed in every case a high *syn*-selectivity. Substituents appeared to affect the outcome of the reaction through their strong affinity to the surface of the titanium particles rather than through altering the reduction potential or electronic density of the carbonyl moiety.



Scheme 4.10: Pinacol Cross-coupling reactions

Entry	R	Time (min)	Yield[a]	Ratio (*syn*:*anti*)
1	4-F	22	40%[b]	-
2	4-Me	24	41%[b]	-
3	4-Me_2N	40	76%[c]	88:12
4	4-MeO	30	68%[c]	91:9
5	3-MeO	40	61%[c]	80:20
6	4-OH	30	64%[c]	85:15
7	4-CO_2Me	45	55%[c]	71:29
8	3,4-$(MeO)_2$	30	65%[c]	79:21
9	4-NHCOPh	40	70%[c]	80:20
10	4-$CONEt_2$	45	66%[c]	74:26

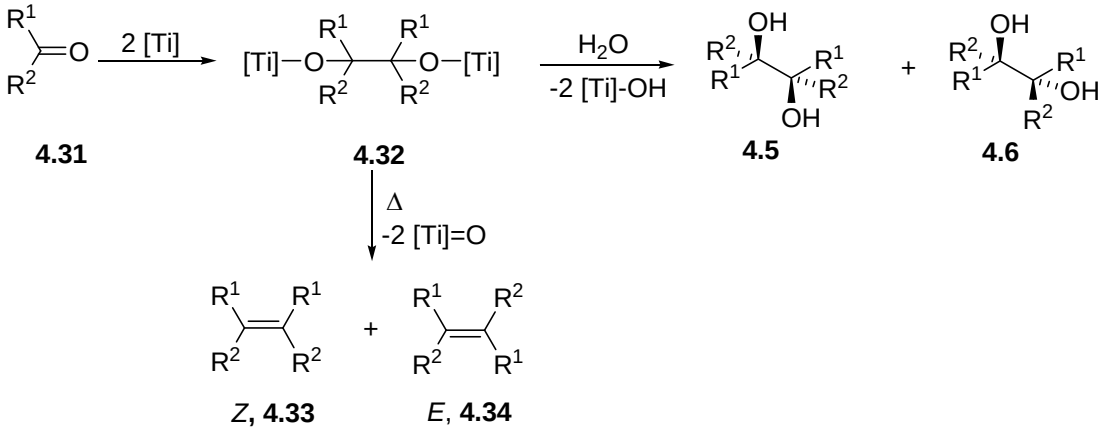
[a]: isolated yield of cross-coupling product **4.28**; [b]: mixture of the three coupling products was obtained;
[c]: ratio of the three compounds (**4.28**: **4.29**:**4.30**) ranged from 7:1:1 to 3:1:0.9

Table 4.3: Conditions for the preparation of unsymmetrical pinacols

4.4. McMurry reactions

The low valent titanium-mediated pinacol reaction is the first step in an important alkenation reaction, now termed the McMurry reaction. In 1973, Tyrlik and Wolochowics[47] discovered that $TiCl_3$-Mg in THF reductively coupled aldehydes and ketones **4.31** to produce alkenes **4.33** and **4.34**. On the other hand Mukaiyama *et al.*[46] found that, depending on the reaction conditions, the $TiCl_4$-Zn system selectively coupled aromatic aldehydes or ketones **4.31** to

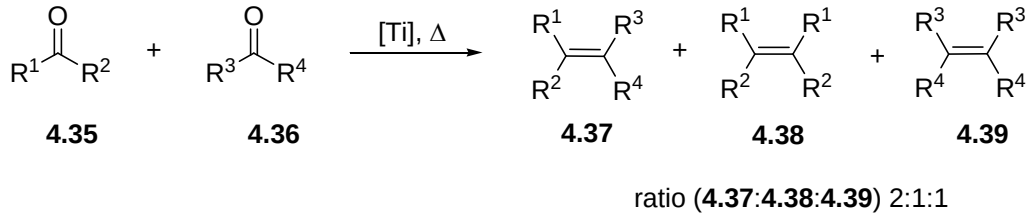
produce either 1,2-diols **4.5** and **4.6** or alkenes **4.33** and **4.34**. In 1974, McMurry and Fleming[61] described a method for the reductive coupling of aldehydes or ketones that employed $TiCl_3$ and $LiAlH_4$, and this paper gave rise to the reaction name. The McMurry reaction has been widely used and comprehensively reviewed.[62-64] In the vast majority of cases, its mechanism is accepted to involve the conversion of ketones or aldehydes **4.31** into ketyl radicals which couple to give titanopinacolate intermediates **4.32**, which are then deoxygenated to give *E* and *Z* alkenes **4.33** and **4.34** (Scheme 4.11). Given the close relationship between the McMurry and titanium-mediated pinacol reactions, it is also worth considering what is known about McMurry cross-couplings.



Scheme 4.11: McMurry coupling reactions

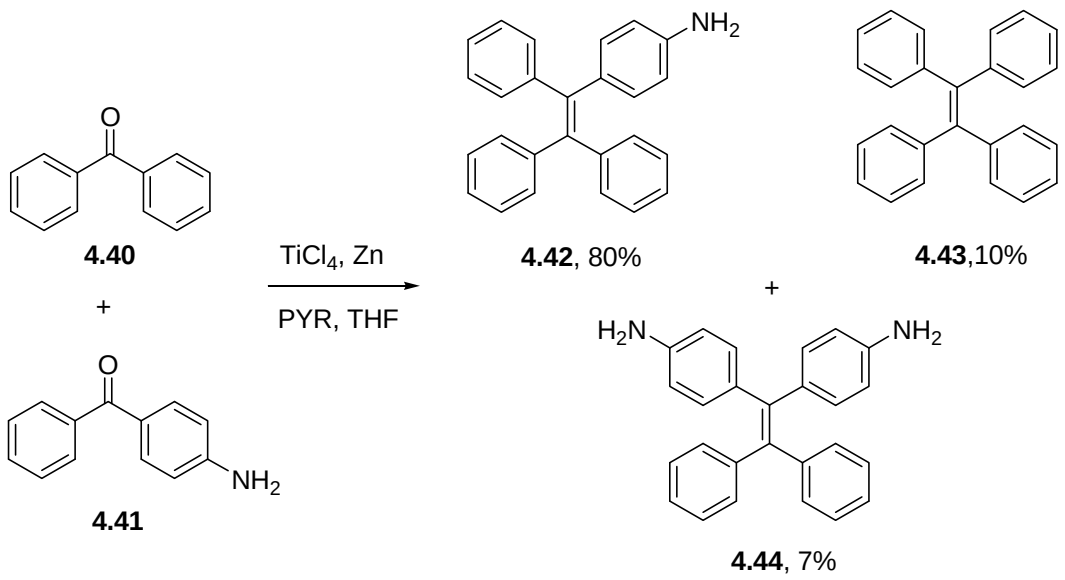
4.5. McMurry cross-coupling reactions

The intermolecular McMurry alkenation reaction is usually limited to the synthesis of symmetrical alkenes by dimerisation of a ketone or aldehyde. When a mixture of two different carbonyl compounds **4.35** and **4.36** is subjected to McMurry alkenation conditions, generally a mixture of the cross-coupled product **4.37** and the two homo-coupled **4.38** and **4.39** is produced, with the ratio of products biased away from the statistical 2:1:1 by preferential homo-coupling of the more easily reduced coupling partner (Scheme 4.12).[62,65] Generally, the way to get good conversion of a carbonyl compound into the cross-coupled product is to use an excess of the other carbonyl component.



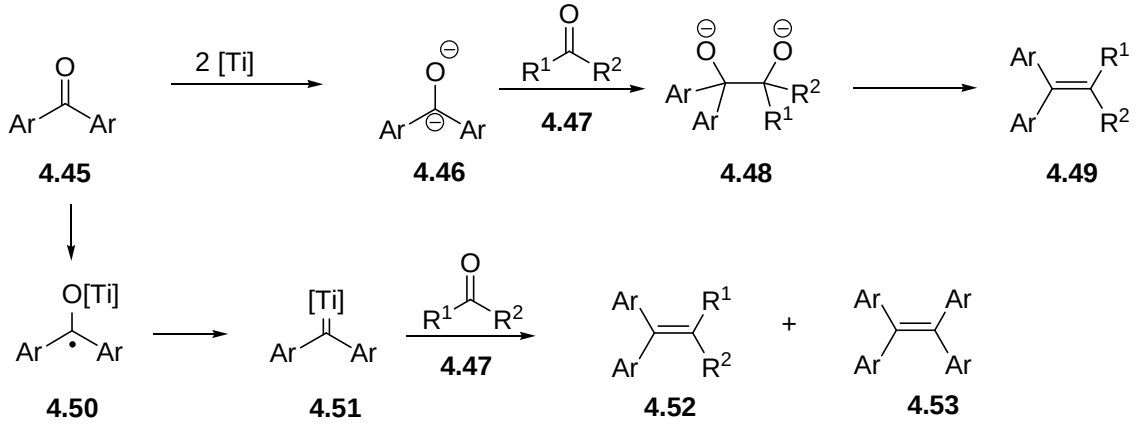
Scheme 4.12: McMurry cross-coupling reaction

The ratio can also be altered to favour cross-coupling if the two carbonyl compounds have similar reduction potentials and one of the two carbonyl compounds has a group that coordinates to the metal.[60,66,67] For example, Duan *et al*. reported cross-coupling between benzophenone **4.40** and diaryl ketone **4.41** (Scheme 4.13). The presence of the amino group favoured the formation of the cross-coupling **4.42** over the homo-coupling products **4.43** and **4.44**.



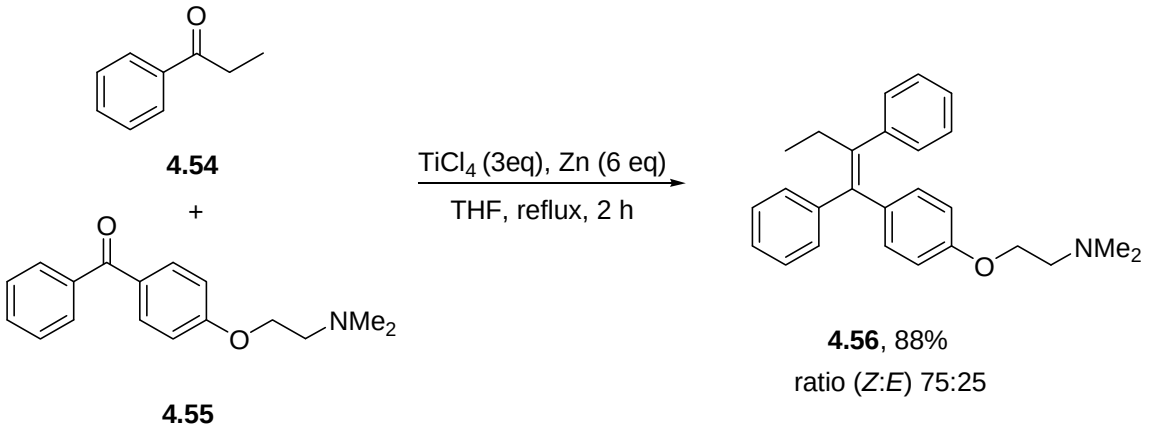
Scheme 4.13: McMurry cross-coupling reaction

If only one of the coupling partners is a diaryl compound, cross-coupling can also occur because such compounds are very easily reduced. Cross-coupling reaction may take place either through double reduction to a dianion **4.46** and nucleophilic attack on the other partner[62] **4.47** or possibly titanium carbenoid generation **4.51** and alkylidenation (Scheme 4.14).[64]



Scheme 4.14: McMurry cross-coupling reaction

A McMurry cross-coupling reaction of this type has been used as the key step in the synthesis of the anti-tumor drug tamoxifen **4.56** and several of its analogues (Scheme 4.15).[68]

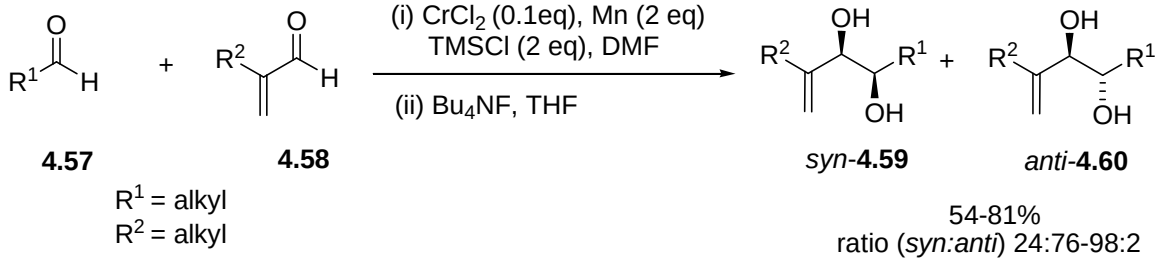


Scheme 4.15: Example of a cross-coupling reaction

In summary, the problem with intermolecular carbonyl coupling is that homo-coupling competes. This is particularly problematic when one coupling partner is significantly more easily reduced as it will preferentially homo-couple. There are isolated examples of successful pinacol and McMurry cross-couplings but generally to be successful a large excess of the less reactive carbonyl group must be used.

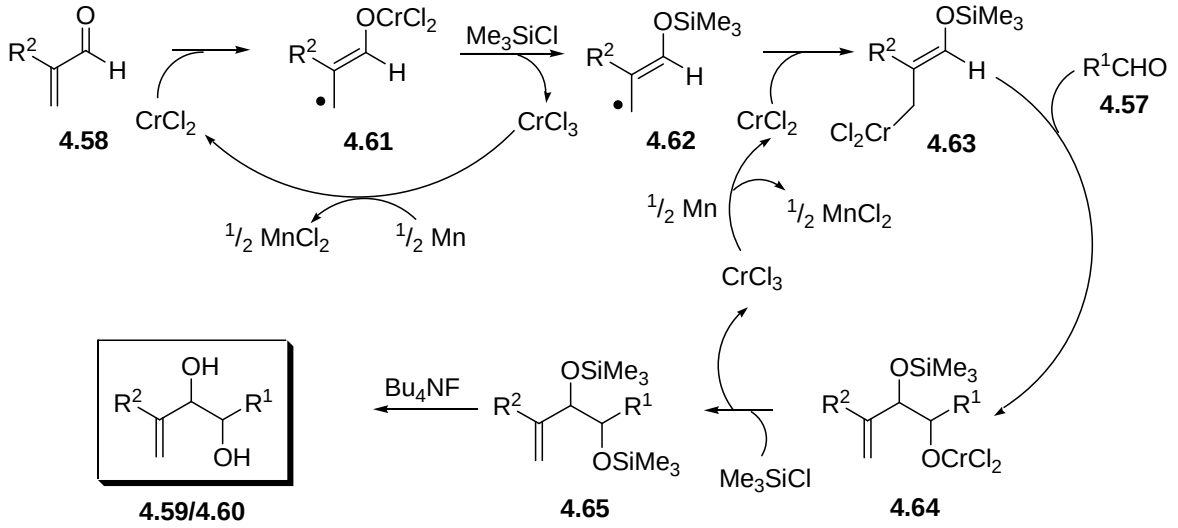
4.6. Alternative pinacol-like approach to 1,2-diols using chromium reagents

A chromium catalyzed pinacol-like cross coupling reaction of α,β-unsaturated carbonyl compounds and aldehydes has been reported by Groth and co-workers.[69,70] Various vinyl ketones were coupled with aldehydes to afford 1,2-diols diastereoselectively. Then they extended the method to chromium-catalysed cross-couplings of sterically demanding acroleins **4.58** and a variety of aldehydes **4.57** to afford highly substituted pinacols **4.59** and **4.60** (Scheme 4.16).



Scheme 4.16: Chromium-catalysed coupling reactions

Ketyl radicals are not intermediates in this pinacol-like reaction (Scheme 4.17). Rather, reduction of the acroleins derivative **4.58** gives an allyl chromium reagent **4.63**. A mixture of *E*- and *Z*- allyl chromium species **4.63** reacts with aldehyde **4.57** *via* a nucleophilic reaction and affords a mixture of *syn* and *anti*-pinacols **4.59** and **4.60**.



Scheme 4.17: Proposed mechanism for a chromium-catalysed pinacol-like reaction

The origin of the diastereoselectivity is believed to be substrate dependent. Indeed, they observed increase of the *syn*-diastereoselectivity as R^2 becomes bulkier. While α-branched acroleins lead predominantly to 1,2-*syn*-diols, 1,2-*anti*-diols are preferred with linear alkyl side chains. They also showed the importance of trimethylsilyl chloride to increase the *syn*-selectivity.[71]

Although pinacol-like cross-coupling reactions catalysed by chromium catalysts are efficient reactions with high yields, and high and controlled diastereoselectivity, the reaction relies on using an α,β-unsaturated carbonyl compounds as one of the substrates and its mechanism is different from the pinacol reaction.

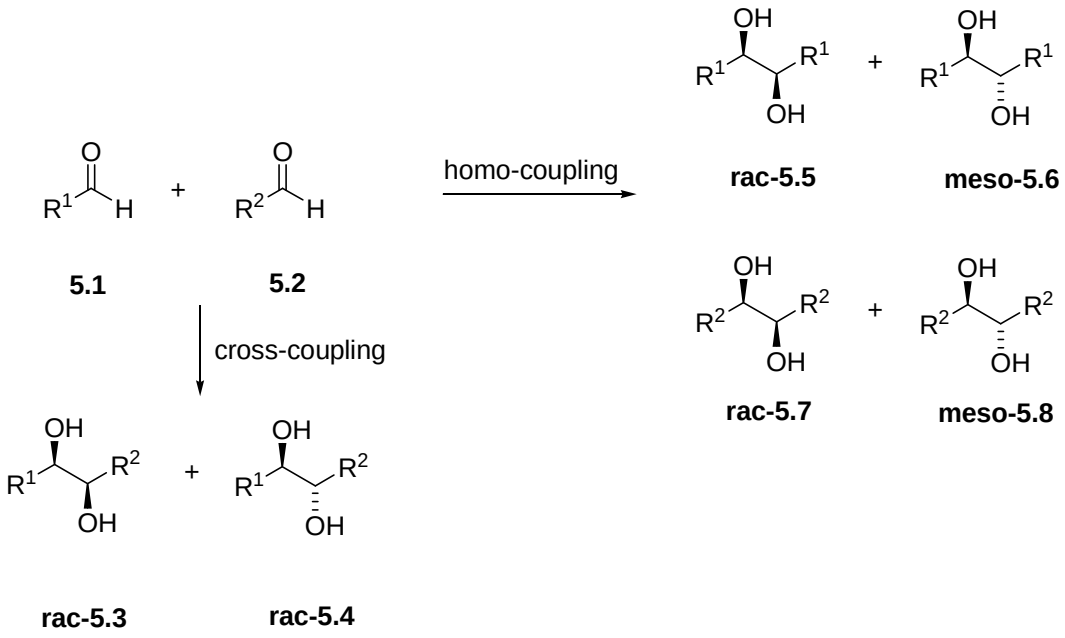
4.7. Conclusion

Pinacol and McMurry coupling reactions are among the most useful synthetic methods for forming carbon–carbon bonds, and have served as the key step in the synthesis of various natural and synthetic products. However, a general method of carrying out pinacol cross-couplings is needed. Our new approach to this is described in the next chapter.

5. Application of Solid-Phase Synthesis to Pinacol Cross-Coupling

5.1. Hypothesis

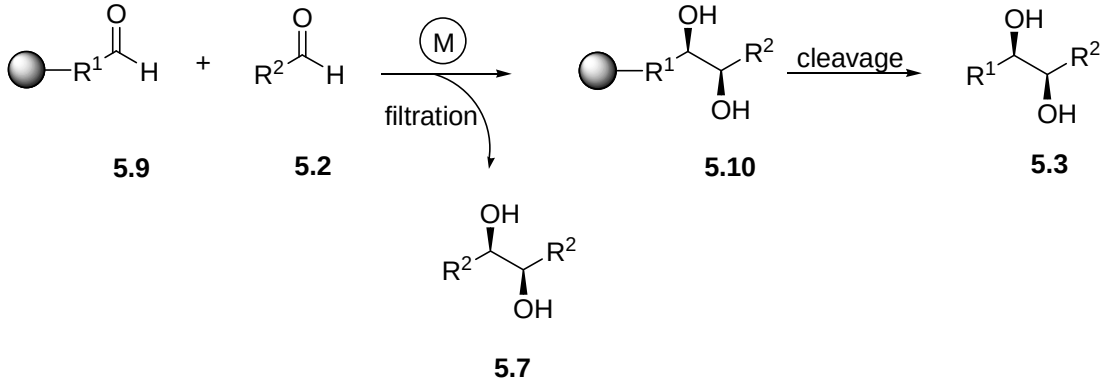
Although the pinacol homo-coupling reaction has been widely used, the cross-coupling reaction has not been exploited so much. The difficulty resides in the homo-coupling by-products generated in the reactions (Scheme 5.1). Thus, aldehydes **5.1** and **5.2** can cross-couple to give 1,2-diols **5.3** and **5.4**, but can also form homo-coupled products **5.5**, **5.6**, **5.7** and **5.8**. If one of the aldehydes (**5.1**) is much more easily reduced then the homo-coupled product **5.5** and **5.6** will be produced rapidly. The homo-coupled product **5.7** and **5.8** will also form as there would no longer be any aldehyde **5.1** available. Diastereoselective pinacol reactions reduce the number of possible products but do not overcome the competition between homo-coupling and cross-coupling.



Scheme 5.1: Homo- and cross-coupling reactions

As discussed in chapter 3, recently there has been great interest in SPOS because the use of polymer supports makes purification steps easier. Pseudo-dilution is a less exploited property of synthesis on resin but we proposed to demonstrate that this property might overcome the problem with the pinacol cross-coupling

reaction. The more easily reduced carbonyl compound **5.1** would be attached to an insoluble support (**5.9**). The second reactant **5.2** would be in solution and addition of the low–valent metal would begin by generating an immobilised ketyl radical from the more reactive partner (Scheme 5.2). Homo-coupling on resin would be prevented by pseudo-dilution effect and only the cross–coupling product **5.10** would form on the resin so that 1,2-diols **5.3** would be obtained after cleavage from resin. Any homo-dimers **5.7** produced in solution would be removed by filtration. Furthermore, formation of the homo-dimer **5.7** would be minimized because it is the product of homo-coupling of the less reactive carbonyl compound. In this way, the cross–coupling reaction would be optimized. Reagent systems known to favour the *syn*-diastereomer would be employed so that a single diol would be produced.

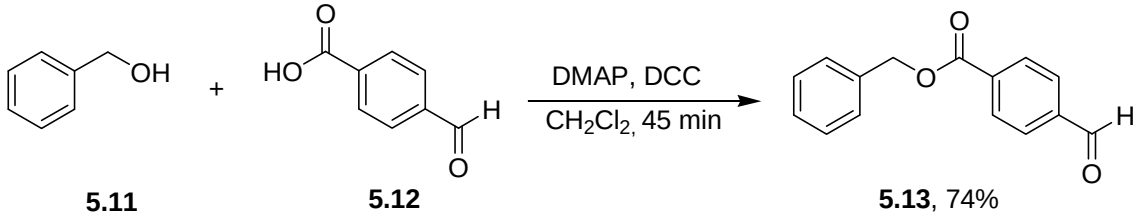


Scheme 5.2: Pinacol coupling reaction on solid-phase

5.2. Solution phase synthesis

The first work took place in solution phase and consisted of a simulation of the linkage between the resin and the substrate in order to enable the observation of potential problems and to overcome these prior to transfer to solid-phase synthesis.

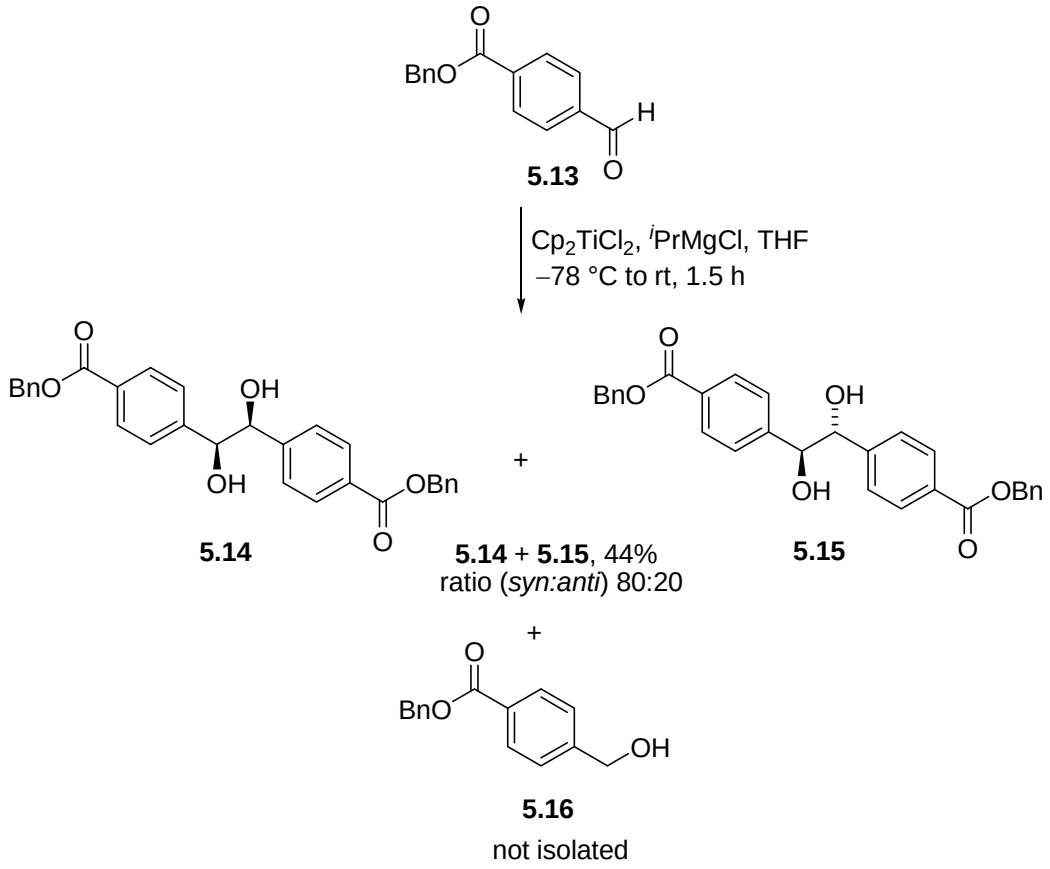
The first substrate chosen **5.12** contained an aldehyde for the pinacol coupling and a carboxylic acid group for making an ester linkage with resins. Steglich esterification[72] with benzyl alcohol **5.11** (which mimics hydroxymethylpoly styrene) gave the benzyl ester **5.13** in good yield (Scheme 5.3) and permitted us to explore the homo-coupling reaction.



5.11 **5.12** **5.13**, 74%

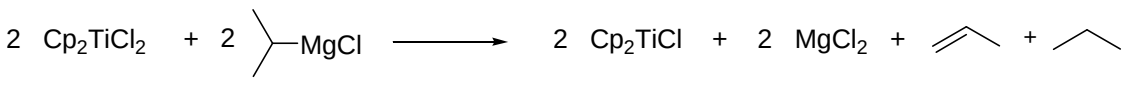
Scheme 5.3: Preparation of the substrate

As previously seen, Yamamoto *et al.*[51] and Handa and Inanaga,[50] both reported a highly stereoselective pinacol coupling mediated by titanium-magnesium complexes. Their results convinced us to carry out reactions using the Cp_2TiCl_2 /^{i}PrMgCl system (Scheme 5.4). By adaptation of their method, pinacol coupling of aldehyde **5.13** gave 1,2-diols **5.14** and **5.15** with a good *syn*-selectivity. Several clues allowed us to determine the ratio of isomers obtained. Firstly, Handa and Inanaga[50] reported determination of the *syn*:*anti*-ratio of isomers by ^{1}H NMR analysis (400 MHz) and established that the proton α to the hydroxyl group in 1,2-*syn*-isomer appears 0.1-0.2 ppm higher field than the one in 1,2-*anti*-isomer. Moreover, we saw in the last chapter that Yamamoto *et al.*[51] observed formation of the *syn*-isomer as the major compound in the homo-coupling of benzaldehyde using the Cp_2TiCl_2/ ^{i}PrMgI system. Thus, we assumed that the proton α to -OH in the 1,2-*syn*-isomer **5.14** corresponds to the signal at 4.67 ppm whereas the same proton in the 1,2-*anti*-isomer **5.15** corresponds to the signal at 4.93 ppm. However, despite the good selectivity, the combined isolated yield of diols **5.14** and **5.15** was low and there was a side-product, the alcohol **5.16**. This was not isolated from other minor impurities but from the ^{1}H NMR analysis of this fraction we were able to identify the CH_2 α to OH as a singlet at 4.70 ppm ($CDCl_3$).



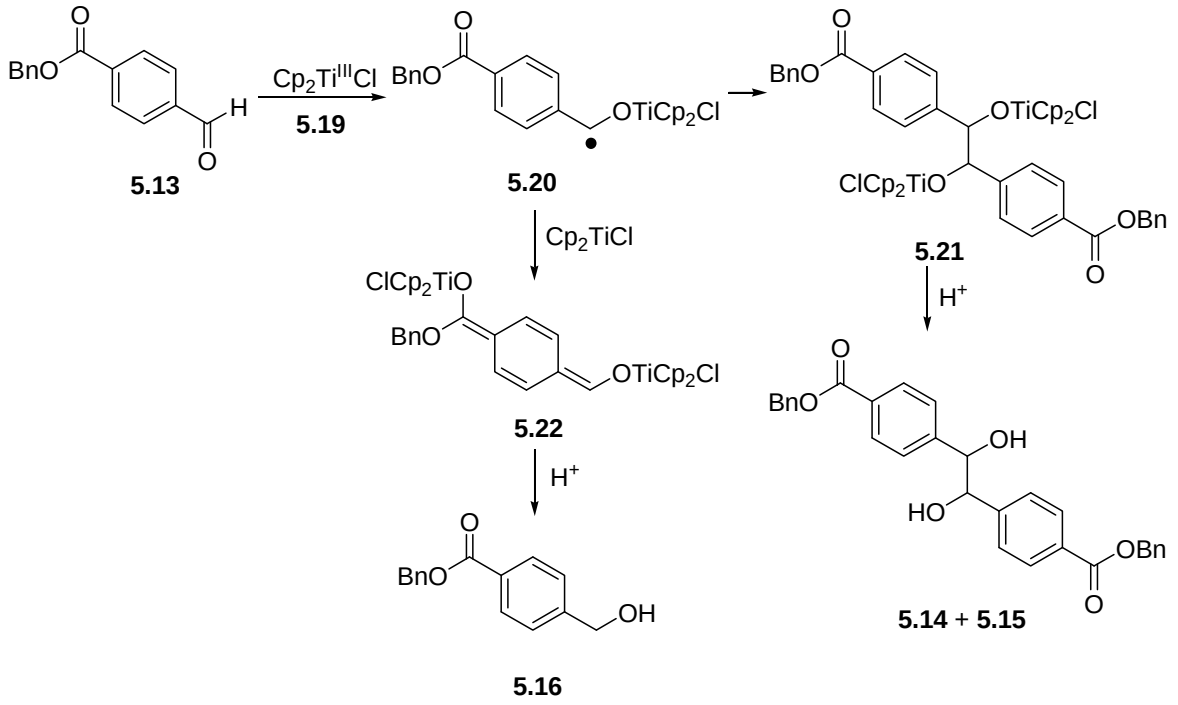
Scheme 5.4: Homo-coupling of aldehyde 5.13

The typical mechanism proposed that reduction of titanocene dichloride **5.17** with the Grignard reagent, ^{i}PrMgCl **5.18**, gave the titanium(III) reagent **5.19** used to promote pinacol coupling reactions (Scheme 5.5). Single electron reduction of aldehyde **5.13** would produce a ketyl radical **5.20**, which would dimerize to form the titanopinacolate intermediate **5.21** (Scheme 5.6). Hydrolysis of the titanopinacolate intermediate **5.21** would provide the 1,2-diols **5.14** and **5.15**. However, if the ketyl radical **5.20** was reduced by a second equivalent of titanocene chloride **5.19** before it had the opportunity to dimerize, then extended enolate **5.22** would be formed and so provide the by-product **5.16,** upon quench.



5.17 **5.18** **5.19**

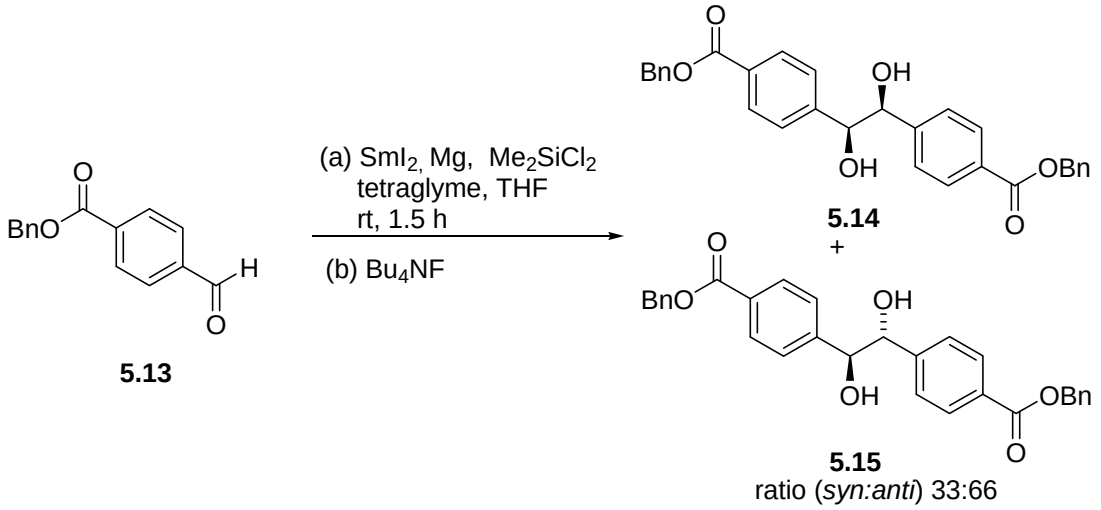
Scheme 5.5: Reduction of titanocene dichloride



Scheme 5.6: Hypothetic mechanism for the formation of alcohol 5.16

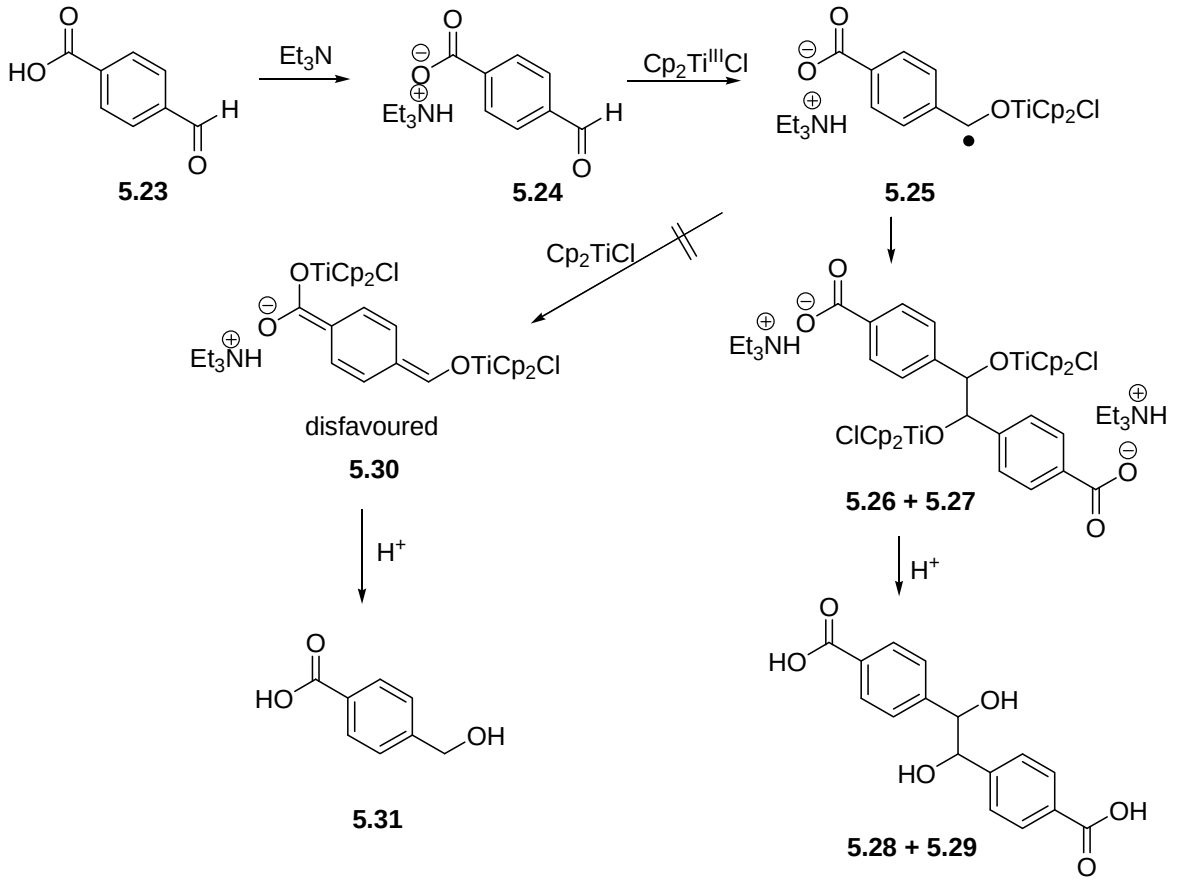
Attempts to prevent the formation of the by-product **5.16**, by increasing the concentration of the aldehyde **5.13** (0.8 M up to 2 M) and / or decreasing the number of equivalents of titanocene dichloride **5.17** (2.0 to 1.5 eq) led to an improvement in terms of proportion of compounds observed (**5.14 + 5.15:5.16** 64:34 to 74:26). However, the alcohol **5.16** remained a side-product in this homo-coupling reaction.

Recently, Aspinall *et al.*[73] reported a catalytic pinacol coupling using SmI_2 / Mg as the reducing agent. The addition of a chelating ligand (tetraglyme) to the SmI_2-promoted pinacol coupling influenced the diastereoselectivity of the reaction in favour of the 1,2-*anti*-isomer in the case of aromatic aldehydes. In order to compare with results obtained using the titanium system, we performed homo-coupling of aldehyde **5.13** using the same system (Scheme 5.7).



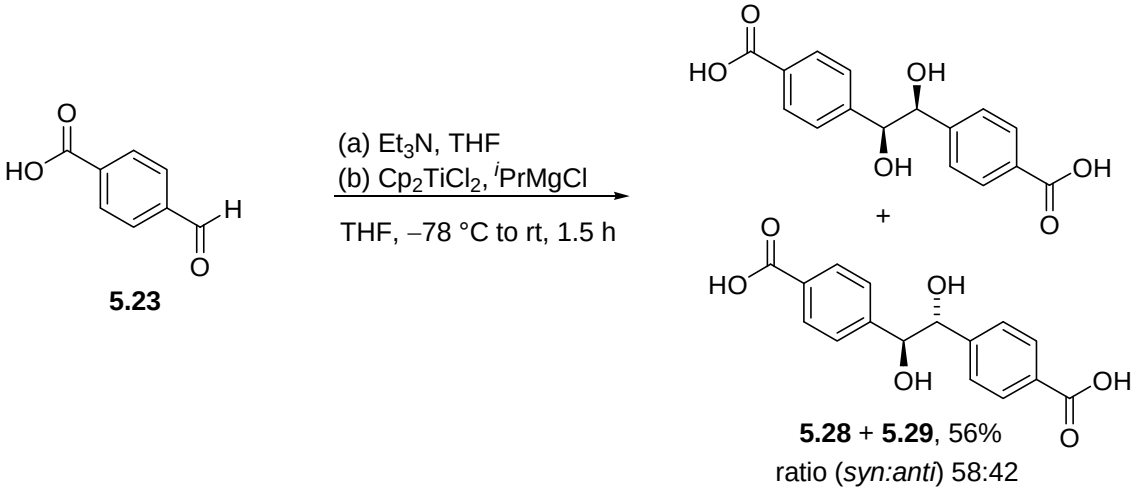
Scheme 5.7: Samarium mediated pinacol coupling

As expected, analysis of the ^{1}H NMR spectrum of the crude mixture showed the formation of 1,2-diols **5.14** and **5.15** as a mixture of 1,2- *syn* and 1,2-*anti*-isomers with a preference for the 1,2-*anti*-isomer **5.15**. Traces of alcohol **5.16** were also reported which confirmed that the presence of a carboxylic ester in the *para* position is not ideal for the pinacol coupling reaction. Consequently, the strategy was modified to reduce the electron-withdrawal by using the carboxylate salt of triethylamine **5.24.** This was expected to reduce the formation of the alcohol by-product **5.31** while mimicking the immobilization of aldehyde **5.23** on an amino-functionalised resin (Scheme 5.8). The carboxylate function present on the substrate **5.24** should disfavour the double reduction as this would generate a trianion **5.30** (regarding the polar covalent O-Ti bond as ionic) from ketyl radical **5.25**.



Scheme 5.8: Carboxylate salt of triethylamine

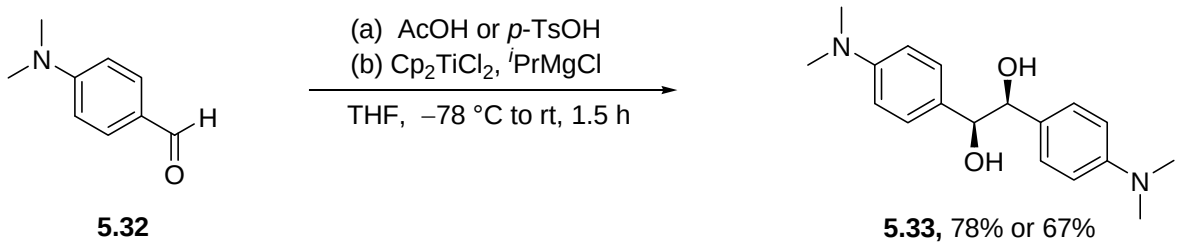
After stirring the aldehyde **5.23** with triethylamine, the resulting salt **5.24** was added to the preformed titanium reagent and converted into an inseparable mixture of 1,2-*syn*- and 1,2-*anti*-diols **5.28** and **5.29** with a modest yield following acidic work-up (Scheme 5.9). Formation of alcohol **5.31** was avoided; nevertheless an optimization of the system was required as the diastereoselectivity was poor.



Scheme 5.9: Homo-coupling reaction of aldehyde 5.23

The temperature of the reaction was more carefully controlled in order to optimise diastereoselectivity. A slow increase of the temperature from −78 to −30 °C over 5 h led to an incomplete reaction and a small amount of starting material **5.23** was recovered. A mixture of both isomers **5.28** and **5.29** was noticed. However, the temperature of the reaction did not have any effect on the diastereoselectivity [ratio (*syn:anti*) 57:43].

Next, reversing the polarity of the resin-substrate interaction by using 4-(di methylamino)benzaldehyde and resin-bound acid was investigated. This new strategy might permit a capture–release strategy of amine with acidic ion-exchange resin (carboxylic acid resins or MP-TsOH). The resin linkage was first simulated by the use of acetic acid (Scheme 5.10). 4-(Dimethylamino) benzaldehyde **5.32** was stirred in a solution of AcOH in THF at 25 °C until it dissolved. The mixture was then added to the preformed titanium reagent at −78 °C and left at rt for 1.5 h. After quenching with 1N HCl to hydrolyse the titanopinacolate intermediate, treatment with base, extraction and evaporation, ^{1}H NMR analysis of the crude mixture revealed the formation of a single isomer and the 1,2-*syn*-diol **5.33** was then isolated in very good yield (78 %).



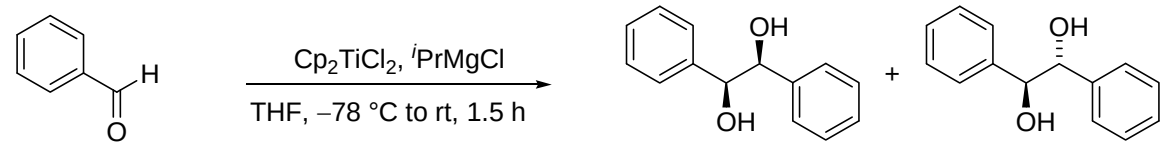
5.32

5.33, 78% or 67%
Syn only

Scheme 5.10: Homo-coupling of 4-(dimethylamino)benzaldehyde 5.32

The same conditions were used with a stronger acid, *p*-TsOH (Scheme 5.10). The pinacol coupling product **5.33** was obtained in good yield (67 %) and as expected only the 1,2-*syn*-isomer **5.33** was isolated. With good conditions for homo-coupling reactions in hand, the next target was a cross–coupling reaction.

The first coupling partner investigated was a simple aromatic aldehyde, benzaldehyde **5.34** (= **4.7**, see Scheme 4.2). First, homo-coupling of the benzaldehyde **5.34** was performed under standard conditions in order to identify this potential by–product in the cross-coupling reaction (Scheme 5.11). The coupling products **5.35** and **5.36** were obtained with a poor yield but with excellent diastereoselectivity [ratio(*syn:anti*) 94:6].

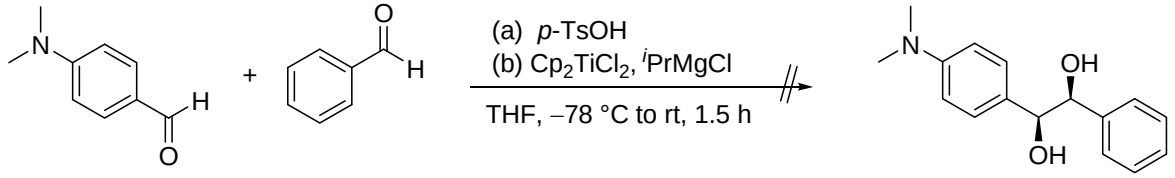


5.34

5.35 + 5.36, 10%
ratio (*syn:anti*) 94:6

Scheme 5.11: Homo-coupling reaction of benzaldehyde 5.34

The cross–coupling of aminoaldehyde **5.32** and benzaldehyde **5.34** was conducted in presence of *p*–TsOH and with the Cp_2TiCl_2/ $^{i}PrMgCl$ system; nonetheless neither the desired product **5.37** nor the homo-coupling products were identified in the crude mixture (Scheme 5.12). We recovered unchanged aldehydes.



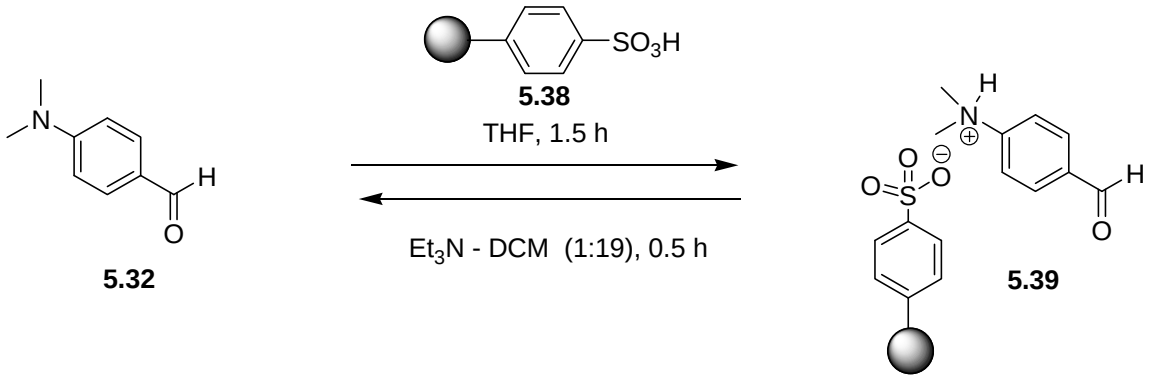
5.32 **5.34** **5.37**

Scheme 5.12: Cross-coupling reaction

Consequently, the solid-phase synthesis was investigated to demonstrate that this cross-coupling issue would be improved on solid support.

5.3. Solid-phase synthesis

To begin with, the loading of the substrate **5.32** onto resin had to be considered. *p*-Toluenesulfonic acid resin **5.38** (= **3.8**, see Figure 3.6) was naturally selected. The loading consisted in stirring beads of resin with a solution of aldehyde **5.32** in THF. Employing an indirect analysis to determine the yield of loading, we finally set optimum conditions of loading at 5.0 eq. of aldehydes **5.32** and 1.0 eq of resin **5.38** for 1.5 h at 25 °C (Scheme 5.13). Cleavage was performed by stirring kans containing compound **5.39** in a solution of Et_3N in CH_2Cl_2 for 0.5 h, and the quantity of aldehyde isolated used to calculate a loading of 1.63 mmol g^{-1}.

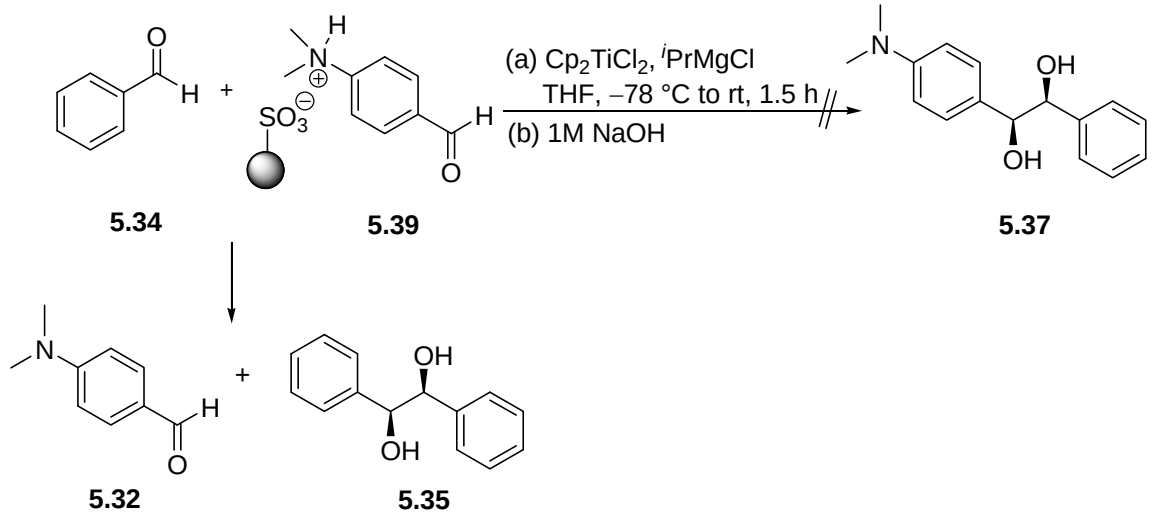


5.32 **5.39**

Scheme 5.13: Loading and cleavage of resin 5.38

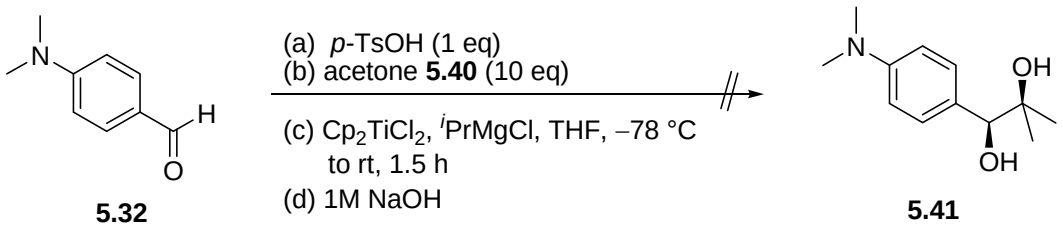
The cross-coupling was attempted with 1 eq of benzaldehyde **5.34** (Scheme 5.14). The cross-coupling product **5.37** was not observed instead we recovered

the homo-coupling product of benzaldehyde **5.35** and starting amino compound **5.32** which seemed to be cleaved from the resin by $Cp_2Ti^{III}Cl$.



Scheme 5.14: Cross-coupling reaction in solid-phase

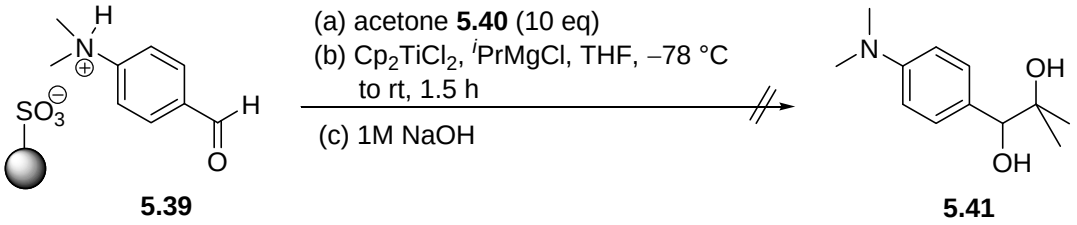
The decision was taken to change the coupling partner and work with acetone **5.40** (Scheme 5.15), which is less easily reduced. Homo-coupling of acetone was considered less likely. A solution of aldehyde **5.32** was treated with *p*-TsOH in THF at 25 °C to give the salt. A solution of acetone **5.40** (10 eq) was added and the mixture transferred into the preformed low valent titanium reagent at −78 °C. The mixture was stirred for 1.5 h at rt before quenching. As expected, the heterocoupling product **5.41** was not observed; on the other hand we identified the homo-coupling product **5.33** of aldehyde **5.32** in the crude mixture.



Scheme 5.15: Heterocoupling reaction attempt

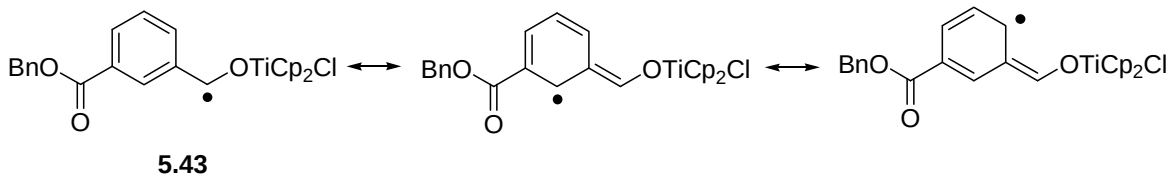
In solid–phase synthesis the formation of the homo-coupling product **5.33** would be stopped by the pseudo-dilution effect. Consequently, we were not expecting

to observe any homo-coupling products of aminobenzaldehyde **5.32** or acetone **5.40** and the cross coupling should be formed. Unfortunately, in solid-phase synthesis, the reaction run under standard conditions produced only starting material **5.32** after treatment with base (Scheme 5.16). Clearly, immobilised 4-(dimethylamino)benzaldehyde **5.39** was not an ideal substrate for the pinacol cross-coupling.



Scheme 5.16: Cross-coupling on solid support

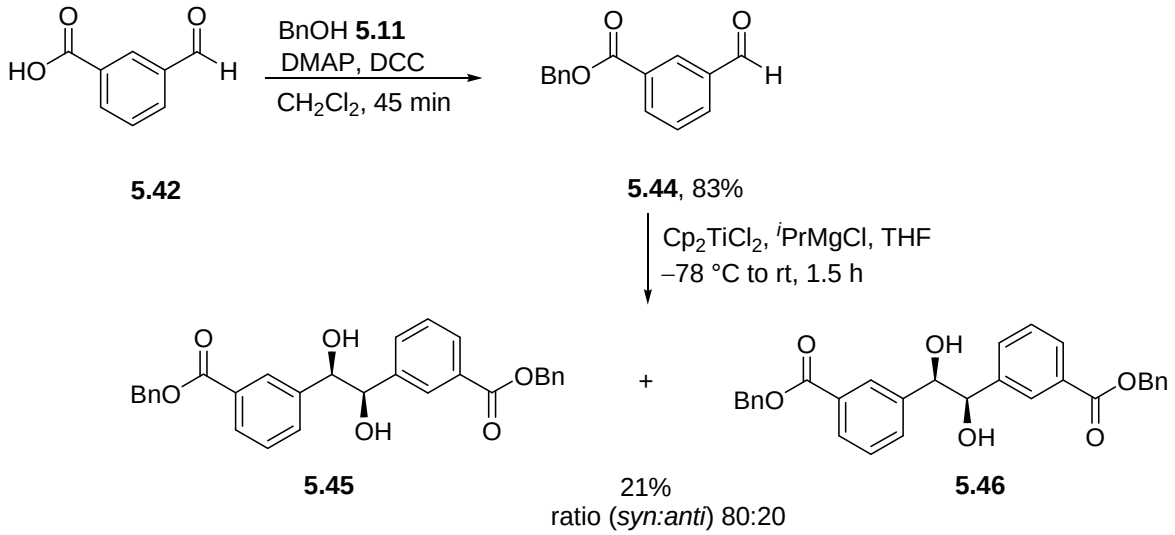
The choice of a new substrate was orientated towards carboxybenzaldehyde as described in our first strategy, however this time we chose *meta*-substitution of the carboxylic function. The use of *m*-carboxybenzaldehyde **5.42** for a pinacol coupling would not lead to the formation of the product of double reduction as observed for the *para*-substituted substrate (Scheme 5.6), as a second electron transfer to radical **5.20** gives extended enolate **5.22** (Scheme 5.6), but a second electron transfer to radical **5.43** would not and so is disfavoured (Scheme 5.17).



Scheme 5.17: Resonance forms

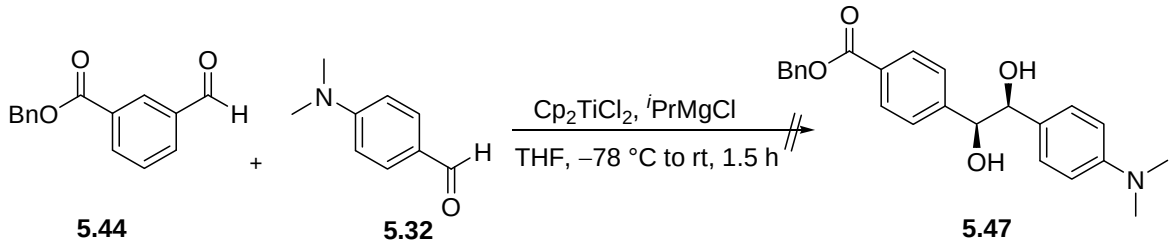
Following the same logic as before, the resin linkage was first simulated. Therefore, benzoate **5.44** was prepared in excellent yield following conditions previously described (Scheme 5.18). Pinacol coupling of aldehyde **5.44** was carried out using titanocene dichloride and ^{i}PrMgCl at −78 °C. After usual work-up, 1,2-diols **5.45** and **5.46** were isolated as an inseparable mixture of diastereoisomers [ratio(*syn:anti*) 80:20] in a very poor yield (21%). The ratio of diastereomers obtained was determined as previously reported for diols **5.14**

and **5.15** (Scheme 5.4). Thus, we assumed that the proton α to -OH in the 1,2-*syn*-isomer **5.45** corresponds to the signal at 4.67 ppm whereas the same proton in the 1,2-*anti*-isomer **5.46** corresponds to the signal at 4.82 ppm ($CDCl_3$).



Scheme 5.18: Homo-coupling of aldehyde 5.44

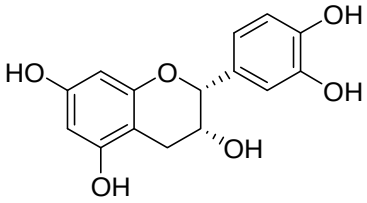
After that, a cross–coupling reaction was conducted with the substrate **5.44** in order to form the 1,2-diol **5.47** (Scheme 5.19). After reaction, the cross–coupling product **5.47** was not observed. Instead we recovered the homo-coupling product **5.33** (from earlier scheme) of aldehyde **5.32** in 57% yield. This result confirms that the aminobenzaldehyde **5.32** homo-coupled faster than aldehyde **5.44** as we did not observe any homo-coupling product **5.45** and also homo-coupling is preferred to cross-coupling reaction. The result was unexpected as aldehyde **5.32** is electron rich and would be expected to be reduced more slowly than aldehyde **5.44**. We realised that the same problem would occur if a resin-bound analogue of aldehyde **5.44** was used.



Scheme 5.19: Attempt of cross-coupling reaction

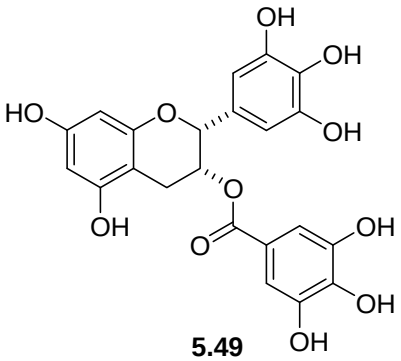
At the same time, a new objective emerged, synthesis of catechins with a pinacol cross-coupling on solid-support as a key step. Catechins are present in nearly all teas made from *Camellia sinensis* (Figure 5.1). Catechins are also present in the human diet in chocolate, fruits, vegetables and wine and are found in many other plant species. There is evidence that (−)-epicatechin **5.48** (Figure 5.2) can reduce the risk of four of the major health problems: stroke, heart failure, cancer and diabetes.[74] Similarly, oral administration or topical application of the antioxidant (−)-epigallocatechin-3-gallate **5.49** (Figure 5.2) helps protect the skin from UV radiation-induced damage and tumor formation.[75]

Figure 5.1: *Camellia sinensis*



5.48

(−)-Epicatechin

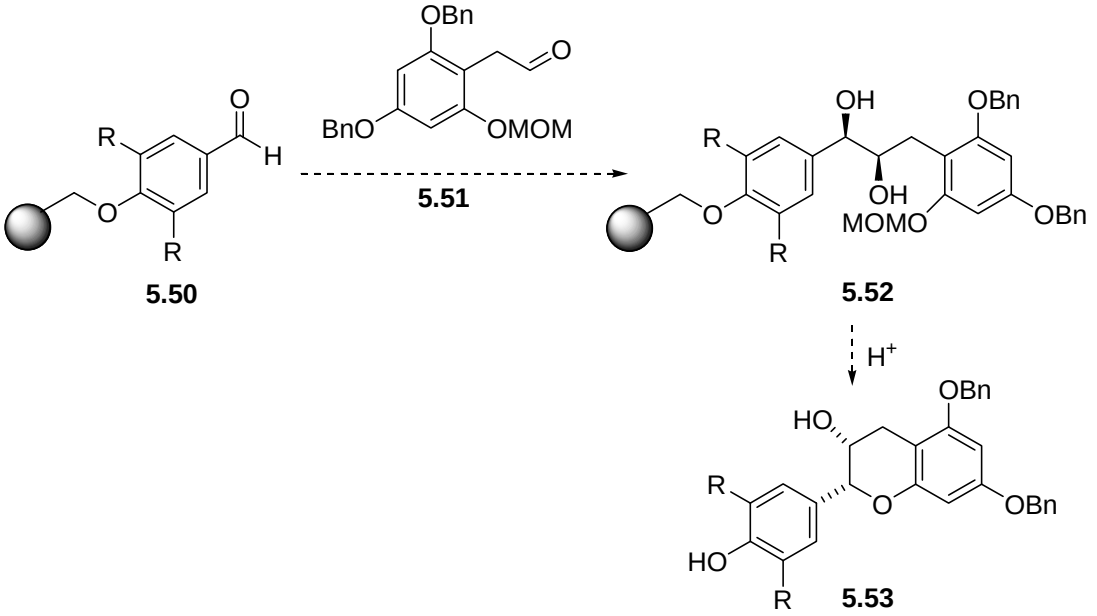


5.49

(−)-Epigallocatechin-3-gallate

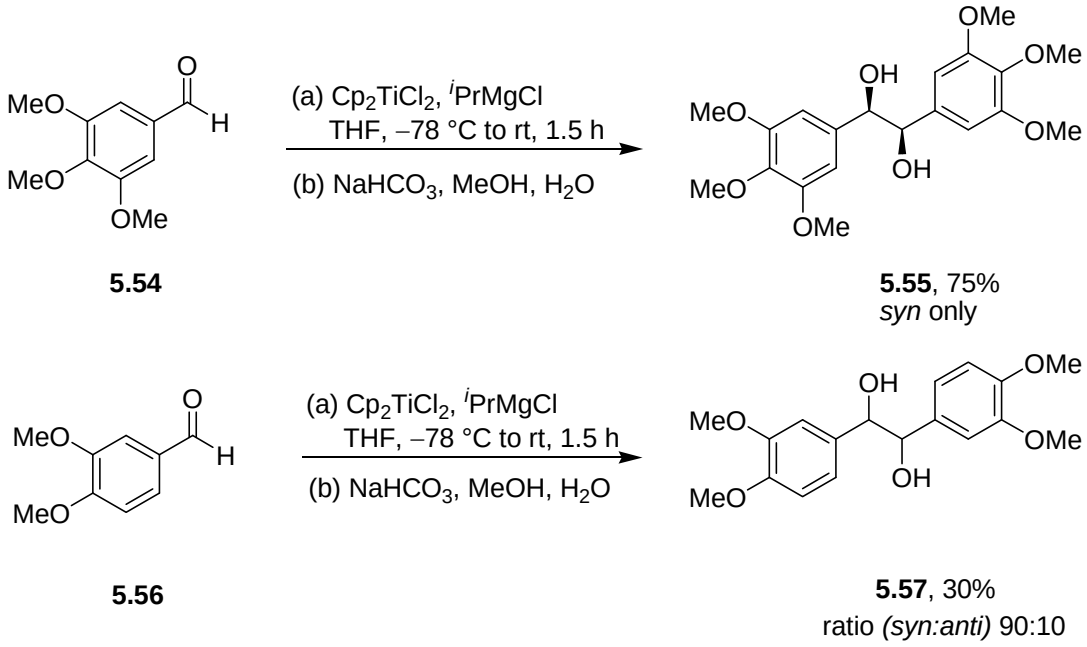
Figure 5.2: Catechins formed in tea

The idea was to carry out a cross-coupling reaction of aldehyde **5.50** supported on Wang resin with fully protected aldehyde **5.51** (Scheme 5.20). Then cleavage under acidic conditions would yield the catechin-like product **5.53**. The aromatic aldehyde **5.50** would be expected to be reduced more easily than aliphatic aldehyde **5.51** and pseudo-dilution would avoid homo-coupling.



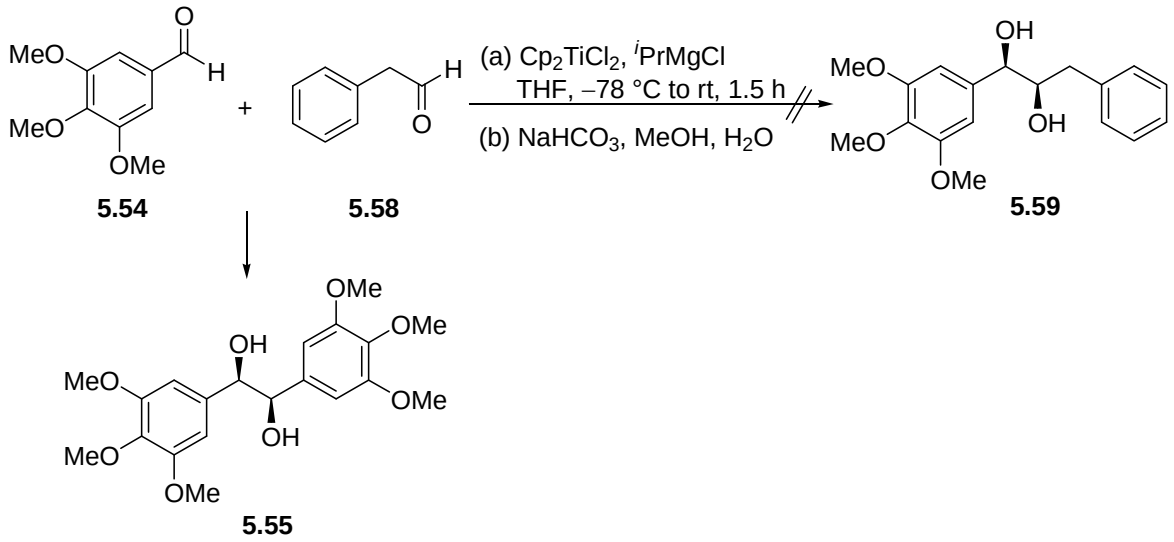
Scheme 5.20: Towards the synthesis of catechins

Following the same tactic as before, we investigated at first the homo-coupling reaction of two chosen substituted substrates (Scheme 5.21): 3,4,5–tri-methoxy benzaldehyde **5.54** and 3,4–dimethoxybenzaldehyde **5.56**. Under standard conditions, 1,2-*syn*-diols **5.55** and **5.57** were isolated with excellent diastereoselectivity. The poor yield observed with compound **5.56** is explained by difficulties met in handling the crude mixture and several filtrations during work up which led to the loss of material. Considering other NMR analyses of 1,2-diols in this chapter, we assumed that the peak observed at 4.49 ppm ($CDCl_3$) as a singlet was the proton α to -OH in the 1,2-*syn*-isomer as the proton α to -OH in the 1,2-*anti*-isomer usually appears closer to 4.70 ppm. Furthermore, 1,2-diols **5.57** were obtained as a mixture of *syn* and *anti*-isomers**.** The proton α to -OH in the 1,2-*syn*-isomer corresponds to the signal at 4.43 ppm whereas the same proton in the 1,2-*anti*-isomer corresponds to the signal at 4.60 ppm ($CDCl_3$), which confirms the supposition concerning the other compound **5.55**.



Scheme 5.21: Homo-coupling of methoxybenzaldehydes 5.54 and 5.56

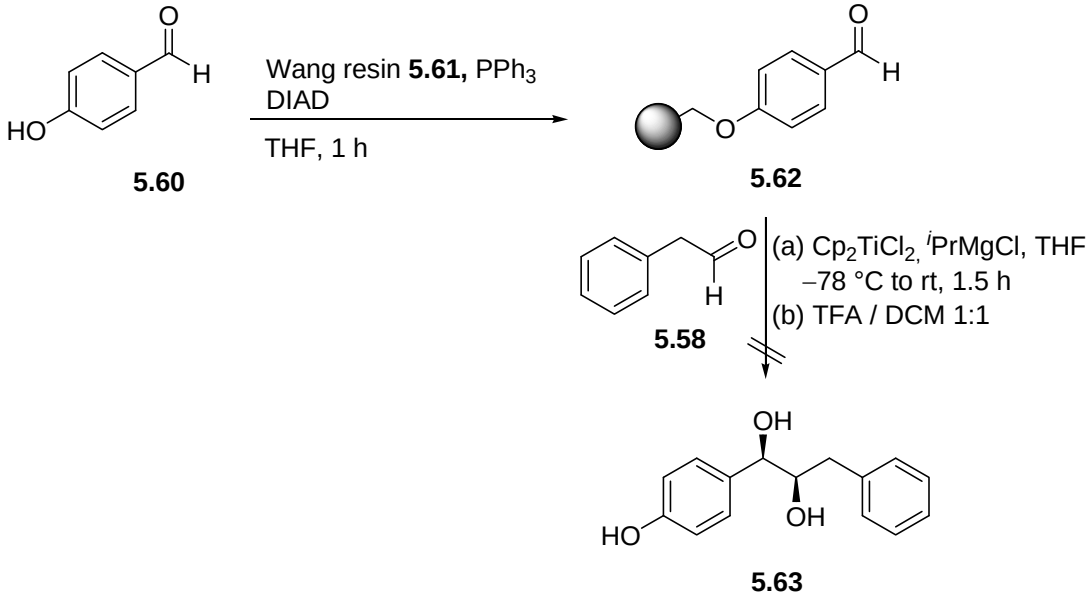
Next, the objective was to proceed to the cross-coupling between the substrate **5.54** and phenylacetaldehyde **5.58** to obtain cross-coupling products **5.59** (Scheme 5.22). The reaction was carried out under standard conditions. As expected, the desired 1,2-diol **5.59** was not formed, instead phenylacetaldehyde **5.58** and the homo-coupling product **5.55** were recovered.



Scheme 5.22: Cross-coupling reaction

In order to prove that solid-phase synthesis would improve the cross-coupling reaction, we considered the loading of a model susbtrate **5.60** onto Wang resin

5.61 (= **3.4**, see Figure 3.5) (Scheme 5.23). The loading was done with 5.0 eq of 4-hydroxybenzaldehyde **5.60** and 1.0 eq of resin **5.61** under Mitsunobu conditions. The loading was assumed to be total. Then, pinacol coupling of this supported substrate **5.62** with phenyl acetaldehyde **5.58** was performed under standard conditions. Results were not those hoped for: no 1,2-diol **5.63** was identified and the crude mixture following cleavage appeared to contain many unidentified by-products. At this stage, we concluded that our solid-phase synthesis approach to the pinacol cross-coupling was not likely to succeed.



Scheme 5.23: Pinacol coupling reaction

5.4. Conclusion

In this project, we demonstrated a couple of interesting points concerning pinacol homo-coupling reactions induced by $Cp_2TiCl_2/^iPrMgCl$. The presence of an electron-withdrawing group in the *para*-position of an aromatic aldehyde leads to the formation of the product of double reduction. The formation of this by-product may be avoided by using an electron-withdrawing group in *meta*-position or by using a carboxylate salt. Although homo-coupling reactions proceeded well, cross-coupling reactions were never observed. Immobilization of an aldehyde that could homo-couple prevented any reaction with the substrate and a coupling partner in solution simply homo-coupled if it was sufficiently easy to reduce.

Part C

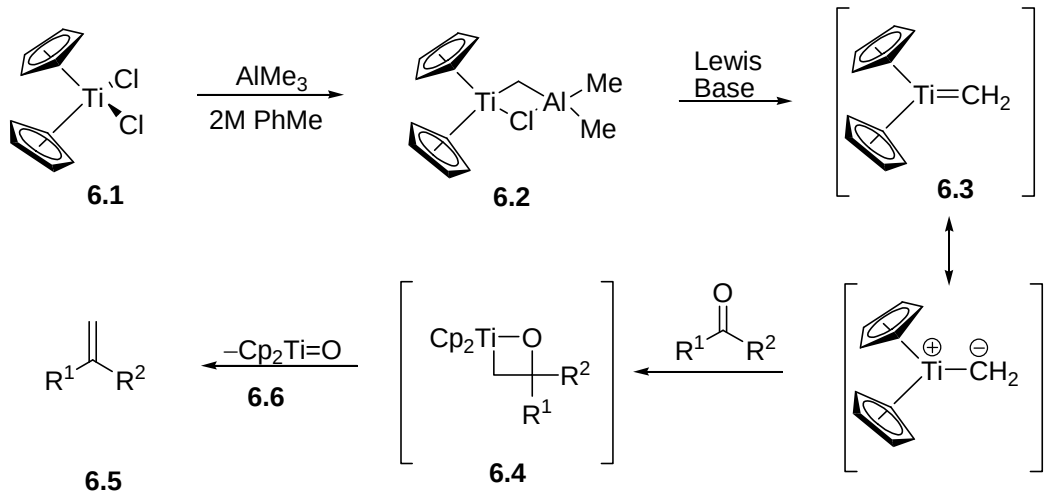
6. Alkenation Reactions using Titanium-Based Reagents

The conversion of carbonyl groups, such as esters, amides, thioesters, and carbonates into alkenes is commonly undertaken with titanium-based carbenoids due to the lack of reactivity of traditional alkenation methods (Wittig, HWE, Julia, Peterson alkenation) or the undesired cleavage of the ester (or amide) bond. Furthermore, Wittig-type reactions require basic conditions, which are not suitable for easily enolisable carbonyl derivatives. A range of titanium-alkylidenes have been designed to overcome these issues. They are not basic, so there is no risk of epimerization of a sensitive chiral centre α to carbonyl groups or *retro*-Michael additions (RMA). Small and reactive, they react with even hindered carbonyl groups. This class of reagents have been recently reviewed,[76] however a brief overview will be given in the following section.

6.1. Tebbe reagent

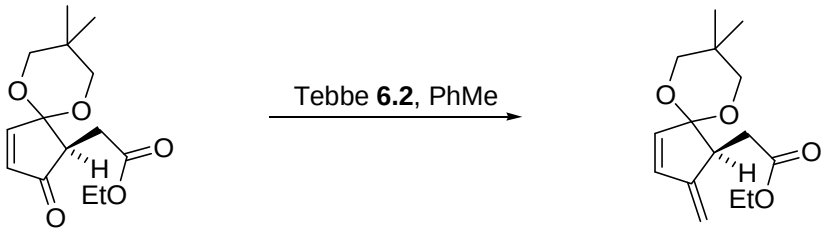
First reported by Tebbe *et al*.[77] in 1978, the Tebbe reagent **6.2** is a titanium-aluminium complex usually prepared using the definitive procedure provided by Pine *et al*.[78] in 1990. Its preparation consists of reaction of titanocene dichloride **6.1** (= **5.17**, see Scheme 5.5) with $AlMe_3$ in toluene (Scheme 6.1). However the reagent is now commercially available as a solution in toluene. The titanium-aluminium metallacycle **6.2** is activated by a base (pyridine, THF) to form the reactive species **6.3**, which is a highly reactive titanocene methylidene responsible for methylenation of carbonyl compounds. The methylidene **6.3** is a typical Schrock carbene being an electron-deficient (16e) complex of titanium in a high formal oxidation state (Ti^{IV}). It is nucleophilic at carbon and electrophilic at titanium. The nucleophilic reagent can react with a wide range of carbonyl compounds to give alkenes **6.5** via the decomposition of oxatitanacyclobutane **6.4** in a manner similar to oxaphosphetane in the Wittig reaction. The driving

force in this reaction is the irreversible formation of a strong Ti-O double bond in oxide **6.6**.



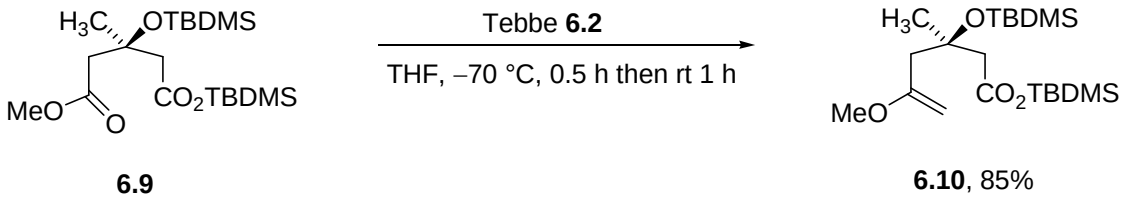
Scheme 6.1: Preparation and use of Tebbe reagent

The Tebbe reagent **6.2** can methylenate a broad range of carbonyl compounds including aldehydes, ketones, esters, thioesters, amides and carbonates. A range of substrates can be found in the review by Hartley and McKiernan.[79] Due to the nucleophilic nature of the reagent, the reactivity of the Tebbe reagent is dependent on the electrophilicity of the substrate. In that way, selective methylenation can be achieved in the presence of different types of carbonyl groups. For example, aldehydes and ketones are methylenated preferentially to esters or amides as they are more electrophilic as described by Fukuyama and Liu[80] in the synthesis of diene **6.8** (Scheme 6.2).



Scheme 6.2: Example of selectivity of Tebbe reagent

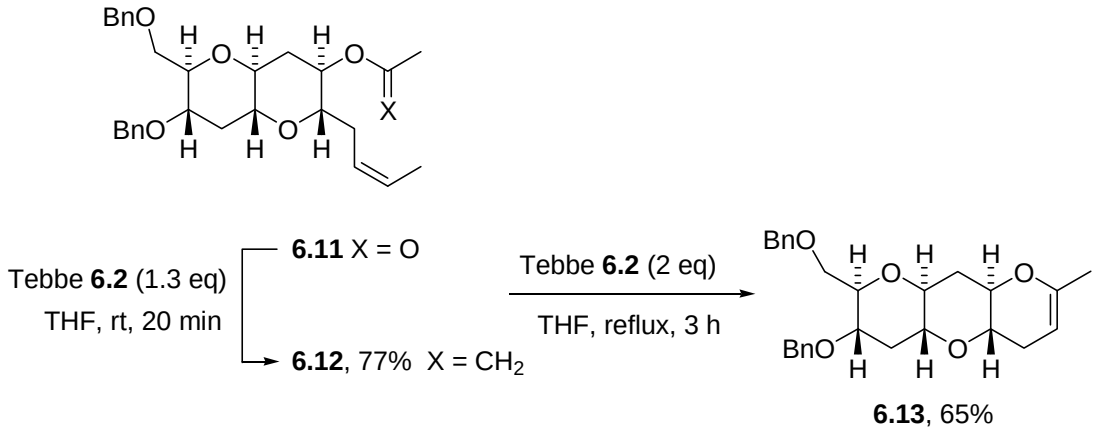
Steric factors also play a role in determining the reactivity of a substrate (Scheme 6.3). In Tebbe methylenation of esters, Müller *et al*.[81] reported methylenation at the less sterically hindered of the two carbonyl groups. The reaction proceeded with 1 eq of Tebbe reagent **6.2** and at low temperature to provide the enol ether **6.10** in very good yield.



6.9 **6.10**, 85%

Scheme 6.3: Example of regioselectivity

Nicolaou and co-workers[82] showed that the Tebbe reagent **6.2** may catalyse ring-closing metathesis (RCM). Indeed they reported that methylenation of ester **6.11** with the Tebbe reagent at room temperature gave the enol ether **6.12** and further addition of the Tebbe reagent led to the cyclisation at higher temperature (Scheme 6.4). This tandem methylenation-RCM can be done as a one-pot procedure.



6.13, 65%

Scheme 6.4: RCM catalysed by Tebbe reagent

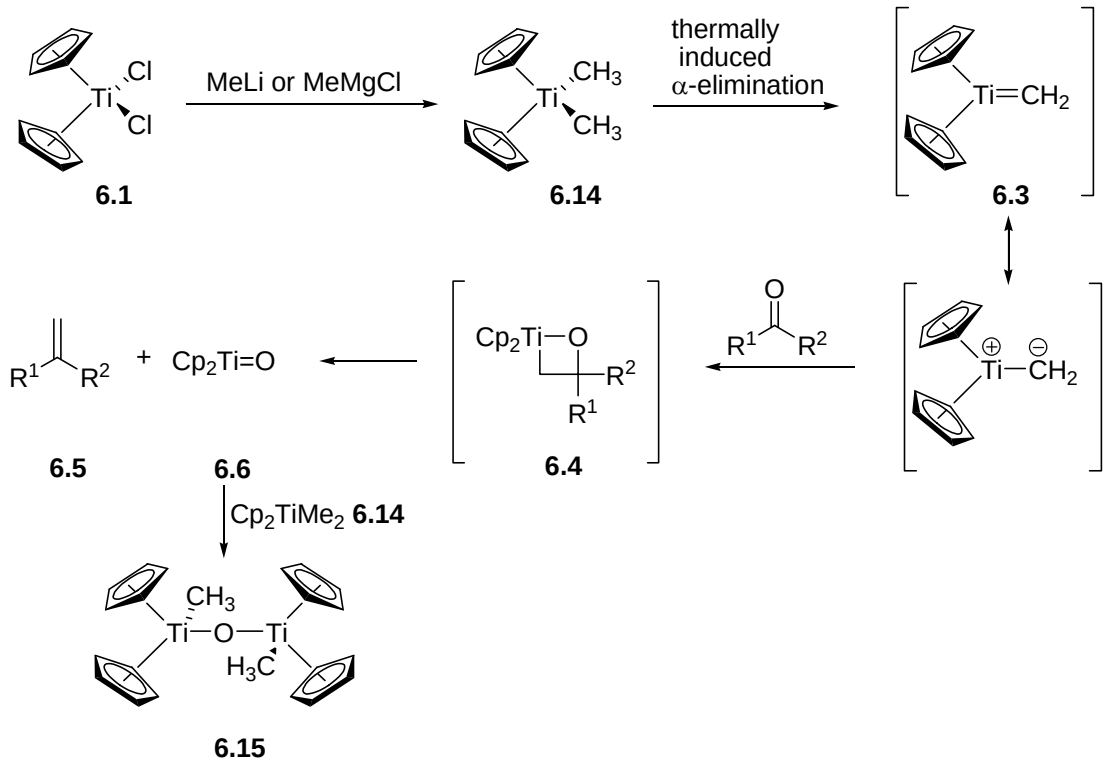
Although the Tebbe reagent has the ability to methylenate a wide range of carbonyl compounds, it has the disadvantage of being limited to methylenation.[76] Moreover, the Tebbe reagent and products of its decomposition are Lewis acidic. The Tebbe reagent is also highly air and moisture sensitive making its handling delicate.

6.2. Petasis reagent

Developed as an alternative to the Tebbe reagent, dimethyltitanocene (DMT) **6.14** was used as a methylenating agent of carbonyl derivatives (esters, ketones and amides) by Petasis and Bzowej[83,84] and is easily prepared by reacting MeLi or MeMgCl with Cp_2TiCl_2 (Scheme 6.5). Definitive procedures for the preparation and storage have been provided by Payack *et al.*;[85] moreover a similar procedure is suitable for the preparation of the reagent on more than a kilogram scale.[86]

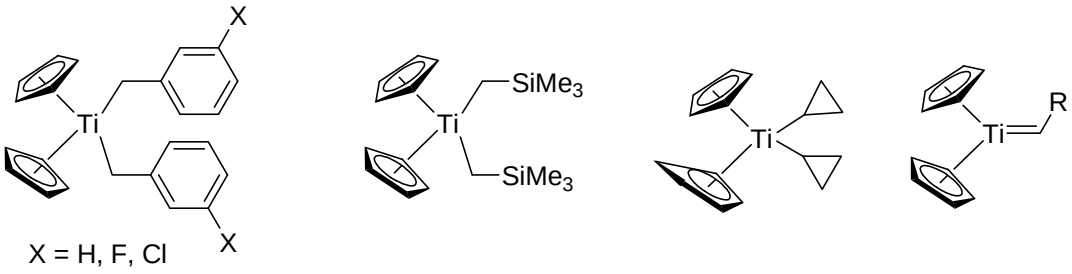
DMT is relatively stable to air and moisture unlike the Tebbe reagent and can be stored for several months if kept at 4 °C and diluted with THF or toluene (10 wt %) as DMT is not stable in a solid state.[87] Furthermore, the Petasis reagent is non-pyrophoric. Another advantage over the Tebbe reagent is the absence of Lewis acidic by-products. Petasis *et al.*[83,88] showed that when DMT **6.14** is heated to 60-75 °C either in THF or toluene, the reactive titanium methylidene **6.3** is formed, which reacts rapidly in the presence of a carbonyl compound to give the alkene **6.5** *via* the oxatitanacyclobutane **6.4** and titanium oxide **6.6**. The titanocene dimer **6.15** is obtained by further reaction of titanium oxide **6.6** with DMT **6.14**.

Hughes *et al.*[89] have provided strong evidence that the methylenation reaction proceeds by generation of the Schrock carbene **6.3** *via* heat-induced α-elimination, and that represents the rate-determining step of the reaction. The methylidene **6.3** can now be generated by microwave irradiation making the reaction quicker, cleaner and requiring fewer equivalents of reagent.[90,91] Furthermore, the oxatitanacyclobutane **6.4** has now been observed by mass spectroscopy which supports the mechanism.[92]



Scheme 6.5: Preparation and use of DMT 6.14

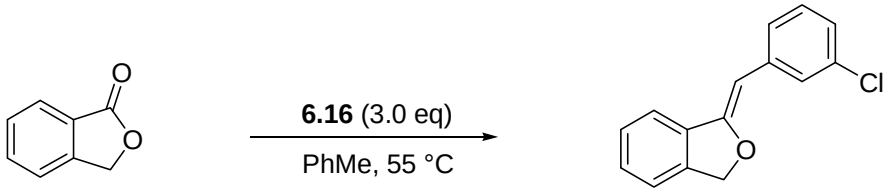
Like the Tebbe reagent **6.2**, DMT **6.14** can selectively methylenate aldehydes and ketones in the presence of esters, amides or carbamates or selectively methylenates the less hindered of two esters.[93] However, DMT will also methylenate highly strained β-lactones[94,95] where Tebbe methylenation is unsuccessful. A variety of others carboxylic acid derivatives are also converted into useful hetero-substituted alkenes with DMT e.g. silyl esters, thioesters, selenoesters, acylsilanes anhydrides, amides etc.[76,79] Above all, the Petasis reagent is not limited to methylenation as the Tebbe reagent is. Functionalised Petasis reagents can be prepared as demonstrated by Petasis and Bzowej.[84] Reagents **6.16**, **6.17** and **6.18** (Figure 6.1) are all converted into Schrock carbenes **6.19** upon heating and can effectively alkylidenate carbonyl compounds.



6.16 **6.17** **6.18** **6.19**

Figure 6.1: Functionalised Petasis reagents

For example, the lactone **6.20** is converted into enol ether **6.21** in quantitative yield and with complete *Z*-selectivity by treatment with functionalised Petasis reagent **6.16** (Scheme 6.6).[84]

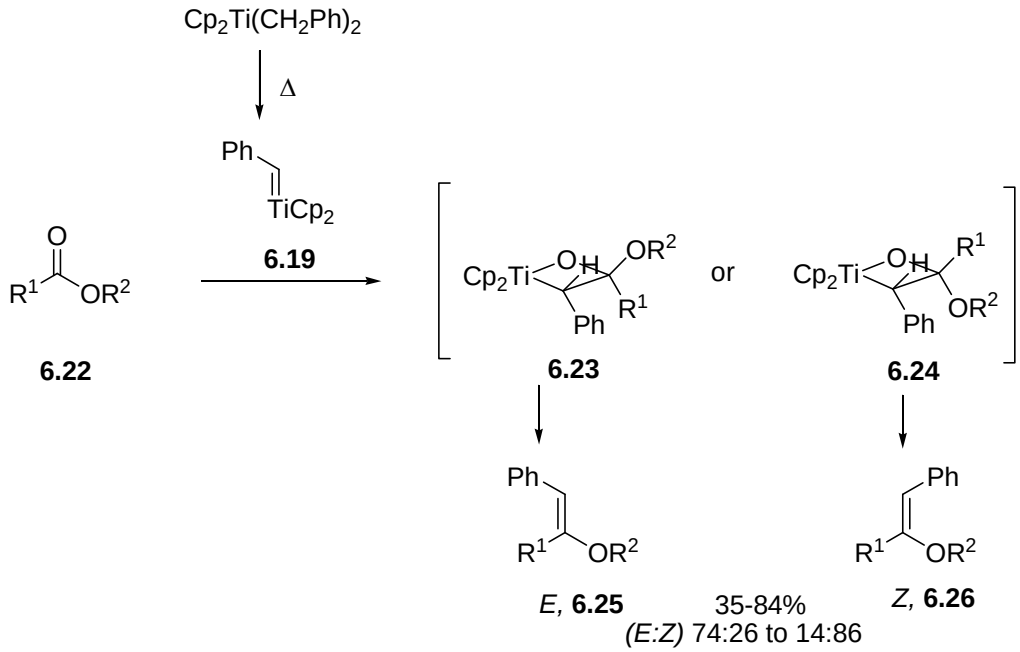


6.20 **6.21**, 100%

Scheme 6.6: Example of the use of a functionalised Petasis reagent

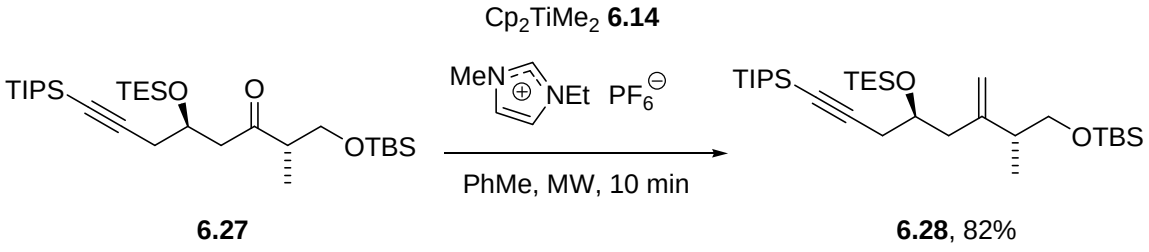
The *Z*-selectivity of the alkene can be explained by considering the oxatitanacyclobutane intermediates **6.23** and **6.24** formed during the alkylidenation (Scheme 6.7). In cases where R^1 is large, the *Z*-alkene **6.26** is favoured in order to minimize steric interactions between the phenyl and R^1 groups. When R^2 is large, the formation of intermediate **6.24** will be disfavoured. However the oxygen acts as a spacer and helps to minimize steric interactions between a large R^2 group and the phenyl group, so this interaction is less significant.[96]

These reagents are useful for alkylidenation of carbonyl compounds only if they do not have a hydrogen atom on an sp^3 carbon β to titanium, as if they do, the β-elimination is faster than α-elimination and the Schrock carbene is not generated.



Scheme 6.7: Selectivity in alkylidenation with functionalised Petasis reagents

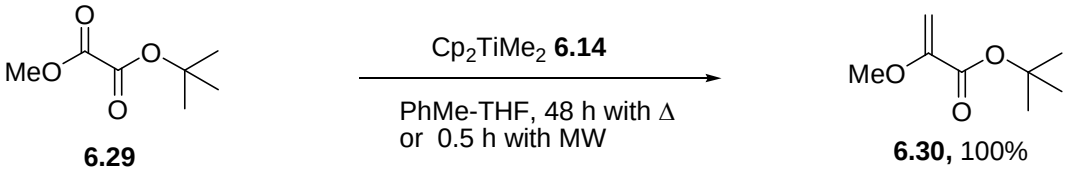
In 2003, Gaunt *et al*.[97] reported the synthesis of an intermediate of the synthesis of Spongistatin 1 with a Petasis methylenation as a key step. Treatment of the ketone **6.27** with Petasis reagent **6.14** in toluene at 120 °C generated alkene **6.28** in 71% yield. The reaction proved to be much more efficient when carried out under microwave irradiations forming the alkene **6.28** after 10 min in 82% yield (Scheme 6.8). By adding a small amount of ionic liquid (1-ethyl-3-methyl imidazoline hexafluorophosphate) to the solvent, they increased the solvent heating temperature[98] and minimized safety problem due to over pressurization of the sealed reaction vessels.[99]



Scheme 6.8: Microwave assisted Petasis methylenation

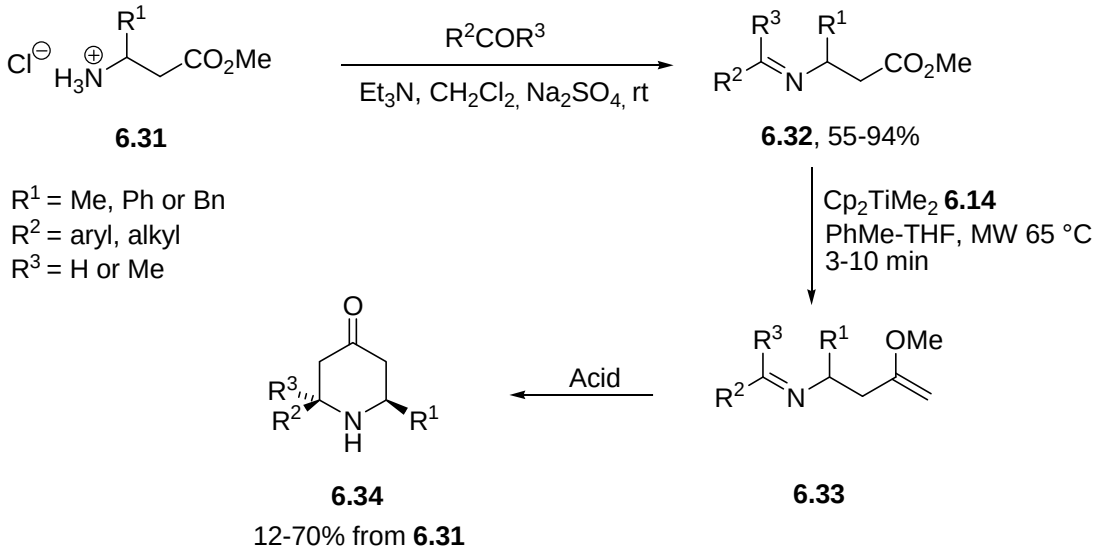
Later, Galagher and co-workers[90] found that under microwave conditions, Petasis alkenation of oxalate **6.29** gave complete conversion to the enol ether **6.30** in

30 min instead of 48 h under thermal conditions (Scheme 6.9). They observed selectivity towards the less hindered carbonyl group.



Scheme 6.9: Microwave-assisted Petasis methylenation

Recently, Adriaenssens and Hartley[100] produced a highly diastereoselective route to 2,6-disubstituted piperidinones using microwave-assisted Petasis methylenation as one of the key steps (Scheme 6.10). A chemoselective methylenation of the ester group of the preformed imine **6.32** using DMT and microwave heating provided the enol ether **6.33**. Cyclisation of the enol ether under acidic conditions gave piperidinones **6.34** in modest to good yield.



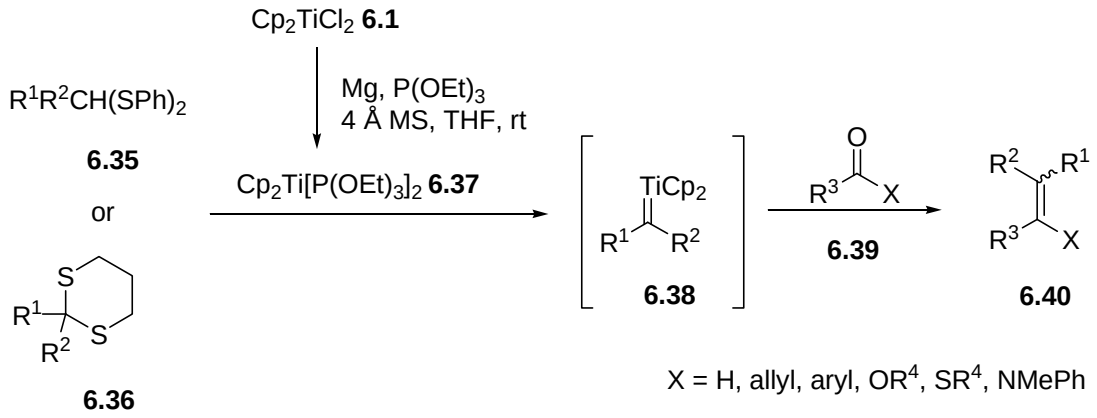
Scheme 6.10: Synthesis of piperidinones

The popular Petasis methylenation of carbonyl groups presents many advantages due to its air and moisture stability and the easy preparation of the reagent. It will cleanly methylenate a wide range of carbonyls groups and titanium containing impurities are easily removed by precipitation and filtration. The reaction conditions are non basic (unlike Wittig) so the epimerization of chiral centres can be avoided. The absence of Lewis acidic by-products (unlike Tebbe)

results in the tolerance of a wider range of functionality. The Petasis methylenation with microwave assistance is particularly attractive. Disadvantages are the high temperature required to induce α-elimination and the excess reagent needed to get completion of the reaction.

6.3. Takeda reagent

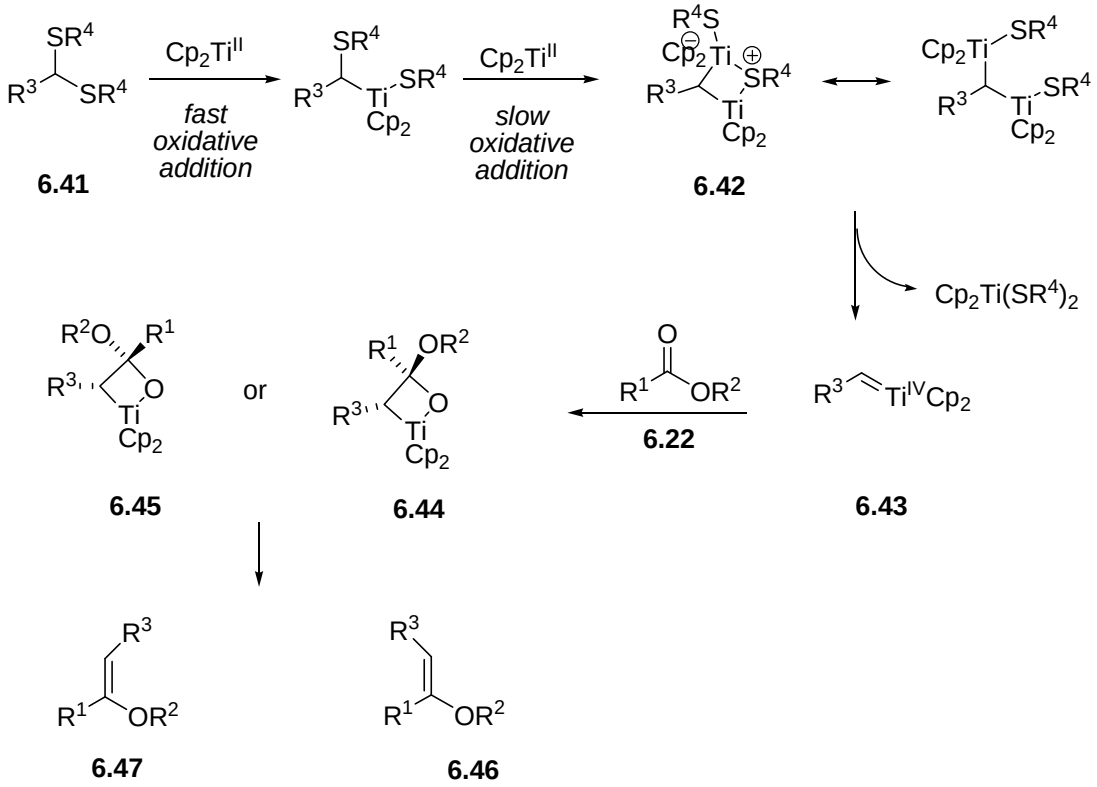
Takeda and co-workers reported that reduction of thioacetals **6.35** or **6.36** by a low-valent titanium(II) reagent **6.37** produced the titanium(IV) alkylidenes **6.38** which were then used to alkylidenate carbonyl derivatives **6.39** and produce alkenes **6.40** (Scheme 6.11). Reduction of titanocene dichloride **6.1** with excess magnesium turnings and $P(OEt)_3$ in THF provides the reagent **6.37**.[101] The addition of 4 Å molecular sieves is essential as the reduction of thioacetals is considerably retarded by traces of water. A range of thioacetals can be used. Allylic, benzylic or alkyl thioacetals are suitable substrates for generating alkylidenating reagents **6.38**. However, methylenation is ineffective under Takeda conditions. Moreover diphenyldithioacetals **6.35** and 1,3-dithianes **6.36** are both reduced effectively but diphenyldithioacetals **6.35** are more easily reduced.[102]



Scheme 6.11: Desulfurisation of thioacetals

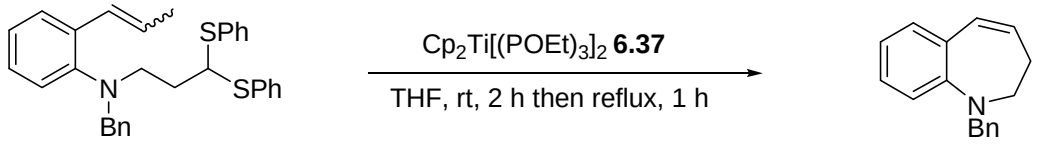
This method was applied to alkylidenation of a wide variety of carbonyl derivatives **6.39**. The reaction proceeds well with a variety of aldehydes and ketones;[101] it could also be achieved with carboxylic esters,[101] lactones,[101] thioesters[103] or *N*-methylanilides.[104] The mechanism for the alkylidenation of

esters is believed to be as follow (Scheme 6.12).[76] A low-valent titanium(II) species reduces thioacetal **6.41**, prepared by treatment of the corresponding aldehyde or ketone with thiols in the presence of a Lewis acid. The bimetallic complex **6.42** is formed as an intermediate in the generation of the titanium alkylidene **6.43** which reacts with esters **6.22** to form oxatitanacyclobutanes **6.44** and **6.45**. The geometry of the alkene formed follows the same rules as for the Petasis reagents since the mechanism of reaction of the Schrock carbene **6.43** is the same in both cases. Esters afford mostly *Z*-enol ether **6.47**,[101] however the selectivity is often modest. Alkylidenation of aldehydes and ketones shows very poor stereoselectivity.



Scheme 6.12: Mechanism for the Takeda alkylidenation

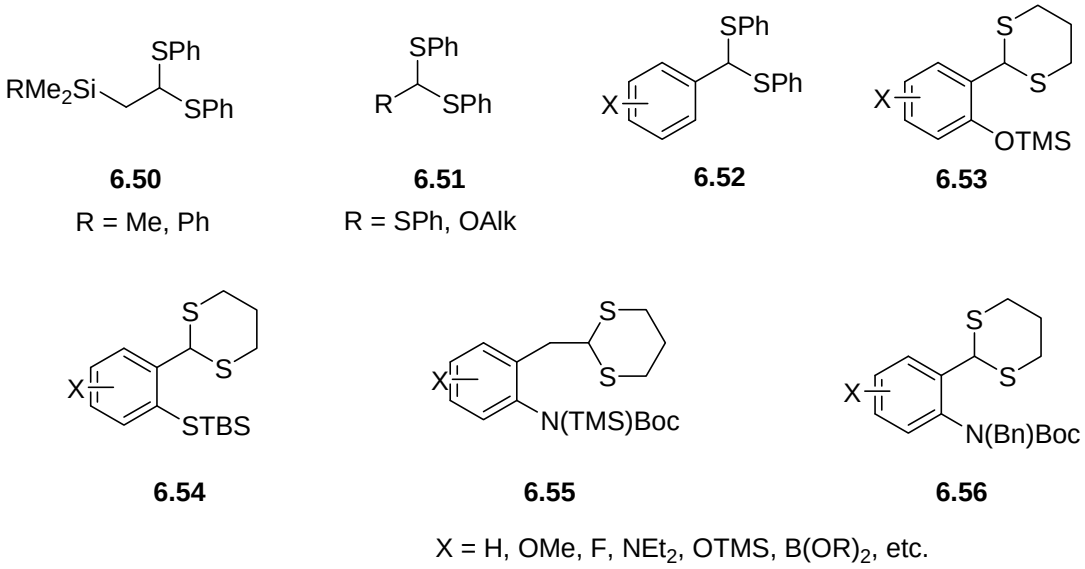
Under Takeda conditions, titanium alkylidenes are thought to be the active species as they have been shown to catalyse alkene metathesis[79] (Scheme 6.13). Indeed, it has been reported that RCM of thioacetal **6.48** proceeds upon treatment with low-valent titanocene **6.37** at room temperature and then heating under reflux to provide the cyclic amine **6.49** in good yield.[105]



6.48 **6.49**, 77%

Scheme 6.13: RCM catalysed by Takeda reagent

An advantage of the Takeda procedure is that titanium alkylidenes can be functionalised as they can be generated from a wide range of thioacetals **6.50**-**6.56** (Figure 6.2). Takeda generated alkylidenating agents from thioacetals **6.50** and **6.51**.[106-108] Hartley and co-workers developed several functionalised thioacetals **6.52-6.56** for the synthesis of bicyclic aromatic heterocycles[109,110,111,112,113] and Knaus' group reported the use of benzylic thioacetal **6.52** for the synthesis of alkenes.[114]



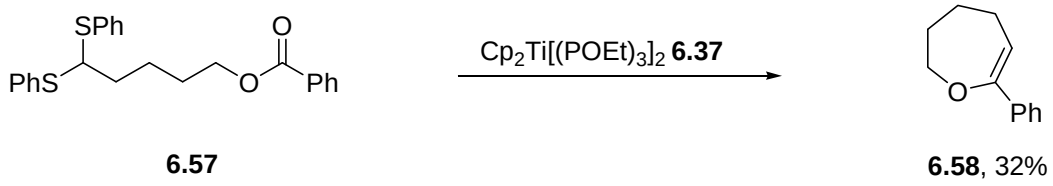
6.50 R = Me, Ph **6.51** R = SPh, OAlk **6.52** **6.53**

6.54 **6.55** **6.56**

X = H, OMe, F, NEt_2, OTMS, $B(OR)_2$, etc.

Figure 6.2: Functionalised thioacetals

The Takeda reaction has been used to produce various challenging heterocycles[115] (Scheme 6.14). The thioacetal **6.57** was reduced by low-valent titanium species **6.37** which induced intramolecular alkylidenation of the ester group and then gave the 7-membered cyclic enol ether **6.58** in a modest yield due to competing intermolecular reactions.

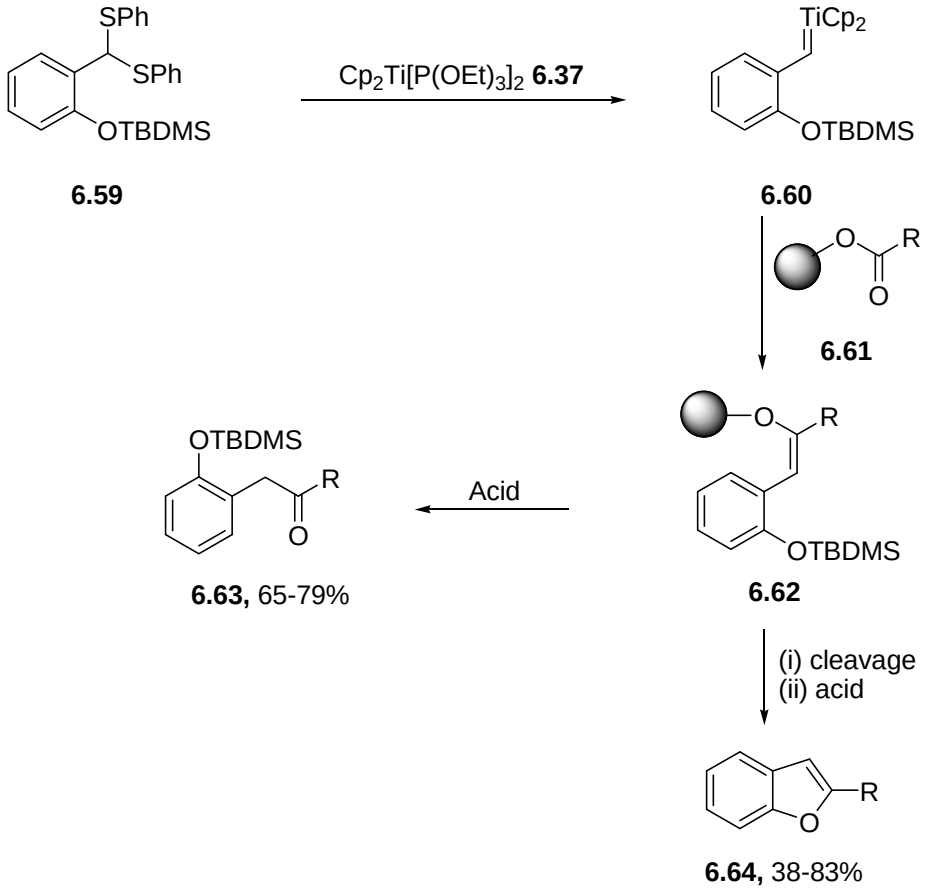


6.57 **6.58**, 32%

Scheme 6.14: Intramolecular alkylidenation

However, despite of the fact that a broad range of functionalities tolerate the Takeda reaction conditions, some groups may affect the titanium reagent as described by Macleod *et al.*[110] for unprotected primary amino groups, which prevent the formation of an effective alkylidenating reagent.[109] Dechlorination of aryl chlorides can also be observed.

A disadvantage of Takeda's procedure resides in the requirement for an excess of titanocene **6.1** (at least 3 eq) and $P(OEt)_3$ (at least 6 eq) which makes the purification of the products problematic. Hartley and co-workers introduced the concept of a Takeda alkylidenation on solid-phase which makes the purification a simple matter of washing[109,116] and the reagent also allowed the introduction of functionality in the alkylidenation step. Thioacetal **6.59** was treated with low valent titanium complex **6.37** to generate the titanium benzylidene **6.60** that benzylidenated Wang resin-bound esters **6.61** to give enol ethers **6.62** (Scheme 6.15). Treatment with acid led to cleavage from the resin and provided the ketones **6.63**, while deprotection of the silyl ether and then treatment with acid led to cyclisation and gave benzofurans **6.64**.

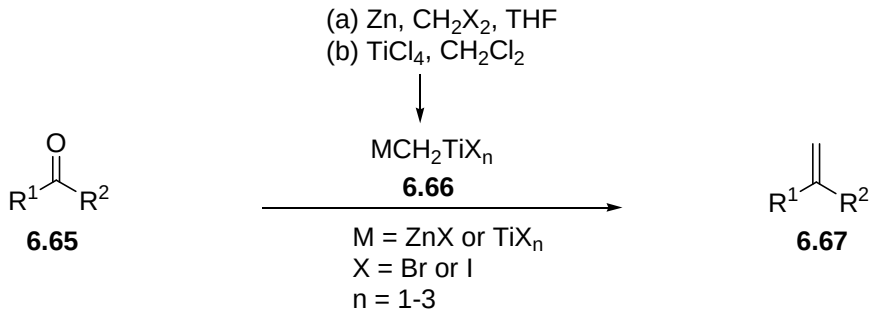


Scheme 6.15: Takeda alkylidenation on solid-phase

The key advantages of the Takeda alkylidenation are the range of alkylidenating reagents that can be prepared, the mildness of the reaction conditions (rt) and the absence of Lewis acidic conditions. The main disadvantages include a poor selectivity in alkylidenation of aldehydes and ketones, no methylenation and the excess of reagents.

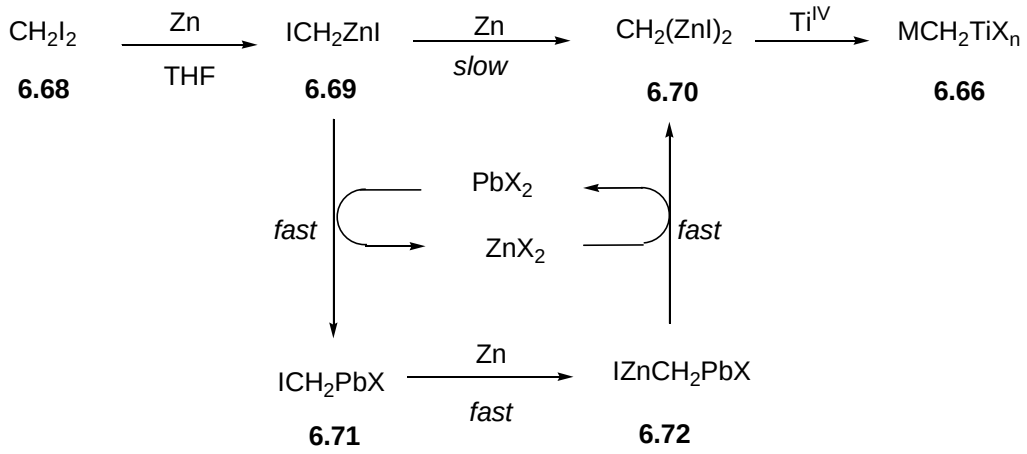
6.4. 1,1-Bimetallic reagents

In 1978, Takai and co-workers[117] reported the methylenation of ketones **6.65** using a new type of titanium carbenoid generated by the addition of $TiCl_4$ in dichloromethane to a suspension of dibromomethane and zinc dust in THF at rt. The new reactive species is presumably a 1,1-bimetallic titanium complex **6.66** (Scheme 6.16).



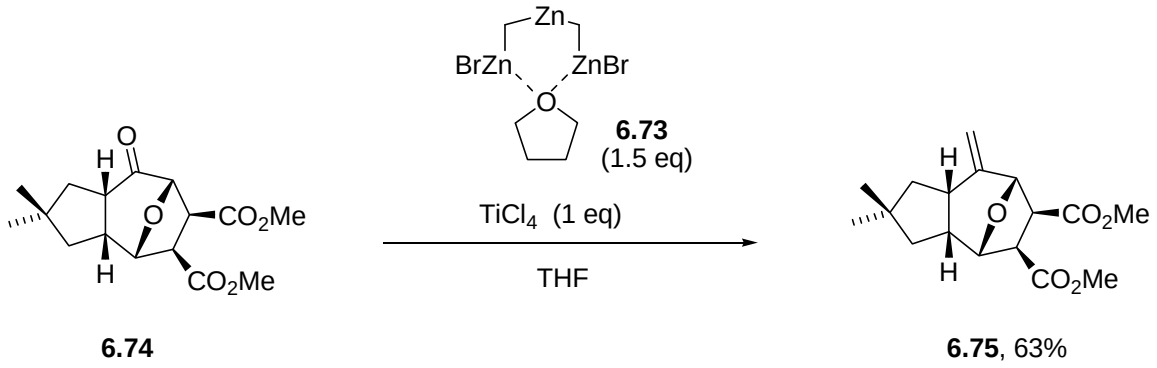
Scheme 6.16: 1,1-Bimetallic titanium carbenoid

The reaction mechanism is not clear (Scheme 6.17). It would seem that diiodomethane **6.68** is rapidly converted into zinc carbenoid **6.69** followed by a second very slow insertion to give the geminal dizinc **6.70**. The addition of lead(II) chloride accelerates the formation of the geminal dizinc **6.70** as it acts as a catalyst.[118] Takai suggested that transmetallation from zinc to lead occurs and gives the carbenoid **6.71** which is more easily reduced by zinc to produce carbenoid **6.72** as the Pb-C bond has a greater covalent character. A last transmetallation from lead to zinc gives geminal dizinc[79] **6.70** which can react with titanium(IV) chloride and form methylenating reagent **6.66**.



Scheme 6.17: Proposed mechanism

Tochtermann and co-workers[119] suggested an alternative to the geminal dizinc **6.70** using the commercially available Nysted reagent **6.73** in order to methylenate ketones (Scheme 6.18). Methylenation of ketone **6.74** took place at room temperature in the presence of Nysted reagent **6.73** (1.5 eq) and $TiCl_4$ (1 eq) and gave the alkene **6.75** in good yield.

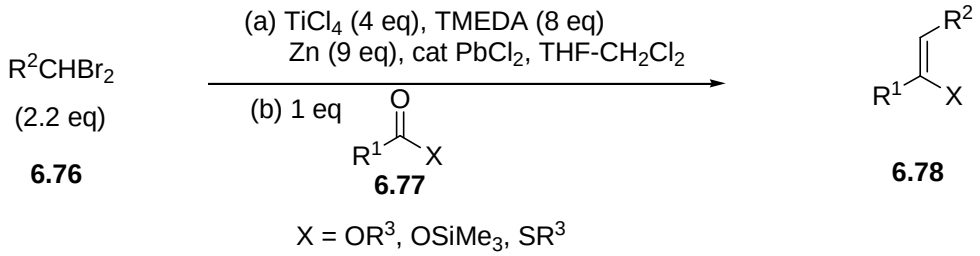


6.74 **6.75**, 63%

Scheme 6.18: Methylenation with Nysted reagent

6.5. Takai reagents

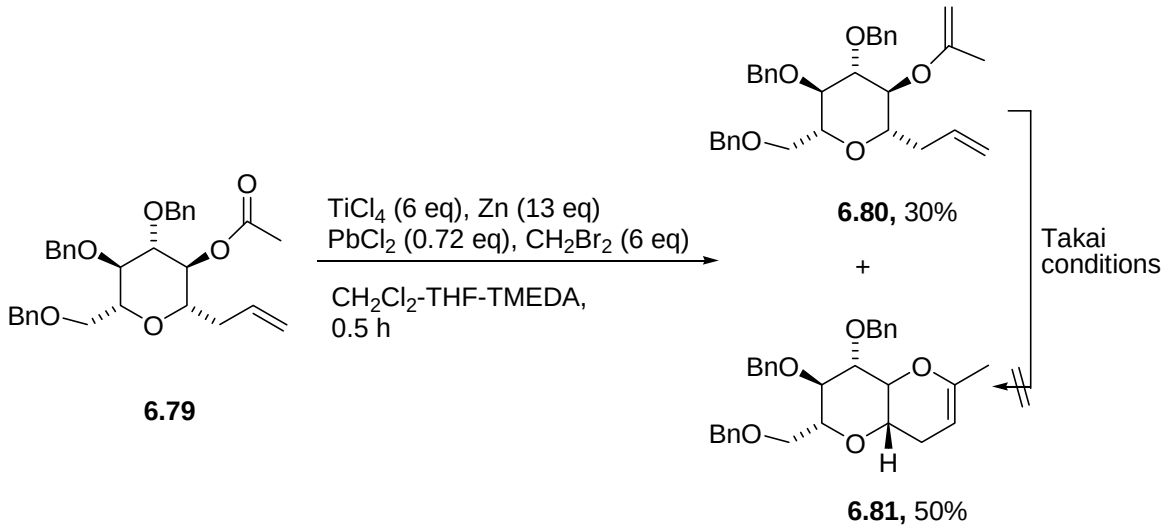
In 1987 Takai and co-workers[120] provided new reagents prepared from 1,1-dibromoalkanes **6.76** (2.2 eq), zinc (9 eq) and $TiCl_4$ (4 eq) and TMEDA (8 eq) in THF (Scheme 6.19). Although the reaction mechanism is still to be established, the presence of lead(II) is reported to be vital for the success of the reaction.[118] A definitive procedure for the preparation of this reagent has been published.[121] These reagents have been used to convert a range of carbonyl compounds **6.77** (including esters, silyl esters and thioesters) into *Z*-hetero-substituted alkenes **6.78** (*E* in the case of enamine). The stereoselectivity is governed by steric interactions.



Scheme 6.19: Takai reagent

Alkylidenation usually gives better yields than methylenation. Many functional groups are tolerated when esters are alkylidenated under Takai conditions including ethers, alkenes, acetals, silyl ethers, and vinyl and aryl halides.[76] The alkylidenes may be functionalised. However this has only been demonstrated for THP acetals[122] and for trimethylsilylmethylenation of esters.[123]

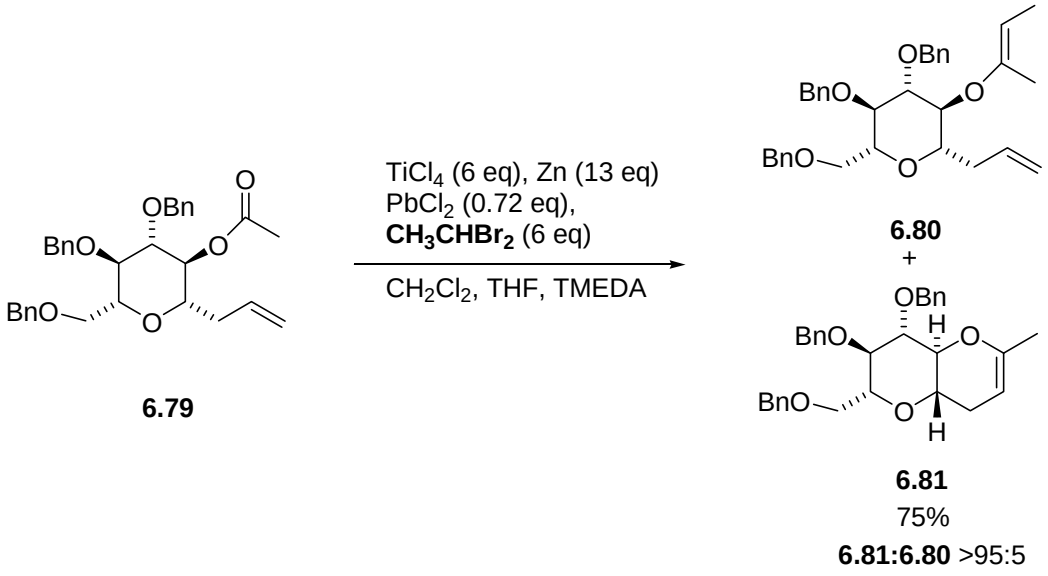
Takai alkylidenation conditions have the advantage that they are mild and involve a one-pot procedure which allows alkylidenation of a range of carbonyl derivatives with good stereoselectivity. It shows better reactivity than the Petasis reagent and a lower Lewis acidity compared to the Tebbe reagent. The mechanism of the Takai alkylidenation is not known however recent works presented by Rainier and co-workers[124] would confirm formation of titanium alkylidenes. Indeed in a first paper,[125] Rainier reported the conversion of *C*-glycoside **6.79** into cyclic enol ether **6.81** and acyclic enol ether **6.80** under Takai conditions (Scheme 6.20). Submitted to the same conditions, the acyclic enol ether **6.80** was not converted into the cyclic enol ether **6.81**. Consequently, unlike the Tebbe and Petasis reagents which can react preferentially with esters and then catalyse RCM, the Takai methylenating reagent does not catalyse RCM. However, it can generate an alkylidenating species by a metathesis process from an allyl group and then methylenate an intramolecular carbonyl group inducing cyclisation.[125] To enable this metathesis process, the methylenating reagent has to be a titanium methylidene rather than a 1,1-bimetallic species.



Scheme 6.20: Takai methylenation

Later, Rainier and co-workers[124] found that the nature of the alkylidenating reagent conditions affects the results of the reaction (Scheme 6.21). While the titanium methylidene reagent converted *C*-glycoside **6.79** into a mixture (62:38) of cyclic and acyclic compounds **6.81**: **6.80** (Scheme 6.20), the corresponding

titanium ethylidene reagent gave almost exclusively the cyclic enol ether **6.81** (Scheme 6.21).

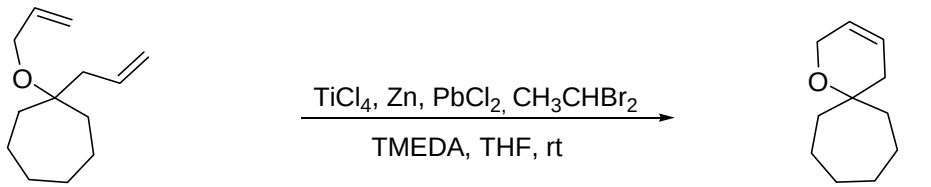


6.79

6.81
75%
6.81:6.80 >95:5

Scheme 6.21: Titanium alkylidene reaction

Furthermore, he found that the ethylidene reagent can catalyse RCM even at room temperature as shown by the conversion of diene **6.82** into the spirocyclic ether **6.83** in quantitative yield (Scheme 6.22).[124]



6.82

6.83, 100%

Scheme 6.22: Reduced titanium-mediated diene RCM

7. Microwave Assisted Organic Synthesis (MAOS)

7.1. Background

Located between IR radiation and radio waves,[126] microwave irradiation is electromagnetic irradiation in the frequency of 0.3 to 300 GHz. For industrial and scientific purposes, the microwave frequency has been imposed at 2.45 GHz in order to avoid interactions with telecommunications and radar equipments. The microwave concept is based on the ability of a specific material (solvent or reagent) to absorb microwave energy and convert it into heat caused by two main mechanisms: dipolar polarization or ionic conduction.[127,128] At microwave frequency, irradiation of the sample results in the dipoles or ions aligning with the applied electric field. As this electric field is alternating, the dipoles or ion field attempts to realign itself with the oscillating electric field and in this process energy is lost in the form of heat through molecular friction and dielectric loss (ε"), which is indicative of the efficiency with which electromagnetic radiation is converted into heat.[128] The amount of heat generated is directly linked to the ability of the dipole to align itself at the frequency of the oscillation of electric field. If the dipole does not have enough time to realign or aligns too fast, no heat is generated. The 2.45 GHz frequency avoids these two extremes. The ability of a substrate to generate heat under microwave irradiation is dependent on its dielectric properties (loss factor tan δ and permittivity).[127] The higher tan δ, the better is the absorption of the electromagnetic energy and consequently the more rapid is the heating (Table 7.1). Furthermore, if tan δ >0.5, the solvent is classified as highly microwave absorbing; if tan δ is 0.1-0.5 it is a medium microwave absorber and if tan δ <0.1, the solvent is a low microwave absorber.

Solvent	tan δ	Solvent	tanδ
Ethylene glycol	1.350	THF	0.047
Ethanol	0.941	Toluene	0.040
Water	0.123	Hexane	0.020

Table 7.1: Loss factors of different solvents

However a solvent with a low loss factor is not excluded from microwave reactions as dielectric properties of substrates, reagents or catalysts will allow sufficient heating. Moreover, polar additives such as ionic liquids can be added to the reaction to increase the absorbance level of the medium. Heating reactions with traditional equipment (oil, sand baths or heating mantles) is a slow and inefficient method for transferring energy to the system. It depends on the thermal conductivity of materials resulting in the temperature of the vessel exceeding that of the reaction mixture; it creates a hot surface on the reaction vessel where products, substrates and reagents decompose over time (wall effects). In contrast, microwave irradiations directly heat the reactants and solvents. An example is provided below (Figure 7.1) where heating performed with microwave irradiation (left) and heating performed with an oil bath (right) are compared. After 1 min of microwave irradiation, the whole volume is heated whereas with the oil bath only the walls of the tube become hot.

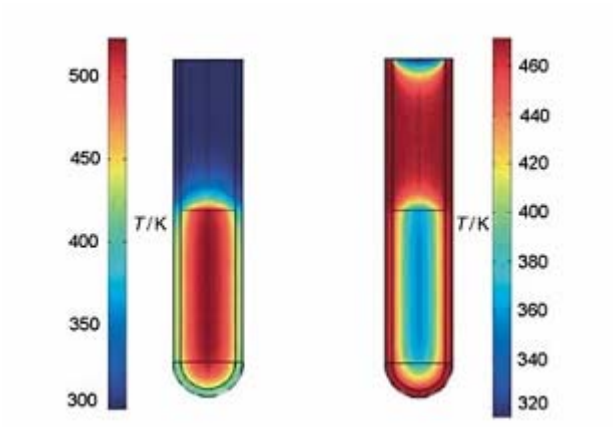


Figure 7.1: Temperature profiles with microwave irradiation (left) and oil bath (right)[127]

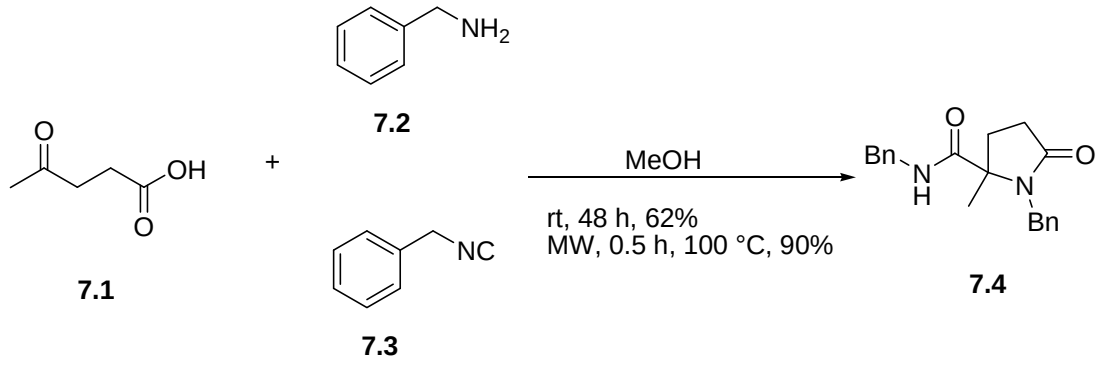
Appropriate vessels have been designed to allow the temperature increase to be uniform throughout the sample, leading to fewer by-products or product decomposition. An efficient internal heat transfer results in minimized wall effects.

Since the first report on the use of microwave heating to accelerate organic reactions by Giguere *et al.*[129] and Gedye *et al.*[130] in 1986, the MAOS has become increasingly popular (over 2000 publications). Many reasons might explain this passion including the commercial availability of microwave equipment designed for chemists. Above all, what makes this technique attractive is a shortened

reaction time (from hours to minutes), reduction of side reactions, an increase on yields and improvement of reproducibility. Moreover, the development of solvent-free techniques has also improved the safety aspects of the method. In the next section, I will briefly show a few notable applications of microwave heating to organic reactions which are most relevant to the chemistry developed in this thesis.

7.2. A microwave-assisted Ugi reaction

Among all the synthetic applications of microwave irradiations developed over the last 20 years, those involving the Ugi reaction or alkenation reactions are particularly relevant to my work. The Ugi reaction is a multi-component reaction developed by Ugi[131] in 1962 which involves condensation of an amine, an aldehyde or ketone, a carboxylic acid and an isocyanide to yield an α-acylaminoamide. The reaction of levulinic acid **7.1** with benzylamine **7.2** and benzylisonitrile **7.3** has been reported to proceed at room temperature in methanol to give the lactam derivatives **7.4** in moderate yields over a period of 48 h (Scheme 7.1).[132] Tye and Whittaker[133] have demonstrated that this reaction can be speeded-up significantly by performing the reaction under sealed-vessel microwave conditions. A reaction time of 30 min at 100 °C produced a better yield than the same process at room temperature.



Scheme 7.1: Ugi reaction at rt or under microwave irradiation

7.3. Petasis methylenation

The use of microwave irradiation to carry out Petasis methylenation has already been described in the chapter about titanium-mediated alkylidenation reactions (Chapter 6).

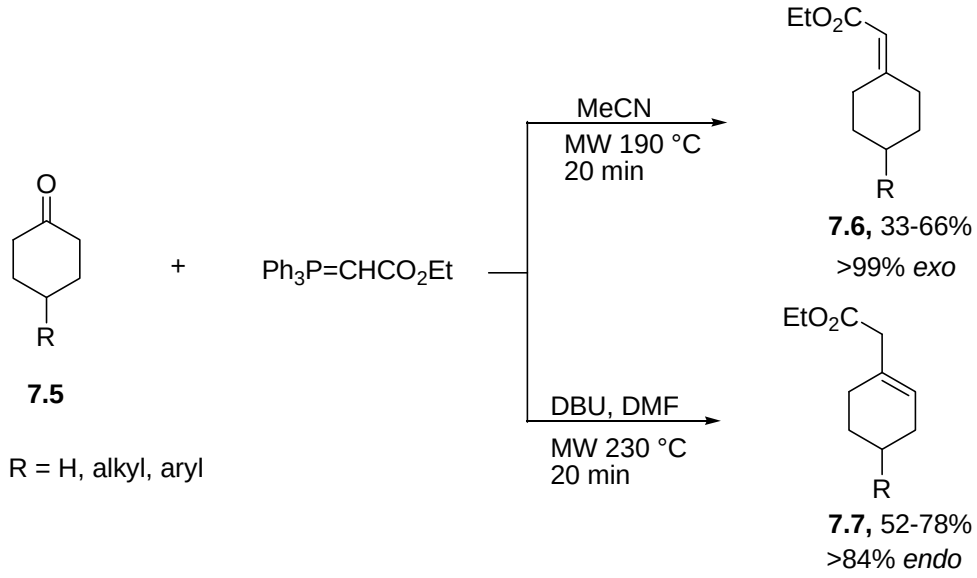
7.4. Microwave-assisted solid-phase organic synthesis

Sometimes solid-phase synthesis exhibits drawbacks such as slow reactions, solvation problems and degradation of the polymer support because of long reaction times. Microwave-assisted synthesis is able to overcome some of these issues. It has been demonstrated that resins (polystyrenes, rink amide, Merrifield, Wang etc.) can bear microwave irradiations for short periods of time even at temperatures above 200 °C. Kappe and co-workers[134] demonstrated that loading Merrifield and Wang resins using Gisin's method[35] under high temperature microwave heating accelerated significantly the reaction (from 12-48 h to 3-15 min) and increased the loading. A variety of reactions on solid-support have been assisted by microwave heating including the Ugi reaction,[135] peptide synthesis,[136] transition metal mediated synthesis[137] and multicomponent reactions.[138,139] However, the lack of suitable technology that would combine microwave heating and automated solid phase synthesis (i.e filtration and washings) makes this technology not fully exploited.

7.5. Wittig reaction

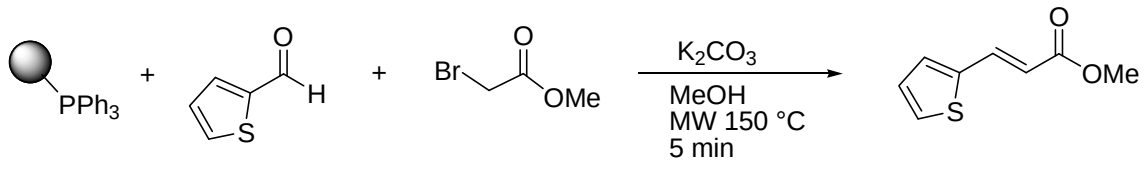
Wittig alkenation is an important transformation in organic synthesis. Dai and co-workers reported a study on the first regioselective microwave-assisted Wittig reactions of ketones with a stabilized phosphorus ylide.[140] They observed that the regioselectivity of the Wittig reaction of 4-substituted cyclohexanone **7.5** with a stabilized phosphorus ylide under microwave heating can be controlled (Scheme 7.2). The reaction carried out at 190 °C in acetonitrile produced the

exo olefin **7.6** whereas reaction at 230 °C in DMF in presence of DBU led to isomerisation to give the thermodynamically more stable *endo* compound **7.7**.



Scheme 7.2: Microwave-assisted Wittig reaction

The microwave-assisted Wittig reaction has also been applied to solid-phase synthesis. Westman[141] described a one-pot method for the formation of alkenes using the Wittig reaction and combining microwave heating and a supported triethylphosphine reagent **7.8** (Scheme 7.3). Yields were always greater than 80% and in most cases 95%. However the purification of products was done in a fully automated system which renders the process not accessible to everybody.

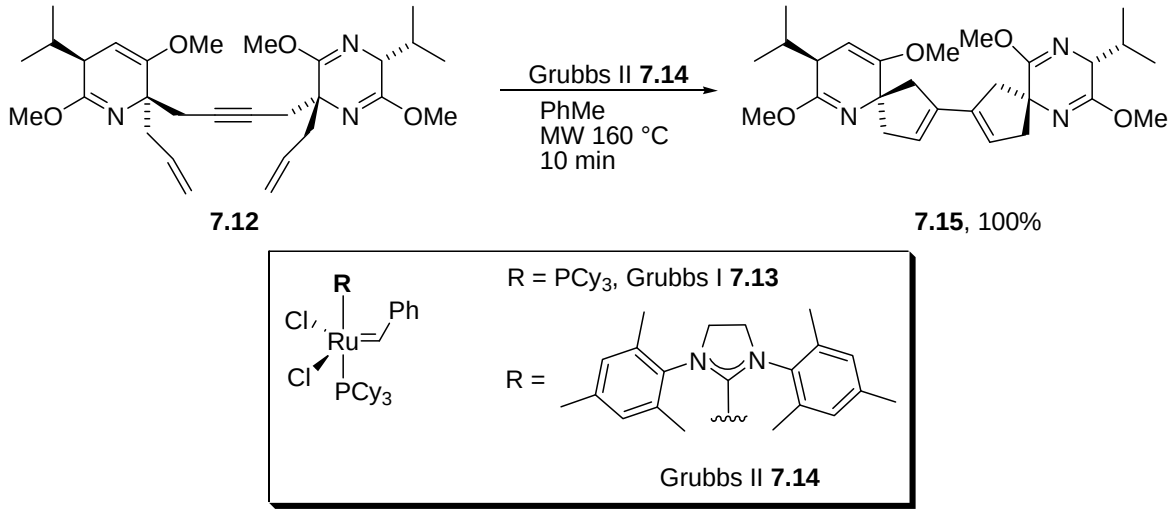


Scheme 7.3: Microwave-assisted Wittig reaction supported on solid-support

7.6. Ring closing metathesis reaction

Metathesis reactions generally require at moderate heating for several hours in order to get complete conversion. RCM under microwave irradiation has been reported to be complete within minutes or even seconds.[127] Efskind and

Undheim[142] reported the RCM reaction of dienyne **7.12** using Grubbs second generation catalyst **7.14** (Scheme 7.4). Usually, the reaction proceeded in toluene at 85 °C over a period of 9 h after multiple addition of fresh catalyst (3 x 10 mol%) and provided the compound **7.15** in 92% yield. Under microwave irradiations, the complete conversion took place in 10 min at 160 °C (5 mol% of catalyst) in toluene. They explained that the suppression of wall effects by microwave irradiation led to an increase in the catalyst lifetime.



Scheme 7.4: Microwave-assisted RCM

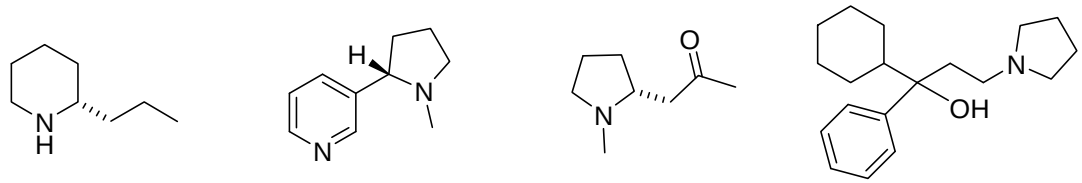
7.7. Conclusion

Many types of reactions can be carried out using microwave heating. In 2006 Kappe and Dallinger[128] counted more than 3000 examples published in literature since the first reports in 1986 and microwaves are an essential tool for the production of new compounds in pharmaceutical industry. Their use leads to dramatically reduced reaction times, higher yields and cleaner reactions. One of the major disadvantages of this technology is the cost of equipment. Scaling up reactions is another drawback of the technique. Most of the published examples were carried out on small scale (<1 g). However, MAOS is a promising technique which knows a rapid expansion.

8. Short Routes to Alkaloids using the Petasis Reagent

Used as drugs, potions, medicines, teas and poisons for 4000 years, alkaloids constitute one of the widest classes of natural products being synthesized by living organisms.[143] The extraordinary diversity of alkaloid structures and biological properties has long interested chemists. It was in the early 19th century that therapeutically active compounds were first isolated with the first crude drug investigation carried out on opium.[143] The first total synthesis of an alkaloid was reported in 1886 by Ladenburg for the synthesis of (+)-coniine **8.1**.[144] Many alkaloids have been used for hundreds of years in medicine and some are still important drugs today. Pharmaceutical industries have used and will continue to use alkaloids as biological tools and as lead compounds for development of new drugs. Many alkaloids serve as models for the synthesis of analogues with better properties.

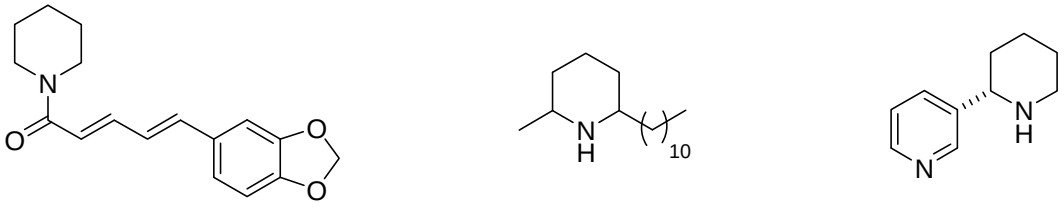
The pyrrolidine motif is present in numerous natural alkaloids such as nicotine **8.2** and hygrine **8.3** isolated from tobacco and coca leaves (Figure 8.1). It is found in many pharmaceutical drugs such as procyclidine **8.4**, an anticholinergic drug principally used for the treatment of Parkinson disease.



8.1 **8.2** **8.3** **8.4**

Figure 8.1: Pyrrolidine and piperidine cores in alkaloids and drugs

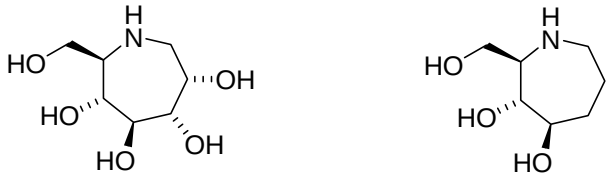
The piperidine structural motif is found in several natural alkaloids presenting biological activity as well, such as piperine **8.5** (black pepper),[145] the fire ant toxins, the solenopsin **8.6** (secreted as a mixture of stereoisomers),[146] the nicotine analogue anabasine **8.7** (Figure 8.2) or coniine **8.1**[144] (Figure 8.1).



8.5 **8.6** **8.7**

Figure 8.2: Piperidines in natural alkaloids

The synthesis of 7-membered amino cycles is also of interest. α-Glycosidase inhibitors have proved to be efficient drugs in the treatment of diabetes, HIV infection, viral infections or cancer as they inhibit the hydrolysis of the glycosidic linkage. A common strategy for designing such inhibitors is based on the mimicry of glycosides and for this purpose, a large number of nitrogen-containing, "sugar-shaped" heterocycles have been synthesized including azepanes **8.8** and **8.9** (Figure 8.3).[147] I explored three short routes for accessing alkaloids using microwave-assisted Petasis methylenation as the key step.



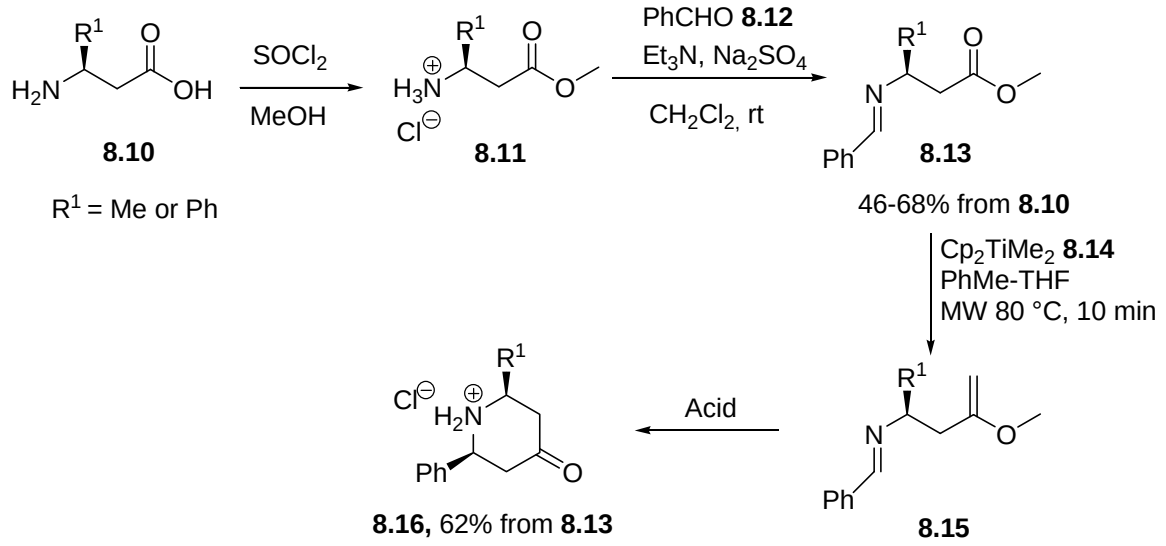
8.8 **8.9**

Figure 8.3: Substituted azepanes mimicking glycosides

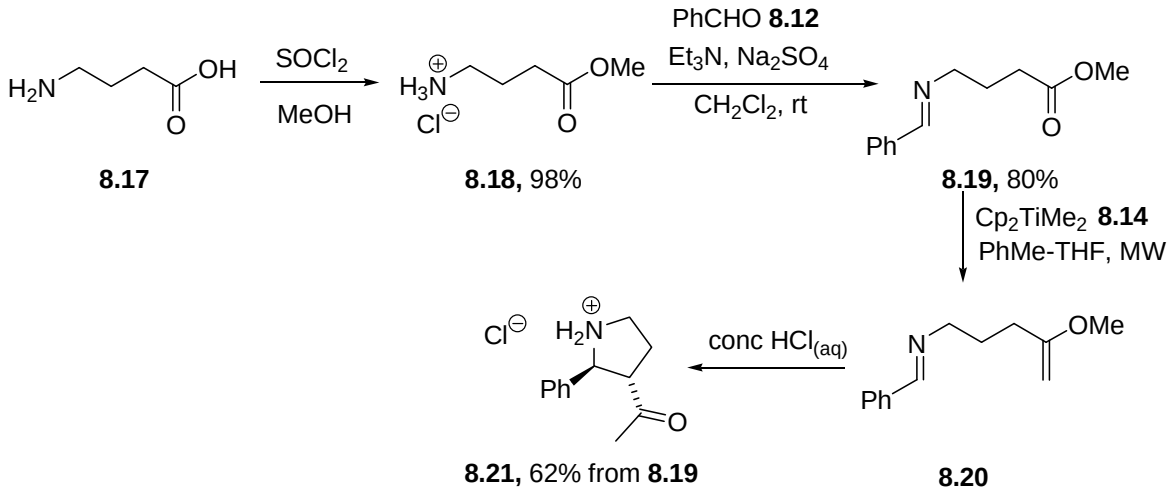
8.1. Synthesis of pyrrolidine or azepane alkaloids

As seen in chapter 6, titanium carbenoids can easily convert carboxylic acid derivatives directly into hetero-substituted alkenes.[76,79] A range of titanium carbenoids could be used to methylenate esters as seen in the literature[77,83,148,149] but methylenation of methyl esters in the presence of imines is best carried out using the Petasis reagent **8.14** (= **6.14**, see Scheme 6.5).[100] As reported by Adriaenssens and Hartley,[100] esters **8.13** were easily prepared from amino acids **8.10** and cleanly converted into enol ethers **8.15** by using microwave-assisted Petasis methylenation. Cyclisation of enol ether **8.15** was

easy and was done under acidic conditions to give cyclic amines **8.16** (Scheme 8.1). During this investigation, Adriaenssens discovered that ketone **8.21** (R^1 = H, R^2 = Ph) could be prepared from the γ-amino butyric acid (GABA) **8.17** (Scheme 8.2).



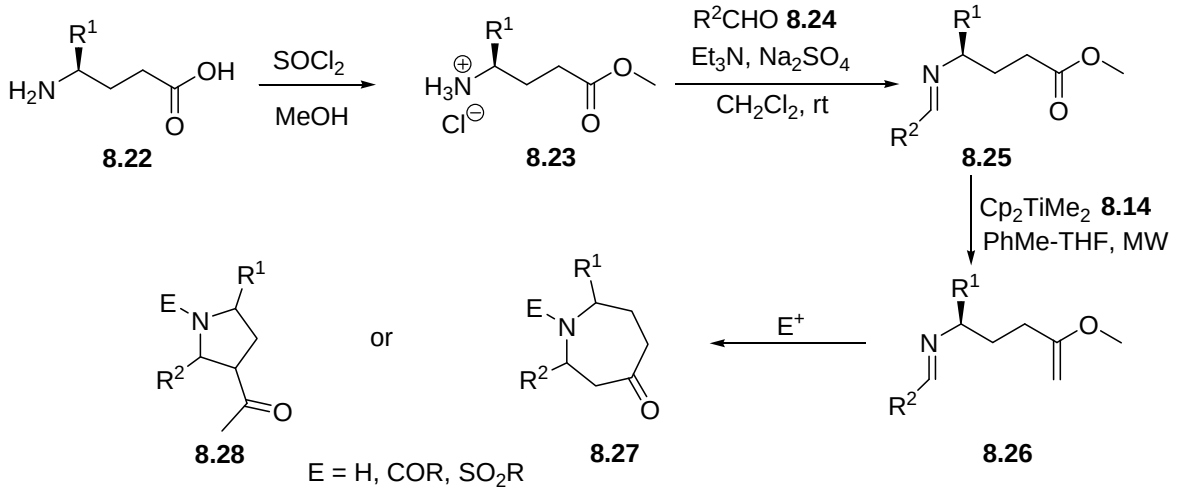
Scheme 8.1: Previous research in the group



Scheme 8.2: Previous research in the group

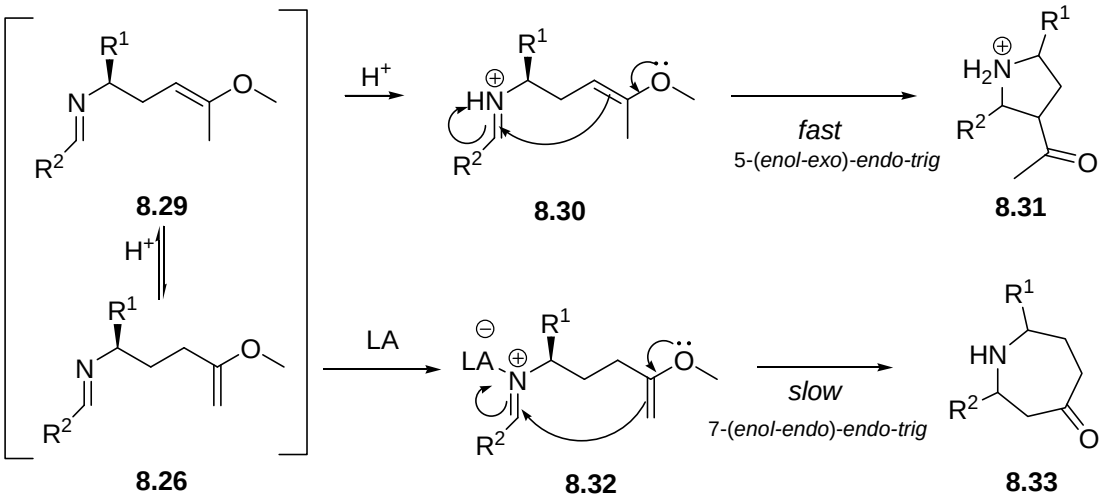
We thought that by following the same strategy a range of pyrrolidine alkaloids **8.28** might be prepared and by changing the cyclisation conditions azepanes **8.27** might also be accessed (Scheme 8.3). Therefore, we proposed to exploit this reaction sequence to allow general stereocontrolled access to azepanes

8.27 and pyrrolidines **8.28** by varying the type of amino acid **8.22**, aldehydes or ketones **8.24** and cyclisation conditions.



Scheme 8.3: Synthesis of cyclic amines using Petasis reagent

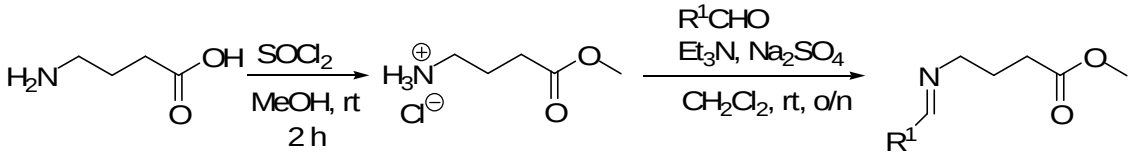
We assumed that by varying the nature of the acid, Lewis acid or electrophile used in the cyclisation step, we might orientate the reaction towards a pyrrolidine ring or towards an azepane. Indeed, treatment of the enol ether **8.26** with a Brönsted acid was expected to isomerise enol ether **8.29** and so generate an iminium intermediate **8.30** (Scheme 8.4), which would cyclise to give after hydrolysis the ammonium salt **8.31**. On the other hand, the use of a Lewis acid to treat the enol ether **8.26** would provide the 7-membered ring **8.33** *via* a 7-(*enol-endo*)-*endo-trig* cyclisation of iminium complex **8.32**.



Scheme 8.4: Towards a 5- or 7-membered ring

Results and discussion

In my first route, γ-aminobutyric acid (GABA) **8.17** was used as the starting material, which was converted into the methyl ester **8.18** by treatment with thionyl chloride in methanol (Scheme 8.5). The hydrochloride salt **8.18** was cleanly isolated in 95% yield, then following a procedure described by Blommaert *et al.*,[150] various imines **8.19** and **8.37-8.39** were formed by condensation of the methyl ester **8.18** with the corresponding aldehydes **8.12** and **8.34-8.36** in the presence of triethylamine (Table 8.1).



8.17 **8.18**, 95% **8.19, 8.37-8.39**

Scheme 8.5: Towards the synthesis of imino esters

Entry	R^1	Aldehydes	Imino esters	Yield
1	Ph-	**8.12**	**8.19**	71%
2	$CH_3CH_2(CH_3)CH$-	**8.34**	**8.37**	94%
3	2,4-$(CH_3O)_2C_6H_3$-	**8.35**	**8.38**	23%
4	(*E*)-C_6H_5CH=CH-	**8.36**	**8.39**	17% [a]

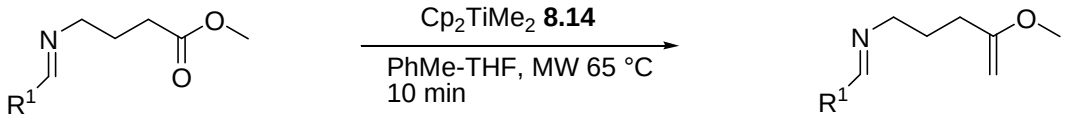
[a]: yield calculated from analysis of the crude NMR

Table 8.1: Summary of yields for the synthesis of imino esters

All these imines were highly unstable and therefore purification was quite delicate which explains the modest yield obtained for imine **8.38**. After aqueous work up, distillation under reduced pressure using a Kugelrohr apparatus was preferred. However, careful monitoring of the temperature and the advancement of the purification were necessary. The imino ester **8.39** was observed by NMR analysis of the crude mixture (17%), but the compound decomposed during distillation and characterization was not carried out.

According to conditions established by Adriaenssens and Hartley,[100] the Petasis reagent **8.14**, prepared as described by Payack *et al.* [85] would allow conversion

of esters into enol ethers under microwave irradiation. Although there are examples reported of selective reaction of nucleophilic organometallic reagents with the imine group of imino esters,[151] Adriaenssens and Hartley[100] had shown that the Petasis reagent methylenates the ester selectively under mild microwave conditions. Irradiation of esters **8.19**, **8.37-8.38** with the Petasis reagent **8.14** in a sealed vessel for 10 min provided enol ethers **8.20**, **8.40-8.41** in modest to excellent yield (Scheme 8.6, Table 8.2). Titanium residues were removed by precipitation by treating the crude mixtures with hexane under sonication and due to the relative instability of enol ethers, the cyclisation was investigated without further purification.



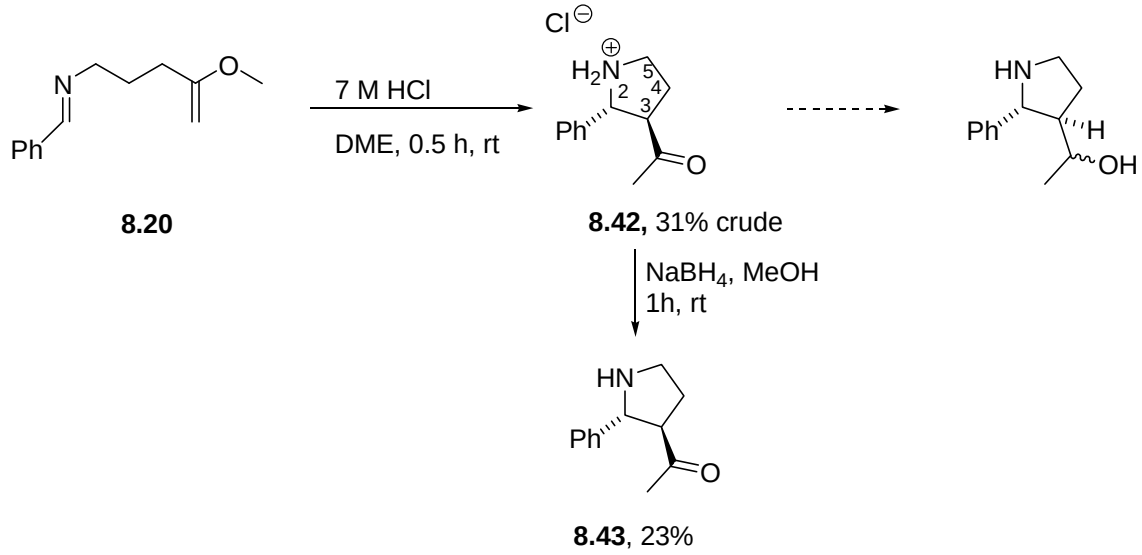
8.19, 8.37-8.38 **8.20, 8.40-8.41**

Scheme 8.6: Petasis methylenation

Entry	R^1	Imino esters	DMT **8.14** (eq)	Enol ethers	Yield
1	Ph-	**8.19**	6.1	**8.20**	84%
2	$CH_3CH_2(CH_3)CH$-	**8.37**	6.1	**8.40**	100%
3	2,4-$(CH_3O)_2C_6H_3$-	**8.38**	8.2	**8.41**	28%

Table 8.2: Summary of yields for the synthesis of enol ethers

Many different conditions were attempted to cyclise the enol ether **8.20** (Table 8.3). Most conditions gave only decomposition (entries 1-4). The only conditions which proved to be at all effective for the cyclisation of enol ether **8.20** was the use of 7 M or Conc HCl in DME (0.1 M) (entries 5 and 6). A compound assumed to be the hydrochloride salt **8.42** was produced in poor yield and identified from the ^{1}H NMR of the crude mixture (Scheme 8.7) [^{1}**H NMR** (400 MHz, $CDCl_3$) δ_H: 2.00-2.08 (4H, m, CH_3 and CH^AH^B-4), 2.41-2.50 (1H, m, CH^AH^B-4), 3.03-3.14 (1H, m, CH^AH^B-5), 3.36-3.44 (1H, m, CH^AH^B-5), 3.50 (1H, q, *J* 9.4 Hz, CH-3), 4.56-4.63 (1H, m, CH-2), 7.25-7.31 (3H, m, Ar-H), 7.54-7.56 (2H, m, Ar-H), 9.63 (1H, br s, NH_2), 10.39 (1H, br s, NH_2)].



Scheme 8.7: Cyclisation of enol ether 8.20

Due to purification issues, this compound was never isolated. Later, this result was supported by further data collected during an attempt at reduction of the ketone, where the free amine **8.43** was isolated in poor yield. Although the cyclisation of enol ethers **8.40** and **8.41** were attempted under the same conditions (entries 7, 8), none of the desired products was detected.

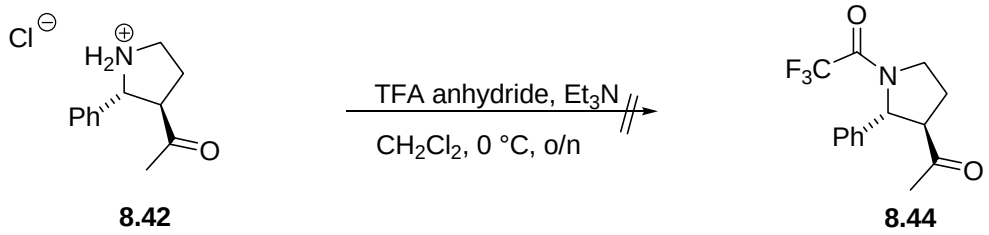
Entry	R^1	Enol ethers	Cyclisation conditions	Yield
1	Ph-	**8.20**	Conc HCl, 0.5 h, rt	-
2	Ph-	**8.20**	7 M HCl, 0.5 h, rt	-
3	Ph-	**8.20**	TsOH (2.5 eq), DME, o/n, rt	-
4	Ph-	**8.20**	TsOH (2.0 eq), DME, o/n, rt	-
5	Ph-	**8.20**	7 M HCl, DME, 0.5 h, rt	**8.42**[a], 31%
6	Ph-	**8.20**	Conc HCl, DME, 0.5 h, rt	**8.42**[a], 9%
7	$CH_3CH_2(CH_3)CH$-	**8.40**	Conc HCl, DME, 0.5 h, rt	-
8	2,4-$(CH_3O)_2C_6H_5$-	**8.41**	Conc HCl, DME, 0.5 h, rt	-

a: crude yield compounds not purified

Table 8.3: Summary of cyclisation conditions

Another attempt at purification involved the derivatisation of the ammonium salt **8.42** (Scheme 8.8). Reaction of cyclic amine **8.42** with trifluoroacetic

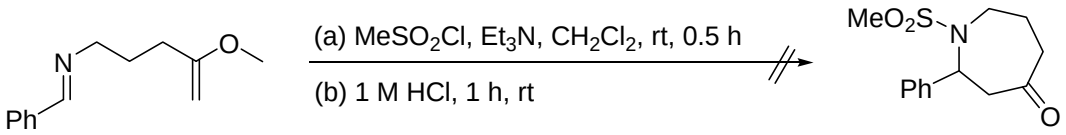
anhydride in presence of triethylamine failed to give the amide **8.44**. Decomposition of the compound was noted.



8.42 **8.44**

Scheme 8.8: Derivatisation of salt 8.42

In order to access the azepane, we decided to activate the imine **8.20** (Scheme 8.9). Reaction of mesyl chloride with enol ether **8.20** in presence of triethylamine in dichloromethane followed by treatment with aqueous acid did not give the desired amine **8.45**. NMR analysis of the crude mixture before acidic conditions revealed that hydrolysis of the imine had occurred. Another reaction carried out with trifluoroacetic anhydride under the same conditions led to the same conclusion.



8.20 **8.45**

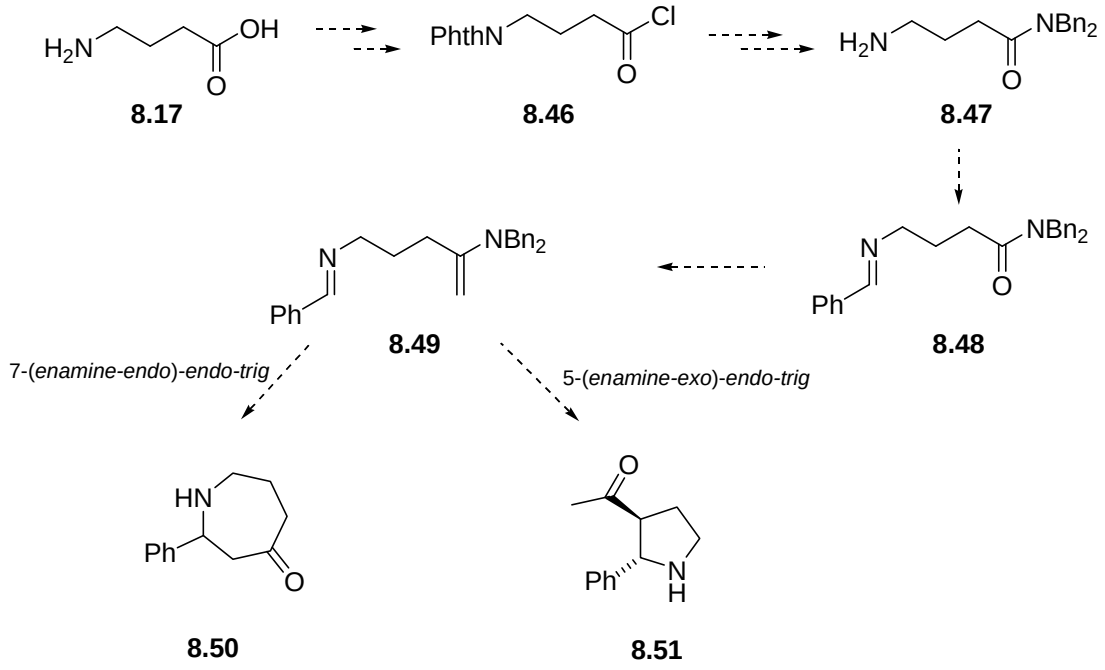
Scheme 8.9: Attempt of cyclisation

These results were not enough to convince us of the likely sucess of this approach. Therefore we proposed another route to access to pyrrolidines or azepanes by using microwave-assisted Petasis methylenation and considering the methylenation of an amide.

8.2. Synthesis of pyrrolidine or azepane alkaloids

This new route would allow access to alkaloids starting from the same amino acid, GABA **8.17** (Scheme 8.10). First, protection of the amino group of the

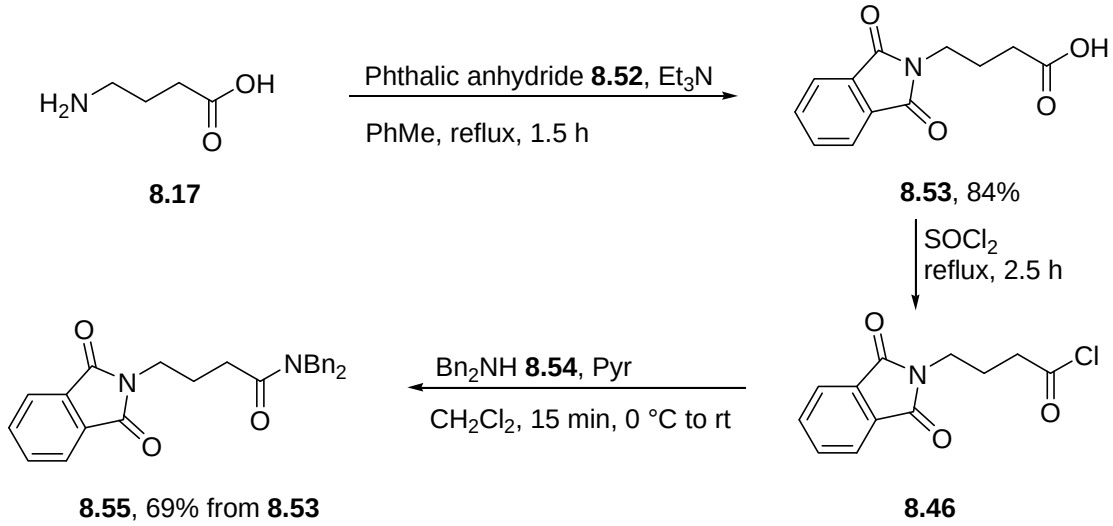
GABA **8.17** would allow the formation of acid chloride **8.46** followed by formation of the dibenzylamide. Deprotection would generate the amine **8.47** and then according to conditions previously described, the imine **8.48** would be formed. The amide would be selectively methylenated using the Petasis reagent assisted by microwave heating. The difference with the preceding route relies on this step as an enamine **8.49** would be formed instead of enol ether. Cyclisation performed under acidic conditions would provide cyclic amines **8.50** or **8.51**.



Scheme 8.10: A new route to alkaloids

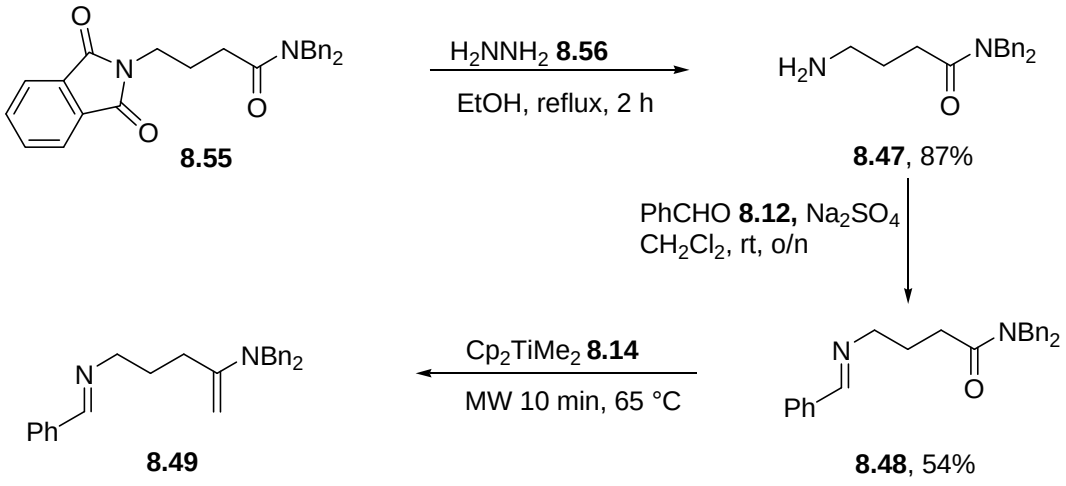
Results and discussion

According to the procedure provided by Kruper *et al.*,[152] the free amine of γ-aminobutyric acid **8.17** was protected using phthalic anhydride **8.52** in the presence of triethylamine (Scheme 8.11). The acid **8.53** obtained in excellent yield was then treated with thionyl chloride at reflux for 2.5 h. After removal of $SOCl_2$ under reduced pressure and without further purification, the acid chloride **8.46** was directly used in a reaction with a solution of dibenzylamine **8.54** and pyridine in CH_2Cl_2.[153] This Schotten-Baumann reaction[154,155] led to the production of the amide **8.55** in good yield.



Scheme 8.11: Synthesis of the amide 8.55

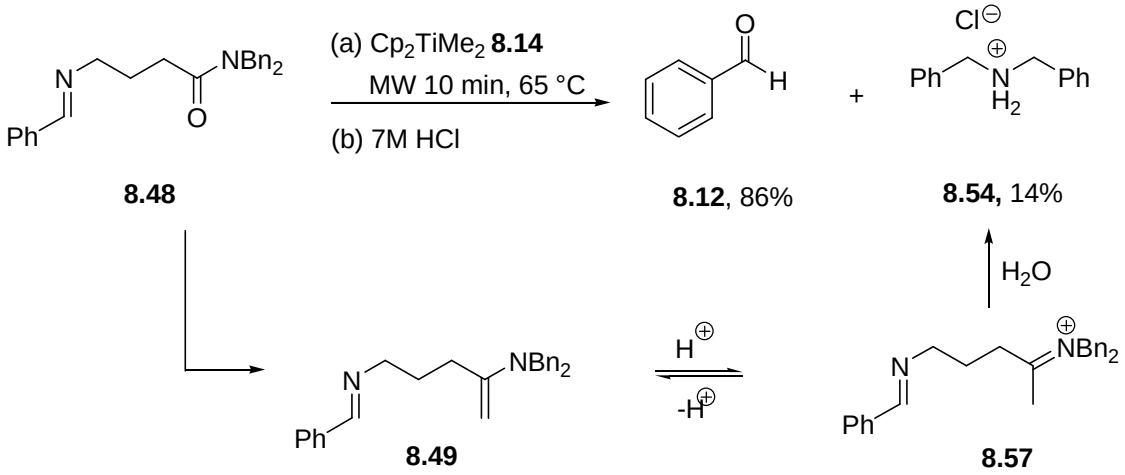
Deprotection of the phthalimide **8.55** using hydrazine **8.56** in ethanol at reflux followed by reaction of the free-amine **8.47** with benzaldehyde **8.12** provided the imino amide **8.48** in 54% yield (Scheme 8.12).[150,156] Petasis methylenation of the amide **8.48** was carried out under standard microwave conditions. However, the use of 6.0 eq of the Petasis reagent **8.14** at 65 °C resulted in a complex mixture, so it was decided to carry out Petasis methylenation and then treat the resulting mixture with acid.



Scheme 8.12: Synthesis of the enamine 8.49

Methylenation of amides have already been reported[84] and from further investigations, it appeared that the iminium ion **8.57** in equilibrium with the enamine **8.49** when there is a proton source suffered hydrolysis rather than

cyclisation (Scheme 8.13). After treatment with 7 M HCl, we recovered benzaldehyde **8.12** from the hydrolysis of the imine part and dibenzylamine hydrochloride salt **8.54** from the enamine part.

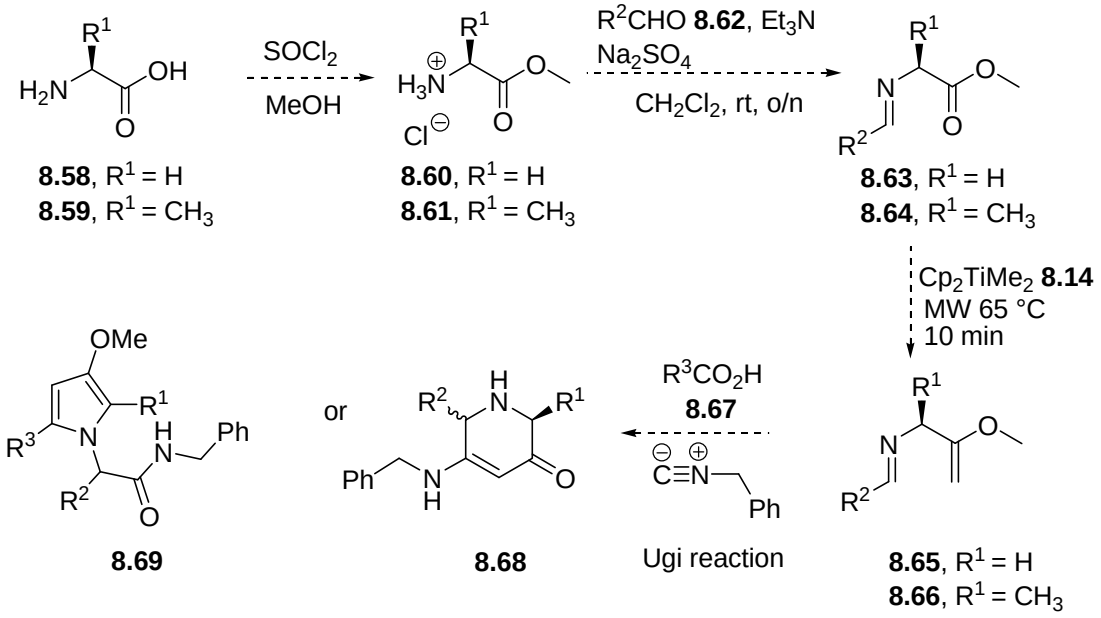


Scheme 8.13: Decomposition of the substrate under Petasis conditions

The desired amines were not obtained as hydrolysis of the enamine occurred. A final approach to the synthesis of cyclic amines using the Petasis reagent was then investigated, which combined methylenation with the Ugi reaction.

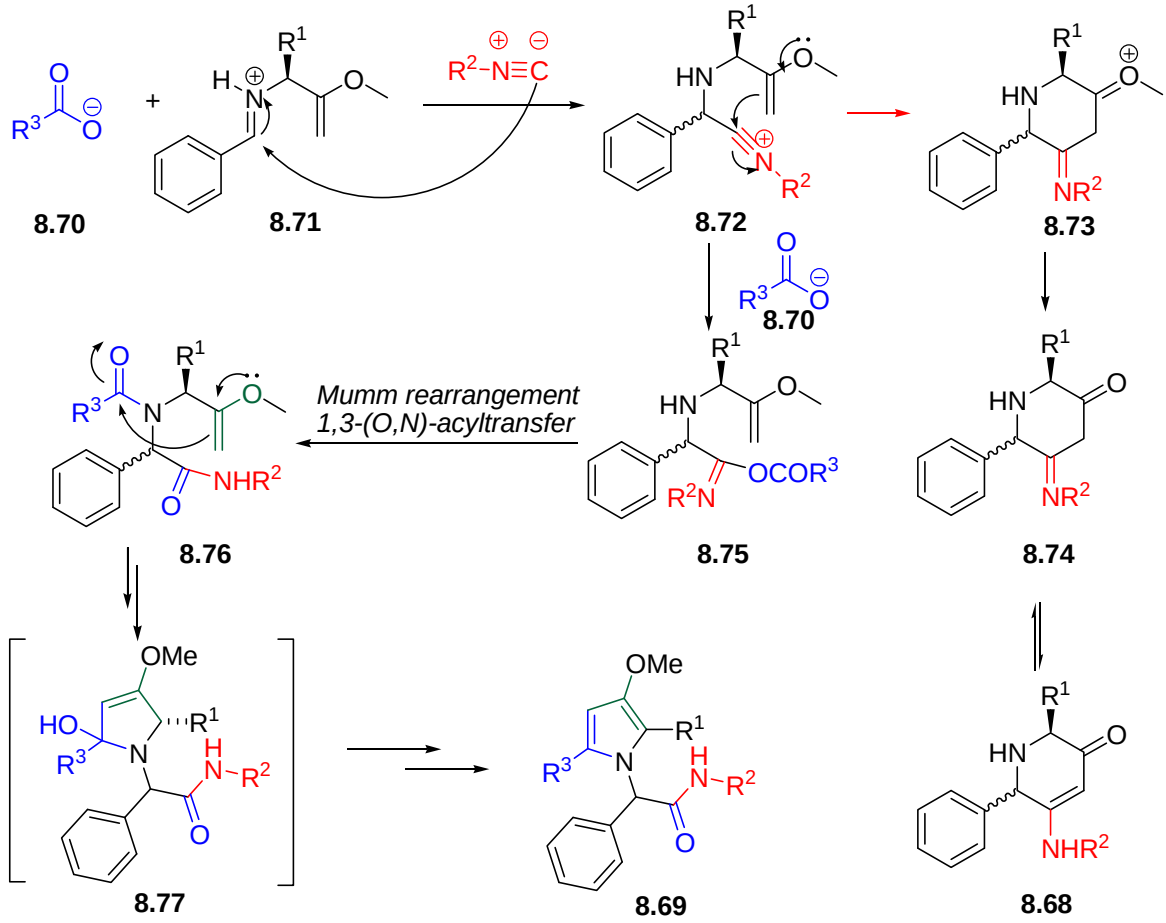
8.3. Synthesis of pyrrole or piperidinone alkaloids using the Ugi reaction

Petasis methylenation and Ugi reaction were key steps in this new route to alkaloids. Following a similar strategy to that seen in section 8.1, pyrrole or piperidinone alkaloids would be prepared starting from glycine **8.58** or (*S*)-alanine **8.59** (Scheme 8.14). Formation of imines **8.63** and **8.64** would be performed as previously described then selective methylenation of esters would provide enol ethers **8.65** and **8.66**. As described in the previous chapter, the Ugi reaction is a multicomponent reaction involving an imine, an isocyanide and a carboxylic acid **8.67**. Recently Tye and Whittaker[133] have provided an optimized version of this reaction assisted by microwave heating. We proposed to use the Ugi reaction as a cyclisation step.



Scheme 8.14: A new route to alkaloids

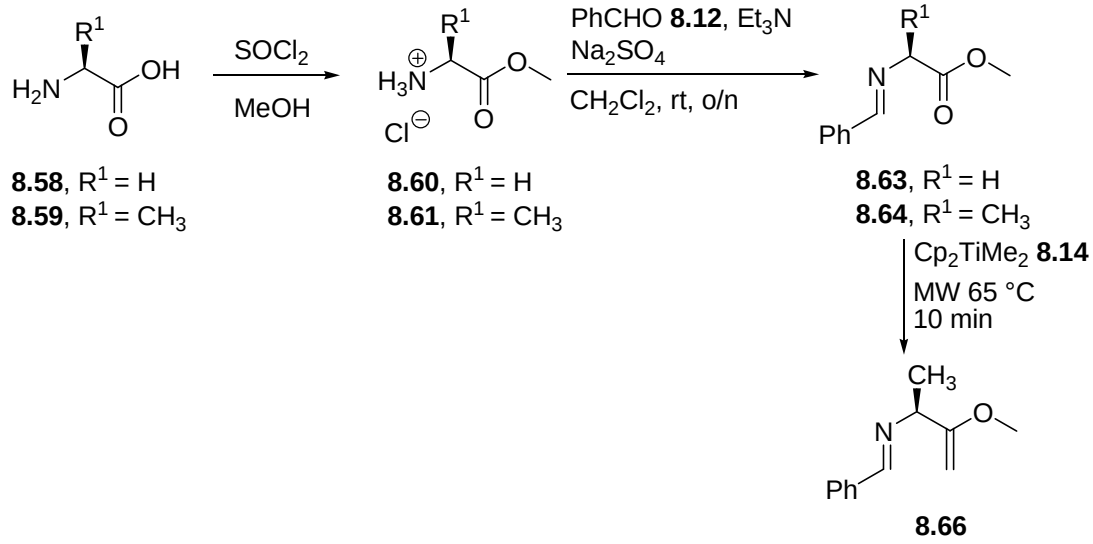
Indeed, we believed that applying the Ugi conditions on enol ethers **8.65** and **8.66** would generate cyclic amines **8.68** or **8.69**. The proposed mechanisms for the potential cyclisations are shown in Scheme 8.15. Under acidic conditions, nucleophilic addition of the isocyanide on the iminium species **8.71** would result in the formation of nitrilium intermediates **8.72** which could cyclise *via* a 6-(*enol-endo*)-*exo-trig* cyclisation and the resulting enol ether hydrolyse to give the piperidinone **8.68** or a second nucleophilic addition takes place with the carboxylate **8.70** and provide the intermediate **8.75**. Then a Mumm rearrangement would yield the compound **8.76.** Finally, a 5-(*enol-endo*)-*exo-trig* cyclisation would allow the formation of the cyclic compound **8.69**.



Scheme 8.15: Proposed mechanisms of cyclisations

Results and discussion

The first step consisted in the formation of methyl esters. Treatment of the amino acid **8.58** or **8.59** with thionyl chloride in methanol gave esters **8.60** and **8.61** in excellent yield (Scheme 8.16, Table 8.4). Then the formation of imines **8.63** and **8.64** was carried out under well-known conditions.[150] However, although the imine **8.63** was observed in the crude mixture, the compound decomposed during the removal of excess aldehyde by distillation. Similarly imine **8.64** gave a poor yield. The use of the Petasis reagent **8.14** under microwave irradiation allowed the conversion of the imine **8.64** into enol ether **8.66** and the cyclisation *via* an Ugi reaction was considered.

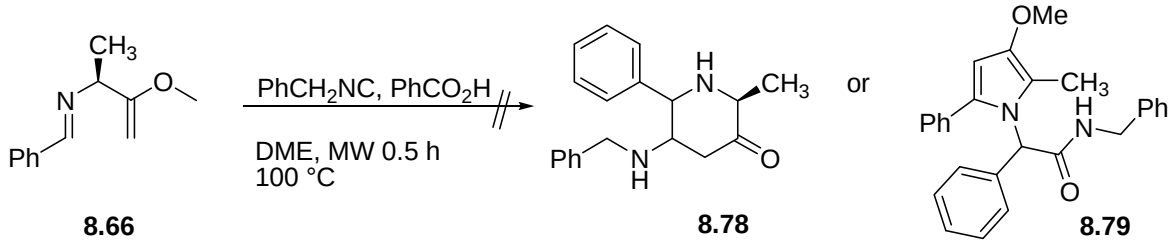


Scheme 8.16: Towards the synthesis of enol ethers

Entry	R^1	AA	Methyl esters and yield	Imines and yield	Enol ethers and yield
1	H	**8.58**	**8.60,** 98%	**8.63,** -	-
2	CH_3	**8.59**	**8.61,** 92%	**8.64,** 19%	**8.66,** 36%

Table 8.4: Summary of yields

In Tye and Whittaker's studies,[133] benzylisonitrile and benzoic acid were chosen to carry out the Ugi reaction (Scheme 8.17). Therefore a solution of imine **8.66** (1.0 eq), benzoic acid (0.7 eq) and benzylisonitrile (0.7 eq) in dry DME (0.4 mL) was heated in a sealed tube by microwave irradiation at 100 °C for 0.5 h. The crude mixture, after a basic work-up showed decomposed materials. This first unpromising result together with the severe stench of the reagents used discouraged further exploration.



Scheme 8.17: Ugi reaction

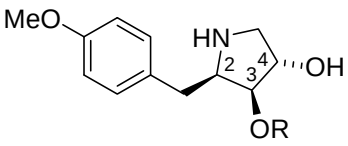
8.4. General conclusions

To sum up, we tested three short routes towards the synthesis of 5-, 6- or 7-membered cyclic amines starting from amino acids with Petasis methylenation as a key step. As expected, selective methylenation of esters to give imino enol ethers generally proceeded well. Concerning cyclisations, despite various conditions attempted (acids and Ugi reaction), there was nothing to encourage further investigations. Methylenation of amide **8.48** under microwave heating is an unsolved problem. It is tricky to be sure if there was competition between hydrolysis of the enamine and cyclisation or if the methylenation had not taken place at all and hydrolysis of the amide and imine happened during the acidic work up.

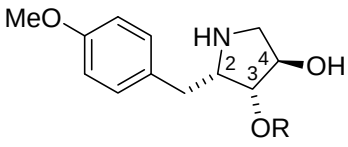
9. Previous Syntheses of Anisomycin

9.1. Background

(−)-Anisomycin **9.1**, also know as flagecidin, is a pyrrolidine antibiotic[157] first isolated from the fermentation of various *Streptomyces* species by Sobin and Tanner of Pfizer in 1954.[158] Its structure was initially elucidated in 1965[159] but the relative and absolute stereochemistry were modified three years later on the basis of ^{1}H NMR analysis[160] and X-ray crystallography[161] to the (2*R*,3*S*,4*S*) configuration[162] (Figure 9.1).



(−)-**9.1,** R = Ac, (−)-anisomycin
(−)-**9.2,** R = H, (−)-deacetylanisomycin



(+)-**9.1**, R = Ac, (+)-anisomycin
(+)-**9.2**, R = H, (+)-deacetylanisomycin

Figure 9.1: Structures of Anisomycin and derivatives

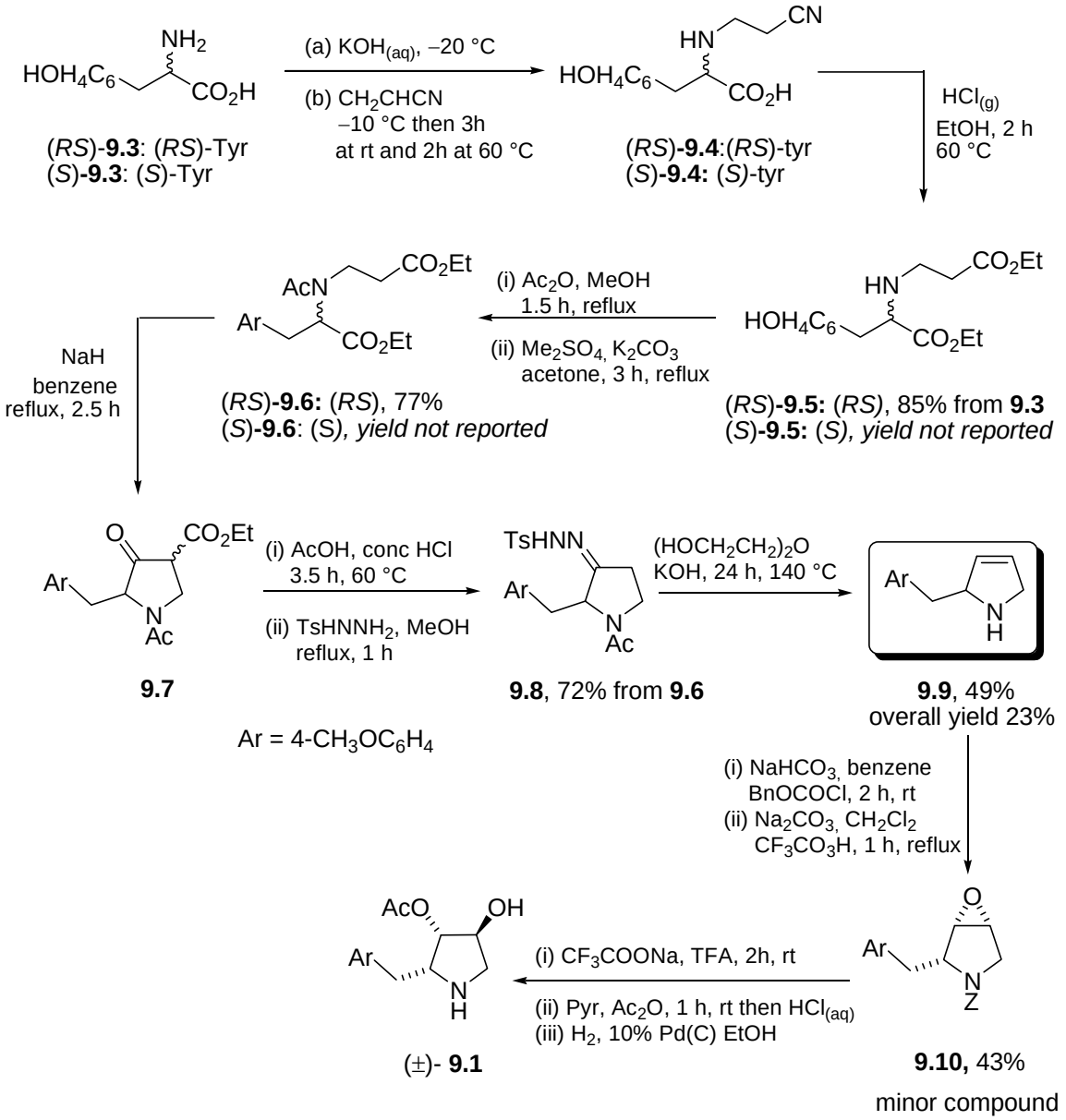
(−)-Anisomycin **9.1** has become a valuable tool in molecular biology as it exhibits selective and potent activity against protozoa and certain strains of fungi. It has been used successfully in clinical trials for the treatment of both amoebic dysentery and trichomonas vaginitis.[163] Anisomycin **9.1** is also known as a peptidyl transferase inhibitor binding to eukaryotic ribosomes.[164] This natural product and its deacetyl derivative **9.2** show fungicide[163] activity as well (Figure 9.1). More recently it has been found that (−)-anisomycin **9.1** displays high *in vitro* antitumor activity [IC_{50} in the range of 0.05-0.34 μM against LU99 (human lung carcinoma) and MCF7 (human breast cancer cell)].[165,166]

A structure-activity relationship indicated that the diverse biological activities are due to the presence of the chiral pyrrolidine skeleton resulting in considerable synthetic interest.[167] Quite a number of enantioselective syntheses of this simple natural product have been reported since 1970.[168] In most of them, anisomycin **9.1** was obtained by transformation of deacetylanisomycin **9.2** accessed *via* various chiral pool starting materials.

About 25 syntheses of anisomycin **9.1** (racemic or enantiopure) or the precursor deacetylanisomycin **9.2** can be found in literature. A short review of the most impressive routes established to access anisomycin is given here. The few total syntheses of racemic anisomycin are described first and then those of enantiopure anisomycin. The nature of the starting material has been chosen as the criterion of classification of the enantioselective routes and so the discussion is divided into four categories: enantioselective routes starting from an amino acid, from a diol, from a sugar or from a diverse range of other substrates.

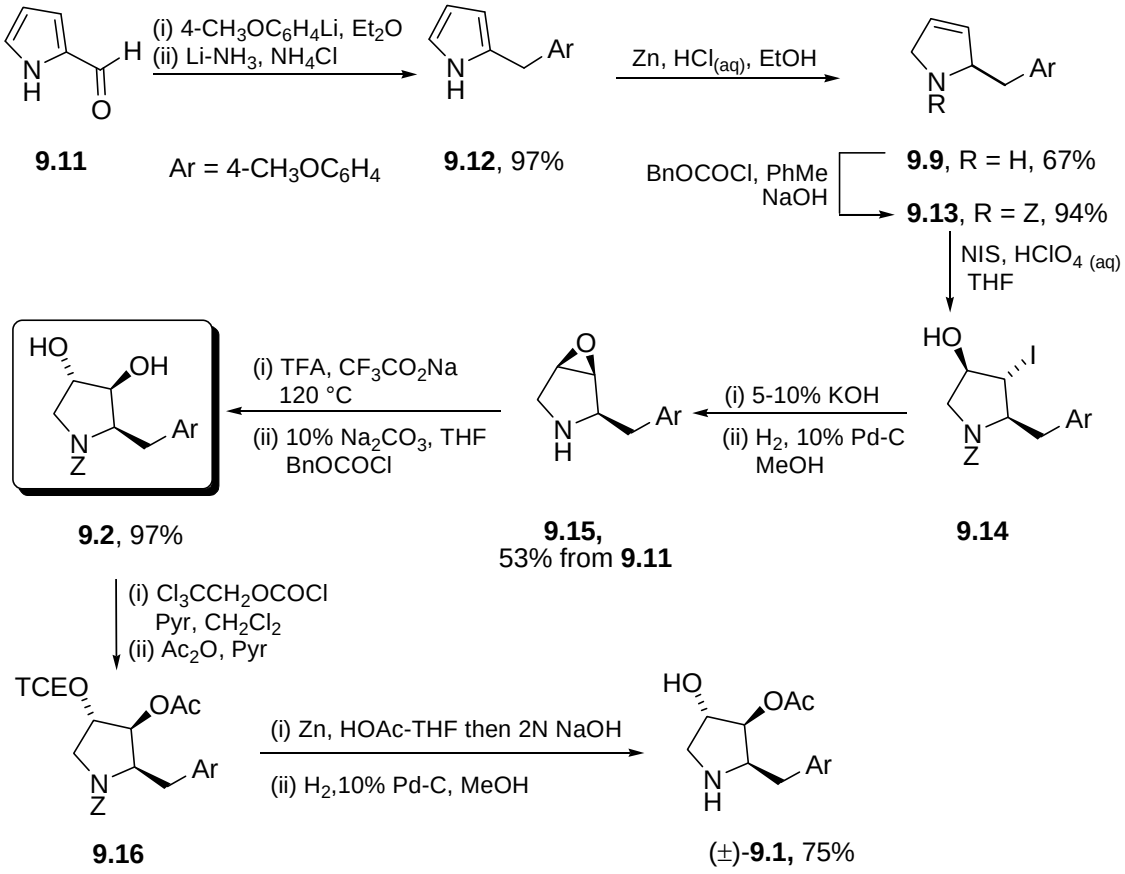
9.2. Racemic syntheses of anisomycin

Only two total syntheses of (±)-anisomycin **9.1** have been reported so far; first in 1969 by Oida and Ohki[169] and later by Schumacher and Hall.[170] Considering Butler's[171] demonstration of tyrosine, glycine and methionine involvement in the biosynthesis of anisomycin, Oida and Ohki proposed a total synthesis of (±)-anisomycin in 15 steps from (*RS*)- or (*S*)-tyrosine **9.3** (Scheme 9.1). The pyrrolidine compound **9.7** was obtained after a few steps *via* a Dieckmann condensation which led to the loss of the enantiomeric purity in the case of (*S*)-tyrosine **9.3**. Then epoxidation of the pyrroline **9.9** using pertrifluoroacetic acid was carried out and yielded a mixture of the *syn*-epoxide and *anti*-epoxide **9.10** in a ratio of 5:1. The epoxides were separated by chromatography and treatment of *anti*-epoxide with acetic acid/ NaOAc then mesylation followed by treatment with base provided the minor *syn*-epoxide **9.10** in good yield**.** The epoxide ring **9.10** was then opened using trifluoroacetic acid followed by acylation and deprotection of the amine. The major drawback of this sequence came from random acylation at the last stage requiring separation of isomers. This resulted in an overall isolated yield of 1%.



Scheme 9.1: Oida and Ohki's synthesis of (±)-anisomycin

In 1982, Schumacher and Hall[170] reported a convenient and efficient diastereoselective total synthesis of (±)-anisomycin **9.1** from pyrrole-2-carboxaldehyde **9.11** where the overall isolated yield was better than 40% and the synthesis required 13 steps (Scheme 9.2). First steps involved formation of the carbon skeleton of anisomycin by using an alkylation-reduction technique. Thus, the 4-methoxybenzylpyrrole **9.12** was prepared in two steps from the pyrrole-2-carboxaldehyde **9.11**. Next steps involved the introduction of the correct stereochemistry.



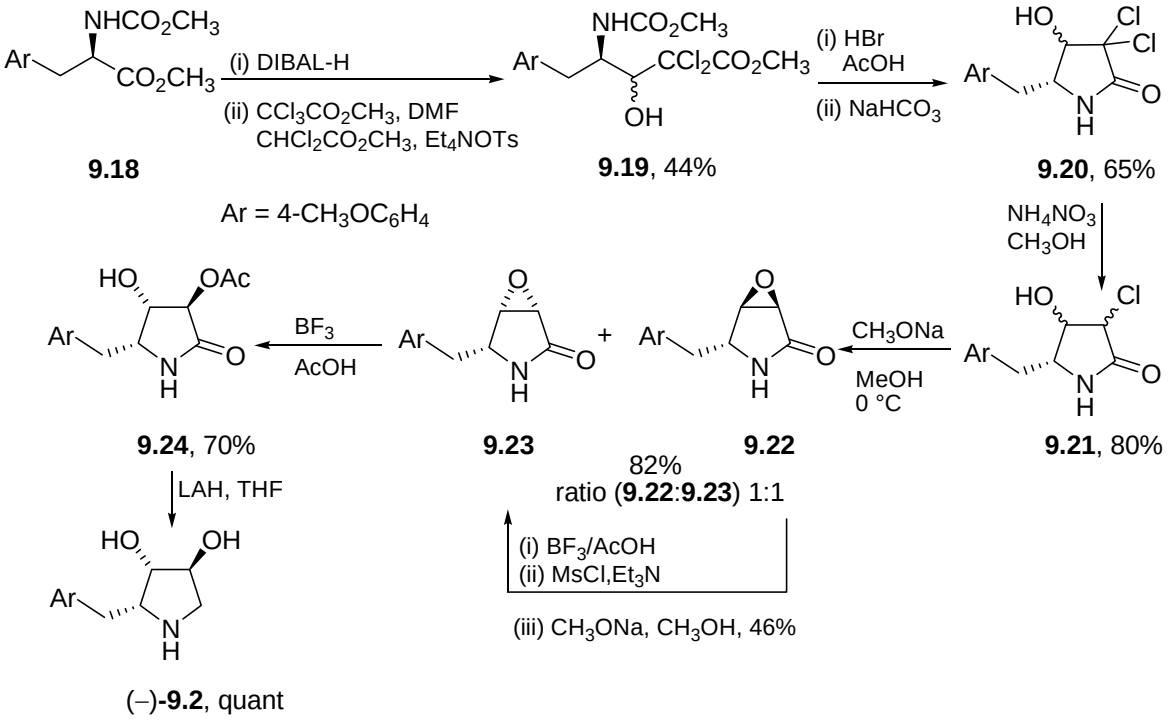
Scheme 9.2: Schumacher and Hall's total synthesis of (±)-anisomycin

Reduction of pyrrole **9.12** followed by protection of the amine as a benzyl carbamate and formation of the halohydrin followed by treatment with base allowed selective formation of the *syn*-epoxide **9.15**. The key step of this synthesis was the regioselective, stereospecific ring opening of the *syn*-epoxide **9.15** and this was followed by a selective protection-acetylation-deprotection reaction sequence. The ring opening reaction must be performed on the free-amine epoxide since the regioselectivity is lost with the *N*-protected *syn*-epoxide. Furthermore the regioselectivity of the step was extremely dependent on the conditions of the reaction. Biological tests carried out by Schumacher indicated the synthetic (±)-anisomycin **9.1** to possess half of the activity of the natural isomer.

Based on these publications, pyrroline **9.9**[169] and deacetylanisomycin **9.2**[170] are reported as final products in many syntheses, since they may be transformed into anisomycin **9.1** by well-documented sequences.[172,173]

9.3. Chiral pool syntheses from amino acids

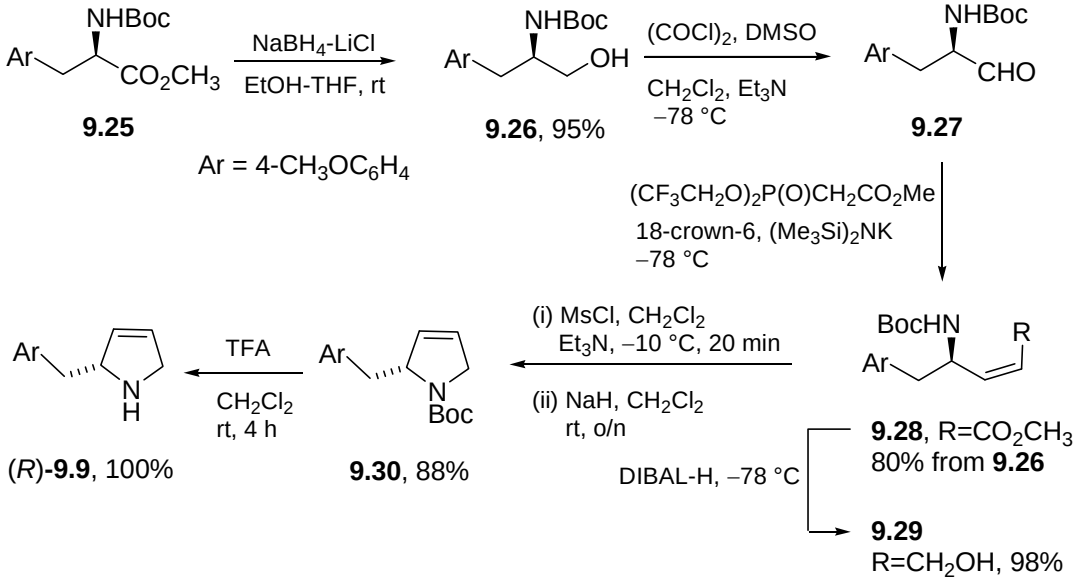
Shono and Kise[174] reported the first synthesis of (−)-anisomycin **9.1** from an amino-acid, (*R*)-tyrosine in which the addition of electrochemically generated enolate of methyl dichloroacetate is used as a key reaction in a 12 step sequence (Scheme 9.3).



Scheme 9.3: Shono and Kise's formal synthesis of (−)-anisomycin 9.1

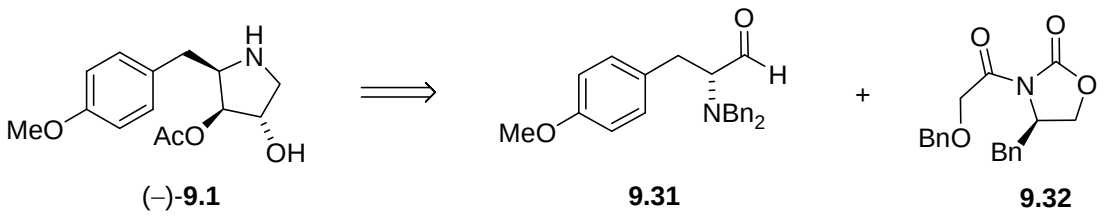
Electrochemical reduction of methyl trichloroacetate using a cell equipped with carbon rod electrodes and coupling with the aldehyde prepared from protected (*R*)-tyrosine gave alcohols **9.19**. After hydrolysis with acid and treatment with $NaHCO_3$, a mixture of 3,4-*syn* and 3,4-*anti*-γ-lactams **9.20** was isolated in good yield. A selective reduction to monochloride and treatment of the mixture with CH_3ONa at 0 °C afforded epoxy-γ-lactams **9.22** and **9.23** in a 1:1 ratio. After separation, lactam **9.22** can be converted into lactam **9.23** *via* acidic ring opening, mesylation and treatment with base. (−)-Deacetylanisomycin **9.2** was accessed from *syn*-epoxide **9.23** after treatment with BF_3/AcOH and reduction. Shono referred to Schumacher's procedure to convert intermediate **9.2** into (−)-anisomycin **9.1**.

At about the same time, Jegham and Das[175] reported a completely different approach to (+) and (−)-anisomycin **9.1** *via* a short synthesis of (*R*)-pyrroline **9.9** and its isomer (*S*)- **9.9** from (*R*)- and (*S*)-tyrosine (Scheme 9.4). From a fully protected (*R*)-tyrosine **9.25**, reduction of the ester function with $NaBH_4$-LiCl followed by Swern oxidation provided the aldehyde **9.27**. Chain extension *via* modified HWE reaction afforded the *Z*-isomer of α,β-unsaturated ester **9.28.** Then reduction to the alcohol **9.29**, mesylation, intramolecular cyclisation and *N*-Boc-deprotection led to the desired pyrroline (−)-**9.9** with an overall yield of 62% from **9.25**. (+)-Isomer **9.9** was prepared in the same manner.



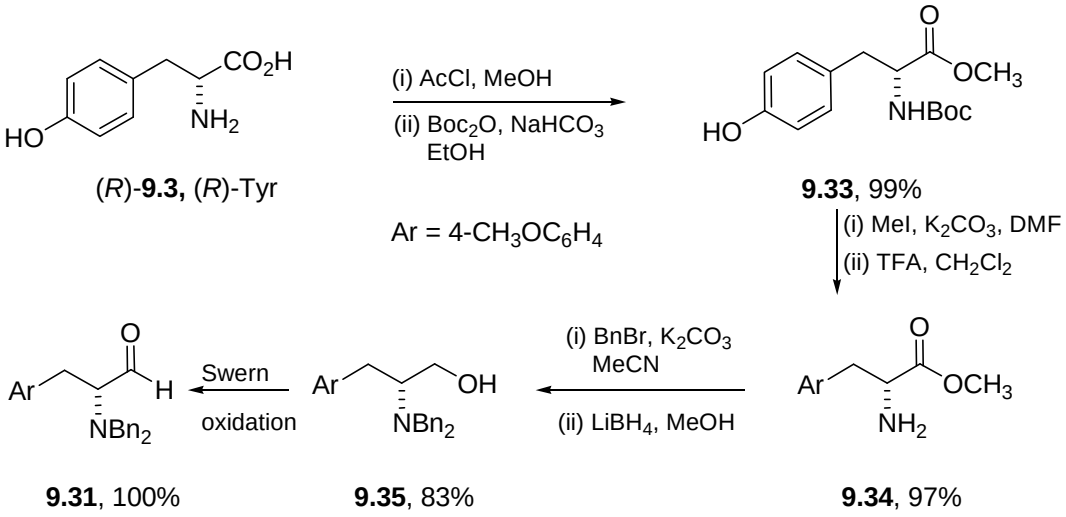
Scheme 9.4: Jegham and Das' formal synthesis

Later, Hulme and Rosser[176] envisaged an alternative approach using a tyrosine-derived aldehyde **9.31** and the glycolate derivative **9.32** of Evans' oxazolidinone to allow a highly efficient synthesis of anisomycin **9.1** (Scheme 9.5).



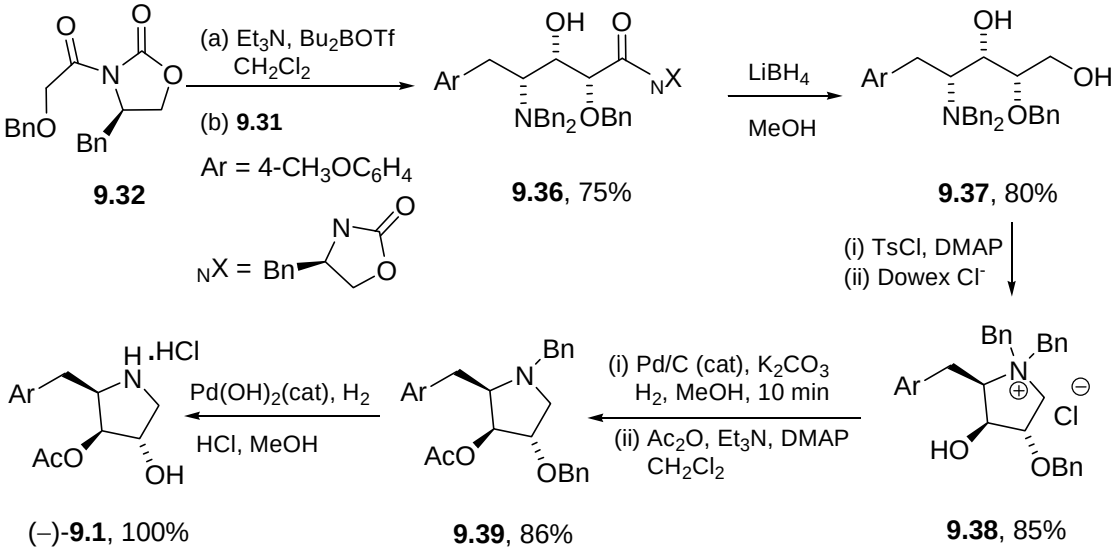
Scheme 9.5: Hulme and Rosser's approach

Tyrosine derivative aldehyde **9.31** was easily prepared from (*R*)-tyrosine (*R*)-**9.3** in 7 steps and 80% overall yield (Scheme 9.6). A few protection and deprotection reactions allowed methylation of the phenol and produced the ester **9.34**. *N,N*-Dibenzylation followed by reduction of the ester provided the amino alcohol **9.35** in excellent yield. The desired aldehyde **9.31** was obtained after Swern oxidation.



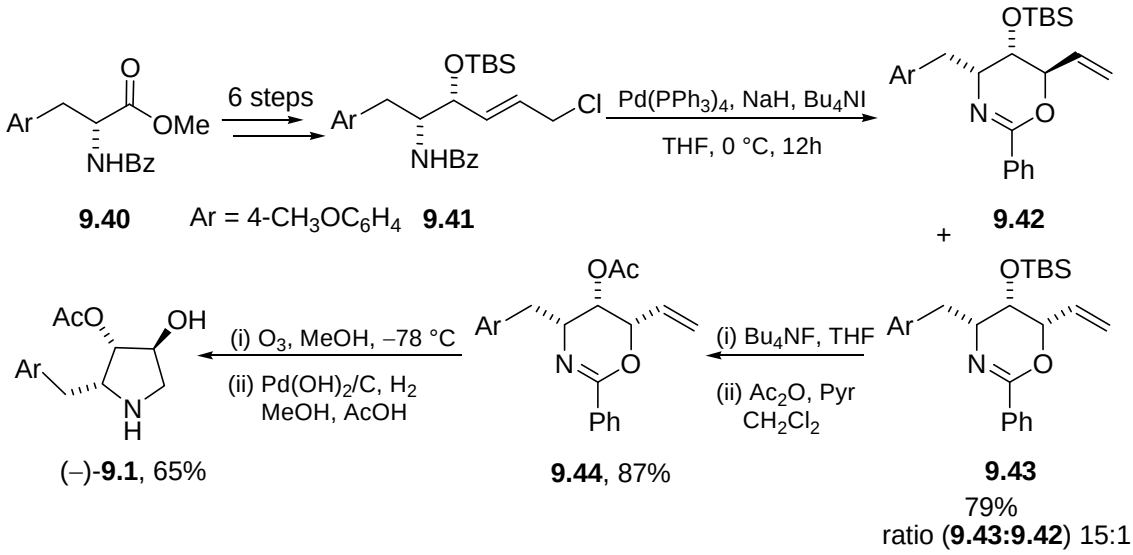
Scheme 9.6: Synthesis of Tyrosine-Derived aldehyde 9.31

The intermediate **9.32** was prepared prior to the synthesis from (4*R*)-benzyloxazolidine-2-one.[176,177] Then Evans' aldol reaction of compound **9.32** with aldehyde **9.31** provided the all *syn*-aldol **9.36** as the major diastereoisomer (Scheme 9.7). Reductive removal of the chiral auxiliary followed by selective tosylation of the primary alcohol and treatment with Dowex resin-1% HCl afforded the pyrrolidinium chloride salt **9.38**. Finally, partial deprotection, acylation and total debenzylation allowed isolation of (−)-anisomycin **9.1**. This rapid synthesis of (−)-anisomycin **9.1** (13 steps) proceeded in an overall yield of 35% and with excellent diastereoselectivity.



Scheme 9.7: Hulme and Rosser's synthesis of (−)-anisomycin 9.1

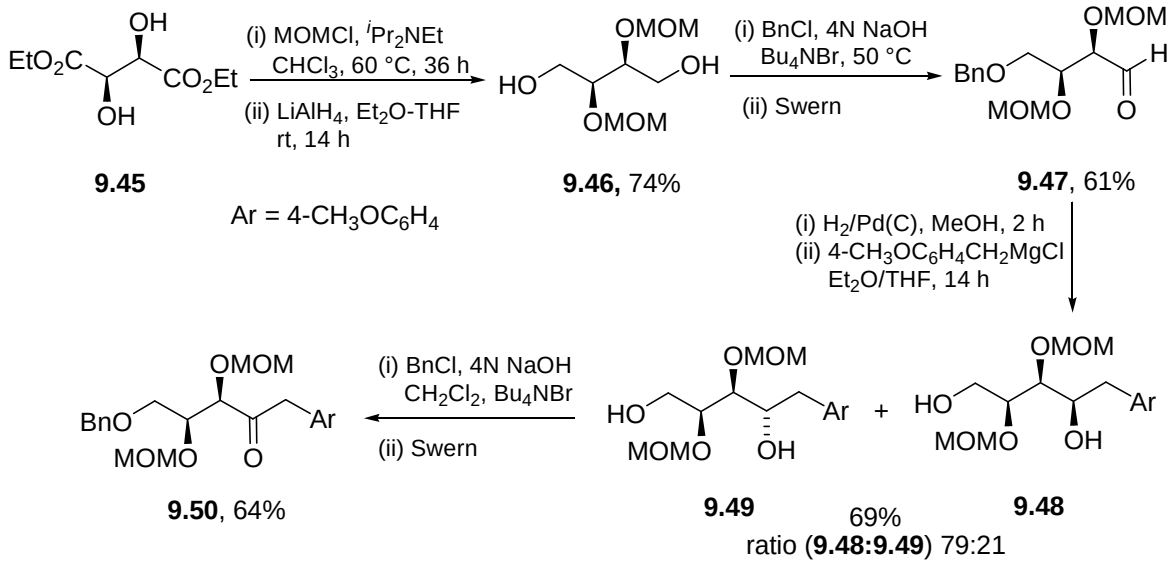
Recently, Joo *et al.*[178] reported an asymmetric synthetic method for the preparation of (−)-anisomycin **9.1** utilizing oxazine **9.43** (Scheme 9.8). The longest linear sequence consisted of 11 steps from the methyl ester **9.40** of *N*-benzoyl (*R*)-tyrosine and proceeded in 27% yield. The key step is a Pd(0)-catalyzed intramolecular formation of oxazine **9.43** and this is followed by ozonolysis of the alkene to expose the aldehyde and catalytic hydrogenation to give the pyrrolidine ring *via* imine formation.



Scheme 9.8: Joo *et al.*'s total synthesis

9.4. Chiral pool syntheses from tartaric acid

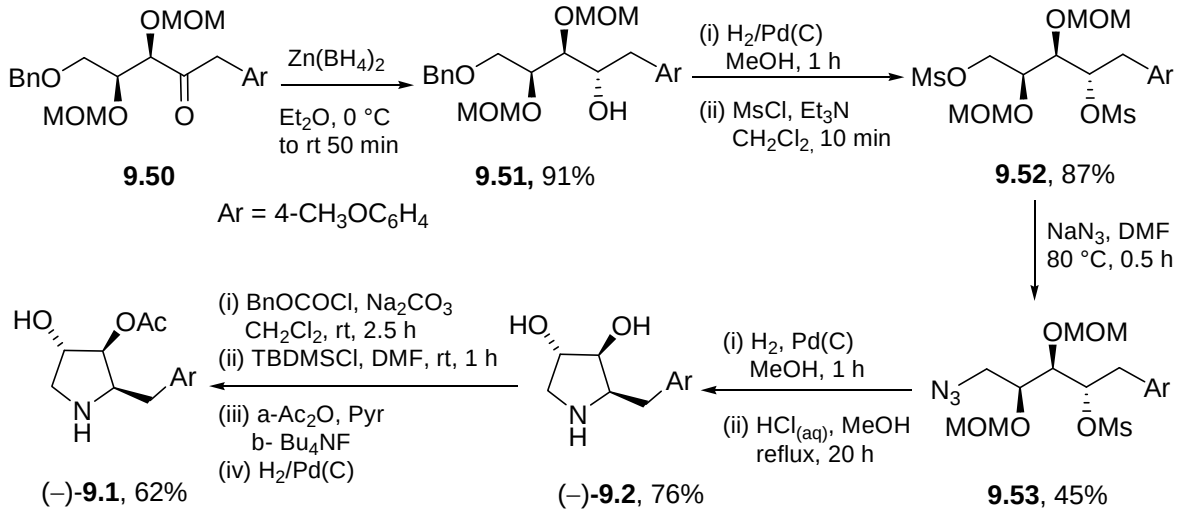
Five total syntheses of anisomycin **9.1** from the chiral pool have been reported starting from tartaric acid or an ester derivative. They take advantage of the presence of two hydroxyl groups with the required relative stereochemistry in the starting material. In the late 60's, Wong *et al.*[179] reported a synthesis from tartaric acid and Felner and Schenker[180] demonstrated one from diethyl tartrate in 1970. However both approaches were non stereoselective and resulted in very low overall yields. 16 years later Iida *et al.*[173] described an approach relying on stereocontrolled reduction of a ketone requiring no separation of isomers, together with a more efficient technique for the acetylation of deacetylanisomycin **9.2** (Scheme 9.9). The synthesis starts from diethyl L-tartrate **9.45** and allows preparation of L-threose derivative **9.47** (in 3 steps), which is used as a chiral building block. Then, after hydrogenation and Grignard addition of 4-methoxybenzylmagnesium chloride, alcohols **9.48** and **9.49** (isolated as a mixture of diastereoisomers) were converted into the ketone **9.50** *via* Swern oxidation.



Scheme 9.9: Iida *et al.*'s total synthesis

Treatment with zinc borohydride provided alcohol **9.51** with perfect control of the diastereoselectivity (>99:1) *via* chelation control (Scheme 9.10). The pyrrolidine ring was easily accessed from the monoazide **9.53**, prepared after debenzylation and mesylation of alcohol **9.51**. Hydrogenation of the monoazide

9.53 gave an amine which spontaneously cyclised *via* a concerted intramolecular displacement of the mesylate and produced after MOM-deprotection the deacetylanisomycin **9.2**. Common problems of random acetylation of intermediate **9.2** were overcome by doing a selective protection of the less hindered C-4 hydroxyl group with bulky TBDMSCl followed by acetylation and deprotection reactions. The bulky silyl protecting group approaches from the less sterically hindered side, thus the opposite side to the bulky *p*-methoxybenzyl group at the C-2 position.

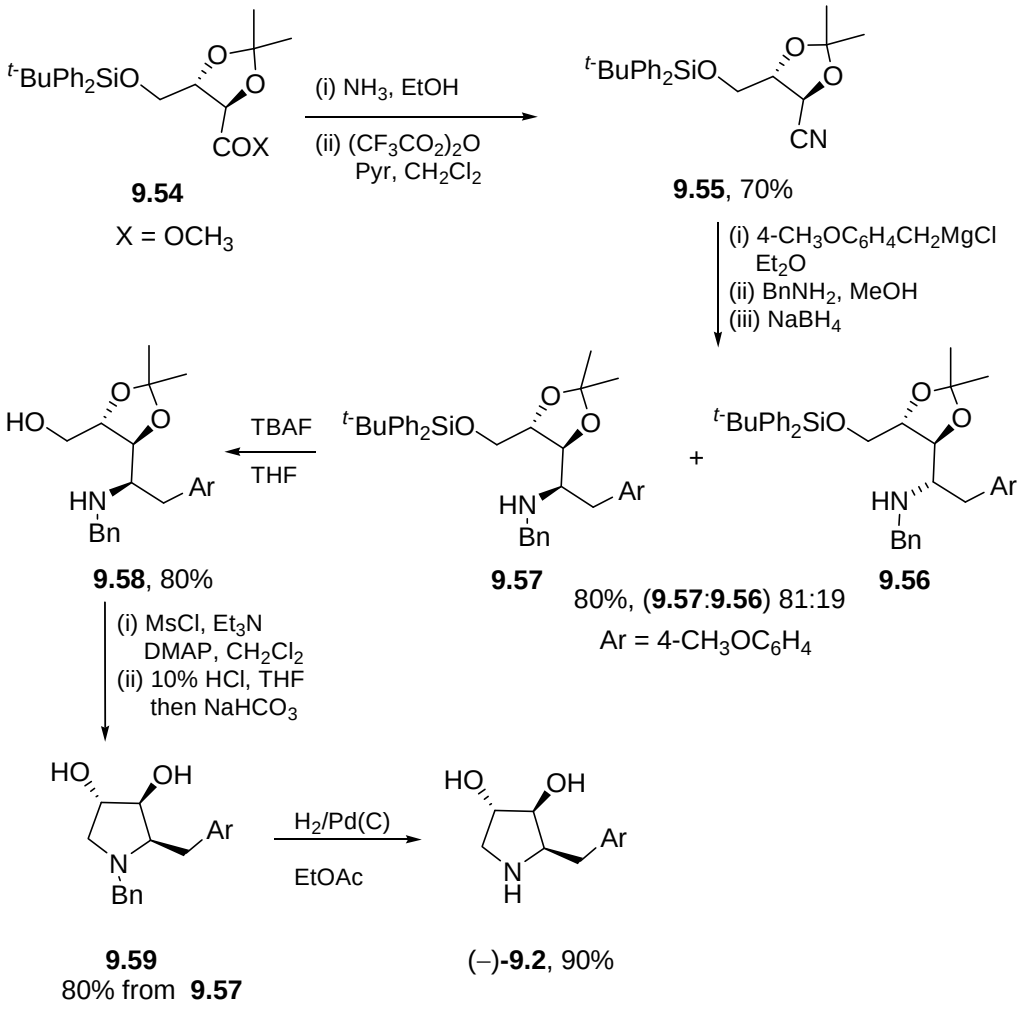


Scheme 9.10: Iida *et al*.'s total synthesis

The route presented the advantages that it was original and did not need separation of diastereoisomers; however, the sequence was long with an average of 16 steps in the longest linear sequence (to **9.1**) and an overall yield of 2% from diethyl tartrate. Schwardt *et al*.[166] proposed a really similar but improved approach with a 12 steps sequence from diethyl L-tartrate **9.45** giving 23% overall yield. Stereoselective Grignard reaction is a key step and formation of the pyrrolidine ring proceeds by intramolecular Mitsunobu reaction. Then selective acetylation was carried out after silylation of the C-4 hydroxyl group and proper protection of the cyclic amine.

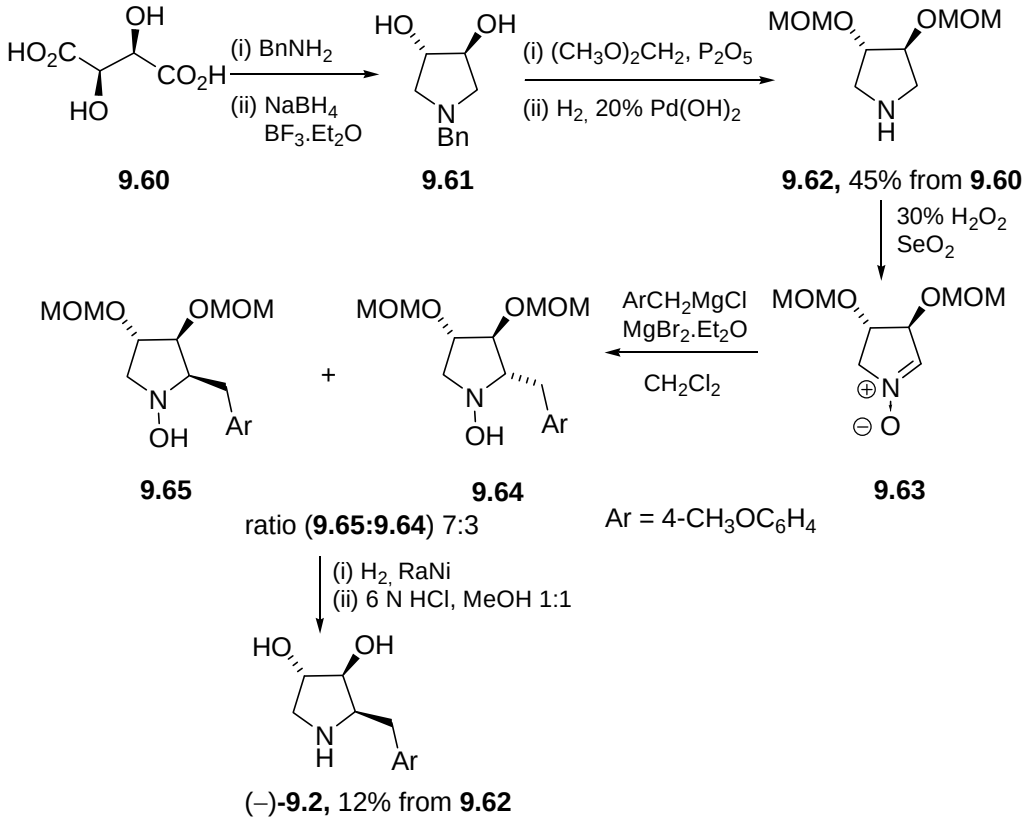
Although relatively similar, Hutin *et al*.'s[181] concise synthesis (10 steps) of (−)-deacetylanisomycin **9.2** is based on the stereoselective reductive alkylation of protected trihydroxynitrile **9.55** prepared from L-tartaric acid derivative **9.54** (the ester **9.54** was easily prepared from tartaric acid in three steps) (Scheme

9.11). After condensation of 4-methoxybenzylmagnesium chloride with nitrile **9.55** followed by *trans*-imination, reduction of the imine with sodium borohydride afforded a 19:81 mixture of diastereomers **9.56**: **9.57** in 80% overall yield from nitrile **9.55.** After separation, primary alcohol **9.58** was prepared from amine **9.57** and was then regioselectively mesylated. After acidic cleavage of the acetonide **9.58**, the resulting aminodiol cyclised to give *N*-benzyldeacetylanisomycin **9.59**. Catalytic hydrogenation afforded deacetyl anisomycin **9.2**.



Scheme 9.11: Hutin *et al.*'s synthesis of deacetylanisomycin

Ballini *et al.*[182] used an original route to prepare (−)-anisomycin **9.1** from L-tartaric acid **9.60** (Scheme 9.12). The key step consisted of an attack by a Grignard reagent on the α-carbon atom of a nitrone system **9.63**. The sequence proceeded in 11 steps to deacetyl intermediate (-)-**9.2** and in 5% overall yield from tartaric acid **9.60**.

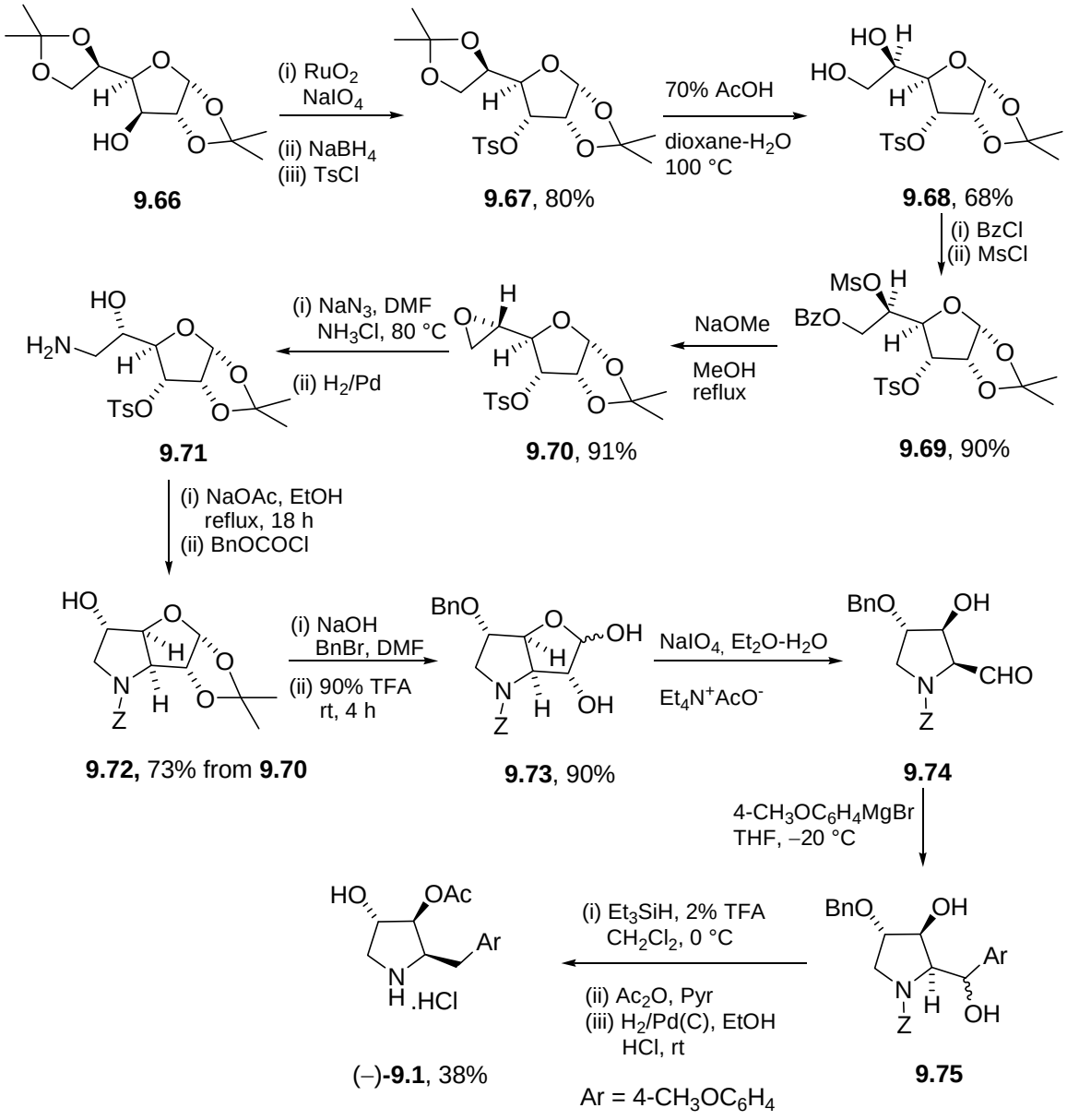


Scheme 9.12: Ballini *et al*.'s formal route

9.5. Chiral pool synthesis from sugars

Carbohydrates constitute one of nature's richest sources of chirality and Moffat and co-workers[183] were first to describe syntheses of anisomycin starting from D-glucose (Scheme 9.13). The sequence is consistent with production of (−)-anisomycin, but the optical rotation reported was positive and did not agree with the literature they cited as in agreement.[158] They carried out an 18 step (8.5% overall yield) synthesis of (−)-anisomycin **9.1** starting from the protected α-D-glucofuranose **9.66.** After conversion into α-D-allofuranose **9.67**, the epoxide **9.70** was formed and allowed access to the amino furanose **9.71**. Heating under reflux for 18 h in the presence of sodium acetate led to cyclisation and after full protection of the amino and hydroxyl groups and deprotection of the diol, the bicycle **9.73** was produced. Oxidative cleavage of the diol with sodium periodate gave aldehyde **9.74**. Introduction of the aromatic substituent was carried out as usual with a Grignard reaction. Hydrogenation of benzylic alcohol **9.75** proceeded by treatment with trimethylsilane in the

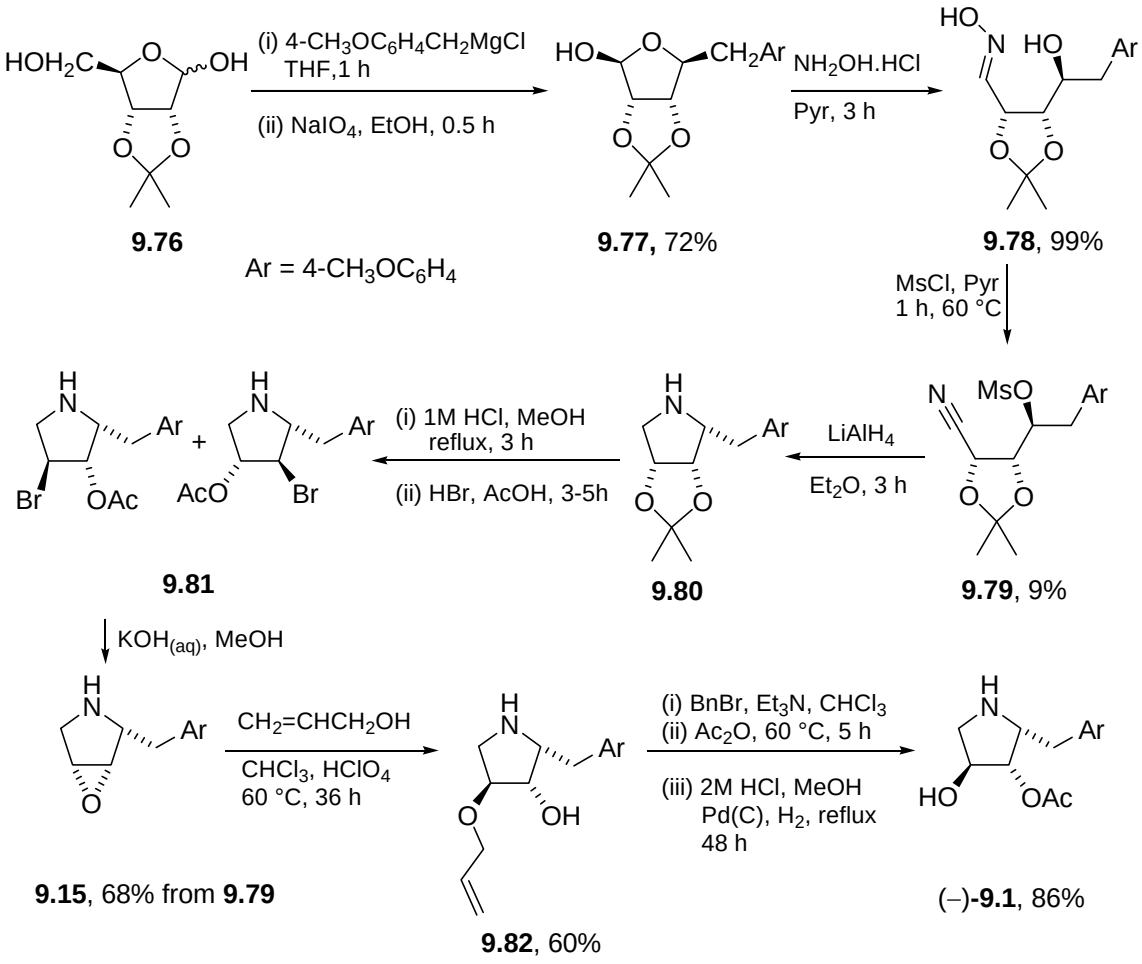
presence of an acid (ionic hydrogenation) and this was followed by acetylation and removal of the protecting group to give (−)-anisomycin **9.1**.



Scheme 9.13: Moffat and co-workers' total synthesis

A few years later, Buchanan *et al.*[184] reported a route starting from D-ribose **9.76**, which was very similar to Moffat's sequence (Scheme 9.14). Reaction with 4-methoxybenzylmagnesium chloride followed by oxidative cleavage of the resulting diol gave hemiacetal **9.77**. Oxime **9.78** obtained after reaction with hydroxylamine hydrochloride was converted into a nitrile derivative **9.79** which cyclised when treated with $LiAlH_4$ to give the pyrrolidine **9.80**. After hydrolysis of the acetonide, treatment of diols with hydrogen bromide in acetic acid gave bromo derivatives **9.81** which were further converted into epoxide **9.15.** This

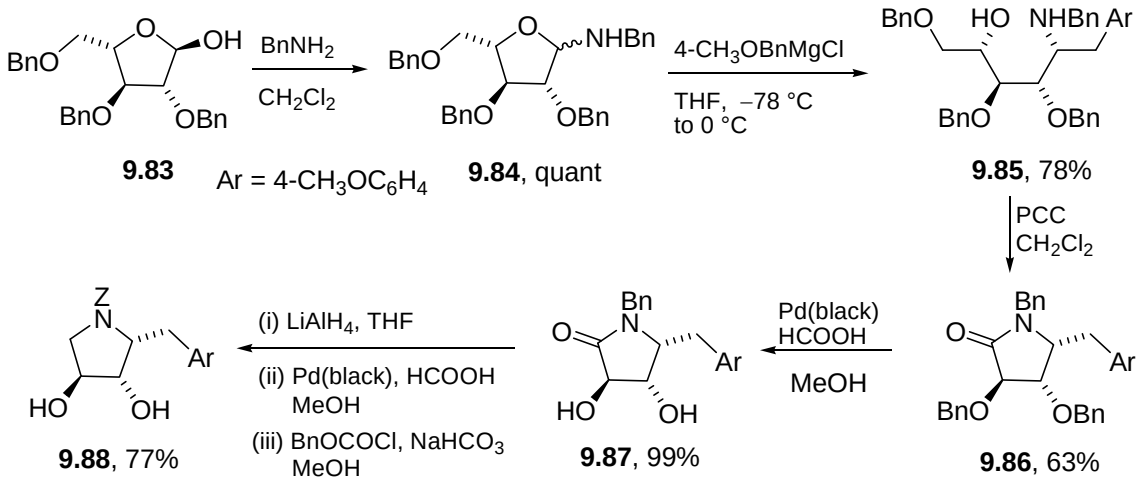
epoxide has already been described as an intermediate in Oida's or Schumacher's synthesis (Scheme 9.1 and Scheme 9.2). Regioselective opening of the epoxide **9.15** provided the allylic ether **9.82**, which was then transformed into an *N*-benzyl-*O*-acetyl derivative. (−)-Anisomycin **9.1** was accessed after removal of the protecting group by hydrogenation. This sequence is relatively short (11 steps) nevertheless the overall yield of 4% is modest.



Scheme 9.14: Buchanan *et al.*'s synthesis

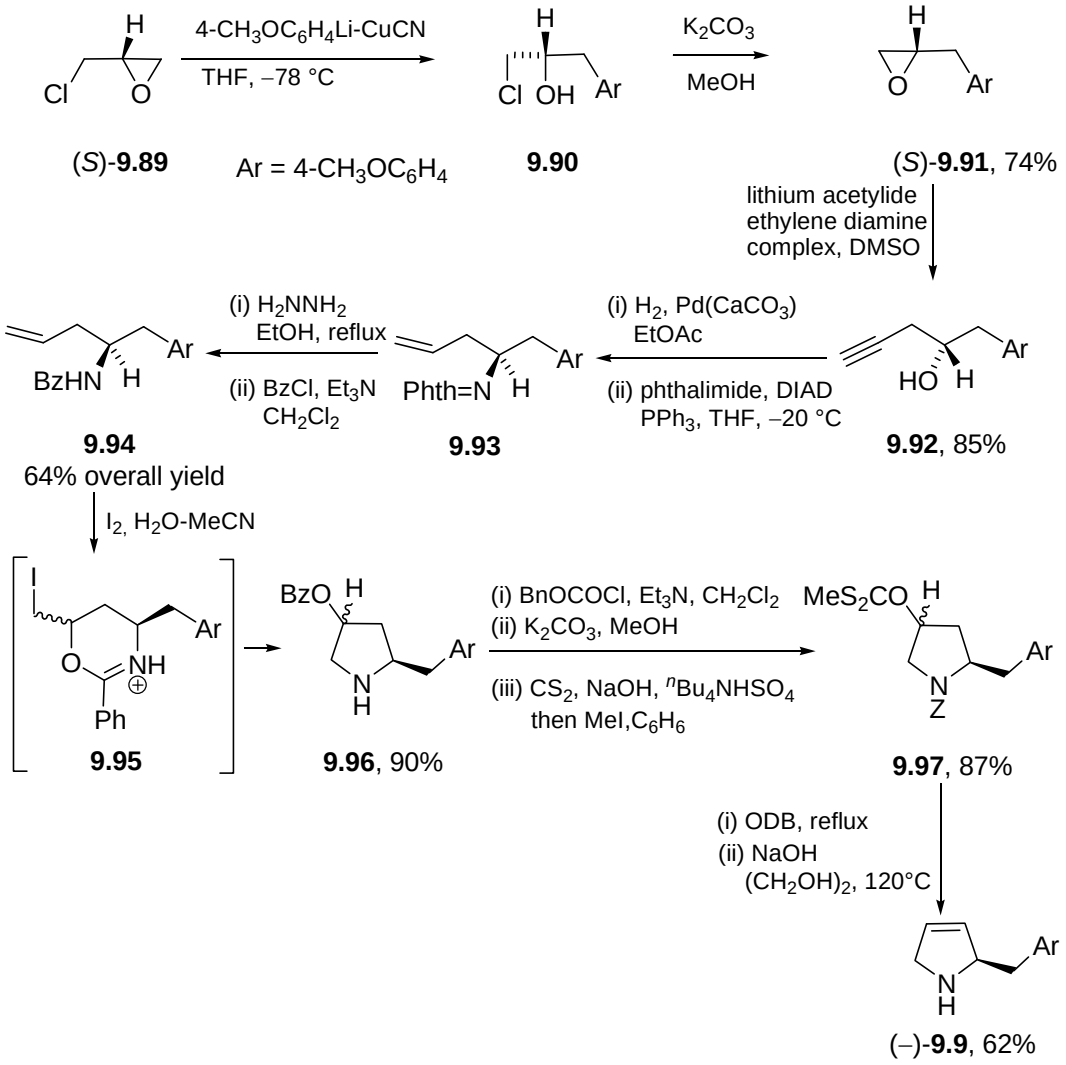
The sequence disclosed at the same time by Baer and Zamkanei[185] was advantageous from an economical point of view, because it began from D-galactose which is cheaper than D-ribose or 1,2,5,6-di-*O*-isopropylene-D-glucose **9.66**. However the synthesis reported by Yoda *et al.*[186] in 1995 was particularly good (Scheme 9.15). Commercially available 2,3,5-tri-*O*-benzyl-β-L-arabino furanose **9.83** was converted into furanosylamine **9.84** which reacted smoothly with 4-methoxybenzylmagnesium chloride in high yield. Then under oxidative conditions, the lactam **9.86** was produced and this was followed by removal of

N- and *O*-benzyl protection. Treatment with benzyl chloroformate provided the pyrrolidine **9.88**. Thus (−)-anisomycin **9.1** would be available in 9 steps following Iida[173] route for the transformation of pyrrolidine **9.88** to (−)-**9.1**.



Scheme 9.15: Yoda *et al*.'s synthesis

In 1989, a route to (−)-anisomycin **9.1** from (*S*)-epichlorohydrin **9.89** prepared from D-mannitol was reported (Scheme 9.16).[187] The (*S*)-oxirane **9.91** was isolated after treatment of (*S*)-epichlorohydrin **9.89** with a cyanylcuprate derived from 4-bromoanisole and then treatment of alcohol **9.90** with methanolic potassium carbonate. Interestingly, Takano *et al.* showed that the (*R*)-enantiomer **9.89** can be converted into (*S*)-oxirane **9.91** as well. However, a longer route is required. The oxirane **9.91** was easily transformed into amide **9.94** through a series of simple reactions. Then the amide **9.94** was exposed to 3 eq of iodine in aqueous acetonitrile for 3 days and provided the pyrrolidine **9.96** as a 2:1 mixture of epimers at C-4. Without separation, the mixture was successively submitted to *N*-protection, *O*-debenzoylation, and *O*-activation and finally, 3-pyrroline **9.9** was isolated as the major regioisomer (the minor being 4-pyrroline) after conversion of compound **9.96** into xanthate **9.97** and then elimination upon thermolysis in *O*-dichlorobenzene (ODB) at reflux.

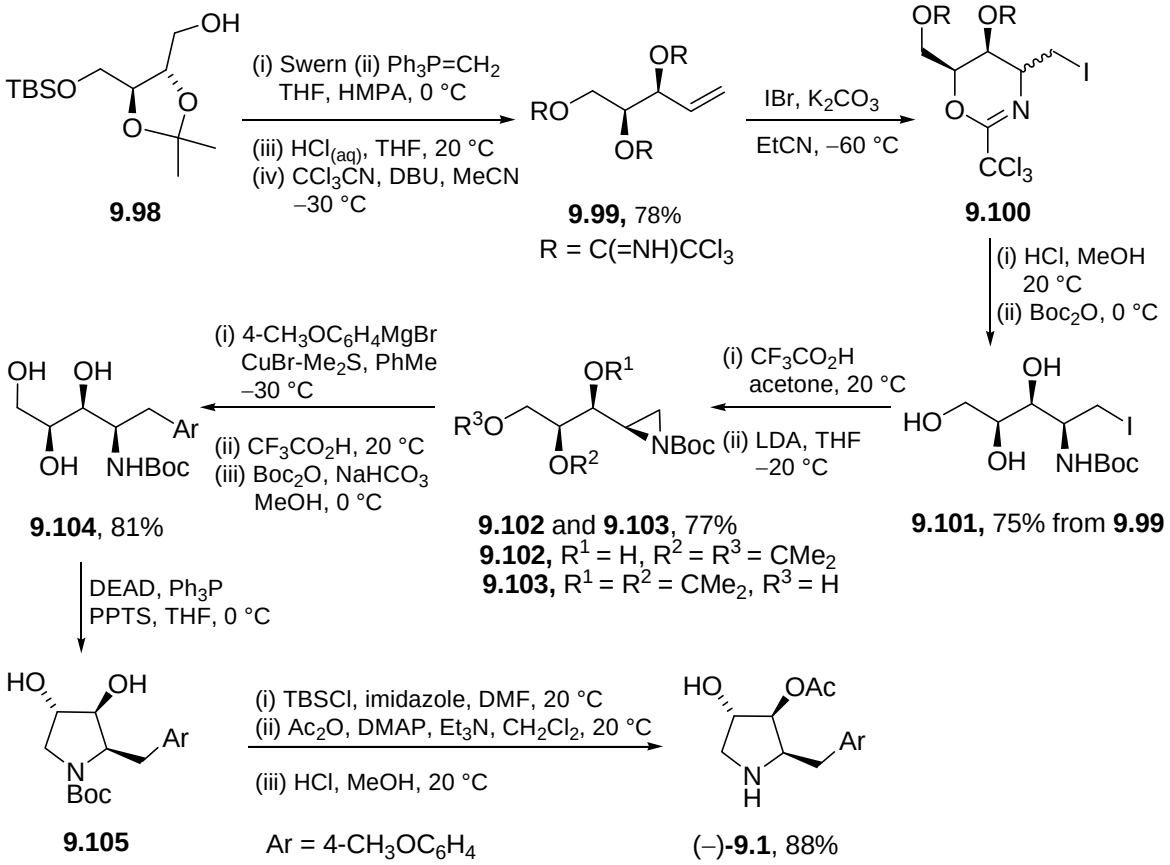


Scheme 9.16: Takano *et al.*'s formal synthesis

Reddy *et al.*[167] gave another approach starting from D-mannitol and providing (+)-deacetylanisomycin **9.2**. Grignard reaction and intramolecular cyclisation reactions are key steps in the the formal synthesis of (+)-anisomycin (11% overall yield in 10 steps).

An asymmetric amidation of (2*S*,3*S*)-pent-4-ene-1,2,3-triol **9.99** derived from L-threitol was a key step in Kang and Choi's[188] total synthesis of (−)-anisomycin **9.1** (Scheme 9.17). Reaction of acetimidate derivative **9.99** with iodine monobromide afforded 6-membered ring giving a mixture of isomers **9.100**. Methanolysis and Boc protection allowed isolation of the all *syn*-isomer **9.101** in good overall yield from acetimidate **9.99**. After total protection of hydroxyl groups and formation of aziridines **9.102: 9.103**, the aromatic substituent was introduced using an organocuprate. Then, the pyrrolidine **9.105** was formed

under Mitsunobu conditions and this was followed by silylation, acetylation and finally *N*-Boc deprotection under acidic conditions. (−)-Anisomycin **9.1** was produced over 16 steps. A really similar but nevertheless shorter route (12 steps) was published in 1996 by Veith *et al.*[189] starting from L-threitol using a Grignard reaction as the key step.

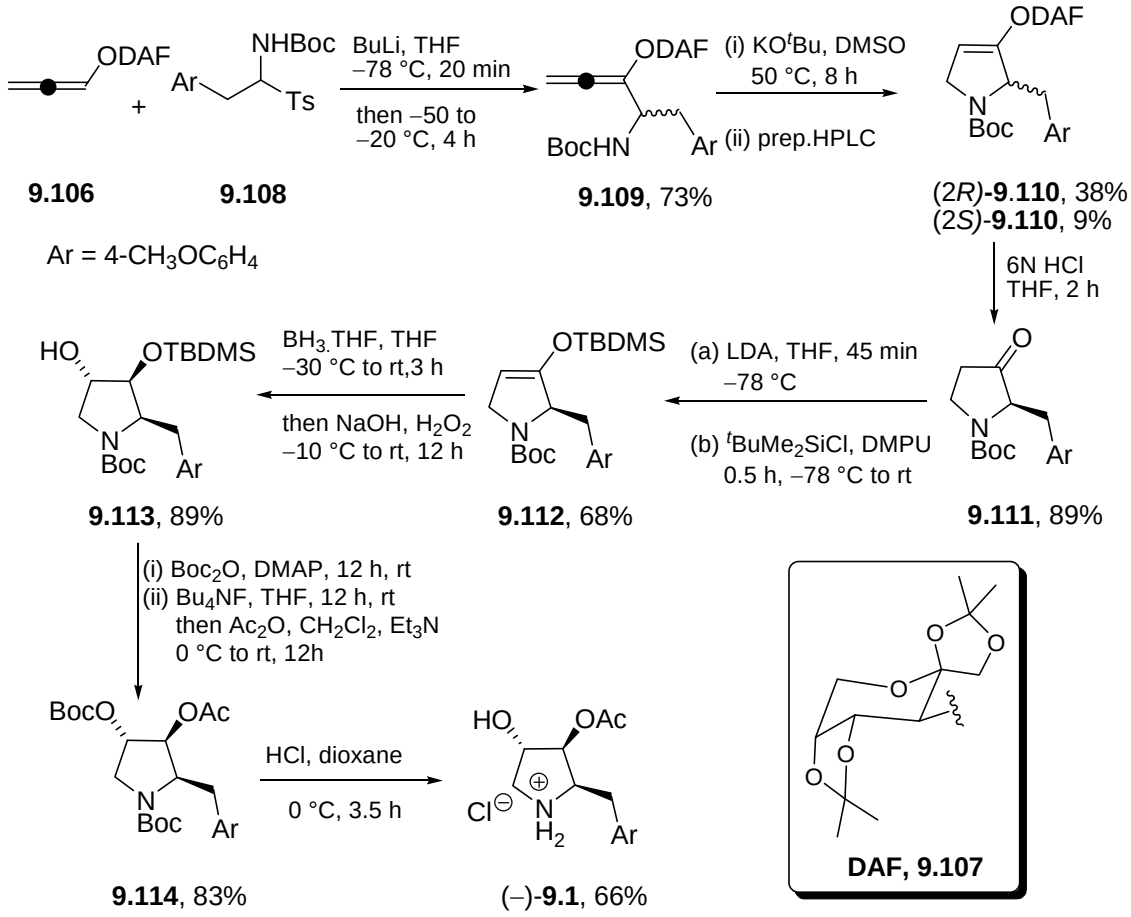


Scheme 9.17: Kang and Choi's total synthesis

9.6. Asymmetric synthesis

(−)-Anisomycin **9.1** was accessed from the allene **9.106** bearing a fructose derivative (DAF) **9.107** as a chiral auxiliary in 10 steps in 8% overall yield (Scheme 9.18).[168] Since none of the chiral centres or atom of DAF are included in the final product this is an asymmetric synthesis rather than a synthesis from the chiral pool. DAF-allene **9.106** was deprotonated with BuLi and condensed with sulfonyl derivatives **9.108** to afford compound **9.109** in good yield but as a 2:1 mixture of isomers. Submitted to strongly basic conditions, compound **9.109** cyclised and produced the two diastereoisomers **9.110** in 65%. HPLC permitted

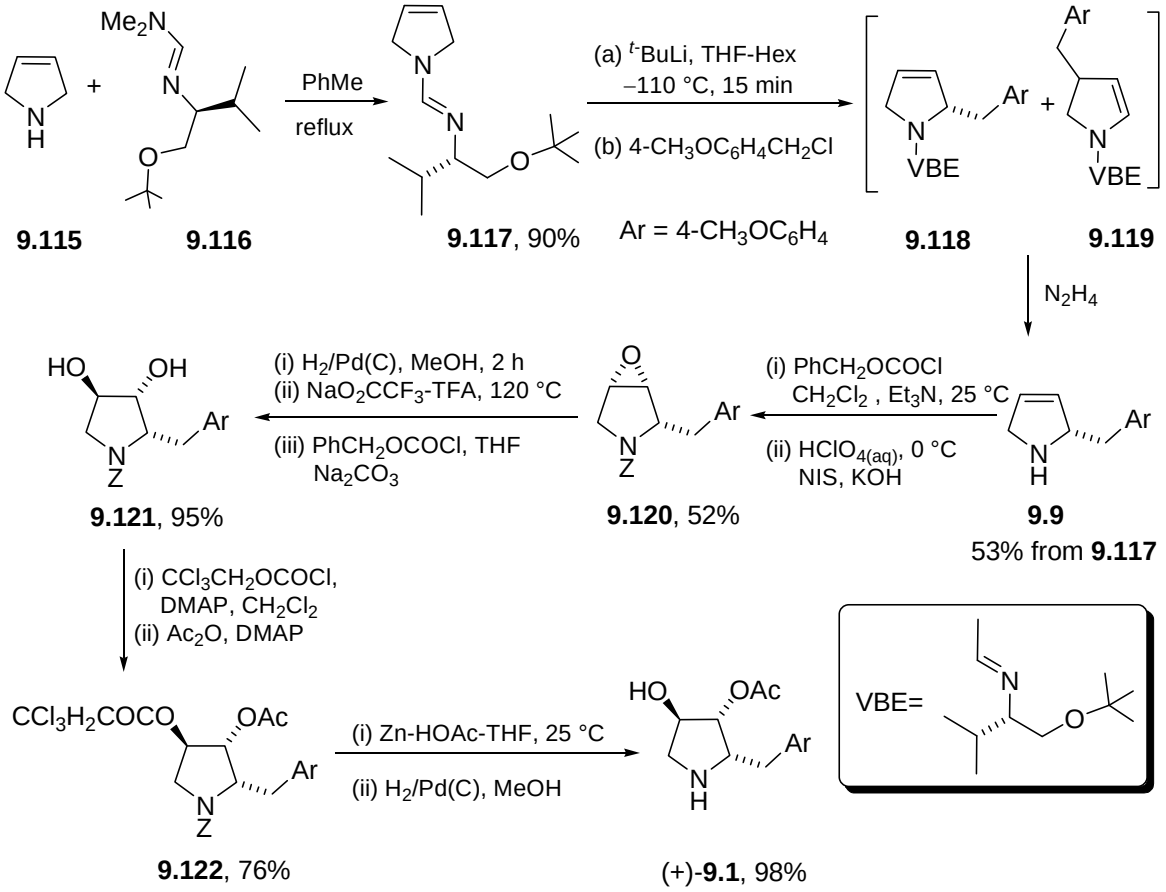
isolation of (2*R*)-**9.110** in 38% yield. By treatment with $HCl_{(aq)}$, pyrroline (2*R*)-**9.110** was converted into 2-substituted *N*-protected pyrrolidinone (2*R*)- **9.111** in good yield. Then conversion of pyrrolidinone **9.111** into enol ether **9.112** was followed by hydroboration (BH_3 in THF) and oxidative work up and afforded the monoprotected diols with high yield and excellent diastereoselectivity. A one pot *O*-Boc and acetyl protection allowed the formation of intermediate **9.114.** Last transformations consisted in *O*- and *N*-deprotection with HCl in dioxane. The major drawback of the method is the moderate diastereoselectivity of the first step.



Scheme 9.18: Kaden *et al.*'s total synthesis

An asymmetric synthesis of the unnatural enantiomer, (+)-anisomycin **9.1** was based on an enantioselective alkylation using a chiral auxiliary (Scheme 9.19).[172] Treatment of dihydropyrrole **9.115** with (*S*)-valinol derivative **9.116** provided the key intermediate **9.117.** *M*etallation followed by treatment with *p*-methoxybenzyl chloride produced regioisomeric compounds **9.118** and **9.119**, resulting from direct and allyl transposed alkylation. When treated with

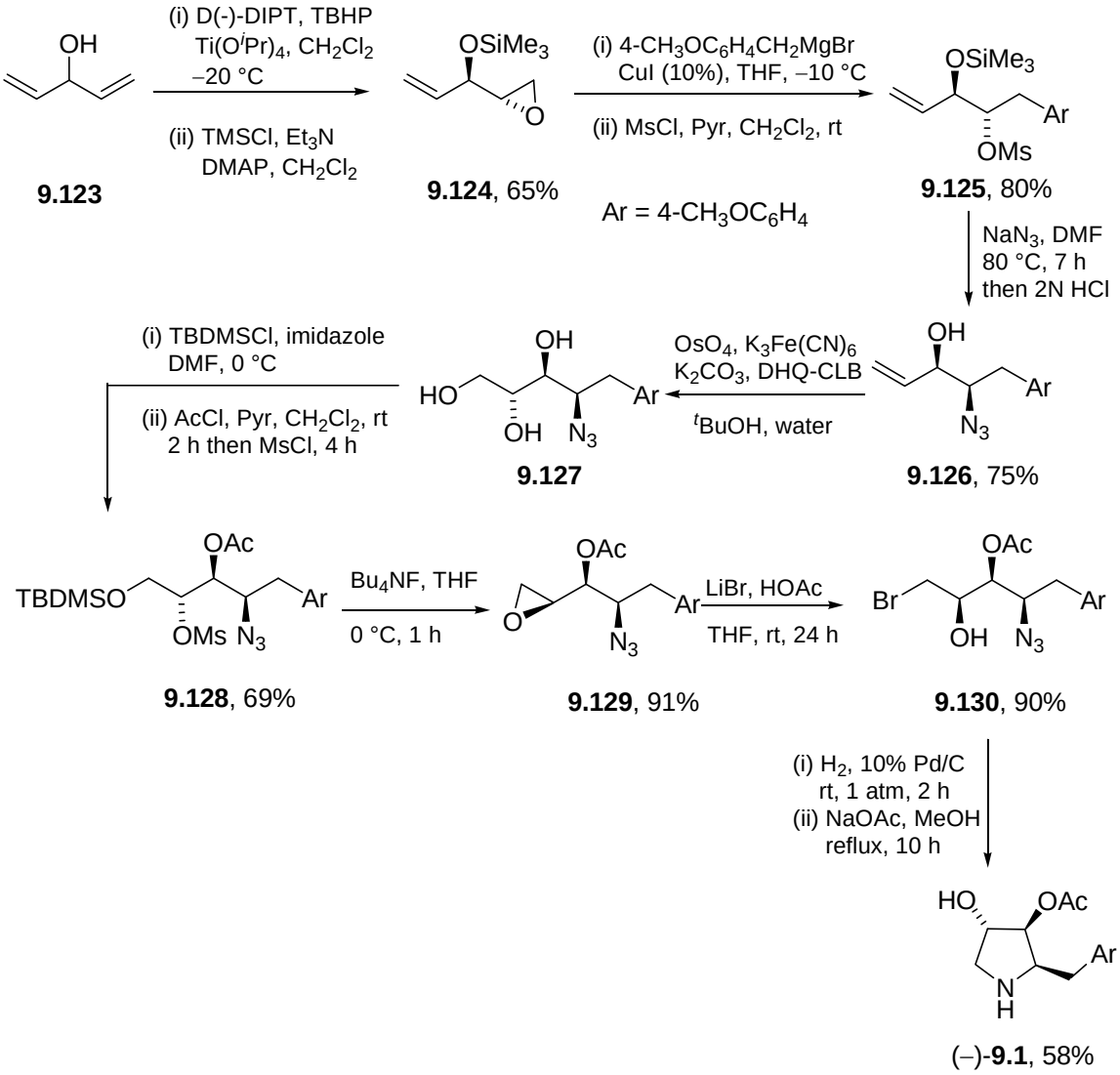
hydrazine, the free amine **9.9** was obtained from compound **9.118** whereas the undesired compound **9.119** decomposed. The synthesis was then continued according to the route established by Schumacher and Hall[170] and described earlier (Scheme 9.2). The (+)-anisomycin **9.1** was accessed in 11 steps and in 22% overall yield from key intermediate **9.117** and 85-90% ee. The use of (*R*)-valinol would undoubtedly furnish the natural anisomycin.



Scheme 9.19: Meyer and Dupré's total synthesis

In 1991, a team published a relatively long total synthesis (19 steps) of (−)-anisomycin **9.1** relying on Sharpless oxidation and epoxidation.[190] The cyclisation to obtain the pyrrolidine ring appeared in an early stage of the synthesis and then the synthesis was built around the ring whereas most of the syntheses seen so far formed the ring in a late step. A few years later, Shi and Lin[191] prepared (−)-anisomycin **9.1** (in 10 steps and 12% overall yield) *via* Sharpless asymmetric epoxidation and Sharpless asymmetric dihydroxylation reaction begining from divinylcarbinol **9.123** (Scheme 9.20). DHQ-CLB (Figure 9.2) was used as the

chiral ligand in the dihydroxylation and $K_3Fe(CN)_6$ as co-oxidant. The pyrrolidine ring was formed by intramolecular alkylation.



Scheme 9.20: Shi and Lin's total synthesis

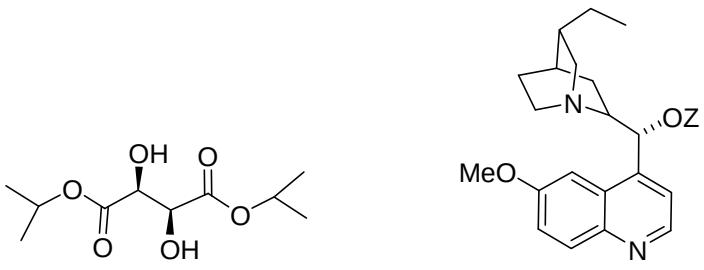
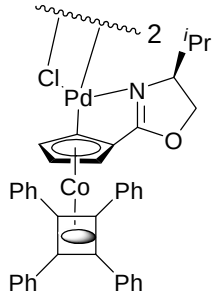


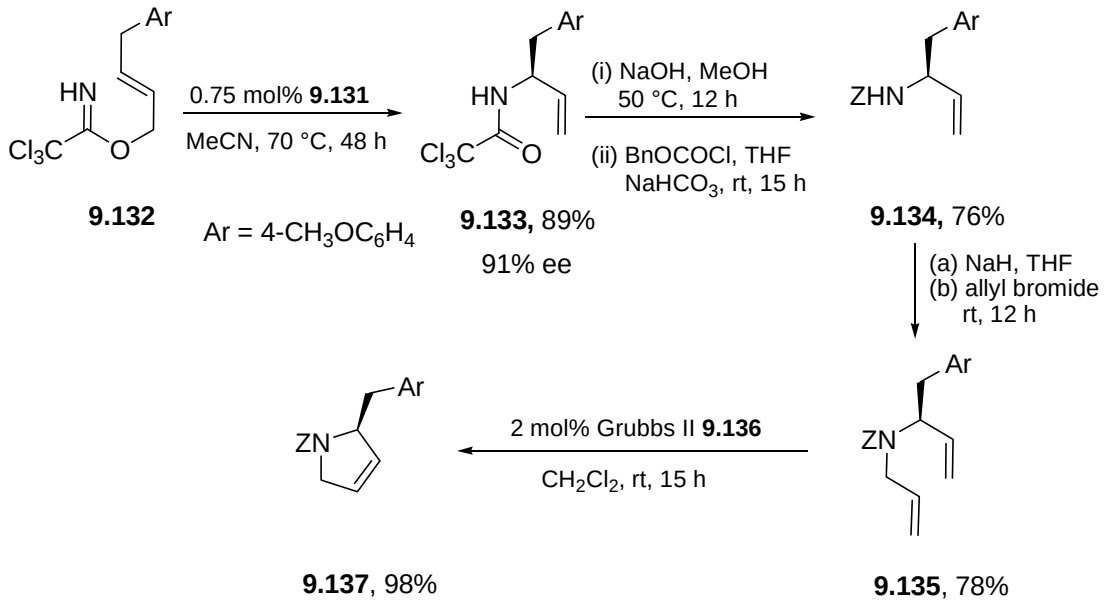
Figure 9.2: Reagents used in Shi's synthesis

Finally, Nomura and Richards[192] recently published a synthesis of anisomycin **9.1**. Pyrroline **9.137** was rapidly accessed from trichloroacetimidate **9.132** after Overman rearrangement and RCM. The use of chloride-bridged cobalt oxazoline palladacycle catalyst **9.131** (Figure 9.3) gave trichloroacetamide **9.133** in high yield and an ee of 91%. After hydrolysis and *Z*-protection, allylation proceeded satisfactory to give amino diene **9.135**. Then RCM with Grubbs II catalyst **9.136** (= **7.14**, see Scheme 7.4) allowed isolation of pyrroline **9.137** with an overall yield of 58%. Nomura suggested that (+)-anisomycin could then be accessed by following the routes of Schumacher[170] or Meyers[172].



9.131

Figure 9.3: Chloride-bridged cobalt oxazoline palladacycle catalyst



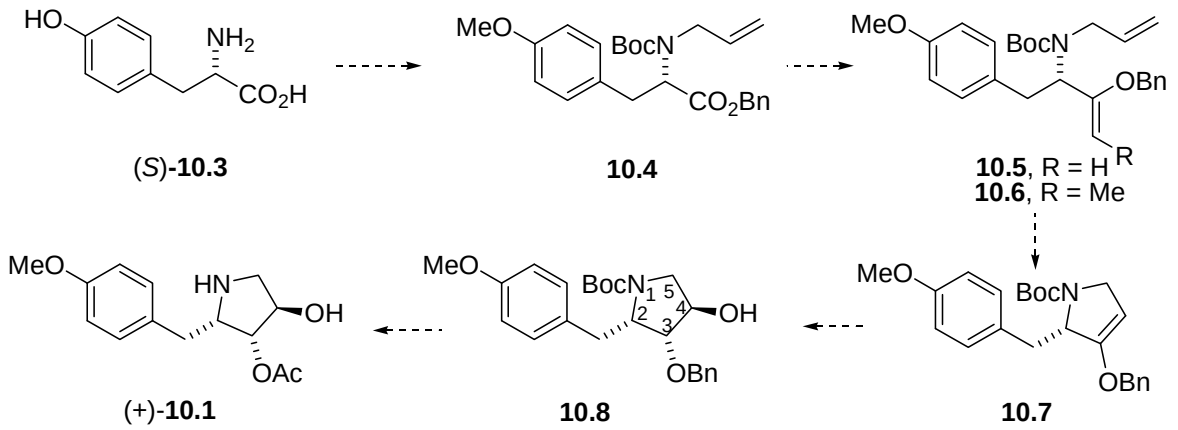
9.132 Ar = 4-$CH_3OC_6H_4$ **9.133,** 89% 91% ee **9.134,** 76%

9.137, 98% **9.135**, 78%

Scheme 9.21: Nomura and Richards' formal synthesis of (+)-anisomycin

10. A Titanium Reagent Based Approach to the Synthesis of Anisomycin

About 25 syntheses of anisomycin **10.1** (=**9.1**, see Figure 9.1) or its precursor deacetylanisomycin **10.2** (=**9.2**, see Figure 9.1) have been reported since 1970. All syntheses of this natural product containing only three stereogenic centres involve many steps.[168] The main structural problem is the existence of an acetoxy and a hydroxyl group in an *anti*-arrangement. More efficient approaches to anisomycin are of continuing interest. Meyers has proposed that "*Those engaged in asymmetric synthesis should periodically prepare the unnatural enantiomer to demonstrate that the method truly fulfils the requirements set forth and provide those enantiomers which are either available in very short supply or are, in fact, nonexistent.*"[172] Following Meyers' wisdom, we initially proposed to make (+)-anisomycin **10.1** from (*S*)-tyrosine **10.3** (=**9.3**, see Scheme 9.1) which is the natural enantiomer of the amino acid (Scheme 10.1). The originality in our sequence would reside in the alkylidenation of benzyl ester **10.4** using a titanium carbenoid as a key step followed by a ring closing metathesis reaction to form the pyrroline **10.7**. Hydroboration would then give the key 3,4-*anti* relationship in alcohol **10.8**. This would then be easily converted into (+)-anisomycin **10.1** by taking advantage of the orthogonality of protecting groups according to Iida's and Kaden's works (Scheme 9.10, Scheme 9.18).[168,173]



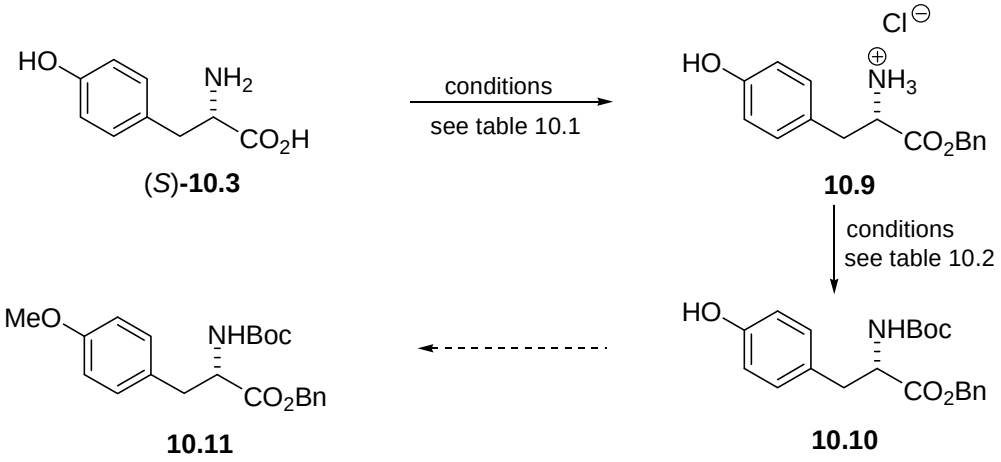
Scheme 10.1: Proposed strategy

10.1. Introduction to the first approach based on tyrosine as starting material

First steps of the sequence involved introducing orthogonal protecting groups and methylation of tyrosine. The carboxylic acid would be protected as a benzyl ester and *N*-Boc-protection would be used for the amino group. The order of these reactions can be varied. Our initial investigation started with benzylation of the carboxylic acid and then *N*-Boc-protection and *O*-methylation.

10.2. Preparation of *N*-allyl esters

Benzylation of (*S*)-tyrosine (*S*)-**10.3** was attempted following various different processes (Scheme 10.2, Table 10.1).



Scheme 10.2: Strategy A

Esterification of (*S*)-tyrosine (*S*)-**10.3** using benzyl alcohol, *p*-toluenesulfonic acid and *p*-toluenesulfonyl chloride (Table 10.1, entry 1) yielded the hydrochloride salt **10.9** while reaction with benzyl alcohol in presence of thionyl chloride (entry 2) failed to give the desired product and left starting materials unreacted.

Entry	(*S*)-Tyr	BnOH	Reagents	Conditions	Yield of **10.9**
1	1.0 eq	19.2 eq	*p*-TsOH (1.0 eq) *p*-TsCl (1.2 eq)	80 °C, 1.5 h	7.4%
2	1.0 eq	17.0 eq	$SOCl_2$ (1.1 eq) or (2.5 eq)	rt then reflux, 2.5 h	-
3	1.0 eq	2.9 eq	*p*-TsOH (1.1 eq) MW 300 W	rt, 60 s	-
4	1.0 eq	5.2 eq	TPA (3.7 eq)	THF, rt, 0.5 h	-
5	1.0 eq	35 eq	AcCl (3.0 eq)	Reflux, 4 h	23%
6	1.0 eq	45 eq	Conc HCl	Benzene, 100 °C, 2.5 h	40%

Table 10.1: Benzylation conditions

More original methods were investigated such as *p*-toluenesulfonic acid under microwave irradiations (Table 6, entry 3) or use of triphosgene (TPA) (entry 4); however all attempts were unsuccessful. Another noteworthy method (entry 5) adapted from the procedure of Hulme and Rosser[176] used benzyl alcohol and acetyl chloride at reflux for 4 hours, but the yield was modest. The optimum result obtained was using benzyl alcohol and concentrated HCl in benzene (entry 6), a procedure described by Viswanatha and Hruby.[193] The main problem in using benzyl alcohol is its removal at the end of the reaction. Its boiling point is 203 °C under atmospheric pressure. Removal by distillation was attempted but most of the time, the crude mixture appeared to decompose before the total removal of the alcohol. Moreover in many attempts, the number of equivalents of benzyl alcohol used was such that the benzyl alcohol hid both reactant and product in the ^{1}H NMR spectrum of the crude mixture. The relatively low solubility of the salt **10.9** in common deuterated solvents appeared to be another issue in analysing the compound. Thus, we decided to carry out the *N*-Boc protection of compound **10.9** without further attempts at optimisation of benzylation, in order to check the good progress of the sequence but keeping in mind that the benzylation step had to be optimized later.

Five different conditions were tested for *N*-Boc protection of benzyl ester **10.9** (Scheme 10.2). Methods such as Boc anhydride in the presence of sodium bicarbonate / ethanol or in presence of water were not effective (Table 7, entries 1-3). They left starting material unreacted. On the other hand, an adaptation of the procedure reported by Hirai *et al*.[194] proved to be the

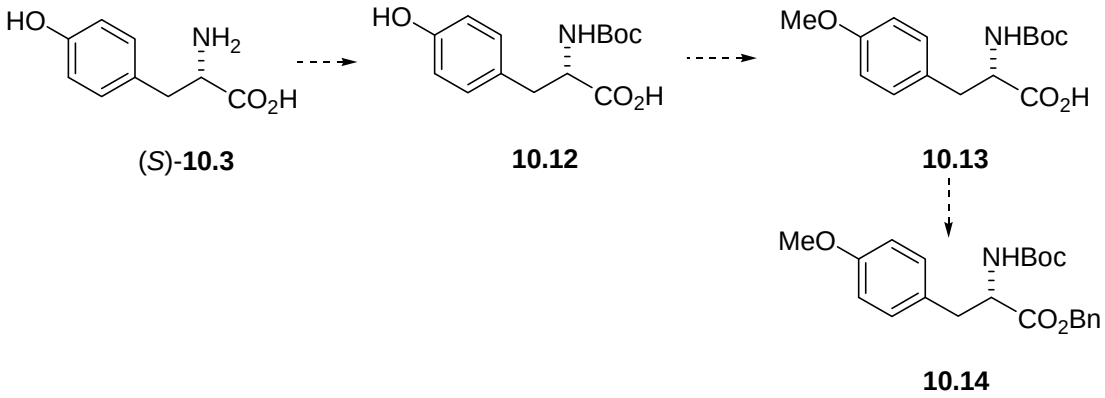
optimum method (entry 4) giving *N*-Boc-(*S*)-tyrosine benzyl ester **10.10** in high yield with no purification needed. Another reaction deserved our attention (entry 5). Using Boc anhydride in cyclohexane overnight,[195] the desired compound **10.10** was observed in the crude mixture with a small impurity. As a purification step was required, we preferred the previous conditions.

Entry	Ester **10.9** (eq)	Boc_2O (eq)	Reagents	Conditions	Yield of **10.10**
1	1.0	1.5	$NaHCO_3$ (2 eq) THF/MeOH	rt, o/n	SM
2	1.0	1.1	H_2O	30 °C, 2.5 h	SM
3	1.0	1.0	EtOH/$NaHCO_3$	rt, o/n	SM
4	1.0	1.1	Et_3N (1.6 eq) H_2O/dioxane	rt, o/n	87%
5	1.0	1.0	cyclohexane	rt, o/n	86%[a]

[a]: minor impurity present

Table 10.2: Conditions for *N*-Boc protection

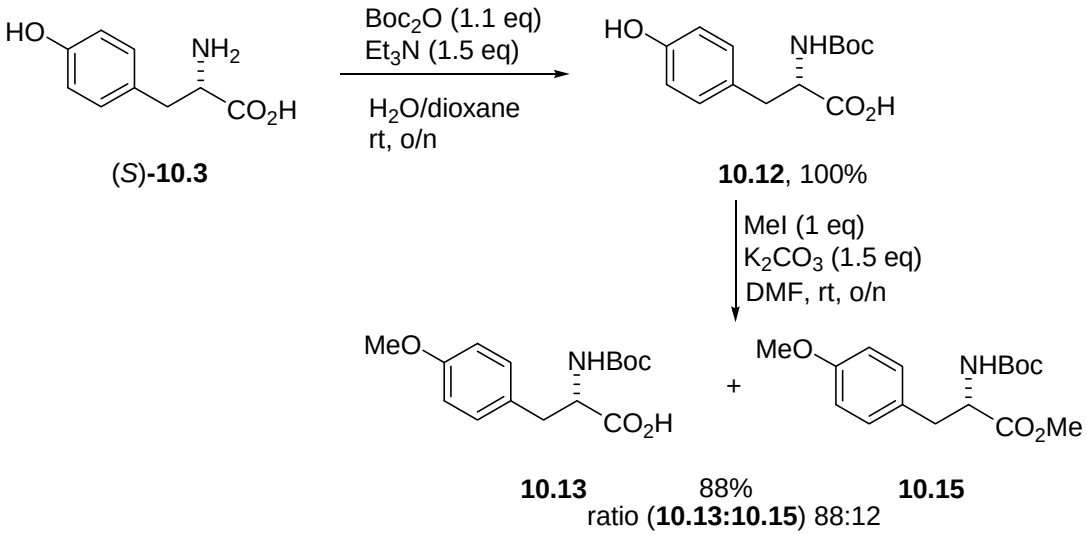
Having optimum conditions in hand for the amine protection but issues with formation of the benzyl ester, we considered reversing the two first steps and thus, beginning the sequence with *N*-Boc protection of the free amine **10.3** followed by *O*-methylation of the phenol **10.12** and finally benzylation of the acid **10.13** (Scheme 10.3).



Scheme 10.3: Strategy B

N-Protection of (*S*)-tyrosine (*S*)-**10.3** was carried out according to the procedure described above (Scheme 10.4). *N*-Boc-(*S*)-tyrosine **10.12** was obtained quantitatively. *O*-Methylation of the free phenolic hydroxyl group using

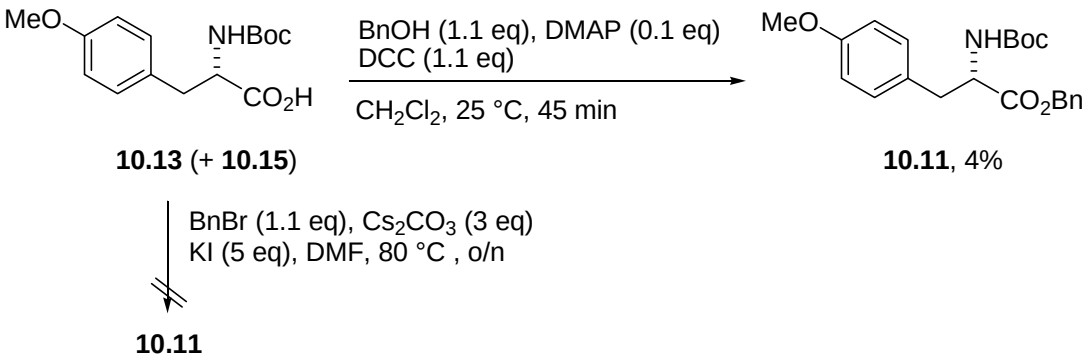
iodomethane (1.5 eq) and potassium carbonate in DMF overnight provided a 41:59 mixture of the acid **10.13** and the methyl ester **10.15,** whereas the use of only 1.0 eq of MeI improved this ratio to 88:12.



Scheme 10.4: First results in strategy B

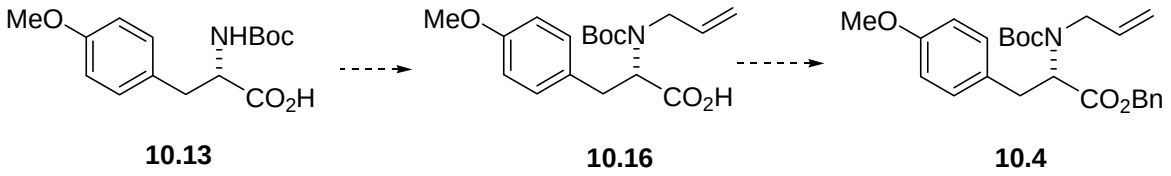
Purification of acid **10.13** was attempted but proved unsucessful and so without further efforts to improve conditions, attempts were made at benzylation of this mixture.

Esterification using the coupling reagent DCC and the nucleophilic catalyst DMAP provided traces of the ester **10.11** (Scheme 10.5). Results were not encouraging and I proved to be allergic to DCC, so further attempts at benzylation using this method were deemed too risky. The use of benzyl bromide in the presence of cesium carbonate and potassium iodide in DMF left starting materials unreacted.



Scheme 10.5: Benzylation conditions

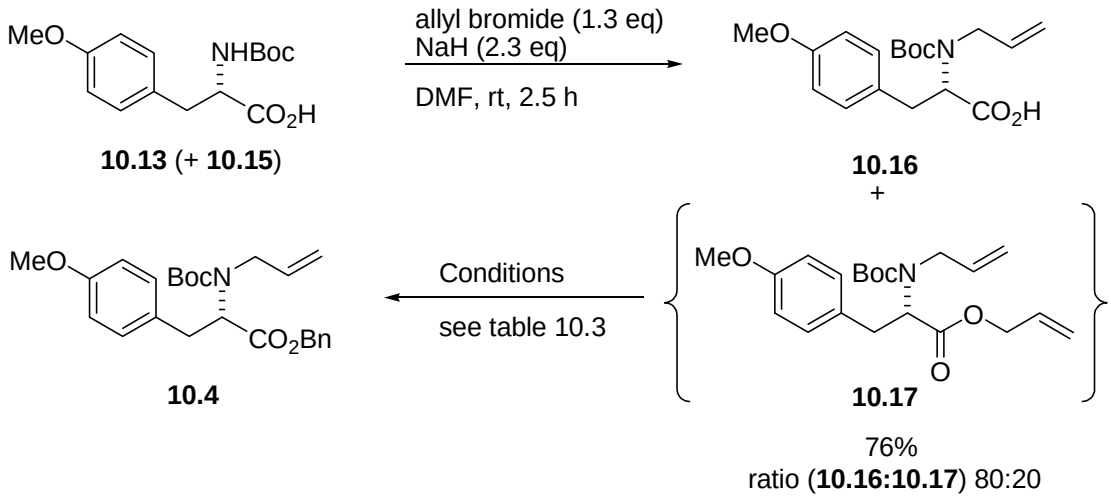
At the same time, a slightly different option stood out (Scheme 10.6). Allylation of the *N*-Boc protected amine **10.13** would be done prior to benzylation of the acid functionality.



10.13 **10.16** **10.4**

Scheme 10.6: Strategy C

The 88:12 mixture of **10.13** and **10.15** reacted with allyl bromide in presence of sodium hydride and provided mainly *N*-allyl-*N*-Boc-*O*-methyl-(*S*)-tyrosine **10.16** and traces of a minor compound which might be compound **10.17** (Scheme 10.7).[110] The presence of the desired acid was only confirmed from the ^{1}H NMR spectrum of the mixture. [^{1}H NMR of the acid **10.16** (400 MHz, $CDCl_3$) δ_H: 1.34 (9H, s, ^{t}Bu), 2.90-3.20 (2H, m, CH_2-3), 3.30 (3H, s, OMe), 4.42-4.53 (2H, m, CH_2N), 4.93 (1H, br s, CH-2), 5.33 (1H, d, *J* 16.8 Hz, =C*H*^{A}H^B), 5.19 (1H, d, *J* 10.5 Hz, =CH^A*H*^{B}), 5.92-6.02 (1H, m, C*H*=CH^{A}H^B), 6.76 (2H, d, *J* 8.0 Hz, H3" and H5"), 6.94-7.03 (2H, m, H2" and H6")]. The mixture was used without further purification in the benzylation reaction as compounds were not separable (Table 10.3).



10.13 (+ **10.15**) **10.16** + **10.4** **10.17**

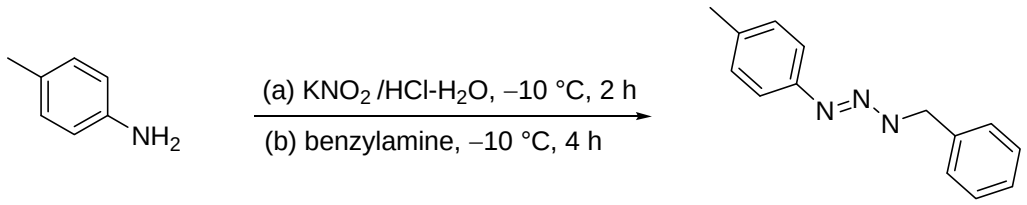
Scheme 10.7: Synthesis of fully protected tyrosine 10.4

All benzylation conditions tested are summed up in Table 10.3. Firstly, reactions carried out with benzyl bromide in presence of potassium carbonate or cesium carbonate (entries 1-4) left starting materials unreacted. After benzylation with benzyl alcohol and acetyl chloride (entries 5-6), adapting the conditions reported by Hulme and Rosser,[176] distillation of the alcohol led to the decomposition of the crude material before dryness. A last reaction was attempted with benzyl bromide in the presence of sodium hydride (Table 3, entry 7). Unfortunately, unreacted starting materials were recovered.

Entry	Acid **10.16**	Reagents	Conditions	Results
1	1.0 eq	BnBr (2 eq), K_2CO_3 (4eq)	DMF, rt, 3 h	SM
2	1.0 eq	BnBr (2 eq), K_2CO_3 (4 eq),	DMF, rt, o/n	SM
3	1.0 eq	BnBr (2 eq), Cs_2CO_3 (6 eq), KI (10 eq)	DMF, 80 °C, o/n	SM
4	1.0 eq	BnBr (18 eq), Cs_2CO_3 (3.8 eq), KI (9.4 eq)	DMF, 80 °C, o/n	SM
5	1.0 eq	BnOH (65 eq), AcCl (3 eq)	reflux, 4 h	decomposed
6	1.0 eq	BnOH (2.0 eq), AcCl (1 eq)	reflux, 4 h	decomposed
7	1.0 eq	BnBr (2 eq), NaH (2 eq)	DMF, rt, 2 h	SM
8	1.0 eq	Triazene **10.19** (2.5 eq), 5N HCl	Et_2O/THF rt, o/n	decomposed

Table 10.3: Benzylation conditions

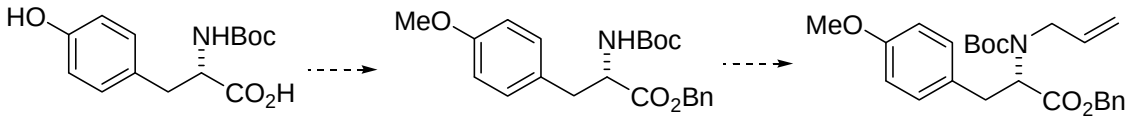
An alternative approach to benzylation was then investigated with a triazene reagent **10.19**. The chemistry and applications of triazenes have a long history dating back to the 19th century.[196] The most convenient synthesis of triazene **10.19** was provided by Mangia and Scandroglio.[197] The synthesis involves reacting *p*-toluidine **10.18** with potassium nitrite in acidic conditions (Scheme 10.8). Benzylamine is then added to the diazonium salt to form the 1-benzyl-3-*p*-tolyltriazene **10.19**. However, benzylation of acid **10.16** using triazene reagent **10.19** was unsuccessful (Scheme 10.7, Table 10.3, entry 8). Indeed after 12 h and appropriate work-up, an intractable mixture was obtained.



10.18 **10.19**, 100%

Scheme 10.8: Synthesis of the triazene reagent 10.19

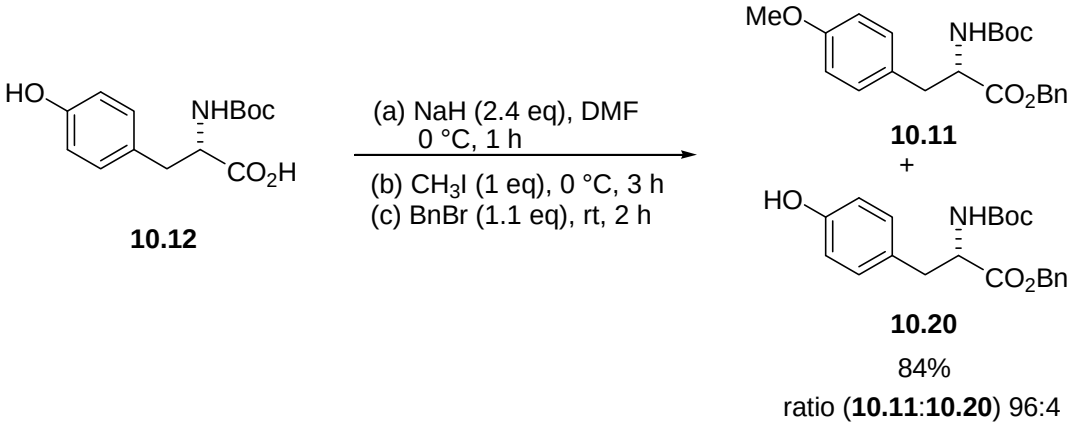
Lastly, a paper published by Rosenberg *et al.*[198] provided a solution to our problem. They reported a one-pot methylation-benzylation of the *N*-Boc-(*S*)-tyrosine **10.12** and therefore gave us a new route to exploit (Scheme 10.9).



10.12 **10.11** **10.4**

Scheme 10.9: Strategy D

Sodium hydride and iodomethane were successively added to a solution of *N*-Boc-(*S*)-tyrosine **10.12** in DMF followed by addition of benzyl bromide to give a 96:4 mixture of methyl ether **10.11** and phenol **10.20** (Scheme 10.10).

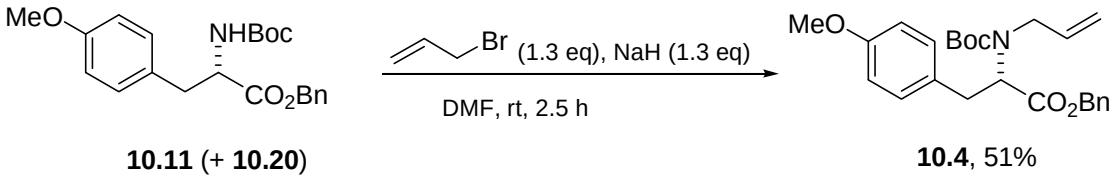


10.12

10.11
+
10.20
84%
ratio (**10.11**:**10.20**) 96:4

Scheme 10.10: One pot *O*-methylation-benzylation

Separation being impossible, the mixture was allylated without further purification following the procedure previously described (Scheme 10.11). This gave the desired precursor for alkylidenation.

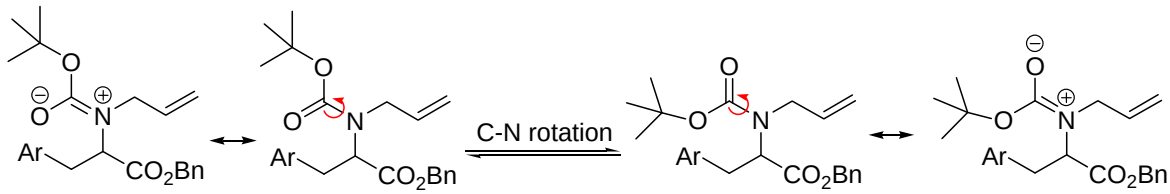


10.11 (+ **10.20**) **10.4**, 51%

Scheme 10.11: *N*-**allylation**

10.3. Analysis of complexities in NMR data of esters

The ^{1}H NMR spectrum of ester **10.4** appeared more complicated than might be expected. Indeed in carbamates as in amides, the rotation about the C-N bond is slow because of delocalization of the nitrogen lone pair (Figure 10.1). At room temperature, this rotation is not fast enough on the NMR timescale, causing broadening of the peaks or sometimes resulting in two sets of signals i.e. a mixture of rotamers. This may also be observed in the ^{13}C NMR spectrum.



Ar = 4-MeOC$_6$H$_4$

Figure 10.1: Rotamers of carbamate 10.4

The rate of the rotation is defined by the Arrhenius equation (where A is a pre-exponential factor, R is the gas constant; Ea is the activation energy and T the temperature of the analysis).

$$k = A \times e^{\left(-\frac{E_a}{RT}\right)}$$ **Arrhenius Equation**

The exponential term is a function of the temperature. Therefore, increasing the temperature of the analysis has the effect of increasing the rate of the rotation so that the ^{1}H NMR spectrum reflects an average of the two rotamers. A

well-resolved average spectrum was observed at T= 363 K (i.e. 90 °C). This phenomenon was observed for all tertiary carbamates.

This ^{1}H NMR analysis highlighted another phenomenon: diastereotopicity of protons (Figure 10.2). Indeed, C-3 and C-1' methylene units have diastereotopic protons because of the stereogenic centre nearby and in each case the geminal protons appear as two different signals in an ABX system. One double doublet is observed for H^{B}-3 with a geminal coupling constant (14.1 Hz) and a *trans*-vicinal coupling constant (9.1 Hz) whereas H^{A}-3 appears as one double doublet with a *gauche* vicinal coupling constant (6.1 Hz) and a geminal coupling constant (14.1 Hz).

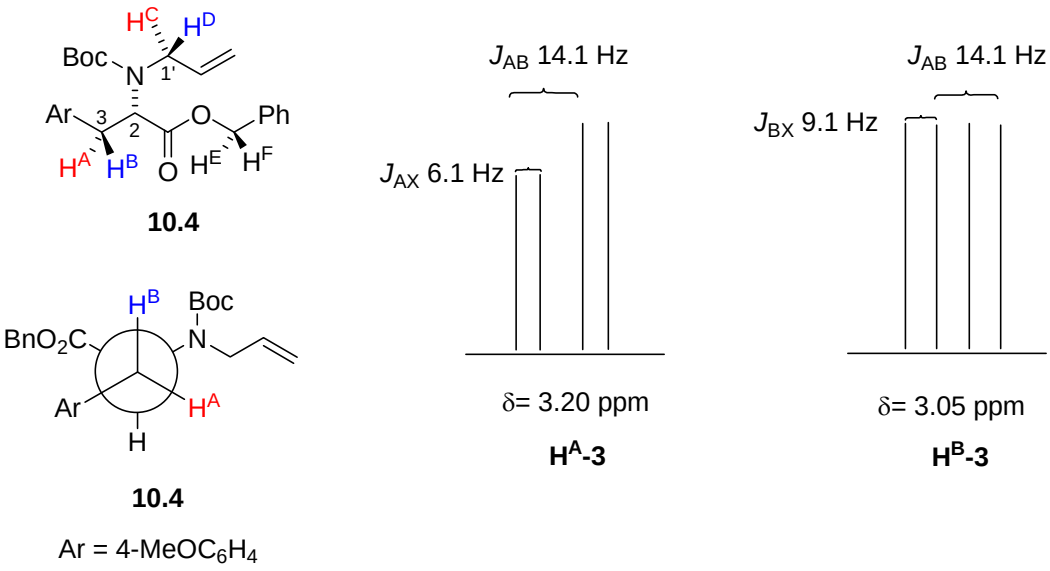


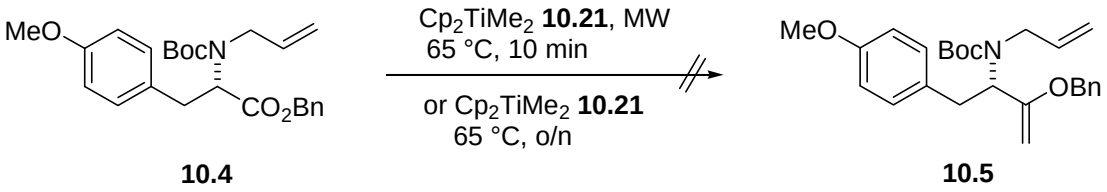
Figure 10.2: Diastereotopicity

The benzylic protons H^{E} and H^{F} are diastereotopic too (Figure 10.2). However in compound **10.4**, H^{E} and H^{F} have the same chemical shift and appear as a singlet, on the other hand in compound **10.11**, they are different and appear as two doublets with a *J* value of 12 Hz.

10.4. Titanium-based strategies for ring-closing

Alkylidenation of ester **10.4** was investigated using standard conditions established in the Hartley group,[100] employing the Petasis reagent **10.21** (=**6.14**,

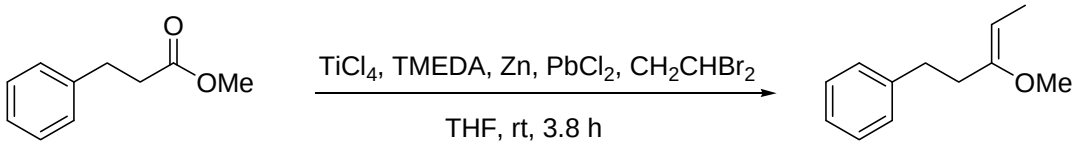
see Scheme 6.5) under microwave irradiations for 10 min (Scheme 10.12). The substrate decomposed under these conditions whereas an attempt at methylenation using dimethyltitanocene **10.21** without microwave irradiation left the starting material unreacted.



10.4 **10.5**

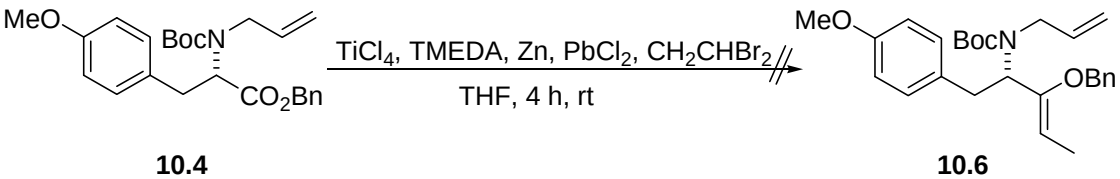
Scheme 10.12: Methylenation using Petasis reagent

Following an adaptation of Takai's procedure reported by Rutherford *et al.*,[199] the titanium carbenoid formed *in situ* from titanium tetrachloride, zinc and 1,1-dibromoethane in the presence of TMEDA transformed ester **10.22** into enol ether **10.23** in modest yield (Scheme 10.13). Therefore, adaptation of this procedure to our substrate **10.4** was expected to generate enol ether **10.6** (Scheme 10.14). Unfortunately, the benzyl ester **10.4**, which is very sterically hindered, did not react under Takai conditions. Thus, we had to consider another way of forming the pyrrolidine ring.



10.22 **10.23**, 58%

Scheme 10.13: Alkylidenation under Takai conditions

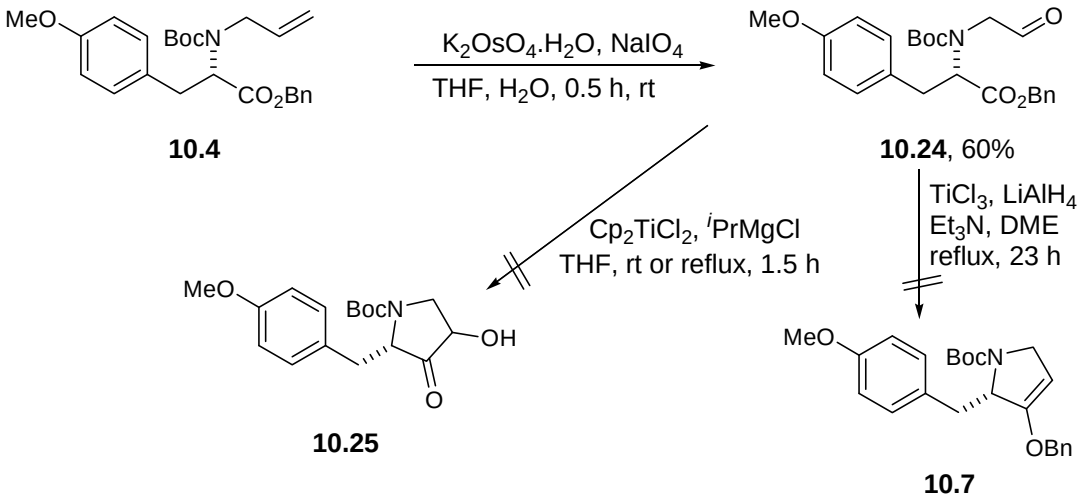


10.4 **10.6**

Scheme 10.14: Alkylidenation under Takai conditions

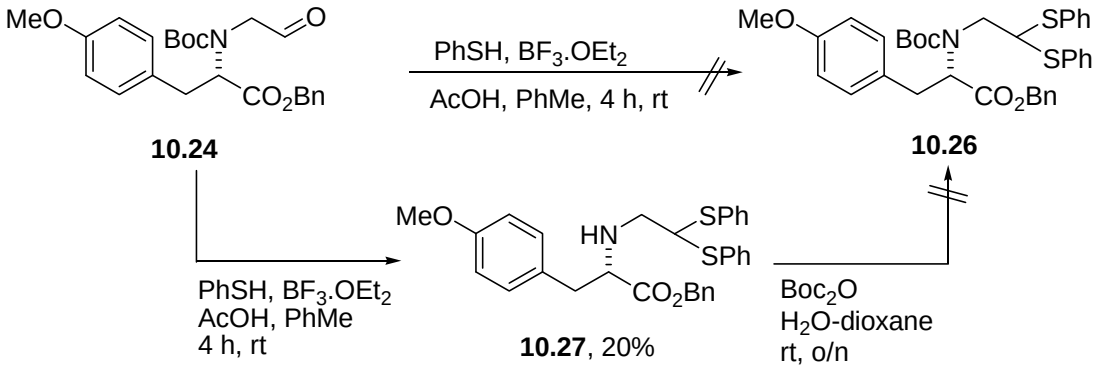
Alkene **10.4** was converted into aldehyde **10.24**, which, we hoped, could be cyclized using low valent titanium chemistry (Scheme 10.15). Attempted

cyclisation using McMurry conditions provided an intractable mixture[200,201] while reaction at room temperature with a low valent titanium reagent prepared from titanocene dichloride and ^{i}PrMgCl left the starting aldehyde **10.24** unreacted.[50,56] Increasing the temperature of the reaction did not provide any improvement. Indeed, heating under reflux in THF for 1.5 h caused decomposition of the substrate.



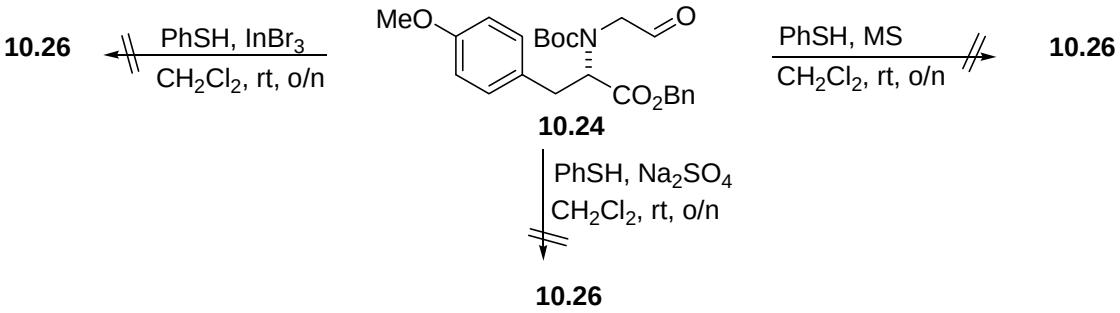
Scheme 10.15: Formation of 5-membered ring

The next route we considered required the formation of thioacetal **10.26** from aldehyde **10.24** in order to perform an intramolecular alkylidenation under Takeda conditions. Reaction of the aldehyde **10.24** with thiophenol and $BF_3.OEt_2$ in acetic acid led to removal of the Boc group and provided the free amine **10.27** in modest yield (Scheme 10.16). Furthermore, the reaction suffered from problems of reproducibility as thioacetal **10.27** was not observed afterwards despite several later attempts at this transformation. An attempt to reprotect amine **10.27** failed under standard conditions.



Scheme 10.16: Formation of thioacetal

The conditions of thioacetal formation were changed to overcome the problem of deprotection of the amine **10.24** (Scheme 10.17). First, the reaction was attempted in non-acidic conditions with sodium sulfate or molecular sieves as dehydrating agents. After overnight reactions, starting materials were recovered unchanged. Ceschi *et al.*[202] reported a chemoselective dithioacetalization of aldehydes catalyzed by indium tribromide. The same procedure adapted to our substrate **10.24** led to a mixture of impurities; nothing noteworthy was identified.

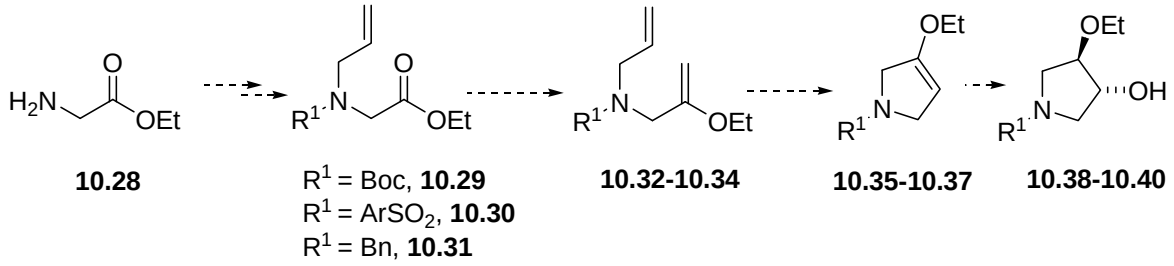


Scheme 10.17: Attempts of dithioacetalization

Taking into consideration difficulties met through this sequence, we decided to test the route with a simple substrate which would allow a better understanding of the issues and allow pursuit of an appropriate solution.

10.5. Model studies using glycine-derivatives

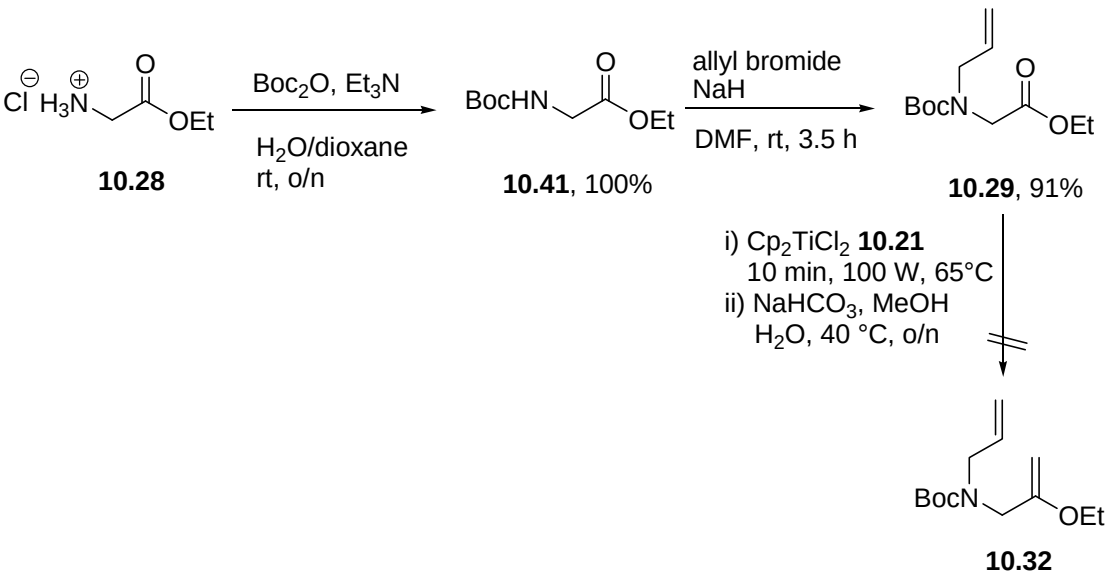
The purpose of this new route was to reproduce the sequence previously described using glycine ethyl ester **10.28** and vary conditions and protecting groups in order to get a better control of the situation (Scheme 10.18).



10.28 | R^1 = Boc, **10.29**; R^1 = $ArSO_2$, **10.30**; R^1 = Bn, **10.31** | **10.32-10.34** | **10.35-10.37** | **10.38-10.40**

Scheme 10.18: Model sequence with glycine ethyl ester 10.28

Amino acid **10.28** was *N*-Boc protected in quantitative yield and this was followed by allylation of the secondary amine **10.41** to give the carbamate **10.29** in high yield (Scheme 10.19). A first attempt at methylenating the ester **10.29** using the Petasis reagent **10.21** under microwave irradiation was unsuccessful. The compound was lost during the purification of the crude mixture due to instability and difficulty in detecting it. Furthermore, the use of carbamates gave rise to the problem of rotamers making spectroscopic analysis difficult.

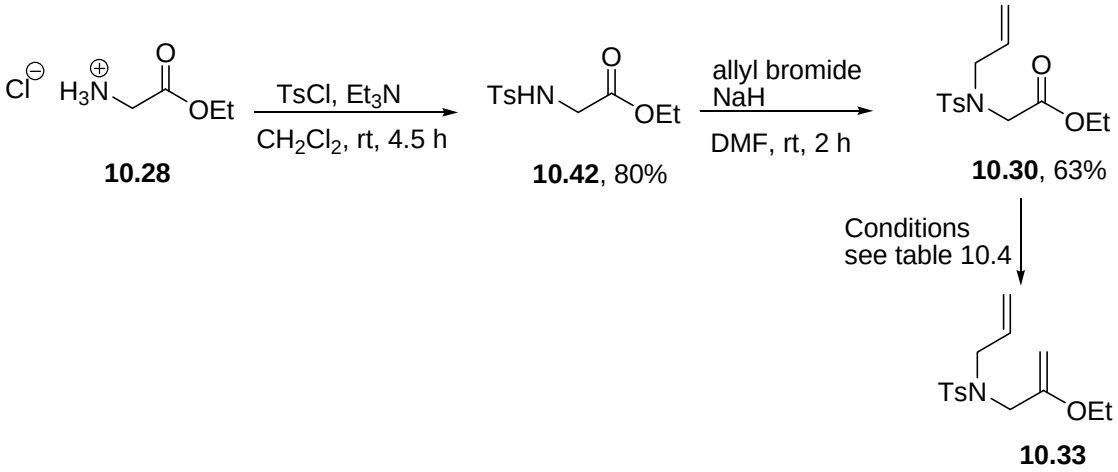


10.28 | **10.41**, 100% | **10.29**, 91% | **10.32**

Scheme 10.19: Carbamate series

Since we had also shown that *N*-Boc protection does not survive the use of boron trifluoride in the preparation of thioacetals, the protection of the amino group was changed.

Sulfonamides presented an opportunity to overcome difficulties met with carbamates. They do not give rise to rotamers and should survive the formation of the thioacetal. The ethyl ester of glycine **10.28** was protected with tosyl chloride to give sulfonamide **10.42** in high yield (Scheme 10.20).[203]



Scheme 10.20: Sulfonamide series

Allylation of sulfonamide **10.42** then provided the ester **10.30** in good yield. Various conditions were attempted for methylenation of the ester **10.30** using the Petasis reagent **10.21** (Table 10.4). Entry 1, reaction under Hartley group conditions, resulted in formation of a complex mixture. Due to the instability of the enol ether on silica, we chose to submit this crude mixture to acidic treatment in order to obtain the ketone derivative **10.43** which might be purified by chromatography. Thus, treatment of the mixture with 1 M HCl in THF for 1 h provided the ketone **10.43** in very low isolated yield. The isolation of ketone **10.43** is proof of the formation of enol ether **10.33** and consequently the success of the reaction. Nevertheless conditions needed to be improved. The same conditions were reproduced with chromatography on alumina as a purification step and this gave both the enol ether **10.33** and a side-product **10.44** formed by methylenation and loss of the allyl chain. However sulfonamide **10.44** was not totally clean and due to its instability and high volatility, this compound was only identified by ^{1}H NMR spectroscopy.

Conditions were obviously too harsh. At the same time, methylenation was carried out under milder conditions (Table 10.4, entry 3) and the result confirmed our supposition. Microwave irradiation caused break down of the molecule whereas thermal conditions allowed the conversion of the ester **10.30** into enol ether **10.33** but even after 72 h of reaction, the yield obtained remained modest (entry 5).

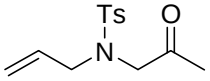
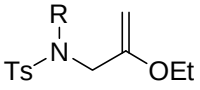
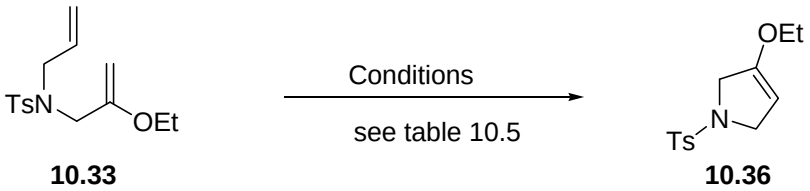
Entry	Cp_2TiMe_2 **10.21**	Conditions	Purification system	Result
1	3.0 eq	MW 65°C, 10 min	1 M HCl, THF	 **10.43**, 5%
2	3.0 eq	MW 65°C, 10 min	Al_2O_3 column	 **10.33**, R = allyl, 21% **10.44**, R = H, 37%
3	3.0 eq	65°C, 9.5 h	Al_2O_3 column	**10.33**, 25%
4	3.0 eq	65°C, 24 h	Al_2O_3 column	**10.33**, 38%
5	3.0 eq	65°C, 72 h	Al_2O_3 column	**10.33**, 39%

Table 10.4: Methylenation conditions

With the enol ether **10.33** in hand, the ring closing metathesis appeared to be a good option to generate the pyrroline ring **10.36** (Scheme 10.21).



10.33 **10.36**

Scheme 10.21: Ring closing metathesis

Use of Grubbs 1st generation catalyst **10.45** (= **7.13**, see Scheme 7.4) (6 mol%) under standard conditions did not provide the desired compound **10.36** as we recovered starting material (Table 10.5, entry 1). A second try using 30 mol% of catalyst yielded ketones **10.43** and **10.47** after acidic treatment and chromatography column (Table 10.5, entry 2). As explained earlier, both ketones are derived from enol ether precursors. We could then conclude that the ring closing reaction did not take place. Grubbs 2nd generation catalyst **10.46**

(5 mol%) (= **7.14**, see Scheme 7.4) did not provide any better results (Table 10.5, entry 3). After purification, we were able to isolate ketone **10.43** in modest yield.

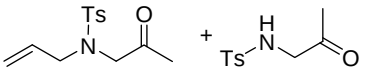
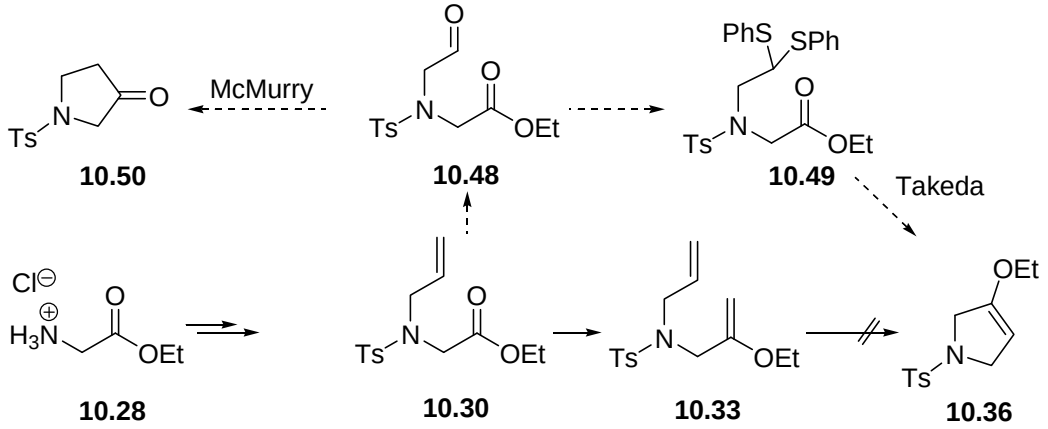
Entry	Catalyst	Conditions	Treatment	Result
1	Grubbs I **10.45** 6 mol%	CH_2Cl_2, 0.01 M, 1.5 h, 50°C	Concentration	SM **10.33**
2	Grubbs I **10.45** 30 mol%	CH_2Cl_2, 0.2 M, 6 h, 50°C	i) 1M HCl-THF ii) SiO_2 column	 **10.43**, 65% + **10.47**, 35%
3	Grubbs II **10.46** 5 mol%	CH_2Cl_2 0.01 M, 1 h, 50°C	i) Al_2O_3 column ii) 1 M HCl, THF	**10.43**, 46%

Table 10.5: Ring closing metathesis

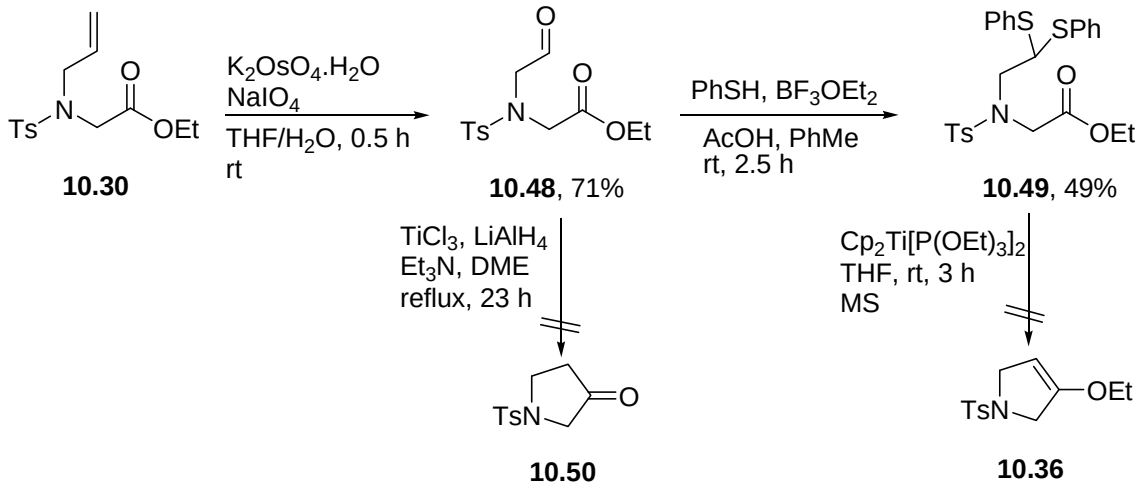
It would probably be worth trying the reaction with a higher loading (*i.e.* 30 mol%) of Grubbs 2nd generation **10.46** but the cost of the catalyst discouraged us. An interesting perspective would be to consider regeneration of the catalyst in order to use it several times and then lower the cost of the step. Research into catalyst recycling has been done by others and solutions are available with ionic liquid-supported ruthenium carbene complex,[204] fluorous polyacrylate bound ruthenium carbene complex,[205] polyethylene glycol-supported (PEG) carbene complex,[205,206,207] butyldiethylsilyl polystyrene-supported ruthenium carbene complex,[208,209] vinyl polystyrene-supported ruthenium carbene complex[210] and poly-divinylbenzene-supported ruthenium carbene complex.[211] The PEG supported catalyst represents the most attractive option from an economic point of view. Grubbs 1st generation catalyst **10.45** can be immobilized on PEG in 6 steps, metathesis of some substrates takes place with 5 mol% loading and the catalyst can be reused after simple precipitation for up to 8 runs.

Considering the failure of RCM, we decided to prepare aldehyde **10.48** in order to perform an intramolecular alkylidenation under Takeda conditions or a McMurry type reaction (Scheme 10.22).



Scheme 10.22: A new pathway

From the ester **10.30**, the aldehyde **10.48** was accessed without any difficulty following the conditions we had used previously (Scheme 10.23). Two distinct options were considered for the aldehyde **10.48:** the use of aldehyde **10.48** directly in a McMurry type reaction using $TiCl_3$-$LiAlH_4$[201] or formation of the thioacetal **10.49** in order to carry out a cyclisation under Takeda conditions. The reaction of $TiCl_3/LiAlH_4$ with aldehyde **10.48** did not produce the expected cyclic compound **10.50**, whereas the formation of the thioacetal **10.49** proceeded without any problems in a modest yield.



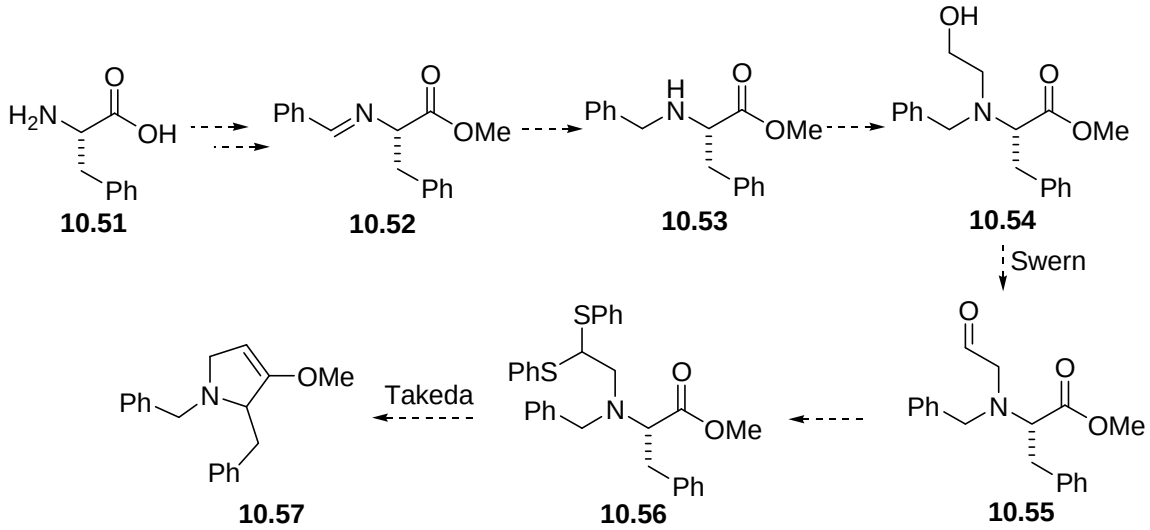
Scheme 10.23: Towards the five-membered ring

The Takeda reaction was problematic. The reaction is highly water sensitive and requires a large excess of reagents so the analysis of the ^1H NMR spectrum of the crude mixture was complicated by the presence of reagents such as $P(OEt)_3$ which hide significant areas of the spectrum. A small portion of the starting

material **10.49** was recovered; other fractions could not be properly identified but seemed to be products of decomposition. As the behaviour of sulfonamides under Takeda conditions was unknown, we considered that the reaction may have led to the loss of the tosylate group before or after cyclisation. In both cases the resulting compounds would probably be too volatile to be observed. A solution would be to add a heavy substituent on the chain so we might isolate these products and conclude if the deprotection occurs before or after cyclisation. Anyway, the protecting group had to be changed as the sulfonamide appeared not to survive the Takeda reaction. To increase the mass and better mimic tyrosine, phenylalanine was used as the starting amino acid. The amino group would be protected with a benzyl group which was known to be tolerated under Takeda conditions.[212]

10.6. Model studies using phenylalanine-derivatives

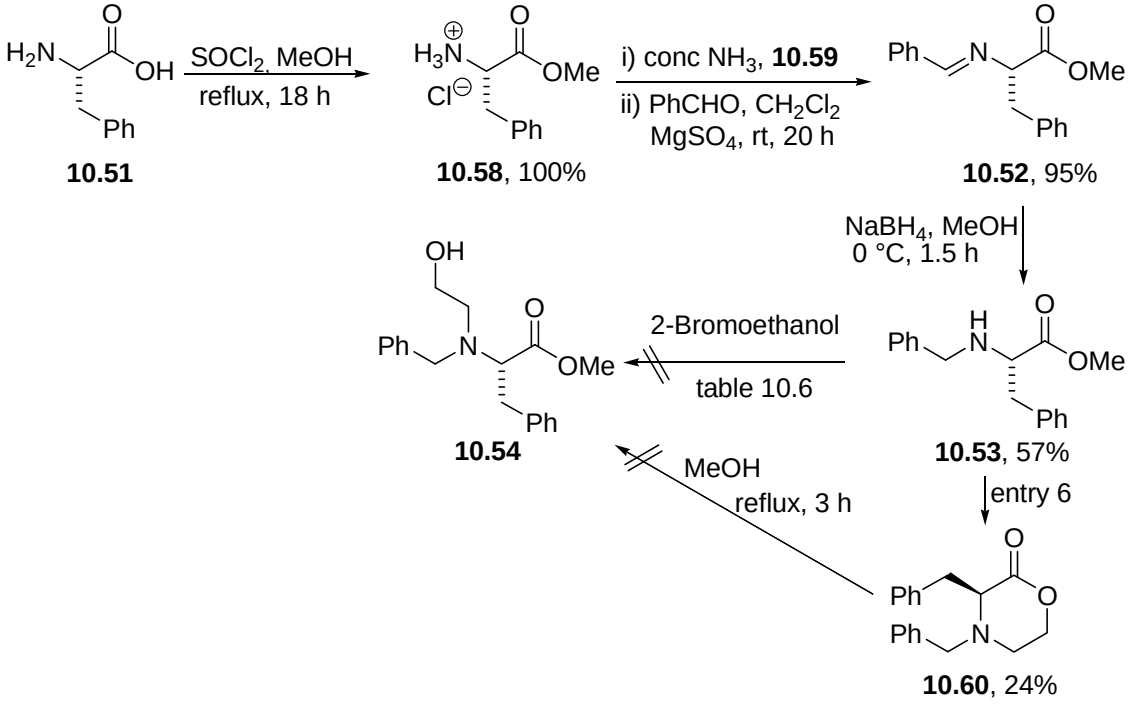
At first, we thought of connecting a ß-hydroxyethyl chain and then oxidizing the alcohol *via* Swern oxidation to give aldehyde **10.55** which would allow access to thioacetal **10.56** (Scheme 10.24).



Scheme 10.24: Effective sequence

The first step consisted in formation of the methyl ester **10.58** using methanol and thionyl chloride (Scheme 10.25).[213] The hydrochloride salt **10.58** was isolated in quantitative yield and then treated with concentrated ammonia to obtain the free amine in excellent yield. The imine **10.52** was formed by

reaction of free amine with benzaldehyde and then reduced to give the secondary amine **10.53**.[214] Several attemps were made to introduce the ß-hydroxyethyl chain to the amine **10.53** (Table 10.6).[215,216,217,218]



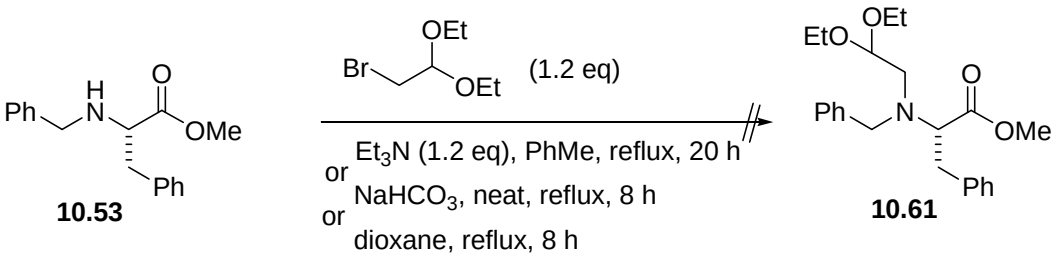
Scheme 10.25: Access to the amine 10.54

Each time starting material was recovered except for conditions using 2-bromo ethanol and Et_3N in toluene.[217] The morpholinone **10.60** was isolated in low yield. According to the literature,[219] it would be possible to open the lactone to get an ester using methanol at reflux. Unfortunately, we recovered the amine **10.53**.

Entry	2-Bromoethanol	Reagents	Conditions	Results
1	20 eq	NaI, DIPEA (10 eq)	MeOH, 50 °C, 21 h	SM **10.53**
2	20 eq	NaI, DIPEA (10 eq)	130 °C, 1 h	decomposition
3	2 eq	Dry K_2CO_3 (2 eq)	MeOH, 74 °C, 68 h	SM **10.53**
4	20 eq	neat	140 °C, 15 min	decomposition
5	1 eq	neat	MW 100W, 85 °C, 10 min	decomposition
6	1.2 eq	Et_3N (1.2 eq)	toluene, reflux, 20 h	**10.60,** 24%
7	2.5 eq	TBAI (2.5 eq) DIPEA (2.5 eq)	DMF, reflux, 7 h	SM **10.53**
8	1.2 eq	DIPEA (1.2 eq)	toluene, reflux, 20 h	decomposition
9	1.2eq	DIPEA (1.2 eq)	toluene, reflux, 7 h	SM **10.53**

Table 10.6: Conditions for the formation of compound 10.54

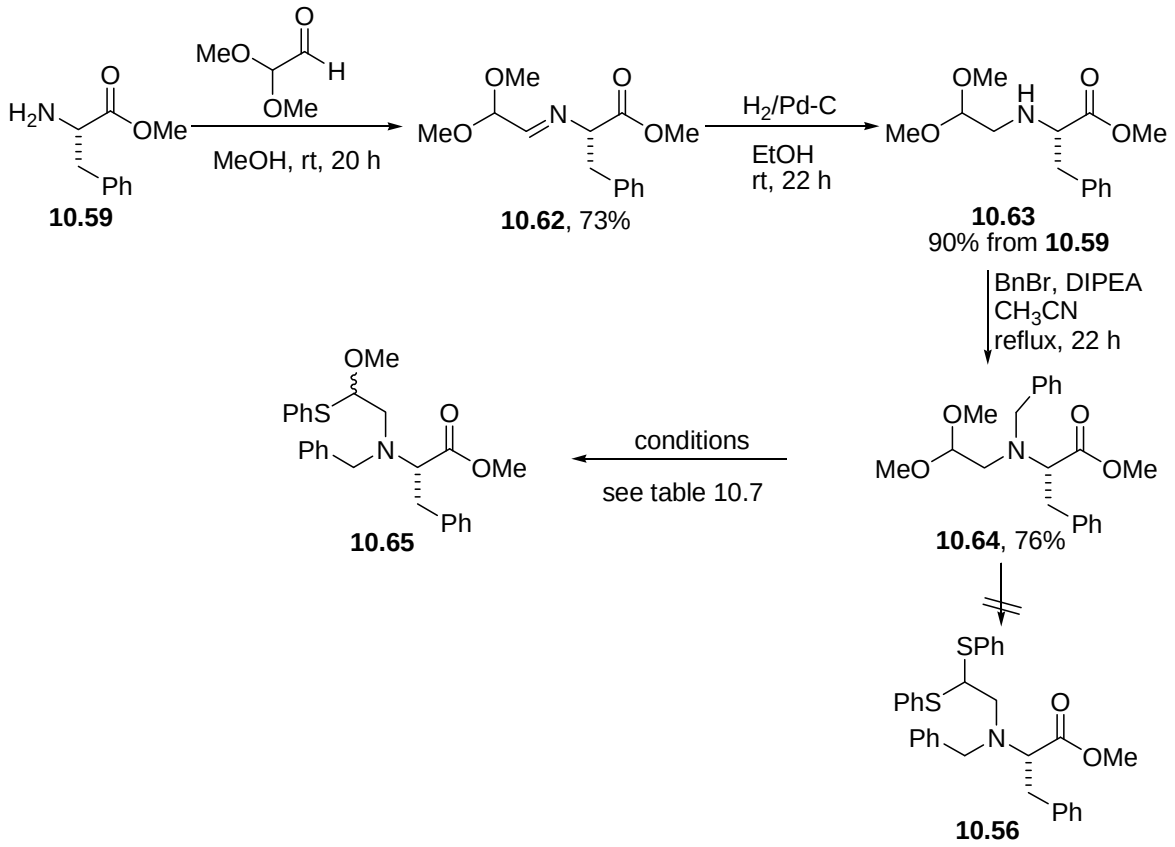
Another route considered involved starting from the secondary amine **10.53** and connecting an acetal instead of an alcohol, in order to avoid the formation of the morpholinone. The thioacetal **10.56** would be directly accessible from the acetal **10.61**. The reaction of the amine **10.53** with bromoacetaldehyde diethylacetal in toluene did not yield the expected acetal **10.61**; starting material was recovered (Scheme 10.26). Different conditions came up with the same result.[220,221]



Scheme 10.26: Attempt of formation of diethyl acetal 10.61

In an alternative route, reaction of the methyl ester of phenylalanine **10.59** with dimethoxyacetaldehyde in CH_2Cl_2 provided the imine **10.62** in high yield (Scheme 10.27). Reduction of the imine **10.62** using sodium borohydride in methanol gave the amine **10.63** in 6% yield, whereas the reduction using catalytic hydrogenation furnished the amine **10.63** in very high yield over two

steps. Benzylation of the secondary amine **10.63** in acetonitrile gave the acetal **10.64** in very good yield.



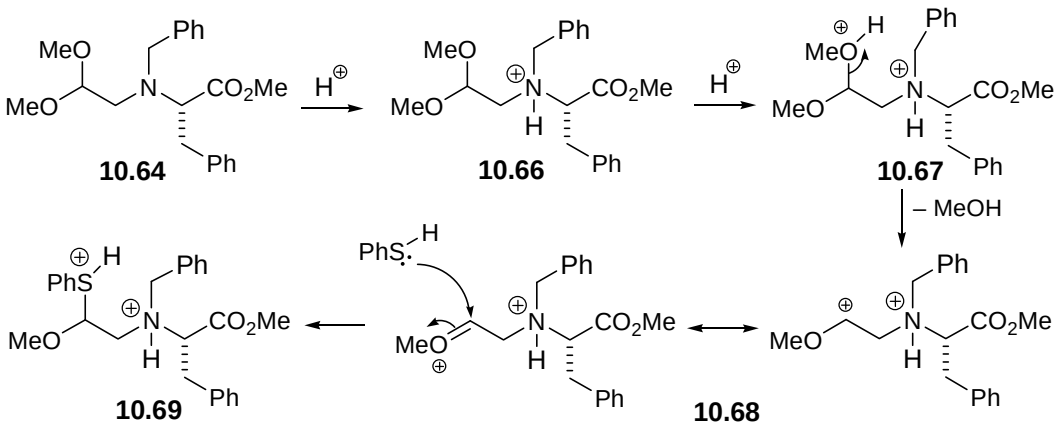
Scheme 10.27: Using dimethoxyacetaldehyde

The next step was the formation of the substrate for the Takeda reaction (Scheme 10.27). However, conversion of the acetal **10.64** into thioacetal **10.56** represented a problem and screening of conditions had to be performed (Table 10.7). Standard conditions ($BF_3.OEt_2$ 1.1 or 2.3 eq at rt) were not successful (entries 1-2). Increasing the temperature led to the formation of some mixed acetal **10.65** (entry 3). Conditions proposed by Park and co-workers[222] or Nishio *et al.*[223] did not provide any better results (entries 4-5). Use of molten tetrabutylammonium bromide (TBAB) and thiophenol (entry 6) as described by Ranu[224] did not give the thioacetal **10.56,** however the formation of the mixed acetal **10.65** was greatly improved producing starting material **10.64** and mixed acetal **10.65** in a ratio 17:83.

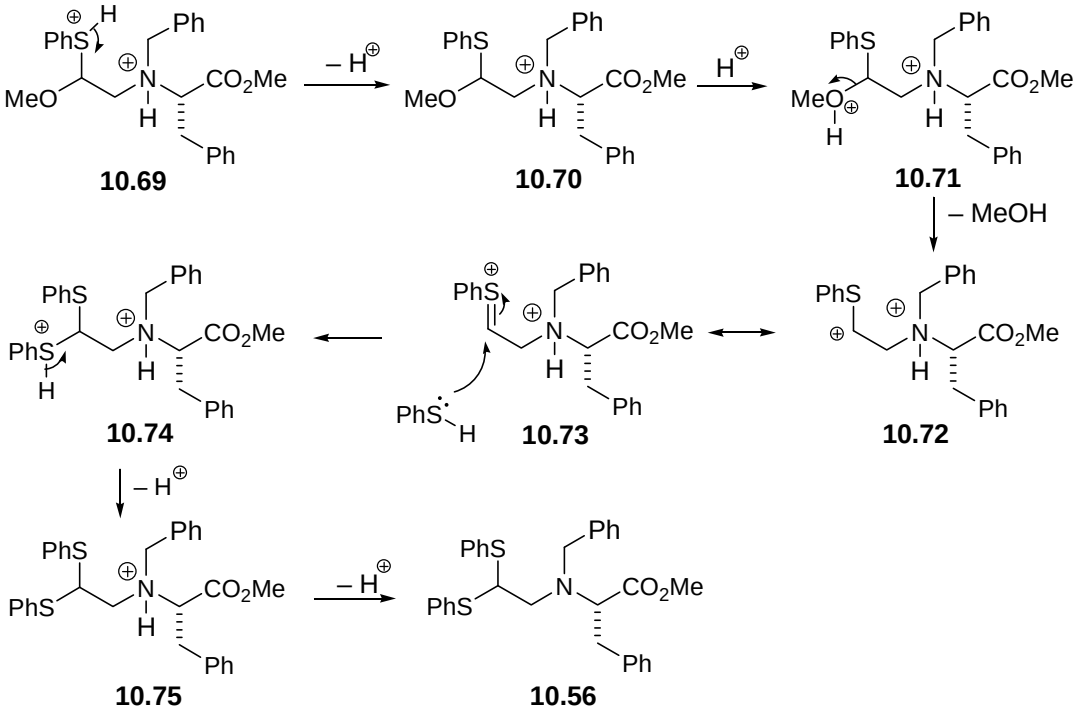
Entry	Reagents	Conditions	Ratio (**10.64**: **10.65**)
1	PhSH (2.3 eq), $BF_3.OEt_2$ (1.1 eq), AcOH	Toluene, rt, 3 h	100:0
2	PhSH (2.3 eq), $BF_3.OEt_2$ (2.3 eq), AcOH	Toluene, rt, 3 h	100:0
3	PhSH (2.3 eq), $BF_3.OEt_2$ (2.3 eq), AcOH	Toluene, reflux, 4 h	86:14
4	PhSH (2.1 eq), $MgBr_2$ (2.1 eq)	Et_2O, rt, 2 h	100:0
5	PhSH (2.2 eq), *p*-TsOH (0.11 eq)	Toluene, reflux, 5 h	decomposition
6	PhSH (2.3 eq), molten TBAB (30 mol%)	neat, 130 °C, 2 h	17:83

Table 10.7: Conditions for the formation of mixed acetal 10.65

The difficulties with obtaining thioacetal **10.56** from acetal **10.64** were probably due to the presence of a basic nitrogen atom that would be protonated under acidic conditions (Scheme 10.28 and Scheme 10.29). Even when no additional acid is added, thiophenol is sufficiently acidic (pKa 6.6) to protonate the amino group and give the ammonium salt **10.66** (pKa approximately 10). Protonation of the acetal and in particular loss of the methanol to give resonance stabilised carbocation **10.68** will be disfavoured by the close proximity of the positive charge, so this is only possible when a high temperature and an ionic liquid are used. Even then the reaction stops at the mixed acetal, because resonance stabilisation of the di-cation **10.72** that would be produced by loss of the second methanol is poor due to poor orbital overlap between the lone pair on sulfur and the empty p-orbital on carbon, and the sulfur is cross-conjugated with the phenyl ring.[225]

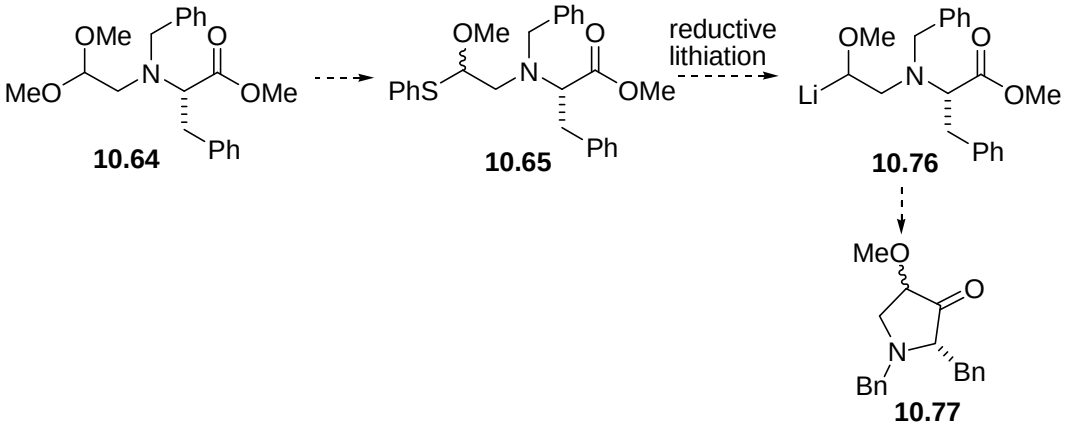


Scheme 10.28: Difficulties with thioacetal formation



Scheme 10.29: Difficulties with thioacetal formation

Instead of trying to obtain what we could not have, we considered what was possible with what we had. Obtaining the thioacetal **10.56** was obviously not possible but we had good conditions for the formation of the mixed acetal **10.65**. Cohen *et al*. reported a number of examples of reductive lithiation of thioacetals with reagents such as lithium naphthalenide **10.78** (LN),[226,227] lithium 1-(dimethylamino)naphthalenide **10.79** (LDMAN)[228,229,230,231] or lithium 4,4'-di-*tert*-butylbiphenylide **10.80** (LDBB)[232,233] (Figure 10.3) followed by reaction with an electrophile. They found that mixed acetals were good starting materials for reductive lithiation as well. Although an intramolecular version of the reaction had never been considered, we considered the reductive lithiation of mixed acetal **10.65** would give the organolithium **10.76** which would spontaneously cyclise by condensation with the ester group and then form the pyrrolidine **10.77** (Scheme 10.30).



Scheme 10.30: Possible strategy from acetal 10.64

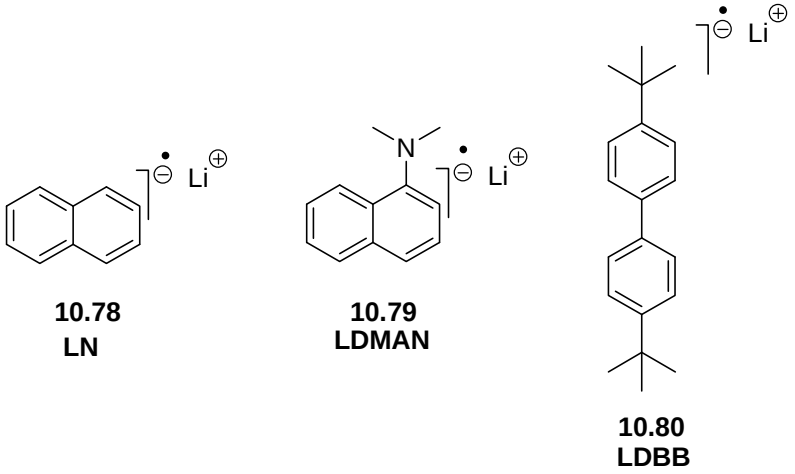
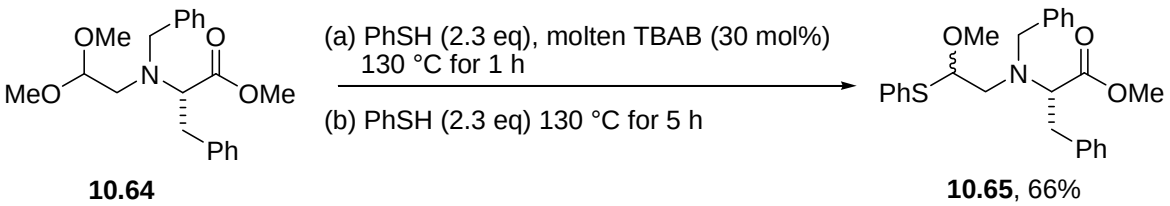


Figure 10.3: Cohen's reducing agents

Initially, the formation of the mixed acetal **10.65** was optimised (Scheme 10.31). After addition of 4.6 eq of thiophenol in two batches and 6 h at 130 °C, the mixed acetal **10.65** was isolated in good yield.



Scheme 10.31: Synthesis of acetal 10.65

The reductive lithiation was investigated by adaptation of Cohen's procedures (Table 10.8).[229] Cohen demonstrated that LN **10.78** is capable of rapid reductive

lithiation of thioacetals to give α-lithiothioethers.[226,227] The reagent is readily prepared by stirring naphthalene dissolved in THF with lithium ribbon at 25 °C for 6 h. A dark green colour indicates the formation of the radical anion. A solution of acetal **10.65** in THF was added to the reagent prepared in this way and at −78 °C. However despite various different conditions (Table 10.8, entries 1-4) no reaction was observed. Cohen had also developed a reagent, LDMAN **10.79**, [228,229,230,231] prepared by stirring 1-(dimethylamino)naphthalene with lithium ribbon in THF at −45 °C. Cohen had noted that this reagent appeared to decompose to give 1-lithionaphthalene above −45 °C. After obtaining the characteristic dark green-blue colour, a solution of mixed acetal **10.65** in THF was added to LDMAN (10 eq) at −78 °C and the mixture left for 15 min. After chromatography, we collected a mixture of the starting *N,N*-(dimethylamino) naphthalene and a minor product masked by the large excess of LDMAN (Table 10.8, entry 5). Reducing the number of equivalents of LDMAN did not reduce the problem (Table 10.8, entry 6). A major disadvantage of this method is the separation of compounds from excess *N,N*-(dimethylamino)naphthalene. Whether the reaction works or not, starting acetal **10.65** or cyclised compound **10.77** (Scheme 10.30) would have similar properties and are hardly separable from the starting naphthalene.

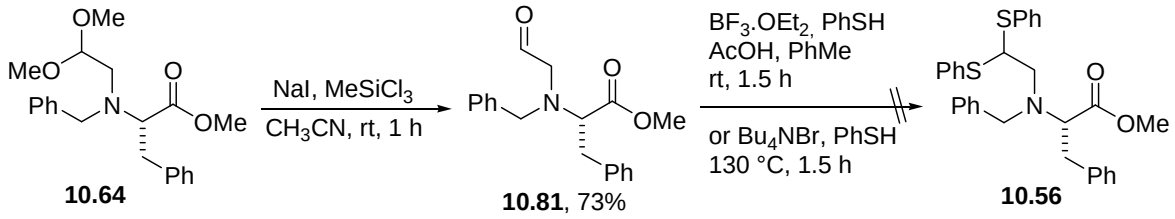
Entry	Reagent	Conditions	Results
1	LN **10.78** (2 eq)	THF, −78 °C, 45 min	SM **10.65**
2	LN **10.78** (2 eq)	THF, −78 °C to rt over 2 h	SM **10.65**
3	LN **10.78** (2.1 eq)	THF, rt, 15 min	SM **10.65**
4	LN **10.78** (2 eq)	THF, −78 °C, 0.5 h then rt, 25 min	SM **10.65**
5	LDMAN **10.79** (10 eq)	THF, −78 °C, 15 min	DMAN
6	LDMAN **10.79** (2.5 eq)	THF, −78 °C, 1 h	decomposition
7	LDBB **10.80** (2.1 eq)	THF, −78 °C, 2 h then rt, 10 min	?

Table 10.8: Conditions for the reductive lithiation

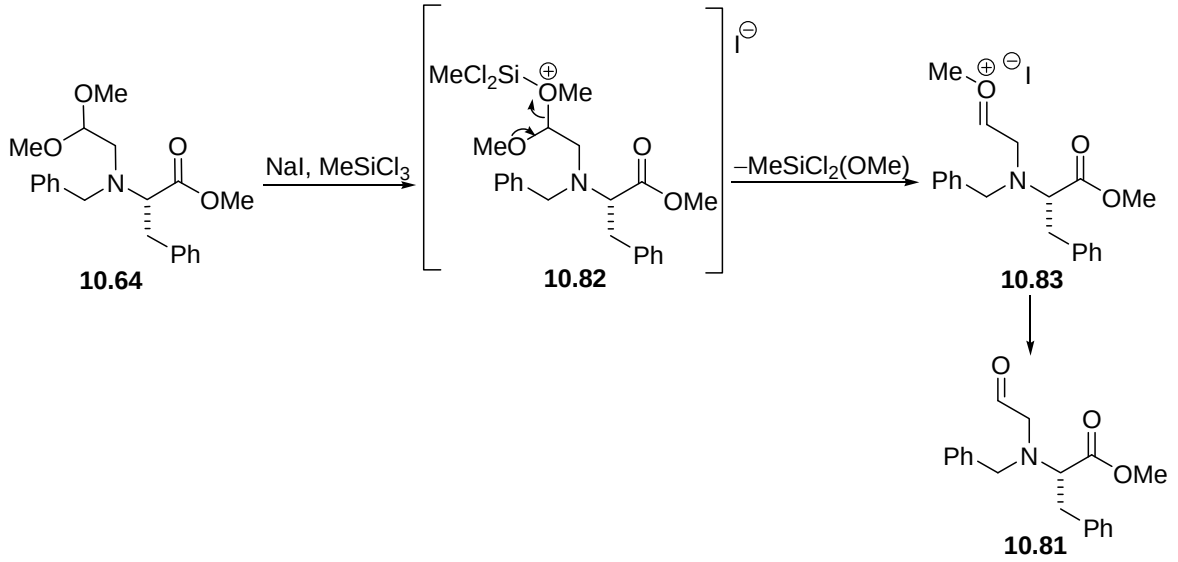
Cohen's group also demonstrated reductive lithiation of thioacetals with the radical anion lithium *p,p'*-di-*tert*-butylbiphenylide (LDBB).[232,233] LDBB proved to be a more powerful reducing agent than LN and led to higher yields than LDMAN.

Furthermore, since the desired product **10.77** is an amine, separation from LDBB would be possible by extraction with acid. Thus, after formation of the radical anion at 0 °C, LDBB was cooled to −78 °C and the solution of mixed acetal **10.65** in THF was added. After 2 h of reaction and despite an acid-base work up, the major fraction we obtained contained a large amount of starting DBB as well as a minor non identified compound which might be the starting acetal but ^{1}H NMR signals were masked by the excess of reagent.

After these results, we decided to concentrate on obtaining thioacetal **10.56** for intramolecular Takeda reaction. Various conditions for converting acetal **10.64** into aldehyde **10.81** were tried (Scheme 10.32). Adaptation of the procedure described by Gomez-Gallego *et al.*[234] with $FeCl_3$ left starting material **10.64** unreacted whereas treatment under acidic conditions (6N HCl) resulted in decomposition of the substrate. Olah *et al.*[235] furnished the solution with a procedure that allowed conversion of dimethyl acetals into carbonyl compound after reaction with a trichloromethylsilane / sodium iodide reagent in acetonitrile. A probable mechanism has been proposed by Olah's group. Dimethyl acetal **10.64** reacts rapidly with trichloromethylsilane / sodium iodide reagent to form the unstable intermediate **10.82**, which is rapidly transformed into carbonyl **10.81** (Scheme 10.33). Aldehyde **10.81** was obtained without any difficulties and in excellent yield under these conditions. Attempted conversion of the aldehyde into a thioacetal **10.56** according to standard condition widely described herein was unsuccessful. Moreover, another unsuccessful effort to make the thioacetal derivative using thiophenol in TBAB encouraged us to stop further investigations of this approach.



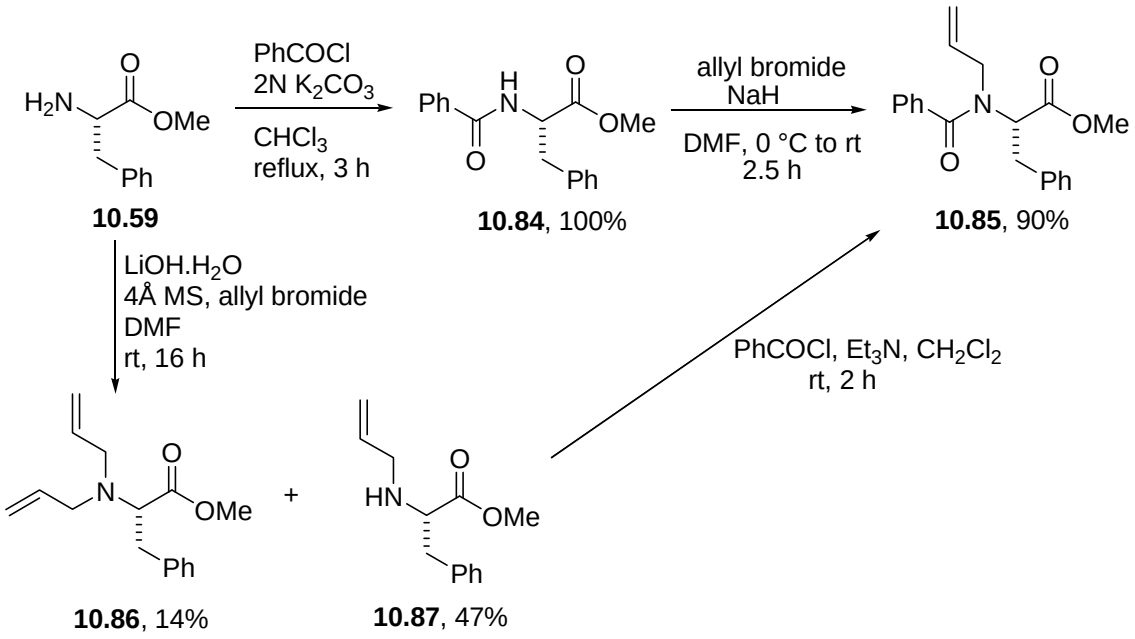
Scheme 10.32: Synthesis of thioacetal 10.56



Scheme 10.33: Probable mechanism for the cleavage of dimethyl acetals

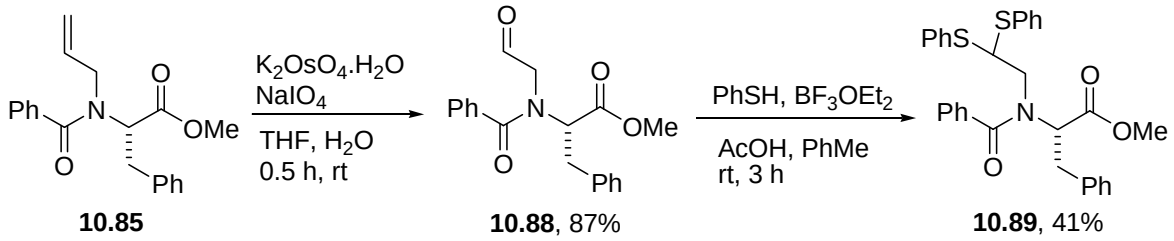
The presence of a basic amino group in acetal **10.64** and in aldehyde **10.81** was believed to be responsible for the failure of routes to thioacetal **10.56**. Acid-sensitive Boc protection had prevented access to thioacetal **10.26**, and sulfonamides had proved unstable under Takeda conditions. We therefore investigated the use of a robust benzamide protecting group.

Amide **10.85** was obtained *via* two different paths (Scheme 10.34). First, amidation of phenylalanine methyl ester **10.59** using benzoyl chloride proceeded quantitatively.[236] Reaction of benzamide **10.84** with allyl bromide provided a mixture that was very difficult to analyse and purify, whereas the amide **10.85** was easily accessed after reaction of amine **10.59** with allyl bromide in the presence of lithium hydroxide[237] followed by benzoylation under basic conditions.[238] Bis-allyl compound **10.86** was isolated as a by-product of the allylation.



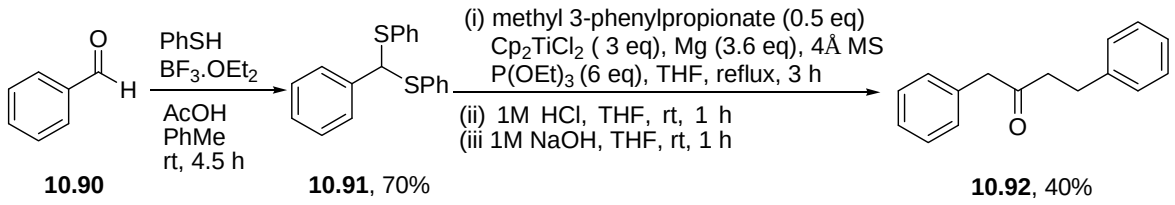
Scheme 10.34: Synthesis of amide 10.85

Oxidative cleavage of the allyl group in benzamide **10.85** gave aldehyde **10.88** and then the thioacetal **10.89** was finally accessed under standard conditions (Scheme 10.35).



Scheme 10.35: Synthesis of thioacetal 10.89

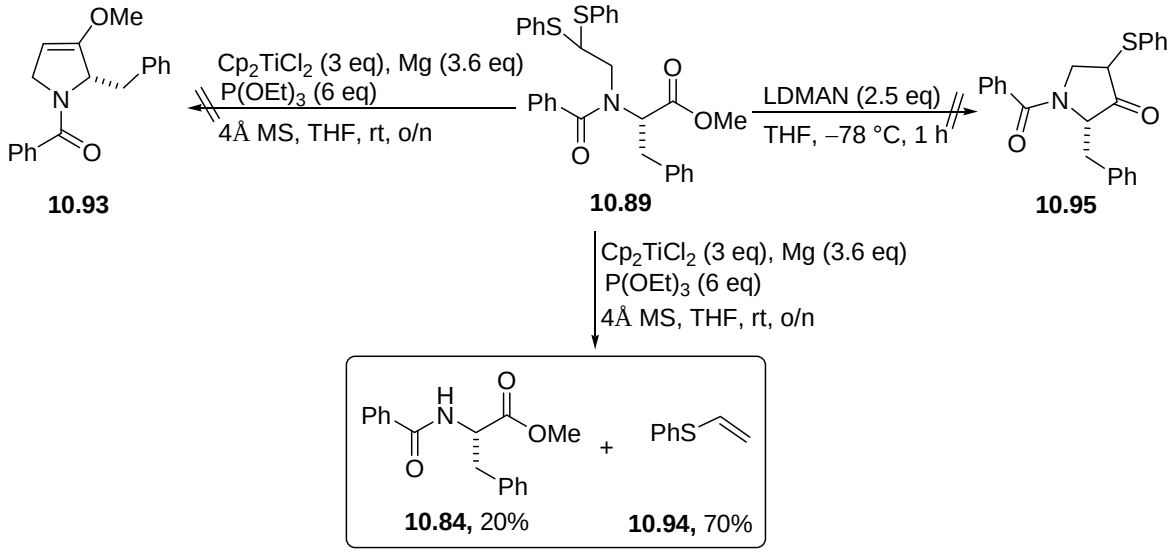
The Takeda reaction is a delicate reaction so it was necessary to test the reaction on a simple compound instead of on our precious substrate **10.89** (Scheme 10.36). Thus, thioacetal **10.91** was formed by reaction of benzaldehyde **10.90** with thiophenol in the presence of acid. The Takeda reaction was then carried out and after 3 h of reflux and an acid-base work up, the ketone **10.92** was isolated in modest yield.



10.90 **10.91**, 70% **10.92**, 40%

Scheme 10.36: Takeda reaction with thioacetal 10.91

Next the reaction was investigated on thioacetal **10.89** in order to obtain pyrroline **10.93** (Scheme 10.37). Unfortunately instead of cyclisation, fragmentation of the thioacetal chain occurred and the ester **10.84** and the sulfide **10.94** were isolated as the main products.

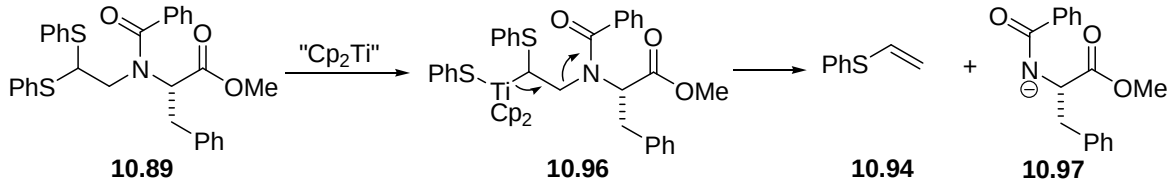


10.93 **10.89** **10.95**

10.84, 20% **10.94,** 70%

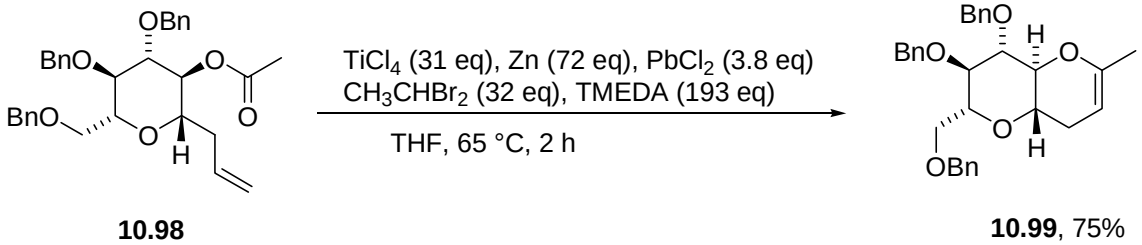
Scheme 10.37: Towards five-membered rings

This result is consistent with insertion of the low valent titanium species into the carbon sulfur bond and then rapid fragmentation to give vinyl sulfide **10.94** and stabilised anion **10.97** (Scheme 10.38). Unfortunately, groups that allow the formation of the thioacetal starting material by reducing the basicity of the nitrogen atom will stabilise anions and so favour this fragmentation. Clearly, anisomycin cannot be made in this way.



Scheme 10.38: Proposed mechanism

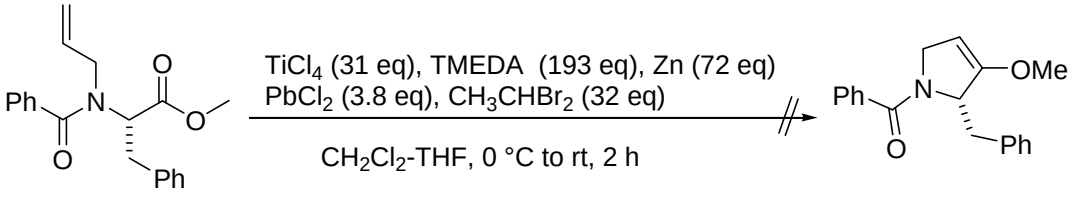
An attempt at reductive lithiation using *in situ*-generated LDMAN **10.79** did not show more promising results. A complex mixture was obtained that did not encourage us to carry on with this approach. Lyer and Rainier's[124] interesting results concerning alkene ester cyclisations under Takai conditions then attracted our attention (Scheme 10.39). They had subjected enol ether **10.98** to the *in situ*-generated titanium ethylidene reagent and were able to isolate the cyclic enol ether **10.99** as the only identifiable product in high yield.



10.98 **10.99**, 75%

Scheme 10.39: Olefinic ester cyclisation

Naturally, we applied these conditions to a similar substrate, the *N*-allyl ester **10.85** (Scheme 10.40). After 2 h of reaction at rt, we identified unreacted starting material **10.85** in the crude mixture. However, considering the huge amount of reagents required to induce the metathesis-alkylidenation reaction, it is not difficult to imagine that some product may have been masked.

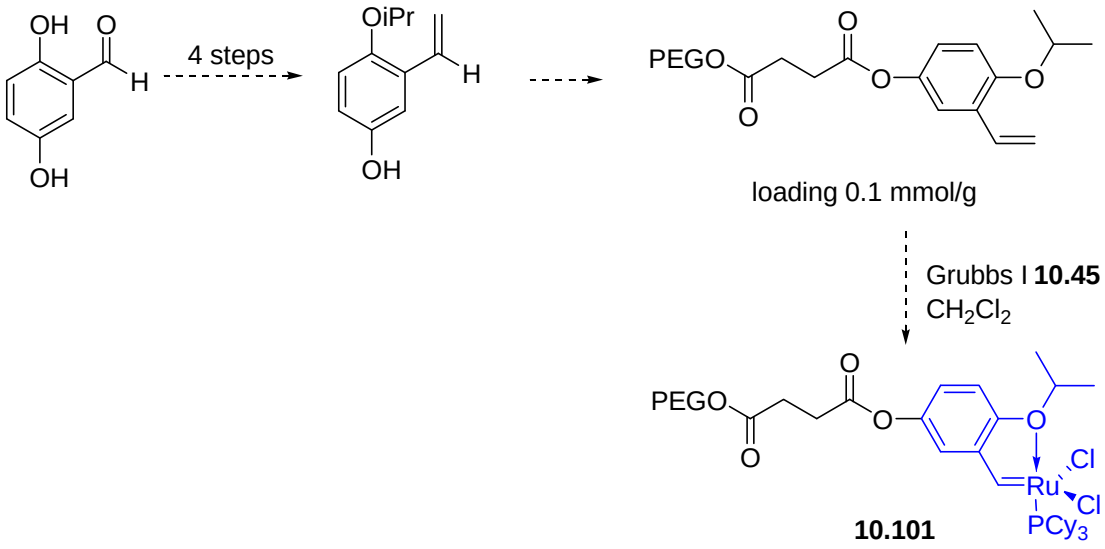


10.85 **10.100**

Scheme 10.40: Cyclisation under Takai conditions

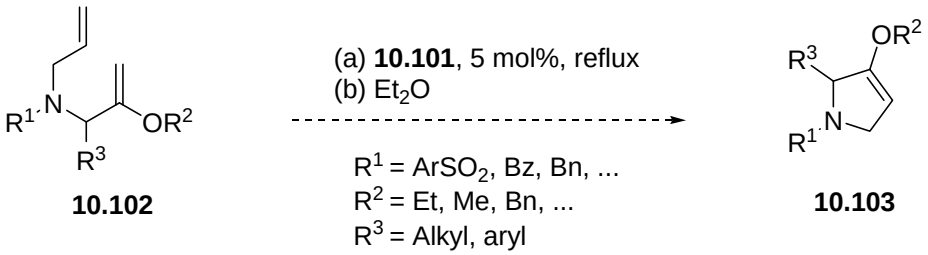
10.7. Conclusion and other potential routes

To sum up, we explored various pathways and different model strategies towards the synthesis of (+)-anisomycin F1 and its enantiomer starting from amino acids. Accessing the thioacetal substrates for Takeda reaction proved to be difficult and when this was achieved, fragmentation rather than cyclisation was observed. RCM also failed, though it may have been possible with higher catalyst loading. Indeed the use of RCM on insoluble support is an interesting and not investigated approach to access the alkaloid. PEG represents an attractive support as described by Yao and Motta.[206,207] The catalyst can be easily accessed in 6 steps from Grubbs 1st generation **10.45** (Scheme 10.41) and if successful on our substrate would be reused several times.



Scheme 10.41: Synthesis of the catalyst

The metathesis reaction would be performed on a substrate like amine **10.102** in dichloromethane and the catalyst would be regenerated by precipitation with Et_2O (Scheme 10.42). I believe the conversion into pyrrolines **10.103** would proceed after having chosen appropriate protecting groups for amine and ester.

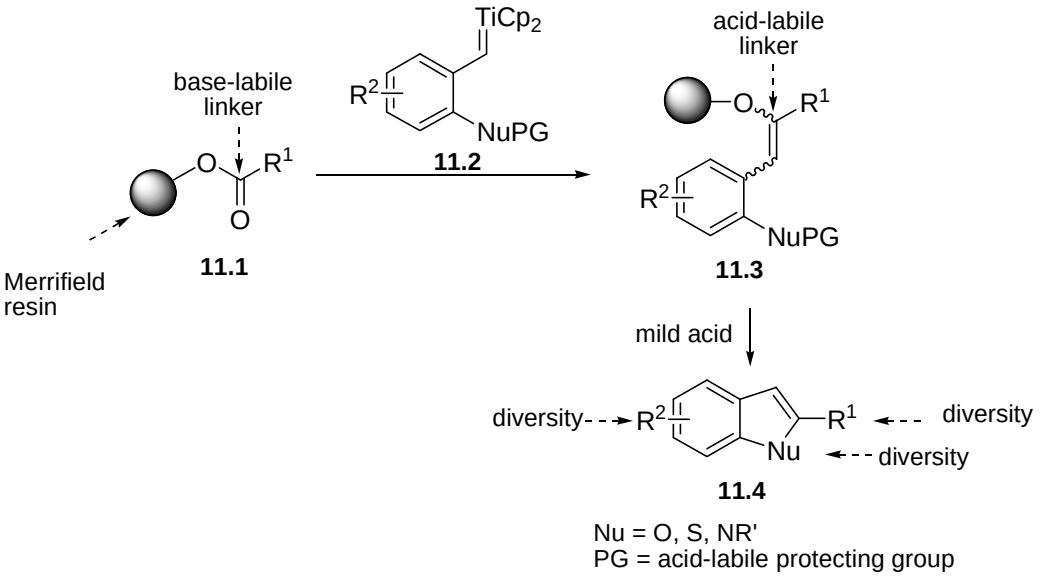


10.102 **10.103**

Scheme 10.42: RCM with PEG supported ruthenium carbene complex

11. Synthesis of Pyrrolines using the Takeda Reaction on Solid-Phase

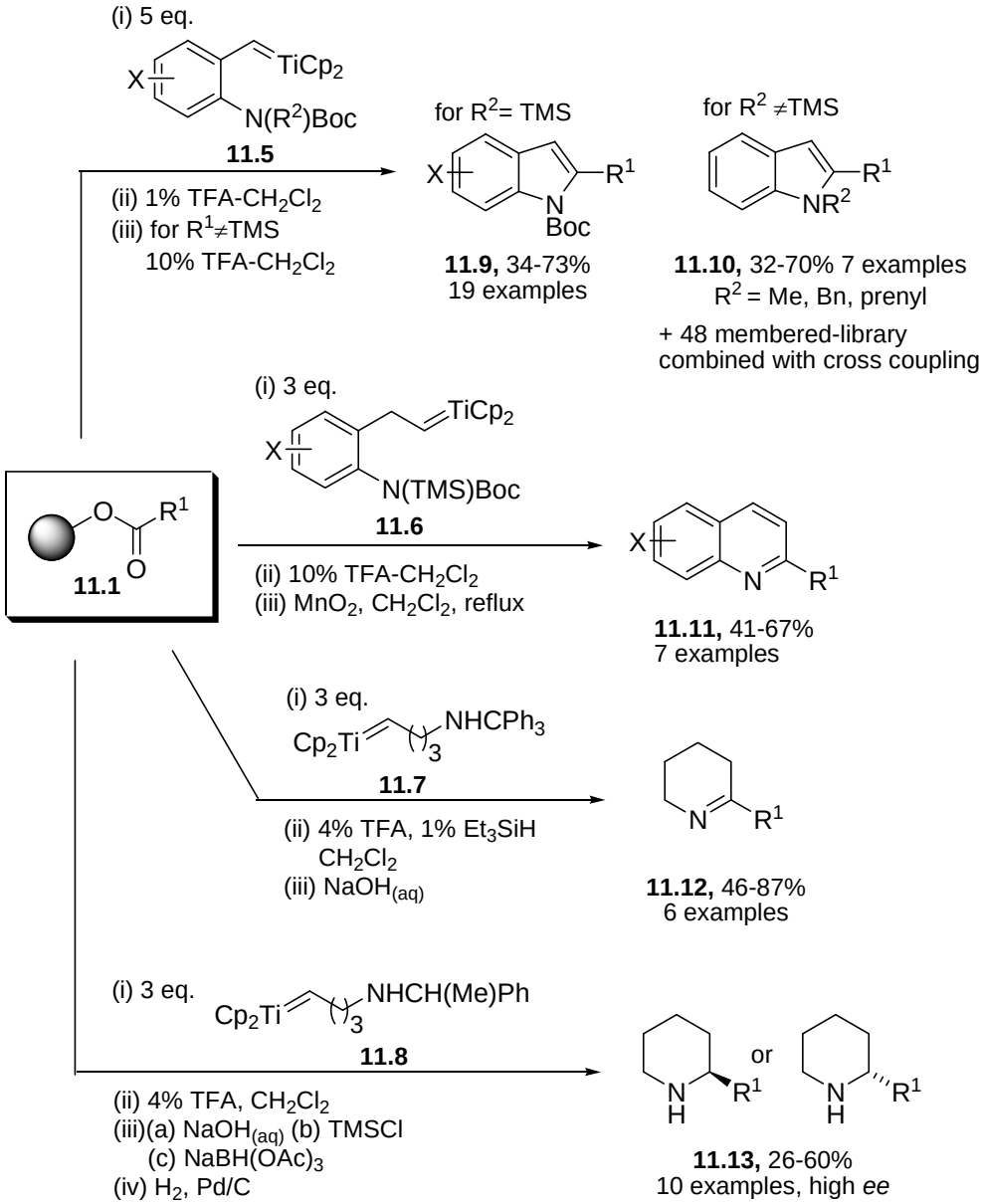
As seen in chapter 6, esters can easily be converted into enol ethers by the use of titanium carbenoids. A range of reagents could be used to alkylidenate esters but only Takeda's and Takai's procedures allow hydrogen atoms β to the titanium atom. Sequences to *N*-containing heterocycles (indoles, quinolines, cyclic imines) have been previously reported within Hartley's group using an alkylidenation reaction on solid-supported esters as a key step.[110,113,239,240] The general strategy uses titanium alkylidene reagents **11.2** containing a masked nucleophile, generated from thioacetals by Takeda's method (Scheme 11.1).



Scheme 11.1: Previous work in the group

These convert resin-bound esters **11.1**, which are fairly acid-stable, into very acid-sensitive enol ethers **11.3**. Treatment with mild acid leads to cleavage from resin and cyclisation to give bicyclic heteroaromatic compounds **11.4** with multiple sites of diversity and no trace of the site of attachment to the resin. The linker is switched to one cleaved under orthogonal conditions ensuring that any unreacted ester **11.1** remains attached to the resin and so the heterocycles **11.4** are produced in high purity. The term "chameleon catch" was introduced by Barrett and co-workers to describe this switch in the nature of a linker.[241,242] In theory, it allows greater diversity to arise from each resin-bound ester **11.1** as

other products would be available from cleaving at the ester stage (e.g. carboxylic acids, alcohols etc.). The advantage of this strategy is that it overcomes the problematic purification so characteristic of Takeda's method. Simple washing of the loaded resin with various solvents is all that is required at the end of the reaction. The Hartley team[243] have used titanium carbenoids **11.5** to generate *N*-Boc and *N*-alkyl indoles[110] **11.9** and **11.10** from resin-bound esters **11.1** (Scheme 11.2).

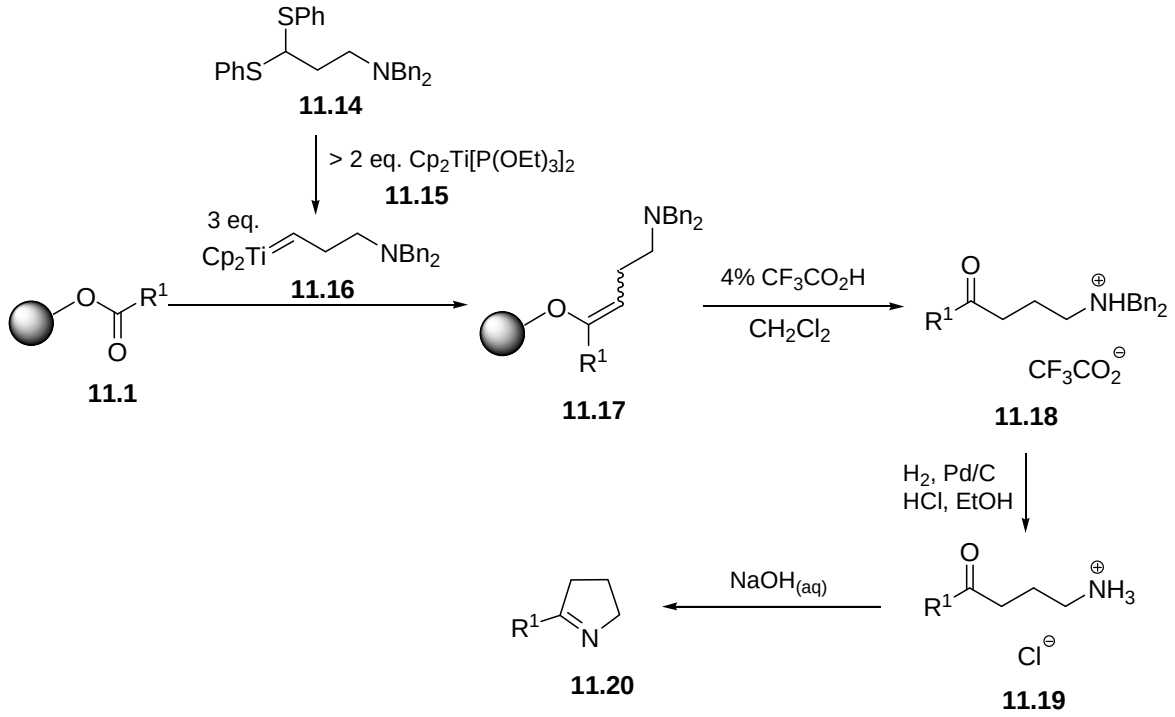


groups included in libraries:
X = OH, OMe, OCH_2O, F, NMe_2, B(pin)
R^1 = Me, ^{n}Pr, CHMeEt, $CH_2CH(Me)(CH_2)_3CHMe_2$, $(CH_2)_2NEt_2$, Ph, $(CH_2)_2Ph$, CH(Me)Ph
$CH{=}CMe_2$, *m*-$MeOC_6H_4$, *p*-$MeOC_6H_4$, 3-furyl, cyclohexen-4-yl
yields based on original loading of Merrifield resin

Scheme 11.2: Previous work in the group

This approach allows indoles to be obtained in modest to excellent yields based on resin loading. A range of functionality is tolerated within the titanium benzylidene reagents. Following this strategy, syntheses of libraries of quinolines[113] **11.11**, various cyclic imines[239,240] **11.12** and enantiomerically enriched piperidines[239] **11.13** were achieved too using alkylidene complexes **11.6** and **11.7** and enantiopure titanium alkylidenes (*S*)-**11.8** and (*R*)-**11.8**.

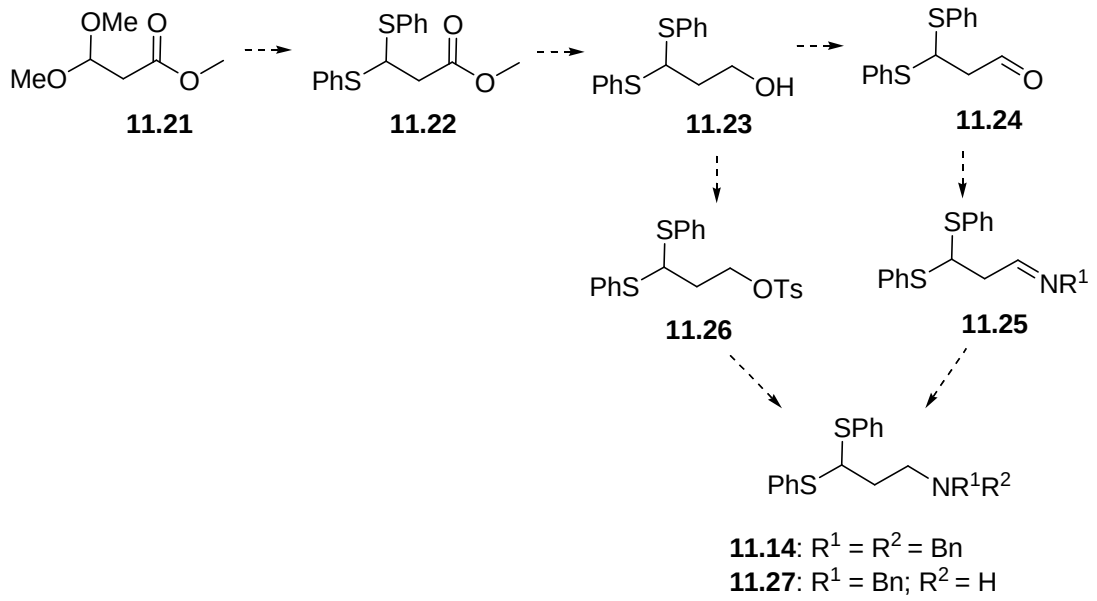
We aimed to enlarge the scope of reagents to allow the synthesis of pyrrolines (Scheme 11.3). The biological importance of pyrrolidines has already been discussed in chapter 8. Thioacetal **11.14** would be used to generate the alkylidenating reagent **11.16** under Takeda conditions. Resin-bound esters **11.1** (previously prepared in the group by reacting carboxylic acids with Merrifield resin in the presence of Cs_2CO_3 and KI[35]) would be converted into enol ether **11.17** using the titanium alkylidene reagent **11.16**. Cleavage from the resin would give trifluoroacetate salts **11.18** which would cyclise after deprotection and so allow access to a range of pyrrolines **11.20**.



Scheme 11.3: General strategy

Thioacetal **11.14** would be synthesized in a few steps from methyl 3,3-dimethoxypropanoate **11.21** (Scheme 11.4). Conversion of methyl acetal **11.21** into thioacetal **11.22** would be followed by reduction to give primary alcohol

11.23. Then, amines **11.14** or **11.27** would be isolated after tosylation of alcohol and reaction of tosylate **11.26** with the appropriate amines. An alternative route to amine **11.27** would involve oxidising alcohol **11.23** to aldehyde **11.24**, formation of imine **11.25** and reduction to give the amine **11.27**.



Scheme 11.4: Access to thioacetals

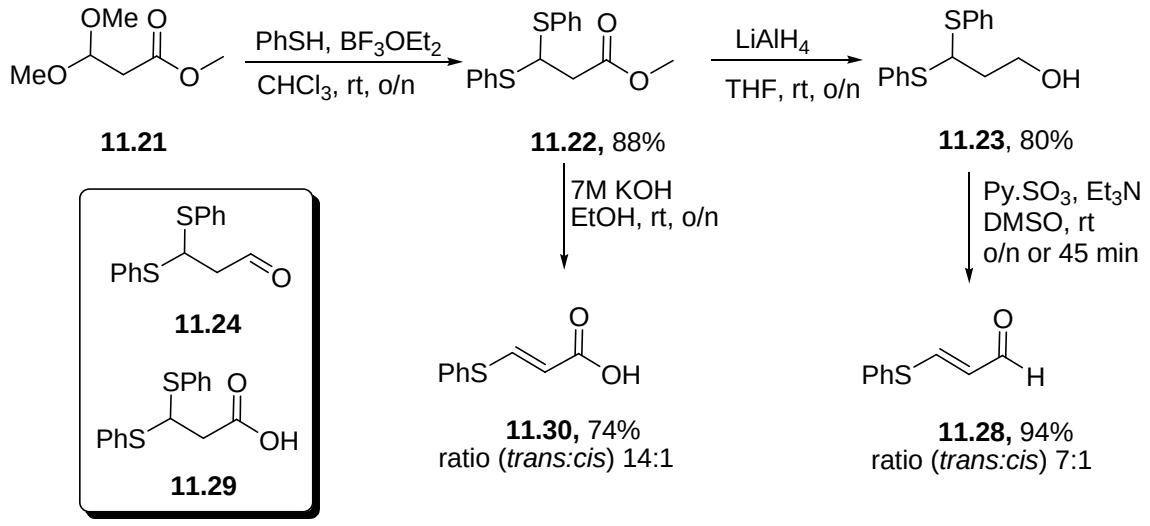
The benzyl protecting group was chosen as protection of the terminal amine because of its high stability in particular during alkylidenation. Moreover, removal was expected to proceed easily and cleanly by catalysed hydrogenolysis.

11.1. Results and discussion

Our route started with the synthesis of the thioacetal **11.22** in excellent yield from methyl 3,3-dimethoxypropanoate **11.21** by treatment with thiophenol and boron trifluoride in chloroform (Scheme 11.5).[115] Reduction following the procedure described by Rahim *et al.*,[115] gave alcohol **11.23** in good yield. Attempted formation of aldehyde **11.24** by reaction of alcohol **11.23** with the pyridine sulphur trioxide complex and triethylamine in DMSO was unsuccessful.[239,244] Indeed, the oxidation took place but was rapidly followed by an elimination step leading to the generation of α,ß-unsaturated aldehyde **11.28**. Decreasing the reaction time from 12 h to 45 min did not give any

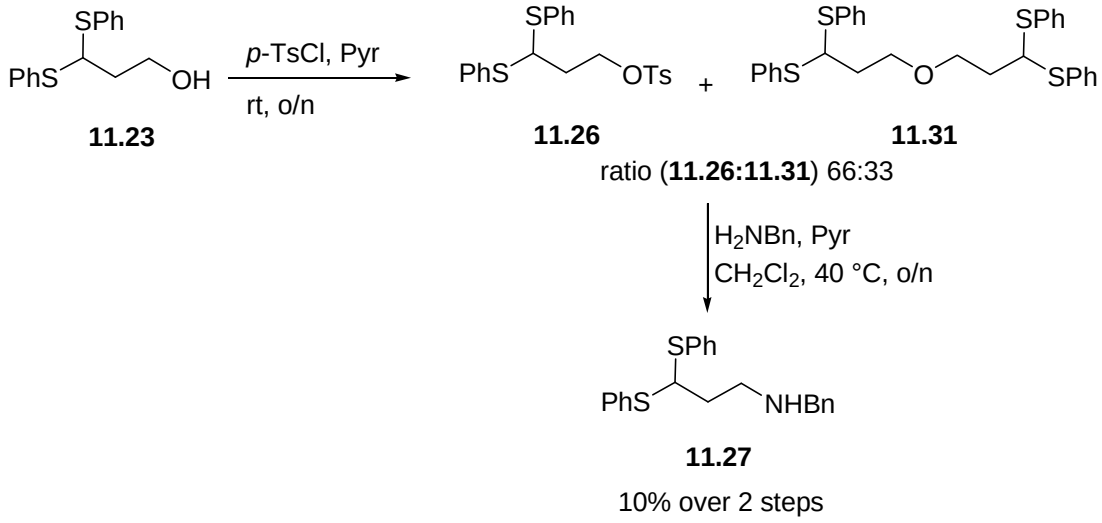
improvement while using 2.5 eq of DMSO instead of 10 eq left the starting material unreacted.

A route *via* amide formation was then considered, but treatment of ester **11.22** with base failed to give the corresponding acid **11.29** and provided the α,ß-unsaturated acid **11.30** instead.



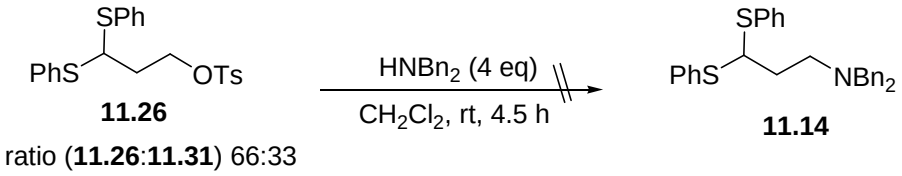
Scheme 11.5: Sequence towards the aldehyde 11.28

Introduction of the amino group by *N*-alkylation was then considered. Alcohol **11.23** was converted into the tosylate **11.26** (Scheme 11.6)[105] but the tosylation proved to be problematic and a 66:33 mixture of tosylate **11.26** and dimer **11.31** was isolated. Attempts to purify the tosylate **11.26** by chromatography were unsuccessful due to the high instability of the compound, so the crude mixture was used in the next step without further purification. Tosylate **11.26** was converted into amine **11.27**, but the yield was poor.



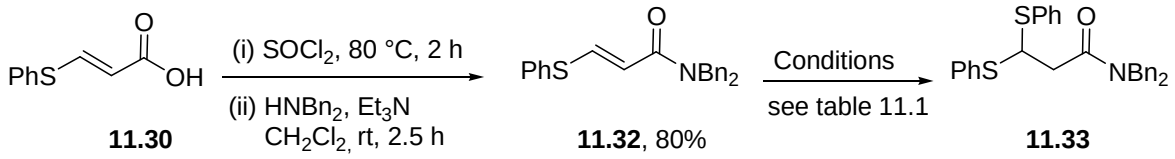
Scheme 11.6: Formation of amine 11.27

Synthesis of amine **11.14** was attempted *via* reaction of tosylate **11.26** with dibenzylamine, but after 4.5 h, the starting material was recovered and no further investigations were carried out on this step (Scheme 11.7).



Scheme 11.7: Synthesis of amine 11.14

Next, we proposed a new route to dibenzylamine **11.14** *via* formation of an amide **11.32** from acid **11.30**, then thioacetal formation followed by reduction (Scheme 11.8). The acrylic acid **11.30** is commercially available as an *E,Z* mixture and we used this mixture as the starting material in this sequence. Acid **11.30** was converted into the acid chloride by treatment with thionyl chloride.[222] The acid chloride was used directly in the reaction with dibenzylamine. Production of α,ß-unsaturated amide **11.32** proceeded in excellent yield. Then, formation of thioacetal **11.33** was undertaken. The use of standard conditions (PhSH/ $BF_3.OEt_2$) left the starting material **11.32** unchanged (Table 11.1, entry 1) while reaction with thiophenol and TBAB provided a 71:29 mixture of starting material **11.32** and desired compound **11.33** (entry 2).[224]



11.30 **11.32**, 80% **11.33**

Scheme 11.8: Towards the thioacetal 11.33

Use of acetic acid with the standard conditions at rt improved this ratio (**11.32**: **11.33**) to 37:63 but still the reaction was not complete and separation proved to be difficult (entry 3). Finally, reaction at 80 °C overnight provided the thioacetal **11.33** in 52% yield (entry 4).

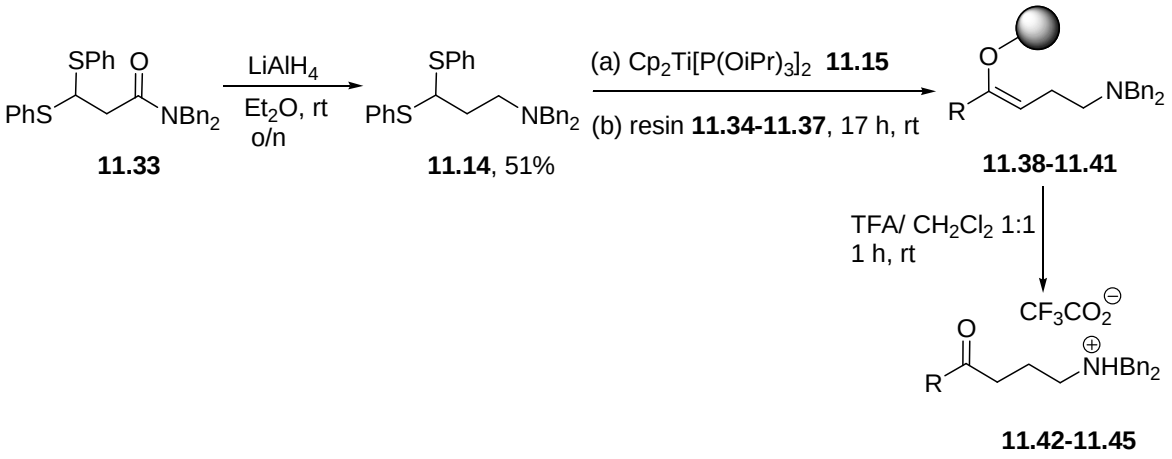
Entry	Amide **11.32**	Reagents	Ratio (**11.32**: **11.33**)
1	1 eq	$BF_3.OEt_2$ (1.1 eq), PhSH (1 eq), $CHCl_3$, rt, 2.5 h	SM **11.32**
2	1 eq	PhSH (2.3 eq), TBAB (30 mol%), 130 °C, 20 h	71:29
3	1 eq	$BF_3.OEt_2$ (1.2 eq), PhSH (2.5 eq), AcOH, PhMe, rt, 20 h	37:63
4	1 eq	$BF_3.OEt_2$ (1.2 eq), PhSH (2.5 eq), AcOH, PhMe, 80 °C, 20 h	**11.33**, 52%[a]

[a]: isolated yield

Table 11.1: Conditions for the formation of thioacetal 11.33

With thioacetal **11.33** in hand, the amine **11.14** was accessed easily by reduction with $LiAlH_4$ (Scheme 11.9). Next, the Takeda reaction was investigated. Resins were prepared by previous members of the lab by treatment of Merrifield resin with the desired carboxylic acid under Gisin's conditions.[110] Prior to the Takeda reaction on solid support, every reagent (including the resin in the MacroKan) were dried by azeotrope with toluene and left under high vacuum for 2 h to avoid the presence of water. Amine **11.14** was treated with 4 eq of pre-formed low valent titanocene complex **11.15.**[109,116,239] After 15 min, Merrifield resin-bound esters **11.34-11.37** were added and the mixtures were left at rt overnight (Table 11.2, entries 1-3). The resulting enol ethers **11.38-11.41** (Scheme 11.9) were cleaved from the resin under mild acid conditions (TFA/CH_2Cl_2 1:1) to give the ammonium salt **11.42-11.44** in excellent yields based on the original loading of the Merrifield resin. The sequence with resin-

bound ester **11.37** did not go cleanly and a complex mixture of compounds was produced (entry 4).



Scheme 11.9: Synthesis of ketones 11.42-11.45

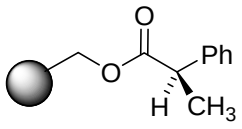
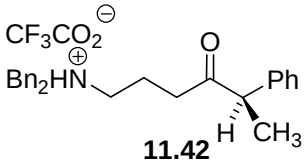
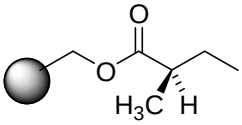
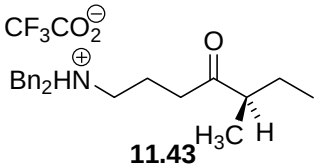
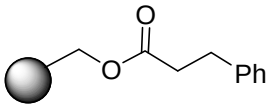
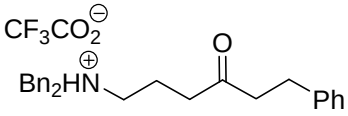
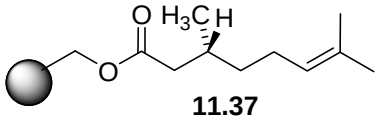
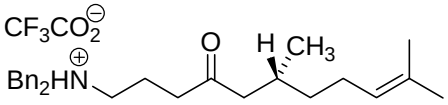
Entry	Resins	Ketones	Yield
1	 **11.34**	 **11.42**	71%
2	 **11.35**	 **11.43**	70%
3	 **11.36**	 **11.44**	76%
4	 **11.37**	 **11.45**	mixture

Table 11.2: Results of the Takeda reaction in solid-phase synthesis

^{1}H NMR analysis of salts **11.42** to **11.44** highlighted the diastereotopicity of the benzylic protons (Figure 11.1). Each proton appears as a double doublet with a geminal coupling constant (13 Hz) and a coupling to NH (5 Hz).

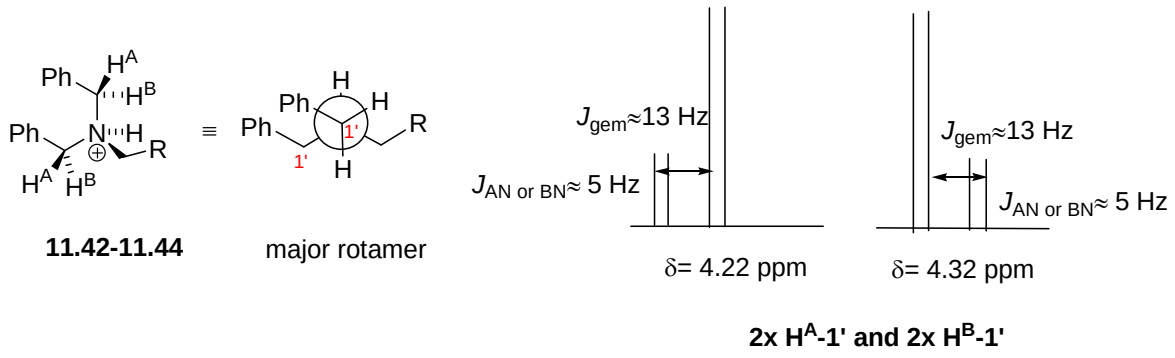
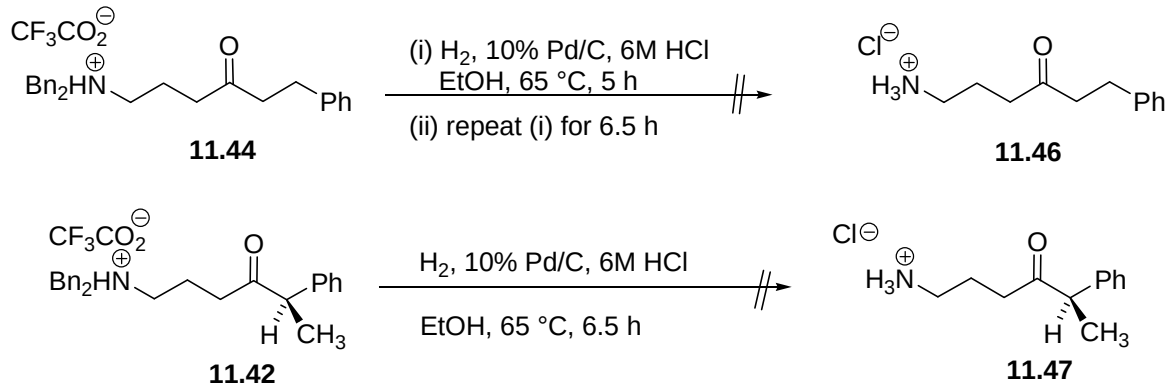


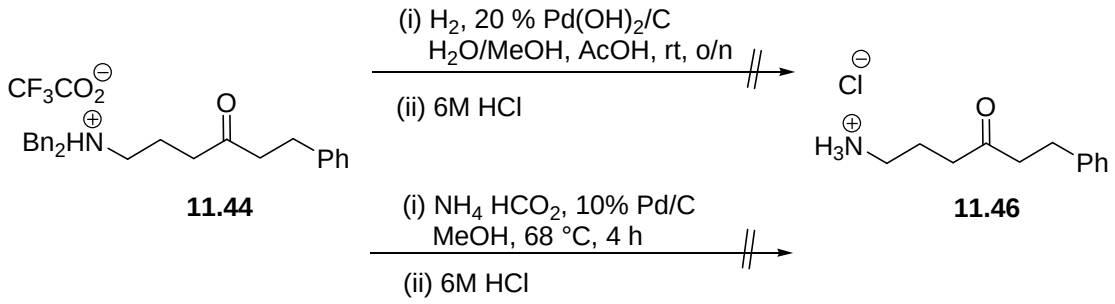
Figure 11.1: Diastereotopicity

With ketones **11.42-11.44** in hand, the next step consisted in removal of the *N*-benzyl protecting group under catalytic hydrogenolysis. Several conditions were tested (Scheme 11.10). Debenzylation of ketone **11.44** in EtOH and HCl (2 eq)[239] in the presence of Pd/C (25 mol%) under hydrogen (atm pressure) at 65 °C for 11.5 h gave the starting material as the hydrochloride salt. Similarly, hydrogenolysis carried out on substrate **11.42** under same conditions left the starting material unreacted. The *N*-benzyl protection appeared to be highly stable.



Scheme 11.10: Hydrogenation reactions

Davies and Ichihara[245] reported a quantitative debenzylation of a tyrosine derivative but when the hydrogenolysis conditions were used for ketone **11.44,** the starting material was recovered unchanged except as a different salt (Scheme 11.11). Using transfer hydrogenation as described by Purchase and Goel[246] followed by addition of $HCl_{(aq)}$ did not lead to the desired compound **11.46** and also gave the hydrochloride salt of the starting ketone **11.44**.



Scheme 11.11: Hydrogenation reactions

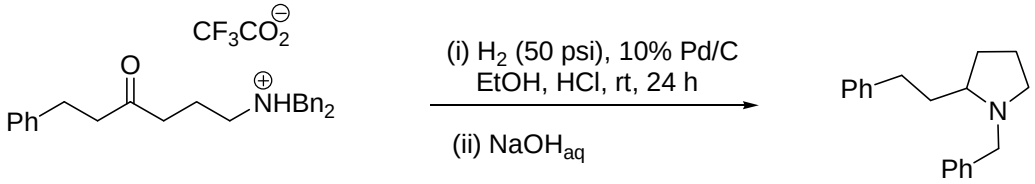
High pressure hydrogenation might solve the problem and an H-Cube® reactor was available in the department (Figure 11.2). This generates the hydrogen gas necessary for the reaction *in situ* from electrolysis of water. A key feature is the ability to pressurize up to 100 bar and heat up to 100 °C. Furthermore, a large range of catalysts packed in cartridges is available so that no filtrations are required. The substrate is passed through the cartridge under a continuous flow and reactions scales may vary from 10 mg to 10 g.

Figure 11.2: H-Cube® reactor

Unfortunately, a spare part was required for the apparatus and I did not have the opportunity to use it or to make further progress within this project due to time constraint. However, I was followed by Iain Thistlethwaite, an MSci student

in the team, who investigated the hydrogenolysis of dibenzylamines with the H-Cube® reactor.

Iain failed to get the H-Cube® reactor operational so he accessed a Cook hydrogenation facility. Reactions were run at rt for reasons of scale, but pressures of 50 psi (3.4 atm) could be achieved. The trifluoroacetate salt **11.44** was reacted in the Cook hydrogenator and then basified. Rather than the desired pyrroline, *N*-benzyl pyrrolidine **11.48** was produced.



11.44 **11.48**

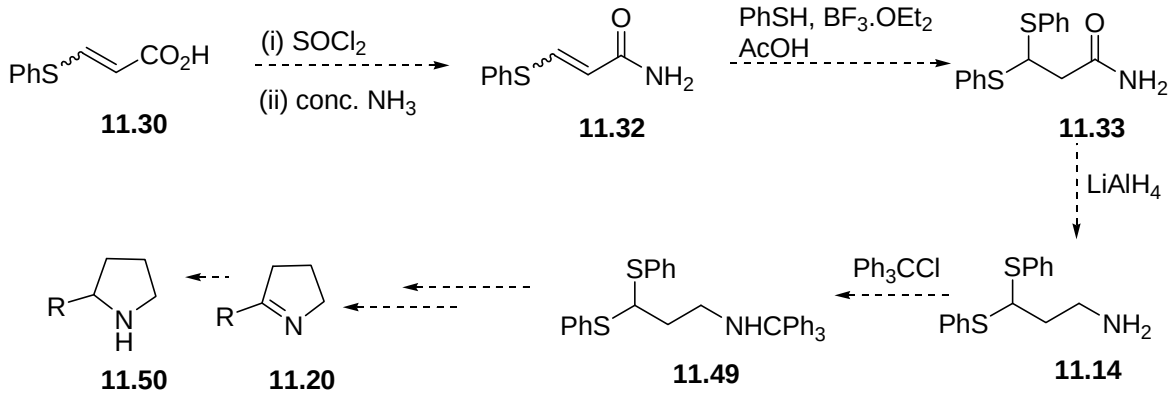
Scheme 11.12: Hydrogenolysis of salt 11.44

11.2. Conclusion and opening remarks

A successful sequence for the solid phase synthesis of amino ketones has been demonstrated. Hydrogenolysis of ammonium salts **11.42**, **11.44** were attempted at atmospheric pressure but did not provide the expected free amine. Under pressurized atmosphere, the *N*-benzyl pyrrolidine **11.48** was formed from hydrogenolysis of trifluoroacetate salt **11.44** and this has opened up the possibility of accessing a library of *N*-alkylated 2-substituted pyrrolidines. However the reaction requires optimization and better purification of the *N*-alkylated pyrrolidines product **11.48**. Other debenzylation conditions such as Pearlman's catalyst (20% $Pd(OH)_2/C$) or higher reaction temperature might be worth trying.

Another option remains unexplored (Scheme 11.13), which is changing the stable benzyl protection for trityl protection. The reaction sequence would start as previously with formation of amide **11.32** followed by reaction with thiophenol in the presence of $BF_3.OEt_2$ and glacial acetic acid to give thioacetal **11.33**. The amide **11.33** would then be reduced to the amine **11.15** and protected with trityl chloride to give thioacetal **11.49**. This synthetic route should allow access

to the desired cyclic imine products **11.20** and pyrrolidine products **11.50** as the cleavage and deprotection steps are known to be successful in the synthesis of the 6-membered cyclic imines.[239]



Scheme 11.13: Alternative routes

Part D

12. Experimental

12.1. General experimental details

All reactions were carried out under an inert atmosphere unless otherwise stated, using oven-dried glassware. Solutions were added *via* syringe unless otherwise stated.

DME was freshly distilled from sodium-benzophenone and stored with molecular sieves; diisopropylamine was freshly distilled from NaOH pellets. DMF was distilled from CaH_2 under reduced pressure and stored over 4 Å molecular sieves; benzyl alcohol was freshly distilled from KOH under reduced pressure; acetone was distilled from anhydrous $CaSO_4$ and stored over 4 Å molecular sieves. Benzyl bromide was distilled from $MgSO_4$ in the dark under reduced pressure. Pyridine was freshly distilled from KOH pellets. Diethyl ether, tetrahydrofuran, dichloromethane, toluene and acetonitrile were dried using a Puresolv© solvent drying system prior to use. Petroleum ethers refer to the fraction boiling at 40-60 °C. Brine refers to a saturated sodium chloride solution.

With the exception of Cp_2TiMe_2 produced via the method of Payack *et al.*,[85] reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. Cp_2TiCl_2 (Titanocene dichloride) was purchased from STREM Fine Chemicals or Sigma-Aldrich. Lithium was purchased from Sigma-Aldrich as a ribbon (0.38 mm thick, 23 mm wide, 99.9%). *p*-toluenesulfonic acid monohydrate was dried prior to use by azeotrope with toluene. *p*-toluenesulfonyl chloride was dried prior to use putting in solution in diethyl ether, washed with 10% NaOH until the solution became colorless and then dried (Na_2SO_4) and crystallised. Triethylamine, TMEDA were freshly distilled from CaH_2 and stored over 4 Å molecular sieves. Thiophenol was freshly distilled from $CaCl_2$ under reduced pressure. $P(OEt)_3$ was freshly distilled from CaH_2 under reduced pressure. TBAB was rescrystallised from benzene/ *n*-hexane (1:3) prior

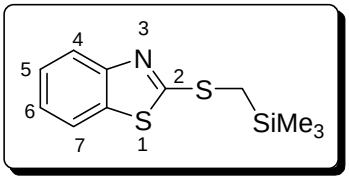
to use. The molarity of the ^{n}BuLi was checked by titration with 1,3-diphenyl-2-propanone *p*-toluenesulfonyl hydrazone prior to use.
The solid-phase syntheses were carried out using resin derived from commercially available Merrifield resin, Wang resin or *p*-toluenesulfonic acid polymer bound with the loadings described in the general procedures below and contained in IRORI Macrokan™ (porous polypropylene reactors with an internal volume 2.4 mL and a pore size of 74 μm).

Reactions were monitored by TLC performed on Merck Kieselgel 60 F_{254} plates or Alugram® SIL G/UV_{254} and visualization was performed using a UV light (365 nm) and potassium permanganate or iodine with heat. Purification by column chromatography was carried out using Fluorochem Silica gel 60 Å (mesh size 35-70 μm) as the stationary phase or Sigma-Aldrich Aluminium oxide (activated, neutral, Brockmann I, 150 mesh, 58 Å) previously deactivated with water (6% w/w) as the stationary phase. All distillations of compounds were carried out bulb to bulb in a Kugelrohr apparatus. Methylenation reactions were carried out in a CEM Focused Microwave Synthesis System, model Discover®.

Melting points were measured using Gallenkamp apparatus and are uncorrected. IR spectra were recorded using KBr powder, NaCl plates on JASCO FT/IR 4100 spectrometer or on FTIR-8400S Shimadzu infrared spectrophotometer. NMR spectra were recorded using a Bruker AV400 FT or DPX/400 spectrometer at room temperature unless otherwise stated. Chemical shifts in ^{1}H NMR are given in ppm relative to trimethylsilane. Chemical shifts in ^{13}C NMR spectra are given in ppm relative to $CDCl_3$ (77.0 ppm) or DMSO-d_6 (39.5 ppm) as internal standard. High temperature NMR experiments were carried out in DMSO-d_6 at 90 °C. All NMR *J* values are given in Hz. CH_3, CH_2, CH, and C in ^{13}C NMR spectra were assigned using DEPT. Mass spectra were recorded on a JEOL JMS-700 High Resolution Mass Spectrometer by the analytical services of the University of Glasgow. Optical rotations were determined using a Autopol® V automatic polarimeter. [α] values were measured at the concentration and temperature stated for a path length of 1 dm and a wavelength of 589 nm (Sodium D line). Elemental analyses were carried out on a Exeter Analytical Elemental Analyser EA 440.

12.2. Experimental to chapter 2

2-(Trimethylsilylmethylthio)benzothiazole 2.1



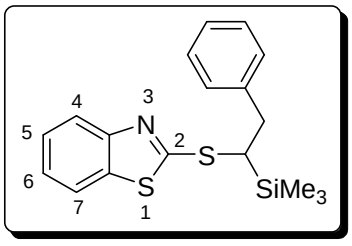
$C_{11}H_{15}NS_2Si$
MW: 253.46

Following the procedure described by Katritzky *et al.*,[13] (chloromethyl) trimethylsilane (0.5 mL, 3.6 mmol, 1.0 eq) was added to a stirred mixture of K_2CO_3 (594 mg, 4.30 mmol, 1.2 eq) and thiol **2.11** (599 mg, 3.58 mmol, 1.0 eq) in dry acetone (4 mL) at 25 °C under argon. The mixture was stirred overnight, and then filtered. The filtrate was concentrated under reduced pressure. Flash chromatography [SiO_2, petroleum ether-Et_2O (100:0-95:5)] gave the sulfide **2.1** (675 mg, 75%) as needles.

R_f [SiO_2, petroleum ether-Et_2O (90:10)] 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.00 (9H, s, $SiMe_3$), 2.41 (2H, s, SCH_2Si), 7.05 (1H, t, *J* 7.8 Hz, H5 or H6), 7.19 (1H, t, *J* 7.6 Hz, H5 or H6), 7.52 (1H, d, *J* 7.9 Hz, H4 or H7), 7.67 (1H, d, *J* 8.1 Hz, H4 or H7). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[247]

2-[2'-Phenyl-1'-(trimethylsilyl)ethylthio]benzothiazole 2.12



$C_{18}H_{21}NS_2Si$
MW: 343.58

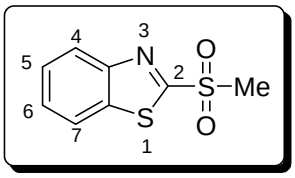
^{n}BuLi [2.3 M in hexane] (0.92 mL, 2.12 mmol, 2.1 eq) was added drop-wise to a stirring solution of freshly distilled diisopropylamine (0.31 mL, 2.21 mmol, 2.2 eq) in dry THF (1.9 mL) at −78 °C under argon. The solution was stirred for 15 min at −78 °C. Silane **2.1** (500 mg, 1.98 mmol, 2.0 eq) in dry THF (2.6 mL) was added drop-wise and the solution left to stir for 1 h at −78 °C. Benzyl bromide (0.12 mL, 1.0 mmol, 1.0 eq) was added drop-wise to the solution which

was left to stir for 4 h. Distilled water and Et_2O were added and the biphasic solution was warmed to rt. The aqueous layer was extracted with Et_2O (3 ×), the organics were washed with brine (2 ×) and then dried ($MgSO_4$). The solvent was evaporated under reduced pressure. Flash chromatography [SiO_2, petroleum ether-Et_2O (100:0-95:5)] gave the sulfide **2.12** (269 mg, 79%) as an oil.

$\mathbf{R_f}$ [SiO_2, petroleum ether (100)] 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.00 (9H, s, $SiMe_3$), 3.09 (2H, d, *J* 7.2 Hz, PhC*H*$_2$CHS), 3.57 (1H, t, *J* 7.2 Hz, PhCH$_2$C*H*S), 7.03 (1H, t, *J* 7.8 Hz, H5 or H6), 7.11-7.18 (3H, m, H5 or H6 and Ph), 7.27-7.32 (3H, m, Ph), 7.60 (1H, d, *J* 8.0 Hz, H4 or H7), 7.76 (1H, d, *J* 8.0 Hz, H4 or H7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 0.00 (CH_3), 38.33 (CH), 40.18 (CH_2), 123.05 (CH), 123.57 (CH), 126.18 (CH), 128.02 (CH), 128.58 (CH), 130.32 (CH), 131.49 (CH), 137.68 (C), 142.25 (C), 155.44 (C), 170.35 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1603 (C=C), 1250 ($SiMe_3$). **MS** (CI^+) *m/z* (%): 344 [(M+H)$^+$, 100], 168 [(BT-SH$_2$)$^+$, 55]. **HRMS** (CI^+): 344.0960. [(M+H)$^+$, $C_{18}H_{22}NS_2Si$ requires 344.0963]. All data were consistent with the literature.[13]

2-(Methylsulfonyl)benzothiazole 2.16



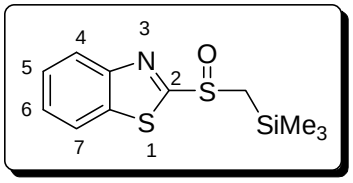
$C_8H_7NO_2S_2$
MW: 213.28

A solution of sulfide **2.1** (304 mg, 1.20 mmol, 1.0 eq) in methanol (4.6 mL) was added to a solution of oxone® (2.19 g, 3.56 mmol, 3.0 eq) in water (5 mL). The mixture was left to stir overnight and then diluted with water. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The organics were washed with water (1 ×) then brine (1 ×) and the solvent was removed under reduced pressure. The sulfone **2.16** was obtained without further purification as a yellow oil (250 mg, 98%).

$\mathbf{R_f}$ [SiO_2, petroleum ether-Et_2O (70:30)] 0.25

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.42 (3H, s, C*H*$_3$), 7.53 (2H, ddd, *J* 1.1, 7.3 and 8.1 Hz, H5 or H6), 7.58 (1H, t, *J* 7.4 Hz, H5 or H6), 8.02 (1H, br d, *J* 7.6 Hz, H4 or H7), 8.21 (1H, br d, *J* 8.3 Hz, H4 or H7). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[248]

2-(Trimethylsilylmethylsulfinyl)benzothiazole 2.29



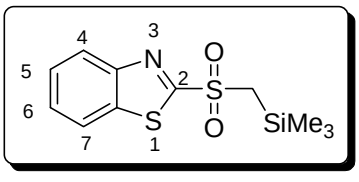
$C_{11}H_{15}NOS_2Si$
MW: 269.46

Oxone® (4.65 g, 7.56 mmol, 6.0 eq) was dissolved in water (10 mL) at 58 °C. This solution was allowed to cool to rt and then added to a mixture of sulfide **2.1** (318 mg, 1.26 mmol, 1.0 eq), acetone (1.1 mL, 15 mmol, 12 eq) and sat $NaHCO_{3(aq)}$ (10 mL) in CH_2Cl_2 (2.7 mL) at 0 °C. The mixture was left to stir at 0 °C for 0.5 h and then at 20 °C for 2 h. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-Et_2O (100:0-70:30)] gave the sulfoxide **2.29** (192 mg, 57%) as a yellow oil.

R_f [SiO_2, petroleum ether-Et_2O (70:30)] 0.34

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.00 (9H, s, $SiMe_3$), 2.53 (1H, d, *J* 13.8 SCH^AH^BSi), 2.61 (1H, d, *J* 13.7 Hz, SCH^AH^BSi), 7.21 (1H, ddd, *J* 1.2, 7.2 and 8.1 Hz, H5 or H6), 7.28 (1H, ddd, *J* 1.2, 7.2 and 8.2 Hz, H5 or H6), 7.72 (1H, ddd, *J* 0.6, 1.3 and 8.1 Hz, H4 or H7), 7.79 (1H, ddd, *J* 0.6, 1.3 and 8.1 Hz, H4 or H7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 0.00 (CH_3), 47.46 (CH_2), 123.06 (CH), 124.57 (CH), 126.90 (CH), 127.58 (CH), 136.88 (C), 154.40 (C), 181.43 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1557 (C=C), 1250 ($SiMe_3$), 1042 (S=O). **MS** (CI^+) *m/z* (%): 270 [$(M+H)^+$, 100]. **HRMS** (CI^+): 270.0438. [$(M+H)^+$, $C_{11}H_{16}NOS_2Si$ requires 270.0443].

2-(Trimethylsilylmethylsulfonyl)benzothiazole 2.15



$C_{11}H_{15}NO_2S_2Si$
MW: 285.46

Procedure A: The reaction was carried out accroding to the procedure described for compound **2.29** using oxone® (2.03 g, 3.30 mmol, 6.0 eq), water (4.4 mL), sulfoxide **2.29** (148 mg, 0.55 mmol, 1.0 eq), acetone (0.48 mL, 6.6 mmol, 12.0

eq) and sat $NaHCO_{3(aq)}$ (4.4 mL) in CH_2Cl_2 (1.2 mL).Flash chromatography [SiO_2, hexane-EtOAc (100:0-90:10)] gave the sulfone **2.15** (75 mg, 48%) as an oil.

R_f [SiO_2, hexane-EtOAc (70:30)] 0.68

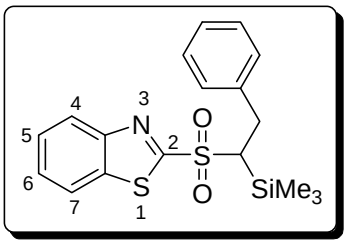
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.29 (9H, s, $SiMe_3$), 3.14 (2H, s, CH_2SiMe_3), 7.49 (1H, t, *J* 7.4 Hz, H5 or H6), 7.54 (1H, t, *J* 7.7 Hz, H5 or H6), 7.92 (1H, d, *J* 7.9 Hz, H4 or H7), 8.10 (1H, d, *J* 8.2 Hz, H4 or H7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 0.00 (CH_3), 46.28 (CH_2), 122.91 (CH), 125.69 (CH), 128.04 (CH), 128.28 (CH), 137.04 (C), 152.99 (C), 169.68 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1554 (C=C), 1320 and 1150 (SO_2 asymm and sym stretching), 1253 ($SiMe_3$). **MS** (CI^+) *m/z* (%): 286 [$(M+H)^+$, 88], 214 [$(BT\text{-}SO_2Me+H)^+$, 90], 136 [$(BT+H)^+$, 100]. **HRMS** (CI^+): 286.0389 [$(M+H)^+$, $C_{11}H_{16}NO_2S_2Si$ requires 286.0392]. **Microanalysis**: Theory C: 46.32% H: 5.26% N: 4.91%; Results C: 46.31% H: 5.24% N: 4.86%.

Procedure B: Oxone® (18.07 g, 29.39 mmol, 3.0 eq) was dissolved in water (39 mL) at 58 °C. After cooling, this solution was added to a stirred mixture of sulfide **2.1** (2.47 g, 9.74 mmol, 1.0 eq), acetone (4.3 mL, 59 mmol, 6.0 eq) and sat $NaHCO_{3(aq)}$ (77 mL) in CH_2Cl_2 (21 mL) at 0 °C. The mixture was left to stir at 0 °C for 0.5 h and then at 20 °C for 1 h. After 1 h, acetone (4.3 mL) was added. The solution was cooled down to 0 °C and a solution of oxone® (18.07 g, 29.39 mmol, 3.0 eq) in water (39 mL) was added. The reaction was left to stir at 0 °C for 0.5 h and then 1 h at 20 °C. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organics were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The crude was submitted to the same process again. The sulfone **2.15** was obtained without further purification as yellow needles (2.41 g, 86%).

mp: 80-82 °C

Data as above.

2-[2'-Phenyl-1'-(trimethylsilyl)ethylsulfonyl]benzothiazole 2.13



$C_{18}H_{21}NO_2S_2Si$
MW: 375.58

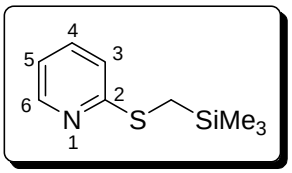
The reaction was carried out according to the procedure described for compound **2.29** using oxone® (1.63 g, 2.65 mmol, 6.2 eq), water (3.5 mL), sulfide **2.12** (146 mg, 0.43 mmol, 1.0 eq), acetone (0.4 mL, 5.3 mmol, 12 eq) and sat $NaHCO_{3(aq)}$ (3.5 mL) in CH_2Cl_2 (0.95 mL). Flash chromatography [SiO_2, petroleum ether-Et_2O (100:0-80:20)] gave a 44:56 mixture of the sulfoxide and the sulfone **2.13** (58 mg) as an oil. The crude was submitted to a second oxidation using oxone® (295 mg, 0.48 mmol, 3.0 eq), water (0.64 mL), the crude mixture from the previous crude mixture (58 mg, 0.16 mmol, 1.0 eq), acetone (0.1 mL, 1.0 mmol, 6.0 eq) and sat $NaHCO_{3(aq)}$ (1.3 mL) in CH_2Cl_2 (0.34 mL) at 0 °C. The mixture was left to stir at 0 °C for 0.5 h and then at 20 °C for 1 h. After 1 h, acetone (0.1 mL, 1.0 mmol, 6.0 eq) was added. The solution was cooled down to 0 °C and a solution of oxone® (295 mg, 0.48 mmol, 3.0 eq) in water (0.64 mL) was added. The reaction was left to stir at 0 °C for 0.5 h and then 1 h at 20 °C. The organic layer was separated and the aqueous layer extracted with CH_2Cl_2 (3 ×). The combined organics were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The sulfone **2.13** was obtained without further purification as an oil (38 mg, 24%).

R_f [SiO_2, petroleum ether-Et_2O (70:30)] 0.58

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.28 (9H, s, $SiMe_3$), 3.06 (1H, dd, *J* 5.9 and 15.6 Hz, PhC*H*^{A}H^B), 3.14 (1H, dd, *J* 7.2 and 15.4 Hz, PhCH^A*H*^{B}), 3.78 (1H, t, *J* 6.6 Hz, $PhCH_2$C*H*S), 6.74-6.87 (5H, m, Ph), 7.42 (1H, ddd, *J* 1.5, 7.3 and 7.8 Hz, H5 or H6), 7.47 (1H, ddd, *J* 1.5, 7.2 and 7.7 Hz, H5 or H6), 7.79 (1H, ddd, *J* 0.7, 1.5 and 8.3 Hz, H4 or H7), 7.97 (1H, ddd, *J* 0.8, 1.5 and 8.3 Hz, H4 or H7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 0.00 (CH_3), 33.06 (CH_2), 56.85 (CH), 122.83 (CH), 125.91 (CH), 127.12 (CH), 127.98 (CH), 128.29 (CH), 128.85 (CH), 129.15 (CH), 137.65 (C), 138.41 (C), 153.31 (C), 168.73 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1603 (C=C), 1314 and 1143 (SO_2 asymm and sym stretching), 1253 ($SiMe_3$). **MS** (Cl^+) *m/z* (%):

376 [$(M+H)^+$, 100], 304 [$(M+H)^+ - H_2C{=}SiMe_2$, 67], 177 [$(M+H)^+$ – BT-SO_2H, 21], 136 [$(BT+H)^+$, 95], 89 (90). **HRMS** (CI^+): 376.0862 [$(M+H)^+$, $C_{18}H_{22}NO_2S_2Si$ requires 376.0861].

2-[(Trimethylsilyl)methylthio]pyridine 2.31



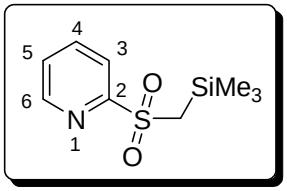
$C_9H_{15}NSSi$
MW: 197.37

Following the procedure described by Kohra *et al.*,[22] (chloromethyl) trimethylsilane (2.5 mL, 18 mmol, 1.0 eq) was added to a stirred mixture of K_2CO_3 (2.99 g, 21.6 mmol, 1.2 eq), KI (1.50 g, 9.03 mmol, 0.5 eq) and thiol **2.30** (2.00 g, 18.0 mmol, 1 eq) in absolute ethanol (20.6 mL) under argon. The mixture was stirred at reflux for 2.3 h. The mixture was then cooled down and filtered. The filtrate was concentrated under reduced pressure. Addition of ethyl acetate led to the formation of a precipitate. After filtration, the filtrate was concentrated under reduced pressure and gave the sulfide **2.31** as a yellow oil (3.03 g, 85%).

R_f [SiO_2, petroleum ether – ethyl acetate (97:3)] 0.27

^{1}H NMR (400 MHz, Methanol-d_4) δ_H: 0.14 (9H, s, $SiMe_3$), 2.32 (2H, s, SCH_2Si), 7.04 (1H, ddd, *J* 1.0, 4.8 and 7.3 Hz, H5), 7.30 (1H, td, *J* 1.1 and 8.1 Hz, H3), 7.60 (1H, ddd, *J* 1.8, 7.3 and 8.1 Hz, H4), 8.32 (1H, ddd, *J* 1.0, 1.8 and 5.0 Hz, H6). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[22]

2-[(Trimethylsilyl)methylsulfonyl]pyridine 2.32



$C_9H_{15}NO_2SSi$
MW: 229.37

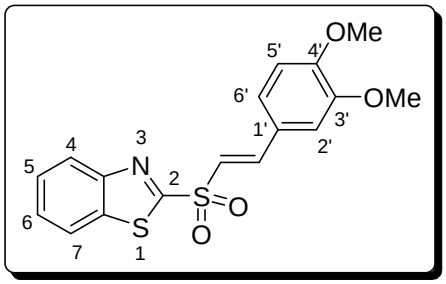
The reaction was carried out according to procedure B using oxone® (17.50 g, 28.47 mmol, 3.0 eq), in water (38 mL), sulfide **2.31** (1.87 g, 9.47 mmol, 1.0 eq),

acetone (4.2 mL, 57 mmol, 6.0 eq) and sat $NaHCO_{3(aq)}$ (75 mL) in CH_2Cl_2 (20 mL). The sulfone **2.32** was obtained (1.82 g, 84%) as crystals.

R_f [SiO_2, petroleum ether-Et_2O (50:50)] 0.59

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.05 (9H, s, $SiMe_3$), 2.79 (2H, s, CH_2Si), 7.26 (1H, ddd, *J* 1.2, 4.7 and 7.6 Hz, H5), 7.68 (1H, td, *J* 1.3 and 7.7 Hz, H3), 7.80 (1H, ddd, *J* 1.0, 7.6 and 7.7 Hz, H4), 8.46 (1H, ddd, *J* 1.0, 1.3 and 4.9 Hz, H6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 0.26 (CH_3), 43.44 (CH_2), 121.06 (CH), 127.50 (CH), 138.75 (CH), 150.50 (CH), 160.67(C). **IR** ν_{max} (ATR)/cm^{-1}: 1578 (C=C), 1300 and 1125 (SO_2 asymm and sym stretching), 1242 ($SiMe_3$). **MS** (CI^+) *m/z* (%): 230 [$(M+H)^+$, 100] . **HRMS** (CI^+): 230.0673 [$(M+H)^+$, $C_9H_{16}NO_2SSi$ requires 230.0671]. **Microanalysis**: Theory C: 47.16% H: 6.55%; N: 6.11% Results C: 47.05% H: 6.49% N: 6.10%.

(*E*)-2-(3',4'-Dimethoxystyrylsulfonyl)benzothiazole 2.34



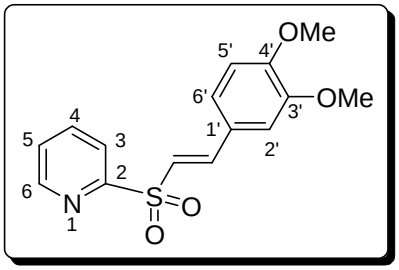
$C_{17}H_{15}NO_4S_2$
MW: 361.44

^{n}BuLi [2.12 M in hexane] (0.28 mL, 0.59 mmol, 1.1 eq) was added drop-wise to a stirring solution of freshly distilled diisopropylamine (0.1 mL, 0.7 mmol, 1.3 eq) in dry THF (1.4 mL) at −78 °C under argon. The solution was left to stir for 15 min at −78 °C. The resulting LDA was added drop-wise to a stirring solution of sulfone **2.15** (150 mg, 0.53 mmol, 1.0 eq) and veratraldehyde **2.33** (138 mg, 0.83 mmol, 1.6 eq) in dry THF (1.4 mL). The solution was warmed to rt and allowed to stir for 2 h. Distilled water and Et_2O were added and the organic layer was washed with sat $NH_4Cl_{(aq)}$ (1 ×), sat $NaHCO_{3(aq)}$ (1 ×), water (1 ×), brine (1 ×) then dried ($MgSO_4$). The solvent was evaporated under reduced pressure. Flash chromatography [SiO_2, petroleum ether-Et_2O (98:2-70:30)] gave the vinyl sulfone **2.34** (121 mg, 63%) as a yellow solid.

R_f [SiO_2, petroleum ether-Et_2O (30:70)] 0.44

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.76 (3H, s, OC*H*$_3$), 3.79 (3H, s, OC*H*$_3$), 6.76 (1H, d, *J* 8.2 Hz, H5'), 6.95 (1H, s, H2'), 6.96 (1H, d, *J* 15.0 Hz, BT-SO_2C*H*=), 7.04 (1H, d, *J* 8.2 Hz, H6'), 7.41 (1H, t, *J* 8.2 Hz, H5 or H6), 7.45 (1H, t, *J* 8.0 Hz, H5 or H6), 7.70 (1H, d, *J* 15.2 Hz, ArC*H*=), 7.83 (1H, d, *J* 7.6 Hz, H4 or H7), 8.02 (1H, d, *J* 7.8 Hz, H4 or H7). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 54.92 (CH_3), 55.02 (CH_3), 109.0 (CH), 109.97 (CH), 120.04 (CH), 121.25 (CH), 123.57 (CH), 123.72 (C), 124.20 (CH), 126.51 (CH), 126.77 (CH), 135.78 (C), 146.06 (CH), 148.25 (C), 151.46 (C), 151.77 (C), 166.43 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1604 (C=C), 1595 (C=C), 1328 and 1138 (SO_2 asymm and sym stretching), 1241 (C-O). **MS** (EI) *m/z* (%): 361 ($M^{+\cdot}$, 35), 296 (90), 162 [$(MeO)_2C_6H_3CCH^{+\cdot}$, 100]. **HRMS** (EI): 361.0439 (M^+, $C_{17}H_{15}NO_4S_2$ requires 361.0443].

(*E*)-2-(3',4'-Dimethoxystyrylsulfonyl)pyridine 2.35



$C_{15}H_{15}NO_4S$
MW: 305.35

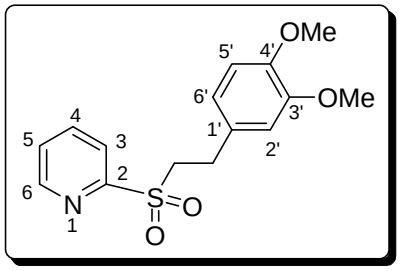
In a same way, the reaction was carried out using ^{n}BuLi [2.11 M in hexane] (2.3 mL, 4.8 mmol, 1.1 eq), diisopropylamine (0.7 mL, 5.2 mmol, 1.2 eq) in dry THF (11.6 mL), sulfone **2.32** (1.00 g, 4.37 mmol, 1.0 eq) and veratraldehyde **2.33** (1.09 g, 6.56 mmol, 1.5 eq) in dry THF (11.3 mL). Flash chromatography [SiO_2, CH_2Cl_2–MeOH (100:0 – 90:10)] gave the vinyl sulfone **2.35** (772 mg, 58%) as a yellow solid.

R_f [SiO_2, CH_2Cl_2–MeOH (95:5)] 0.61

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.90 (3H, s, OC*H*$_3$), 3.92 (3H, s, OC*H*$_3$), 6.58 (1H, d, *J* 8.1 Hz , H5'), 6.88 (1H, d, *J* 15.4 Hz, PyrSO_2C*H*=), 7.02 (1H, s, H2'), 7.13 (1H, d, *J* 8.1 Hz, H6'), 7.60-7.64 (1H, m, H5), 7.72 (1H, d, *J* 15.4 Hz, ArC*H*=), 7.96 (1H, t, *J* 7.5 Hz, H4), 8.14 (1H, d, *J* 7.6 Hz, H3), 8.76-8.79 (1H, m, H6) . **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 55.96 (CH_3), 110.09 (CH), 111.06 (CH), 121.77 (CH), 121.85 (CH), 123.83 (CH), 125.29 (C), 126.98 (CH), 138.17 (CH), 145.19 (CH), 149.34 (C), 150.37 (CH), 152.06 (C), 158.89 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1597 (C=C),

1303 and 1141 (SO_2 asymm and sym stretching), 1269 (C-O ether). **MS** (EI) *m/z* (%): 305 ($M^{+\cdot}$, 10), 240 (94), 179 (74), 162 [$(MeO)_2C_6H_3C{\equiv}CH^{+\cdot}$, 100], 147 (37). **HRMS** (EI): 305.0723 (M^+, $C_{15}H_{15}NO_4S$ requires 305.0722).

(*E*)-2-(3',4'-Dimethoxyphenylethylsulfonyl)pyridine 2.36



$C_{15}H_{17}NO_4S$
MW: 307.36

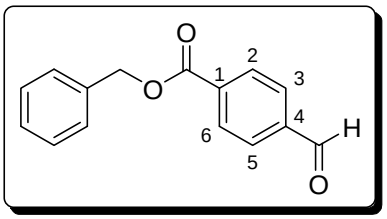
$NaBH_4$ (40.0 mg, 1.05 mmol, 6.0 eq) was added to a solution of alkene **2.35** (53.5 mg, 0.18 mmol, 1.0 eq) in THF (0.9 mL). The reaction was stirred for 4 h at 80 °C. Then water was added and the aqueous layer was extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, CH_2Cl_2-MeOH (100:0–95:5)] gave the alkyl sulfone **2.36** (27 mg, 49%) as an oil.

R_f [SiO_2, CH_2Cl_2-MeOH (95:5)] 0.63

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.05 (2H, t, *J* 8.1 Hz, C*H*$_2$), 3.68 (2H, t, *J* 8.2 Hz, C*H*$_2$), 3.84 (6H, s, OC*H*$_3$), 6.66 (1H, s, H2'), 6.69 (1H, d, *J* 8.3 Hz, H6'), 6.74 (1H, d, *J* 8.1 Hz, H5'), 7.53-7.79 (1H, m, H5), 7.93-8.00 (1H, m, H3), 8.06-8.12 (1H, m, H4), 8.73-8.74 (1H, m, H6). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 26.02 (CH_2), 38.07 (CH_3), 51.39 (CH_2), 53.91 (CH_3), 109.40 (CH), 109.61 (CH), 118.54 (CH), 120.24 (CH), 125.40 (CH), 127.98 (C), 136.18 (CH), 145.96 (C), 147.06 (C), 148.15 (CH), 155.34 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1593 (C=C), 1313 and 1165 (SO_2 asymm and sym stretching), 1265 (C-O ether). **MS** (EI) *m/z* (%): 307 ($M^{+\cdot}$, 7), 164 [$(MeO)_2C_6H_3CHCH_2^{+\cdot}$, 100], 149 (42). **HRMS** (EI): 307.0880 (M^+, $C_{15}H_{17}NO_4S$ requires 307.0878).

12.3. Experimental to chapter 5

Benzyl 4-formylbenzoate 5.13



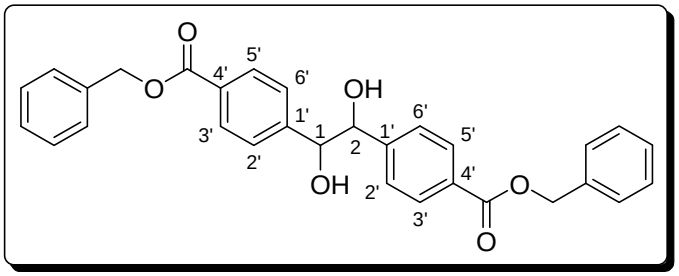
$C_{15}H_{12}O_3$
MW: 240.25

Following a procedure described by Gennari *et al.*[249], a solution of 4-formyl benzoic acid **5.12** (8.00 g, 53.3 mmol, 1.0 eq), benzyl alcohol **5.11** (6.1 mL, 59 mmol, 1.1 eq) and DMAP (651 mg, 5.32 mmol, 0.1 eq) in dry CH_2Cl_2 (120 mL) under argon was treated with a solution of DCC (12.10 g, 58.64 mmol, 1.1 eq) in dry CH_2Cl_2 (80 mL). The mixture was stirred at 25 °C for 45 min then cooled down to 0 °C. DCU was removed by filtration and the precipitate washed with cold CH_2Cl_2 (2 ×). The filtrate was washed with H_2O (2 ×), 10% AcOH (250 mL) and H_2O (1 ×). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, hexane – CH_2Cl_2 (80:20 – 40:60)] gave the aldehyde **5.13** (9.45 g, 74%) as a solid.

R_f [SiO_2, hexane – CH_2Cl_2 (20:80)] 0.47

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.26 (2H, s, C*H*$_2$Ph), 7.25 – 7.40 (5H, m, Ar-H), 7.85 (2H, d, *J* 8.4 Hz, H2 and H6), 8.18 (2H, d, *J* 8.4 Hz, H3 and H5), 10.01 (1H, s, CHO). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 67.36 (CH_2), 128.38 (CH), 128.54 (CH), 128.72 (CH), 129.55 (CH), 130.34 (CH), 135.12 (C), 135.55 (C), 139.23 (C), 165.44 (C), 191.69 (CH). NMR spectral data in agreement with those previously reported in the literature.[249]

(1*RS*, 2*RS*)- and (1*RS*, 2*SR*)-1,2-Bis[4'-(benzyloxycarbonyl)phenyl]ethanol-1,2-diols 5.14:5.15



$C_{30}H_{26}O_6$
MW: 482.52

Procedure A: A 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.3 mmol, 2.2 eq) was added to a stirred suspension of titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (10 mL) under argon at rt. After 0.5 h, the mixture was cooled to −78 °C and the aldehyde **5.13** (360 mg, 1.50 mmol, 1.0 eq) was added. The mixture was stirred for 5 min and then allowed to warm to rt over 1.5 h. The reaction was quenched by addition of 1 M $HCl_{(aq)}$ (20 mL) and the mixture was stirred for 0.5 h. The organic layer was separated and washed with brine (3 ×). The aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, hexane–ethyl acetate (80:20 – 50:50)] gave 1,2-diols **5.14** and **5.15** (160 mg, 44%) as an inseparable 80:20 mixture of the 1,2-*syn* and 1,2-*anti*–isomers as a yellow oil.

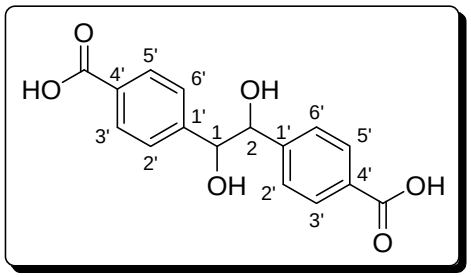
R_f [SiO_2, hexane–ethyl acetate (50:50)] 0.45

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.67 (2H^{syn}, s, C*H*OH), 4.93 (2H^{anti}, s, C*H*OH), 5.28 (4H^{syn}, s, CH_2Ph), 5.29 (4H^{anti}, s, CH_2Ph), 7.09 – 8.11 (18H^{syn} and 18H^{anti}, m, Ar-H). **^{13}C NMR** of major isomer (100 MHz, $CDCl_3$) δ_C: 66.84 (CH_2), 78.71 (CH), 127.03 (CH), 128.29 (CH), 128.34 (CH), 128.65 (CH), 129.62 (CH), 129.81 (C), 135.90 (C), 144.67 (C), 166.19 (C). **IR** ν_{max} (KBr)/cm^{-1}: 3465 (OH), 2956 (CH sp^3), 1690 (C=O ester), 1495 (Ph). **MS** (FAB) *m/z* (%): 483 [(M+H)$^+$, 3], 148 (24), 92 ($C_6H_5CH_2^+$, 100). **HRMS** (FAB): 483.1813 [(M+H)$^+$, $C_{30}H_{27}O_6$ requires 483.1808].

Procedure B: Schlenk tube was charged with magnesium turnings (154 mg, 6.43 mmol, 6.4 eq). After vigorous stirring for 1 h under argon to activate the magnesium, a solution of 0.1 M SmI_2 in THF (4.0 mL, 0.40 mmol, 0.4 eq), dichlorodimethylsilane (0.05 mL, 0.4 mmol, 0.4 eq) and tetraglyme (0.09 mL, 0.4 mmol, 0.4 eq) were added successively to the magnesium. A mixture of the aldehyde **5.13** (240 mg, 1.0 mmol, 1.0 eq), dichlorodimethylsilane (0.1 mL, 0.8 mmol, 0.82 eq) and dry THF (4 mL) was then added drop-wise via a syringe pump at such a rate as to retain the blue colour. After the addition, the mixture was filtered, quenched with Bu_4NF (10 mL) and washed with brine (10 mL). The mixture was evaporated under reduced pressure and the product was extracted by continuous extraction with Et_2O (200 mL), overnight. The solvent was removed under reduced pressure. After analysis of the crude mixture, 1,2-diols

was observed as a mixture (66:33) of *anti* and 1,2-*syn*-diols **5.14:5.15**. Data as above.

(1*RS*, 2*RS*)- and (1*RS*, 2*SR*)-1,2-Bis(4'-carboxyphenyl)ethane-1,2-diols 5.28:5.29



$C_{16}H_{14}O_6$
MW: 302.28

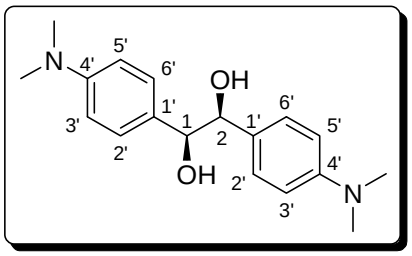
Triethylamine (0.20 mL, 1.5 mmol, 1.0 eq) was added to 4-carboxybenzaldehyde **5.23** (225 mg, 1.50 mmol, 1.0 eq) in dry THF (5.0 mL) under argon at rt. Meanwhile, a 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.4 mmol, 2.3 eq) was added to a suspension of Cp_2TiCl_2 **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (7 mL) under argon at rt. The reaction was stirred for 0.5 h. The first mixture was added to the mixture containing the titanium complex at −78 °C. The mixture was stirred for 5 min at −78 °C and warmed up to rt over 1.5 h. The reaction was quenched by 1 M $HCl_{(aq)}$ (10 mL) and the mixture was stirred for 0.5 h. The organic layer was separated and washed with brine (3 ×). The aqueous layer was extracted with ethyl acetate (3 ×). The combined organic layers were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Because of a difference of solubility in $CHCl_3$, the crude mixture was placed in a minimal amount of $CHCl_3$ and filtered. The filtrate contained the titanocene complexes while the solid was purified by flash chromatography [SiO_2, $CHCl_3$-MeOH (80:20-60:40)] and gave an inseparable 58:42 mixture of the 1,2-*syn* and 1,2-*anti*-isomers **5.28:5.29** (126 mg, 56%) as a cream powder.

R_f [SiO_2, $CHCl_3$-MeOH (70:30)] 0.22

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 4.66 (2H^{syn}, s, C*H*OH), 4.73 (2H^{anti}, s, C*H*OH), 5.52 (2H^{syn}, s, OH), 5.63 (2H^{anti}, s, OH), 7.23 (4H^{anti}, d, *J* 8.3 Hz, H3' and H5'), 7.35 (4H^{syn}, d, *J* 8.3 Hz, H3' and H5'), 7.75 (4H^{anti}, d, *J* 8.3 Hz, H2' and H6'), 7.83 (4H^{syn}, d, *J* 8.3 Hz, H2' and H6'), 12.82 (2H^{syn}, s, CO_2H). **^{13}C NMR** (100 MHz,

DMSO-d_6) δ_C: 76.49 (CH), 76.71 (CH), 127.16 (CH), 127.42 (CH), 128.33 (CH), 128.43 (CH), 129.08 (C), 129.16 (C), 147.30 (C), 148.11 (C), 167.30 (C), 167.35 (C). **IR** ν_{max} (KBr)/cm^{-1}: 3544 (OH), 3450 (OH), 1685 (C=O acid), 1429 (C=C). Compound reported in the literature without spectroscopic data provided.[250]

(1*RS*, 2*RS*)-1,2-Bis[4'-(*N*,*N*-dimethylamino)phenyl]ethane-1,2-diols 5.33



$C_{18}H_{24}N_2O_2$
MW: 300.40

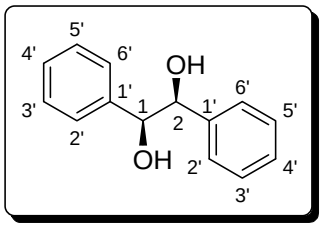
Procedure C: A 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.4 mmol, 2.3 eq) was added to a stirred suspension of titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (5 mL) under argon at rt. After 0.5 h, the solution was cooled to −78 °C and a solution of acetic acid (0.10 mL, 1.7 mmol, 1.1 eq) and 4-(*N,N*-dimethylamino)benzaldehyde **5.32** (224 mg, 1.50 mmol, 1.0 eq) in dry THF (7 mL) were added under argon at rt. The mixture was stirred for 5 min and allowed to warm to rt over 1.5 h. The reaction was quenched by addition of 1 M $HCl_{(aq)}$ (10 mL) and the mixture was stirred for 0.5 h. The organic layer containing titanium residues was separated. The aqueous layer was treated by addition of 1 M $NaOH_{(aq)}$ until pH 9 and extracted with CH_2Cl_2 (3 ×). This organic layer was washed with brine (3 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, CH_2Cl_2–Et_2O (100:0–50:50)] gave the 1,2-*syn*-diols **5.33** (177 mg, 78%) as a green oil.

R_f [SiO_2, CH_2Cl_2–Et_2O (50:50)] 0.60

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.84 (12H, s, NCH_3), 4.60 (2H, s, C*H*OH), 6.57 (4H, d, *J* 8.6 Hz, H3' and H5'), 6.96 (4H, d, *J* 8.8 Hz, H2' and H6'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 40.60 (CH_3), 78.64 (CH), 112.26 (CH), 127.84 (CH), 128.23 (C), 150.18 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3562 (OH), 2957 (CH sp^3), 1610 (C=C), 1516 (C=C), 1260 (C–N). **MS** (EI) *m/z* (%): 300 ($M^{+\cdot}$, 0.4), 282 ($M^{+\cdot} - H_2O$, 36), 254 (65), 253 (100), 237 ($M^{+\cdot} - H_2O$ and Me_2NH, 61), 150 ($Me_2NC_6H_4CHOH^+$, 63), 148 (68). **HRMS** (EI): 300.1842 (M^+, $C_{18}H_{24}O_2N_2$ requires 300.1838). NMR spectral data in agreement with those previously reported in the literature.[251]

Procedure D: A 2 *M* solution of ^{i}Pr*M*gCl in THF (1.7 mL, 3.4 mmol, 2.3 eq) was added to a stirred suspension of titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (5 mL) under argon at rt. After 0.5 h, the solution was cooled to −78 °C and a solution of *p*-TsOH (258 mg, 1.36 mmol, 0.9 eq) and 4-(*N,N*-dimethylamino)benzaldehyde **5.32** (224 mg, 1.50 mmol, 1.0 eq) were added in dry THF (7 mL) under argon at rt. The mixture was stirred for 5 min and allowed to warm to rt over 1.5 h. The reaction was quenched by addition of 1 M $HCl_{(aq)}$ (10 mL) and the mixture was stirred for 0.5 h. The organic layer was separated. The aqueous layer was treated by addition of 1 M $NaOH_{(aq)}$ until pH 9 and extracted with CH_2Cl_2 (3 ×). This organic layer was washed with brine (2 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, CH_2Cl_2–Et_2O (100:0–50:50)] gave the 1,2-*syn*-diols **5.33** (151 mg, 67%) as a green oil. Data as above.

(1*RS*,2*RS*)-1,2-Diphenyl ethane-1,2-diols 5.35:5.36



$C_{14}H_{14}O_2$
MW: 214.26

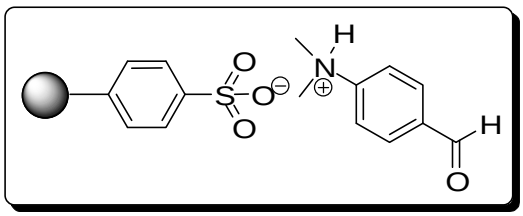
The reaction was carried out according to procedure A using a 2 *M* solution of ^{i}Pr*M*gCl in THF (1.7 mL, 3.4 mmol, 1.7 eq), titanocene dichloride **5.17** (747 mg, 3.00 mmol, 1.5 eq) in dry THF (10 mL) and benzaldehyde **5.34** (0.2 mL, 2.0 mmol, 1.0 eq). The crude mixture was dissolved in a minimal amount of $CHCl_3$ and filtered. The filtrate was treated with 1 M $NaOH_{(aq)}$ and stirred for 10 min. The mixture was filtered through a pad of Celite®. The filtrate was extracted with diethyl ether (2 ×). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography [SiO_2, hexane–ethyl acetate (90:10–60:40)] gave the 1,2-diols (16 mg, 10%) as an inseparable 94:6 mixture of the *syn*- and *anti*-isomers **5.35:5.36** as yellow crystals.

R_f [SiO_2, hexane–ethyl acetate (3:2)] 0.37

Data on syn–isomer only **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 2.80 (2H, br s, OH), 4.64 (2H, s, C*H*OH), 7.04 – 7.08 (4H, m, H2' and H6'), 7.15 – 7.20 (6H, m, H3', H4' and H5'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 79.15 (CH), 126.96 (CH), 127.98

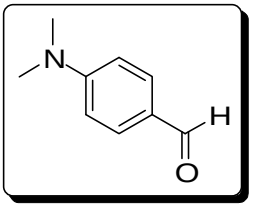
(CH), 128.17 (CH), 139.83 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3368 (OH), 2923 (CH sp^3). **MS** (EI) *m/z* (%): 214 ($M^{+\cdot}$, 0.1), 107 ($C_6H_5CHOH^+$, 100), 83 (49), 79 (90), 77 ($C_6H_5^+$, 65). (CI^+) *m/z* (%): 197 [$(M+H)^+ - H_2O$, 100], 107 ($C_6H_5CHOH^+$, 29). **HRMS** (CI^+): 197.0963 [$(M+H)^+ - H_2O$, $C_{14}H_{13}O$ requires 197.0966]. All Data are consistent with the literature.[252,253]

Loading of 4-toluenesulfonic acid resin 5.38



A solution of 4-(*N,N*-dimethylamino)benzaldehyde **5.32** (564 mg, 3.78 mmol, 5.0 eq) in dry THF (10 mL) was added to a flask containing resin-bound toluenesulfonic acid **5.38** (252 mg of macroporous resin, 30-60 mesh, with a loading of 2.0 mmol. g^{-1}, 1.0 eq) contained in an IRORI MacroKan™ (porous polypropylene reactors with an internal volume of 2.4 mL, and a pore size of 74 μm) under argon. The mixture was stirred at rt for 1.5 h and then the MacroKan™ was removed from the flask and washed with THF (5 ×) then alternately with CH_2Cl_2 and MeOH (2 ×), and finally with CH_2Cl_2 (1 ×) then Et_2O (1 ×), before the combined washings were evaporated under reduced pressure.

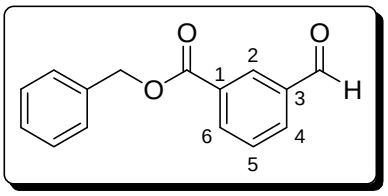
Cleavage of 4-toluenesulfonic acid resin



$C_9H_{11}NO$
MW: 149.19

The MacroKan™ **5.39** was stirred in a solution of Et_3N - CH_2Cl_2 (1:19) for 1.25 h at rt under argon. The MacroKan™ was then washed with THF (5 ×), then alternately with CH_2Cl_2 and MeOH (2 ×), and finally with CH_2Cl_2 (1 ×) then Et_2O (1 ×), before the combined washings were evaporated under reduced pressure. The aldehyde **5.32** was recovered (61 mg) yielding 54% of loading.

Benzyl 3-formylbenzoate 5.44



$C_{15}H_{12}O_3$
MW: 240.25

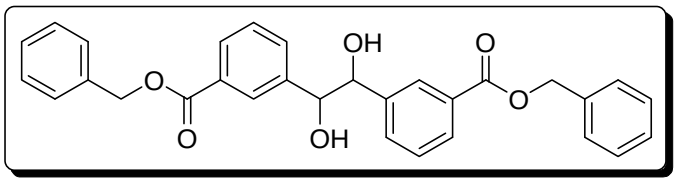
The reaction was carried out following the procedure described for compound **5.13** using 3-formylbenzoic acid **5.42** (1.00 g, 6.66 mmol, 1.0 eq), benzyl alcohol **5.11** (0.80 mL, 7.3 mmol, 1.1 eq), DMAP (82 mg, 0.67 mmol, 0.1 eq) in dry CH_2Cl_2 (15 mL) and a solution of DCC (1.51 g, 7.32 mmol, 1.1 eq) in CH_2Cl_2 (10 mL). Flash chromatography [SiO_2, hexane–CH_2Cl_2 (80:20–40:60)] gave the ester **5.44** (1.33 g, 83%) as an amorphous solid.

R_f [SiO_2, hexane–CH_2Cl_2 (20:60)] 0.40

mp: 55 – 57 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.32 (2H, s, C*H*$_2$Ph), 7.25 – 7.39 (5H, m, Ar-H), 7.53 (1H, t, *J* 7.6 Hz, H5), 8.00 (1H, d, *J* 7.8 Hz, H4 or H6), 8.25 (1H, d, *J* 7.8 Hz, H4 or H6), 8.48 (1H, s, H2), 9.98 (1H, s, C*H*O). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 67.29 (CH_2), 128.45 (CH), 128.55 (CH), 128.74 (CH), 129.34 (CH), 131.25 (C), 131.44 (CH), 133.20 (CH), 135.34 (CH), 135.59 (C), 136.56 (C), 165.35 (C), 191.43 (CH). **IR** ν_{max} (KBr)/cm^{-1}: 3062 (CH sp^2), 2830 (CH sp^3), 1704 (C=O), 1592 (C=C). **MS** (CI$^+$) *m/z* (%): 241 [(M+H)$^+$, 100%], 151 (30), 91 ($C_6H_5CH_2^+$, 52). **HRMS** (CI$^+$): 241.0862. [(M+H$^+$), $C_{15}H_{13}O_3$ requires 241.0865]. **Microanalysis**: Theory C: 74.92% H: 5.03%; Results C: 74.84% H: 4.99%.

(1*RS*,2*RS*)- and (1*RS*,2*SR*)-1,2-Bis[3'-(benzyloxycarbonyl)phenyl]ethane-1,2-diols 5.45:5.46



$C_{30}H_{26}O_6$
MW: 482.52

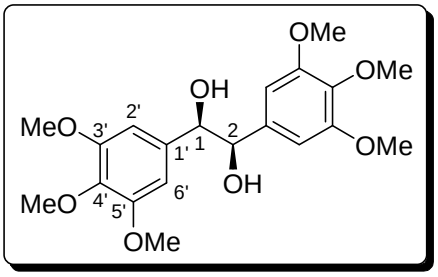
The reaction was carried out according to procedure A using a 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.4 mmol, 2.3 eq), titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (10 mL) and the aldehyde **5.44** (360 mg,

1.49 mmol, 1.0 eq). After acidic treatment, the red crude mixture was stirred for 5 min with 1 M $NaOH_{(aq)}$ (25 mL) and then filtered through Celite®. The filtrate was extracted with ethyl acetate (3 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, hexane–ethyl acetate (80:20–50:50)] gave 1,2-diols (76.7 mg, 21%) as an inseparable 80:20 mixture of *syn*- and *anti*-isomers **5.45:5.46** as a yellow oil.

R_f [SiO_2, hexane–ethyl acetate (50:50)] 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 4.67 ($2H^{syn}$, s, C*H*OH), 4.82 ($2H^{anti}$, s, C*H*OH), 5.19 ($4H^{anti}$, s, CH_2Ph), 5.20 ($4H^{syn}$, s, CH_2Ph), 7.10-7.18 (6H, m, Ar-H), 7.24 – 7.31 (12H, m, Ar-H), 7.73-7.84 (18H, m, Ar-H). **^{13}C NMR** of major isomer (100 MHz, $CDCl_3$) δ_C: 65.75 (CH_2), 76.23 (CH^{anti}), 77.43 (CH^{syn}), 127.08 (CH), 127.17 (CH), 127.25 (CH), 127.56 (CH), 128.24 (CH), 128.72 (C), 130.80 (CH), 134.79 (C), 139.15 (C), 165.22 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3466 (OH), 2925 (CH sp^3), 1717 (C=O ester), 1497 (Ph). **MS** (CI^+) *m/z* (%): 305 (45), 241 ($C_6H_5CH_2OCOC_6H_4CHOH^+$, 100), 151 (51), 91 ($C_6H_5CH_2^+$, 80).

(1*RS*,2*RS*)-1,2-Bis(3',4',5'-trimethoxyphenyl)ethane-1,2-diols 5.55



$C_{20}H_{26}O_8$
MW: 394.42

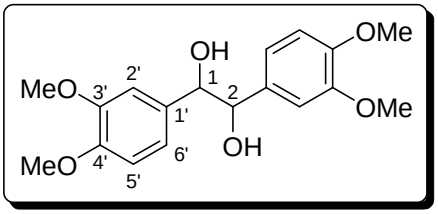
The reaction was carried out according to procedure A using a 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.4 mmol, 2.3 eq), titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (10 mL) and the aldehyde **5.54** (295 mg, 1.50 mmol, 1.0 eq). The combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. Sodium bicarbonate (6.70 g), methanol (103 mL) and water (4 mL) were added to the crude mixture. The mixture was heated to 40 °C overnight and then cooled to rt. The titanium residues were removed by filtration. The solution was evaporated under reduced pressure. Water (150 mL) and CH_2Cl_2 (75 mL) were added and the mixture shaken. The organic layer was separated, dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, CH_2Cl_2–MeOH (99:1–95:5)] gave

the 1,2-*syn*-diols **5.55** (221 mg, 75%) as an amorphous solid. $\mathbf{R_f}$ [SiO_2, CH_2Cl_2-MeOH (95:5)] 0.47

mp: 172 – 174 °C

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.66 (12H, s, 4 × OC*H*$_3$), 3.73 (6H, s, 2 × OC*H*$_3$), 4.49 (2H, s, C*H*OH), 6.28 (4H, s, 2 × H2' and 2 × H6'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 56.07 (CH_3), 60.85 (CH_3), 79.24 (CH), 103.78 (CH), 135.47 (C), 137.37 (C), 152.88 (C). **IR** ν_{max} (KBr)/cm^{-1}: 3482 (OH), 2966 (CH sp^2), 2939 (CH sp^3), 1592 (C=C arom). **MS** (EI) *m/z* (%): 394 [$M^{+\cdot}$, 1], 376 [$M^{+\cdot} - H_2O$, 3], 360 (13), 347 (8), 345 (7), 198 [$(MeO)_3C_6H_2CH_2OH^{+\cdot}$, 100]. ($CI^+$) *m/z* (%): 377 [$(M+H)^+ - H_2O$, 60], 197 [$(MeO)_3C_6H_2CHOH^+$, 100]. **HRMS** (EI): 394.1627. [M^+, $C_{20}H_{26}O_8$ requires 394.1628]. **Microanalysis**: Theory C: 60.91% H: 6.60%; Results C: 60.64% H: 6.71%. Compound reported in the literature without spectroscopic data provided.

(1*RS*,2*RS*)- and (1*RS*,2*SR*)-1,2-Bis(3',4'-dimethoxyphenyl)ethane-1,2-diols 5.57



$C_{18}H_{22}O_6$
MW: 334.36

In a same way, the reaction was carried out using a 2 M solution of ^{i}PrMgCl in THF (1.7 mL, 3.4 mmol, 2.3 eq), titanocene dichloride **5.17** (747 mg, 3.00 mmol, 2.0 eq) in dry degassed THF (10 mL) and the aldehyde **5.56** (250 mg, 1.50 mmol, 1.0 eq). Flash chromatography [SiO_2, CH_2Cl_2 - MeOH (100:0-98:2)] gave the 1,2-diols **5.57** as an inseparable 90:10 mixture of *syn*- and *anti*-isomers as a yellow amorphous solid after recrystallisation in $CHCl_3$ (75 mg, 30%).

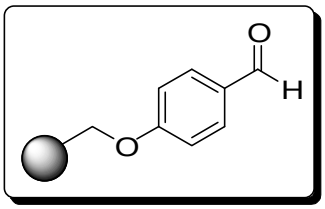
$\mathbf{R_f}$ [SiO_2, CH_2Cl_2-MeOH (95:5)] 0.40

mp: 150-152 °C ($CHCl_3$)

Data on syn-isomer only.**^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 3.63 (6H, s, OC*H*$_3$), 3.71 (6H, s, OC*H*$_3$), 4.43 (2H, s, C*H*OH), 6.47-6.49 (4H, m, H2' and H6'), 6.58 (2H, d, *J* 8.6 Hz, H5'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 55.74 (CH_3), 55.79 (CH_3), 78.96 (CH), 110.02 (CH), 110.48 (CH), 119.57 (CH), 132.55 (C), 148.37 (C),

148.60 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3532 (OH), 1603 (C=C). **MS** (EI) *m/z* (%): 316 ($M^{+\cdot}$ – H_2O, 15), 300 ($M^{+\cdot}$ – H_2O and – CH_4, 26), 287 ($M^{+\cdot}$ – H_2O and – $\cdot CH{=}O$, 100), 167 [$(MeO)_2C_6H_3CHOH^+$, 70]. **HRMS** (EI): 334.1414. [M^+, $C_{18}H_{22}O_6$ requires 334.1416]. **Microanalysis**: Theory C: 64.67% H: 6.59%; Results C: 64.83% H: 6.67%. Compound reported in the literature without spectroscopic data provided.[254,255]

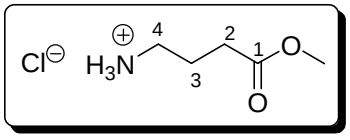
Loading of Wang resin with 4-hydroxybenzaldehyde 5.60



A solution of DIAD (1.1 mL, 5.6 mmol, 5.6 eq) in dry THF (6 mL) was added drop-wise at 0 °C to a stirred solution of 4-hydroxybenzaldehyde **5.60** (613 mg, 5.02 mmol, 5.0 eq), PPh_3 (1.38 g, 5.25 mmol, 5.2 eq) and a flask containing resin-bound Wang resin **5.61** (591 g of maroporous resin, 150–300 μm, with a loading of 1.7 mmol. g^{-1}, 1.0 eq) contained in an IRORI MacroKan™ (porous polypropylene reactors with an internal volume of 2.4 mL, and a pore size of 74 μm) under argon in dry THF (12 mL). After addition, the mixture was stirred at rt for 1 h and then the MacroKan™ was removed from the flask and washed with THF (5 ×) then alternately with CH_2Cl_2 and MeOH (4 ×), and finally with Et_2O (1 ×), before the combined washings were evaporated under reduced pressure.

12.4. Experimental to chapter 8

Methyl 4-aminobutanoate hydrochloride salt 8.18



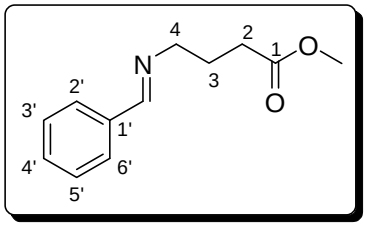
$C_5H_{12}ClNO_2$
MW: 153.61

Thionyl chloride (7.1 mL, 97 mmol, 2.0 eq) was added drop-wise to a stirred solution of γ-aminobutyric acid **8.17** (5.00 g, 48.5 mmol, 1.0 eq) in MeOH

(59 mL) at −10 °C under argon. The solution was stirred for 5 min, and then allowed to warm to rt and stirred for 2 h. The resulting mixture was evaporated under reduced pressure. Washing the crude product with hot hexane left the hydrochloride salt of the amino ester **8.18** as an amorphous solid (7.02 g, 95%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.82 (2H, qn, *J* 7.6 Hz, CH_2-3), 2.45 (2H, t, *J* 7.3 Hz, CH_2-2), 2.75-2.83 (2H, m, C*H*$_2$N), 3.61 (3H, s, OC*H*$_3$), 8.06-8.18 (3H, br s, N*H*$_3$). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[256]

Methyl 4-(benzylidenamino)butanoate 8.19

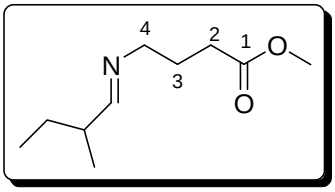


$C_{12}H_{15}NO_2$
MW: 205.25

Triethylamine (3.6 mL, 26 mmol, 2.0 eq) and benzaldehyde **8.12** (1.7 mL, 17 mmol, 1.3 eq) were added to a stirred suspension of the amino ester **8.18** (2.00 g, 13.1 mmol, 1.0 eq) and Na_2SO_4 (2.23 g, 15.7 mmol, 1.0 eq) in dry CH_2Cl_2 (40 mL) under argon at rt. After stirring overnight, the mixture was filtered off and washed with water (2 ×), brine (1 ×), then dried ($MgSO_4$) and the solvent was removed under reduced pressure. Excess reagents were removed at 120 °C under reduced pressure to leave the imine **8.19** (1.90 g, 71%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.96 (2H, qn, *J* 7.0 Hz, C*H*$_2$-3), 2.35 (2H, t, *J* 7.4 Hz, C*H*$_2$-2), 3.56 (2H, t, *J* 6.8 Hz, C*H*$_2$N), 3.58 (3H, s, OC*H*$_3$), 7.39-7.42 (3H, m, H3', H4' and H5'), 7.71-7.73 (2H, m, H2' and H6'), 8.19-8.21 (1H, br s, C*H*=N). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[257]

Methyl 4-(2'-methylbutylideneamino)butanoate 8.37



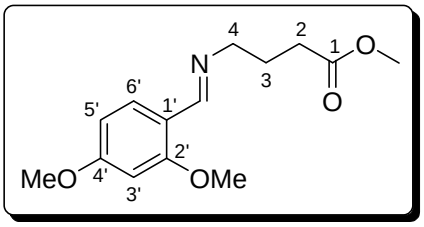
$C_{10}H_{19}NO_2$
MW: 185.26

In a same way, the reaction was carried out using triethylamine (2.0 mL, 14 mmol, 2.0 eq), 2-methylbutyraldehyde **8.34** (1.0 mL, 9.3 mmol, 1.3 eq), the hydrochloride salt **8.18** (1.12 g, 7.32 mmol, 1.0 eq) and Na_2SO_4 (1.24 g, 8.73 mmol, 1.2 eq) in dry CH_2Cl_2 (22 mL). The imine **8.37** was obtained as a brown oil (1.27 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.87 (3H, t, *J* 6.9 Hz, C*H*$_3$CH$_2$), 1.00 (3H, d, *J* 6.2 Hz, C*H*$_3$CH), 1.26-1.48 (2H, m, C*H*$_2$CH$_3$), 1.90 (2H, apparent qn, *J* 7.1 Hz, CH$_2$-3), 2.18 (1H, septet, *J* 6.7 Hz, C*H*CH$_3$), 2.30 (2H, t, *J* 7.5 Hz, CH$_2$-2), 3.35 (2H, t, *J* 6.8 Hz, C*H*$_2$N), 3.63 (3H, s, OC*H*$_3$), 7.43 (1H, d, *J* 6.0 Hz, C*H*N).

Due to the relative instability of this compound, we decided to carry on the next step without more characterization.

Methyl 4-(2',4'-dimethoxybenzylidenamino)butanoate 8.38

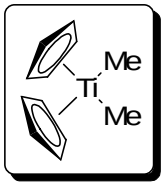


$C_{14}H_{19}NO_4$
MW: 265.30

In a same way, the reaction was carried out using triethylamine (2.0 mL, 14 mmol, 2.0 eq), 2,4-dimethoxybenzaldehyde **8.35** (1.58 g, 9.51 mmol, 1.3 eq), the hydrochloride salt **8.18** (1.12 g, 7.34 mmol, 1.0 eq) and Na_2SO_4 (1.24 g, 8.73 mmol, 1.2 eq) in dry CH_2Cl_2 (22 mL). Excess reagents were removed at 150 °C under reduced pressure to leave the imine **8.38** as a brown oil (443 mg, 23%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.04 (2H, qn, *J* 6.9 Hz, C*H*$_2$-3), 2.43 (2H, t, *J* 7.6 Hz, C*H*$_2$-2), 3.62 (2H, dt, *J* 1.3 and 6.4 Hz, C*H*$_2$N), 3.68 (3H, s, OC*H*$_3$), 3.85 (3H, s, OC*H*$_3$), 3,86 (3H, s, OC*H*$_3$), 6.45 (1H, d, *J* 2.3 Hz, H3'), 6.53 (1H, dd, *J* 2.3 and 8.7 Hz, H5'), 7.89 (1H, d, *J* 8.6 Hz, H6'), 8.61 (1H, br s, C*H*=N). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 26.33 (CH_2), 31.84 (CH_2), 51.52 (CH_3), 55.44 (CH_3), 55.47 (CH_3), 60.70 (CH_2), 98.03 (CH), 105.29 (CH), 117.89 (C), 128.42 (CH), 157.01 (CH), 159.98 (C), 162.97 (C), 174.09 (C). **MS** (EI) *m/z* (%): 265 ($M^{+\cdot}$, 43), 234 ($M^{+\cdot}$ – MeO$^{\cdot}$, 25), 192 ($M^{+\cdot}$ – $^{\cdot}CH_2CO_2Me$, 98), 178 ($M^{+\cdot}$ – $^{\cdot}CH_2CH_2CO_2Me$, 40), 164 [$(MeO)_2C_6H_3C{\equiv}NH^+$, 70%], 149 (100).

Petasis reagent: dimethyltitanocene 8.14

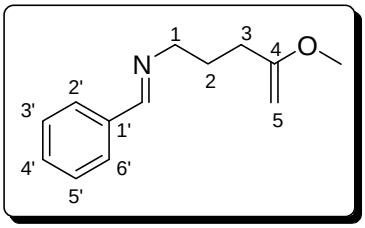


$C_{12}H_{16}Ti$
MW: 208.12

Following the procedure described by Payack *et al.*,[85] a 1.4 M solution of MeMgBr (137 mL, 192 mmol, 2.3 eq) in toluene-THF (30:10) was added drop-wise to a stirred solution of titanocene dichloride **6.1** (21.00 g, 84.3 mmol, 1.0 eq) in dry toluene (230 mL) previously chilled to −5 °C over 1 h with the internal temperature maintained under 8 °C. The resulting orange slurry was stirred for 4 h. Meanwhile, a stirred solution of 6% aqueous ammonium chloride was chilled to 1 to 2 °C. When the formation of dimethyltitanocene was judged complete (assayed by NMR), the toluene / THF reaction mixture was poured into ammonium chloride saturated aqueous solution via a cannula over a period of 0.5 h maintaining an internal temperature between 0 and 5 °C in both flasks. Toluene (15 mL) was used to rinse the reaction flask. The aqueous phase of this biphasic mixture was then removed. The organic layer was washed sequentially with cold water (3 × 50 mL) and brine (50 mL), and then dried (Na_2SO_4). The organic layer was filtered and carefully concentrated under reduced pressure. The resulting orange slurry was assayed by ^{1}H NMR spectroscopy to be 29 weight percent dimethyltitanocene **8.14**. The reagent was diluted with dry THF until 1.32 M to be stored more than a week and stored at 4 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.05 (6H, s, Me), 6.18 (10 H, s, Cp). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[85]

***N*-benzyliden-4-methoxypent-4-en-1-amine 8.20**



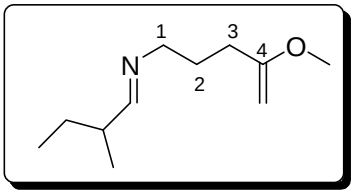
$C_{13}H_{17}NO$
MW: 203.28

Following the procedure described by Adriaenssens,[258] a 1.32 M solution of Cp_2TiMe_2 **8.14** (1.0 mL, 1.4 mmol, 6.1 eq) in toluene / THF (1:1 by mass) was

added to the imino ester **8.19** (46 mg, 0.22 mmol, 1.0 eq) and sealed in a 10 mL microwave tube under argon. This mixture was irradiated under 100 W microwave power to raise the internal temperature to 65 °C for 10 min before cooling. The resultant black solution was concentrated under reduced pressure and then hexane was added. The hexane extract was submitted to sonication and then filtered off. The solvent was removed under reduced pressure to yield the crude enol ether **8.20**, as an orange oil which was used directly in the cyclisation reaction (38 mg, 84%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.05 (2H, qn, *J* 7.2 Hz, C*H*$_2$-2), 2.34 (2H, t, *J* 7.2 Hz, C*H*$_2$-3), 3.70 (3H, s, OC*H*$_3$), 3.80 (2H, dt, *J* 1.5 and 6.8 Hz , C*H*$_2$N), 4.03 (2H, s, C*H*$_2$=), 7.55-7.60 (3H, m, H3', H4' and H5'), 7.85-7.93 (2H, m, H2' and H6'), 8.40-8.42 (1H, br s, C*H*=N). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[258]

4-Methoxy-*N*-(2'-methylbutyliden)pent-4-en-1-amine 8.40



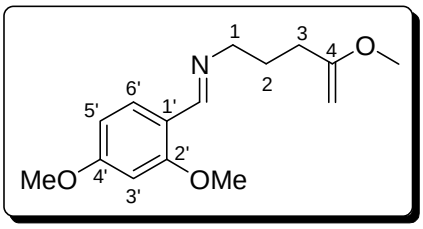
$C_{11}H_{21}NO$
MW: 183.29

In a same way, the reaction was carried out using a 1.32 M solution of Cp_2TiMe_2 **8.14** (2.5 mL, 3.3 mmol, 6.1 eq), the imino ester **8.37** (100 mg, 0.54 mmol, 1.0 eq) and yielded the crude enol ether **8.40**, as an orange oil, which was used directly in the cyclisation reaction (99 mg, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.03 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.19 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 1.50-1.71 (2H, m, C*H*$_2$CH$_3$), 1.94 (2H, qn, *J* 7.1 Hz, CH$_2$-2), 2.24 (2H, t, *J* 7.1 Hz, CH$_2$-3), 2.36 (1H, septet, *J* 6.7 Hz, C*H*CH$_3$), 3.50 (2H, t, *J* 6.8 Hz, C*H*$_2$N), 3.66 (3H, s, OC*H*$_3$), 3.96 (1H, d, *J* 1.9 Hz, C*H*^{A}H^B=), 3.98 (1H, d, *J* 2.1 Hz, CH^A*H*^{B}=), 7.59 (1H, d, *J* 6.3 Hz, C*H*N).

Due to the relative instability of this compound, we decided to carry on the next step without more characterization.

N-(2',4'-Dimethoxybenzyliden)-4-methoxypent-4-en-1-amine 8.41



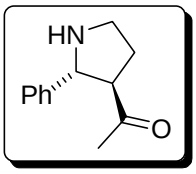
$C_{15}H_{21}NO_3$
MW: 263.33

In a same way, the reaction was carried out using a 1.32 M solution of Cp_2TiMe_2 **8.14** (2.4 mL, 3.2 mmol, 8.2 eq), the imino ester **8.38** (104 mg, 0.39 mmol, 1.0 eq) and yielded the crude enol ether **8.41**, as an orange oil, which was used directly in the cyclisation reaction (29 mg, 28%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.02-2.08 (2H, m, C*H*$_2$-2), 2.31 (2H, t, *J* 7.2 Hz, C*H*$_2$-3), 3.68 (3H, s, OC*H*$_3$), 3.74 (2H, dt, *J* 1.3 and 6.8 Hz, C*H*$_2$N), 3.99 (3H, s, OC*H*$_3$), 4.00 (3H, s, OC*H*$_3$), 4.03 (1H, d, *J* 1.8 Hz, C*H*^{A}H^B=), 4.04 (1H, d, *J* 2.1 Hz, CH^A*H*^{B}=), 6.59 (1H, d, *J* 2.2 Hz, H3'), 6.67 (1H, dd, *J* 2.3 and 8.6 Hz, H5'), 8.07 (1H, d, *J* 8.6 Hz, H6'), 8.74 (1H, br s, C*H*=N).

Due to the relative instability of this compound, we decided to carry on the step after without more characterization.

(2*R*,3*R*)-2-phenyl-3-methyloxo-pyrrolidine 8.43



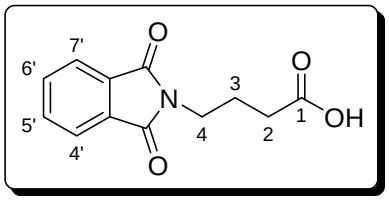
$C_{12}H_{15}NO$
MW: 189.25

A solution of $NaBH_4$ (37 mg, 1.0 mmol, 6.0 eq) in methanol (1 mL) was added to a stirred aqueous solution of crude mixture **8.42** (0.16 mmol, 1.0 eq) in MeOH/ H_2O (75% v/v, 0.9 mL). After stirring 1 h, the solvent was removed under reduced pressure and the aqueous slurry was extracted with $CHCl_3$, then dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, hexane–ethyl acetate (90:10–70:30)] gave the free amine **8.43** (7 mg, 23%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.01 (3H, s, CH_3), 2.07-2.14 (2H, m, CH_2-5), 3.00-3.06 (2H, m, CH_2-4), 3.13-3.18 (1H, m, CH-3), 4.25 (1H, d, *J* 7.3 Hz, CH-2),7.16-

7.21 (2H, m, Ar-H), 7.24-7.31 (3H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 30.00 (CH_2), 30.23 (CH_3), 46.76 (CH_2), 60.08 (CH), 65.10 (CH),126.73 (CH), 127.38 (CH), 128.61 (CH), 143.11 (C), 209.28 (C).

4-(1',3'-Dioxoisoindolin-2-yl)butanoic acid 8.53

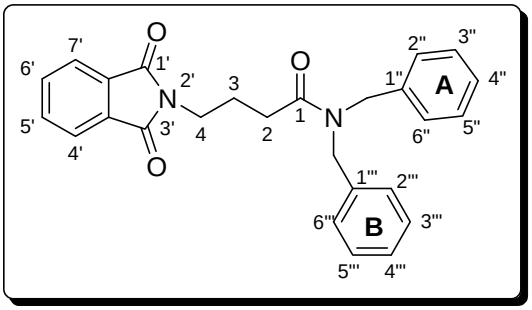


$C_{12}H_{11}NO_4$
MW: 233.22

Following the procedure described by Kruper *et al.*,[152] phthalic anhydride **8.52** (14.8 g, 100 mmol, 1.0 eq), γ-aminobutyric acid **8.17** (10.30 g, 100 mmol, 1.0 eq), triethylamine (1.3 mL, 9.3 mmol, 0.1 eq) were placed in a round bottom flask equipped with a Dean Stark trap and condenser. The mixture was brought to reflux and water was removed azeotropically over 1.5 h period. The solution was allowed to cool and stand overnight at rt. The resulting crystals were filtered off, washed with hexane and dried ($MgSO_4$). The crude crystals were then washed with 5% of $HCl_{(aq)}$ (250 mL) and cold water (100 mL). The acid **8.53** was obtained as an amorphous solid (23.3 g, 84%) after recrystallisation from MeOH - H_2O (30:70).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.96 (2H, qn, *J* 7.1 Hz, C*H*$_2$-3), 2.35 (2H, t, *J* 7.4 Hz, C*H*$_2$-2), 3.70 (2H, t, *J* 7.0 Hz, C*H*$_2$N), 7.64-7.66 (2H, m, H5' and H6'), 7.77-7.79 (2H, m, H4' and H7'). Spectral data in agreement with those previously reported in the literature.[152,259]

N,N-Dibenzyl-4-(1',3'-dioxoisoindolin-2'-yl)butanamide 8.55



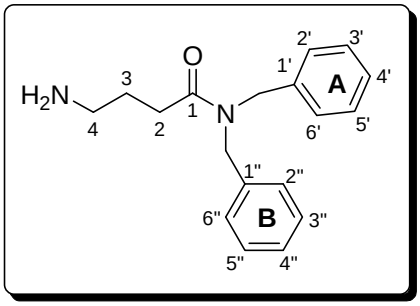
$C_{26}H_{24}N_2O_3$
MW: 412.48

A solution of acid **8.53** (10 g, 43 mmol, 1.0 eq) in thionyl chloride (40.7 mL, 558 mmol, 13.0 eq) was heated to reflux over 2.5 h. The solvent was then removed under reduced pressure. The crude mixture was immediately diluted with dry CH_2Cl_2 (6 mL). The solution was added drop-wise to a stirred solution of dibenzylamine **8.54** (9.1 mL, 47 mmol, 1.1 eq), dry pyridine (3.8 mL, 47 mmol, 1.1 eq) and dry CH_2Cl_2 (25 mL) at 0 °C. This stirred solution was allowed to warm to rt over 15 min and was then acidified with dilute aqueous HCl (5% by volume). Layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 x). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. The amide **8.55** was obtained after recrystallisation in diethyl ether-pentane (95:5) (v/v) as a cream amorphous solid (12.18 g, 69%).

mp: 98-100 °C (ether-pentane)

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.03 (2H, qn, *J* 7.0 Hz, C*H*$_2$-3), 2.40 (2H, t, *J* 7.3 Hz, C*H*$_2$-2), 3.71 (2H, t, *J* 6.8 Hz, C*H*$_2$-4), 4.35 (2H, s, NC*H*$_2$Ph), 4.53 (2H, s, NC*H*$_2$Ph), 7.05 (2H, d, *J* 7.0 Hz, H2" and H6" or H2"' and H6"'), 7.15 (2H, d, *J* 6.8 Hz, H2" and H6" or H2"' and H6"'), 7.18-7.27 (6H, m, H4", H5", H6" and H4"', H5"' and H6"'), 7.63- 7.65 (2H, m, H5' and H6'), 7.75-7.77 (2H, m, H4' and H7'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 24.42 (CH_2), 30.52 (CH_2), 37.56 (CH_2), 48.35 (CH_2), 49.90 (CH_2), 123.25 (CH), 126.37 (CH), 127.40 (CH), 127.58 (CH), 128.28 (CH), 128.63 (CH), 128.96 (CH), 132.12 (C), 133.92 (CH), 136.43 (C), 137.34 (C), 168.45 (C), 172.33 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3053 (CH sp^2), 2937 (CH sp^3), 1651 (C=O amide). **MS** (EI) *m/z* (%): 412 ($M^{+\cdot}$, 12), 321 ($M^{+\cdot}$ – Bn$^{\cdot}$, 32), 216 ($M^{+\cdot}$ – Bn$^{\cdot}$ and – PhCH=NH, 47), 160 (PhthCH$_2^+$, 29), 106 (PhCH=NH$_2^+$, 100), 91 (Bn$^+$, 61). **HRMS** (EI): 412.1786 (M^+, $C_{26}H_{24}N_2O_3$ requires 412.1787). **Microanalysis**: Theory C: 75.73% H: 5.83% N: 6.80%; Results C: 75.38% H: 6.05 % N: 6.85%.

4-Amino-*N*,*N*-dibenzylbutanamide 8.47

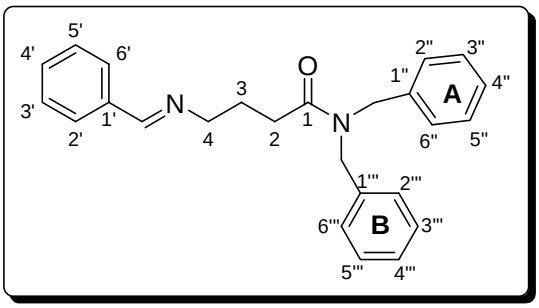


$C_{18}H_{22}N_2O$
MW: 282.38

Amide **8.55** (5.00 g, 12.1 mmol, 1.0 eq) was heated at reflux with hydrazine hydrate **8.56** (18 mL, 370 mmol, 30.5 eq) and ethanol (77 mL) for 2 h. The reaction mixture was then cooled to 0 °C. A precipitate, which appeared upon cooling, was removed by filtration. The filtrates were concentrated under reduced pressure to remove ethanol, then re-dissolved in ethyl acetate and washed with a sat $NaHCO_{3(aq)}$. The aqueous layer was extracted with ethyl acetate (2 ×). The combined organic layers were washed with brine (1 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The desired amine **8.47** was obtained as a yellow oil (2.97 g, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.83 (2H, qn, *J* 7.1 Hz, C*H*$_2$-3), 2.42 (2H, t, *J* 7.4 Hz, C*H*$_2$-2), 2.72 (2H, t, *J* 7.0 Hz, C*H*$_2$-4), 3.05 (2H, br s, N*H*$_2$), 4.37 (2H, s, NC*H*$_2$Ph), 4.51 (2H, s, NC*H*$_2$Ph), 7.05 (2H, d, *J* 6.9 Hz, H2' and H6' or H2" and H6"), 7.12 (2H, d, *J* 7.3 Hz, H2' and H6'or H2" and H6"), 7.15-7.30 (6H, m, H3', H4', H5' and H3", H4", H5"). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 29.71 (CH_2), 31.90 (CH_2), 41.24 (CH_2), 48.21 (CH_2), 49.94 (CH_2), 126.39 (CH), 127.42 (CH), 127.66 (CH), 128.19 (CH), 128.64 (CH), 128.97 (CH), 136.48 (C), 137.34 (C), 173.49 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3361 (NH), 1636 (C=O amide), 1495 (C=C). **MS** (EI) *m/z* (%): 282 ($M^{+\cdot}$, 5), 239 [$(CH_3CONBn_2)^{+\cdot}$, 43], 196 [$(PhCH{=}NHBn)^+$, 9], 148 (32), 106 ($PhCH{=}NH_2^+$, 96), 91 (Bn^+, 100). **HRMS** (EI): 282.1735 (M^+, $C_{18}H_{22}N_2O$ requires 282.1732).

N,N-Dibenzyl-4-(benzylidenamino)butanamide 8.48



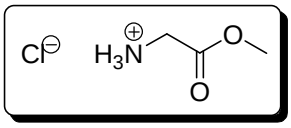
$C_{25}H_{26}N_2O$
MW: 370.49

Benzaldehyde **8.12** (0.3 mL, 3 mmol, 1.2 eq) was added to a stirred suspension of the amine **8.47** (737 mg, 2.61 mmol, 1.0 eq) and Na_2SO_4 (358 mg, 2.52 mmol, 1.0 eq) in dry CH_2Cl_2 (7 mL) under argon at rt. After stirring overnight, the mixture was filtered and the filtrate washed with water (2 ×), then brine (1 ×), and then dried ($MgSO_4$) and the solvent was removed under reduced pressure. Excess reagents were removed at 100 °C under reduced pressure to leave the imine **8.48** (517 mg, 54%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.06 (2H, qn, *J* 6.9 Hz, C*H*$_2$-3), 2.50 (2H, t, *J* 7.3 Hz, C*H*$_2$-2), 3.61 (2H, t, *J* 6.5 Hz, C*H*$_2$-4), 4.37 (2H, s, NC*H*$_2$Ph), 4.54 (2H, s, NC*H*$_2$Ph), 7.05 (2H, d, *J* 6.6 Hz, H2" and H6" or H2"' and H6"'), 7.15 (2H, d, *J* 6.6 Hz, H2" and H6" or H2"' and H6"'), 7.18-7.34 (9H, m, H3', H4', H5' and H3", H4", H5" and H3"', H4"', H5"'), 7.57-7.59 (2H, m, H2' and H6'), 8.15-8.17 (1H, br s, C*H*=N).

Due to the relative instability of this compound, we decided to carry on the next step without more characterization.

Methyl 2-aminoethanoate hydrochloride salt 8.60



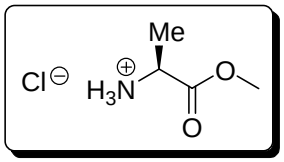
$C_3H_8ClNO_2$
MW: 125.55

The reaction was carried out following the procedure described for compound **8.18** using thionyl chloride (0.4 mL, 6 mmol, 2.0 eq), glycine **8.58** (225 mg, 3.00 mmol, 1.0 eq) in MeOH (4.0 mL). Washing the crude product with hot hexane left the hydrochloride salt of the amino ester **8.60** as an amorphous solid (366 mg, 98%).

mp= 155-157 °C

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 3.74 (3H, s, OC*H*$_3$), 3.84 (2H, s, C*H*$_2$), 8.48 (3H, br s, N*H*$_3$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 39.43 (CH_3), 52.48 (CH_2), 168.06 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3415 (NH), 1752 (C=O). **MS** (FAB) *m/z* (%): 90 [(M^+, ammonium cation), 14], 79 (100). **HRMS** (FAB): 90.0555 [(M^+, ammonium cation), $C_4H_8NO_2$ requires 90.0554]. NMR spectral data in broad agreement with those previously reported in $CDCl_3$. ^{1}H NMR and IR spectral data in broad agreement with those previously reported in D_2O.[260]

Methyl 2(*S*)-aminopropanoate hydrochloride salt 8.61

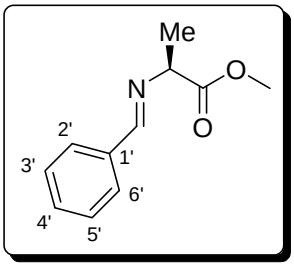


$C_4H_{10}ClNO_2$
MW: 139.58

In a same way, the reaction was carried out using thionyl chloride (3.9 mL, 53 mmol, 2.0 eq) and a solution of *L*-alanine **8.59** (2.37 g, 26.6 mmol, 1.0 eq) in MeOH (32 mL). Washing the crude product with hot hexane provided the hydrochloride salt of the amino ester **8.61** as an amorphous solid (3.40 g, 92%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.43 (3H, d, *J* 7.1 Hz, C*H*$_3$CH), 3.74 (3H, s, OC*H*$_3$), 4.05 (1H, q, *J* 7.2 Hz, C*H*CH$_3$), 8.74 (3H, br s, N*H*$_3$). **^{13}C NMR** (100 MHz, DMSO-d_6) δ_C: 15.53 (CH_3), 47.63 (CH), 52.63 (CH_3), 170.26 (C). **IR** ν_{max} (ATR) /cm^{-1}: 3570 (NH), 2956 (CH sp^3), 1741 (C=O ester), 1602 (NH). **MS** (CI^+) *m/z* (%): 104 [(M^+, ammonium cation), 100]. **HRMS** (CI^+): 104.0709 [(M^+, ammonium cation), $C_4H_{10}NO_2$ requires 104.0712]. NMR spectral data in broad agreement with those previously reported in $CDCl_3$.[261]

Methyl 2(*S*)-(benzylidenamino)propanoate 8.64

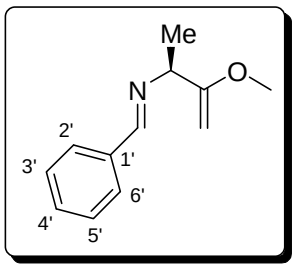


$C_{11}H_{13}NO_2$
MW: 191.23

The reaction was carried out following the procedure described for compound **8.19** using triethylamine (1.0 mL, 7.2 mmol, 2.0 eq), benzaldehyde **8.12** (0.48 mL, 4.7 mmol, 1.3 eq), the amino ester **8.61** (500 mg, 3.58 mmol, 1.0 eq) and Na_2SO_4 (307 mg, 2.16 mmol, 0.6 eq) in dry CH_2Cl_2 (11 mL). Excess reagents were removed at 140 °C under reduced pressure to leave the imine **8.64** (132 mg, 19%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.44 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 3.74 (3H, s, OC*H*$_3$), 4.05 (1H, q, *J* 6.8 Hz, C*H*CH$_3$), 7.30-7.35 (3H, m, H3', H4' and H5'), 7.68-7.70 (2H, m, H2' or H6'), 8.22 (1H, br s, C*H*=N). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[262]

N-benzyliden-3-methoxybut-3-en-2-amine 8.66



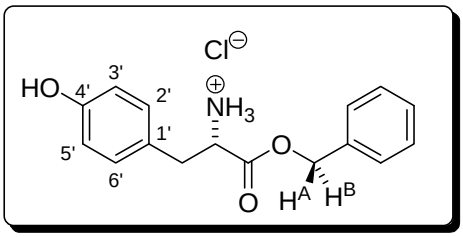
$C_{12}H_{15}NO$
MW: 189.25

The reaction was carried out as described for compound **8.20** using a 1.32 M solution of Cp_2TiMe_2 **8.14** (1.4 mL, 1.8 mmol, 6.0 eq) and the imino ester **8.64** (58.6 mg, 0.31 mmol, 1.0 eq). The solvent was removed under reduced pressure to yield the crude enol ether **8.66**, as a yellow oil which was used directly in the cyclisation reaction (21 mg, 36%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.58 (3H, d, *J* 6.8 Hz, C*H*$_3$CH), 3.73 (3H, s, OC*H*$_3$), 4.08 (1H, q, *J* 6.8 Hz, C*H*CH$_3$), 4.15 (1H, d, *J* 2.3 Hz, C*H*^{A}H^B=), 4.35 (1H, d, *J* 2.2 Hz, CH^A*H*^{B}=), 7.55-7.56 (3H, m, H3', H4' and H5'), 7.91-7.94 (2H, m, H2' and H6'), 8.44 (1H, s, C*H*=N). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[263]

12.5. Experimental to chapter 10

Benzyl 2(*S*)-amino-3-(4'-hydroxyphenyl)propanoate hydrochloride salt 10.9



$C_{16}H_{18}ClNO_3$
MW: 307.77

Procedure A: (*S*)-tyrosine **10.3** (1.00 g, 5.52 mmol, 1.0 eq), *p*-TsOH (1.05 g, 5.52 mmol, 1.0 eq) and *p*-TsCl (1.26 g, 6.61 mmol, 1.2 eq) were added to dry benzyl alcohol (11 mL, 106 mmol, 19 eq) and the mixture was heated at 80 °C for 1.5 h under argon. Benzyl alcohol was removed by distillation. The mixture was diluted with $CHCl_3$ (110 mL). Then, 1 M $NaHCO_{3\ (aq)}$ (110 mL) was added to the mixture. The mixture was shaken and the layers were separated. The organic layer was concentrated to about 50 mL and 7.5 M HCl in dioxane (1 mL) was added to the solution. A precipitate was formed, which was recrystallised from methanol-ether to give the ester **10.9** as an amorphous solid (127 mg, 7.4%).

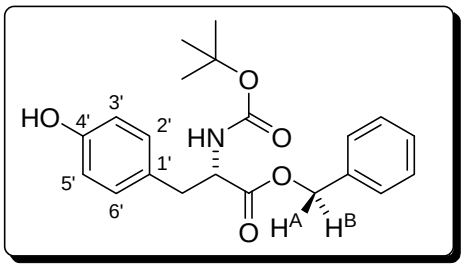
Procedure B: Following the procedure described by Viswanatha and Hruby,[193] a mixture of (*S*)-tyrosine **10.3** (1.40 g, 7.73 mmol, 1.0 eq), conc HCl (4 mL) and benzyl alcohol (40 mL, 387 mmol, 50 eq) was heated at 100 °C for 15 min to give a clear solution. Benzene (20 mL) was added and the solution was heated at 100 °C and water was removed azeotropically for 2.5 h. Conc HCl (1 mL) was added and heating was continued for another 0.5 h. The mixture was cooled and diluted with diethyl ether (50 mL). The mixture was extracted with 1 M $HCl_{(aq)}$ (5 × 20 mL) and water (2 × 20 mL). The aqueous layer was washed with diethyl ether (2 ×) and the pH was brought to pH 9 with 2 M $NH_4OH_{(aq)}$. The mixture was left overnight. The solid was filtered off, washed with water (2 ×) and dried ($MgSO_4$). The solid was stirred with acetone (100 mL) and filtered to give tyrosine (10 mg). The filtrate was concentrated under reduced pressure to give the ester **10.9** as a yellow gum, which solidified (842 mg, 40%).

Procedure C: Acetyl chloride (3.0 mL, 42 mmol, 3.0 eq) was added to a stirred solution of dry benzyl alcohol (50 mL, 483 mmol, 35 eq) at 0 °C. The solution was stirred for 15 min at 0 °C under argon and then (*S*)-tyrosine **10.3** (2.50 g, 13.8 mmol, 1.0 eq) was added portion-wise to the solution. The resulting solution was heated at reflux for 4 h before removing benzyl alcohol by distillation. The ester **10.9** was obtained as a cream solid (981 mg, 23 %).

mp: decomposed above 300 °C

^{1}H NMR (400 MHz, Methanol-d_4) δ_H: 3.05-3.15 (2H, m, CH_2CH), 4.27 (1H, t, *J* 7.0 Hz, C*H*CH$_2$), 5.21 (1H, d, *J* 11.8 Hz, OCH^AH^{B}Ph), 5.25 (1H, d, *J* 12.0 Hz, OCH^AH^BPh), 6.71 (2H, d, *J* 8.4 Hz, H3' and H5'), 6.97 (2H, d, *J* 8.4 Hz, H2' and H6'), 7.31-7.39 (5H, m, Ph). **^{13}C NMR** (100 MHz, Methanol-d_4) δ_C: 36.81 (CH_2), 55.40 (CH), 69.24 (CH_2), 116.95 (CH), 125.57 (C), 129.69 (CH), 129.82 (CH), 129.98 (CH), 131.73 (CH), 136.19 (C), 158.36 (C), 170.21 (C). **IR** ν_{max} (KBr)/cm^{-1}: 3404 (NH), 3138 (OH), 1739 (C=O). **MS** (FAB) *m/z* (%): 272 [(M^+, ammonium cation), 100], 93 (43). **HRMS** (FAB): 272.1285. [(M^+, ammonium cation), $C_{16}H_{18}NO_3$ requires 272.1287]. **$[\alpha]_D^{26}$** −16.12, (*c* 1.04, MeOH). ^{1}H NMR spectral data in broad agreement with those previously reported in a mixture $CDCl_3$-DMSO-d_6.[193]

Benzyl 2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-hydroxyphenyl)propanoate 10.10



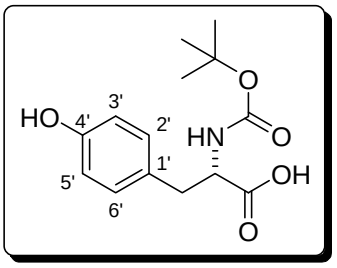
$C_{21}H_{25}NO_5$
MW: 371.43

Prodecure A: A solution of Boc_2O (373 mg, 1.71 mmol, 1.1 eq) in dioxane (1.6 mL) was added to a solution of (*S*)-tyrosine benzyl ester **10.9** (421 mg, 1.55 mmol, 1.0 eq) and Et_3N (0.35 mL, 2.5 mmol, 1.6 eq) in water (1.8 mL) at rt. After being stirred for 24 h, the reaction was acidified with 10 % $HCl_{(aq)}$ at 0 °C and then extracted with ethyl acetate (3 ×). The combined organic layers were washed with 5% $HCl_{(aq)}$ (2 ×). The ester **10.10** was obtained as a brown oil (498 mg, 87%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.25 (9H, s, ^{t}Bu), 2.86-2.89 (2H, m, C*H*$_2$CH), 4.43-4.49 (1H, m, C*H*CH$_2$), 4.96 (1H, d, *J* 12.3 Hz, OC*H*^{A}H^{B}Ph), 5.05 (1H, d, *J* 12.0 Hz, OCH^A*H*^{B}Ph), 5.11 (1H, d, *J* 8.3 Hz, N*H*), 6.60 (2H, d, *J* 8.4 Hz, H3' and H5'), 6.75 (2H, d, *J* 8.2 Hz, H2' and H6'), 7.15-7.24 (5H, m, Ph). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[194]

Procedure B: A solution of Boc_2O (338 mg, 1.55 mmol, 1.0 eq) in cyclohexane (0.3 mL) was added at 10 °C to a solution of (*S*)-tyrosine benzyl ester **10.9** (421 mg, 1.55 mmol, 1.0 eq) in cyclohexane (0.70 mL). After 20 h at 20 °C, the organic layer was washed with 0.01 N $HCl_{(aq)}$ and sat $NaHCO_{3(aq)}$. The solvent was removed under reduced pressure. The ester **10.10** was obtained as a brown oil (497 mg, 86%). Data as above.

2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-hydroxyphenyl)propanoic acid 10.12

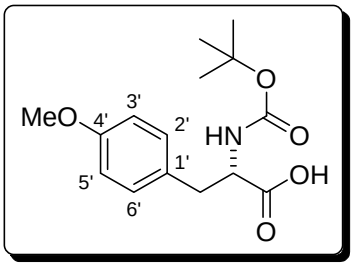


$C_{14}H_{19}NO_5$
MW: 281.30

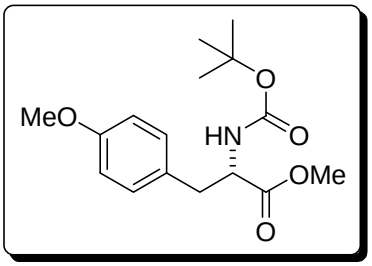
Following the procedure described by Jung and Lazarova,[264] triethylamine (5.8 mL, 42 mmol, 1.5 eq) was added to a solution of (*S*)-tyrosine **10.3** (5.00 g, 27.6 mmol, 1.0 eq) in dioxane/ water (1:1)(100 mL). The reaction flask was cooled to 0 °C and Boc_2O (6.60 g, 30.2 mmol, 1.1 eq) was added in one batch. After 0.5 h, the mixture was allowed to warm to rt and stirred overnight. The reaction mixture was then concentrated and the residue was diluted with water. The aqueous layer was extracted with ethyl acetate (3 ×), acidified to pH 1 with 1 M $HCl_{(aq)}$ and back extracted with ethyl acetate (2 ×). The combined organic extracts were washed with brine (1 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The acid **10.12** was obtained without further purification as a white foam (7.76 g, 100%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.36 (9H, s, ^{t}Bu), 2.93-3.01 (2H, m, C*H*$_2$CH), 4.47-4.52 (1H, m, C*H*CH$_2$), 5.00 (1H, d, *J* 8.4 Hz, N*H*), 5.87 (1H, br s, OH), 6.66 (2H, d, *J* 8.1 Hz, H3' and H5'), 6.98 (2H, d, *J* 8.2 Hz, H2' and H6'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[264]

2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-methoxyphenyl)propanoic acid 10.13 and methyl 2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-methoxyphenyl)propanoate 10.15



$C_{15}H_{21}NO_5$
MW: 295.33

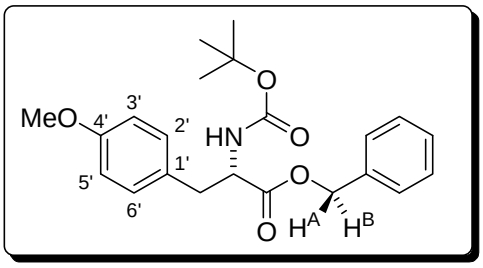


$C_{16}H_{23}NO_5$
MW: 309.36

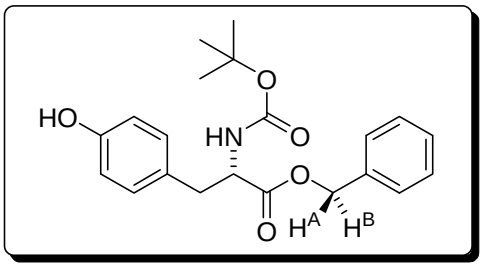
Iodomethane (1.7 mL, 28 mmol, 1.0 eq), K_2CO_3 (5.72 g, 41.4 mmol, 1.5 eq), *N*-Boc-(*S*)-tyrosine **10.12** (7.76 g, 27.6 mmol, 1.0 eq) and anhydrous DMF (20 mL) were stirred under argon at rt overnight. The reaction mixture was quenched with water (10 mL) and extracted with CH_2Cl_2 (3 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. The acid **10.13** was obtained in a 88:12 mixture of the acid **10.13** and the ester **10.15** as a yellow liquid (5.04 g, 88% mass recovery). The mixture was used without further purification.

Data on acid only **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 1.33 (9H, s, ^{t}Bu), 2.85-2.97 (2H, m, C*H*$_2$CH), 3.61 (3H, s, OMe), 4.38-4.43 (1H, m, C*H*CH$_2$), 5.10 (1H, d, *J* 7.4 Hz, N*H*), 6.71 (2H, d, *J* 8.2 Hz, H3' and H5'), 6.86 (2H, d, *J* 8.2 Hz, H2' and H6'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[265]

Benzyl 2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-methoxyphenyl) propanoate 10.11 and benzyl 2(*S*)-[*N*-(tert-butoxycarbonyl)amino]-3-(4'-hydroxyphenyl) propanoate 10.20



$C_{22}H_{27}NO_5$
MW: 385.45



$C_{21}H_{25}NO_5$
MW: 371.43

Procedure A: Following the procedure described by Rosenberg *et al.*,[198] sodium hydride [80% in mineral oil] (2.56 g, 85.4 mmol, 2.4 eq) was added to a solution of *N*-Boc-(*S*)-tyrosine **10.12** (10.04 g, 35.73 mmol, 1.0 eq) in anhydrous DMF (146 mL) at 0 °C under argon. After 1 h, iodomethane (2.2 mL, 36 mmol, 1.0 eq) was added and the reaction was stirred at 0 °C for 3 h. Benzyl bromide (4.7 mL, 39 mmol, 1.1 eq) was added and the reaction was allowed to warm to rt and was stirred for 2 h. The reaction was quenched with acetic acid (2.2 mL), poured into sat $NaHCO_{3(aq)}$ and extracted with ethyl acetate (3 ×). The organic layer was washed with brine (1 ×) and dried ($MgSO_4$). Then the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether–Et_2O (100:0–75:25)] gave a 96:4 inseparable mixture of the ether **10.11** and the alcohol **10.20** (8.48 g, 84% mass recovery) as an orange oil.

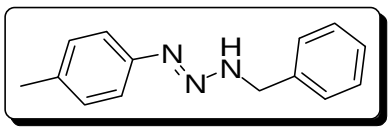
R_f [SiO_2, petroleum ether–Et_2O (70:30)] 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.47 (9H, s, ^{t}Bu), 3.07 (2H, m, CH_2CH), 3.79 (3H, s, OMe), 4.61-4.66 (1H, m, C*H*CH_2), 5.10 (1H, br s, N*H*), 5.13 (1H, d, *J* 11.9 Hz, OCH^AH^{B}Ph), 5.22 (1H, d, *J* 12.2 Hz, OCH^AH^BPh), 6.80 (2H, d, *J* 8.2 Hz, H3' and H5'), 6.99 (2H, d, *J* 8.2 Hz, H2' and H6'), 7.29-7.42 (5H, m, Ph). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 28.37 (CH_3), 37.39 (CH_2), 54.67 (CH), 55.19 (CH_3), 67.06 (CH_2), 79.85 (C), 113.98 (CH), 127.86 (C), 128.48 (CH), 128.61 (CH), 130.37 (CH), 135.32 (C), 155.18 (C), 158.65 (C), 171.87 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3370 (N-H), 1715 (C=O ester), 1612 (N-H), 1511 (C=C). **MS** (CI$^+$) *m/z* (%): 386 [(M+H)$^+$, 12], 250 [(M+H)$^+$ − BnO_2CH], 215 (100). **HRMS** (CI$^+$): 386.1964 [(M+H)$^+$, $C_{22}H_{28}NO_5$

requires 386.1967]. $[\alpha]_D^{24}$ −1.75, (*c* 1.07, $CHCl_3$). ^1H NMR and MS spectral data consistent with the literature.[198]

Procedure B: A solution of the 41:59 mixture of *N*-Boc-*O*-methoxy-(*S*)-tyrosine **10.13** and *N*-Boc-*O*-methoxy-(*S*)-tyrosine methyl ester **10.15** (4.00 g, 13.6 mmol, 1.0 eq), BnOH (1.5 mL, 15 mmol, 1.1 eq) and DMAP (166 mg, 1.36 mmol, 0.1 eq) in CH_2Cl_2 (21 mL) under argon was treated with a solution of DCC (3.10 g, 15.0 mmol, 1.1 eq) in CH_2Cl_2 (31 mL). The mixture was stirred at 25 °C for 45 min then cooled to 0 °C. The filtrate was washed with water (2 x), 10% AcOH. A precipitation was observed. The precipitate was removed by filtration and washed with cold CH_2Cl_2. The filtrate was washed with H_2O (2 x). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. Flash chromatography [cyclohexane – EtOAc (80:20 – 70:30)] gave the desired compound **10.11** (214 mg, 4%) as a uncolor oil. R_F [SiO_2, cyclohexane – EtOAc (70:30)] 0.56. Data as above

1-Benzyl-3-(4'-methylphenyl)triazene 10.19

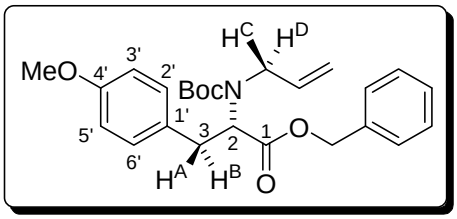


$C_{14}H_{15}N_3$
MW: 225.29

A mixture of crushed ice (50.00 g) and conc HCl (28 mL) was added to *p*-toluidine **10.18** (10.00 g, 93.33 mmol, 1.0 eq) at −10 °C. A solution of potassium nitrite (9.29 g, 109 mmol, 1.17 eq) in water (30 mL) was slowly added with continued stirring for 1 h until a positive starch-potassiun iodide test was obtained and the mixture was stirred for an additional hour. The mixture was then brought to pH 6.8-7.2 at 0 °C with a cold solution of sat $NaCO_{3(aq)}$. The solution was added slowly to a vigorously stirred mixture of Na_2CO_3 (30.00 g), 35% $benzylamine_{(aq)}$ (60 mL) and crushed ice (20.00 g). The reaction mixture was kept at −10 °C during the addition, and stirred for 4 h at rt. The solution was extracted with diethyl ether (3 ×). The combined organic extracts were dried (Na_2SO_4) and concentrated under reduced pressure to give the triazene **10.19** as a red solid (21.00 g, 100%), which was sufficiently pure for the next step.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.25 (3H, s, Me), 3.76 (1H, s, N*H*), 4.71 (2H, s, CH_2), 7.05 (2H, d, *J* 7.9 Hz, Ar-H), 7.14-7.28 (7H, m, Ar-H). **IR** ν_{max} (NaCl)/cm^{-1}: 3220 (NH), 1643 (C=C), 1519 (NH). **MS** (EI) *m/z* (%): 106 ($C_6H_5CH{=}NH_2^+$, 20), 91 ($C_6H_5CH_2^+$, 100). **HRMS** (EI): 225.1267 (M^+, $C_{14}H_{15}N_3$ requires 225.1266). Compound reported in the literature without spectroscopic data provided.[266]

Benzyl 2(*S*)-[*N*-allyl-*N*-(tert-butoxycarbonyl) amino]-3-(4''-methoxyphenyl)propanoate 10.4



$C_{25}H_{31}NO_5$
MW: 425.52

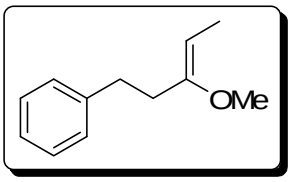
Sodium hydride [80% in mineral oil] (506 mg, 16.9 mmol, 1.3 eq) was added portion-wise to a solution of the amine **10.11** and alcohol **10.20** (4.99 g, 13.0 mmol, 1.0 eq) and allyl bromide (1.5 mL, 17 mmol, 1.3 eq) in anhydrous DMF (75 mL) at 0 ^oC under argon. The reaction mixture was then allowed to warm to rt and stirred for 5.5 h. After this time, the reaction mixture was carefully poured into iced-water and extracted into ethyl acetate (2 $\times$). The combined organics were then washed with water (3 $\times$), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether–Et_2O (100:0–85:15)] gave the ester **10.4** (2.8 mg, 51%) as an oil.

R_f [SiO_2, petroleum ether–Et_2O (70:30)] 0.33

^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C) δ_H: 1.34 (9H, s, ^{t}Bu), 3.05 (1H, dd, *J* 9.3 and 14.2 Hz, C*H*^{A}H^B-3), 3.20 (1H, dd, *J* 5.8 and 14.0 Hz, CH^A*H*^{B}-3), 3.41 (1H, dd, *J* 6.2 and 15.6 Hz, NC*H*^{C}H^D), 3.71-3.77 (4H, m, OCH_3 and NCH^C*H*^{D}), 4.37-4.41 (1H, m, C*H*-2), 4.90-5.15 (4H, m, =CH_2 and OCH_2Ph), 5.49-5.58 (1H, m, C*H*=), 6.82 (2H, d, *J* 8.9 Hz, H3' and H5'), 7.09 (2H, d, *J* 8.9 Hz, H2' and H6'), 7.28-7.34 (5H, m, Ph). **^{13}C NMR** (100 MHz, DMSO-d_6 at 90 °C) δ_C: 27.95 (CH_3), 34.59 (CH_2), 49.99 (CH_2), 55.18 (CH), 61.00 (CH_3), 66.06 (CH_2), 69.75 (CH_2), 79.60 (C), 113.94 (CH), 127.63 (CH), 127.83 (CH),128.21 (CH), 129.89 (C), 130.06 (CH), 134.63 (CH), 135.91 (C), 154.20 (C), 158.21 (C), 170.41 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1739 (C=O), 1693 (C=O), 1647 (C=C), 1246 (C-O ether), 1163 (C-O ester). **MS** (CI^+) *m/z*

(%): 426 [(M+H)$^+$, 77], 370 (100), 326 (91). **HRMS**: 426.2281 [(M+H)$^+$, $C_{25}H_{31}NO_5$ requires 426.2280]. **[α]$_D^{26}$** −27.69, (*c* 1.4, $CHCl_3$).

3-Methoxy-5-phenylpent-2(*Z*)-ene 10.23

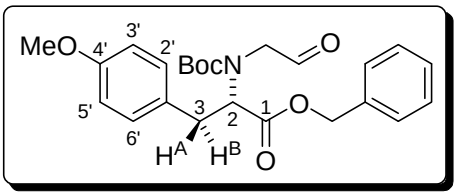


$C_{12}H_{16}O$
MW: 176.25

$TiCl_4$ (2.7 mL, 25 mmol, 4.0 eq) was added slowly to a stirred solution of freshly distilled THF (42 mL) at 0 °C under argon. Freshly distilled and dry TMEDA (7.4 mL, 49 mmol, 8.0 eq) was added drop-wise to the solution. After 0.5 h at 0 °C, Zinc (3.59 g, 54.9 mmol, 9.0 eq) (previously activated by washing several times with 5% $HCl_{(aq)}$, H_2O, acetone, Et_2O and drying under vacuum) was added to the mixture at 0 °C in many portions in such a manner that the temperature remained at 0 °C. Then $PbCl_2$ (75 mg, 0.27 mmol, 44 meq) was added and the resulting suspension was warmed to 25 °C. A solution of methyl 3-phenyl propionate **10.22** (0.95 mL, 6.1 mmol, 1.0 eq) and 1.1-dibromoethane (1.2 mL, 13 mmol, 2.2 eq) in dry THF (1.6 mL) was added via an addition funnel over a period of 10 min at 25 °C and stirring was continued for 3.8 h. The reaction mixture was then cooled to 0 °C and sat $K_2CO_{3(aq)}$ (10 mL) was added. After stirring at 0 °C for an additional 15 min, the mixture was poured into Et_2O (40 mL) and then passed through a short column of basic alumina (pre-treated by shaking with 6% weight of water) to filter off the solid formed during the quench. The layers were separated and the aqueous layer extracted with Et_2O, the combined ethered extracts were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was treated with hexane and the insoluble precipitate formed was filtered off by passing through a short column of basic alumina eluting with hexane. Removal of solvents under reduced pressure gave the enol ether **10.23** as an oil (624 mg, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.66 (3H, m, C*H*$_3$CH), 2.44-2.52 (2H, m, C*H*$_2$), 2.78-2.87 (2H, m, C*H*$_2$), 3.65 (3H, s, OC*H*$_3$), 4.67 (1H, q, *J* 6.8 Hz, C*H*CH$_3$), 7.24-7.38 (5H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[267]

Benzyl 2(*S*)-[*N*-(tert-butoxycarbonyl)-*N*-(2'-oxoethyl)amino]-3-(4''-methoxyphenyl) propanoate 10.24



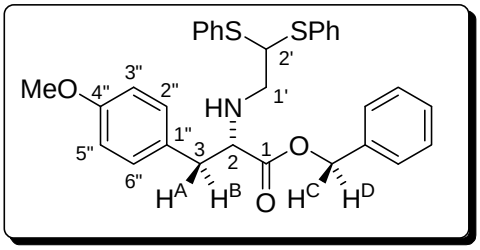
$C_{24}H_{29}NO_6$
MW: 427.49

A suspension of $K_2OsO_4.2H_2O$ (30 mg, 0.08 mmol, 2 mol%) in deionised water (1.5 mL) was added to a stirred solution of alkene **10.4** (1.71 g, 4.02 mmol, 1.0 eq) in THF (11 mL) at rt. Then $NaIO_4$ (2.58 g, 12.1 mmol, 3.0 eq) in water (23 mL) was added over 0.5 h. After stirring at rt for a further 0.5 h, the reaction was diluted with Et_2O (50 mL) and quenched with sat $Na_2S_2O_{3(aq)}$ (40 mL). The aqueous layer was extracted with Et_2O (3 ×) and the combined organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-Et_2O (100:0-30:70)] gave the aldehyde **10.24** (1.02 g, 60%) as an oil.

R_f [SiO_2, petroleum ether–Et_2O (40:60)] 0.58

^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C) δ_H: 1.29 (9H, s, ^{t}Bu), 3.02 (1H, dd, *J* 9.8 and 14.3 Hz, C*H*^{A}H^B-3), 3.19 (1H, dd, *J* 5.6 and 14.3 Hz, CH^A*H*^{B}-3), 3.70 (5H, m, OCH_3 and C*H*$_2$N), 4.78-4.87 (1H, br s, H2), 5.08 (2H, s, OC*H*$_2$Ph), 6.82 (2H, d, *J* 7.8 Hz, H3' and H5'), 7.12 (2H, d, *J* 7.6 Hz, H2' and H6'), 7.28-7.41 (5H, m, Ph), 9.12 (1H, s, CHO). **^{13}C NMR** (100 MHz, DMSO-d_6 at 90 °C) δ_C: 27.73 (CH_3), 34.51 (CH_2), 55.20 (CH_2), 55.57 (CH), 66.36 (CH_3), 69.74 (CH_2), 80.70 (C), 114.06 (CH), 127.32 (CH), 127.77 (CH), 127.98 (CH), 128.29 (CH), 129.98 (C), 135.73 (C), 154.49 (C), 158.32 (C), 170.39 (C), 199.36 (CH). **IR** ν_{max} (NaCl)/cm^{-1}: 1735 (C=O ester), 1698 (C=O aldehyde), 1513 (C=C). **MS** (CI$^+$) m/z (%): 428 [(M+H)$^+$, 15], 372 [(M+H)$^+$ – $(CH_3)_2C{=}CH_2$, 100], 328 [(M+H)$^+$ – $(CH_3)_2C{=}CH_2$ and CO_2, 29]. **HRMS** (CI$^+$): 428.2070. [(M+H)$^+$, $C_{24}H_{30}NO_6$ requires 428.2073]. **$[\alpha]_D^{24}$** –7.67, (*c* 2.3, $CHCl_3$).

Benzyl 2(*S*)-*N*-[2',2'-*bis*(phenylthio)ethylamino]-3-(4''-methoxyphenyl) propanoate 10.27



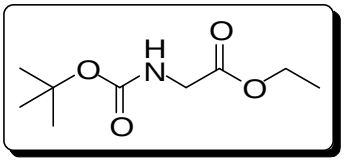
$C_{31}H_{31}NO_3S_2$
MW: 529.71

$BF_3.OEt_2$ (0.1 mL, 0.55 mmol, 1.1 eq) was added to a solution of aldehyde **10.24** (200 mg, 0.47 mmol, 1.0 eq), thiophenol (0.1 mL, 1.1 mmol, 2.3 eq) and acetic acid (0.40 mL) in dry toluene (1 mL) under argon. After 4 h, the reaction mixture was diluted with CH_2Cl_2 (10 mL) and washed with water (3 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, hexane-ethyl acetate (100:0-70:30)] gave the thioacetal **10.27** (50 mg, 20%) as an oil.

R_f [SiO_2, hexane-ethyl acetate (60:40)] 0.32

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.96 (1H, br s, N*H*), 2.71 (1H, dd, *J* 5.8 and 12.5 Hz, C*H*^{A}H^B-3), 2.83 (2H, d, *J* 7.0 Hz, C*H*$_2$N), 2.89 (1H, dd, *J* 6.7 and 12.5 Hz, CH^A*H*^{B}-3), 3.43 (1H, t, *J* 6.8 Hz, C*H*-2'), 3.68 (3H, s, OC*H*$_3$), 4.35 (1H, t, *J* 6.2 Hz, C*H*-2), 4.93 (1H, d, *J* 12.2 Hz, OCH^C*H*^{D}Ph), 4.97 (1H, d, *J* 12.2 Hz, OC*H*^{C}H^{D}Ph), 6.70 (2H, d, *J* 8.7 Hz, H3" and H5"), 6.97 (2H, d, *J* 8.7 Hz, H2" and H6"), 7.10-7.36 (15H, m, 3 x Ph). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 37.67 (CH_2), 50.45 (CH_2), 54.17 (CH_3), 57.29 (CH), 61.95 (CH), 65.45 (CH_2), 112.86 (CH),126.66 (CH), 126.78 (CH), 127.14 (CH), 127.20 (CH), 127.37 (CH), 127.81 (CH), 129.13 (CH), 129.17 (CH), 131.51 (CH), 131.82 (CH), 132.44 (C), 132.61 (C), 134.47 (C), 157.44 (C), 172.92 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3442 (N-H stretching), 1732 (C=O), 1612 (NH bending). **MS** (CI$^+$) *m/z* (%): 530 [(M+H)$^+$, 74], 422 [(M+H)$^+$ – $HOCH_2C_6H_5$, 100], 420 [(M+H)$^+$ – HSPh, 58], 312 [(M+H)$^+$ – $HOCH_2C_6H_5$ and – HSPh, 32], 286 [(M+H)$^+$ – CH_2=C(SPh)$_2$, 34], 167 (63). **HRMS** (CI$^+$): 530.1813. [(M+H)$^+$, $C_{31}H_{32}NO_3S_2$ requires 530.1824]. **[α]$_D^{25}$** + 0.43, (*c* 0.7, $CHCl_3$).

Ethyl 2-[*N*-(*tert*-butoxycarbonylamino)]acetate 10.41

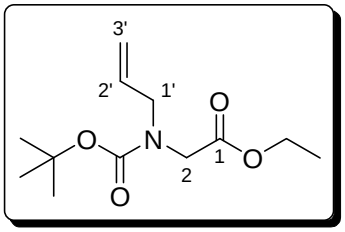


$C_9H_{17}NO_4$
MW: 203.24

The reaction was carried out according to procedure described for compound **10.10** using triethylamine (6.0 mL, 43 mmol, 2.0 eq) and a stirred solution of glycine ethyl ester hydrochloride **10.28** (3.00 g, 21.5 mmol, 1.0 eq) in dioxane/water (1:1) (69 mL). The carbamate **10.41** was obtained without further purification as an oil (4.37 g, 100%).

^{1}H NMR (400 MHz, DMSO-d_6) δ_H: 1.20 (3H, t, *J* 7.0 Hz, C*H*$_3$CH$_2$), 1.40 (9H, s, ^{t}Bu), 3.67 (2H, d, *J* 6.0 Hz, C*H*$_2$N), 4.09 (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 6.57 (1H, br s, N*H*). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[268,269]

Ethyl 2-[*N*-allyl-*N*-(*tert*-butoxycarbonyl)amino]acetate 10.29



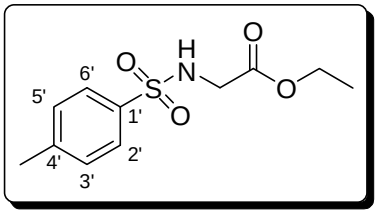
$C_{12}H_{21}NO_4$
MW: 243.30

The reaction was carried out according to procedure described for compound **10.4** using sodium hydride [80% in mineral oil] (837 mg, 27.7 mmol, 1.3 eq), carbamate **10.41** (4.36 g, 21.5 mmol, 1.0 eq) and allyl bromide (2.4 mL, 28 mmol, 1.3 eq) in anhydrous DMF (119 mL). The ester **10.29** was obtained (4.74 g, 91%) as a yellow liquid.

R_f [SiO_2, petroleum ether-Et_2O (70:30)] 0.48

1H NMR (400 MHz, DMSO-d6 at 90 °C) δ_H: 1.20 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 1.39 (9H, s, ^{t}Bu), 3.75-3.88 (4H, m, CH_2-2 and CH_2-1'), 4.12 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 5.09 (1H, d, *J* 10.3 Hz, C*H*^{A}H^B=), 5.13 (1H, d, *J* 17.4 Hz, CH^A*H*^{B}=), 5.71 (1H, m, C*H*=). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[270]

Ethyl 2-(*p*-toluenesulfonamido)acetate 10.42



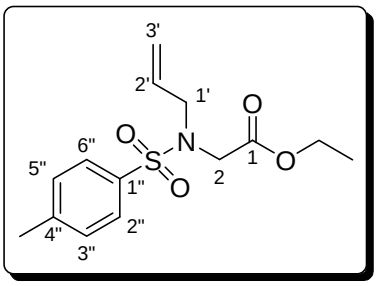
$C_{11}H_{15}NO_4S$
MW: 257.31

Following the procedure described by Shipov *et al.*,[203] triethylamine (2.0 mL, 14 mmol, 2.0 eq) was added to a cooled suspension of glycine ethyl ether hydrochloride salt **10.28** (1.00 g, 7.16 mmol, 1.0 eq) in dry CH_2Cl_2 (14 mL), then *p*-TsCl (1.37 g, 7.16 mmol, 1.0 eq) was added portion-wise. The reaction mixture was stirred at 21 °C for 4.5 h under argon. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The mixture was dissolved in Et_2O and the excess of triethylamine was removed by washing with 1 M $HCl_{(aq)}$ (2 ×), then the aqueous layer was extracted with Et_2O (3 ×). The combined organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. The sulfonamide **10.42** was obtained without further purification as a yellow oil (1.48 g, 80%).

R_f [SiO_2, petroleum ether–ethyl acetate (70:30)] 0.36

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.11 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 2.35 (3H, s, CH$_3$Ar), 3.69 (2H, d, *J* 5.1 Hz, C*H*$_2$N), 4.01 (2H, q, *J* 7.2 Hz, C*H*$_2$CH$_3$), 5.00 (1H, br s, N*H*), 7.24 (2H, d, *J* 8.1 Hz, H3' and H5'), 7.68 (2H, d, *J* 8.3 Hz, H2' and H6'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 13.99 (CH_3), 21.55 (CH_3), 44.17 (CH_2), 61.92 (CH_2), 127.29 (CH), 129.76 (CH), 136.12 (C), 143.84 (C), 168.79 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3221 (NH), 1732 (C=O ester), 1620 (NH). **MS** (EI) *m/z* (%): 257 ($M^{+\cdot}$, 18), 184 ($TsNHCH_2^+$, 100), 155 ($CH_3C_6H_4SO_2^+$, 94), 91 ($CH_3C_6H_4^+$, 84). **HRMS** (EI): 257.0725 (M^+, $C_{11}H_{15}NO_4S$ requires 257.0722). **Microanalysis**: Theory C: 51.36% H: 5.84% N: 5.45%; Results C: 51.34% H: 5.89% N: 5.51%.

Ethyl 2-(*N*-allyl-*p*-toluenesulfonamido)acetate 10.30



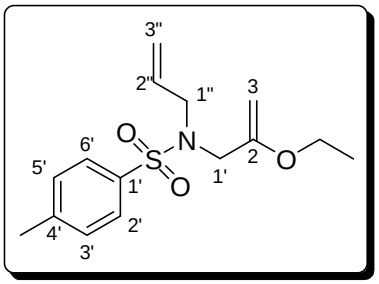
$C_{14}H_{19}NO_4S$
MW: 297.37

The reaction was carried out following the procedure described for compound **10.29** using sodium hydride [80% in mineral oil] (3.04 g, 102 mmol, 1.3 eq), sulfonamide **10.42** (20.17 g, 78.5 mmol, 1.0 eq) and allyl bromide (8.8 mL, 100 mmol, 1.3 eq) in anhydrous DMF (436 mL). Flash chromatography [SiO_2, petroleum ether–ethyl acetate (95:5–80:20)] gave the ester **10.30** (14.52 g, 63%) as an oil.

R_f [SiO_2, petroleum ether–ethyl acetate (70:30)] 0.71

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.19 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 2.42 (3H, s, C*H*$_3$Ar), 3.90 (2H, d, *J* 6.4 Hz, C*H*$_2$-1'), 4.00 (2H, s, C*H*$_2$-2), 4.08 (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 5.16 (1H, d, *J* 17.6 Hz, C*H*^{A}H^B=), 5.18 (1H, d, *J* 10.9 Hz, CH^A*H*^{B}=), 5.64-5.74 (1H, m, C*H*=), 7.30 (2H, d, *J* 7.7 Hz, H3" and H5"), 7.74 (2H, d, *J* 7.8 Hz, H2" and H6"). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 14.04 (CH_3), 21.52 (CH_3), 47.00 (CH_2), 50.74 (CH_2), 61.20 (CH_2), 119.81 (CH_2), 127.37 (CH), 129.58 (CH), 132.30 (CH), 136.89 (C), 143.19 (C), 168.85 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1739 (C=O ester), 1644 (C=C allyl), 1597 (C=C arom). **MS** (CI$^+$) *m/z* (%): 298 [(M+H)$^+$, 24], 89 (100). **HRMS** (CI$^+$): 298.1108 [(M+H)$^+$, $C_{14}H_{20}NO_4S$ requires 298.1113].

***N*-allyl-*N*-(2-ethoxyprop-2-en-1-yl)-*p*-toluenesulfonamide 10.33**



$C_{15}H_{21}NO_3S$
MW.: 295.40

Procedure A: A 1.07 M solution of Cp_2TiMe_2 **10.21** (3.2 mL, 3.4 mmol, 3.0 eq) in toluene-THF (1:1 by mass) was added to the ester **10.30** (344 mg, 1.16 mmol, 1.0 eq) and sealed in a 10 mL microwave tube under argon. The mixture was

irradiated over 10 min under 100 W microwave power to raise the internal temperature to 65 °C before cooling. The resultant black solution was concentrated under reduced pressure. Flash chromatography [Al_2O_3, petroleum ether–CH_2Cl_2 (80:20–60:40)] gave the enol ether **10.33** (71 mg, 21%) as a brown oil.

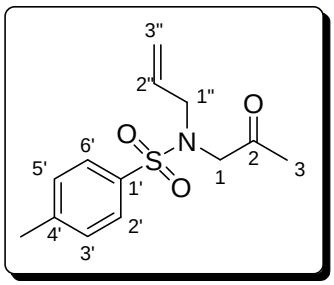
R_f [Al_2O_3, petroleum ether-CH_2Cl_2 (60:40)] 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ_H:1.05 (3H, t, *J* 6.9 Hz, C*H*$_3$CH$_2$), 2.34 (3H, s, C*H*$_3$Ar), 3.50 (2H, q, *J* 7.0 Hz, C*H*$_2$CH$_3$), 3.76-3.77 (4H, m, 2 x C*H*$_2$N), 3.89 (1H, d, *J* 2.3 Hz, C*H*^{A}H^B-3), 3.98 (1H, d, *J* 2.3 Hz, CH^A*H*^{B}-3), 5.08 (1H, d, *J* 9.1 Hz, C*H*^{C}H^D-3"), 5.09 (1H, d, *J* 17.3 Hz, CH^C*H*^{D}-3"), 5.55-5.65 (1H, m, C*H*=), 7.19 (2H, d, *J* 8.1 Hz, H3' and H5'), 7.66 (1H, d, *J* 8.3 Hz, H2' and H6'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 14.19 (CH_3), 21.45 (CH_3), 49.21 (CH_2), 49.81 (CH_2), 62.96 (CH_2), 84.61 (CH_2), 118.91 (CH_2), 127.61 (CH), 129.05 (CH), 132.86 (CH), 137.78 (C), 142.92 (C), 157.28 (C). **IR** ν_{max} (ATR)/cm^{-1}: 2980 (CH sp^3 and sp^2), 1631 (C=C), 1599 (C=C arom), 1155 (C-O ether).

Due to the relative instability of this compound, we decided to carry onto the next step without more characterization

Procedure B: A 1.07 M solution of Cp_2TiMe_2 **10.21** (4.6 mL, 5.0 mmol, 3.0 eq) in toluene-THF (1:1 by mass) was added to the ester **10.30** (49.1 mg, 1.65 mmol, 1.0 eq) and the mixture stirred under argon at 65 °C in the dark for 24 h. After this time, the mixture was diluted with petroleum ether and filtered. The filtrate was concentrated under reduced pressure. Flash chromatography [Al_2O_3, petroleum ether–ethyl acetate (100:0–50:50)] then gave the enol ether **10.33** (187 mg, 38%) as a yellow oil. Data as above.

N-allyl-*N*-(2-oxopropyl)-*p*-toluenesulfonamide 10.43



$C_{13}H_{17}NO_3S$
MW: 267.34

Procedure C: The reaction was carried out according to procedure A using a 1.07 M solution of Cp_2TiMe_2 **10.21** (3.2 mL, 3.4 mmol, 3.0 eq) in toluene-THF (1:1 by mass) and the ester **10.30** (344 mg, 1.16 mmol, 1.0 eq). The resultant black solution was concentrated under reduced pressure. 1 M $HCl_{(aq)}$ (10 mL) was added to a solution of the crude mixture in THF (11 mL). The mixture was stirred for 1 h at 21 °C. After this time, the reaction mixture was poured into water and extracted into ethyl acetate (3 ×). The combined organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [petroleum ether-Et_2O (100:0–80:20)] gave the ketone **10.43** (15 mg, 5%) as a yellow oil.

R_f [SiO_2, petroleum ether-Et_2O (70:30)] 0.33

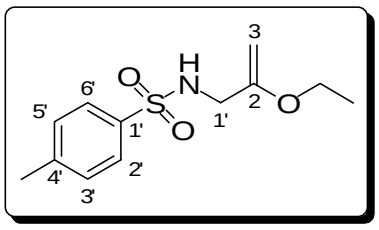
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.11 (3H, s, C*H*$_3$CO), 2.37 (3H, s, C*H*$_3$Ar), 3.74 (2H, d, *J* 6.6 Hz, C*H*$_2$-1"), 3.84 (2H, s, C*H*$_2$-1), 5.07 (1H, qd, *J* 1.3 and 17.0 Hz, C*H*^{A}H^B=), 5.11 (1H, qd, *J* 1.1 and 10.1 Hz, CH^A*H*^{B}=), 5.59 (1H, ddt, *J* 10.1, 16.8 and 6.7 Hz, C*H*=), 7.24 (2H, d, *J* 7.8 Hz, H3' and H5'), 7.64 (2H, d, *J* 7.6 Hz, H2' and H6'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 19.84 (CH_3), 25.31 (CH_3), 49.79 (CH_2), 53.83 (CH_2), 118.64 (CH_2), 125.67 (CH), 127.98 (CH), 130.37 (CH), 134.32 (C), 141.97 (C), 202.30 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 1734 (C=O ketone), 1643 (C=C). **MS** (CI^+) *m/z* (%): 268 [$(M+H)^+$, 87], 157 ($CH_3C_6H_4SO_2H_2^+$, 39), 136 (55), 112 [$(CH_2$=CHCH=NHCH$_2$COCH$_3)^+$, 100]. **HRMS** (CI^+): 268.1006 [$(M+H)^+$, $C_{13}H_{18}NO_3S$ requires 268.1007].

Procedure D: Grubbs 1st generation catalyst **10.45** (50 mg, 60 μmol, 30 mol%) was added to a stirred solution of enol ether **10.33** (58 mg, 0.20 mmol, 1.0 eq) in dry CH_2Cl_2 (1 mL) under argon. The mixture was stirred at 50 °C for 6 h. The solvent was removed under reduced pressure. The crude mixture was then stirred with THF (2 mL) and 1 M HCl (5 mL) for 1 h. The reaction was quenched with water and the aqueous layer extracted with ethyl acetate. The organic layer was dried ($MgSO_4$) and then concentrated under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-70:30)] gave the ketone **10.43** (34 mg, 65%) as an oil. Data as above.

Procedure E: Grubbs 2nd generation catalyst **10.46** (11 mg, 10 μmol, 5 mol%) was added to a stirred solution of enol ether **10.33** (69 mg, 0.23 mmol, 1.0 eq)

in dry CH_2Cl_2 (23 mL) under argon. The mixture was stirred at 50 °C for 1 h. The solvent was removed under reduced pressure. Flash chromatography [Al_2O_3, hexane-ethyl acetate (100:0-80:20)] gave the ketone **10.43** (28 mg, 46%) as an oil. Data as above.

N-(2-ethoxyprop-2-en-1-yl)-*p*-toluenesulfonamide 10.44

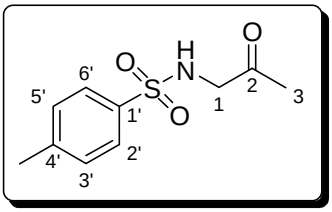


$C_{12}H_{17}NO_3S$
MW: 255.33

The reaction was carried out according to procedure A using a 1.07 M solution of Cp_2TiMe_2 **10.21** (3.2 mL, 3.4 mmol, 3.0 eq) in toluene-THF (1:1 by mass) and the ester **10.30** (344 mg, 1.16 mmol, 1.0 eq). Flash chromatography [Al_2O_3, petroleum ether–CH_2Cl_2 (80:20–60:40)] gave the enol ether **10.44** (110 mg, 37%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.18 (3H, t, *J* 6.9 Hz, CH_2CH_3), 2.42 (3H, s, $ArCH_3$), 3.53 (2H, q, *J* 7.0 Hz, OCH_2), 3.59 (2H, d, *J* 6.3 Hz, CH_2), 3.84 (1H, br s, CH^AH^B=), 3.98 (1H, br s, CH^AH^B=), 4.90 (1H, br s, NH), 7.28 (2H, d, *J* 8.1 Hz, Ar), 7.74 (2H, d, *J* 8.2 Hz, Ar).

N-(2-oxopropyl)-*p*-toluenesulfonamide 10.47



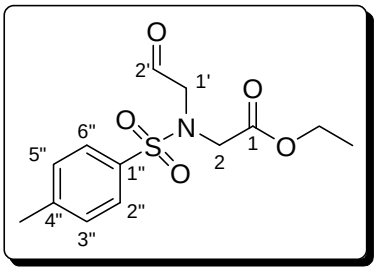
$C_{10}H_{13}NO_3S$
MW: 227.28

The reaction was carried out according to procedure D using Grubbs 1st generation catalyst **10.45** (50 mg, 60 μmol, 30 mol%) and a stirred solution of enol ether **10.33** (58 mg, 0.20 mmol, 1.0 eq) in dry CH_2Cl_2 (1 mL). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-70:30)] gave the ketone **10.47** (15 mg, 35%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.15 (3H, s, CH_3CO), 2.44 (3H, s, CH_3Ar), 3.71 (2H, br s, CH_2N), 5.48-5.51 (1H, m, N*H*), 7.32 (2H, d, *J* 8.1 Hz, H3' and H5'), 7.67

(2H, d, *J* 8.1 Hz, H2' and H6'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[271]

Ethyl 2-[*N*-(2'-oxoethyl)-*p*-toluenesulfonamido]acetate 10.48



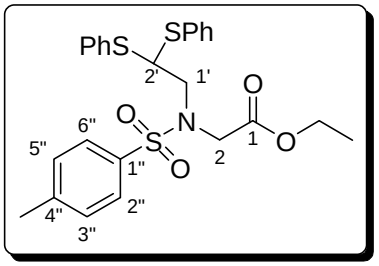
$C_{13}H_{17}NO_5S$
MW: 299.34

The reaction was carried out according to procedure described for compound **10.24** using $K_2OsO_4.2H_2O$ (50 mg, 0.13 mmol, 2 mol%) in deionised water (2.7 mL), a stirred solution of alkene **10.30** (2.00 g, 6.73 mmol, 1.0 eq) in THF (19 mL) and $NaIO_4$ (4.32 g, 20.2 mmol, 3.0 eq) in water (39 mL).Flash chromatography [SiO_2, petroleum ether–ethyl acetate (100:0-40:60)] gave the aldehyde **10.48** (1.42 g, 71%) as a yellow oil.

R_f [SiO_2, petroleum ether–ethyl acetate (60:40)] 0.41

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.21 (3H, t, *J* 7.2 Hz, C*H*$_3$CH$_2$), 2.43 (3H, s, C*H*$_3$Ar), 3.98 (2H, s, C*H*$_2$-2), 4.08-4.14 (4H, m, C*H*$_2$-1' and C*H*$_2$CH$_3$), 7.33 (2H, d, *J* 8.1 Hz, H3" and H5"), 7.69 (2H, d, *J* 8.3 Hz, H2" and H6"), 9.70 (1H, s, C*H*O). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 13.99 (CH_3), 21.03 (CH_3), 49.99 (CH_2), 57.40 (CH_2), 61.48 (CH_2), 127.60 (CH), 130.29 (CH), 135.58 (C), 143.97 (C), 168.48 (C), 198.18 (CH). **IR** ν_{max} (ATR)/cm^{-1}: 2983 (CH sp^3), 1732 (C=O aldehyde and ester), 1597 (C=C arom). **MS** (FAB) *m/z* (%): 300 [(M+H)$^+$, 100]. **HRMS** (FAB): 300.0905 [(M+H)$^+$, $C_{13}H_{18}NO_5S$ requires 300.0906].

Ethyl 2-{*N*-[2',2'-*bis*(phenylthio)ethyl]-*p*-toluenesulfonamido}acetate 10.49



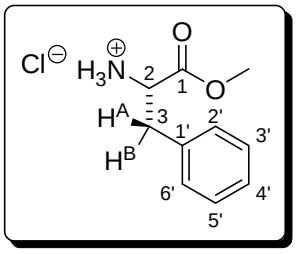
$C_{25}H_{27}NO_4S_3$
MW: 501.68

The reaction was carried out according to procedure described for compound **10.27** using $BF_3.OEt_2$ (0.54 mL, 4.31 mmol, 1.1 eq), aldehyde **10.48** (1.17 mg, 3.92 mmol, 1.0 eq), thiophenol (0.92 mL, 9.00 mmol, 2.3 eq) and acetic acid (3.5 mL) in dry toluene (9 mL). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-60:40)] gave the thioacetal **10.49** (957 mg, 49%) as an oil.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.49

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.12 (3H, t, *J* 7.1 Hz, C*H*$_3$CH$_2$), 2.36 (3H, s, C*H*$_3$Ar), 3.52 (2H, d, *J* 7.1 Hz, C*H*$_2$-1'), 3.98 (2H, q, *J* 7.1 Hz, C*H*$_2$CH$_3$), 4.37 (2H, s, C*H*$_2$-2), 4.82 (1H, t, *J* 7.2 Hz, C*H*-2'), 7.14 (2H, d, *J* 8.1 Hz, H3" and H5"), 7.32-7.38 (8H, m, H2" and H6" and Ar-H), 7.49 (4H, d, *J* 7.3 Hz, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 13.43 (CH_3), 20.99 (CH_3), 50.54 (CH_2), 51.81 (CH_2), 57.20 (CH), 60.73 (CH_2), 126.93 (CH), 127.46 (CH), 128.57 (CH), 128.83 (CH), 131.99 (CH), 132.89 (C), 135.36 (C), 142.99 (C), 168.27 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1737 (C=O ester), 1577 (C=C). **MS** (FAB) *m/z* (%): 524 [$(M+Na)^+$, 100], 392 (86), 237 (99). **HRMS** (FAB): 524.0999 [$(M+Na)^+$, $C_{25}H_{27}NO_4S_3Na$ requires 524.1000].

Methyl 2(*S*)-amino-3-phenylpropanoate, hydrochloride salt 10.58

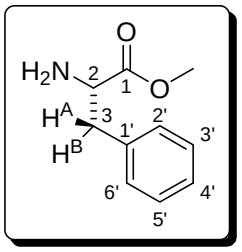


$C_{10}H_{14}ClNO_2$
MW: 215.68

Following the procedure described by Hvidt and Szarek,[213] *(S)*-phenylalanine **10.51** (21.00 g, 127 mmol, 1.0 eq) was added to a stirred solution of thionyl chloride (11.0 mL, 152 mmol, 1.2 eq) in methanol (350 mL) and the resulting mixture heated under reflux for 18 h. The mixture was then evaporated under reduced pressure, affording in quantitative yield (27.31 g) a crystalline product **10.58** that was used without further purification.

^{1}H NMR (400 MHz, D_2O) δ_H: 3.15 (1H, dd, *J* 7.6 and 13.9 Hz, C*H*^{A}H^B-3), 3.27 (1H, dd, *J* 5.8 and 13.9 Hz, CH^A*H*^{B}-3), 3.76 (3H, s, OC*H*$_3$), 4.35 (1H, dd, *J* 5.8 and 7.6 Hz, C*H*N), 7.20-7.22 (2H, m, H2' and H6'), 7.30-7.37 (3H, m, H3', H4' and H5'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[213]

Methyl 2(*S*)-amino-3-phenylpropanoate 10.59

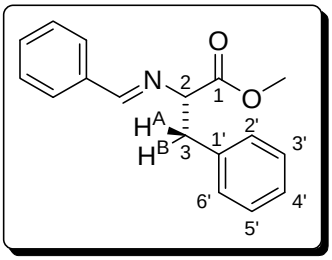


$C_{10}H_{13}NO_2$
MW: 179.22

Following the procedure described by Garner and Kaniskan,[214] a solution of (*S*)-phenylalanine methyl ester hydrochloride salt **10.58** (27.31 g, 127.0 mmol) in dry CH_2Cl_2 was shaken with concentrated aqueous ammonia solution (2 ×). The organic layer was dried ($MgSO_4$), filtered and the solvent was removed under reduced pressure to afford the free amine **10.59** as a liquid (21.49 g, 95%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.42 (2H, br s, NH_2), 2.84 (1H, dd, *J* 7.8 and 13.4 Hz, CH^AH^B-3), 3.07 (1H, dd, *J* 5.1 and 13.6 Hz, CH^AH^B-3), 3.68-3.73 (4H, m, OCH_3 and C*H*N), 7.17 (2H, d, *J* 7.6 Hz, H2' and H6'), 7.21-7.31 (3H, m, H3', H4' and H5'). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 41.10 (CH_2), 51.97 (CH), 55.84 (CH_3), 126.82 (CH), 128.56 (CH), 129.26 (CH), 137.23 (C), 175.45 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3383 (NH_2), 3003 (CH sp^2), 1734 (C=O ester). **MS** (FAB) *m/z* (%): 180 [(M+H)$^+$, 100]. **HRMS** (FAB): 180.1027 [(M+H)$^+$, $C_{10}H_{14}NO_2$ requires 180.1025]. **$[\alpha]_D^{22}$** + 28.85, (*c* 1.26, $CHCl_3$).

Methyl 2(*S*)-(*N*-benzylidenamino)-3-phenylpropanoate 10.52

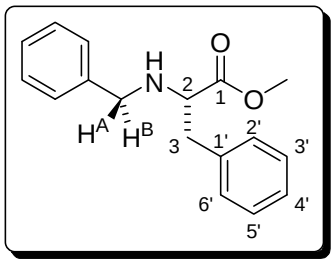


$C_{17}H_{17}NO_2$
MW: 267.32

Benzaldehyde (4.7 mL, 47 mmol, 1.0 eq) was added to a stirred mixture of free amine **10.59** (10.01 g, 55.92 mmol, 1.2 eq) in dry CH_2Cl_2 (280 mL) and $MgSO_4$. The mixture was stirred at rt under argon for 20 h. After filtration, the solvent was removed under reduced pressure and the crude product **10.52** (14.95 g, quant) was used in the next step without purification due to its instability.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.15 (1H, dd, *J* 8.8 and 13.4 Hz, C*H*^{A}H^B-3), 3.37 (1H, dd, *J* 5.1 and 13.6 Hz, CH^A*H*^{B}-3), 3.73 (3H, s, OC*H*$_3$), 4.17 (1H, dd, *J* 5.1 and 8.8 Hz, C*H*N), 7.14-7.24 (5H, m, Ph), 7.36-7.40 (3H, m, H3', H4' and H5'), 7.66-7.69 (2H, m, H2' and H6'), 7.90 (1H, s, C*H*=N). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[214]

Methyl 2(*S*)-(*N*-benzylamino)-3-phenylpropanoate 10.53

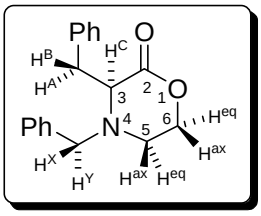


$C_{17}H_{19}NO_2$
MW: 269.34

Following the procedure described by Garner and Kaniskan,[214] $NaBH_4$ (3.18 g, 84.1 mmol, 1.5 eq) was added to a stirred solution of imine **10.52** (15.00 g, 56 mmol, 1.0 eq) in methanol (135 mL) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 1.5 h, at which point acetone was added and the mixture was concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water (2 ×). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to yield the amine **10.53** as an oil (8.62 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.80 (1H, br s, N*H*), 2.95 (2H, d, *J* 7.1 Hz, C*H*$_2$CH), 3.53 (1H, t, *J* 6.8 Hz, C*H*CH$_2$), 3.62 (3H, s, OC*H*$_3$), 3.63 (1H, d, *J* 13.1 Hz, NHC*H*^{A}H^{B}Ph), 3.73 (1H, d, *J* 13.1 Hz, NHCH^A*H*^{B}Ph), 7.15 (2H, d, *J* 7.1 Hz, H2' and H6'), 7.19-7.28 (8H, m, Ph, H3', H4' and H5'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[214]

3(*S*),4-Dibenzylmorpholin-2-one 10.60



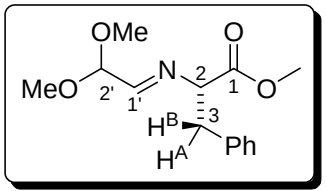
$C_{18}H_{19}NO_2$
MW: 281.35

A stirred solution of amine **10.53** (309 mg, 1.15 mmol, 1.0 eq), triethylamine (0.2 mL, 1.4 mmol, 1.2 eq) and 2-bromoethanol (0.1 mL, 1.4 mmol, 1.2 eq) in dry toluene (2.4 mL) was heated under reflux under argon for 20 h. After cooling, the mixture was filtered and the filtrate concentrated under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–50:50)] gave the morpholine **10.60** (78 mg, 24%) as a yellow oil.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.36

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.38 (1H, ddd, *J* 2.5, 10.1 and 12.6 Hz, C*H*-5^{ax}), 2.72 (1H, dt, *J* 12.6 and 2.5 Hz, C*H*-5^{eq}), 3.11 (1H, dd, *J* 4.7 and 14.0 Hz, CH^A*H*^{B}), 3.22 (1H, dd, *J* 4.7 and 14.0 Hz, C*H*^{A}H^B), 3.31 (1H, d, *J* 13.1 Hz, CH^X*H*^{Y}), 3.60 (1H, t, *J* 4.7 Hz, C*H*^{C}), 3.75 (1H, dt, *J* 2.2 and 10.4 Hz, C*H*-6^{ax}), 3.96 (1H, d, *J* 13.4 Hz, C*H*^{X}H^Y), 4.02 (1H, dt, *J* 10.7 and 2.8 Hz, C*H*-6^{eq}), 7.15-7.25 (10H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[272]

Methyl 2(*S*)-[*N*-(2,2'-dimethoxyethylidenamino]-3-phenylpropanoate 10.62

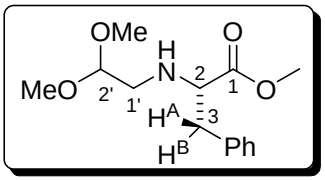


$C_{14}H_{19}NO_4$
MW: 265.30

Dimethoxyacetaldehyde [60% in water] (3.0 mL, 20 mmol, 1.1 eq) was added to a stirred solution of amine **10.59** (3.27 g, 18.3 mmol, 1.0 eq) in methanol (52 mL). The mixture was stirred at rt for 20 h. After filtration, excess dimethoxyacetaldehyde was removed at 125 °C under reduced pressure to leave the imine **10.62** (3.26 g, 73%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.08 (1H, dd, *J* 4.3 and 13.7 Hz, C*H*^{A}H^B-3), 3.18 (3H, s, OC*H*$_3$), 3.30-3.32 (4H, m, CO_2CH_3 and C*H*N), 3.72 (3H, s, OC*H*$_3$), 4.06 (1H, dd, *J* 4.7 and 13.7 Hz, CH^A*H*^{B}-3), 4.63 (1H, d, *J* 4.3 Hz, C*H*-2'), 7.12-7.27 (6H, m, Ar-H and C*H*=N).

Methyl 2(*S*)-[*N*-(2',2'-dimethoxyethylamino)]-3-phenylpropanoate 10.63



$C_{14}H_{21}NO_4$
MW: 267.32

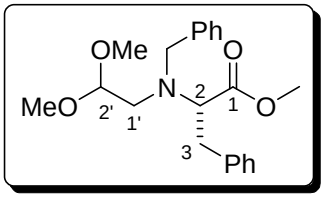
Procedure A: The reaction was carried out according to the procedure described for compound **10.53** using the imine **10.62** (871 mg, 3.29 mmol, 1.0 eq prepared from 589 mg of amine **10.59**), methanol (8 mL) and sodium borohydride (187 mg, 4.94 mmol, 1.5 eq). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–50:50)] gave the amine **10.63** (54 mg, 6%) as a yellow oil.

R_f [SiO_2, petroleum ether-ethyl acetate (70:30)] 0.28

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.71 (1H, br s, N*H*), 2.52 (1H, dd, *J* 5.1 and 11.9 Hz, C*H*^{A}H^B-3), 2.67 (1H, dd, *J* 5.9 and 12.0 Hz, CH^A*H*^{B}-3), 2.88 (2H, d, *J* 7.1 Hz, CH_2N), 3.23 (3H, s, OCH_3), 3.24 (3H, s, OCH_3), 3.46 (1H, t, *J* 7.1 Hz, C*H*-2'), 3.47 (3H, s, CO_2CH_3), 4.33 (1H, t, *J* 5.4 Hz, NC*H*CH_2), 7.10-7.23 (5H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 36.62 (CH_2), 48.21 (CH_2), 50.40 (CH_3), 52.01 (CH_3), 52.64 (CH_3), 61.93 (CH), 102.67 (CH), 125.62 (CH), 127.34 (CH), 128.15 (CH), 136.38 (C), 173.61 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1734 (C=O). **MS** (CI$^+$) *m/z* (%): 268 [(M+H)$^+$, 100], 236 [MeOCH=CHNH$_2^+$CH(Bn)CO_2Me, 78], 208 [(MeO)$_2$CHCH$_2$NH$_2^+$CH=CHPh, 52], 180 {$^+$[H_3NCH(Bn)CO_2Me], 78}. **HRMS** (CI$^+$): 268.1539 [(M+H)$^+$, $C_{14}H_{22}NO_4$ requires 268.1549]. **$[\alpha]_D^{23}$** + 1.78, (*c* 1.32, $CHCl_3$).

Procedure B: 10% Palladium on carbon (120 mg) was added to a stirred solution of imine **10.62** (1.09 g, 4.10 mmol, 1.0 eq, prepared from 1.08 g of amine **10.59**) in ethanol (37 mL). The atmosphere was changed to H_2 and the reaction was stirred at rt for 22 h. The mixture was filtered and the solvent removed under reduced pressure to yield the amine **10.63** as a yellow oil (980 mg, 90% over 2 steps). Data as above.

Methyl 2(*S*)-[*N*-benzyl-*N*-(2',2'-dimethoxyethyl)amino]-3-phenylpropanoate 10.64



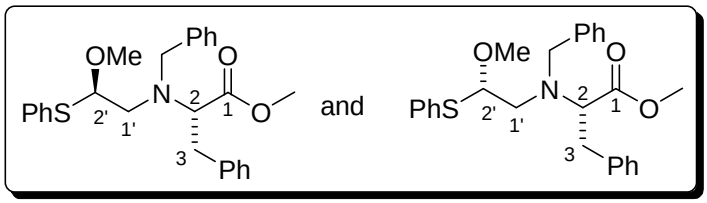
$C_{21}H_{27}NO_4$
MW: 357.44

Benzyl bromide (2.0 mL, 18 mmol, 1.5 eq) was added to a stirred solution of amine **10.63** (3.18 g, 11.9 mmol, 1.0 eq) and DIPEA (4.2 mL, 24 mmol, 2.0 eq) in dry CH_3CN (18 mL) under argon. The mixture was stirred at 70 °C for 22 h. The mixture was then evaporated under reduced pressure. The resulting mixture was dissolved in water and the aqueous layer extracted with ethyl acetate (3 ×). The organics were washed with water (2 ×), 0.1 N HCl (1 ×), water (1 ×) and then dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–90:10)] gave the ester **10.64** (3.23 g, 76%) as an oil.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.68 (1H, dd, *J* 5.3 and 14.1 Hz, C*H*^{A}H^B-3), 2.75 (1H, dd, *J* 4.8 and 14.1 Hz, CH^A*H*^{B}-3), 2.84 (1H, dd, *J* 7.9 and 14.0 Hz, C*H*^{C}H^D-1'), 3.02 (1H, dd, *J* 7.2 and 14.0 Hz, CH^C*H*^{D}-1'), 3.12 (3H, s, OC*H*$_3$), 3.15 (3H, s, OC*H*$_3$), 3.57 (3H, s, OC*H*$_3$), 3.60 (1H, d, *J* 14.4 Hz, NC*H*^{E}H^{F}Ph), 3.70 (1H, t, *J* 7.6 Hz, C*H*-2'), 3.93 (1H, d, *J* 14.1 Hz, NCH^E*H*^{F}Ph), 4.07 (1H, dd, *J* 4.9 and 5.3 Hz, NC*H*CH$_2$), 7.03-7.16 (10H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 35.97 (CH_2), 50.87 (CH_3), 52.79 (CH_3), 53.34 (CH_3), 53.97 (CH_2), 55.89 (CH_2), 64.55 (CH), 104.79 (CH), 125.97 (CH), 126.67 (CH), 127.87 (CH), 127.97 (CH), 128.48 (CH), 129.10 (CH), 138.19 (C), 139.32 (C), 172.87 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1732 (C=O ester). **MS** (CI$^+$) *m/z* (%): 358 [(M+H)$^+$, 92], 326 [MeOCH$^+$CH$_2$N(Bn)CH(Bn)CO$_2$Me, 100]. **HRMS** (CI$^+$): 358.2014 [(M+H)$^+$, $C_{21}H_{28}NO_4$ requires 358.2018]. **$[\alpha]_D^{23}$** –20.59, (*c* 1.18, $CHCl_3$).

Methyl 2(*S*)-[*N*-benzyl-*N*-2'(*RS*)-methoxy-2'-(phenylthio)ethylamino]-3-phenylpropanoate 10.65



$C_{26}H_{29}NO_3S$
MW 435.58

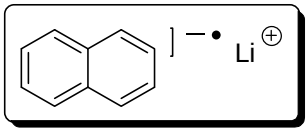
A mixture of acetal **10.64** (200 mg, 0.56 mmol, 1.0 eq) and freshly distilled thiophenol (0.13 mL, 1.3 mmol, 2.3 eq) was added to molten TBAB (55 mg, 0.17 mmol, 30 mol%) at 130 °C and the whole mixture was stirred at 130 °C under argon for 1 h. After 1 h, more thiophenol (0.13 mL, 1.3 mmol, 2.3 eq) was added and the mixture was left to stir at 130 °C for 5 h. Then the mixture was diluted with CH_2Cl_2 and washed with water (2 ×). The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–95:5)] gave a 1:1 mixture of epimeric acetals **10.65** (161 mg, 66%) as an oil. *Data for (2S,2'R)-***10.65** *and (2S,2'S)-***10.65***.*

R_f [SiO_2, petroleum ether-ethyl acetate (90:10)] 0.41

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.80 (1H$^{a\ or\ b}$, dd, *J* 8.5 and 14.3 Hz, C*H*^{A}H^B-3$^{a\ or\ b}$), 2.85 (1H$^{a\ or\ b}$, dd, *J* 7.6 and 14.2 Hz, C*H*^{A}H^B-3$^{a\ or\ b}$), 2.91-3.03 (6H, m, C*H*$_2$-1' and CH^A*H*^{B}-3$^{a\ and\ b}$), 3.24 (3H$^{a\ or\ b}$, s, OC*H*$_3$$^{a\ or\ b}$), 3.25 (3H$^{a\ or\ b}$, s, OC*H*$_3$$^{a\ or\ b}$), 3.53 (3H$^{a\ or\ b}$, s, CO_2C*H*$_3$$^{a\ or\ b}$), 3.55 (3H$^{a\ or\ b}$, s, CO_2C*H*$_3$$^{a\ or\ b}$), 3.56 (1H$^{a\ or\ b}$, d, *J* 13.9 Hz, NCH^C*H*^{D}Ph$^{a\ or\ b}$), 3.64 (1H$^{a\ or\ b}$, t, *J* 7.8 Hz, CH-2'$^{a\ or\ b}$), 3.70 (1H$^{a\ or\ b}$, d, *J* 14.7 Hz, NCH^C*H*^{D}Ph$^{a\ or\ b}$), 3.74 (1H$^{a\ or\ b}$, t, *J* 7.9 Hz, CH-2'$^{a\ or\ b}$), 3.92 (1H$^{a\ or\ b}$, d, *J* 14.4 Hz, NC*H*^{C}H^{D}Ph$^{a\ or\ b}$), 3.97 (1H$^{a\ or\ b}$, d, *J* 14.1 Hz, NC*H*^{C}H^{D}Ph$^{a\ or\ b}$), 4.26 (1H$^{a\ or\ b}$, dd, *J* 3.8 and 8.3 Hz, C*H*N$^{a\ or\ b}$), 4.45 (1H$^{a\ or\ b}$, dd, *J* 4.3 and 7.6 Hz, C*H*N$^{a\ or\ b}$), 6.97-7.28 (30H, m, Ar-H$^{a\ and\ b}$). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 35.35 (CH_2), 35.38 (CH_2), 50.15 (CH_3), 54.98 (CH_2), 55.00 (CH_2), 55.16 (CH_3), 55.58 (CH_2), 55.66 (CH_2), 64.05 (CH_3), 64.48 (CH), 89.24 (CH), 91.21 (CH), 125.16 (CH), 125.18 (CH), 125.85 (CH), 125.87 (CH),125.90 (CH), 126.21 (CH), 126.29 (CH), 127.08 (CH), 127.10 (CH), 127.13 (CH), 127.61 (CH), 127.67 (CH), 127.73 (CH), 128.22 (CH), 128.24 (CH), 132.06 (CH), 132.09 (CH), 132.56 (C), 132.63 (C), 137.18 (C), 137.32 (C), 138.39 (C), 138.59 (C), 172.15 (C), 172.24 (C). **IR** ν_{max} (ATR)/cm^{-1}: 2951 (CH sp^2), 1733 (C=O ester), 1495 (C=C). **MS** (FAB) *m/z* (%): 436 [(M+H)$^+$, 13],

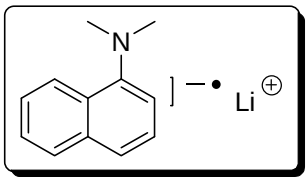
326 [MeOCH$^+$CH$_2$N(Bn)CH(Bn)CO$_2$Me, 39], 282 [$^+$CH$_2$N(Bn)CH(Bn)CO$_2$Me, 100]. **HRMS** (FAB): 436.1949 [(M+H)$^+$, $C_{26}H_{30}NO_3S$ requires 436.1946]. **[α]$_D^{22}$** −97.74, (*c* 3.6, $CHCl_3$)

Lithium naphthalenide (LN) 10.78



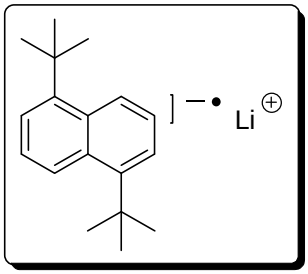
Following the procedure described by Cohen and Weisenfeld,[273] to a flame-dried flask, which was continually purged with argon was added dry and degassed THF (10 mL) and lithium ribbon (51 mg, 7.4 mmol, 1.0 eq). Naphthalene (738 mg, 5.76 mmol, 1.0 eq) was slowly added. The dark green color of the radical anion appeared within 10 min. The mixture was stirred for 6 h, after which it was presumed that the LN **10.78** had formed completely and a 0.58 M solution had therefore been prepared.

Lithium 1-(*N,N*-dimethylamino)naphthalenide (LDMAN) 10.79



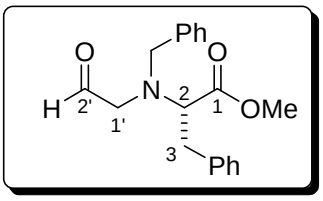
Following the procedure described by Cohen *et al.*,[229] to a flame-dried flask, which was continually purged with argon was added dry and degassed THF (10 mL) and lithium ribbon (40 mg, 5.8 mmol, 1.0 eq). The mixture was then cooled to −55 °C. 1-(*N,N*-dimethylamino)naphthalene (0.8 mL, 5.1 mmol, 1.0 eq) was slowly added. The dark green color of the radical anion appeared within 10 min. The mixture was stirred for 3.5 h, after which it was presumed that the LDMAN **10.79** had formed completely and a 0.5 M solution had therefore been prepared.

Lithium 4,4'-di-*tert*-butylbiphenylide (LDBB) 10.80



Following the procedure described by Cohen and Doubleday,[233] to a flame-dried flask, which was continually purged with argon was added dry and degassed THF (6.4 mL) and lithium ribbon (23 mg, 3.3 mmol). The mixture was then cooled to 0 °C. 4,4'-Di-*tert*-butylbiphenyl (765 mg, 2.88 mmol) was slowly added. The dark green color of the radical anion appeared within 10 min. The mixture was stirred for 5 h, after which it was presumed that the LDBB **10.80** had formed completely and a 0.5 M solution had therefore been prepared.

Methyl 2(*S*)-[*N*-benzyl-*N*-(2'-oxoethyl)amino]-3-phenylpropanoate 10.81



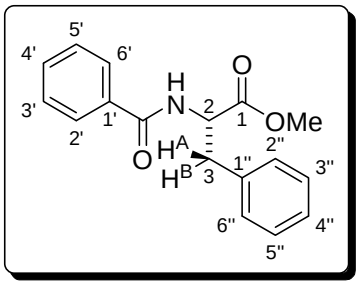
$C_{19}H_{21}NO_3$
MW: 311.37

Trichloromethylsilane (0.14 mL, 1.12 mmol, 2.0 eq) and acetal **10.64** (200 mg, 0.56 mmol, 1.0 eq) were added successively to a stirred solution of NaI (210 mg, 1.40 mmol, 2.5 eq) in dry CH_3CN (2.2 mL) under argon at rt and the mixture stirred for 1 h. The reaction was then quenched with water and extracted with CH_2Cl_2. The organics were washed with sat $Na_2S_2O_{3(aq)}$ (1 ×), H_2O (1 ×), brine (1 ×) and then dried (Na_2SO_4). The solvent was removed under reduced pressure to give the aldehyde **10.81** (127 mg, 73%) without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.86 (1H, dd, *J* 8.5 and 14.0 Hz, C*H*^{A}H^B-3), 3.05 (1H, dd, *J* 7.1 and 13.9 Hz, CH^A*H*^{B}-3), 3.29 (1H, dd, *J* 2.3 and 18.2 Hz, C*H*^{C}H^D-1'), 3.43 (1H, d, *J* 18.2 Hz, CH^C*H*^{D}-1'), 3.61-3.67 (5H, m, OC*H*$_3$, C*H*N and NC*H*^{E}H^{F}Ph), 3.79 (1H, d, *J* 13.6 Hz, NCH^E*H*^{F}Ph), 7.03-7.22 (10H, m, Ar-H), 9.24 (1H, d, *J* 2.0 Hz, C*H*O). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 36.21 (CH_2), 51.36 (CH_3), 57.33

(CH_2), 60.35 (CH_2), 65.16 (CH), 126.58 (CH), 127.55 (CH), 128.32 (CH), 128.39 (CH), 129.00 (CH), 129.15 (CH), 137.51 (C), 137.77 (C), 172.51 (C), 202.80 (CH). **IR** ν_{max} (ATR)/cm^{-1}: 1726 (C=O), 1269 (C-O ester). **MS** (CI^+) *m/z* (%): 312 [$(M+H)^+$, 100]. **HRMS** (FAB): 312.1598 [$(M+H)^+$, $C_{19}H_{22}NO_3$ requires 312.1600]. **$[\alpha]_D^{24}$** – 51.80, (*c* 1.1, $CHCl_3$).

Methyl 2(*S*)-benzamido-3-phenylpropanoate 10.84



$C_{17}H_{17}NO_3$
MW: 283.32

Procedure A: Following the procedure described by Nadia *et al.*,[274] benzoyl chloride (0.9 mL, 7.7 mmol, 1.0 eq) was added dropwise to a stirred solution of amine **10.59** (1.38 g, 7.71 mmol, 1.0 eq), 2 N K_2CO_3 (9.6 mL, 19.3 mmol, 2.5 eq) in $CHCl_3$ (154 mL). The mixture was heated under reflux for 3 h. The reaction was then quenched with water and the aqueous layer was extracted with $CHCl_3$ (3 ×). The combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure to give the amide **10.84** (2.18 g, 100%), which was used without further purification.

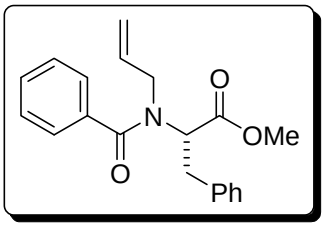
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.22 (1H, dd, *J* 5.6 and 13.9 Hz, C*H*^{A}H^B-3), 3.29 (1H, dd, *J* 5.8 and 13.9 Hz, CH^A*H*^{B}-3), 3.76 (3H, s, OC*H*$_3$), 5.09 (1H, td *J* 5.8 and 7.6 Hz, C*H*N), 6.59 (1H, d, *J* 7.3 Hz, N*H*), 7.13-7.15 (2H, m, H2'' and H6"), 7.25-7.32 (3H, m, H3'', H4" and H5"), 7.39-7.44 (2H, m, H2' and H6'), 7.48-7.53 (1H, m, H4'), 7.71-7.74 (2H, m, H3' and H5'). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[274]

Procedure B: Titanocene dichloride (709 mg, 2.85 mmol, 3.0 eq), Mg (83 mg, 3.4 mmol, 3.6 eq) [pre-dried at 250 °C overnight] and freshly activated 4 Å molecular sieves (500 mg) were twice heated gently, under reduced pressure for about 1 min shaking the flask between heatings and then placed under Ar. Dry THF (1 mL) was added followed by freshly distilled $P(OEt)_3$ (1.0 mL, 5.7 mmol,

6.0 eq). After stirring for 3 h at rt, a solution of dithiane **10.89** (500 mg, 0.95 mmol, 1.0 eq) in dry THF (2.7 mL) was added to the mixture and stirred overnight at rt. The reaction was quenched by addition of 1 M NaOH and the resulting insoluble materials were filtered off through Celite®. The filtrate was extrated with Et_2O (3 ×). The combined organic layers were dried (K_2CO_3). The solvent removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether (100)] gave the amide **10.84** (53 mg, 20%) as yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 3.23 (1H, dd, *J* 5.2 and 13.9 Hz, C*H*^{A}H^B-3), 3.30 (1H, dd, *J* 5.1 and 13.4 Hz, CH^A*H*^{B}-3), 3.77 (3H, s, OC*H*$_3$), 5.06-5.11 (1H, m, C*H*N), 6.72 (1H, br s, N*H*), 7.14-7.16 (2H, m, H2'' and H6"), 7.25-7.30 (3H, m, H3'', H4" and H5"), 7.41-7.44 (2H, m, H2' and H6'), 7.49-7.53 (1H, m, H4'), 7.73-7.75 (2H, m, H3' and H5').

Methyl 2(*S*)-(*N*-allylbenzamido)-3-phenylpropanoate 10.85



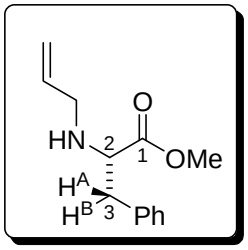
$C_{20}H_{21}NO_3$
MW: 323.39

Following the procedure described by Poulsen and Bornaghi,[238] benzoyl chloride (4.3 mL, 37 mmol, 2.0 eq) was added to a stirred solution of amine **10.84** (4.04 g, 18.5 mmol, 1.0 eq), triethylamine (5.2 mL, 37 mmol, 2.0 eq) in dry CH_2Cl_2 (84 mL). The mixture was stirred at rt under argon for 3 h. The reaction mixture was then diluted with CH_2Cl_2 and washed with 1 N HCl (1 ×), brine (1 ×) and the organic layer was dried ($MgSO_4$). The solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-70:30)] gave the amide **10.85** (5.39 g, 90%) as an oil.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.30

^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C) δ_H: 3.23-3.37 (2H, m, NCHC*H*$_2$), 3.65-3.84 (2H, m, NC*H*$_2$CH), 3.71 (3H, s, OC*H*$_3$), 4.52-4.56 (1H, m, NC*H*CH$_2$), 5.02-5.07 (2H, m, C*H*$_2$=), 5.54-5.66 (1H, m, C*H*=), 7.15-7.43 (10H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[238]

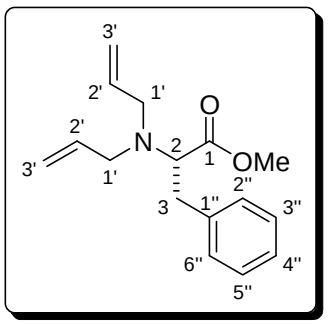
Methyl 2(*S*)-(*N*-allylamino)-3-phenylpropanoate 10.87



$C_{13}H_{17}NO_2$
MW: 219.28

Lithium hydroxide monohydrate (1.00 g, 24 mmol, 2.15 eq) was added to activated 4 Å molecular sieves (5 g) in anhydrous DMF (62 mL) and then the suspension was vigorously stirred for 20 min. The amine **10.59** (2.00 g, 11.2 mmol, 1.0 eq) was added and the mixture was stirred for 45 min. Allyl bromide (1.16 mL, 13.4 mmol, 1.2 eq) was added to the suspension and then the mixture was allowed to stir for 16 h under argon at rt. After filtration, the combined filtrate was washed with water (2 ×) and dried (Na_2SO_4). The solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–50:50)] gave the amine **10.87** (1.15 g, 47%) as a yellow oil.
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.62 (1H, br s, N*H*), 2.95 (2H, d, *J* 6.8 Hz, NCH_2CH), 3.11 (1H, tdd, *J* 1.3, 6.3 and 13.9 Hz, CH^AH^B-3), 3.26 (1H, tdd, *J* 1.3, 5.8 and 13.9 Hz, CH^AH^B-3), 3.55 (1H, apparent t, *J* 6.8 Hz, NC*H*CH$_2$), 3.63 (3H, s, OCH_3), 5.06 (1H, qd, *J* 1.3 and 10.2 Hz, CH^AH^B=), 5.11 (1H, qd, *J* 1.5 and 17.2 Hz, CH^AH^B=), 5.80 (1H, tdd, *J* 6.0, 10.2 and 17.2 Hz, C*H*=), 7.16-7.30 (5H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[275]

Methyl 2(*S*)-[*N,N-bis*(allyl)amino]-3-phenylpropanoate 10.86



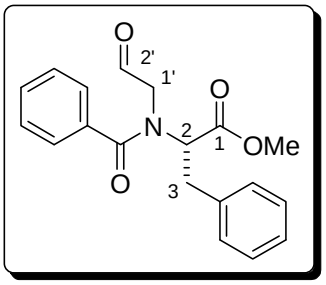
$C_{16}H_{21}NO_2$
MW: 259.34

In the same way, the reaction was carried out using lithium hydroxide monohydrate (1.00 g, 23.8 mmol, 2.15 eq), activated 4 Å molecular sieves (5 g)

in anhydrous DMF (62 mL), the amine **10.59** (2.00 g, 11.2 mmol, 1.0 eq) and allyl bromide (1.16 mL, 13.4 mmol, 1.2 eq). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0–50:50)] gave the amine **10.86** (413 mg, 14%) as an oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.80 (1H, dd, *J* 7.1 and 13.6 Hz, C*H*^{A}H^B-3), 2.96 (1H, dd, *J* 7.8 and 13.6 Hz, C*H*^{A}H^B-3), 2.99 (2H, dd, *J* 7.4 and 14.2 Hz, 2 x NCH^C*H*^{D}-1'), 3.26-3.29 (2H, ddd, *J* 1.6, 4.8 and 14.5 Hz, 2 x NC*H*^{C}H^D-1'), 3.51 (3H, s, OC*H*$_3$), 3.62 (1H, apparent t, *J* 7.6 Hz, NC*H*CH$_2$), 4.97 (2H, m, 2 x C*H*^{E}H^F=), 5.04 (2H, qd, *J* 1.6 and 17.2 Hz, 2 x CH^E*H*^{F}=), 5.53-5.63 (2H, m, C*H*=), 7.06-7.09 (3H, m, H3'', H4" and H5"), 7.13-7.16 (2H, m, H2'' and H6"). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[276]

Methyl 2(*S*)-[*N*-(2'-oxoethyl)benzamido]-3-phenylpropanoate 10.88



$C_{19}H_{19}NO_4$
MW: 325.36

The reaction was carried out according to the procedure described for compound **10.24** using $K_2OsO_4.2H_2O$ (46 mg, 0.12 mmol, 2 mol%) in deionised water (2.4 mL), alkene **10.85** (2.00 g, 6.19 mmol, 1.0 eq) in THF (17 mL) at rt and $NaIO_4$ (3.97 g, 18.6 mmol, 3.0 eq) in water (36 mL). Flash chromatography [SiO_2, petroleum ether–ethyl acetate (70:30-30:70)] gave the aldehyde **10.88** (1.746 g, 87%) as a yellow oil.

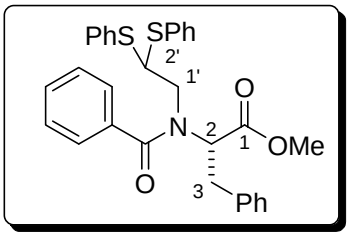
R$_f$ [SiO_2, petroleum ether-ethyl acetate (20:80)] 0.41

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.90 (1H, dd, *J* 3.8 and 11.2 Hz, C*H*^{A}H^B-3), 3.21 (1H, dd, *J* 3.6 and 13.9 Hz, CH^A*H*^{B}-3), 3.78 (3H, s, OC*H*$_3$), 3.95 (1H, d, *J* 17.2 Hz, NC*H*^{C}H^D-1'), 4.29 (1H, d, *J* 17.2 Hz, NCH^C*H*^{D}-1'), 4.75 (1H, m, NC*H*CH$_2$), 6.92-6.94 (4H, m, Ar-H), 7.27-7.38 (6H, m, Ar-H), 9.55 (1H, br s, C*H*O).

^{13}C NMR (100 MHz, $CDCl_3$) δ_C: 35.64 (CH_2), 51.64 (CH_2), 52.28 (CH), 59.79 (CH_3), 125.99 (CH), 126.80 (CH), 127.89 (CH), 128.31 (CH), 128.55 (CH), 129.38 (CH), 133.63 (C), 134.89 (C), 170.04 (C), 172.31 (C), 197.16 (CH). **IR** ν_{max} (ATR)/cm^{-1}:

1732 (C=O), 1639 (C=O), 1265 (C-O ester). **MS** (CI^+) *m/z* (%): 326 [$(M+H)^+$, 100]. **HRMS** (CI^+): 326.1398 [$(M+H)^+$, $C_{19}H_{20}NO_4$ requires 326.1392]. **$[\alpha]_D^{23}$** – 66.96, (*c* 2.2, $CHCl_3$)

Methyl 2(*S*)-{*N*-[2',2'-*bis*(phenylthio)ethyl]benzamido}-3-phenylpropanoate 10.89



$C_{31}H_{29}NO_3S_2$
MW: 527.70

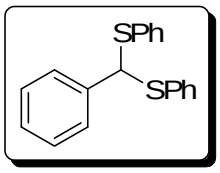
The reaction was carried out according to the procedure described for compound **10.27** using $BF_3.OEt_2$ (0.74 mL, 5.9 mmol, 1.1 eq), aldehyde **10.88** (1.75 g, 5.37 mmol, 1.0 eq), thiophenol (1.30 mL, 12.4 mmol, 2.3 eq) and glacial acetic acid (4.7 mL) in dry toluene (12.2 mL). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-80:20)] gave the thioacetal **10.89** (1.16 g, 41%) as prisme.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.44

mp: 63-65 °C

^{1}H NMR (400 MHz, DMSO-d_6 at 90 °C) δ_H: 3.14 (1H, dd, *J* 8.8 and 13.9 Hz, C*H*^{A}H^B-3), 3.25 (1H, dd, *J* 6.1 and 14.2 Hz, CH^A*H*^{B}-3), 3.41-3.53 (1H, m, NC*H*^{C}H^D-1'), 3.62 (3H, s, OC*H*$_3$), 3.67-3.74 (1H, m, NCH^C*H*^{D}-1'), 4.45-4.49 (1H, m, NC*H*CH$_2$), 4.82-4.88 (1H, m, NCH$_2$C*H*), 7.01-7.45 (20H, m, Ar-H). **^{13}C NMR** (100 MHz, DMSO-d_6 at 90 °C δ_C: 34.99 (CH_2), 51.77 (CH_3), 51.80 (CH), 55.49 (CH_2), 59.56 (CH), 126.55 (CH), 126.81 (CH), 127.65 (CH), 127.82 (CH), 128.21 (CH), 128.31 (CH), 128.98 (CH), 129.00 (CH), 129.09 (CH), 129.59 (CH), 131.58 (CH), 131.87 (CH), 133.20 (C), 133.89 (C), 135.60 (C), 137.17 (C), 169.99 (C), 170.01 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1735 (C=O ester), 1641 (C=O amide). **MS** (CI^+) *m/z* (%): 528 [$(M+H)^+$, 58], 418 [$(M+H)^+$ – PhSH, 100] **HRMS** (CI^+): 528.1671 [$(M+H)^+$, $C_{31}H_{30}NO_3S_2$ requires 528.1667]. **Microanalysis**: Theory C: 70.59% H: 5.50% N: 2.66%; Results C: 70.57% H: 5.50% N: 2.83%. **$[\alpha]_D^{23}$** –117.39, (*c* 1.5, $CHCl_3$)

Bis(phenylthio)methylbenzene 10.91



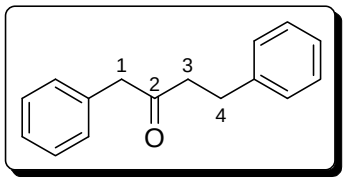
$C_{19}H_{16}S_2$
MW: 308.46

In a same way, the reaction was carried out using $BF_3.OEt_2$ (1.3 mL, 10.4 mmol, 1.1 eq), benzaldehyde **10.90** (0.96 mL, 9.4 mmol, 1.0 eq), thiophenol (2.2 mL, 22 mmol, 2.3 eq) and glacial acetic acid (8.3 mL) in dry toluene (21.5 mL). Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-95:5)] gave the thioacetal **10.91** (2.04 mg, 70%) as a solid.

R_f [SiO_2, petroleum ether-ethyl acetate (95:5)] 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.42 (1H, s, C*H*), 7.21-7.28 (9H, m, Ar-H), 7.32-7.37 (6H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[277]

1,4-Diphenylbutan-2-one 10.92



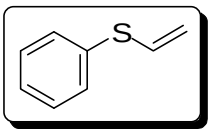
$C_{16}H_{16}O$
MW: 224.30

The reaction was carried out according to the procedure B described for compound **10.84** using titanocene dichloride (727 mg, 2.92 mmol, 3.0 eq), Mg (87 mg, 3.5 mmol, 3.6 eq) and 4 Å molecular sieves (515 mg), dry THF (4.9 mL) and dry $P(OEt)_3$ (1.0 mL, 5.8 mmol, 6.0 eq) and a solution of dithiane **10.91** (300 mg, 0.97 mmol, 1.0 eq) in THF (3 mL). Removal of solvent under reduced pressure gave the crude enol ether derivative. The crude liquid was quickly passed through a short column of silica [petroleum ether-ethyl acetate (100:0-95:5) to remove excess of $P(OEt)_3$. The resulting crude was then dissolved in THF (5 mL) and stirred with 1 M HCl (5 mL) for 1 h at rt. Water was added and the aqueous layer was extracted with EtOAc (3 ×). The combined organics were then dried ($MgSO_4$) and removal of the solvent under reduced pressure gave a mixture of the ketone **10.92** and 3-phenylpropanoic acid. Therefore a solution of this mixture in THF (5 mL) was treated with 1 M NaOH (5 mL) and stirred for 1 h at

rt. The reaction was stopped by addition of water and the aqueous layer was extracted with EtOAc (3 ×). The organic layer was then dried ($MgSO_4$) and the solvent removed under reduced pressure to give the pure ketone **10.92** (44 mg, 40%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.69 (2H, t, *J* 6.9 Hz, CH_2-4), 2.79 (2H, t, *J* 6.9 Hz, CH_2-3), 3.58 (2H, s, CH_2-1), 7.06-7.24 (10H, m, Ar-H).^{1}H NMR spectral data in agreement with those previously reported in the literature.[278]

Phenyl vinyl sulfide 10.94



C_8H_8S
MW: 136.21

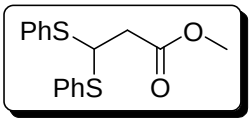
The reaction was carried out according to the procedure B described for compound **10.84** using titanocene dichloride (709 mg, 2.85 mmol, 3.0 eq), Mg (83 mg, 3.4 mmol, 3.6 eq) and 4 Å molecular sieves (500 mg), dry THF (1 mL), dry $P(OEt)_3$ (1.0 mL, 5.7 mmol, 6.0 eq) and dithiane **10.89** (500 mg, 0.95 mmol, 1.0 eq) in dry THF (2.7 mL). Flash chromatography [SiO_2, petroleum ether (100)] gave the sulfide **10.94** (46 mg, 70%) as yellow oil.

R_f [SiO_2, petroleum ether (100)] 0.69

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.32 (1H,d, *J* 16.6 Hz, CH^AH^B=), 5.24 (1H, d, *J* 9.6 Hz, CH^AH^B=), 6.54 (1H, dd, *J* 9.6 and 16.6 Hz, C*H*=), 7.22-7.53 (5H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[279]

12.6. Experimental to chapter 11

Methyl 3,3-*bis*(phenylthio)propanoate 11.22



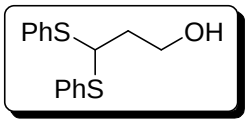
$C_{16}H_{16}O_2S_2$
MW: 304.43

Following the procedure described by Rahim *et al.*,[115] $BF_3.OEt_2$ (8.9 mL, 71 mmol, 2.0 eq) was added to a stirred solution of methyl acetal **11.21** (5.0 mL, 35 mmol, 1.0 eq) and thiophenol (7.2 mL, 71 mmol, 2.0 eq) in $CHCl_3$ (35 mL) at

0°C under argon. After 20 h at rt, the reaction mixture was quenched by addition of water and the aqueous layer was extracted with $CHCl_3$ (3 ×). The organic layer was washed with water (2 ×) and dried (Na_2SO_4). The solvent was removed under reduced pressure. The thioacetal **11.22** was obtained as an oil (9.47 g, 88%) and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.81 (2H, d, *J* 7.3 Hz, C*H*$_2$CH), 3.68 (3H, s, OC*H*$_3$), 4.81 (1H, t, *J* 7.3 Hz, CH$_2$C*H*), 7.31-7.32 (6H, m, Ar-H), 7.48-7.50 (4H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[280]

3,3-*Bis*(phenylthio)propan-1-ol 11.23



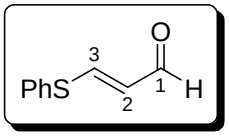
$C_{15}H_{16}OS_2$
MW: 276.42

Following the procedure described by Rahim *et al.*,[115] a solution of ester **11.22** (8.14 g, 26.7 mmol, 1.0 eq) in dry THF (20 mL) was added to a suspension of $LiAlH_4$ (1.14 g, 30.0 mmol, 1.12 eq) in dry THF (30 mL) at 0 °C under argon. After being stirred overnight at rt, the reaction was quenched by dropwise addition of 1 M NaOH and the insoluble materials were filtered off through Celite®. The filtrate was extracted with Et_2O (3 ×). The organics were dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-90:10)] gave the alcohol **11.23** (8.28 g, 80%) as an oil.

R_f [SiO_2, petroleum ether-ethyl acetate (70:30)] 0.56

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.70 (1H, br s, O*H*), 2.01 (2H, td, *J* 5.8 and 6.8Hz, CHC*H*$_2$), 3.88 (2H, t, *J* 5.8 Hz, C*H*$_2$OH), 4.64 (1H, t, *J* 6.8 Hz, C*H*CH$_2$), 7.25-7.33 (6H, m, Ar-H), 7.46-7.49 (4H, m, Ar-H). ^{1}H NMR spectral data in agreement with those previously reported in the literature.[115]

3-(Phenylthio)acrylaldehyde 11.28

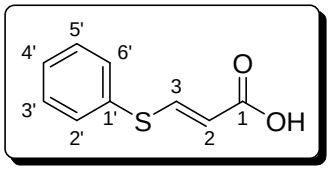


C_9H_8OS
MW: 164.22

DMSO (4.8 mL) and triethylamine (6.5 mL, 47 mmol, 7.0 eq) were added to a stirred solution of alcohol **11.23** (1.84 g, 6.67 mmol, 1.0 eq) in dry DCM (51 mL) at rt under argon. After cooling to 0 °C, sulfur trioxide pyridine (4.20 g, 26.7 mmol, 4.0 eq) was added in batches. The reaction mixture was stirred overnight at rt. The mixture was then quenched with sat $NaHCO_{3(aq)}$. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The organic layers were washed with water (1 ×), brine (1 ×) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give the α,β-unsaturated aldehyde **11.28** as an *E*:*Z* mixture (7:1) (1.03 g, 94%). Due to the relative instability of this compound, the crude mixture was used in the next step without further purification.

Data on *E*-isomer only from the crude mixture ^{1}H NMR (400 MHz, $CDCl_3$) δ_H : 5.93 (1H, dd, *J* 7.8 and 15.0 Hz, CH-2), 7.20-7.31 (3H, m, Ph), 7.43-7.50 (2H, m, Ph), 7.68 (1H, d, *J* 15.0 Hz, CH-3), 9.43 (1H, d, *J* 7.8 Hz, C*H*O).

3-(Phenylthio)acrylic acid 11.30



$C_9H_8O_2S$
MW: 180.22

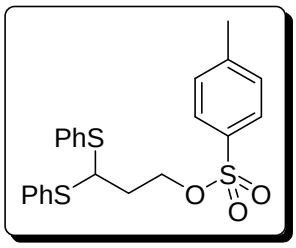
7 M KOH (19 mL) was added to a stirred solution of ester **11.22** (500 mg, 1.64 mmol, 1.0 eq) in EtOH (31 mL) and the reaction was left to stir overnight at rt. The reaction mixture was then poured into water and the aqueous layer washed with Et_2O (3 ×). The organic layer was discarded. The aqueous layer was acidified with 6 M HCl and extracted with Et_2O (3 ×). The organics were dried ($MgSO_4$) and flash chromatography [SiO_2, petroleum ether-ethyl acetate (90:10-50:50)] gave the acid **11.30** (219 mg, 74%) as a powder and a 14:1 mixture of *E*:*Z* compounds.

mp: 104-106 °C

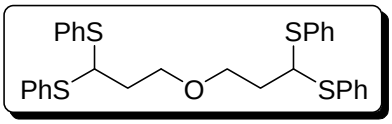
R_f [SiO_2, petroleum ether-ethyl acetate (60:40)] 0.43

Data on *E*-isomer only ^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 5.61 (1H, d, *J* 15.2 Hz, CH-2), 7.40-7.43 (3H, m, H3', H4' and H5'), 7.48-7.50 (2H, m, H2' and H6'), 7.92 (1H, d, *J* 15.2 Hz, CH-3).**^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 114.30 (CH), 129.80 (CH), 129.88 (CH), 129.92 (C),133.18 (CH), 150.39 (CH), 170.42 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3250 (OH), 2972 (CH sp^2), 1705 (C=O). **MS** (CI^+) *m/z* (%): 181 [$(M+H)^+$, 100]. **HRMS** (CI^+): 181.0327. [$(M+H)^+$, $C_9H_9SO_2$ requires 181.0323]. **Microanalysis**: Theory C: 60.00% H: 4.45%; Results C: 60.29% H: 4.62%. Commercial compound reported in the literature without spectroscopic data provided.[281,282]

3,3-*Bis*(phenylthio)propyl 4'-toluenesulfonate 11.26
***bis*[3,3'-*bis*(phenylthio)prop-1-yl ether 11.31**



$C_{22}H_{22}O_3S_3$
MW: 430.60



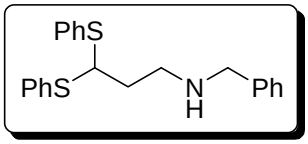
$C_{30}H_{30}OS_4$
MW: 534.82

Procedure A: A solution of alcohol **11.23** (514 mg, 1.86 mmol, 1.0 eq) in dry pyridine (0.43 mL) was added dropwise to a stirred solution of *p*-toluenesulfonyl chloride (398 mg, 2.09 mmol, 1.12 eq) in dry pyridine (0.45 mL) at 0 °C under argon. The mixture was stirred for 16 h at rt under argon. The mixture was then diluted with water and extracted with Et_2O (3 ×). The combined organics were washed with 1 M HCl (2 ×), water (2 ×) and brine (1 ×) and then dried (Na_2SO_4). The solvent was removed under reduced pressure to afford a 2:1 mixture of tosylate and dimer **11.26:11.31** (428 mg). The crude mixture was used in the next step without further purification due to the instability of the tosylate **11.26,** but characterization of tosylate **11.26** and dimer **11.31** were carried out later on.

Procedure B: In a same way, the reaction was carried out using alcohol **11.23** (489 mg, 1.77 mmol, 1.0 eq) in dry pyridine (0.41 mL) and *p*-toluenesulfonyl chloride (1.35 g, 7.09 mmol, 4.0 eq) in dry pyridine (1.5 mL). After 2 h at rt

under argon, the mixture was treated as previously described. The solvent was removed under reduced pressure to afford tosylate **11.26** (566 mg, 74%). The crude mixture was used in the next step without further purification due to the instability of the tosylate **11.26**.

N-benzyl-3,3-*bis*(phenylthio)propan-1-amine 11.27

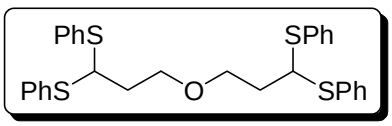


$C_{22}H_{23}NS_2$
MW: 365.55

Benzylamine (0.08 mL, 0.69 mmol, 1.1 eq) was added to a stirred solution of the crude mixture tosylate **11.26**: dimer **11.31** (428 mg) in dry CH_2Cl_2 (1.0 mL) at 0 °C under argon. Then dry pyridine (0.07 mL) was added to the mixture at 0 °C. The reaction mixture was left to stir for 12 h at rt and then maintained at 40 °C for 4 h. The mixture was diluted with water and the organic materials extracted with Et_2O (3 ×). The combined organics were dried and solvent removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-70:30)] gave the amine **11.27** (64 mg, 10% over 2 steps) as well as the dimer **11.31** (94 mg) and the tosylate **11.26** (44 mg).

R_f [SiO_2, petroleum ether-ethyl acetate (50:50)] 0.58

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.52 (1H, br s, N*H*), 2.02 (2H, apparent q, *J* 6.8 Hz, CHC*H*$_2$), 2.90 (2H, t, *J* 6.7 Hz, C*H*$_2$NH), 3.72 (2H, s, C*H*$_2$Ph), 4.61 (1H, t, *J* 6.9 Hz, C*H*CH$_2$), 7.22-7.32 (11H, m, Ar-H), 7.43-7.47 (4H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 36.04 (CH_2), 46.34 (CH_2), 53.69 (CH_2), 55.97 (CH), 126.94 (CH), 127.66 (CH), 128.06 (CH), 128.37 (CH), 128.88 (CH), 132.67 (CH), 134.11 (C), 140.15 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3059 (CH sp^3), 2920 (CH sp^2), 1581 (NH). **MS** (CI$^+$) *m/z* (%): 366 [(M+H)$^+$, 100]. **HRMS** (CI$^+$): 366.1354 [(M+H)$^+$, $C_{22}H_{24}NS_2$ requires 366.1350].



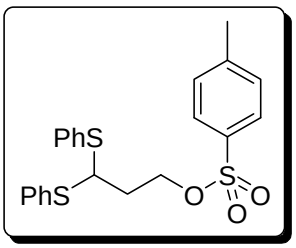
$C_{30}H_{30}OS_4$
MW: 534.82

Dimer **11.31**: yellow oil

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.87

R_f [SiO_2, petroleum ether (100)] 0.53

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.16 (4H, td, *J* 6.3 and 7.1 Hz, 2 x CHC*H*$_2$), 3.71 (4H, t, *J* 6.3 Hz, 2 x C*H*$_2$O), 4.55 (2H, t, *J* 7.1 Hz, 2 x C*H*CH_2), 7.20-7.25 (12H, m, Ar-H), 7.38-7.41 (8H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 37.13 (CH_2), 41.05 (CH_2), 54.19 (CH), 127.20 (CH), 128.23 (CH), 131.69 (CH), 132.25 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 2959 (CH sp^3), 1661 (C=C),1024 (C-O).



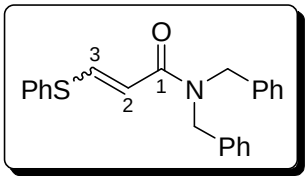
$C_{22}H_{22}O_3S_3$
MW: 430.60

Tosylate **11.26**: yellow oil

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.48

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.12 (2H, td, *J* 5.8 and 7.3 Hz, CHC*H*$_2$), 2.43 (3H, s, C*H*$_3$Ar), 4.27 (2H, t, *J* 6.0 Hz, C*H*$_2$O), 4.43 (1H, t, *J* 7.1 Hz, C*H*CH_2), 7.29-7.31 (8H, m, Ar-H), 7.38-7.41 (4H, m, Ar-H), 7.74 (2H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 21.69 (CH_3), 34.92 (CH_2), 53.91 (CH), 67.38 (CH_2), 127.94 (CH), 128.13 (CH), 129.05 (CH), 129.91 (CH), 132.77 (C),133.02 (CH), 138.76 (C), 144.88 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 2918 (CH sp^3), 1597 (C=C), 1362 and 1176 (SO_2).

N,N-Dibenzyl-3-(phenylthio)acrylamide 11.32



$C_{23}H_{21}NOS$
MW: 359.48

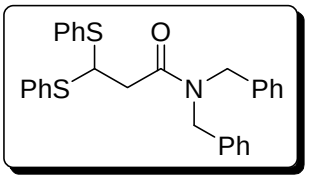
$SOCl_2$ (0.61 mL, 8.36 mmol, 1.5 eq) was added to a commercial mixture of *E:Z* acrylic acid **11.30** (1.00 g, 5.56 mmol, 1.0 eq). The reaction was stirred for 2 h under argon at 80 °C. The mixture was then concentrated under reduced pressure and immediately dissolved in dry CH_2Cl_2 (3.3 mL). Dibenzylamine (1.2 mL, 6.1 mmol, 1.1 eq), triethylamine (0.8 mL, 5.6 mmol, 1.0 eq) were added dropwise to the stirred solution at 0 °C under argon. This stirred solution was

allowed to warm to rt for 2.5 h and was then made acidic with 1 M HCl. The aqueous layer was extracted with CH_2Cl_2 (3 ×). The combined organics were dried ($MgSO_4$) and the solvent removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-70:30)] gave a 1.8:1 *E:Z* mixture of amide **11.32** (1.54 g, 80%) as a yellow oil.

R_f [SiO_2, petroleum ether-ethyl acetate (80:20)] 0.42

Data on *E* and *Z*-isomers. **^{1}H NMR** (400 MHz, $CDCl_3$) δ_H: 4.38 ($2H^E$, s, C*H*$_2$Ph), 4.50 ($2H^Z$, s, C*H*$_2$Ph), 4.65 ($2H^E$, s, C*H*$_2$Ph), 4.71 ($2H^Z$, s, C*H*$_2$Ph), 6.18 ($1H^E$, d, *J* 14.4 Hz, C*H*-3), 6.27 ($1H^Z$, d, *J* 9.9 Hz, C*H*-3), 7.06-7.46 ($30H^{E+Z}$, m, Ar-H), 7.50-7.53 ($1H^Z$, m, C*H*-2), 7.92 ($1H^E$, d, *J* 14.4 Hz, C*H*-2). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 47.33 (CH_2, *Z*), 47.91 (CH_2, *E*), 48.84 (CH_2, *E*), 48.90 (CH_2, *Z*), 110.81 (CH, *Z*), 113.91 (CH, *E*), 125.36 (CH), 125.43 (CH), 126.37 (CH), 126.55 (CH), 126.49 (CH), 126.80 (CH), 127.23 (CH), 127.51 (CH), 127.52 (CH), 127.55 (CH), 127.80 (CH), 127.84 (CH), 127.92 (CH), 127.94 (CH), 128.18 (CH), 128.41 (CH), 129.82 (CH), 130.51 (C), 131.11 (CH), 131.51 (CH), 135.57 (CH), 135.61 (C), 136.30 (C), 136.54 (C), 144.46 (CH, *E*), 147.32 (CH, *Z*), 164.57 (C), 166.09 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3085 (CH sp^2), 2922 (CH sp^3), 1629 (C=O), 1563 (C=C). **MS** (EI) *m/z* (%): 359 ($M^{+\cdot}$, 40), 268 ($M^{+\cdot}$ – Bn$^{\cdot}$, 60), 251 (100), 210 (57). **HRMS** (EI): 359.1346 [M^+, $C_{23}H_{21}NOS$ requires 359.1344].

N,*N*-Dibenzyl-3,3-*bis*(phenylthio)propanamide 11.33



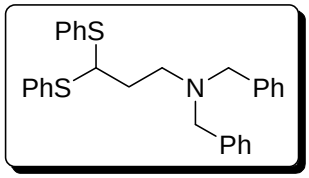
$C_{29}H_{27}NOS_2$
MW: 469.66

$BF_3.OEt_2$ (0.85 mL, 6.78 mmol, 1.2 eq) was added to a stirred solution of alkene **11.32** (2.03 g, 5.65 mmol, 1.0 eq), thiophenol (1.5 mL, 14 mmol, 2.5 eq) and glacial acetic acid (5.0 mL) in dry toluene (13.0 mL) at 0 °C under argon. After overnight at 80 °C, the reaction mixture was diluted with CH_2Cl_2 and washed with water (3 ×), dried ($MgSO_4$) and the solvent was removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-92:8)] gave the thioacetal **11.33** (1.39 g, 52%) as a yellow oil.

R_f [SiO_2, petroleum ether-ethyl acetate (90:10)] 0.41

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.85 (2H, d, *J* 7.1 Hz, CHC*H*$_2$), 4.27 (2H, s, C*H*$_2$Ph), 4.57 (2H, s, C*H*$_2$Ph), 5.09 (1H, t, *J* 7.0 Hz, C*H*CH$_2$), 7.17-7.28 (16H, m, Ar-H), 7.37-7.40 (4H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 38.29 (CH_2), 47.71 (CH_2), 48.97 (CH_2), 53.06 (CH), 125.33 (CH), 126.46 (CH), 126.67 (CH), 126.82 (CH), 127.26 (CH), 127.59 (CH), 127.95 (CH), 127.97 (CH), 131.54 (CH),132.82 (C), 135.01 (C), 135.92 (C), 168.98 (C). **IR** ν_{max} (NaCl)/cm^{-1}: 3028 (CH sp^2), 2918 (CH sp^3), 1643 (C=O), 1438 (CH sp^3). **MS** (EI) *m/z* (%): 360 ($M^{+\cdot}$ – PhS$^{\cdot}$, 53), 250 ($M^{+\cdot}$ – PhS$^{\cdot}$ and PhSH, 26), 196 [PhCH=NH$^+$Bn, 45], 91 (Bn$^+$, 100). **HRMS** (EI): 469.1529 [M^+, $C_{29}H_{27}NOS_2$ requires 469.1534].

N,*N*-Dibenzyl-3,3-*bis*(phenylthio)prop-1-yl-amine 11.14



$C_{29}H_{29}NS_2$
MW: 455.68

A solution of amide **11.33** (1.28 g, 2.73 mmol, 1.0 eq) in anhydrous diethyl ether (3.0 mL) was added dropwise to a supension of $LiAlH_4$ (135 mg, 3.55 mmol, 1.3 eq) in anhydrous diethyl ether (3.0 mL) at 0 °C under argon. After stirring overnight at rt, the mixture was carefully quenched with acetone then water and a white insoluble precipitate formed was filtered out. The filtrate was extracted with CH_2Cl_2 (3 ×) whereas the precipitate was taken up into water, then basify with 1 M NaOH. The aqueous layer was extracted with CH_2Cl_2 (3 ×). Combined organic layers were dried ($MgSO_4$) and solvent removed under reduced pressure. Flash chromatography [SiO_2, petroleum ether-ethyl acetate (100:0-98:2)] gave the amine **11.14** (627 mg, 51%) as prisms.

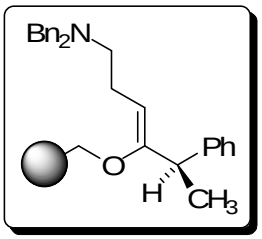
mp: 52-55 °C

R$_f$ [SiO_2, petroleum ether-ethyl acetate (95:5)] 0.46

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 2.00 (2H, apparent q, *J* 6.6 Hz, CHC*H*$_2$), 2.70 (2H, t, *J* 6.6 Hz, CH$_2$C*H*$_2$N), 3.48 (4H, s, 2 x NC*H*$_2$Ph), 4.50 (1H, t, *J* 6.7 Hz, C*H*CH$_2$), 7.18-7.26 (16H, m, Ar-H), 7.34-7.36 (4H, m, Ar-H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 33.40 (CH_2), 50.72 (CH_2), 55.41 (CH), 58.30 (CH_2), 126.90 (CH), 127.55 (CH), 128.22 (CH), 128.84 (CH), 128.87 (CH), 132.52 (CH), 134.20 (C), 139.32 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3024 (CH sp^3), 1581 (C=C), 1442 (CH sp^3), 732 and 694 (CH sp^2).

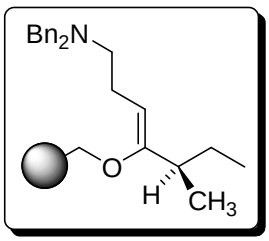
MS (EI) *m/z* (%): 455 ($M^{+\cdot}$, 32), 210 (100), 91 (Bn^+, 90). **HRMS** (EI): 455.1745 [M^+, $C_{29}H_{29}NS_2$ requires 455.1741]. **Microanalysis**: Theory C: 76.48% H: 6.37% N: 3.08% Results C: 76.51% H: 6.45% N: 3.30%

Resin-Bound enol ether 11.38.



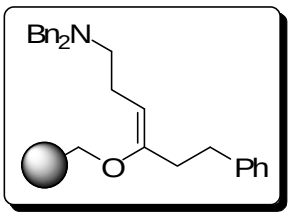
Titanocene dichloride (971 mg, 3.90 mmol, 12.0 eq), Mg (104 mg, 4.29 mmol, 13.2 eq) [pre-dried at 250 °C overnight] and freshly activated 4 Å molecular sieves (500 mg) were twice heated gently, under reduced pressure for about 1 min shaking the flask between heatings and then placed under argon. Dry THF (5.0 mL) was added followed by freshly distilled and dry $P(OEt)_3$ (1.3 mL, 7.8 mmol, 24 eq). After stirring for 3 h at rt, a solution of thioacetal **11.14** (413 mg, 0.91 mmol, 2.8 eq) in dry THF (5.0 mL) was added to the mixture via a cannula and stirred for 15 min. A MacroKan™ containing the resin-bound ester **11.34** [0.325 mmol/MacroKan™ previously prepared in the group from Merrifield resin with a loading of 1.83 mmol (chloride) g^{-1}] that had been dried by azeotrope with toluene and then purged with argon was added. After 17 h the MacroKan™ was removed from the flask and washed with THF (7 ×) then alternately with MeOH and DCM (3 ×), and finally with MeOH then Et_2O (2 ×). The MacroKan™ was then dried under vacuum.

Resin-Bound enol ether 11.39.



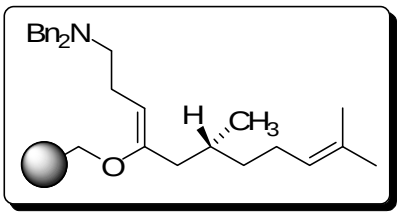
In the same way as above, the resin bound enol ether **11.39** was prepared from titanocene dichloride (971 mg, 3.90 mmol, 12.0 eq), Mg (104 mg, 4.29 mmol, 13.2 eq), $P(OEt)_3$ (1.3 mL, 7.8 mmol, 24 eq), thioacetal **11.14** (414 mg, 0.91 mmol, 2.8 eq) and a MacroKan™ containing the resin-bound ester **11.35** [0.325 mmol /MacroKan™]. The MacroKan™ was then dried under vacuum.

Resin-Bound enol ether 11.40.



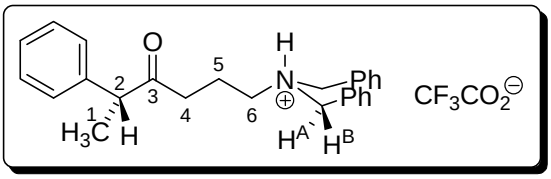
In the same way as above, the resin bound enol ether **11.40** was prepared from titanocene dichloride (926 mg, 3.72 mmol, 12.0 eq), Mg (100 mg, 4.09 mmol, 13.2 eq), $P(OEt)_3$ (1.0 mL, 7.4 mmol, 24 eq), thioacetal **11.14** (396 mg, 0.87 mmol, 2.8 eq) and a MacroKan™ containing the resin-bound ester **11.36** [0.31 mmol /MacroKan™]. The MacroKan™ was then dried under vacuum.

Resin-Bound enol ether 11.41.



In the same way as above, the resin bound enol ether **11.41** was prepared from titanocene dichloride (971 mg, 3.90 mmol, 12.0 eq), Mg (104 mg, 4.29 mmol, 13.2 eq), $P(OEt)_3$ (1.3 mL, 7.8 mmol, 24 eq), thioacetal **11.14** (413 mg, 0.91 mmol, 2.8 eq) and a MacroKan™ containing the resin-bound ester **11.37** [0.325 mmol /MacroKan™ prepared from Merrifield resin]. The MacroKan™ was then dried under vacuum.

6-(*N*,*N*-Dibenzylamino)-2(*S*)-phenylhexan-3-one, trifluoroacetate salt 11.42

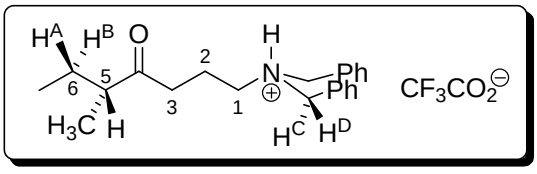


$C_{28}H_{30}F_3NO_3$
MW: 485.54

The MacroKan™ was shaken with 4% TFA in dry CH_2Cl_2 (5 mL) for 1 h. The solution was removed and the reactor was washed with CH_2Cl_2 (4 ×). The combined organics were concentrated under reduced pressure to give the amino ketone salt **11.42** (112 mg, 71 %) as brown oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.37 (3H, d, *J* 6.9 Hz, C*H*$_3$CH), 1.93-2.00 (2H, m, C*H*$_2$-5), 2.37-2.42 (2H, m, C*H*$_2$-4), 2.84-2.90 (2H, m, C*H*$_2$-6), 3.70 (1H, q, *J* 6.8 Hz, CH$_3$C*H*), 4.07-4.18 (2H, m, 2 × NC*H*^{A}H^{B}Ph), 4.28-4.34 (2H, m, 2 × NCH^A*H*^{B}Ph), 7.11-7.13 (2H, m, Ar-H), 7.28-7.33 (3H, m, Ar-H), 7.37-7.45 (10H, m, Ar-H), 10.44-10.51 (1H, br s, N*H*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 16.98 (CH_3), 18.01 (CH_2), 37.57 (CH_2), 50.69 (CH_2), 52.93 (CH), 56.83 (CH_2), 127.55 (CH), 127.71 (CH), 128.08 (CH), 129.14 (C), 129.52 (CH), 130.32 (CH), 130.93 (CH), 139.69 (C), 210.46 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3030 (CH sp^2), 3010 (CH sp^3), 2612 (NH), 1713 (C=O), 1600 (C=C), 1140 (CF_3). **MS** (FAB) *m/z* (%): 372 [(M$^+$, ammonium cation), 100]. **HRMS** (FAB): 372.2328 [(M$^+$, ammonium cation), $C_{26}H_{30}NO$ requires 372.2327]. **[α]$_D^{28}$** – 17.93, (*c* 1.2, EtOH)

1-(*N*,*N*-Dibenzylamino)-5(*S*)-methylheptan-4-one, trifluoroacetate salt 11.43



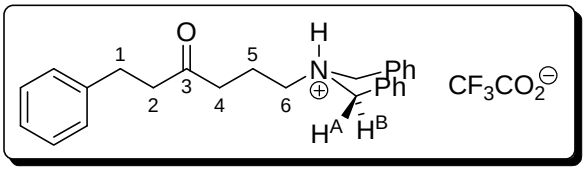
$C_{24}H_{30}F_3NO_3$
MW: 437.50

The reaction was carried out according to conditions described above and the amino ketone salt **11.43** was prepared as a brown oil (100 mg, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 0.72 (3H, t, *J* 7.3 Hz, C*H*$_3$CH$_2$), 0.91 (3H, d, *J* 7.0 Hz, C*H*$_3$CH), 1.25 (1H, qdd, *J* 7.3, 6.9 and 14.9 Hz, C*H*^{A}H^B-6), 1.50 (1H, qdd, *J* 7.3, 6.9 and 14.7 Hz, CH^A*H*^{B}-6),1.93-1.98 (2H, br s, CH$_2$-2), 2.32 (1H, sex, *J* 6.9 Hz, C*H*CH$_3$), 2.39-2.44 (2H, m, C*H*$_2$-1), 2.98-3.05 (2H, m, C*H*$_2$-3), 4.15 (2H, m,

NC*H*^{C}H^{D}Ph), 4.27 (2H, m, NCH^{C}*H*^{D}Ph), 7.34-7.38 (10H, m, Ar-H), 10.24-10.35 (1H, br s, N*H*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 10.43 (CH_3), 14.58 (CH_3), 16.95 (CH_2), 24.83 (CH_2), 37.12 (CH_2), 46.68 (CH), 50.56 (CH_2), 56.00 (CH_2), 127.33 (C), 128.51 (CH), 129.28 (CH), 129.83 (CH), 214.65 (C). **IR** ν_{max} (ATR)/cm^{-1}: 1670 (C=O), 1458 (C=C), 1137 (CF_3). **MS** (FAB) *m/z* (%): 324 [(M^+, ammonium cation), 100]. **HRMS** (FAB): 324.2328 [(M^+, ammonium cation), $C_{22}H_{30}NO$ requires 324.2327]. **[α]$_D^{28}$** + 5.44, (*c* 1.8, EtOH).

6-(*N,N*-Dibenzylamino)-1-phenylhexan-3-one, trifluoroacetate salt 11.44



$C_{28}H_{30}F_3NO_3$
MW: 485.54

The reaction was carried out according to conditions described above and the amino ketone salt **11.44** was prepared as brown needles (114 mg, 76 %).
mp: 50-55 °C
^{1}H NMR (400 MHz, $CDCl_3$) δ_H: 1.94-1.97 (2H, m, C*H*$_2$-5), 2.45 (2H, t, *J* 5.6 Hz, C*H*$_2$-4), 2.71 (2H, t, *J* 7.3 Hz, C*H*$_2$-1), 2.84 (2H, t, *J* 7.3 Hz, C*H*$_2$-2), 3.13-3.14 (2H, m, C*H*$_2$-6), 4.22 (2H, dd, *J* 5.3 and 13.2 Hz, 2 × NC*H*^{A}H^{B}Ph), 4.32 (2H, dd, *J* 4.1 and 13.2 Hz, 2 × NCH^{A}*H*^{B}Ph), 7.13-7.15 (2H, m, Ar-H), 7.19-7.30 (3H, m, Ar-H), 7.37-7.39 (4H, m, Ar-H), 7.43-7.50 (6H, m, Ar-H), 11.08-11.26 (1H, br s, N*H*). **^{13}C NMR** (100 MHz, $CDCl_3$) δ_C: 17.74 (CH_2), 29.72 (CH_2), 39.44 (CH_2), 43.98 (CH_2), 50.48 (CH_2), 56.65 (CH_2), 126.30 (CH), 128.25 (C), 128.29 (CH), 128.59 (CH), 129.52 (CH), 130.28 (CH), 131.05 (CH), 140.44 (C), 207.07 (C). **IR** ν_{max} (ATR)/cm^{-1}: 3033 (CH sp^3), 2782 (CH sp^2), 2626 (NH), 1711 (C=O), 1672 (C=O), 1602 (C=C), 1453 (CH sp^3), 1134 (CF_3). **MS** (FAB) *m/z* (%): 372 [(M^+, ammonium cation), 100]. **HRMS** (FAB): 372.2323 [(M^+, ammonium cation), $C_{26}H_{30}NO$ requires 372.2327].

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