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NOVEL METATHESIS APPLICATIONS: SYNTHESIS OF NEW AZAHETEROCYCLES BY HOMOGENEOUS CATALYSIS

Thesis submitted in fulfillment of the requirements
For the degree of Doctor (PhD) in Applied Biological Sciences:
Chemistry

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Nieuwe toepassingen van metathese: synthese van nieuwe azaheterocyclische verbindingen door homogene katalyse

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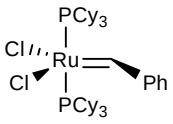
List of Abbreviations

Ac	Acetyl
ADMEP	Acyclic diene metathesis polymerization (= ADMET)
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl

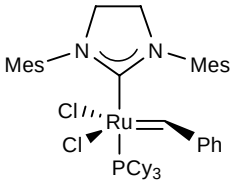
Catalyst **A**



First Generation Grubbs' catalyst

Bis(tricyclohexylphosphine) benzylidine ruthenium dichloride

Catalyst **B**



Second generation Grubbs' catalyst

Benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine) ruthenium

CM	Cross metathesis
cod	Cycloocta-1,5-diene
COSY	Correlated Spectroscopy
Cy	Cyclohexyl
DDQ	2,3-Dicyano-5,6-dichloro-parabenzoquinone
DMAP	4-Dimethylamino pyridine
DMF	Dimethyl formamide
DMP	Dimethyl phosphite
DMPU	N,N'-Dimethyl propylene ureua, tetrahydro-pyrimidin-2-one
DMSO	Dimethyl sulfoxide
DQFCOSY	Double quantum filtered correlated spectroscopy
HMBA	Hexamethylenebis(acetamide)
HMBC	Heteronuclear multiple bond correlation
*i*Bu	iso-butyl
*i*Pr	iso-propyl
KHMDS	Potassium 1,1,1,3,3,3-hexamethyldisilazane
KO*t*Bu	Potassium *t*-butoxide

LiHMDS	Lithium 1,1,1,3,3,3-hexamethyldisilazane
Mes	Mesityl, 2,4,6-trimethyl-phenyl
Ms	Mesyl
MW	Microwave
NHC	*N*-heterocyclic carbene
NMP	*N*-methylpyrrolidinon
PEG	Poly(ethylene glycol)
PG	Protecting group
Ph	Phenyl
PHF	Precultured heart fragment
QSAR	Quantitative structure-activity relationship
RCEYM	Ring-closing enyne metathesis
RCM	Ring-closing metathesis
ROCM	Ring-opening cross metathesis
ROMP	Ring-opening metathesis polymerization
RT	Room temperature
SES	Trimethylsilylethanesulfonyl
SIMES	Saturated Imidazole *N*-Mesityl, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene
*t*Bu	Tertiary butyl
TBAF	Tetrabutylammonium fluoride
TCQ	Tetrachloroquinone (chloranil)
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMSBr	Trimethylsilyl bromide
Tos	Tosyl

1 Introduction and Goals

Our ecosystem is severely tested by the ever increasing needs of today's "society of consumers" and the continuously growing population. The concept of sustainable development strives for an evolution in balance with the ecosystem which implies that the current and future use of energy and natural resources does not exceed the carrying capacity of the Earth. It would be foolish to think that this can be achieved without switching to a less energy- and resource-consuming way of producing and consuming.

A lot of research these days is focussed on the use of bioresources as a source of raw material in the chemical industry.[1] Whether resources for the chemical industry are renewable or not is irrelevant to the fact that one always has to try to achieve a specific chemical transformation in the most efficient way in order to limit the amount of waste and used energy. It is in this perspective that the use of catalysts has to be seen. A catalyst is a substance that makes a reaction go faster, by decreasing the activation energy, without being consumed in this reaction. In this way certain processes can be achieved that otherwise would demand an immense energy input or would not be possible at all.

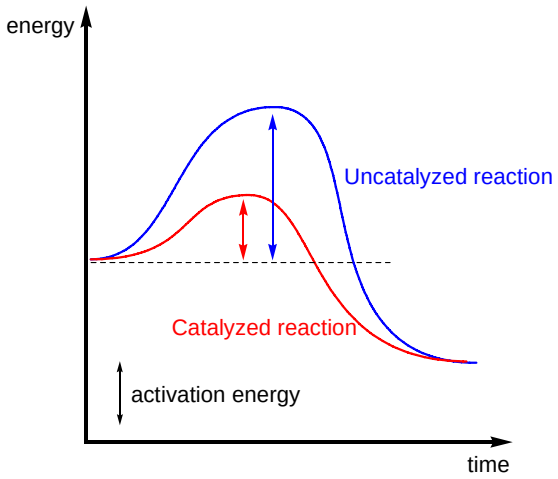


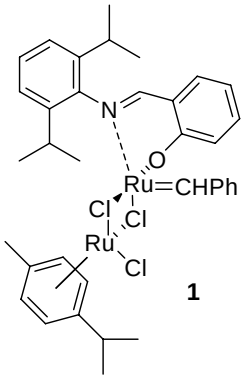
Figure 1: Difference in activation energy between catalyzed and uncatalyzed reaction.

Almost 80% of all processes in the chemical industry use catalysts. Famous examples are the production of NH_3 in the Haber process (Fe catalyst, 140 million tonnes per year), the synthesis of nitric acid (Pt/Rh catalyst, 60 million tonnes per year), the synthesis of sulfuric acid (V_2O_5 catalyst, 140 million tonnes per year) and the production of margarine by hydrogenation of vegetable oils (Ni catalyst, 2 million tonnes per year).[2] Catalysts are found in many different forms. Roughly, catalysis can be divided in three classes: homogeneous catalysis, heterogeneous catalysis and biocatalysis. The best known biocatalysts are called enzymes which are responsible for many fundamentally important reactions in living organisms. In heterogeneous catalysis the

catalyst and the involved reaction components are present in a different phase (e.g. solid catalyst in liquid). In homogeneous catalysis both the catalyst and reaction components are distributed to the molecular level in a single phase.

It is the goal of this work to use homogeneous catalysis for the synthesis of fine chemicals. More precise, compounds will be targeted that are very difficult to synthesize in a non-catalytic way and that are biologically important or closely related to a biologically important group of compounds. Attention will be focussed on three major groups: pyrroles, hydantoins and benzo-fused heterocycles. Since the synthesis of new molecules almost always consists of many different synthetic steps, it is virtually impossible to perform every single transformation in a catalytic way. Therefore, in this thesis, only the key transformation will be performed using homogeneous catalysis. The work in this thesis is based on ring-closing metathesis (RCM), a catalytic process in which two carbon-carbon double bonds are broken and one new carbon-carbon double bond is formed. Furthermore, attempts will be made to achieve multiple transformations (both catalytic and non-catalytic) in a single synthetic operation thus decreasing the amount of steps needed to obtain a certain compound.

During previous research at our department using a novel bimetallic catalyst **1**,[3] it was found that diallylamines **2** are converted to pyrroles **3** instead of to the expected pyrrolines **4**.



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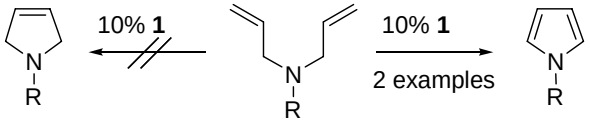
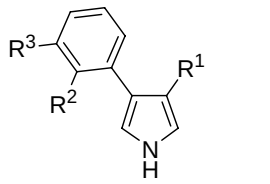
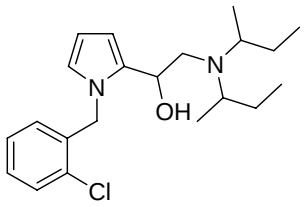


4 **2** **3**

Since the importance of the pyrrole nucleus is evident by its presence in both natural and synthetic biologically active compounds,[4] the abovementioned new entry towards this interesting heterocycle has to be further explored. Some examples of physiologically active pyrroles are pyrrolnitrin **5** (antifungal) and derivative fenpiclonil **6**,[5] viminol **7**[6] (analgesic), the antibacterial heterocycle **8**[7] and antimycobacterial compound **9**[8] to name but a few.



5 $R^1 = R^3 = Cl$, $R^2 = NO_2$
6 $R^1 = CN$, $R^2 = R^3 = Cl$



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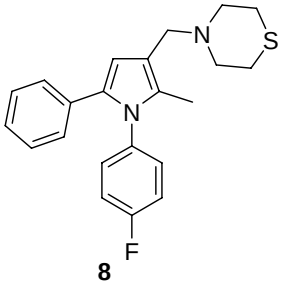

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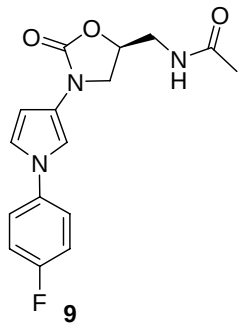

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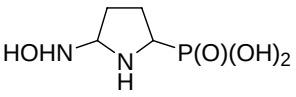
The prime goal will be to establish the general nature of this pyrrole formation and develop a standard protocol that can be used for the synthesis of a variety of mono- and polycyclic pyrroles. Once a workable protocol for the catalytic synthesis of pyrroles has been developed, an attempt will be made to use this methodology for the synthesis of phosphonylated pyrroles. Phosphonylated azaheterocycles are an important class of compounds with high biological potential as conformationally restricted bioisosteres of amino acids. Some interesting activities are shown by azaheterocyclic five-membered rings with phosphonates at various positions like compound **10** (bactericidal, fungicidal, herbicidal) and compound **11** (antibiotic).[9]



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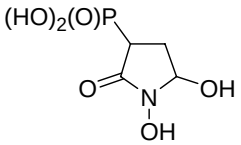
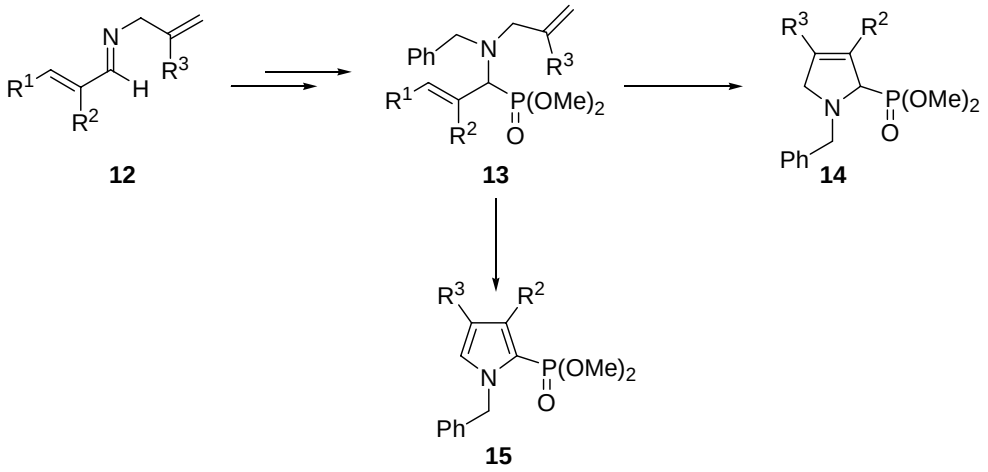


11

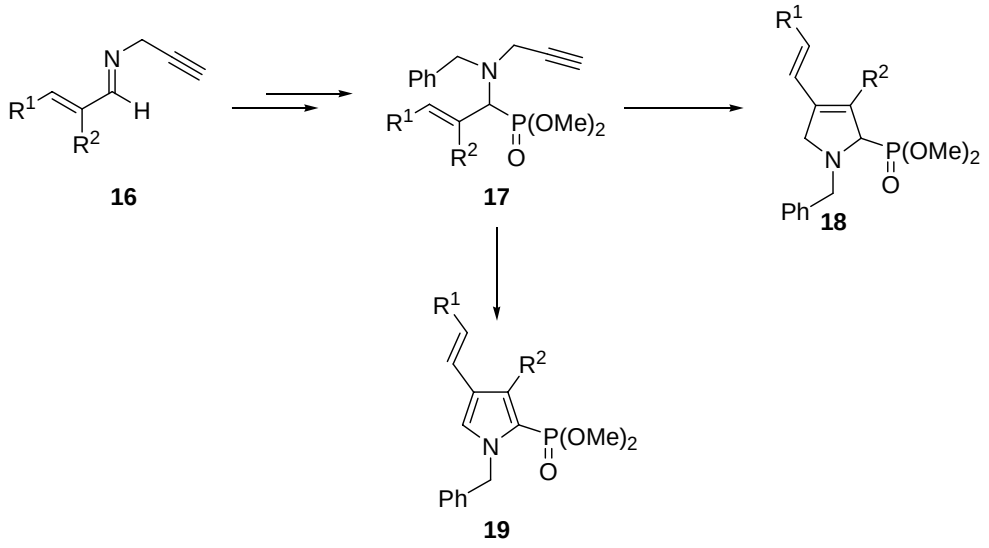
Only a limited amount of research on the synthesis of the aromatic counterpart of phosphonylated five-membered rings has been performed, however, leaving much room for new developments in this field. An attempt will be made to convert imines **12**, versatile compounds in organic synthesis,[10] to α-aminophosphonates **13**.



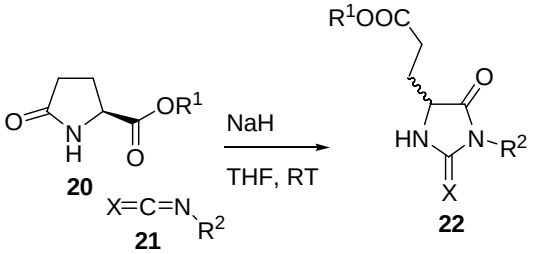
12 **13** **14** **15**

Under standard RCM conditions these compounds should be converted to pyrrolines **14** whereas the 'to be developed protocol' should be able to convert them to pyrroles **15**.

Next to this sequence, a ring-closing enyne metathesis (RCEYM) approach will also be envisaged which also leads to phosphonylated pyrroles and pyrrolines. RCEYM is even more atom-efficient than RCM since all atoms from the starting material are retained in the end product. For this, suitable imines **16** have to be converted to α-aminophosphonates **17**. These compounds can then be converted to pyrrolines **18** or to pyrroles **19**, depending on the conditions used. Since intramolecular RCEYM reactions between a terminal alkyne and a non-terminal alkene have not been systematically studied in the literature, an extra effort will be made in order to unravel the details concerning the precise reaction mechanism.

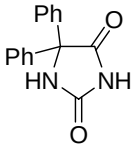


Preliminary research at our department has shown that pyroglutamates **20** undergo an interesting ring-transformation upon reaction with isocyanates **21** leading to hydantoins **22**.[11]



Hydantoins have been extensively studied and are reported to possess a wide range of biological activities. Phenetoin **23**, for example, was already synthesized in 1908[12] and is now still the drug of choice for the treatment of certain types of epileptic seizures. Compounds with general

structure **24** are known for their fungicidal, herbicidal and bactericidal properties. Dibromantin (R^1 = R^2 = Br) for example is a disinfectant used for water purification and glycoserve (R^1 = R^2 = CH_2OH) is a pesticide used in paints. A well known fungicide containing the hydantoin nucleus is iprodione **25**. Allantoin **26** was originally isolated from the comfrey plant (*Symphytum officinale* L., Dutch: smeerwortel) and is used for its healing and anti-irritating properties in a lot of skincare products like shaving cream, to help heal minor cuts. It is also frequently used in toothpaste, shampoos, lipsticks, lotions, ... Dantrolene **27** is a muscle relaxant that is used in cases of muscle spasticity for example for persons with ecstasy (XTC) intoxication. Finally, fosphenytoin **28** is a water soluble prodrug of phenetoin. In the body it is hydrolyzed to yield phosphate, formaldehyde and phenetoin **23**.



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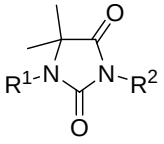

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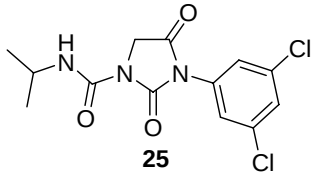
R^1, R^2 = Cl, Br, CH_2OH, H



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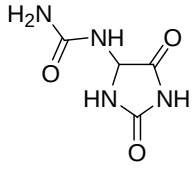

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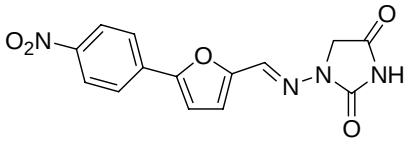

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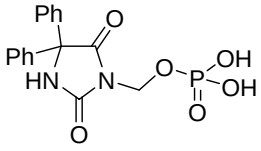
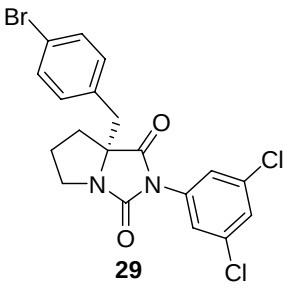


28

Furthermore, several hydantoin derivatives with an extra fused ring show some interesting medicinal properties. Bicyclic compound **29** is an inhibitor for the LFA-1/ICAM interactions (Leukocyte Function-Associated antigen-1 / InterCellular Adhesion Molecule).[13] Derivatives **30** are androgen receptor antagonists and may play an important role in the treatment of prostate cancer.[14] Finally, hydantoins **31** bind selectively to certain receptors involved in regulating a variety of neurotransmitters in the central nervous system.[15]



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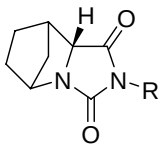

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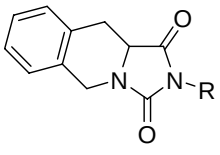
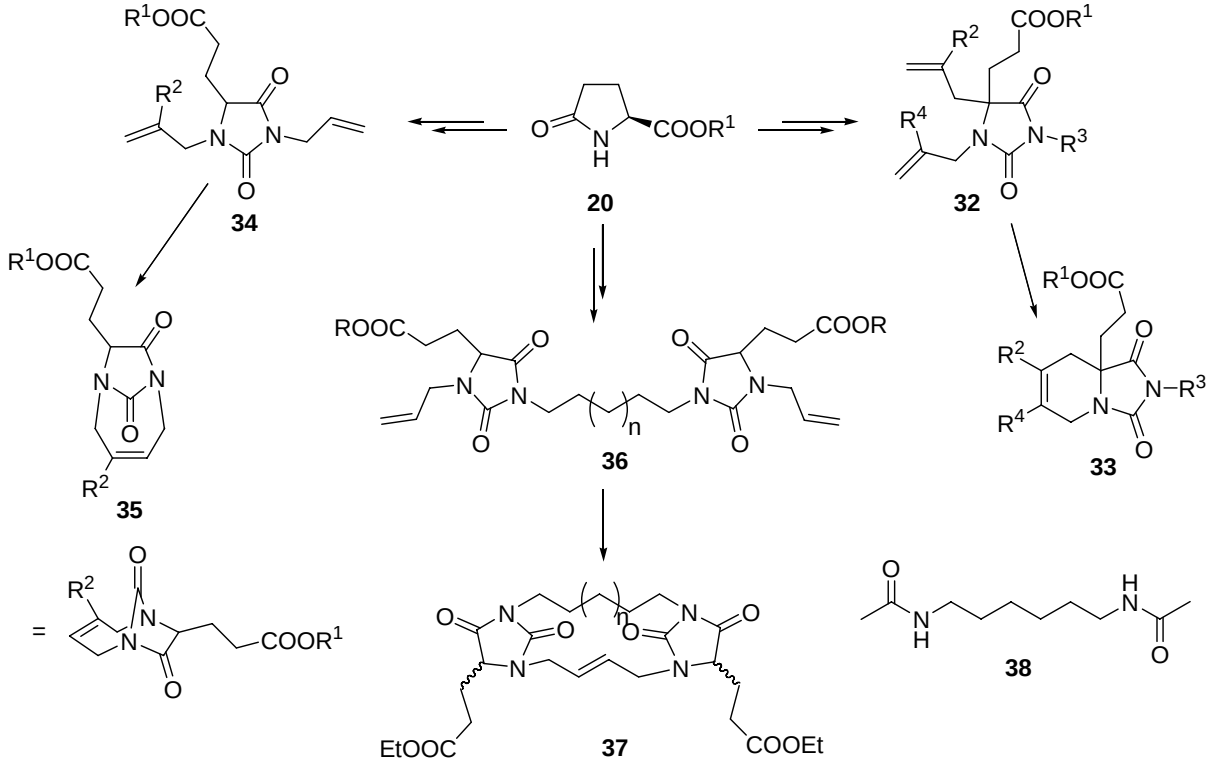


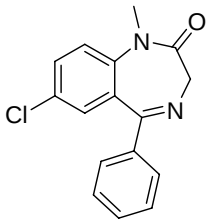
31

Attempts will be made to synthesize polycyclic hydantoin derivatives **33** starting from pyroglutamates **20**. Functionalization of the pyroglutamate at the 2-position, subsequent ring-

transformation and *N*-functionalization should lead to **32**. With the two double bonds ready for cyclization, treatment with a metathesis catalyst should produce derivatives **33**. Reaction of **20** with allylisocyanate followed by *N*-functionalization should yield **34**. Ring-closing of **34** could lead to derivatives **35** containing a seven-membered ring. Also the reaction of pyroglutamates with diisocyanates leading to derivatives **36** will be investigated. Bis-hydantoins, usually dimers of phenetoin or related compounds, have been tested as analogues of HMBA **38** (hexamethylenebis(acetamide)) and might prove effective in cancer treatment.[16,17] The problem with these compounds is their poor water solubility, requiring high doses. Since derivatives **36** have an ester moiety on a side chain, the increased polarity might lead to an activity at lower concentrations. Attempts will be made to cyclize these compounds to macrocyclic derivatives **37**.



Finally, a new entry will be developed towards benzo-annulated heterocycles. Benzo-fused compounds, and especially seven-membered ring systems, have received a lot of attention over the years because of their ubiquitous appearance in natural products and modern pharmaceuticals.[18] Two important examples are diazepam **39** (Valium®) and flurazepam (Dalmadorm®) **40**, mostly used in psychotherapy. Other commercially available drugs include capsazepine **41**, used to treat respiratory disorders like astma,[19] benazepril **42**, used to lower blood pressure in case of hypertension, hart failure and stroke and finally fenoldopam **43**, a rapid vasodilator.



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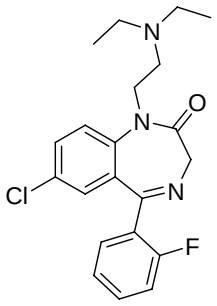

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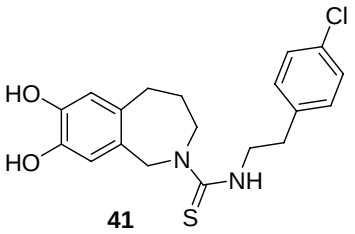

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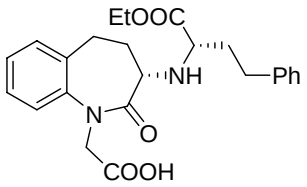
Derivatives of type **44** are inhibitors of acetylcholinesterase and may find application in the treatment of Alzheimer's disease.[20]



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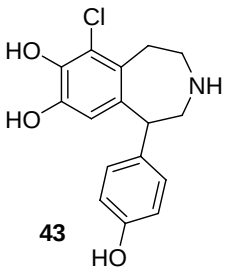

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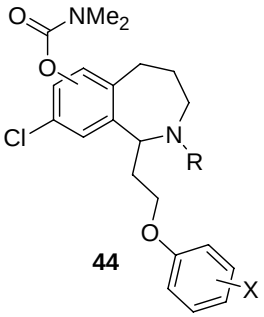
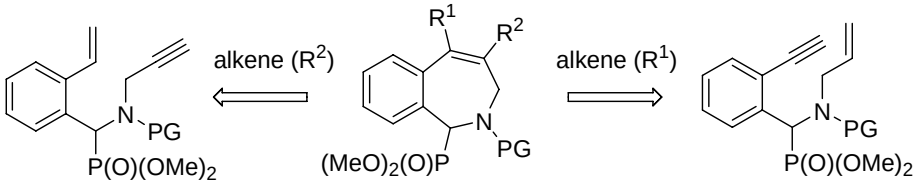


44

So far only one entry to 1*H*-2-benzazepine-1-ylphosphonates **45** has been reported in the literature.[21] Furthermore, only a few papers have been published in the field of seven-membered azaheterocyclic phosphonates, although some of these compounds show interesting biological properties like bone-resorption inhibitory activity.[22] An attempt will be made to synthesize these compounds starting from α-aminophosphonates **46** or **47** using a tandem enyne-metathesis—cross metathesis with an alkene.



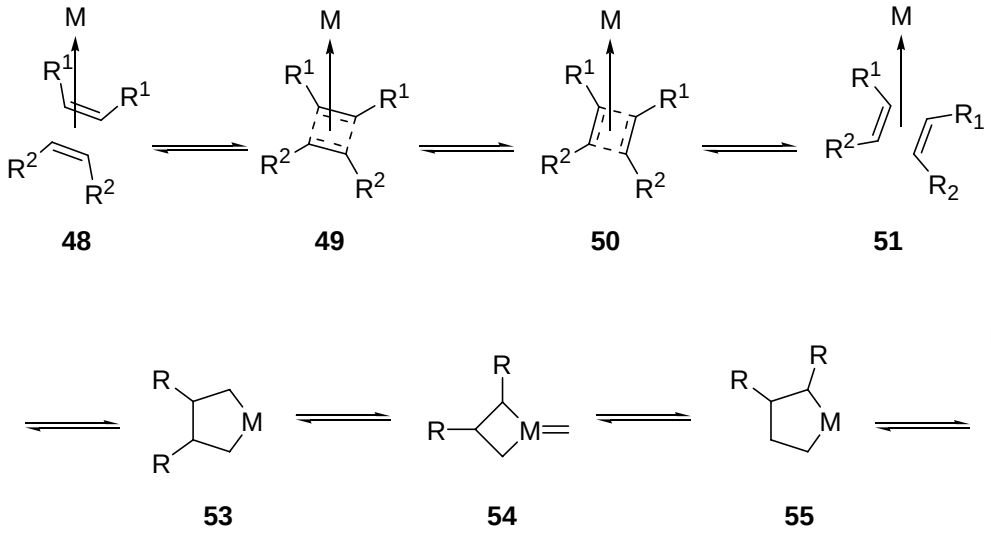
46 **45** **47**

The same methodology will be used to try to synthesize other benzo-annulated phosphonylated heterocycles like benzoxazonines and benzoxazepines.

2 Literature Overview on Ring-Closing Metathesis

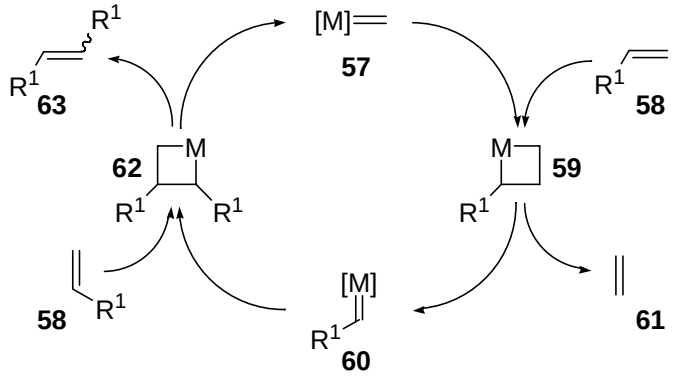
2.1 History of RCM

In 2005, the Nobel Prize in Chemistry was awarded jointly to Yves Chauvin, Robert H. Grubbs and Richard R. Schrock "for the development of the metathesis method in organic synthesis". The discovery of catalyzed metathesis dates from the 1950s in industry when Ziegler observed the polymerization of ethylene. Later on, polymers were obtained starting from norbornene, cycloheptene, cyclooctene, cyclododecene and it was observed that propene was converted to ethylene and butene. The mechanisms behind these reactions were not understood and instead of defined catalysts mixtures of compounds (like MoO_3 on alumina combined with $LiAlH_4$ or $AlⁱBu_3$, WCl_6 combined with Et_3Al, Et_2AlCl or $EtAlCl_2$) were used to achieve these conversions. Several mechanistic hypotheses were formulated to explain these results like the metal-coordinated 'quasicyclobutane' model of Calderon[23,24] who proposed a pairwise exchange of alkylidenes (**48**-**51**) and the metallacyclopentane model of Grubbs (**52**-**56**).[25]

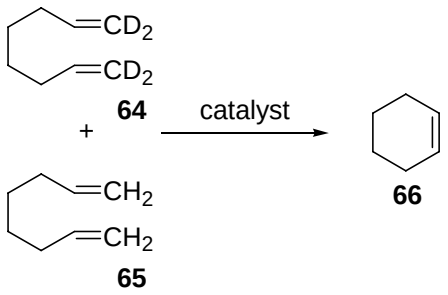


In 1971 Chauvin proposed a non-pairwise mechanism with a metal carbene as the acting catalyst which connects two terminal alkenes into an internal alkene with the formation of ethylene.[26] Every step in the reaction is an equilibrium, but the removal of ethylene drives the reaction to completion. The metal alkylidene plays a central role in this mechanism. In a first step the metal methylidene **57** reacts with an alkene **58** to form a metallacyclobutane **59**. This four-membered ring cleaves with the formation of a new metal alkylidene **60** and ethylene **61**. The ethylene formed contains one methylene from the catalyst and one from the starting alkene. The metal alkylidene **60** again reacts with a molecule of alkene **58** to form a new metallacyclobutane **62**.

Upon decomposition, the internal alkene **63** is formed and the methylidene carbene **57** is regenerated.

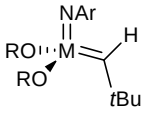


After extensive experimental work, this mechanism became accepted as *the* mechanism for metathesis. A famous experiment performed by Grubbs lies at the basis of this acceptance. A 1:1 mixture of 1,1,8,8-tetradeutero-1,7-octadiene **64** and 1,7-octadiene **65** was treated with a catalyst to produce cyclohexene **66** and a statistical mixture of deuterium labeled ethylenes. Statistical analysis had shown that the kinetic products formed in the non-pairwise mechanism (Chauvin) should appear in a 1:2:1 ratio whereas in the pairwise mechanism (Calderon) a 1:1.6:1 mixture should be formed. It was found that a 1:2:1 mixture was formed, which could only be explained by the Chauvin mechanism.[27] Experiments carried out later with other labeled compounds also pointed towards the Chauvin mechanism.[28,29]

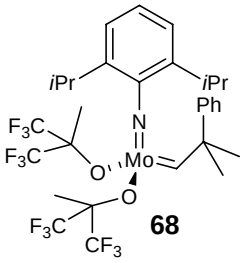


	non-pairwise	pairwise
$H_2C{=}CH_2$	1	1
$H_2C{=}CD_2$	2	1.6
$D_2C{=}CD_2$	1	1

This insight in the reaction mechanism prompted chemists to try to synthesize stabile alkylidene carbenes that could catalyze metathesis reactions, rather than working with the *in situ* generated undefined catalysts used up to that time. It wasn't until the mid 1980s however that a stable metal carbene was synthesized by Schrock and his co-workers that showed metathesis activity.[30] The work of Schrock resulted in the synthesis of a whole family of Mo and W based catalysts possessing very high metathesis activity with general formula **67**, some of them are commercially available like **68**.[31,32,33]

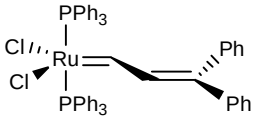


67

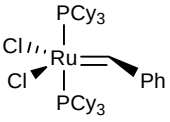


68

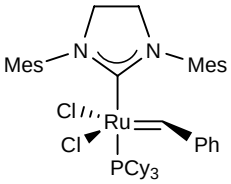
Although Schrock's catalysts are stable and well defined, they are very sensitive to moisture and air. In 1992 Grubbs and co-workers reported the first well defined ruthenium carbene complex **69** that did not only show good metathesis activity, but was also air-stable and could be used under standard lab conditions.[34] Three years later, the PPh_3 ligands were replaced by PCy_3 (tricyclohexylphosphine) ligands and the vinylidene carbene by a benzylidene carbene; catalyst **A** which would later be called the "first-generation Grubbs' catalyst" was born.[35] In order to increase both the activity of the catalyst and its lifetime, one of the phosphine ligands was replaced by a cyclic bis-amino carbene ligand.[36] This catalyst **B** with greater thermal stability is now known as the "second-generation Grubbs' catalyst".



69

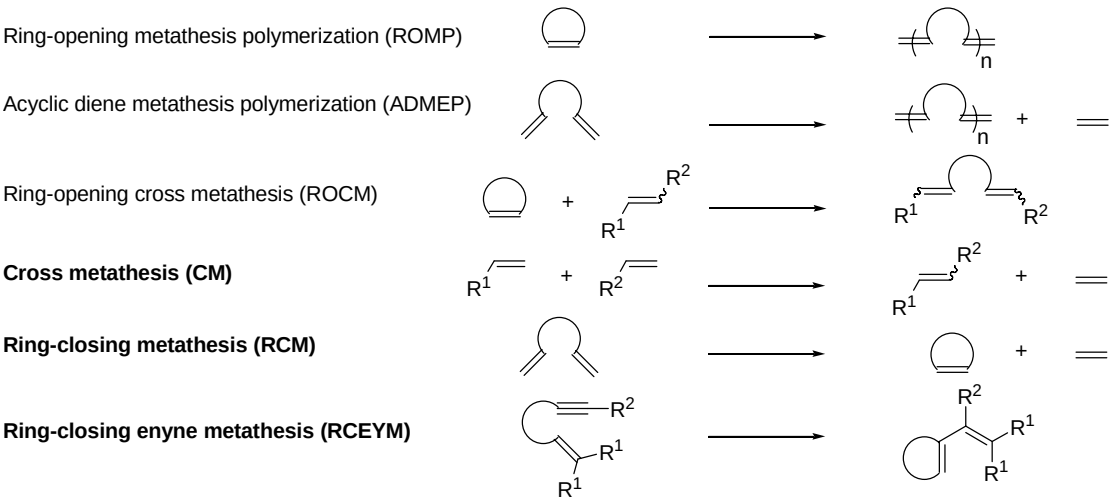


A



B

The Grubbs' catalysts, with their ease of handling and tolerance to a wide variety of functional groups, have offered synthetic chemists opportunities to explore a whole range of new reactions. These reactions can be classified into different classes. In this thesis ring-closing metathesis (RCM), cross metathesis (CM) and ring-closing enyne metathesis (RCEYM) are used.



As a consequence of the 'ease of handling' of these catalysts, the number of articles dealing with metathesis has grown exponentially over the years. To illustrate this, figure 2 shows the cumulative amount of articles found in Web of Knowledge containing the term 'ring-closing metathesis' in the title, keywords or abstract between 1995 and 2005.

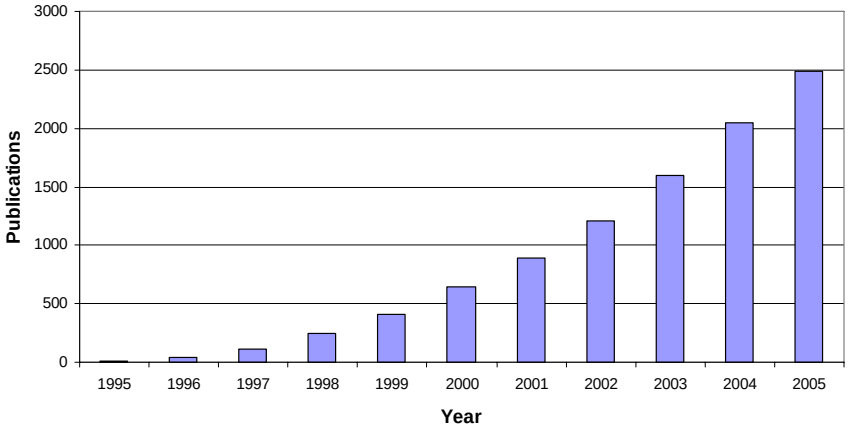


Figure 2: Cumulative amount of articles found in Web of Knowledge containing the term 'ring-closing metathesis' in the title, keywords or abstract between 1995 and 2005.

2.2 RCM in organic synthesis; a short appetizer

2.2.1 The Chauvin mechanism applied to the Grubbs' catalysts

The Grubbs' catalysts are Ru(II) based 16 valence-electron complexes with a general formula like **70** (L = ligand). In this form, they are stable and inert and can be stored for years without decomposition. When brought in solution, however, a phosphine ligand can dissociate to form the active 14 valence-electron complex **71**. An alkene, present in the solution, can act as a new ligand to form another 16 valence-electron complex **72**. A [2+2] cycloaddition results in the formation of ruthenacyclobutane **73**, with 14 valence-electrons and the oxidation state of ruthenium changes to IV.[37] The dissociation of the phosphine ligand, the initiation step, occurs much faster (about two orders of magnitude) in the first generation complex (L = PCy_3) than in the second generation complex (L = SIMES, Saturated Imidazole *N*-Mesityl, 1,3-dimesityl-4,5-dihydroimidazol-2-ylidene). This is more than compensated, however, by the selectivity towards alkenes versus phosphines (about four orders of magnitude) for the second generation complex compared to the first generation complex. This results in an overall greater activity of the catalyst bearing a *N*-heterocyclic carbene (NHC) ligand. In a series of experiments, Grubbs was able to determine the rate constants k_1 and k_2 of the different Ru-complexes in reaction with ethylvinylether as well as the Gibbs free activation energies for phosphine dissociation (Table 1).[38,39]

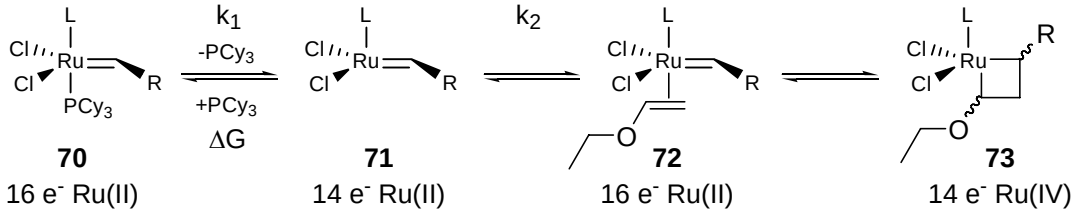
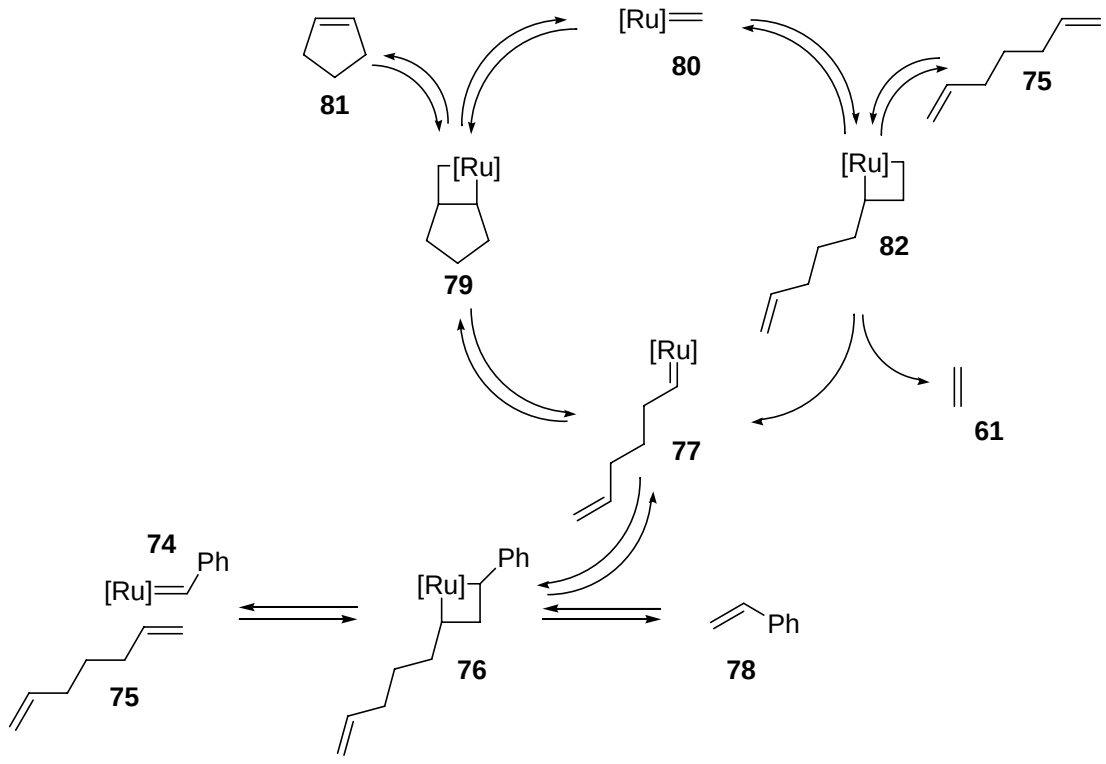


Table 1: rate constants k_1 and k_2 of reaction with ethylvinylether and Gibbs free activation energies for phosphine dissociation of different Ru-complexes

L = PCy_3	L = SIMES
ΔG = 83.2 kJ/mol ± 0.3 kJ/mol	ΔG = 96.2 kJ/mol ± 1.7 kJ/mol
$k_1/k_2 = 1.3x10^4$	k_1/k_2 = 1.25

From these results it is clear that although the formation of the active species is quite slow for the second generation catalyst (larger ΔG), the association with an alkene occurs extremely fast resulting in an overall much greater activity (in this case about four orders of magnitude).

The complete catalytic cycle for ring-closing of 1,6-heptene **75** is depicted in the scheme below. After the active species **74** is formed by dissociation of the phosphine ligand, the alkene can associate with one of its double bonds. For clarity reasons, the ruthenium with all its remaining ligands is depicted as [Ru]. A [2+2] cycloaddition produces ruthenacyclobutane **76** which forms styrene **78**, as a side product, and new carbene **77** after cycloreversion.

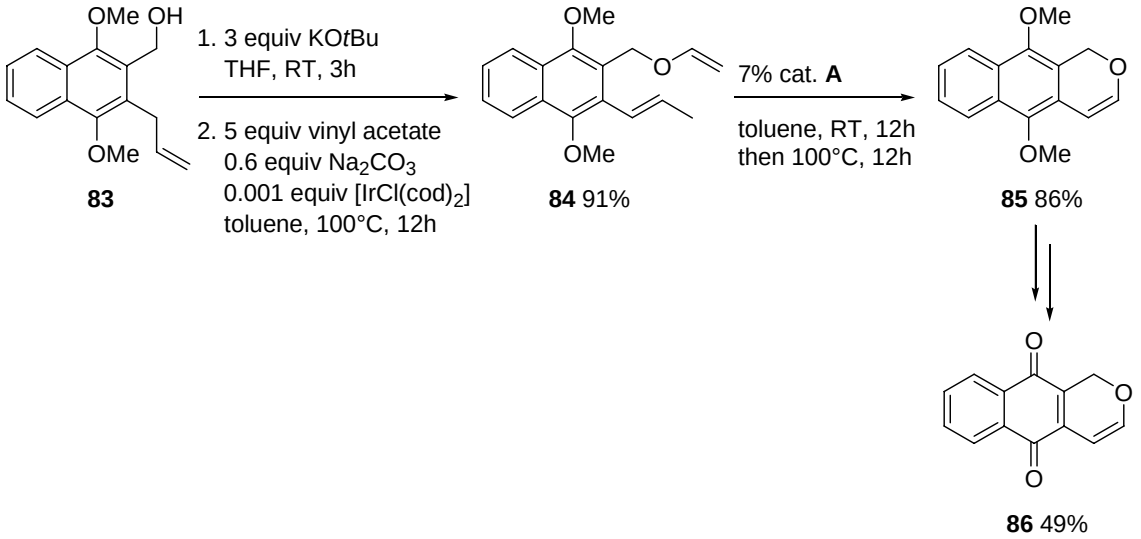


Now the other double bond can associate with the ruthenium and another cycloaddition leads to bicyclic compound **79**. Cycloreversion forms the end product cyclopentene **81** and methylidene carbene **80**. This carbene is considered as the propagating species that is continuously regenerated during the course of the reaction. The cycle continues with association and subsequent cycloaddition of another molecule of substrate, forming **82**, which decomposes with formation of **77** and ethylene **61**. Since all steps in this reaction sequence are in fact equilibria, removal of ethylene from the mixture drives the reaction to completion.

2.2.2 Ring-closing metathesis in action

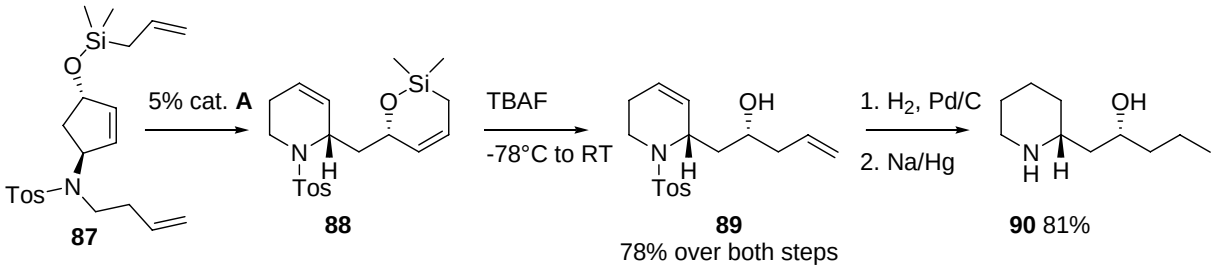
As stated before, the number of reports on the use of RCM has grown exponentially. Therefore, a systematic overview of this subject can not be presented here. The interested reader is kindly invited to consult following reviews for more information: olefin metathesis,[40,41,42,43,44] non-metathetic behaviour of Grubbs' carbenes,[45] Ru complexes with bidentate carbenes,[46] enyne metathesis,[47,48] group-selective ring-closing enyne metathesis,[49] Ru complexes with bidentate Schiff base ligands for organic and polymer synthesis,[50] tandem and stepwise metathesis/non-metathesis processes,[51,52] molybdenum and tungsten catalysts,[53] metathesis in total synthesis,[54] RCM for the construction of aromatic compounds,[55] the evolution of metathesis,[56,57] synthesis of oxygen- and nitrogen-containing heterocycles by RCM,[58] synthesis of phosphorus and sulfur heterocycles by RCM,[59] metathesis/hydrogenation tandems,[60] synthesis of peptidomimetics, sugars and alkaloids by RCM,[61] factors influencing ring-closure,[62] cross-metathesis.[63] In what follows, a very short summary of some interesting examples of RCM in organic synthesis will be given, although this is merely 'scratching the surface'. Two important developments, namely the use of RCM for the synthesis of aromatic compounds and RCM in a tandem reaction sequence will be dealt with in more detail later.

Pentalongin **86** is a natural product from the Central-East African medicinal plant *Pentas longiflora* Oliv., which is used in the region for treatment of malaria and certain skin diseases. Starting from dimethoxynaphthalene derivative **83**, the RCM substrate **84** was synthesized in two steps; the first being isomerization of the allylic double bond and the second vinylation of the primary alcohol. Treatment of this precursor with first generation catalyst **A** resulted in the formation of **85**, the reduced and protected form of pentalongin. This compound was transformed in 3 additional steps to the target compound **86**.[64]



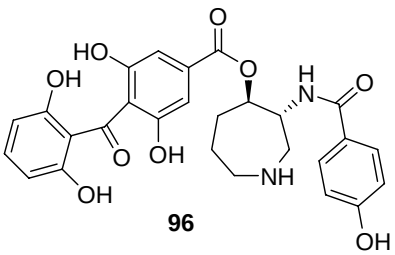
83 **84** 91% **85** 86% **86** 49%

An elegant approach to the piperidine alkaloid (−)-halosaline **90** using a combination of ring-opening metathesis and ring-closing metathesis, also called ring shuffling metathesis, was developed by Blechert.[65] Functionalized cyclopentene derivative **87** was treated with first generation catalyst **A** resulting in opening of the five-membered ring and the formation of two less strained six-membered rings **88**. After cleavage of the O-Si bond, **89**, the double bonds were reduced and the *N*-atom was deprotected to yield **90**.

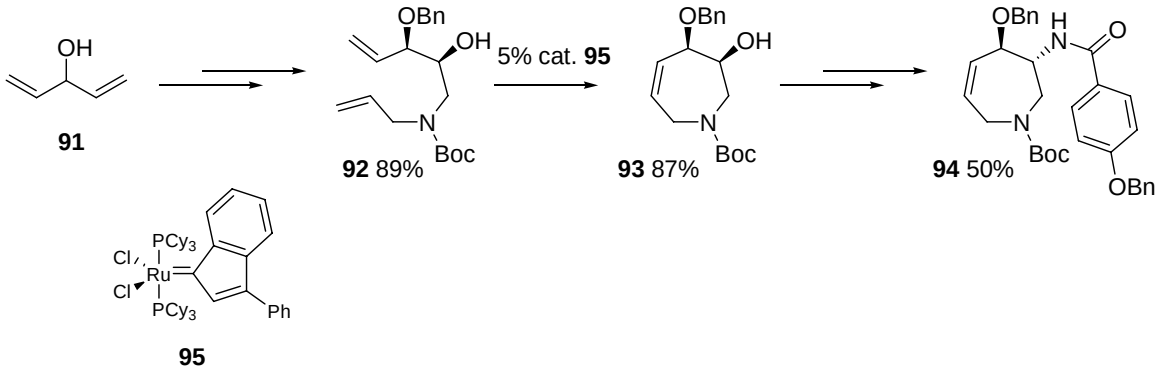


87 **88** **89** 78% over both steps **90** 81%

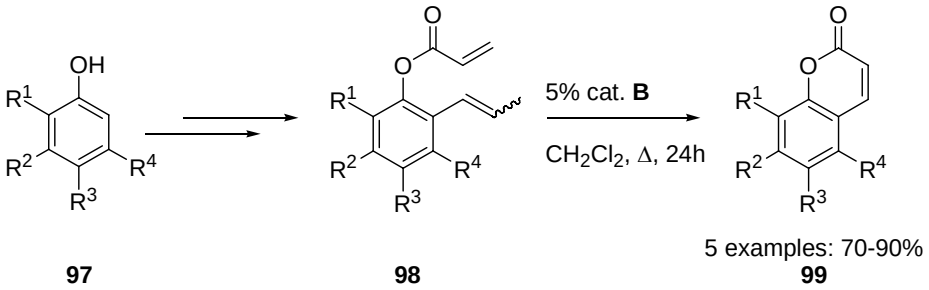
The alkaloid (−)-balanol **96**, with a hexahydroazepine nucleus, is a new lead structure in the quest for protein kinase C inhibitors. A total synthesis to form the seven-membered core of this compound was developed by Fürstner.[66] Commercially available alcohol **91** was converted to the RCM substrate **92** in four steps in 89% yield. Treatment of this compound with catalyst **95** effects the formation of the seven-membered ring **93** which is converted to **94** in three steps in 50% yield.



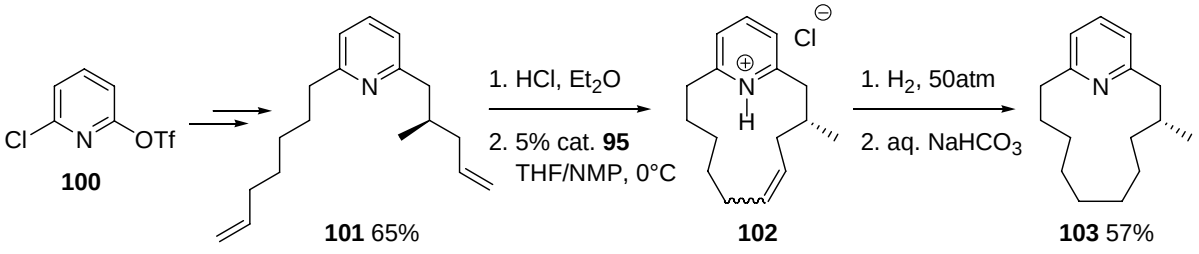
96



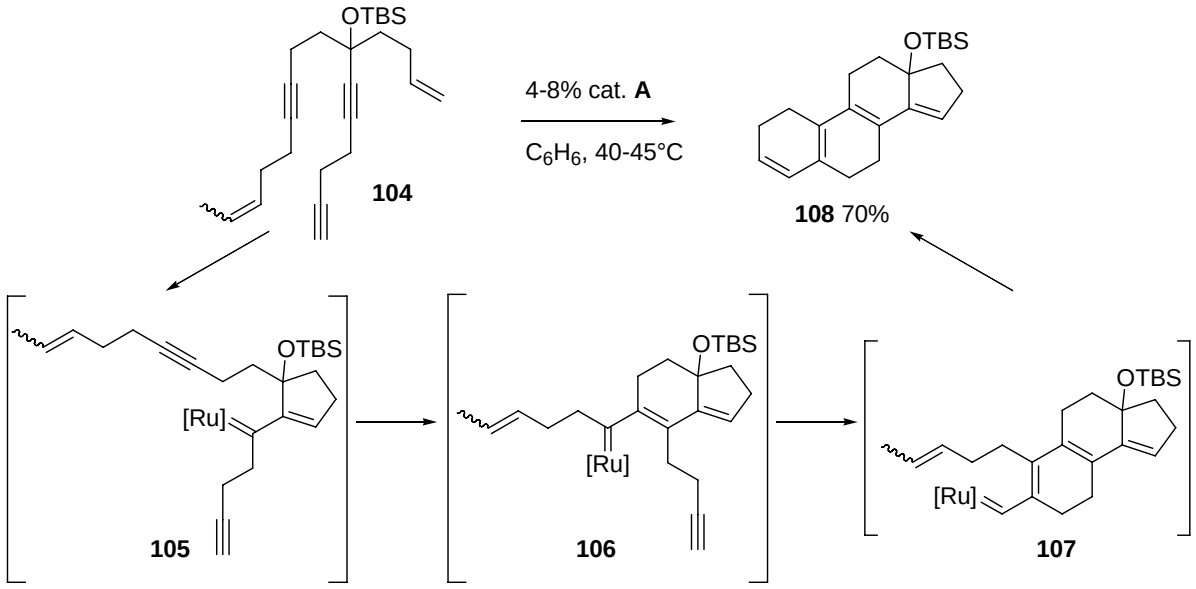
Coumarins are widespread in nature as physiologically active components of plants and show interesting biological properties like antimicrobial, anticancer and anti-HIV activity. Commercially available phenols **97** were transformed in four straightforward steps to α,β-unsaturated esters **98**. When subjected to the action of the second generation catalyst **B**, these compounds were cyclized to coumarins **99**.[67] A similar approach to coumarins, with substituents at the α,β-unsaturated bond, was independently developed by Grubbs.[68]



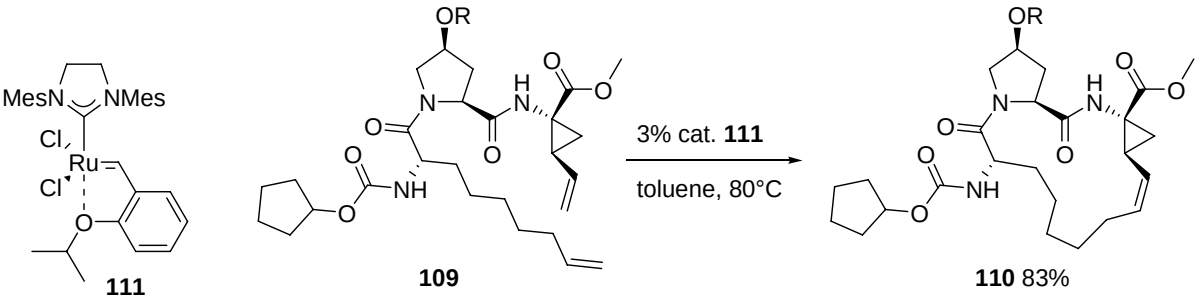
The odour compound of animal origin (R)-(−)-muscopyridine **103**, has attracted a lot of attention from organic chemists but was only recently very efficiently synthesized by Fürstner.[69] The synthesis is based on two key reactions. The first one being an alkyl-aryl cross-coupling catalyzed by an iron-salen complex and the second being RCM. Functionalized pyridine **100** is transformed in two iron-salen catalyzed cross-couplings to open chain derivative **101** in about 65% yield. Treatment of the HCl salt of **101** with catalyst **95** gives **102** as an *E*/*Z* mixture. This crude mixture was placed under a high pressure H_2 atmosphere and after a basic workup muscopyridine **103** was obtained in 57%.



In relay metathesis, an acyclic precursor containing two double and several triple bonds is cyclized to a polycyclic entity. A very nice example of this was reported by Grubbs and truly shows the power of this technique.[70] Thus (dienyl)polyalkyne **104** was transformed in a single step to the tetracyclic compound **108** possessing the steroid skeleton. The catalyst initiates at the terminal double bond and then reacts with the nearest triple bond to form a new ring **105**. Every triple bond acts as an anchor that keeps the catalyst attached to the molecule. The catalysts moves from one triple bond to the next, from **105** to **106** to **107**, and after the final cyclization the catalyst is split off and ready to react with another molecule of **104**.



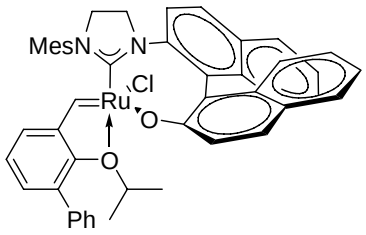
Recently the first ever use of RCM for production scale synthesis was described by German researchers at Boehringer Ingelheim.[71,72] The fifteen-membered macrocycle **110** is a precursor of the antiviral drug BILN 2061 ZW, which has been developed against the Hepatitis C virus. In total, 400 kg of compound **110** was needed and this was achieved by conducting the cyclization of **109** in batches of 20.2 kg diene in toluene at 80 °C.



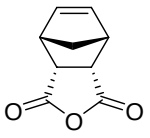
In order to prevent dimerization instead of cyclization, the reaction has to be run at a very low concentration of 14.64 mmol/l, i.e. 7.3 g of diene **109** per litre toluene. The second generation

Hoveyda-Grubbs catalyst **111** was used with a loading set to about 3 mol%. This means that about 493 g of catalyst was needed for each reaction run!

A relatively new chapter in metathesis is the synthesis of chiral Ru complexes like catalyst **112**.[73] The usefulness of this kind of catalysts is shown by several examples like the asymmetric ring-opening/cross metathesis of substrate **113** in the presence of an alkene **58**. After the reaction, the catalyst can be recovered up to 96%. The ring-opened compounds **114** are obtained in reasonable yield and good enantioselective excess. The same catalyst was used for the enantioselective ring-closing of ether **115**. Dihydro pyran **116** was obtained in excellent yield with reasonable enantiomeric excess.



112

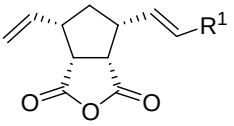


113

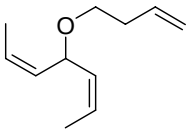
2 equiv. R^1 **58**

0.5-10% cat. **112**

THF, 50°C



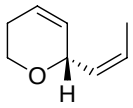
80-82% ee
57-71%
114



115

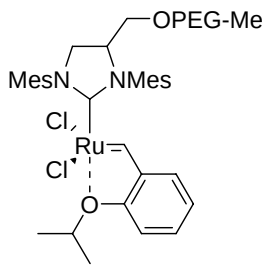
10% cat. **104**

$ClCH_2CH_2Cl$, 60°C

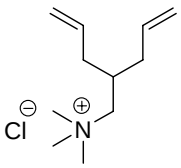


76% ee, 98%
116

Very recently Grubbs reported on the synthesis and evaluation of the new catalyst **117**, with a poly(ethylene glycol) (PEG) chain attached to the nondissociating NHC ligand.[74] This very polar side chain makes the catalyst soluble in methanol and water. The remarkable stability of the ruthenium carbene was again proven by conducting RCM in water. Thus quaternary ammonium salt **118** could by cyclized to **119** in excellent yield. Also cross metathesis proved to be possible, shown by dimerization of allyl alcohol **120** to **121**. The use of PEG as support for metathesis catalysts has also been reported by other research groups.[75]



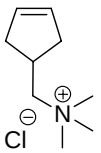
117



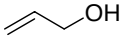
118

5% cat. **117**

H_2O, 45°C, 12h



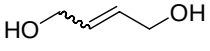
119 >95%



120

5% cat. **117**

H_2O, 45°C, 12h



121 >95%

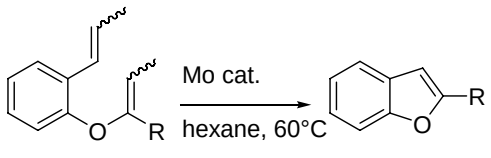
2.3 RCM as a basis for the synthesis of aromatic compounds

2.3.1 Introduction

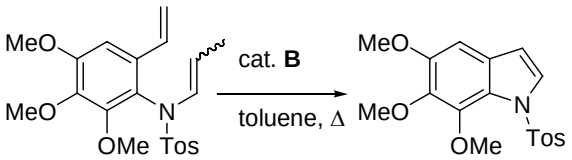
At the beginning of this PhD in august 2003, there was no general route to aromatic compounds using RCM. In the following years, however, this became a new 'hot topic' in organic synthesis. The strategy developed in this work is based on a one-pot combination of ring-closing metathesis and oxidation in which both the ruthenium catalyst and the oxidant are present at the beginning of the reaction. To this date, no other research group has developed a similar protocol. In what follows an overview is presented of the different strategies developed in recent years used to synthesize aromatic compounds by RCM.

2.3.2 Direct formation of aromatic compounds by RCM

Evidently, the easiest way to construct aromatic compounds by RCM is choosing the correct starting material that upon cyclization immediately leads to the aromatic compound. Although this strategy leads directly to the desired compounds, it has limited use due to the non-availability and stability of suitable starting materials. This strategy was applied for the synthesis of benzofurans **123** using a Mo based catalyst for the cyclization of enol ethers **122**.[76] A very similar strategy can be applied for the synthesis of indoles **125**. In this case the second generation Grubbs' catalyst **B** was used to cyclize enamines **124**.[77] These enamines were obtained by isomerization of the double bond using catalyst **B** modified with 1 equivalent of vinyloxytrimethylsilane. The second generation catalyst was later used for the synthesis of a number of phenanthrenes[78,79] and ring-fused carbazoles.[80]



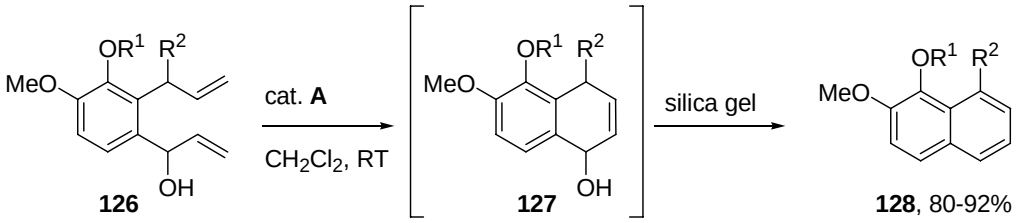
122 **123**, 87%



124 **125**, 83%

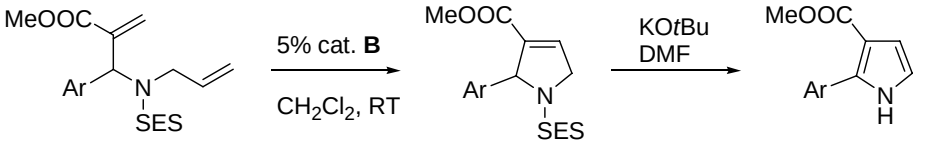
2.3.3 RCM followed by elimination of a leaving group

Another strategy used to obtain aromatic compounds is incorporating a proper leaving group in the ring that upon elimination leads to aromatization. This strategy was used for the first time in 2001 for the synthesis of a number of naphthalene derivatives **128**.[81] The diene precursors **126** were cyclized to **127** using the first generation Grubbs' catalyst **A** and aromatized by dehydration using silica gel. A very similar combination of cyclization and elimination of water was used for the synthesis of a benzimidazole in the presence of TsOH.[82]



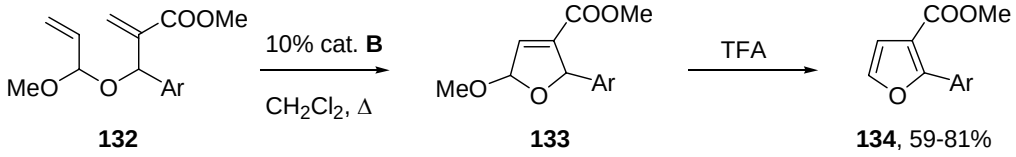
126 **127** **128**, 80-92%

A general approach to pyrroles was developed by Lamaty and coworkers.[83] They observed that trimethylsilylethanesulfonyl (SES)-protected[84] pyrrolines **130**, formed by cyclization of **129** using second generation catalyst **B**, aromatize to the corresponding pyrroles **131** upon base-induced deprotection of the *N*-atom. The same group had previously observed the formation of pyridines upon fluoride-induced deprotection of the PEG-supported SES-group on tetrahydropyridines.[85]

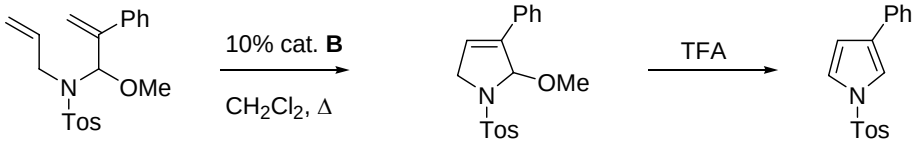


129 **130**, 90-98% **131**, 66-88%

Donohoe and coworkers came up with an approach to furans and pyrroles by TFA promoted elimination of methanol after cyclization.[86] In a first step, diene precursors **132** and **135** were treated with second generation catalyst **B** in refluxing CH_2Cl_2. When this mixture was treated with TFA, the ring-closed products **133** and **136** aromatized to the corresponding furan **134** and pyrrole **137**. The main drawback of this procedure, however, was the purification of these aromatic compounds. Therefore, the reaction had to be performed in two steps with intermediate purification of **133** and **136**.



132 **133** **134**, 59-81%

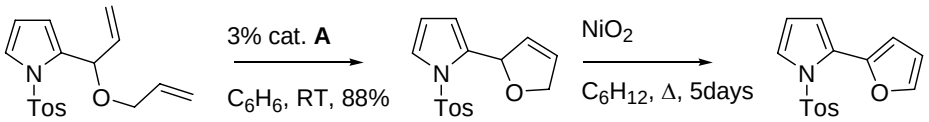


135 **136** **137**, 74%

2.3.4 RCM followed by oxidation

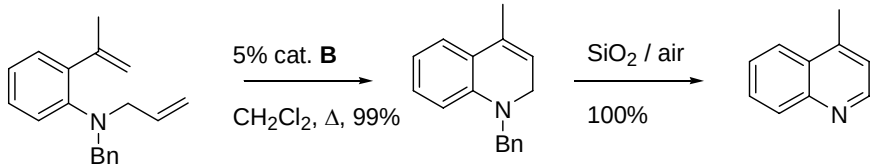
The new entry to pyrroles developed in this work is based on a combination of RCM and oxidation and will be described in detail later on. Here, an overview is presented of other oxidation methods recently described.

In 2000, Robertson and co-workers were able to construct the bis-aromatic compound **140** in two steps starting from pyrrole **138**.[87] They used a NiO_2 promoted oxidation of compound **139** but obtained only 8% of the desired compound after 5 days of reflux in cyclohexane.



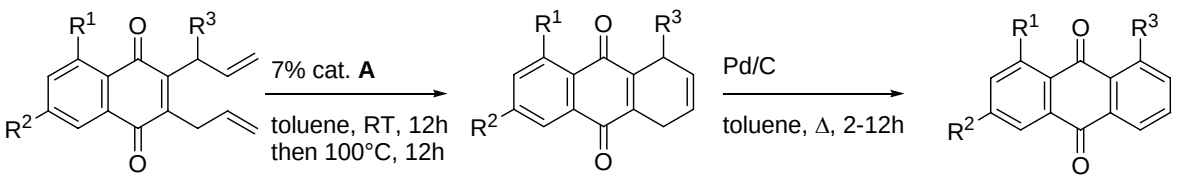
138 **139** **140**, 8%

Two different research groups were able to obtain quinolines after removal of the protecting group on the *N*-atom followed by spontaneous oxidation. In the first strategy compound **141** is cyclized towards **142** and subsequently the benzyl group is split off during chromatography. The *N*-deprotected form of **142** spontaneously oxidized to **143**.[88]



141 **142** **143**

In 2004, De Kimpe and co-workers disclosed a new entry to anthraquinones **146** in two high-yielding steps starting from diallylated naphthoquinones **144**. The first step is ring-closing catalyzed by first generation complex **A** and the second an oxidative aromatization of **145** by treatment with Pd/C in refluxing toluene.[89]

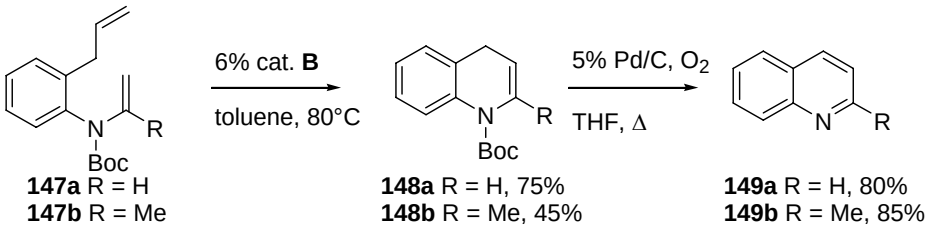


5 examples: 88-94% 5 examples: 88-96%

144 **145** **146**

Another research group used a very similar strategy to obtain quinolines **149**. The cyclized compound **148** is refluxed in THF under O_2 atmosphere in the presence of Pd/C resulting in

aromatization and deprotection of nitrogen.[90] A similar strategy with another protecting group (CO_2Me) was later used by the same research group.[91]

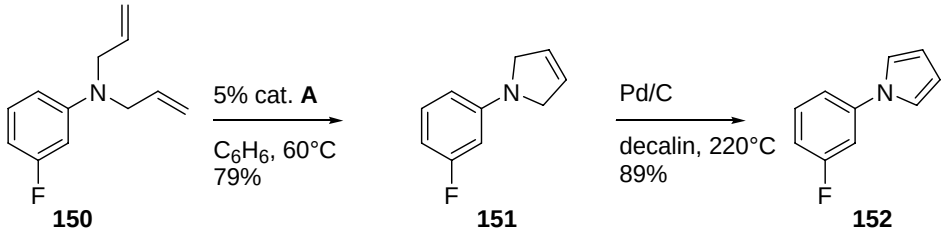


147a R = H
147b R = Me

148a R = H, 75%
148b R = Me, 45%

149a R = H, 80%
149b R = Me, 85%

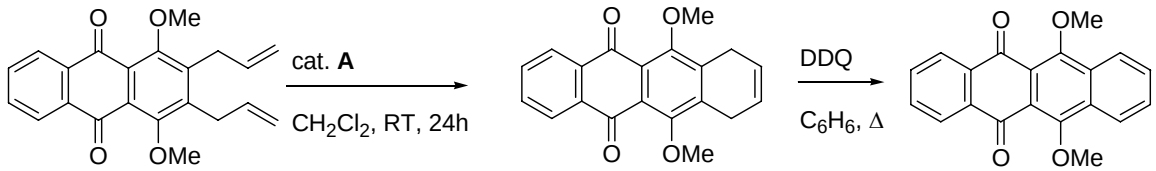
Recently another Pd/C promoted aromatization was disclosed by heating cyclized compounds **151** and **154** to 220 °C in decalin. In this fashion, pyrrole **152** and quinoline **155** could be obtained. The authors report that during the cyclization of **153** the acetyl group is spontaneously split off and the double bond isomerizes.[92]



150 **151** **152**

153 **154** **155**

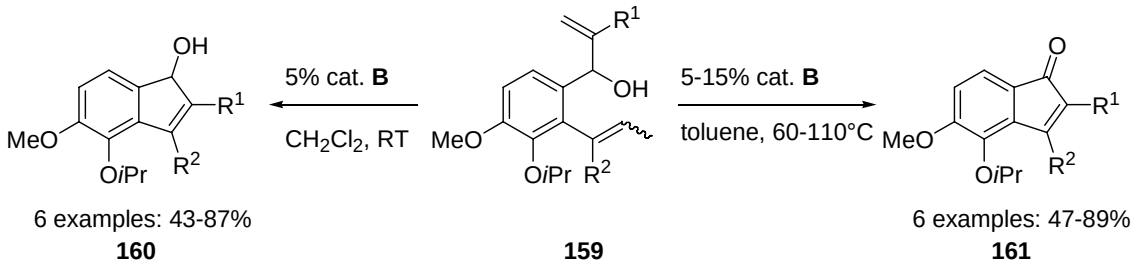
A new benzoannulation protocol leading to various quinone derivatives consists of RCM followed by oxidation with DDQ. An example is 5,12-naphthacenedione **158** which is obtained in a one-pot two-step protocol starting from **156**.[93] The sequence has to be performed in two steps because of incompatibility between the metathesis catalyst and DDQ.



156 **157** **158** 49% overall

Finally, there are some reports in the literature of spontaneous aromatization upon prolonged heating of the reaction mixtures. Generally decomposition products of the metathesis catalyst are thought to be responsible for this. Examples include the formation of pyrroles,[94,95] furans[96] and indenones.[97] It should be noted, however, that the aromatizations in the first two cases are side

reactions observed with only one or a few derivatives whereas the metathesis of compounds **159** can be directed towards the indenols **160** or indenones **161** depending on the applied conditions.



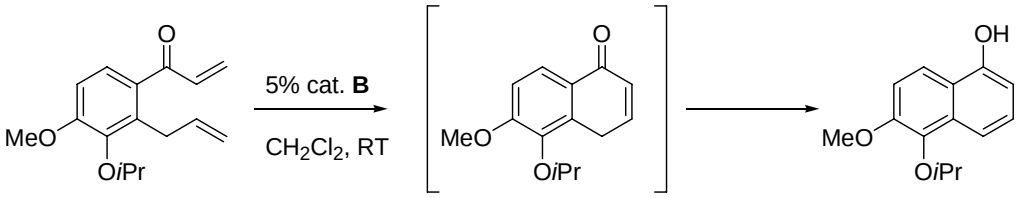
6 examples: 43-87%
160

159

6 examples: 47-89%
161

2.3.5 RCM combined with tautomerization

The first compound to be synthesized by a combination of RCM and tautomerization was naphthol **164** reported by de Koning.[98] When α,β-unsaturated ketone **162** was treated with second generation catalyst **B** it was immediately converted to **164** without a trace of intermediate **163**.

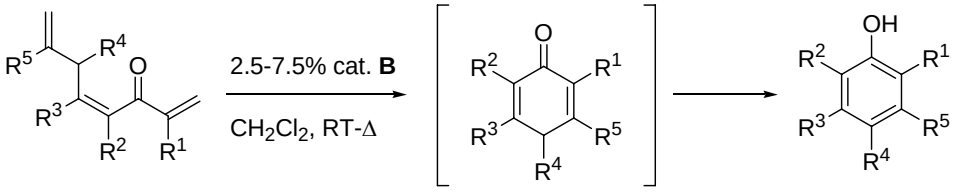


162

163
Not observed

164 69%

A similar strategy was used for the synthesis of phenols **167**. The only limitation is the number of substituents, as it was observed that an acyclic precursor **165** bearing more than three substituents did not cyclize.[99]



165

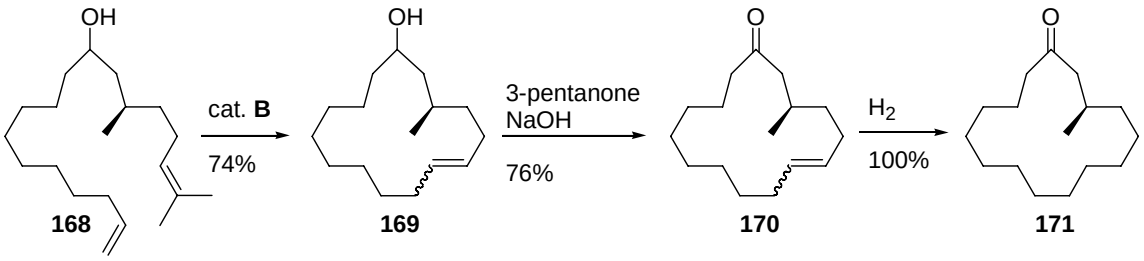
166

167
40-97%

2.4 RCM in a tandem reaction sequence

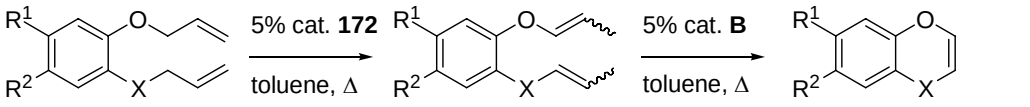
2.4.1 Tandem metathesis/hydrogenation

The first reaction to be performed in a tandem sequence with RCM was hydrogenation. To achieve this, the mixture obtained after the ring-closing step is simply placed under a H_2 atmosphere which turns the ruthenium catalyst into a metal-hydride species, able to reduce double bonds. One of the most famous examples, the synthesis of (R)-muscone **171**, was published by Grubbs.[100] In a first step the secondary alcohol **168** is cyclized towards **169** which is converted to ketone **170** by transfer hydrogenation in the presence of 3-pentanone and NaOH. Finally the mixture is placed under a H_2 atmosphere which results in the chemoselective reduction of the double bond. It is important to notice that a single Ru source is used for all three transformations.



2.4.2 Combination of RCM and isomerization

The isomerization of a double bond can be achieved either before or after the metathesis step. A lot of work based on a combination of isomerization catalyzed by **172**[101,102] and RCM has been performed by van Otterlo and co-workers. In a series of papers they describe the synthesis of benzo[1,4]dioxins **175a**, benzoxazines **175b**, benzofurans **178** and a 1,5-benzothiazepine **181**, all based on the same strategy.[103,104,105]



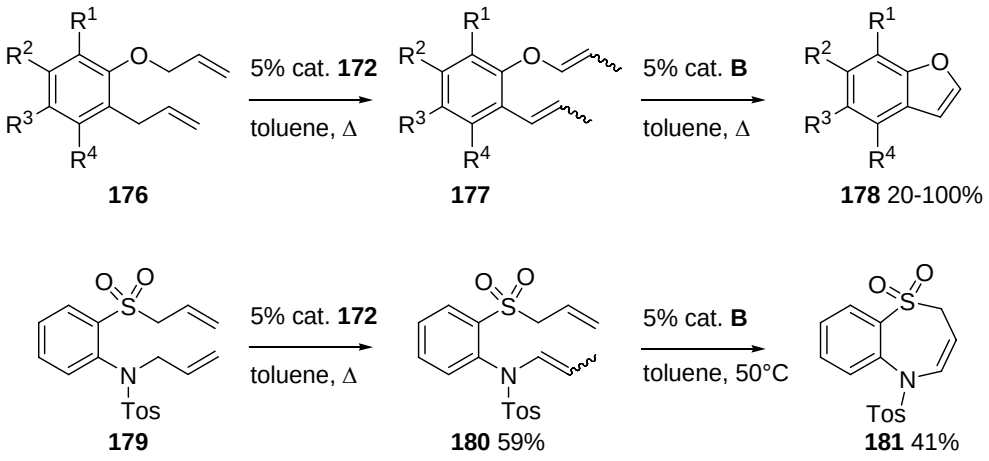
173a X = O
173b X = NTos

174a X = O
174b X = NTos

175a X = O, 70-90%
175b X = NTos, 71-90%

$RuClH(CO)(PPh_3)_3$ **172**

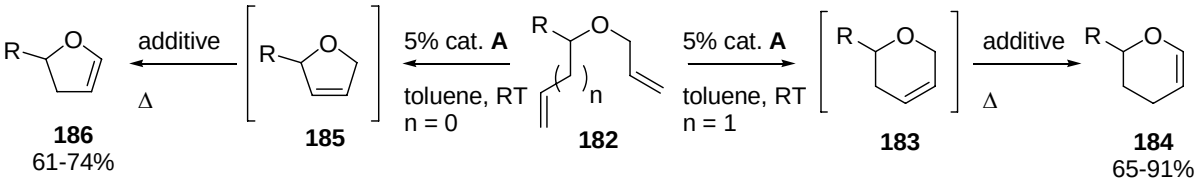
In some cases the reaction is performed without isolation nor purification of the isomerized compounds.



176 **177** **178** 20-100%

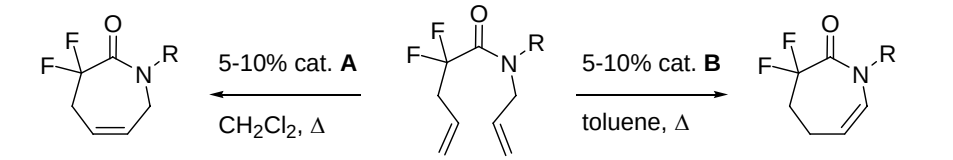
179 **180** 59% **181** 41%

Isomerization after cyclization can be performed by adding certain additives to the reaction mixture in order to convert the metathesis catalyst to a Ru-H species, or by applying more drastic reaction conditions. The first additive used to create the hydride species was a mixture of H_2 and N_2 (5/95).[106] A more practical approach was developed by Schmidt who used organic (ethyl vinyl ether, triethylsilane and isopropanol in combination with NaOH) and inorganic (NaH and $NaBH_4$) additives to achieve this conversion.[107,108] In this way 3,4-dihydro-2H-pyrans **184** and 2,3-dihydro-furans **186** could be obtained without isolation of the metathesis products **183** and **185**.



186 61-74% **185** **182** **183** **184** 65-91%

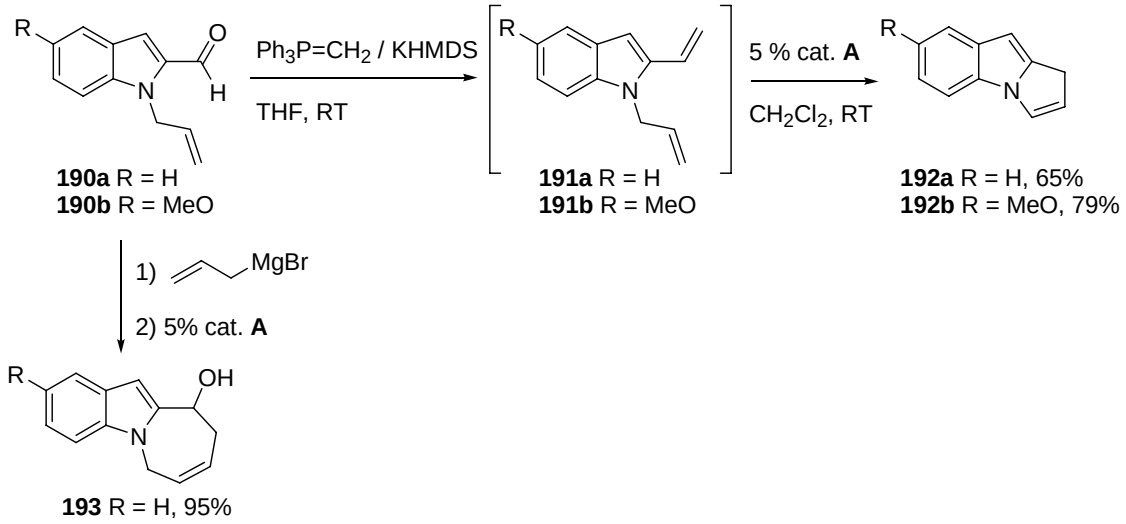
The addition of an extra reagent can be avoided by allowing the metathesis catalyst to decompose after cyclization has occurred. Upon decomposition, the catalyst is transformed into an undefined Ru-H species which is able to bring about isomerization. This strategy was used for the synthesis of a variety of five- to eight-membered rings. Depending on the applied reaction conditions, fluorinated amides **187** are converted to **189** or to the isomerized compounds **188**.[109]



4 examples: 70-95% **189** **187** 6 examples: 70-93% **188**

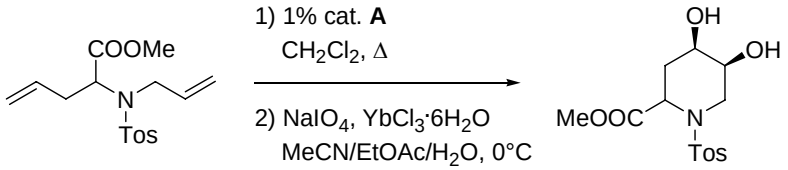
2.4.3 Combination of a Grignard or Wittig reaction with RCM

During research on the mitosene skeleton, it was found that certain intermediates in the envisaged reaction sequence are unstable. This meant that either a new strategy had to be adopted or the isolation of these intermediates had to be avoided. It was found that compounds **191**, created by a Wittig reaction on **190**, are very unstable and break down rapidly. It proved possible, however, to perform an RCM on the unpurified reaction mixture (after extraction and changing of solvent) and obtain **192** in very good overall yield. After the ring-closing, the double bond of the newly formed five-membered ring spontaneously shifts towards the *N*-atom. The same group reported the instability of the secondary alcohol obtained by a Grignard reaction between **190a** and allylmagnesium bromide. Again this problem was circumvented by immediately performing the metathesis reaction. The overall yield of **193** is excellent.[110] Another research group performed an enantioselective Grignard reaction, using a BINAP ligand, in the presence of Cu in combination with RCM.[111]



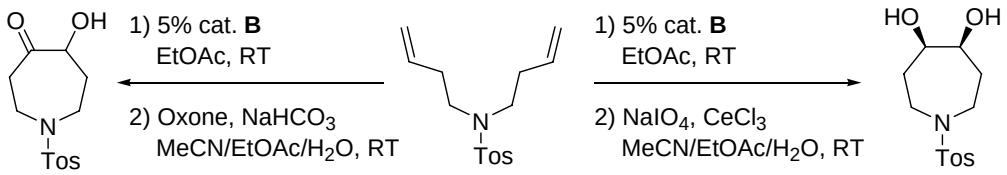
2.4.4 Combination of RCM and dihydroxylation or α-ketohydroxylation

The first report of a metathesis/dihydroxylation sequence was made by Blechert.[112] After the metathesis, the ruthenium carbene is converted to the oxidative RuO_4 species by treatment with 1.2-1.6 equivalents of $NaIO_4$ (the stoichiometric oxidant) and a catalytic amount of $YbCl_3 \cdot 6H_2O$ in a 3:3:1 mixture of MeCN/EtOAc/H_2O. A number of six- and seven-membered nitrogen and oxygen heterocycles were prepared in this fashion such as piperidine **195**, obtained in excellent yield starting from **194**. Instead of RCM also cross metathesis is possible, in this case acyclic dihydroxylated compounds are obtained.



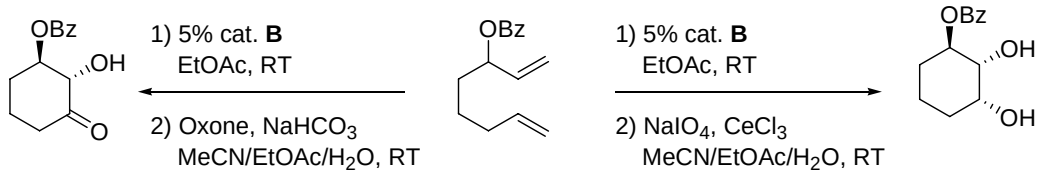
194 **195** 88%

The main disadvantage of this approach is the fact that both steps have to be performed in different solvents since the dihydroxylation didn't work in CH_2Cl_2. This technique was refined and expanded, however, by Snapper and co-workers.[113] By performing the RCM in EtOAc and afterwards pouring this mixture in MeCN/H_2O (6:1) containing a catalytic amount of $CeCl_3$ and a stoichiometric amount of $NaIO_4$, the need for solvent removal was avoided. By changing $NaIO_4$ to oxone, they were able to achieve α-ketohydroxylation instead of dihydroxylation. In this way a number of five- six- and seven-membered α-hydroxyketones were produced as well as linear ones when used in combination with cross metathesis. Compound **196** could thus be converted to **197** or to **198** depending on the oxidant used.



198 65% **196** **197** 65%

Control experiments showed that the oxidation does not occur in the absence of the Ru-complex, proving that this is really necessary for the oxidation. The dihydroxylation reaction can proceed with high diastereoselectivity when a stereocenter is proximal to the olefin. This is proven by the selective conversion of **199** to **201**. When the α-ketohydroxylation was performed on the same unsymmetrical substrate, however, regioisomers **200** are obtained.

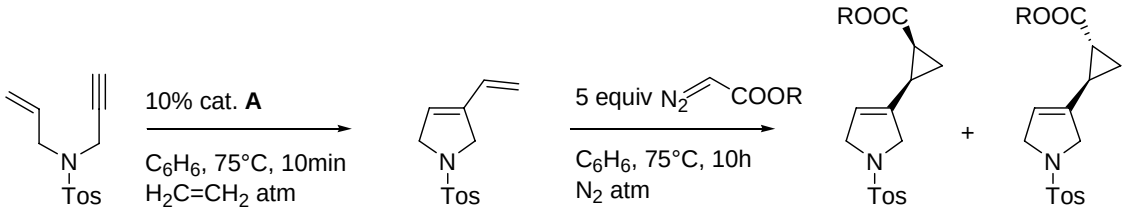


200 60% (2:1) **199** **201** 81%

2.4.5 RCM followed by cyclopropanation

The same research group that developed the α-ketohydroxylation also came up with a combination of ring-closing enyne metathesis with cyclopropanation.[114] Treatment of a precursor like **202** containing an yne and an ene moiety with first generation catalyst **A** under ethylene

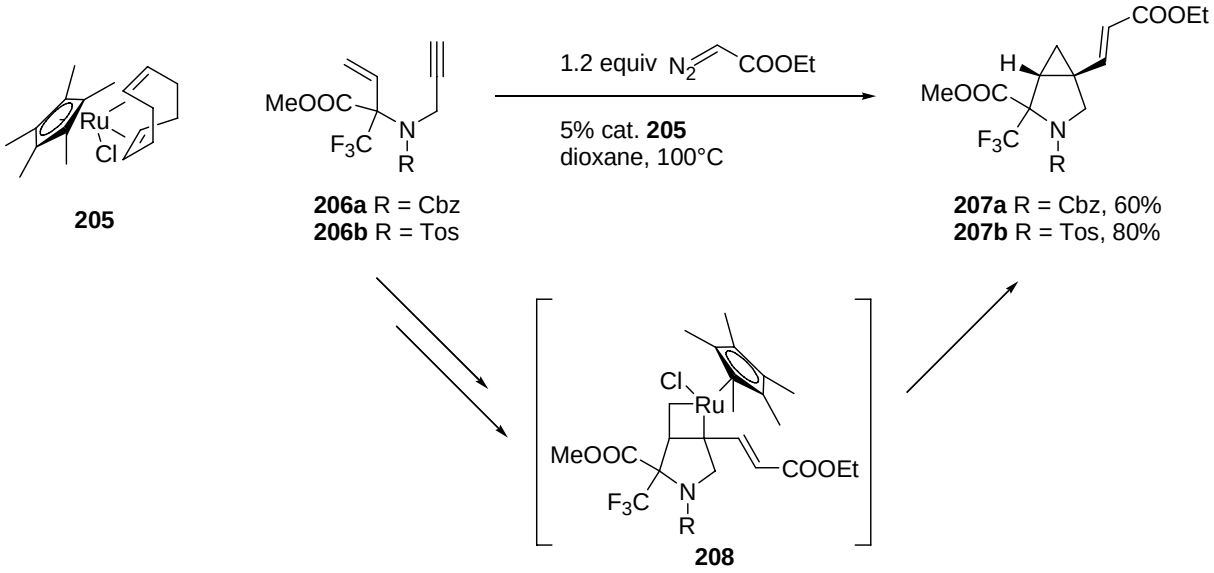
atmosphere, the so called Mori conditions,[115] results in the formation of intermediate 1,3-dienes like **203**. Subsequently, the ethylene atmosphere was changed into a N_2 atmosphere and 5 equivalents of a suitable diazo compound were added. This results in cyclopropanation at the more accessible olefin. The obtained compounds **204** are the (*E*)- and (*Z*)-cyclopropyl stereoisomers.



202 **203**

204a R = Et, 65%, *E*/*Z* 2.2/1
204b R = *t*Bu, 71%, *E*/*Z* 2.7/1

A complementary reaction sequence, cyclopropanation at the least accessible olefin, was developed by Dixneuf and co-workers.[116,117] They didn't use a Grubbs-type catalyst for the ring-closing of **206**, however, but catalyst **205**. This catalyst is in fact a pre-catalyst; treatment with a diazocompound turns it into a ruthenium carbene species that is able to perform ring-closing enyne metathesis. The cyclopropane is formed because the intermediate ruthenacyclobutane **208** favours reductive elimination leading to **207** rather than [2+2] cycloreversion.



205

206a R = Cbz
206b R = Tos

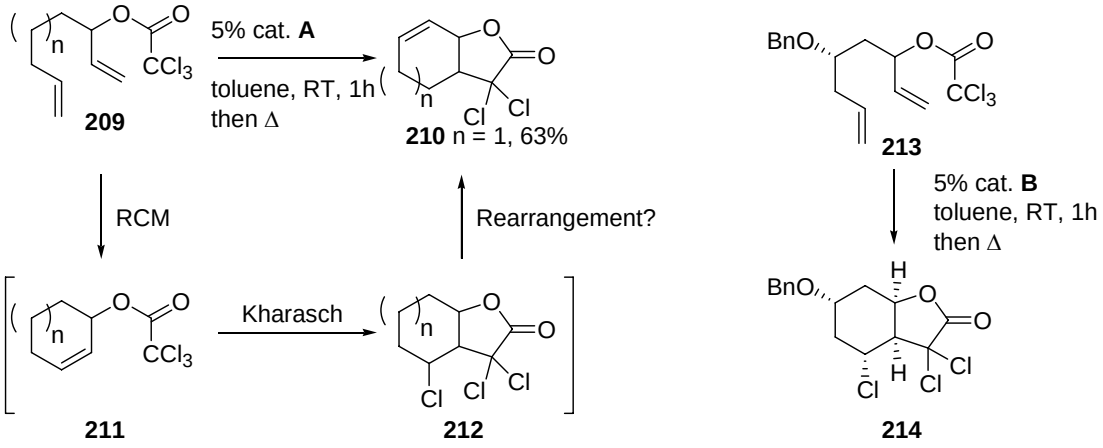
207a R = Cbz, 60%
207b R = Tos, 80%

208

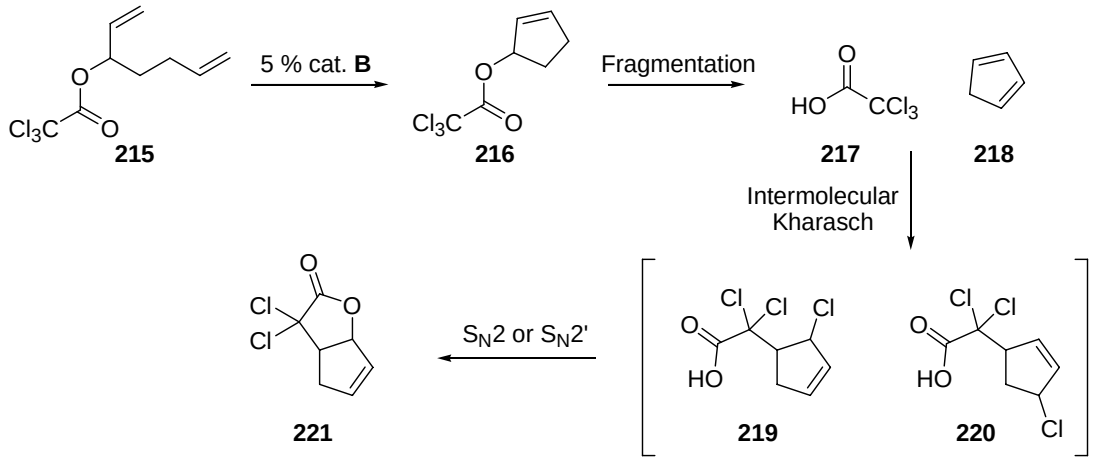
2.4.6 RCM combined with radical atom transfer cyclization

It was not long after Quayle[118,119] reported that the Grubbs' catalysts act as efficient catalysts in intramolecular Kharasch reactions, that Schmidt used this in a tandem sequence with RCM.[120] The tandem sequence is based on the fact that RCM occurs at ambient temperature whereas the generation of radicals requires reflux conditions. It was expected that cyclization of **209** would lead to intermediate **211** which could undergo a radical cyclization to yield trichlorinated

compound **212**. The isolated compound of this sequence, however, was **210** apparently resulting from dechlorination and double bond migration. With an extra substituent on the alkyl chain, like in **213**, the isolated compound was the expected trichlorinated bicyclic lactone **214**.

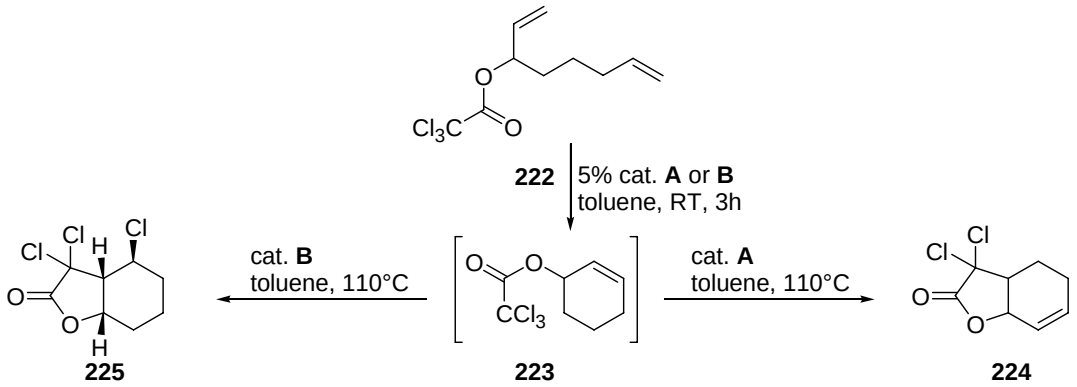


Quayle was able to reveal the true nature of this rearrangement. By running an experiment in deuterated toluene inside an NMR, he was able to follow the exact course of the reaction.[121] As a test substrate, **215** was treated with second generation catalyst **B** resulting in cyclopentene **216**. This compound is extremely labile and fragments into trichloroacetic acid **217** and cyclopentadiene **218**. Upon heating, an intermolecular Kharasch reaction takes place between these two compounds resulting in the formation of **219** and **220**. Both compounds then further react to the observed product **221** by S_N2 or S_N2'. The same mechanism is applicable for the formation of derivative **210**.



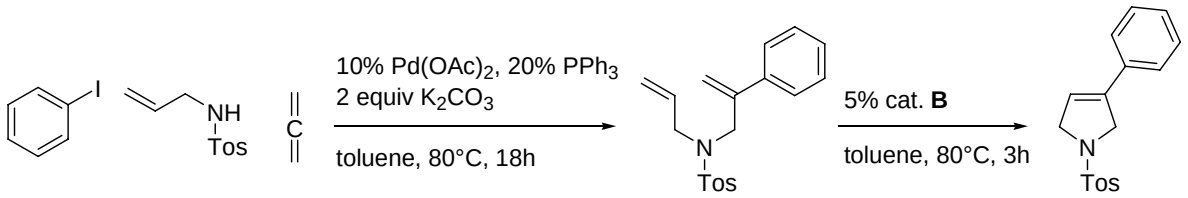
Strangely enough, the catalyst used can determine the course of the reaction. It was found that subjecting **222** to the tandem RCM/Kharasch sequence can lead either to **224** or **225**. When the first generation catalyst **A** is used, the ring-closed product **223** rearranges to give unsaturated

lactone **224**. When the second generation catalyst **B** is used, on the other hand, intramolecular Kharasch reaction takes place to yield trichlorinated compound **225**. Very similar work was performed by Snapper.[122]

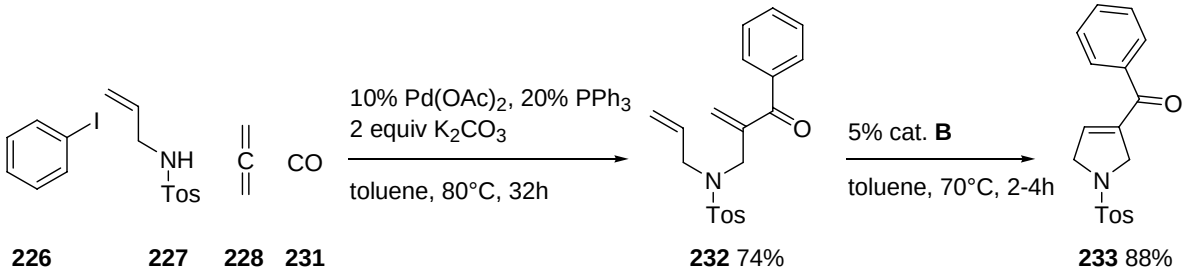


2.4.7 RCM combined with 1,3-dipolar cycloaddition

Two research groups developed a new Pd(0) catalyzed three component process involving allenylation of aryl iodides to generate palladium species which react with nitrogen nucleophiles to afford 1,6- and 1,7-dienes.[123,124] Thus, for example, tertiary amine **229** could be prepared by reacting iodobenzene **226** with secondary amine **227** under an atmosphere of allene **228**. In a second step, this amine could be cyclized to pyrroline **230** using second generation catalyst **B**.

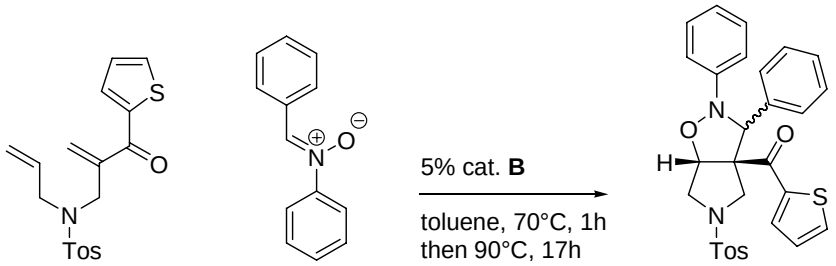


This process was transformed to a four component reaction by working under an atmosphere of CO (1 atm) and allene (1 atm).[125] Thus compound **232**, containing an α,β-unsaturated ketone, was obtained and in a separate step cyclized towards **233**.



The obtained unsaturated compounds proved to be ideal substrates for 1,3-dipolar cycloadditions with imines and nitrones. It was even possible to perform the RCM and the cycloaddition in one

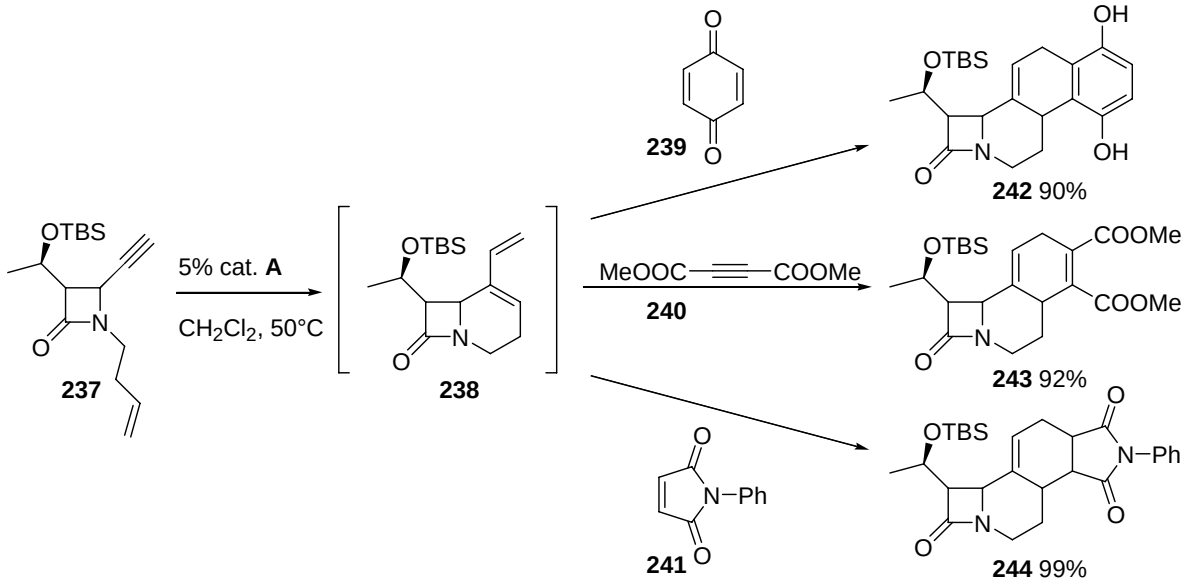
pot.[126] Thus, a mixture of secondary amine **234** and nitrone **235** was treated with the second generation catalyst for 1 hour at 70 °C and then for 17 hours at 90 °C. The diastereomeric mixture of **236** was isolated in 59% yield.



234 **235** **236** 59%

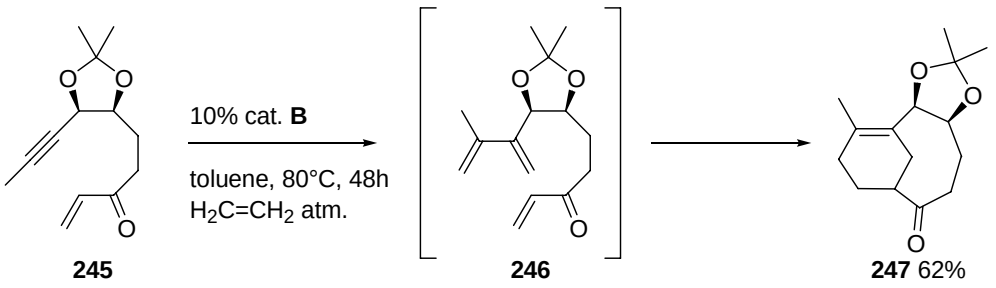
2.4.8 RCM followed by a Diels-Alder reaction

A lot of reports have been published regarding the combination of ring-closing enyne metathesis and Diels-Alder reactions.[127,128] A nice example is the synthesis of polycyclic β-lactams via a one-pot reaction sequence.[129] Treatment of β-lactam **237** in a pressure tube with first generation catalyst **A** results in the formation of diene **238**. Subsequently, different dienophiles (like 1,4-benzoquinone **239**, dimethylacetylene dicarboxylate **240** or *N*-phenyl maleimide **241**) can be added, the temperature is raised to 80 °C and tricyclic **243** or tetracyclic compounds **242** and **244** are formed in high yields.



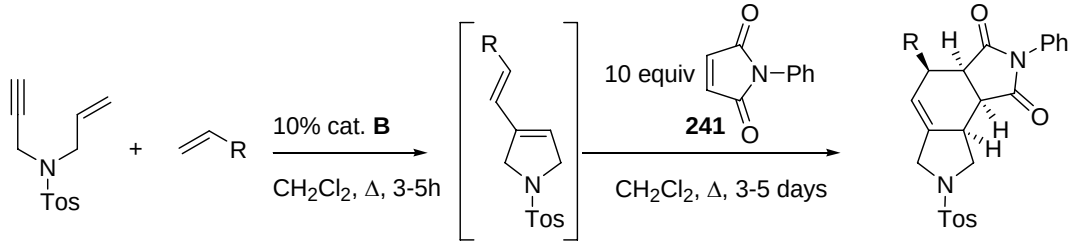
237 **238** **239** **240** **241** **242** 90% **243** 92% **244** 99%

A combination of RCEYM with an intramolecular Diels-Alder was used for the synthesis of a bicyclo[5.3.1]undecene, a structural subunit of taxol. Unsaturated ketone **245** was treated with second generation catalyst **B** to form triene **246** via cross-metathesis with ethylene. Upon prolonged heating, this compound cyclizes to form the desired bicyclic skeleton **247**.[130]



245 **246** **247** 62%

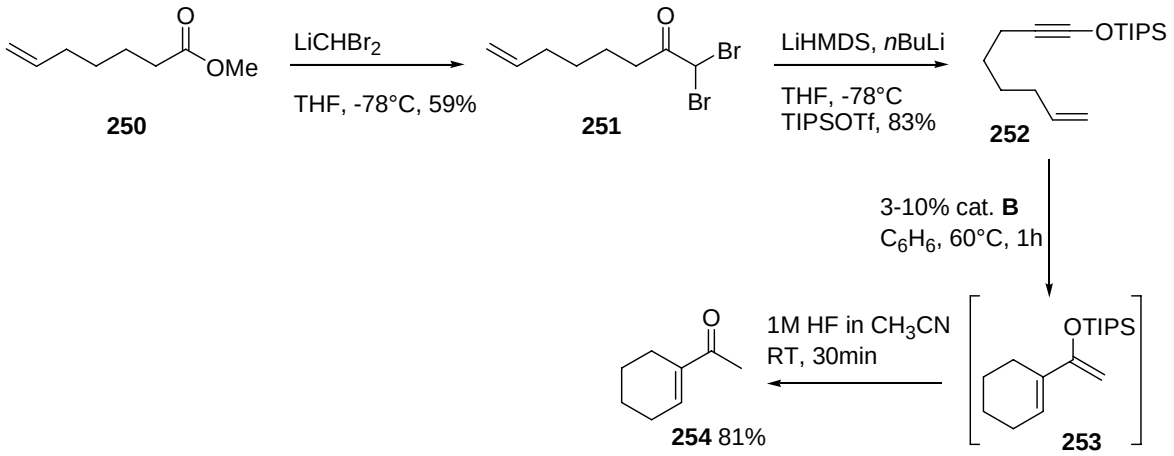
Finally, a three component tandem enyne metathesis, diene-ene metathesis followed by Diels-Alder reaction was used to synthesize very complex tricyclic compounds with four stereocenters. A mixture of **202** and 5 equivalents of an alkene **58** was treated with second generation catalyst **B** in refluxing CH_2Cl_2. The produced diene **248** is then treated with 10 equivalents of dienophile **241** resulting in very slow conversion to **249**.[131]



202 **58** **248** **249**
6 examples 71-83%

2.4.9 RCM followed by Si-O bond cleavage

Kozmin reported on the use of RCM followed by cleavage of a Si-O bond for the synthesis of functionalized enones starting from readily accessible precursors.[132] In a first step, ester **250** was transformed to the corresponding dibromoketone **251** by treatment with $LiCHBr_2$.

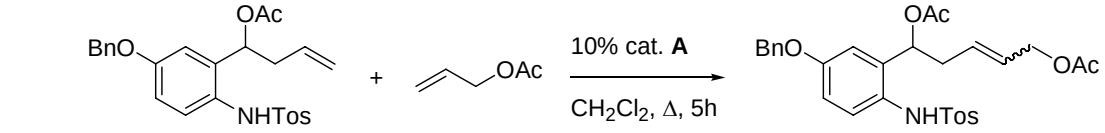


250 **251** **252** **253** **254** 81%

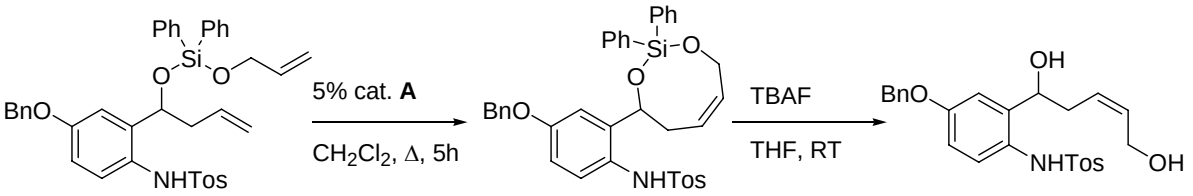
Next, this product was subjected to a Kowalski rearrangement[133,134] by treatment with a mixture of LiHMDS and BuLi and silylated using triisopropylsilyl trifluoromethanesulfonate (TIPSOTf) to obtain enyne **252**. After cyclization using second generation catalyst **B**, the *O*-protecting group in

253 was removed using HF in CH_3CN and unsaturated ketone **254** was obtained in 81% yield. By this procedure, a variety of highly functionalized enones could be prepared in high yield.

Several groups have used a combination of RCM and Si-O bond cleavage to obtain a *cis* carbon-carbon double bond.[135,136] An attempted cross-metathesis between **255** and **256** led to **257** in poor yield (max 42%) and as an *E*/*Z*-mixture (ratio from 4:1 to 6:1). If the coupling is aided by a silicon tether, like in **258**, the RCM results in the formation of eight-membered ring **259** which can be opened with TBAF to yield **260** with a double bond exclusively in the *Z*-configuration.[137]



255 **256** **257** 15-42% *E*/*Z* 4:1-6:1



258 **259** 86% **260** 84%

3 Results and Discussion

3.1 Introduction

The results in this thesis are divided into 3 chapters: the synthesis of pyrroles by an RCM/oxidation strategy, the synthesis of polycyclic hydantoins and the synthesis of benzo-fused heterocycles. This thesis is partly based on eight papers, published in peer-reviewed SCI-journals, referred to in the text by the Roman numerals I-VIII. In the following chapters, a comprehensive overview of the published results will be given and the main conclusions will be highlighted. More details regarding the experimental set-up, additional mechanistic considerations, exact reaction conditions and specific introductions can be found in the papers.

Part 1: synthesis of pyrroles by an RCM/oxidation strategy:

I. N. Dieltiens, C. V. Stevens, D. De Vos, B. Allaert, R. Drozdzak, F. Verpoort, **Tetrahedron Lett. 2004**, *45*, 8995–8998. Pyrrole synthesis using a tandem Grubbs' carbene-$RuCl_3$ catalytic system. (SCI Impact Factor 2.477)

II. N. Dieltiens, C. V. Stevens, B. Allaert, F. Verpoort, **Arkivoc 2005**, *i*, 92-97. A new protocol for pyrrole synthesis by a combination of ring-closing metathesis and in situ oxidative aromatization. (SCI Impact Factor 0.694)

III. K. Moonen, N. Dieltiens, C. V. Stevens, **J. Org. Chem. 2006**, *71*, 4006-4009. Synthesis of 2-Phosphonopyrroles via a One-Pot RCM/Oxidation Sequence. (SCI Impact Factor 3.675)

IV. N. Dieltiens, K. Moonen, C. V. Stevens, **Chem. Eur. J. 2007**, *13*, 203-214. Enyne Metathesis-Oxidation Sequence for the Synthesis of 2-Phosphono Pyrroles, Proof of the "Yne-then-Ene" Pathway. (SCI Impact Factor 4.907)

Part 2: synthesis of polycyclic hydantoins:

V. N. Dieltiens, D. D. Claeys, V. V. Zhdankin, V. N. Nemykin, B. Allaert, F. Verpoort, C. V. Stevens, **Eur. J. Org. Chem. 2006**, 2649-2660. The Pyroglutamate Hydantoin Rearrangement. (SCI Impact Factor 2.548)

VI. N. Dieltiens, D. D. Claeys, C. V. Stevens, **J. Org. Chem. 2006**, *71*, 3863-3868. Synthesis of *N*(3),*N*(3)-Polymethylene-bis-hydantoins and Their Macrocyclic Derivatives. (SCI Impact Factor 3.675)

Part 3: synthesis of benzo-fused heterocycles:

VII. N. Dieltiens, C. V. Stevens, **Synlett 2006**, *17*, 2771-2776. Domino Ring-Closing Enyne Metathesis—Cross-Metathesis Approach to 1-Phosphonylated Benzazepines. (SCI Impact Factor 2.693)

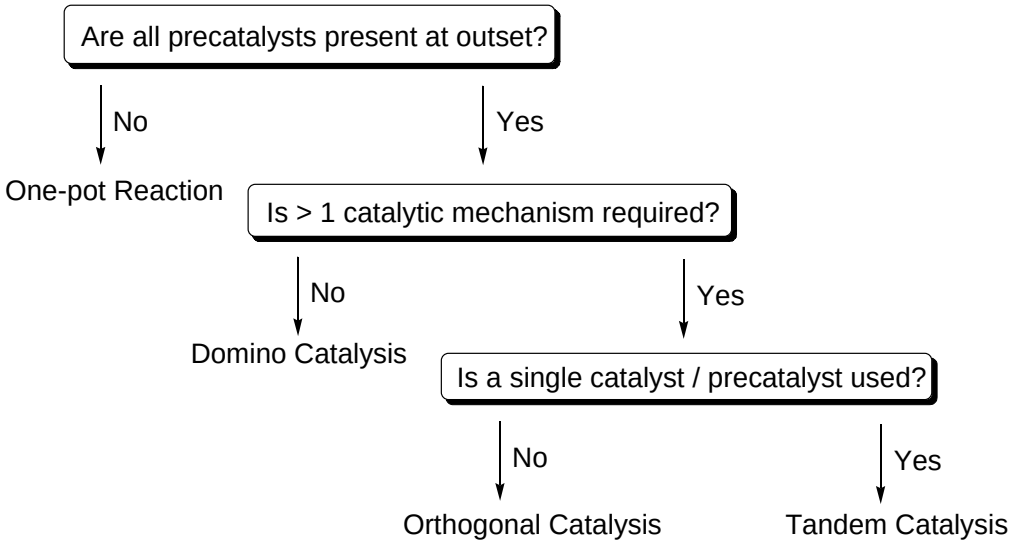
VIII. N. Dieltiens, C. V. Stevens, **Org. Lett. 2007**, *9*, 465-468. Metal-Free Entry to Phosphonylated Isoindoles by a Cascade of 5-*exo*-dig Cyclization, a [1,3]-Alkyl Shift, and Aromatization under Microwave Heating. (SCI Impact Factor 4.368)

3.2 Synthesis of pyrroles by an RCM/oxidation strategy

3.2.1 Introduction

Due to the omnipresent nature and the wide variety of biological activities of the pyrrole nucleus, this ring system has been the subject of intense investigation over the years. Next to the classical methods like the Knorr, Paal-Knorr and Hantzsch syntheses, many new entries to functionalized pyrroles like cyanopyrroles,[138] halogenated pyrroles,[139,140,141,142,143] annulated pyrroles[144] and others[145] have been developed. These new methods include microwave synthesis,[146] ruthenium catalyzed synthesis,[147] palladium catalyzed multicomponent coupling,[148] titanium catalyzed synthesis,[149] and many more. The interested reader is kindly requested to consult some interesting reviews for more detailed information regarding pyrrole syntheses.[4,150,151]

The taxonomy used in this work is based on the flowchart outlined below.[152] In order to classify a one-pot process with multiple catalytic transformations a number of questions have to be answered:



The transformations can be roughly categorized into four groups depending on criteria like the presence of the catalysts at the beginning of the reaction, the number of catalytic mechanisms and the number of catalysts used.

3.2.2 Orthogonal tandem catalysis for pyrrole synthesis (Paper I)

Initial experiments focused on the use of bimetallic complex **1**.[153] A number of diallylamines **2** were prepared under straightforward conditions either by refluxing the corresponding amines **261** with allylbromide in CH_3CN with NEt_3 as a base, or by reacting diallylamine **262** with electrophiles.

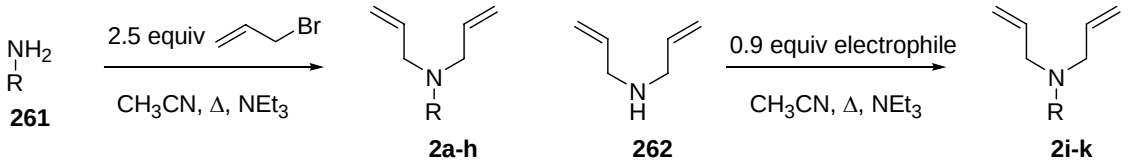


Table 2: Synthesis of diallylamines **2a-k**

2	**R**	Yield (%)
a	*p*-FC_6H_4	95
b	*o,o*-$Cl_2C_6H_3$	92
c	Bn	99
d	$CH(CH_3)COOEt$	96
e	CH_2COOMe	88
f	CH(Ph)COOEt	82
g	$CH_2P(O)(OEt)_2$	47
h	*o*-$MeOC_6H_4$	98
i	$CH_2CH_2CH_2Ph$	75
j	CH_2CN	94
k	CH_2CH_2CN	74

A final group of diallylamines with an R-group attached to a double bond was made by alkylation of secondary amines **263** with a proper electrophile. Secondary amines **263** were made by a reductive amination from benzaldehyde and allylamine or by allylation of methyl glycinate. Amine **2q** was made by treating **2o** with morpholine.

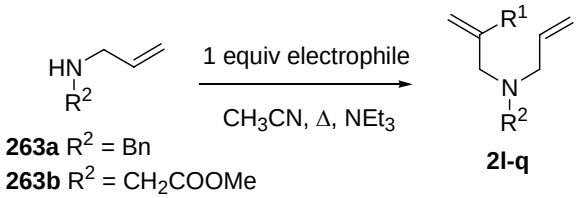


Table 3: Synthesis of diallylamines **2l-q**

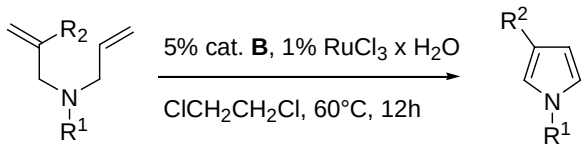
2	R^1	R^2	Yield (%)
l	CH_3	Bn	92
m	Cl	Bn	79
n	Br	COOMe	80
o	CH_2Cl	Bn	68[¥]
p	COOEt	Bn	82
q	CH_2morpholine	Bn	75

[¥] 3 eq. electrophile were used

Although the synthesis of these amines is very straightforward, most of them were purified using column chromatography in order to remove trace amounts of secondary amines which would poison the catalyst. A selection of these amines (**a**, **b**, **d**, **e**, **f**, **g** and **i**) were treated with complex **1** and heated to 60 °C in chlorobenzene for 14 hours. Not in a single case, however, could pyrrole formation be observed, even after numerous repetitions, extra purification of the substrates and resynthesizing the catalyst. In most cases only starting material and decomposition products could be detected. The fact that no pyrroles were formed could not be

attributed to the change of substrates since **2e** and **2g** were exactly the same compounds as used in previous research. The only reasonable explanation would be that the pyrrole formation in the original experiments could not be attributed to complex **1**. At a very early stage, this work seemed to be a dead-end street.

Rationalizing these observations in combination with literature data, led to the belief that another ruthenium species might have been responsible for the oxidative aromatization and that the original starting point of this research, namely the special activity of complex **1**, was wrong. It was proposed that maybe some $RuCl_3$, used in the synthesis of **1**, was still present in the catalyst and caused the oxidative aromatization. According to this hypothesis two different catalytic processes were active; the first being ring-closure catalyzed by the metathesis catalyst and the second being oxidative dehydrogenation catalyzed by $RuCl_3$. Indeed, it was found that subjecting a variety of amines **2** in a pressure tube to a tandem catalytic system of the 'standard' second generation metathesis catalyst **B** in combination with $RuCl_3$ under ultrasound conditions results in the production of pyrroles **3**. The ultrasound was used to obtain a fine dispersion of the $RuCl_3$ since this additive is poorly soluble. Although reasonable conversions are obtained, the purification on a silica column causes a significant drop in yield. Unfortunately, compounds **2m** and **2n** bearing a vinylic halogen or **2p** bearing an ester on the double bond could not be converted to the corresponding pyrroles. In these cases a mixture was formed of dimerized material, product with the allyl group split off and remaining starting product. Compounds **2o** and **2q** were converted to the pyrroles but the presence of a good leaving group caused decomposition during purification, probably by formation of aza-fulvenes.

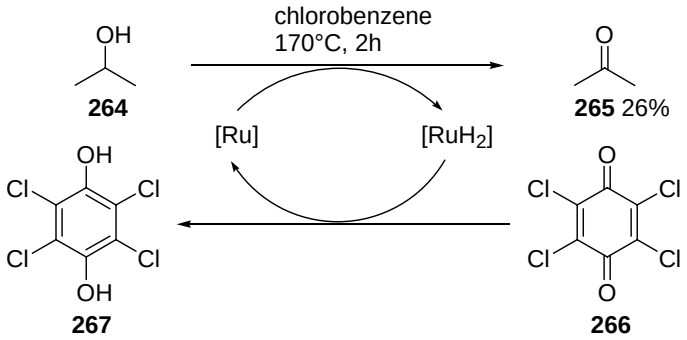


2 **3**

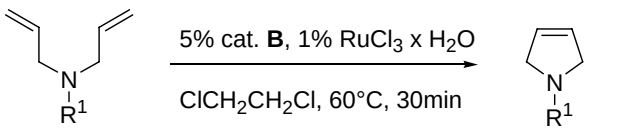
Table 4: Synthesis of pyrroles **3** by combination of 2nd gen. Grubbs' and $RuCl_3$

R^1	R^2	Conversion	Yield
Bn	H	74%	**3a** 55%
$CH(CH_3)COOEt$	H	78%	**3b** 57%
CH_2COOMe	H	91%	**3c** 63%
$CH_2P(O)(OEt)_2$	H	71%	**3d** 60%
o-$MeOC_6H_4$	H	95%	**3e** 74%
CH_2CN	H	30%	**3f** 0%
CH_2CH_2CN	H	44%	**3g** 30%
Bn	CH_3	69%	**3h** 50%
Bn	CH_2morpholine	82%	**3i** 0%
Bn	Cl	0%	**3k** 0%
COOMe	Br	0%	**3l** 0%
Bn	CH_2Cl	56%	**3m** 0%
Bn	COOEt	0%	**3n** 0%

Already in 1974, Japanese scientists had noticed that $RuCl_3$ x H_2O can act as hydrogen transfer catalyst in the oxidation of isopropanol **264** to acetone **265** with simultaneous reduction of chloranil **266** (tetrachloroquinone, TCQ) to the corresponding hydroquinone **267**.[154] They also observed that the speed of this reaction was greatly increased (73% conversion) using $RuCl_2(PPh_3)_3$, a more soluble Ru-complex.



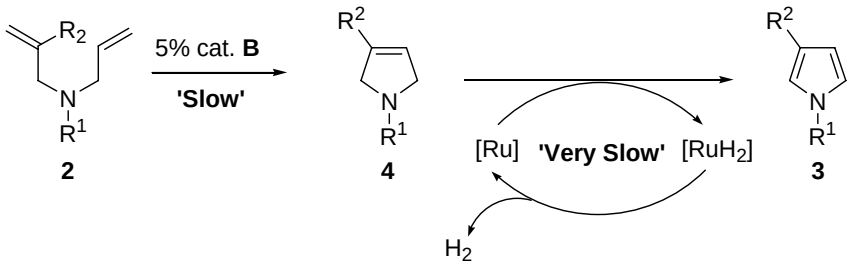
Very recently both German[155] and English[156] researchers reported that $RuCl_3$, in the presence of various phosphine ligands, is able to oxidize alcohols to the corresponding ketones in the absence of a hydrogen acceptor. This means that the ruthenium-hydride intermediates decompose with the formation of hydrogen gas. In our case, the phosphine ligand is *in situ* released by the Grubbs' catalyst creating a catalytic system very similar to the one described by these researchers. A strange observation was, however, that some pyrrole formation is also observed when no $RuCl_3$ is added. In this case the oxidation of the pyrroline to the pyrrole is much slower and no complete conversion is obtained. This can be explained by assuming that not only $RuCl_3$ but also decomposition products of the catalyst act as hydrogen acceptors. This hypothesis is supported by the discovery that metathesis catalysts form metal-hydride compounds upon prolonged heating.[157] It should also be noted that no pyrrole is formed when an electron withdrawing group is present at nitrogen. Thus **2r** and **2s** were very rapidly and quantitatively converted to pyrrolines **4r** and **4s**. This explains why no direct pyrrole formation was observed by researchers working with a tosyl-, Boc-, or SES-protecting group on nitrogen.



2r R^1 = Boc
2s R^1 = Tos

4r R^1 = Boc
4s R^1 = Tos

When the conversion of diallylamines to pyrroles is monitored by NMR, both the pyrroline **4** and the pyrrole **3** are observed next to the starting material. This proofs that the ring-closing step proceeds quite slow and the oxidation from the pyrroline to the pyrrole occurs very slow.



Usually it takes about 12 hours to obtain a reasonable conversion to the pyrrole. This slow conversion might be attributed to catalyst poisoning by the substrate **2** and/or pyrroline **4**.

3.2.3 Domino reaction sequence for pyrrole synthesis (Paper II)

In order to accelerate the conversion of the pyrroline to the pyrrole, a hydrogen acceptor was added to the reaction mixture to increase the speed by which the $[RuH_2]$ species is converted back to the [Ru] species. The oxidation of pyrrolines to pyrroles is usually performed with DDQ.[158,159,160] Evaluation of three different quinones (DDQ, duroquinone and TCQ) showed that the last one is the best oxidant since the first one destroys the metathesis catalyst and the second one doesn't affect the oxidation rate at all. In a comparative test, it was also found that $RuCl_3$ is not really required as a hydrogen transfer catalyst since the reaction works equally well in the absence of this reagent. Thus, diallylamines could be very rapidly converted to pyrroles in a one-pot domino reaction sequence. In this case, obviously, a stoichiometric amount of oxidant is required. The intermediate pyrrolines **4** were never observed, proving that the oxidation to the pyrroles occurs very fast. Another observation was that the ring-closing step from **2** to **4** also occurs faster. This is probably because the pyrroline, which poisons the catalyst, is quickly removed from the reaction mixture by conversion to the pyrrole which does not contaminate the catalyst. In this case only the remaining starting material will diminish the activity of the catalyst. Usually it takes only about 2 hours to obtain reasonable conversion to the pyrrole.

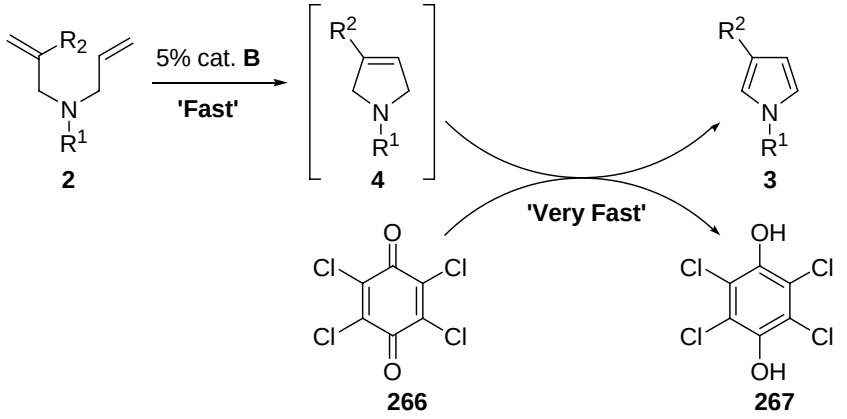
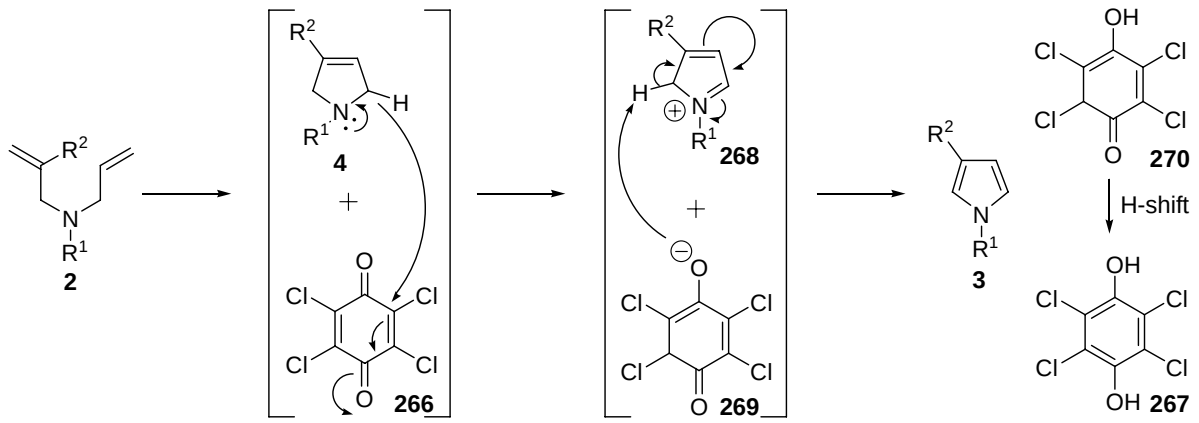


Table 5: Synthesis of pyrroles **3** by combination of 2nd gen. Grubbs' and TCQ

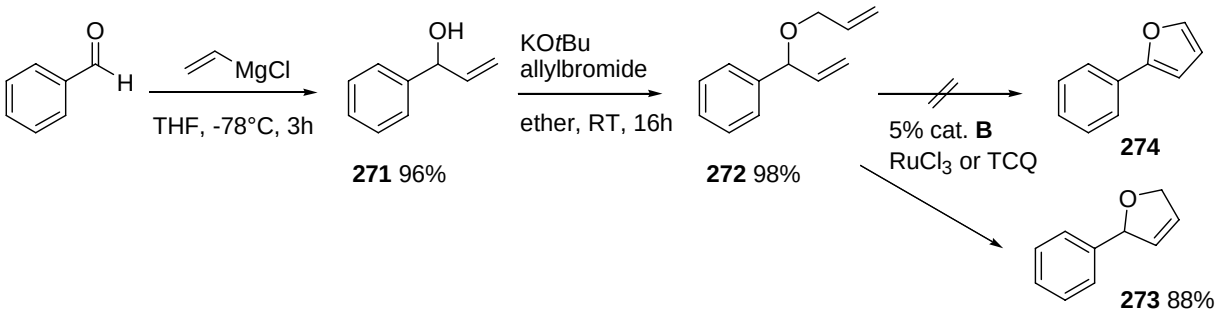
R^1	R^2	Conversion
Bn	H	**3a** 100%
CH_2COOMe	H	**3c** 96%
$CH_2P(O)(OEt)_2$	H	**3d** 95%
o-$MeOC_6H_4$	H	**3e** 100%
Bn	CH_3	**3h** 93%
Bn	CH_2morpholine	**3i** 90%

A possible mechanism for this reaction sequence is outlined below. After ring-closing metathesis, the electron lone pair on nitrogen of the intermediate 3-pyrroline **4** initiates the aromatization by expelling a hydride which immediately reacts with quinone **266**. This assumption is consistent with the observation that diallylamines with strong electron withdrawing groups on nitrogen do not aromatize. Possibly, both donor and acceptor are coordinated to the transition metal centre in this step, thus facilitating the H-transfer. In the next step, the intermediate iminium-ion **268** loses a proton and aromatizes to the pyrrole **3**. In a final step, a keto-enol tautomeric shift converts **270** to hydroquinone **267**.



3.2.4 Attempted synthesis of furans

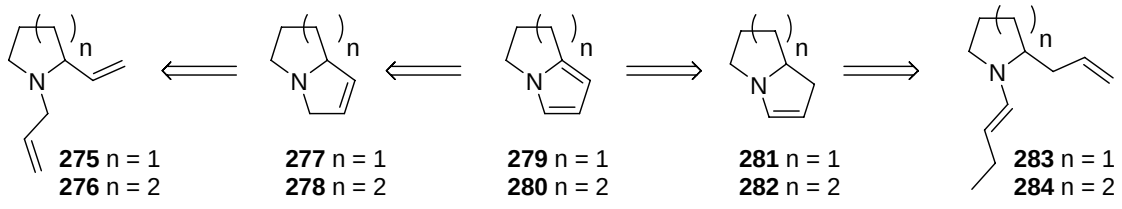
An attempt was made to expand this methodology for the synthesis of furans. In a first step alcohol **271** was obtained in 96% yield by treating benzaldehyde with vinylmagnesium chloride. This alcohol was allylated at oxygen using allylbromide and KO*t*Bu as a base. Treatment of **272** with the second generation catalyst **B** resulted in very fast conversion to dihydrofuran **273**. It proved impossible, however, to oxidize this compound to furan **274** using $RuCl_3$ or TCQ.

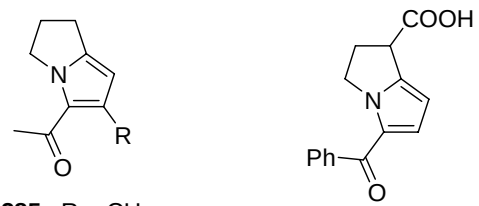


3.2.5 Attempted synthesis of bicyclic pyrroles

Having established this new entry to pyrroles, an attempt was made to use this methodology for the synthesis of bicyclic derivatives such as **279** and **280**. Azabicyclic compounds with a nitrogen at a bridgehead position have attracted the attention of synthetic chemists for many years.[161,162] The 2,3-dihydro-1*H*-pyrrolizine skeleton **279** is present in a number of Maillard components **285a** and **285b**, formed by heating a model system of L-proline and 1,3-dihydroxyacetone.[163,164] It can also be found in ketorolac **286**, an anti-inflammatory agent with analgesic and antipyretic properties. The 5,6,7,8-tetrahydro-indolizine **280** nucleus can be found for example in natural compounds, present in herbs used in traditional Chinese medicine, that delay replicative senescence in certain human cells.[165]

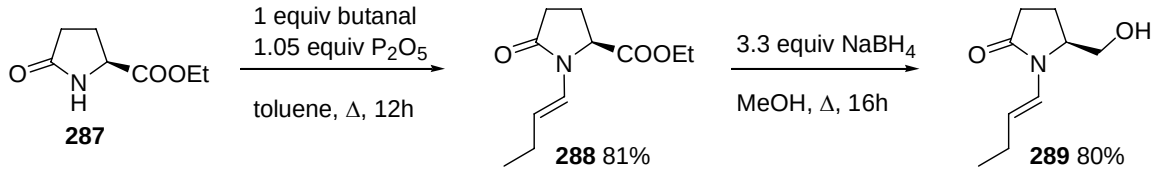
Retrosynthetic analysis shows that these compounds can be obtained by oxidative aromatization of **277** and **278** which are obtained by RCM of derivatives **275** and **276**. Alternatively they could also be obtained by oxidative aromatization of cyclic enamines **281** and **282** which are obtained by ring-closing of **283** and **284**.



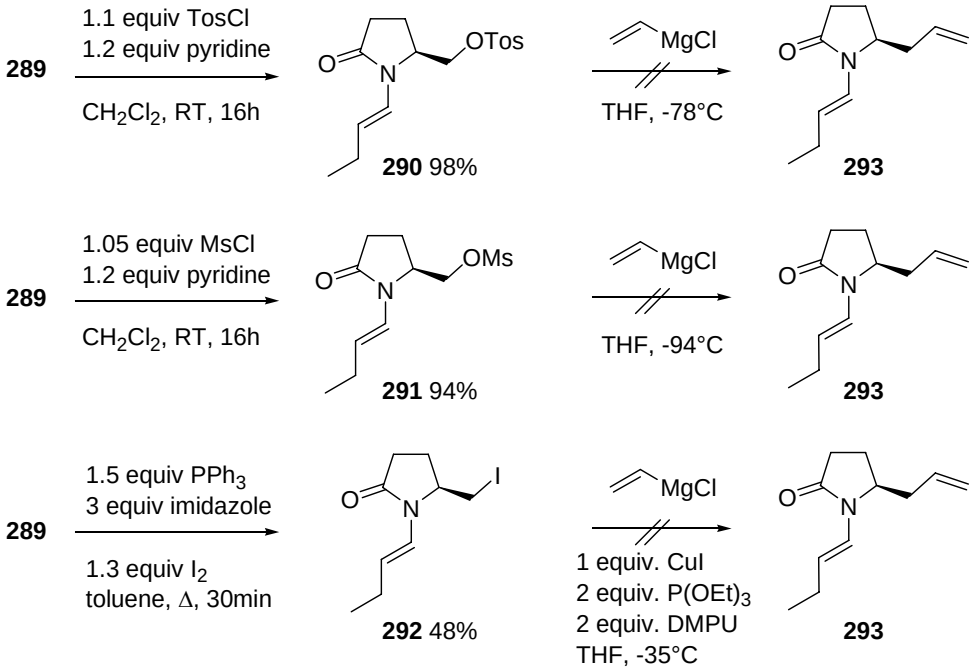


Derivatives of type **283** were targeted starting from pyroglutamate **287**, since some expertise on pyroglutamate chemistry was present at our department[166,167] and pyroglutamates can be easily functionalized at various positions.[168] Treatment of **287** with butanal in the presence of P_2O_5 in a

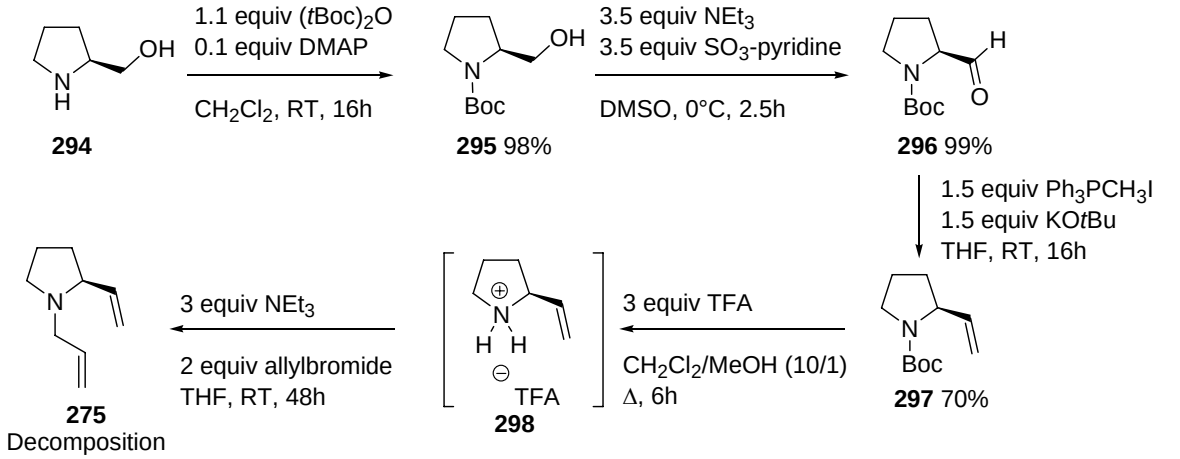
Dean-Stark trap led to enamide **288** after column chromatography and bulb-to-bulb distillation.[169] Reduction of the ester function using $NaBH_4$ in methanol gave alcohol **289**.



The alcohol function was converted to different leaving groups (**290**, **291**, **292**) under straightforward conditions in order to substitute this with a Grignard reagent (vinylmagnesium chloride) to introduce the second double bond. Not in a single case, however, the desired compound **293** could be obtained in pure form. A number of competing reactions, namely opening of the lactam ring and elimination of the leaving group with formation of a double bond, caused the formation of inseparable mixtures.

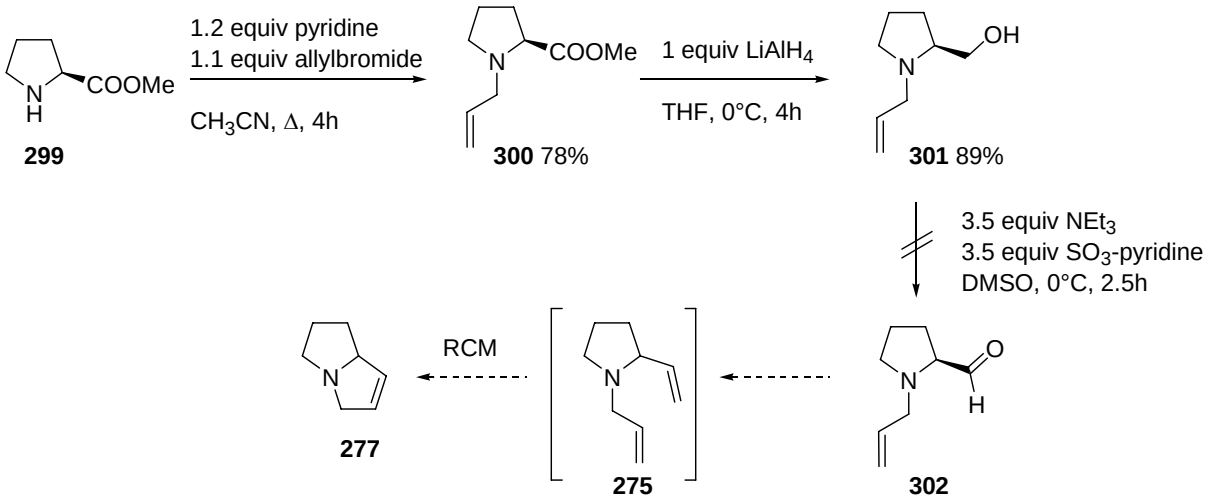


Two different routes to obtain derivatives of type **275** were designed starting from prolinol **294** and methyl prolinate **299**, respectively. After protection of the *N*-atom of **294** with a Boc-group, the alcohol **295** was oxidized to the aldehyde **296**. A Wittig reaction completed the synthesis of the first double bond. Upon deprotection of compound **297** a volatile secondary amine would be formed, therefore this compound was isolated as its TFA salt **298**.

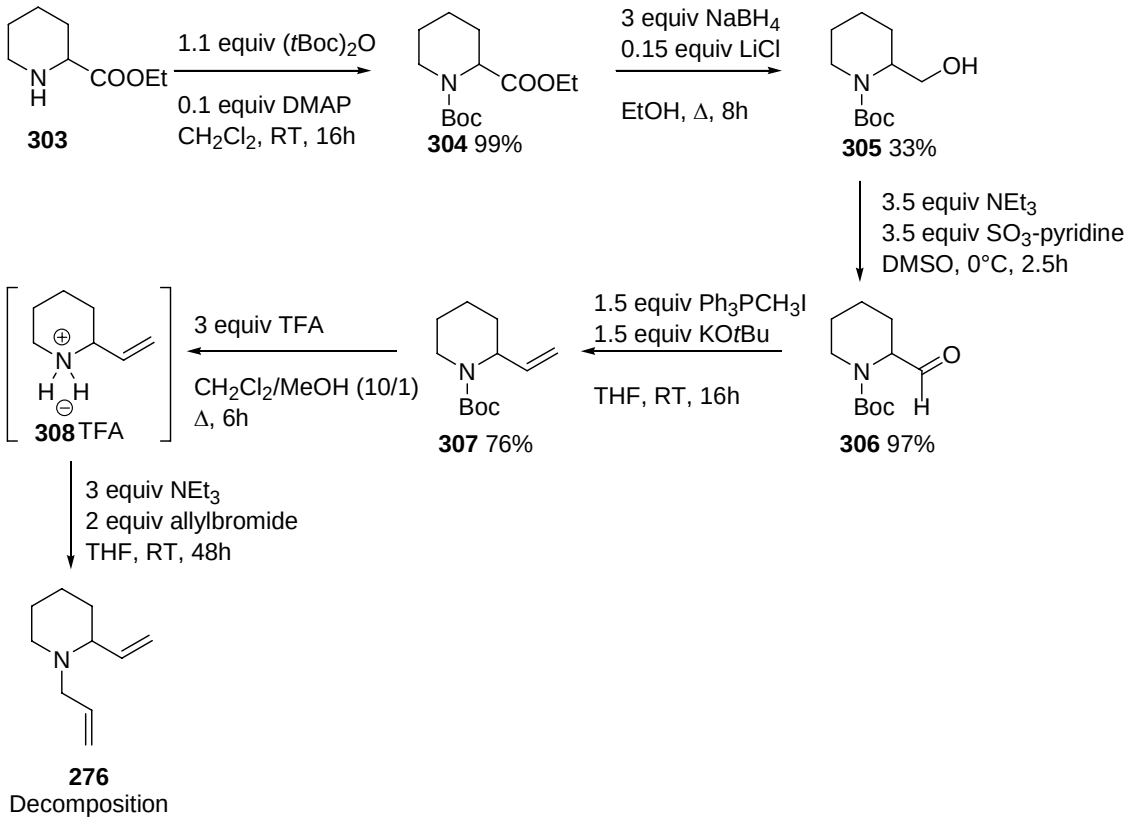


Treatment of this salt with triethylamine and allylbromide in THF resulted in the formation of the desired compound **275**. Unfortunately, this compound proved to be extremely unstable and decomposed within minutes upon concentration. Because the crude mixture still contains allylbromide, TFA and a large amount of triethylamine, direct RCM on this mixture is probably not possible.

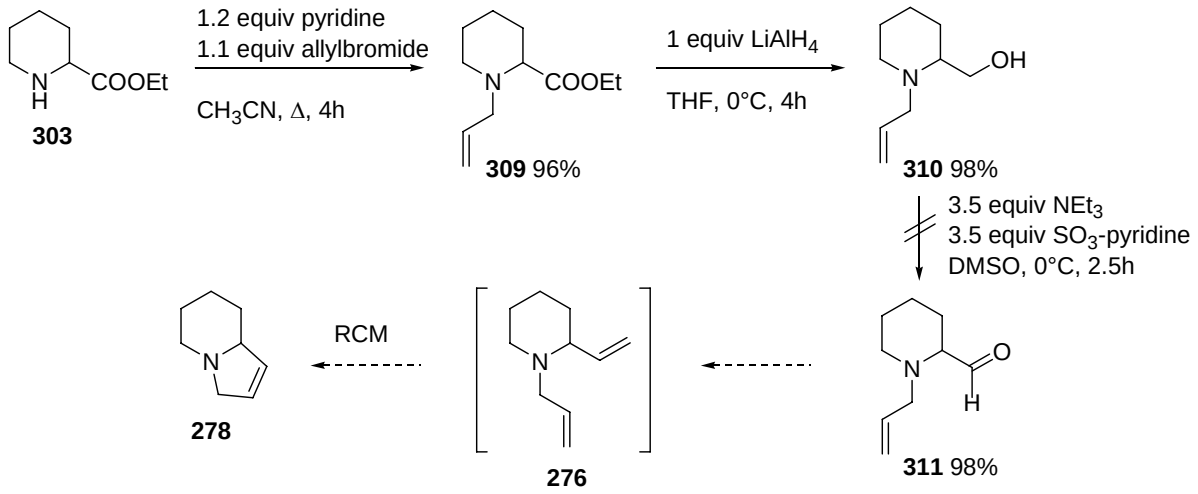
Therefore, a second route to **275** was evaluated. This strategy was planned to end with a Wittig-reaction. Since this reaction can be combined in a tandem sequence with RCM, this strategy could possibly avoid the problems associated with the instability of **275**. Thus, **299** was allylated at the *N*-atom and the ester **300** was reduced to **301**. Unfortunately, the oxidation of alcohol **301** to the corresponding aldehyde **302** proved to be a problem. Although some aldehyde was formed, judging from the crude ^{1}H NMR spectrum, the main part of the reaction mixture proved to consist of decomposition material.



A final attempt was made to access the 5,6,7,8-tetrahydro-indolizine **280** skeleton by RCM/oxidation from derivatives **276**. A strategy very similar to the one attempted for the synthesis of derivatives **275** was followed. In a first route, the *N*-atom of ethyl pipecolinate **303** was protected with a Boc-group. Ester **304** was reduced to alcohol **305** using $NaBH_4$ and a catalytic amount of LiCl. Oxidation to aldehyde **306** and subsequent Wittig olefination gave derivative **307**. Deprotection of **307** and subsequent allylation of the TFA salt **308** gave **276** that unfortunately decomposed rapidly as was the case for compound **275**.

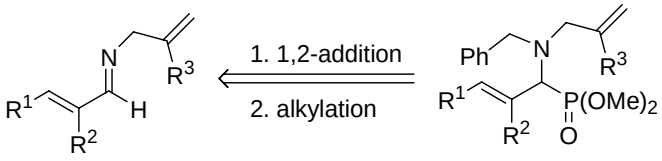


The second route also ran into the same problems as encountered during the synthesis of **275**. Although allylation of **303** to **309** and subsequent reduction with $LiAlH_4$ to **310** proceeded smoothly, the attempted oxidation to **311** brought an early end to this route since mostly decomposition material was formed. The attempts to synthesize bicyclic pyrroles were abandoned in this stage to pursue other, hopefully more fruitful routes.

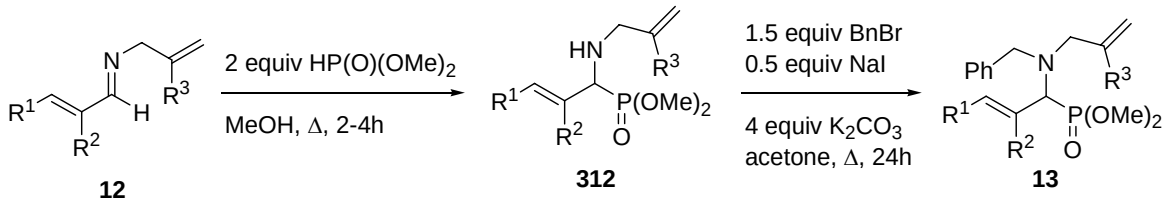


3.2.6 Synthesis of 2-phosphonopyrroles via an RCM/oxidation sequence (Paper III)

Bearing in mind the developed RCM/oxidation methodology, both phosphonylated pyrrolines **14** and pyrroles **15** should be accessible from the same α-aminophosphonate **13** depending on the reaction conditions used. The problem in obtaining compounds **13** is that they need to be formed by a regioselective 1,2-addition of a phosphorus nucleophile onto imines **12**, followed by alkylation of the *N*-atom. Initial experiments using silylated phophites as a nucleophile resulted in the formation of a mixture of a variety of compounds that could not be purified or properly analyzed at that time. Ongoing research at our department revealed, however, that both the phosphorus nucleophile used and the steric hindrance of the substituents greatly affect the course of this reaction and allow the selective synthesis of 1,2-adducts, 1,4-adducts or even tandem 1,4-1,2-addition products.[170,171,172] This insight and research paved the way for the straightforward synthesis of compounds **13**.



Thus, imines **12** could simply be phosphonylated with complete 1,2-regioselectivity by refluxing in methanol in the presence of two equivalents of dimethyl phosphite. An acid/base extraction proves sufficient to purify compounds **312**. Since secondary amines are well known to poison the Grubbs' catalysts, the nitrogen had to be protected prior to metathesis. Due to the electron withdrawing nature of the phosphonate in combination with the steric hindrance, these compounds are very poor nucleophiles, so that alkylation requires long reaction times, good electrophiles (like benzylbromide) and the use of NaI as a catalyst.

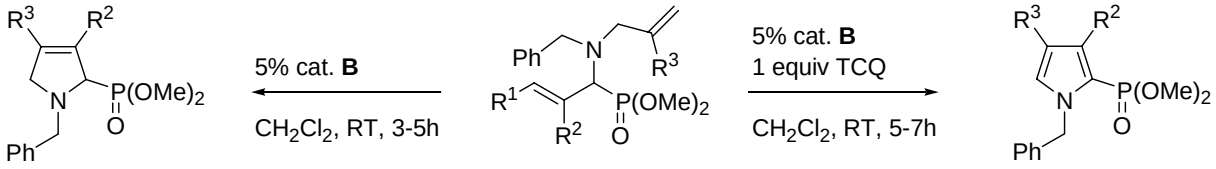


12 **312** **13**

Table 6: Synthesis of α-aminophosphonates **312** and **13**

Entry	R^1	R^2	R^3	312 (%)	13 (%)
a	Ph	H	H	95	61
b	Ph	Me	H	90	50
c	Me	Bn	H	27	50
d	Ph	isoamyl	H	88	54
e	Me	Ph	H	80	35
f	Me	CH_2CH_2Ph	H	44	92
g	Ph	H	Me	74	86

The domino reaction sequence using *in situ* oxidative aromatization with TCQ proved to work excellent on these substrates. Both pyrrolines **14** and pyrroles **15** could be formed in good yield at room temperature upon treatment with second generation catalyst **B**. The fact that these substrates could be cyclized under such mild conditions can most probably be attributed to the electron withdrawing nature of the phosphonate group, which lowers the nucleophilicity of the *N*-atom. As a consequence the substrate is less likely to poison the catalyst. In a control experiment, it was demonstrated that oxidation of the isolated pyrrolines **14** with TCQ in the absence of second generation catalyst **B** proceeds significantly slower than in the domino reaction. Probably both hydrogen donor and acceptor are brought together by simultaneous coordination to the metal centre, followed by direct hydrogen transfer from the pyrroline to the TCQ.

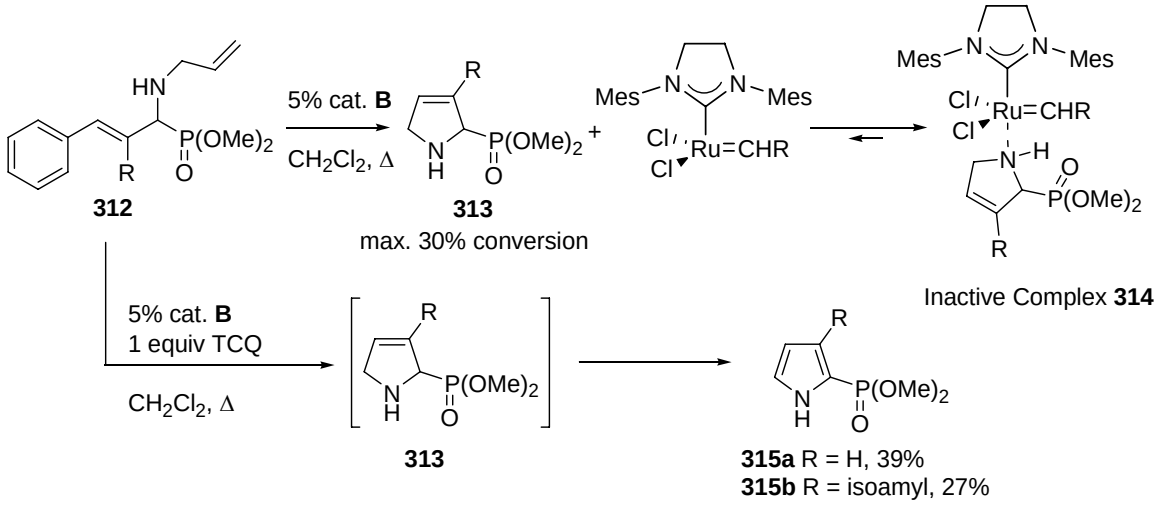


14 **13** **15**

Table 7: Synthesis of 2-phosphonylated pyrrolines **14** by RCM and pyrroles **15** by RCM/oxidation sequence using TCQ

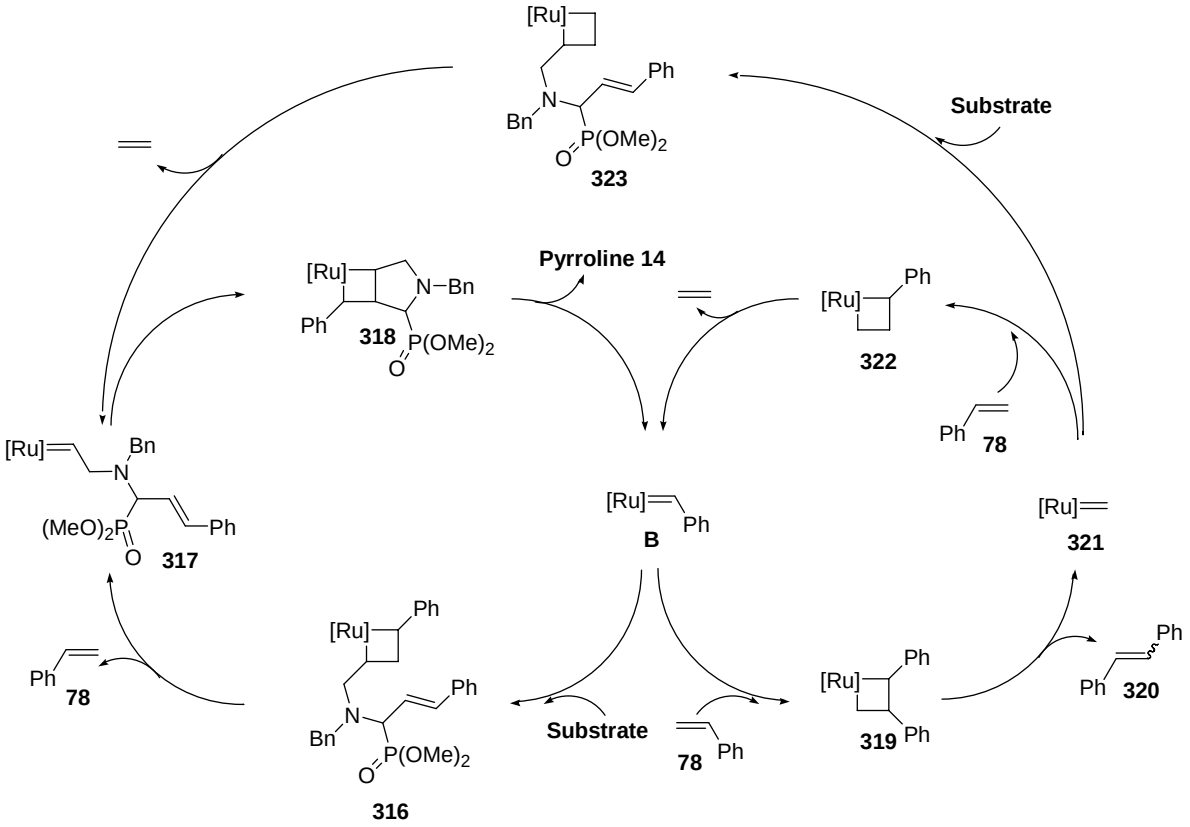
Entry	R^1	R^2	R^3	14 (%)	15 (%)
a	Ph	H	H	44	75
b	Ph	Me	H	58	84
c	Me	Bn	H	62	72
d	Ph	isoamyl	H	70	70
e	Me	Ph	H	54	75
f	Me	CH_2CH_2Ph	H	-	71
g	Ph	H	Me	-	-

As mentioned before, secondary amines poison the Grubbs' catalysts because they coordinate too strong to the central ruthenium metal. When the RCM was attempted on amines **312** the reaction stops at about 30% conversion. This proves that especially pyrrolines **313** tend to poison the catalyst. This comes as no surprise since cyclic amines are always much more nucleophilic than their acyclic counterparts due to the lowered steric hindrance of the alkyl chains which are tightly held back in the ring. In the pyrrole ring, however, the nitrogen lone pair is not nucleophilic anymore since it is part of the aromatic system.



When TCQ is added to the secondary amines **312** together with second generation catalyst **B**, the 'poisonous' pyrrolines **313** are immediately oxidized to the 'benign' pyrroles **315**. In this fashion, the formation of inactive complexes like **314** is inhibited and 100% conversion is obtained. Unfortunately, an immense drop in yield is observed during purification by column chromatography.

The substrates **13** and **312** bear one terminal and one non-terminal alkene. Initiation of the metathesis occurs, for steric reasons, on the terminal double bond. The cyclobutane **316** fragments with formation of a new carbene **317** and styrene **78**. The new carbene cyclizes to **318** which forms the pyrroline **14** and regenerates the active species of catalyst **B** upon cycloreversion. No ethylene is formed in this cycle which is very strange since the formation of ethylene is considered to be crucial to shift the equilibrium to the end product. Styrene **78** builds up in the reaction mixture, however, and starts to compete with the substrate for reaction with the catalyst. Thus in a second catalytic cycle, styrene is dimerized to stilbene **320**, which precipitates from the mixture, and methylidene carbene **321** is generated. This carbene can react either with styrene to **322** or with substrate to **323**. Both cyclobutanes generate ethylene upon cycloreversion. Thus in contrast to the normal metathesis cycle, in this case ethylene is generated in two secondary catalytic pathways.



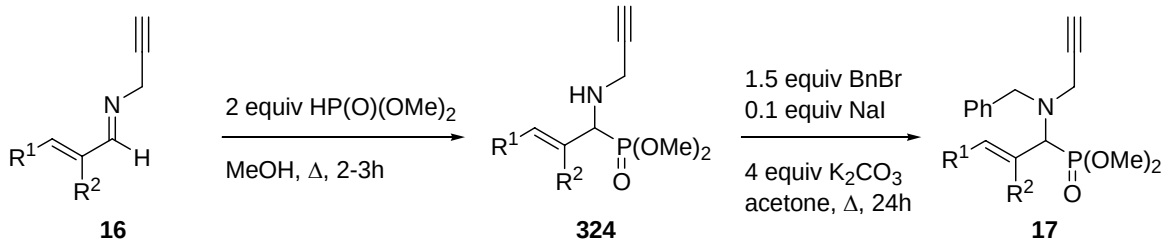
3.2.7 Synthesis of 2-phosphonopyrroles via an RCEYM/oxidation sequence (Paper IV)

As stated before, ring-closing metathesis has been applied for the synthesis of a wide variety of ring systems. The very related enyne metathesis, involving the reaction between an alkene and an alkyne, has received far less attention. Unlike olefin metathesis, all carbon atoms from the starting material are retained in the end-product which contains a synthetically useful 1,3-diene moiety. In the literature overview, a number of sequential reactions using RCM has been presented. Such sequential reactions have hardly been developed for enyne metathesis. So far, only a one-pot combination of enyne metathesis with a Diels-Alder reaction or a cyclopropanation has been reported.

As previously described, suitable diallylamines can be converted to the corresponding 3-pyrrolines upon treatment with the second generation Grubbs' catalyst and *in situ* oxidized to the pyrrole nucleus in a one-pot protocol by the addition of tetrachloroquinone (TCQ). The correct choice of the oxidizing agent, however, is crucial, since DDQ caused decomposition of the metathesis catalyst, illustrating the delicate balance of this one-pot reaction sequence. Since enyne metathesis involves different ruthenium-species intermediates, it was hard to predict if TCQ would be able to oxidize the pyrrolines to the corresponding pyrroles while not affecting the metathesis reaction.

Thus α,β-unsaturated *N*-propargyl aldimines **16** were phosphonylated with complete regioselectivity, using the same protocol as for the synthesis of derivatives **312**, resulting in the

formation of aminophosphonates **324** in good yield. Subsequent benzylation provided the substrates **17** for the ring-closing/oxidation step.

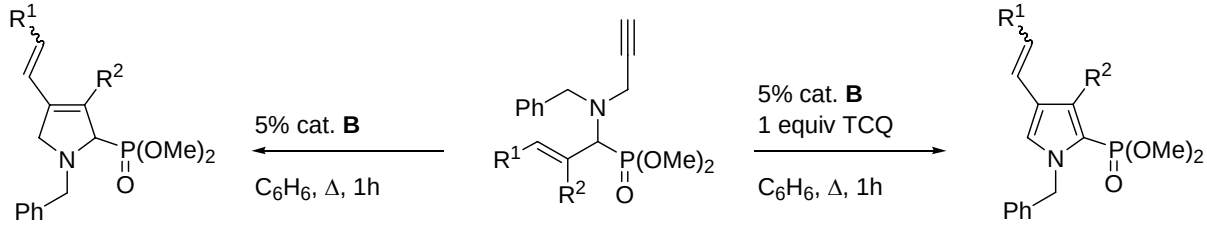


16 **324** **17**

Table 8: Synthesis of α-aminophosphonates **324** and **17**

Entry	R^1	R^2	324 (%)	17 (%)
a	2-furyl	H	69	54
b	CH_3	Ph	82	68
c	Ph	CH_3	92	65
d	propyl	H	95	60
e	Ph	H	70	64
f	isopropyl	H	65	46

It was found, however, that conversion of these derivatives to pyrrolines **18** upon treatment with second generation catalyst **B** in refluxing CH_2Cl_2 is very slow. More than 12h were needed to achieve complete conversion. When the reaction was carried out in refluxing benzene, however, complete conversion was achieved in less than 30 minutes. The addition of 1 equivalent TCQ to the reaction mixture resulted in complete conversion to pyrroles **19** in about the same time. Large substituents R^2 are not very well tolerated in these reactions. In the case of **17b**, no metathesis was observed but only catalytic deprotection of the propargyl amine.



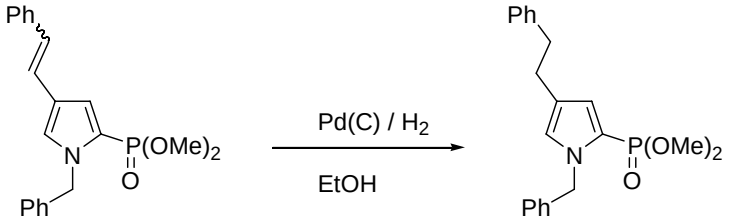
18 **17** **19**

Table 9: Synthesis of 2-phosphonylated pyrrolines **18** by RCEYM and pyrroles **19** by RCEYM/oxidation sequence using TCQ

Entry	R^1	R^2	18 (%) (*E*:*Z*)	19 (%) (*E*:*Z*)
a	2-furyl	H	68 (78:22)	78 (75:25)
b	CH_3	Ph	0	0
c	Ph	CH_3	88 (100:0)	85 (100:0)
d	propyl	H	78 (100:0)	48 (79:21)
e	Ph	H	86 (82:18)	82 (82:18)
f	isopropyl	H	75 (64:36)	‡

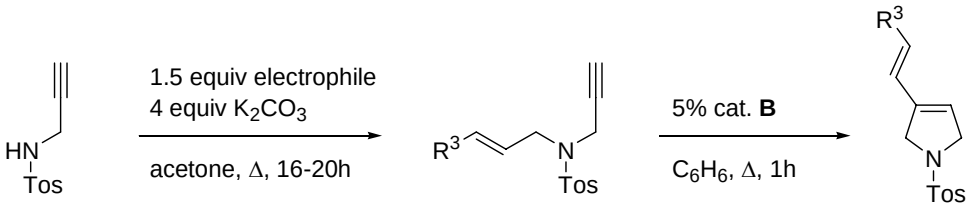
‡the pyrrole could not be obtained in sufficient purity

Because of the formation of an (*E*/*Z*)-mixture in combination with the phosphorus coupling, the spectra of these compounds can sometimes be quite difficult to interpret. In order to be sure that indeed an (*E*/*Z*)-mixture is formed, compound **19e** was treated with Pd(C) under a hydrogen atmosphere. The reduction of the double bond led, as expected, to the formation of **325** as the only compound.



19e **325**

In order to investigate the effect of other substituents on the double bond, enynes **327** were prepared by alkylation of **326**. It was shown that a variety of substituents are tolerated with no significant effect on the yield of the cyclization. Due to the electron withdrawing properties of the tosyl group, the pyrrolines **328** cannot be oxidized to the pyrroles.



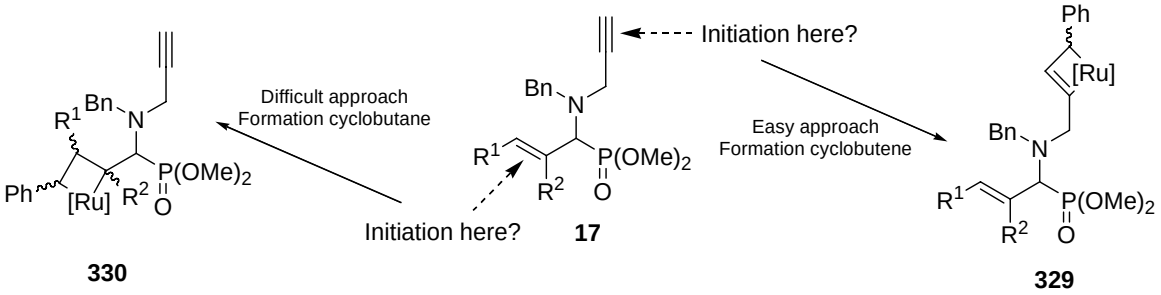
326 **327** **328**

Table 10: Synthesis of *N*-Tos pyrrolines **328** by RCEYM

Entry	R^3	Yield 328 (%)	*E*:*Z*
g	CH_2Cl	86	100/0
h	CH_2Br	76	100/0
i	4-chloro-phenoxymethyl	73	63/37
j	Ph	89	100/0

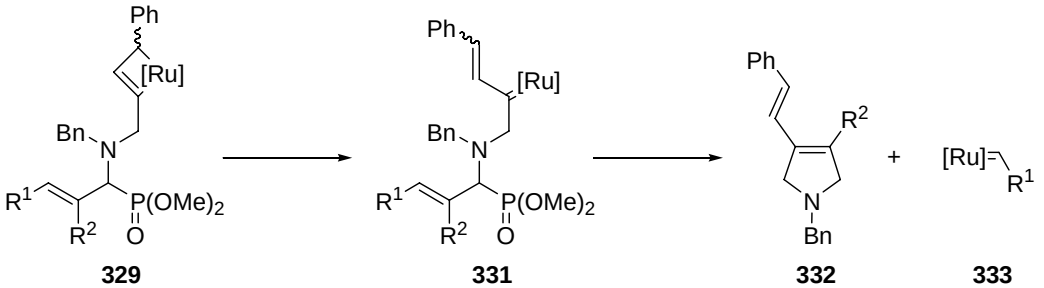
The history of RCM is laced with experiments designed to determine the exact mechanism of a certain reaction. Since enyne metathesis reactions of acyclic olefins, other than terminal olefins, with terminal alkynes have not been studied systematically, research to determine this mechanism can contribute to a better understanding of RCEYM. More precisely, the question whether the reaction proceeds via the "yne-then-ene" or the "ene-then-yne" mechanism is still often raised. The "yne-then-ene" mechanism is commonly postulated for the Ru-catalyzed enyne RCM reaction. In this pathway, the reaction starts at the alkyne moiety with formation of a metallacyclobutene. Recent kinetic studies, however, have brought up evidence for the "ene-then-yne" pathway in cross enyne metathesis[173] and enyne metathesis with terminal olefins.[174] In

this pathway, the reaction starts at the alkene with formation of a metallacyclobutane. This has created a gap in the mechanistic insights of RCEYM that has to be addressed.

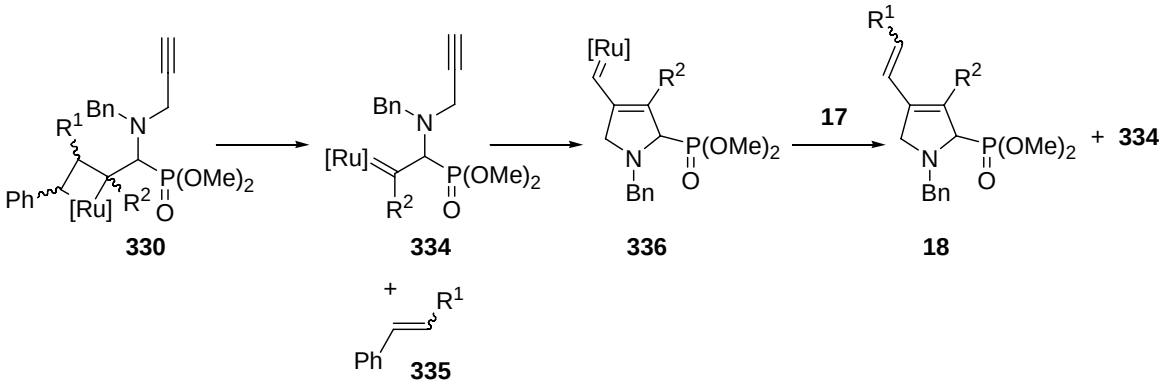


This is exemplified by the possible reaction pathways of compound **17**. When the catalyst initiates at the triple bond, there is little steric hindrance but cycloaddition forms a cyclobutene **329**. In case of initiation at the double bond, the approach is more difficult due to steric hindrance but a less strained cyclobutane **330** is formed. As mentioned before, when both multiple bonds are terminal (R^1 = H) and as a consequence steric hindrance is comparable for both pathways, the catalyst chooses the formation of the cyclobutane over the cyclobutene. Since both pathways lead to the same final product, other information is necessary in order to distinguish between these two mechanisms.

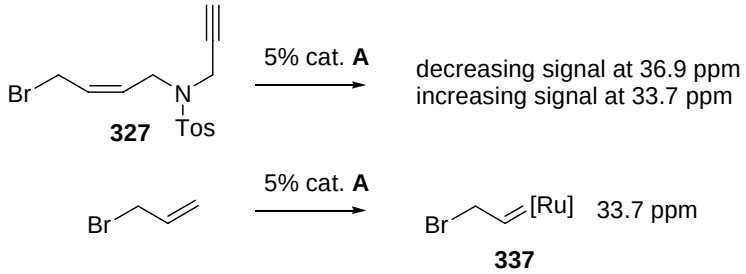
In case of initiation at the triple bond, cyclobutene **329** opens with formation of **331**. Intramolecular cycloaddition and subsequent cycloreversion leads to pyrroline **332** and new catalyst **333**. This pyrroline has got a phenyl group where the R^1 group was expected to be. This phenyl group used to be attached to the catalyst and was transferred to the substrate during the reaction. Next to this pyrroline, a new carbene **333** is formed with the R^1 group attached to it as alkylidene ligand. This new catalyst can continue the catalytic cycle and transfer the R^1 group to a newly formed pyrroline.



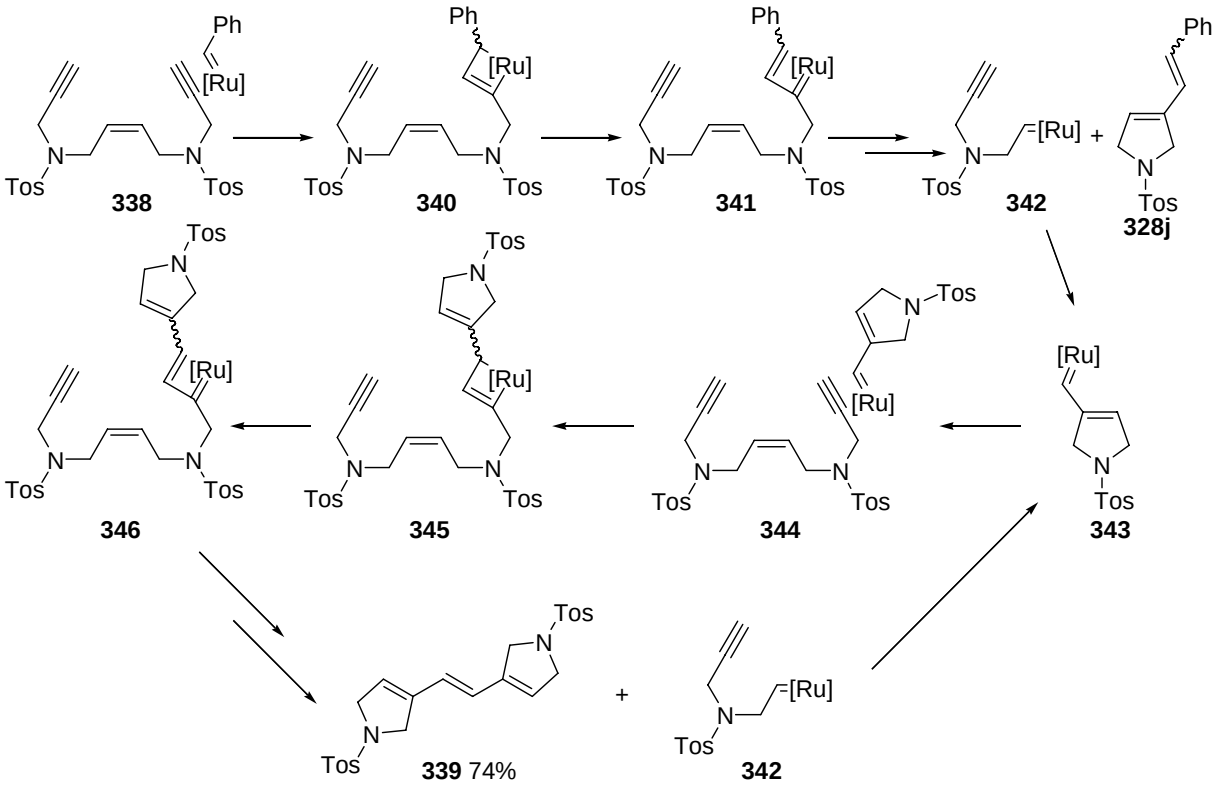
In case of initiation at the double bond, cyclobutane **330** opens with formation of **334** and side product **335**. Carbene **334** cyclizes to **336** which has to do a cross metathesis with another molecule of substrate **17** in order to create pyrroline **18** and to regenerate carbene **334**. In this case, no pyrroline side product like **332** or a new carbene like **333** are formed.



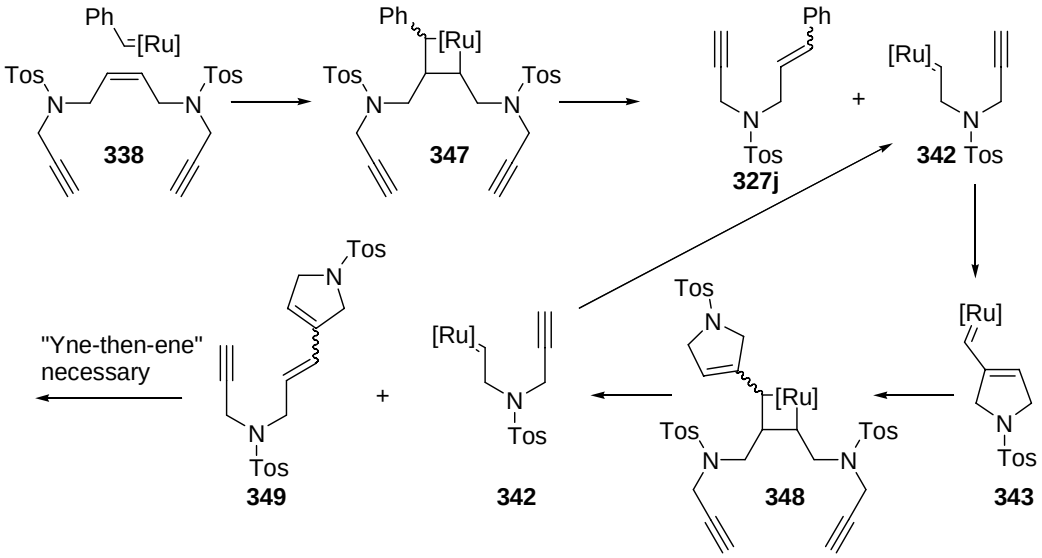
Careful analysis of the reaction mixtures revealed the presence of side product **332** in every case, in about the same amount as the catalyst loading (about 5%). Not in a single case, products like **335** could be observed. This was a first indication that the "yne-then-ene" pathway is active. In order to obtain further evidence, an attempt was made to detect the newly formed carbenoid species **333** since this is only formed in the first pathway. To detect this compound, derivative **327h** was dissolved in C_6D_6 treated with first generation catalyst **A** and the reaction was performed inside the NMR. The reaction could easily be monitored using ^{31}P NMR. In the beginning of the reaction one strong signal is observed at 36.9 ppm which belongs to the Grubbs' catalyst. Next this signal slowly decreased and at the same time a new signal appeared at 33.7 ppm. In order to attribute this signal to **337**, allylbromide was treated in a separate experiment with first generation catalyst **A** resulting in the appearance of the same signal. This proves that it was indeed this ruthenium species that was formed during enyne metathesis of **327h**.



In order to obtain additional proof for the mechanism, enediyne **338** was synthesized since this compound would, depending on the reaction pathway, lead to a different compound. Treatment of this compound with 5 mol% of the second generation catalyst **B** in refluxing benzene led to the formation of conjugated triene **339** in 74% yield after purification with concomitant formation of 5% **328j**. This result can only be explained by accepting the "yne-then-ene" pathway. This reaction also represents the first example of a conjugated triene being formed by enyne-metathesis.

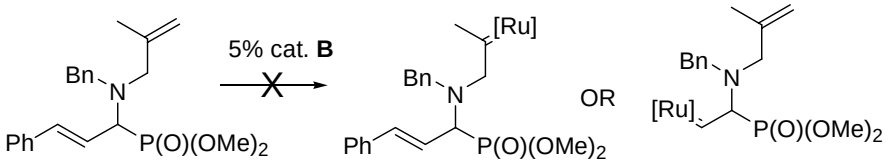


This result can only be obtained when the "yne-then-ene" pathway is active since the "ene-then-yne" pathway does not lead to the formation of the observed end product as outlined in the scheme below.



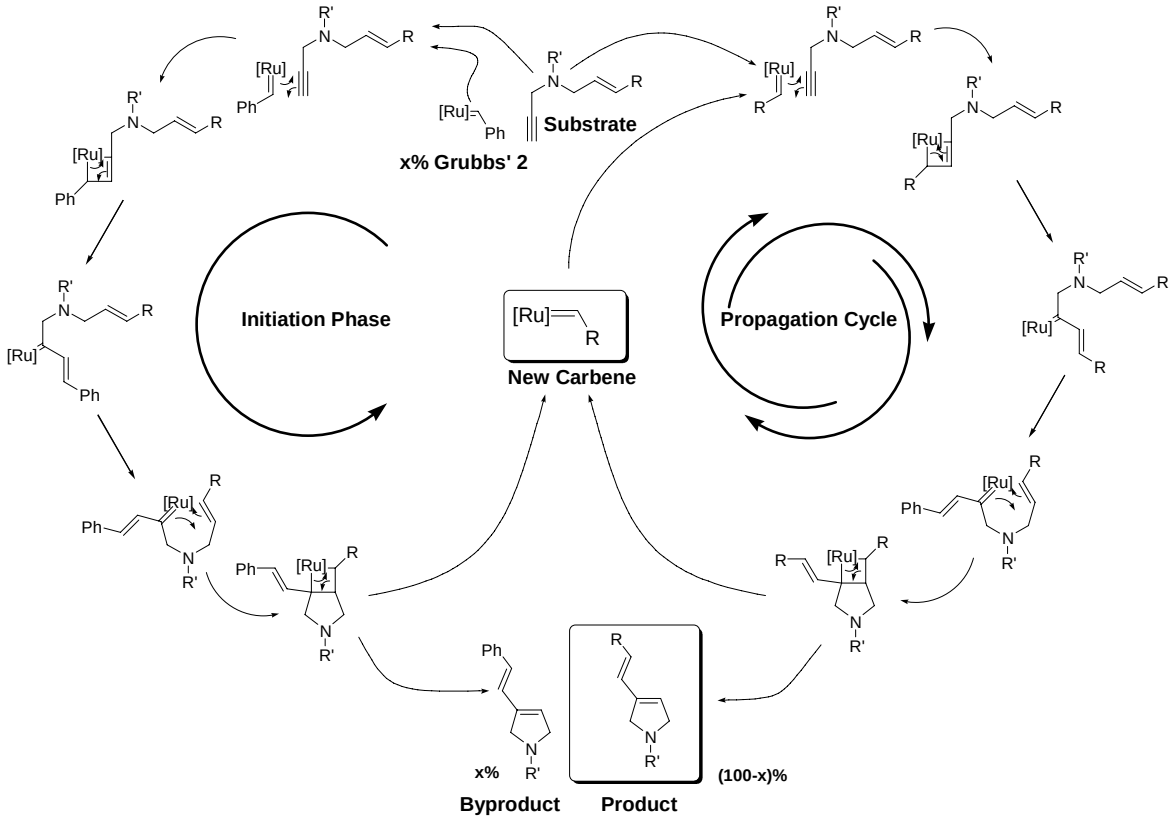
Finally, evaluating **13g** as a substrate showed that no metathesis occurred at all when a 2-methylallyl substituent is introduced at nitrogen. Initiation at either double bond would result in a ruthenium species **350** or **351** with limited steric hindrance at the other double bond, especially compared to intermediates like **331**. Even switching of solvent to refluxing toluene (110 °C) or

chlorobenzene (132 °C) did not result in any metathesis activity. This shows that removing the yne-moiety has a very dramatic effect on the reactivity of these compounds.



13g **350** **351**

All these observations lead to the proposal of a complete catalytic cycle as depicted below. In the initiation phase, the substrate reacts with the Grubbs' carbene to yield, after a sequence of cycloadditions and cycloreversions, the byproduct and the new carbene. This new carbene can then react further with another molecule of substrate to produce the final product with regeneration of the carbene, after a sequence of cycloadditions and cycloreversions. In the case of complete initiation of the metathesis catalyst, x% of catalyst gives rise to a mixture of x% byproduct and (100-x)% of product upon completion of the reaction.



3.2.8 Conclusion

In the first part of this thesis a new entry towards pyrroles was developed using a combination of ring-closing metathesis mediated by the second generation Grubbs' catalyst and oxidative

aromatization. At first, $RuCl_3$ was used as an additive for the conversion of the intermediate pyrrolines to the corresponding pyrroles. Although this reaction works fine, it usually takes more than 12 hours to obtain satisfactory conversion at 60 °C under ultrasound conditions. The reaction time could be dramatically reduced by adding a strong hydrogen acceptor, namely tetrachloroquinone, to the reaction mixture. In this case $RuCl_3$ is no longer required as a hydrogen transfer catalyst. The reaction time is reduced to about 2 hours in this fashion. Substrates bearing a strong electron withdrawing group on the *N*-atom, however, could not be oxidized. The application of this methodology on α-aminophosphonates containing two double bonds allowed the straightforward synthesis of phosphonylated pyrroles. This conversion also occurs in a one-pot fashion and under very mild conditions. In a control experiment, it was demonstrated that oxidation of the isolated pyrrolines with TCQ in the absence of the second generation catalyst **B** proceeds significantly slower than in the domino reaction. Probably both hydrogen donor and acceptor are brought together by simultaneous coordination to the metal centre, followed by direct hydrogen transfer from the pyrroline to the TCQ. It seems that the phosphonate group is just electron withdrawing enough to lower the nucleophilicity of the *N*-atom to allow the RCM to occur at room temperature while still allowing oxidation of the pyrrolines to the corresponding pyrroles. The first combination of ring-closing enyne metathesis with oxidation was developed by treatment of α-aminophosphonates containing a double and a triple bond with the second generation Grubbs' catalyst in refluxing benzene in the presence of TCQ. This reaction sequence allows the synthesis of highly functionalized 2-phosphonylated pyrroles. A detailed mechanistic investigation revealed that the reaction follows the "yne-then-ene" pathway. The proof of this reaction mechanism is based on the formation of certain end and sideproducts, spectroscopic data and finally on the difference in reactivity of different substrates. During the initiation phase, the Grubbs' carbene is converted to a new ruthenium-carbene which continues the propagation cycle.

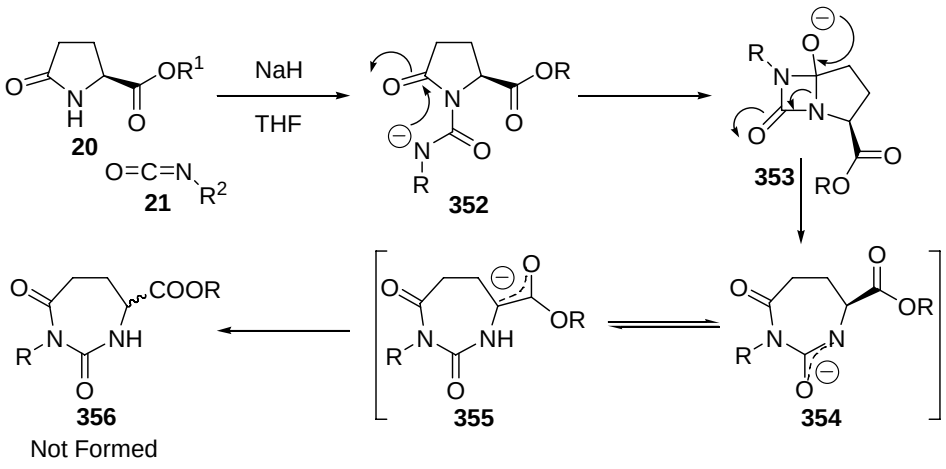
3.3 Synthesis of polycyclic hydantoins

3.3.1 Introduction

The story of hydantoin starts in 1861 when Adolph von Baeyer discovered this compound by hydrogenolysis of allantoin, hence it's name.[175] The first classical synthetic pathway, known as the Urech reaction, comprises to reaction of amino acids with potassium cyanate and allows the synthesis of 5-monosubstituted hydantoins.[176] Another famous method is known as the Bucherer-Bergs method, comprising the condensation of carbonyl compounds with potassium cyanide and ammonium carbonate.[177] This reaction allows the synthesis of both 5-mono and 5,5-disubstituted hydantoins. Since then a vast amount of new entries towards this interesting heterocycle have been described. This interest is driven by the discovery of a wide variety of biological activities like anticonvulsant, neuro-protective, antihypertensive, antibacterial, antiviral, analgesic,... activities and many, many more. The recent developments in hydantoin chemistry have been excellently reviewed by Gütschow.[178]

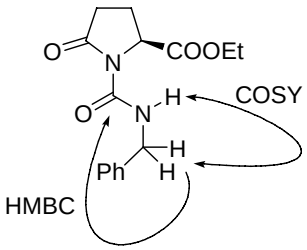
3.3.2 Synthesis of bicyclic hydantoin derivatives (Paper V)

At first the reaction of pyroglutamates **20** with isocyanates **21** was misinterpreted as leading to perhydro-1,3-diazepine-2,4-diones **356**.[179] It was found that when a mixture of **20** with an isocyanate is treated with NaH in diethylether, a precipitate is formed during the reaction, which after workup proved to be the sodium salt of the expected carbamoyllactam **352** in high purity. If the reaction is performed in THF on the other hand, no precipitate is formed and after workup a compound was isolated which gave a different but very similar ^{1}H NMR spectrum. It was assumed that intermediate **352**, which is apparently soluble in THF, reacts intramolecularly by a nucleophilic attack on the lactam ring with formation of the unstable intermediate **353**. This intermediate decomposes with loss of ring-strain to form the seven-membered ring anions **354** and **355**.

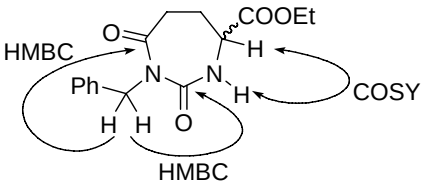


These anions are in equilibrium with each other, causing racemization of the chiral centre (this was proven by quenching the reaction with D_2O) and upon workup resulted in what was thought to be **356** as a 1:1 mixture of its enantiomers.

In the past, 1-carbamoyl-2-pyrrolidinones **352** were incorrectly identified as perhydro-1,3-diazepine-2,4-diones **356**. For example the natural product squamolone was originally identified as a seven-membered ring (of type **356**) but later turned out to be a five-membered ring (of type **352)**.[180] Also a claim of the preparation of these seven-membered rings by cyclization of 4-ureidobutyric acids with thionyl chloride[181] was later corrected by another research group.[182] This last research group gave some spectroscopic guidelines which would allow discrimination between compounds **352** and **356**. In the 2D-correlated spectra, certain long range correlations should be visible in case of the seven-membered ring that are not present in the five-membered ring. Since we believed we had both derivatives in hands, we could compare all spectral data.



352e



356e

Indeed we observed the predicted HMBC (Heteronuclear Multiple Bond Correlation) couplings between the CH_2 of the benzyl group on the tertiary nitrogen atom to the urea and the lactam carbonyl in the compound with proposed structure **356e**. Also a COSY (Correlated Spectroscopy) coupling between the NH and the proton in α-position of the ester was observed. All these couplings could not be found for the carbamoylated lactam **352e** and as a consequence these and other derivatives were identified as seven-membered rings.[183]

X-ray analysis that was carried out later proved, however, that the compounds produced are in fact hydantoin derivatives **22**. Apparently the intermediate **352** performs an intramolecular nucleophilic attack on the ester carbonyl with formation of bicyclic intermediate **357** and expulsion of an alkoxide anion. The alkoxide anion in turn can open this bicyclic intermediate with formation of anions **358** and **359**. These anions are in equilibrium with each other, causing racemization of the chiral centre and upon work up resulted in hydantoin derivatives **22** as a 1:1 mixture of their enantiomers.

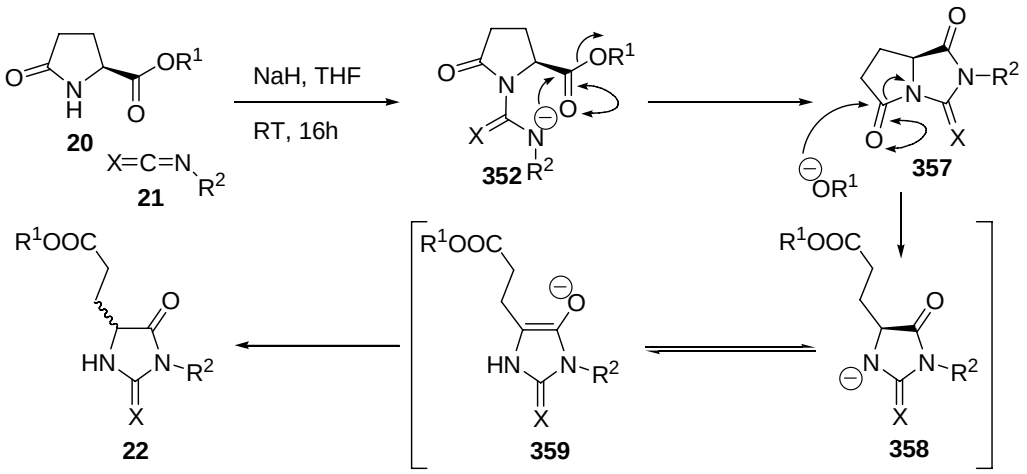
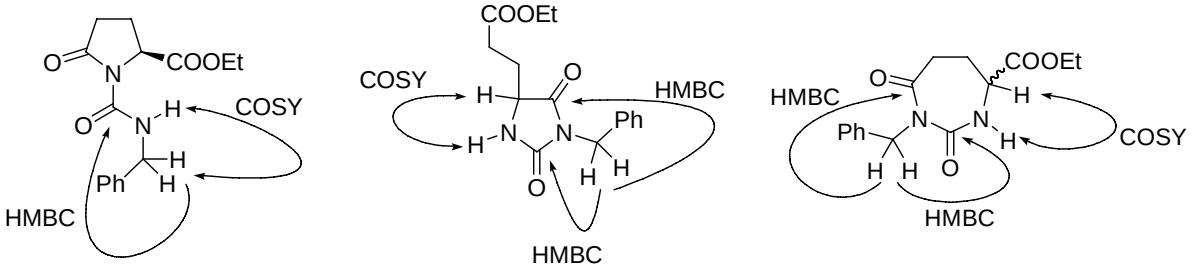


Table 11: Synthesis of hydantoins **22** by ring-transformation from pyroglutamates **20**

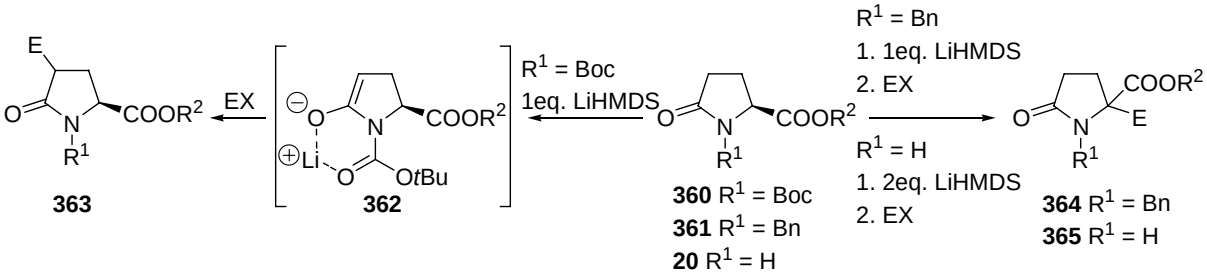
Entry	R^1	X	R^2	Yield 22 (%)
a	Bn	O	Ph	56
b	Bn	O	CH_2CH_2Cl	50
c	Bn	S	Ph	42
d	Et	O	Ph	89
e	Et	O	Bn	87
f	Et	O	CH_2CH_2Cl	81
g	Et	O	allyl	48
h	Me	O	Ph	81

The same methodology was performed on different combinations of pyroglutamate esters and isocyanates. We were pleased to find that different esters underwent the same reaction, although, in some cases, traces of carbamoyllactam could be observed due to the poor solubility of this intermediate in THF. It is important to notice, however, that in diethylether the sodium salts of intermediates **352** precipitate. As a consequence the end product formed depends on the solvent used.

As shown below, all the predicted and observed HMBC- and COSY-couplings for the seven-membered ring are also present in case of the hydantoin derivative, this explains the misinterpretation of the spectral data.



The attractiveness in using pyroglutamates as a building block lies in the fact that the site of alkylation can be directed by changing the protecting group on nitrogen. Alkylation of *N*-Boc protected pyroglutamates **360** results in *C*(4) functionalized derivatives **363** whereas alkylation of *N*-benzyl **361** or *N*-unprotected **20** pyroglutamates occurs at the 2-position, resulting in **364** and **365**.[184,185] The regioselectivity of the alkylation of *N*-Boc protected pyroglutamates was explained by the formation of a stabilized Li-salt **362** which directs the alkylation to the 4-position. This stabilized intermediate cannot be formed in *N*-benzyl or *N*-unprotected derivatives, thus resulting in alkylation at the 2-position.



The first step in the sequence towards the bicyclic derivatives **33** is alkylation of the pyroglutamate at the 2-position. As mentioned above, alkylation of pyroglutamates at this position has been described before, but this method is rather unpractical with the need for stringent time and temperature control. During a series of experiments, the alkylation of benzyl pyroglutamate with allylbromide was optimized. In each experiment benzyl alcohol was formed by fragmentation of the ester. This kind of fragmentation in the absence of water has been observed before.[167] The main conclusion of these experiments is that the anion at *C*(2) is quite unstable and the time it is present in the mixture should be kept to a minimum. In order to realize this, the electrophile can already be mixed with the pyroglutamate prior to deprotonation. It was found that excellent results can be obtained when a mixture of the pyroglutamate and the electrophile is treated with 2.1 equivalents of LiHMDS at –40 °C.[186] Even when using several equivalents of electrophile, no *N*-alkylation was observed. This methodology can not be followed, however, when base-sensitive electrophiles are used (e.g. in case of **365e** and **365f**). The electrophile used for entry **d**, (1-bromomethyl-vinyl)-benzene, was obtained following a literature procedure.[187] Compound **365i** was obtained by treating **365b** with morpholine but is added to the table for the sake of completion.

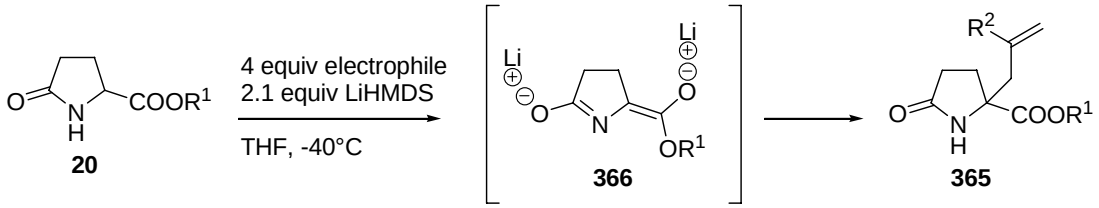


Table 12: Alkylation of pyroglutamates **20** at the 2-position towards **365**

Entry	R^1	R^2	Yield 365 (%)
a	Et	H	72
b	Et	CH_2Cl	62
c	Et	CH_3	84
d	Et	Ph	70
e	Et	Cl	46
f	Et	Propyne at *C*(2)	20
g	Bn	H	83
h	Bn	CH_2Cl	40
i	Et	CH_2morpholine	60

All following reactions were carried out on the ethyl ester since working with the benzyl esters often caused decomposition and subsequent purification problems. Furthermore, the ring-transformation to the hydantoins gives lower yields for these derivatives. The ring-transformation of compounds **365** to the hydantoins was then performed using different isocyanates. Unfortunately, bulky substituents at the 2-position prevent the substrate from reacting with the isocyanate, even at elevated temperatures. In these cases only unreacted starting material could be recovered. Also compound **365f**, with a propyne substituent at *C*(2), gave a mixture of compounds upon reaction with isocyanates and was therefore not used further.

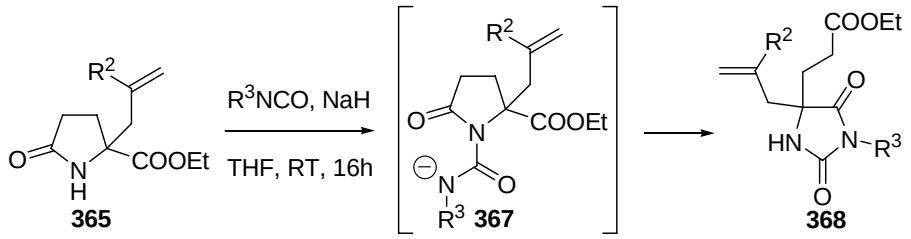
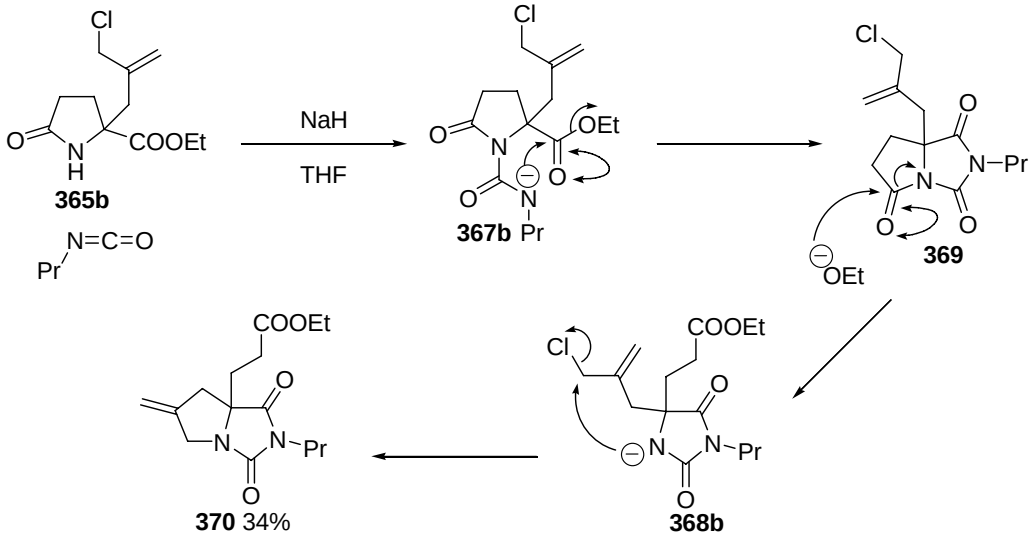


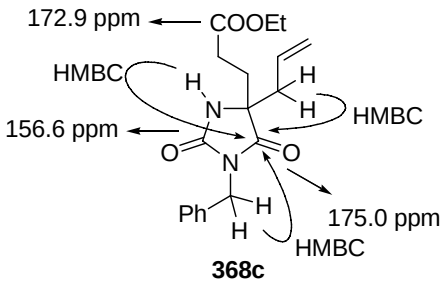
Table 13: Synthesis of hydantoins **368** by ring-transformation from pyroglutamates **365**

Entry	R^2	R^3	Yield 368 (%)
a	H	Pr	61
b	H	Ph	70
c	H	Bn	45
d	Cl	Pr	66
e	CH_3	Pr	63

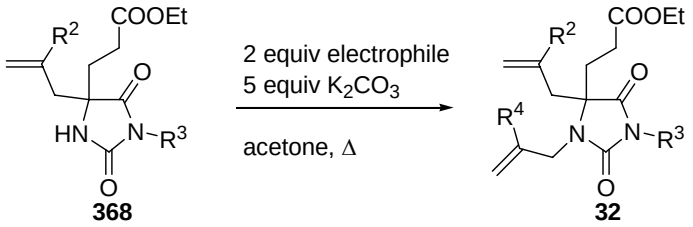
When compound **365b** was treated with propyl isocyanate and NaH in THF, the bicyclic hydantoin derivative **370** is formed. The intermediate carbamoylated lactam **367b** cyclizes as expected to compound **369** with formation of ethoxide. This bicyclic compound is opened by ethoxide to give anion **368b**. Normally this anion is stable and quenched by the addition of water. In this case, however, a good leaving group is present and an intramolecular substitution of the allylic chloride leads to the tetrahydro-pyrrolo[1,2-c]imidazol-7a-yl derivative **370** in 34% yield after purification.



The ^{1}H NMR and ^{13}C NMR spectra of compounds **368** are again not completely conclusive to determine whether or not the rearrangement has indeed taken place. In order to distinguish these compounds from the intermediate lactams **367**, the 2D spectra are extremely useful. In the HMBC spectrum the protons of the allyl substituent, of the benzyl group and on the secondary *N*-atom all couple to the same carbon at 175.0 ppm. These couplings could never be observed in case of the carbamoylated lactams.



The next step in the reaction sequence is the introduction of a second double bond by alkylation of *N*(1). Normally, when *N*-unsubstituted hydantoins are treated with alkyl halides, reaction occurs at *N*(3). Functionalization of both nitrogen atoms, or of *N*(1) in case *N*(3) already bears a substituent, requires very harsh conditions. It was found that the only way to alkylate these compounds cleanly at *N*(1) in good yield was to reflux them with 2 equivalents of electrophile and 5 equivalents of finely ground K_2CO_3 in acetone for several days. The compounds **32** are obtained pure after filtration of the solids and evaporation of the volatiles. In some cases, column chromatography was necessary to remove the excess of electrophile.

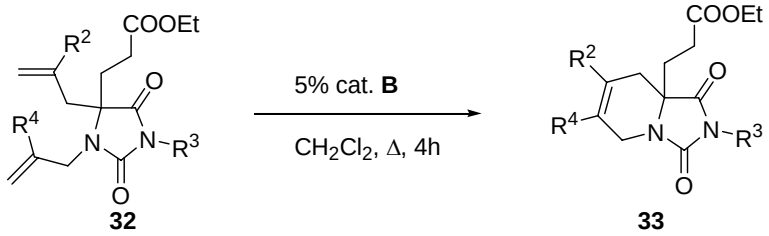


368 **32**

Table 14: Alkylation at *N*(1) of hydantoins **368** towards **32**

Entry	R^2	R^3	R^4	Yield 32 (%)
a	H	Pr	H	98
b	H	Ph	H	98
c	H	Bn	Cl	70
d	H	Ph	CH_3	99
e	H	Bn	CH_2Cl	72
f	H	Bn	COOEt	45
g	Cl	Pr	H	83
h	CH_3	Pr	H	98

The last step in the sequence is the ruthenium catalyzed cyclization. Treatment of these compounds with 5% second generation catalyst **B** in refluxing CH_2Cl_2 resulted in clean conversion to the desired compounds **33**. When a halogen is present at the double bond, **32c** and **32g**, more drastic conditions are required.[188,189] In this case switching to refluxing benzene is necessary to obtain cyclization. Since compound **32f** has a very electron poor double bond, it is in fact an α,β-unsaturated ester, the second generation Hoveyda-Grubbs catalyst **111** was used because this catalyst proved to be superior with electron deficient olefins.[190]



32 **33**

Table 15: Synthesis of bicyclic hydantoin derivatives **33** by RCM on substrates **32**

Entry	R^2	R^3	R^4	Yield 33 (%)
a	H	Pr	H	93
b	H	Ph	H	88
c	H	Bn	Cl	75
d	H	Ph	CH_3	79
e	H	Bn	CH_2Cl	85
f	H	Bn	COOEt	55¥
g	Cl	Pr	H	77
h	CH_3	Pr	H	86

¥the second generation Hoveyda-Grubbs catalyst **111** was used

It was possible to obtain single crystals from compound **33b** which made it possible to perform X-ray analysis (Fig. 3).

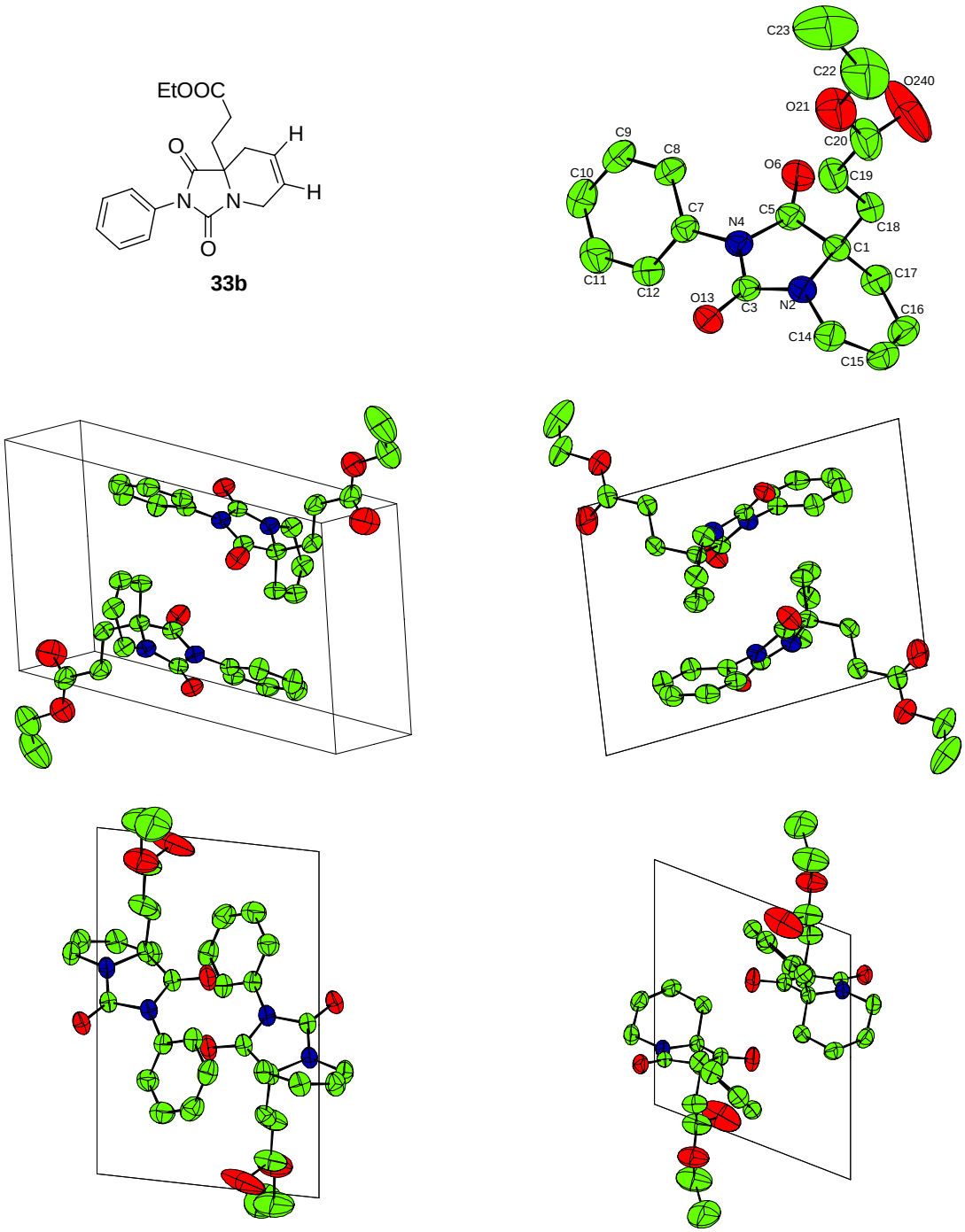


Figure 3: X-ray structure of compound **33b**.

In conclusion, it can be stated that a straightforward four-step protocol for the synthesis of bicyclic hydantoin derivatives starting from pyroglutamates was developed. This procedure starts with alkylation of the pyroglutamate at the 2-position, followed by ring-transformation to the hydantoin nucleus upon reaction with an isocyanate. Next, *N*-alkylation and ring-closing metathesis provides the heavily substituted bicyclic compounds (Fig. 4).

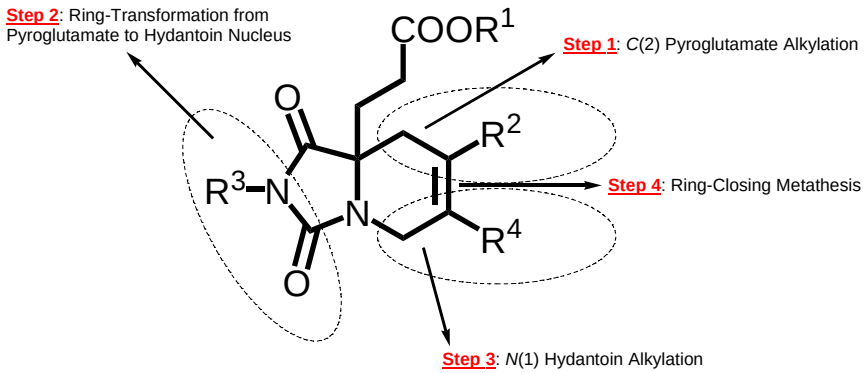
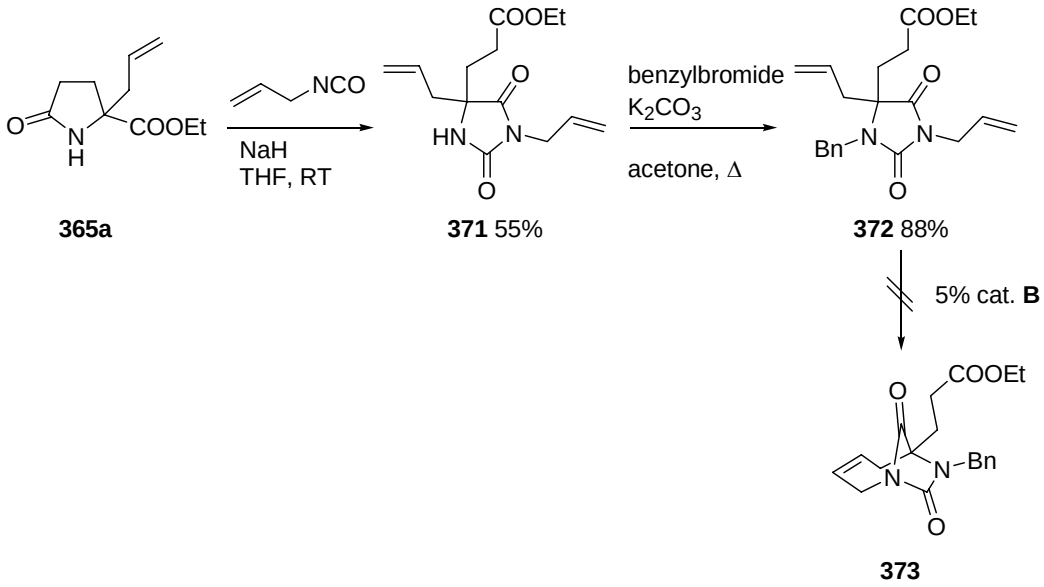


Figure 4: Four-step approach towards bicyclic hydantoin derivatives.

3.3.3 Attempted synthesis of other bicyclic hydantoin derivatives

Attempts were made to synthesize two other diazabicyclic compounds using the same methodology. First, compound **373** was targeted. A mixture of functionalized pyroglutamate **365a** and allylisocyanate was treated with NaH in THF to produce hydantoin **371**. This compound was alkylated using benzylbromide to **372** in refluxing acetone and K_2CO_3 as a solid base. When compound **372** was treated with 5% second generation catalyst **B** in refluxing CH_2Cl_2 a mixture of different compounds was obtained. Probably, the envisaged compound **373** is too strained resulting in polymerization of **372** rather than in cyclization. Compound **373** could not be purified from this mixture. Lowering the concentration of the reaction in order to favour cyclization over polymerization gave no better result.

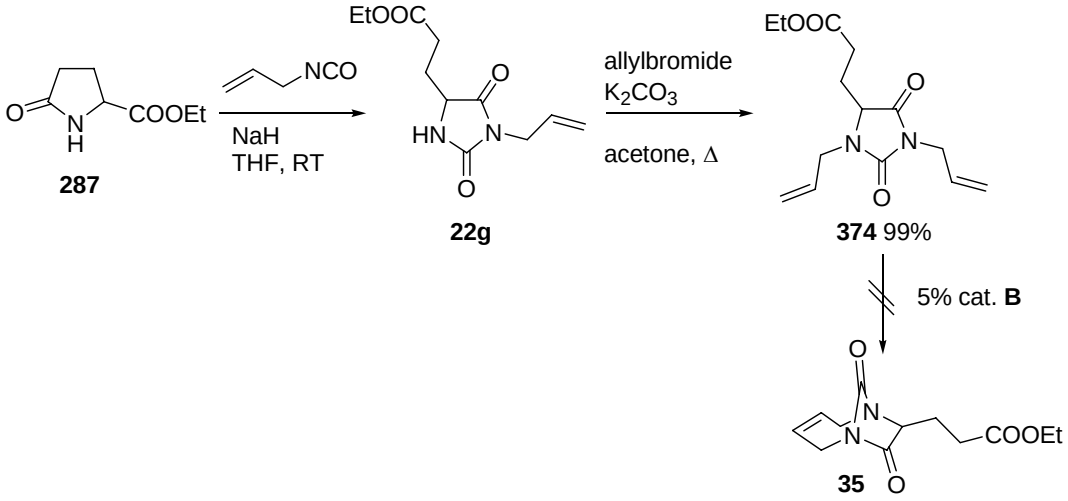


365a **371** 55% **372** 88%

373

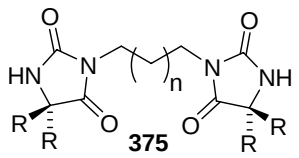
Secondly, compound **35** was targeted. A mixture of ethyl pyroglutamate **287** and allyl isocyanate was treated with NaH in THF. The obtained compound **22g** was alkylated using allylbromide in refluxing acetone in the presence of K_2CO_3. Treatment of compound **374** at room temperature with 5% second generation catalyst **B** in CH_2Cl_2 did not result in any reaction. Raising the temperature of the mixture to reflux did result in reaction. Spectroscopic analysis of the crude

reaction mixture revealed certain signals that could be attributed to compound **35**, however, a great number of undesired compounds, probably resulting from polymerization, were also formed and the targeted structure could not be purified from this mixture.



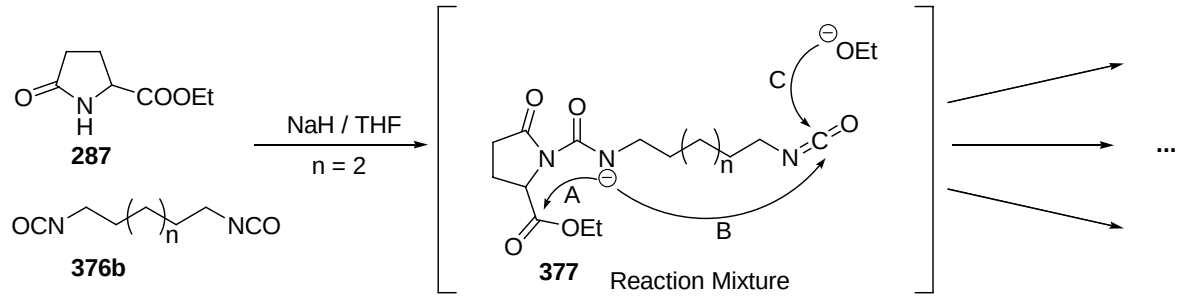
3.3.4 Synthesis of bis-hydantoins and their macrocyclic derivatives (Paper VI)

The pyroglutamate-hydantoin rearrangement could prove a very powerful method to make *N*(3),*N*(3)-polymethylene-bis-hydantoins with general structure **375**. In the past, this kind of compounds has been made by reaction of a hydantoin with an α,ω-dihaloalkane under basic conditions.[191] As mentioned before, the functionalization of hydantoins at the 3-position occurs quite easily, but side reactions at *N*(1) also occur resulting in mixtures of compounds that are difficult to purify and usually result in quite low yields. Starting from pyroglutamates would avoid the problem of *N*(3)-selectivity and also allows the synthesis of highly functionalized derivatives since pyroglutamates can easily be derivatised.



When the developed method was applied to a mixture of pyroglutamate **287** and diisocyanate **376b**, however, a mixture of a variety of compounds was formed. The formation of this mixture can be explained by taking a closer look at the reaction mixture. Once a pyroglutamate has reacted with one of the isocyanate moieties, the intermediate **377** can react in different ways. Route A is active in the normal rearrangement and leads to the bicyclic intermediates. The intermediate can also avoid forming this strained bicyclic compound by reacting towards the second isocyanate moiety, route B. A third possibility, route C, is that ethoxide anions, formed by

route A, react with the isocyanate instead of opening the bicyclic compound. Besides these three reactions also others can be proposed.



An earlier observation, namely that the sodium salts of the carbamoylated lactams precipitate in diethylether, came to rescue. When a mixture of pyroglutamate **287** and diisocyanate **376** in ether was treated with NaH, a white precipitate is formed. This precipitate dissolves during acidic workup using aqueous NH_4Cl and the dimers **379** were isolated in high yield and purity.

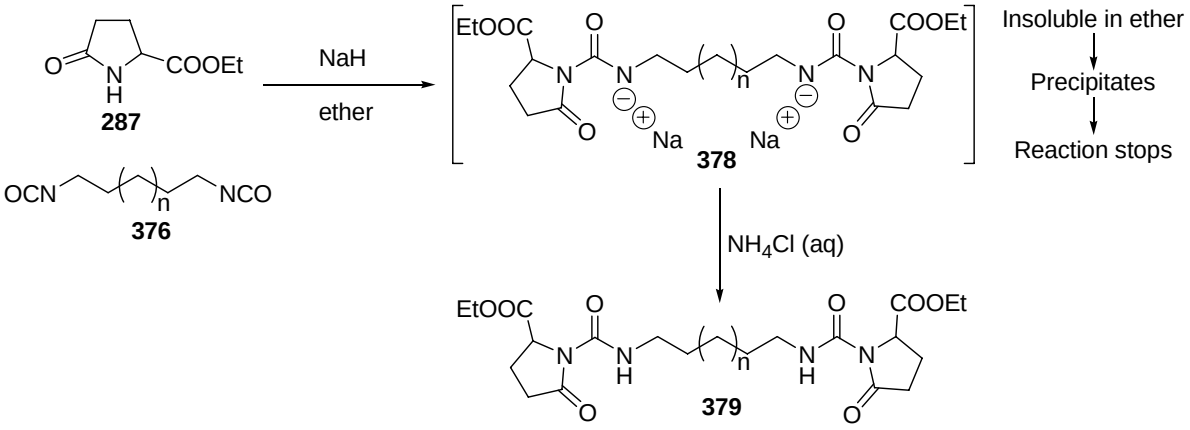


Table 16: Synthesis of bis-carbamoylated lactams **379**

Entry	n	Yield 379 (%)
a	0	97
b	2	99
c	4	99
d	8	99

The most convenient way to achieve the ring rearrangement towards the bis-hydantoins was to dissolve these dimers in absolute ethanol followed by treatment with 2.2 equivalents of KO*t*Bu. Two reaction pathways can be proposed for this rearrangement. In the first pathway, the lactam rings of **379** are opened by ethoxide resulting in acyclic compound **380**. This dianion is in equilibrium with dianion **381** and cyclization of the latter with expulsion of ethoxide leads to the bis-hydantoins **382**. Alternatively, the rearrangement can also follow the same course as when performed in THF. Deprotonation of nitrogen and cyclization of **383** leads to intermediate **384**

which is opened by ethoxide to give **382**. Possibly, both pathways may be active, but this isn't a problem since they both lead to the same compound.

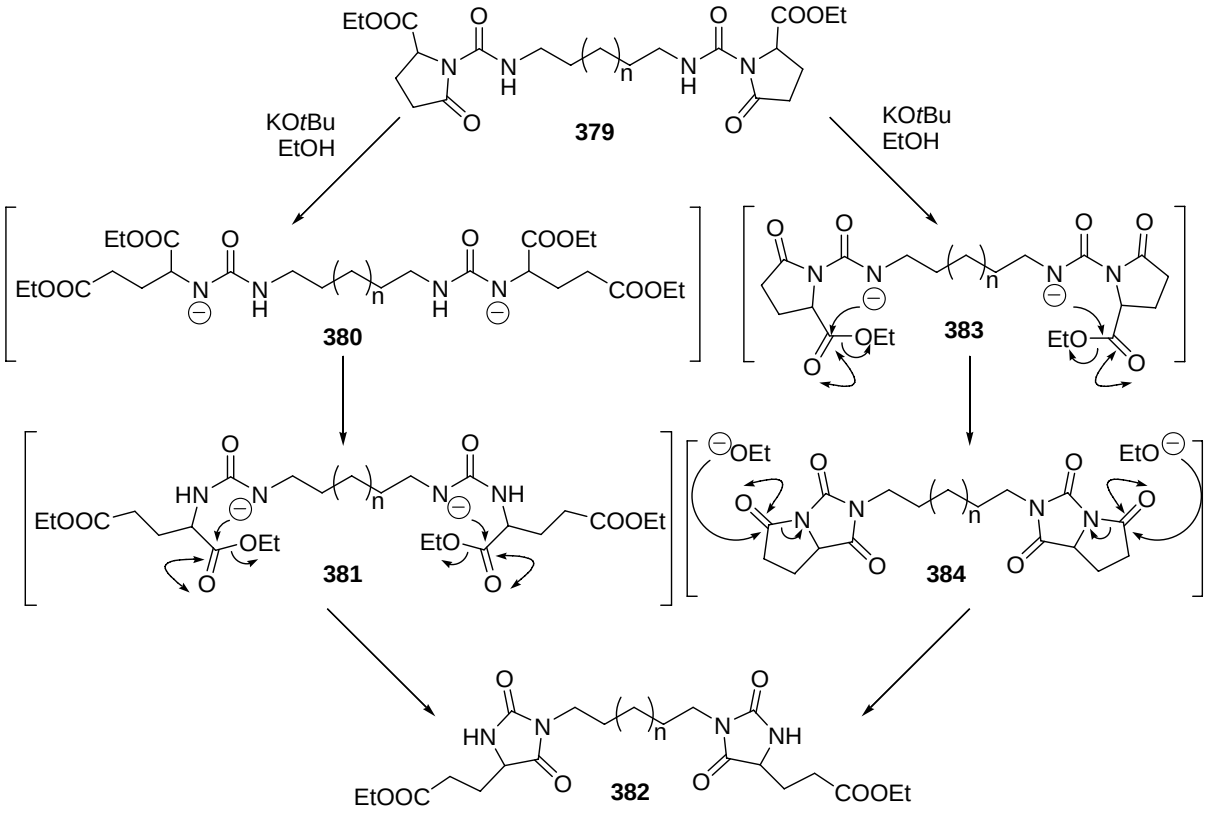


Table 17: Synthesis of bis-hydantoins **382**

Entry	n	Yield 382 (%)
a	0	98
b	2	97
c	4	99
d	8	99

Again straightforward ^{1}H NMR and ^{13}C NMR measurements are not sufficient to distinguish between compounds **379** and **382**, as can be seen from figures 5-8. However, having both compounds in hand, 2-dimensional spectroscopy clearly allowed the unambiguous determination. In the case of **379**, there is a coupling in the COSY spectrum between the NH-protons and the CH_2 next to the nitrogen. On the other hand, the NH protons of **382** show a coupling to the proton next to the carbonyl and not to the CH_2, proving that this methylene is connected to a tertiary nitrogen. Furthermore, the protons of the CH_2 next to nitrogen of **379** only couple to the urea carbonyl in the HMBC spectrum, whereas in the case of **382** they couple to both the urea and the lactam carbonyl. Another distinctive feature is the shift of the NH-protons. Intramolecular hydrogen bridge formation in **379** to the lactam carbonyl causes a downfield shift, resulting in a typical value of 8.3 ppm whereas the value in the case of **382** is typically around 6.3 ppm.

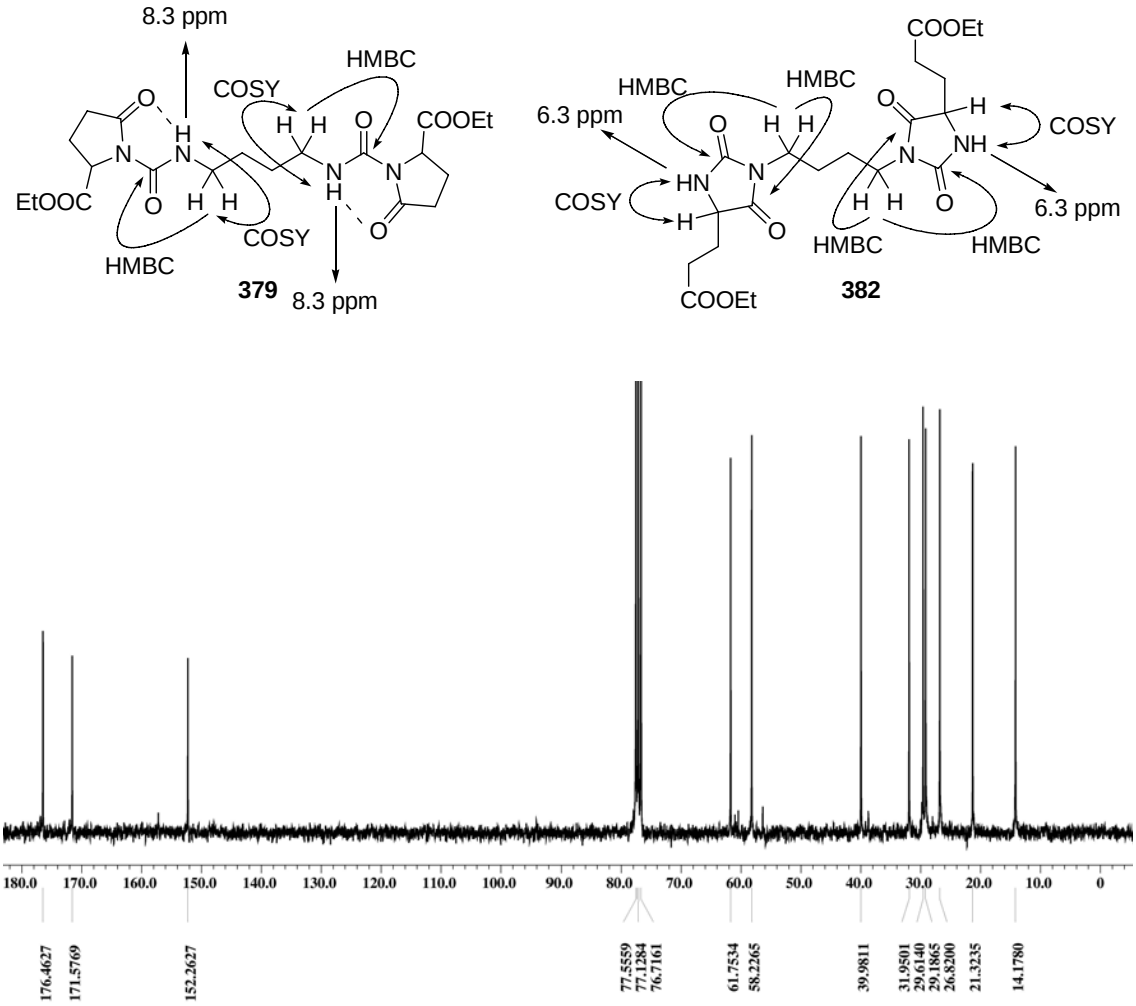


Figure **5**: ^{13}C spectrum of **379c**.

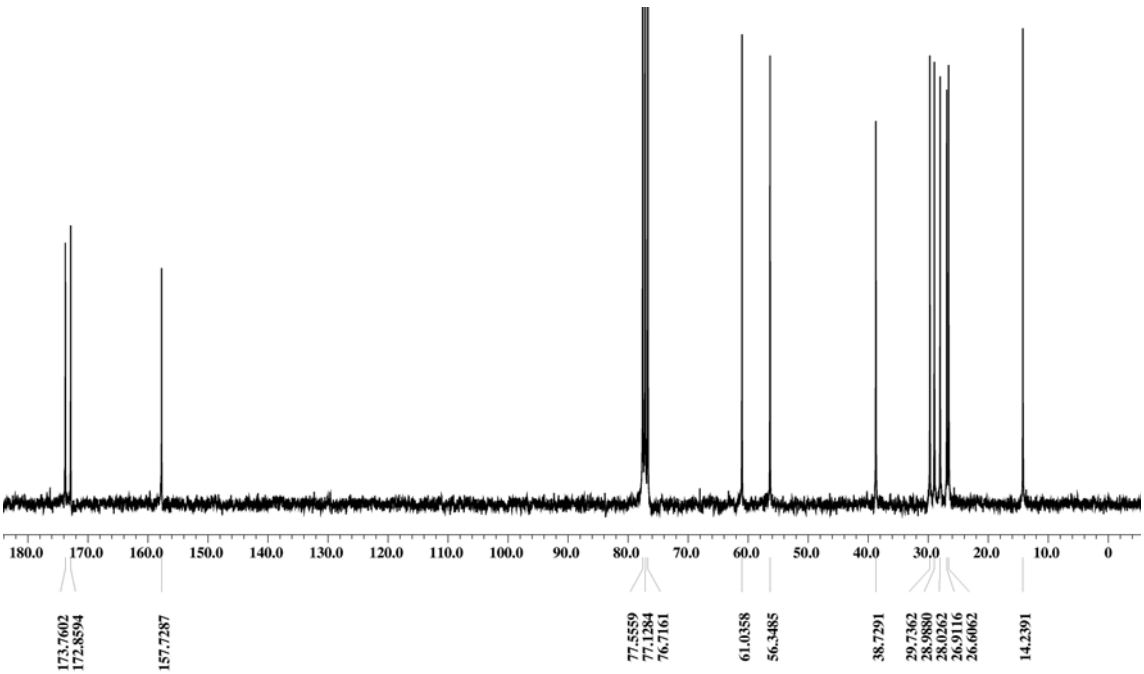


Figure **6**: ^{13}C spectrum of **382c**.

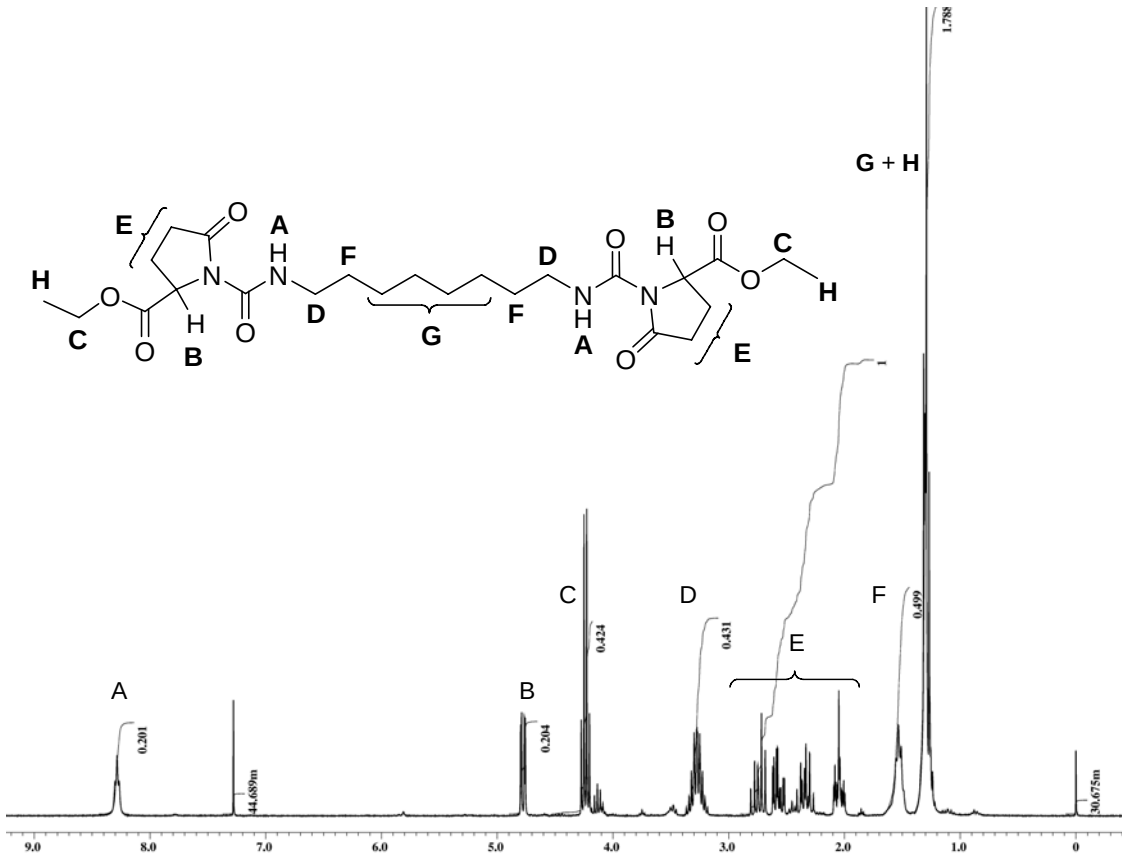


Figure **7**: ^{1}H spectrum of **379c**.

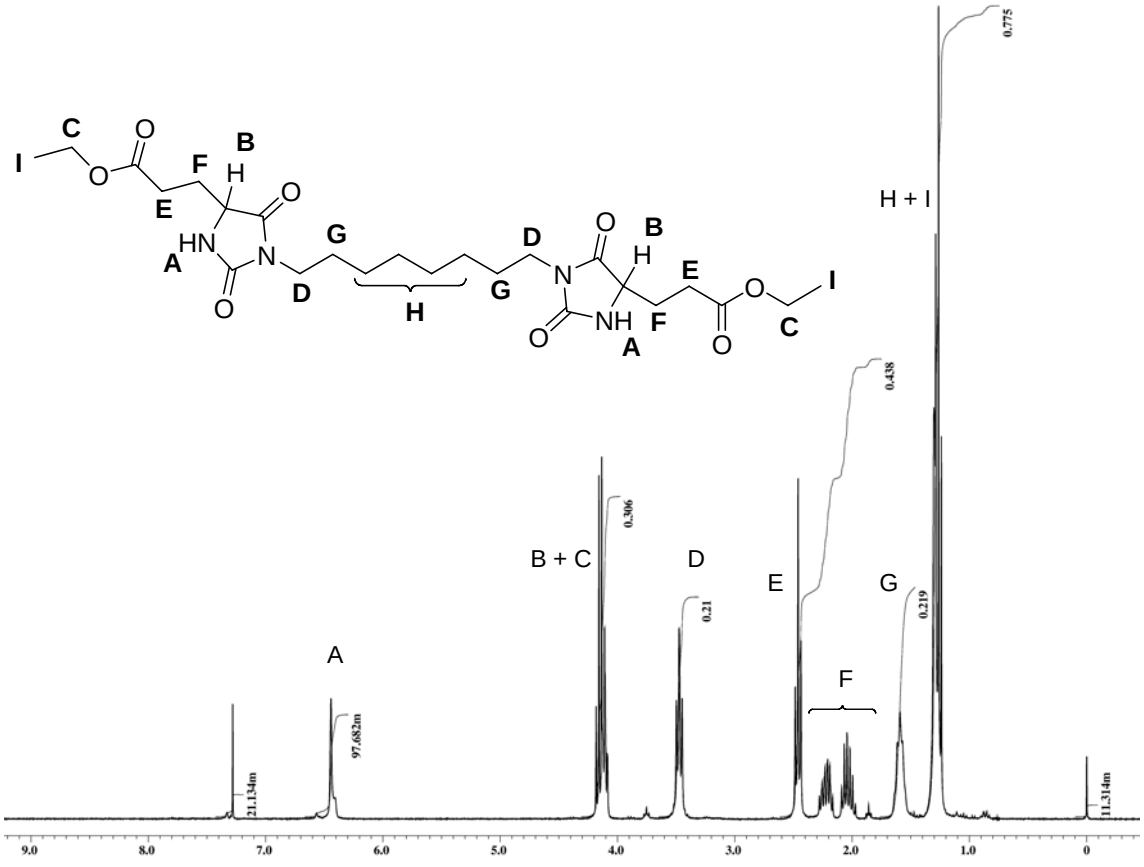


Figure **8**: ^{1}H spectrum of **382c**.

Alkylation at *N*(1) was performed by the same procedure as for the synthesis of compounds **32**. Thus compounds **36** were obtained clean and in good yield after filtration and evaporation of the solids or column chromatography.

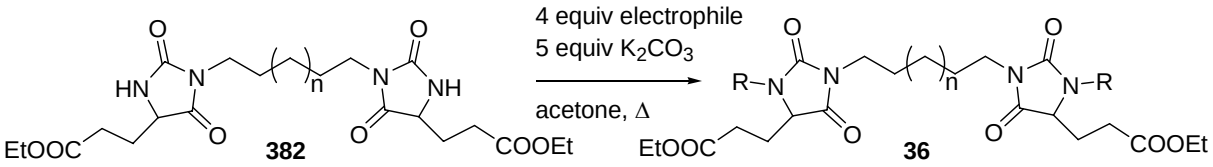


Table 18: Alkylation at *N*(1) of bis-hydantoins **382** towards **36**

Entry	n	R	Yield 36 (%)
a	0	allyl	98
b	2	allyl	98
c	2	CH_2CCCH_3	99
d	4	allyl	98
e	4	*o*-bromobenzyl	84
f	4	*m*-fluorobenzyl	86
g	8	allyl	98

In order to prevent free rotation around the central polymethylene axis, we wanted to evaluate the possibility to use ring-closing metathesis for the macrocyclization of derivatives **36a**, **b**, **d** and **g**. Treatment of these compounds with 5% second generation catalyst **B** resulted in reasonably clean conversion to tricyclic compounds **37**. Due to the great polarity of these compounds quite a drop in yield was observed during purification.

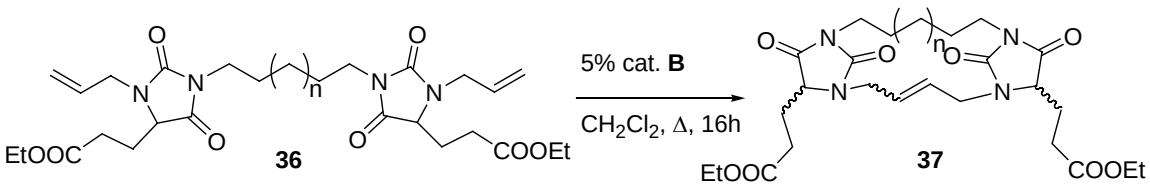


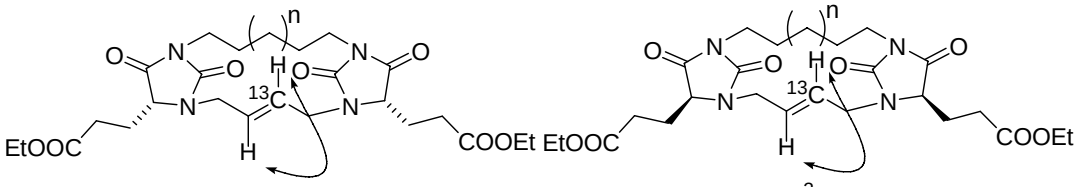
Table 19: Synthesis of macrocycles **37** by RCM on substrates **36**

Entry	n	Outer ringsize	Yield 37 (%)
a	0	16	46
b	2	18	58
c	4	20	54
d	8	24	41

Spectral analysis of compounds **37** revealed that they are present in two forms (1:1 ratio). This could indicate that an (*E,Z*)-mixture around the double bond is formed during the metathesis. It was also possible that the two forms are diastereoisomers since these compounds have two racemic centres. Since these compounds are symmetrical entities, the $^3J_{HH}$ coupling constant between the two alkene protons is absent because they are magnetically equivalent. It was,

however, possible to separate the two forms of compound **37c** by column chromatography. Now it was possible to prove whether they were diastereoisomers or (*E,Z*)-isomers. Firstly, it was observed that treatment with base of one form of **37c** resulted in equilibration to the mixture of both forms. Secondly, hydrogenation of the two forms gave two different compounds **385a** en **385b**. These results can only be explained by assuming that the two compounds were diastereoisomers.

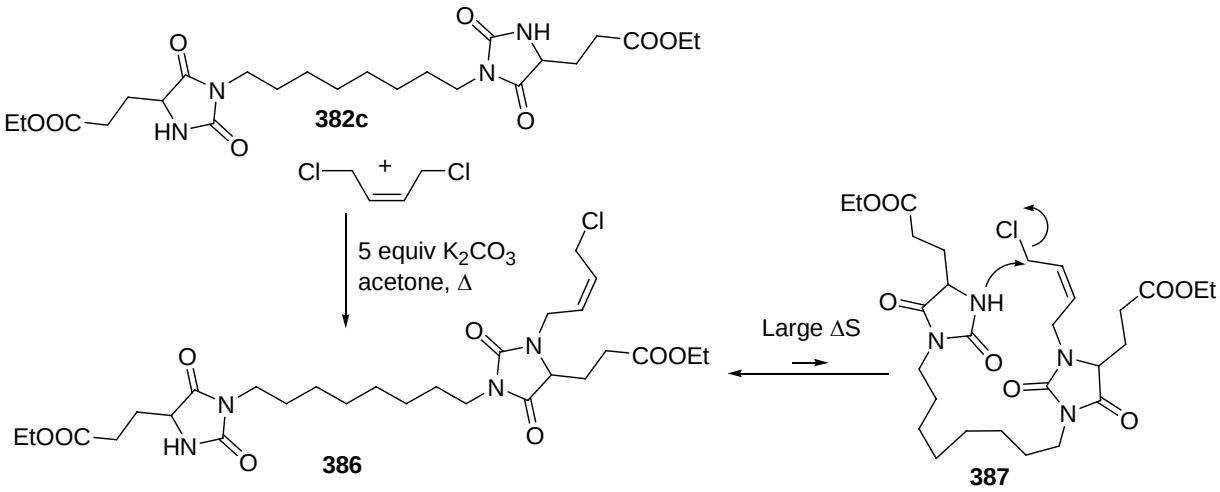
However, the question then arose whether the *trans*- or *cis*-fused cycles were produced. As mentioned before, the $^{3}J_{HH}$ couplings are absent and cannot be used to determine the configuration of the double bond. The symmetry of the molecule could be circumvented, however, by taking the ^{13}C satellites of the alkene protons into account of one pair of enantiomers of **37c**. When one of the two alkene carbon atoms is a ^{13}C isotope, the symmetry is lost due to the presence of a magnetically active ^{13}C in place of an inactive ^{12}C. In this case, the two isotopomers give two separate signals (br d, 5.14 ppm, 14.3 Hz and br d, 5.12 ppm, 14.9 Hz). They are not each other's mirror image because of the two other chiral centres. A $^{3}J_{H,H}$ coupling of 14.3 and 14.9 Hz is observed, pointing to the *trans*-geometry.



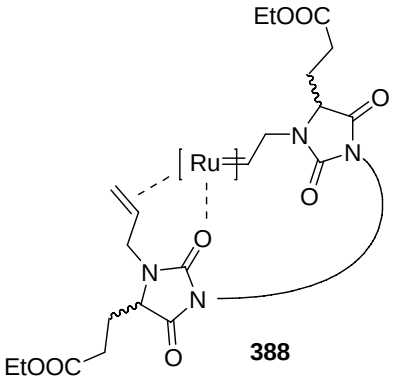
37c n = 4
isotopomer 1

37c n = 4
isotopomer 2

One could argue that these macrocyclic compounds could also be obtained by reaction of derivatives **382** with an α,ω-dihaloalkane. Treatment of **382c** with *cis*-1,4-dichloro-2-butene resulted in a mixture, however, of starting material, mono-alkylated product **386** and cyclized material (<10%). In order for a ring to be formed, an energy activation barrier ΔG has to be taken. This barrier is comprised of two parts namely the enthalpy of activation ΔH, which is associated with the energy required to bring the reacting atoms together against the ring strain and repulsive forces and the entropy of activation ΔS which is associated with the ease by which an ordered transition state is formed from a randomly moving molecule. In this case a very large ring is formed thus ΔH is very small since no ring strain is present. On the other hand ΔS is very negative since mono-alkylated compound **386** has to give up a lot of freedom to adopt the right conformation **387** which can react.



The fact that these derivatives are so difficult to cyclize in this fashion, again proves the importance of RCM as macrocyclization method. Probably, chelation complexes of type **388** are formed during metathesis, effectively bringing the two alkene moieties in the correct position. Complexation of the ruthenium centre with functional groups across the molecule lowers the ΔS needed to achieve the proper conformation. This illustrates the essential role of functional groups as a relay in order to form macrocyclic compounds by RCM.[192,193]



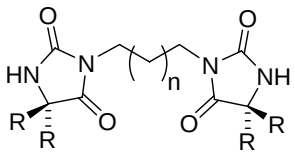
3.3.5 Anti-invasive activity on human breast cancer cell lines

3.3.5.1 Introduction

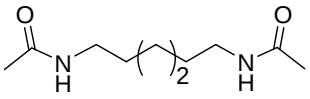
Cancer is the result of a number of genetic mutations that lead to functional alterations of certain cells. Cancer cells differ from their normal counterparts in the following aspects: growth, differentiation, tissue integrity and anoikis. When a cancer develops, the cells start to divide in an uncontrolled way and penetrate and damage the surrounding tissue. The causes of cancer can be divided into internal factors and external factors. The most important internal factors are errors in the DNA and a weakened immune system. The most important external factors include smoking, drinking, viruses, several chemical substances, radiation etc. In Flanders every day 84 people are diagnosed with cancer, which equals about 30000 per year. After cardiac affections, cancer is the

most important cause of death. Among the male population prostate cancer is the most occurring (28,6 %), followed by lung cancer (17,9 %) and colon cancer (13,6 %). Among the female population breast cancer is the most occurring (35,5 %), followed by colon cancer (13,9 %) and uterus cancer (5,4 %).[194] Treatment of cancer is done by surgery, radiotherapy, chemotherapy or a combination of those.

As mentioned in the introduction of this work, bis-hydantoins have in the past been tested as analogues of HMBA **38**. HMBA is an agent that induces differentiation of certain types of tumor cells to nonmalignant phenotypes. This implies that it works not by killing the cancer cells but by inducing them to differentiate and to express characteristics of the normal nontransformed counterpart. This is a promising approach to cancer therapy, potentially without many of the disadvantages of cytotoxic agents. HMBA has even had some modest success in clinical trials. The doses required to achieve sufficient blood levels in human patients, however, led to some undesirable side effects. It was found that compounds **375a** and **375c** were 10 times more potent than HMBA itself. The activity of **375b** was low, probably due to its insolubility.[16,17,195] Since derivatives **36** have an ester moiety on a side chain, the increased polarity might lead to an activity at lower concentrations.



375a n = 4, R = Me
375b n = 4, R = Ph
375c n = 3, R = Me



38

3.3.5.2 The chick heart invasion essay

The screening of several hydantoin derivatives for their anti-invasive activity was performed in cooperation with the department of Gynaecological Oncology and the department of Experimental Cancerology at the Ghent University Hospital.

The screening assay chosen, is based on the *in vitro* confrontation of cancer cells with a fragment of normal tissue (Fig. 9). Heart tissue fragments are dissected from 9-days old chicken embryos and precultured to obtain living spheres with a standard diameter of 0.4 mm. These precultured heart fragments (PHF's) are confronted with standard aggregates (diameter 0.2 mm) of invasive test cells like human MCF-7/6 mammary carcinoma cells. The aggregates become attached to the PHF's by incubation on a semi-solid agar bed overnight and are then transferred as individual

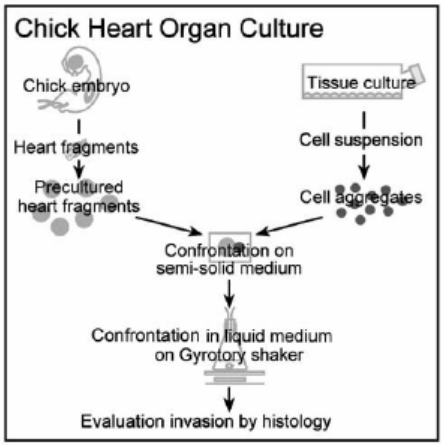


Figure 9: Protocol for the chick heart invasion assay.

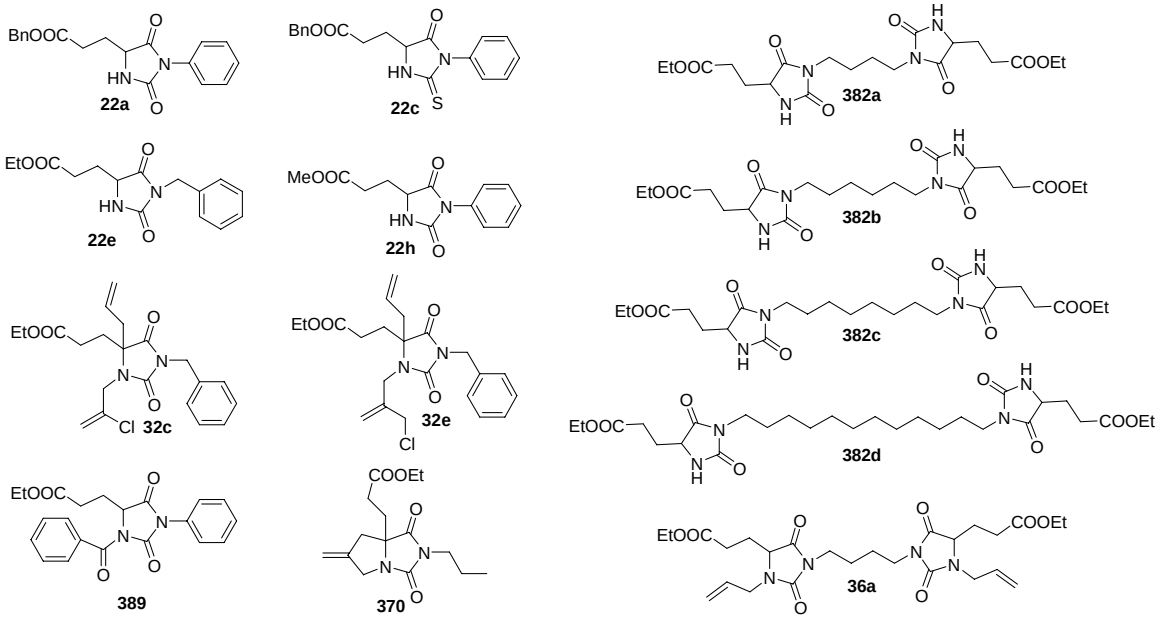
pairs into Erlenmeyer flasks for suspension culture in liquid medium. The cultures are treated with the compounds at concentrations ranging from 100 μm to 1 μm. After 8 days of incubation on a Gyrotory shaker, the cultures are fixed and embedded in paraffin for histology. After serial sectioning and staining of the sections with hematoxylin and eosin, the interaction of the tumor cells with the PHF can be reconstructed tri-dimensionally from microscopic analysis of all sections.[196]

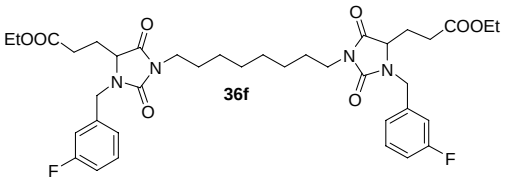
The invasion was scored as follows:

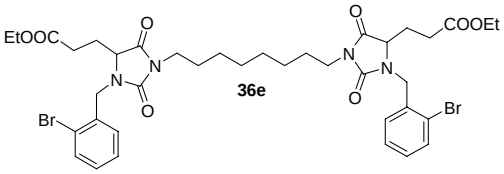
- Grade 0: only PHF can be found and no confronting cells can be observed
- Grade 1: the confronting test cells are attached to the PHF and do not occupy the heart tissue
- Grade 2: occupation of the PHF is limited to the outer fibroblast-like and myoblast cell layers
- Grade 3: the confronting cells have occupied the PHF but have left more than half of the original amount of heart tissue intact
- Grade 4: the confronting cells have occupied more than half of the original volume of the PHF

3.3.5.3 Results

A total number of 15 compounds were selected for screening in the *in vitro* tests. These include *N*(3) functionalized hydantoins (**22a**, **22c**, **22e**, **22h**), hydantoins functionalized at *N*(3) and *N*(1) (**32c**, **32e**, **389**, **370**), bis-hydantoins (**382a**, **382b**, **382c**, **382d**) and functionalized bis-hydantoins (**36a**, **36e**, **36f**).







In a first screening, 13 compounds were added to the liquid medium containing the PHF and the human MCF-7/6 mammary carcinoma cells in a concentration of 100 μm. In every batch of tests a number of control experiments are included in order to check the activity of the cancer cells. This is necessary because after a number of cell divisions mutations start to accumulate that can alter the normal activity of the cancer cells. As can be seen from these results (table 20) a number of compounds completely block the invasion of the cancer cells into the heart tissue whereas in the control experiments the heart fragments have almost completely been destroyed (Fig. 10). The compounds showing the highest activity (score 1) do not immediately show structural resemblance. Sometimes a great difference in activity is observed depending on the substituents present on the hydantoin nucleus. This is the case for **36e** and **36f** where the only difference is the nature and position of the halogen. Although this test is performed at a very high concentration, it is well suited for selecting active compounds and detect toxicity towards the benign cells as is the case for compounds **22c** and **22e**.

Table 20: Anti-invasive activity of several hydantoin derivatives at 100 μm

Product	Invasion Grade	Remark
22a	4	
22c	1	Toxic for PHF
22e	1	Toxic for PHF
22h	3	
32c	1	
389	2	
382a	4	
382b	2	
382c	1	
382d	3	
36a	3	
36e	3	
36f	1	
Control	4	
Control	4	

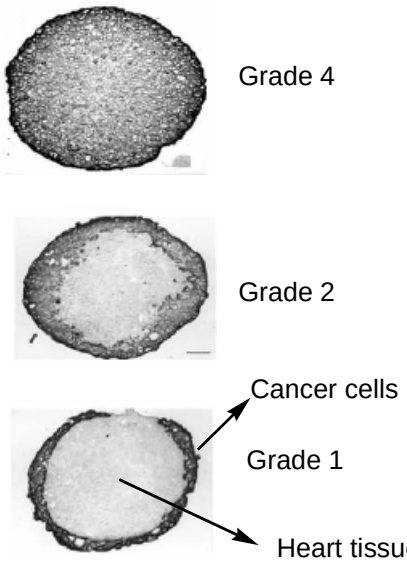


Figure 10: Example PHF's with invasion grades 4, 2 and 1.

In a second series of experiments, the most active non-toxic compounds from the previous test and the untested compounds were screened for activity at a concentration of 10 μm. It should be noted that in these tests the control experiments clearly showed a decrease in the activity of the cancer cells. This means that it's difficult to compare these results with the previous tests and draw conclusions. It can still be seen, however, that some compounds also prevent invasion at

this lower concentration. A rather strange result is obtained from compound **382d** that showed an activity of only 3 at 100 μm but seems to be more active at 10 μm.

Table 21: Anti-invasive activity of several hydantoin derivatives at 10 μm

Product	Invasion Grade batch 1	Invasion Grade batch 2
32e	1	
370	2	
382c	1	
382d	1	0
36f	1	2
389	1	
Control	2	2

The final experiments were performed at 1 μm. Also in this case, a decreased activity of the cancer cells was observed. The fact, however, that a strong invasion (score 3) was observed in some cases, shows that the cancer cells are still reasonably active. It is clear that the activity at this low concentration is rather poor.

Table 22: Anti-invasive activity of several hydantoin derivatives at 1 μm

Product	Invasion Grade
382c	3
382d	2
36f	3
Control	2

3.3.5.4 Predicting the activity

Quantitative structure-activity relationships (QSAR's) have been used in the past to develop models in order to estimate and predict biological or toxicological behaviour of organic molecules using computational descriptors solely derived from chemical structures. Very recently an artificial neural network was constructed that used a nonlinear combination of a large number of descriptors derived from 93 anti-invasive compounds. This model was able to predict accurately the anti-invasive activity of 46 other compounds.[197] If this model is able to predict the activity of the synthesized hydantoins, this would provide the opportunity to screen compounds prior to their synthesis. This would give the chance to target new compounds that are predicted to be active rather than randomly synthesize derivatives. The model calculates an anti-invasive activity score (I_index) representing the activity of the compounds at different concentration. The compounds are classified using this I_index depending on the concentration at which they inhibit invasion of the cancer cells into the PHF (grade 0 or grade 1).

Table 23: I_index in relation to concentration needed for anti-ivasive activity

Concentration (μm)	**Activity**	**Anti-invasive activity score (I_index)**
>100	Low	1
100	Fair	2
10	Good	3
1	Active	4

Unfortunately, the model proved to be completely useless for the compounds prepared in this thesis. As can be seen in the table below products **36a**, **36e** and **36f** are all predicted to possess very low activity while in reality **36f** shows good activity. Compounds **382a**, **382c** and **382d** are all predicted to be very active while in fact **382a** is completely inactive.

Table 24: Predicted anti-invasive activity score of several hydantoin derivatives

Product	**Predicted anti-invasive activity score (I_index)**
36a	1.39
36e	1.16
36f	1.09
382a	3.51
382c	3.56
382d	3.53

For other derivatives there was also no correlation between the predicted and observed activity. Although this model is based on a wide variety of compounds including chalcones, chromenones, catechins, (poly)phenolics, methoxyflavones, pyrazoles, oxazoles, indolones and others, the hydantoins seem to be a bridge too far.

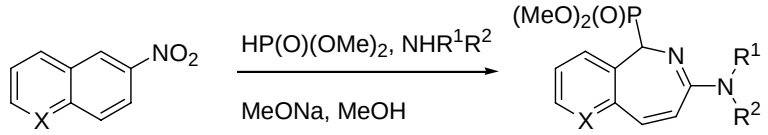
3.3.6 Conclusion

In the second part of this thesis entries towards new polycyclic hydantoin derivatives were developed starting from pyroglutamates. A short four-step approach was successful for the synthesis of hydantoin derivatives that are annelated to a six-membered ring. Also a new entry towards bis-hydantoins was developed by reaction of pyroglutamates with bis-isocyanates and subsequent ring-transformation. The compounds could be converted to their macrocyclic derivatives using the second generation Grubbs' catalyst in refluxing CH_2Cl_2. A number of the synthesized compounds were screened for their anti-invasive activity on human breast cancer cell lines. It can be stated that some of the synthesized bis-hydantoins show some good anti-invasive activity and are non-toxic to the heart tissue used in the *in vitro* tests. Unfortunately, the activity of these compounds cannot be accurately predicted using a nonlinear QSAR model. Therefore, further research is needed to shed light on the mode of action of these structures in order to allow the synthesis of more active compounds. In a further stage *in vivo* tests will have to be performed to validate these results.

3.4 Synthesis of benzo-fused heterocycles

3.4.1 Synthesis of 1-phosphonylated benzazepines (Paper VII)

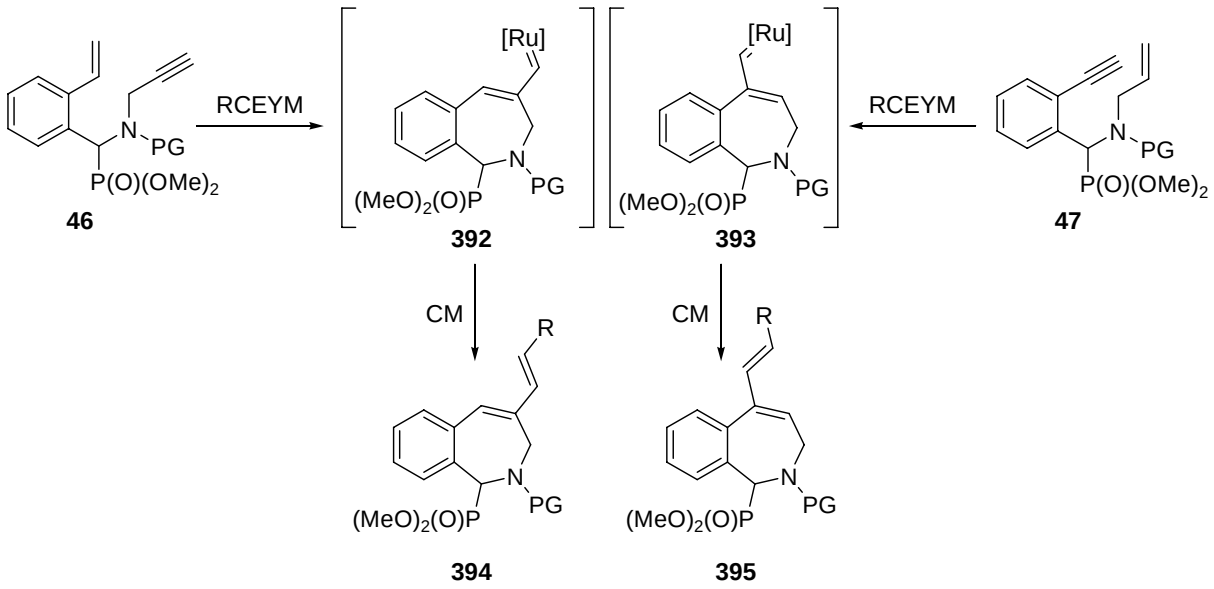
Seven-membered azaheterocyclic phosphonates are very rare in literature. As mentioned in the introduction, only one entry to 1-phoshonylated benzazepines has been described.[21] This rearrangement involves the reaction of a dialkyl phosphite and amines with bicyclic aromatic nitro compounds **390** to afford compounds **391**.



390 **391**

6 examples: 65-82%

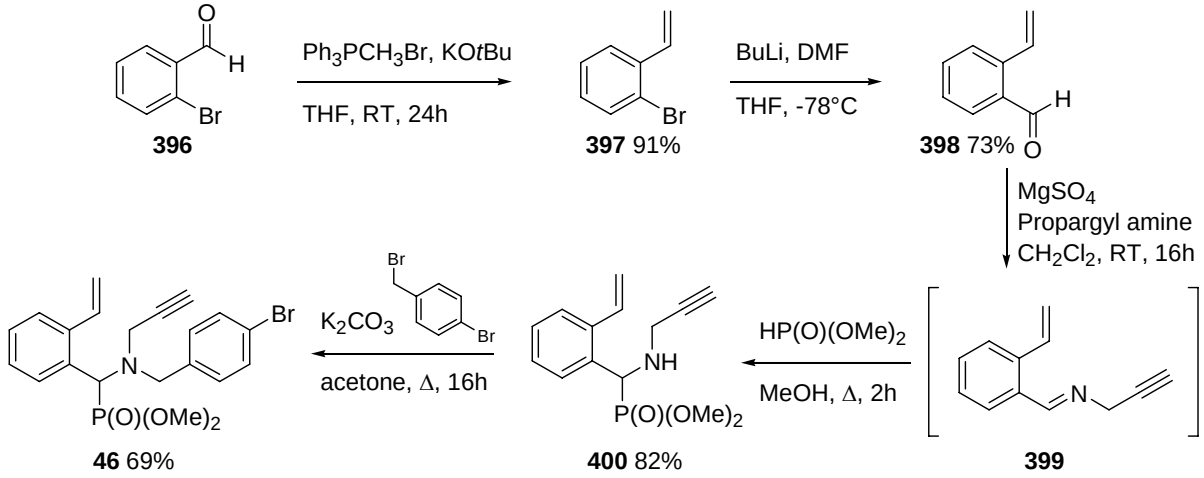
The lack of straightforward entries towards this interesting heterocyclic scaffold provides the opportunity to develop new pathways targeting related compounds. Ring-closing enyne metathesis seems a very attractive method to obtain these compounds since it is not only very atom-efficient but it also provides the possibility of immediately functionalising the intermediately formed diene by cross-metathesis with an alkene. Thus α-aminophosphonates **46** and **47** have to be synthesized and treated with a metathesis catalyst to produce vinylic carbenes **392** and **393**. These intermediates can undergo cross-metathesis with an alkene to form **394** and **395**. The advantage of this strategy is that only two compounds, **46** and **47**, have to be used as starting material. These compounds can be transformed to a variety of benzazepines depending on the addition of a certain alkene to the reaction mixture.



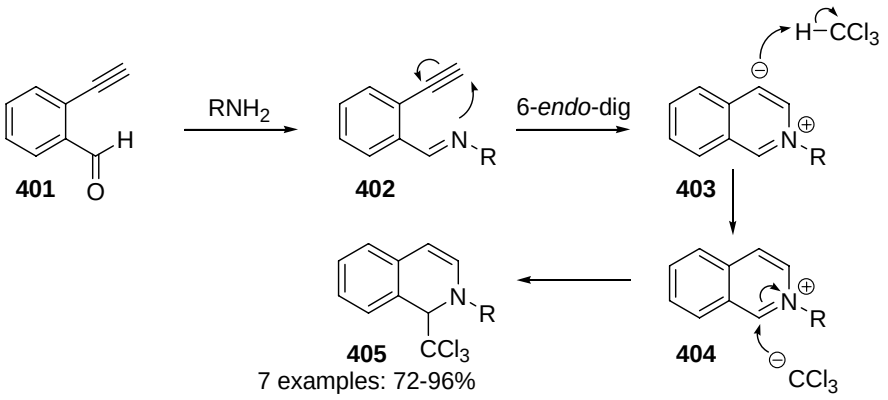
46 **392** **393** **47**

394 **395**

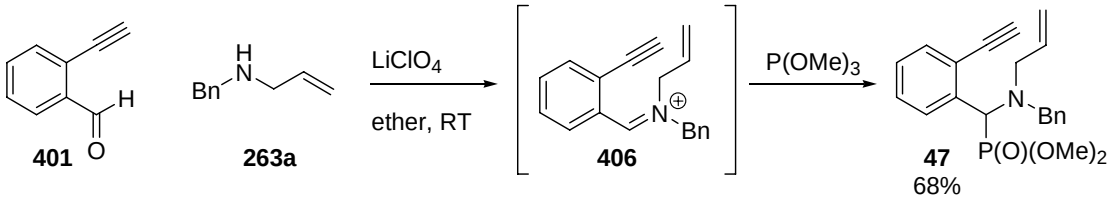
The first building block **46** was synthesized in four steps starting from commercially available aldehyde **396**. In the first step, the aldehyde was converted to an alkene via a Wittig reaction using methyltriphenylphosphonium bromide and KO*t*Bu as a base. The formylation of alkene **397** was performed with DMF after Li-halogen exchange with BuLi at -78 °C. The obtained aldehyde **398** was converted to imine **399** by treatment with propargylamine and $MgSO_4$ in CH_2Cl_2. This imine was immediately phosphonylated using dimethyl phosphite in methanol and isolated using an acid-base extraction. The *N*-atom of **400** was protected using *p*-bromobenzylbromide and K_2CO_3 as a solid base in refluxing acetone. The first building block **46** was isolated in 69% yield after column chromatography.



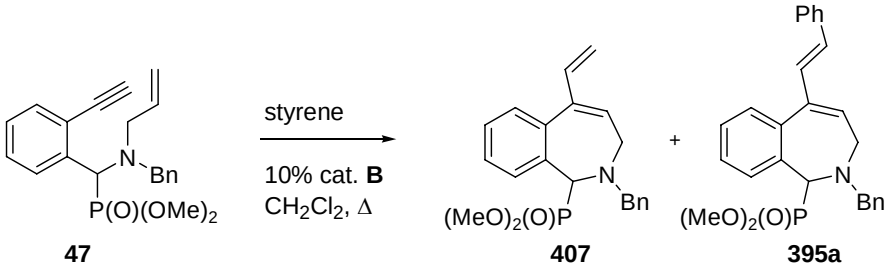
A very similar approach towards the second building block **47** was attempted. When commercially available aldehyde **401** was treated with primary amines in the presence of $MgSO_4$ in CH_2Cl_2, a complex reaction mixture was formed instead of the expected imines **402**. Apparently these imines are quite unstable. An attempt was made to form the imine followed by an immediate reaction with dimethyl phosphite by running the imination reaction in dry methanol in the presence of $MgSO_4$. Although ^{31}P NMR revealed the formation of an α-aminophosphonate, this reaction was far from clean and the desired compound could not be purified from this mixture. Recently, Asao and co-workers revealed the nature of the instability of imines **402**.[198] Apparently an intramolecular 6-*endo*-dig reaction takes place by attack of the nitrogen lone pair onto the inactivated triple bond. This results in the formation of zwitterionic intermediate **403**. When the reaction is performed in chloroform, a proton is abstracted from the solvent to produce **404**. Subsequent attack of $^{-}CCl_3$ provides 1,2-dihydroisoquinolines **405**.



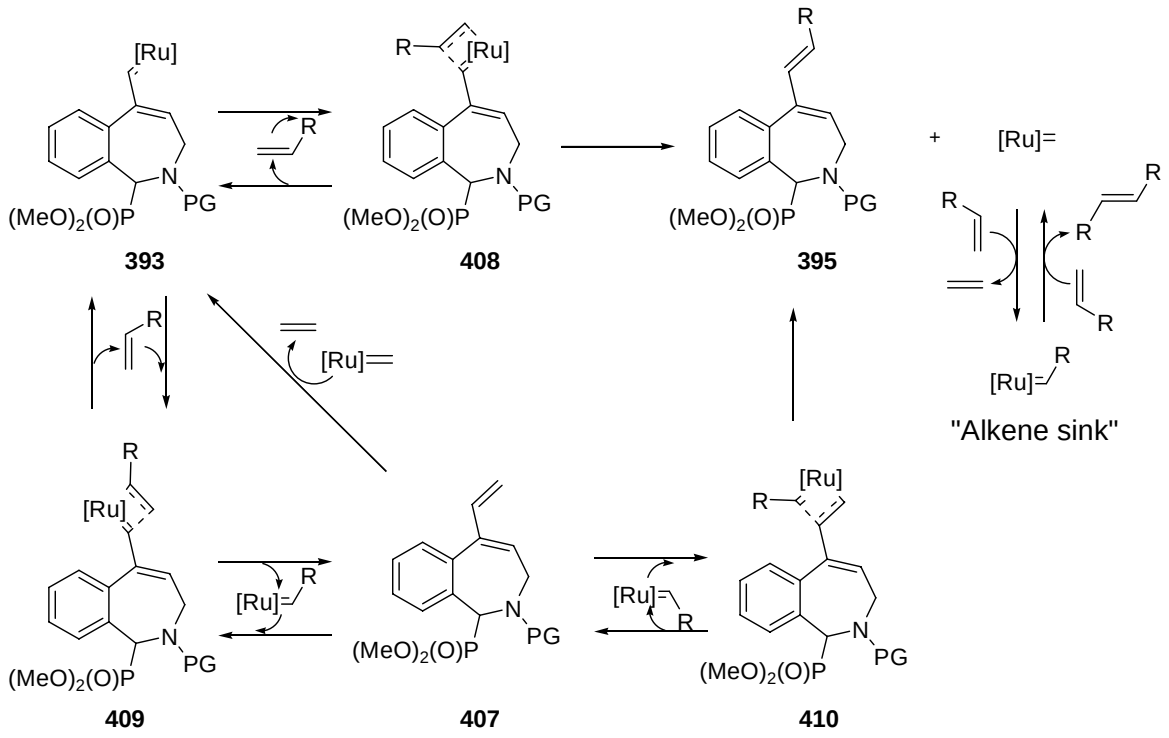
In order to circumvent the instability of imines **402**, a one-pot three-component coupling mediated by $LiClO_4$ was attempted.[199] Thus, a mixture of aldehyde **401** and two equivalents of amine **263a** was treated with $LiClO_4$ in ether. This results in the formation of iminium ion **406** which is stabilized by $LiClO_4$. Subsequent addition of trimethyl phosphite to this mixture results in the formation of the desired compound **47**. Although this reaction work fine, a difficult purification is necessary to remove the excess of amine resulting in a decreased yield of the aminophosphonate. The second building block **47** was isolated in 68% yield after column chromatography.



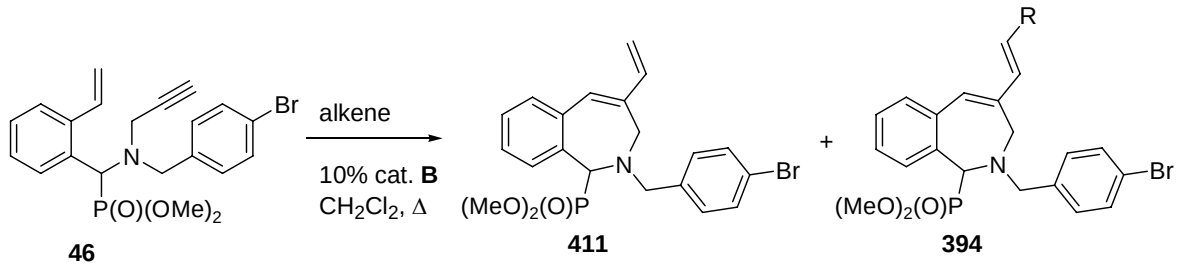
Having both building blocks in hands, a first reaction was performed to test the envisaged route. Thus compound **47** was treated with 5 equivalents of styrene and 10% second generation catalyst **B** in refluxing CH_2Cl_2. Spectroscopic analysis of the reaction mixture after 30 minutes revealed that the major compound present was **407**. The conversion of this compound to the desired compound **395a** proceeded extremely slow. It was found, however, that the addition of an extra five equivalents of styrene speeds up this conversion significantly.



This reaction pattern can be explained by looking at the complete reaction cycle of this conversion. In a first step, vinylic carbene **393** is formed. This compound can react with the alkene in two different ways: with the R-group pointing away from the metallic centre (**408**) or with the R-group towards the metallic centre (**409**). In the first case the desired end product **395** is produced after the cycloreversion. In the second case the unwanted byproduct **407** is formed after cycloreversion which can react in three different ways: 1) conversion to **393** via **409**, 2) conversion to **393** by reaction with the methylidene carbene and production of ethylene or 3) conversion to **395** after reaction with the alkylidene carbene via **410**. During the course of the reaction, the alkene is not only incorporated in the end product but also dimerized in the "alkene sink" with regeneration of the methylidene carbene and production of ethylene. This explains the fact that adding an extra amount of alkene speeds up the conversion of **407** to **395** since the dimerized alkene remains relatively inert in the reaction mixture. In all cases, however, about 10% of **407** remained present which had to be removed by flash chromatography.

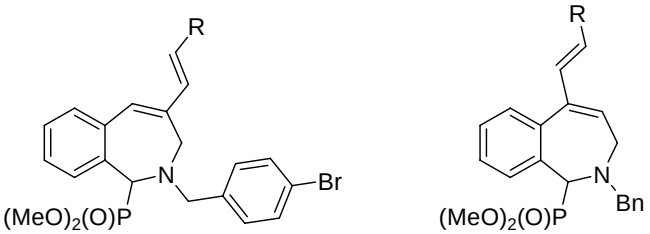


Upon evaluation of the reaction between **46** and styrene, it was found that in this case it is not necessary to add an extra amount of alkene. Only very small signals were present in the ^{1}H NMR spectrum that could tentatively be attributed to **411**. This can be explained in two ways. The first possibility is that the formation of metallacyclobutanes of type **408** is favoured, immediately leading to the end products. The second possibility is that the intermediate product **411** is converted much faster to the final compound than the alkene is being dimerized.



46 **411** **394**

A total of six 1-phosphonylated benzazepines of type **394** and **395** could be obtained in reasonable yield after column chromatography in this fashion. In two cases an (*E*/*Z*)-mixture was obtained. The (*E*/*Z*)-ratio observed does not provide any information about the configuration of the intermediate metallacyclobutanes or of the initial metathesis products since Grubbs has proven that isomerization of double bonds can occur by secondary metathesis reactions leading to the thermodynamically favoured configuration.[200]



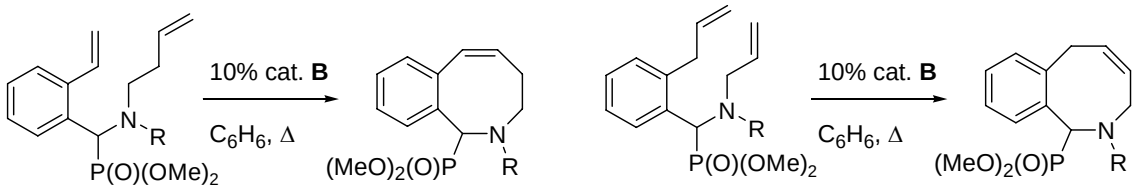
394 **395**

Table 25: Synthesis of 1-phosphonylated benzazepines **394** and **395**

Substrate	Product	R	Yield (%)	*E*/*Z*
46	**394a**	Ph	69	100/0
46	**394b**	CH_2CH_2Br	50	100/0
46	**394c**	$CH_2CH_2CH_2CH_3$	70	100/0
47	**395a**	Ph	78	100/0
47	**395b**	$CH_2Si(CH_3)_3$	74	66/34
47	**395c**	$CH_2CH_2COCH_3$	68	67/33

3.4.2 Synthesis of 1-phosphonylated benzazocines

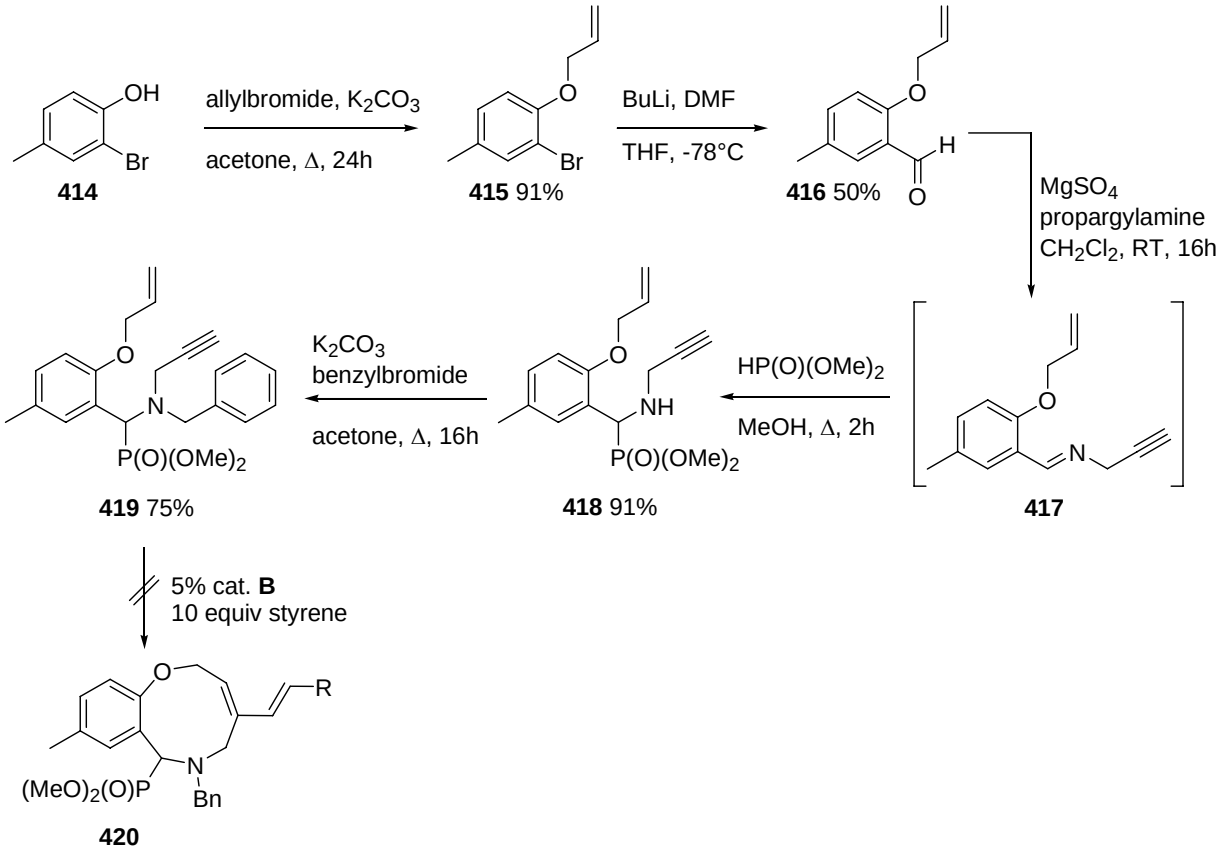
In closely related research, a very similar methodology was used for the synthesis of previously undescribed 1-phosphonylated benzazocines.[201] Thus α-aminophosphonates **412a** and **412b** were prepared and treated with the second generation Grubbs' catalyst **B** in refluxing benzene. The benzo-fused eight-membered rings **413a** and **413b** were isolated in reasonable yield.



412a **413a** **412b** **413b**

3.4.3 Attempted synthesis of other benzo-fused heterocycles by RCEYM or RCM

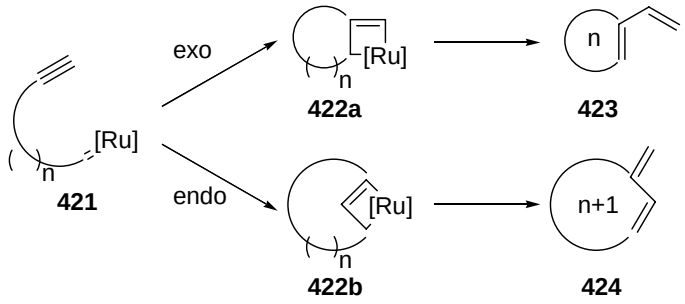
In a first pathway, phosphonylated benzoxazonines were targeted, nine-membered rings containing one oxygen and one nitrogen atom fused with an aromatic six-membered ring. In a first step, 2-bromo-4-methylphenol **414** was allylated at oxygen using allylbromide and K_2CO_3 in refluxing acetone. After a basic workup compound **415** was obtained in 91% yield. This compound was formylated with DMF after Li-halogen exchange resulting in **416** in 50% yield after column chromatography. Conversion of the aldehyde to imine **417** with propargylamine and subsequent phosphonylation gave **418** in excellent yield after acid/base extraction. Finally benzylation gave substrate **419**.



No reaction was observed when enyne **419** was treated with 10 mol% second generation catalyst **B** and 5 equivalents of styrene in refluxing CH_2Cl_2 for an overnight period. When the solvent was changed to refluxing benzene, however, almost complete consumption of the starting material was obtained after 16 hours. Unfortunately, a complex mixture was obtained which proved impossible to purify. Switching to 4-bromobutene as an alkene gave no better result. When no alkene was added, only unreacted starting material was recovered. Derivatives **420** could never be obtained.

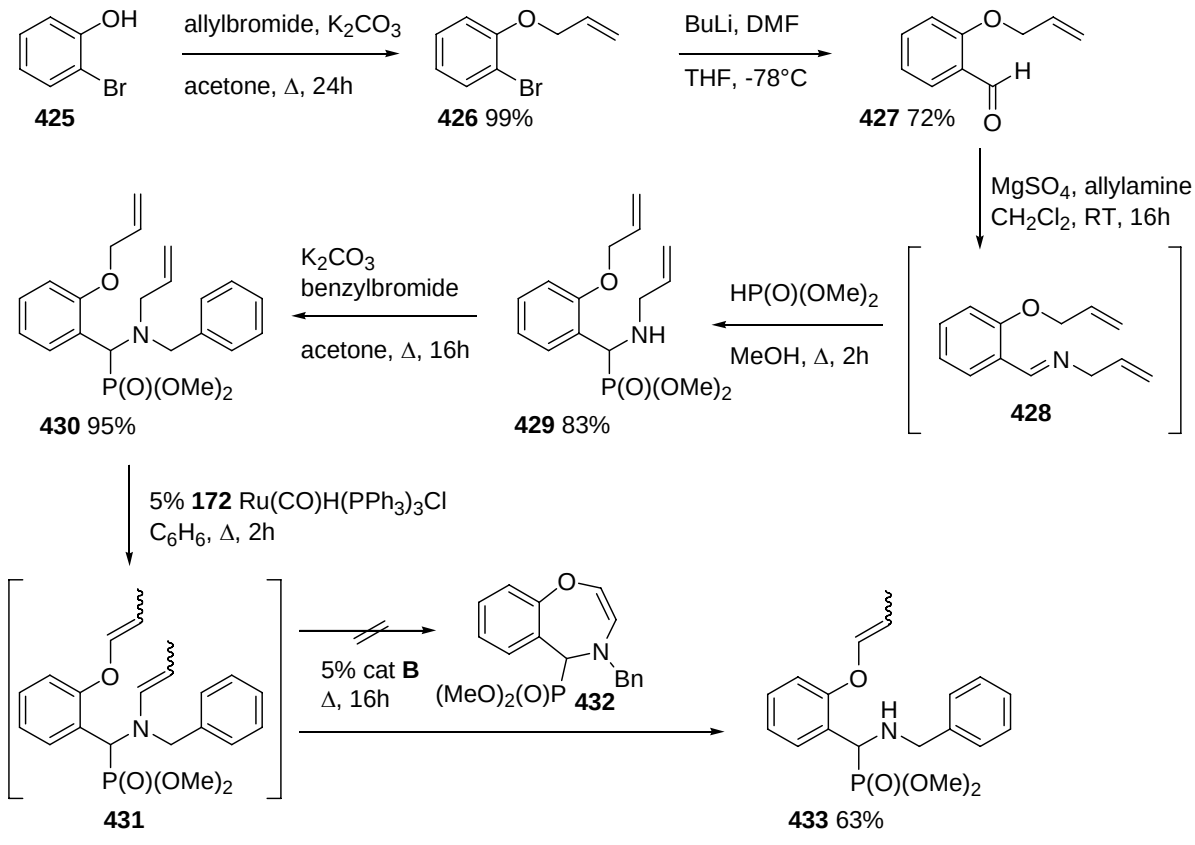
The formation of these mixtures can be explained by mechanistic work done by Hansen and Lee.[202,203] The problem with the use of RCEYM for the synthesis of macrocycles is the control of *exo* or *endo* ring-closure. The initially formed carbene **421** normally reacts in an *exo*-mode with

the formation of bicyclic intermediate **422a**. When this opens and reacts further, the expected product **423** is observed.



When n is large, however, reaction can also proceed via the *endo*-mode leading to intermediate **422b**. When this compound reacts further, another compound **424** is formed having a larger ring than expected. It is possible that in this case both the *exo* and *endo* pathways are occurring leading to the observed mixtures. Furthermore, cross-metathesis with the alkene could lead to (*E/Z*)-mixtures as was observed for derivatives **395**.

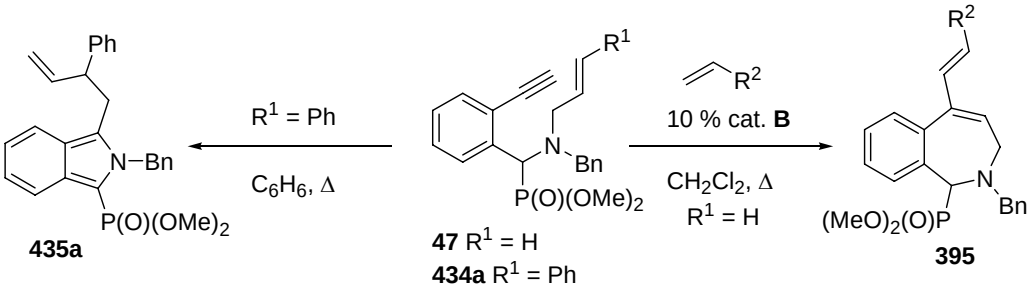
This route was abandoned and an attempt was made to obtain benzoxazepines, seven-membered rings containing one oxygen and one nitrogen atom fused with an aromatic six-membered ring, via an isomerization-RCM sequence. Compound **430**, the required substrate, was obtained in a very similar way used to synthesize **419**.



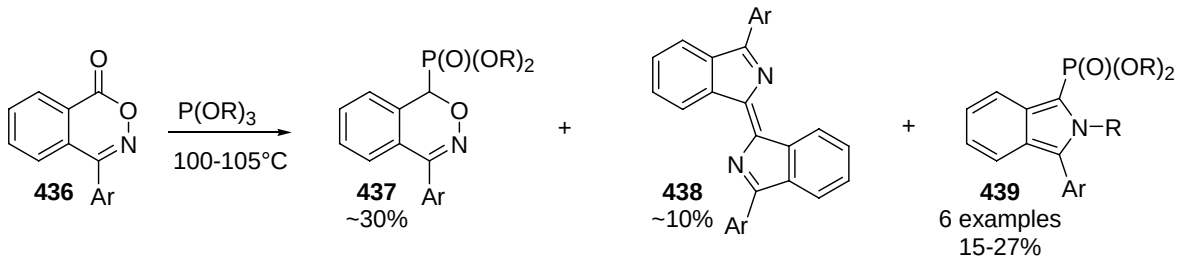
In a first step, 2-bromophenol **425** was allylated at oxygen using allylbromide and K_2CO_3 in refluxing acetone. After a basic workup compound **426** was obtained in 99% yield. This compound was formylated with DMF after Li-halogen exchange resulting in **427** in 72% yield after column chromatography. Conversion of the aldehyde to imine **428** with allylamine and subsequent phosphonylation gave **429** in excellent yield after acid/base extraction. Finally benzylation gave substrate **430**. The idea was to treat **430** with catalyst **172** in order to isomerize the double bonds and then cyclize **431** with the RCM catalyst towards the envisaged structure **432**. Unfortunately, only compound **433** could be isolated from the reaction mixture resulting from decomposition of **431**. It seems that especially the enamine is unstable. This problem might be solved by placing an electron withdrawing group on the *N*-atom, but this route was not pursued.

3.4.4 Microwave induced synthesis of phosphonylated isoindoles (Paper VIII)

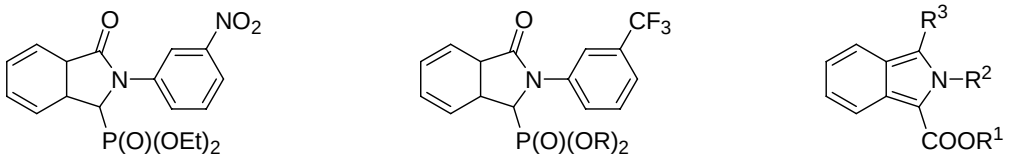
In a previous chapter, it was explained how compound **47** was used in a domino enyne metathesis—cross-metathesis with an alkene for the synthesis of benzazepines **395**. In extension of this research an enyne metathesis with a non-terminal alkene **434a** was attempted, as was very successful in paper IV. This would avoid the need of adding a great number of equivalents of alkene to the reaction mixture. It was found, however, that **434a** was quite inert towards the second generation Grubbs' catalyst, even in refluxing benzene. After two weeks of refluxing, however, spectroscopic analysis revealed the formation of a trace amount of new compound with a ^{31}P NMR shift around 15 ppm. This was recognized as a phosphorus attached to an sp^2-carbon. The trace amount was isolated and identified as isoindole **435a**.



Phosphonylated isoindoles and related compounds are rarely described in the literature. In fact, only one entry to phosphonylated isoindoles could be found from the reaction of 2,3-benzoxazin-1-ones **436** with trialkyl phosphites at high temperature. This reaction results in the formation of a mixture containing about 30% **437**, about 10% **438** and **439**. From this mixture, the isoindoles **439** could be purified in a rather low yield.[204]

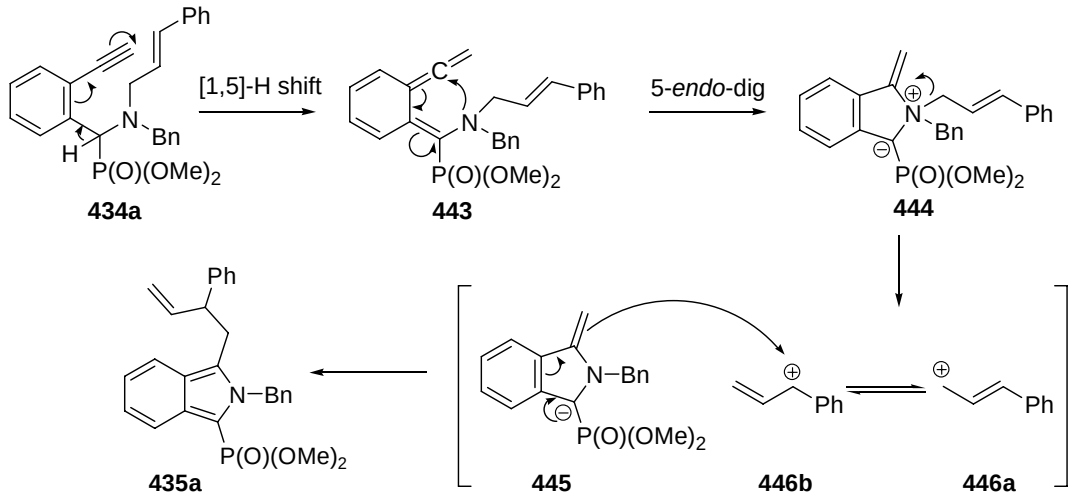


Few entries towards phosphonylated dihydro isoindoles and isoindolinones have been reported in the literature. The latter are known for their plant growth regulating properties. Compound **440** is effective against the weed cocklebur (*Xanthium pennsylvanicum* Wallr., Dutch: stekelnoot) at 56 kg/ha.[205] Compound **441** can alter some growth-related properties (like stature reduction and axillary bud development) in soybean plants at 0.35 kg/ha.[206] Isoindoles possessing an alkoxycarbonyl group, the bio-isosteric counterpart of the phosphonate, on the 1-position **442** have been patented as appetite depressants.[207]

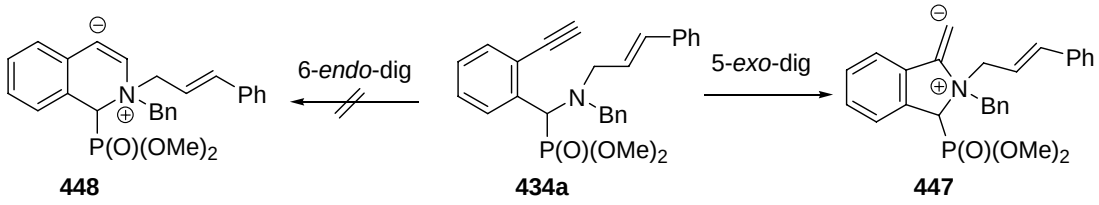


440 **441** **442**

In light of this interesting range of biological activities, an attempt was made to develop an easy protocol for the synthesis of phosphonylated isoindoles starting from compounds like **434a**. Since the transformation of **434a** to **435a** is obviously not a metathesis process, the reaction was repeated in refluxing benzene without a metal catalyst. It required several days, however, to achieve some conversion to **435a**. At first, it was thought that the reaction proceeded via a [1,5]-shift of the acidic proton in α-position of the phosphonate of **434a** followed by 5-*endo*-dig attack of the nitrogen atom onto the central allene carbon atom of **443**. The zwitterionic form **444** could then fragment into anion **445** and cations **446a** and **446b**. The anion can then react with **446b** at the phenylated position to yield **435a**. Next, the rearrangement was evaluated in CH_3CN since the formation and stability of ionic intermediates might be improved in a more polar solvent. It was found that the reaction indeed proceeds faster, but it takes still several days to obtain reasonable conversion. The first step in this sequence is assumed to be rate determining since aromaticity of the benzene ring is lost. The addition of NEt_3 to a refluxing solution of **434a** in CH_3CN, in order to facilitate the proton shift, did not result in an increased reaction rate and caused decomposition (appearance of signals in the 0-5 ppm region in the ^{31}P NMR). Also the addition of $NEt(iPr)_2$ did not result in a more efficient conversion. These observations may suggest that the reaction does not proceed via the proposed pathway.

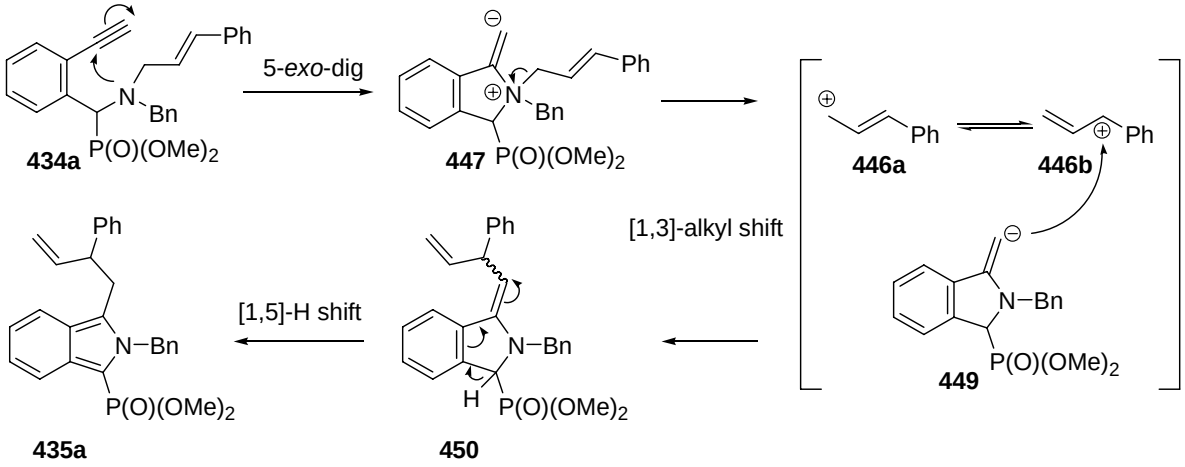


If the reaction is thermally driven, increasing the temperature should result in a faster conversion to **435a**. Unfortunately, refluxing in DMF, DMSO or NMP did not result in a clean reaction; again the appearance of signals in the 0-5 ppm region in the ^{31}P NMR was noticed. Finally a high-temperature short-time approach was evaluated using microwave technology. When using benzene, a quite apolar solvent, very slow heating was observed. Polar solvents, on the other hand, are heated very fast as their component molecules are forced to rotate with the field and lose energy in collisions. Thus it was observed that CH_3CN heats up very rapidly, but the reaction was not as clean as expected. After a number of experiments, a mixture of benzene/CH_3CN in a 1/1 ratio at 165 °C proved to be the ideal solvent system for the ring-transformation. The first step in this transformation probably involves a direct addition of the nitrogen lone pair onto the triple bond in a 5-*exo*-dig fashion to **447**. Although *endo* dig cyclizations are more favoured than *exo* dig cyclizations, in this case the *endo* cyclization would lead to a less stable secondary anion **448**. Although the anion **448** is benzylic, the electron pair resides in an sp-orbital that is perpendicular to the p-orbitals of the aromatic system. As a consequence no additional stabilization by conjugation with this aromatic system is to be expected. Indeed it is found in the literature that this kind of *exo* cyclizations are the most common pathways followed by substrates bearing terminal alkynes.[208,209]



The zwitterionic intermediate **447** subsequently fragments with formation of anion **449** and cations **446a** and **446b**. Anion **449** reacts with **446b** with formation of **450**. The overall result

of the fragmentation and recombination corresponds to a [1,3]-alkyl shift. The rearrangement ends with a [1,5]-H shift resulting in aromatization towards **435a**.



In order to prove the general nature of this rearrangement, a number of α-aminophosphonates like **434a** had to be prepared. A number of secondary amines **454a-h** were prepared by a straightforward reductive amination between suitable unsaturated aldehydes **452** and amines **451**.[210] Thus the formed imines **453** were treated with $NaBH_4$ in methanol for an overnight period and the produced secondary amines were isolated using a simple extraction. These amines were converted to the α-aminophosphonates **434a-i** using the three component coupling mediated by $LiClO_4$. Although this reaction works fine, a very difficult purification is necessary in order to remove the excess of amine. Very often column chromatography is not possible since both the aminophosphonate and the amine have a very similar R_f value. In some cases, the aminophosphonates could be crystallised from the mixture; in other cases the excess amine could be removed by washing with acidified water since the protonated aminophosphonates are poorly water soluble and remained in the organic phase. It was also observed that during the synthesis of compounds **434** sometimes some isoindole (<10%) was formed if the reaction was allowed to stir for a prolonged time, probably by activation of the triple bond by $LiClO_4$. All the synthesized α-aminophosphonates could be converted to the isoindoles by heating to 165 °C in a 1/1 mixture benzene/CH_3CN under microwave conditions. In order to assure that complete conversion occurred, a sample can be taken directly from the reaction mixture and analyzed using ^{31}P NMR. When this revealed the presence of remaining starting material, the pressure tube was put back in the microwave for an additional period of time. In every case the recombination of the anion occurs with the most stabile resonance form of the cation.

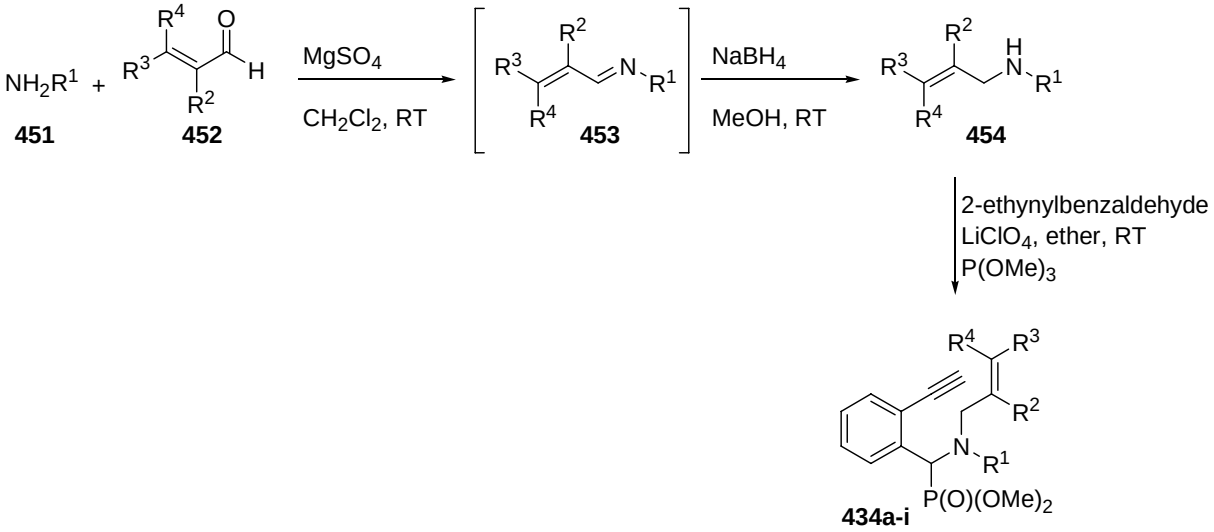


Table 26: Synthesis of secondary amines **454** and α-aminophosphonates **434**

Entry	R^1	R^2	R^3	R^4	Yield 454 (%)	Yield 434 (%)
a	Bn	H	Ph	H	98	68
b	Bn	H	H	H	99‡	68
c	Pr	H	*p*-$MeOC_6H_4$	H	97	81
d	*p*-MeBn	H	CH_3	CH_3	68	48
e	CH_2CH_2Ph	H	*i*Pr	H	86	56
f	*m*-FC_6H_4	H	H	H	94	72
g	CH_2CH_2*p*-ClPh	-$CH_2CH_2CH_2CH_2$-		H	88	59
h	Bu	CH_3	Ph	H	49	88
i	Allyl	H	H	H	-	79¥

‡ allylamine was used in combination with benzaldehyde
¥ commercially available diallylamine was used

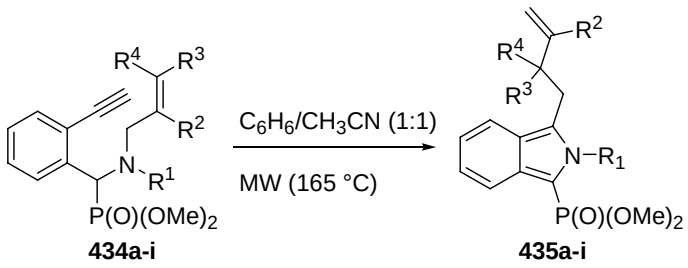
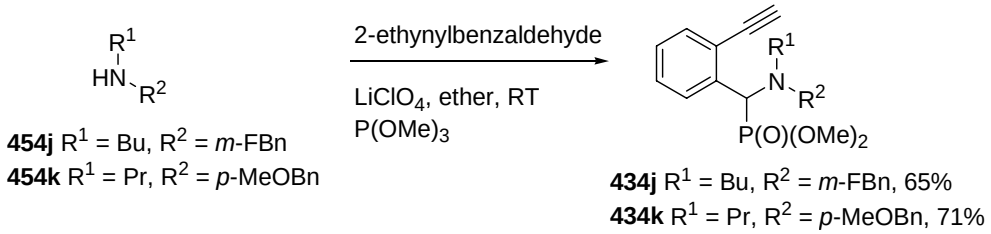


Table 27: Microwave induced rearrangement of **434** towards isoindoles **435**

Substrate	Time (min)	Yield 435a-i (%)
434a	90	82
434b	70	76
434c	90	68
434d	95	47
434e	80	71
434f	150	63
434g	180	40
434h	80	40
434i	60	98

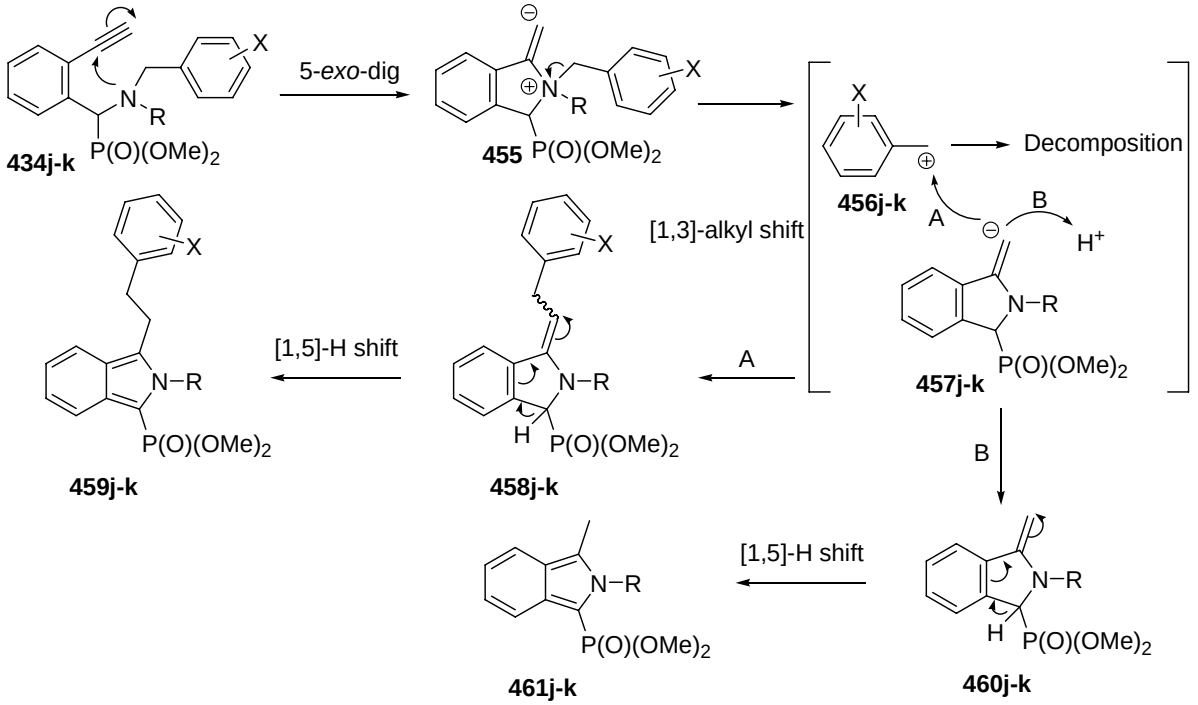
During all these rearrangements, allylic cations are formed. In order to check if this is really a prerequisite, amines **454j-k** were prepared by reductive amination from functionalized benzaldehydes and primary amines and subsequent conversion to aminophosphonates **434j-k**.



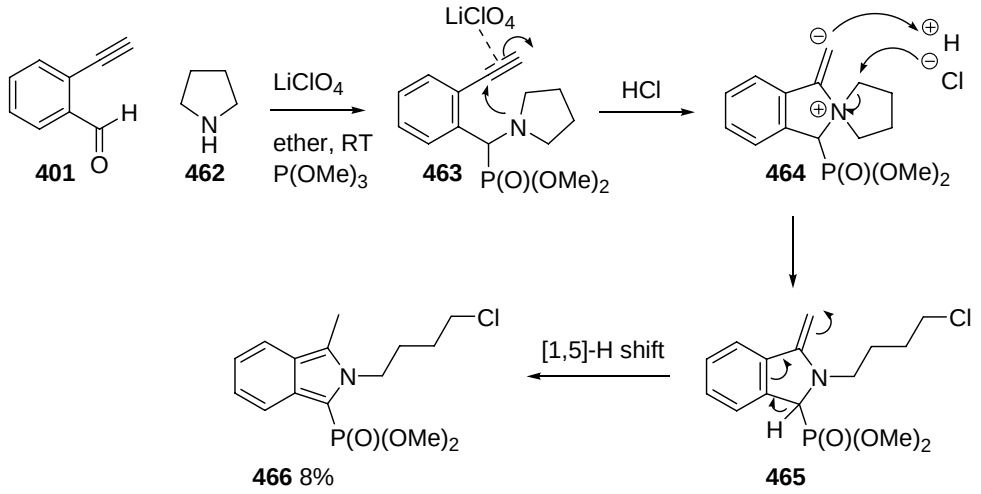
454j R^1 = Bu, R^2 = *m*-FBn
454k R^1 = Pr, R^2 = *p*-MeOBn

434j R^1 = Bu, R^2 = *m*-FBn, 65%
434k R^1 = Pr, R^2 = *p*-MeOBn, 71%

It was found that these compounds require higher temperatures in order to react. This can be explained by the necessity of forming a less stabilized benzylic cation **456** instead of an allylic cation. Furthermore, next to the expected products **459j-k** also side products were formed that were identified as **461j-k**. Normally, route A is followed in which anions **457** recombine with cations **456** and produce **459** after the proton shift. Apparently, benzylic cations **456** are not stable enough and decompose in the reaction mixture. As a consequence, there is a shortage of reaction partners for the anions **457**. These anions can then abstract a proton from a molecule of substrate or from a trace amount of water to form compounds **460** (route B). These compounds also aromatize via a [1,5]-H shift to produce the observed side products **461**. Depending on the applied time/temperature profile a different ratio of **459**/**461** is obtained. It proved impossible, however, to separate these two compounds. It should be noted that not in a single case migration of the alkyl chain was observed.



The fact that alkyl migration does not occur in combination with the observation that $LiClO_4$ can slightly activate the triple bond, allowed the 'trapping' of a zwitterionic intermediate. Thus, a mixture of 2-ethynylbenzaldehyde **401** and pyrrolidine **462** was stirred in a concentrated solution of $LiClO_4$ in ether and treated with trimethyl phosphite resulting in the formation of aminophosphonate **463**. By activation of the triple bond by $LiClO_4$, a small amount of zwitterionic compound **464** is formed. Under these conditions, this intermediate did not fragment, since a non-stabilized primary cation would have been formed. After four hours, this mixture was quenched by the addition of 3N HCl. The zwitterionic intermediate reacted with HCl producing compound **466** by aromatization of **465**. This compound could be purified by column chromatography and was obtained pure in 8% yield.



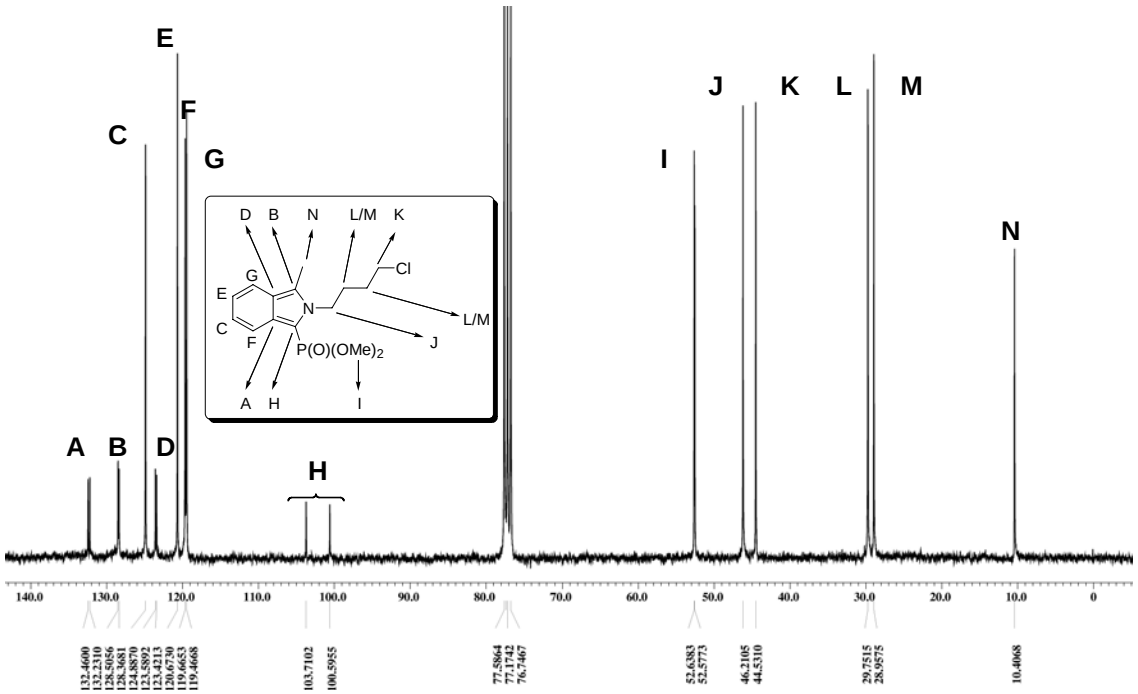
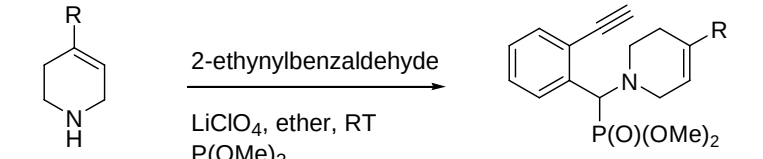


Figure **11:** ^{13}C spectrum of isoindole **466**.

Figure 11 shows the typical ^{13}C pattern displayed by these phosphonylated isoindoles. All four carbon atoms (A, B, D and H) from the five-membered ring appear as doublets as is the case for the phosphonylated pyrroles. A very large C-P coupling of about 235 Hz is observed for carbon H which is attached to the phosphonate function. A remarkable deshielding is observed for carbon C. This can probably be attributed to the 1,4-relationship with the electron withdrawing phosphonate.

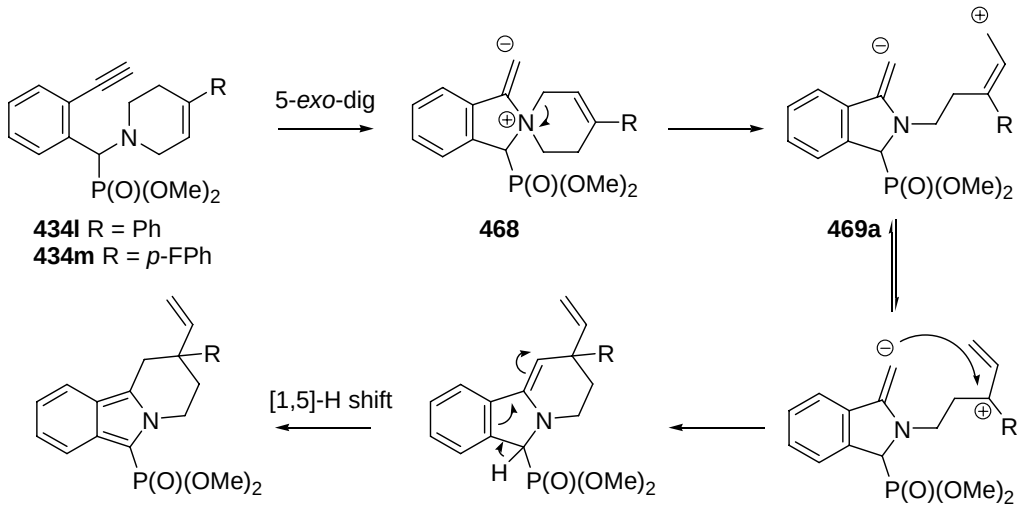
When the allylic group that migrates is incorporated in an extra ring, the anion and cation will remain attached to each other during the reaction. Thus compounds **434l-m** were easily prepared from the commercially available amines **467a-b**.



467a R = Ph
467b R = *p*-FPh

434l R = Ph, 75%
434m R = *p*-FPh, 62%

As expected, heating **434l-m** under microwave conditions resulted in the formation of tricyclic compounds **471a-b**. The fragmentation of the zwitterionic intermediate **468** results in the formation of **469a** and resonance form **469b**. An intramolecular attack forms an additional six-membered ring **470**. Finally, aromatization produces isoindoles **471a-b**.



434l R = Ph
434m R = *p*-FPh

468

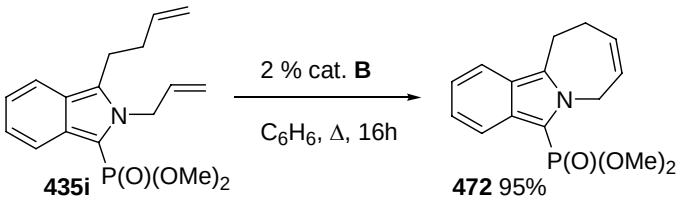
469a

469b

470

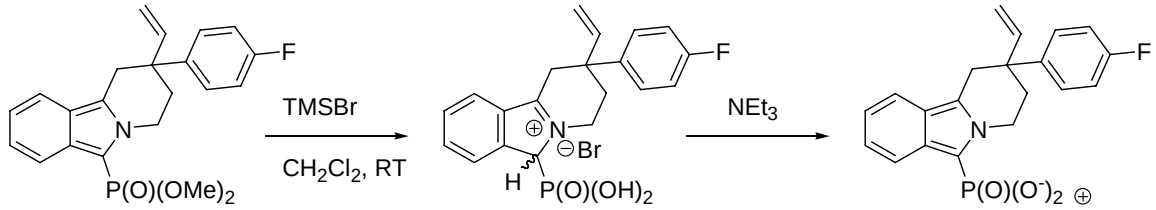
471a R = Ph, 68%
471b R = *p*-FPh, 82%

Derivative **435i** proved to be an excellent substrate for ring-closing metathesis. It was converted to azepino isoindole **472** in high yield by treatment with 2 mol% second generation catalyst **B** in refluxing benzene.



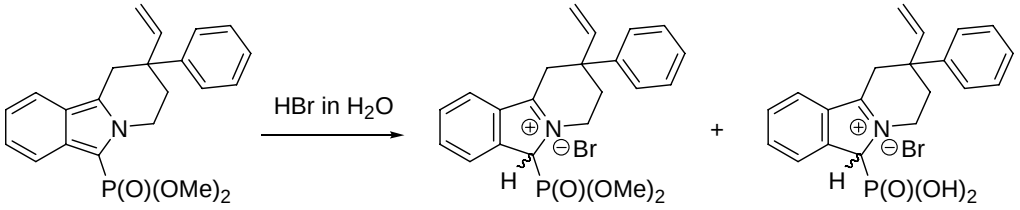
435i **472** 95%

Some attempts were made to convert the phosphonates to the free phosphonic acids. Thus compound **471b** was treated with 3 equivalents of TMSBr in dry dichloromethane. After 1 hour, water was added and all solvents were removed. Analysis by ^{31}P NMR revealed the formation of a 1:1 mixture of two compounds. At first it was thought that the starting material was only partially deprotected. The same mixture was obtained, however, when the reaction was repeated with 5, 10 or 15 equivalents of TMSBr. Possibly, a diasteriomeric isoindolium salt **473** is formed during this reaction. Unfortunately, due to the poor solubility of this compound, no complete spectroscopic analysis could be performed. The hypothesis of the formation of this diastereomeric salt is supported by the fact that the multiplicity disappears upon addition of NEt_3. The presumably formed salt **474**, however, could also not be fully characterized due to its insolubility in a variety of solvents.



471b **473** **474**

Further evidence for the formation of a isoindolium salt was obtained by treating **471a** with 4 equivalents HBr in H_2O (33% w/w). After stirring for 10 minutes at room temperature, the volatiles were removed and the ^{31}P NMR showed the presence of four compounds which were tentatively identified as diastereomers **475** and diastereomers **476**. If the compound was stirred for 2 hours in the presence of HBr, complete conversion to **476** was obtained. Also in this case, however, a practically insoluble compound was obtained.



471a **475** **476**

3.4.5 Conclusion

In the third and final part of this thesis two new entries to benzo-fused azaheterocyclic phosphonates have been developed. The first protocol uses a combination of enyne-metathesis with cross-metathesis and leads to phosponylated benzazepines. The advantage of this strategy is that it required the synthesis of only two substrates, with a terminal double and triple bond, that depending on the addition of a certain alkene to the reaction mixture are transformed into different seven-membered rings. The treatment of very similar substrates containing a non-terminal double bond with a metathesis catalyst did not lead to the expected seven-membered rings but produced phosphonylated isoindoles instead. This thermally driven rearrangement starts with an attack of a tertiary nitrogen on a non-activated carbon-carbon triple bond in a 5-*exo*-dig fashion, followed by a [1,3]-alkyl shift with eventual aromatization. This pathway represents the first high yielding entry to phosphonylated isoindoles. The same strategy could also be used for the synthesis of compounds containing an additional six- or seven-membered ring.

4 Supplementary Experimental Part

4.1 General methods

4.1.1 NMR spectroscopy

High resolution ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were run on a Jeol JNM-EX 300 NMR. Peak assignments were obtained with the aid of DEPT, HSQC, COSY, DQFCOSY, HMBC spectra. The compounds were diluted in deuterated solvents and the used solvent is indicated for each compound. As internal standard tetramethylsilane (TMS) was used. Multiplicities are described by using the following abbreviation: s = singlet, d = doublet, t = triplet, q = quadruplet, p = pentuplet, m = multiplet, br = broad, ps = pseudo.

4.1.2 Mass spectroscopy

Low resolution mass spectra were recorded on an Agilent 1100 Series VS mass spectrometer using a direct inlet system (ES, 4000V). Some volatile samples were recorded on a HP 6890 GC coupled with a HP 5973 MSD (Mass selective detector; quadrupole). High resolution mass spectra were recorded on a Finnigan MAT 95 XP-API-GC-Trap tandem mass spectrometer system.

4.1.3 Infrared spectroscopy

IR spectra were obtained from a Perkin Elmer Spectrum One infrared spectrometer. For liquid samples the spectra were collected by preparing a thin film of compound between two sodium chloride plates. The crystalline compounds were mixed with potassium bromide and pressed until a transparent potassium bromide plate was obtained.

4.1.4 Melting point

Melting points of crystalline compounds were measured with a Büchi 540 apparatus.

4.1.5 Column chromatography

The purification of reaction mixtures was performed by column chromatography using a glass column with silica gel (particle size 0.035-0.070 mm, pore diameter ca. 6 nm). Solvent systems were determined via initial TLC analysis (Merck Kieselgel $60F_{254}$, precoated 0.25 mm). As detection methods UV light, adsorption with iodine vapours or colouring with $KMnO_4$ was used.

4.1.6 Dry solvents

Diethyl ether, tetrahydrofuran and toluene were distilled from sodium and sodium benzophenone ketyl, while dichloromethane was distilled from calcium hydride before use. Methanol was

refluxed in the presence of magnesium metal for two hours, then distilled and kept over molecular sieves.

4.1.7 Microwave reactions

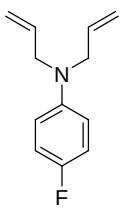
All microwave reactions were performed in the *CEM Focused Microwave™ Synthesis System, Model Discover*, with a selectable power output from 0-300 watts. The reactions were performed in 10 ml thick walled Pyrex reaction vessels closed with a Septa cap and equiped with a small stirring bar. The temperature control system uses a non-contact infrared sensor to measure temperature on the bottom of the vessel and is used in a feedback loop with the on-board computer to regulate the temperature from 25-250 °C by adjusting the power output (1 watt increments). The pressure control, *IntelliVent™ Pressure Control System*, uses an indirect measurement of the pressure by sensing changes in the external deflection of the septa on the top of the sealed pressure vessel. Stirring is performed by a rotating magnetic plate located below the floor of the microwave cavity. Cooling of the vessel after the reaction is performed by a stream of clean air onto the vessel which decreases the temperature of a 2 ml solution from ~150 °C to ~40 °C in less then 120 seconds. A ramp time of maximum 5 minutes is used during which the temperature increases from RT to the desired temperature. This temperature is maintained during the course of the reaction for the indicated time.

4.2 Synthesis of diallylamines

4.2.1 Alkylation of amines using allylbromide

Amines **2a-h** were prepared by alkylation of the corresponding amines with allylbromide. To a solution of 20 mmol amine in 100 ml CH_3CN was added 50 mmol allylbromide and 70 mmol NEt_3. This mixture was refluxed until TLC analysis showed complete consumption of the starting material. After cooling this mixture was poured into a separation funnel containing 150 ml $NaHCO_3$ (aq, sat). This mixture was extracted three times with 50 ml ethyl acetate and dried with $MgSO_4$. After removal of the volatiles an additional purification using column chromatography was sometimes necessary.

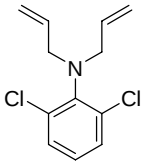
N,N-diallyl-4-fluoroaniline (2a)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.86-3.88 (m, 4H, 2 x NCH_2), 5.13-5.20 (m, 4H, m, 2 x HC=C$\underline{H}_2$), 5.77-5.89 (m, 2H, 2 x $\underline{H}C=CH_2$), 6.59-6.65 (m, 2H, CH_{arom}), 6.84-6.92 (m, 2H CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 55.54 (2 x NCH_2), 113.73 (d, *J* = 7 Hz, CH_{arom}), 115.54 (d, *J* = 22 Hz, CH_{arom}), 116.3 (2 x HC=$\underline{C}H_2$), 134.2 (2 x H$\underline{C}$=CH_2), 145.6 ($NC_{q,arom}$), 155,46 (d, *J* = 235 Hz, $FC_{q,arom}$). **^{19}F-NMR (282 MHz, $CDCl_3$) δ:** -

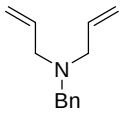
129.2 **IR (cm^{-1}) ν_{max}:** 1513. **MS: m/z (%):** 191 (M^+,100), 164 (97), 148 (42), 122 (63), 95 (45), 75 (13), 41 (26). **Yield:** 95%.

N,N-diallyl-2,6-dichloroaniline (2b)



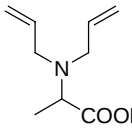
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.74-3.77 (m, 4H, 2 x NCH_2), 5.00-5.20 (m, 4H, 2 x HC=C$\underline{H}_2$), 5.80-5.93 (m, 2H, 2 x $\underline{H}C=CH_2$), 6.98 (dd, *J* = 3.0 Hz, *J* = 7.7 Hz, 1H, CHC$\underline{H}$CH), 7.25-7.27 (m, 2H, C$\underline{H}$CHC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 55.37 (2 x N$\underline{C}H_2$), 116.87 (2 x HCH=$\underline{C}H_2$), 126,38 (CH_{arom}), 129.00 (CH_{arom}), 136.09 (2 x H$\underline{C}$=CH_2), 136,72 ($C_{q,arom}$), 144.72 ($C_{q,arom}$). **IR (cm^{-1}) ν_{max}:** 1641. **MS: m/z (%):** 245/243/241 (M^+,41), 214 (45), 206 (100), 171,9 (49), 164 (45). **Yield:** 92%.

Diallyl benzylamine (2c)



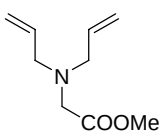
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.10 (dt, *J* = 6.4 Hz, *J* = 1.2 Hz, 4H, 2 x NC$\underline{H}_2$CH), 3.60 (s, 2H, NCH_2Ph), 5.06-5.28 (m, 4H, 2 x HC=C$\underline{H}_2$), 5.91 (ddt, *J* = 6.4 Hz, *J* = 10.3 Hz, *J* = 16.9 Hz, 2H, 2 x $\underline{H}C=CH_2$), 6.98-7.27 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 56.46 (2 x N$\underline{C}H_2$CH), 57.59 (NCH_2Ph), 117.75 (2 x HC=$\underline{C}H_2$), 127,01 (CH_{arom}), 128.31 (2 x CH_{arom}), 129.08 (2 x CH_{arom}), 135,72 (2 x H$\underline{C}$=CH_2), 139.21 ($C_{q,arom}$). **IR (cm^{-1}) ν_{max}:** 1643 (C=C). **MS: m/z (%):** 187 (M^+,100), 91 (49). **Yield:** 99%.

Ethyl 2-(diallylamino)propanoate (2d)



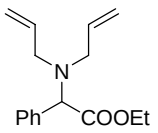
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.27 (d, *J* = 7.2 Hz, 3H, C$\underline{H}_3$CH), 1.28 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 3.14 (dd, *J* = 7.0 Hz, *J* = 14.4 Hz, 2H, 2 x NC$\underline{H}_A\underline{H}_B$), 3.27 (ddt, *J* = 1.4 Hz, *J* = 5.5 Hz, *J* = 14.4 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 3.58 (q, *J* = 7.2 Hz, 1H, C$\underline{H}CH_3$), 4.08-4.23 (m, 2H, C$\underline{H}_2CH_3$), 5.09-5.23 (m, 4H, 2 x HC=C$\underline{H}_2$), 5.75-5.88 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.35 (CH_3), 14.88 (CH_3), 53.49 (2 x NCH_2), 57.23 ($\underline{C}H_2CH_3$), 60.04 ($\underline{C}HCH_3$), 116.95 (2 x HC=$\underline{C}H_2$), 136.55 (2 x H$\underline{C}$=CH_2), 173.78 (C=O). **IR (cm^{-1}) ν_{max}:** 1732 (C=O), 1643 (C=C). **MS: m/z (%):** no M^+, 156 (9), 124 (100), 41 (17). **Chromatography:** EtOAc (100) R_f = 0.65. **Yield:** 99%.

Methyl diallylamino acetate (2e)



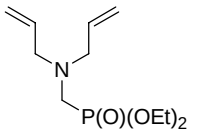
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.24 (d, *J* = 6.6 Hz, 4H, 2 x NC$\underline{H}_2$CH), 3.32 (s, 2H, NC$\underline{H}_2$COOMe), 3.69 (s, 3H, CH_3), 5.13-5.24 (m, 4H, 2 x HC=C$\underline{H}_2$), 5.86 (ddt, *J* = 6.6 Hz, *J* = 10.2 Hz, *J* = 17.2 Hz, 2H, 2 x $\underline{H}C=CH_2$), 6.98-7.27 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 51.39 (N$\underline{C}H_2$COOMe), 57.27 (2 x N$\underline{C}H_2$CH), 118.20 (2 x HC=$\underline{C}H_2$), 135,24 (2 x H$\underline{C}$=CH_2), 171.75 (C=O). **IR (cm^{-1}) ν_{max}:** 1643 (C=C), 1741 (C=O). **MS: m/z (%):** 169 (M^+, 0.6), 110 (M^+-COOMe, 100). **Chromatography:** Hex/EtOAc (70/30) R_f = 0.34. **Yield:** 88%.

Ethyl diallylaminophenylacetate (2f)



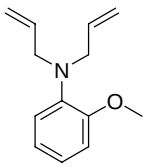
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 3.22 (d, *J* = 6.3 Hz, 4H, 2 x NCH_2), 4.11-4.29 (m, 2H, $C\underline{H}_2CH_3$), 4.59 (s, 1H, CHPh), 5.11-5.20 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.76-5.90 (m, 2H, 2 x $\underline{H}C=CH_2$), 7.26-7.43 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 ($CH_2\underline{C}H_3$), 53.19 (NCH_2), 60.23 ($\underline{C}H_2CH_3$), 67.50 (CHPh), 117.34 (2 x $HC=\underline{C}H_2$), 127.84 (CH_{arom}), 128.34 (CH_{arom}), 128.63 (CH_{arom}), 135.78 (2 x $H\underline{C}=CH_2$), 137.00 ($C_{q,arom}$), 171.72 (C=O). **IR (cm^{-1}) ν_{max}:** 1736 (C=O), 1642 (C=C). **MS: m/z (%):** no M^+, 186 (100), 104 (7), 91 (9), 41 (12). **Yield:** 82%.

Diethyl diallylaminomethylphosphonate (2g)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (t, *J* = 7.1 Hz, 3H, $CH_2\underline{C}H_3$), 1.33 (t, *J* = 6.9 Hz, 3H, $CH_2C\underline{H}_3$), 2.87 (d, *J* = 10.9 Hz, 2H, $NC\underline{H}_2P(O)(OEt)_2$), 3.25 (d, *J* = 6.3 Hz, 4H, 2 x $NC\underline{H}_2CH$), 4.06-4.20 (m, 4H, 2 x $C\underline{H}_2CH_3$), 5.17-5.23 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.76-5.96 (m, 2H, 2 x $\underline{H}C=CH_2$), 6.98-7.27 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 16.50 (d, *J* = 4.8 Hz, 2 x $CH_2\underline{C}H_3$), 48.19 (d, *J* = 163.6 Hz, $N\underline{C}H_2P(O)(OEt)_2$), 58.09 (d, *J* = 7.3 Hz, 2 x $N\underline{C}H_2CH$), 61.90 (d, *J* = 3.6 Hz, 2 x $\underline{C}H_2CH_3$), 118.17 (d, *J* = 7.3 Hz, 2 x $HC=\underline{C}H_2$), 135,04 (2 x $H\underline{C}=CH_2$), 171.75 (C=O). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 26.35. **IR (cm^{-1}) ν_{max}:** 1030 (P-O), 1260 (P=O), 1643 (C=C). **MS: m/z (%):** 247 (M^+, 3), 110 (M^+-$P(O)(OEt)_2$, 100). **Chromatography:** Hex/EtOAc (30/70) R_f = 0.30. **Yield:** 47%.

N,N-diallyl-N-(2-methoxyphenyl)amine (2h)



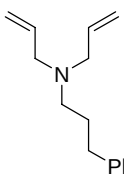
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.75 (dd, *J* = 1.1 Hz, *J* = 6.4 Hz, 4H, 2 x NCH_2), 3.87 (s, 3H, OCH_3), 5.09-5.19 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.82 (ddt, *J* = 6.4 Hz, *J* = 10.2 Hz, *J* = 17.1 Hz, 2H, 2 x $\underline{H}C=CH_2$), 6.84-6.99 (m, 4H, CH_{arom}).). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 54.67 (2 x NCH_2), 55.48 (OCH_3), 111.83 (CH_{arom}), 117.22 (2 x $HC=\underline{C}H_2$), 117.33 (CH_{arom}), 120.76 (CH_{arom}), 121.31 (CH_{arom}), 122.63 (CH_{arom}), 135.61 (2 x $H\underline{C}=CH_2$), 139.85 (C_{arom}), 153.59 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1594, 1642. **MS: m/z (%):** 203 (M^+,100), 176 (53), 162 (47), 134 (35). **Chromatography:** Hex/EtOAc (95/5) R_f = 0.28. **Yield:** 98%.

4.2.2 Alkylation of diallylamine

Amines **2i-k** were prepared by alkylation of commercially available diallylamine with electrophiles. To a solution of 30 mmol diallylamine in 100 ml CH_3CN was added 10 mmol electrophile and 30 mmol NEt_3. This mixture was refluxed until TLC analysis showed complete consumption of the starting material. After cooling this mixture was poured into a separation funnel containing 150 ml $NaHCO_3$ (aq, sat). This mixture was extracted three times with 50 ml

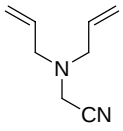
ethyl acetate and dried with $MgSO_4$. After removal of the volatiles an additional purification using column chromatography was sometimes necessary.

N-allyl-N-(3-phenylpropyl)-2-propen-1-amine (2i)



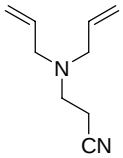
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.55-1.70 (m, 2H, $NCH_2C\underline{H}_2$), 2.45-2.51 (m, 2H, $NC\underline{H}_2CH_2$), 2.58-2.63 (m, 2H, $C\underline{H}_2Ph$), 3.07-3.10 (m, 4H, 2 x $NC\underline{H}_2CH$), 5.09-5.19 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.78-5.92 (m, 2H, 2 x $\underline{H}C=CH_2$), 7.14-7.30 (m, 5H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 28.87 ($NC\underline{H}_2CH_2$), 33.80 ($NCH_2C\underline{H}_2$), 52.93 ($\underline{C}H_2Ph$), 56.93 (2 x $NC\underline{H}_2CH$), 117.54 (2 x $HC=\underline{C}H_2$), 125.85 (CH_{arom}), 128.41 (CH_{arom}), 128.52 (CH_{arom}), 135.75 (2 x $H\underline{C}=CH_2$), 142.45 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1642. **MS: m/z (%):** 215 (M^+,3), 110 (100), 91 (13), 41 (14). **Yield:** 75%.

(Diallylamino)acetonitrile (2j)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.17 (d, *J* = 6.6 Hz, 4H, 2 x $NC\underline{H}_2CH$), 3.56 (s, 2H, NCH_2CN), 5.22-5.36 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.72-5.85 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 40.73 ($N\underline{C}H_2CN$), 57.02 (2 x $N\underline{C}H_2CH$), 114.60 (CN), 119.31 (2 x $HC=\underline{C}H_2$), 134.14 (2 x $H\underline{C}=CH_2$). **IR (cm^{-1}) ν_{max}:** 1644 (C=C), 2232 (CN). **MS: m/z (%):** 136 (M^+, 32), 135 (11), 121 (22), 109 (97), 107 (30), 96 (31), 95 (39), 68 (59), 67 (25), 42 (100), 41 (94). **Chromatography:** Hex/EtOAc (1/1) R_f = 0.52. **Yield:** 94%.

3-(Diallylamino)propanenitrile (2k)

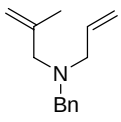


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.45 (t, *J* = 7.0 Hz, 2H, CH_2CN), 2.80 (t, *J* = 7.0 Hz, 2H, $NC\underline{H}_2CH_2$), 3.14 (dt, *J* = 1.2 Hz, *J* = 6.6 Hz, 4H, 2 x $NC\underline{H}_2CH$), 5.15-5.25 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.77-5.91 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 16.27 ($\underline{C}H_2CN$), 48.39 ($N\underline{C}H_2CH_2$), 56.64 (2 x $N\underline{C}H_2CH$), 117.73 (2 x $HC=\underline{C}H_2$), 118.96 (CN), 135.24 (2 x $\underline{H}C=CH_2$). **IR (cm^{-1}) ν_{max}:** 1643 (C=C), 2249 (CN). **MS: m/z (%):** 150 (M^+, 4), 123 (10), 110 (100), 81 (9), 68 (10), 42 (11), 41 (40). **Yield:** 74%.

4.2.3 Alkylation of allylbenzylamine

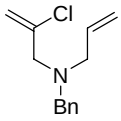
Amines **2l-q** were prepared by alkylation of allylbenzylamine or methyl *N*-allylglycine with electrophiles. To a solution of 30 mmol secondary amine in 100 ml CH_3CN was added 33 mmol electrophile and 45 mmol NEt_3. This mixture was refluxed until TLC analysis showed complete consumption of the starting material. After cooling this mixture was poured into a separation funnel containing 150 ml $NaHCO_3$ (aq, sat). This mixture was extracted three times with 50 ml ethyl acetate and dried with $MgSO_4$. After removal of the volatiles an additional purification using column chromatography was sometimes necessary.

N-allyl-N-benzyl-2-methyl-2-propen-1-amine (2l)



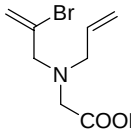
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.76 (s, 3H, CH_3), 2.93 (s, 2H, NCH_2C), 3.01 (dd, *J* = 1.1 Hz, *J* = 6.2 Hz, 2H, $NC\underline{H}_2CH$), 3.53 (s, 2H, CH_2Ph), 4.85 (d, *J* = 0.8 Hz, 1H, $C=C\underline{H}_A\underline{H}_B$), 4.94 (d, *J* = 0.8 Hz, 1H, $C=CH_A\underline{H}_B$), 5.11-5.23 (m, 2H, $HC=C\underline{H}_2$), 5.81-5.94 (m, 1H, $\underline{H}C=CH_2$), 7.20-7.36 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 20.93 (CH_3), 56.46 (NCH_2CH), 57.88 ($\underline{C}H_2Ph$), 60.67 ($N\underline{C}H_2C$), 112.72 ($C=\underline{C}H_2$), 117.18 ($HC=\underline{C}H_2$), 126.84 (CH_{arom}), 128.29 (CH_{arom}), 128.81 (CH_{arom}), 136.29 ($H\underline{C}=CH_2$), 140.06 ($C_{q,arom}$), 144.12 (C_q). **IR (cm^{-1}) ν_{max}:** 1644 (C=C), 1698 (C=C). **MS: m/z (%):** 201 (M^+, 18), 160 (70), 91 (100). **Chromatography:** Hex/EtOAc (95/5) R_f = 0.23. **Yield:** 92%.

N-allyl-N-benzyl-2-chloro-2-propen-1-amine (2m)



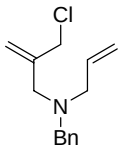
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.13 (d, *J* = 6.1 Hz, 2H, $NC\underline{H}_2CH$), 3.22 (s, 2H, NCH_2C), 3.65 (s, 2H, $NC\underline{H}_2Ph$), 5.15-5.26 (m, 2H, $HC=C\underline{H}_2$), 5.34 (s, 1H, $ClC=C\underline{H}_A\underline{H}_B$), 5.48 (s, 1H, $ClC=CH_A\underline{H}_B$), 5.80-5.94 (m, 1H, $\underline{H}C=CH_2$), 7.22-7.37 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 56.33 (NCH_2), 57.63 ($N\underline{C}H_2Ph$), 59.75 ($N\underline{C}H_2CCl$), 113.96 ($ClC=\underline{C}H_2$), 117.89 ($HC=\underline{C}H_2$), 127.21 (CH_{arom}), 128.48 (CH_{arom}), 128.87 (CH_{arom}), 135.54 ($H\underline{C}=CH_2$), 139.87 (C_{arom} or CCl), 140.44 (C_{arom} or CCl). **IR (cm^{-1}) ν_{max}:** 1635 (C=C). **MS: m/z (%):** 222.2/224.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (95/5) R_f = 0.23. **Yield:** 79%.

Methyl [allyl(2-bromo-2-propenyl)amino]acetate (2n)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.34 (dt, *J* = 1.2 Hz, *J* = 6.6 Hz, 2H, $NC\underline{H}_2CH$), 3.45 (s, 2H, $C\underline{H}_2COOMe$), 3.52 (s, 2H, $NC\underline{H}_2CBr$), 3.70 (s, 3H, CH_3), 5.14-5.26 (m, 2H, $HC=C\underline{H}_2$), 5.58 (dd, *J* = 0.8 Hz, *J* = 1.4 Hz, 1H, $BrC=C\underline{H}_A\underline{H}_B$), 5.78-5.91 (m, 1H, $\underline{H}C=CH_2$), 5.90 (dd, *J* = 1.4 Hz, *J* = 2.8 Hz, 1H, $BrC=CH_A\underline{H}_B$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 51.43 (CH_3), 53.11 ($N\underline{C}H_2COOMe$), 56.58 (NCH_2CH), 61.52 ($N\underline{C}H_2CBr$), 118.18 ($HC=\underline{C}H_2$), 118.69 ($CBr\underline{C}H_2$), 131.57 (CBr), 135.35 ($H\underline{C}=CH_2$), 171.70 (C=O). **IR (cm^{-1}) ν_{max}:** 1629 (br. C=C), 1741 (br. C=O). **MS: m/z (%):** no M^+, 188/190 (100, M^+-COOMe), 128 (48), 41 (35). **Chromatography:** Hex/EtOAc (7/3) R_f = 0.66. **Yield:** 80%.

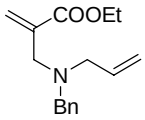
N-allyl-N-benzyl-N-[2-(chloromethyl)prop-2-enyl]amine (2o)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.98-3.05 (m, 2H, $NC\underline{H}_2CH$), 3.13 (s, 2H, $NC\underline{H}_2C$), 3.54 (d, *J* = 10.7 Hz, 1H, $NC\underline{H}_A\underline{H}_BPh$), 3.54 (d, *J* = 10.7 Hz, 1H, $NCH_A\underline{H}_VPh$), 4.13 (s, 2H, CH_2Cl), 5.10-5.27 (m, 4H, $HC=C\underline{H}_2$ + $C=C\underline{H}_2$), 5.80-5.94 (m, 1H, $\underline{H}C=CH_2$), 7.22-7.39 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 46.30 (CH_2Cl), 56.53 (NCH_2), 56.57 (NCH_2), 58.09 (NCH_2), 117.12 ($HC=\underline{C}H_2$), 117.83 ($C=\underline{C}H_2$), 128.43 (CH_{arom}), 128.57 (CH_{arom}), 128.99 (CH_{arom}), 135.88 ($H\underline{C}=CH_2$), 139.54 ($\underline{C}=CH_2$), 143.83 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1644 (C=C). **MS:**

m/z (%): 237 (M^+, 3), 235 (M^+, 10), 200 (28), 160 (60), 91 (100). **Chromatography:** Hex/EtOAc (8/2) R_f = 0.77. **Yield:** 68%.

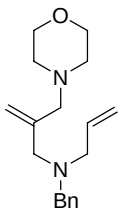
Ethyl 2-{[allyl(benzyl)amino)]methyl}acrylate (2p)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (dt, *J* = 1.7 Hz, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 3.04 (dd, *J* = 1.0 Hz, *J* = 6.2 Hz, 2H, $NC\underline{H}_2CH$), 3.33 (s, 2H, $NC\underline{H}_2C$), 3.57 (s, 2H, $C\underline{H}_2Ph$), 4.17 (dq, *J* = 1.4 Hz, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 5.09-5.21 (m, 2H, $HC=C\underline{H}_2$), 5.78-5.91 (m, 2H, $\underline{H}C=CH_2$ + $C=C\underline{H}_aH_b$), 6.23 (dd, *J* = 1 Hz, *J* = 2.1 Hz, 1H, $C=CH_a\underline{H}_b$), 7.18-7.36 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.32 ($COOCH_2\underline{C}H_3$), 53.89 ($N\underline{C}H_2C$), 56.64 ($N\underline{C}H_2CH$), 57.98 ($\underline{C}H_2Ph$), 60.62 ($COO\underline{C}H_2CH_3$), 117.36 ($HC=\underline{C}H_2$), 125.76 ($C=\underline{C}H_2$), 126.95 (CH_{arom}), 128.29 (CH_{arom}), 128.64 (CH_{arom}), 135.83 ($H\underline{C}=CH_2$), 138.67 (C_{arom}), 139.56 ($\underline{C}=CH_2$), 167.09 (C=O). **IR (cm^{-1}) ν_{max}:** 1717 (C=O), 1640 (C=C). **MS: m/z (%):** 259 (M^+, 1), 218 (16), 168 (83), 160 (17), 146 (28), 122 (19), 91 (100). **Chromatography:** Hex/EtOAc (95/5) R_f = 0.29. **Yield:** 82%.

N-allyl-N-benzyl-N-[2-(morholin-4-ylmethyl)prop-2-enyl]amine (2q)

Compound **2o** (0.32 g, 1.36 mmol) is dissolved into CH_3CN (10 ml), morpholine (0.35 g, 4.08 mmol) is added and the mixture is refluxed until TLC analysis showed that all starting material was consumed. The mixture is cooled and aqueous $NaHCO_3$ (15 ml) is added. The mixture is extracted with EtOAc, and the organics are dried ($MgSO_4$) and filtered. The solvent is removed *in vacuo*, and the residue is purified by column chromatography. The compound was obtained in 75% yield.



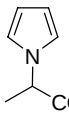
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.35 (t, *J* = 4.6 Hz, 4H, 2 x $NCH_{2morph.}$), 2.93 (s, 2H, NCH_2C), 3.00 (s, 2H, NCH_2C), 3.01-3.03 (m, 2H, $NC\underline{H}_2CH$), 3.53 (s, 2H, $NC\underline{H}_2Ph$), 3.63 (t, *J* = 4.6 Hz, 4H, 2 x OCH_2), 5.05-5.29 (m, 4H, $HC=\underline{C}H_2$ + $C=C\underline{H}_2$), 5.80-5.94 (m, 1H, $\underline{H}C=CH_2$), 7.19-7.35 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 53.77 (2x $NCH_{2morph.}$), 56.61 (NCH_2), 57.48 (NCH_2), 58.09 (NCH_2), 62.41 (NCH_2), 67.22 (2x CH_2O), 114.90 ($C=\underline{C}H_2$), 117.07 ($HC=\underline{C}H_2$), 126.81 (CH_{arom}),128.22 (CH_{arom}),128.78 (CH_{arom}), 136.26 ($H\underline{C}=CH_2$), 139.99 ($C_{q.arom}$), 144.00 ($\underline{C}=CH_2$). **IR (cm^{-1}) ν_{max}:** 1651 (C=C). **MS: m/z (%):** 287 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (8/2) R_f = 0.32. **Yield:** 75%.

4.3 Synthesis of pyrroles using the $RuCl_3$ or the TCQ method

The general procedure for the synthesis of pyrroles using a combination of the second generation Grubbs' catalyst and $RuCl_3$ is presented in paper I. The general procedure for the synthesis of pyrroles using a combination of the second generation Grubbs' catalyst and TCQ is presented in paper II. The spectral data of pyrroles **3a** (Hex/EtOAc (9/1) R_f = 0.55), **3c** (Hex/EtOAc (1/1) R_f =

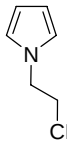
0.7), **3d** (Hex/EtOAc (2/8) R_f = 0.3), **3e** (Hex/EtOAc (9/1) R_f = 0.4) and **3h** (Hex/EtOAc (9/1) R_f = 0.6) can also be found in paper II.

Ethyl 2-(1*H*-pyrrol-1-yl)propanoate (3b)



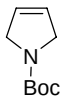
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.72 (d, *J* = 7.3 Hz, 3H, $CHC\underline{H}_3$), 4.18 (q, *J* = 7.2 Hz, 2H, $C\underline{H}_2CH_3$), 4.75 (q, *J* = 7.3 Hz, 1H, $C\underline{H}CH_3$), 6.19 (t, *J* = 2.2 Hz, 2H, 2 x NCHC$\underline{H}$), 6.76 (t, *J* = 2.2 Hz, 2H, 2 x NCH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.18 ($CH_2\underline{C}H_3$), 18.42 ($CH\underline{C}H_3$), 57.14 ($\underline{C}H_2CH_3$), 61.65 ($\underline{C}HCH_3$), 108.61 (2 x NCH$\underline{C}$H), 119.79 (2 x NCH), 171.36 (C=O). **IR (cm^{-1}) ν_{max}:** 1741 (br. C=O). **MS: m/z (%):** 167 (M^+, 45), 95 (10), 94 (100). **Chromatography:** Hex/EtOAc (6/4) R_f = 0.77.

3-(1*H*-pyrrol-1-yl)propanenitrile (3g)



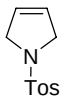
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.77 (t, *J* = 6.7 Hz, 2H, CH_2CN), 4.20 (t, *J* = 6.7 Hz, 2H, NCH_2), 6.20 (t, *J* = 2.1 Hz, 2H, 2 x NCHC$\underline{H}$), 6.71 (t, *J* = 2.1 Hz, 2H, 2 x NCH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 20.97 (CH_2CN), 45.17 (NCH_2), 109.63 (2 x NCH$\underline{C}$H), 117.37 (CN), 120.46 (2 x NCH). **IR (cm^{-1}) ν_{max}:** 2250 (CN). **MS: m/z (%):** 120 (M^+, 79), 80 (100), 78 (12), 53 (23). **Chromatography:** Hex/EtOAc (6/4) R_f = 0.65.

***Tert*-butyl 2,5-dihydro-1H-pyrrole-1-carboxylate (4r)**



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.48 (s, 9H, *t*Bu), 4.11 (dt, *J* = 12.9 Hz, *J* = 2.1 Hz, 4H, 2 x $C\underline{H}_2$), 5.73-5.81 (m, 2H, $\underline{H}C{=}C\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 28.61 (*t*Bu), 52.93 (CH_2), 53.19 (CH_2), 79.37 (C_q), 125.85 (CH), 125.96 (CH), 154.42 (C=O). **IR (cm^{-1}) ν_{max}:** 1625 (C=C), 1705 (br. C=O). **MS: m/z (%):** 169 (M^+, 6), 114 (24), 113 (32), 112 (40), 96 (40), 69 (28), 68 (65), 57 (100), 41 (41).

1-[(4-Methylphenyl)sulfonyl]-2,5-dihydro-1*H*-pyrrole (4s)

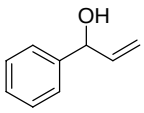


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.43 (s, 3H, CH_3), 4.12 (br s, 4H, 2 x CH_2), 5.65 (br s, 2H, $\underline{H}C{=}C\underline{H}$), 7.32 (*J* = 8.1 Hz, 2H, 2 x CH_{arom}), 7.72 (dt, *J* = 1.9 Hz, *J* = 8.1 Hz, 2H, 2 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 21.61 (CH_3), 54.93 (2xCH_2), 125.53 ($CH_{arom.}$), 127.50 ($CH_{arom.}$), 129.86 (C), 134.31 (C), 143.54 (HC=CH). **IR (cm^{-1}) ν_{max}:** 1595 (C=C). **MS: m/z (%):** 223 (50), 155 (50), 91 (100), 68 (85), 41 (16). **Chromatography:** Hex/EtOAc (1/2) R_f = 0.74. **Mp. (°C):** 126.

4.4 Attempted synthesis of furans

4.4.1 Synthesis of 1-phenylprop-2-en-1-ol (271)

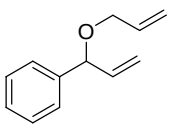
In dry THF (10 ml) benzaldehyde (1 g, 9.43 mmol) is dissolved and the flask is cooled to -78 °C under N_2 atmosphere. Via a syringe vinylmagnesium chloride (6.12 ml of a 15% solution, 9.91 mmol) is added and the mixture is slowely heated to room temperature over a period of 3 hours. After this time NH_4Cl (5 ml, aq, sat) and water (10 ml) are added and the mixture is extracted with ether (3 x 20 ml). After drying with $MgSO_4$ and evaporation of the solvent, the alcohol is obtained pure in 96% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.00 (br s, 1H, OH), 5.18-5.21 (m, 2H, HC=C$\underline{H}_2$), 5.35 (dt, *J* = 17.1 Hz, *J* = 1.3 Hz, 1H, C$\underline{H}$OH), 6.00-6.11 (m, 1H, $\underline{H}$C=CH_2), 7.35-7.37 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 75.27 (CHOH), 115.18 (HC=$\underline{C}H_2$), 126.81 (2 x CH_{arom}), 127.77 (CH_{arom}), 128,69 (2 x CH_{arom}), 140.72 (H$\underline{C}$=CH_2), 143.10 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1643 (C=C), 3246 (br OH). **MS: m/z (%):** 134 (M^+, 53), 133 (100), 115 (35), 105 (64), 92 (50), 91 (29), 79 (55), 77 (58).

4.4.2 Synthesis of [1-(allyloxy)prop-2-enyl]benzene (272)

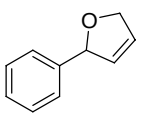
Alcohol **271** (0.5 g, 3.73 mmol) is dissolved in dry ether (10 ml) and KO*t*Bu (0.47 g, 4.1 mmol) is added after which the mixture is stirred for 30 minutes. Next allylbromide (0.99 g, 8.2 mmol) is added and stirring is continued for 16 hours. After this time NH_4Cl (5 ml, aq, sat) and water (10 ml) are added and the mixture is extracted with ether (3 x 20 ml). After drying with $MgSO_4$ and evaporation of the solvent, the ether is obtained pure in 98% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 3.93-4.05 (m, 2H, OCH_2), 4.81 (d, *J* = 6.6 Hz, 1H, OCH), 5.16-5.33 (m, 4H, 2 x HC=C$\underline{H}_2$), 5.88-6.01 (m, 2H, 2 x $\underline{H}$C=CH_2), 7.24-7.36 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 69.34 (OCH_2), 82.23 (OCH), 116.41 (HC=$\underline{C}H_2$), 116.95 (HC=$\underline{C}H_2$), 127.04 (2 x CH_{arom}), 127.80 (CH_{arom}), 128.61 (2 x CH_{arom}), 134.99 ($CH_2H\underline{C}$=CH_2), 139.07 (CH$\underline{C}$=CH_2), 141.15 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1645 (C=C), 1687 (C=C). **MS: m/z (%):** no M^+, 133 (45), 117 (67), 115 (52), 105 (100), 91 (24).

4.4.3 Synthesis of 2-phenyl-2,5-dihydrofuran (273)

Ether **272** (0.1 g, 0.57 mmol) is dissolved in dry CH_2Cl_2 (5 ml) and the second generation Grubbs' catalyst (0.005 g, 0.0057 mmol) is added after which the mixture is refluxed for 30 minutes. Next the mixture is filtered over a small silica plug and after evaporation of the solvent dihydrofuran is obtained pure in 88% yield.

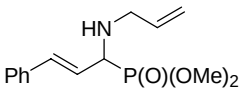


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 4.78 (dddd, *J* = 1.7 Hz, *J* = 2.5 Hz, *J* = 4.1 Hz, *J* = 12.8 Hz, 1H, HC=C<u>H</u>), 4.87 (dddd, *J* = 1.7 Hz, *J* = 2.5 Hz, *J* = 6.0 Hz, *J* = 12.8 Hz, 1H, <u>H</u>C=CH), 5.80 (ddd, *J* = 1.7 Hz, *J* = 4.1 Hz, *J* = 7.9 Hz, 1H, C<u>H</u>Ph), 5.75-5.92 (m, 1H, OC<u>H</u>$_A$H$_B$), 6.02-6.06 (m, 1H, OCH$_A$<u>H</u>$_B$), 7.28-7.38 (m, 5H, Ph). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 75.92 (OCH_2), 88.00 (OCH), 126.49 (2 x CH_{arom}), 126.73 (HC=CH), 127.91 (CH_{arom}), 128.60 (2 x CH_{arom}), 130.05 (H<u>C</u>=CH), 142.11 (C_{arom}). **IR (cm^{-1}) ν_{max}:** 1680 (C=C), 1725 (C=C). **MS: m/z (%):** 146 (M^+, 62), 145 (58), 117 (40), 115 (61), 105 (100), 77 (29).

4.5 Synthesis of 2-phosphonopyrroles

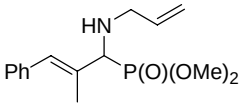
The general procedure for the synthesis of α-aminophosphonates like **312a-g** and **324a-f** by phosphonylation of an aldimine is described in paper IV. The benzylation of **312a-g** towards **13a-g** and the conversion of these compounds to 2-phosphonopyrrolines **14a-e** and 2-phosphonopyrroles **15a-f** is described in paper III. Paper III also contains the spectroscopic data of **13a**, **14a** and **15a**. Paper IV contains the complete spectroscopic characterization and general procedure for the synthesis of all compounds obtained by RCEYM and RCEYM in combination with oxidation.

Dimethyl *(2E)*-1-allylamino-3-phenylprop-2-enylphosphonate (312a)



^{1}H NMR (300 MHz, ppm) δ: 1.91 (br s, 1H, NH), 3.21 (dd, *J* = 14.0 Hz, *J* = 6.3 Hz, 1H, NC<u>H</u>$_A$H$_B$), 3.41 (dd, *J* = 14.0 Hz, *J* = 5.2 Hz, 1H, NCH$_A$<u>H</u>$_B$), 3.72-3.84 (m, 7H, CHP + 2 x OMe), 5.12-5.22 (m, 2H, HC=C<u>H</u>$_2$), 5.86 (dddd, *J* = 17.2 Hz, *J* = 10.3 Hz, *J* = 6.7 Hz, *J* = 5.2 Hz, 1H, <u>H</u>C=CH$_2$), 6.10 (ddd, *J* = 15.9 Hz, *J* = 8.7 Hz, *J* = 5.8 Hz, C<u>H</u>CHPh), 6.62 (dd, *J* = 15.9 Hz, *J* = 4.7 Hz, 1H, C<u>H</u>Ph), 7.23-7.42 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 50.09 (d, *J* = 16.2 Hz, NCH_2), 53.57 (d, *J* = 6.9 Hz, OMe), 53.73 (d, *J* = 8.1 Hz, OMe), 57.72 (d, *J* = 156.9 Hz, CHP), 116.96 (HC=<u>C</u>H$_2$), 123.91 (d, *J* = 6.9 Hz, <u>C</u>HCHPh), 126.64 (CH_{arom}), 128.09 (CH_{arom}), 128.72 (CH_{arom}), 134.70 (d, *J* = 6.9 Hz, CHPh), 135.97 (H<u>C</u>=CH$_2$), 136.34. **^{31}P NMR (121 MHz, ppm) δ:** 26.77. **IR (cm^{-1}) ν_{max}:** 3308 (NH), 1247 (P=O), 1033 (br P-O). **MS m/z (%):** 282 ($M+H^+$, 100). **MP (°C):** 54.1. **Yield:** 95%.

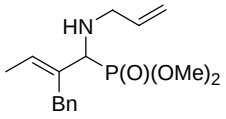
Dimethyl *(2E)*-1-allylamino-2-methyl-3-phenylprop-2-enylphosphonate (312b)



^{1}H NMR (300 MHz, ppm) δ: 1.90 (br s, 1H, NH), 1.99 (dd, *J* = 3.3 Hz, *J* = 1.4 Hz, 3H, CH_3), 3.13 (dd, *J* = 13.9 Hz, *J* = 6.9 Hz, 1H, NC<u>H</u>$_A$H$_B$), 3.33 (dd, *J* = 13.9 Hz, *J* = 5.2 Hz, 1H, NCH$_A$<u>H</u>$_B$), 3.70 (d, *J* = 21.5 Hz, 1H, CHP), 3.78 (d, *J* = 10.5 Hz, 3H, OMe), 3.83 (d, *J* = 10.7 Hz, OMe), 5.12-5.29 (m, 2H, HC=C<u>H</u>$_2$), 5.81-5.94 (m, 1H, <u>H</u>C=CH$_2$), 6.55 (d, *J* = 4.1 Hz, C<u>H</u>Ph), 7.21-7.37 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 15.40 (CH_3), 49.86 (d, *J* = 18.5 Hz, NCH_2), 53.48 (d, *J* = 6.9 Hz, OMe), 53.65 (d, *J* = 8.1 Hz, OMe), 62.97 (d, *J* = 153.5 Hz, CHP), 116.99 (HC=<u>C</u>H$_2$), 126.84 (CH_{arom}), 128.28 (CH_{arom}), 129.07

(CH_{arom}), 130.48 (d, J= 12.7 Hz, CHPh), 132.67 (d, J= 4.6 Hz, C=CH), 136.05 (HC=CH_2), 137.28 (d, J= 2.3 Hz, $C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 26.98. **IR (cm^{-1}) ν_{max}:** 3470 (NH), 1248 (P=O), 1039 (br P-O). **MS m/z (%):** 296 ($M+H^+$, 81), 186 ($M+H^+$-P(O)$(OMe)_2$, 100). **Yield:** 90%.

Dimethyl *(2E)*-1-allylamino-2-benzyl-but-2-enylphosphonate (312c)

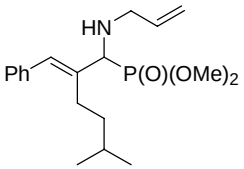


^{1}H NMR (300 MHz, ppm) δ: 1.54 (br s, 1H, NH), 1.87 (dd, J = 6.3 Hz, J = 5.8 Hz, 3H, CH_3), 2.68 (dd, J = 14.0 Hz, J = 6.6 Hz, 1H, NCH_AH_B), 2.99 (dd, J = 14.0 Hz, J = 5.5 Hz, 1H, NCH_AH_B), 3.34-3.40 (m, 1H, CH_AH_BPh), 3.41 (d, J = 21.7 Hz, 1H, CHP), 3.68-3.82 (m, 1H, CH_AH_BPh), 3.73 (d, J= 10.5 Hz, 3H, OMe), 3.78 (d, J= 10.5 Hz, OMe), 4.75-4.90 (m, 2H, HC=CH_2), 5.49-5.63 (m, 1H, HC=CH_2), 5.81 (ps p, $J \approx$ 6.3 Hz, CHCH_3), 7.15-7.30 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.15 (CH_3), 35.23 (CH_2Ph), 49.57 (d, J= 16.2 Hz, NCH_2), 53.05 (d, J= 6.9 Hz, OMe), 53.86 (d, J= 6.9 Hz, OMe), 58.90 (d, J= 154.6 Hz, CHP), 116.32 (HC=CH_2), 124.93 (d, J = 11.5 Hz, HCCH_3), 126.25, 128.46, 128.90, 133.31 (d, J= 3.5 Hz, C=CH), 136.09 (HC=CH_2), 139.41 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 27.40. **IR (cm^{-1}) ν_{max}:** 3321 (NH); 1238 (P=O), 1074, 1026 (P-O). **MS m/z (%):** 310 ($M+H^+$, 100). **MP (°C):** 78-80. **Yield:** 27%.

Dimethyl 1-allylamino-2-isopentyl-3-phenyl-propenylphosphonate (312d)

Mixture of two isomers: 79% E and 21% Z.

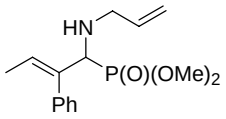
Major and minor isomer are indicated as M and m respectively whenever possible.



^{1}H NMR (300 MHz, ppm) δ: 0.85-0.96 (m, 2 x 3H, CH_3), 1.27-1.49 (m, 2 x 5H, CH_3 + CH + CH_AH_B), 1.53-1.71 (m, 2x1H, CH_AH_B), 1.89 (br s, 2x1H, NH), 2.11-2.20 (m, 1H, CCH_AH_B, M), 2.22-2.37 (m, 2H, CCH_2, m), 2.50-2.60 (m, 1H, CCH_AH_B, M), 2.84 (dd, J= 13.8 Hz, J = 6.3 Hz, 1H, NCH_AH_B, m), 3.17 (dd, J_{AB} = 14.0 Hz, J = 5.5 Hz, 1H, NCH_AH_B, M), 3.13-3.20 (m, 1H, NCH_AH_B, m), 3.40 (dd, J_{AB} = 13.8 Hz, J = 3.9 Hz, 1H, NCH_AH_B, M), 3.66 (d, J = 20.6 Hz, 1H, CHP, M), 3.77 (d, J = 10.5 Hz, 2 x 3H, OCH_3), 3.78 (d, J = 10.5 Hz, 3H, OCH_3, m), 3.83 (d, J = 10.5 Hz, 3H, OCH_3, M), 4.25 (d, J = 22.6 Hz, 1H, CHP, m), 4.83-4.90 (m, 2H, HC=CH_2, m), 5.11-5.25 (m, 2H, HC=CH_2, M), 5.61-5.74 (m, 1H, HC=CH_2, m), 5.81-5.94 (m, 1H, HC=CH_2, M), 6.67 (d, J = 5.5 Hz, 1H, CHPh, M), 6.70 (br s, 1H, CHPh, m), 7.20-7.36 (m, 2 x 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 13.99 (CH_3, M), 14.08 (CH_3, m), 22.34 (CH_3, M), 22.74 (CH_3, m), 27.83 (d, J= 2.3 Hz, CH_2, M), 28.08 (CH_2, m), 30.58 (CCH_2CH_2, m), 30.89 (d, J= 2.3 Hz, CH_2, M), 31.85 (CH, m), 32.00 (CH, M), 49.62 (d, J= 16.2 Hz, NCH_2, m), 49.84 (d, J= 16.2 Hz, NCH_2, M), 52.95 (d, J= 6.9 Hz, OMe, m), 53.26 (d, J= 6.9 Hz, OMe, M), 53.45 (d, J= 6.9 Hz, OMe, m), 53.87 (d, J= 6.9 Hz, OMe, M), 54.78 (d, J= 156.9 Hz, CHP, m), 59.74 (d, J= 152.3 Hz, CHP, M), 116.60 (HC=CH_2, m + M), 126.63 (CH_{arom}), 128.18 (CH_{arom}), 128.22 (CH_{arom}), 128.48 (CH_{arom}), 128.60 (d, J = 13.9 Hz,

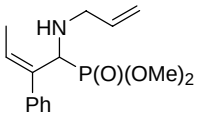
CHPh, M), 130.53 (d, *J*= 13.9 Hz, CHPh, m), 135.75 (H<u>C</u>=CH_2, m), 136.24 (H<u>C</u>=CH_2, M), 136.42 (C_q), 137.34 (C_q), 137.38 (C_q), 137.43 (C_q), 137.49 (C_q). **^{31}P NMR (121 MHz, ppm) δ:** 26.94 (M), 27.64 (m). **IR (cm^{-1}) ν_{max}:** 3329 (NH), 1246 (P=O), 1052, 1035 (P-O). **MS: m/z (%):** 352 ($M+H^+$, 53), 242 ($M+H^+$-$PO(OMe)_2$, 100). **Yield:** 88%.

Dimethyl *(2E)*-1-allylamino-2-phenyl-but-2-enylphosphonate (*E*-(312e))



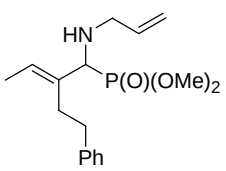
^{1}H NMR (300 MHz, ppm) δ: 1.66 (dd, *J* = 6.6 Hz, *J* = 5.2 Hz, 3H, CH_3), 1.84 (br s, 1H, NH), 3.23 (dd, *J* = 13.7 Hz, *J* = 6.6 Hz, 1H, NC<u>H_A</u>H_B), 3.44 (dd, *J* = 13.7 Hz, *J* = 5.2 Hz, 1H, NCH_A<u>H_B</u>), 3.64 (d, *J* = 10.5 Hz, 3H, OMe), 3.66 (d, *J* = 10.7 Hz, 3H, OMe), 3.80 (d, *J* = 22.6 Hz, 1H, CHP), 5.10-5.22 (m, 2H, HC=C<u>H_2</u>), 5.80-5.97 (m, 2H, <u>H</u>C=CH_2 + C<u>H</u>CH_3), 7.22-7.40 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.79 (d, *J*= 2.3 Hz, CH_3), 49.70 (d, *J*= 17.3 Hz, NCH_2), 52.88 (d, *J*= 6.9 Hz, OMe), 53.35 (d, *J* = 6.9 Hz, OMe), 60.82 (d, *J*= 156.9 Hz, CHP), 116.69 (HC=CH_2), 127.86 (CH_{arom}), 127.24 (d, *J*= 10.4 Hz, <u>C</u>HCH_3), 127.97 (2 x CH_{arom}), 129.01 (2 x CH_{arom}), 135.68 (br CPh), 136.05 (H<u>C</u>=CH_2), 138.83 (d, *J* = 3.5 Hz, $C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 26.87. **IR (cm^{-1}) ν_{max}:** 3469 (NH), 1244 (P=O), 1039 (br P-O). **MS: m/z (%):** 296.3 ($M+H^+$, 100), 186.2 ($M+H^+$-$PO(OMe)_2$, 84). **Chromatography:** Hex/EtOAc (2/8) R_f = 0.20. **Yield:** 52%.

Dimethyl *(2Z)*-1-allylamino-2-phenyl-but-2-enylphosphonate (*Z*-(312e))



^{1}H NMR (300 MHz, ppm) δ: 1.86 (dd, *J* = 7.2 Hz, *J* = 4.7 Hz, 3H, CH_3), 1.89 (br s, 1H, NH), 3.00 (dd, *J* = 13.7 Hz, *J* = 6.9 Hz, 1H, NC<u>H_A</u>H_B), 3.18 (dd, *J* = 13.7 Hz, *J* = 5.2 Hz, 1H, NCH_A<u>H_B</u>), 3.73 (d, *J* = 10.5 Hz, 3H, OMe), 3.79 (d, *J* = 10.5 Hz, 3H, OMe), 4.29 (d, *J* = 26.4 Hz, 1H, CHP), 5.05-5.12 (m, 2H, HC=C<u>H_2</u>), 5.71-5.84 (m, 1H, <u>H</u>C=CH_2), 5.97 (dq, *J* = 7.2 Hz, *J* = 4.1 Hz, 1H, C<u>H</u>CH_3), 7.20-7.59 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.34 (CH_3), 50.17 (d, *J*= 18.5 Hz, NCH_2), 53.35 (d, *J*= 8.1 Hz, OMe), 53.82 (d, *J*= 6.9 Hz, OMe), 54.62 (d, *J*= 160.4 Hz, CHP), 117.11 (HC=<u>C</u>H_2), 127.17 (CH_{arom}), 127.25 (2 x CH_{arom}), 128.36 (2 x CH_{arom}), 130.56 (d, *J*= 11.5 Hz, <u>C</u>HCH_3), 136.14 (H<u>C</u>=CH_2), 136.76 (CPh), 140.86 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 27.40. **IR (cm^{-1}) ν_{max}:** 3469 (NH), 1246 (P=O), 1058, 1032 (br P-O). **MS: m/z (%):** 296.3 ($M+H^+$, 100), 186.2 ($M+H^+$-$PO(OMe)_2$, 39). **Chromatography:** Hex/EtOAc (2/8) R_f = 0.24. **Yield:** 10%.

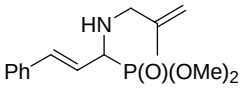
Dimethyl *(2E)*-1-allylamino-2-(2-phenylethyl)but-2-enylphosphonate (312f)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.71 (t, *J* = 6.05 Hz, 3H, CH_3), 1.76 (s, 1H, NH), 2.28-2.81 (m, 4H, CH_2CH_2), 3.07 (dd, *J* = 14.1 Hz, *J* = 6.3 Hz, 1H, NC<u>H_A</u>H_B), 3.27 (dd, *J* = 14.1 Hz, *J* = 5.1 Hz, 1H, NCH_A<u>H_B</u>), 3.50 (d, *J* = 21.5 Hz, 1H, CHP), 3.74 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.80 (d, *J* = 10.2 Hz, 3H, OCH_3), 5.09-5.22 (m, 2H, C=CH_2), 5.66 (dq, *J* = 6.6 Hz, *J* = 6.2 Hz, 1H, CH_3C<u>H</u>), 5.77-5.88 (m,

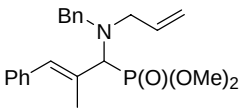
1H, $\underline{H}C=CH_2$), 7.16-7.32 (m, 5H, Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 13.43 (CH_3), 31.42 ($\underline{C}H_2Ph$), 34.42 ($C\underline{C}H_2$), 49.68 (d, *J* = 16.2 Hz, NCH_2), 52.90 (d, *J* = 6.9 Hz, OCH_3), 53.55 (d, *J* = 6.9 Hz, OCH_3), 60.17 (d, *J* = 154.6 Hz, CHP), 116.26 ($C=\underline{C}H_2$), 125.16 (d, *J* = 11.5 Hz, $CH_3\underline{C}H$), 125.82 (2 x CH_{arom}), 128.28 (2 x CH_{arom}), 133.73 (d, *J* = 3.5 Hz, $H\underline{C}=CH_2$), 136.29 ($C_{q\ arom}$), 141.97 ($\underline{C}=CH_2$). **^{31}P NMR (121 MHz, ppm) δ:** 27.56 **IR (cm^{-1}) ν_{max}:** 3324 (NH), 1246 (P=O), 1031 (P-O). **MS: m/z (%):** 324.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/8) R_f = 0,32. **Yield:** 44%.

Dimethyl *(2E)*-1-[(2-methylprop-2-enyl)amino]-3-phenyl-prop-2-enylphosphonate (312g)



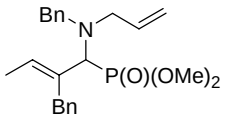
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.75 (s, 4H, NH + CH_3), 3.16 (d, *J* = 14.3 Hz, 1H, $NC\underline{H}_AH_B$), 3.29 (d, *J* = 14.3 Hz, 1H, $NCH_A\underline{H}_B$), 3.71 (ddd, *J* = 0.8 Hz, *J* = 8.5 Hz, *J* = 19.5 Hz, 1H, CHP), 3.80 (d, *J* = 9.6 Hz, 3H, OCH_3), 3.83 (d, *J* = 9.6 Hz, 3H, OCH_3), 4.88 (s, 1H, $C=C\underline{H}_AH_B$), 4.90 (s, 1H, $C=CH_A\underline{H}_B$), 6.11 (ddd, *J* = 5.6 Hz, *J* = 8.5 Hz, *J* = 15.8 Hz, 1H, $C\underline{H}CHP$), 6.62 (dd, *J* = 4.5 Hz, *J* = 15.8 Hz, 1H, $PhC\underline{H}$), 7.23-7.42 (m, 5H, Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 20.68 (CH_3), 53.22 (d, *J* = 16.1 Hz, NCH_2), 53.51 (d, *J* = 6.9 Hz, OCH_3), 53.80 (d, *J* = 7.0 Hz, OCH_3), 57.45 (d, *J* = 156.9 Hz, CHP), 111.99 ($C=\underline{C}H_2$), 124.02 (d, *J* = 6.9 Hz, $\underline{C}HCHP$), 126.64 (2 x CH_{arom}), 128.05 (CH_{arom}), 128.70 (2 x CH_{arom}), 134.64 (d, *J* = 13.8 Hz, PhCH), 136.37 ($C_{q\ arom}$), 143.03 ($\underline{C}=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 26.9 **IR (cm^{-1}) ν_{max}:** 1057 (P-O), 1244 (P=O), 3460 (NH). **MS: m/z (%):** 296.7 ($M+H^+$, 100). **Yield:** 74%.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-methyl-3-phenyl-prop-2-enylphosphonate (13b)



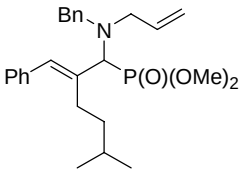
^{1}H NMR (300 MHz, ppm) δ: 2.07 (s, 3H, CH_3), 3.25 (dd, J_{AB} = 14.2 Hz, *J* = 7.4 Hz, 1H, $NC\underline{H}_AH_B$), 3.62-3.70 (m, 1H, $NCH_A\underline{H}_B$), 3.72 (d, *J* = 10.5 Hz, 3H, OMe), 3.72-3.86 (m, 2H, CHP + $C\underline{H}_AH_BPh$), 3.84 (d, *J* = 10.5 Hz, 3H, OMe), 4.18 (dd, J_{AB} = 13.8 Hz, *J* = 2.5 Hz, 1H, $CH_A\underline{H}_BPh$), 5.15-5.26 (m, 2H, $HC=C\underline{H}_2$), 5.79-5.92 (m, 1H, $\underline{H}C=CH_2$), 6.66 (br s, 1H, CHPh), 7.20-7.39 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 18.63 (d, *J*= 6.9 Hz, CH_3), 52.86 (d, *J*= 8.1 Hz, OMe), 52.98 (d, *J*= 6.9 Hz, OMe), 63.92 (d, *J*= 153.5 Hz, CHP), 117.83 ($HC=\underline{C}H_2$), 126.82 (CH_{arom}), 127.02 (CH_{arom}), 128.21 (CH_{arom}), 128.28 (CH_{arom}), 128.88 (CH_{arom}), 129.12 (CH_{arom}), 131.95 (d, *J*= 4.6 Hz, $\underline{C}$=CH), 132.38 (d, *J*= 11.5 Hz, CHPh), 136.49 ($H\underline{C}=CH_2$), 137.40 ($C_{q,arom}$), 139.80 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 27.35. **IR (cm^{-1}) ν_{max}:** 1247 (P=O), 1037 (br P-O). **MS m/z (%):** 386 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (3/2) R_f = 0.26. **Yield:** 50%.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-benzyl-but-2-enylphosphonate (13c)



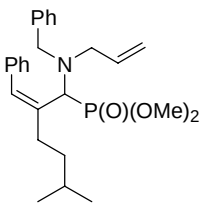
^{1}H NMR (300 MHz, ppm) δ: 1.83 (d, *J* = 6.6 Hz, 3H, CH_3), 3.20 (d, *J* = 14.9 Hz, 1H, $CC\underline{H}_A\underline{H}_BPh$), 3.34-3.39 (m, 2H, NCH_2CH), 3.46 (d, *J* = 10.5 Hz, 3H, OMe), 3.53 (d, *J* = 20.6 Hz, 1H, CHP), 3.66 (d, *J* = 10.5 Hz, 3H, OMe), 3.68-3.74 (m, 1H, $CCH_A\underline{H}_BPh$), 3.86-3.88 (m, 2H, NCH_2Ph), 5.05-5.16 (m, 2H, $HC=C\underline{H}_2$), 5.73 (ddt, *J* = 17.3 Hz, *J* = 10.2 Hz, *J* = 6.5 Hz, 1H, $\underline{H}C=CH_2$), 6.27 (q, *J* = 6.6 Hz, 1H, $C\underline{H}CH_3$), 6.92 (d, *J* = 6.6 Hz, 2H, 2 x CH_{arom}), 7.10-7.39 (m, 8H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.44 (CH_3), 35.74 (d, *J* = 11.5 Hz, $C\underline{C}H_2Ph$), 51.81 (d, *J* = 6.9 Hz, OMe), 52.65 (d, *J* = 6.9 Hz, OMe), 54.20 (d, *J* = 3.5 Hz, $N\underline{C}H_2CH$), 54.91 (br NCH_2Ph), 58.41 (d, *J* = 140.8 Hz, CHP), 117.6 ($HC=\underline{C}H_2$), 126.06 (CH_{arom}), 126.98 (CH_{arom}), 127.71 (d, *J* = 5.8 Hz, $\underline{C}HCH_3$), 128.29 (CH_{arom}), 128.81 (CH_{arom}), 129.2,2 (CH_{arom}), 133.22 (d, *J* = 10.4 Hz, $\underline{C}$=CH), 137.16 ($H\underline{C}=CH_2$), 139.45 ($CCH_2\underline{C}_{q,arom}$), 140.29 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 28.84. **IR (cm^{-1}) ν_{max}:** 1236 (P=O), 1053, 1030 (P-O). **MS m/z (%):** 400 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (1/1) R_f = 0.45. **Yield:** 50%.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-isopentyl-3-phenyl-prop-2-enylphosphonate (*E*-(13d))



^{1}H NMR (300 MHz, ppm) δ: 0.83-0.88 (m, 3H, CH_3), 1.12-1.35 (m, 6H, CH_3 + CH_2 + CH), 2.05-2.17 (m, 1H, $C\underline{H}_A\underline{H}_BC$), 2.40-2.49 (m, 1H, $CH_A\underline{H}_BC$), 3.42-3.57 (m, 2H, NCH_2), 3.75 (d, *J* = 10.5 Hz, 3H, OMe), 3.83 (d, *J* = 21.5 Hz, 1H, CHP), 3.87 (d, *J* = 10.5 Hz, 3H, OMe), 3.96 (d, *J* = 13.7 Hz, 1H, $C\underline{H}_A\underline{H}_BPh$), 4.04 (dd, *J* = 13.7 Hz, *J* = 3.9 Hz, 1H, $CH_A\underline{H}_BPh$), 5.15-5.28 (m, 2H, $HC=C\underline{H}_2$), 5.77-5.90 (m, 1H, $\underline{H}C=CH_2$), 7.12 (br s, 1H, CHPh), 7.21-7.35 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.07 (CH_3), 22.37 (CH_3), 28.02 (CH_2), 31.27 (d, *J* = 10.4 Hz, $C\underline{C}H_2CH_2$), 31.81 (CH), 52.05 (d, *J* = 6.9 Hz, OMe), 53.11 (d, *J* = 6.9 Hz, OMe), 54.25 (d, *J* = 4.6 Hz, NCH_2), 55.08 (d, *J* = 4.6 Hz, NCH_2Ph), 58.72 (d, *J* = 144.2 Hz, CHP), 117.68 ($HC=\underline{C}H_2$), 126.65 (CH_{arom}), 126.97 (CH_{arom}), 128.17 (CH_{arom}), 128.20 (CH_{arom}), 128.74 (CH_{arom}), 129.10 (CH_{arom}), 131.36 (d, *J* = 5.8 Hz, CHPh), 136.96 ($H\underline{C}=CH_2$), 137.15 (d, *J* = 8.1 Hz, $\underline{C}$=CH), 137.68 ($C_{q,arom}$), 139.96 ($CH_2\underline{C}_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 28.72 **IR (cm^{-1}) ν_{max}:** 1247 (P=O), 1058, 1029 (P-O), **MS: m/z (%):** 442 ($M+H^+$, 100), 332 ($M+H^+$-$PO(OMe)_2$, 32). **Chromatography:** Hex/EtOAc (1/1) R_f = 0.50. **Yield:** 34%.

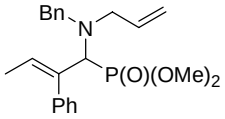
Dimethyl *(2Z)*-1-(allylbenzylamino)-2-isopentyl-3-phenyl-prop-2-enylphosphonate (*Z*-(13d))



^{1}H NMR (300 MHz, ppm) δ: 0.84-0.96 (m, 3H, CH_3), 1.32-1.46 (m, 4H, CH_3 + CH), 1.61-1.72 (m, 2H, CH_2), 2.40-2.63 (m, 2H, CH_2C), 3.05 (dd, *J* = 14.3 Hz, *J* = 7.4 Hz, 1H, $NC\underline{H}_A\underline{H}_B$), 3.47-3.57 (m, 1H, $NCH_A\underline{H}_B$), 3.55 (d, *J* = 14.0 Hz, 1H,

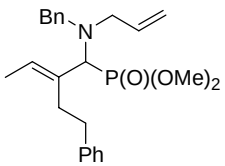
$C\underline{H}_AH_BPh$), 3.69 (d, *J* = 10.7 Hz, 3H, OMe), 3.71 (d, *J* = 10.7 Hz, 3H, OMe), 4.05 (dd, *J* = 14.0 Hz, *J* = 1.9 Hz, 1H, $CH_A\underline{H}_BPh$), 4.54 (d, *J* = 24.8 Hz, 1H, CHP), 4.71-4.87 (m, 2H, $HC=C\underline{H}_2$), 5.52-5.65 (m, 1H, $\underline{H}C=CH_2$), 6.70 (br s, 1H, CHPh), 7.07-7.35 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.22 (CH_3), 22.84 (CH_3), 28.60 (CH_2), 32.01 (CH), 33.54 ($C\underline{C}H_2CH_2$), 52.55 (d, *J* = 6.9 Hz, OMe), 53.08 (d, *J* = 6.9 Hz, OMe), 54.74 (d, *J* = 8.1 Hz, NCH_2), 55.55 (d, *J* = 8.1 Hz, NCH_2Ph), 56.82 (d, *J* = 156.9 Hz, CHP), 117.28 ($HC=\underline{C}H_2$), 126.69 (CH_{arom}), 128.06 (CH_{arom}), 128.37 (CH_{arom}), 128.44 (CH_{arom}), 128.89 (CH_{arom}), 131.05 (d, *J* = 13.9 Hz, CHPh), 135.83 ($H\underline{C}=CH_2$), 136.99 ($\underline{C}=CH$), 137.92 ($C_{q,arom}$), 139.93 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 27.79. **IR (cm^{-1}) ν_{max}:** 1249 (P=O), 1059, 1031 (P-O). **MS: m/z (%):** 442 ($M+H^+$, 100), 332 (19, $M+H^+$-$PO(OMe)_2$, 19). **Chromatography:** Hex/EtOAc (1/1) R_f = 0.58. **Yield:** 11%.

Dimethyl *(2E)*-1-(allylbenzylamino)-2-phenyl-but-2-enylphosphonate (13e)



^{1}H NMR (300 MHz, ppm) δ: 1.69 (d, *J* = 6.3 Hz, 3H, CH_3), 2.95 (dd, *J* = 13.9 Hz, *J* = 7.6 Hz, 1H, $NC\underline{H}_AH_B$), 3.43 (d, *J* = 13.5 Hz, 1H, $C\underline{H}_AH_BPh$), 3.44-3.51 (m, 1H, $NCH_A\underline{H}_B$), 3.70 (d, *J* = 10.5 Hz, 3H, OMe), 3.82 (d, *J* = 10.7 Hz, 3H, OMe), 4.03 (d, *J* = 24.5 Hz, 1H, CHP), 4.02-4.08 (m, 1H, $CH_A\underline{H}_BPh$), 4.84-5.01 (m, 2H, $HC=C\underline{H}_2$), 5.60-5.74 (m, 1H, $\underline{H}C=CH_2$), 6.41 (qd, *J* = 6.8 Hz, *J* = 1.7 Hz, 1H, $C\underline{H}CH_3$), 7.04-7.36 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 15.10 (CH_3), 52.63 (d, *J* = 6.9 Hz, OMe), 53.27 (d, *J* = 6.9 Hz, OMe), 54.35 (d, *J* = 6.9 Hz, NCH_2), 55.27 (d, *J* = 6.9 Hz, $N\underline{C}H_2Ph$), 60.81 (d, *J* = 156.9 Hz, CHP), 117.58 ($HC=\underline{C}H_2$), 126.76 (CH_{arom}), 127.95 (CH_{arom}), 128.13 (CH_{arom}), 128.95 (CH_{arom}), 129.09 (d, *J* = 4.6 Hz, $\underline{C}HCH_3$), 134.12 (d, *J* = 8.1 Hz, CPh), 136.47 ($H\underline{C}=CH_2$), 139.43 ($CH_2\underline{C}_{q,arom}$), 141.51 (d, *J* = 13.9 Hz, $C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 27.19. **IR (cm^{-1}) ν_{max}:** 1246 (P=O), 1057, 1036 (P-O). **MS: m/z (%):** 386 ($M+H^+$, 100), 276 ($1M+H^+$-$PO(OMe)_2$, 10). **Chromatography:** Hex/EtOAc (1/1) R_f = 0.30. **Yield:** 25%. - The minor *(2Z)*-isomer could not be obtained in pure form.

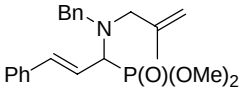
Dimethyl *(2E)*-1-(allylbenzylamino)-2-(2-phenylethyl)but-2-enylphosphonate (13f)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.64 (d, *J* = 6.8 Hz, 3H, CH_3), 2.23-2.33 (m, 1H, $C\underline{H}_AH_BPh$), 2.47-2.57 (m, 3H, $C\underline{H}_2CH_A\underline{H}_BPh$), 3.32 (dd, *J* = 13.8 Hz, *J* = 6.1 Hz, 1H, $NC\underline{H}_AH_BCH$), 3.44 (ddd, *J* = 13.8 Hz, *J* = 6.6 Hz, *J* = 4.3 Hz, 1H, $NCH_A\underline{H}_BCH$), 3.65-3.81 (m, 2H, CHP + $NC\underline{H}_AH_BPh$), 3.68 (d, *J* = 10.6 Hz, 3H, OCH_3), 3.83 (d, *J* = 10.7 Hz, 3H, OCH_3), 3.92 (dd, *J* = 13.8 Hz, *J* = 1.1 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.11-5.25 (m, 2H, $C=CH_2$), 5.79 (ddt, *J* = 16.6 Hz, *J* = 10.5 Hz, *J* = 6.5 Hz, 1H, $NCH_2C\underline{H}$), 6.05 (q, *J* = 6.8 Hz, 1H, $CH_3C\underline{H}$), 7.10-7.38 (m, 10H, Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 13.69 (CH_3), 32.95 (d, *J* = 10.7 Hz, $\underline{C}H_2Ph$), 34.58 ($C\underline{C}H_2$), 52.10 (d, *J* = 8.1 Hz, OCH_3), 52.87 (d, *J* = 7.0 Hz, OCH_3), 54.09 (d, *J* = 4.6 Hz, $N\underline{C}H_2CH$), 54.84 (d, *J* = 3.4 Hz, NCH_2Ph), 59.23 (d, *J* = 143.1 Hz, CHP), 117.76 ($C=\underline{C}H_2$), 125.89 (CH_{arom}), 126.98 (CH_{arom}), 127.38 (d, *J* = 5.8 Hz, $CH_3\underline{C}H$), 128.29 (2 x

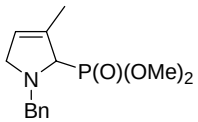
CH_{arom}), 128.38 (2 x CH_{arom}), 128.52 (2 x CH_{arom}), 129.10 (2 x CH_{arom}), 133.48 (d, *J* = 8.0 Hz, H<u>C</u>=CH_2), 137.12 ($C_{q\ arom}$), 140.17 ($C_{q\ arom}$), (141.97 (<u>C</u>=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 29.01 **IR (cm^{-1}) ν_{max}:** 1028 (P-O), 1241 (P=O). **MS: m/z (%):** 414.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (4/6) R_f = 0,41. **Yield:** 92%.

Dimethyl *(2E)*-1-[benzyl(2-methylprop-2-enyl)amino]-3-phenylprop-2-enylphosphonate (13g)



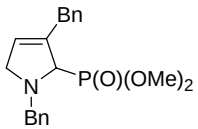
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.79 (s, 3H, CH_3), 3.02 (d, *J* = 12.7 Hz, 1H, NC<u>H</u>$_A$H$_B$Ph), 3.47 (d, *J* = 13.8 Hz, 1H, NC<u>H</u>$_A$H$_B$C), 3.51 (d, *J* = 12.7 Hz, 1H, NCH$_A$<u>H</u>$_B$Ph), 3.68 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.82 (d, *J* = 10.7 Hz, 3H, OCH_3), 3.82 (dd, *J* = 9.8 Hz, *J* = 23.7 Hz, 1H, CHP), 4.22 (dd, *J* = 13.8 Hz, *J* = 2.2 Hz, 1H, NCH$_A$<u>H</u>$_B$C),4.91 (s, 1H, C=C<u>H</u>$_A$H$_B$), 4.98 (s, 1H, C=CH$_A$<u>H</u>$_B$), 6.38 (ddd, *J* = 6.3 Hz, *J* = 9.8 Hz, *J* = 15.7 Hz, 1H, C<u>H</u>CHP), 6.70 (dd, *J* = 3.0 Hz, *J* = 15.7 Hz, 1H, PhC<u>H</u>), 7.22-7.45 (m, 5H, Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 20.64 (CH_3), 52.85 (d, *J* = 6.9 Hz, OCH_3), 53.31 (d, *J* = 6.9 Hz, OCH_3), 55.14 (d, *J* = 6.9 Hz, N<u>C</u>H$_2$C), 57.84 (d, *J* = 8.1 Hz, NCH_2Ph), 59.01 (d, *J* = 160.4 Hz, CHP), 113.63 (C=<u>C</u>H$_2$), 119.74 (<u>C</u>HCHP), 126.75 (2 x CH_{arom}), 127.10 (CH_{arom}), 128.22 (CH_{arom}), 128.40 (2 x CH_{arom}), 128.75 (2 x CH_{arom}), 128.84 (2 x CH_{arom}), 136.40 ($C_{q\ arom}$), 137.28 (d, *J* = 15.0 Hz, PhCH), 139.57 ($C_{q\ arom}$), 143.53 (<u>C</u>=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 27.48 **IR (cm^{-1}) ν_{max}:** 1029 (P-O), 1246 (P=O). **MS: m/z (%):** 386.7 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (4/6) R_f = 0,47. **MP (°C):** 78.5. **Yield:** 86%.

Dimethyl 1-benzyl-3-methyl-2,5-dihydro-1*H*-pyrrol-2-ylphosphonate (14b)



^{1}H NMR (300 MHz, ppm) δ: 1.86 (br s, 3H, CH_3), 3.19-3.47 (m, 1H, NC<u>H</u>$_A$H$_B$), 3.63 (d, *J* = 13.2 Hz, 1H, C<u>H</u>$_A$H$_B$Ph), 3.63-3.74 (m, 1H, NCH$_A$<u>H</u>$_B$), 3.82 (d, *J* = 10.7 Hz, 6H, 2 x OMe), 3.92 (m, 1H, CHP), 4.28 (d, *J* = 13.2 Hz, 1H, CH$_A$<u>H</u>$_B$Ph), 5.49-5.52 (m, 1H, HC=C), 7.21-7.39 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.81 (CH_3), 53.19 (d, *J*= 8.1 Hz, OMe), 53.36 (d, *J*= 6.9 Hz, OMe), 59.87 (d, *J*= 8.1 Hz, NCH_2), 60.56 (d, *J* = 5.8 Hz, N<u>C</u>H$_2$Ph), 70.84 (d, *J* = 174.2 Hz, CHP), 124.78 (d, *J* = 12.7 Hz, H<u>C</u>=C), 126.92 (CH_{arom}), 128.25 (CH_{arom}), 128.60 (CH_{arom}), 133.43 (d, *J*= 4.6 Hz, HC=<u>C</u>), 139.37 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 24.69. **IR (cm^{-1}) ν_{max}:** 1249 (P=O), 1057, 1029 (P-O). **MS m/z (%):** 282 ($M+H^+$, 100). **Yield:** 58%.

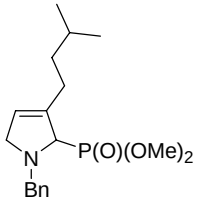
Dimethyl 1-benzyl-3-benzyl-2,5-dihydro-1*H*-pyrrol-2-ylphosphonate (14c)



^{1}H NMR (300 MHz, ppm) δ: 3.20-3.34 (m, 1H, NC<u>H</u>$_A$H$_B$), 3.43 (br d, *J* = 16.2 Hz, 1H, CC<u>H</u>$_A$H$_B$Ph), 3.60 (d, *J* = 13.2 Hz, 1H, NC<u>H</u>$_A$H$_B$Ph), 3.63-3.76 (m, 2H, NCH$_A$<u>H</u>$_B$, CCH$_A$<u>H</u>$_B$Ph), 3.80 (d, *J* = 10.5 Hz, 3H, OMe), 3.82 (d, *J* = 10.5 Hz, 3H, OMe), 3.89-3.94 (m, 1H, CHP), 4.13 (d, *J* = 13.2 Hz, 1H, NCH$_A$<u>H</u>$_B$Ph), 5.43-5.48 (m, 1H, HC=C),

7.20-7.34 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 35.33 (CH_2Ph), 53.29 (d, *J* = 6.9 Hz, OMe), 53.39 (d, *J* = 8.1 Hz, OMe), 59.93 (d, *J* = 6.9 Hz, NCH_2), 60.65 (d, *J* = 6.9 Hz, $N\underline{C}H_2$Ph), 69.04 (d, *J* = 173.1 Hz, CHP), 125.76 (d, *J* = 11.5 Hz, $H\underline{C}$=C), 126.37 (CH_{arom}), 127.06 (CH_{arom}), 128.34 (CH_{arom}), 128.49 (CH_{arom}), 128.73 (CH_{arom}), 129,15 (CH_{arom}), 137.67 (d, *J* = 4.6 Hz, HC=$\underline{C}$), 138.89 ($C_{q,arom}$), 139.24 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 24.69. **IR (cm^{-1}) ν_{max}:** 1245 (P=O), 1056, 1029 (P-O). **MS m/z (%):** 358 ($M+H^+$, 100), 248 ($M+H^+$-$PO(OMe)_2$, 34). **Yield:** 62%.

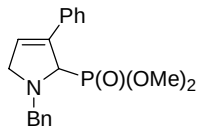
Dimethyl 1-benzyl-3-isopentyl-2,5-dihydro-1*H*-pyrrol-2-ylphosphonate (14d)



^{1}H NMR (300 MHz, ppm) δ: 0.90 (ps t, *J* = 6.7 Hz, 3H, CH_3), 1.25-1.38 (m, 4H, CH_3 + CH), 1.42-1.55 (m, 2H, CH_2), 2.06-2.31 (m, 2H, CH_2C), 3.20-3.34 (m, 1H, $NC\underline{H}_AH_B$), 3.63 (d, *J* = 13.2 Hz, 1H, $NC\underline{H}_AH_B$Ph), 3.65-3.78 (m, 1H, $NCH_A\underline{H}_B$), 3.80 (d, *J* = 10.2 Hz, 3H, OMe), 3.81 (d, *J* = 10.2 Hz, 3H, OMe), 3.93-3.99 (m, 1H, CHP), 4.24 (d, *J* = 13.2 Hz, 1H, $NCH_A\underline{H}_B$Ph), 5.51 (br s, 1H, HC=C), 7.21-7.38 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.15 (CH_3), 22.59 (CH_3), 27.28 (CH_2), 28.76 ($C\underline{C}H_2CH_2$), 31.64 (CH), 53.36 (d, *J* = 6.9 Hz, 2 x OMe), 60.02 (d, *J* = 8.1 Hz, NCH_2), 60.81 (d, *J* = 6.9 Hz, CH_2Ph), 69.87 (d, *J* = 174.2 Hz, CHP), 123.28 (d, *J* = 11.5 Hz, $H\underline{C}$=C), 127.01 (CH_{arom}), 128.34 (CH_{arom}), 128.67 (CH_{arom}), 138.34 (d, *J* = 4.6 Hz, HC=$\underline{C}$), 139.45 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 24.91. **IR (cm^{-1}) ν_{max}:** 1249 (P=O), 1058, 1032 (P-O). **MS m/z (%):** 338 ($M+H^+$, 100), 228 ($M+H^+$-$PO(OMe)_2$, 17). **Yield:** 70%.

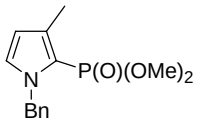
Dimethyl 1-benzyl-3-phenyl-2,5-dihydro-1*H*-pyrrol-2-ylphosphonate (14e)

Could only be isolated together with small amounts of pyrrole **15e** because of spontaneous oxidation during the work-up procedure and product handling. Spectral data given below are determined from the mixture and are indicative.



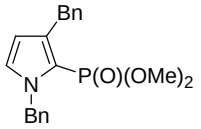
^{1}H NMR (300 MHz, ppm) δ: 3.51 (d, *J* = 10.5 Hz, 3H, OMe), 3.52-3.60 (m, 1H, $NC\underline{H}_AH_B$), 3.64 (d, *J* = 10.5 Hz, 3H, OMe), 3.82 (d, *J* = 13.2 Hz, 1H, $NC\underline{H}_AH_B$Ph), 3.93-4.05 (m, 1H, $NCH_A\underline{H}_B$), 4.15 (d, *J* = 13.2 Hz, 1H, $NCH_A\underline{H}_B$Ph), 4.54-4.59 (m, 1H, CHP), 6.17-6.19 (m, 1H, HC=C), 7.19-7.45 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 53.20 (d, *J* = 6.9 Hz, 2 x OMe), 60.60 (d, *J* = 4.5 Hz, NCH_2), 61.22 (d, *J* = 9.2 Hz, CH_2Ph), 68.67 (d, *J* = 173.1 Hz, CHP), 126.98 (d, *J* = 11.5 Hz, CH), 127.06 (CH_{arom}), 127.24 (CH_{arom}), 127.89 (CH_{arom}), 128.25 (CH_{arom}), 128.43 (CH_{arom}), 128.84 (CH_{arom}), 134.05 ($C_{q,arom}$), 137.52 (d, *J* = 3.5 Hz, CPh), 139.12 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 24.64.

Dimethyl 1-benzyl-3-methyl-1*H*-pyrrol-2-ylphosphonate (15b)



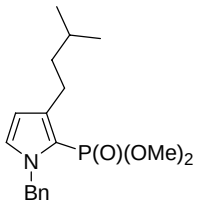
^{1}H NMR (300 MHz, ppm) δ: 2.29 (d, *J* = 1.4 Hz, 3H, CH_3), 3.53 (d, *J* = 11.7 Hz, 6H, 2 x OMe), 5.38 (s, 2H, NCH_2), 6.07-6.09 (m, 1H, CH), 6.82 (dd, *J* = 5.0 Hz, *J* = 2.5 Hz, 1H, NCH), 7.07-7.35 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 12.93 (CH_3), 52.03 (d, *J* = 4.6 Hz, 2 x OMe), 52.46 (NCH_2), 111.25 (d, *J* = 15.0 Hz, CH), 113.49 (d, *J* = 226.1 Hz, CP), 126.91 (CH_{arom}), 127.38 (CH_{arom}), 128.54 (d, *J* = 12.7 Hz, NCH), 128.50 (CH_{arom}), 133.47 (d, *J* = 18.5 Hz, NCC), 138.6 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 14.82. **IR (cm^{-1}) ν_{max}:** 1249 (P=O), 1025 (br P-O). **MS m/z (%):** 280 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/3) R_f = 0.27. **Yield:** 84%.

Dimethyl 1,3-dibenzyl-1*H*-pyrrol-2-ylphosphonate (15c)



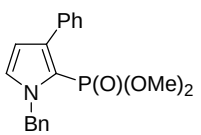
^{1}H NMR (300 MHz, ppm) δ: 3.47 (d, *J* = 11.6 Hz, 6H, 2 x OMe), 4.11 (s, 2H, CCH_2Ph), 5.38 (s, 2H, NCH_2), 6.02 (dd, *J* = 4.2 Hz, *J* = 2.5 Hz, 1H, CH), 6.84 (dd, *J* = 5.0 Hz, *J* = 2.5 Hz, 1H, NCH), 7.07-7.35 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 33.06 (CCH_2Ph), 52.07 (d, *J* = 5.8 Hz, 2 x OMe), 52.48 (NCH_2), 110.89 (d, *J* = 16.2 Hz, CH), 113.47 (d, *J* = 226.0 Hz, CP), 125.70 (CH_{arom}), 126.92 (CH_{arom}), 127.43 (CH_{arom}), 128.19 (CH_{arom}), 128.51 (CH_{arom}), 128.73 (d, *J* = 11.5 Hz, NCH), 128.80 (CH_{arom}), 137.15 (d, *J* = 18.5 Hz, NCC), 138.44 ($C_{q,arom}$), 141.78 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 14.39. **IR (cm^{-1}) ν_{max}:** 1240 (P=O), 1023 (br P-O). **MS m/z (%):** 356 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/3) R_f = 0.29. **Yield:** 72%.

Dimethyl 1-benzyl-3-isopentyl-1*H*-pyrrol-2-ylphosphonate (15d)



^{1}H NMR (300 MHz, ppm) δ: 0.87-0.92 (m, 3H, CH_3), 1.28-1.40 (m, 4H, CH + CH_3), 1.54-1.64 (m, 2H, CH_2), 2.69 (t, *J* = 7.8 Hz, 2H, CC$H_2$$CH_2$), 3.52 (d, *J* = 11.6 Hz, 6H, 2 x OMe), 5.38 (s, 2H, NCH_2), 6.13 (dd, *J* = 4.1 Hz, *J* = 2.8 Hz, 1H, CH), 6.84 (dd, *J* = 5.1 Hz, *J* = 2.8 Hz, 1H, NCH), 7.06-7.32 (m, 5H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 14.18 (CH_3), 22.67 (CH_3), 26.96 (CC$H_2$$CH_2$), 31.03 ($CH_2$), 31.89 (CH), 52.08 (d, *J* = 5.8 Hz, 2 x OMe), 52.47 (NCH_2), 109.86 (d, *J* = 15.0 Hz, CH), 112.92 (d, *J* = 226.1 Hz, CP), 126.95 (CH_{arom}), 127.42 (CH_{arom}), 128.55 (CH_{arom}), 128.71 (d, *J* = 12.7 Hz, NCH), 138.78 ($C_{q,arom}$), 139.38 (d, *J* = 19.6 Hz, NCC). **^{31}P NMR (121 MHz, ppm) δ:** 14.87. **IR (cm^{-1}) ν_{max}:** 1250 (P=O), 1025 (br P-O). **MS m/z (%):** 336 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/3) R_f = 0.46. **Yield:** 70%.

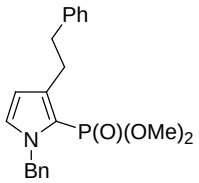
Dimethyl 1-benzyl-3-phenyl-1*H*-pyrrol-2-ylphosphonate (15e)



^{1}H NMR (300 MHz, ppm) δ: 3.36 (d, *J* = 11.6 Hz, 6H, 2 x OMe), 5.57 (s, 2H, NCH_2), 6.29 (dd, *J* = 4.0 Hz, *J* = 2.5 Hz, 1H, CH), 6.94 (dd, *J* = 5.0 Hz, *J* = 2.5

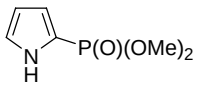
Hz, 1H, NCH), 7.19-7.46 (m, 10H, Ph). **^{13}C NMR (75 MHz, ppm) δ:** 52.09 (d, *J* = 5.8 Hz, 2 x OMe), 52.95 (NCH_2), 110.98 (d, *J* = 13.9 Hz, CH), 113.79 (d, *J* = 226.1 Hz, CP), 126.88 (CH_{arom}), 127.32 (CH_{arom}), 127.58 (CH_{arom}), 128.57 (CH_{arom}), 128.66 (d, *J* = 12.7 Hz, NCH), 129.46 (CH_{arom}), 135.99 ($C_{q,arom}$), 137.46 (d, *J* = 18.5 Hz, NCC), 138.28 ($C_{q,arom}$). **^{31}P NMR (121 MHz, ppm) δ:** 13.77. **IR ν_{max} (cm^{-1}):** 1249 (P=O), 1053, 1028 (br., P-O). **MS m/z (%):** 342 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/3) R_f = 0.30. **Yield:** 75%.

Dimethyl 1-benzyl-3-(2-phenylethyl)-1*H*-pyrrol-2-ylphosphonate (15f)



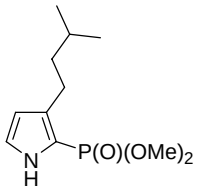
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.87-2.92 (m, 2H, CH_2Ph), 3.01-3.06 (m, 2H, CH_2CH_2Ph), 3.47 (d, *J* = 11.6 Hz, 6H, 2 x OCH_3), 5.37 (s, 2H, NCH_2), 6.13 (dd, *J* = 4.1 Hz, *J* = 2.5 Hz, 1H, NCHCH), 6.84 (dd, *J* = 5.0 Hz, *J* = 2.5 Hz, 1H, NCH), 7.03-7.35 (m, 10H, Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 29.19 (CH_2CH_2Ph), 37.89 (CCH_2), 52.11 (d, *J* = 5.8 Hz, 2 x OCH_3), 52.52 (NCH_2), 110.12 (d, *J* = 16.2 Hz, NCHCH), 113.32 (d, *J* = 225.0 Hz, CP), 125.81 (CH_{arom}), 126.87 (2 x CH_{arom}), 127.47 (CH_{arom}), 128.29 (2 x CH_{arom}), 128.58 (2 x CH_{arom}), 128.62 (d, *J* = 12.7 Hz, NCH), 128.75 (2 x CH_{arom}), 138.24 (d, *J* = 19.6 Hz, NCC), 138.75 ($C_{q\ arom}$), 142.32 ($C_{q\ arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 14.52 **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1248 (P=O). **MS: m/z (%):** 370.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (6/4) R_f = 0,27. **Yield:** 71%.

Dimethyl 1*H*-pyrrol-2-ylphosphonate (315a)



^{1}H-NMR (300 MHz, ppm) δ: 3.73 (d, *J* = 11.6 Hz, 6H, 2 x OMe), 6.29-6.33 (m, 1H, CH), 6.73-6.76 (m, 1H, NCCH), 7.07-7.10 (m, 1H, NCH). **^{13}C-NMR (75 MHz, ppm) δ:** 53.00 (d, *J* = 5.8 Hz, 2 x OMe), 109.93 (d, *J* = 15.0 Hz, CH), 115.16 (d, *J* = 230.8 Hz, CP), 118.65 (d, *J* = 17.3 Hz, NCCH), 124.59 (d, *J* = 12.7 Hz, NCH). **^{31}P-NMR (121 MHz, ppm) δ:** 15.01. **IR ν (cm^{-1}):** 3199 (NH), 1244 (P=O), 1029 (br P-O). **MS m/z (%):** 175 ($M+H^+$, 100). **Chromatography:** EtOAc R_f = 0.20. **Yield:** 39%.

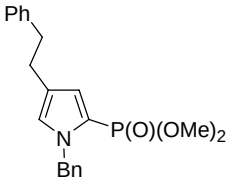
Dimethyl 3-isopentyl-1*H*-pyrrol-2-ylphosphonate (315b)



^{1}H-NMR (300 MHz, ppm) δ: 0.86-0.92 (m, 3H, CH_3), 1.25-1.41 (m, 4H, CH + CH_3), 1.52-1.63 (m, 2H, CH_2), 2.58 (t, *J* = 7.8 Hz, 2H, CCH_2CH_2), 3.71 (d, *J* = 11.6 Hz, 6H, 2 x OMe), 6.18-6.21 (m, 1H, CH), 6.93-6.97 (m, 1H, NCH). **^{13}C-NMR (75 MHz, ppm) δ:** 14.04 (CH_3), 22.54 (CH_3), 26.28 (CCH_2CH_2), 30.64 (CH_2), 31.70 (CH), 52.44 (d, *J* = 5.8 Hz, 2 x OMe), 110.82 (d, *J* = 15.0 Hz, CH), 111.74 (d, *J* = 229.6 Hz, CP), 123.35 (d, *J* = 11.5 Hz, NCH), 135.21 (d, *J* = 18.5 Hz, NCC). **^{31}P-NMR (121 MHz, ppm) δ:** 16.21. **IR ν (cm^{-1}):** 3215 (NH), 1245 (P=O), 1030, 1053 (P-O). **MS m/z (%):** 246 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc (2/3) R_f = 0.23. **Yield:** 27%. **Purity:** 90%.

Dimethyl 1-benzyl-4-[2-phenylethyl]-1H-pyrrol-2-ylphoshonate (325)

Compound **19e** (70 mg, 0.19 mmol) was dissolved in absolute ethanol (10 ml) and subjected to catalytic reduction using H_2 (3 bar) and Pd/C (5%) at room temperature for 16 hours. After this time the mixture was filtered over a small silica plug and the solvent was removed *in vacuo*. The reduced compound is obtained quantitatively.

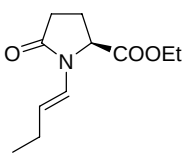


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.73-2.88 (m, 4H, CH_2CH_2), 3.58 (d, 6H, *J* = 11.3 Hz, 2 x OCH_3), 5.26 (s, 2H, NCH_2), 6.62 (dd, 1H, *J* = 1.9 Hz, *J* = 5.5 Hz, NCH), 6.69 (dd, 1H, *J* = 1.9 Hz, *J* = 3.3 Hz, NCCH), 7.05-7.33 (m, 10H, 2 x Ph). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 28.59 ($CH_2\underline{C}H_2Ph$), 37.37 ($\underline{C}H_2CH_2Ph$), 52.30 (NCH_2), 52.72 (d, *J* = 5.8 Hz, 2 x OCH_3), 116.99 (d, *J* = 238.4 Hz, CP), 122.15 (d, *J* = 17.3 Hz, $NC\underline{C}H$), 124.25 (d, *J* = 13.8 Hz, $NCH\underline{C}$), 125.91 (CH_{arom}), 127.06 (d, *J* = 9.2 Hz, NCH), 127.12 (2 x CH_{arom}), 127.62 (CH_{arom}), 128.31 (2 x CH_{arom}), 128.60 (2 x CH_{arom}), 128.63 (2 x CH_{arom}), 138.14 (C_{arom}), 142.02 ($NCH_2\underline{C}_{arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$) δ:** 13.8. **IR (cm^{-1}) ν_{max}:** 1255 (P=O), 1023. **MS: m/z (%):** 370.8 ($M+H^+$, 100).

4.6 Attempted synthesis of bicyclic pyrroles

4.6.1 Synthesis of (5S)-ethyl 1-(but-1-enyl)-5-oxopyrrolidine-2-carboxylate (288)

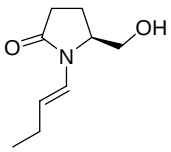
In a dry flask ethyl pyroglutamate (5 g, 32 mmol) and butanal (2.31 g, 32 mmol) are dissolved into toluene (40 ml). To this mixture is added P_2O_5 (4.78 g, 33.7 mmol) and the flask is fitted with a Dean-Stark apparatus. After 12 hours of refluxing the mixture is cooled and carefully poured into a separation funnel containing 200 ml $NaHCO_3$ (aq, sat). This mixture is extracted with diethyl ether (3 x 100 ml) and dried with $MgSO_4$. After removal of the solids the product is distilled (Kugelrohr, 155-160 °C, 3 mmHg) and further purified using column chromatography (diethyl ether, R_f = 0.44). The compound is obtained as an oil in 52% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.99 (t, *J* = 7.4 Hz, 3H, $CH_2C\underline{H}_3$), 1.27 (t, *J* = 7.2 Hz, 3H, $COOCH_2C\underline{H}_3$), 2.02-2.17 (m, 3H, $C\underline{H}_2CH_3$ + $COCH_2C\underline{H}_AH_B$), 2.29-2.50 (m, 2H, $COC\underline{H}_AH_BCH_A\underline{H}_B$), 2.55-2.70 (m, 1H, $COCH_A\underline{H}_B$), 4.23 (q, *J* = 7.2 Hz, 2H, $COOC\underline{H}_2CH_3$), 4.36 (dd, *J* = 1.8 Hz, *J* = 9.2 Hz, 1H, NCH), 4.90 (dt, *J* = 6.9 Hz, *J* = 14.7 Hz, 1H, $NCH=C\underline{H}$), 6.83 (d, *J* = 14.7 Hz, 1H, $NC\underline{H}=CH$). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 13.46 (CH_3), 13.98 (CH_3), 22.70 (CH_2), 23.14 ($\underline{C}H_2CH_3$), 29.60 ($CO\underline{C}H_2$), 58.43 ($COO\underline{C}H_2CH_3$), 61.34 (NCH), 114.00 ($NCH=\underline{C}H$), 122.05 ($N\underline{C}H=CH$), 171.39 (C=O), 172.69 (C=O). **IR (cm^{-1}) ν_{max}:** 1667 (C=C), 1712 (C=O), 1743 (C=O). **MS: m/z (%):** 212 ($M+H^+$, 100).

4.6.2 Synthesis of (5S)-1-[(1E)-but-1-enyl]-5-(hydroxymethyl)pyrrolidin-2-one (289)

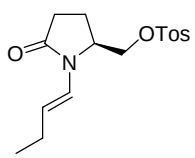
In a dry flask enamide **288** (1.42 g, 6.73 mmol) is dissolved into dry methanol (15 ml). Carefully $NaBH_4$ (0.28 g, 7.4 mmol) is added and the mixture is refluxed for 2 hours. After this period, the flask is cooled and again very carefully $NaBH_4$ (0.28 g, 7.4 mmol) is added and the mixture is again refluxed for 2 hours. After this again very carefully a final amount of $NaBH_4$ (0.28 g, 7.4 mmol) is added and the mixture is again refluxed for 2 hours. After cooling, 50 ml of $NaHCO_3$ (aq, sat) is added and the methanol is removed *in vacuo*. The remaining part is extracted with CH_2Cl_2 (3 x 25 ml) and dried with $MgSO_4$. After evaporation of the solvent the alcohol is purified by column chromatography and obtained as an oil in 72% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.02 (t, *J* = 7.4 Hz, 3H, CH_3), 1.95-2.23 (m, 4H, $C\underline{H}_2CH_3$ + CH_2), 2.26-2.40 (m, 1H, $COCH_A\underline{H}_B$), 2.62 (dt, *J* = 2.6 Hz, *J* = 8.5 Hz, 1H, $COCH_A\underline{H}_B$), 3.64 (dd, *J* = 2.5Hz, *J* = 11.4 Hz, 1H, $C\underline{H}_AH_BOH$), 3.78 (dd, *J* = 4.8 Hz, *J* = 11.4 Hz, 1H, $CH_A\underline{H}_BOH$), 4.00-4.03 (m, 1H, NCH), 4.65 (br s, 1H, OH), 5.15 (dt, *J* = 7.0 Hz, *J* = 14.9 Hz, 1H, NCH=C$\underline{H}$), 6.69 (d, *J* = 14.9 Hz, 1H, NC$\underline{H}$=CH). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 14.24 (CH_3), 21.55 (CH_2), 23.43 ($\underline{C}H_2CH_3$), 30.62 ($CO\underline{C}H_2$), 58.26 (CH_2OH), 60.53 (NCH), 114.93 (NCH=$\underline{C}$H), 121.47 (N$\underline{C}$H=CH), 173.90 (C=O). **IR (cm^{-1}) ν_{max}:** 1663 (C=C), 1682 (br. C=O), 3391 (br. OH). **MS: m/z (%):** 170 ($M+H^+$, 100). **Chromatography:** CH_2Cl_2/MeOH 93/7 R_f = 0.31.

4.6.3 Synthesis of {(2S)-1-[(1E)-but-1-enyl]-5-oxopyrrolidin-2-yl}methyl 4-methyl benzenesulfonate (290)

In a dry flask alcohol **289** (0.59 g, 3.49 mmol) is dissolved into dry CH_2Cl_2 (10 ml). To this solution tosylchloride (0.80 g, 4.18 mmol) and pyridine (0.33 g, 4.18 mmol) are added and the mixture is stirred for 16 hours at room temperature. Next the mixture is poured into a separation funnel containing 50 ml $NaHCO_3$ (aq, sat), extracted with CH_2Cl_2 (3 x 10 ml) and dried with $MgSO_4$. After evaporation of the solvent the product is purified by column chromatography and obtained as a white solid in 98% yield.

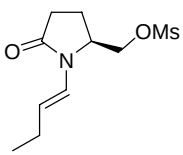


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, *J* = 7.1 Hz, 3H, CH_3), 1.91-2.67 (m, 6H, $C\underline{H}_2CH_3$ + $C\underline{H}_2C\underline{H}_2$), 2.46 (s, 3H, Ph$C\underline{H}_3$), 4.07-4.15 (m, 3H, NCH + CH_2O), 4.73 (dt, *J* = 7.1 Hz, *J* = 14.9 Hz, 1H, NCH=C$\underline{H}$), 6.50 (d, *J* = 14.9 Hz, 1H, NC$\underline{H}$=CH), 7.36 (d, *J* = 8.1 Hz, 2 x CH_{arom}), 7.74 (d, *J* = 8.1 Hz, 2 x CH_{arom}). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 14.22 (CH_3), 21.51 (CH_2), 21.71 (Ph$\underline{C}H_3$), 23.42 ($\underline{C}H_2CH_3$), 30.09 ($CO\underline{C}H_2$), 54.84 (CH_2O), 67.34 (NCH), 114.50 (NCH=$\underline{C}$H), 121.10 (N$\underline{C}$H=CH), 128.03 (2 x CH_{arom}), 130.08 (2 x CH_{arom}), 132.19 ($SC_{q,arom}$), 145.35 ($C_{q,arom}$), 172.66 (C=O). **IR (cm^{-1}) ν_{max}:** 1664

(C=C), 1689 (C=O). **MS: m/z (%):** 324.2 ($M+H^+$, 100). **Chromatography:** EtOAc R_f = 0.53. **MP (°C):** 62.5-63. α^{589nm} = -37.2° (c = 11.02 mg/ml in CH_2Cl_2).

4.6.4 Synthesis of {(2S)-1-[(1E)-but-1-enyl]-5-oxopyrrolidin-2-yl}methyl methane sulfonate (291)

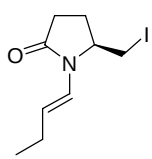
In a dry flask alcohol **289** (1 g, 5.92 mmol) is dissolved into dry CH_2Cl_2 (20 ml) and placed into an ice bath. To this solution pyridine (0.51 g, 6.5 mmol), mesylchloride (0.48 ml, 6.21 mmol) and DMAP (0.07 g, 0.59 mmol) are added and the mixture is stirred for 16 hours at room temperature. Next the mixture is poured into a separation funnel containing 50 ml $NaHCO_3$ (aq, sat), extracted with CH_2Cl_2 (3 x 10 ml) and dried with $MgSO_4$. After evaporation of the solvent the product is purified by column chromatography and obtained as an oil in 94% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.04 (t, *J* = 7.4 Hz, 3H, CH_3), 1.76-2.69 (m, 6H, $C\underline{H}_2CH_3$ + $C\underline{H}_2C\underline{H}_2$), 3.01 (s, 3H, SCH_3), 4.18-4.25 (m, 1H, NCH), 4.31 (dd, *J* = 2.6 Hz, *J* = 10.5 Hz, 1H, $C\underline{H}_AH_BO$), 4.37 (dd, *J* = 4.7 Hz, *J* = 10.5 Hz, 1H, $CH_A\underline{H}_BO$), 5.11 (dt, *J* = 6.7 Hz, *J* = 14.7 Hz, 1H, NCH=C<u>H</u>), 6.78 (d, *J* = 14.7 Hz, 1H, N<u>C</u>H=CH). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 14.28 (CH_3), 21.40 (CH_2), 23.40 ($\underline{C}H_2CH_3$), 29.98 ($CO\underline{C}H_2$), 37.26 (SCH_3), 54.94 (NCH), 67.42 (OCH_2), 114.89 (NCH=<u>C</u>H), 121.22 (N<u>C</u>H=CH), 172.80 (C=O). **IR (cm^{-1}) ν_{max}:** 1694 (br C=C + C=O). **MS: m/z (%):** 248.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 2/8 R_f = 0.33.

4.6.5 Synthesis of (5S)-1-[(1E)-but-1-enyl]-5-(iodomethyl)pyrrolidin-2-one (292)

In a dry flask alcohol **289** (1 g, 5.92 mmol) is dissolved into dry toluene (60 ml). To this solution triphenylphosphine (2.33 g, 8.88 mmol) is added and the mixture is refluxed for 15 minutes. After this time 10 ml of toluene is removed by distillation. The mixture is cooled to room temperature and imidazole (1.21 g, 17.8 mmol) and iodine (1.95 g, 7.69 mmol) are added. The mixture is refluxed for 30 minutes after which the solvent is removed *in vacuo*. Next EtOAc (75 ml) is added and the organic layer is washed with brine (25 ml). After drying with $MgSO_4$ the remainder is dissolved in a 1:1 mixture of EtOAc:hexanes and placed in the freezer. The liquid layer is decanted from the white precipitate (Ph_3PO) and purified by column chromatography. The compound is obtained as an oil in 48% yield.



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.03 (t, *J* = 7.4 Hz, 3H, CH_3), 1.73-2.70 (m, 6H, $C\underline{H}_2CH_3$ + $C\underline{H}_2C\underline{H}_2$), 3.16-3.45 (m, 2H, CH_2I), 4.09 (t, *J* = 8.3 Hz, 1H, NCH), 5.04 (dt, *J* = 7.0 Hz, *J* = 14.9 Hz, 1H, NCH=C<u>H</u>), 6.73 (d, *J* = 14.9 Hz, 1H, N<u>C</u>H=CH). **^{13}C -NMR (75 MHz, $CDCl_3$) δ:** 8.74 (CH_2I), 14.39 (CH_3), 23.45 (CH_2), 24.03

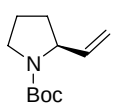
($\underline{C}H_2CH_3$), 29.72 ($CO\underline{C}H_2$), 56.61 (NCH), 114.46 (NCH=$\underline{C}$H), 121.15 (N$\underline{C}$H=CH), 172.05 (C=O). **IR (cm^{-1}) ν_{max}:** 1691 (br C=C + C=O). **MS: m/z (%):** 280.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 8/2 R_f = 0.24.

4.6.6 Synthesis of tert-butyl (2S)-2-hydroxymethyl-pyrrolidine-1-carboxylate (295) and tert-butyl (2S)-2-formyl-pyrrolidine-1-carboxylate (296)

Both compounds were obtained following a literature procedure and the obtained spectroscopic data was in agreement with the reported data.[211]

4.6.7 Synthesis of tert-butyl (2S)-2-vinylpyrrolidin-1-carboxylate (297)

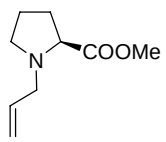
In a dry flask methyltriphenylphosphonium iodide (4.57 g, 11.3 mmol) is dissolved in 30 ml dry THF and KO*t*Bu (2.62 g, 11.6 mmol) is added. This mixture is stirred for 15 minutes under inert N_2 atmosphere. Next aldehyde **296** (1.5 g, 7.54 mmol) is dissolved into dry THF (20 ml) and added to the mixture which is stirred for an overnight period. After this time 30 ml of water is added and the mixture is extracted with ether (3 x 50 ml). The organic layer is washed with brine (20 ml) and dried with $MgSO_4$. After removal of the solvent, the remainder is dissolved in a 1:1 mixture of ether:hexanes and placed in the freezer. The liquid layer is decanted from the white precipitate (Ph_3PO) and purified by column chromatography. The compound is obtained as an oil in 70% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.44 (s, 9H, *t*Bu), 1.66-2.13 (m, 4H, 2 x CH_2), 3.63 (br s, 2H, NCH_2), 4.25 (br s, 1H, NCH), 5.02 (br s, 1H, HC=C$\underline{H}_A$$H_B$), 5.06 (br s, 1H, HC=C$H_A$$\underline{H}_B$), 5.73 (br s, 1H, $\underline{H}$C=CH_2). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 22.29 (CH_2), 27.93 ((CH_3)$_3$), 31.61 (CH_2), 45.72 (NCH_2), 58.67 (NCH), 78.11 (C_q), 113.02 (HC=$\underline{C}H_2$), 138.70 (H$\underline{C}$=CH_2), 153.73 (C=O). **IR (cm^{-1}) υ_{max}:** 1644 (C=C), 1692 (C=O). **MS (ESI): m/z (%):** 198.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 9/1 R_f = 0.23. α^{589nm} = -14.4° (c = 10.40 mg/ml in CH_2Cl_2).

4.6.8 Synthesis of methyl (2S)-1-allylpyrrolidine-2-carboxylate (300)

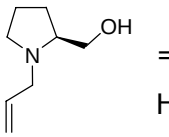
Methyl prolinate **299** (5 g, 39 mmol) is dissolved in acetonitrile (50 ml). To this solution pyridine (3.67 g, 47 mmol) and allylbromide (5.16 g, 43 mmol) are added. The mixture is refluxed for 4 hours. After this time all the volatiles are removed *in vacuo* and the residue is dissolved in EtOAc (50 ml) and saturated aqueous $NaHCO_3$ (50 ml). After extracting with EtOAc (3 x 25 ml) and drying with $MgSO_4$ the compound is obtained pure as an oil in 78% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.79-2.22 (m, 4H, 2 x CH_2), 2.38 (dd, *J* = 7.7 Hz, *J* = 16.0 Hz, 1H, $NCH_AH_BCH_2$), 3.09-3.18 (m, 3H, NCH + $NCH_AH_BCH_2$ + NCH_AH_BCH), 3.71 (dd, *J* = 6.5 Hz, *J* = 13.1 Hz, 1H, NCH_AH_BCH), 3.72 (s, 3H, CH_3), 5.07-5.21 (m, 2H, $HC=CH_2$), 5.85-5.99 (m, 1H, $HC=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 22.74 (CH_2), 29.06 (CH_2), 51.17 (OCH_3), 52.99 (NCH_2CH_2), 57.25 (NCH_2CH), 64.65 (NCH), 116.81 ($HC=CH_2$), 135.06 ($HC=CH_2$), 173.93 (C=O). **IR (cm^{-1}) υ_{max}:** 1644 (C=C), 1736 (C=O). **MS (ESI): m/z (%):** 170.2 ($M+H^+$, 100). α^{589nm} = -99.8° (c = 11.32 mg/ml in CH_2Cl_2).

4.6.9 Synthesis of [(2S)-1-allylpyrrolidin-2-yl]methanol (301)

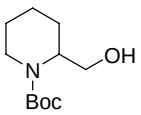
Ester **300** (5.1 g, 30.1 mmol) is dissolved in dry THF (50 ml) and placed in an ice bath under N_2 atmosphere. Very carefully $LiAlH_4$ (1.14 g, 30.1 mmol) is added. The mixture is stirred for 4 hours at 0 °C. After this time water (2 ml) is added drop wise and the solution is stirred for an additional hour at room temperature. The mixture is filtered over $MgSO_4$ and the solvent is removed. The compound is obtained pure as an oil in 89% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.66-1.96 (m, 4H, 2 x CH_2), 2.30 (dd, *J* = 7.3 Hz, *J* = 15.8 Hz, 1H, $NCH_AH_BCH_2$), 2.60-2.77 (m, 2H, NCH + NCH_AH_BCH), 2.92 (dd, *J* = 7.3 Hz, *J* = 13.6 Hz, 1H, NCH_AH_BCH), 3.05-3.17 (m, 1H, $NCH_AH_BCH_2$), 3.36-3.44 (m, 2H, NCH_AH_BOH + $NCH_AH_BCH_2$), 3.63 (dd, *J* = 10.8 Hz, *J* = 3.6 Hz, 1H, NCH_AH_BOH), 5.10 (dd, *J* = 1.2 Hz, *J* = 9.5 Hz, 1H, $HC=CH_AH_B$), 5.19 (dd, *J* = 1.2 Hz, *J* = 17.2 Hz, 1H, $HC=CH_AH_B$), 5.89 (dddd, *J* = 5.5 Hz, *J* = 7.3 Hz, *J* = 9.5 Hz, *J* = 17.2 Hz, 1H, $HC=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 22.77 (CH_2), 27.63 (CH_2), 54.26 (NCH_2CH_2), 57.75 (NCH_2CH), 62.85 (OCH_2), 64.47 (NCH), 116.78 ($HC=CH_2$), 135.76 ($HC=CH_2$). **IR (cm^{-1}) υ_{max}:** 1644 (C=C), 3400 (br OH). **MS (ESI): m/z (%):** 142.5 ($M+H^+$, 100). α^{589nm} = -36.8° (c = 10.34 mg/ml in CH_2Cl_2).

4.6.10 Synthesis of tert-butyl 2-(hydroxymethyl)piperidine-1-carboxylate (305)

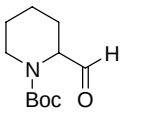
Ester **304** (5 g, 19.5 mmol) is dissolved in dry ethanol (50 ml) and placed in an ice bath under N_2 atmosphere. Very carefully $NaBH_4$ (2.21 g, 58.4 mmol) and LiCl (0.12 g, 2.92 mmol) are added. The mixture is refluxed for 8 hours. After this time 1N HCl is added until the pH is 7. The mixture is extracted with EtOAc (3 x 30 ml) and dried with $MgSO_4$. After removal of the solvent the residue is redissolved in CH_2Cl_2 (15 ml) and the precipitates are removed by filtration. The solvent is removed from the filtrate and the compound is obtained pure after column chromatography as a solid in 33% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.40-1.52 (m, 2H, CH_2), 1.46 (s, 9H, *t*Bu), 1.55-1.71 (m, 4H, 2 x CH_2), 2.87 (t, *J* = 12.3 Hz, 1H, $NC\underline{H}_AH_B$), 3.61 (dd, *J* = 5.8 Hz, *J* = 10.9 Hz, 1H, $OC\underline{H}_AH_B$), 3.82 (dd, *J* = 9.2 Hz, *J* = 10.9 Hz, 1H, $OCH_A\underline{H}_B$), 3.94 (br d, *J* = 12.3 Hz, 1H, $NCH_A\underline{H}_B$), 4.26-4.31 (m, 1H, NCH). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 19.74 (CH_2), 25.31 (CH_2), 25.37 (CH_2), 28.51 ((CH_3)$_3$), 40.03 (NCH_2), 52.64 (NCH), 61.89 (OCH_2), 79.94 (C_q), 156.43 (C=O). **IR (cm^{-1}) υ_{max}:** 1680 (br C=O), 3436 (br OH). **MS (ESI): m/z (%):** 238.3 ($M+Na^+$, 100). **MP (°C):** 64-66.

4.6.11 Synthesis of tert-butyl 2-formylpiperidine-1-carboxylate (306)

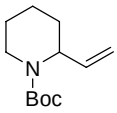
Alcohol **305** (1.35 g, 6.27 mmol) is dissolved in DMSO (10 ml) and placed in an ice bath under Ar atmosphere. To this solution NEt_3 (3.08 ml, 22 mmol) is added and the mixture is stirred for 15 minutes. After this time SO_3-pyridine complex (3.49 g, 21.9 mmol) is added in three portions over 40 minutes at room temperature. Next the reaction is placed in an ice bath and stirring is continues for 2.5 hours. After this period ice is added (25 g) and the mixture is extracted with CH_2Cl_2 (4 x 20 ml). The organic phase is washed consecutively with citric acid (20 ml, 50% in water), water (20 ml), $NaHCO_3$ (20 ml, aq, sat) and water (20 ml). After drying with $MgSO_4$ and removal of the solvent the compound is obtained pure in 97% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.02-1.63 (m, 14H, *t*Bu + $C\underline{H}_AH_B$+ 2 x CH_2), 2.01-2.11 (m, 1H, $CH_A\underline{H}_B$), 2.79 (br s, 1H, $NC\underline{H}_AH_B$), 3.89 (br s, $NCH_A\underline{H}_B$), 4.47 (br s, 1H, NCH), 9.47 (s, 1H, HCO). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 20.96 (CH_2), 23.60 (CH_2), 24.73 (CH_2), 28.42 ((CH_3)$_3$), 43.14 (br NCH_2), 61.51 (br NCH), 80.33 (C_q), 155.00 (br C=O), 201.32 (C=O). **IR (cm^{-1}) υ_{max}:** 1694 (C=O), 1735 (C=O). **MS (GCMS): m/z (%):** 184 (M^+-COH, 20), 140 (M^+-O*t*Bu, 20), 128 (100).

4.6.12 Synthesis of tert-butyl 2-vinylpiperidine-1-carboxylate (307)

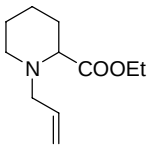
In a dry flask methyltriphenylphosphonium iodide (3.41 g, 8.44 mmol) is dissolved in 25 ml dry THF and KO*t*Bu (0.98 g, 8.53 mmol) is added. This mixture is stirred for 15 minutes under inert N_2 atmosphere. Next aldehyde **306** (1.2 g, 5.63 mmol) is dissolved into dry THF (15 ml) and added to the mixture which is stirred for an overnight period. After this time 30 ml of water is added and the mixture is extracted with ether (3 x 40 ml). The organic layer is washed with brine (20 ml) and dried with $MgSO_4$. After removal of the solvent, the remainder is dissolved in a 1:1 mixture of ether:hexanes and placed in the freezer. The liquid layer is decanted from the white precipitate (Ph_3PO) and purified by column chromatography. The compound is obtained as an oil in 76% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.24-1.82 (m, 15H, *t*Bu + 3 x CH_2), 2.83 (br t, *J* = 13.1 Hz, 1H, NCH_AH_B), 3.95 (br d, *J* = 13.1 Hz, 1H, NCH_AH_B), 4.79 (br s, 1H, NCH), 5.04 (dt, *J* = 1.4 Hz, *J* = 17.1 Hz, 1H, $HC=CH_AH_B$), 5.17 (dt, *J* = 1.4 Hz, *J* = 10.6 Hz, 1H, $HC=CH_AH_B$), 5.75 (ddd, *J* = 4.1 Hz, *J* = 10.6 Hz, *J* = 17.1 Hz, 1H, $HC=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 19.57 (CH_2), 25.64 (CH_2), 28.51 ($(CH_3)_3$), 29.02 (CH_2), 39.78 (NCH_2), 52.56 (NCH), 79.34 (C_q), 115.54 ($HC=CH_2$), 137.00 ($HC=CH_2$), 155.75 (C=O). **IR (cm^{-1}) υ_{max}:** 1640 (C=C), 1694 (C=O). **MS (ESI): m/z (%):** 212.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 9/1 R_f = 0.43.

4.6.13 Synthesis of ethyl 1-allylpiperidine-2-carboxylate (309)

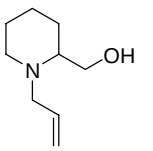
Ethyl pipecolinate **303** (4 g, 25 mmol) is dissolved in acetonitrile (40 ml). To this solution pyridine (2.42 g, 30.6 mmol) and allylbromide (3.39 g, 28 mmol) are added. The mixture is refluxed for 4 hours. After this time all the volatiles are removed *in vacuo* and the residue is dissolved in EtOAc (50 ml) and saturated aqueous $NaHCO_3$ (50 ml). After extracting with EtOAc (3 x 25 ml) and drying with $MgSO_4$ the compound is obtained pure as an oil in 96% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.28 (t, *J* = 7.2 Hz, CH_3), 1.33-2.19 (m, 6H, 3 x CH_2), 2.89-3.35 (m, 5H, 2 x NCH_2 + NCH), 4.11-4.23 (m, 2H, OCH_2), 5.12-5.18 (m, 2H, $HC=CH_2$), 5.83-5.97 (m, 1H, $HC=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 13.74 (CH_3), 22.07 (CH_2), 24.90 (CH_2), 29.09 (CH_2), 49.81 (NCH_2CH_2), 58.91 (NCH_2CH), 59.54 (OCH_2), 63.72 (NCH), 117.10 ($HC=CH_2$), 134.67 ($HC=CH_2$), 172.68 (C=O). **IR (cm^{-1}) υ_{max}:** 1643 (C=C), 1733 (C=O). **MS (ESI): m/z (%):** 198.2 ($M+H^+$, 100).

4.6.14 Synthesis of (1-allylpiperidin-2-yl)methanol (310)

Ester **309** (4.1 g, 21 mmol) is dissolved in dry THF (35 ml) and placed in an ice bath under N_2 atmosphere. Very carefully $LiAlH_4$ (0.79 g, 21 mmol) is added. The mixture is stirred for 4 hours at 0 °C. After this time water (1.5 ml) is added drop wise and the solution is stirred for an additional hour at room temperature. The mixture is filtered over $MgSO_4$ and the solvent is removed. The compound is obtained pure as an oil in 98% yield.



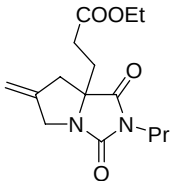
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.22-1.85 (m, 6H, 3 x CH_2), 2.18-2.37 (m, 2H, $NCH_AH_BCH_2$ + NCH), 2.92-3.20 (m, 2H, $NCH_AH_BCH_2$ + NCH_AH_BCH), 3.40-3.52 (m, 2H, NCH_AH_BCH + CH_AH_BOH), 3.78 (dd, *J* = 3.7 Hz, *J* = 11.0 Hz,1H, CH_AH_BOH), 5.12-5.22 (m, 2H, $HC=CH_2$), 5.80-5.94 (m, 1H, $HC=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ

23.46 (CH_2), 23.71 (CH_2), 27.15 (CH_2), 50.71 (NCH_2CH_2), 55.68 (NCH_2CH), 60.40 (NCH), 61.52 (CH_2OH), 116.18 ($HC=CH_2$), 133.48 ($HC=CH_2$). **IR (cm^{-1}) υ_{max}:** 1643 (C=C), 3370 (br OH). **MS (ESI): m/z (%):** 156.2 ($M+H^+$, 100).

4.7 Synthesis of hydantoins by rearrangement of pyroglutamates

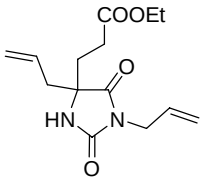
Typical procedures for the synthesis and complete spectroscopic description of compounds **22a-h**, **365a-i**, **368a-e**, **32a-h** and **33a-h** can be found in paper V.

4.7.1 Ethyl 3-(6-methylene-1,3-dioxo-2-propyltetrahydro-1H-pyrrolo[1,2-c]imidazol-7a(5H)-yl)propanoate (370)



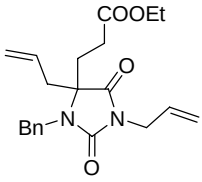
^{1}H-NMR (300 MHz, CDCl3) δ: 0.93 (t, *J* = 7.3 Hz, 3H, $NCH_2CH_2CH_3$), 1.24 (t, *J* = 7.2 Hz, 3H, CH_3), 1.65 (sextet, *J* = 7.3 Hz, 2H, NCH_2CH_2), 2.03-2.28 (m, 4H, CH_2CH_2), 2.43-2.73 (m, 2H, CCH_2), 3.45 (dt, *J* = 7.3 Hz, *J* = 13.3 Hz, 1H, $NCH_AH_BCH_2$), 3.49 (dt, *J* = 7.3 Hz, *J* = 13.3 Hz, 1H, $NCH_AH_BCH_2$), 3.73 (d + small splitting, *J* = 15.5 Hz, 1H, NCH_AH_BC), 4.09 (dq, *J* = 7.2 Hz, *J* = 10.5 Hz, 1H, $CH_AH_BCH_3$), 4.12 (dq, *J* = 7.2 Hz, *J* = 10.5 Hz, 1H, $CH_AH_BCH_3$), 4.32 (d + small splitting, *J* = 15.5 Hz, 1H, NCH_AH_BC), 5.11 (p, *J* = 2.1 Hz, 1H, $C=CH_AH_B$), 5.15 (p, *J* = 2.1 Hz, 1H, $C=CH_AH_B$). **^{13}C-NMR (75 MHz, CDCl3) δ:** 11.19 (CH_3, pr), 14.18 (CH_3), 21.35 (NCH_2CH_2), 29.16 (CH_2), 29.42 (CH_2), 40.73 (NCH_2CH_2), 40.78 (CCH_2C), 48.68 (NCH_2C), 60.78 (OCH_2), 71.78 (C_q), 110.12 ($HC=CH_2$), 144.93 ($C=CH_2$), 159.73 (NC=ON), 172.42 (C=O), 175.03 (C=O). **MS (ESI) m/z (%):** 295.8 ($M+H^+$, 100). **IR (cm-1, KBr) υ_{max}:** 1714 (C=O), 1774 (C=O). **Chromatography:** Hex/EtOAc/ether 7/3/2 R_f = 0.36. **Yield:** 34%.

4.7.2 Ethyl 3-(1,4-diallyl-2,5-dioxo-imidazolidin-4-yl)propionate (371)



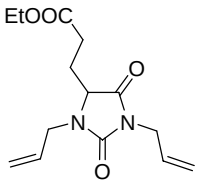
^{1}H-NMR (300 MHz, CDCl3) δ: 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 2.05-2.31 (m, 4H, CH_2CH_2), 2.44 (dd, *J* = 7.4 Hz, *J* = 14.0 Hz, 1H, CH_AH_BCH), 2.52 (dd, *J* = 7.6 Hz, *J* = 14.0 Hz, 1H, CH_AH_BCH), 4.07-4.16 (m, 2H, NCH_2), 4.12 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 5.16-5.28 (m, 4H, 2 x $HC=CH_2$), 5.62-5.86 (m, 2H, 2 x $HC=CH_2$). **^{13}C-NMR (75 MHz, CDCl3) δ:** 14.19 (CH_3), 28.76 (CH_2), 31.16 (CH_2), 40.70 (NCH_2), 41.46 (CH_2CH), 61.02 (OCH_2), 64.59 (C_q), 118.23 ($HC=CH_2$), 121.36 ($HC=CH_2$), 130.03 ($HC=CH_2$), 131.15 ($HC=CH_2$), 156.69 (NC=ON), 172.81 (C=O), 174.98 (C=O). **MS (ESI) m/z (%):** 281.2 ($M+H^+$, 100). **IR (cm-1, KBr) vmax:** 1645 (C=C), 1714 (C=O), 1777 (C=O). **Chromatography:** Hex/EtOAc 6/4 R_f = 0.23. **Yield:** 55%.

4.7.3 Ethyl 3-(1,4-diallyl-3-benzyl-2,5-dioxo-imidazolidin-4-yl)propionate (372)



^{1}H-NMR (300 MHz, CDCl3) δ: 1.18 (t, *J* = 7.1 Hz, 3H, CH_3), 1.73-2.15 (m, 4H, CH_2CH_2), 2.47 (dd, *J* = 6.7 Hz, *J* = 14.2 Hz, 1H, $C\underline{H}_A\underline{H}_BCH$), 2.54 (dd, *J* = 7.3 Hz, *J* = 14.2 Hz, 1H, $CH_A\underline{H}_BCH$), 4.00 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.10 (dd, *J* = 5.2 Hz, *J* = 14.4 Hz, 1H, $NCH_A\underline{H}_B$), 4.12 (dd, *J* = 5.9 Hz, *J* = 14.4 Hz, 1H, $NCH_A\underline{H}_B$), 4.29 (d, *J* = 15.3 Hz, 1H, $NC\underline{H}_A\underline{H}_BPh$), 4.68 (d, *J* = 15.3 Hz, 1H, $NC\underline{H}_A\underline{H}_BPh$), 4.98-5.05 (m, 2H, $HC=C\underline{H}_2$), 5.19-5.38 (m, 3H, $\underline{H}C=C\underline{H}_2$), 5.74-5.87 (m, 1H, $\underline{H}C=CH_2$), 7.25-7.44 (m, 5H, Ph). **^{13}C-NMR (75 MHz, CDCl3) δ:** 14.21 (CH_3), 27.97 (CH_2), 29.87 (CH_2), 39.60 ($\underline{C}H_2CH$), 41.16 (NCH_2), 43.77 ($N\underline{C}H_2Ph$), 60.68 (OCH_2), 68.55 (C_q), 118.55 ($HC=\underline{C}H_2$), 121.09 ($HC=\underline{C}H_2$), 128.15 (CH_{arom}), 128.89 (2 x CH_{arom}), 129.01 (2 x CH_{arom}), 129.62 ($H\underline{C}=CH_2$), 131.24 ($H\underline{C}=CH_2$), 137.19 ($C_{q,arom}$), 156.49 (NC=ON), 171.73 (C=O), 173.76 (C=O). **MS (ESI) m/z (%):** 371.2 ($M+H^+$, 100). **IR (cm-1, KBr) vmax:** 1710 (C=O), 1733 (C=O), 1769 (C=O). **Chromatography:** Hex/EtOAc 2/1 R_f = 0.40. **Yield:** 88%.

4.7.4 Ethyl 3-(1,3-diallyl-2,5-dioxo-imidazolidin-4-yl)propionate (374)



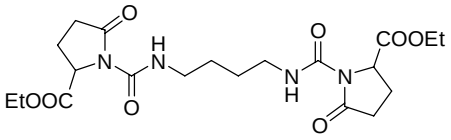
^{1}H-NMR (300 MHz, CDCl3) δ: 1.25 (t, *J* = 7.1 Hz, 3H, CH_3), 2.02-2.14 (m, 1H, $CHC\underline{H}_A\underline{H}_B$), 2.17-2.44 (m, 3H, $COC\underline{H}_2$ + $CHCH_A\underline{H}_B$), 3.62 (dd, *J* = 7.7 Hz, *J* = 15.7 Hz, 1H, $NC\underline{H}_A\underline{H}_B$), 4.04 (dd, *J* = 3.0 Hz, *J* = 6.6 Hz, 1H, $C\underline{H}CH_2$), 4.10 (dd, *J* = 1.7 Hz, *J* = 3.0 Hz, 1H, $NC\underline{H}_A\underline{H}_B$), 4.12 (dd, *J* = 1.4 Hz, *J* = 3.2 Hz, 1H, $NCH_A\underline{H}_B$), 4.13 (q, *J* = 7.1 Hz, 2H, $C\underline{H}_2CH_3$), 4.37 (ddt, *J* = 1.3 Hz, *J* = 5.0 Hz, *J* = 15.7 Hz, 1H, $NCH_A\underline{H}_B$), 5.19-5.29 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.34-5.95 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, CDCl3) δ:** 14.24 (CH_3), 23.80 (CH_2), 28.22 (CH_2), 41.07 (NCH_2), 43.54 (NCH_2), 57.81 (CH), 60.93 (OCH_2), 118.28 ($HC=\underline{C}H_2$), 119.51 ($HC=\underline{C}H_2$), 131.21 ($H\underline{C}=CH_2$), 131.73 ($H\underline{C}=CH_2$), 155.97 (NC=ON), 172.20 (C=O), 172.37 (C=O). **MS (ESI) m/z (%):** 281.2 ($M+H^+$, 100). **IR (cm-1, KBr) vmax:** 1646 (C=C), 1661 (C=C), 1713 (C=O), 1772 (C=O). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.55. **Yield:** 99%.

4.8 Synthesis of bis-hydantoins and derivatives

4.8.1 Synthesis of bis-carbamoyl lactams 379

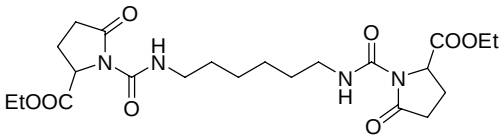
The general procedure of this synthesis can be found in paper VI.

Ethyl 1-({[4-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)butyl]amino} carbonyl)-5-oxopyrrolidine-2-carboxylate (379a)



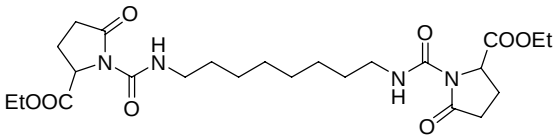
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.60 (t, *J* = 3.0 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.00-2.10 (m, 2H, 2 x $CHC\underline{H}_AH_B$), 2.25-2.45 (m, 2H, 2 x $CHCH_A\underline{H}_B$), 2.57 (ddd, *J* = 17.6 Hz, *J* = 3.4 Hz, *J* = 9.5 Hz, 2H, 2 x $COC\underline{H}_AH_B$), 2.74 (ddd, *J* = 17.6 Hz, *J* = 9.9 Hz, *J* = 9.9 Hz, 2H, 2 x $COCH_A\underline{H}_B$), 3.23-3.40 (m, 4H, 2 x $NC\underline{H}_2$), 4.24 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.77 (dd, *J* = 9.5 Hz, *J* = 2.6 Hz, 2H, 2 x C<u>H</u>), 8.31 (t, *J* = 5.5 Hz, 2H, 2 x NH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.15 (2 x CH_3), 21.28 (2 x $CH\underline{C}H_2$), 27.02 (2 x $NCH_2\underline{C}H_2$), 31.87 (2 x $CO\underline{C}H_2$), 39.51 (2 x $N\underline{C}H_2$), 58.20 (2 x <u>C</u>H), 61.72 (2 x $\underline{C}H_2CH_3$), 152.29 (2 x NC=ON), 171.50 (2 x NC=O), 176.48 (2 x C=OO). **IR (cm^{-1}) ν_{max}:** 1694 (C=O), 1721 (br C=O), 3317 (NH). **MS: m/z (%):** 455.7 ($M+H^+$, 100). **HRMS:** calcd for $C_{20}H_{30}N_4O_8$ ($M + H^+$), 455.21364; found, 455.21475. **Yield:** 97%.

Ethyl 1-({[6-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)hexyl]amino} carbonyl)-5-oxopyrrolidine-2-carboxylate (379b)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.35 (t, *J* = 6.9 Hz, 4H, 2 x $N(CH_2)_2C\underline{H}_2$), 1.55 (p, *J* = 6.9 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.04 (dddd, *J* = 13.3 Hz, *J* = 9.7 Hz, *J* = 3.2 Hz, *J* = 3.0 Hz, 2H, 2 x $CHC\underline{H}_AH_B$), 2.34 (dddd, *J* = 13.3 Hz, *J* = 9.8 Hz, *J* = 9.7 Hz, *J* = 9.6 Hz, 2H, 2 x $CHCH_A\underline{H}_B$), 2.57 (ddd, *J* = 17.6 Hz, *J* = 9.7 Hz, *J* = 3.2 Hz, 2H, 2 x $COC\underline{H}_AH_B$), 2.74 (ddd, *J* = 17.6 Hz, *J* = 9.7 Hz, *J* = 9.8 Hz, 2H, 2 x $COCH_A\underline{H}_B$), 3.23 (ddt, *J* = 13.3 Hz, *J* = 6.9 Hz, *J* = 5.4 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 3.32 (ddt, *J* = 13.3 Hz, *J* = 6.9 Hz, *J* = 5.4 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 4.24 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.78 (dd, *J* = 3.0 Hz, *J* = 9.6 Hz, 2H, 2 x C<u>H</u>), 8.29 (t, *J* = 5.4 Hz, 2H, 2 x NH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.18 (2 x CH_3), 21.32 (2 x $CH\underline{C}H_2$), 26.55 (2 x $N(CH_2)_2\underline{C}H_2$), 29.58 (2 x $NCH_2\underline{C}H_2$), 31.93 (2 x $CO\underline{C}H_2$), 39.87 (2 x $N\underline{C}H_2$), 58.23 (2 x <u>C</u>H), 61.75 (2 x $\underline{C}H_2CH_3$), 152.29 (2 x NC=ON), 171.56 (2 x NC=O), 176.46 (2 x C=OO). **IR (cm^{-1}) ν_{max}:** 1693 (C=O), 1721 (C=O), 1743 (C=O), 3319 (NH). **MS: m/z (%):** 483.8 ($M+H^+$, 100). **HRMS:** calcd for $C_{22}H_{34}N_4O_8$ ($M + H^+$), 483.24494; found, 483.24594. **Yield:** 99%.

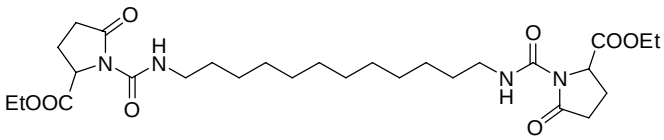
Ethyl 1-({[8-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)octyl]amino} carbonyl)-5-oxopyrrolidine-2-carboxylate (379c)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.30 (m, 8H, 2 x $N(CH_2)_2C\underline{H}_2C\underline{H}_2$), 1.53 (p, *J* = 6.7 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.05 (ddt, *J* = 13.1 Hz, *J* = 9.9 Hz, *J* = 3.1 Hz, 2H, 2 x $CHC\underline{H}_AH_B$), 2.34 (ddt, *J* = 13.1

Hz, *J* = 9.6 Hz, *J* = 9.8 Hz, 2H, 2 x CHCH$_A$H$_B$), 2.57 (ddd, *J* = 17.6 Hz, *J* = 9.6 Hz, *J* = 3.1 Hz, 2H, 2 x COCH$_A$H$_B$), 2.74 (ddd, *J* = 17.6 Hz, *J* = 9.8 Hz, *J* = 9.9 Hz, 2H, 2 x COCH$_A$H$_B$), 3.23 (ddt, *J* = 13.3 Hz, *J* = 6.7 Hz, *J* = 5.4 Hz, 2H, 2 x NCH$_A$H$_B$), 3.32 (ddt, *J* = 13.3 Hz, *J* = 6.6 Hz, *J* = 5.4 Hz, 2H, 2 x NCH$_A$H$_B$), 4.24 (q, *J* = 7.2 Hz, 4H, 2 x CH$_2$CH$_3$), 4.78 (dd, *J* = 3.1 Hz, *J* = 9.6 Hz, 2H, 2 x CH), 8.28 (t, *J* = 5.4 Hz, 2H, 2 x NH). **^{13}C-NMR (75 MHz, CDCl$_3$) δ:** 14.18 (2 x CH$_3$), 21.32 (2 x CHCH$_2$), 26.82 (2 x N(CH$_2$)$_2$CH$_2$), 29.19 (2 x N(CH$_2$)$_3$CH$_2$), 29.61 (2 x NCH$_2$CH$_2$), 31.95 (2 x COCH$_2$), 39.98 (2 x NCH$_2$), 58.23 (2 x CH), 61.75 (2 x CH$_2$CH$_3$), 152.26 (2 x NC=ON), 171.58 (2 x NC=O), 176.46 (2 x C=OO). **IR (cm^{-1}) ν_{max}:** 1694 (C=O), 1723 (C=O), 1746 (C=O), 3318 (NH). **MS: m/z (%):** 511.7 (M+H$^+$, 100). **HRMS:** calcd for $C_{24}H_{38}N_4O_8$ (M + H$^+$), 511.27624; found, 511.27666. **Yield:** 99%.

Ethyl 1-({[12-({[2-(ethoxycarbonyl)-5-oxopyrrolidin-1-yl]carbonyl}amino)dodecyl] amino}carbonyl)-5-oxopyrrolidine-2-carboxylate (379c)

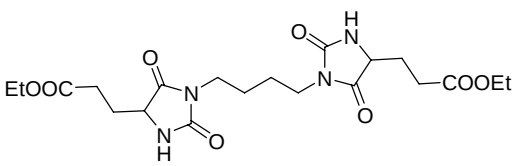


^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.25-1.31 (m, 16H, 2 x N(CH$_2$)$_2$(CH$_2$)$_4$), 1.29 (t, *J* = 7.2 Hz, 6H, 2 x CH$_3$), 1.54 (p, *J* = 6.7 Hz, 4H, 2 x NCH$_2$CH$_2$), 2.05 (ddt, *J* = 13.1 Hz, *J* = 9.9 Hz, *J* = 2.9 Hz, 2H, 2 x CHCH$_A$H$_B$), 2.33 (ddt, *J* = 13.1 Hz, *J* = 9.8 Hz, *J* = 9.4 Hz, 2H, 2 x CHCH$_A$H$_B$), 2.57 (ddd, *J* = 17.6 Hz, *J* = 9.8 Hz, *J* = 2.9 Hz, 2H, 2 x COCH$_A$H$_B$), 2.74 (ddd, *J* = 17.6 Hz, *J* = 9.9 Hz, *J* = 9.4 Hz, 2H, 2 x COCH$_A$H$_B$), 3.24 (br dt, *J* = 13.2 Hz, *J* = 6.7 Hz, 2H, 2 x NCH$_A$H$_B$), 3.31 (br dt, *J* = 13.2 Hz, *J* = 6.7 Hz, 2H, 2 x NCH$_A$H$_B$), 4.24 (q, *J* = 7.2 Hz, 4H, 2 x CH$_2$CH$_3$), 4.78 (dd, *J* = 9.4 Hz, *J* = 2.9 Hz, 2H, 2 x CH), 8.28 (t, *J* = 5.3 Hz, 2H, 2 x NH). **^{13}C-NMR (75 MHz, CDCl$_3$) δ:** 14.18 (2 x CH$_3$), 21.34 (2 x CHCH$_2$), 26.94 (2 x N(CH$_2$)$_2$CH$_2$), 29.34 (2 x N(CH$_2$)$_3$CH$_2$), 29.58 (2 x N(CH$_2$)$_4$CH$_2$), 29.61 (2 x N(CH$_2$)$_5$CH$_2$), 29.66 (2 x NCH$_2$CH$_2$), 31.95 (2 x COCH$_2$), 40.04 (2 x NCH$_2$), 58.24 (2 x CH), 61.75 (2 x CH$_2$CH$_3$), 152.28 (2 x NC=ON), 171.58 (2 x NC=O), 176.45 (2 x C=OO). **IR (cm^{-1}) ν_{max}:** 1694 (C=O), 1723 (C=O), 1746 (C=O), 3318 (NH). **MS: m/z (%):** 567.5 (M+H$^+$, 100). **MP (°C):** 99.4-101. **HRMS:** calcd for $C_{28}H_{46}N_4O_8$ (M + H$^+$), 567.33884; found, 567.34103. **Yield:** 99%.

4.8.2 Synthesis of bis-hydantoins 382

The general procedure of this synthesis can be found in paper VI.

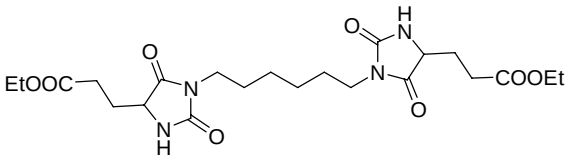
3-(1-{4-[4-(2-Ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-butyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (382a)



^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.26 (t, *J* = 7.2 Hz, 6H, 2 x CH$_3$), 1.63 (br s, 4H, 2 x NCH$_2$CH$_2$), 2.03 (ddt, *J* = 13.9 Hz, *J* = 7.2 Hz, *J* = 7.3 Hz, 2H, 2 x

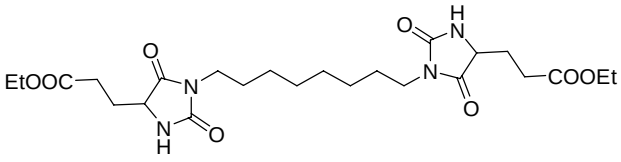
C<u>H</u>$_A$H$_B$CH), 2.20 (ddt, *J* = 13.9 Hz, *J* = 7.3 Hz, *J* = 6.3 Hz, 2H, 2 x CH$_A$<u>H</u>$_B$CH), 2.47 (t, *J* = 7.3 Hz, 2H, COCH$_2$), 3.52 (br s, 4H, 2 x NC<u>H</u>$_2$), 4.14 (q, *J* = 7.2 Hz, 4H, 2 x C<u>H</u>$_2$CH$_3$), 4.10 (dd, *J* = 7.2 Hz, *J* = 6.3 Hz, 2H, 2 x C<u>H</u>), 6.29 (s, 2H, 2 x NH). **^{13}C-NMR (75 MHz, CDCl$_3$) δ:** 14.25 (2 x CH$_3$), 25.16 (2 x NCH$_2$<u>C</u>H$_2$), 26.94 (2 x CH<u>C</u>H$_2$), 29.87 (2 x CO<u>C</u>H$_2$), 38.03 (2 x N<u>C</u>H$_2$), 56.44 (2 x <u>C</u>H), 61.07 (2 x <u>C</u>H$_2$CH$_3$), 157.38 (2 x NC=ON), 172.92 (2 x C=OO), 173.73 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1713 (br C=O), 1764 (C=O), 3249 (NH). **MS: m/z (%):** 455.7 (M+H$^+$, 100). **MP (°C):** 124-127. **HRMS:** calcd for $C_{20}H_{30}N_4O_8$ (M + H$^+$), 455.21364; found, 455.21467. **Yield:** 98%.

3-(1-{6-[4-(2-Ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-hexyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (382b)



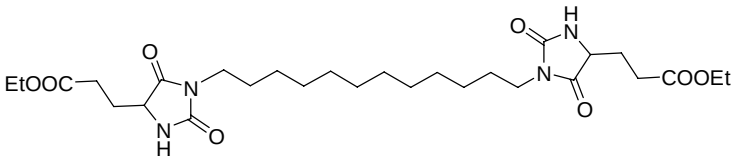
^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.26 (t, *J* = 7.1 Hz, 6H, 2 x CH$_3$), 1.33 (br s, 4H, 2 x N(CH$_2$)$_2$C<u>H</u>$_2$), 1.61 (br p, *J* = 6.9 Hz, 4H, 2 x NCH$_2$C<u>H</u>$_2$), 2.02 (ddt, *J* = 14.3 Hz, *J* = 7.1 Hz, *J* = 6.4 Hz, 2H, 2 x CHC<u>H</u>$_A$H$_B$), 2.22 (ddt, *J* = 14.3 Hz, *J* = 5.5 Hz, *J* = 7.1 Hz, 2H, 2 x CHCH$_A$<u>H</u>$_B$), 2.46 (t, *J* = 7.1 Hz, 4H, 2 x COC<u>H</u>$_2$), 3.48 (t, *J* = 6.9 Hz, 4H, 2 x NC<u>H</u>$_2$), 4.10 (dd, *J* = 5.5 Hz, *J* = 6.4 Hz, 2H, 2 x C<u>H</u>), 4.15 (q, *J* = 7.1 Hz, 4H, 2 x C<u>H</u>$_2$CH$_3$), 6.16 (s, 2H, 2 x NH). **^{13}C-NMR (75 MHz, CDCl$_3$) δ:** 14.25 (2 x CH$_3$), 26.21 (2 x N(CH$_2$)$_2$<u>C</u>H$_2$), 26.93 (2 x CH<u>C</u>H$_2$), 27.90 (2 x NCH$_2$<u>C</u>H$_2$), 29.81 (2 x CO<u>C</u>H$_2$), 38.56 (2 x N<u>C</u>H$_2$), 56.36 (2 x <u>C</u>H), 61.05 (2 x <u>C</u>H$_2$CH$_3$), 157.48 (2 x NC=ON), 172.89 (2 x C=OO), 173.71 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1712 (C=O), 1774 (C=O), 3338 (NH). **MS: m/z (%):** 483.3 (M+H$^+$, 100). **MP (°C):** 95-98. **HRMS:** calcd for $C_{22}H_{34}N_4O_8$ (M + H$^+$), 483.24494; found, 483.24577. **Yield:** 97%.

3-(1-{8-[4-(2-Ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-octyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (382c)



^{1}H-NMR (300 MHz, CDCl$_3$) δ: 1.26 (t, *J* = 7.2 Hz, 6H, 2 x CH$_3$), 1.30 (br s, 8H, 2 x N(CH$_2$)$_2$(C<u>H</u>$_2$)$_2$), 1.59 (p, *J* = 6.8 Hz, 4H, 2 x NCH$_2$C<u>H</u>$_2$), 2.03 (ddt, *J* = 14.7 Hz, *J* = 7.5 Hz, *J* = 6.2 Hz, 2H, 2 x CHC<u>H</u>$_A$H$_B$), 2.22 (ddt, *J* = 14.7 Hz, *J* = 7.5 Hz, *J* = 6.7 Hz, 2H, 2 x CHCH$_A$<u>H</u>$_B$), 2.46 (t, *J* = 7.5 Hz, 4H, 2 x COC<u>H</u>$_2$), 3.47 (t, *J* = 6.8 Hz, 4H, 2 x NC<u>H</u>$_2$), 4.11 (dd, *J* = 6.2 Hz, *J* = 6.7 Hz, 2H, 2 x C<u>H</u>), 4.15 (q, *J* = 7.2 Hz, 4H, 2 x C<u>H</u>$_2$CH$_3$), 6.41 (s, 2H, 2 x NH). **^{13}C-NMR (75 MHz, CDCl$_3$) δ:** 14.24 (2 x CH$_3$), 26.61 (2 x N(CH$_2$)$_2$<u>C</u>H$_2$CH$_2$), 26.91 (2 x CH<u>C</u>H$_2$), 28.03 (2 x NCH$_2$<u>C</u>H$_2$), 28.99 (2 x N(CH$_2$)$_3$<u>C</u>H$_2$), 29.74 (2 x CO<u>C</u>H$_2$), 38.73 (2 x N<u>C</u>H$_2$), 56.35 (2 x <u>C</u>H), 61.04 (2 x <u>C</u>H$_2$CH$_3$), 157.73 (2 x NC=ON), 172.86 (2 x C=OO), 173.76 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (br. C=O), 1774 (C=O), 3331 (NH). **MS: m/z (%):** 511.7 (M+H$^+$, 100). **MP (°C):** 102.5-103.5. **HRMS:** calcd for $C_{24}H_{38}N_4O_8$ (M + H$^+$), 511.27624; found, 511.27767. **Yield:** 99%.

3-(1-{12-[4-(2-Ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-dodecyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (382d)

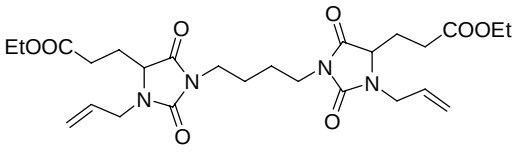


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24-1.29 (br s, 16H, 2 x $N(CH_2)_2(C\underline{H}_2)_4$), 1.26 (t, *J* = 7.0 Hz, 6H, 2 x CH_3), 1.60 (p, *J* = 6.9 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.03 (ddt, *J* = 13.8 Hz, *J* = 7.0 Hz, *J* = 6.4 Hz, 2H, 2 x $CHC\underline{H}_AH_B$), 2.22 (ddt, *J* = 13.8 Hz, *J* = 7.0 Hz, *J* = 6.0 Hz, 2H, 2 x $CHCH_A\underline{H}_B$), 2.46 (t, *J* = 7.0 Hz, 4H, 2 x $CO\underline{C}H_2$), 3.48 (t, *J* = 6.9 Hz, 4H, 2 x $NC\underline{H}_2$), 4.10 (dd, *J* = 6.4 Hz, *J* = 6.0 Hz, 2H, 2 x $C\underline{H}$), 4.15 (q, *J* = 7.0 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 6.24 (s, 2H, 2 x NH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 26.74 (2 x $NCH_2CH_2\underline{C}H_2$), 26.89 (2 x $CH\underline{C}H_2$), 28.09 (2 x $NCH_2\underline{C}H_2$), 29.16 (2 x $N(CH_2)_3\underline{C}H_2$), 29.48 (2 x $N(CH_2)_4\underline{C}H_2\underline{C}H_2$), 29.77 (2 x $CO\underline{C}H_2$), 38.84 (2 x $N\underline{C}H_2$), 56.36 (2 x $\underline{C}H$), 61.05 (2 x $\underline{C}H_2CH_3$), 157.62 (2 x NC=ON), 172.87 (2 x C=OO), 173.73 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1703 (br. C=O), 1773 (C=O), 3314 (NH). **MS: m/z (%):** 567.5 ($M+H^+$, 100). **MP (°C):** 94-96. **HRMS:** calcd for $C_{28}H_{46}N_4O_8$ ($M + H^+$), 567.33884; found, 567.34079. **Yield:** 99%.

4.8.3 Synthesis of bis-hydantoins 36 by N(1) alkylation of 382

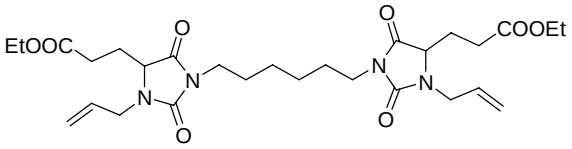
The general procedure of this synthesis can be found in paper VI.

3-(3-Allyl-1-{4-[3-allyl-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-butyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36a)



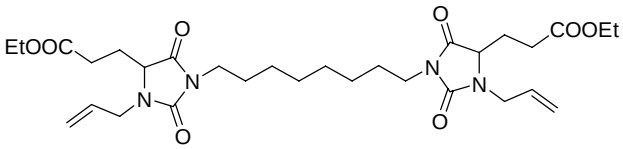
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.64 (br s, 4H, 2 x $NCH_2C\underline{H}_2$), 2.00-2.12 (m, 2H, 2 x $C\underline{H}_AH_BCH$), 2.18-2.42 (m, 6H, 2 x $C\underline{H}_2CH_AH_BCH$), 3.53 (br s, 4H, 2 x $NC\underline{H}_2$), 3.62 (dd, *J* = 15.7 Hz, *J* = 7.4 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 4.01 (dd, *J* = 3.0 Hz, *J* = 6.6 Hz, 2H, 2 x $C\underline{H}$), 4.13 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.34 (dd, *J* = 15.7 Hz, *J* = 5.0 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 5.24 (d, *J* = 4.7 Hz, 2H, 2 x $HC=C\underline{H}_AH_B$), 5.28 (s, 2H, 2 x $HC=CH_A\underline{H}_B$), 5.70-5.83 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 23.80 (2 x $CH\underline{C}H_2$), 25.29 (2 x $NCH_2\underline{C}H_2$), 28.24 (2 x $CO\underline{C}H_2$), 38.29 (2 x $N\underline{C}H_2$), 43.54 (2 x $N\underline{C}H_2CH$), 57.78 (2 x $\underline{C}H$), 60.90 (2 x $\underline{C}H_2CH_3$), 119.45 (2 x $HC=\underline{C}H_2$), 131.80 (2 x $H\underline{C}=CH_2$), 156.25 (2 x NC=ON), 172.39 (2 x C=O), 172.57 (2 x C=O). **IR (cm^{-1}) ν_{max}:** 1645 (C=C), 1709 (br C=O), 1769 (C=O). **MS: m/z (%):** 535.7 ($M+H^+$, 100). **HRMS:** calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$), 535.27624; found, 535.27686. **Yield:** 98%.

3-(3-Allyl-1-{6-[3-allyl-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-hexyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36b)



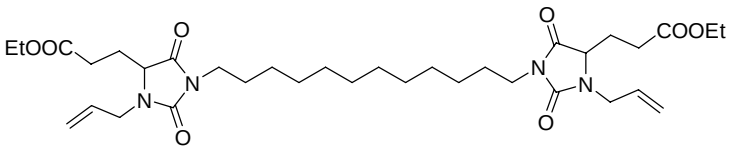
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.34 (br s, 4H, 2 x $N(CH_2)_2\underline{C}H_2$), 1.61-1,66 (m, 4H, 2 x $NCH_2\underline{C}H_2$), 2.01-2.13 (m, 2H, 2 x $CH\underline{C}H_AH_B$), 2.19-2.42 (m, 6H, 2 x $CHCH_A\underline{H_B}\underline{C}H_2$), 3.49 (t, *J* = 7.1 Hz, 4H, 2 x $NC\underline{H}_2$), 3.61 (dd, *J* = 15.7 Hz, *J* = 7.7 Hz, 2H, 2 x $NC\underline{H_A}H_B$), 4.01 (dd, *J* = 6.3 Hz, *J* = 2.8 Hz, 2H, 2 x C<u>H</u>), 4.13 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.35 (dd, *J* = 15.7 Hz, *J* = 4.7 Hz, 2H, 2 x $NCH_A\underline{H_B}$), 5.24 (d, *J* = 4.4 Hz, 2H, 2 x $HC{=}C\underline{H_A}H_B$), 5.28 (s, 2H, 2 x $HC{=}CH_A\underline{H_B}$), 5.70-5.83 (m, 2H, 2 x $\underline{H}C{=}CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), 23.74 (2 x $CH\underline{C}H_2$), 26.27 (2 x $N(CH_2)_2\underline{C}H_2$), 27.98 (2 x $NCH_2\underline{C}H_2$), 28.18 (2 x $CO\underline{C}H_2$), 38.84 (2 x $N\underline{C}H_2$), 43.48 ($N\underline{C}H_2CH$), 57.71 (2 x <u>C</u>H), 60.88 (2 x $\underline{C}H_2CH_3$), 119.39 (2 x $HC{=}\underline{C}H_2$), 131.80 (2 x $H\underline{C}{=}CH_2$), 156.37 (2 x NC=ON), 172.39 (2 x C=O), 172.57 (2 x C=O). **IR (cm^{-1}) ν_{max}:** 1645 (C=C), 1709 (C=O), 1737 (C=O), 1768 (C=O). **MS: m/z (%):** 563.3 ($M+H^+$, 100). **HRMS:** calcd for $C_{28}H_{42}N_4O_8$ ($M + H^+$), 563.30754; found, 563.30994. **Yield:** 98%.

3-(3-Allyl-1-{8-[3-allyl-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-octyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36d)



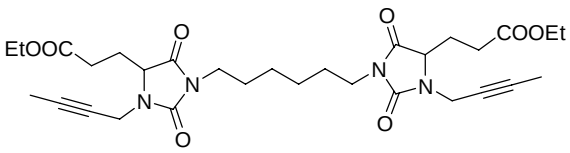
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.30 (br s, 8H, 2 x $N(CH_2)_2(\underline{C}H_2)_2$), 1.60 (p, *J* = 7.1 Hz, 4H, 2 x $NCH_2\underline{C}H_2$), 2.04-2.13 (m, 2H, 2 x $CH\underline{C}H_AH_B$), 2.18-2.38 (m, 6H, 2 x $CHCH_A\underline{H_B}\underline{C}H_2$), 3.47 (dt, *J* = 13.5 Hz, *J* = 7.1 Hz, 2H, 2 x $NC\underline{H_A}H_BCH_2$), 3.50 (dt, *J* = 13.5 Hz, *J* = 7.1 Hz, 2H, 2 x $NCH_A\underline{H_B}CH_2$), 3.61 (dd, *J* = 15.6 Hz, *J* = 7.6 Hz, 2H, 2 x $NC\underline{H_A}H_BCH$), 4.00 (dd, *J* = 3.2 Hz, *J* = 6.5 Hz, 2H, 2 x C<u>H</u>), 4.13 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.35 (dd, *J* = 15.6 Hz, *J* = 5.0 Hz, 2H, 2 x $NCH_A\underline{H_B}CH$), 5.23 (d, *J* = 6.3 Hz, 2H, 2 x $HC{=}C\underline{H_A}H_B$), 5.28 (s, 2H, 2 x $HC{=}CH_A\underline{H_B}$), 5.69-5.83 (m, 2H, 2 x $\underline{H}C{=}CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 23.77 (2 x $CH\underline{C}H_2$), 26.71 (2 x $N(CH_2)_2\underline{C}H_2$), 28.10 (2 x $NCH_2\underline{C}H_2$), 28.19 (2 x $CO\underline{C}H_2$), 29.05 (2 x $N(CH_2)_3\underline{C}H_2$), 39.02 (2 x $N\underline{C}H_2CH_2$), 43.49 (2 x $N\underline{C}H_2CH$), 57.72 (2 x <u>C</u>H), 60.90 (2 x $\underline{C}H_2CH_3$), 119.38 (2 x $HC{=}\underline{C}H_2$), 131.82 (2 x $H\underline{C}{=}CH_2$), 156.43 (2 x NC=ON), 172.40 (2 x C=O), 172.58 (2 x C=O). **IR (cm^{-1}) ν_{max}:** 1645 (C=C), 1709 (C=O), 1732 (C=O), 1769 (C=O). **MS: m/z (%):** 591.8 ($M+H^+$, 100). **HRMS:** calcd for $C_{30}H_{46}N_4O_8$ ($M + H^+$), 591.33884; found, 591.34042. **Chromatography:** Hex/EtOAc (4/6) R_f = 0.47. **Yield:** 98%.

3-(3-Allyl-1-{12-[3-allyl-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-dodecyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36g)



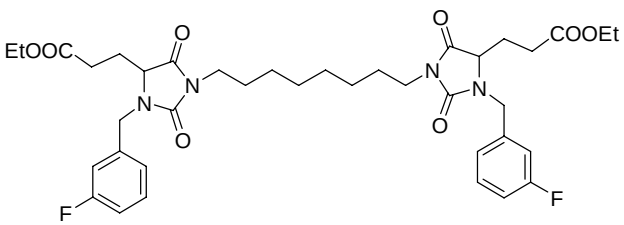
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.25-1.28 (m, 16H, 2 x $NCH_2CH_2(C\underline{H}_2)_4$), 1.60 (p, *J* = 6.3 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.05-2.13 (m, 2H, 2 x $CHC\underline{H}_AH_B$), 2.18-2.36 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.48 (dt, *J* = 8.4 Hz, *J* = 6.3 Hz, 2H, 2 x $NC\underline{H}_AH_BCH_2$), 3.49 (dt, *J* = 8.4 Hz, *J* = 6.3 Hz, 2H, 2 x $NCH_A\underline{H}_BCH_2$), 3.61 (dd, *J* = 15.6 Hz, *J* = 3.6 Hz, 2H, 2 x $NC\underline{H}_AH_BCH$), 4.01 (dd, *J* = 3.0 Hz, *J* = 6.3 Hz, 2H, 2 x $C\underline{H}$), 4.13 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.35 (dd, *J* = 15.6 Hz, *J* = 4.8 Hz, 2H, 2 x $NCH_A\underline{H}_BCH$), 5.23 (d, *J* = 5.0 Hz, 2H, 2 x $HC=C\underline{H}_AH_B$), 5.28 (s, 2H, 2 x $HC=CH_A\underline{H}_B$), 5.69-5.82 (m, 2H, 2 x $\underline{H}C=CH_2$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), 23.74 (2 x $CH\underline{C}H_2$), 26.80 (2 x $N(CH_2)_2\underline{C}H_2$), 28.16 (2 x $NCH_2\underline{C}H_2$), 29.20 (2 x $CO\underline{C}H_2$), 29.52 (2 x $N(CH_2)_3\underline{C}H_2$), 29.57 (2 x $N(CH_2)_4(\underline{C}H_2)_2$), 39.07 (2 x $N\underline{C}H_2CH_2$), 43.46 (2 x $N\underline{C}H_2CH$), 57.69 (2 x $\underline{C}H$), 60.87 (2 x $\underline{C}H_2CH_3$), 119.33 (2 x $HC=\underline{C}H_2$), 131.83 (2 x $H\underline{C}=CH_2$), 156.45 (2 x NC=ON), 172.39 (2 x C=O), 172.57 (2 x C=O). **IR (cm^{-1}) ν_{max}:** 1645 (C=C), 1710 (C=O), 1732 (C=O), 1770 (C=O). **MS: m/z (%):** 647.5 ($M+H^+$, 100). **HRMS:** calcd for $C_{34}H_{54}N_4O_8$ ($M + H^+$), 647.40144; found, 647.40224. **Chromatography:** Hex/EtOAc (4/6) R_f = 0.44. **Yield:** 98%.

3-(3-But-2-ynyl-1-{6-[3-but-2-ynyl-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-hexyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36c)



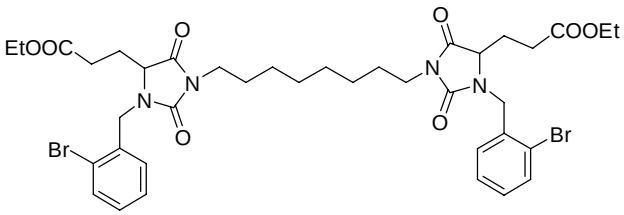
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.27 (br s, 4H, 2 x $N(CH_2)_2C\underline{H}_2$), 1.60 (p, *J* = 7.1 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 1.80 (t, *J* = 2.3 Hz, 6H, 2 x CCH_3), 2.13-2.37 (m, 8H, 2 x $CHC\underline{H}_2C\underline{H}_2$), 3.46 (dt, *J* = 13.3 Hz, *J* = 7.1 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 3.49 (dt, *J* = 13.3 Hz, *J* = 7.1 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 3.79 (dq, *J* = 17.6 Hz, *J* = 2.3 Hz, 2H, 2 x $NC\underline{H}_AH_BC$), 4.12 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.19 (dd, *J* = 5.5 Hz, *J* = 3.3 Hz, 2H, 2 x $C\underline{H}$), 4.46 (dq, *J* = 17.6 Hz, *J* = 2.3 Hz, 2H, 2 x $NCH_A\underline{H}_BC$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 3.54 (2 x $C\underline{C}H_3$), 14.25 (2 x CH_3), 23.75 (2 x $CH\underline{C}H_2$), 26.29 (2 x $N(CH_2)_2\underline{C}H_2$), 27.97 (2 x $NCH_2\underline{C}H_2$), 28.45 (2 x $CO\underline{C}H_2$), 31.22 (2 x $N\underline{C}H_2C$), 38.96 ($N\underline{C}H_2CH_2$), 57.92 (2 x $\underline{C}H$), 60.87 (2 x $\underline{C}H_2CH_3$), 72.07 (2 x $\underline{C}CH_3$), 81.50 (2 x $NCH_2\underline{C}$), 156.37 (2 x NC=ON), 172.42 (4 x C=O). **IR (cm^{-1}) ν_{max}:** 1710 (br C=O), 1771 (C=O), 2231 (alkyne). **MS: m/z (%):** 587.7 ($M+H^+$, 100). **HRMS:** calcd for $C_{30}H_{42}N_4O_8$ ($M + H^+$), 587.30754; found, 587.30760. **Chromatography:** Hex/EtOAc (4/6) R_f = 0.35. **Yield:** 99%.

3-[1-{8-[4-(2-Ethoxycarbonyl-ethyl)-3-(3-fluoro-benzyl)-2,5-dioxo-imidazolidin-1-yl]-octyl}-3-(3-fluoro-benzyl)-2,5-dioxo-imidazolidin-4-yl]-propionic acid ethyl ester (36f)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.24 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.33 (br s, 8H, 2 x $N(CH_2)_2(C\underline{H}_2)_2$), 1.62 (p, *J* = 7.2 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.00-2.40 (m, 8H, 2 x $CHC\underline{H}_2C\underline{H}_2$), 3.50 (dt, *J* = 13.5 Hz, *J* = 7.2 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_BCH_2$), 3.53 (dt, *J* = 13.5 Hz, *J* = 7.2 Hz, 2H, 2 x $NCH_A\underline{H}_BCH_2$), 3.83 (dd, *J* = 3.2 Hz, *J* = 6.5 Hz, 2H, 2 x C<u>H</u>), 4.12 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.13 (d, *J* = 14.9 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_BPh$), 4.95 (d, *J* = 14.9 Hz, 2H, 2 x $NCH_A\underline{H}_BPh$), 6.97-7.06 (m, 3H, CH_{arom}), 7.29-7.36 (m, 1H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 23.67 (2 x $CH\underline{C}H_2$), 26.73 (2 x $N(CH_2)_2\underline{C}H_2$), 28.10 (2 x $NCH_2\underline{C}H_2$), 28.18 (2 x $CO\underline{C}H_2$), 29.06 (2 x $N(CH_2)_3\underline{C}H_2$), 39.16 (2 x $N\underline{C}H_2CH_2$), 44.24 (2 x $N\underline{C}H_2Ph$), 57.59 (2 x <u>C</u>H), 60.96 (2 x $\underline{C}H_2CH_3$), 115.12 (d, *J* = 4.6 Hz, 2 x CH_{arom}), 115.40 (d, *J* = 3.5 Hz, 2 x CH_{arom}), 123.88 (d, *J* = 2.3 Hz, 2 x CH_{arom}), 130.71 (d, *J* = 8.1 Hz, 2 x CH_{arom}), 138.32 (d, *J* = 6.9 Hz, 2 x C_{arom}), 163.15 (d, *J* = 246.9 Hz, 2 x FC_{arom}), 156.83 (2 x NC=ON), 172.34 (4 x C=O). **IR (cm^{-1}) ν_{max}:** 1708 (C=O), 1769 (C=O). **^{19}F-NMR (282 MHz, $CDCl_3$) δ:** -111.74 (dt, *J* = 8.7 Hz, *J* = 6.1 Hz). **MS: m/z (%):** 727.8 ($M+H^+$, 100). **HRMS:** calcd for $C_{38}H_{48}F_2N_4O_8$ ($M + H^+$), 727.35130 found, 727.35429. **Chromatography:** Hex/EtOAc (3/7) R_f = 0.61. **Yield:** 86%.

3-(3-(2-Bromo-benzyl)-1-{8-[3-(2-bromo-benzyl)-4-(2-ethoxycarbonyl-ethyl)-2,5-dioxo-imidazolidin-1-yl]-octyl}-2,5-dioxo-imidazolidin-4-yl)-propionic acid ethyl ester (36e)



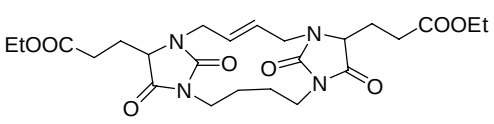
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.32 (br s, 8H, 2 x $N(CH_2)_2(C\underline{H}_2)_2$), 1.62 (p, *J* = 7.4 Hz, 4H, 2 x $NCH_2C\underline{H}_2$), 2.11-2.39 (m, 8H, 2 x $CHC\underline{H}_2C\underline{H}_2$), 3.50 (dt, *J* = 13.5 Hz, *J* = 7.4 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_BCH_2$), 3.53 (dt, *J* = 13.5 Hz, *J* = 7.4 Hz, 2H, 2 x $NCH_A\underline{H}_BCH_2$), 3.84 (dd, *J* = 3.3 Hz, *J* = 5.8 Hz, 2H, 2 x C<u>H</u>), 4.12 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.37 (d, *J* = 15.5 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_BPh$), 5.00 (d, *J* = 15.5 Hz, 2H, 2 x $NCH_A\underline{H}_BPh$), 7.15-7.22 (m, 1H, CH_{arom}), 7.28-7.37 (m, 2H, CH_{arom}), 7.54-7.59 (m, 1H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.27 (2 x CH_3), 24.03 (2 x $CH\underline{C}H_2$), 26.74 (2 x $N(CH_2)_2\underline{C}H_2$), 28.12 (2 x $NCH_2\underline{C}H_2$), 28.26 (2 x $CO\underline{C}H_2$), 29.09 (2 x $N(CH_2)_3\underline{C}H_2$), 39.13 (2 x $N\underline{C}H_2CH_2$), 44.65 (2 x $N\underline{C}H_2Ph$), 57.94 (2 x <u>C</u>H), 60.91 (2 x $\underline{C}H_2CH_3$), 123.70 (2 x BrC_{arom}), 128.17 (2 x CH_{arom}), 129.94 (2 x CH_{arom}), 130.75 (2 x CH_{arom}), 133.35 (2 x CH_{arom}), 135.01 (2 x C_{arom}), 156.77 (2 x NC=ON), 172.31 (2 x C=OO), 172.40 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1732 (C=O), 1770 (C=O). **MS: m/z (%):** 847.5;849.5;851.5 ($M+H^+$,

100). **HRMS:** calcd for $C_{38}H_{48}{}^{79}Br_2N_4O_8$ (M + H^+), 847.19116; found, 847.19501. **Chromatography:** Hex/EtOAc (3/7) R_f = 0.61. **Yield:** 84%.

4.8.4 Synthesis of macrocycles 37 by RCM

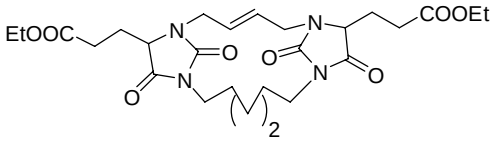
The general procedure of this synthesis can be found in paper VI.

3-[16-(2-Ethoxycarbonyl-ethyl)-8,15,17,18-tetraoxo-1,6,9,14-tetraaza-tricyclo [12.2.1.1^{6,9}]octadec-3-en-7-yl]-propionic acid ethyl ester (37a) (diastereomer 1, *diastereomer 2*, not assigned)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.25 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), *1.26* (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.46-1.75 (m, 8H, 2 x NCH_2CH_2), 2.03-2.23 (m, 8H, 2 x $CHCH_2$), 2.26-2.64 (m, 8H, 2 x $CHCH_2CH_2$), 3.35 (d, *J* = 13.8 Hz, 2H, 2 x $NCH_AH_BCH_2$), 3.40 (d, *J* = 17.6 Hz, 2H, 2 x NCH_AH_BCH), 3.56-3.65 (m, 6H, $NCH_AH_BCH_2$ + *NCH_2CH_2*), 3.70-3.90 (m, 2 x *NCH_AH_BCH*), 4.06-4.19 (m, 8H, 2 x NCH_AH_BCH + 2 x *NCH_AH_BCH* + 2 x CH + 2 x *CH*), 4.12 (q, *J* = 7.1 Hz, 8H, 2 x CH_2CH_3), 5.83 (t, *J* = 3.4 Hz, 2H, HC=CH), *5.90* (t, *J* = 3.7 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), *22.71* (2 x NCH_2CH_2), 23.23 (2 x NCH_2CH_2), 23.74 (2 x $CHCH_2$), 28.58 (2 x $COCH_2$), *28.76* (2 x $COCH_2$), *37.72* (2 x NCH_2CH_2), 38.00 (2 x NCH_2CH_2), 42.55 (2 x NCH_2CH), 58.01 (2 x CH), *58.72* (2 x CH), 60.87 (2 x CH_2CH_3), 128.61 (HC=CH), 157.33 (2 x NC=ON), 172.60 (2 x C=OO), *172.75* (2 x C=OO), 172.91 (2 x NC=O). *173.18* (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1767 (C=O). **MS: m/z (%):** 507.7 (M+H^+, 100). **HRMS:** calcd for $C_{24}H_{34}N_4O_8$ (M + H^+), 507.24494; found, 507.24700. **Chromatography:** Hex/EtOAc (3/7) R_f = 0.24. **Yield:** 46%.

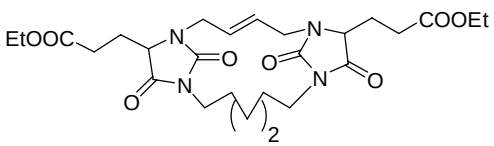
3-[18-(2-Ethoxycarbonyl-ethyl)-8,17,19,20-tetraoxo-1,6,9,16-tetraaza-tricyclo [14.2.1.1^{6,9}]icos-3-en-7-yl]-propionic acid ethyl ester (37b) (diastereomer 1)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.15-1.30 (m, 4H, 2 x $N(CH_2)_2CH_2$), 1.24 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.62-1.74 (m, 4H, 2 x NCH_2CH_2), 2.00-2.16 (m, 2H, 2 x $CHCH_AH_B$), 2.17-2.52 (m, 6H, 2 x $CHCH_AH_BCH_2$), 3.43-3.49 (m, 4H, 2 x $NCH_AH_BCH_2$ + NCH_AH_BCH), 3.57 (ddd, *J* = 13.8 Hz, *J* = 6.3 Hz, *J* = 3.9 Hz, 2H, 2 x $NCH_AH_BCH_2$), 4.04 (dd, *J* = 2.9 Hz, *J* = 6.5 Hz, 2H, 2 x CH), 4.11 (q, *J* = 7.2 Hz, 4H, 2 x CH_2CH_3), 4.35 (d, *J* = 16.0 Hz, 2H, 2 x NCH_AH_B), 5.35 (t, *J* = 2.2 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), 23.60 (2 x $CHCH_2$), 27.48 (2 x $N(CH_2)_2CH_2$), 27.83 (2 x NCH_2CH_2), 28.45 (2 x $COCH_2$), 39.58 (2 x NCH_2CH_2), 41.83 (2 x NCH_2CH), 57.71 (2 x CH), 60.91 (2 x CH_2CH_3), 126.31 (HC=CH), 156.97 (2 x NC=ON), 172.57 (2 x C=OO), 172.71 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1769 (C=O).

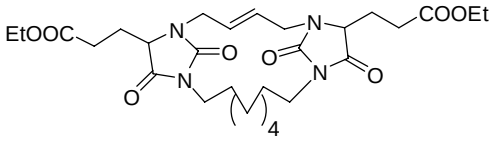
MS: m/z (%): 535.2 ($M+H^+$, 100). **HRMS:** calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$), 535.27624; found, 535.27723. **Chromatography:** Hex/EtOAc (2/8) R_f = 0.42.

3-[18-(2-Ethoxycarbonyl-ethyl)-8,17,19,20-tetraoxo-1,6,9,16-tetraaza-tricyclo [14.2.1.1^{6,9}]icos-3-en-7-yl]-propionic acid ethyl ester (37b) (diastereomer 2)



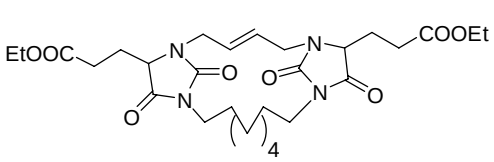
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16-1.35 (m, 4H, 2 x $N(CH_2)_2C\underline{H}_2$), 1.26 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.58-1.75 (m, 4H, 2 x $NCH_2C\underline{H}_2$), 1.97-2.09 (m, 2H, 2 x $CHC\underline{H}_A\underline{H}_B$), 2.13-2.55 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.43-3.49 (m, 4H, 2 x $NC\underline{H}_A\underline{H}_BCH_2$ + $NC\underline{H}_A\underline{H}_BCH$), 3.48 (ddd, *J* = 13.3 Hz, *J* = 6.4 Hz, *J* = 3.8 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_BCH_2$), 3.58 (ddd, *J* = 13.3 Hz, *J* = 3.9 Hz, *J* = 3.8 Hz, 2H, 2 x $NCH_A\underline{H}_BCH_2$), 3.68 (dt, *J* = 16.2 Hz, *J* = 2.4 Hz, 2H, 2 x $NC\underline{H}_A\underline{H}_B$), 4.04 (dd, *J* = 3.6 Hz, *J* = 7.2 Hz, 2H, 2 x $C\underline{H}$), 4.09 (d, *J* = 16.2 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 4.14 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 5.63 (t, *J* = 2.4 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.27 (2 x CH_3), 24.25 (2 x $CH\underline{C}H_2$), 26.79 (2 x $N(CH_2)_2\underline{C}H_2$), 27.58 (2 x $NCH_2\underline{C}H_2$), 28.56 (2 x $CO\underline{C}H_2$), 38.94 (2 x $N\underline{C}H_2CH_2$), 42.35 (2 x $N\underline{C}H_2CH$), 58.10 (2 x $\underline{C}H$), 60.88 (2 x $\underline{C}H_2CH_3$), 128.22 ($H\underline{C}=\underline{C}H$), 156.86 (2 x NC=ON), 172.71 (2 x C=OO), 172.97 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1768 (C=O). **MS: m/z (%):** 535.2 ($M+H^+$, 100). **HRMS:** calcd for $C_{26}H_{38}N_4O_8$ ($M + H^+$), 535.27624; found, 535.27786. **Chromatography:** Hex/EtOAc (2/8) R_f = 0.38. (Still contains 14% of diastereomer 1). **Total yield:** 58%.

3-[20-(2-Ethoxycarbonyl-ethyl)-8,19,21,22-tetraoxo-1,6,9,18-tetraaza-tricyclo [16.2.1.1^{6,9}]docos-3-en-7-yl]-propionic acid ethyl ester (37c) (diastereomer 1)



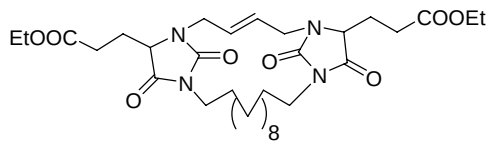
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.16-1.36 (m, 8H, 2 x $N(CH_2)_2(C\underline{H}_2)_2$, 1.25 (t, *J* = 7.2 Hz, 6H, 2 x CH_3), 1.52-1.74 (m, 4H, 2 x $NCH_2C\underline{H}_2$), 1.97-2.09 (m, 2H, 2 x $CHC\underline{H}_A\underline{H}_B$), 2.17-2.43 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.47-3.63 (m, 6H, 2 x $NC\underline{H}_2CH_2$ + 2 x $NC\underline{H}_A\underline{H}_BCH$), 4.03 (dd, *J* = 2.9 Hz, *J* = 6.5 Hz, 2H, 2 x $C\underline{H}$), 4.12 (q, *J* = 7.2 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 4.47 (d, *J* = 16.2 Hz, 2H, 2 x $NCH_A\underline{H}_BCH$), 5.42 (t, *J* = 1.9 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), 23.46 (2 x $CH\underline{C}H_2$), 25.83 (2 x $N(CH_2)_2\underline{C}H_2$), 27.93 (2 x $NCH_2\underline{C}H_2$), 28.26 (2 x $CO\underline{C}H_2$), 29.06 (2 x $N(CH_2)_3\underline{C}H_2$), 39.23 (2 x $N\underline{C}H_2CH_2$), 41.08 (2 x $N\underline{C}H_2CH$), 57.10 (2 x $\underline{C}H$), 60.94 (2 x $\underline{C}H_2CH_3$), 126.37 ($H\underline{C}=\underline{C}H$), 156.69 (2 x NC=ON), 172.46 (2 x C=OO), 172.52 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1770 (C=O). **MS: m/z (%):** 563.7 ($M+H^+$, 100). **HRMS:** calcd for $C_{28}H_{42}N_4O_8$ ($M + H^+$), 563.30754; found, 563.30876. **Chromatography:** Hex/EtOAc (3/7) R_f = 0.26.

3-[20-(2-Ethoxycarbonyl-ethyl)-8,19,21,22-tetraoxo-1,6,9,18-tetraaza-tricyclo [16.2.1.1^{6,9}]docos-3-en-7-yl]-propionic acid ethyl ester (37c) (diastereomer 2)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.14-1.29 (m, 8H, 2 x $N(CH_2)_2(C\underline{H}_2)_2$, 1.26 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.50-1.73 (m, 4H, 2 x $NCH_2C\underline{H}_2$), 1.96-2.08 (m, 2H, 2 x $CHC\underline{H}_AH_B$), 2.16-2.56 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.56 (t, *J* = 5.7 Hz, 4H, 2 x $NC\underline{H}_2CH_2$), 3.81 (d, *J* = 5.7 Hz, 2H, $NC\underline{H}_AH_B$), 4.02 (dd, *J* = 3.5 Hz, *J* = 7.1 Hz, 2H, 2 x C<u>H</u>), 4.09-4.16 (m, 2H, 2 x $NCH_A\underline{H}_B$), 4.14 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$), 5.53 (t, *J* = 2.3 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.24 (2 x CH_3), 24.10 (2 x $CH\underline{C}H_2$), 25.66 (2 x $N(CH_2)_2\underline{C}H_2$), 27.80 (2 x $NCH_2\underline{C}H_2$), 28.27 (2 x $CO\underline{C}H_2$), 29.02 (2 x $N(CH_2)_3\underline{C}H_2$), 38.97 (2 x $N\underline{C}H_2CH_2$), 41.97 (2 x $N\underline{C}H_2CH$), 58.13 (2 x <u>C</u>H), 60.85 (2 x $\underline{C}H_2CH_3$), 127.06 (H<u>C</u>=<u>C</u>H), 156.60 (2 x NC=ON), 172.54 (2 x C=OO), 172.77 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1710 (C=O), 1770 (C=O). **MS: m/z (%):** 563.7 (M+H$^+$, 100). **HRMS:** calcd for $C_{28}H_{42}N_4O_8$ (M + H$^+$), 563.30754; found, 563.30774. **Chromatography:** Hex/EtOAc (3/7) R_f = 0.22. Still contains 17% of diastereomer 1). **Total yield:** 54%.

3-[24-(2-Ethoxycarbonyl-ethyl)-8,23,25,26-tetraoxo-1,6,9,22-tetraaza-tricyclo [20.2.1.1^{6,9}]hexacos-3-en-7-yl]-propionic acid ethyl ester (37d) (50:50 mixture of diastereomers)

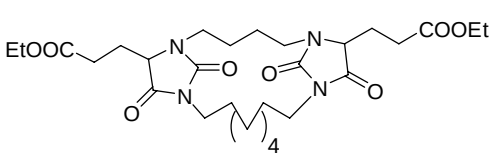


^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.23-1.28 (m, 44H, 2 x $N(CH_2)_2(C\underline{H}_2)_8$ + 4 x CH_3), 1.50-1.75 (m, 8H, 4 x $NCH_2C\underline{H}_2$), 1.93-2.07 (m, 4H, 4 x $CHC\underline{H}_AH_B$), 2.18-2.52 (m, 12H, 4 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.39-3.55 (m, 8H, 4 x $NC\underline{H}_2CH_2$), 3.61 (d, *J* = 16.4 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 3.76 (d, *J* = 15.6 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 4.03 (dd, *J* = 3.2 Hz, *J* = 7.0 Hz, 4H, 4 x CH), 4.13 (q, *J* = 7.1 Hz, 8H, 4 x $C\underline{H}_2CH_3$), 4.22 (d, *J* = 15.6 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 4.40 4.22 (d, *J* = 16.4 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 5.56 (br t, *J* = 2.9 Hz, 2H, HC=CH), 5.60 (br t, *J* = 2.6 Hz, 2H, HC=CH). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (4 x CH_3), 23.69 (2 x $CH\underline{C}H_2$), 24.07 (2 x $CH\underline{C}H_2$), 26.21 (2 x $N(CH_2)_2\underline{C}H_2$), 26.41 (2 x $N(CH_2)_2\underline{C}H_2$), 27.21 (2 x $NCH_2\underline{C}H_2$), 27.35 (2 x $NCH_2\underline{C}H_2$), 27.66 (2 x $CO\underline{C}H_2$), 27.84 (4 x $N(CH_2)_3\underline{C}H_2$), 27.89 (2 x $CO\underline{C}H_2$), 28.22 ((4 x $N(CH_2)_4(\underline{C}H_2)_2$), 39.00 (2 x $N\underline{C}H_2CH_2$), 39.19 (2 x $N\underline{C}H_2CH_2$), 41.34 (2 x $N\underline{C}H_2CH$), 42.06 (2 x $N\underline{C}H_2CH$), 57.57 (2 x <u>C</u>H), 58.10 (2 x <u>C</u>H), 60.90 (2 x $\underline{C}H_2CH_3$), 60.94 (2 x $\underline{C}H_2CH_3$), 127.24 (H<u>C</u>=<u>C</u>H), 127.54 (H<u>C</u>=<u>C</u>H), 156.49 (2 x NC=ON), 156.52 (2 x NC=ON), 172.39 (2 x C=O), 172.43 (2 x C=O), 172.52 (2 x C=O), 172.65 (2 x C=O). **IR (cm^{-1}) ν_{max}:** 1713 (C=O), 1732 (C=O), 1770 (C=O). **MS: m/z (%):** 619.8 (M+H$^+$, 100). **HRMS:** calcd for $C_{32}H_{50}N_4O_8$ (M + H$^+$), 619.37014; found, 619.37291. **Chromatography:** Hex/EtOAc (4/6) R_f = 0.17. **Yield:** 41%.

4.8.5 Synthesis of 385a and 385c by reduction of compound 37c

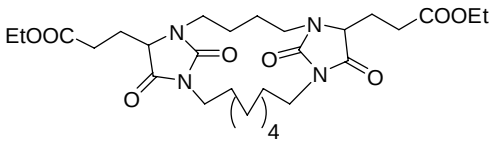
One diastereomer of **37c** (100 mg, 0.18 mmol) was dissolved in absolute ethanol (5 ml) and subjected to catalytic reduction using H_2 (3 bar) and Pd/C (10%) at room temperature for 16 hours. After this time the mixture was filtered over a small silica plug and the solvent was removed *in vacuo*. The reduced compounds are obtained quantitatively.

10,21,25,26-tetraoxo-1,6,11,20-tetraaza-tricyclo[18.4.1.1^{6,11}]hexacosane-7,24-dicarboxylic acid diethyl ester (385a) (reduction **37c** diastereomer 1)



^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.14-1.36 (m, 8H, 2 x $N(CH_2)_2(C\underline{H})_2$, 1.25 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.50 (br s, 4H, 2 x $NCH_2C\underline{H}_2$), 1.54-1.69 (m, 4H, 2 x $NCH_2C\underline{H}_2$), 1.97-2.10 (m, 2H, 2 x $CHC\underline{H}_AH_B$), 2.18-2.45 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 2.99 (br d, *J* = 14.2 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 3.42-3.62 (m, 4H, 2 x $NC\underline{H}_2CH_2$), 3.80 (br d, *J* = 14.2 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 4.08 (dd, *J* = 2.8 Hz, *J* = 6.6 Hz, 2H, 2 x $C\underline{H}$), 4.12 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.28 (2 x CH_3), 23.54 (2 x $CH\underline{C}H_2$), 24.85 (2 x $NCH_2\underline{C}H_2$), 28.19 (2 x $NCH_2\underline{C}H_2$), 28.30 (2 x $CO\underline{C}H_2$), 29.40 (2 x $N(CH_2)_3\underline{C}H_2$), 39.16 (2 x $N\underline{C}H_2CH_2$), 39.94 (2 x $N\underline{C}H_2CH_2$), 56.81 (2 x $\underline{C}H$), 61.01 (2 x $\underline{C}H_2CH_3$), 156.90 (2 x NC=ON), 172.49 (2 x C=OO), 172.66 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1706 (C=O), 1731 (C=O), 1768 (C=O). **MS: m/z (%):** 565.8 ($M+H^+$, 100). **HRMS:** calcd for $C_{28}H_{44}N_4O_8$ ($M + H^+$), 565.32319; found, 565.32582.

10,21,25,26-tetraoxo-1,6,11,20-tetraaza-tricyclo[18.4.1.1^{6,11}]hexacosane-7,24-dicarboxylic acid diethyl ester (385b) (reduction **37c** diastereomer 2)



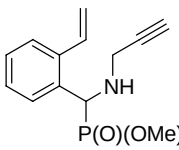
^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.14-1.36 (m, 8H, 2 x $N(CH_2)_2(C\underline{H})_2$, 1.27 (t, *J* = 7.1 Hz, 6H, 2 x CH_3), 1.51-1.66 (m, 8H, 2 x $NCH_2C\underline{H}_2$ + 2 x $NCH_2C\underline{H}_2$), 1.98-2.11 (m, 2H, 2 x $CHC\underline{H}_AH_B$), 2.23-2.50 (m, 6H, 2 x $CHCH_A\underline{H}_BC\underline{H}_2$), 3.26 (br d, *J* = 14.3 Hz, 2H, 2 x $NC\underline{H}_AH_B$), 3.52 (br d, *J* = 14.3 Hz, 2H, 2 x $NCH_A\underline{H}_B$), 3.54 (t, *J* = 5.6 Hz, 4H, 2 x $NC\underline{H}_2CH_2$), 4.02 (dd, *J* = 3.0 Hz, *J* = 6.9 Hz, 2H, 2 x $C\underline{H}$), 4.15 (q, *J* = 7.1 Hz, 4H, 2 x $C\underline{H}_2CH_3$). **^{13}C-NMR (75 MHz, $CDCl_3$) δ:** 14.25 (2 x CH_3), 24.29 (2 x $CH\underline{C}H_2$), 25.78 (2 x $NCH_2\underline{C}H_2$), 28.10 (2 x $NCH_2\underline{C}H_2$), 28.18 (2 x $CO\underline{C}H_2$), 29.34 (2 x $N(CH_2)_3\underline{C}H_2$), 38.81 (2 x $N\underline{C}H_2CH_2$), 40.81 (2 x $N\underline{C}H_2CH_2$), 58.26 (2 x $\underline{C}H$), 60.88 (2 x $\underline{C}H_2CH_3$), 156.93 (2 x NC=ON), 172.54 (2 x C=OO), 172.69 (2 x NC=O). **IR (cm^{-1}) ν_{max}:** 1709 (C=O), 1731 (C=O), 1768 (C=O). **MS: m/z (%):** 565.8 ($M+H^+$, 100). **HRMS:** calcd for $C_{28}H_{44}N_4O_8$ ($M + H^+$), 565.32319; found, 565.32452.

4.9 Synthesis of 1-phosphonylated benzazepines

General procedures for the synthesis of compounds **397a-c** and **395a-c** as well as their complete spectroscopic description can be found in paper VII.

4.9.1 Synthesis of dimethyl (prop-2-ynylamino)(2-vinylphenyl)methylphosphonate (400)

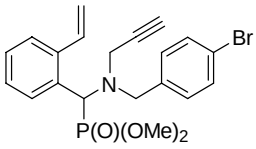
The synthesis of 1-bromo-2-vinyl-benzene **397** and 2-vinyl-benzaldehyde **398** was performed following a literature procedure.[212] Aldehyde **398** (1.54 g, 11.6 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and 1.1 equivalents of propargylamine (0.71 g, 12.8 mmol) and $MgSO_4$ (4.21 g) were added. The mixture was allowed to stir at room temperature for 24 hours. After filtration of the solids and removal of the volatiles, the obtained imine was directly used for the synthesis of the α-aminophosphonate **400**. Thus the imine is dissolved in 30 ml of MeOH in a round bottom flask. Then, 2 equivalents of dimethyl phosphite (DMP) (2.57 g, 23 mmol) is added and the mixture is refluxed for 2 hours. After removing the solvent under vacuum, the resulting oil is dissolved in 20 ml of diethyl ether and added to a separatory funnel containing 20 ml of 1 M HCl. Both phases are vigorously mixed and the organic phase is removed from the funnel. The aqueous phase is washed twice with 10 ml of diethyl ether, added to 20 ml of dichloromethane and then neutralized using 3 M NaOH until slightly alkaline. Both phases are vigorously mixed and the organic phase is now collected. The aqueous phase is extracted twice more with 10 ml of dichloromethane and the combined organic phases are dried using $MgSO_4$. The compound is obtained in pure form after filtration and evaporation of the solvent in 82% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.19 (br s, 1H, NH), 2.23 (t, *J* = 2.3 Hz, 1H, CCH_{alkyne}), 3.15 (br d, *J* = 17.1 Hz, 1H, $NC\underline{H}_A H_B C$), 3.44 (dd, *J* = 2.3 Hz, *J* = 17.1 Hz, 3H, $NCH_A\underline{H}_B C$), 3.56 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.72 (d, *J* = 10.5 Hz, 3H, OCH_3),4.79 (d, *J* = 18.5 Hz, 1H, CHP), 5.36 (d, *J* = 10.9 Hz, 1H, $HC=C\underline{H}_A H_B$), 5.61 (d, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 7.18 (dd, *J* = 10.9 Hz, *J* = 17.3 Hz, 1H, $\underline{H}C=CH_2$), 7.27-7.37 (m, 2H, 2 x CH_{arom}), 7.46 (d, *J* = 7.2 Hz, 1H, $PCHCCCH_{arom}$), 7.59-7.62 (m, 1H, $PCHCC\underline{H}_{arom}$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 35.86 (d, *J* = 18.5 Hz), 53.59 (d, *J* = 5.8 Hz), 53.67 (d, *J* = 5.8 Hz), 53.88 (d, *J* = 155.8 Hz), 72.50, 81.08, 117.38, 127.06 (d, *J* = 2.3 Hz), 128.12 (d, *J* = 3.5 Hz), 128.21 (d, *J* = 5.8 Hz), 128.67 (d, *J* = 3.5 Hz), 131.52 (d, *J* = 5.8 Hz), 134.63, 138.96 (d, *J* = 6.9 Hz). **^{31}P-NMR (MHz, $CDCl_3$):** δ 26.44. **IR (cm^{-1}) υ_{max}:** 1031 (br P-O), 1247 (P=O), 2104 (alkyne), 3293 (br NH). **MS (ESI): m/z (%):** 280.2 ($M+H^+$, 87), 170.2 (M^+-$P(O)(OMe)_2$, 100).

4.9.2 Synthesis of dimethyl [(4-bromobenzyl)(prop-2-ynyl)amino](2-vinylphenyl) methylphosphonate (46)

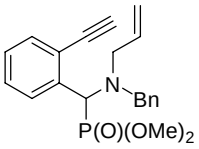
To a roundbottom flask, compound **400** (0.7 g, 2.5 mmol) is added together with K_2CO_3 (1.38 g, 10 mmol), NaI (0.04 g, 0.25 mmol) and 10 ml of acetone. Then 4-bromobenzyl bromide (1.25 g, 5.0 mmol) is added and the mixture is refluxed during 24h. After this time the solids are removed by filtration and the solvent by evaporation under reduced pressure. The compound was obtained in pure form as a pale yellow oil after column chromatography in 69% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (t, *J* = 2.2 Hz, 1H, CCH_{alkyne}), 3.16 (dd, *J* = 2.2 Hz, *J* = 17.6 Hz, 1H, $NC\underline{H}_A H_B C$), 3.27 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.44 (dt, *J* = 2.2 Hz, *J* = 17.6 Hz, 3H, $NCH_A\underline{H}_B C$), 3.74-3.92 (m, 2H, NCH_2Ph), 3.79 (d, *J* = 10.8 Hz, 3H, OCH_3), 4.69 (d, *J* = 17.3 Hz, 1H, CHP), 5.36 (dd, *J* = 1.0 Hz, *J* = 11.0 Hz, 1H, $HC=C\underline{H}_A H_B$), 5.63 (dd, *J* = 1.0 Hz, *J* = 16.8 Hz, 1H, $HC=CH_A\underline{H}_B$), 7.23 (dd, *J* = 11.0 Hz, *J* = 16.8 Hz, 1H, $\underline{H}C=CH_2$), 7.26-7.54 (m, 7H, 7 x CH_{arom}), 7-87-7.90 (m, 1H, $PCHCC\underline{H}_{arom}$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 39.52 (d, *J* = 10.4 Hz), 52.55 (d, *J* = 8.1 Hz), 53.23 (d, *J* = 6.9 Hz), 54.09 (d, *J* = 6.9 Hz), 58.94 (d, *J* = 155.8 Hz), 73.71, 78.38, 117.04, 120.78, 126.72, 127.60, 128.22, 130.02 (d, *J* = 3.5 Hz), 130.48, 131.12, 131.48 (d, *J* = 3.5 Hz), 134.46, 137.33, 138.80 (d, *J* = 8.1 Hz). **^{31}P-NMR (MHz, $CDCl_3$):** δ 26.20. **IR (cm^{-1}) υ_{max}:** 1031 (P-O), 1058 (P-O), 1250 (P=O), 2101 (alkyne). **MS (ESI): m/z (%):** 448.2/450.2 ($M+H^+$, 100), 422.2/424.2 (M^+-vinyl, 8), 338.3/340.3 (M^+-$P(O)(OMe)_2$, 20). **Chromatography:** Hex/EtOAc 6/4 R_f = 0.23.

4.9.3 Synthesis of dimethyl (allylbenzylamino)(2-ethynylphenyl)methylphosphonate (47)

In a dry flask, 2-ethynylbenzaldehyde (0.5 g, 3.84 mmol) is dissolved into dry diethylether (6 ml). To this solution is added $LiClO_4$ (3.07 g, 28.8 mmol, dried for 24h at 110 °C). This mixture is stirred for 5 minutes. Subsequently allylbenzylamine (1.13 g, 7.69 mmol, dissolved in 1 ml dry diethylether) is added. This mixture is stirred for 20 minutes after which $P(OMe)_3$ is added (0.71 g, 5.76 mmol). The reaction is stirred for 30 minutes after which water is very carefully added (20 ml). The mixture is extracted with CH_2Cl_2 (3 x 20 ml) and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained compound was purified using column chromatography and obtained in 68% yield as a white solid.

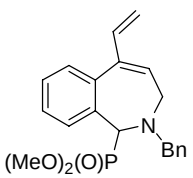


^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 1H, CCH), 3.06 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 1H, $NC\underline{H}_A H_B CH$), 3.44 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.52 (d, *J* = 14.2 Hz, 1H, $NC\underline{H}_A H_B Ph$), 3.66 (ddd, *J* = 1.5 Hz, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H, $NCH_A\underline{H}_B CH$), 3.96 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.23 (d, *J* = 14.2 Hz, 1H,

$NCH_A\underline{H}_BPh$), 5.03 (d, *J* = 24.5 Hz, 1H, CHP), 5.09 (d, *J* = 10.8 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.18 (dd, *J* = 1.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.83 (dddd, *J* = 4.5 Hz, *J* = 7.2 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz, 1H, $\underline{H}C=CH_2$), 7.19-7.44 (m, 7H, 7 x CH_{arom}), 7.56 (d, *J* = 7.7 Hz, 1H, PCHCC$\underline{H}$), 7.97 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 52.94 (d, *J* = 6.9 Hz, OCH_3), 53.72 (d, *J* = 6.9 Hz, OCH_3), 54.28 (d, *J* = 8.1 Hz, $N\underline{C}H_2CH$), 55.18 (d, *J* = 8.1 Hz, $N\underline{C}H_2Ph$), 58.64 (d, *J* = 161.5 Hz, CHP), 81.98 ($\underline{C}CH$), 82.08 ($C\underline{C}H$), 117.41 ($HC=\underline{C}H_2$), 124.18 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 126.80 (CH_{para}, Ph), 128.11 (3 x CH_{arom}), 128.64 (3 x CH_{arom}), 130.74 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.39 (PCHCC$\underline{C}$H), 135.77 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 135.99 ($H\underline{C}=CH_2$), 139.96 (C_q, Ph). **^{31}P-NMR (MHz, $CDCl_3$):** δ 26.25. **IR (cm^{-1}) υ_{max}:** 1035 (P-O),1058 (P-O), 1246 (P=O), 1642 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 370.2 ($M+H^+$, 100). **MP (°C):** 86-87. **Chromatography:** Hex/EtOAc 4/6 R_f = 0.27.

4.9.4 Dimethyl 2-benzyl-5-vinyl-2,3-dihydro-1H-2-benzazepin-1-ylphosphonate (407)

During the synthesis of compounds **395a-c** about 10% of side product **407** is formed. This compound can be isolated using column chromatography.



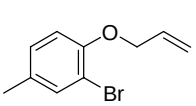
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.77 (dd, *J* = 7.0 Hz, *J* = 12.0 Hz, 1H, $NC\underline{H}_AH_BCH$), 3.05 (dd, *J* = 7.0 Hz, *J* = 12.0 Hz, 1H, $NCH_A\underline{H}_BCH$), 3.48 (d, *J* = 10.2 Hz, 3H, OCH_3), 3.63 (d, *J* = 12.9 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.65 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.00 (d, *J* = 12.9 Hz, 1H, $NCH_A\underline{H}_BPh$), 4.30 (d, *J* = 25.1 Hz, 1H, CHP), 5.23 (dd, *J* = 1.2 Hz, *J* = 10.8 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.35 (dd, *J* = 1.2 Hz, *J* = 17.5 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.19 (t, *J* = 7.0 Hz, 1H, $NCH_2C\underline{H}$), 6.58 (dd, *J* = 10.8 Hz, *J* = 17.5 Hz, 1H, $\underline{H}C=CH_AH_B$), 7.24-7.47 (m, 9H, 9 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 50.00 (d, *J* = 5.8 Hz, $N\underline{C}H_2CH$), 52.97 (d, *J* = 6.9 Hz, OCH_3), 53.07 (d, *J* = 6.9 Hz, OCH_3), 61.59 (d, *J* = 10.4 Hz, $N\underline{C}H_2Ph$), 65.10 (d, *J* = 170.8 Hz, CHP), 116.57 ($HC=\underline{C}H_2$), 127.38 (CH_{para}, Ph), 127.83 (CH_{arom}), 127.91 (CH_{arom}), 128.05 ($NCH_2\underline{C}H$), 128.38 (2 x CH_{arom}), 129.27 (CH_{arom}), 129.47 (2 x CH_{arom}), 131.69 (d, *J* = 10.4 Hz, PCHC$\underline{C}$H), 133.07 (d, *J* = 2.3 Hz, PCH$\underline{C}$), 137.77 ($H\underline{C}=CH_2$), 137.81 (d, *J* = 5.8 Hz, PCHC$\underline{C}$), 138.63 (C_q, Ph), 143.51 ($NCH_2CH\underline{C}$). **^{31}P-NMR (MHz, $CDCl_3$):** δ 26.06. **IR (cm^{-1}) υ_{max}:** 1031 (P-O),1057 (P-O), 1249 (P=O), 1601 (C=C). **MS (ESI): m/z (%):** 370.2 ($M+H^+$, 100), 260.2 (M^+-$P(O)(OMe)_2$, 30). **Chromatography:** Hex/EtOAc 2/8 R_f = 0.33.

4.10 Attempted synthesis of other benzo-fused heterocycles

4.10.1 Synthesis of 1-(allyloxy)-2-bromo-4-methylbenzene (415)

In a dry flask 2-bromo-4-methylphenol (5 g, 27 mmol) is dissolved in acetone (100 ml). To this solution allylbromide (12.94 g, 107 mmol) and K_2CO_3 (14.76 g, 107 mmol) are added. The mixture is refluxed for 48 hours. After cooling, the mixture is filtered and all the volatiles are

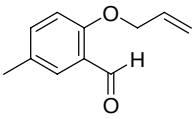
removed *in vacuo*. The residue is dissolved in CH_2Cl_2 (50 ml) and washed with $NaHCO_3$ (20 ml, aq, sat). After drying of the organic layer with $MgSO_4$ the compound is obtained pure as an oil in 91% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (s, 3H, CH_3), 4.57 (dt, *J* = 1.9 Hz, *J* = 5.0 Hz, 2H, OC$\underline{H}_2$), 5.29 (dq, *J* = 1.9 Hz, *J* = 10.5 Hz, 1H, HC=C$\underline{H}_A$H$_B$), 5.47 (dq, *J* = 1.9 Hz, *J* = 17.2 Hz, 1H, HC=CH$_A\underline{H}_B$), 6.05 (ddt, *J* = 5.0 Hz, *J* = 10.5 Hz, *J* = 17.2 Hz, 1H, $\underline{H}$C=CH$_A$H$_B$), 6.78 (d, *J* = 8.5 Hz, 1H, CH_{arom}), 7.02 (dd, *J* = 2.2 Hz, *J* = 8.5 Hz, 1H, CH_{arom}), 7.36 (d, *J* = 2.2 Hz, 1H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 20.32 (CH_3), 69.89 (O$\underline{C}H_2$), 112.11 (Br$C_{q,arom}$), 113.71 (CH_{arom}), 117.62 (HC=$\underline{C}H_2$), 128.95 (CH_{arom}), 131.76 ($C_{q,arom}$), 132.99 (CH_{arom}), 133.88 (H$\underline{C}$=CH$_2$), 152.93 (O$C_{q,arom}$). **IR (cm^{-1}) υ_{max}:** 1648 (C=C). MS (ESI): m/z (%): 226/228 ($M+H^+$, 100).

4.10.2 Synthesis of 2-(allyloxy)-5-methylbenzaldehyde (416)

In a dry flask compound **415** (5 g, 22 mmol) is dissolved in dry THF (100 ml). The flask is placed under inert N_2 atmosphere in an acetone bath at -78 °C. To this solution BuLi (9 ml of a 2.5 M solution in hexanes, 22 mmol) is added and the mixture is stirred for 30 minutes at -78 °C. Next DMF (1.77 g, 24 mmol) is added and the mixture is stirred for 1 hour at -78 °C and 1 hour at room temperature. After that time very carefully brine is added (30 ml) and $NaHCO_3$ (30 ml, aq, sat). The mixture is extracted with EtOAc (3 x 50 ml). After drying with $MgSO_4$ the compound is obtained pure as an oil after column chromatography in 50% yield.

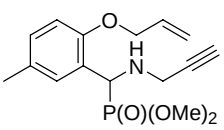


^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.31 (s, 3H, CH_3), 4.63 (dt, *J* = 1.4 Hz, *J* = 4.9 Hz, 2H, OC$\underline{H}_2$), 5.33 (dq, *J* = 1.4 Hz, *J* = 10.5 Hz, 1H, HC=C$\underline{H}_A$H$_B$), 5.44 (dq, *J* = 1.4 Hz, *J* = 17.3 Hz, 1H, HC=CH$_A\underline{H}_B$), 6.07 (ddt, *J* = 4.9 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz, 1H, $\underline{H}$C=CH$_A$H$_B$), 6.88 (d, *J* = 8.5 Hz, 1H, CH_{arom}), 7.33 (dd, *J* = 2.2 Hz, *J* = 8.5 Hz, 1H, CH_{arom}), 7.64 (d, *J* = 2.2 Hz, 1H, CH_{arom}), 10.51 (s, 1H, HC=O). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 20.35 (CH_3), 69.37 (O$\underline{C}H_2$), 113.01 (CH_{arom}), 118.02 (HC=$\underline{C}H_2$), 124.86 ($C_{q,arom}$), 128.49 (CH_{arom}), 130.37 ($C_{q,arom}$), 132.66 (H$\underline{C}$=CH$_2$), 136.60 (CH_{arom}), 159.15 (O$C_{q,arom}$), 190.02 (C=O). **IR (cm^{-1}) υ_{max}:** 1613 (C=C), 1686 (C=O). **MS (ESI): m/z (%):** 177.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 10/1 R_f = 0.41.

4.10.3 Synthesis of dimethyl [2-(allyloxy)-5-methylphenyl](prop-2-ynylamino) methylphosphonate (418)

Aldehyde **416** (1.9 g, 11 mmol) was dissolved in dry CH_2Cl_2 (30 ml) and propargylamine (0.89 g, 16 mmol) and $MgSO_4$ (2.59 g) were added. The mixture was allowed to stir at room temperature for 24 hours. After filtration of the solids and removal of the volatiles, the obtained imine was directly used for the synthesis of the α-aminophosphonate **417**. Thus the imine is dissolved in 50

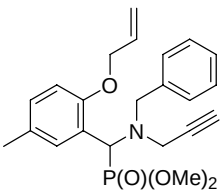
ml of MeOH in a round bottom flask. Then, dimethyl phosphite (DMP) (2.37 g, 22 mmol) is added and the mixture is refluxed for 2 hours. After removing the solvent under vacuum, the resulting oil is dissolved in 20 ml of diethyl ether and added to a separatory funnel containing 20 ml of 1 M HCl. Both phases are vigorously mixed and the organic phase is removed from the funnel. The aqueous phase is washed twice with 10 ml of diethyl ether, added to 20 ml of dichloromethane and then neutralized using 3 M NaOH until slightly alkaline. Both phases are vigorously mixed and the organic phase is now collected. The aqueous phase is extracted twice more with 10 ml of dichloromethane and the combined organic phases are dried using $MgSO_4$. The compound is obtained in pure form after filtration and evaporation of the solvent in 91% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.13 (br s, 1H, NH), 2.18 (t, *J* = 2.1 Hz, 1H, CH_{alkyne}), 2.29 (s, 3H, CH_3), 3.22 (dd, *J* = 2.5 Hz, *J* = 17.1 Hz, 1H, $NC\underline{H}_AH_B$), 3.43 (ddd, *J* = 1.2 Hz, *J* = 2.1 Hz, *J* = 17.1 Hz, 1H, $NCH_A\underline{H}_B$), 3.59 (d, *J* = 10.6 Hz, 3H, OCH_3), 3.79 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.55 (dt, *J* = 1.5 Hz, *J* = 5.0 Hz, 2H, $OC\underline{H}_2$), 4.96 (d, *J* = 19.6 Hz, CHP), 5.26 (dq, *J* = 1.5 Hz, *J* = 10.5 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.43 (dq, *J* = 1.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.05 (ddt, (dq, *J* = 5.0 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz, 1H, $OCH_2C\underline{H}$), 6.78 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.04 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.31 (s, 1H, 1 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 20.74 (CH_3), 36.38 (d, *J* = 18.5 Hz, NCH_2), 50.83 (d, *J* = 158.1 Hz, PCH), 53.48 (d, *J* = 6.9 Hz, OCH_3), 53.68 (d, *J* = 6.9 Hz, OCH_3), 69.51 ($O\underline{C}H_2$), 71.92 (CH_{alkyne}), 81.36 (C_{alkyne}), 112.41 (CH_{arom}), 117.22 ($HC=\underline{C}H_2$), 123.12 (d, *J* = 3.5 Hz, $C_{q,arom}$), 129.47 (d, *J* = 4.6 Hz, CH_{arom}), 129.59 (d, *J* = 2.3 Hz, CH_{arom}), 130.51 (d, *J* = 2.3 Hz, $C_{q,arom}$), 133.48 ($OCH_2\underline{C}H$), 154.84 (d, *J* = 6.9 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 27.01. **IR (cm^{-1}) υ_{max}:** 1034 (br P-O), 1245 (P=O), 1644 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 324.3 ($M+H^+$, 100).

4.10.4 Synthesis of Dimethyl [2-(allyloxy)-5-methylphenyl][benzyl(prop-2-ynylamino)] methylphosphonate (419)

In a flask compound **418** (3.14 g, 9.71 mmol) is dissolved in acetone (50 ml) and K_2CO_3 (5.05 g, 39 mmol), NaI (0.15 g, 0.97 mmol) and benzylbromide (3.32 g, 19 mmol) are added and the mixture is refluxed during 24h. After this time the solids are removed by filtration and the solvent by evaporation under reduced pressure. The compound was obtained in pure form as a pale yellow oil after column chromatography in 75% yield.

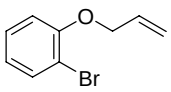


^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.12 (t, *J* = 2.2 Hz, 1H, CH_{alkyne}), 2.32 (s, 3H, CH_3), 3.27 (dd, *J* = 2.2 Hz, *J* = 17.2 Hz, 1H, $NC\underline{H}_AH_B$), 3.47 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.55 (d, *J* = 13.1 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.56 (dt, *J* = 2.2 Hz, *J* = 17.2 Hz, 1H, $NCH_A\underline{H}_B$), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.16 (d, *J* = 13.1 Hz,

1H, $NCH_A\underline{H}_BPh$), 4.54 (dt, *J* = 1.5 Hz, *J* = 5.2 Hz, 2H, $OC\underline{H}_2$), 5.11 (d, *J* = 21.5 Hz, CHP), 5.25 (dq, *J* = 1.5 Hz, *J* = 10.7 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.40 (dq, *J* = 1.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.05 (ddt, (dq, *J* = 5.2 Hz, *J* = 10.7 Hz, *J* = 17.3 Hz, 1H, $OCH_2C\underline{H}$), 6.81 (dd, *J* = 1.1 Hz, *J* = 8.3 Hz, 1H, CH_{arom}), 7.07 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.21-7.42 (m, 5H, 5 x CH_{arom}), 7.66 (s, 1H, 1 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 20.87 (CH_3), 40.71 (d, *J* = 10.4 Hz, NCH_2), 53.04 (d, *J* = 6.9 Hz, OCH_3), 53.88 (d, *J* = 8.1 Hz, OCH_3), 54.38 (d, *J* = 163.8 Hz, PCH), 55.41 (d, *J* = 8.1 Hz, NCH_2Ph), 69.60 ($O\underline{C}H_2$), 72.62 (CH_{alkyne}), 80.14 (C_{alkyne}), 112.20 (CH_{arom}), 117.36 ($HC=\underline{C}H_2$), 121.89 ($C_{q,arom}$), 127.13 (CH_{arom}), 128.25 (2 x CH_{arom}), 129.25 (2 x CH_{arom}), 131.96 (d, *J* = 4.6 Hz, CH_{arom}), 133.61 ($OCH_2\underline{C}H$), 139.10 ($C_{q,arom}$), 155.13 (d, *J* = 9.2 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 26.35. **IR (cm^{-1}) υ_{max}:** 1033 (P-O), 1059 (P-O), 1240 (br P=O), 1608 (C=C). **MS (ESI): m/z (%):** 414.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/7 R_f = 0.39.

4.10.5 Synthesis of 1-(allyloxy)-2-bromobenzene (426)

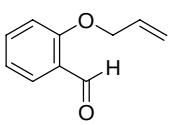
The synthesis of this compound follows the same procedure as for compound **415**. The compound was obtained in 99% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.60 (dt, *J* = 1.6 Hz, *J* = 4.9 Hz, 2H, $OC\underline{H}_2$), 5.31 (dq, *J* = 1.7 Hz, *J* = 10.5 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.49 (dq, *J* = 1.7 Hz, *J* = 17.2 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.06 (ddt, *J* = 4.9 Hz, *J* = 10.5 Hz, *J* = 17.2 Hz, 1H, $\underline{H}C=CH_AH_B$), 6.80-7.55 (m, 4H, 4 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 69.72 ($O\underline{C}H_2$), 112.40 ($BrC_{q,arom}$), 113.68 (CH_{arom}), 117.83 ($HC=\underline{C}H_2$), 122.09 (CH_{arom}), 128.48 (CH_{arom}), 132.72 ($H\underline{C}=CH_2$), 133.51 (CH_{arom}), 155.03 ($OC_{q,arom}$). **IR (cm^{-1}) υ_{max}:** 1649 (C=C). **MS (GCMS): m/z (%):** 212/214 (M^+, 100).

4.10.6 Synthesis of 1-(allyloxy)benzaldehyde (427)

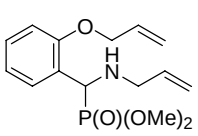
The synthesis of this compound follows the same procedure as for compound **416**. The compound was obtained in 72% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 4.66 (dt, *J* = 1.4 Hz, *J* = 5.2 Hz, 2H, $OC\underline{H}_2$), 5.34 (dq, *J* = 1.4 Hz, *J* = 10.6 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.46 (dq, *J* = 1.4 Hz, *J* = 17.3 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.08 (ddt, *J* = 5.2 Hz, *J* = 10.6 Hz, *J* = 17.3 Hz, 1H, $\underline{H}C=CH_AH_B$), 6.97-7.06 (m, 2H, 2 x CH_{arom}), 7.50-7.56 (m, 1H, 1 x CH_{arom}), 7.83-7.86 (m, 1H, CH_{arom}), 10.54 (s, 1H, HC=O). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 69.23 ($O\underline{C}H_2$), 112.91 (CH_{arom}), 118.17 ($HC=\underline{C}H_2$), 122.09 (CH_{arom}), 125.15 ($C_{q,arom}$), 128.52 (CH_{arom}), 132.46 ($H\underline{C}=CH_2$), 133.96 (CH_{arom}), 161.03 ($OC_{q,arom}$), 189.90 (C=O). **IR (cm^{-1}) υ_{max}:** 1689 (br C=O). **MS (ESI): m/z (%):** 163.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 10/1 R_f = 0.31.

4.10.7 Synthesis of dimethyl allylamino[2-(allyloxy)phenyl]methylphosphonate (429)

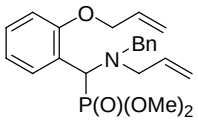
The synthesis of this compound follows the same procedure as for compound **418**. The compound was obtained in 83% yield.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.01 (br s, 1H, NH), 3.05 (dd, *J* = 6.6 Hz, *J* = 13.8 Hz, 1H, $NC\underline{H}_AH_B$), 3.21 (dd, *J* = 5.2 Hz, *J* = 13.8 Hz, 1H, $NCH_A\underline{H}_B$), 3.54 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.80 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.57 (br d, *J* = 4.6 Hz, 2H, $OC\underline{H}_2$), 4.78 (d, *J* = 21.5 Hz, CHP), 5.05-5.46 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.78-5.91 (m, 1H, $NCH_2C\underline{H}$), 5.98-6.11 (m, 1H, $OCH_2C\underline{H}$), 6.88 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.01 (t, *J* = 7.4 Hz, 1H, CH_{arom}), 7.22-7.28 (m, 1H, 1 x CH_{arom}), 7.51 (d, *J* = 7.4 Hz, 1H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 50.23 (d, *J* = 16.2 Hz, NCH_2), 51.42 (d, *J* = 158.1 Hz, PCH), 53.36 (d, *J* = 6.9 Hz, OCH_3), 53.68 (d, *J* = 6.9 Hz, OCH_3), 69.22 ($O\underline{C}H_2$), 112.08 (CH_{arom}), 116.69 ($HC=\underline{C}H_2$), 117.41 ($HC=\underline{C}H_2$), 121.22 (d, *J* = 6.9 Hz, CH_{arom}), 124.67 ($C_{q,arom}$), 128.92 (2 x CH_{arom}), 132.27 ($OCH_2\underline{C}H$), 136.23 ($NCH_2\underline{C}H$), 156.72 (d, *J* = 6.9 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 27.47. **IR (cm^{-1}) υ_{max}:** 1032 (br P-O), 1242 (P=O), 1599 (C=C), 1644 (C=C). **MS (ESI): m/z (%):** 312.3 ($M+H^+$, 100).

4.10.8 Synthesis of dimethyl (allylbenzylamino)[2-(allyloxy)phenyl]methyl phosphonate (430)

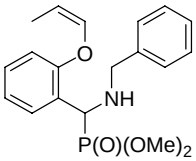
The synthesis of this compound follows the same procedure as for compound **419**. The compound was obtained in 95% yield.



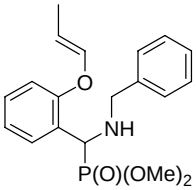
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.92 (dd, *J* = 7.8 Hz, *J* = 14.1 Hz, 1H, $NC\underline{H}_AH_B$), 3.29 (d, *J* = 14.0 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.62 (ddd, *J* = 1.9 Hz, *J* = 4.1 Hz, *J* = 14.1 Hz, 1H, $NCH_A\underline{H}_B$), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.24 (d, *J* = 14.0 Hz, 1H, $NC\underline{H}_AH_BPh$), 4.53 (dt, *J* = 1.4 Hz, *J* = 5.4 Hz, 2H, $OC\underline{H}_2$), 5.04 (d, *J* = 25.3 Hz, CHP), 5.07-5.34 (m, 4H, 2 x $HC=C\underline{H}_2$), 5.76-5.91 (m, 1H, $NCH_2C\underline{H}$), 5.95 (ddt, *J* = 5.4 Hz, *J* = 10.6 Hz, *J* = 17.2 Hz, 1H, $OCH_2C\underline{H}$), 6.92 (d, *J* = 8.3 Hz, 1H, CH_{arom}), 7.00 (t, *J* = 7.7 Hz, 1H, CH_{arom}), 6.91-7.39 (m, 6H, 6 x CH_{arom}), 7.88 (d, *J* = 7.7 Hz, 1H, CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 52.43 (d, *J* = 167.3 Hz, PCH), 52.67 (d, *J* = 6.9 Hz, OCH_3), 53.91 (d, *J* = 6.9 Hz, OCH_3), 54.61 (d, *J* = 9.2 Hz, $N\underline{C}H_2CH$), 55.52 (d, *J* = 8.1 Hz, $N\underline{C}H_2Ph$), 69.43 ($O\underline{C}H_2$), 112.25 (CH_{arom}), 117.25 ($HC=\underline{C}H_2$), 117.71 ($HC=\underline{C}H_2$), 120.46 (CH_{arom}), 121.62 (d, *J* = 6.9 Hz, $C_{q,arom}$), 126.75 (CH_{arom}), 128.09 (2 x CH_{arom}), 128.87 (2 x CH_{arom}), 129.41 (CH_{arom}), 132.22 (d, *J* = 4.6 Hz, CH_{arom}), 133.22 ($OCH_2\underline{C}H$), 136.74 ($NCH_2\underline{C}H$), 140.28 ($C_{q,arom}$), 157.18 (d, *J* = 11.5 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 27.23. **IR (cm^{-1}) υ_{max}:** 1035 (P-O), 1058 (P-O), 1238 (P=O), 1598 (C=C), 1643 (C=C). **MS (ESI): m/z (%):** 402.2 ($M+H^+$, 100).

4.10.9 Synthesis of (1Z) and (1E) dimethyl (benzylamino)[2-(prop-1-enyloxy)phenyl] methylphosphonate (433)

Compound **430** (0.15 g, 0.374 mmol) is dissolved in benzene (7.5 ml). Next $ClRu(CO)H(PPh_3)_3$ (0.0178 g, 5 mol%) is added and the mixture is refluxed for 2 hours under N_2 atmosphere. After this period the second generation Grubbs' catalyst (0.016 g, 5 mol%) is added and refluxing is continued for 16 hours. Silica gel is added on which the product is coated by removal of the solvent *in vacuo*. The compound is obtained as an E/Z mixture (3:7) in 63% combined yield.



MAJOR: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.63 (dd, *J* = 1.7 Hz, *J* = 6.9 Hz, 3H, CH_3), 2.27 (br s, 1H, NH), 3.54 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.55-3.77 (m, 2H, NCH_2 major + minor), 3.78 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.72 (d, *J* = 21.2 Hz, CHP), 4.87 (p, *J* = 6.3 Hz, 1H, OCHC<u>H</u>), 6.31 (dq, *J* = 1.7 Hz, *J* = 6.3 Hz, 1H, OC<u>H</u>CH), 6.91-7.70 (m, 9H, 9 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 9.46 (CH_3), 51.43 (d, *J* = 156.9 Hz, PCH), 51.50 (d, *J* = 17.3 Hz, NCH_2), 53.37 (d, *J* = 6.9 Hz, OCH_3), 53.84 (d, *J* = 6.9 Hz, OCH_3), 107.83 (OCH<u>C</u>H), 114.95 (CH_{arom}), 122.97 (d, *J* = 3.5 Hz, CH_{arom}), 125.12 ($C_{q,arom}$), 127.18 (CH_{arom}), 128.40 (2 x CH_{arom}), 128.52 (2 x CH_{arom}), 129.09 (CH_{arom}), 132.19 (d, *J* = 9.2 Hz, CH_{arom}), 139.42 ($C_{q,arom}$), 140.98 (OCH), 155.82 (d, *J* = 6.9 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 26.87. **IR (cm^{-1}) υ_{max}:** 1031 (br P-O), 1251 (P=O), 1669 (C=C). **MS (ESI): m/z (%):** 362.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.26.



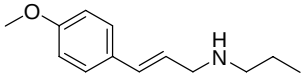
MINOR: ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.65 (dd, *J* = 1.5 Hz, *J* = 6.7 Hz, 3H, CH_3), 2.27 (br s, 1H, NH), 3.54 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.79 (d, *J* = 10.7 Hz, 3H, OCH_3), 3.55-3.77 (m, 2H, NCH_2 major + minor), 4.66 (d, *J* = 21.2 Hz, CHP), 5.29 (dq, *J* = 6.7 Hz, *J* = 12.4 Hz, 1H, OCHC<u>H</u>), 6.33 (dq, *J* = 1.5 Hz, *J* = 12.4 Hz, 1H, OC<u>H</u>CH), 6.91-7.70 (m, 9H, 9 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$):** δ 12.33 (CH_3), 51.59 (d, *J* = 17.3 Hz, NCH_2), 51.63 (d, *J* = 156.9 Hz, PCH), 53.37 (d, *J* = 6.9 Hz, OCH_3), 53.93 (d, *J* = 5.8 Hz, OCH_3), 108.61 (OCH<u>C</u>H), 115.57 (CH_{arom}), 123.07 (d, *J* = 2.3 Hz, CH_{arom}), 125.25 ($C_{q,arom}$), 127.18 (CH_{arom}), 128.40 (2 x CH_{arom}), 128.52 (2 x CH_{arom}), 129.09 (CH_{arom}), 132.05 (d, *J* = 2.3 Hz, CH_{arom}), 139.50 ($C_{q,arom}$), 142.20 (OCH), 155.77 (d, *J* = 8.1 Hz, $OC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$):** δ 26.82. **IR (cm^{-1}) υ_{max}:** 1031 (br P-O), 1251 (P=O), 1669 (C=C). **MS (ESI): m/z (%):** 362.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.26.

4.11 Synthesis of phosphonylated isoindoles

4.11.1 Synthesis of secondary amines 454

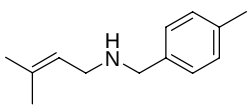
All secondary amines were synthesized using a reductive amination. A suitable aldehyde was dissolved in dry CH_2Cl_2 and 1 equivalent of amine and 2 equivalents of $MgSO_4$ were added. The mixture was allowed to stir at room temperature for 24 hours. After filtration of the solids and removal of the volatiles, the obtained aldimines were dissolved in dry MeOH. To this solution 1.1 equivalent of $NaBH_4$ was carefully added and stirring was continued for 4 hours. The reaction was quenched by the addition of $NaHCO_3$ (sat, aq) and the MeOH was removed under reduced pressure. The residue was extracted with CH_2Cl_2 and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained amines **184a-h** were obtained pure.

N-[(2E)-3-(4-methoxyphenyl)prop-2-enyl]-N-propylamine (454c)



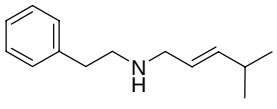
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H, CH_3), 1.55 (sextet, *J* = 7.3 Hz, 2H, $C\underline{H}_2CH_3$), 1.94 (s, 1H, NH), 2.63 (t, *J* = 7.3 Hz, 2H, $NC\underline{H}_2CH_2$), 3.40 (dd, *J* = 1.2 Hz, *J* = 6.5 Hz, 2H, $NC\underline{H}_2CH$), 3.80 (s, 3H, $PhOCH_3$), 6.18 (dt, *J* = 15.7 Hz, *J* = 6.5 Hz, 1H, $\underline{H}C$=CHPh), 6.47 (d, *J* = 15.7 Hz, 1H, $\underline{H}CPh$), 6.84 (d, *J* = 8.8 Hz, 2H, 2 x CH_{arom}), 7.31 (d, *J* = 8.5 Hz, 2H, 2 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.86 ($CH_2\underline{C}H_3$), 23.28 ($\underline{C}H_2CH_3$), 51.40 ($N\underline{C}H_2CH_2$), 52.03 ($N\underline{C}H_2CH$), 55.04 (OCH_3), 113.91 (2 x CH_{arom}), 126.41 ($H\underline{C}$=CHPh), 127.36 (2 x CH_{arom}), 129.96 ($C_{q,arom}$), 130.54 (HC=$\underline{C}$HPh), 159.01 (C_q, Ph). **IR (cm^{-1}) ν_{max}:** 1608 (C=C), 3300 (br NH). **MS (ESI): m/z (%):** No $M+H^+$, 147.2 (M^+-NC_3H_8, 100). **Yield:** 97%.

N-(4-methylbenzyl)-N-(3-methylbut-2-enyl)amine (454d)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.62 (br s, 3H, CH_3), 1.72 (br s, 3H, CH_3), 1.77 (s, 1H, NH), 2.33 (s, 3H, CH_3), 3.22 (d, *J* = 6.9 Hz, $NC\underline{H}_2CH$), 3.74 (s, 2H, $NC\underline{H}_2C$), 5.28 (t x septet, *J* = 6.9 Hz, *J* = 1.4 Hz, 1H, $NCH_2C\underline{H}$), 7.11-7.26 (m, 4H, 4 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.16 ($CH_2\underline{C}H_3$), 16.73 ($C\underline{C}H_3$), 20.65 ($\underline{C}H_2CH_3$), 32.44 ($NCH_2\underline{C}H_2$), 49.10 ($N\underline{C}H_2CH_2$), 58.35 ($N\underline{C}H_2C$), 125.51 ($\underline{C}HPh$), 126.20 (CH_{arom}), 128.14 (2 x CH_{arom}), 128.96 (2 x CH_{arom}), 137.33 ($C\underline{C}H_3$), 138.20 ($C_{q,arom}$). **IR (cm^{-1}) ν_{max}:** 1655 (C=C), 2950 (br NH). **MS (ESI): m/z (%):** 204.5 ($M+H^+$, 100). **Yield:** 68%.

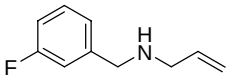
N-[(2E)-4-methylpent-2-enyl]-N-(2-phenylethyl) amine (454e)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.97 (d, *J* = 6.8 Hz, 6H, 2 x CH_3), 1.30 (br s, 1H, NH), 2.26 (octet, *J* = 6.8 Hz, 1H, CH), 2.78-2.90 (m, 4H, CH_2CH_2), 3.19 (d, *J* = 5.8 Hz, 2H, $NC\underline{H}_2CH$), 5.39-5.58 (m, 2H, $\underline{H}C$=C$\underline{H}$Ph), 7.17-7.32 (m, 5H, 5 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 22.51 (2 x CH_3),

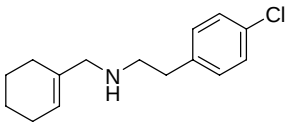
30.91 (<u>C</u>H(CH_3)$_2$), 36.53 (<u>C</u>H_2Ph), 50.65 (N<u>C</u>$H_2$$CH_2$), 51.75 (N<u>C</u>$H_2$CH), 125.24 (H<u>C</u>=CHPh), 126.18 (CH_{arom}), 128.38 (2 x CH_{arom}), 128.80 (2 x CH_{arom}), 139.73 (HC=<u>C</u>HPh), 140.22 (C_q, Ph). **IR (cm^{-1}) ν_{max}:** 1604 (C=C), 2958 (br NH). **MS (ESI): m/z (%):** 204.5 (M+H$^+$, 100). **Yield:** 86%.

Allyl-(3-fluorobenzyl)amine (454f)



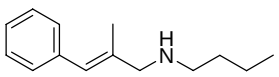
^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.53 (br s, 1H, NH), 3.27 (dt, *J* = 1.2 Hz, *J* = 6.1 Hz, 2H, NC<u>H</u>$_2$CH), 3.79 (s, 2H, NC<u>H</u>$_2$Ph), 5.31 (dq, *J* = 1.2 Hz, *J* = 10.2 Hz, 1H, HC=C<u>H</u>$_A$H$_B$), 5.20 (dq, *J* = 1.2 Hz, *J* = 17.1 Hz, 1H, HC=CH$_A$<u>H</u>$_B$), 5.92 (ddt, *J* = 6.1 Hz, *J* = 10.2 Hz, *J* = 17.1 Hz, 1H, <u>H</u>C=CH$_2$), 6.91-7.32 (m, 4H, 4 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 51.74 (N<u>C</u>H_2CH), 52.65 (N<u>C</u>H_2Ph), 113.83 (d, *J* = 21.9 Hz, CH_{arom}), 114.96 (d, *J* = 20.8 Hz, CH_{arom}), 116.21 (HC=<u>C</u>H_2), 123.70 (d, *J* = 3.5 Hz, CH_{arom}), 129.86 (d, *J* = 8.1 Hz, CH_{arom}), 136.67 (H<u>C</u>=CH$_2$), 143.12 (d, *J* = 6.9 Hz, $CH_{q,arom}$), 163.08 (d, *J* = 245.8 Hz, $FC_{q,arom}$). **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -113.41 (dd, *J* = 9.8 Hz, *J* = 16.8 Hz). **IR (cm^{-1}) ν_{max}:** 1590 (C=C), 1616 (C=C), 1644 (C=C), 2823 (br NH). **MS (ESI): m/z (%):** 166.3 (M+H$^+$, 100). **Yield:** 94%.

N-(4-methylbenzyl)-N-(3-methylbut-2-enyl)amine (454g)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.48 (br s, 1H, NH), 1.52-1.67 (m, 4H, CH_2CH_2), 1.87-1.94 (m, 2H, CC<u>H</u>$_2$), 1.96-2.05 (m, 2H, HCC<u>H</u>$_2$), 2.74-2.84 (m, 4H, NCH_2CH_2), 3.11 (s, 2H, NCH_2), 5.54 (br s, HC), 7.14 (d, 2H, *J* = 8.4 Hz, 2H, 2 x CH_{arom}), 7.26 (d, 2H, *J* = 8.4 Hz, 2H, 2 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 22.61 (CH_2), 22.82 (CH_2), 25.14 (HC<u>C</u>H_2), 26.96 (C<u>C</u>H_2), 35.81 (<u>C</u>H_2Ph), 50.32 (N<u>C</u>$H_2$$CH_2$), 56.13 (N<u>C</u>$H_2$C), 122.86 (H<u>C</u>=C), 128.61 (2 x CH_{arom}), 130.14 (2 x CH_{arom}), 131.93 ($ClC_{q,arom}$), 135.97 ($C_{q,arom}$), 138.77 (<u>C</u>=CH). **IR (cm^{-1}) ν_{max}:** 1670 (C=C), 2925 (NH). **MS (ESI): m/z (%):** 250.2/252.2 (M+H$^+$, 100). **Yield:** 88%.

N-butyl-N-[(2E)-2-methyl-3-phenylprop-2-enyl]amine (454h)

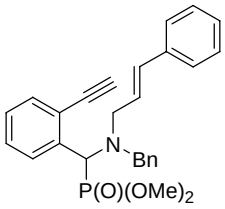


^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.93 (t, *J* = 7.3 Hz, 3H, CH_3), 1.36 (s, 1H, NH), 1.37 (sextet, *J* = 7.3 Hz, 2H, C<u>H</u>$_2$CH$_3$), 1.47-1.57 (m, 2H, NCH_2C<u>H</u>$_2$), 1.89 (d, *J* = 1.1 Hz, 3H, CH_3), 2.63 (t, *J* = 7.2 Hz, NC<u>H</u>$_2$$CH_2$), 3.32 (s, 2H, NC<u>H</u>$_2$C), 6.34 (br s, 1H, C<u>H</u>Ph), 7.17-7.35 (m, 5H, 5 x CH_{arom}). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.16 (CH_2<u>C</u>H$_3$), 16.73 (C<u>C</u>H$_3$), 20.65 (<u>C</u>H$_2$CH$_3$), 32.44 (NCH_2<u>C</u>H$_2$), 49.10 (N<u>C</u>$H_2$$CH_2$), 58.35 (N<u>C</u>$H_2$C), 125.51 (<u>C</u>HPh), 126.20 (CH_{arom}), 128.14 (2 x CH_{arom}), 128.96 (2 x CH_{arom}), 137.33 (C<u>C</u>H$_3$), 138.20 ($C_{q,arom}$). **IR (cm^{-1}) ν_{max}:** 1655 (C=C), 2950 (br NH). **MS (ESI): m/z (%):** 204.5 (M+H$^+$, 100). **Yield:** 49%.

4.11.2 Synthesis of α-aminophosphonates 434

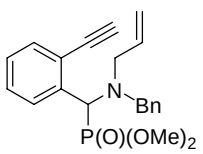
In a dry flask, 2-ethynylbenzaldehyde (0.5g, 3.84 mmol) is dissolved into diethylether (6 ml). To this solution is added $LiClO_4$ (3.06 g, 28.8 mmol, dried for 24h at 110 °C). This mixture is stirred for 5 minutes. Subsequently secondary amine **454** is added (7.69 mmol, dissolved in 1ml dry diethylether). This mixture is stirred for 20 minutes after which $P(OMe)_3$ is added (0.71 g, 5.76 mmol). The reaction is stirred for 30 minutes after which water is very carefully added (20 ml). The mixture is extracted with CH_2Cl_2 (3 x 20ml) and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained compounds were purified using either crystallization, column chromatography or acid/base extraction.

Dimethyl [benzyl-(3-phenylprop-2-enyl)amino](2-ethynylphenyl)methylphosphonate (434a)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.01 (s, 1H, CCH), 3.20 (dd, *J* = 7.4 Hz, *J* = 14.6 Hz, 1H, NCH_AH_BCH), 3.45 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.63 (d, *J* = 14.0 Hz, 1H, NCH_AH_BPh), 3.75 (ddt, *J* = 2.5 Hz, *J* = 5.2 Hz, *J* = 14.6 Hz, 1H, NCH_AH_BCH), 3.91 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.33 (d, *J* = 14.2 Hz, 1H, NCH_AH_BPh), 5.12 (d, *J* = 24.0 Hz, 1H, CHP), 6.18 (ddd, *J* = 15.7 Hz, *J* = 7.4 Hz, *J* = 5.2 Hz, 1H, HC=CHPh), 6.48 (d, *J* = 15.7 Hz, 1H, HCPh), 7.17-7.58 (m, 13H, 13 x CH_{arom}), 8.00 (d, *J* = 8.0 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 53.04 (d, *J* = 6.9 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 53.70 (d, *J* = 8.1 Hz, NCH_2CH), 55.48 (d, *J* = 6.9 Hz, NCH_2Ph), 58.85 (d, *J* = 160.1 Hz, CHP), 82.11 (CCH), 82.17 (CCH), 124.15 (d, *J* = 12.7 Hz, PCHCC), 126.34 (2 x CH_{arom}), 126.86 (CH_{arom}), 127.35 (CH_{arom}), 127.70 (HC=CHPh), 128.11 (CH_{arom}), 128.18 (2 x CH_{arom}), 128.57 (3 x CH_{arom}), 128.72 (3 x CH_{arom}), 130.73 (d, *J* = 3.5 Hz, PCHCCH), 132.58 (CHPh), 133.45 (PCHCCCH), 135.98 (d, *J* = 5.8 Hz, PCHC), 137.38 (C_q, Ph), 140.00 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.47. **IR (cm^{-1}) ν_{max}:** 1032 (P-O), 1056 (P-O), 1248 (P=O), 1641 (C=C), 2090 (alkyne). **MS (ESI): m/z (%):** 446.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.18. **Yield:** 68%.

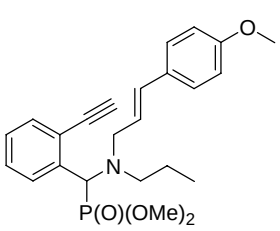
Dimethyl (allylbenzylamino)(2-ethynylphenyl)methylphosphonate (434b)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.04 (s, 1H, CCH), 3.06 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 1H, NCH_AH_BCH), 3.44 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.52 (d, *J* = 14.2 Hz, 1H, NCH_AH_BPh), 3.66 (ddd, *J* = 1.5 Hz, *J* = 4.5 Hz, *J* = 14.6 Hz, 1H, NCH_AH_BCH), 3.96 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.23 (d, *J* = 14.2 Hz, 1H, NCH_AH_BPh), 5.03 (d, *J* = 24.5 Hz, 1H, CHP), 5.09 (d, *J* = 10.8 Hz, 1H, $HC=CH_AH_B$), 5.18 (dd, *J* = 1.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_AH_B$), 5.83 (dddd, *J* = 4.5 Hz, *J* = 7.2 Hz, *J* = 10.5 Hz, *J* = 17.3 Hz, 1H, $HC=CH_2$), 7.19-7.44 (m, 7H, 7 x CH_{arom}), 7.56 (d, *J* = 7.7 Hz, 1H, PCHCCH), 7.97 (d, *J* = 8.0 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 52.94 (d, *J* = 6.9 Hz, OCH_3), 53.72 (d, *J*

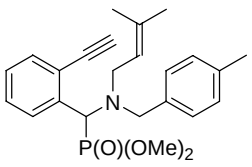
= 6.9 Hz, OCH_3), 54.28 (d, *J* = 8.1 Hz, N<u>C</u>H_2CH), 55.18 (d, *J* = 8.1 Hz, N<u>C</u>H_2Ph), 58.64 (d, *J* = 161.5 Hz, CHP), 81.98 (<u>C</u>CH), 82.08 (C<u>C</u>H), 117.41 (HC=<u>C</u>H_2), 124.18 (d, *J* = 12.7 Hz, PCHC<u>C</u>), 126.80 (CH_{para}, Ph), 128.11 (3 x CH_{arom}), 128.64 (3 x CH_{arom}), 130.74 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 133.39 (PCHCC<u>C</u>H), 135.77 (d, *J* = 5.8 Hz, PCH<u>C</u>), 135.99 (H<u>C</u>=CH_2), 139.96 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.25. **IR (cm^{-1}) ν_{max}:** 1035 (P-O),1058 (P-O), 1246 (P=O), 1642 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 370.2 ($M+H^+$, 100). **MP (°C):** 86-87. **Chromatography:** Hex/EtOAc 4/6 R_f = 0.27. **Yield:** 68%.

Dimethyl (2-ethynylphenyl) [(propyl)[(2E)-3-(4-methoxyphenyl)prop-2-enyl]amino] methylphosphonate (434c)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.86 (t, *J* = 7.3 Hz, 3H, CH_3), 1.55 (sextet, *J* = 7.3 Hz, 2H, C<u>H</u>$_2$$CH_3$), 2.51 (ddd, *J* = 5.5 Hz, *J* = 7.3 Hz, *J* = 12.9 Hz, 1H, NC<u>H</u>$_A$$H_B$$CH_2$), 2.74-2.81 (m, 1H, NC$H_A$<u>H</u>$_B$$CH_2$), 3.07 (dd, *J* = 7.6 Hz, *J* = 14.3 Hz, 1H, NC<u>H</u>$_A$$H_B$CH), 3.22 (s, 1H, CCH), 3.47 (d, *J* = 9.6 Hz, 3H, OCH_3), 3.79 (s, 3H, PhOCH_3), 3.90-3.94 (m, 1H, NCH_A<u>H</u>$_B$CH), 3.92 (d, *J* = 10.5 Hz, 3H, OCH_3), 5.02 (d, *J* = 24.8 Hz, 1H, CHP), 6.04 (ddd, *J* = 14.7 Hz, *J* = 7.6 Hz, *J* = 5.5 Hz, 1H, <u>H</u>C=CHPh), 6.41 (d, *J* = 14.7 Hz, 1H, <u>H</u>CPh), 6.83 (d, *J* = 8.2 Hz, 2H, 2 x CH_{arom}), 7.25-7.41 (m, 2H, 2 x CH_{arom}), 7.26 (d, *J* = 8.3 Hz, 2H, 2 x CH_{arom}), 7.56 (d, *J* = 7.4 Hz, 1H, PCHCC<u>H</u>), 7.93 (d, *J* = 7.7 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.74 (CH$_2$<u>C</u>H$_3$), 21.31 (<u>C</u>H$_2$CH$_3$), 52.76 (d, *J* = 6.9 Hz, OCH_3), 53.07 (d, *J* = 10.4 Hz, N<u>C</u>H$_2$CH$_2$), 54.10 (d, *J* = 6.9 Hz, OCH_3), 54.20 (d, *J* = 5.8 Hz, N<u>C</u>H$_2$CH), 58.95 (d, *J* = 162.7 Hz, CHP), 81.54 (<u>C</u>CH), 82.38 (C<u>C</u>H), 114.00 (2 x CH_{arom}), 124.01 (d, *J* = 12.7 Hz, PCHC<u>C</u>), 126.32 (H<u>C</u>=CHPh), 127.42 (2 x CH_{arom}), 127.91 (CH_{arom}), 128.66 (CH_{arom}), 130.32 ($C_{q,arom}$), 130.73 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 131.30 (HC=<u>C</u>HPh), 133.39 (PCHCC<u>C</u>H), 136.12 (d, *J* = 6.9 Hz, PCH<u>C</u>), 159.01 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.11. **IR (cm^{-1}) ν_{max}:** 1034 (P-O),1058 (P-O), 1248 (P=O), 1607 (C=C), 2098 (alkyne). **MS (ESI): m/z (%):** 428.3 ($M+H^+$, 100). **MP (°C):** 99-101. **Yield:** 81%.

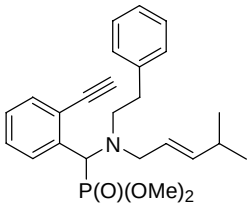
Dimethyl [(4-methylbenzyl)-(3-methylbut-2-enyl)amino](2-ethynylphenyl)methyl phosphonate (434d)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 3.03 (dd, *J* = 6.7 Hz, *J* = 13.5 Hz, 1H, NC<u>H</u>$_A$$H_B$CH), 3.06 (s, 1H, CCH), 3.40-3.51 (m, 1H, NCH_A<u>H</u>$_B$CH), 3.44 (d, *J* = 10.4 Hz, 3H, OCH_3), 3.53 (d, *J* = 13.8 Hz, 1H, NC<u>H</u>$_A$$H_B$Ph), 3.89 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.15 (d, *J* = 13.8 Hz, 1H, NCH_A<u>H</u>$_B$Ph), 5.04 (d, *J* = 24.2 Hz, 1H, CHP), 5.26 (t*septet, *J* = 6.6 Hz, *J* = 1.2 Hz, 1H, <u>H</u>C=C), 7.06-7.43 (m, 6H, 6 x CH_{arom}), 7.55 (d, *J* = 7.7 Hz, 1H, PCHCC<u>H</u>), 7.96 (d, *J* = 8.0 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 18.19 (CH_3), 21.22 (CH_3), 26.06 (CH_3),

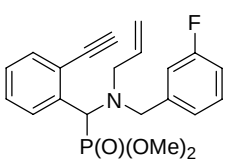
49.05 (d, *J* = 9.2 Hz, N<u>C</u>H$_2$CH), 52.87 (d, *J* = 6.9 Hz, OCH$_3$), 53.75 (d, *J* = 6.9 Hz, OCH$_3$), 55.15 (d, *J* = 8.1 Hz, N<u>C</u>H$_2$Ph), 58.86 (d, *J* = 160.4 Hz, CHP), 81.77 (C<u>C</u>H), 82.91 (<u>C</u>CH), 122.14 (H<u>C</u>=C), 124.08 (d, *J* = 11.5 Hz, PCHC<u>C</u>), 127.88 (CH$_{arom}$), 128.63 (CH$_{arom}$), 128.70 (4 x CH$_{arom}$), 130.79 (d, *J* = 3.5 Hz, PCHCC<u>C</u>H), 133.33 (PCHCC<u>C</u>H), 134.95 (C$_{q,arom}$), 136.17 (d, *J* = 6.8 Hz, PCH<u>C</u>), 136.28 (C$_q$), 137.19 (C$_{q,arom}$). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 26.56. **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1057 (P-O), 1245 (P=O), 1637 (C=C), 2101 (alkyne). **MS (ESI): m/z (%):** 412.3 (M+H$^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R$_f$ = 0.32. **MP (°C):** 101.5. **Yield:** 48%.

Dimethyl (2-ethynylphenyl)[[(2E)-4-methylpent-2-enyl(2-phenylethyl)]amino]methyl phosphonate (434e)



^{1}H-NMR (300 MHz, CDCl$_3$): δ 0.95 (d, *J* = 6.9 Hz, 3H, CH$_3$), 0.96 (d, *J* = 6.9 Hz, 3H, CH$_3$), 2.26 (octet, *J* = 6.9 Hz, 1H, CH), 2.69-2.85 (m, 3H, C<u>H$_2$</u>Ph + NC<u>H$_A$H$_B$</u>CH$_2$), 2.99-3.11 (m, 2H, NCH$_A$<u>H$_B$</u>CH$_2$ + NC<u>H$_A$H$_B$</u>CH), 3.33 (s, 1H, CCH), 3.45 (d, *J* = 10.4 Hz, 3H, OCH$_3$), 3.80 (d, *J* = 10.4 Hz, 3H, OCH$_3$), 3.76-3.84 (m, 1H, NCH$_A$<u>H$_B$</u>CH), 5.05 (d, *J* = 24.5 Hz, 1H, CHP), 5.33 (ddd, *J* = 15.4 Hz, *J* = 7.0 Hz, *J* = 5.6 Hz, 1H, NCH$_2$C<u>H</u>), 5.52 (dd, *J* = 15.4 Hz, *J* = 6.9 Hz, 1H, C<u>H</u>CH(CH$_3$)$_2$), 7.12-7.51 (m, 7H, 7 x CH$_{arom}$), 7.55 (d, *J* = 7.4 Hz, 1H, PCHCC<u>H</u>), 7.89 (d, *J* = 7.7 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 22.51 (CH$_3$), 22.56 (CH$_3$), 30.99 (CH), 34.23 (<u>C</u>H$_2$Ph), 52.49 (d, *J* = 10.4 Hz, N<u>C</u>H$_2$CH$_2$), 52.80 (d, *J* = 8.1 Hz, OCH$_3$), 54.16 (d, *J* = 5.8 Hz, N<u>C</u>H$_2$CH + OCH$_3$), 59.51 (d, *J* = 163.8 Hz, CHP), 81.91 (C<u>C</u>H), 82.55 (<u>C</u>CH), 123.81 (d, *J* = 12.7 Hz, PCHC<u>C</u>), 124.78 (NCH$_2$<u>C</u>H), 125.89 (CH$_{arom}$), 127.96 (CH$_{arom}$), 128.26 (2 x CH$_{arom}$), 128.78 (CH$_{arom}$), 129.18 (2 x CH$_{arom}$), 130.60 (d, *J* = 3.5 Hz, PCHCC<u>H</u>), 133.44 (CH$_{arom}$), 136.25 (d, *J* = 4.6 Hz, PCH<u>C</u>), 140.54 (H<u>C</u>CH(<u>C</u>H$_3$)$_2$), 140.58 (C$_{q,arom}$). **^{31}P-NMR (MHz, CDCl$_3$): δ** 25.95. **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1060 (P-O), 1246 (P=O), 1604 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 426.2 (M+H$^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R$_f$ = 0.56. **Yield:** 56%.

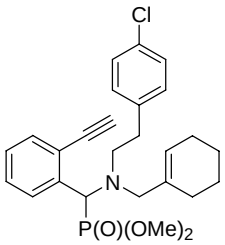
Dimethyl [allyl(3-fluorobenzyl)amino](2-ethynylphenyl)methylphosphonate (434f)



^{1}H-NMR (300 MHz, CDCl$_3$): δ 3.05 (dd, *J* = 7.6 Hz, *J* = 14.3 Hz, 1H, NC<u>H$_A$H$_B$</u>CH), 3.06 (s, 1H, CCH), 3.44 (d, *J* = 10.7 Hz, 3H, OCH$_3$), 3.53 (d, *J* = 14.4 Hz, 1H, NC<u>H$_A$H$_B$</u>Ph), 3.71 (ddd, *J* = 2.0 Hz, *J* = 4.6 Hz, *J* = 14.3 Hz, 1H, NCH$_A$<u>H$_B$</u>CH), 3.91 (d, *J* = 10.7 Hz, 3H, OCH$_3$), 4.21 (d, *J* = 14.4 Hz, 1H, NCH$_A$<u>H$_B$</u>Ph), 4.99 (d, *J* = 24.8 Hz, 1H, CHP), 5.10 (dd, *J* = 10.6 Hz, *J* = 1.0 Hz, 1H, HC=C<u>H$_A$H$_B$</u>), 5.18 (dd, *J* = 1.0 Hz, *J* = 17.0 Hz, 1H, HC=CH$_A$<u>H$_B$</u>), 5.83 (dddd, *J* = 4.6 Hz, *J* = 7.6 Hz, *J* = 10.6 Hz, *J* = 17.0 Hz, 1H, <u>H</u>C=CH$_2$), 6.87-7.44 (m, 6H, 6 x CH$_{arom}$), 7.56 (d, *J* = 7.7 Hz, 1H, PCHCC<u>H</u>), 7.96 (d, *J* = 7.7 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 53.00 (d, *J* = 6.9 Hz, OCH$_3$), 53.62 (d, *J* = 6.9 Hz, OCH$_3$), 54.47 (d, *J* = 6.9 Hz, N<u>C</u>H$_2$CH), 54.65 (d, *J* = 8.1 Hz, N<u>C</u>H$_2$Ph), 58.53 (d, *J* = 161.5 Hz, CHP), 81.91 (<u>C</u>CH), 82.11 (C<u>C</u>H), 113.62 (d, *J* = 20.8 Hz, CH$_{arom}$), 115.26

(d, *J* = 21.9 Hz, CH_{arom}), 117.60 (HC=$\underline{C}H_2$), 124.08 (d, *J* = 2.3 Hz, CH_{arom}), 124.18 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 128.17 (CH_{arom}), 128.75 (CH_{arom}), 129.38 (d, *J* = 8.1 Hz, CH_{arom}), 130.64 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 133.45 (PCHCC$\underline{C}$H), 135.48 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 135.79 (H$\underline{C}$=CH_2), 142.90 (d, *J* = 6.9 Hz, C_q, Ph), 163.03 (d, *J* = 224.6 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.03. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -113.90 (dt, *J* = 6.6 Hz, *J* = 9.2 Hz). **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1058 (P-O), 1248 (P=O), 1615 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 388.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 6/4 R_f = 0.13. **Yield:** 72%.

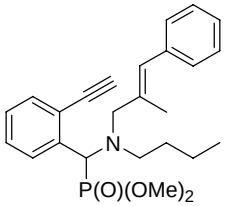
Dimethyl {[(cyclohex-1-en-1-ylmethyl)[2-(4-chlorophenyl)ethyl]]amino}(2-ethynyl phenyl)methylphosphonate (434g)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.53-1.61 (m, 4H, $CH_2\underline{C}H_2$), 1.86-1.97 (m, 4H, HCC$\underline{H}_2$ + CC$\underline{H}_2$), 2.57-2.68 (m, 1H, NC$\underline{H}_A$H$_B$CH$_2$), 2.74 (t, *J* = 6.6 Hz, 2H, NCH$_2$C$\underline{H}_2$), 2.84 (d, *J* = 12.9 Hz, NC$\underline{H}_A$H$_B$), 2.96-3.05 (m, 1H, NCH$_A$$\underline{H}_BCH_2$), 3.31 (s, 1H, CH_{alkyne}), 3.44 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.65 (d, *J* = 12.9 Hz, NCH$_A$$\underline{H}_B$), 3.82 (d, *J* = 10.7 Hz, 3H, OCH_3), 5.03 (d, *J* = 24.8 Hz, 1H, CHP), 5.52 (br s, 1H, CH), 7.09 (d, *J* = 8.4 Hz, 2H, 2 x CH_{arom}), 7.21 (d, *J* = 8.4 Hz, 2H, 2 x CH_{arom}), 7.29-7.39 (m, 2H, 2 x CH_{arom}), 7.57 (d, *J* = 7.4 Hz, 1H, PCHCC$\underline{H}$), 7.85 (d, *J* = 8.0 Hz, 1H, PCHCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 22.73 (CH_2), 22.91 (CH_2), 25.38 (CH_2), 26.77 (CH_2), 33.74 ($\underline{C}H_2$Ph), 52.58 (d, *J* = 10.4 Hz, N$\underline{C}H_2CH_2$), 52.91 (d, *J* = 6.9 Hz, OCH_3), 53.59 (d, *J* = 6.9 Hz, OCH_3), 59.00 (d, *J* = 162.7 Hz, CHP), 59.26 (d, *J* = 5.8 Hz, N$\underline{C}H_2$C), 81.71 (C$\underline{C}$H), 82.55 ($\underline{C}$CH), 123.87 (d, *J* = 12.7 Hz, PCHC$\underline{C}$), 124.72 (CH), 127.96 (CH_{arom}), 128.32 (2 x CH_{arom}), 128.73 (CH_{arom}), 130.37 (2 x CH_{arom}), 130.64 (d, *J* = 3.5 Hz, PCHC$\underline{C}$H), 131.57 ($ClC_{q,arom}$), 133.44 (CH_{arom}), 135.96 ($C_{q,arom}$), 136.06 (d, *J* = 5.8 Hz, PCH$\underline{C}$), 139.24 ($\underline{C}$=CH). **^{31}P-NMR (MHz, $CDCl_3$): δ** 26.21. **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1060 (P-O), 1244 (P=O), 2097 (alkyne). **MS (ESI): m/z (%):** 472.2/474.2 ($M+H^+$, 100). **MP (°C):** 103-104. **Yield:** 59%.

Dimethyl (2-ethynylphenyl){butyl[(2E)-2-methyl-3-phenylprop-2-enyl]amino}methyl phosphonate (434h)

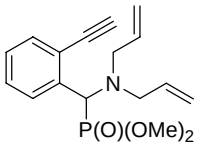
For purification of **434h**, the mixture obtained after drying with $MgSO_4$ was dissolved in ether (100 ml) and washed twice with HCl (3N, 25 ml) to remove the excess of secondary amine. Afterwards the organic layer is made basic with NaOH (aq, 3N),extracted with ether three times (50 ml) and dried with $MgSO_4$.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.3 Hz, 3H, $CH_2C\underline{H}_3$), 1.20-1.43 (m, 2H, $C\underline{H}_2CH_3$), 1.54 (m, 2H, $NCH_2C\underline{H}_2$), 1.92 (s, 3H, CCH_3), 2.44 (ddd, *J* = 6.1 Hz, *J* = 6.9 Hz, *J* = 12.9 Hz, 1H, NC$\underline{H}_A$H$_B$CH$_2$), 2.81-2.92 (m, 1H,

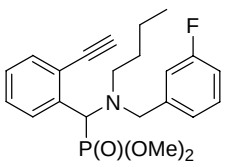
$NCH_AH_BCH_2$), 2.90 (d, *J* = 13.8 Hz, 1H, NCH_AH_BC), 3.21 (s, 1H, CCH), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.84 (d, *J* = 13.8 Hz, 1H, NCH_AH_BC), 3.91 (d, *J* = 10.7 Hz, 3H, OCH_3), 5.05 (d, *J* = 25.6 Hz, 1H, CHP), 6.43 (s, 1H, HC=C), 7.17-7.43 (m, 7H, 7 x CH_{arom}), 7.57 (d, *J* = 7.4 Hz, 1H, PCHCCH), 7.93 (d, *J* = 8.0 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.27 (CH_2CH_3), 16.65 (CCH_3), 20.56 (CH_2CH_3), 30.47 (NCH_2CH_2), 51.00 (d, *J* = 11.5 Hz, NCH_2CH_2), 52.84 (d, *J* = 6.9 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 58.30 (d, *J* = 163.8 Hz, CHP), 60.97 (d, *J* = 5.8 Hz, NCH_2C), 81.45 (CCH), 82.32 (CCH), 124.19 (d, *J* = 12.7 Hz, PCHCC), 126.11 (HC=C), 126.81 (CH_{arom}), 127.94 (CH_{arom}), 128.12 (2 x CH_{arom}), 128.63 (CH_{arom}), 128.93 (2 x CH_{arom}), 130.80 (d, *J* = 3.5 Hz, PCHCCH), 133.42 (PCHCCCH), 135.76 (d, *J* = 6.9 Hz, PCHC), 137.35 (C=CH), 138.45 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.38. **IR (cm^{-1}) ν_{max}:** 1036 (P-O),1059 (P-O), 1244 (P=O), 1598 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 426.2 ($M+H^+$, 100). **Yield:** 88%.

Dimethyl (diallylamino)(2-ethynylphenyl)methylphosphonate (434i)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.06 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 2H, 2 x NCH_AH_BCH), 3.26 (s, 1H, CCH), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.66 (ddt, *J* = 2.2 Hz, *J* = 2.5 Hz, *J* = 14.6 Hz, 2H, 2 x NCH_AH_BCH), 3.90 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.97 (d, *J* = 24.2 Hz, 1H, CHP), 5.10 (d, *J* = 10.5 Hz, 2H, 2 x $HC=CH_aH_b$), 5.19 (d, *J* = 17.2 Hz, 2H, 2 x $HC=CH_aH_b$), 5.75-5.88 (m, 2H, 2 x $HC=CH_2$), 7.27-7.41 (m, 2H, 2 x CH_{arom}), 7.72 (d, *J* = 7.5 Hz, 1H, PCHCCH), 7.92 (d, *J* = 7.7 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 52.82 (d, *J* = 6.9 Hz, OCH_3), 54.05 (d, *J* = 8.1 Hz, 2 x NCH_2CH), 54.15 (d, *J* = 6.9 Hz, OCH_3), 58.91 (d, *J* = 163.8 Hz, CHP), 81.97 (CCH), 82.26 (CCH), 117.04 (2 x $HC=CH_2$), 123.95 (d, *J* = 12.7 Hz, PCHCC), 127.99 (CH_{arom}), 128.70 (CH_{arom}), 130.66 (d, *J* = 4.6 Hz, PCHCCH), 133.42 (CH_{arom}), 136.00 (d, *J* = 4.6 Hz, PCHC), 136.15 (2 x $HC=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.16. **IR (cm^{-1}) ν_{max}:** 1047 (br P-O), 1239 (P=O), 1642 (C=C), 2095 (alkyne). **MS (ESI): m/z (%):** 320.2 ($M+H^+$, 100). **MP (°C):** 97. **Yield:** 79%.

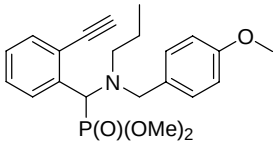
Dimethyl (2-ethynylphenyl) [(butyl)(3-fluorobenzyl)amino]methylphosphonate (434j)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.81 (t, *J* = 7.4 Hz, 3H, CH_3), 1.09-1.36 (m, 2H, CH_2CH_3), 1.48 (p, *J* = 7.2 Hz, 2H, NCH_2CH_2), 2.45 (dt, *J* = 6.6 Hz, *J* = 13.0 Hz, 1H, $NCH_AH_BCH_2$), 2.70-2.80 (m, 1H, $NCH_AH_BCH_2$), 3.14 (s, 1H, CCH), 3.37 (d, *J* = 14.3 Hz, 1H, NCH_AH_BPh), 3.46 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.92 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.37 (d, *J* = 14.3 Hz, 1H, NCH_AH_BPh), 5.02 (d, *J* = 25.3 Hz, 1H, CHP), 6.87-7.43 (m, 6H, 6 x CH_{arom}), 7.57 (d, *J* = 7.5 Hz, 1H, PCHCCH), 7.95 (d, *J* = 7.7 Hz, 1H, PCHCCCH). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 14.10 (CH_3), 20.32 (CH_2CH_3), 30.32 (NCH_2CH_2), 51.32 (d, *J* = 10.4 Hz, NCH_2CH_2), 52.92 (d, *J* = 8.1 Hz, OCH_3), 53.63 (d, *J* = 6.9 Hz, OCH_3), 55.61 (d, *J* = 5.8 Hz, NCH_2Ph), 58.30 (d, *J* = 163.8 Hz, CHP), 81.62 (CCH), 82.11 (CCH), 113.56 (d, *J* = 20.8 Hz, CH_{arom}), 115.37 (d, *J* = 21.9 Hz, CH_{arom}), 124.17 (d, *J* = 2.3 Hz, CH_{arom}), 124.23

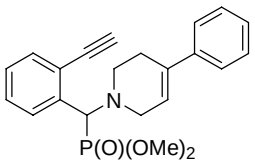
(d, *J* = 11.5 Hz, PCHC<u>C</u>), 128.09 (CH_{arom}), 128.70 (CH_{arom}), 129.38 (d, *J* = 8.1 Hz, CH_{arom}), 130.71 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 133.47 (PCHCC<u>C</u>H), 135.47 (d, *J* = 6.9 Hz, PCH<u>C</u>), 143.36 (d, *J* = 6.9 Hz, C_q, Ph), 163.00 (d, *J* = 224.6 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.37. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -114.00 (dt, *J* = 5.3 Hz, *J* = 9.5 Hz). **IR (cm^{-1}) ν_{max}:** 1036 (P-O),1058 (P-O), 1249 (P=O), 1614 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 404.2 ($M+H^+$, 100). **MP (°C):** 67. **Yield:** 65%.

Dimethyl (2-ethynylphenyl)[(4-methoxybenzyl)(propyl)amino]methylphosphonate (434k)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.77 (t, *J* = 7.3 Hz, 3H, CH_3), 1.42-1.57 (m, 2H, $C\underline{H}_2CH_3$), 2.41 (ddd, *J* = 4.8 Hz, *J* = 8.3 Hz, *J* = 13.0 Hz, 1H, $NC\underline{H}_AH_BCH_2$), 2.61-2.72 (m, 1H, $NCH_A\underline{H}_BCH_2$), 3.16 (s, 1H, CCH), 3.27 (d, *J* = 13.5 Hz, 1H, $NC\underline{H}_AH_BPh$), 3.47 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.79 (s, 3H, $PhOC\underline{H}_3$), 3.91 (d, *J* = 10.7 Hz, 3H, OCH_3), 4.32 (d, *J* = 13.5 Hz, 1H, $NCH_A\underline{H}_BPh$), 5.04 (d, *J* = 25.3 Hz, 1H, CHP), 6.83 (d, *J* = 8.7 Hz, 2H, 2 x CH_{arom}), 7.26-7.56 (m, 2H, 2 x CH_{arom}), 7.28 (d, *J* = 8.7 Hz, 2H, 2 x CH_{arom}), 7.57 (d, *J* = 6.0 Hz, 1H, PCHCC<u>H</u>), 7.96 (d, *J* = 7.7 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 11.66 ($CH_2\underline{C}H_3$), 21.17 ($\underline{C}H_2CH_3$), 52.82 (d, *J* = 6.9 Hz, OCH_3), 52.98 (d, *J* = 10.4 Hz, $N\underline{C}H_2CH_2$), 53.80 (d, *J* = 6.9 Hz, OCH_3), 55.31 ($PhO\underline{C}H_3$), 55.39 (d, *J* = 5.8 Hz, NCH_2), 58.44 (d, *J* = 163.8 Hz, CHP), 81.50 ($C\underline{C}H$), 82.20 ($\underline{C}CH$), 113.42 (2 x CH_{arom}), 124.19 (d, *J* = 12.7 Hz, PCHC<u>C</u>), 127.97 (CH_{arom}), 128.66 (CH_{arom}), 129.89 (2 x CH_{arom}), 130.82 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 132.37 ($C_{q,arom}$), 133.41 ($C_{q,arom}$), 135.77 (d, *J* = 6.9 Hz, PCH<u>C</u>), 158.51 ($C_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 26.31. **IR (cm^{-1}) ν_{max}:** 1034 (P-O), 1057 (P-O), 1246 (P=O), 1612 (C=C), 2099 (alkyne). **MS (ESI): m/z (%):** 402.2 ($M+H^+$, 100). **MP (°C):** 82. **Yield:** 71%.

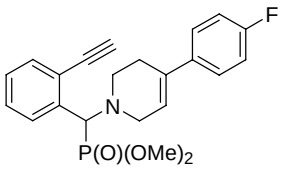
Dimethyl [(2-ethynylphenyl)-(4-phenyl-3,6-dihydro-2H-pyridin-1-yl)methyl] phosphonate (434l)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.44-2.66 (m, 2H, $NCH_2C\underline{H}_2$), 2.75 (ddd, *J* = 4.4 Hz, *J* = 7.3 Hz, *J* = 11.4 Hz, 1H, $NC\underline{H}_AH_BCH_2$), 3.31 (dt, *J* = 4.6 Hz, *J* = 11.4 Hz, 1H, $NCH_A\underline{H}_BCH_2$), 3.34 (s, 1H, CCH), 3.43 (d, *J* = 2.9 Hz, 1H, $NC\underline{H}_AH_B$), 3.44 (d, *J* = 2.9 Hz, 1H, $NCH_A\underline{H}_B$), 3.50 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.92 (d, *J* = 22.0 Hz, 1H, CHP), 6.02 (br s, 1H, CH), 7.18-7.41 (m, 7H, 7 x CH_{arom}), 7.57 (dt, *J* = 7.7 Hz, *J* = 1.1 Hz, 1H, PCHCC<u>H</u>), 7.94 (dt, *J* = 7.9 Hz, *J* = 2.5 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 28.29 ($NCH_2\underline{C}H_2$), 47.97 (d, *J* = 6.9 Hz, $N\underline{C}H_2CH_2$), 51.57 (d, *J* = 11.5 Hz, $N\underline{C}H_2CH$), 53.06 (d, *J* = 8.1 Hz, OCH_3), 54.06 (d, *J* = 6.9 Hz, OCH_3), 63.07 (d, *J* = 161.5 Hz, CHP), 82.15 ($\underline{C}CH$), 82.24 ($C\underline{C}H$), 122.00 ($H\underline{C}$=C), 123.85 (d, *J* = 11.5 Hz, PCHC<u>C</u>), 124.84 (2 x CH_{arom}), 127.02 (CH_{arom}), 128.06 (CH_{arom}), 128.37 (2 x

CH_{arom}), 128.83 (CH_{arom}), 130.33 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 133.27 (PCHCC<u>C</u>H), 134.54 ($C_{q,arom}$), 135.12 (d, *J* = 2.0 Hz, PCH<u>C</u>), 140.80 (HC=<u>C</u>). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 24.96. **IR (cm^{-1}) ν_{max}:** 1036 (P-O), 1058 (P-O), 1245 (P=O), 1654 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 382.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.16. **Yield:** 75%.

Dimethyl [(2-ethynylphenyl)-(4-(4-fluorophenyl)-3,6-dihydro-2H-pyridin-1-yl)methyl] phosphonate (434m)

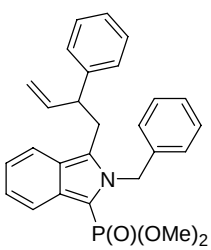


^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42-2.61 (m, 2H, $NCH_2C\underline{H}_2$), 2.74 (ddd, *J* = 4.4 Hz, *J* = 7.4 Hz, *J* = 11.4 Hz, 1H, $NC\underline{H}_AH_BCH_2$), 3.30 (dt, *J* = 3.3 Hz, *J* = 11.4 Hz, 1H, $NCH_A\underline{H}_BCH_2$), 3.34 (s, 1H, CCH), 3.43 (br s, 2H, NCH_2), 3.50 (d, *J* = 10.5 Hz, 3H, OCH_3), 3.88 (d, *J* = 10.5 Hz, 3H, OCH_3), 4.91 (d, *J* = 22.0 Hz, 1H, CHP), 5.96 (br s, 1H, CH), 6.98 (t, *J* = 8.5 Hz, 2H, 2 x CH_{arom}), 7.26-7.44 (m, 4H, 4 x CH_{arom}), 7.57 (d, *J* = 7.6 Hz, 1H, PCHCC<u>H</u>), 7.93 (d, *J* = 8.0 Hz, 1H, PCHCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 28.53 ($NCH_2\underline{C}H_2$), 47.91 (d, *J* = 8.1 Hz, $N\underline{C}H_2CH_2$), 51.49 (d, *J* = 11.5 Hz, $N\underline{C}H_2CH$), 53.09 (d, *J* = 8.1 Hz, OCH_3), 54.00 (d, *J* = 6.9 Hz, OCH_3), 63.04 (d, *J* = 161.5 Hz, CHP), 82.12 (<u>C</u>CH), 82.24 (C<u>C</u>H), 115.13 (d, *J* = 20.8 Hz, 2 x CH_{arom}), 121.86 (H<u>C</u>=C), 123.83 (d, *J* = 11.5 Hz, PCHC<u>C</u>), 126.36 (d, *J* = 20.8 Hz, 2 x CH_{arom}), 128.08 (CH_{arom}), 128.84 (CH_{arom}), 130.30 (d, *J* = 3.5 Hz, PCHC<u>C</u>H), 133.28 (PCHCC<u>C</u>H), 133.64 (HC=<u>C</u>), 135.11 ($C_{q,arom}$), 136.91 (d, *J* = 3.5 Hz, PCH<u>C</u>), 162.06 (d, *J* = 245.8 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 24.93. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -115.83 (tt, *J* = 9.8 Hz, *J* = 5.7 Hz). **IR (cm^{-1}) ν_{max}:** 1035 (P-O), 1057 (P-O), 1227 (P=O), 1602 (C=C), 2100 (alkyne). **MS (ESI): m/z (%):** 400.2 ($M+H^+$, 100). **MP (°C):** 76-77. **Chromatography:** Hex/EtOAc 4/6 R_f = 0.21. **Yield:** 62%.

4.11.3 Microwave induced synthesis of isoindoles 435

In a dry reaction tube, compounds **434** (0.5 mmol) are dissolved into a mixture of acetonitrile (3 ml) and benzene (3 ml). This solution is heated in a microwave to 165 °C for 60 minutes. After this period of time the progress of the reaction is checked by ^{31}P NMR from a sample taken directly from the mixture. If this reveals the presence of remaining starting material, the reaction is placed back inside the microwave and is again heated to 165 °C. After complete conversion the compound is coated on silica gel by removal of the volatiles *in vacuo* and purified by column chromatography.

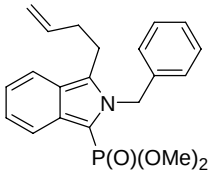
Dimethyl 2-benzyl-3-(2-phenylbut-3-enyl)-2H-isoindol-1-ylphosphonate (435a)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.17 (dd, *J* = 7.5 Hz, *J* = 15.1 Hz, 1H, $C\underline{H}_AH_BCH$), 3.43 (dd, *J* = 7.5 Hz, *J* = 15.1 Hz, 1H, $CH_A\underline{H}_BCH$), 3.48 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.49 (d, *J* = 11.6 Hz, 3H, OCH_3), 3.62 (ps q, *J* = 7.5 Hz, C<u>H</u>Ph), 4.98 (1H, d, *J* = 17.1 Hz, HC=C$\underline{H}_A$$H_B$), 5.07 (1H, d, *J* = 10.3 Hz,

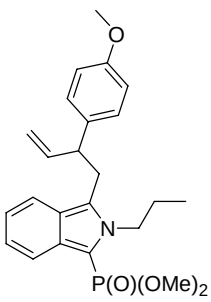
HC=CH$_A$H$_B$), 5.19 (d, *J* = 16.8 Hz, 1H, NCH$_A$H$_B$Ph), 5.53 (d, *J* = 16.8 Hz, 1H, NCH$_A$H$_B$Ph), 6.10 (ddd, *J* = 17.1 Hz, *J* = 10.3 Hz, *J* = 7.5 Hz, 1H, HC=CH$_2$), 6.74-7.53 (m, 13H, 13 x CH$_{arom}$), 7.95 (d, *J* = 8.5 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 32.18 (CH$_2$CH), 49.63 (NCH$_2$), 50.20 (CHPh), 52.33 (d, *J* = 3.5 Hz, 2 x OCH$_3$), 103.63 (d, *J* = 231.9 Hz, PC), 115.71 (HC=CH$_2$), 119.89 (CH$_{arom}$), 120.15 (CH$_{arom}$), 121.13 (CH$_{arom}$), 124.05 (d, *J* = 12.7 Hz, PCCC), 124.84 (CH$_{arom}$), 125.74 (2 x CH$_{arom}$), 127.02 (CH$_{arom}$), 127.39 (CH$_{arom}$), 127.65 (2 x CH$_{arom}$), 128.69 (4 x CH$_{arom}$), 131.07 (d, *J* = 9.2 Hz, NC), 133.00 (d, *J* = 17.3 Hz, PCC), 137.79 (C$_q$, Ph), 140.06 (HC=CH$_2$), 142.80 (C$_q$, Ph). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 14.66. **IR (cm^{-1}) ν$_{max}$:** 1022 (P-O), 1049 (P-O), 1242 (P=O), 1702 (C=C). **MS (ESI): m/z (%):** 446.3 (M+H$^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R$_f$ = 0.34. **Yield:** 82%.

Dimethyl 2-benzyl-3-but-3-enyl-2H-isoindol-1-ylphosphonate (435b)



^{1}H-NMR (300 MHz, CDCl$_3$): δ 2.25 (ps q, *J* = 7.5 Hz, 2H, CH$_2$CH), 3.02 (t, *J* = 7.3 Hz, 2H, CH$_2$CH$_2$), 3.55 (d, *J* = 11.5 Hz, 6H, 2 x OCH$_3$), 4.97 (d, *J* = 10.7 Hz, 1H, HC=CH$_A$H$_B$), 4.98 (d, *J* = 16.3 Hz, 1H, HC=CH$_A$H$_B$), 5.77 (ddt, *J* = 7.3 Hz, *J* = 10.7 Hz, *J* = 16.3 Hz, 1H, HC=CH$_2$), 5.84 (s, 2H, NCH$_2$), 6.87 (d, *J* = 6.6 Hz, 2 x CH$_{arom}$), 7.05 (t, *J* = 7.6 Hz, CH$_{arom}$), 7.17-7.29 (m, 4H, 4 x CH$_{arom}$), 7.62 (d, *J* = 8.5 Hz, PCCCH), 7.93 (d, *J* = 8.8 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 24.93 (NCCH$_2$), 33.97 (CH$_2$CH), 50.12 (NCH$_2$), 52.48 (d, *J* = 5.8 Hz, 2 x OCH$_3$), 103.57 (d, *J* = 234.2 Hz, PC), 116.05 (HC=CH$_2$), 119.86 (CH$_{arom}$), 120.03 (CH$_{arom}$), 121.04 (CH$_{arom}$), 123.43 (d, *J* = 12.7 Hz, PCCC), 124.94 (CH$_{arom}$), 125.93 (2 x CH$_{arom}$), 127.48 (CH$_{arom}$), 128.72 (2 x CH$_{arom}$), 132.80 (d, *J* = 9.2 Hz, NC), 132.82 (d, *J* = 17.3 Hz, PCC), 137.01 (HC=CH$_2$), 137.80 (C$_q$, Ph). **^{31}P-NMR (121 MHz, CDCl$_3$): δ** 14.80. **IR (cm^{-1}) ν$_{max}$:** 1023 (P-O), 1049 (P-O), 1241 (P=O), 1698 (C=C). **MS (ESI): m/z (%):** 370.2 (M+H$^+$, 100). **Chromatography:** Hex/EtOAc 55/45 R$_f$ = 0.25. **Yield:** 76%.

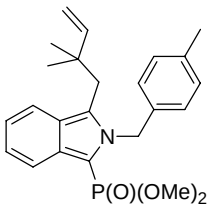
Dimethyl 3-[2-(4-methoxyphenyl)but-3-enyl]-2-propyl-2H-isoindol-1-ylphosphonate (435c)



^{1}H-NMR (300 MHz, CDCl$_3$): δ 0.92 (t, *J* = 7.4 Hz, 3H, CH$_3$), 1.66-1.80 (m, 2H, CH$_2$CH$_3$), 3.24 (dd, *J* = 8.0 Hz, *J* = 14.6 Hz, 1H, CH$_A$H$_B$CH), 3.47 (dd, *J* = 7.2 Hz, *J* = 14.6 Hz, 1H, CH$_A$H$_B$CH), 3.67 (d, *J* = 11.8 Hz, 3H, OCH$_3$), 3.68 (d, *J* = 11.6 Hz, 3H, OCH$_3$), 3.67-3.74 (m, 1H, CHPh), 3.76 (s, 3H, PhOCH$_3$), 4.00 (ddd, *J* = 6.3 Hz, *J* = 9.5 Hz, *J* = 14.0 Hz, 1H, NCH$_A$H$_B$), 4.22 (ddd, *J* = 6.3 Hz, *J* = 9.5 Hz, *J* = 14.0 Hz, 1H, NCH$_A$H$_B$), 5.01 (dt, *J* = 1.3 Hz, *J* = 17.1 Hz, 1H, HC=CH$_A$H$_B$), 5.08 (dt, *J* = 1.3 Hz, *J* = 10.2 Hz, HC=CH$_A$H$_B$), 6.11 (ddd, *J* = 17.1 Hz, *J* = 10.2 Hz, *J* = 7.0 Hz, 1H, HC=CH$_2$), 6.74-7.51 (m, 7H, 7 x CH$_{arom}$), 7.85 (d, *J* = 8.5 Hz, 1H, PCCCCH). **^{13}C-NMR (75 MHz, CDCl$_3$): δ** 11.38 (CH$_2$CH$_3$), 25.58 (CH$_2$CH$_3$), 32.22

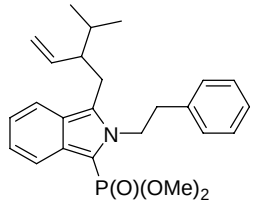
($\underline{C}H_2CH$), 48.25 (NCH_2), 49.39 ($\underline{C}HPh$), 52.37 (d, J = 5.8 Hz, 2 x OCH_3), 55.34 ($PhOCH_3$), 102.33 (d, J = 234.2 Hz, $P\underline{C}$), 114.05 (2 x CH_{arom}), 115.30 ($HC=\underline{C}H_2$), 119.77 (2 x CH_{arom}), 120.69 (CH_{arom}), 123.77 (d, J = 13.8 Hz, $PCC\underline{C}$), 124.52 (CH_{arom}), 128.54 (2 x CH_{arom}), 130.41 (d, J = 9.2 Hz, $N\underline{C}$), 132.64 (d, J = 18.5 Hz, $PC\underline{C}$), 134.84 (C_q, Ph), 140.51 ($H\underline{C}=CH_2$), 158.60 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.23. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1049 (P-O), 1246 (P=O), 1698 (C=C). **MS (ESI): m/z (%):** 428.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.15. **Yield:** 68%.

Dimethyl 3-(2,2-dimethylbut-3-enyl)-2-(4-methylbenzyl)-2H-isoindol-1-ylphosphonate (435d)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12 (s, 6H, 2 x $C\underline{H}_3$), 2.27 (s, 3H, CH_3), 3.47 (d, J = 11.5 Hz, 6H, 2 x OCH_3), 4.93 (dd, J = 17.4 Hz, J = 1.1 Hz, 1H, $HC=C\underline{H}_A\underline{H}_B$), 4.97 (dd, J = 10.7 Hz, J = 1.1 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.82 (s, 2H, NCH_2), 5.84 (dd, J = 10.7 Hz, J = 17.4 Hz, 1H, $\underline{H}C=CH_2$), 6.58 (d, J = 7.8 Hz, 2 x CH_{arom}), 7.02 (d, J = 7.8 Hz, 2 x CH_{arom}), 7.05-7.21 (m, 2H, 2 x CH_{arom}), 7.62-7.65 (m, 1H, $PCCC\underline{H}$), 7.93 (d, J = 8.8 Hz, 1H, $PCCCC\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 21.09 (CH_3), 27.57 (2 x CH_3), 37.52 ($NC\underline{C}H_2$), 39.81 ($\underline{C}(CH_3)_2$), 50.21 (NCH_2), 52.30 (d, J = 4.6 Hz, 2 x OCH_3), 104.03 (d, J = 233.1 Hz, $P\underline{C}$), 111.82 ($HC=\underline{C}H_2$), 120.02 (CH_{arom}), 120.93 (CH_{arom}), 121.19 (CH_{arom}), 124.64 (CH_{arom}), 123.94 (d, J = 12.7 Hz, $PCC\underline{C}$), 125.50 (2 x CH_{arom}), 129.28 (2 x CH_{arom}), 130.86 (d, J = 9.2 Hz, $N\underline{C}$), 132.11 (d, J = 17.3 Hz, $PC\underline{C}$), 134.84 (C_q, Ph), 136.95 (C_q, Ph), 147.04 ($H\underline{C}=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.79. **IR (cm^{-1}) ν_{max}:** 1023 (P-O), 1051 (P-O), 1243 (P=O), 1638 (C=C). **MS (ESI): m/z (%):** 412.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.22. **Yield:** 47%.

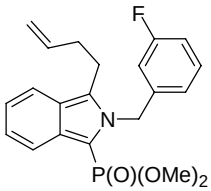
Dimethyl 3-[2-isopropylbut-3-enyl]-2-(2-fenylethyl)-2H-isoindol-1-ylphosphonate (435e)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.95 (d, J = 6.4 Hz, 3H, CH_3), 0.96 (d, J = 6.4 Hz, 3H, CH_3), 1.70 (octet, J = 6.4 Hz, 1H, $C\underline{H}(CH_3)_2$), 2.24 (tt, J = 6.4 Hz, J = 9.8 Hz, 1H, $CH_2C\underline{H}$), 2.76 (dd, J = 9.8 Hz, J = 14.9 Hz, 1H, $C\underline{H}_A\underline{H}_BCH$), 2.98 (dd, J = 6.4 Hz, J = 14.9 Hz, 1H, $CH_A\underline{H}_BCH$), 3.05-3.20 (m, 2H, CH_2Ph), 3.74 (d, J = 11.6 Hz, 3H, OCH_3), 3.75 (d, J = 11.5 Hz, 3H, OCH_3), 4.61 (dd, J = 1.7 Hz, J = 17.1 Hz, 1H, $HC=C\underline{H}_A\underline{H}_B$), 4.61-4.79 (m, 2H, NCH_2), 4.82 (dt, J = 1.7 Hz, J = 9.8 Hz, $HC=CH_A\underline{H}_B$), 5.63 (dt, J = 17.1 Hz, J = 9.8 Hz, 1H, $\underline{H}C=CH_2$), 6.98-7.33 (m, 7H, 7 x CH_{arom}), 7.52 (d, J = 8.5 Hz, 1H, $PCCC\underline{H}$), 7.86 (d, J = 8.8 Hz, 1H, $PCCCC\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 18.85 (CH_3), 20.90 (CH_3), 27.90 ($\underline{C}H_2CH$), 31.46 ($\underline{C}H(CH_3)_2$), 38.88 ($\underline{C}H_2Ph$), 48.90 (NCH_2), 51.51 ($\underline{C}HCH=CH_2$), 52.53 (d, J = 4.6 Hz, 2 x OCH_3), 101.81 (d, J = 234.2 Hz, $P\underline{C}$), 116.76 ($HC=\underline{C}H_2$), 119.60 (CH_{arom}), 120.14 (CH_{arom}), 120.54 (CH_{arom}), 123.73 (d, J

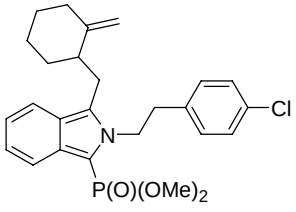
= 12.7 Hz, PCC<u>C</u>), 124.73 (CH_{arom}), 126.90 (CH_{arom}), 128.81 (2 x CH_{arom}), 129.01 (2 x CH_{arom}), 132.13 (d, *J* = 10.4 Hz, N<u>C</u>), 132.73 (d, *J* = 17.3 Hz, PC<u>C</u>), 138.23 (C_q, Ph), 138.58 (H<u>C</u>=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.44. **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1049 (P-O), 1247 (P=O), 1660 (C=C). **MS (ESI): m/z (%):** 426.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.32. **Yield:** 71%.

Dimethyl 3-but-2-enyl-2-(3-fluorobenzyl)-2H-isoindol-1-ylphosphonate (435f)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.26 (ps q, *J* = 7.4 Hz, 2H, C<u>H</u>$_2$CH), 3.01 (t, *J* = 7.4 Hz, 2H, NCC<u>H</u>$_2$), 3.59 (d, *J* = 11.6 Hz, 6H, 2 x OCH_3), 4.95-5.01 (m, 2H, HC=C<u>H</u>$_2$), 5.77 (ddt, *J* = 7.4 Hz, *J* = 9.9 Hz, *J* = 17.3 Hz, 1H, <u>H</u>C=CH_2), 5.85 (s, *2*H, NC<u>H</u>$_2$Ph), 6.57 (d, *J* = 9.6 Hz, 1H, CH_{arom}), 6.69 (d, *J* = 7.7 Hz, 1H, CH_{arom}), 6.92 (dt, *J* = 8.4 Hz, *J* = 0.8 Hz, 1H, CH_{arom}), 7.04-7.26 (m, 3H, 3 x CH_{arom}), 7.62 (d, *J* = 8.5 Hz, 1H, PCCC<u>H</u>), 7.90 (d, *J* = 8.8 Hz, 1H, PCCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.88 (NC<u>C</u>H_2), 33.97 (<u>C</u>H_2CH), 49.60 (NCH_2), 52.52 (d, *J* = 5.8 Hz, 2 x OCH_3), 103.69 (d, *J* = 234.2 Hz, P<u>C</u>), 113.04 (d, *J* = 23.1 Hz, CH_{arom}), 114.45 (d, *J* = 21.9 Hz, CH_{arom}), 116.18 (HC=<u>C</u>H_2), 119.89 (CH_{arom}), 119.96 (CH_{arom}), 121.21 (CH_{arom}), 121.58 (d, *J* 3.5 Hz, CH_{arom}), 123.48 (d, *J* = 13.9 Hz, PCC<u>C</u>), 125.13 (CH_{arom}), 130.30 (d, *J* = 8.1 Hz, CH_{arom}), 132.64 (d, *J* = 17.3 Hz, N<u>C</u>), 132.70 (d, *J* = 17.3 Hz, PC<u>C</u>), 136.86 (H<u>C</u>=CH_2), 140.49 (d, *J* = 6.9 Hz, $C_{q,arom}$), 163.23 (d, *J* = 245.8 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.56. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -112.48 (dt, *J* = 5.3 Hz, *J* = 7.2 Hz). **IR (cm^{-1}) ν_{max}:** 1025 (P-O), 1050 (P-O), 1243 (P=O), 1617 (C=C). **MS (ESI): m/z (%):** 388.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.36. **Yield:** 63%.

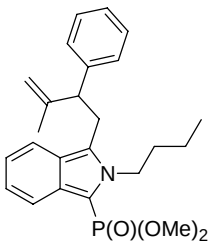
Dimethyl [2-[2-(4-chlorophenyl)-ethyl]-3-(2-methylene-cyclohexylmethyl)--2H-isoindol-1-yl]-phosphonate (435g)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.12-1.70 (m, 6H, 3 x CH_2), 1.99-2.10 (m, 1H, C<u>H$_A$H$_B$</u>), 2.30-2.38 (m, 2H, CH_2C<u>H</u> + C<u>H$_A$H$_B$</u>), 2.88 (dd, *J* = 10.3 Hz, *J* = 14.7 Hz, 1H, NCC<u>H$_A$H$_B$</u>), 3.03 (dd, *J* = 4.3 Hz, *J* = 14.7 Hz, 1H, NCCH$_A$<u>H$_B$</u>), 3.09-3.17 (m, 2H, C<u>H$_2$</u>Ph), 3.77 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.78 (d, *J* = 11.5 Hz, 3H, OCH_3), 4.62 (1H, s, C=C<u>H$_A$H$_B$</u>), 4.64 (dt, *J* = 8.0 Hz, *J* = 13.8 Hz, 1H, NC<u>H$_A$H$_B$</u>), 4.74 (dt, *J* = 7.9 Hz, *J* = 13.8 Hz, 1H, NCH$_A$<u>H$_B$</u>), 4.76 (1H, s, C=CH$_A$<u>H$_B$</u>), 6.99-7.28 (m, 6H, 6 x CH_{arom}), 7.53 (d, *J* = 8.5 Hz, 1H, PCCC<u>H</u>), 7.82 (d, *J* = 8.5 Hz, 1H, PCCCC<u>H</u>). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.97 (CH_2), 27.90 (NC<u>C</u>H_2), 28.47 (CH_2), 33.39 (CH_2), 35.75 (CH_2), 38.23 (NCH_2<u>C</u>H_2), 43.49 (CH), 48.53 (NCH_2), 52.68 (d, *J* = 3.5 Hz, 2 x OCH_3), 102.27 (d, *J* = 235.4 Hz, P<u>C</u>), 105.92 (C=<u>C</u>H_2), 119.45 (CH_{arom}), 120.22 (CH_{arom}), 120.78 (CH_{arom}), 123.93 (d, *J* = 12.7 Hz, PCC<u>C</u>), 124.93 (CH_{arom}), 128.89 (2 x CH_{arom}), 130.44 (2 x CH_{arom}), 132.02 (d, *J* = 9.2 Hz, N<u>C</u>), 132.45 (d, *J* = 17.3 Hz, PC<u>C</u>), 132.78 ($ClC_{q,arom}$), 136.57

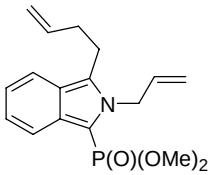
($C_{q,arom}$), 152.22 ($\underline{C}$=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.25. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1049 (P-O), 1245 (P=O), 1644 (C=C). **MS (ESI): m/z (%):** 472.2/474.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.26. **Yield:** 40%.

Dimethyl 2-butyl-3-(3-methyl-2-phenylbut-3-enyl)-2H-isoindol-1-ylphosphonate (435h)



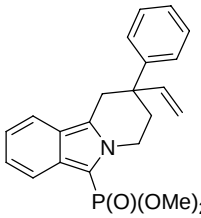
^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.89 (t, *J* = 7.6 Hz, 3H, CH_3), 1.29 (sextet, *J* = 7.6 Hz, 2H, $C\underline{H_2}CH_3$), 1.59 (p, *J* = 7.6 Hz, 2H, $NCH_2C\underline{H_2}$), 1.66 (s, 3H, CH_3), 3.22 (dd, *J* = 9.5 Hz, *J* = 13.3 Hz, 1H, $C\underline{H_A}H_BCH$), 3.54-3.77 (m, 3H, $CH_A\underline{H_B}C\underline{H}$ + $NC\underline{H_A}H_B$), 3.64 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.65 (d, *J* = 11.6 Hz, 3H, OCH_3), 4.10 (dt, *J* = 7.6 Hz, *J* = 14.0 Hz, 1H, $NCH_A\underline{H_B}$), 5.08 (s, 1H, $HC=C\underline{H_A}H_B$), 5.11 (s, 1H, $HC=CH_A\underline{H_B}$), 6.85-7.20 (m, 7H, 7 x CH_{arom}), 7.42 (d, *J* = 8.3 Hz, 1H, PCCC$\underline{H}$), 7.86 (d, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 13.77 ($CH_2\underline{C}H_3$), 20.17 ($\underline{C}H_2CH_3$), 22.79 ($C\underline{C}H_3$), 30.83 ($\underline{C}H_2CH$), 34.12 ($NCH_2\underline{C}H_2$), 46.13 (NCH_2), 52.36 (d, *J* = 3.5 Hz, 2 x OCH_3), 52.87 ($\underline{C}$HPh), 101.90 (d, *J* = 234.2 Hz, P$\underline{C}$), 111.05 (C=$\underline{C}H_2$), 119.54 (CH_{arom}), 119.82 (CH_{arom}), 120.58 (CH_{arom}), 123.63 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.46 (CH_{arom}), 127.01 (CH_{arom}), 127.82 (2 x CH_{arom}), 128.44 (2 x CH_{arom}), 130.75 (d, *J* = 9.2 Hz, N$\underline{C}$), 132.77 (d, *J* = 17.3 Hz, PC$\underline{C}$), 141.86 (C_q, Ph), 147.09 ($\underline{C}$=CH_2). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.24. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1048 (P-O), 1251 (P=O), 1701 (C=C). **MS (ESI): m/z (%):** 426.5 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.20. **Yield:** 40%.

Dimethyl 2-allyl-3-but-3-enyl-2H-isoindol-1-ylphosphonate (435i)



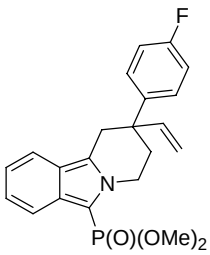
^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.43 (ps q, *J* = 7.4 Hz, 2H, $CH_2C\underline{H_2}CH$), 3.07 (t, *J* = 7.4 Hz, 2H, $C\underline{H_2}CH_2$), 3.71 (d, *J* = 11.6 Hz, 6H, 2 x OCH_3), 4.74 (br d, *J* = 17.1 Hz, *J* = 1.5 Hz, 1H, $NCH_2HC=C\underline{H_A}H_B$), 5.03 (br d, *J* = 10.3 Hz, 1H, $HC=C\underline{H_A}H_B$), 5.09 (br d, *J* = 17.1 Hz, 1H, $HC=CH_A\underline{H_B}$), 5.16 (dq, *J* = 10.5 Hz, *J* = 1.5 Hz, 1H, $NCH_2HC=CH_A\underline{H_B}$), 5.23 (dt, *J* = 1.5 Hz, *J* = 4.8 Hz, 2H, NCH_2), 5.86 (ddt, *J* = 7.4 Hz, *J* = 10.3 Hz, *J* = 17.1 Hz, 1H, $\underline{H}C=CH_2$), 6.03 (ddt, *J* = 4.8 Hz, *J* = 10.5 Hz, *J* = 17.1 Hz, 1H, $NCH_2\underline{H}C=CH_2$), 7.00-7.06 (m, 1H, CH_{arom}), 7.15-7.20 (m, 1H, CH_{arom}), 7.15-7.20 (m, 1H, CH_{arom}), 7.58-7.62 (m, 1H, CH_{arom}), 7.87 (d, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 24.68 ($NC\underline{C}H_2$), 34.06 ($CH_2\underline{C}H_2CH$), 48.96 (NCH_2), 52.62 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.77 (d, *J* = 234.2 Hz, P$\underline{C}$), 116.00 (HC=$\underline{C}H_2$), 116.14 ($NCH_2CH=\underline{C}H_2$), 119.79 (CH_{arom}), 119.83 (CH_{arom}), 120.84 (CH_{arom}), 123.25 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.80 (CH_{arom}), 132.44 (d, *J* = 9.2 Hz, N$\underline{C}$), 132.57 (d, *J* = 18.5 Hz, PC$\underline{C}$), 134.31 ($NCH_2H\underline{C}=CH_2$), 137.12 ($H\underline{C}=CH_2$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 14.97. **IR (cm^{-1}) ν_{max}:** 1022 (P-O), 1050 (P-O), 1241 (P=O), 1641 (C=C). **MS (ESI): m/z (%):** 320.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 55/45 R_f = 0.25. **Yield:** 98%.

Dimethyl 2-phenyl-2-vinyl-1,2,3,4-tetrahydropyrido[2,1-a]isoindol-6-ylphosphonate (471a)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.41 (ddd, *J* = 5.6 Hz, *J* = 7.1 Hz, *J* = 13.3 Hz, 1H, $NCH_2C\underline{H}_AH_B$), 2.57 (ddd, *J* = 5.3 Hz, *J* = 7.7 Hz, *J* = 13.3 Hz, 1H, $NCH_2CH_A\underline{H}_B$), 3.49 (s, 2H, $NCC\underline{H}_2$), 3.64 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.66 (d, *J* = 11.6 Hz, 3H, OCH_3), 4.30 (ddd, *J* = 5.3 Hz, *J* = 7.1 Hz, *J* = 14.1 Hz, 1H, $NC\underline{H}_AH_B$), 4.50 (ddd, *J* = 5.6 Hz, *J* = 7.7 Hz, *J* = 14.1 Hz, 1H, $NCH_A\underline{H}_B$), 5.01 (d, *J* = 17.4 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.17 (d, *J* = 10.7 Hz, 1H, $HC=CH_A\underline{H}_B$), 6.03 (dd, *J* = 10.7 Hz, *J* = 17.4 Hz, 1H, $\underline{H}C=CH_2$), 7.03-7.36 (m, 7H, 7 x CH_{arom}), 7.61-7.65 (m, 1H, CH_{arom}), 7.89 (d, *J* = 8.4 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 32.70 ($NC\underline{C}H_2$), 32.81 ($NCH_2\underline{C}H_2$), 42.24 (C_q), 43.66 (NCH_2), 52.39 (d, *J* = 3.5 Hz, OCH_3), 52.44 (d, *J* = 4.6 Hz, OCH_3), 101.65 (d, *J* = 235.4 Hz, P$\underline{C}$), 114.32 ($HC=\underline{C}H_2$), 119.12 (CH_{arom}), 119.51 (CH_{arom}), 120.49 (CH_{arom}), 121.74 (d, *J* = 13.9 Hz, PCC$\underline{C}$), 126.47 (2 x CH_{arom}), 129.96 (CH_{arom}), 128.44 (d, *J* = 9.2 Hz, N$\underline{C}$), 128.73 (2 x CH_{arom}), 133.28 (d, *J* = 18.5 Hz, PC$\underline{C}$), 143.47 ($H\underline{C}=CH_2$), 144.08 (C_q, Ph). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.29. **IR (cm^{-1}) ν_{max}:** 1021 (P-O), 1047 (P-O), 1243 (P=O), 1623 (C=C). **MS (ESI): m/z (%):** 382.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 1/1 R_f = 0.14. **Yield:** 68%.

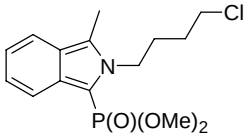
Dimethyl 2-(4-fluorophenyl)-2-vinyl-1,2,3,4-tetrahydropyrido[2,1-a]isoindol-6-ylphosphonate (471b)



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.38 (dt, *J* = 6.3 Hz, *J* = 13.8 Hz, 1H, $NCH_2C\underline{H}_AH_B$), 2.52 (dt, *J* = 6.3 Hz, *J* = 13.8 Hz, 1H, $NCH_2CH_A\underline{H}_B$), 3.45 (s, 2H, $NCC\underline{H}_2$), 3.65 (d, *J* = 11.5 Hz, 3H, OCH_3), 3.67 (d, *J* = 11.5 Hz, 3H, OCH_3), 4.27 (dt, *J* = 6.3 Hz, *J* = 14.7 Hz, 1H, $NC\underline{H}_AH_B$), 4.51 (dt, *J* = 6.3 Hz, *J* = 14.7 Hz, 1H, $NCH_A\underline{H}_B$), 4.99 (d, *J* = 17.6 Hz, 1H, $HC=C\underline{H}_AH_B$), 5.17 (d, *J* = 10.7 Hz, 1H, $HC=CH_A\underline{H}_B$), 5.99 (dd, *J* = 10.7 Hz, *J* = 17.6 Hz, 1H, $\underline{H}C=CH_2$), 6.93-7.26 (m, 6H, 6 x CH_{arom}), 7.62 (dt, *J* = 0.9 Hz, *J* = 8.5 Hz, 1H, CH_{arom}), 7.89 (dt, *J* = 0.9 Hz, *J* = 8.5 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 32.85 ($NC\underline{C}H_2$), 32.94 ($NCH_2\underline{C}H_2$), 41.87 (C_q), 43.60 (NCH_2), 52.39 (d, *J* = 4.6 Hz, OCH_3), 52.42 (d, *J* = 4.6 Hz, OCH_3), 101.84 (d, *J* = 236.5 Hz, P$\underline{C}$), 114.46 ($HC=\underline{C}H_2$), 115.47 (d, *J* = 21.9 Hz, 2 x CH_{arom}), 119.05 (CH_{arom}), 119.51 (CH_{arom}), 120.58 (CH_{arom}), 121.73 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 125.13 (CH_{arom}), 128.09 (d, *J* = 11.5 Hz, N$\underline{C}$), 128.22 (d, *J* = 8.1 Hz, 2 x CH_{arom}), 133.24 (d, *J* = 18.5 Hz, PC$\underline{C}$), 139.77 (d, *J* = 3.5 Hz, $C_{q,arom}$), 143.38 ($H\underline{C}=CH_2$), 161.64 (d, *J* = 246.9 Hz, $FC_{q,arom}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.17. **^{19}F-NMR (282 MHz, $CDCl_3$): δ** -115.68 - -155.78 (m). **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1048 (P-O), 1238 (P=O), 1602 (C=C), 1623 (C=C), 1636 (C=C), 1702 (C=C). **MS (ESI): m/z (%):** 400.2 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.17. **Yield:** 82%.

4.11.4 Synthesis of dimethyl 2-(4-chlorobutyl)-3-methyl-2H-isoindol-1-ylphosphonate (466)

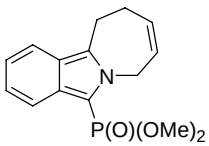
In a dry flask, 2-ethynylbenzaldehyde (0.5 g, 3.84 mmol) is dissolved into diethylether (6 ml). To this solution is added $LiClO_4$ (3.06 g, 28.8 mmol, dried for 24h at 110 °C). This mixture is stirred for 5 minutes. Subsequently pyrrolidine is added (0.55 g, 7.69 mmol) dissolved in 1 ml dry diethylether. This mixture is stirred for 20 minutes after which $P(OMe)_3$ is added (0.71 g, 5.76 mmol). The reaction is stirred for 4 hours after which HCl (3N, 20 ml) is very carefully added. The mixture is extracted with CH_2Cl_2 (3 x 20 ml) and dried using $MgSO_4$. After filtration of the solids and removal of the volatiles, the obtained compound was purified using column chromatography.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.88-2.02 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.61 (s, 3H, CH_3), 3.59 (t, *J* = 6.2 Hz, 2H, $C\underline{H}_2Cl$), 3.73 (d, *J* = 11.3 Hz, 6H, 2 x OCH_3), 4.55 (t, *J* = 7.6 Hz, 2H, $NC\underline{H}_2$), 7.02 (t, *J* = 8.0 Hz, 1H, CH_{arom}), 7.17 (t, *J* = 8.0 Hz, 1H, CH_{arom}), 7.56 (d, *J* = 8.0 Hz, 1H, PCCC$\underline{H}$), 7.80 (d, *J* = 8.0 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 10.41 (CH_3), 28.96 (CH_2), 29.75 (CH_2), 44.53 ($ClCH_2$), 46.21 (NCH_2), 52.61 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.16 (d, *J* = 235.4 Hz, P$\underline{C}$), 119.47 (CH_{arom}), 119.67 (CH_{arom}), 120.67 (CH_{arom}), 123.51 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 124.89 (CH_{arom}), 128.44 (d, *J* = 10.4 Hz, N$\underline{C}$), 132.35 (d, *J* = 17.3 Hz, PC$\underline{C}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ** 15.16. **IR (cm^{-1}) ν_{max}:** 1024 (P-O), 1048 (P-O), 1245 (P=O), 1710 (C=C). **MS (ESI): m/z (%):** 330.2/332.3 ($M+H^+$, 100). **Chromatography:** EtOAc R_f = 0.59. **Yield:** 8%.

4.11.5 Synthesis of dimethyl 10,11-dihydro-7H-azepino[2,1-a]isoindol-5-ylphosphonate (472)

Compound **435i** (0.2 g, 0.63 mmol) was dissolved in benzene (20 ml) and the second generation Grubbs' catalyst (5 mol%, 0.011 g, 0.013 mmol) was added. The reaction was allowed to reflux for 16h under a N_2-atmosphere. The product was coated on silica gel by removal of the solvent *in vacuo* and purified by column chromatography.



^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.42-2.48 (m, 2H, $CH_2C\underline{H}_2CH$), 3.38 (t, *J* = 6.0 Hz, 2H, $C\underline{H}_2CH_2CH$), 3.72 (d, *J* = 11.5 Hz, 6H, 2 x OCH_3), 5.24-5.28 (m, 2H, NCH_2), 5.75-5.94 (m, 2H, $\underline{H}C{=}C\underline{H}$), 7.03 (ddd, *J* = 1.0 Hz, *J* = 6.6 Hz, *J* = 8.4 Hz, 1H, CH_{arom}), 7.16 (ddd, *J* = 1.0 Hz, *J* = 6.6 Hz, *J* = 8.7 Hz, 1H, CH_{arom}), 7.58 (ddt, *J* = 1.0 Hz, *J* = 2.2 Hz, *J* = 8.4 Hz, 1H, PCCC$\underline{H}$), 7.90 (dt, *J* = 1.0 Hz, *J* = 8.7 Hz, 1H, PCCCC$\underline{H}$). **^{13}C-NMR (75 MHz, $CDCl_3$): δ** 21.86 ($NC\underline{C}H_2$), 28.13 ($CH_2\underline{C}H_2CH$), 43.98 (NCH_2), 52.59 (d, *J* = 4.6 Hz, 2 x OCH_3), 102.46 (d, *J* = 234.2 Hz, P$\underline{C}$), 119.08 (CH_{arom}), 119.75 (CH_{arom}), 120.72 (CH_{arom}), 122.26 (d, *J* = 12.7 Hz, PCC$\underline{C}$), 122.62 (H$\underline{C}$=CH), 124.44 (CH_{arom}), 132.09 (d, *J* = 17.3 Hz, PC$\underline{C}$), 133.15 ($NCH_2\underline{C}H$), 133.87 (d, *J* = 9.2 Hz, N$\underline{C}$). **^{31}P-NMR (121 MHz, $CDCl_3$): δ**

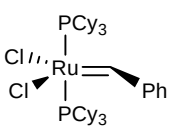
15.26. **IR (cm^{-1}) v_{max}:** 1025 (P-O), 1047 (P-O), 1224 (P=O), 1694 (C=C). **MS (ESI): m/z (%):** 292.3 ($M+H^+$, 100). **Chromatography:** Hex/EtOAc 4/6 R_f = 0.20. **Yield:** 95%.

5 Summary and Perspectives

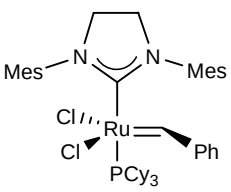
Almost 80% of all processes in the modern chemical industry use catalysts. This can be attributed to a continuing quest of researchers to achieve a specific chemical transformation in the most efficient way in order to limit the amount of waste and used energy. Catalysts are found in many different forms. Roughly, catalysis can be divided into three classes: homogeneous catalysis, heterogeneous catalysis and biocatalysis. The best known biocatalysts are called enzymes which are responsible for many fundamentally important reactions in living organisms. In heterogeneous catalysis the catalyst and the involved reaction components are present in a different phase (e.g. solid catalyst in liquid). In homogeneous catalysis both the catalyst and reaction components are distributed to the molecular level in a single phase.

In this work homogeneous catalysis was used to target compounds that are very difficult to synthesize in a non-catalytic way and that are biologically important or closely related to a biologically important group of compounds. Attention was focussed on three major groups: pyrroles, hydantoins and benzo-fused heterocycles. Furthermore, successful efforts were made to achieve multiple transformations (both catalytic and non-catalytic) in a single synthetic operation thus decreasing the amount of steps needed to obtain a certain compound.

The key reaction in this thesis is ring-closing metathesis, a process in which two carbon-carbon double bonds are broken and one new carbon-carbon double bond is formed, catalyzed by certain ruthenium complexes. In 2005, three researchers, namely Yves Chauvin, Robert H. Grubbs and Richard R. Schrock, received the Nobel Prize in Chemistry for the development of the metathesis method in organic synthesis. Although the discovery of catalyzed metathesis dates from the 1950s in industry, it was only in 1992 that Grubbs and co-workers reported the first well defined ruthenium carbene complex that did not only show good metathesis activity, but was also air-stable and could be used under standard lab conditions. Three years later, an even more active catalyst **i**, which would later be called the "first-generation Grubbs' catalyst", was described. The "second-generation Grubbs' catalyst" **ii** with increased activity and greater thermal stability, was presented in 1999.

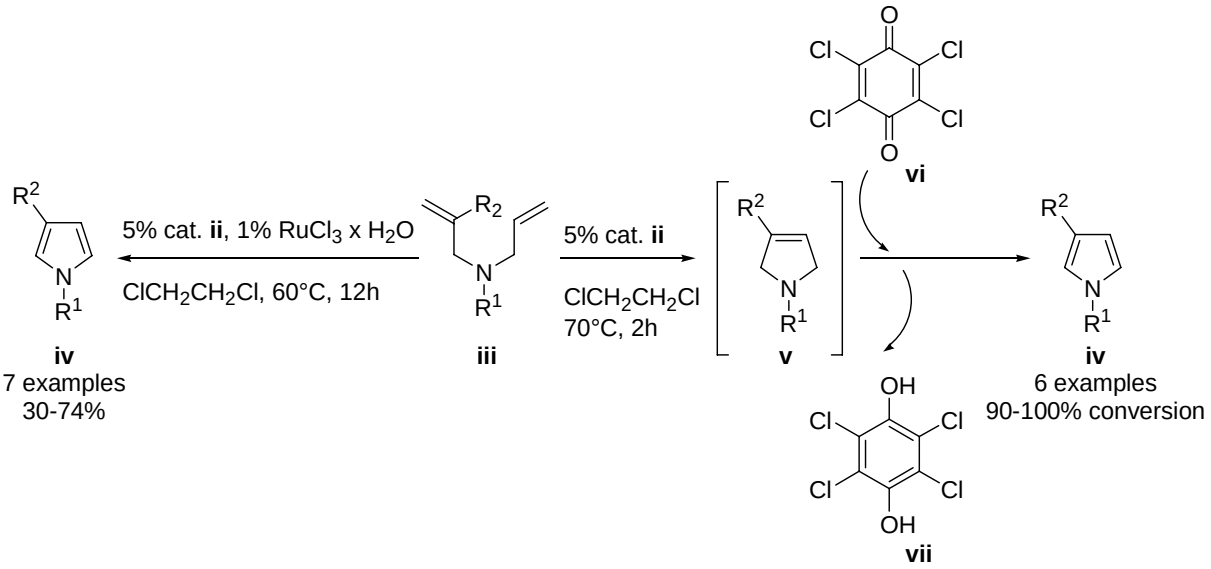


i



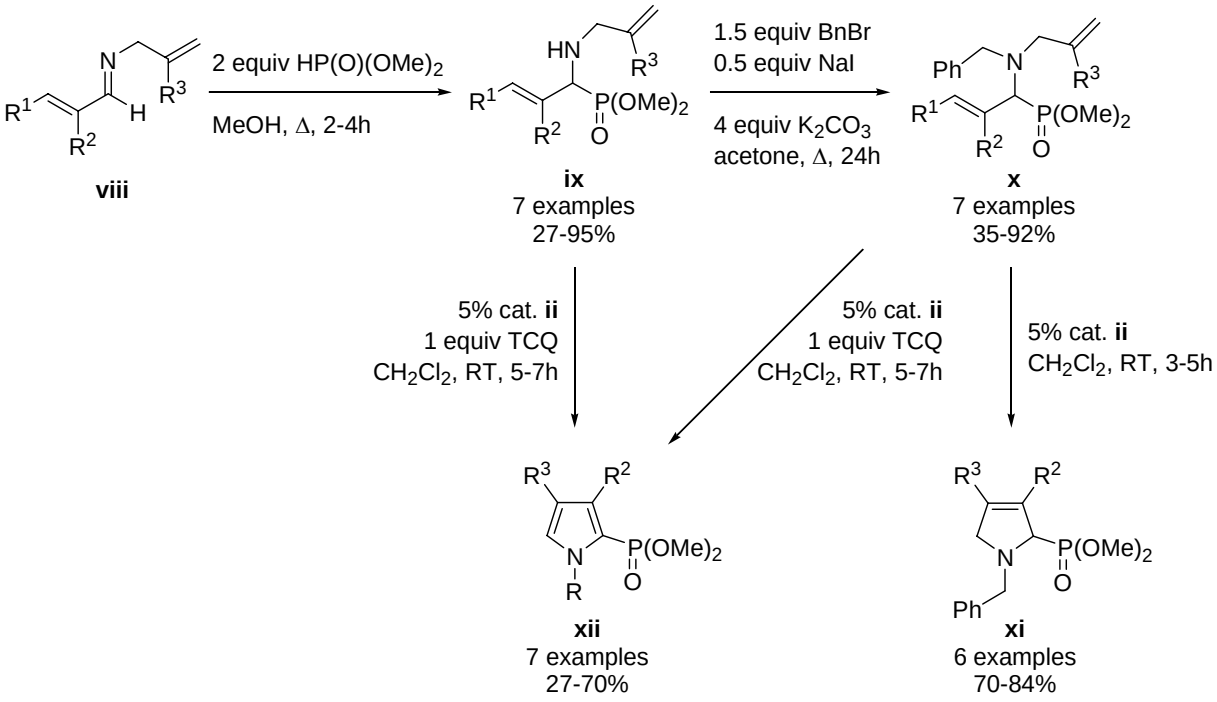
ii

The starting point of this research was the special activity of a new ruthenium based bimetallic catalyst. Earlier work had suggested that this catalyst converts diallylamines **iii** directly to the corresponding pyrroles **iv** instead of to the expected pyrrolines **v**. It was proven, however, that this hypothesis was not correct and that rather $RuCl_3$ x H_2O, present as impurity in the catalyst, facilitates the conversion of pyrrolines to pyrroles. Thus, in a first part of this PhD a new entry to this interesting azaheterocyclic compound was developed comprising the ring-closing of diallylamines **iii** using the commercially available second generation Grubbs' catalyst **ii** in combination with catalytic oxidative aromatization using $RuCl_3$ x H_2O. Although this reaction works fine, it usually takes more than 12 hours to obtain satisfactory conversion to the pyrroles at 60 °C under ultrasound conditions. Especially the oxidative dehydrogenation step proved to proceed very slowly. The reaction time could be dramatically reduced by adding a strong hydrogen acceptor, namely tetrachloroquinone **vi** which is reduced to **vii**, to the reaction mixture. The correct choice of the oxidizing agent, however, is crucial since duroquinone didn't influence the oxidation rate and DDQ caused decomposition of the metathesis catalyst. This illustrates the delicate balance of this one-pot reaction sequence. It was also found that in this case $RuCl_3$ x H_2O is no longer required as a hydrogen transfer catalyst. The reaction time is reduced to about 2 hours in this fashion. In this case, obviously, a stoichiometric amount of oxidant is consumed. Substrates bearing a strong electron withdrawing group on the *N*-atom, however, could not be oxidized. This explains why no direct pyrrole formation was observed by researchers working with a tosyl-, Boc-, or SES-protecting group on nitrogen.



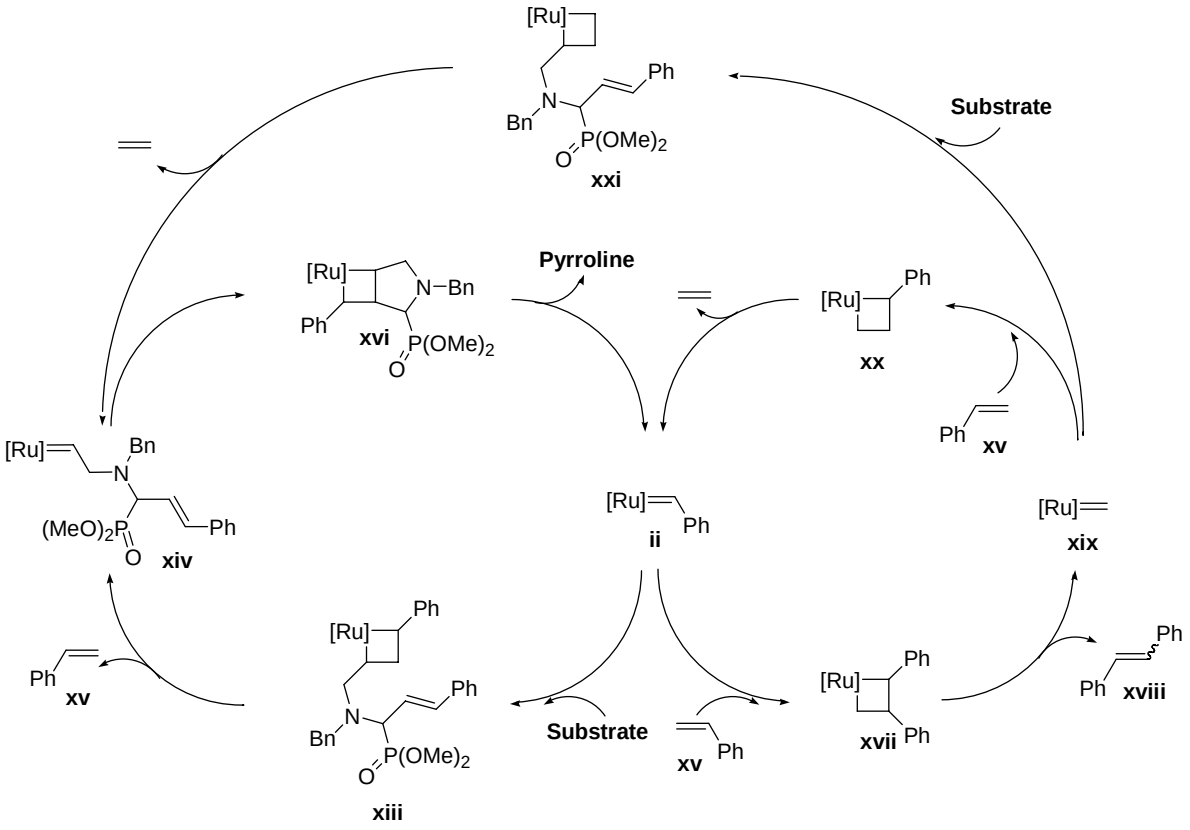
Phosphonylated azaheterocycles are an important class of compounds with high biological potential as conformationally restricted bioisosteres of amino acids. Some interesting activities are shown by azaheterocyclic five-membered rings with phosphonates at various positions. The synthesis of the aromatic counterparts of phosphonylated five-membered rings, however, has

received far less attention over the years. Application of the developed RCM/oxidation methodology on α-aminophosphonates **x** containing two double bonds allowed the straightforward synthesis of phosphonylated pyrrolines and pyrroles. In a first step, imines **viii** were phosphonylated with complete 1,2-regioselectivity by treatment with dialkyl phosphites in refluxing methanol. The *N*-atom of the obtained α-aminophosphonates **ix** was protected with a benzyl group by refluxing in acetone with K_2CO_3 as a base, benzylbromide as electrophile and NaI as catalyst. These compounds **x** could easily be converted, under very mild conditions, to the corresponding pyrrolines **xi** or pyrroles **xii**, depending on the addition of TCQ to the reaction mixture. When the RCM was attempted on secondary amines **ix**, the reaction stops at about 30% conversion. This proves that especially pyrrolines tend to poison the catalyst. In the pyrrole ring, the nitrogen lone pair is no longer nucleophilic since it is part of the aromatic system. When TCQ is added to the secondary amines **ix** together with the metathesis catalyst **ii**, the 'poisonous' pyrrolines are immediately oxidized to the 'benign' pyrroles. In this fashion, 100% conversion could be obtained. Unfortunately, an immense drop in yield is observed during purification by column chromatography.



In a control experiment, it was demonstrated that oxidation of the isolated pyrrolines with TCQ in the absence of the second generation catalyst **ii** proceeds significantly slower than in the domino reaction. Probably, both hydrogen donor and acceptor are brought together by simultaneous coordination to the metal centre, followed by direct hydrogen transfer from the pyrroline to the TCQ. It seems that the phosphonate group is just electron withdrawing enough to lower the nucleophilicity of the *N*-atom to allow the RCM to occur at room temperature while still allowing oxidation of the pyrrolines to the corresponding pyrroles.

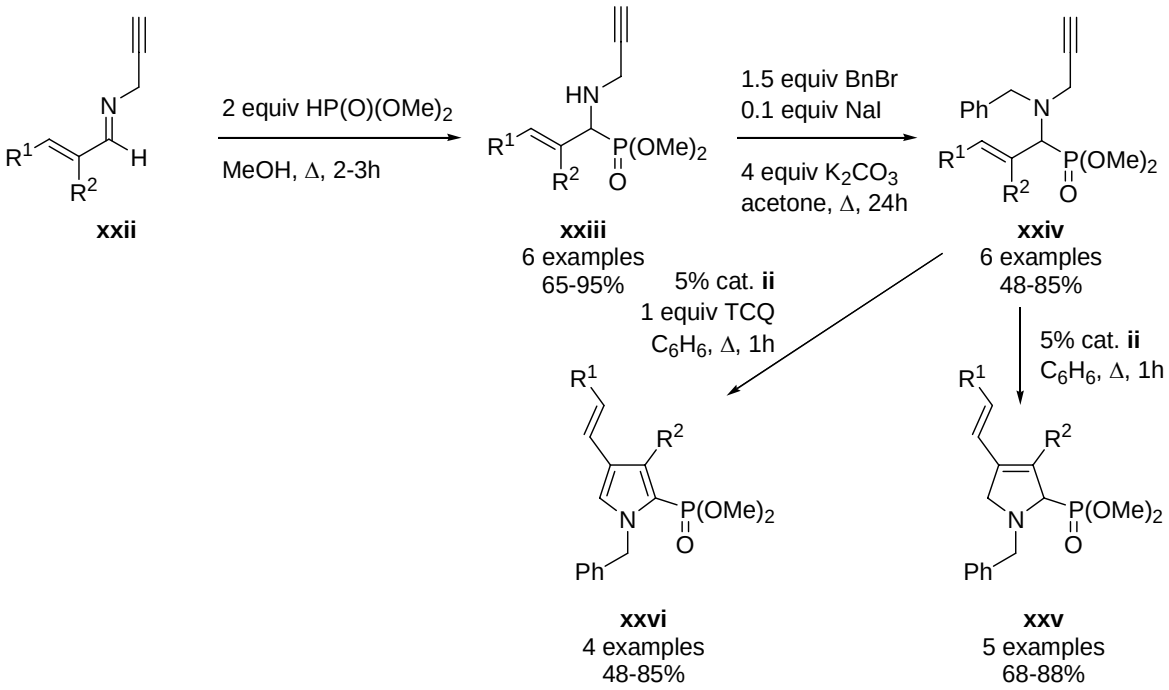
The substrates **ix** and **x** bear one terminal and one non-terminal alkene. Initiation of the metathesis occurs, for steric reasons, on the terminal double bond. The cyclobutane **xiii** fragments with formation of a new carbene **xiv** and styrene **xv**. The new carbene cyclizes to **xvi** which forms the pyrroline and regenerates the active species of catalyst **ii** upon cycloreversion. No ethylene is formed in this cycle which is unconventional since the formation of ethylene is considered to be crucial to shift the equilibrium to the end product. The styrene **xv** builds up in the reaction mixture, however, and starts to compete with the substrate for reaction with the catalyst. Thus, in a second catalytic cycle, styrene is dimerized to stilbene **xviii**, which precipitates from the mixture, and methylidene carbene **xix** is generated. This carbene can react either with styrene to **xx** or with substrate to **xxi**. Both cyclobutanes generate ethylene upon cycloreversion. Thus, in contrast to the normal metathesis cycle, in this case ethylene is generated in two secondary catalytic pathways.



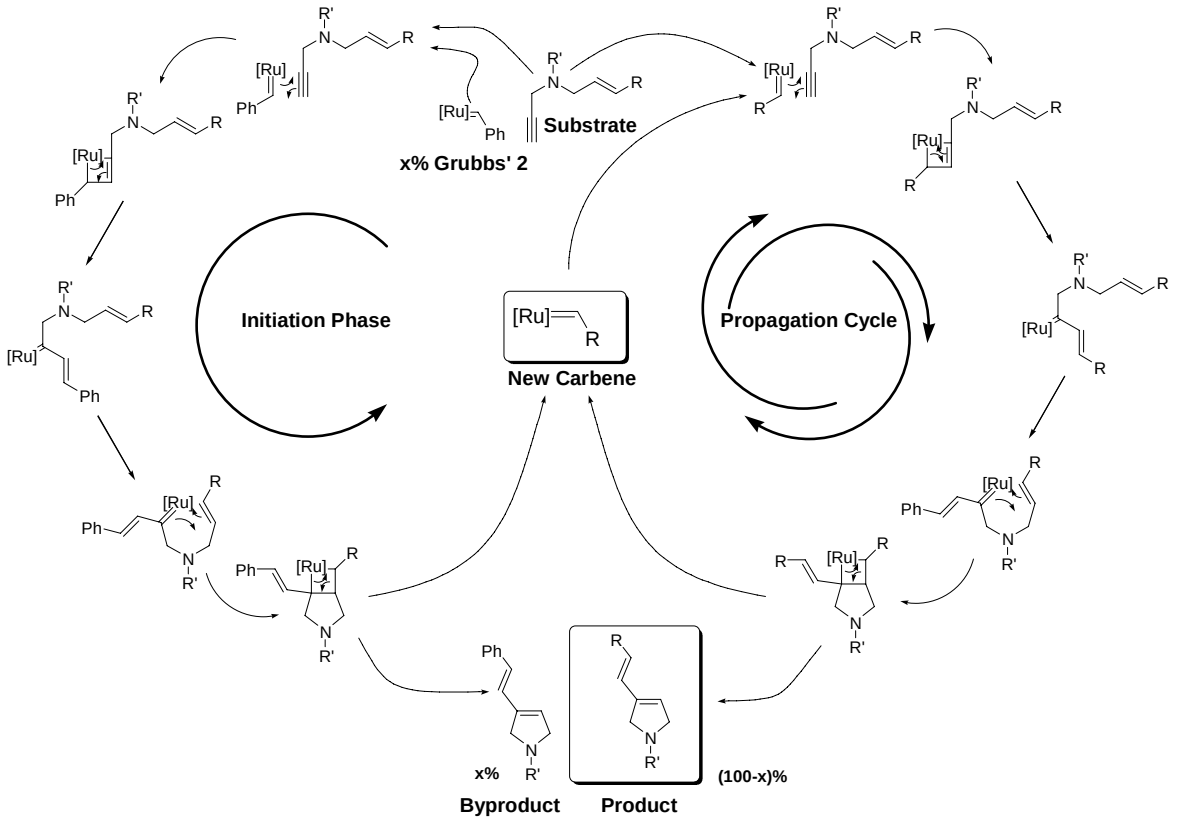
Enyne metathesis, involving reaction between an alkene and an alkyne, has received far less attention than RCM. Sequential reactions, for example, have hardly been developed for enyne metathesis. So far, only a one-pot combination of enyne metathesis with a Diels-Alder reaction or a cyclopropanation has been reported. Unlike olefin metathesis, all carbon atoms from the starting material are retained in the end product which contains a synthetically useful 1,3-diene moiety. Despite its usefulness, however, little is known about the mechanism of the reaction.

More precisely, the question whether the reaction proceeds via the "yne-then-ene" or the "ene-then-yne" mechanism is still often raised.

The first combination of ring-closing enyne metathesis with oxidation was developed by treatment of α-aminophosphonates **xxiv** containing a double and a triple bond with the second generation Grubbs' catalyst **ii** in refluxing benzene in the presence of TCQ. The substrates for this reaction were made in two straightforward steps starting from imines **xxii**. In a first step these imines were phosphonylated with complete 1,2-regioselectivity by treatment with dialkyl phosphites in refluxing methanol. The *N*-atom of the obtained α-aminophosphonates **xxiii** was protected with a benzyl group by refluxing in acetone with K_2CO_3 as a base, benzylbromide as electrophile and NaI as catalyst.

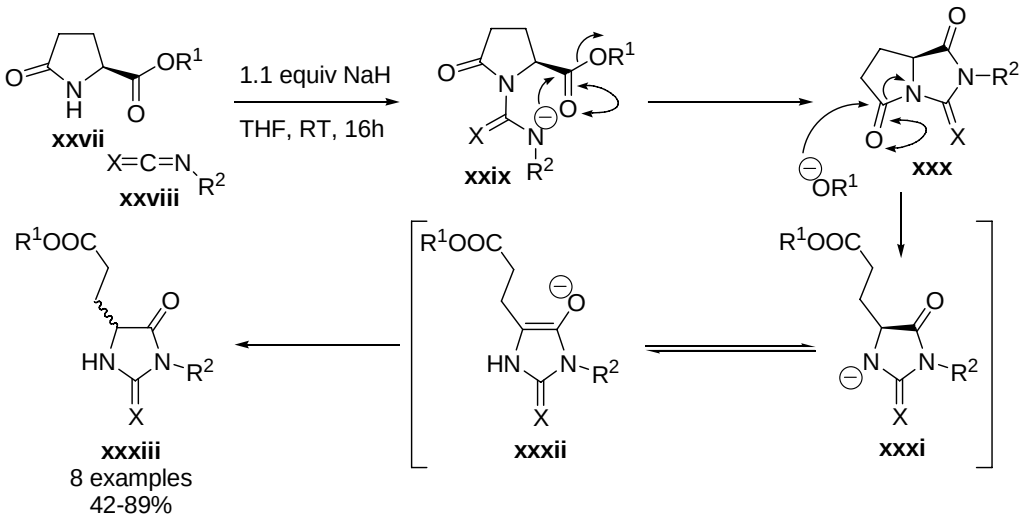


This RCEYM/oxidation sequence on substrates **xxiv** allows the synthesis of highly functionalized 2-phosphonylated pyrrolines **xxv** and pyrroles **xxvi**. A detailed mechanistic investigation revealed that the reaction follows the "yne-then-ene" pathway. The proof of this reaction mechanism is based on the formation of certain end and sideproducts, spectroscopic data and finally on the difference in reactivity of different substrates. During the initiation phase, the Grubbs' carbene is converted to a new ruthenium-carbene which continues the propagation cycle.

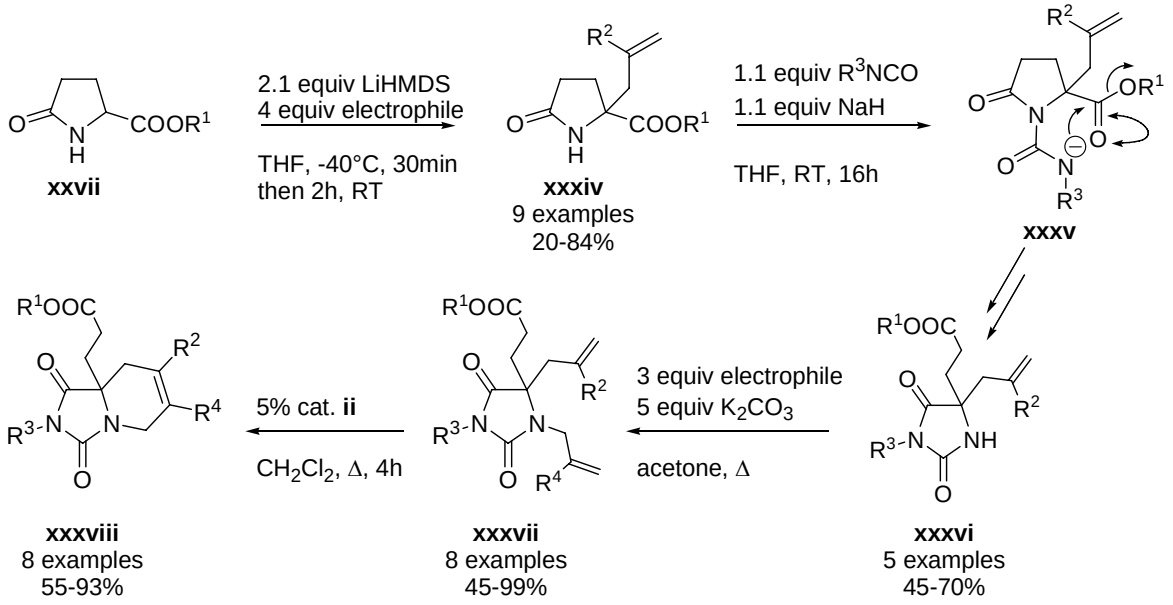


In the second part of this thesis entries towards new polycyclic hydantoin derivatives were developed starting from pyroglutamates. Hydantoins have been extensively studied and are reported to possess a wide range of biological activities. Furthermore, several hydantoin derivatives with an extra fused ring show some interesting medicinal properties.

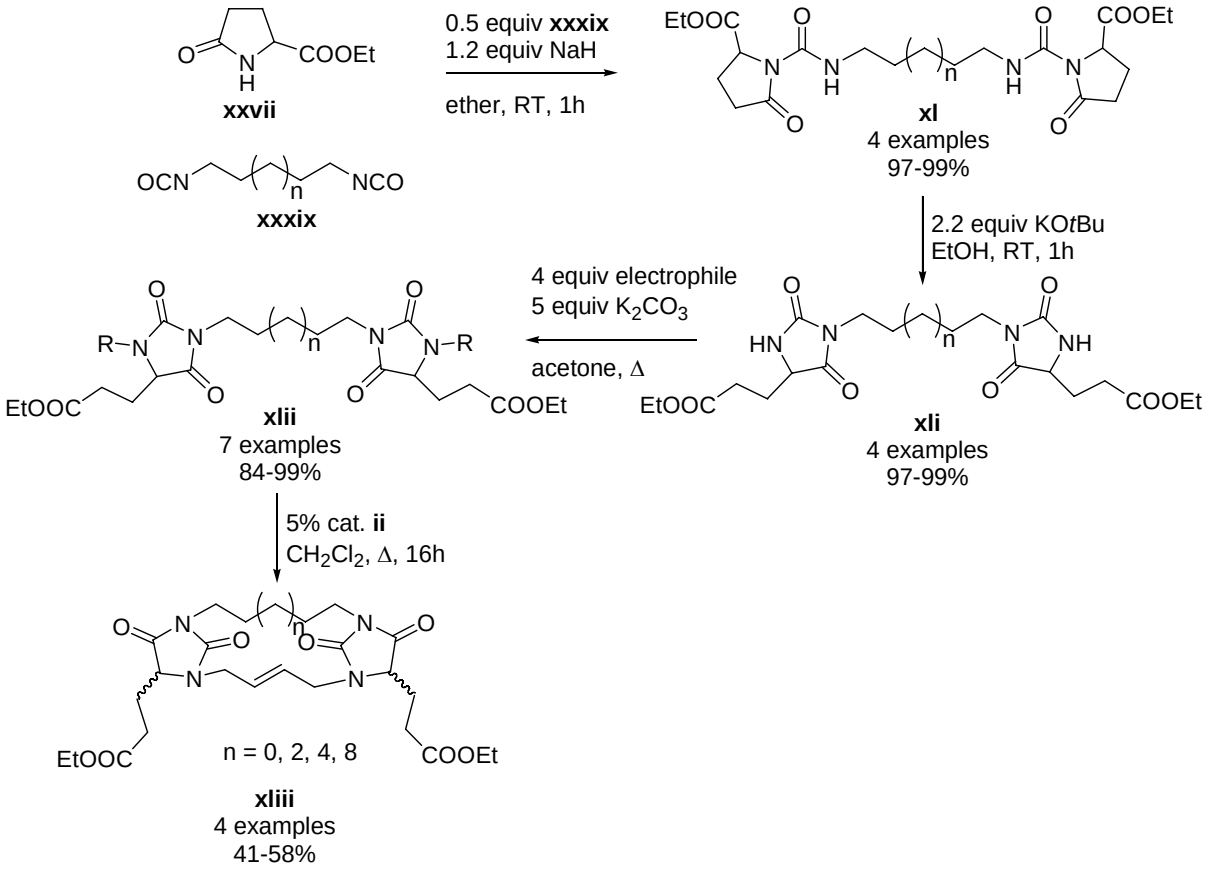
When a mixture of a pyroglutamate **xxvii** and an isocyanate **xxviii** is treated with NaH in diethyl ether, a precipitate is formed during the reaction, which after workup proved to be the sodium salt of the expected carbamoyllactam **xxix** in high purity. If the reaction is performed in THF on the other hand, no precipitate is formed since intermediate **xxix** reacts intramolecularly by a nucleophilic attack on the carbonyl of the ester function followed by expulsion of an alkoxide anion, resulting in the formation of bicyclic intermediate **xxx**. The alkoxide anion in turn can open this bicyclic intermediate with formation of anions **xxxi** and **xxxii**. These anions are in equilibrium with each other, causing racemization of the chiral centre. Work up results in hydantoin derivatives **xxxiii** as a 1:1 mixture of their enantiomers.



This ring-transformation was successfully used in a short 4-step approach for the synthesis of hydantoin derivatives **xxxviii** that are annelated to a six-membered ring. In a first step, pyroglutamates **xxvii** are alkylated at the 2-position using LiHMDS and a proper electrophile. It was found that excellent results can be obtained when a mixture of the pyroglutamate and the electrophile is treated with 2.1 equivalents of LiHMDS at –40 °C. Even when using several equivalents of electrophile, no *N*-alkylation was observed. Treatment of a solution of **xxxiv** and an isocyanate in THF with NaH results in the formation of carbamoylated lactam **xxxv** which rearranges with formation of the hydantoin nucleus **xxxvi**. These compounds are cleanly alkylated at *N*(1) towards **xxxvii** in good yield by refluxing them with 2 equivalents of electrophile and 5 equivalents of finely ground K_2CO_3 in acetone for several days. Treatment of these compounds with 5% second generation catalyst **ii** in refluxing CH_2Cl_2 resulted in clean conversion to the desired compounds **xxxviii**.



Also a new entry towards *N*(3),*N*(3)-polymethylene-bis-hydantoins was developed. Bis-hydantoins, usually dimers of phenetoin or related compounds, have in the past been tested as analogues of HMBA and might prove effective in cancer treatment. In this work, bis-hydantoins **xli** were obtained by reaction of pyroglutamate **xxvii** with bis-isocyanates **xxxix** and subsequent ring-transformation of bis-carbamoylated lactams **xl** using KO*t*Bu in ethanol.

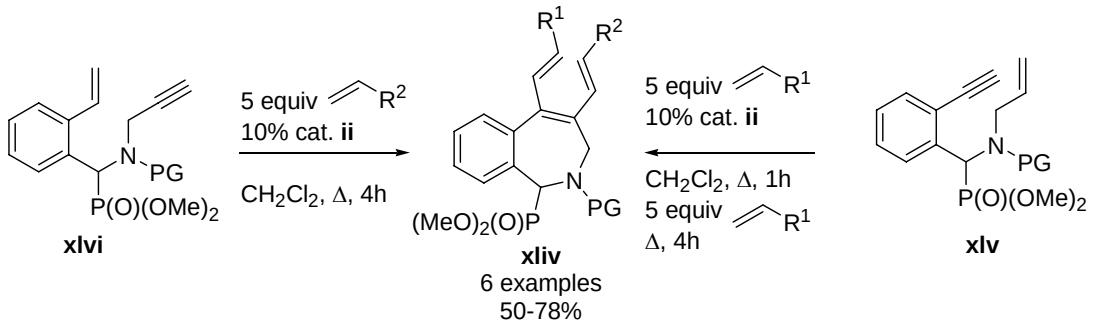


These compounds **xli** are cleanly alkylated at *N*(1) towards **xlii** in good yield by refluxing with 4 equivalents of electrophile and 5 equivalents of finely ground K_2CO_3 in acetone. The compounds with allyl groups at *N*(1) could be converted to their macrocyclic derivatives **xliii** using the second generation Grubbs' catalyst **ii** in refluxing CH_2Cl_2. It was proven that only the *trans*-isomers are isolated. The presence of only one isomer around the double bound can be explained by secondary metathesis reactions since it is known that macrocycles isomerise to produce a thermodynamically controlled (*E/Z*) ratio regardless the stereochemistry of the initial alkene.

A number of the synthesized hydantoins were screened for their anti-invasive activity on human breast cancer cell lines. The screening assay chosen is based on the *in vitro* confrontation of cancer cells with a fragment of normal heart tissue dissected from 9-days old chicken embryos. It can be stated that some of the synthesized bis-hydantoins show some good anti-invasive activity at a concentration of 100 μm and 10 μm. Furthermore, these compounds can be very easily prepared on a large scale and are non-toxic to the heart tissue used in the *in vitro* tests.

Unfortunately, the activity of these compounds cannot be accurately predicted using a nonlinear QSAR model. Further research is therefore needed to shed light on the mode of action of these structures in order to allow the synthesis of more active compounds. In a further stage, *in vivo* tests will have to be performed to validate these results.

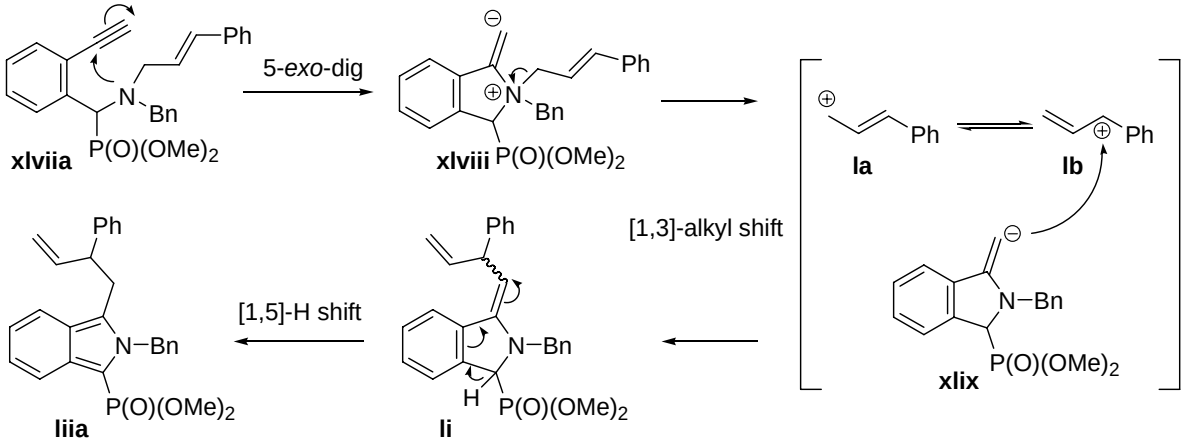
In the third part of this thesis, entries towards new benzo-fused compounds, namely 1*H*-2-benzazepine-1-ylphosphonates and phosphonylated isoindoles, were developed. Benzo-fused compounds, and especially seven-membered ring systems with famous examples like diazepam (Valium®) and flurazepam (Dalmadorm®), have received a lot of attention over the years because of their ubiquitous appearance in natural products and modern pharmaceuticals.
The first protocol for the synthesis of 1*H*-2-benzazepine-1-ylphosphonates **xliv** uses a combination of enyne-metathesis with cross-metathesis. A refluxing mixture of compound **xlv** and 5 equivalents of an alkene in CH_2Cl_2 was treated with 10 mol% of the second generation Grubbs' catalyst **ii**. An additional amount of alkene (5 equiv) has to be added after 2 hours. This observation was explained by looking at the complete reaction cycle. During the course of the reaction, the alkene is not only incorporated in the end product but also dimerized in the "alkene sink" with regeneration of the methylidene carbene and production of ethylene. Upon evaluation of the reaction between **xlvi** and alkenes, it was found that in this case it is not necessary to add an extra amount of alkene. The advantage of this strategy is that it required the synthesis of only two substrates, with a terminal double and triple bond, that depending on the addition of a certain alkene to the reaction mixture are transformed into different seven-membered rings.



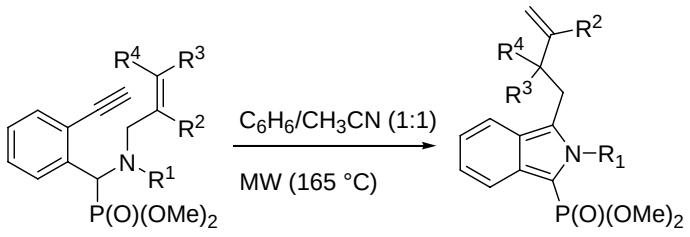
xlvi **xliv** 6 examples 50-78% **xlv**

The treatment of very similar substrates **xlvii** containing a non-terminal double bond with a metathesis catalyst did not lead to the expected seven-membered rings but produced phosphonylated isoindoles instead. Phosphonylated isoindoles and related compounds are rarely described in the literature. In fact, only one low yielding entry to phosphonylated isoindoles could be found. Furthermore, few entries towards related compounds like phosphonylated dihydro isoindoles and isoindolinones have been reported in the literature. The latter are known for their plant growth regulating properties.

It was found that this rearrangement is thermally driven. After a number of experiments the yield and conversion rate could be optimized by heating the substrates in a mixture of benzene/CH_3CN in a 1/1 ratio at 165 °C under microwave conditions. The first step in this transformation probably involves a direct addition of the nitrogen lone pair onto the triple bond in a 5-*exo*-dig fashion to **xlviii**. The zwitterionic intermediate **xlviii** subsequently fragments with formation of anion **xlix** and cations **Ia** and **Ib**. Anion **xlix** reacts with **Ib** with formation of **li**. The overall result of the fragmentation and recombination corresponds to a [1,3]-alkyl shift. The rearrangement ends with a [1,5]-H shift resulting in aromatization towards **lii**. This pathway represents the first ever high yielding entry to phosphonylated isoindoles.



The general nature of this rearrangement was proven by preparing a number of α-aminophosphonates **xlvii** and subjecting them to the same conditions. These α-aminophosphonates were prepared using a three component coupling between ethynylbenzaldehyde, secondary amines and trimethyl phosphite mediated by $LiClO_4$. The isoindoles **lii** were isolated in good yield.

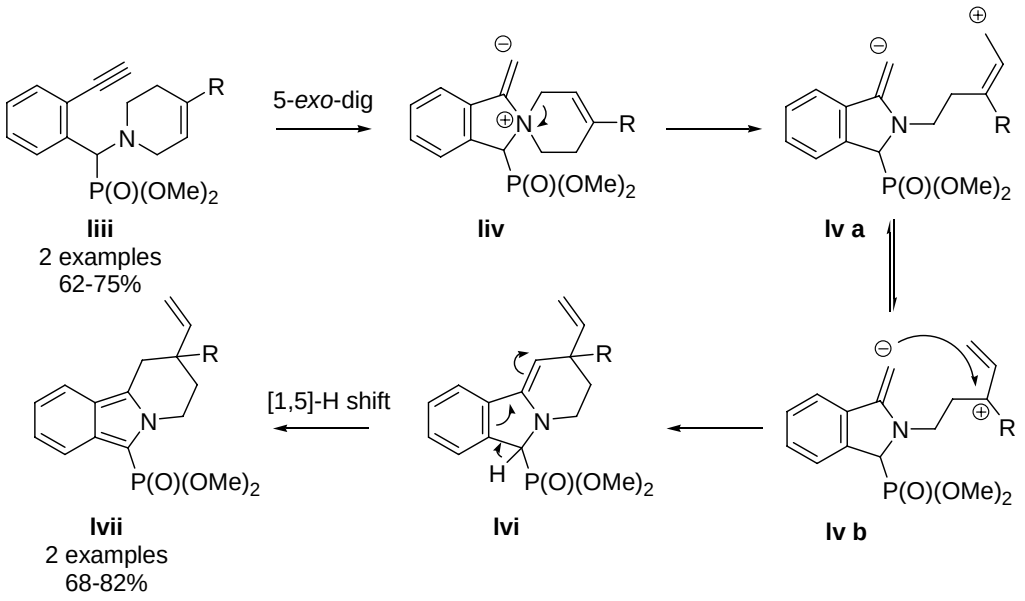


xlvii
9 examples
48-88%

lii
9 examples
40-98%

When the allylic group that migrates is incorporated in an extra ring, the anion and cation will remain attached to each other during the reaction. As expected, heating **liii** under microwave conditions resulted in the formation of tricyclic compounds **lvii**. The fragmentation of the

zwitterionic intermediate **liv** results in the formation of **lva** and resonance form **lvb**. An intramolecular attack forms an additional six-membered ring **lvi**. Finally, aromatization produces isoindoles **lvii**.



From the results in this research, some perspectives to future work have to be formulated. Firstly, a new entry towards pyrroles using a combination of RCM or RCEYM with oxidation has been developed. This will allow researchers to efficiently construct this interesting azaheterocyclic compound and its phosphonylated derivatives. In order to evaluate the biological potential of these compounds, deprotection of the phosphonates might be necessary. New catalytic systems, for example on a solid support, may allow the synthesis of these compounds on a larger scale. Possibly, this methodology can also be extended for the synthesis of other heterocycles. It is unlikely, however, that for example furans or thiophenes can be made in a one-pot sequence since most probably the metathesis catalyst will be destroyed by the use of stronger oxidants. In the future, development of other metathesis catalysts could allow the synthesis of more substituted derivatives and allow the use of other oxidants. The mechanistic insights in RCEYM will help researchers to explain the formation of certain end and byproducts in the reaction mixture.

The new entry to hydantoin derivatives might prove very powerful when combined with enantioselective reactions on the pyroglutamate. Future biological screening of compounds obtained in this thesis might reveal their working mechanisms and can possibly direct the synthesis to more active structures. The hydrolysis of the ester moiety in the screened compounds will produce more polar compounds with even better water solubility and possibly increased activity.

The combination of enyne-metathesis with cross-metathesis for the synthesis of 1*H*-2-benzazepine-1-ylphosphonates allows the synthesis of a variety of benzo-fused azepines depending on the addition of a certain alkene. The obtained diene could be further functionalized by a Diels-Alder reaction with a variety of dienophiles, leading to more complex structures in one synthetic effort.

The rearrangement towards phosphonylated isoindoles is a very promising reaction since it could possibly be applied to the synthesis of other heterocycles. Thus, instead of starting from 2-ethynylbenzaldehyde one could envisage routes starting from 3-ethynyl-furan-2-carbaldehyde or 3-ethynyl-pyridine-2-carbaldehyde. Reactions with internal alkynes instead of terminal ones, might lead to isoquinoline derivatives after a rearrangement that starts with a 6-*endo*-dig attack instead of the 5-*exo*-dig attack described in this work.

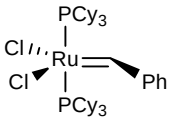
In conclusion, a large variety of azaheterocyclic compounds has been made accessible by ring-closing metathesis reactions. These include five-, six- and seven-membered rings next to a number of macrocyclic derivatives. Furthermore, the combination of RCM with oxidative dehydrogenation provides a new straightforward entry to aromatic compounds. The results obtained in this thesis offer the possibility to other researchers to further develop this interesting chemistry.

6 Samenvatting en Perspectieven

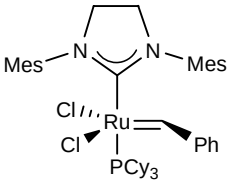
Bijna 80% van alle processen in de moderne chemische industrie maken gebruik van katalysatoren. Dit kan verklaard worden door de voortdurende zoektocht van onderzoekers om een specifieke chemische transformatie te verwezenlijken op de meest efficiënte manier teneinde zowel de hoeveelheid afval als de hoeveelheid gebruikte energie te beperken. Katalysatoren komen voor onder veel verschillende vormen. Ruwweg kan katalyse ingedeeld worden in drie klassen: homogene katalyse, heterogene katalyse en biokatalyse. De best gekende biokatalysatoren zijn enzymes die instaan voor een aantal fundamenteel belangrijke processen in levende organismen. Bij heterogene katalyse zijn de katalysator en de reactiecomponenten aanwezig in een verschillende fase (bijvoorbeeld een vaste katalysator in een vloeistof). Bij homogene katalyse zijn de katalysator en de reactiecomponenten in dezelfde fase tot op het moleculaire niveau verdeeld.

In dit werk werd gebruikt gemaakt van homogene katalyse om verbindingen aan te maken die heel moeilijk te bereiden zijn op niet-katalytische wijze en die tevens een zeker biologisch belang hebben of nauw verwant zijn aan een biologisch belangrijke klasse van verbindingen. De aandacht werd gefocust op drie grote groepen: pyrrolen, hydantoines en benzo-gefuseerde heterocyclische verbindingen. Bovendien werden een aantal succesvolle pogingen ondernomen om meerdere transformaties (zowel katalytische als niet-katalytische) te verwezenlijken in één enkele synthetische handeling, waardoor dus het aantal stappen nodig om een bepaald product te bekomen, verminderd werd.

De sleutelreactie in deze thesis is ringsluitings metathese, een proces waarbij twee koolstof-koolstof dubbele bindingen gebroken worden en één nieuwe koolstof-koolstof dubbele binding gevormd wordt, gekatalyseerd door bepaalde ruthenium complexen. In 2005 ontvingen drie onderzoekers, namelijk Yves Chauvin, Robert H. Grubbs en Richard R. Schrock, de Nobelprijs Chemie voor de ontwikkeling van de metathese methodologie in de organische synthese. Alhoewel de ontdekking van gekatalyseerde metathese reeds dateert van de jaren 1950, werd er pas in 1992 een goed gedefinieerd ruthenium complex ontwikkeld door Grubbs en zijn medewerkers dat niet alleen hoge metathese activiteit vertoonde maar tevens luchtstabiel was en gebruikt kon worden onder standaard labo condities. Drie jaar later werd een nog actievere katalysator **i** beschreven die later de "eerste-generatie Grubbs katalysator" genoemd zou worden. De "tweede-generatie Grubbs katalysator" **ii** met verhoogde activiteit en grotere thermische stabiliteit werd voorgesteld in 1999.

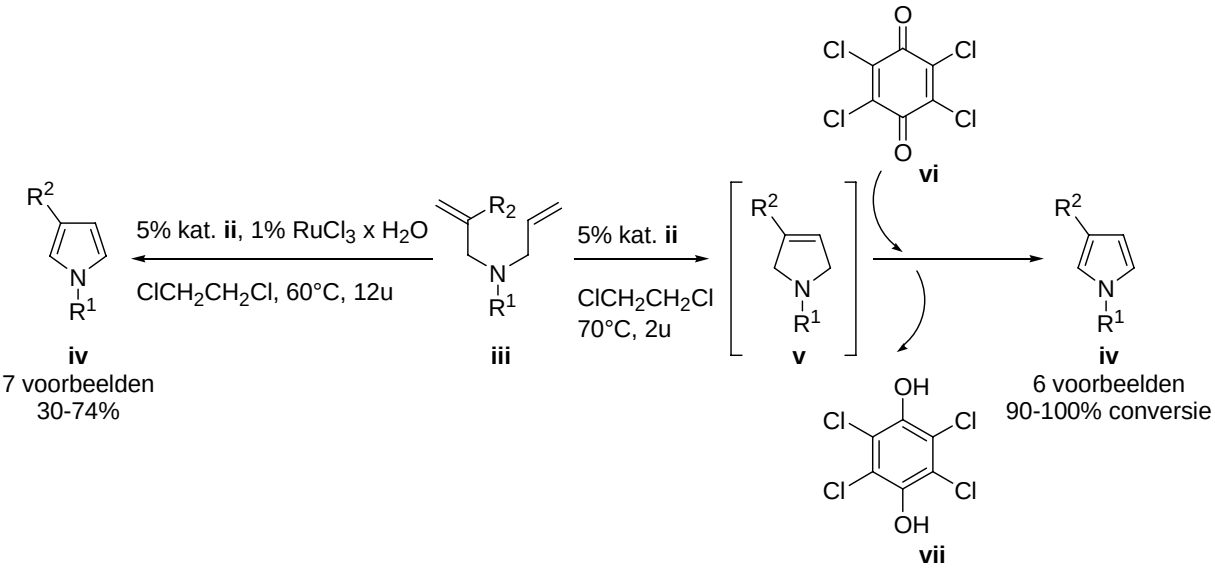


i



ii

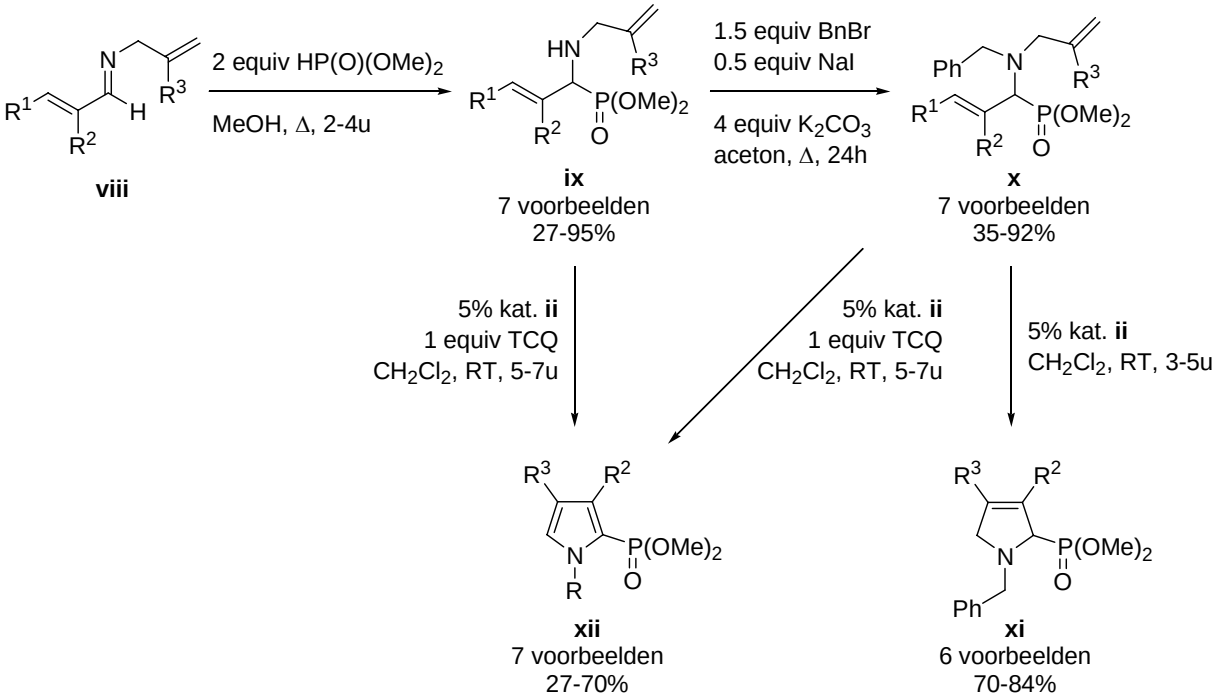
Het oorspronkelijke uitgangspunt van dit onderzoek was de speciale activiteit van een nieuwe bimetallische ruthenium katalysator. Eerder onderzoek had immers gesuggereerd dat deze katalysator diallylamines **iii** rechtstreeks kon omzetten tot de overeenkomstige pyrrolen **iv** in plaats van tot de verwachte pyrrolines **v**. Het werd echter aangetoond dat deze hypothese niet correct was en dat eerder $RuCl_3$ x H_2O, aanwezig als onzuiverheid in de katalysator, de omzetting van pyrrolines naar pyrrolen veroorzaakt. In een eerste deel van dit doctoraat werd er dus een nieuwe toetreding tot deze interessante heterocyclische verbindingen ontwikkeld die bestaat uit de ringsluiting van diallylamines **iii**, door de commercieel beschikbare tweede generatie Grubbs katalysator **ii**, in combinatie met een katalytische oxidatieve aromatizatie door $RuCl_3$ x H_2O. Alhoewel deze reactie betrekkelijk goed werkt, duurt het doorgaans meer dan 12 uren om een aanvaardbare omzetting tot de pyrrolen te verkrijgen bij 60 °C onder ultrasone condities. Er werd opgemerkt dat vooral de oxidatieve dehydrogenatie zeer traag verloopt. De reactietijd kon enorm gereduceerd worden door een sterke waterstof acceptor, namelijk tetrachloorchinon **vi** dat gereduceerd wordt tot **vii**, toe te voegen aan het reactiemengsel. De correcte keuze van het oxidans is echter cruciaal aangezien durochinon de oxidatiesnelheid niet beïnvloedt en DDQ afbraak van de metathese katalysator veroorzaakt.



Dit illustreert de delicate balans van deze eenpotsreactie. Het werd tevens opgemerkt dat $RuCl_3$ x H_2O niet langer nodig was als waterstoftransfer katalysator. Op deze wijze werd de reactietijd teruggebracht tot ongeveer 2 uren. Natuurlijk wordt er in dit geval een stoichiometrische hoeveelheid oxidans verbruikt. Substraten met een sterke elektronenzuigende groep op het *N*-

atoom konden echter niet geoxideerd worden. Dit verklaart waarom directe pyrrool vorming niet geobserveerd werd door onderzoekers die werkten met een tosyl-, Boc-, of SES-beschermende groep op stikstof.

Gefosfonyleerde heterocyclische producten zijn een interessante klasse van verbindingen met groot biologisch potentieel als conformationeel beperkte bio-isosteren van aminozuren. Sommige azaheterocyclische vijfringen met een fosfonaatgroep op variabele positie vertonen interessante biologische activiteit. De synthese van de aromatische tegenhangers van gefosfonyleerde azaheterocyclische vijfringen heeft echter heel wat minder aandacht gekregen over de jaren. Toepassing van de ontwikkelde RCM/oxidatie methodologie op α-aminofosfonaten **x**, die twee dubbele bindingen bevatten, liet de synthese toe van gefosfonyleerde pyrrolines en pyrrolen. In een eerste stap werden imines **viii** gefosfonyleerd met complete 1,2-regioselectiviteit door behandeling met dialkyl fosfieten in kokende methanol. Het *N*-atoom van de verkregen α-aminofosfonaten **ix** werd beschermd met een benzyl groep door te refluxen in aceton met K_2CO_3 als base, benzylbromide als elektrofiel en NaI als katalysator. Deze verbindingen **x** konden eenvoudig en onder heel milde omstandigheden omgezet worden tot de overeenkomstige pyrrolines **xi** of pyrrolen **xii**, afhankelijk van de toevoeging van TCQ aan het reactiemengsel.

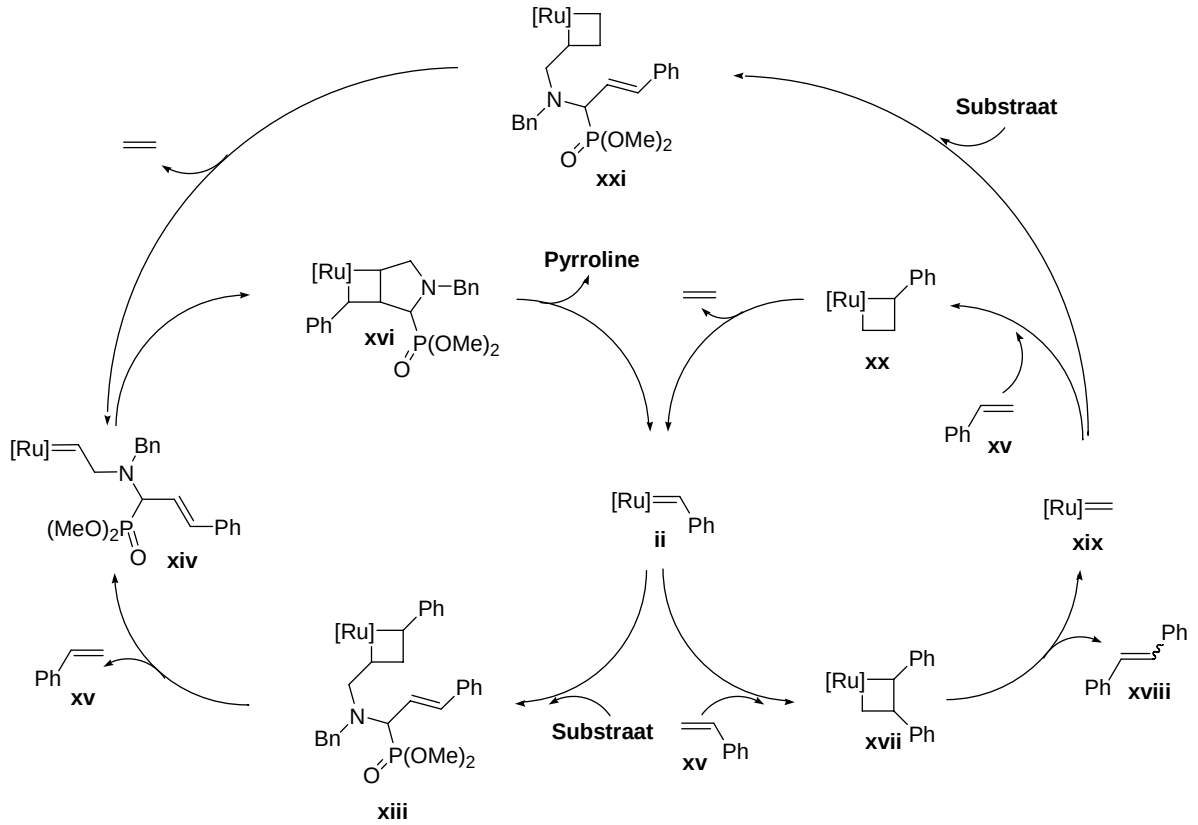


Wanneer de RCM geëvalueerd werd op secundaire amines **ix**, werd opgemerkt dat de reactie stilvalt bij ongeveer 30% omzetting. Dit duidt op het feit dat vooral pyrrolines de katalysator vergiftigen. In de pyrroolring is het vrije elektronenpaar op stikstof immers niet meer nucleofiel aangezien het deel uitmaakt van het aromatisch systeem. Wanneer TCQ samen met de

secundaire amines **ix** wordt toegevoegd aan de metathese katalysator **ii**, worden de complexerende pyrrolines onmiddellijk geoxideerd tot de niet-complexerende pyrrolen. Op deze wijze kon 100% conversie bekomen worden. Jammer genoeg daalde het rendement enorm tijdens de opzuivering via kolom chromatografie.

In een controle experiment werd aangetoond dat de oxidatie van de geïsoleerde pyrrolines met TCQ opvallend trager verloopt in afwezigheid van de tweede generatie katalysator **ii** dan in de domino sequentie. Waarschijnlijk worden zowel waterstofdonor als –acceptor bij elkaar gebracht door simultane coördinatie aan het metallisch centrum, gevolgd door directe waterstof transfer van het pyrroline naar TCQ. Het lijkt dat de fosfonaatgroep net elektronenzuigend genoeg is om de nucleofiliciteit van het *N*-atoom te verlagen zodat de RCM bij kamertemperatuur kan plaatsgrijpen terwijl toch nog steeds de oxidatie van het pyrroline tot het pyrrool mogelijk is.

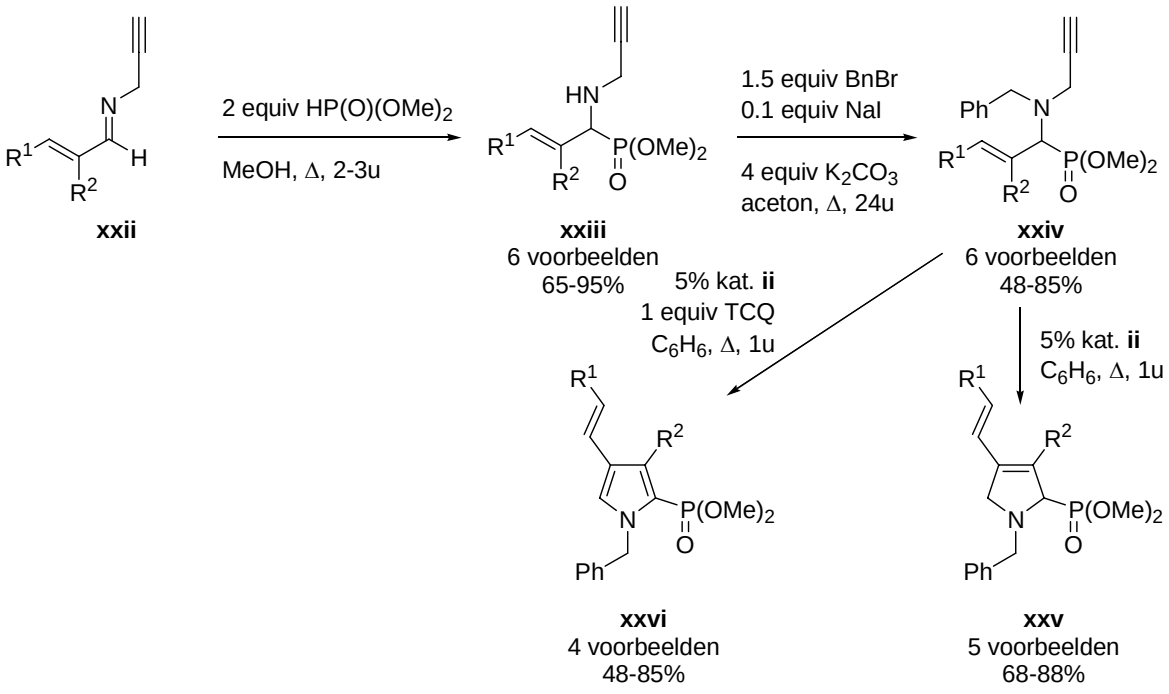
De substraten **ix** en **x** bezitten één eindstandige en één niet-eindstandige dubbele binding. Initiatie van de metathese gebeurt, omwille van sterische redenen, aan de eindstandige dubbele binding. Het cyclobutaan **xiii** fragmenteert met vorming van een nieuw carbeen **xiv** en styreen **xv**. Dit nieuwe carbeen cycliseert tot **xvi** dat het pyrroline vormt en het actieve species van de katalysator regenereert na cycloreversie. In deze cyclus wordt geen etheen gevormd en dat is merkwaardig aangezien de vorming van etheen als cruciaal aanzien wordt om het evenwicht van de reactie naar het eindproduct te verschuiven.



Styreen **xv** accumuleert echter in het reactiemengsel en begint in competitie te treden met het substraat om met de katalysator te reageren. Zo wordt in een tweede katalytische cyclus styreen omgezet tot stilbeen **xviii** dat neerslaat uit het mengsel en wordt het methylideen carbeen **xix** gegenereerd. Dit carbeen kan ofwel reageren met styreen tot **xx** of met substraat tot **xxi**. Beide cyclobutanen genereren etheen tijdens de cycloreversie. In tegenstelling dus tot de normale metathese cyclus, wordt in dit geval etheen gegenereerd in twee secundaire katalytische cycli.

Enyne metathese (RCEYM), dat reactie inhoudt tussen een alkeen en een alkyn, heeft in het verleden veel minder aandacht gekregen dan RCM. Sequentiële reacties, bijvoorbeeld, zijn nauwelijks ontwikkeld voor RCEYM. Tot nu toe zijn enkel een eenpotsreactie van RCEYM met een Diels-Alder reactie of een cyclopropanering beschreven. In tegenstelling tot de olefiene metathese, worden bij RCEYM alle koolstof atomen van het uitgangsproduct ingebouwd in het eindproduct dat een synthetisch bruikbaar 1,3-dieen bevat. Ondanks het grote nut van deze reactie is echter nog relatief weinig bekend over het mechanisme ervan. Meer precies wordt nog vaak de vraag gesteld of de reactie geschiedt via het "yn-dan-een" of via het "een-dan-yn" mechanisme.

De allereerste combinatie van RCEYM met een oxidatie werd ontwikkeld door α-aminofosfonaten **xxiv**, die zowel een dubbele als een driedubbele binding bevatten, te behandelen met de tweede generatie Grubbs katalysator in kokende benzeen in aanwezigheid van TCQ. De substraten voor deze reactie werden bereid in twee eenvoudige stappen uit imines **xxii**. Als eerste stap werden deze imines gefosfonyleerd met volledige 1,2-regioselectiviteit door ze te behandelen met dialkyl fosfiet in kokende methanol.



xxii

xxiii
6 voorbeelden
65-95%

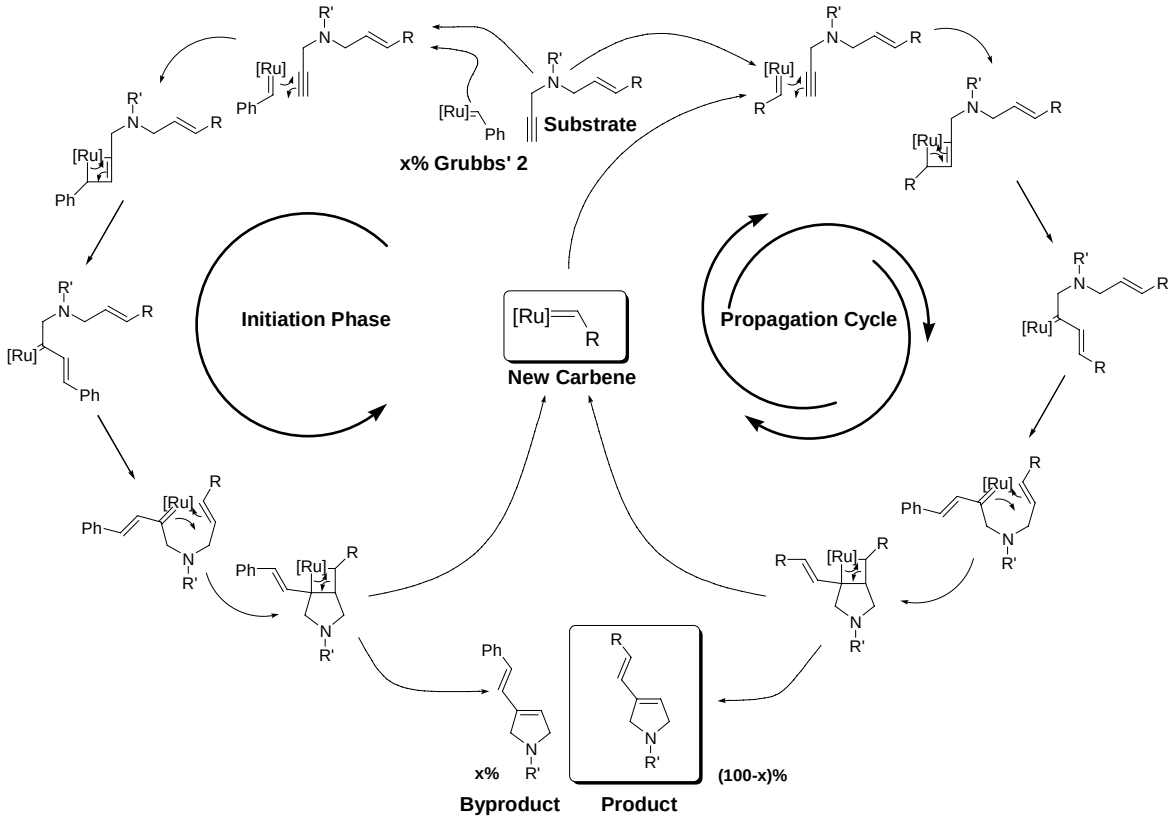
xxiv
6 voorbeelden
48-85%

xxvi
4 voorbeelden
48-85%

xxv
5 voorbeelden
68-88%

Het *N*-atoom van de verkregen α-aminofosfonaten **xxiii** werd beschermd met een benzylgroep door te refluxen in aceton met K_2CO_3 als base, benzylbromide als elektrofiel en NaI als katalysator.

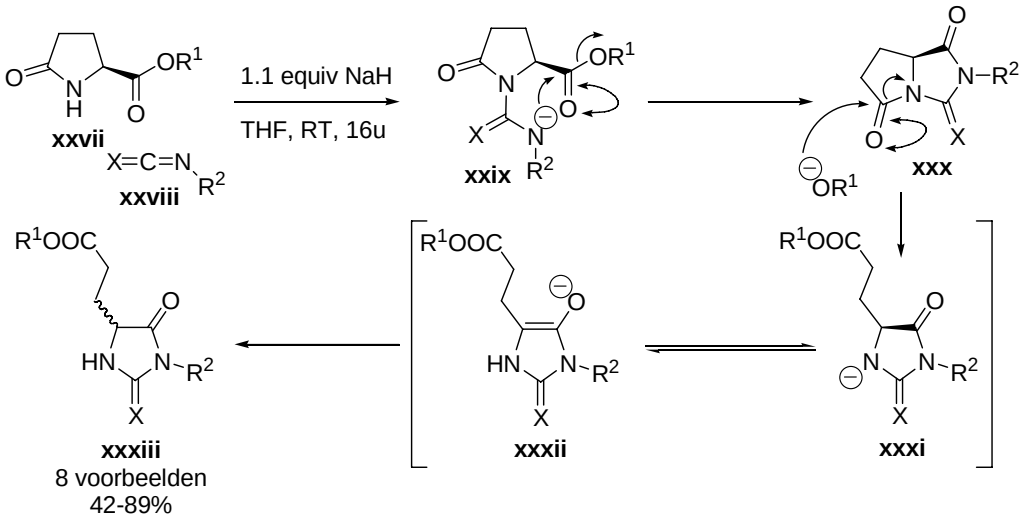
Deze RCEYM/oxidatie sequentie laat de synthese toe van sterk gefunctionaliseerde 2-gefosfonyleerde pyrrolines **xxv** en pyrrolen **xxvi**. Een gedetailleerd mechanistisch onderzoek bracht aan het licht dat de reactie de "yn-dan-een" pathway volgt. Het bewijs voor dit reactiemechanisme is gebaseerd op de vorming van bepaalde eind- en nevenproducten, spectroscopische gegevens en tenslotte op het verschil in reactiviteit van verschillende substraten. Tijdens de initiatie fase wordt het Grubbs carbeen omgezet tot een nieuw ruthenium carbeen dat de propagatie cyclus verder zet.



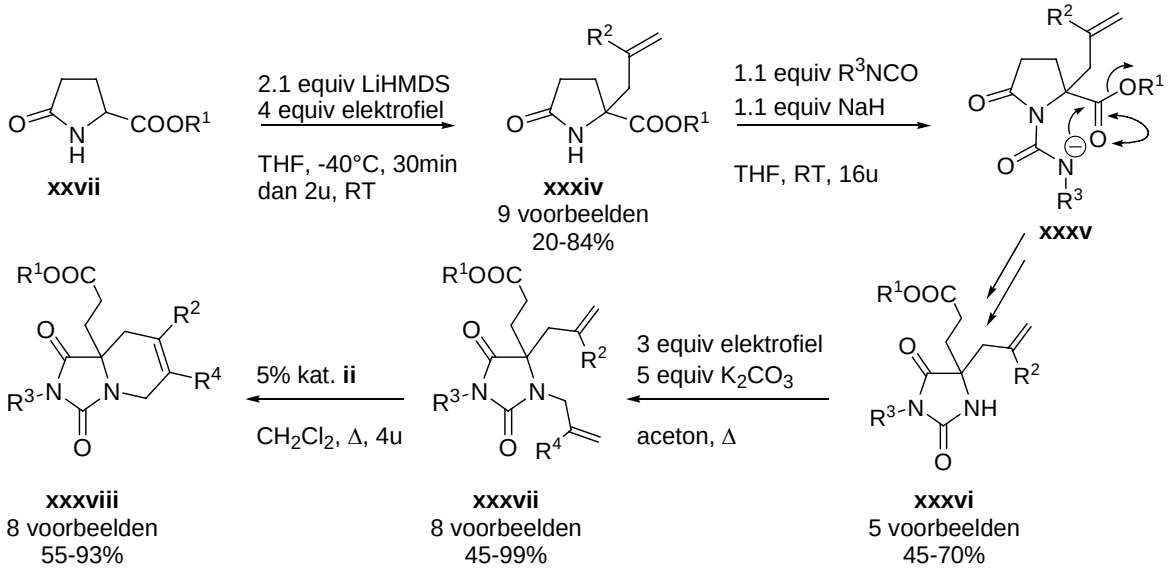
In het tweede deel van deze thesis werd een toetreding tot nieuwe polycyclische hydantoines ontwikkeld vertrekkend van pyroglutamaten. Hydantoines zijn reeds uitgebreid bestudeerd en vertonen een breed gamma aan biologische activiteiten. Tevens vertonen een reeks hydantoine derivaten, die gefuseerd zijn met een extra ring, een aantal interessante medicinale eigenschappen.

Wanneer een mengsel van een pyroglutamaat **xxvii** en een isocyanaat **xxviii** in ether behandeld wordt met NaH, wordt een neerslag gevormd tijdens de reactie die na opwerking het natrium zout bleek te zijn van het verwachte carbamoyl lactam **xxix** in hoge zuiverheid. Indien deze

reactie echter uitgevoerd wordt in THF, wordt er geen neerslag gevormd omdat intermediair **xxix** intramoleculair reageert door een nucleofiele aanval op de carbonylfunctie van het ester, gevolgd door uitstoot van een alkoxide anion en vorming van het bicyclisch intermediair **xxx**. Het alkoxide anion kan op zijn beurt dit bicyclisch intermediair openen met vorming van de anionen **xxxi** en **xxxii**. Deze anionen zijn met elkaar in evenwicht waardoor racemisatie van het chirale centrum optreedt en de hydantoines **xxxiii** geïsoleerd worden als een 1:1 mengsel van enantiomeren.

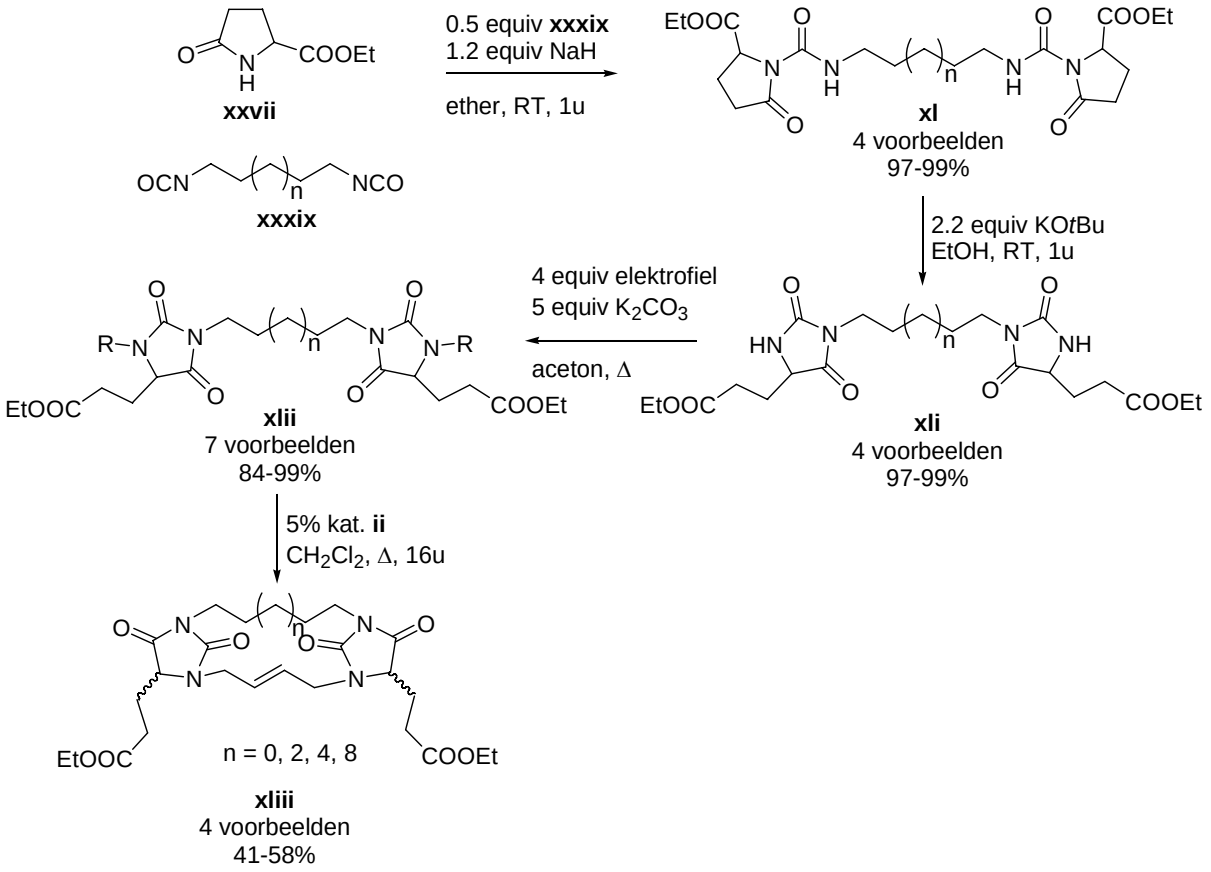


Deze ringtransformatie werd succesvol toegepast in een korte vierstapssequentie voor de synthese van hydantoinederivaten **xxxviii** die gefuseerd zijn met een zesring. In een eerste stap werden pyroglutamaten **xxvii** gealkyleerd op de 2-positie door gebruik te maken van LiHMDS en een gepast elektrofiel.



De studie toonde aan dat uitstekende resultaten bekomen kunnen worden wanneer een mengsel van het pyroglutamaat en elektrofiel behandeld wordt met 2.1 equivalenten LiHMDS bij -40 °C. Zelfs indien meerdere equivalenten elektrofiel gebruikt werden, werd er nooit reactie vastgesteld op het stikstof atoom. Behandeling van een oplossing van **xxxiv** en een isocyanaat in THF met NaH leidt vervolgens tot de vorming van het carbamoyl lactam **xxxv** dat een omlegging ondergaat tot hydantoine **xxxvi**. Deze verbindingen kunnen eenvoudig gealkyleerd worden op *N*(1) tot **xxxvii** door ze enkele dagen te refluxen met 2 equivalenten elektrofiel en 5 equivalenten fijngemalen K_2CO_3 in aceton. Behandeling van deze verbindingen met 5% katalysator **ii** in kokende CH_2Cl_2 leidt tot omzetting naar de gewenste derivaten **xxxviii**.

Tevens werd een nieuwe toetreding tot *N*(3),*N*(3)-polymethyleen-bis-hydantoines ontwikkeld. Bis-hydantoines, meestal dimeren van phenetoin of gelijkaardige producten, zijn in het verleden reeds met succes getest als analogen van HMBA en kunnen mogelijks hun nut bewijzen bij de behandeling van kanker. In dit werk werden bis-hydantoines **xli** verkregen door reactie van pyroglutamaat **xxvii** met bis-isocyanaten en daaropvolgende ringtransformatie van bis-carbamoyl lactamen **xl** in ethanol met KO*t*Bu als base.

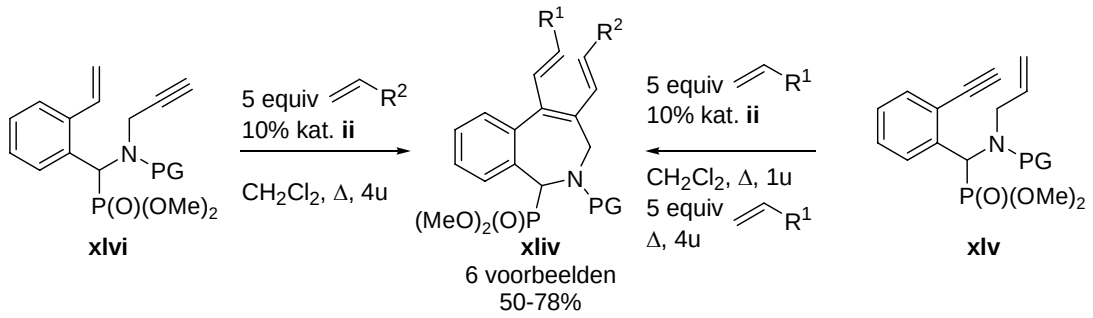


Deze verbindingen **xli** kunnen eenvouding gealkyleerd worden op *N*(1) tot **xlii** door ze te refluxen met 4 equivalenten elektrofiel en 5 equivalenten fijngemalen K_2CO_3 in aceton. De

derivaten met een allyl substituent op *N*(1) konden omgezet worden tot de overeenkomstige macrocyclische derivaten **xliii** door behandeling met de tweede generatie Grubbs katalysator **ii** in kokende CH_2Cl_2. Er werd aangetoond dat enkel de *trans* isomeren geïsoleerd werden. De aanwezigheid van een enkel isomeer ter hoogte van de dubbele binding kan verklaard worden door secundaire metathese reacties, aangezien het geweten is dat macrocyclische verbindingen isomeriseren naar een thermodynamisch gecontroleerde (*E*/*Z*) verhouding los van de stereochemie van het initieel gevormde alkeen.

Een aantal van de gesynthetiseerde hydantoines werd gescreend op hun anti-invasieve activiteit tegen een humane borstkanker cellijn. De gekozen screening assay is gebaseerd op de *in vitro* confrontatie van kankercellen met een fragment normaal hartweefsel dat gedissecteerd werd uit kuiken embryo's van 9 dagen oud. Er kan gesteld worden dat sommige van de aangemaakte bis-hydantoines goede anti-invasieve activiteit vertonen bij een concentratie van 100 μm en 10 μm. Tevens kunnen deze producten heel eenvoudig op grote schaal aangemaakt worden en zijn ze niet toxisch voor het hartweefsel dat gebruikt werd in de *in vitro* test. Jammer genoeg kon de activiteit van deze componenten niet correct voorspeld worden door een niet-lineair QSAR model. Daarom is er verder onderzoek nodig om het exacte werkingsmechanisme van deze structuren te ontrafelen zodat de synthese van meer actieve verbindingen mogelijk wordt. In een verder stadium zullen *in vivo* testen dienen te gebeuren om deze resultaten te valideren.

In het derde deel van deze thesis werden nieuwe toetredingen ontwikkeld naar benzo-gefuseerde verbindingen namelijk 1*H*-2-benzazepine-1-ylfosfonaten en gefosfonyleerde isoindolen. Benzo-gefuseerde verbindingen, en in het bijzonder zevenringen met bekende voorbeelden als diazepam (Valium®) en flurazepam (Dalmadorm®), hebben over de jaren heen veel aandacht gekregen omwille van hun alomtegenwoordigheid in natuurproducten en moderne farmaceutica.
Het eerste protocol voor de synthese van 1*H*-2-benzazepine-1-ylfosfonaten **xliv** maakt gebruik van een combinatie van RCEYM met cross-metathese. Hiertoe werd een refluxend mengsel van **xlv** en 5 equivalenten alkeen in CH_2Cl_2 behandeld met 10 mol% tweede generatie Grubbs' katalysator **ii**. Een extra hoeveelheid alkeen (5 equiv) dient toegevoegd te worden na 2 uren.

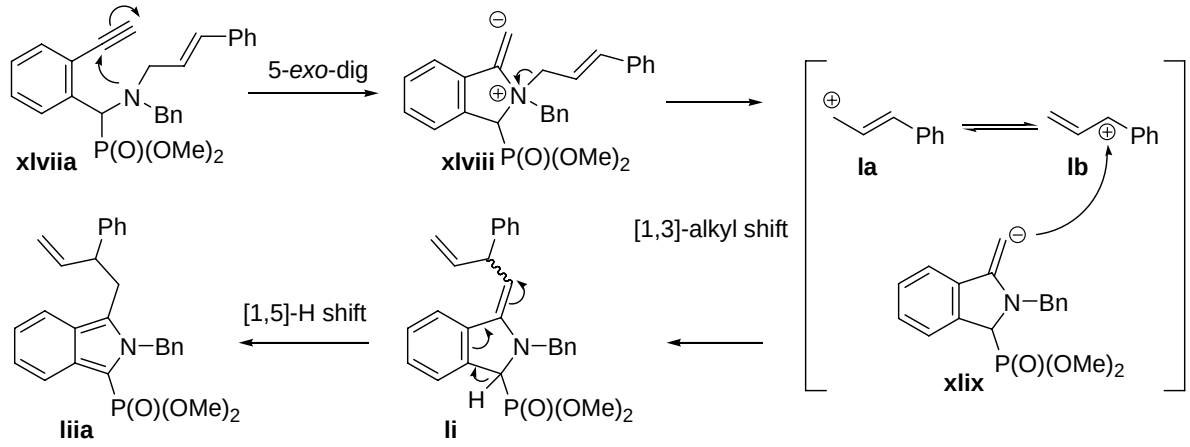


xlvi **xliv** **xlv**

6 voorbeelden
50-78%

Deze observatie werd verklaard door te kijken naar de volledige reactie cyclus. Tijdens het verloop van de reactie wordt het alkeen immers niet enkel ingebouwd in het eindproduct, maar ook gedimeriseerd in de zogenaamde "alkeen-sink" met regeneratie van het methylideen carbeen en productie van etheen. Bij evaluatie van de reactie tussen **xlvi** en alkenen werd vastgesteld dat het in dit geval niet nodig is een extra hoeveelheid alkeen toe te voegen. Het voordeel van deze strategie is dat het slechts de synthese vereist van twee substraten, met een eindstandige dubbele en driedubbele binding, die worden omgezet tot verschillende zevenringen afhankelijk van de toevoeging van een bepaald alkeen aan het reactiemengsel.

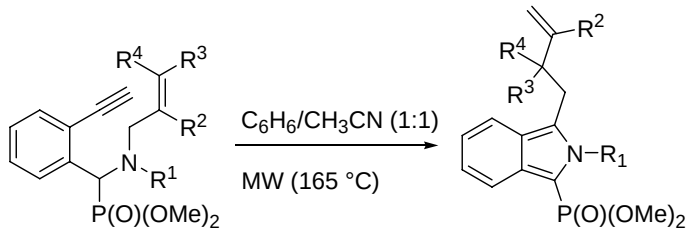
De behandeling van zeer gelijkaardige substraten **xlvii** die een niet-eindstandige dubbele binding bevatten met een metathese katalysator leidde niet tot de verwachte zevenring maar leverde gefosfonyleerde isoindolen. Gefosfonyleerde isoindolen zijn nog maar zelden beschreven in de literatuur. Er werd immers maar één toetreding tot deze producten gevonden, die echter een laag rendement gaf. Bovendien zijn er slechts weinig toetredingen gerapporteerd tot verwante verbindingen zoals gefosfonyleerde dihydroisoindolen en isoindolinonen. Deze laatste zijn gekend omwille van hun plantengroei regulerende eigenschappen.
Er werd gevonden dat deze omlegging thermisch gedreven is. Na een aantal experimenten konden het rendement en de conversiesnelheid geoptimaliseerd worden door de substraten te verhitten in een mengsel van benzeen/CH_3CN in een 1/1 verhouding tot 165 °C onder microgolf condities. De eerste stap in deze transformatie omvat waarschijnlijk een directe aanval van het vrije elektronenpaar van stikstof op de niet geactiveerde driedubbele binding op een 5-*exo*-dig wijze met vorming van **xlviii**.



Het zwitterion **xlviii** fragmenteert vervolgens met vorming van anion **xlix** en kationen **la** en **lb**. Anion **xlix** reageert met **lb** met vorming van **li**. Het resultaat van deze fragmentatie en recombinatie komt overeen met een [1,3]-alkyl shift. De omlegging eindigt met een [1,5]-H shift

die resulteert in aromatisering tot **lii**. Deze reactieweg vertegenwoordigt de eerste efficiënte toetreding tot gefosfonyleerde isoindolen.

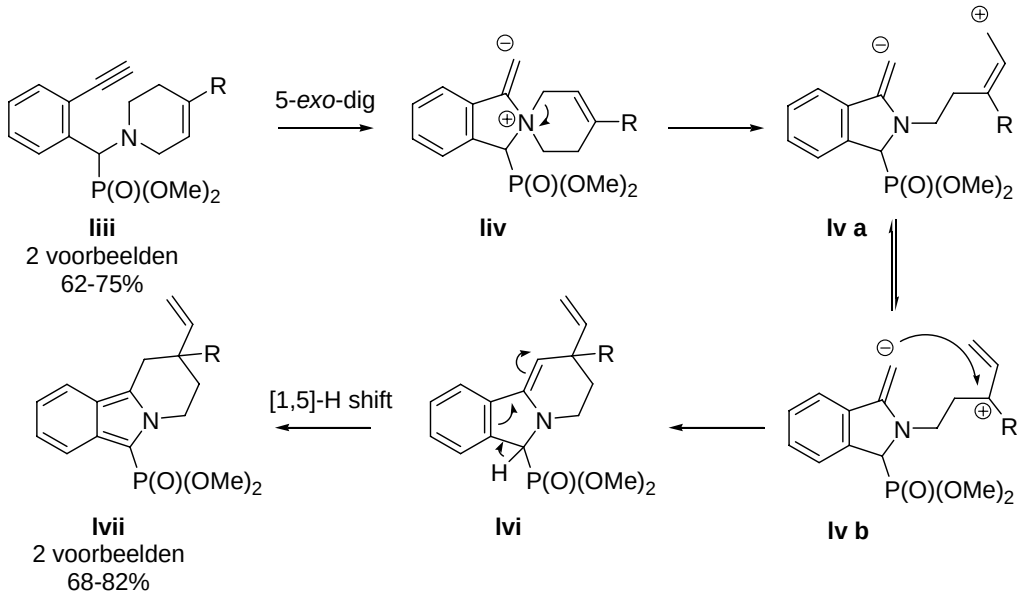
De algemene aard van deze omlegging werd aangetoond door een aantal α-aminofosfonaten **xlvii** te bereiden en te onderwerpen aan dezelfde condities. Deze α-aminofosfonaten werden bereid door gebruik te maken van een driecomponent koppeling tussen ethynylbenzaldehyde, secundaire amines en trimethyl fosfiet in aanwezigheid van $LiClO_4$. De isoindolen **lii** werden geïsoleerd in goed rendement.



xlvii
9 voorbeelden
48-88%

lii
9 voorbeelden
40-98%

Wanneer de migrerende allylische groep geïncorporeerd wordt in een extra ring, blijven het anion en het kation aan mekaar verbonden tijdens de reactie. Zoals verwacht, resulteerde de verhitting van **liii** onder microgolfcondities in de vorming van tricyclische verbindingen **lvii**. De fragmentatie van het zwitterion **liv** resulteert in de vorming van **lva** en resonantie vorm **lvb**. Een intramoleculaire aanval vormt een extra zesring **lvi**. Uiteindelijk zorgt aromatisering voor de vorming van isoindolen **lvii**.



liii
2 voorbeelden
62-75%

liv

lv a

lv b

lvi

lvii
2 voorbeelden
68-82%

Vanuit de resultaten behaald in dit werk, kunnen een aantal perspectieven voor toekomstig werk geformuleerd worden. Initieel werd een nieuwe toetreding tot pyrrolen ontwikkeld, gebruik makend van een combinatie van RCM of RCEYM met oxidatie. Dit zal onderzoekers toelaten deze interessante azaheterocyclische verbindingen, en gefosfonyleerde derivaten, op efficiente wijze te construeren. Teneinde het biologisch potentieel van deze producten te evalueren, kan een ontscherming van het fosfonaat wenselijk zijn. Nieuwe katalytische systemen, bijvoorbeeld op een vaste drager, kunnen toelaten de synthese op een grotere schaal uit te voeren. Mogelijks kan deze methodologie uitgebreid worden voor de synthese van andere heterocyclische verbindingen. Het is echter onwaarschijnlijk dat furanen of thiofenen gemaakt kunnen worden via een éénstapssequentie aangezien waarschijnlijk de metathese katalysator vernietigd zal worden door het gebruik van sterkere oxidanten. In de toekomst zou de ontwikkeling van nieuwe katalysatoren de synthese van meer gesubstitueerde derivaten en het gebruik van sterkere oxidanten kunnen toelaten. Het mechanistisch inzicht in RCEYM zal onderzoekers toelaten de vorming van bepaalde neven- en eindproducten in reactiemengsels te verklaren.
De nieuwe toetreding tot hydantoines kan zich ontpoppen tot een heel krachtige methode indien gecombineerd met enantioselectieve reacties op het pyroglutamaat. Toekomstige biologische screening van de producten gesynthetiseerd in deze thesis zou het exacte werkingsmechanisme aan het licht kunnen brengen en zo de synthese kunnen bijsturen naar meer actieve structuren. De verzeping van het ester kan meer polaire structuren leveren met een hogere wateroplosbaarheid en mogelijks verhoogde activiteit.
De combinatie van RCEYM met cross-metathese voor de synthese van 1*H*-2-benzazepine-1-ylfosfonaten laat de synthese toe van een brede waaier aan benzo-gefuseerde azepines, afhankelijk van de toevoeging van een specifiek alkeen. Het verkregen dieen zou tevens verder gefunctionaliseerd kunnen worden door middel van een Diels-Alder reactie, wat leidt tot meer complexe structuren in één synthetische inspanning.
De omlegging tot gefosfonyleerde isoindolen is een veelbelovende reactie omdat ze mogelijks kan toegepast worden voor de synthese van andere heterocyclische verbindingen. Zo zou gestart kunnen worden van 3-ethynyl-furan-2-carbaldehyde of 3-ethynyl-pyridine-2-carbaldehyde in plaats van 2-ethynylbenzaldehyde. Reacties met interne alkynen in plaats van eindstandige, zou kunnen leiden tot isoquinoline derivaten na een omlegging die begint met een 6-*endo*-dig aanval in plaats van de 5-*exo*-dig aanval zoals hier beschreven.

Samengevat werd een waaier aan azaheterocyclische verbindingen bereid gebruik makend van RCM. Er werden onder andere vijf-, zes-, en zevenringen gesynthetiseerd naast een aantal macrocyclische derivaten. Bovendien biedt de combinatie van RCM met oxidatieve aromatisering een nieuwe toetreding tot aromatische verbindingen. De resultaten uit deze thesis bieden de mogelijkheid aan andere onderzoekers om deze interessante chemie verder te ontwikkelen.

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Appendix 2 – Overview of Structures

About 213 compounds have been described in this thesis. In this appendix a location (page number or paper) is given to each structure which allows the interested reader to quickly retrieve the procedure and spectral data of a certain compound. The synthesized compounds are divided into 9 classes:

1. Diallylamines, propargylamines, pyrroles, pyrrolines (42 compounds)
2. α-Aminophosphonates (46 compounds)
3. 2-Phosphonopyrrolines and 2-phosphonopyrroles (23 compounds)
4. Phosphonylated isoindoles (13 compounds)
5. Phosphonylated benzazepines (7 compounds)
6. Hydantoins and bicyclic derivatives (33 compounds)
7. Bis-hydantoins and bis-carbamoyllactams (20 compounds)
8. Pyroglutamate derivatives (14 compounds)
9. Miscellaneous (15 compounds)

1. Diallylamines, propargylamines, pyrroles, pyrrolines

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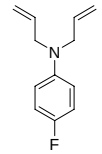
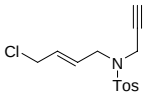
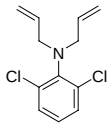
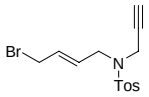
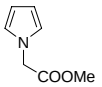
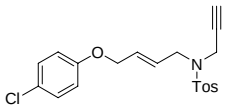
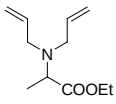
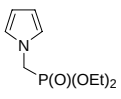
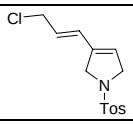
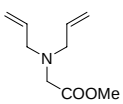
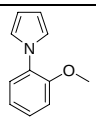
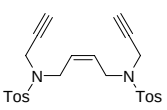
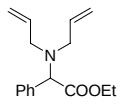
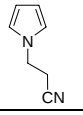
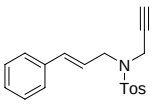
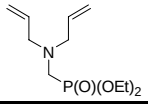
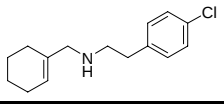
	96		Paper II		Paper IV
	97		102		Paper IV
	97		Paper II		Paper IV
	97		Paper II		Paper IV
	97		Paper II		Paper IV
	98		102		Paper IV
	98		Paper II		143

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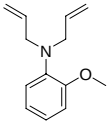
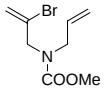
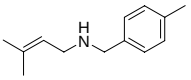
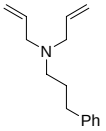
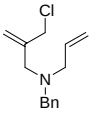
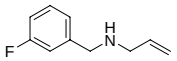
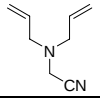
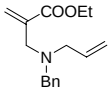
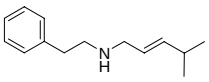
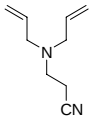
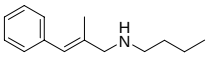
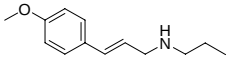
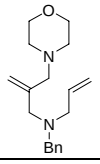
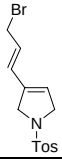
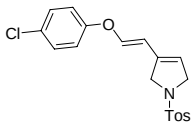
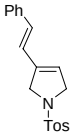
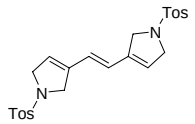
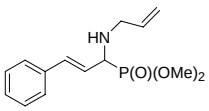
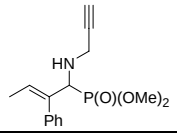
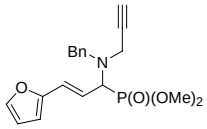
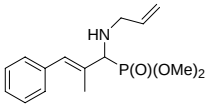
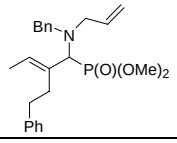
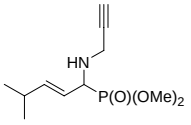
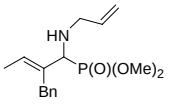
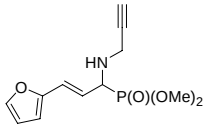
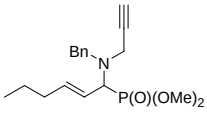
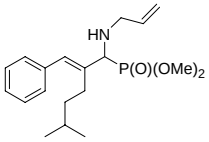
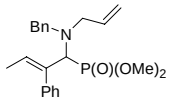
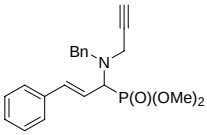
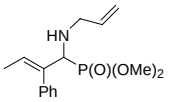
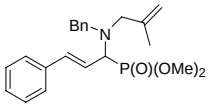
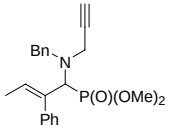
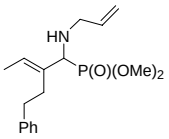
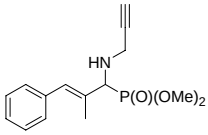
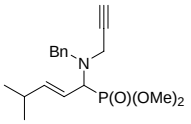
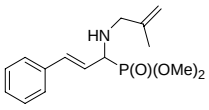
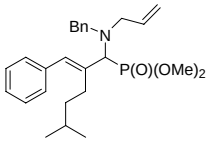
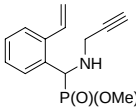
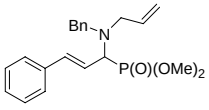
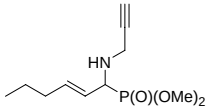
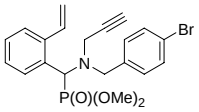
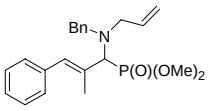
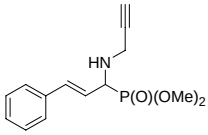
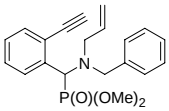
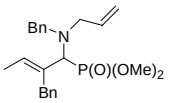
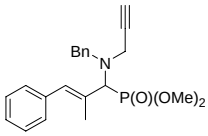
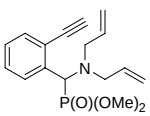
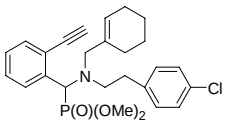
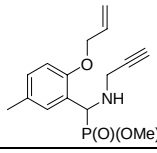
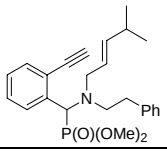
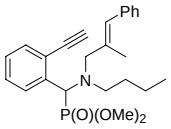
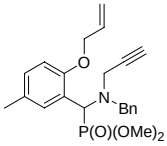
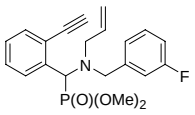
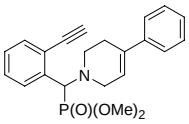
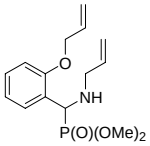
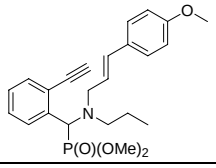
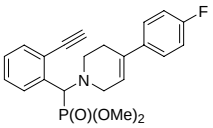
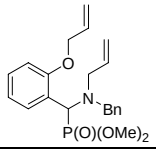
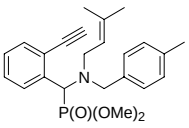
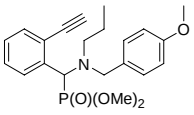
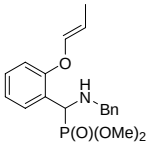
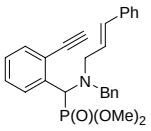
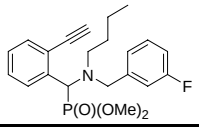
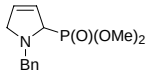
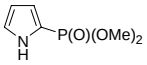
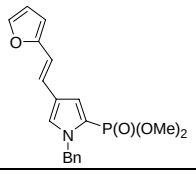
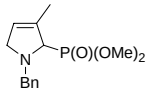
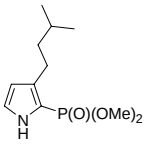
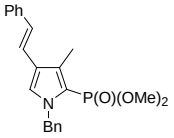
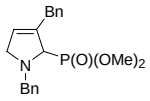
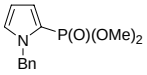
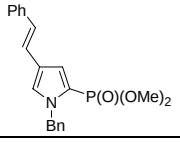
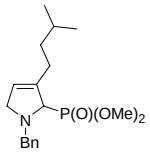
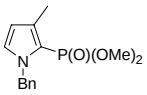
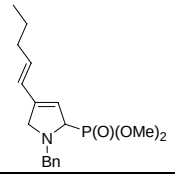
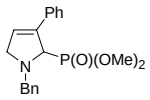
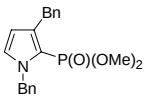
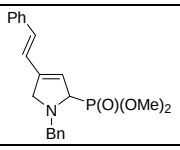
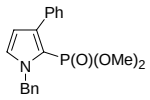
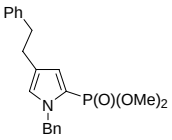
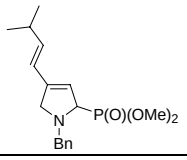
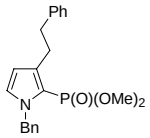
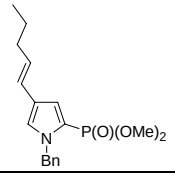
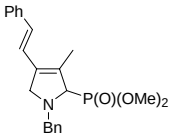
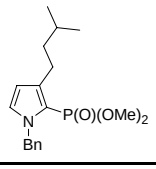
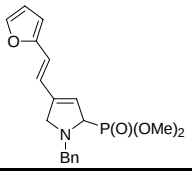
	98		100		142
	99		100		143
	99		101		142
	99		102		143
	100		102		142
	101		Paper IV		Paper IV
	100		Paper IV		Paper IV

2. α-Aminophosphonates

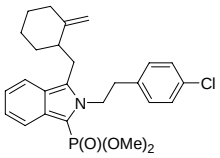
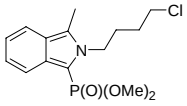
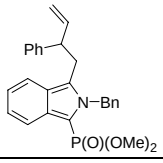
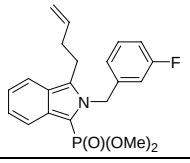
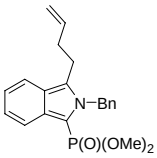
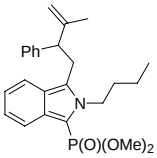
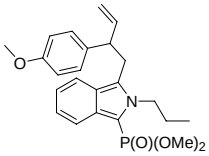
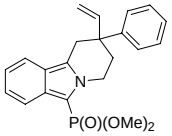
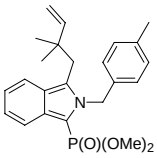
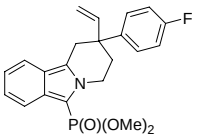
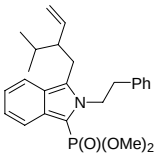
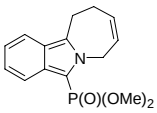
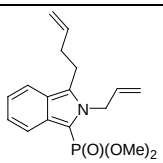
Structure	Location	Structure	Location	Structure	Location
	104		Paper IV		Paper IV
	104		109		Paper IV
	105		Paper IV		Paper IV
	105		109		Paper IV
	106		110		Paper IV
	106		Paper IV		Paper IV
	107		108		134
	Paper III		Paper IV		135
	107		Paper IV		135
	108		Paper IV		148

Structure	Location	Structure	Location	Structure	Location
	147		138		146
	147		138		146
	149		140		145
	150		140		145
	149		141		144
	148				

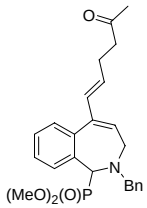
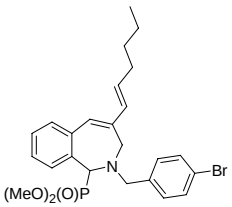
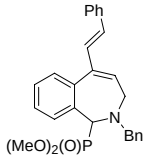
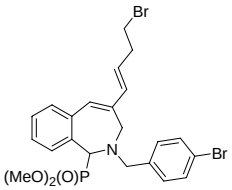
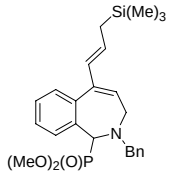
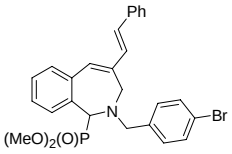
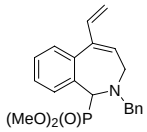
3. 2-Phosphonopyrrolines and 2-phosphonopyrroles

Structure	Location	Structure	Location	Structure	Location
	Paper III		113		Paper IV
	110		113		Paper IV
	110		Paper III		Paper IV
	111		112		Paper IV
	111		112		Paper IV
	112		114		Paper IV
	113		Paper IV		Paper IV
	112		Paper IV		

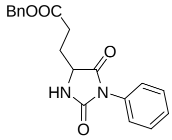
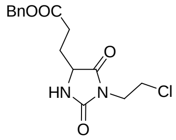
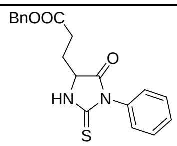
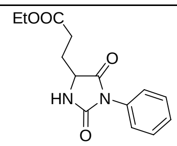
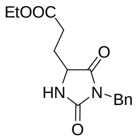
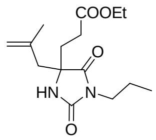
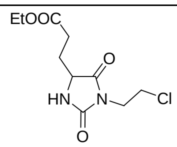
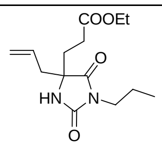
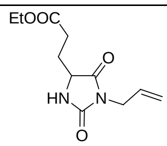
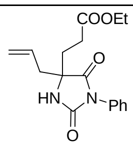
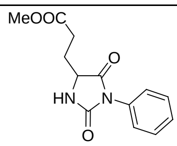
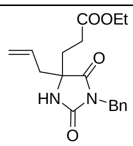
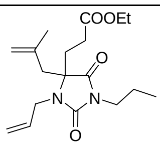
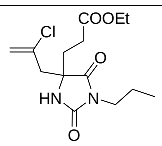
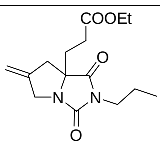
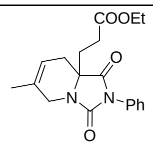
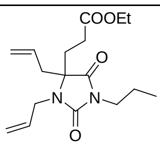
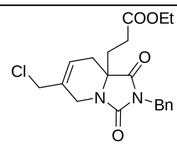
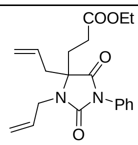
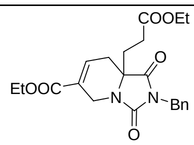
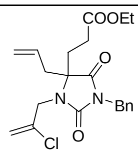
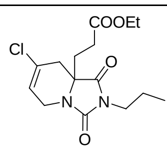
4. Phosphonylated isoindoles

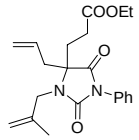
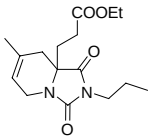
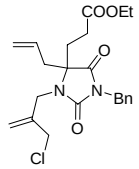
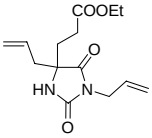
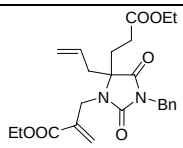
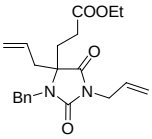
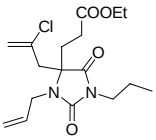
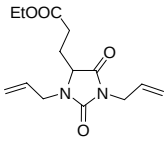
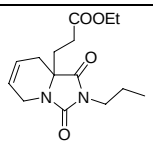
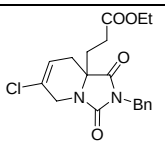
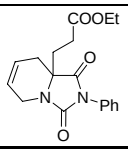
Structure	Location	Structure	Location
	153		156
	150		153
	151		154
	151		155
	152		155
	152		156
	154		

5. Phosphonylated benzazepines

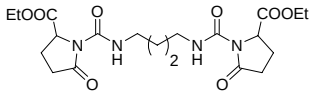
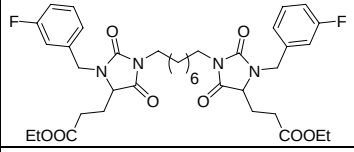
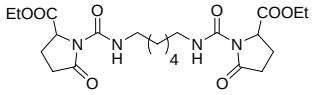
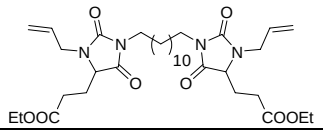
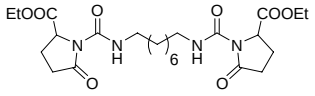
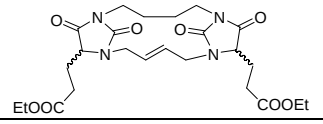
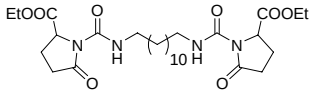
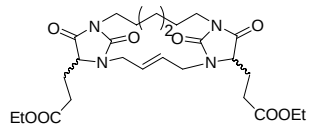
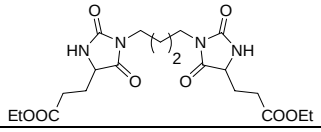
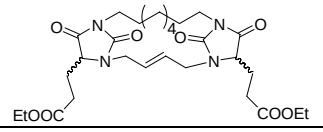
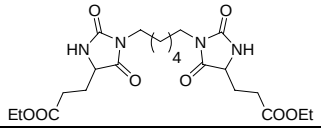
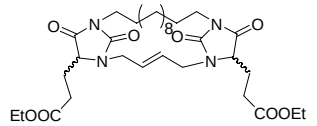
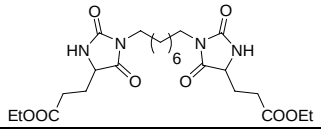
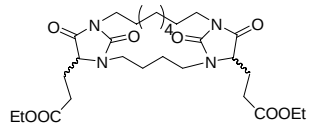
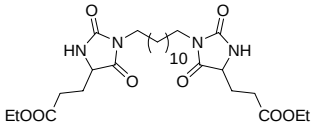
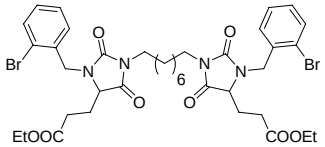
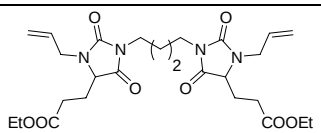
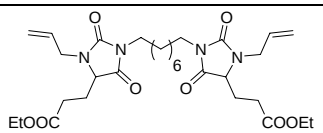
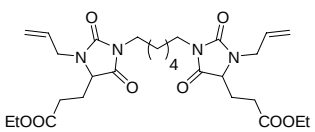
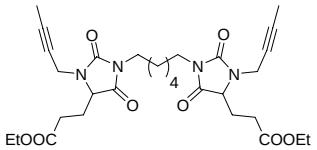
Structure	Location	Structure	Location
	Paper VII		Paper VII
	Paper VII		Paper VII
	Paper VII		Paper VII
	136		

6. Hydantoins

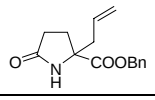
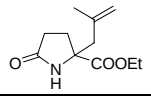
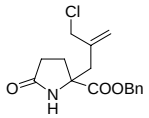
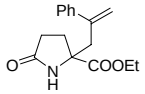
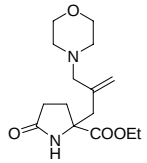
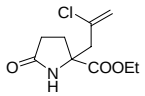
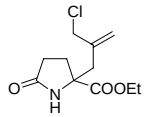
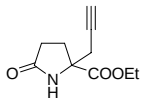
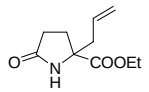
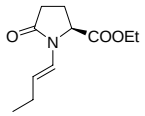
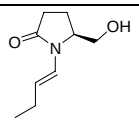
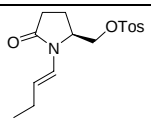
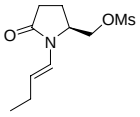
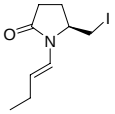
Structure	Location	Structure	Location
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	121		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V

Structure	Location	Structure	Location
	Paper V		Paper V
	Paper V		121
	Paper V		122
	Paper V		122
	Paper V		Paper V
	Paper V		

7. Bis-hydantoins and bis-carbamoyllactams

Structure	Location	Structure	Location
	123		129
	123		128
	123		130
	124		130
	124		131
	125		132
	125		133
	126		129
	126		127
	127		128

8. Pyroglutamate derivatives

Structure	Location	Structure	Location
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		Paper V
	Paper V		114
	115		115
	116		116

9. Miscellaneous

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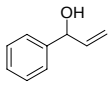
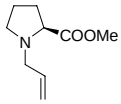
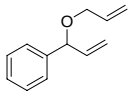
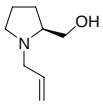
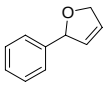
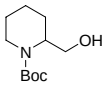
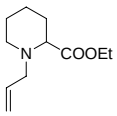
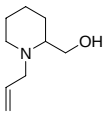
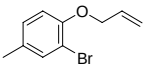
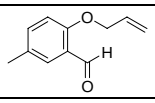
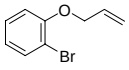
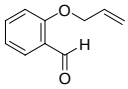
	117		103
	118		103
	118		104
	119		120
	119		120
	120		137
	137		139
	139		

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EDUCATION

1993-1998:	Secondary School: Sint-Lodewijkscollege, Lokeren. Latin-Mathematics
1998-2003:	Bio-engineer Chemistry Ghent University, graduated with great distinction Thesis: 'Ringopening-ringclosing methodology for the synthesis of pyroglutamate analogues' Promoter: Prof. dr. ir. C.V. Stevens
February 2003:	Intensive Socrates programme: 'Agriculture: Source of raw material for industry' BOKU University, Vienna
2004-2006:	Master of Economics and Business Administration option: Business Economics Ghent University, graduated with distinction Thesis: 'Biofuels on the Dutch market; a study of the economic chances, consequences, barriers and supportive measures' Promotor: dr. J. Albrecht

CAREER

August 2003 - Present:	PhD student, BOF-research project Department of Organic Chemistry, Faculty of Bioscience Engineering Ghent University Title: 'Novel metathesis applications: synthesis of new azaheterocycles by homogeneous catalysis' Promoter: Prof. dr. ir. C.V. Stevens
From june 2007:	Production engineer at LANXESS Rubber N.V. (Zwijndrecht)

SCIENTIFIC CAREER

Publications in international SCI-journals with peer review (a1):

- **N. Dieltiens**, C. V. Stevens, D. De Vos, B. Allaert, R. Drozdzak, F. Verpoort, *Tetrahedron Lett.* **2004**, *45*, 8995–8998. Pyrrole synthesis using a tandem Grubbs' carbene-$RuCl_3$ catalytic system.
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- B. Allaert, **N. Dieltiens**, N. Ledoux, C. Vercaemst, P. Van Der Voort, C. V. Stevens, A. Linden, F. Verpoort, *J. Mol. Catal A-Chem*. **2006***, 260,* 221-226*.* Synthesis and activity for ROMP of bidentate Schiff base substituted second generation Grubbs catalysts.
- **N. Dieltiens**, C. V. Stevens, *Synlett* **2006**, *17,* 2771-2776. Domino Ring-Closing Enyne Metathesis—Cross-Metathesis Approach to 1-Phosphonylated Benzazepines.

- **N. Dieltiens**, K. Moonen, C. V. Stevens, *Chem. Eur. J.* **2007**, *13*, 203-214. Enyne Metathesis-Oxidation Sequence for the Synthesis of 2-Phosphono Pyrroles, Proof of the "Yne-then-Ene" Pathway.
- **N. Dieltiens**, C. V. Stevens, *Org. Lett.* **2007**, *9,* 465-468. Metal-Free Entry to Phosphonylated Isoindoles by a Cascade of 5-*exo*-dig Cyclization, a [1,3]-Alkyl Shift, and Aromatization under Microwave Heating.
- K. G. R. Masschelein, C. V. Stevens, **N. Dieltiens**, D. D. Claeys, Tetrahedron **2007**, in press. Exploiting the regioselectivity of pyroglutamate alkylations for the synthesis of 6-azabicyclo[3.2.1]octanes and 4-azabicyclo[3.3.0] octanes.

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- B. Allaert, **N. Dieltiens**, C. Stevens, R. Drozdzak, I. Dragutan, V. Dragutan, F. Verpoort, NATO Advanced Study Institute (ASI), Kluwer Academic Publishers, Dordrecht, The Netherlands, *in preparation*. Towards New Generations of Metathesis Metal-Carbene Precatalysts.

Abstracts at conferences (posters):

- L. De Buyck, F. Ghelfi, A. Mucci, U. P. Pagnoni, **N. Dieltiens**, A. F. Parsons. Synthetic utility of 2,2-dichlorocarboxylic acids. 10th Belgian Organic Synthesis Symposium, July 12-16 2004, Louvain-la-Neuve, Belgium.
- **N. Dieltiens**, C. V. Stevens, B. Allaert, F. Verpoort. Ring-closing metathesis-oxidation sequence for pyrrole synthesis. 8th Sigma-Aldrich organic synthesis meeting. Dec 2-3, 2004, Spa, Belgium.
- C. V. Stevens, **N. Dieltiens**, D. D. Claeys. Straightforward ring opening of pyroglutamates for the synthesis of perhydro 2,4-dioxo-1,3-diazepines. 6th Annual Florida Heterocyclic Course and Conference. March 3-6, 2005. University of Florida, Gainsville, US.
- **N. Dieltiens**, D. D. Claeys, C. V. Stevens. Synthesis of bicyclic hydantoin derivatives via a ring transformation-RCM sequence. 9th Sigma-Aldrich organic synthesis meeting. Dec 1-2, 2005, Spa, Belgium.
- **N. Dieltiens**, K. Moonen, C. V. Stevens. Enyne metathesis: a convenient way of making heterocycles. 10th Sigma-Aldrich organic synthesis meeting. Dec 7-8, 2006, Spa, Belgium.
- K. G. R. Masschelein, **N. Dieltiens**, D. D. Claeys, T. Rammeloo, C. V. Stevens. Exploiting the regioselectivity of pyroglutamate alkylations. 10th Sigma-Aldrich organic synthesis meeting. Dec 7-8, 2006, Spa, Belgium.
- S. Van der Jeught, **N. Dieltiens**, I. Laureyn, C. V. Stevens. Synthesis of analogues of fosmidomycin, a promising antimalarial compound. 10th Sigma-Aldrich organic synthesis meeting. Dec 7-8, 2006, Spa, Belgium.

Abstracts at conferences (oral presentations):

- **N. Dieltiens**, D. D. Claeys, C. V. Stevens. Straightforward synthesis of complex hydantoin derivatives *via* a rearrangement-RCM sequence. Journées Nord-Ouest Européennes des Jeunes Chercheurs. April 13-14, 2006, Villeneuve d'Ascq, France.
- **N. Dieltiens**, K. Moonen, C. V. Stevens. Orthogonal tandem catalysis and domino reactions for the synthesis of (2-phosphono) pyrroles. Bilateral Scientific Cooperation Flanders-Hungary, New entries towards highly functionalized bicyclic, chiral and spirocyclic pyrrolidines and the synthesis of 3-functionalized azetidin-2-carboxylates. July 10, 2006, Ghent, Belgium.

Participation to conferences:

- Conformationally constrained amino acids and opioid peptides: synthesis, chiral analysis and biological activity. Sept 19, 2003, Ghent University.
- 7th Sigma-Aldrich organic synthesis meeting. Dec 4-5, 2003, Spa, Belgium.
- Detection of antimutagenic and anticarcinogenic properties of southern African plant species and their isolated components. Oct 22, 2004, Ghent University.
- "Synthesis an Biosynthesis of Antibiotics" Prof. J. E. Baldwin (Oxford University). The 2004 Lilly European distinguished lectureship organised in the frame of MeRinOS group activities. Nov 17, 2004, Facultés N.D. de le Paix, Namur, Belgium.
- 8th Sigma-Aldrich organic synthesis meeting. Dec 2-3, 2004, Spa, Belgium.
- 9th Sigma-Aldrich organic synthesis meeting. Dec 1-2, 2005, Spa, Belgium.
- 10th Sigma-Aldrich organic synthesis meeting. Dec 7-8, 2006, Spa, Belgium.